STEP-UP TO USMLE STEP 1

2015 EDITION

Michael McInnis • Samir Mehta
Chris Lewis • Sonia Mehta • Sonul Mehta
Adam J. Mirarchi • Edmund A. Milder

500+ “Quick Hits” and mnemonics highlight key facts for USMLE Step 1
Systems-based approach covers only the details you need
NEW! Includes expanded coverage of Immunology concepts
350 online USMLE-style questions, with complete answer-explanations
STEP-UP TO USMLE Step 1 2015
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Michael McInnis, MD
Internal Medicine
Chief Educator
Doctors in Training.com, LLC
Fort Worth, Texas

Samir Mehta, MD
Assistant Professor
Department of Orthopaedic Surgery
Chief, Orthopaedic Trauma Service
The Hospital of the University of Pennsylvania
Philadelphia, Pennsylvania

Chris Lewis, MD
Family Medicine
Chief Educator
Doctors in Training.com, LLC
Austin, Texas
Sonia Mehta, MD  
Fellow  
Emory Eye Center  
Emory University  
Atlanta, Georgia  

LCDR Edmund A. Milder, MC USNR  
Department of Pediatrics  
Naval Medical Center  
San Diego, California  

Sonul Mehta, MD  
Assistant Professor  
Department of Ophthalmology  
Hospital of the University of Pennsylvania  
Philadelphia, Pennsylvania  

Adam J. Mirarchi, MD  
Assistant Professor  
Department of Orthopaedic Surgery  
Oregon Health & Science University  
Portland, Oregon
We would like to extend our thanks to all the reviewers and contributors to previous editions and extend special thanks to the contributors to this edition who have helped review and update this text to reflect the most current knowledge in their respective fields.

JENNIFER SHUFORD, MD
Infectious Disease
Austin, Texas

HAMPTON RICHARDS, MD
Obstetrics and Gynecology
Dallas, Texas

ADAM ODEH, PhD
Microbiology and Immunology
Fort Worth, Texas

TIMOTHY L. McCAVIT, MD, MS
Pediatric Hematology/Oncology
Dallas, Texas
Interested in medical publishing? Contribute to Step-Up!

Student suggestions and feedback are always welcomed and appreciated by the Step-Up team. Please send feedback and suggestions for new study material and test-taking strategies by writing to the authors at the website provided. Students can also directly submit new mnemonics, quick hits, tables, and figures. For each original entry incorporated into the text, students’ names will be listed and personally acknowledged in the next edition. If duplicate entries are received, the first to submit will be acknowledged.

To make an entry or provide feedback and suggestions, simply visit http://www.lww.com and click Contact LWW.

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As the first national licensure exam encountered during a medical career, the USMLE Step 1 is often a source of anxiety for the medical student.

As with most things in life, having a systematic plan can be helpful in approaching what at first seems like an enormous task—preparing for the boards. The authors of *Step-Up to the USMLE Step 1* have created this guide below to direct you in effectively preparing for and excelling on the boards.

The first section of the guide will introduce you to the exam and the test makers. It will also familiarize you with the exam structure, content, testing environment, and interface. Finally, it will review how the test is scored and how to register for the exam.

The second section of the guide details successful preparation strategies. In this section, you will learn tips for creating study schedules and gathering study materials as well as strategies for effective studying.

---

**THE EXAM: THE USMLE STEP 1**

**The National Board of Medical Examiners**

The USMLE is a joint endeavor by the National Board of Medical Examiners (NBME) and Federation of State Medical Boards (FSMB). Step 1 is the first of three exams medical students and graduates need to pass in order to become licensed physicians in the United States. The NBME was founded in 1915 in Philadelphia, Pennsylvania and administered its first exam in 1916. The first exams were largely essay based and were organized around testing the basic science subjects of anatomy, physiology, biochemistry, pathology, pharmacology, microbiology, and behavioral science. The exam has evolved over the years. In the early 1990s, after years of culminated efforts, the USMLE was introduced. This test embraced the systems-based practice of medicine and adopted a clinically oriented question format. In 1992, Step 1 replaced the Federation Licensing Examination (FLEX) and now serves as the single exam for international medical graduates seeking U.S. medical licensure. In 1999, the test became computer based, and in 2005, the FRED software was adopted.

**Test Structure**

The exam consists of 322 questions administered in seven blocks of 46 questions each with 60 minutes per block (Table 1). The eighth block is a survey consisting of 11 questions. Students are allotted 45 minutes of authorized break time that can be taken anytime between blocks.

Breaks can be taken between blocks when you wish. Figure 1 shows two suggested test day schedules. The first schedule is the traditional one-break schedule made for the student who likes one large midday break (Figure 1). The second schedule is for those students who prefer multiple breaks in order to stay fresh and to prevent testing fatigue. Both schedules may be modified to individual preferences.

---

**QUICK HIT**

After the seventh block, a screen appears to move on to the eighth block. The eighth block is not a question block. It is a survey of your testing experience consisting of 11 questions. Don’t be fooled!
Test Content

The exam consists of multiple-choice questions; each question contains a question stem followed by five or more answer choices. Nearly 75% of questions begin with a clinical vignette or patient scenario. Students may also be asked direct questions. What kinds of questions are not seen on the test? Question stems including “all of the following except,” “not,” and matching-style questions are never included in Step 1 exams.

Often, examinees will be presented with answer choices that are partially correct. In these instances, it is important to pick the option that best answers the statement in the question stem and move on.

Prior to test day, take the exam tutorial offered on the NBME website. On exam day, skip the tutorial and gain an extra 15 minutes of break time.
Questions may range in difficulty from medium to hard. Although the questions vary from test to test and year to year, the proportion of question difficulty does not change.

Something important for you to remember: Anywhere from 10% to 20% of questions seen on exam day are experimental questions that are not scored. Therefore, when presented with a difficult question with options that seem partially correct, it is important to select an answer that best fits and move on.

Test Environment

In general, Prometric centers share a generic design. There is the reception area where you will register on the morning of the exam, place your belongings in a locker, and return to take breaks. Beyond this is the examination area where only certain items are allowed: a government-issued identification card (typically a driver's license or passport) and a locker key. Everything else, including cell phones, pagers, digital watches, PDAs, books, notes, wallets, food, and beverages, goes into the locker. The examination area consists of a series of cubicles with computers. Test-takers are given noise reducer muffs, a dry-erase board, markers, and a dry eraser to use as needed during the exam. Proctors walk through the rooms periodically to make sure test rules are obeyed. When taking an authorized break after a block is completed, you will need to leave the examination area, present an identification card, and sign a book. The process is repeated when you return to the testing area after the break. When you return to the cubicle, the computer will ask for your candidate identification number, which is written at the top of the dry erase board. As soon as you enter the candidate identification number into the computer, the next testing block begins.

Test Interface

The NBME offers an online tutorial that reviews exam procedures and the testing interface. Briefly, the testing interface for each block consists mainly of a single question and answer choices below it (Figure 2). Above this is a panel with several icons. Clicking on the appropriate icons allows you to perform that specific function. Clicking on the “mark” button will mark the question for that block, allowing you to return to the question at the end of the set. Next to the mark button are navigation buttons including a “previous” button and “next” button. These move you back one question or forward one question. Clicking on the “labs” button displays the normal lab values screen. Four options are offered: blood, hematologic, cerebrospinal, and sweat/urine/BMI. You can also write a note next to the text by clicking on the “notes” button. Finally, clicking the “calculator” button brings up a calculator to use for basic math functions.

On the left part of the screen is a panel with a running list of 46 questions. The question that is currently being viewed is highlighted in blue. Incomplete questions have a dot next to the item number and completed questions have no dot. When you mark questions with the mark function, a flag appears next to that question. You can directly click on that question to return to it at any time before the block ends.

Test Scoring

Examinees receive their score via an electronic score report 3 to 6 weeks after taking the exam. The score report consists of three key pieces of information. First, it states whether the examinee has passed or failed. Second, it displays a score in a three-digit scale and a two-digit scale that reflects how well the examinee performed on the content of the exam. The mean score on the exam is 227 with a standard deviation of 22. Passing on the three-digit scale is 192, which corresponds to 75 on the two-digit scale. The minimum passing score is subject to change by the NBME. Finally, there is a table depicting the examinee’s performance profile by basic science subject and organ system. The examinee's medical school also receives a report containing pass/fail status, digit score, and group performance profile. During the residency application process, residency programs receive a transcript containing pass/fail status and the digit score without the performance profile (Figure 3).
When preparing for the exam, there are two objectives. One objective should be to pass the exam so that you can be on your way to becoming a licensed physician in the United States. Also, passing the exam is often linked to proceeding to the third year of medical school and getting your medical degree. A second objective is doing the best you can so that you can make yourself a competitive applicant for the residency of your choice. Certain highly competitive residency programs such as orthopaedic surgery and ophthalmology use Step 1 scores in the selection process.

A 45-year-old man has just undergone a successful heart transplant for dilated cardiomyopathy and has been placed on cyclosporin as an immunosuppressive agent. Three weeks later he develops cough, chest pain, and intermittent fevers and is diagnosed with right upper lobe pneumonia. Which antibiotic would be best to avoid a state of cyclosporin toxicity?

- A. Erythromycin
- B. Azithromycin
- C. Clarithromycin
- D. Ciprofloxacin
- E. Norfloxacin

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88% to 93% of the United States and Canadian medical students pass the exam on their first attempt. Compare this to the U.S. bar exam, which has a passing rate of 67%.

The minimum passing score on the USMLE Step 1 is 192. This number generally corresponds to getting 60% to 70% of exam questions right.
It is important to note that the Step 1 score is one of several factors considered in the residency selection process. Programs make use of other applicant characteristics such as clinical rotation grades, research, publications, and reference letters. Having insight into your academic portfolio and defining your personal goals may be helpful in guiding your studies for Step 1.

Registering to Take the Exam

Six to 8 months prior to the anticipated exam date, you will likely be prompted by your school to begin the registration process for taking the exam. The Step 1 application packet can be downloaded from the USMLE website: http://www.usmle.org. Applicants must select a 3-month time period to take the exam (e.g., April–May–June, June–July–August). The application includes a form requiring a passport-sized photo that must be certified by the school registrar. The NBME processes the submitted application and sends out a scheduling permit.

The scheduling permit contains a unique candidate identification number, which is necessary in order to schedule the exam and take the exam. After receiving the scheduling permit, you should attempt to schedule your exam as soon as possible in order to receive the location and time of your choice. Scheduling occurs on a first-come, first-served basis, and testing centers fill up quickly during popular testing times of the year. Specific instructions on scheduling the test are delineated on the scheduling permit. A list of Prometric testing centers nearest you can be found on the Prometric website. Of note, testing centers are closed for the first 2 weeks of January, during major holidays, and generally on Sundays. Also, the exam can be started at different times of the day for those preferring the early or late hours of the day. Generally, Step 1 is taken by second-year medical students finishing their second year of medical school. Some relevant information to consider when scheduling your exam is your second year end date and third year start date. Because most curricula end in May, and students allow themselves a study time of at least 1 month, most students take the exam in June.

If for some reason you need to reschedule your exam, you will need to call or visit the Prometric website. The rescheduled date must fall within the 3-month eligibility period selected earlier during the registration process (also found on your scheduling permit). Also, to avoid a rescheduling fee, Prometric should be contacted before noon EST 5 business days prior to the testing date.

PREPARING FOR THE EXAM: STUDY STRATEGIES

Study Materials

The first step to preparing for the exam is collecting and familiarizing yourself with study materials. You can start this step years before you actually take the exam. When starting medical school, consider purchasing a comprehensive review text such as *Step-Up to the USMLE Step 1*. The purpose of this is to begin reading, annotating, and familiarizing yourself with the test and content of the book. In addition to a comprehensive review text, many students use a variety of resources to prepare for the exam, such as question banks and structured video review courses.

You should also take advantage of USMLE resources officially provided by the NBME. The NBME offers a free sample test: http://www.usmle.org/practice-materials/index.html. For those examinees who would like to practice taking the exam with the testing interface, a mock testing situation can be set up at a Prometric center. This additional service costs $42. Students are provided with a score report at the end, although no explanations are offered online or at the testing center. The Comprehensive Basic Science Self-Assessment (CBSSA) is a 200-question test offered by the NBME, presented in four blocks of 50 questions each. Students must register to take the exam online and are charged $50 for this service. The website to create an account is https://nsasnbme.org/nsasweb/servlet/ma. After taking the test, students are provided with a performance profile outlining the student’s strengths and weaknesses.


Study Schedule

After collecting study materials, the next step is creating a study schedule. Preparation for the USMLE Step 1 can start years before actually taking the exam. As mentioned earlier, as you prepare for your medical school classes, read and annotate review texts along with studying syllabi and textbooks for classes. The purpose of this is to familiarize yourself with the text.

In the months prior to the exam, you should register for the exam, schedule the exam, and collect study materials including a question bank. Familiarize yourself with your study materials and attend campus review sessions.

At least 1 month before the exam, create and follow a study schedule. The purpose of the study schedule is to cover each of the disciplines tested on the exam. Typically, most medical students are provided 1 month to study for the exam. When students are creating a study schedule, oftentimes, the most challenging feat is determining how many days to allocate toward one discipline. Figures 4 and 5 are suggested study schedules that have been successful for students in the past. The first study schedule is organized by organ systems, and the second by basic science.
system and the second by basic science discipline. These schedules are only suggested schedules. Individual schedules should be tailored to your needs, keeping in mind your individual strengths and weaknesses, high-yield topics for the exam, and available time to study.

The suggested study schedules in Figures 4 and 5 assume 28 days available for study, including the day before the USMLE. If you have more or fewer days, adjust the schedule accordingly. For example, if you have 31 days, add ½ day to Behavioral Science, ½ day to Gross Anatomy/Embryology, 1 day off, and 1 day to wrap up. In these suggested schedules, 2 to 3 days are allocated for wrap-up before the exam, 1 to 2 days are scheduled as days off as rewards for doing your work, and 24 days are full study days. In general, when determining the order of subjects to study, the general strategy should be longer term memory subjects early and shorter term memory subjects late (Table 2). Also, when determining how many days to allocate certain subjects or organ systems, provide more days for heavily tested subjects such as pathology and physiology (Table 3).

**Table 2: Order for Organ System and Basic Science Schedule**

<table>
<thead>
<tr>
<th>Order for Organ System Schedule</th>
<th>Order for Basic Science Schedule</th>
</tr>
</thead>
<tbody>
<tr>
<td>Basic concepts/general</td>
<td>Physiology</td>
</tr>
<tr>
<td>Endocrine</td>
<td>Pathology</td>
</tr>
<tr>
<td>Nervous</td>
<td>Behavioral science</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>Microbiology/immunology</td>
</tr>
<tr>
<td>Respiratory</td>
<td>Pharmacology</td>
</tr>
<tr>
<td>Renal</td>
<td>Biochemistry</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>Neuroanatomy</td>
</tr>
<tr>
<td>Musculoskeletal</td>
<td>Gross anatomy/embryology/histology</td>
</tr>
<tr>
<td>Reproductive</td>
<td></td>
</tr>
<tr>
<td>Heme/lymph</td>
<td></td>
</tr>
</tbody>
</table>

**Table 3: Allocation of Days**

<table>
<thead>
<tr>
<th>Allocation of Days by Organ System</th>
<th>Allocation of Days by Basic Science</th>
</tr>
</thead>
<tbody>
<tr>
<td>Organ System</td>
<td>Days</td>
</tr>
<tr>
<td>Nervous</td>
<td>3.5</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>3</td>
</tr>
<tr>
<td>Respiratory</td>
<td>2.5</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>2</td>
</tr>
<tr>
<td>Renal</td>
<td>2.5</td>
</tr>
<tr>
<td>Endocrine</td>
<td>2.5</td>
</tr>
<tr>
<td>Reproductive</td>
<td>2</td>
</tr>
<tr>
<td>Musculoskeletal</td>
<td>2</td>
</tr>
<tr>
<td>Heme/lymph</td>
<td>2</td>
</tr>
<tr>
<td>Basic concepts/general</td>
<td>2</td>
</tr>
</tbody>
</table>
In the month prior to the exam, you should also create and follow a daily schedule. Table 4 contains a sample daily study schedule. The daily schedule should allot time for studying review texts, reading cases/clinical vignettes, and doing questions. While studying texts, you should not only read but also spend time understanding concepts and memorizing key facts. Tools that help with understanding and memorizing information include organizing information into tables, charts, and figures; using mnemonics; and applying information in daily practice, such as in clinics and caring for patients. Books with clinical cases and vignettes are based on this premise and provide an opportunity to integrate studied information. Doing questions is another excellent method of reinforcing and remembering learned information. An online question bank of nearly 500 USMLE-format questions based on commonly tested facts has been included with this text and can be accessed at www.thePoint.lww.com. Make sure you also include in your schedule time to relax and do other things that are important to you (work out, spend time with friends and family, etc.).

The night before the exam, relax and gather your required materials (orange permit slip, government-issued photo ID). Make sure you know how to get to the testing center and have confirmed with the testing center your test time and date. Get a good night’s rest!

**TEST DAY TIPS**

- Bring a cooler with ice, water, juice, or a sports drink. Pack a lunch. Bring some fruits and snacks. (You may not be able to predict what you’re going to want to eat, so it’s better to bring too much than too little.) Eat light, not heavy.
- Consider getting out in the sun and/or stretching during your breaks.
- Bring a light sweater or sweatshirt in case the testing center is cold.
- Don’t forget your ID and USMLE pass.
- Take your breaks when you need them. (Example: 2 sections → break → 2 sections → break → 1 section → break → 2 sections) Some breaks may need to be longer than others. Don’t be afraid to take a small 5-minute bathroom break.
- Expect 5 to 10 questions in each section that you have never seen before. If you expect this, then you won’t become anxious when it happens (and it will happen).
- Bring your own watch to keep track of your break time!
- Consider answering 10 practice questions prior to going into the test center for “warm-up” (but don’t look at the answers, in case you are incorrect).

What should I put on my markerboard prior to the start of the test?

- Don’t write on your markerboard for more than 5 minutes before you start your test.
- Put whatever you want, but you may want to consider the following:
  - Developmental milestones
  - Important pharmacokinetic equations
  - Error square
  - Sensitivity, specificity, PPV, NPV, OR, RR, equations, and square
  - Lung volume diagram

### Table 4 Suggested Daily Study Schedule

<table>
<thead>
<tr>
<th>Time</th>
<th>Activity</th>
</tr>
</thead>
<tbody>
<tr>
<td>8:00 a.m.–12:00 p.m.</td>
<td>Study</td>
</tr>
<tr>
<td>12:00 p.m.–1:00 p.m.</td>
<td>Lunch</td>
</tr>
<tr>
<td>1:00 p.m.–5:00 p.m.</td>
<td>Study</td>
</tr>
<tr>
<td>5:00 p.m.–8:00 p.m.</td>
<td>Exercise, dinner, errands, phone calls</td>
</tr>
<tr>
<td>8:00 p.m.–10:00 p.m. (or 11:00 p.m.)</td>
<td>Questions</td>
</tr>
</tbody>
</table>
Basic Concepts

ENZYME KINETICS

I. Enzymes
A. An enzyme is a protein or nucleic acid molecule that decreases the energy of activation for a reaction (Figure 1-1).
B. Enzymes interact specifically with substrates at an enzyme active site.
C. By lowering the energy of activation, enzymes increase the rate of reaction.
D. Enzymes do not alter the equilibrium of substrates and products, which is concentration dependent, or the free energy released from the reaction.
E. Enzymatic reactions generally require cofactors, such as metals, derivatives of vitamins, or small organic molecules. The vitamins and small organic molecules are often referred to as coenzymes.

QUICK HIT
Genetic mutations leading to inborn errors of metabolism may alter substrate bonding or enzyme activity on a substrate.

II. Kinetics
A. Velocity (V) is the rate of reaction and is dependent on enzyme concentration, substrate concentration, temperature, and pH.
   1. Enzyme concentration: increased enzyme concentration leads to faster rate of reaction.
   2. Substrate concentration: increased concentration leads to increased rate of reaction until a maximum is reached when all enzyme receptor sites are saturated.
   3. Temperature: increased temperature leads to increased rate of reaction up to a maximum, after which enzymes denature.
   4. pH: velocity of a reaction is maximum at its optimal pH. A pH that is either too high or too low leads to a slower reaction or may denature the enzyme.
B. Michaelis–Menten equation
1. Enzymatically catalyzed reactions can be characterized by the Michaelis–Menten equation:
   \[ V = \frac{V_{\text{max}}}{K_m + [S]} \]
   where \( V \) is the velocity of the reaction.
   \( V_{\text{max}} \) is the maximum velocity of the reaction.
   \([S]\) is the substrate concentration.
   \( K_m \) is the Michaelis constant (the substrate concentration at which velocity is one-half of the maximum velocity of a given reaction; \( V = \frac{1}{2} V_{\text{max}} \)).
2. Effect of substrate concentration on reaction velocity (Figure 1-2)

C. Lineweaver–Burk plots (Figure 1-3)
1. A Lineweaver–Burk plot is a linear representation of the Michaelis–Menten equation, which allows for easier interpretation of the maximum velocity of an equation.
   a. Competitive inhibitors increase the \( K_m \) by competing with substrate binding to enzyme at the active site.
   b. Noncompetitive inhibitors decrease the \( V_{\text{max}} \) by bonding to the enzyme (E or ES) outside of the active site.
   c. Irreversible inhibitors inactivate the enzyme with kinetics similar to non-competitive inhibition. Example: Aspirin inhibition of cyclooxygenases.
2. Regulatory enzymes in metabolic pathways are influenced by allosteric interactions and will have nonlinear Lineweaver–Burk plots for their kinetics.
Basic Concepts

\[ V_{\text{max}} \] is decreased by noncompetitive inhibitors

\[ K_m \] is increased by competitive inhibitors

\( V_{\text{max}} \) = Maximum velocity
\( K_m \) = Michaelis constant
\( V \) = Reaction velocity
\( [S] \) = Substrate concentration

**Quick Hit**
When infusing a drug, it takes 4.3 half-lives to achieve 95% of the steady-state concentration.

**Concepts in Pharmacology**

I. Absorption
   A. There are many routes of administration (Figure 1-4).

**Figure 1-4** Routes of drug administration

- Parenteral: IV, IM, SC
- Sublingual
- Inhalation
- Oral
- Transdermal patch
- Topical
- Rectal

IM, intramuscular; IV, intravenous; SC, subcutaneous. (Adapted from Mycek M, Harvey RA, Chompe PC. Lippincott’s Illustrated Reviews: Pharmacology. 2nd ed. Philadelphia, PA: Lippincott-Raven Publishers; 1996/2. Used with permission of Lippincott Williams & Wilkins.)
B. Oral administration is the most common route.
C. Most drugs are absorbed in the duodenum.
   1. Drugs enter the portal circulation.
   2. They are subject to first-pass metabolism by the liver.
D. Other factors that affect absorption include:
   1. Intestinal pH
   2. Whether taken with food (slows transit, allowing for further acid digestion)
   3. Whether the drug is a sustained-release preparation
   4. Whether gastrointestinal diseases or malabsorption syndromes are present

II. Distribution
   \[ V_d = \frac{D}{C} \]
A. \( V_d \), volume of distribution; D, amount of drug in body; C, plasma concentration.
B. Distribution occurs more rapidly with high blood flow, high vessel permeability, and a hydrophobic drug.
C. Binding to plasma proteins (albumin and globulins) accelerates absorption into plasma but slows diffusion into tissues.
D. Many disease states alter distribution:
   1. Edematous states (e.g., cirrhosis, heart failure, nephrotic syndrome) prolong distribution and delay clearance.
   2. Obesity allows for greater accumulation of lipophilic agents within fat cells, increasing distribution and prolonging half-life.
   3. Pregnancy increases intravascular volume, thus increasing \( V_d \).
   4. Hypoalbuminemia allows drugs that are protein bound to have increased availability because of lack of albumin for binding.

III. Pharmacokinetics
A. The effect an agonist has on its receptors depends on concentration.
B. Efficacy is a measure of the maximum effect a drug can produce.
C. Potency is a measure of the amount of drug needed to produce a given effect (Figure 1-5).

**QUICK HIT**
Charged species do not cross the gastrointestinal membrane as readily as uncharged species. Therefore, the percentage of drug in the uncharged state determines the rate of absorption.
\[ \text{pH} = \text{pK}_a + \log \frac{\text{protonated species}}{\text{unprotonated species}} \]

**QUICK HIT**
Acidophilic drugs bind to albumin, whereas basophilic drugs bind to globulins. The administration of a drug that binds to sites already occupied by a drug can displace the first drug. This leads to a surge in free drug, which, in turn, leads to increased activity and elimination.

**QUICK HIT**
Efficacy is equivalent to maximum velocity (\( V_{\text{max}} \)) in enzyme kinetics.

**QUICK HIT**
If a drug is rapidly metabolized by the liver, the amount reaching the target tissues is significantly reduced. Such drugs include propranolol, lidocaine, verapamil, and meperidine.

**QUICK HIT**
Efficacy is equivalent to maximum velocity (\( V_{\text{max}} \)) in enzyme kinetics.

D. Effective dose (ED) and lethal dose (LD)
   1. ED is the dose of the drug that produces the desired effect.
   2. \( ED_{50} \) is the dose of the drug that produces the desired effect in 50% of the population.
   3. LD is the dose of the drug that produces death.
4. LD₅₀ is the dose of the drug that produces death in 50% of the population.
5. Separation of ED and LD determines therapeutic range (Figure 1-6).
6. A drug’s therapeutic index (TI) is a measure of how safe it is to use. TI = LD₅₀/ED₅₀

E. Antagonists (Figure 1-7)

1. Competitive antagonist: competes for the same binding site as the agonist or drug
   a. Increases $K_m$
   b. Does not affect $V_{max}$

2. Noncompetitive antagonist: prevents binding of the agonist or drug to the receptor or prevents activation of the receptor by the agonist
   a. Decreases the efficacy of the agonist
   b. Decreases $V_{max}$ but does not affect $K_m$

3. Complete antagonist: prevents all pharmacologic action(s) of the agonist or drug

4. Partial agonist: binds to the same receptor site as the agonist or drug but has a lower efficacy
F. Pharmacokinetics are affected by disease states:
1. Hyperthyroidism increases the heart’s sensitivity to catecholamines.
2. Patients with cirrhosis are more sensitive to sedative-hypnotics.
3. Patients with cirrhosis and congestive heart failure (CHF) will retain fluids if taking nonsteroidal anti-inflammatory drugs (NSAIDs) because of the role of prostaglandins in maintaining renal function.

IV. Metabolism
A. Drugs may be chemically altered, varying activity or aiding excretion.
B. The enzymatic transformation of drugs usually follows one of two kinetics:
   1. First-order kinetics: a constant fraction of drug is metabolized in a certain unit of time—by far the most common. This arises because drugs have higher affinities for their receptors ($K_d$) than their metabolizing enzymes ($K_m$).
   2. Zero-order kinetics: a constant amount of drug is metabolized in a certain unit of time (e.g., ethanol)—rare.
C. The liver is the primary site of metabolism and uses two sets of reactions:
   1. Phase 1: drugs are modified or portions are removed (cytochrome P450 oxidation, enzymatic reduction, hydrolysis).
   2. Phase 2: conjugation reactions add chemical groupings to the drug (e.g., glucuronidation, sulfate or glutathione conjugation, acetylation, methylation).
D. Prodrugs are drugs that are administered in an inactive form and are metabolically activated by the body.
E. Some drugs are metabolized to toxic products (e.g., acetaminophen).

V. Elimination
A. Most drugs are eliminated in the urine or bile.
B. Volatile drugs can be eliminated through the lungs.
C. Renal excretion
   1. Substances with a molecular weight (MW) <5,000 that are free in the plasma are filtered in the glomerulus.
   2. Higher concentrations of a substance within the tubules may favor some reabsorption.
   3. The proximal convoluted tubule (PCT) may actively secrete a drug.
   4. The urine pH, molecular size, lipid solubility, and negative logarithm of the acid ionization constant ($pK_a$) of the drug affect renal excretion.
D. Biliary excretion
   1. Hepatocytes actively take up the drug from plasma, store it or metabolize it, and release it into the bile duct.
   2. Some drugs are excreted in feces.
   3. Some drugs are reabsorbed in the terminal ileum (enterohepatic cycling).

VI. Special circumstances
A. Geriatric patients
   1. These patients often use multiple prescriptions and over-the-counter medications.
   2. Decreased body size, body water, and serum albumin, along with increased body fat, alter drug distribution.
   3. Decreased phase 1 reactions, liver mass, and liver blood flow all slow metabolism.
   4. Decreased kidney mass, renal blood flow, glomerular filtration rate, and tubular function hamper drug excretion.
B. Pediatric patients
   1. Most drugs cross the placenta to some extent, and their possible effects on the fetus are ranked as category A, B, C, D, and X (A = no evidence of first trimester risk in well-controlled human studies, X = positive evidence of fetal risk, and the risks outweigh the potential benefits).
   2. Absorption
      a. High gastric pH and delayed emptying affect enteral absorption.
      b. High surface area-to-volume ratio affects transdermal administration.
      c. Low muscle mass limits intramuscular (IM) administration to the vastus lateralis in infancy.
   3. Albumin does not reach adult levels until 1 year of age.
4. Both phases of metabolism are deficient to varying degrees until 12 years of age.
5. Specific antibiotics avoided in childhood include quinolones (articular cartilage erosion and tendon damage) and tetracycline (depression of bone and teeth formation).

C. Pharmacogenetics
1. Acetylation of isoniazid
   a. In patients who are slow acetylators, there is increased incidence of neuropathy, bladder cancer, and familial Parkinson disease.
   b. Patients who are rapid acetylators are the majority of the population.
   c. Rate of acetylation also affects metabolism of hydralazine, dapsone, and phenytoin.
2. Succinylcholine sensitivity
   a. Atypical pseudocholinesterase does not hydrolyze succinylcholine effectively.
   b. It leads to prolonged paralysis (succinylcholine apnea).
   c. It is autosomal recessive.
3. Ethanol metabolism
   a. Ethanol is metabolized by two enzymes:
      i. Alcohol dehydrogenase (converts ethanol to acetaldehyde)
      ii. Aldehyde dehydrogenase (converts acetaldehyde to acetate)
   b. Aldehyde dehydrogenase shows diminished activity in certain patients (e.g., approximately 30%–40% of Chinese and Japanese individuals have diminished activity).
   c. Acetaldehyde accumulation leads to facial flushing, headache, nausea, and vomiting.

D. Toxicology (Table 1-1)

<table>
<thead>
<tr>
<th>Poison</th>
<th>Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acetaminophen</td>
<td>N-acetylcysteine</td>
</tr>
<tr>
<td>Amphetamine</td>
<td>Ammonium chloride (acidify urine)</td>
</tr>
<tr>
<td>Arsenic</td>
<td>Dicrimerol, succimer, penicillamine</td>
</tr>
<tr>
<td>Aspirin</td>
<td>Activated charcoal, sodium bicarbonate (alkalinize urine), dialysis</td>
</tr>
<tr>
<td>Atropine</td>
<td>Physostigmine</td>
</tr>
<tr>
<td>Benzodiazepines</td>
<td>Flumazenil</td>
</tr>
<tr>
<td>ß-Blockers</td>
<td>Atropine, activated charcoal, glucagon, calcium chloride</td>
</tr>
<tr>
<td>Carbon monoxide</td>
<td>100% oxygen, hyperbaric oxygen</td>
</tr>
<tr>
<td>Cocaine</td>
<td>Supportive care, benzodiazepines, calcium channel blockers</td>
</tr>
<tr>
<td>Copper</td>
<td>Penicillamine</td>
</tr>
<tr>
<td>Cyanide</td>
<td>Sodium thiosulfate; amyl nitrite plus sodium nitrite</td>
</tr>
<tr>
<td>Digitalis</td>
<td>Activated charcoal, digoxin immune Fab, potassium (if serum potassium level is low), possibly atropine</td>
</tr>
<tr>
<td>Ethylene glycol (antifreeze)</td>
<td>Fomepizole, ethanol, dialysis</td>
</tr>
<tr>
<td>Heparin</td>
<td>Protamine sulfate</td>
</tr>
<tr>
<td>Iron</td>
<td>Deferoxamine</td>
</tr>
<tr>
<td>Isoniazid</td>
<td>Vitamin B₆</td>
</tr>
<tr>
<td>Isopropyl alcohol</td>
<td>Supportive care</td>
</tr>
<tr>
<td>Lead</td>
<td>Succimer, EDTA, dimercaprol</td>
</tr>
<tr>
<td>Mercury</td>
<td>Dimercaprol</td>
</tr>
<tr>
<td>Methanol</td>
<td>Fomepizole, ethanol, dialysis</td>
</tr>
</tbody>
</table>
I. **Sensitivity and specificity (Table 1-2)**

A. Sensitivity (positive in disease) is the probability that a person having a disease will be correctly identified.

B. Specificity (negative in healthy) is the probability that a person who does not have a disease will be correctly identified.

C. Positive predictive value (PPV) is the probability that an individual who tests positive has the disease.

D. Negative predictive value (NPV) is the probability that an individual who tests negative does not have the disease.

II. **Incidence and prevalence (Table 1-2)**

A. Incidence is the number of new individuals who develop an illness in a given time period divided by the total number of individuals at risk for the illness.

B. Prevalence is the number of individuals in the population who have an illness divided by the total population.

C. Example: **Incidence** is the number of intravenous (IV) drug abusers newly diagnosed with HIV in 2013 divided by the number of HIV-negative IV drug abusers in the population in 2013. **Prevalence** is the number of IV drug users in the United States who are currently HIV positive divided by the total population of IV drug users.

### TABLE 1-2  **Sensitivity and Specificity**

<table>
<thead>
<tr>
<th>Disease</th>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>Test Results:</td>
<td>Positive</td>
<td>False Positive (B)</td>
</tr>
<tr>
<td>Terminology</td>
<td>Equation</td>
<td>Definition</td>
</tr>
<tr>
<td>---</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>Sensitivity (positive in disease)</td>
<td>[ \frac{A}{(A+C)} ]</td>
<td>Probability that a person having a disease will be correctly identified</td>
</tr>
<tr>
<td>Specificity (negative in healthy)</td>
<td>[ \frac{D}{(D+B)} ]</td>
<td>Probability that a person who does not have a disease will be correctly identified</td>
</tr>
<tr>
<td>Positive predictive value (PPV)</td>
<td>[ \frac{A}{(A+B)} ]</td>
<td>Probability that an individual who tests positive has the disease</td>
</tr>
<tr>
<td>Negative predictive value (NPV)</td>
<td>[ \frac{D}{(C+D)} ]</td>
<td>Probability that an individual who tests negative does not have the disease</td>
</tr>
<tr>
<td>Prevalence</td>
<td>[ \frac{A+C}{(A+B+C+D)} ]</td>
<td>Total number of cases in a population at a given time</td>
</tr>
<tr>
<td>Incidence</td>
<td>Generally calculated by number of new cases/susceptible population</td>
<td>Number of new cases of disease in the population over a given time</td>
</tr>
</tbody>
</table>

**QUICK HIT**

High-sensitivity tests are better suited for screening purposes, whereas high-specificity tests are used as confirmatory tests.

**QUICK HIT**

For chronic conditions (e.g., diabetes or cirrhosis), the prevalence is higher than the incidence because the long length of the disease process increases prevalence. For conditions that resolve quickly (e.g., strep throat) or are rapidly fatal (e.g., pancreatic cancer), the incidence and prevalence are approximately equal.
III. Key relationships among statistical variables

A. Sensitivity (Sn), false-negative ratio (FNR), negative predictive value (NPV)
   1. Sn and FNR are inversely related: \( Sn = 1 - FNR \).
   2. Therefore, increasing the Sn of a test decreases the FNR (the number of false
negatives) and increases the NPV.
   3. Example: A fasting blood sugar (FBS) > 126 mg/dL is used to diagnose
diabetes. If we lower the threshold to 110 mg/dL, then we will catch more
individuals with diabetes. Statistically, this means decreasing the number
of false negatives (those individuals who test negative but actually have the
disease) and increasing sensitivity.

B. Specificity (Sp), false-positive ratio (FPR), positive predictive value (PPV)
   1. Sp and FPR are inversely related: \( Sp = 1 - FPR \).
   2. Therefore, increasing the Sp of a test decreases the FPR (the number of false
positives) and increases the PPV.
   3. Example: Western blot testing is used as a confirmatory test for HIV because of
its high specificity. The initial screening test is highly sensitive (catches all true
positives, plus some false positives). Western blot is specific; therefore, the false
positives on the first test are shown to be true negatives on the Western blot test.

C. Specificity and sensitivity are inversely related: as Sp increases, Sn decreases and
vice versa.

D. Treatment
   1. Treatment decreases prevalence by shortening duration (remember that preva-
lence = incidence \times duration of disease) (Table 1-2).
   2. Treatment has no effect on incidence.
   3. Adherence, therapy, physician access, early detection \( \rightarrow \) decreases duration \( \rightarrow \)
decreases prevalence.

IV. Research study designs (Table 1-3)

A. Cohort studies
   1. Observational and can be prospective or retrospective

<table>
<thead>
<tr>
<th>TABLE 1-3 Research Study Designs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study</td>
</tr>
<tr>
<td>Case series</td>
</tr>
<tr>
<td>Case-control</td>
</tr>
<tr>
<td>Cohort</td>
</tr>
<tr>
<td>Crossover</td>
</tr>
<tr>
<td>Cross-sectional</td>
</tr>
<tr>
<td>Meta-analysis</td>
</tr>
<tr>
<td>Controlled trial</td>
</tr>
</tbody>
</table>
2. After assessment of exposure to a risk factor, subjects are compared with each other for a period of time.
3. Clinical treatment trial
   a. Highest quality cohort study
   b. Compares the therapeutic benefits of two or more treatments
4. Relative risk
   a. Calculated only for cohort studies
   b. Compares incidence rate in exposed group with incidence rate in unexposed individuals

B. Case-control studies
   1. Retrospective and observational
   2. Subjects with and without disorder are identified, and information on exposure to risk factors is assessed

C. Odds ratio
   1. Calculated in case-control studies; approximates the relative risk
   2. Based on disease occurring with or without exposure
   3. Odds ratio = (A × D)/(B × C) = (A/C)/(B/D) = (A/B)/(C/D)
   
   Where

<table>
<thead>
<tr>
<th>Disease</th>
<th>Exposure: Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>A</td>
<td>B</td>
</tr>
<tr>
<td>No</td>
<td>C</td>
<td>D</td>
</tr>
</tbody>
</table>

V. Biases—A systematic tendency to produce an outcome that differs from the underlying truth
A. Sampling bias—Volunteer subjects in a study may not be representative of the population being studied; as a consequence, the results of the study may not be generalizable to the entire population.
B. Selection bias—Occurs when there is a systematic difference in the way study groups are chosen. One method of decreasing this bias is randomization.
C. Expectancy bias—Occurs when a physician knows which patients are in treatment versus placebo group, causing the physician to draw conclusions supporting the expected outcome. One method of decreasing this bias is a double-blind design.
D. Late-look bias—Results from information being gathered too late to draw conclusions about the disease or exposure of interest from the entire study population. For instance, the more severe cases may have already died.
E. Measurement bias—Describes how information gathered affects information collected. For example, the Hawthorne effect describes how people act differently when being watched.
F. Proficiency bias—This is an issue when comparing the effects of different treatments administered at multiple sites. Physicians at one site may have more skill, thereby providing better treatment.
G. Recall bias—Patients who experience an adverse outcome have a different likelihood of recalling an exposure than do patients who do not have an adverse outcome, independent of the true extent of the exposure.

VI. Disease prevention
A. Primary prevention stops disease occurrence; for example, encouraging use of sun protection to prevent skin cancer.
B. Secondary prevention detects disease early; for example, physician checking for suspicious growths.
C. Tertiary prevention decreases devastating complications of the disease; for example, administering insulin to a diabetic.
VII. Testing and statistical methods

A. Reliability versus validity
1. **Reliability** refers to the reproducibility of test results, which reflects the absence of random variation. Also known as precision.
2. **Validity** refers to the appropriateness of a test's measurements; that is, how closely the test results reflect the truth. Also known as accuracy.
3. **Sensitivity** and **specificity** are measures of validity.

B. Bell curve (Figure 1-8)
1. In a normal distribution, the mean, median, and mode are equal.
   a. **Mean**: average
   b. **Median**: middle value in a sequentially ordered group of numbers
   c. **Mode**: number that appears most often in a group
2. **Skew** refers to the way a peak may be offset.
   a. **Positive skew**: peak is to the left (most scores at low end; mean > median > mode)
   b. **Negative skew**: peak is to the right (most scores at high end; mean < median < mode)
3. A bimodal distribution has two peaks.

C. The **null hypothesis** ($H_0$)
1. Postulates that there is no significant difference between groups
2. A **type I error** occurs when the null hypothesis is rejected when it is true. The $\alpha$ is the probability of making a type I error.
   a. The $\alpha$ value is set by the investigator, usually at 0.05.
   b. The **p value** is the probability that the study results occurred due to chance alone, given the null hypothesis is true.
   c. If $p$ is less than $\alpha$ (usually 0.05), the results are considered "significant," and the null hypothesis is rejected.
3. A **type II error** occurs when the null hypothesis is accepted when it is not true. The $\beta$ is the probability of making a type II error.
4. **Power** is the probability of rejecting the null hypothesis when the null hypothesis is false. Power $= 1 - \beta$. Increasing the sample size increases power. If $p < 0.05$, then the null hypothesis can be rejected.
5. Example
   a. A study is conducted on the influence of medical school on dating frequency.
   b. The null hypothesis would be that medical school students, when compared with 22- to 26-year-olds in the working population, have no difference in dating frequency.
   c. If the p value of the study is less than 0.05 (meaning that there is a statistical difference), then the null hypothesis can be rejected. Thus, it can be stated that medical school decreases dating frequency.

**EXTREME ENVIRONMENTS**

I. **High altitude**

   A. Barometric pressure at sea level is 760 mm Hg. At 20,000 feet above sea level, barometric pressure is 349 mm Hg. Partial pressure of O\(_2\) is 21% of the barometric pressure, regardless of altitude.

   B. To compensate for this lower PO\(_2\) at high altitude, the body makes several physiologic adjustments:
   1. Ventilatory rate increases both acutely and chronically.
   2. Renal excretion of bicarbonate increases to compensate for the respiratory alkalosis caused by increased ventilation.
   3. Erythropoietin production increases to increase red blood cell (RBC) mass.
   4. Numbers of mitochondria and oxidative enzymes increase slightly.

   C. Rapid ascent to high altitude without sufficient acclimatization can result in acute mountain sickness.
   1. Usually occurs 2 hours to 2 days after ascent
   2. Common symptoms include headache and fatigue
   3. Severe illness can result in acute cerebral edema or acute pulmonary edema.
   4. Can be treated with acetazolamide

   D. Individuals who remain at high altitude too long can also develop chronic mountain sickness. The clinical features include:
   1. Increased RBC mass and hematocrit
   2. Increased blood viscosity and decreased tissue blood flow
   3. Elevated pulmonary artery pressure (pulmonary arteries constrict in response to hypoxia)
   4. Right-sided heart enlargement
   5. Systemic arterial pressure begins to fall
   6. CHF

II. **Aviation and space flight**

   A. Gravitational force
   1. 1 G is a force equal to the pull of gravity, and −1 G is an equal force in the opposite direction.
   2. Positive G forces will move blood away from the head (toward the feet), and negative G forces move blood toward the head (away from the feet)

   B. High G environments
   1. Individuals experience a visual “blackout” at 4–6 G, due to pooling of blood in the abdomen and legs, insufficient return of blood to the heart, and insufficient pumping of blood to the brain.
   2. Specialized “G suits” apply pressure to the lower abdomen and legs, to prevent blackouts during high G situations.
   3. During liftoff of a spacecraft liftoff, G forces may reach 8–9 G. To prevent blackout, astronauts liftoff in a semireclining position, transverse to the axis of acceleration.

   C. Individuals who live at zero gravity for extended period undergo several physiological changes:
   1. Decreased blood volume and RBC mass
   2. Decreased muscle strength and work capacity
3. Decreased maximum cardiac output
4. Decreased bone mass due to loss of calcium and phosphate

III. Deep sea medicine
A. Nitrogen narcosis
1. Atmospheric gas is roughly 78% nitrogen. During prolonged exposure to hyperbaric conditions (such as ocean depths), nitrogen dissolves into the neural membranes, causing reduced neuronal excitability.
2. Symptoms of nitrogen narcosis resemble alcohol intoxication. The diver will first become jovial and careless, then drowsy, then he or she experiences loss of strength and coordination.
B. Decompression sickness
1. At the high pressures associated with a deep sea dive, additional nitrogen gas dissolves in the blood.
2. When the diver returns to sea level too rapidly, those gases begin to escape the dissolved state, forming actual bubbles that can occlude blood vessels.
3. Symptoms of decompression sickness (caisson disease, “the bends”) include:
   a. Pain in the joints and muscles of the extremities
   b. Neurologic problems (dizziness, paralysis, or syncope) in 5%–10% of patients
   c. Dyspnea and pulmonary edema, due to occlusion of pulmonary capillaries in approximately 2% of patients
4. Treatment is to put the patient in a hyperbaric chamber and redissolve the gas bubbles, then gradually return the patient to sea-level pressure.

ETHICS AND THE ROLE OF THE PHYSICIAN
I. Ethical principles
A. Beneficence—The physician must act in the patient’s best interest.
B. Autonomy (“self-rule”)
   1. Patient autonomy—The patient has the right to make decisions regarding his or her own body. This includes the right to refuse treatment, or to choose treatments for himself or herself (within reason).
   2. Physician autonomy—The physician has the right to choose which treatments he or she will or will not provide.
C. Nonmaleficence—The physician must not intentionally harm the patient.
D. Justice—The physician must strive to treat patients fairly/equitably.

II. Patient consent
A. Informed consent—The principle of patient autonomy dictates that before a physician performs any procedure or administers treatment, the patient must give consent. The patient must have some understanding of the procedure/treatment, including the risks involved, the expected benefits, and the alternatives to the procedure.
B. Decision-making capacity—In order to give consent, the patient must be determined to have the capacity to make healthcare decisions for himself or herself.
   1. The patient must be able to make a treatment decision and communicate that choice to the healthcare team.
   2. The patient must also be informed of the risks, benefits, and alternatives.
   3. The decision must be consistent with patient’s values.
   4. The patient’s decision has to be stable over time. (However, the patient retains the right to change his or her mind and revoke consent.)
   5. The decision is not based on delusions or hallucinations.
C. Directives—There are several mechanisms that allow a patient to exercise his or her right to patient autonomy in the event that he or she becomes incapacitated.
   1. Power of attorney for healthcare—The patient formally designates an individual to consent in the event of incapacitation.
2. **Advance directive**—The patient gives instructions in advance about the kinds of procedures and treatments he or she would or would not consent to. This can be in oral or written form.

3. A **living will** is one type of written advance directive. It is a legal document that gives treatment instructions to the healthcare team. It is the responsibility of the designated agent to follow the patient's wishes as outlined.

D. **Surrogate decision-maker**
   1. If a patient lacks the capacity to give informed consent, the decision-making responsibilities fall to a surrogate decision-maker.
   2. **Substituted judgment**—The surrogate's decision should be consistent with the patient's stated values, as if the patient were making the decision for himself or herself. Surrogate decisions carry the same legal weight as the patient's decisions.

E. Consent for minors—Treatment of minors requires consent of the parent (or other responsible adult), with certain exceptions:
   1. Emancipated minors (≥16 years old, living on his or her own, and managing his or her own finances)
   2. Treatment of sexually transmitted infections
   3. Treatment related to pregnancy (other than abortion)
   4. Treatment of drug addiction/dependency
   5. Treatment of the child of a minor
   6. Treatment of minor serving a sentence of confinement
   7. Emergency situations where parental consent cannot be obtained

III. **Medical malpractice**—The four basic elements of a malpractice claim are:
   A. **Duty**: The physician had an obligation to provide medical care to the plaintiff.
   B. **Breach of duty**: The physician failed to meet that obligation.
   C. **Harm**: The breach of duty caused some harm or injury to the plaintiff.
   D. **Damage**: The patient has suffered some physical, financial, or emotional loss as a result of the injury.
The Nervous System

DEVELOPMENT

I. Central nervous system (CNS)

A. The CNS includes the brain and spinal cord.
B. The CNS forms from the neural tube.
   1. The basal plate of the neural tube forms motor neurons.
   2. The alar plate of the neural tube forms sensory neurons.
   3. The basal and alar plates are separated by the sulcus limitans.
C. Oligodendrocytes are responsible for myelination, which begins 4 months after conception and is completed by the second year of life.
D. The distal end of the spinal cord, the conus medullaris, is at the level of the third lumbar vertebra (L3) at birth. As the body grows, the cord “ascends” to its final resting position at the first lumbar vertebra (L1) (Figure 2-1).

II. Peripheral nervous system (PNS)

A. The PNS includes the peripheral nerves and the autonomic and sensory ganglia.
B. It is derived from neural crest cells, which give rise to:
   1. Schwann cells
   2. Pseudounipolar cells of the spinal and cranial nerve (CN) ganglia

QUICK HIT
Symptoms of a disc herniation are referred to the myotome and dermatome below the lesion. For example, a herniation of the C4–C5 disc would cause impingement of the C5 nerve root.

Each oligodendrocyte can myelinate several axons, whereas each Schwann cell can only myelinate one axon.
3. Multipolar cells of the autonomic ganglia
4. Pia and arachnoid mater (not part of PNS)
5. Melanocytes (not part of PNS)
6. Epinephrine-producing chromaffin cells of the adrenal gland (not part of PNS)

C. Schwann cells are responsible for myelination, which begins 4 months after conception and is completed by the second year of life.

## CONGENITAL MALFORMATIONS OF THE NERVOUS SYSTEM

Abnormal development of the embryonal components of the nervous system can result in some of the malformations described in Table 2-1.

### TABLE 2-1 Congenital Malformations of the Nervous System

<table>
<thead>
<tr>
<th>Condition</th>
<th>Clinical Features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fetal alcohol syndrome</td>
<td>• Most common cause of mental retardation</td>
</tr>
<tr>
<td></td>
<td>• Cardiac septal defects</td>
</tr>
<tr>
<td></td>
<td>• Facial malformations including widely spaced eyes and long philtrum</td>
</tr>
<tr>
<td></td>
<td>• Growth retardation</td>
</tr>
<tr>
<td>Spina bifida</td>
<td>• Improper closure of posterior neuropore</td>
</tr>
<tr>
<td></td>
<td>• Several forms</td>
</tr>
<tr>
<td></td>
<td>• <strong>Spina bifida occulta</strong> (mildest form)—failure of vertebrae to close around spinal cord (tufts of hair often evident)</td>
</tr>
<tr>
<td></td>
<td>• Spinal meningocele (spina bifida cystica)—meninges extend out of defective spinal canal</td>
</tr>
<tr>
<td></td>
<td>• Meningomyelocele—meninges and spinal cord extend out of spinal canal</td>
</tr>
<tr>
<td></td>
<td>• Rachischisis (most severe form)—neural tissue is visible externally</td>
</tr>
<tr>
<td>Hydrocephaly</td>
<td>• Accumulation of CSF in ventricles and subarachnoid space</td>
</tr>
<tr>
<td></td>
<td>• Caused by congenital blockage of cerebral aqueducts</td>
</tr>
<tr>
<td></td>
<td>• May be caused by <strong>cytomegalovirus</strong> or toxoplasma infection</td>
</tr>
<tr>
<td></td>
<td>• Increased head circumference in neonates</td>
</tr>
<tr>
<td>Dandy–Walker malformation</td>
<td>• Dilation of fourth ventricle, leading to hypoplasia of cerebellum</td>
</tr>
<tr>
<td></td>
<td>• Failure of foramina of Luschka and Magendie to open</td>
</tr>
<tr>
<td></td>
<td>• May result from riboflavin inhibition, posterior fossa trauma, or viral infection</td>
</tr>
<tr>
<td>Anencephaly</td>
<td>• Failure of brain to develop</td>
</tr>
<tr>
<td></td>
<td>• Caused by lack of closure of anterior neuropore</td>
</tr>
<tr>
<td></td>
<td>• Associated with increased maternal α-fetoprotein (AFP)</td>
</tr>
<tr>
<td></td>
<td>• Decreased head circumference in neonates</td>
</tr>
<tr>
<td>Arnold–Chiari malformation</td>
<td>• Herniation of the cerebellar vermis through the foramen magnum</td>
</tr>
<tr>
<td></td>
<td>• Hydrocephaly</td>
</tr>
<tr>
<td></td>
<td>• Myelomeningocele</td>
</tr>
</tbody>
</table>

CSF, cerebrospinal fluid.

## MAJOR RECEPTORS OF THE NERVOUS SYSTEM

### I. Receptors of the sympathetic and parasympathetic nervous systems

A. The sympathetic and parasympathetic nervous systems exert their effects via various receptors scattered throughout the body (Table 2-2).

B. These effects are mediated by the substances shown in Figure 2-2.
II. Neurotoxins and their effects *(Figure 2-3)*

<table>
<thead>
<tr>
<th>Site of Action</th>
<th>Sympathetic Nervous System</th>
<th>Parasympathetic Nervous System</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Receptor</td>
<td>Effect on Site</td>
</tr>
<tr>
<td>Smooth muscle, skin and viscera</td>
<td>$\alpha_1$</td>
<td>Contract</td>
</tr>
<tr>
<td>Smooth and skeletal muscle</td>
<td>$\alpha_1$, $\beta_2$</td>
<td>Contract, Relax</td>
</tr>
<tr>
<td>Smooth muscle of the lung</td>
<td>$\beta_2$</td>
<td>Relax</td>
</tr>
<tr>
<td>Smooth muscle of the gastrointestinal tract</td>
<td>$\beta_2$, $\alpha_1$</td>
<td>Relax intestinal wall, Contract sphincters</td>
</tr>
<tr>
<td>Heart, SA node</td>
<td>$\beta_1$</td>
<td>Increase heart rate</td>
</tr>
<tr>
<td>Heart, ventricles</td>
<td>$\beta_1$</td>
<td>Increase contractility and conduction velocity</td>
</tr>
<tr>
<td>Eye, radial muscle</td>
<td>$\alpha_1$</td>
<td><strong>Mydriasis</strong> (dilation of pupil)</td>
</tr>
<tr>
<td>Eye, sphincter muscle</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Eye, ciliary muscle</td>
<td>$\beta_2$</td>
<td><strong>Relax</strong></td>
</tr>
<tr>
<td>Bladder</td>
<td>$\beta_2$, $\alpha_1$</td>
<td>Relax wall, Contract sphincter</td>
</tr>
<tr>
<td>Uterus</td>
<td>$\alpha_1$, $\beta_2$</td>
<td>Contract, Relax</td>
</tr>
<tr>
<td>Penis</td>
<td>$\alpha_2$</td>
<td>Emission, ejaculation</td>
</tr>
<tr>
<td>Sweat glands</td>
<td>Muscarinic</td>
<td>Secrete</td>
</tr>
<tr>
<td>Pancreas</td>
<td>$\alpha_2$, $\beta_2$</td>
<td><strong>Decrease insulin secretion</strong>, <strong>Increase insulin secretion</strong></td>
</tr>
<tr>
<td>Liver</td>
<td>$\alpha_1$, $\beta_2$</td>
<td>Glycolysis, gluconeogenesis</td>
</tr>
<tr>
<td>Adipose tissue</td>
<td>$\beta_1$, $\beta_2$</td>
<td>Lipolysis</td>
</tr>
</tbody>
</table>

N/A, not applicable; SA, sinoatrial.
A. Cholinergic

B. Noradrenergic

Choline + Acetyl CoA → Acetylcholine (ACH)

ACH → Cholinergic Receptor

Noradrenaline (NE) → Adrenergic Receptor

Tyrosine → DOPA → Dopamine

NE → Uptake 1 → Diffusion, metabolism (MAO)

Benzodiazepines + GABA

Barbiturates + GABA

GABA

Muscarinic (G protein)

Nicotinic (ion channel)

Ach, acetylcholine; AChE, acetylcholinesterase; Bar, barbiturates; BZ, benzodiazepine; ChAT, choline acetyltransferase; CoA, coenzyme A; DOPA, dihydroxyphenylalanine; GABA, \( \gamma \)-aminobutyric acid; MAO, monoamine oxidase; NE, norepinephrine; PLP, pyridoxal phosphate; TCA, tricyclic antidepressant.
The Nervous System

Meninges, flow of cerebrospinal fluid, and pathologic trauma

**TETANUS TOXIN**
Inhibits Renshaw cell release of glycine (an inhibitor) through presynaptic binding.

**strychnine**
Blocks inhibitory neuronal input by binding glycine receptor.

**Black widow spider, scorpion venom**
Presynaptic binding causes excessive release of ACh.

**Botentilum toxin**
Inhibits release of ACh at neuromuscular junction.

**α-Bungarotoxin**
Blocks ACh receptor by binding irreversibly to nicotinic receptors.

**ACh**, acetylcholine.

Hydrocephalus
- CSF volume leading to dilated ventricles and intracranial pressure
- Communicating
  - Blockage in subarachnoid space allowing free flow
- Noncommunicating
  - CSF outflow obstruction
    - Foramina of Luschka and Magendie
    - Foramen of Monro
    - Aqueduct of Sylvius
    - Fourth ventricle
    - Foramen magnum
- Blood–CSF barrier
  - Composed of arachnoid, epithelium of choroid plexus, and capillary endothelium
- Subdural space
  - Between dura and arachnoid
  - Contains arteries which can tear with skull fractures (especially the middle meningeal artery) producing epidural hematomas
- Arachnoid
  - Thin nonvascular layer
  - Between pia and dura mater
- Subarachnoid space
  - Between pia mater and arachnoid
  - Contains CSF
  - Ends at S2
  - Subarachnoid hematomas are often caused by rupture of berry aneurysms
  - The space that CSF is drained from in a lumbar puncture (done between L3 and L4 or L4 and L5 discs)

CSF, cerebrospinal fluid.
Cerebrovascular disease is the most common cause of CNS pathology and the third major cause of death in the United States (Table 2-3).
CLINICAL PRESENTATION: A 26-year-old man was pushed down a flight of stairs in a fight. He briefly lost consciousness, then regained consciousness and went to dinner. After 1 hour at the restaurant, the man lost consciousness again. He was rushed to the emergency room, and after airway, breathing, and circulation were assessed and secured, a computerized tomography (CT) scan of the head was performed. The scan (Figure 2-6A) showed a convex mass over the right parietal lobe. An eye exam showed a fixed and dilated right pupil.

DIFFERENTIALS: Epidural hematoma, subdural hematoma, concussion, brain stem herniation

DIAGNOSTIC TESTS: A CT scan of the head is essential for diagnosis in patients with a history of head trauma with loss of consciousness. An epidural hematoma is seen on CT as a convex mass, which overlays the brain with high attenuation (Figure 2-6A). (Mnemonic: Epidural = convEx). An epidural hematoma is a blood clot between the skull and the dura, caused by laceration of the middle meningeal artery when the temporal bone is fractured. The “classic” presentation is a patient who has a brief loss of consciousness followed by a lucid interval, after which the patient goes into a coma as the hematoma enlarges and compresses the midbrain.

In contrast, a subdural hematoma forms between the dura and the brain (under the dura). It results from venous bleeding (as opposed to arterial in epidural hematomas) after blunt head trauma. The movement of brain relative to the skull causes rupture of bridging veins. Patients at higher risk for incurring a subdural hematoma after trauma are alcoholics and elderly patients. This is because of brain atrophy, which results in more “space” for the superficial bridging veins to move in response to rapid movement, thus increasing the risk of vessel rupture. Another risk factor for a subdural hematoma is anticoagulation therapy. A subdural hematoma on a CT scan appears as a crescent-shaped (concave) hematoma, which is usually less dense than an epidural hematoma because the blood is diluted with cerebrospinal fluid (Figure 2-6B).

CONCUSSION: Brain injury following blunt trauma that usually results in a brief loss of consciousness. Some refer to concussion as a “brain bruise.” Those at increased risk include patients with a history of previous concussions. Concussion is caused by dysfunction of the electrophysiology of the midbrain secondary to impact. Patients experience confusion, dizziness, problems with concentration, and inability to answer questions (or a delay in answering) after awakening.

MANAGEMENT: Treatment for an epidural hematoma includes rapid surgical decompression. Conversely, an acute subdural hematoma can be managed by observation or craniotomy with evacuation, depending on size and severity of symptoms. There is no treatment for a concussion.
The Nervous System

A. Epidural hematoma

B. Subdural hematoma

**LESIONS OF THE CEREBRAL CORTEX** *(Figure 2-7)*

**A. Lateral view**

- Primary somatosensory cortex (3, 1, 2)
  - Lesion causes contralateral loss of touch, vibration, and stereognosis in affected area.
- Primary motor cortex (4)
  - Lesion causes contralateral hemiparesis in affected area.
- Frontal eye field (8)
  - Lesion in left hemisphere causes eyes to look left.
  - Lesion of right hemisphere causes eyes to look right.
- Broca’s speech area of left hemisphere (44, 45)
  - Destruction causes Broca’s (expressive) aphasia. Patient understands spoken word but cannot form fluent sentences.
- Primary visual cortex (17)
  - Lesion causes visual field deficits.
- Auditory association cortex (Wernicke’s speech area of left hemisphere) (22)
  - Destruction causes Wernicke’s aphasia. Patient cannot understand spoken word, and speech is fluid but does not make sense.
- Lesion of right parietal lobe results in left-sided neglect.
  - Patient fails to recognize that the left side of his/her body exists.

**B. Medial view**

- Primary motor cortex (4)
- Premotor cortex (6)
- Primary somatosensory cortex (3, 1, 2)
- Prefrontal cortex (9, 10, 11, 12)
  - Destruction is equivalent to frontal lobotomy and causes inappropriate social behavior, loss of ability to adapt, and decreased desire to work.
- Frontal eye field (8)
- Broca’s speech area of left hemisphere (44, 45)
- Primary visual cortex (17)
- Auditory association cortex (Wernicke’s speech area of left hemisphere) (22)

**IMPORTANT PATHWAYS OF THE SPINAL CORD** *(Figure 2-8)*

**I. Posterior white column (dorsal column medial lemniscus pathway)**

A. The posterior white column is the ascending pathway that conveys discriminatory touch (two-point touch), vibration, proprioception, and stereognosis.

B. The posterior white column receives information at all spinal cord levels from pseudounipolar cells of dorsal root ganglia. This information is conveyed from a variety of receptors:

1. Meissner corpuscles (rate of applied stimulus)
2. Pacinian corpuscles (vibration stimulus)
3. Joint receptors (joint position, proprioception)

**QUICK HIT**

- Klüver–Bucy syndrome is a bilateral lesion of the amygdala nuclei. It results in hypersexuality, docility, and hyperorality.

- Muscle spindles function as the afferent limb of the myotatic (stretch) reflex (e.g., tapping knee with reflex hammer). Ventral horn motor neurons function as the efferent limb.

Muscle spindles are arranged in parallel with the extrafusal muscle fibers; Golgi tendon organs are arranged in series.
Important pathways of the spinal cord

**The Nervous System**

**Midbrain**
- Posterior commissure and center for vertical conjugate gaze
- Superior colliculus
- Spinothalamic tract
- Medial lemniscus
- Dentatothalamic tract
- Red nucleus

**Pons**
- Inferior cerebellar peduncle
- Vestibular nuclei
- Spinal trigeminal nucleus and tract
- CN VIII (Vestibular nerve)
- CN VII
- Nucleus CN VII
- Lateral spinothalamic tract
- MLF
- Medial lemniscus
- Corticospinal tract

**Medulla**
- Nucleus of solitary tract
- Dorsal motor nucleus
- Hypoglossal nucleus
- CN X
- Nucleus ambiguous
- Inferior olivary nucleus
- CN XII
- Medullary pyramid (corticospinal tract)
- Medial lemniscus

**A.** Vascular injury to anterior spinal artery (medial medullary syndrome).
**B.** PICA (posterior inferior cerebellar artery) lesion leading to lateral medullary syndrome.
**C.** Lesion leads to MLF syndrome frequently seen in multiple sclerosis.
**D.** Lesion results in Weber syndrome.
**E.** Sensory homunculus representation in the postcentral gyrus.

---

**CN, cranial nerve; MLF, medial longitudinal fasciculus.**

---

**Posterior white column**
- Spinothalamic tract
- Corticospinal tract

**Spinothalamic tract**

**Corticospinal tract**
The Nervous System

QUICK HIT
In amyotrophic lateral sclerosis (ALS), there is damage to both upper and lower motor neurons, producing symptoms of both spastic and flaccid paresis.

II. Spinothalamic tract
A. The spinothalamic tract is the ascending pathway that conveys pain and temperature from the body.
B. It receives input from free nerve endings of fast (A-type) and slow (C-type) pain fibers.
C. First-order neurons originate in the dorsal root ganglion, enter the spinal cord, and synapse on second-order neurons in the dorsolateral tract of Lissauer (thoracic vertebra level 2 [T2] to lumbar vertebra level 3 [L3]).
D. Second-order neurons ascend while decussating through the ventral white commissure and continue to ascend in the lateral spinothalamic tract, terminating in the VPL nucleus of the thalamus.
E. Third-order neurons originate in the VPL and project to the primary somatosensory cortex.
F. Lesions of the spinothalamic tract produce contralateral loss of pain and temperature sensation beginning one level below that of the lesion.

III. Corticospinal tract
A. The corticospinal tract is the descending pathway that originates in the primary motor cortex.
B. It mediates voluntary movement of striated muscle.
C. First-order neurons project to the posterior limb of the internal capsule, descend through the middle three-fifths of the midbrain’s crus cerebri and base of the pons, decussate in the pyramids of the medulla, and continue down the spinal cord as the corticospinal tract.
D. Corticospinal fibers synapse on second-order neurons of the ventral horn via interneurons.
E. Lesions above the pyramids (upper motor neurons [UMNs]) produce contralateral spastic paresis and a positive Babinski sign (upgoing toes).
F. Lesions below the pyramids (UMNs) produce ipsilateral spastic paresis and a positive Babinski sign.
G. Lesions of the second-order neurons (lower motor neurons [LMNs]) produce flaccid paralysis and fasciculations.

IMPORTANT PATHWAYS OF THE BRAIN STEM AND CEREBRUM
I. Trigeminothalamic pathway
A. The trigeminothalamic pathway is the ascending pathway that conveys pain and temperature from the face (analogous to the spinothalamic tract).
B. It receives input from free nerve endings of fast (A-type) and slow (C-type) pain fibers.
C. First-order neurons originate in the trigeminal ganglion and synapse on second-order neurons in the spinal trigeminal nucleus (ventral trigeminothalamic tract) or principal sensory nucleus of the trigeminal nerve (dorsal trigeminothalamic tract).
D. Second-order neurons of the ventral tract decussate while ascending; however, the dorsal tract neurons remain uncrossed, with termination in the ventral posteromedial (VPM) nucleus of the thalamus.

E. Third-order neurons originate in the VPM nucleus and project to the primary somatosensory cortex.

II. Corticobulbar tract
   A. The corticobulbar tract is the descending pathway that originates in the primary motor cortex.
   B. It mediates voluntary movement of the muscles of facial expression (analogous to the corticospinal tract).
   C. First-order neurons project to the genu of the internal capsule, descend through the anterior one-third of the midbrain's crus cerebri, and synapse in the nucleus of CN VII (facial nucleus).
   D. Second-order neurons innervate the muscles of facial expression (orbicularis oculi, orbicularis oris, buccinator, frontalis, and platysma) via the facial nerve.
   E. The upper face (orbicularis oculi and frontalis muscles) receives bilateral input from the UMN and therefore is unaffected by unilateral cortical lesions.
   F. The lower face (buccinator, orbicularis oris, and platysma) receives only contralateral input.

III. Cerebellar pathway
   A. The cerebellar pathway controls posture and balance, maintains muscle tone, and coordinates motor activity.
   B. The dentatothalamic tract is the major cerebellar tract.
      1. It originates in the dentate nucleus of the cerebellum.
      2. It projects to the ventrolateral nucleus of the thalamus (not the VPL nucleus) via the superior cerebellar peduncle.
      3. Thalamic fibers within the tract project to area 4 (primary motor cortex; see Figure 2-7A).
      4. Cerebral fibers within the tract project to corticospinal neurons.
      5. The pons receives cerebral fibers and sends fibers to the cerebellum, where they terminate on mossy fibers.
   C. Damage to one side of the vestibulocerebellum results in ipsilateral findings. Patient will fall toward the affected side (positive Romberg sign).

IV. Vestibulocochlear pathways
   A. Auditory pathway
      1. The auditory pathway originates from hair cells in the organ of Corti in the cochlea.
      2. Signals are sent down bipolar cell axons and are then relayed to the cochlear nuclei of the pons via the spiral ganglion.
      3. Signals are sent to higher CNS areas and relayed to the cerebral hemisphere via the medial geniculate body of the thalamus.
      4. Fibers terminate in the transverse temporal gyri.
      5. Because of the bilateral projection of information in the auditory pathway, one-sided lesions of this pathway at any point beyond the cochlear nuclei do not produce hearing loss.
      6. Lesions of the cochlear nerve itself will produce ipsilateral hearing loss.
   B. Vestibular pathway
      1. Hair cells of the three semicircular canals encode angular acceleration and deceleration.
      2. Hair cells of the utricle encode linear acceleration.
      3. Information is passed via the vestibular nerve to the vestibular nuclei of the low pons.
      4. Fibers then project to:
         a. The spinal cord
         b. The cerebellum
The Nervous System

3. The thalamus

4. CNs III, IV, and VI via the medial longitudinal fasciculus (MLF)

5. Nystagmus is mediated by the vestibular and oculomotor nuclei, the MLF, and the muscles of ocular movement controlled by CNs III, IV, and VI (Table 2-4).

Table 2-4: Direction of Movement in Types of Nystagmus

<table>
<thead>
<tr>
<th>Form of Nystagmus</th>
<th>Direction of Movement during Fast Phase</th>
<th>Direction of Movement during Slow Phase</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rotary nystagmus (i.e., while spinning in a circle)</td>
<td>Same as direction of rotation</td>
<td>Opposite direction of rotation</td>
</tr>
<tr>
<td>Postrotary nystagmus (i.e., after spinning in a circle)</td>
<td>Opposite direction of rotation</td>
<td>Same as direction of rotation</td>
</tr>
<tr>
<td>Caloric nystagmus</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Warm water placed in one ear</td>
<td>Toward the ear with warm water placed in it</td>
<td>Away from the ear with cold water placed in it</td>
</tr>
<tr>
<td>- Cold water placed in one ear</td>
<td>Away from the ear with warm water placed in it</td>
<td>Toward the ear with cold water placed in it</td>
</tr>
</tbody>
</table>

V. Visual pathways and vision abnormalities (Figure 2-9)

A. Muscles of the eye (Figure 2-10)

B. Horner syndrome

1. It is caused by a lesion of the sympathetic trunk in the neck.
2. Clinical features of the syndrome include ipsilateral ptosis, anhydrosis, flushing of skin, and miosis.

C. Argyll Robertson pupil

1. A pupil that accommodates to near objects but does not react to light
2. Seen in syphilis, systemic lupus erythematosus (SLE), and diabetes mellitus

D. Marcus Gunn pupil (aka afferent defect)

1. It is caused by a relative deficit in the afferent portion of the light reflex pathway.
2. Shining a light in the affected pupil causes minimal bilateral constriction, but shining light in the unaffected pupil causes normal constriction of both pupils.

E. MLF syndrome

1. Caused by a lesion of the MLF and can be unilateral or bilateral
2. Clinical features
   a. The ipsilateral eye (the eye on the side of the MLF lesion) is unable to adduct, and the contralateral eye (the opposite eye) has nystagmus.
   For example, in the cases of right MLF lesions, the right eye is unable to adduct and the left eye has nystagmus when looking left.
   b. Convergence is unaffected.
3. Often seen in multiple sclerosis (MS) and may be seen in stroke

F. Uncal herniation

1. The uncus of the temporal lobe is forced through the opening of the tentorium.
2. Clinical features include (Figure 2-9):
   a. Compression of CN III, leading to fixed and dilated (“blown”) pupil on ipsilateral side
   b. Ophthalmoplegia (paralysis of one or more of the ocular muscles)
   c. Compression of the corticospinal tract leading to ipsilateral hemiparesis
   d. Compression of the posterior cerebral artery leading to contralateral homonymous hemianopsia

QUICK HIT

Injury to CN III (oculomotor) results in ptosis because of loss of the levator palpebrae superioris muscle, exotropia because of the unopposed pull of the lateral rectus, dilation of the pupil because of unopposed pull of the dilator pupillae muscle, and impairment of near vision as a result of loss of accommodation of the ciliary muscle.

QUICK HIT

Horner syndrome is often caused by Pancoast tumor, a lung neoplasm that invades the cervical sympathetic chain.

QUICK HIT

The Marcus Gunn pupil can be diagnosed using the swinging flashlight test. Shining a flashlight in the normal pupil causes constriction of both pupils. Swinging the flashlight quickly to the affected eye causes paradoxical dilation of the pupils.

QUICK HIT

Remember COWS: cold opposite, warm same side for the direction of movement during fast phase of caloric nystagmus.

TABLE 2-4: Direction of Movement in Types of Nystagmus

<table>
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</tr>
<tr>
<td>Postrotary nystagmus</td>
<td>Opposite direction of rotation</td>
<td>Same as direction of rotation</td>
</tr>
<tr>
<td>Caloric nystagmus</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Warm water placed in one ear</td>
<td>Toward the ear with warm water placed in it</td>
<td>Away from the ear with cold water placed in it</td>
</tr>
<tr>
<td>- Cold water placed in one ear</td>
<td>Away from the ear with warm water placed in it</td>
<td>Toward the ear with cold water placed in it</td>
</tr>
</tbody>
</table>

023-060_McInnis_CH002_printer_file.indd   35
023-060_McInnis_CH002_printer_file.indd   35
9/10/14   4:01 AM
9/10/14   4:01 AM
The Nervous System

A. Optic tract

B. Pupillary constriction pathway

C. Lateral conjugate gaze

Legend for lesions:
1. Total blindness
2. Bitemporal hemianopsia—common lesion caused by superiorly growing pituitary tumor
3. Right hemianopsia
4. Right upper quadrantanopsia
5. Right lower quadrantanopsia
6. Right hemianopsia with macular sparing

B. Light shined in one eye causes constriction of both pupils.

C. Abduction of one eye results in adduction of the other eye in individuals with an intact medial longitudinal fasciculus and normal lateral conjugate gaze.

CN, cranial nerve; MLF, medial longitudinal fasciculus.

(Adapted from Chung KW. BRS Gross Anatomy. 2nd ed. Baltimore, MD: Lippincott Williams & Wilkins; 199.1:302, with permission.)
The Nervous System

Muscles of the eye

**Superior rectus muscle**
- Innervated by CN III (oculomotor)
- Causes eye to look upward
- Loss of function causes deviation downward

**Medial rectus muscle**
- Innervated by CN III (oculomotor)
- Causes adduction of the eye
- Loss of function causes abduction

**Lateral rectus muscle**
- Innervated by CN VI (abducens)
- Causes abduction of the eye
- Loss of function causes adduction

**Inferior rectus muscle**
- Innervated by CN III (oculomotor)
- Causes eye to look downward
- Loss of function causes deviation upward

**Superior oblique muscle**
- Innervated by CN IV (trochlear)
- Causes eye to look downward and laterally, also intorts the eye
- Loss of function causes deviation medially and superiorly

**Inferior oblique muscle**
- Innervated by CN III (oculomotor)
- Causes eye to look upward and laterally, also extorts the eye
- Loss of function causes deviation medially and inferiorly

---

**TABLE 2-5** Common Ocular Pathology

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Etiology</th>
<th>Pathology</th>
<th>Clinical Features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetic retinopathy</td>
<td>Proposed mechanism: accumulation of sorbitol in capillary pericytes results in loss of function, leading to retinal ischemia</td>
<td>Nonproliferative type observes microaneurysms, flame hemorrhages, dot and blot hemorrhages, soft exudates (cotton-wool spots), hard exudates (deposits of protein that have leaked from damaged capillaries), venous beading; proliferative type also observes neovascularization and fibrosis</td>
<td>Loss of visual acuity; advanced disease is the major cause of blindness</td>
</tr>
<tr>
<td>Age-related macular degeneration</td>
<td>Proposed mechanism: genetic</td>
<td>Pigmentary changes (drusen), macular hemorrhage or edema</td>
<td>Loss of central vision</td>
</tr>
<tr>
<td>Cataract</td>
<td>Aging, diabetes, galactosemia, Hurler disease, congenital causes (trisomy, myotonic dystrophy, hypoglycemia, TORCH infections)</td>
<td>Opacity of lens as a result of precipitation of sorbitol (diabetes), galactitol (galactosemia), mucopolysaccharide (Hurler disease), lens proteins (senile)</td>
<td>Decreased visual acuity, glare</td>
</tr>
<tr>
<td>Hypertensive retinopathy</td>
<td>High blood pressure → damages capillary walls</td>
<td>Copper wiring, flame hemorrhages, arteriovenous nicking, optic disc swelling (acute rise in blood pressure)</td>
<td></td>
</tr>
<tr>
<td>Atherosclerosis</td>
<td>Atherosclerotic plaque from carotid artery embolizes into ipsilateral retinal artery</td>
<td>Hollenhorst plaque, copper wiring, flame hemorrhages, arteriovenous nicking</td>
<td>Amaurosis fugax (transient loss in vision, classically described as “shade falling over eye”)</td>
</tr>
<tr>
<td>Papilledema</td>
<td>Increased intracranial pressure</td>
<td>Optic disc swelling (bilateral)</td>
<td>Headache; no changes in visual acuity until advanced disease</td>
</tr>
<tr>
<td>Angle-closure glaucoma</td>
<td>Acutely increased intraocular pressure</td>
<td>The lens abuts the posterior surface of the iris, pushing the iris forward and blocking the flow of aqueous humor</td>
<td>Acutely red, painful, rock-hard eye; decreased vision; halos around lights</td>
</tr>
<tr>
<td>Open-angle glaucoma</td>
<td>Chronically increased intraocular pressure</td>
<td>Less well understood; may be due to degeneration of the trabecular meshwork and canal of Schlemm</td>
<td>Gradual onset of loss of peripheral vision</td>
</tr>
</tbody>
</table>

TORCH, toxoplasmosis, other infections, rubella, cytomegalovirus, and herpes simplex virus.
The Nervous System

VI. Taste

A. The solitary nucleus of the medulla receives taste sensation via the solitary tract from three sources:
   1. The anterior two-thirds of the tongue via the chorda tympani nerve of the facial nerve (CN VII)
   2. The posterior third of the tongue via the glossopharyngeal nerve (CN IX)
   3. The epiglottic region of the pharynx via the vagus nerve (CN X)
B. Neurons carrying taste sensations ascend in the ventral tegmental tract to the VPM nucleus of the thalamus.
C. The VPM nucleus of the thalamus sends fibers to the parietal lobe.

VII. Limbic system

A. Mediates behavior and emotion, specifically:
   1. Feeding
   2. Feeling (emotions)
   3. Fighting
   4. Fleeing
   5. Sexual activity
B. Primarily controlled by the hypothalamus and autonomic nervous system
C. Primary components
   1. Anterior nucleus of thalamus
   2. Cingulate gyrus
   3. Mammillary bodies
   4. Septal area
   5. Hippocampus
   6. Amygdala (Table 2-5 and Figures 2-11 and 2-12)

Lesions of the mammillary bodies occur in thiamine deficiency, commonly seen in chronic alcoholism due to malnutrition. Damage results in Korsakoff syndrome, characterized by confusion, severe memory impairment, and confabulation, which is irreversible.

Age-related macular degeneration

Diabetic retinopathy

HYPOTHALAMUS (Figure 2-14)

Paraventricular and supraoptic nuclei
- Regulate water balance
- Produce ADH and oxytocin
- Destruction causes diabetes insipidus

Anterior commissure

Anterior nucleus
- Thermal regulation (dissipation of heat)
- Stimulates parasympathetic NS
- Destruction results in hyperthermia

Preoptic area
- Contains sexual dimorphic nucleus
- Regulates release of gonadotropin hormones

Suprachiasmatic nucleus
- Receives input from retina
- Controls circadian rhythms

Dorsomedial nucleus
- Stimulation results in obesity and savage behavior

Posterior nucleus
- Thermal regulation (conservation of heat)
- Destruction results in inability to thermoregulate
- Stimulates the sympathetic nervous system

Lateral nucleus
- Stimulation induces eating
- Destruction results in starvation

Mammillary body
- Receives input from hippocampal formation
- Contains hemorrhagic lesions in Wernicke encephalopathy

Ventromedial nucleus
- Satiety center
- Destruction results in obesity and savage behavior

ADH, antidiuretic hormone; CN, cranial nerve; NS, nervous system. (Redrawn from Fix JD. High-Yield Neuroanatomy. Baltimore, MD: Lippincott Williams & Wilkins; 1996:44, with permission.)
**QUICK HIT**

Tic douloureux (trigeminal neuralgia) is marked by severe stabbing bursts of pain in the distribution of CN V.

**THALAMUS** (Figure 2-15)

**Ventral anterior nucleus**
- **Input:** Substantia nigra, Globus pallidus
- **Output:** Prefrontal cortex, Orbital cortex, Premotor cortex

**Ventral lateral nucleus**
- **Input:** Cerebellum, Substantia nigra, Globus pallidus
- **Output:** Motor cortex (area 4), Premotor cortex (area 6)

**Ventral posterior lateral nucleus**
- **Input:** Spinothalamic tract, Medial lemniscus
- **Output:** Sensory cortex (areas 3, 1, 2)

**Ventral posterior medial nucleus**
- **Input:** Trigeminothalamic tract, Taste via central tegmental tract from solitary nucleus
- **Output:** Sensory cortex (areas 3, 1, 2)

**Lateral geniculate body**
- **Input:** Optic tract
- **Output:** Visual cortex (area 17), Relays visual information

**Medial geniculate body**
- **Input:** Inferior colliculus (sound)
- **Output:** Auditory cortex (areas 41, 42), Functions in relaying auditory information

**Anterior nucleus**
- **Input:** Mammillary tract and fornix
- **Output:** Cingulate gyrus, Functions in Papez circuit of emotion (limbic system)

**Mediodorsal nucleus**
- **Input:** Substantia nigra, Amygdala, Temporal lobe, Prefrontal cortex
- **Output:** Motor cortex (area 4), Premotor cortex (area 6)

**Centromedian nucleus**
- **Input:** Motor cortex (area 4), Globus pallidus
- **Output:** Caudal nucleus, Putamen, Diffusely to red cortex, Motor cortex (4)

**Pulvinar**
- **Input:** Occipital, Parietal, Posterior temporal lobes
- **Output:** Lateral and medial geniculate bodies, Superior colliculus

**Anterior nucleus**
- **Input:** Mammillary tract and fornix
- **Output:** Cingulate gyrus, Functions in Papez circuit of emotion (limbic system)

**CRANIAL NERVES**

The 12 CNs arise from various nuclei within the brain stem and cortex and serve multiple functions in the body. Their extracranial course is important for locating lesions, which can be tested by asking the patient to perform simple tasks. Table 2-6 outlines important information about CNs I to XII.
### TABLE 2-6 Cranial Nerves

<table>
<thead>
<tr>
<th>Nerve</th>
<th>Site of Exit from Skull</th>
<th>Function</th>
<th>Common Lesions</th>
<th>Test</th>
</tr>
</thead>
<tbody>
<tr>
<td>I—Olfactory</td>
<td>Cribriform</td>
<td>Smell</td>
<td>Cribriform plate fracture, Kallmann syndrome</td>
<td>Smell</td>
</tr>
<tr>
<td>II—Optic</td>
<td>Optic canal</td>
<td>Sight</td>
<td>Figure 2-9</td>
<td>Snellen chart, peripheral vision</td>
</tr>
<tr>
<td>III—Oculomotor</td>
<td>Superior orbital fissure</td>
<td>Parasympathetic to ciliary and sphincter muscles, medial rectus, superior rectus, inferior rectus, inferior oblique</td>
<td>Transtentorial (uncal) herniation, diabetes, Weber syndrome</td>
<td>“H” in space, pupillary light reflexes, convergence</td>
</tr>
<tr>
<td>IV—Trochlear</td>
<td>Superior orbital fissure</td>
<td>Superior oblique muscle</td>
<td>Head trauma</td>
<td>“H” in space</td>
</tr>
<tr>
<td>V—Trigeminal V1—Ophtalmic</td>
<td>Superior orbital fissure</td>
<td>Sensory from medial nose, forehead</td>
<td>Tic douloureux (trigeminal neuralgia)</td>
<td>Facial sensation, open jaw (deviates toward lesion)</td>
</tr>
<tr>
<td>V2—Maxillary</td>
<td>Foramen rotundum</td>
<td>Sensory from lateral nose, upper lip, superior buccal area</td>
<td></td>
<td></td>
</tr>
<tr>
<td>V3—Mandibular</td>
<td>Foramen ovale</td>
<td>Muscles of mastication, tensor tympani, tensor veli palatini; sensory from lower lip, lateral face to lower border of mandible</td>
<td></td>
<td></td>
</tr>
<tr>
<td>VI—Abduces</td>
<td>Superior orbital fissure</td>
<td>Lateral rectus muscle</td>
<td>Medial inferior pontine syndrome</td>
<td>“H” in space</td>
</tr>
<tr>
<td>VII—Facial</td>
<td>Internal acoustic meatus</td>
<td>Parasympathetic to lacrimal, submandibular, and sublingual glands; muscles of facial expression and stapedius, stylohyoid muscle; posterior belly of digastic muscle, sensory from anterior two-thirds of tongue (including taste via chorda tympani)</td>
<td>Bell palsy</td>
<td>Wrinkle forehead, show teeth, puff out cheeks, close eyes tightly</td>
</tr>
<tr>
<td>VIII—Vestibulocochlear</td>
<td>Internal acoustic meatus</td>
<td>Equilibrium, hearing</td>
<td>Acoustic schwannoma</td>
<td>Hearing, nystagmus (slow phase toward lesion)</td>
</tr>
<tr>
<td>IX—Glossopharyngeal</td>
<td>Jugular foramen</td>
<td>Parasympathetic to parotid gland; stylopharyngeus muscle; sensory from pharynx, middle ear, auditory tube, carotid body and sinus, external ear, posterior third of tongue (including taste)</td>
<td>Posterior inferior cerebellar artery (PICA) infarct</td>
<td>Gag reflex (no response ipsilateral to lesion)</td>
</tr>
<tr>
<td>X—Vagus</td>
<td>Jugular foramen</td>
<td>Parasympathetic to body viscera; laryngeal and pharyngeal muscles; sensory from trachea, esophagus, viscera, external ear, epiglottis (including taste)</td>
<td>Thyroidectomy, PICA infarct</td>
<td>Gag reflex (uvula deviates away from lesion)</td>
</tr>
<tr>
<td>XI—Accessory</td>
<td>Jugular foramen</td>
<td>Sternoclidomastoid and trapezius muscles</td>
<td>PICA infarct</td>
<td>Turning head (weakness turning away from lesion), raising shoulder against resistance (ipsilateral)</td>
</tr>
<tr>
<td>XII—Hypoglossal</td>
<td>Hypoglossal canal</td>
<td>Intrinsic tongue muscles</td>
<td>Anterior spinal artery infarct</td>
<td>Tongue protrusion (deviates toward lesion)</td>
</tr>
</tbody>
</table>
CONTENTS OF THE CAVERNOUS SINUS (Figure 2-16)

Contents of the cavernous sinus

- Optic tract and chiasm
- Ophthalmic artery
- Internal carotid artery
- Hypophysis
- Lumina of cavernous sinus
- Arachnoid mater
- Pia mater on surface of brain
- Subarachnoid space with arachnoid trabeculae
- Diaphragma sellae
- Infundibulum
- Oculomotor nerve (CN III)
- Trochlear nerve (CN IV)
- Abducent nerve (CN VI)
- Trigeminal nerve (CN V):
  - Ophthalmic division (V₁)
  - Maxillary division (V₂)
- Diaphragma sellae
- Infundibulum
- Pia mater on surface of brain
- Subarachnoid space

CN, cranial nerve. (From Tank PW, Gest TR. Lippincott Williams & Wilkins Atlas of Anatomy. Baltimore, MD: Wolters Kluwer Health; 2009. Used with permission)

SLEEP (Figure 2-17)

The sleep cycle

- Awake
- REM
- Light sleep
- Moderate sleep
- Deep sleep

I. Sleep–wake cycles

A. Based on circadian rhythms controlled by the suprachiasmatic nucleus of the hypothalamus

B. Serotonin (5-HT) released from the raphe nuclei of the brain stem is important in initiating sleep, whereas the reticular activating system maintains alertness.
C. Sleep is divided in the three non–rapid eye movement (REM) stages (N1, N2, and N3) and REM sleep.
1. An awake, alert individual shows low amplitude, high-frequency (12 to 30 Hz) beta waves on electroencephalogram (EEG).
2. A relaxed individual (still awake but with eyes closed, in preparation for sleep) shows lower frequency (8 to 12 Hz) alpha waves.
3. Stage N1 of sleep (light sleep) shows alpha waves giving way to low-frequency (4 to 7 Hz) theta waves.
4. Stage N2 sleep shows sleep spindles and K-complexes on EEG.
5. Stage N3 sleep (“slow-wave sleep,” deep sleep) shows very low-frequency (0 to 4 Hz) delta waves. Dreaming is possible (though less common than in REM sleep).
6. REM sleep normally occurs at 90-minute intervals and is characterized by high-frequency beta waves, which mirror those seen in the alert individual in the waking state. Most dreaming occurs during REM sleep along with increased brain oxygen consumption, nocturnal erections, and loss of skeletal muscle tone. REM sleep is thought to be important for memory processing and consolidation.

II. Common sleep disorders
A. Insomnia affects 30% of the U.S. population. It is associated with anxiety and leads to daytime sleepiness.
B. Restless leg syndrome is the sensation of unpleasant paresthesias that compels the patient to have voluntary, spontaneous, continuous leg movements. It is usually a primary idiopathic disorder, but it can occur secondary to iron deficiency, end-stage renal disease, diabetic neuropathy, Parkinson disease, pregnancy, rheumatic diseases, varicose veins, and excessive caffeine intake.
C. Nightmares versus night terrors
1. Nightmares are frightening dreams that occur during REM sleep, and patients actually awake from sleep.
2. Night terrors occur during non-REM sleep, and patients may appear to be awake (frightened/screaming, tachycardic, and diaphoretic) but are not actually fully awake. They are often difficult to arouse and usually fall right back to sleep after the episode.
D. Central sleep apnea, affecting less than 0.5% of the population, involves an absence of respiratory effort (for a discussion of obstructive sleep apnea, see Chapter 4).
E. Narcolepsy is seen in 0.04% of the population and is characterized by sudden onset of sleep with rapid onset of REM sleep. It may be associated with hallucinations and cataplexy (sudden loss of muscle tone).
F. Nocturnal enuresis is overnight bed-wetting after 5 years of age (developmental age), when daytime bladder control has been achieved. It is often familial.
1. Treatment is usually delayed until the child is at least 7 years of age.
2. Behavioral interventions are usually first line, including motivational therapy (e.g., star charts), nighttime fluid restriction, scheduled wakening, and enuresis alarms (most effective long-term therapy).
3. Pharmacologic interventions are usually second line and may include short-term imipramine, oral desmopressin, or indomethacin. There is a high likelihood of recurrence upon discontinuation.

SEIZURE TYPES
Seizures are paroxysmal events caused by abnormal and excessive discharges from CNS neurons triggered by a variety of causes (Table 2-7).

The antiepileptic agents, which include several different medications, affect ion channels (Table 2-8). The side effects of these agents are often significant. Because it is frequently necessary to take these agents for long periods, it is important to understand these side effects.
# Table 2-7 Seizure Types

<table>
<thead>
<tr>
<th>Type</th>
<th>Patient</th>
<th>Presentation</th>
<th>Pathology</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Simple partial seizures</td>
<td>All ages</td>
<td>Malfunction of one muscle or muscle group</td>
<td>No loss of consciousness</td>
<td>Phenobarbital</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Sensory distortions</td>
<td></td>
</tr>
<tr>
<td>Jacksonian seizures</td>
<td>All ages (subtype of simple partial)</td>
<td>Expanding area of motor malfunction</td>
<td>Original focus spreads to adjacent areas of cortex</td>
<td>Carbamazepine</td>
</tr>
<tr>
<td>Complex partial seizures</td>
<td>First seizure during first two decades of life may be caused by fever in children 6 months to 5 years of age (febrile seizure)</td>
<td>Incontinence</td>
<td>Single focus</td>
<td>Phenobarbital, carbamazepine (febrile seizures do not require antiseizure medication)</td>
</tr>
<tr>
<td>Absence (petit mal) seizures</td>
<td>Begin at 2–3 years of age Often end with puberty</td>
<td>1–5 seconds loss of consciousness Several episodes per day Blank stare with rapid blinking</td>
<td>Original focus rapidly spreads across both hemispheres</td>
<td>Ethosuximide, valproic acid</td>
</tr>
<tr>
<td>Tonic–clonic (grand mal) seizures</td>
<td>Most common type Encountered in different clinical settings, often in patients with metabolic disorders</td>
<td>Sudden loss of consciousness Loss of postural control and continence Tonic phase (static extension) Clonic phase (jerking movements) Recovery period with exhaustion and disorientation</td>
<td>Original focus rapidly spreads across both hemispheres</td>
<td>Phenobarbital, carbamazepine</td>
</tr>
</tbody>
</table>

# Table 2-8 Antiepileptic Agents

<table>
<thead>
<tr>
<th>Drug</th>
<th>Mechanism of Action</th>
<th>Type(s) of Seizure(s) Controlled</th>
<th>Side Effects</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carbamazepine</td>
<td>Blocks voltage-gated sodium channels by increasing the refractory period</td>
<td>Tonic–clonic (grand mal), partial, Jacksonian</td>
<td>Liver enzyme induction, ataxia, diplopia, blood dyscrasias (agranulocytosis, aplastic anemia), teratogenesis, induction of cytochrome P450</td>
<td>Can be used to treat trigeminal neuralgia</td>
</tr>
<tr>
<td>Ethosuximide</td>
<td>Inhibits certain sodium channels, particularly in certain parts of thalamus that produce cyclic cortical discharges</td>
<td>Absence</td>
<td>Headache, lethargy, diarrhea, urticaria, Stevens–Johnston syndrome</td>
<td></td>
</tr>
<tr>
<td>Phenytoin</td>
<td>Blocks voltage-gated sodium channels by increasing refractory period</td>
<td>Tonic–clonic (grand mal), partial</td>
<td>Liver enzyme induction, ataxia, diplopia, megaloblastic anemia, lupus-like syndrome, nystagmus, sedation, teratogenesis (fetal hydantoin syndrome), peripheral neuropathy, hirsutism, gingival hyperplasia, induction of cytochrome P450, malignant hyperthermia (rare)</td>
<td></td>
</tr>
<tr>
<td>Valproic acid</td>
<td>May affect potassium channels to cause hyperpolarization of neuronal membranes</td>
<td>Absence, tonic–clonic (grand mal), partial</td>
<td>Liver enzyme induction, diarrhea, rarely hepatotoxic, tremor, weight gain, neural tube defects in fetus (spina bifida)</td>
<td>Contraindicated in pregnancy</td>
</tr>
<tr>
<td>Phenobarbital (barbiturate)</td>
<td>Increase inhibitory effects of γ-aminobutyric acid (GABA) by increasing duration of chloride channel opening</td>
<td>Tonic–clonic (grand mal), partial</td>
<td>Liver enzyme induction, sedation, tolerance, dependence, induction of cytochrome P450</td>
<td>First line in pregnant women, children</td>
</tr>
</tbody>
</table>

(continued)
Degenerative diseases can lead to focal or systemic loss of function. Many of the degenerative diseases affecting the CNS are irreversible and are listed in Table 2-9.

**Parkinson disease**, a movement disorder, results from deterioration of the **basal ganglia**. Dopamine production decreases, which in turn increases the relative effects of acetylcholine. Treatment is symptomatic and is aimed at trying to restore the balance between the two hormones (Table 2-10).

### TABLE 2-8 Antiepileptic Agents (Continued)

<table>
<thead>
<tr>
<th>Drug</th>
<th>Mechanism of Action</th>
<th>Type(s) of Seizure(s) Controlled</th>
<th>Side Effects</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benzodiazepines</td>
<td>Increase inhibitory effects of GABA by increasing frequency of chloride channel opening</td>
<td>First line for acute status epilepticus</td>
<td>Sedation, tolerance, dependence</td>
<td>Used for seizures of eclampsia</td>
</tr>
<tr>
<td>(diazepam, lorazepam)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lamotrigine</td>
<td>Blocks voltage-gated sodium channels</td>
<td>Tonic–clonic (grand mal), partial</td>
<td>Stevens–Johnson syndrome</td>
<td></td>
</tr>
<tr>
<td>Gabapentin</td>
<td>Increases GABA release</td>
<td>Tonic–clonic (grand mal), partial</td>
<td>Sedation, ataxia</td>
<td></td>
</tr>
<tr>
<td>Topiramate</td>
<td>Blocks sodium channels, increases GABA action</td>
<td>Tonic–clonic (grand mal), partial</td>
<td>Sedation, weight loss, nephrolithiasis</td>
<td>Also used for migraine prophylaxis</td>
</tr>
</tbody>
</table>

### TABLE 2-9 Degenerative Diseases

<table>
<thead>
<tr>
<th>Disease</th>
<th>Etiology</th>
<th>Clinical Manifestation</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vitamin B₁₂ deficiency</td>
<td>Strict vegetarian diet, <strong>pernicious anemia</strong>, fundal gastritis type A, <em>Diphyllobothrium latum</em></td>
<td><strong>Megaloblastic anemia, peripheral neuropathy, myelin degeneration of posterior white columns, and lateral corticospinal tracts</strong></td>
<td>Megaloblastic anemia component of vitamin B₁₂ deficiency can be treated with folate; however, this will not resolve the peripheral neuropathy component of the deficiency</td>
</tr>
<tr>
<td>Parkinson disease</td>
<td>Decrease in dopamine caused by depletion of cells of substantia nigra and locus coeruleus; similar symptoms may be caused by depression, hydrocephaly, MPTP intoxication</td>
<td><strong>Resting tremors, masked facies, muscular rigidity, shuffling gait, Lewy bodies</strong></td>
<td>Usually appears after 55 years of age; therapy with dopamine precursors or ACh inhibitors</td>
</tr>
<tr>
<td>Poliomyelitis</td>
<td>Poliovirus (RNA); fecal–oral; replicates in pharynx; spreads to CNS</td>
<td><strong>Aseptic meningitis, death of anterior horn cells in spinal cord, paralysis</strong></td>
<td>Killed (Salk) and live-attenuated (Sabin) vaccine available; Sabin vaccine given to children because of IgA response, longer action, and availability of oral form</td>
</tr>
<tr>
<td>Rabies</td>
<td>Rhabdovirus (RNA); spread via saliva</td>
<td><strong>Laryngeal spasm resulting in fear of water, CNS excitability, Negri body inclusions, hippocampal degeneration</strong></td>
<td>Treatment via passive and active immunization at distant sites</td>
</tr>
<tr>
<td>Spongiform encephalopathies (a) Animals</td>
<td><strong>Scrapie (sheep)</strong> – <strong>Bovine spongiform encephalopathy (BSE; cows; aka mad cow disease)</strong></td>
<td><strong>Vacuolization of brain tissue, dementia, ataxia, depictions of the abnormal protein, long incubation (years), rapid death after onset (months)</strong></td>
<td>Diagnosed at autopsy; no treatment; new-variant CJD acquired by eating BSE-contaminated meat; Kuru spread by nonalignment of neurologic tissue; CJD has been spread by corneal transplant and on contaminated neurosurgical equipment</td>
</tr>
</tbody>
</table>

(continued)
### TABLE 2-9 Degenerative Diseases (Continued)

<table>
<thead>
<tr>
<th>Disease</th>
<th>Etiology</th>
<th>Clinical Manifestation</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>(b) Humans</td>
<td>Autosomal recessive; <strong>deficiency of hexosaminidase A</strong> with increase in G&lt;sub&gt;M2&lt;/sub&gt;, ganglioside seizures</td>
<td>Mental retardation, <strong>cherry-red spot on macula</strong>, muscular weakness</td>
<td>Fatal, prenatal diagnosis possible, usually affects cells of CNS</td>
</tr>
<tr>
<td>Tay–Sachs disease</td>
<td>Severe malnutrition (may be secondary to alcoholism)</td>
<td>Degeneration of mammillary bodies, Wernicke–Korsakoff syndrome—psychosis manifested with confusion, ataxia, and confabulation</td>
<td>Wernicke encephalopathy (reversible) and Korsakoff syndrome (irreversible) are both secondary to deficiency caused by alcoholism</td>
</tr>
<tr>
<td>Thiamine deficiency</td>
<td>Autosomal recessive; <strong>decreased ceruloplasmin</strong></td>
<td>Copper accumulation, asterixis, dementia, liver cirrhosis, <strong>Kayser–Fleischer ring</strong> in cornea</td>
<td>Hepatolenticular degeneration of the basal ganglia</td>
</tr>
<tr>
<td>Wilson disease</td>
<td>Ach, acetylcholine; CNS, central nervous system; IgA, immunoglobulin A; MPTP, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### TABLE 2-10 Antiparkinsonian Agents

<table>
<thead>
<tr>
<th>Drug</th>
<th>Mechanism of Action</th>
<th>Side Effects</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Levodopa (<strong>L</strong>-dopa) (dopamine precursor)</td>
<td>More readily crosses the blood–brain barrier, converted to dopamine in the brain by <strong>DOPA decarboxylase</strong></td>
<td>Dyskinesias (following dose), akinesia (between doses), postural hypotension, anorexia, depression, psychosis, arrhythmia</td>
<td>Development of tolerance, wildly varying effectiveness (on–off phenomenon), often necessitates drug holidays</td>
</tr>
<tr>
<td>Carbidopa</td>
<td>Inhibits conversion of L-dopa to dopamine in the periphery by <strong>DOPA decarboxylase</strong></td>
<td>Decreases systemic side effects of L-dopa such as anorexia and nausea</td>
<td>Given with L-dopa, <strong>does not cross the blood–brain barrier</strong>, inhibition of systemic conversion of L-dopa, which reduces L-dopa dosing approximately 75%</td>
</tr>
<tr>
<td>Amantadine</td>
<td>Unclear; may stimulate dopamine receptors, stimulate dopamine release, or inhibit its reuptake</td>
<td>Agitation, restlessness, psychosis, urinary retention</td>
<td>Rapid deterioration of effectiveness over a period of weeks</td>
</tr>
<tr>
<td>Selegiline, rasagiline</td>
<td>Selectively and irreversibly inhibits MAO type B, which metabolizes dopamine</td>
<td>Dyskinesias, hepatic conversion to amphetamine causes insomnia and anorexia</td>
<td>In high doses, inhibition of MAO type A, which is prevalent in the gut, allowing absorption of ingested amines, which can cause <strong>hypertensive crises</strong></td>
</tr>
<tr>
<td>Entacapone, tolcapone</td>
<td>Inhibits COMT, which metabolizes dopamine</td>
<td>Nausea, dyskinesia, orthostatic hypotension</td>
<td>Administered with levodopa/carbidopa to reduce “wearing off” symptoms at the end of dosing interval</td>
</tr>
<tr>
<td>Bromocriptine</td>
<td>Acts as a dopamine receptor agonist</td>
<td>Anorexia, nausea, vomiting, postural hypotension, psychosis</td>
<td>Given as an adjuvant with L-dopa, inhibits release of prolactin and growth hormone and is therefore used for prolactinomas and acromegaly</td>
</tr>
<tr>
<td>Pramipexole, ropinirole</td>
<td>Dopamine receptor agonist</td>
<td>Postural hypotension/syncope, dizziness, sedation, fatigue, hallucinations, abnormal dreams</td>
<td>Also used to treat restless leg syndrome</td>
</tr>
<tr>
<td>Benzotropine</td>
<td>Blocks muscarinic acetylcholine receptors</td>
<td>Atropine-like side effects, inattention, psychosis</td>
<td>Used in combination with dopamine agonists and L-dopa, <strong>improves tremor and rigidity</strong> but has little effect on bradykinesia</td>
</tr>
</tbody>
</table>

COMT, catechol-O-methyltransferase; MAO, monoamine oxidase.
The Nervous System

DISEMYELINATING DISEASES

Loss of the neuronal sheath can lead to impaired nerve conduction, which, in turn, causes deficits and disease (Table 2-11).

DISEASES THAT CAUSE DEMENTIA

Dementia is a chronic progressive deterioration in cognitive ability in which mental faculties, such as executive function, attention span, judgment, memory, mood, and behavior, are affected (Table 2-12).

ACUTE MENINGITIS

Meningitis is an infection of the meninges resulting in an inflammatory reaction characterized by severe headache, fever, photophobia, and positive Kernig and Brudzinski signs. Meningitis in immunocompetent adults is generally caused by Streptococcus pneumoniae or CNS stimulants, which are at the other end of the spectrum from the sedative-hypnotics, usually cause sympathetic stimulation, resulting in increased alertness. They can also lower the seizure threshold. Common drugs of this type are amphetamine, caffeine, cocaine, dextroamphetamine, ephedrine, and methylphenidate.

QUICK HIT

Amantadine, used in the treatment of Parkinson disease, also has antiviral effects and is sometimes used in the prevention and treatment of influenza A.

QUICK HIT

Tay–Sachs disease and Niemann–Pick disease, a deficiency of sphingomyelinase, can both present with a cherry-red spot on the macula.

QUICK HIT

Werdnig–Hoffmann disease is an infantile, autosomal recessive, and lower motor neuron disease similar to ALS.

QUICK HIT

Progressive multifocal leukoencephalopathy is a demyelinating disease caused by JC virus infection of oligodendrocytes. It is seen in patients with immune deficiency.

QUICK HIT

The Nervous System

Amantadine, used in the treatment of Parkinson disease, also has antiviral effects and is sometimes used in the prevention and treatment of influenza A.

Werdnig–Hoffmann disease is an infantile, autosomal recessive, and lower motor neuron disease similar to ALS.

Progressive multifocal leukoencephalopathy is a demyelinating disease caused by JC virus infection of oligodendrocytes. It is seen in patients with immune deficiency.

TABLE 2-11 Demyelinating Diseases of the Nervous System

<table>
<thead>
<tr>
<th>Disease</th>
<th>Etiology</th>
<th>Clinical Manifestation</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amyotrophic lateral sclerosis (ALS, Lou Gehrig disease)</td>
<td>No specific pattern of inheritance, although autosomal dominant in 5% of cases (similar symptoms with some heavy metal poisonings, infections, or tumors)</td>
<td>Both upper and lower motor neuron signs; loss of lateral corticospinal tracts and anterior motor neurons leading to muscle atrophy</td>
<td>Most common motor neuron disease; rapidly fatal course</td>
</tr>
<tr>
<td>Guillain–Barre syndrome</td>
<td>Postviral autoimmune reaction involving peripheral nerves</td>
<td>Muscle weakness and paralysis ascending upward from the lower extremities</td>
<td>Young adults; albuminocytologic dissociation is pathognomonic (high albumin, low cell count)</td>
</tr>
<tr>
<td>Huntington disease</td>
<td>Chromosome 4; CAG repeat base repeat with anticipation</td>
<td>Degeneration of caudate nucleus, onset at 30–40 years of age, athetoid movements, muscular deterioration, dementia</td>
<td>Usually involves acetylcholine (ACh) and /H9253-aminobutyric acid (GABA) neurons</td>
</tr>
<tr>
<td>Krabbe disease</td>
<td>Autosomal recessive; decrease in /H9252-galactocerebrosidase</td>
<td>Loss of myelin from globoid cells and peripheral nerves, mental retardation, blindness, paralysis, globoid bodies in white matter</td>
<td>Usually affects infants, rapidly fatal</td>
</tr>
<tr>
<td>Metachromatic leukodystrophy</td>
<td>Autosomal recessive defect of arylsulfatase A</td>
<td>Progressive paralysis and dementia, loss of myelin, accumulation of sulfatides, nerves stain yellow-brown in color, ataxia</td>
<td>Fatal in first decade</td>
</tr>
<tr>
<td>Multiple sclerosis (MS)</td>
<td>Unknown; more common in northern Europe; more common in women</td>
<td>Multiple focal areas of demyelination; variable course; Triad of MS: intention tremor, scanning speech, nystagmus</td>
<td>Most common demyelinating disease; increased cerebrospinal fluid (CSF) immunoglobulin</td>
</tr>
</tbody>
</table>
Neisseria meningitidis. Conditions predisposing an individual to acute bacterial meningitis as a result of pneumococcus include distant foci of infection (such as otitis, sinusitis, or pneumonia), sickle cell disease (secondary to splenic autoinfarction), alcoholism, or trauma with loss of meningeal integrity. Patients with a deficiency of complement components C5 to C8 are at a greater risk of developing meningococcal meningitis. Haemophilus

### Clinical Vignette 2-2

**Clinical Presentation:** A 28-year-old female presents to the emergency department complaining of numbness in her right leg that lasted several hours, which worsened when she took a warm shower. She also complained of feeling fatigued lately and she remembered that 1 year ago she had an episode of transient unilateral vision loss that resolved and never recurred. Vital signs: temperature = 97.0°F; blood pressure = 122/75 mm Hg; heart rate = 76 bpm; respiration rate = 18 breaths/min. Physical exam is significant for nystagmus, scanning speech, and diminished sensation in the right leg but normal strength.

**Differentials:** Multiple sclerosis (MS), Guillian–Barré syndrome.

**Diagnostic Studies:** Order magnetic resonance imaging (MRI) of the brain and a lumbar puncture (LP). MS should be suspected in young adults with relapsing and remitting neurologic signs and symptoms that do not seem associated to the same area of central nervous system (CNS) white matter. MRI shows demyelinating lesions (plaques) at the angles of the lateral ventricles (which is the classic location of plaques in MS). MS is caused by selective demyelination of the spinal cord and brain, sparing peripheral nervous system (PNS) and gray matter. There are no laboratory tests specific for MS, but LP and cerebrospinal fluid (CSF) analysis will show oligoclonal bands of IgG in 90% of patients with MS. Transient sensory deficits are a common presenting feature of MS, as are visual disturbances caused by optic neuritis. Optic neuritis presents as monocular visual loss, pain on movement of eyes, central scotoma (black spot in center of vision), or decreased pupillary reaction to light. Also, be aware of the Charcot triad: intention tremor, nystagmus, and scanning speech.

**Management:** Treat this patient with high-dose intravenous (IV) corticosteroids, which can shorten an acute attack. After treatment of an acute attack, manage patient with interferon therapy, which should be started early in the course of disease. Treat symptoms of muscle spasticity with baclofen and carbamazepine or gabapentin for neuropathic pain.

### TABLE 2-12 Diseases That Cause Dementia

<table>
<thead>
<tr>
<th>Disease</th>
<th>Etiology</th>
<th>Clinical Manifestation</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alzheimer dementia</td>
<td>Unknown; possibly chromosome 21, degeneration of nucleus basalis of Meynert, decreased choline acetyltransferase</td>
<td>Progressively worsening memory loss, neurofibrillary tangles, senile plaques (amyloid β/A4 protein)</td>
<td>Most common cause of dementia; age of onset is usually 65 years (younger in patients with Down syndrome)</td>
</tr>
<tr>
<td>Multi-infarct dementia</td>
<td>Cerebral atherosclerosis</td>
<td>Stepwise decline of function, signs of dementia and possible motor deficits</td>
<td>Second most common cause of dementia</td>
</tr>
<tr>
<td>Primary HIV dementia</td>
<td>Macrophages, infected with HIV, enter CNS</td>
<td>Onset before immunodeficiency, slow thinking, ataxia, Toxoplasma gondii on autopsy</td>
<td>Most common CNS manifestation of HIV</td>
</tr>
<tr>
<td>Frontotemporal dementia</td>
<td>Unknown; may be familial</td>
<td>Dementia plus personality/behavioral changes; possibly progressive aphasia</td>
<td></td>
</tr>
<tr>
<td>(Pick disease)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dementia with Lewy bodies</td>
<td>Unknown; combination of genetics and environmental factors</td>
<td>Dementia plus parkinsonian features, visual hallucinations, syncope/falls</td>
<td>More common in men</td>
</tr>
</tbody>
</table>

CNS, central nervous system.
**The Nervous System**

**Haemophilus influenzae** type B was once a common cause of meningitis in children, although these numbers have decreased because of widespread vaccination (Table 2-13).

Lumbar puncture (LP) is often performed to confirm a suspected diagnosis of meningitis. The LP usually shows increased neutrophils, increased protein, and decreased glucose if bacterial in origin. Also, organisms may be seen on Gram stain. However, if the CSF contains increased lymphocytes and a normal glucose level, viral agents such as enterovirus, HIV, and herpes simplex virus should be considered (Table 2-14). If the LP shows organisms with a thick capsule when stained with India ink, this suggests *Cryptococcus neoformans*, and the infected individual is most likely immunocompromised as a result of HIV infection. Adults who are immunocompromised are also at risk for developing meningitis caused by *Listeria monocytogenes*.

### NERVOUS SYSTEM TUMORS

Nearly 50% of the tumors occurring within the nervous system are metastases to the brain from tumors elsewhere in the body. The other 50% are primary nervous system tumors. Tables 2-15 and 2-16 list the most common nervous system tumors in adults and children. Seventy percent of adult brain tumors are supratentorial; 70% of childhood brain tumors are infratentorial.

**TABLE 2-13 Common Causes of Meningitis in Various Age Groups**

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Causes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Newborns</td>
<td>Group B streptococci, <em>Escherichia coli</em>, <em>Listeria</em></td>
</tr>
<tr>
<td>Children</td>
<td><em>Haemophilus influenzae</em> b (declining since Hib vaccine introduced)</td>
</tr>
<tr>
<td></td>
<td><em>Streptococcus pneumoniae</em>, <em>Neisseria meningitidis</em>, Enteroviruses</td>
</tr>
<tr>
<td>Adolescents and young adults</td>
<td>Enteroxviruses, <em>N. meningitidis</em>, <em>S. pneumoniae</em>, Herpes simplex virus</td>
</tr>
<tr>
<td>Elderly</td>
<td><em>S. pneumoniae</em>, Gram-negative rods, <em>Listeria</em></td>
</tr>
</tbody>
</table>

**QUICK HIT**

*Toxoplasma gondii* can infect the immunocompromised individual via three routes: undercooked meat, cat feces, or in utero. It is the most common CNS infection in patients with AIDS.

**PREVNAR** is a pneumococcal conjugate vaccine that is being given to children. The goal is to prevent invasive pneumococcal infections. There are two pediatric formulations: one with 7 serotypes, and one with 13 serotypes. The serotypes used to make the immunization are thought to be responsible for the majority of severe, invasive pneumococcal infections. Common, less invasive infections, such as otitis media, are unlikely to be affected because many other serotypes are not included in the vaccine.

**QUICK HIT**

**Tumors of the CNS are usually intracranial, with adult tumors commonly supratentorial and childhood tumors usually infratentorial.**

**TABLE 2-14 Evaluation of Cerebrospinal Fluid to Determine Cause of Meningitis**

<table>
<thead>
<tr>
<th>Laboratory Test</th>
<th>Bacterial</th>
<th>Viral</th>
<th>Fungal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Opening CSF pressure</td>
<td>↑</td>
<td>N</td>
<td>↑</td>
</tr>
<tr>
<td>Lymphocytes</td>
<td>N</td>
<td>↑</td>
<td>↑</td>
</tr>
<tr>
<td>Neutrophils</td>
<td>↑</td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td>Glucose</td>
<td>↓</td>
<td>N</td>
<td>↓</td>
</tr>
<tr>
<td>Protein</td>
<td>↑</td>
<td>N</td>
<td>↑</td>
</tr>
</tbody>
</table>

↑, increased; ↓, decreased; CSF, cerebrospinal fluid; N, normal.
### TABLE 2-15 Nervous System Tumors in Adults

<table>
<thead>
<tr>
<th>Tumor</th>
<th>Presentation</th>
<th>Significant Features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metastatic neoplasms</td>
<td>Headache, focal defects, formation of discrete nodules in brain</td>
<td>Nearly half of all intracranial neoplasm; usually bloodborne; commonly from lung, breast, gastrointestinal, thyroid, kidney, genitourinary, and melanoma</td>
</tr>
<tr>
<td>Glioblastoma (grade IV astrocytoma)</td>
<td>Cerebral hemisphere tumor, irregular mass with necrotic center surrounded by edema seen on CT</td>
<td>Most common primary intracranial neoplasm, poor prognosis, neural tube origin, pseudopalisading arrangement of cells, astrocytes stain with GFAP</td>
</tr>
<tr>
<td>Meningioma</td>
<td>Psammoma bodies, slowly growing, originates in arachnoid cells, follows sinuses</td>
<td>Second most common primary CNS tumor, usually occurs in women, resectable, neural crest origin</td>
</tr>
<tr>
<td>Schwannoma</td>
<td>Tinnitus and hearing loss, ataxic gait, positive Romberg sign, increased intracranial pressure, hydrocephalus, benign</td>
<td>Third most common primary intracranial tumor, neural crest origin, usually occurs in the cerebellopontine angle and involves CN VIII, seen bilaterally in neurofibromatosis type 2 (NF-2)</td>
</tr>
<tr>
<td>Oligodendroglioma</td>
<td>Slow-growing frontal lobe tumor</td>
<td>Rare; clearing of the cytoplasm around the nuclei (perinuclear halo) gives tumor cells a “fried egg” appearance</td>
</tr>
</tbody>
</table>

CN, cranial nerve; CNS, central nervous system; CT, computed tomography; GFAP, glial fibrillary acidic protein.

### TABLE 2-16 Nervous System Tumors in Children

<table>
<thead>
<tr>
<th>Tumor</th>
<th>Presentation</th>
<th>Significant Features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pilocytic astrocytoma (grade I astrocytoma)</td>
<td>Benign, usually posterior fossa, good prognosis</td>
<td>Most common primary brain tumor in children, astrocytes stain with GFAP, eosinophilic Rosenthal fibers</td>
</tr>
<tr>
<td>Medulloblastoma</td>
<td>Cerebellar mass, may compress the fourth ventricle (noncommunicating hydrocephalus), ataxic gait, projectile vomiting</td>
<td>Most common malignant primary brain tumor of childhood, neural tube origin, Homer-Wright rosettes (circular arrangement of tumor cells around a central tangle of fibrils)</td>
</tr>
<tr>
<td>Ependymoma</td>
<td>May compress the fourth ventricle (noncommunicating hydrocephalus)</td>
<td>Neural tube origin; perivascular rosettes (circular arrangement of tumor cells around a central vessel)</td>
</tr>
<tr>
<td>Craniopharyngioma</td>
<td>Endocrine abnormalities, papilledema, bitemporal hemianopsia due to compression of optic chiasm</td>
<td>Enlarged sella turcica, most common supratentorial brain tumor in children, ectodermal origin (Rathke pouch)</td>
</tr>
</tbody>
</table>

GFAP, glial fibrillary acidic protein.

Psammoma bodies are also seen in papillary adenocarcinoma of the thyroid, serous papillary cystadenocarcinoma of the ovary, and malignant mesothelioma.
HEADACHE (Table 2-17)

<table>
<thead>
<tr>
<th>Type</th>
<th>General Characteristics</th>
<th>Clinical Features</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tension</td>
<td>Worsens throughout the day; precipitated by stress, anxiety, and depression; more frequent in women</td>
<td>Tight, bandlike pain encircling the entire head; most intense around the neck or back of head; tenderness in posterior neck muscles</td>
<td>Stress reduction, NSAIDs, acetaminophen, and aspirin if mild/moderate; if severe, TCAs or SSRIs</td>
</tr>
<tr>
<td>Cluster</td>
<td>Usually occurs in middle-aged men, episodic—lasts 2–3 months, with remissions of months to years; occurs around bedtime and lasts 30–90 min</td>
<td>Excruciating periorbital pain (“behind the eye”), unilateral; stabbing or deep, burning pain; accompanied by ipsilateral lacrimation, nasal congestion or discharge, facial flushing</td>
<td>Acute: sumatriptan, oxygen inhalation; Prophylaxis: verapamil taken daily—drug of choice (alternatives: ergotamine, methylin, methylsergide, corticosteroids)</td>
</tr>
<tr>
<td>Migraine</td>
<td>Inherited; caused by serotonin depletion; women &gt; men; family history subtypes: 1. Classic: migraine with aura (aura usually visual such as flashing lights, scotoma, visual distortions) 2. Common: migraine without aura 3. Menstrual</td>
<td>Prodromal phase; severe throbbing or dull achy unilateral headaches, may be generalized; lasts for 4–72 h; pain is aggravated by coughing, physical activity, and bending down; other symptoms include nausea and vomiting, photophobia, and increased sensitivity to smell</td>
<td>Acute: NSAIDs, dihydroergotamine, sumatriptan; Prophylaxis: first line—TCAs and propranolol; second line—verapamil, valproic acid, and methylergide</td>
</tr>
</tbody>
</table>

NSAID, nonsteroidal anti-inflammatory drug; SSRI, selective serotonin reuptake inhibitor; TCA, tricyclic antidepressant.

PSYCHIATRY AND BEHAVIORAL SCIENCE

I. Nonpharmacologic therapeutic modalities (Table 2-18)

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Characteristics</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Biofeedback</td>
<td>Gaining control over physiology via continuous information; motivation and practice required</td>
<td>Used for hypertension, migraine headaches, and tension headaches</td>
</tr>
<tr>
<td>Classical conditioning</td>
<td>A reflexive, natural behavior is elicited in response to a learned stimulus (e.g., ringing of a bell causing salivation)</td>
<td>Aversive conditioning pairs an unwanted response to a painful stimulus; stages include acquisition, extinction, and recovery</td>
</tr>
<tr>
<td>Cognitive therapy</td>
<td>Negative thinking is reorganized into self-affirming, positive thoughts</td>
<td>Short-term psychotherapy used to treat depression and anxiety</td>
</tr>
<tr>
<td>Electroconvulsive therapy (ECT)</td>
<td>Electric current introduced into brain to alter neurotransmitter function; improvement seen faster than with pharmacologic regimens</td>
<td>Used for major depression; safe; effective; retrograde amnesia is a major side effect</td>
</tr>
<tr>
<td>Operant conditioning</td>
<td>Behavior that is not part of the natural repertoire is learned by altering the reward (reinforcement)</td>
<td>Reinforcement can be positive or negative; reward schedule includes continuous, fixed, or variable</td>
</tr>
<tr>
<td>Psychoanalysis</td>
<td>Intensive treatment based on recovering and integrating past experiences from the unconscious via free association; based on Freud's theories</td>
<td>Id—sexual drives and aggression; ego—controls instinct and interacts with the world; superego—morality and conscience</td>
</tr>
<tr>
<td>Systematic desensitization</td>
<td>Classical conditioning technique in which relaxation procedures are combined with increasing doses of anxiety-provoking stimuli</td>
<td>Used to eliminate phobias</td>
</tr>
<tr>
<td>Token economy</td>
<td>Positive reinforcement in which a reward is used to elicit a desired response</td>
<td>Seen often in mental hospitals or parents dealing with children</td>
</tr>
</tbody>
</table>
II. Eating disorders (Table 2-19)

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Characteristics</th>
<th>Treatment</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anorexia nervosa</td>
<td>Body weight &lt;85% of ideal, distorted body image, amenorrhea, intense fear of gaining weight</td>
<td>Supportive care, counseling, cognitive behavioral therapy, family therapy, pharmacotherapy is typically ineffective</td>
<td>Higher incidence in female adolescents, upper middle socioeconomic class; amenorrhea; decreased libido</td>
</tr>
<tr>
<td>Bulimia nervosa</td>
<td>Binge eating, followed by some inappropriate behavior to prevent weight gain (e.g., purging, abuse of laxatives); normal weight</td>
<td>Psychotherapy, pharmacotherapy, with fluoxetine (first line), other SSRIs, TCAs, or MAOIs; bupropion is contraindicated due to risk of seizures</td>
<td>Normal libido, no amenorrhea (unlike anorexics), erosion of tooth enamel, hypokalemic hypochloremic metabolic alkalosis (due to vomiting), hypertrophy of parotid glands</td>
</tr>
<tr>
<td>Binge eating disorder</td>
<td>Binge eating as an expression of deeper psychological problems, no purging, excessive weight gain</td>
<td>Psychotherapy, cognitive behavioral therapy, SSRIs</td>
<td>Patients may have negative attitudes toward food</td>
</tr>
<tr>
<td>Compulsive eating</td>
<td>Binge eating, constant preoccupation with and fantasizing about food</td>
<td>SSRIs, SNRIs, cognitive behavioral therapy</td>
<td>A form of obsessive-compulsive disorder</td>
</tr>
<tr>
<td>Obesity</td>
<td>BMI &gt;30</td>
<td>Dieting and exercise, strict dieting ineffective, bariatric surgery may be useful in selected patients with good dietary compliance</td>
<td>Lower socioeconomic groups, genetics plays a role, increased risk of disease</td>
</tr>
</tbody>
</table>

BMI, body mass index; MAOI, monoamine oxidase inhibitor; SNRI, serotonin-norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor; TCA, tricyclic antidepressant.

III. Drugs of abuse and dependence (Table 2-20)

<table>
<thead>
<tr>
<th>Drug</th>
<th>Mechanism</th>
<th>Intoxication Effect</th>
<th>Withdrawal Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alcohol</td>
<td>Unknown; possible effect at GABA receptor directly on membranes</td>
<td>Sedation, hypnosis, slurred speech, ataxia, loss of motor coordination, Wernicke–Korsakoff syndrome</td>
<td>Malaise, tachycardia, tremors, seizures, delirium tremens, death</td>
</tr>
<tr>
<td>Amphetamine</td>
<td>Release of intracellular stores of catecholamines</td>
<td>Insomnia, irritability, tremor, hyperactive reflexes, arrhythmias, anorexia, psychosis</td>
<td>Lethargy, depression, hunger, craving for drug resulting in bizarre psychological behavior, anxiety</td>
</tr>
<tr>
<td>Barbiturates</td>
<td>Potentiation of GABA action on chloride by increase of duration of chloride channel opening</td>
<td>Mental sluggishness, anesthesis, hypnosis</td>
<td>Restlessness, anxiety, tremor, death</td>
</tr>
</tbody>
</table>
IV. Schizophrenia

A. Diagnostic features
1. Diagnostic criteria:
   a. Hallucinations (usually auditory)
   b. Delusions
   c. Disorganized speech
   d. Disorganized or catatonic behavior
   e. Negative symptoms: flattened affect, social withdrawal, lack of motivation, thought blocking, poor grooming
2. Two of these criteria have to be met over much of the time for at least 1 month, with a significant impact on social/occupational functioning for at least 6 months.

B. Neurotransmitters involved: increased dopamine may be implicated

C. Other features
1. Usually first presents in young adulthood
2. Marijuana use during teenage years is a risk factor
3. Enlarged lateral ventricles and third ventricle

### TABLE 2-20 Drugs of Abuse and Dependence (Continued)

<table>
<thead>
<tr>
<th>Drug</th>
<th>Mechanism</th>
<th>Intoxication Effect</th>
<th>Withdrawal Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benzodiazepines</td>
<td>Potentiation of GABA action on chloride by increase of frequency of chloride channel opening</td>
<td>Sedation, ataxia, mild respiratory depression</td>
<td>Tremors, anxiety, psychosis, seizures</td>
</tr>
<tr>
<td>Caffeine</td>
<td>Translocation of Ca$$^{2+}$$, inhibition of phosphodiesterase (increase in cAMP, cGMP)</td>
<td>Insomnia, anxiety, agitation</td>
<td>Lethargy, irritability, headache</td>
</tr>
<tr>
<td>Cocaine</td>
<td>Blockade of norepinephrine, 5-HT, and dopamine reuptake</td>
<td>Hallucinations, anxiety, arrhythmias, nasal problems, sudden death</td>
<td>Craving, depression, excessive sleeping, fatigue</td>
</tr>
<tr>
<td>Lysergic acid diethylamide (LSD)</td>
<td>5-HT agonist action in the midbrain</td>
<td>Papillary dilation, increased blood pressure and body temperature, piloerection, hallucinations</td>
<td>Flashbacks</td>
</tr>
<tr>
<td>Marijuana</td>
<td>Unknown; tetrahydrocannabinol (THC) is active compound; possible endogenous receptors in brain</td>
<td>Increased appetite, visual hallucinations, increased heart rate, decreased blood pressure Impairment of short-term memory and mental activity</td>
<td>Fatigue, hypersomnia, psychomotor retardation</td>
</tr>
<tr>
<td>Nicotine</td>
<td>Low doses—ganglionic stimulation; high doses—ganglionic blockade</td>
<td>Increased heart rate and blood pressure, irritability, tremors, intestinal cramps</td>
<td>Irritability, anxiety, restlessness, headaches, insomnia, difficulty in concentrating</td>
</tr>
<tr>
<td>Opioids (heroin)</td>
<td>Inhibition of adenylyl cyclase by opioid receptors within the CNS</td>
<td>Constipation, pinpoint pupils, potentially lethal via respiratory depression, sedation</td>
<td>Insomnia, diarrhea, sweating, fever, piloerection</td>
</tr>
<tr>
<td>Phencyclidine (PCP)</td>
<td>Inhibition of dopamine, serotonin, and norepinephrine reuptake</td>
<td>Hostile, bizarre behavior; nystagmus hypersalivation, anesthesia</td>
<td>Sudden onset of violent behavior</td>
</tr>
</tbody>
</table>

cAMP, cyclic adenosine monophosphate; cGMP, cyclic guanosine monophosphate; CNS, central nervous system; GABA, \(\gamma\)-aminobutyric acid; 5-HT, serotonin.
V. Schizophrenia-related disorders

A. Brief psychotic disorder
1. Symptoms of schizophrenia for <1 month
2. Usually stress related

B. Schizophreniform disorder—symptoms of schizophrenia for 1 to 6 months

C. Schizoaffective disorder—schizophrenia/psychosis as the primary disorder, in addition to a secondary mood disorder (either bipolar disorder or depression)

D. Delusional disorder
1. Characterized by non-bizarre delusions that are more than simply overvalued ideas
2. Absence of hallucinations
3. Functioning is not impaired, and behavior is not odd

VI. Antipsychotics (Table 2-21)

Experts theorize that an excess of dopamine in certain areas of the brain is in some way responsible for psychosis. The development of psychosis as a common side effect of treatment of Parkinson disease with dopamine and dopamine agonists supports this theory. It is thought that most antipsychotics exert their effect by blocking dopamine receptors.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Clinical Uses</th>
<th>Side Effects</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Typical antipsychotics (traditional neuroleptics)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>High potency</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Haloperidol, fluphenazine</td>
<td>Schizophrenia, psychosis, halloperidol</td>
<td>EPS (dystonia, akinesia, akathisia, tardive dyskinesia); toxicity results in NMS (rigidity, myoglobinuria, autonomic instability, hyperpyrexia); anticholinergic side effects are less common; prolonged QT syndrome</td>
<td>NMS is treated with dantrolene and dopamine agonists</td>
</tr>
<tr>
<td>Trifluoperazine, thiothixene, loxapine</td>
<td>Schizophrenia, psychosis</td>
<td>Same as haloperidol, variable QT prolongation</td>
<td>These are sometimes inconsistently classified as “moderate potency” neuroleptics</td>
</tr>
<tr>
<td><strong>Typical antipsychotics (traditional neuroleptics)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low potency</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chlorpromazine</td>
<td>Schizophrenia, psychosis</td>
<td>Anticholinergic side effects (dry mouth, constipation); weight gain; some alpha blockade (hypotension) and histamine blockade (sedation); EPS and NMS are less common</td>
<td></td>
</tr>
<tr>
<td>Thioridazine</td>
<td></td>
<td>Same as chlorpromazine, plus high risk of QT prolongation and arrhythmias</td>
<td>Not commonly used</td>
</tr>
<tr>
<td><strong>Atypical antipsychotics</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clozapine</td>
<td>Schizophrenia, useful for both positive and negative symptoms</td>
<td>Agranulocytosis, weight gain, diabetes, low risk of anticholinergic side effects; EPS and NMS occur at lower rates than with typicals</td>
<td>Second-line agent used for refractory schizophrenia, check weekly blood counts due to risk of agranulocytosis</td>
</tr>
<tr>
<td>Olanzapine, quetiapine, risperidone, aripiprazole</td>
<td>Schizophrenia, bipolar disorder</td>
<td>Weight gain, diabetes, low risk of anticholinergic side effects; EPS and NMS occur at lower rates than with typicals</td>
<td>Of these drugs, olanzapine has the highest risk of weight gain and diabetes</td>
</tr>
</tbody>
</table>

EPS, extrapyramidal symptoms; NMS, neuroleptic malignant syndrome.

In its most severe form, extrapyramidal effects may develop into neuroleptic malignant syndrome, a potentially fatal combination of severe rigidity, decreased perspiration, hyperpyrexia, and autonomic instability. Treatment involves immediate discontinuation of antipsychotic medications, supportive measures, and administration of dantrolene.
Antipsychotic drugs have several particular side effects in common. The side effects may be grouped into the following categories: (1) extrapyramidal, (2) anticholinergic, (3) alpha-blocking effects, and (4) histamine receptor effects. Extrapyramidal side effects refer to acute dystonia, bradykinesia, and akathisia. Dystonia presents acutely within the first several days of starting the medication as a muscular spasm, stiffness, and oculogyric crisis. Akathisia presents within the first month of starting the medication as restlessness and a voluntary urge to move. Bradykinesia presents within two months of starting the medication as parkinsonian symptoms (or akinesia in severe cases). Tardive dyskinesia presents after a few months of starting the medication with stereotypic oral facial movements, likely due to dopamine receptor sensitization. Tardive dyskinesia is often irreversible and is most common in older women who have received long-term treatment with high doses. Anticholinergic side effects include dry mouth and constipation. Alpha-blocking effects include hypotension. Histamine receptor effects include sedation. Atypical antipsychotics such as clozapine, olanzapine, risperidone, quetiapine, and aripiprazole have a lower incidence of extrapyramidal and anticholinergic side effects. Finally, antipsychotics also may be antiemetic and have a tendency to lower the seizure threshold.

VII. Depression

A. Major depressive disorder (MDD)
   1. Diagnostic features (SIG E CAPS): sleep disturbances, loss of interest in formerly pleasurable things (anhedonia), guilt, low energy, poor concentration, appetite changes, psychomotor retardation or agitation, suicidal ideation, and depressed mood
   2. Symptoms must be present for at least 2 weeks.
   3. Neurotransmitters involved: decreased norepinephrine (NE) and 5-HT
   4. Decreased REM latency (rapid onset of REM sleep) is commonly seen.
   5. Treatment
      a. Pharmacotherapy: selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants (TCAs), monoamine oxidase inhibitors (MAOIs)
      b. Nonpharmacologic therapies: cognitive behavioral therapy, electroconvulsive therapy (ECT)

B. Atypical depression
   1. Features include hypersomnia, overeating and weight gain, mood reactivity, rejection hypersensitivity
   2. Treatment: MAOIs or SSRIs

C. Postpartum depression
   1. Depression in the postpartum period that exceeds 2 weeks and may persist for longer than a year
   2. Treatment: same as for MDD

D. Dysthymia—A milder form of depression with the same diagnostic features as MDD that lasts at least 2 years

E. Seasonal affective disorder
   1. A form of major depression that occurs during the winter season due to a deficiency of retinal stimulation with light
   2. Treatment: supplemental light therapy daily

VIII. Antidepressants (Table 2-22)

The “amine theory” attributes mood to levels of certain amines such as NE and 5-HT. It is theorized that low levels of these hormones lead to depression, and many of the antidepressants boost amine levels. The sites of action of the antidepressants are represented graphically (Figure 2-18).
### TABLE 2-22  Antidepressants

<table>
<thead>
<tr>
<th>Class of Antidepressant (Specific Agent)</th>
<th>Mechanism of Action</th>
<th>Clinical Uses</th>
<th>Side Effects</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Selective serotonin reuptake inhibitors (SSRIs) (e.g., fluoxetine, paroxetine, sertraline, citalopram)</td>
<td>Inhibit reuptake of 5-HT at neuronal synapses</td>
<td>Major depression, OCD, anxiety disorders, bulimia nervosa</td>
<td>Inhibits liver enzymes, nausea, agitation, sexual dysfunction (anorgasmia), dystonic reactions</td>
<td>Contraindicated with MAOIs secondary to serotonin syndrome (hyperthermia, muscle rigidity, cardiovascular collapse). Allow time for antidepressant effect; usually takes 2–3 weeks</td>
</tr>
<tr>
<td>Serotonin-norepinephrine reuptake inhibitors (SNRIs) (venlafaxine, desvenlafaxine, duloxetine, milnacipran, sibutramine)</td>
<td>Inhibit reuptake of NE and 5-HT at neuronal synapses</td>
<td>Major depression, anxiety disorders, neuropathic pain (duloxetine), fibromyalgia (milnacipran), obesity (sibutramine)</td>
<td>Sedation, nausea, constipation, hypertension, mild sexual dysfunction</td>
<td>Sibutramine is used only as an appetite suppressant for morbid obesity</td>
</tr>
<tr>
<td>Tricyclic antidepressants (TCAs) (amitriptyline, imipramine, nortriptyline, desipramine, clomipramine, doxepin, amoxapine)</td>
<td>Inhibit reuptake of NE and 5-HT at neuronal synapses</td>
<td>Major depression, OCD (clomipramine), nocturnal enuresis (imipramine), panic disorder</td>
<td>Sedation, α-blocking effects (orthostatic hypotension), anticholinergic (tachycardia, dry mouth, urinary retention), hallucinations (in elderly), confusion (elderly) Overdose toxicity results in convulsions, coma, cardiotoxicity (arrhythmias), respiratory depression, hyperpyrexia</td>
<td>Desipramine is the least sedating Used off-label for insomnia</td>
</tr>
<tr>
<td>Monoamine oxidase inhibitors (MAOIs) (isocarboxazid, phenelzine, tranylcypromine)</td>
<td>Inhibit degradation of NE and 5-HT at neuronal synapses</td>
<td>Atypical depression (with hypersomnia, anxiety, sensitivity to rejection, hypochondrasis)</td>
<td>Hypertensive episodes with ingestion of tyramine-containing foods or beta agonists, hyperthermia, convulsions</td>
<td>Contraindicated with SSRIs and meperidine secondary to serotonin syndrome (hyperthermia, muscle rigidity, cardiovascular collapse)</td>
</tr>
<tr>
<td>Other antidepressants</td>
<td>Inhibits reuptake of NE and dopamine</td>
<td>Major depression, smoking cessation</td>
<td>Tachycardia, insomnia, headache, seizure (especially patients with bulimia)</td>
<td>Does not have sexual side effects</td>
</tr>
<tr>
<td>Bupropion</td>
<td>α₂-antagonist → increases release of NE and 5-HT</td>
<td>Major depression (especially with insomnia)</td>
<td>Weight gain, dry mouth, increased appetite, sedation</td>
<td></td>
</tr>
<tr>
<td>Mirtazapine</td>
<td>Blocks NE uptake</td>
<td>Major depression</td>
<td>Sedation, orthostatic hypotension</td>
<td></td>
</tr>
<tr>
<td>Maprotiline</td>
<td>Inhibits 5-HT reuptake</td>
<td>Major depression (especially with insomnia), insomnia</td>
<td>Sedation, nausea, priapism, postural hypotension</td>
<td></td>
</tr>
</tbody>
</table>

5-HT, serotonin; OCD, obsessive-compulsive disorder; NE, norepinephrine.
IX. Anxiety disorders (Table 2-23)

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Characteristics</th>
<th>Neurotransmitter(s) Involved</th>
<th>Treatment</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Panic disorder</td>
<td>Discrete, episodic periods of intense anxiety or discomfort; palpitations; chest pain; sweating; fear of dying</td>
<td>Decreased serotonin, norepinephrine, GABA</td>
<td>Imipramine; behavioral therapy</td>
<td>Associated with mitral valve prolapse; young women predominantly affected; genetic component</td>
</tr>
<tr>
<td>Generalized anxiety disorder</td>
<td>Generalized, persistent anxiety; tension; insomnia; irritability</td>
<td>Decreased serotonin, norepinephrine, GABA</td>
<td>SSRIs, buspirone (Table 2-25), benzodiazepines</td>
<td>Anxiety for more than 6 months</td>
</tr>
<tr>
<td>Posttraumatic stress disorder</td>
<td>Result of trauma, hypervigilance, nightmares, flashbacks</td>
<td>Decreased serotonin, norepinephrine, GABA</td>
<td>Counseling, group therapy, benzodiazepines for symptoms</td>
<td>For the first 3 months after the trauma, it is called acute PTSD; symptoms lasting longer than 3 months is chronic PTSD</td>
</tr>
<tr>
<td>Obsessive-compulsive disorder</td>
<td>Recurrent thoughts and actions; patients are distressed by repetitive actions</td>
<td>Decreased serotonin</td>
<td>Behavioral therapy, clomipramine, trazodone, SSRIs</td>
<td></td>
</tr>
<tr>
<td>Phobias</td>
<td>Irrational, situational fear</td>
<td>Decreased serotonin, norepinephrine, and GABA</td>
<td>Systematic desensitization; propranolol useful for physiologic manifestations</td>
<td>EEG changes</td>
</tr>
</tbody>
</table>

EEG, electroencephalogram; GABA, γ-aminobutyric acid; SSRIs, selective serotonin reuptake inhibitor.

An overdose of a tricyclic antidepressant (TCA) causes delirium, coma, seizures, respiratory depression, and arrhythmias and is potentially fatal and difficult to treat. The large volume of distribution of a TCA makes dialysis relatively ineffective.
X. Other neuropsychiatric disorders and other psychiatric drugs (Tables 2-24 and 2-25)

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Characteristics</th>
<th>Treatment</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bipolar disorder</td>
<td>Rapid speech, decreased need for sleep, hyperenergetic state, impaired judgment followed by a state of depression</td>
<td>Lithium (Table 2-25), certain anticonvulsants, atypical antipsychotics</td>
<td></td>
</tr>
<tr>
<td>Cyclothymic disorder</td>
<td>Alternating between hypomania and mild depression, lasting at least 2 years</td>
<td>Same as bipolar disorder</td>
<td></td>
</tr>
<tr>
<td>Delirium</td>
<td>Impaired cognitive processes, diurnal variation in mood (worse at night—“sundowning”), illusions and hallucinations</td>
<td>Treat the underlying cause</td>
<td>Most common problem in hospitalized patients with psychiatric disorders</td>
</tr>
<tr>
<td>Dissociative disorders</td>
<td>Psychological factors resulting in memory loss and loss of function</td>
<td>Psychotherapy, hypnotherapy, medication for associated symptoms</td>
<td>Includes amnesia, fugue, dissociative identity disorder, depersonalization</td>
</tr>
<tr>
<td>Somatoform disorders</td>
<td>Symptoms of disease occur without related pathology</td>
<td>Psychotherapy and therapeutics may help; variable response</td>
<td>Patients truly believe in having illness, whereas factitious disorders are the result of faking illness</td>
</tr>
<tr>
<td>Factitious disorder</td>
<td>Patient consciously produces signs or symptoms of illness without a conscious motive or external incentive</td>
<td>Treatment of self-induced illness; avoid unnecessary tests and procedures</td>
<td></td>
</tr>
<tr>
<td>Malingering</td>
<td>Patient consciously produces signs or symptoms of illness for secondary gain (avoiding work, obtaining money, drugs, shelter)</td>
<td>Avoid unnecessary tests and procedures</td>
<td>Patients often leave when confronted</td>
</tr>
<tr>
<td>Attention deficit hyperactivity disorder (ADHD)</td>
<td>Hyperactive, poor attention span, highly sensitive to stimuli</td>
<td>Amphetamines (methylphenidate—see Table 2-25)</td>
<td>More common in male children</td>
</tr>
<tr>
<td>Tourette syndrome</td>
<td>Involuntary motor and vocal movements (need both)</td>
<td>Haloperidol, clonidine</td>
<td>Onset occurs in childhood</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Class/Drug</th>
<th>Mechanism of Action</th>
<th>Clinical Uses</th>
<th>Side Effects</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lithium</td>
<td>Unclear; inhibits regeneration of IP$_3$ and DAG; important for many second-messenger systems</td>
<td>Bipolar disorder, acute mania</td>
<td>Tremor, hypothyroidism, teratogenesis, nephrogenic diabetes insipidus</td>
<td>Requires close monitoring of serum levels due to narrow therapeutic window</td>
</tr>
<tr>
<td>Buspirone</td>
<td>5-HT receptor agonist</td>
<td>Generalized anxiety disorder</td>
<td>Dizziness, drowsiness, headache, nausea</td>
<td></td>
</tr>
<tr>
<td>Varenicline</td>
<td>Partial agonist of nicotinic receptor</td>
<td>Smoking cessation</td>
<td>Nausea, headache, insomnia, abnormal dreams</td>
<td></td>
</tr>
<tr>
<td>Methylphenidate</td>
<td>CNS stimulant—blocks presynaptic reuptake of NE and dopamine</td>
<td>Attention deficit hyperactivity disorder, narcolepsy</td>
<td>Insomnia, restlessness</td>
<td>Contraindicated in patients with heart disease or hypertension</td>
</tr>
</tbody>
</table>

5-HT, serotonin; CNS, central nervous system; DAG, diacylglycerol; IP$_3$, inositol trisphosphate; NE, norepinephrine.
### Defense Mechanisms (Table 2-26)

<table>
<thead>
<tr>
<th>Mechanism</th>
<th>Characteristics</th>
<th>Example</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Immature mechanisms</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acting out</td>
<td>Stress is dealt with through actions</td>
<td>After the death of his brother, a priest breaks all the windows in his church.</td>
</tr>
<tr>
<td>Denial</td>
<td>Not accepting the reality of a situation</td>
<td>A woman refuses to consider the possibility of pregnancy after having unprotected intercourse and missing two periods.</td>
</tr>
<tr>
<td>Displacement</td>
<td>Feelings for causal source are transferred to another object</td>
<td>A man kicks his dog after getting fired from his job.</td>
</tr>
<tr>
<td>Dissociation</td>
<td>Loss of memory or change in personality as a result of stressor</td>
<td>A woman who was sexually abused as a child develops another personality.</td>
</tr>
<tr>
<td>Identification</td>
<td>Behavior patterned after another</td>
<td>A teenager smokes pot because his favorite rock star does.</td>
</tr>
<tr>
<td>Intellectualization</td>
<td>Reason is used to cope with anxiety</td>
<td>A physician starts reading textbooks and journal articles about her father’s cancer.</td>
</tr>
<tr>
<td>Isolation of affect</td>
<td>Events are separated from emotion</td>
<td>An airline passenger describes an emergency landing to his family without any emotion.</td>
</tr>
<tr>
<td>Projection</td>
<td>One’s own characteristics are applied to another</td>
<td>A flirtatious man accuses his wife of cheating.</td>
</tr>
<tr>
<td>Rationalization</td>
<td>Analytical reason is used to justify unacceptable feelings</td>
<td>A man claims that his driving under the influence arrest would never have happened if his softball team had won.</td>
</tr>
<tr>
<td>Regression</td>
<td>Feelings are denied and opposite actions are performed</td>
<td>A woman who wants to cheat on her husband instead buys him a new car.</td>
</tr>
<tr>
<td>Repression</td>
<td>Stress-induced behavior that involves returning to a childlike state</td>
<td>Medical students have a food fight during their lunch break on the day of board examinations.</td>
</tr>
<tr>
<td>Repression</td>
<td>Holding back an unacceptable feeling or idea from reaching consciousness</td>
<td>A recent widower feels no sense of loss.</td>
</tr>
<tr>
<td>Splitting</td>
<td>Feelings or stressors are placed in distinct, opposite compartments (i.e., either all good or all bad)</td>
<td>A man in a doctor’s office describes how much he hates the nurses but loves the receptionist.</td>
</tr>
<tr>
<td><strong>Mature mechanisms</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Altruism</td>
<td>One unselfishly assists others</td>
<td>A woman donates her entire estate to her favorite charities upon her death.</td>
</tr>
<tr>
<td>Humor</td>
<td>Humor is used to reduce stress</td>
<td>While stuck in an elevator, a young man makes jokes to ease the tension.</td>
</tr>
<tr>
<td>Sublimation</td>
<td>Unacceptable impulse is directed into a socially accepted action</td>
<td>A boy who got into a lot of fights as a kid decides to become a professional boxer.</td>
</tr>
<tr>
<td>Suppression</td>
<td>Conscious effort to suppress thoughts or feelings</td>
<td>A recent widower actively refuses to think about his deceased wife while packing her things away.</td>
</tr>
</tbody>
</table>
Schizotypal is a personality disorder characterized by odd beliefs or magical thinking. Schizoid is a personality disorder characterized by voluntary social isolation. Neither of these meets the diagnostic criteria for schizophrenia, but both are risk factors for the development of schizophrenia.

### Table 2-27: Personality Disorders

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Characteristics</th>
<th>Example</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CLUSTER A</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Paranoid</td>
<td>Hostile, suspicious, mistrustful, usually male</td>
<td>A patient being prepared for surgery yells at the doctors on rounds because he feels they are gossiping about him.</td>
</tr>
<tr>
<td>Schizoid</td>
<td>Voluntarily socially withdrawn without psychological problems; usually male</td>
<td>A 52-year-old computer programmer lives alone, is not married, has no friends, and is contented.</td>
</tr>
<tr>
<td>Schizotypal</td>
<td>Odd behavior, thoughts, and appearance without psychosis</td>
<td>A woman wears many-layered clothing and inappropriately applied makeup and only talks to people with brown-colored hair.</td>
</tr>
<tr>
<td><strong>CLUSTER B</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Histrionic</td>
<td>Dramatic, overemotional, sexually provocative, unable to maintain close friendships, usually female</td>
<td>A woman exaggerates her suffering over a mild cold and behaves seductively toward the physician.</td>
</tr>
<tr>
<td>Narcissistic</td>
<td>Grandiosity, hypersensitivity to criticism, and lack of empathy</td>
<td>A resident refuses to operate with anyone but the best surgeon in the hospital because he feels it is beneath his talent.</td>
</tr>
<tr>
<td>Antisocial</td>
<td>Inability to conform to societal rules; criminal behavior; more often male, requires diagnosis of conduct disorder as child</td>
<td>A multiple rapist has no concern for his victims or the law.</td>
</tr>
<tr>
<td>Borderline</td>
<td>Unstable, impulsive, suicide attempts, vulnerable to abandonment, usually female, uses splitting</td>
<td>After an argument with her boyfriend, a woman chases him out of her home and later calls him and tells him she cannot live without him.</td>
</tr>
<tr>
<td><strong>CLUSTER C</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Avoidant</td>
<td>Shy, involuntarily (compare to schizoid) withdrawn because fears rejection, usually female</td>
<td>A businesswoman defers speaking during presentations to her project partner and has few friends.</td>
</tr>
<tr>
<td>Obsessive-compulsive</td>
<td>Rigid, perfectionist, stubborn, orderly, found twice as often in males</td>
<td>A businessman works long hours on a project, holding up both the project deadline and his personal life in vain attempts to make it perfect.</td>
</tr>
<tr>
<td>Dependent</td>
<td>Defers decision making; not comfortable with an authority position; insecure; has the ability to make long-lasting relationships ( unlike avoidant); usually female</td>
<td>A third-year resident often accepts on-call duty for other residents, never speaks up when talked down to by the junior residents, and has trouble writing orders.</td>
</tr>
<tr>
<td>Passive-aggressive</td>
<td>Obstinate, inefficient, procrastinating, noncompliant</td>
<td>School student intentionally does poorly on homework because he does not like his teacher.</td>
</tr>
</tbody>
</table>

Quick Hit

**Schizotypal** is a personality disorder characterized by odd beliefs or magical thinking. **Schizoid** is a personality disorder characterized by voluntary social isolation. Neither of these meets the diagnostic criteria for schizophrenia, but both are risk factors for the development of schizophrenia.
**DEVELOPMENT**

I. Heart

A. The cardiovascular system is derived from the **mesoderm**.
B. Paired endocardial heart tubes form in the **cephalic region** of the embryo.
C. Lateral and cephalocaudal folding causes the heart tubes to join together and lie in a ventral location between the primitive mouth and the foregut.
D. The **primitive heart** dilates into five areas, as shown in Figure 3-1. The five embryologic regions and their adult derivatives are as follows:
   1. **Truncus arteriosus** → proximal aorta and proximal pulmonary artery
   2. **Bulbus cordis** → smooth parts of the right ventricle (conus arteriosus) and left ventricles
   3. **Primitive ventricle** → right and left ventricles (trabeculated parts)
   4. **Primitive atrium** → right and left atria
   5. **Sinus venosus** → smooth part of right atrium, the coronary sinus, and oblique vein
E. The lumen of the truncus arteriosus and bulbus cordis is divided into the aorta and **pulmonary trunk** by the aorticopulmonary septum.
F. The septum primum and septum secundum form the **atrial septum**.
G. The **foramen ovale** is a communication between the right and left atria, which is formed by the walls of the septum primum and septum secundum.
   1. It allows blood to flow from the venous side of the circulation to the arterial side without passing through the lungs as a result of higher pressure on the venous side during gestation.
   2. After birth, the foramen ovale closes because of increased arterial pressure that pushes the septum primum against the septum secundum.

**QUICK HIT**

In dextrocardia, the heart is located on the right side in the thorax. An isolated, misplaced heart is often accompanied by multiple anomalies. If all of the body’s organs are transposed (situs inversus—associated with Kartagener syndrome; immotile cilia caused by a defect in the dynein arms resulting in lung disease and male sterility), the heart is often normal.

**Figure 3-1**

Embryologic development of the heart

- **Truncus arteriosus**
- **Bulbus cordis**
- **Primitive ventricle**
- **Primitive atrium**
- **Sinus venosus**

**A**
- Right
- Left

**B**
- **Truncus arteriosus**
- **Bulbus cordis**

**C**
- **Truncus arteriosus**
- **Primitive atrium**
- **Sinus venosus**

**D**
- Superior vena cava
- Aorta
- Left ventricle
- Right atrium

Folding of the developing heart (A–C) during weeks 5–8 into the normal adult heart (D)
H. The aorticopulmonary septum (also called the spiral septum, derived from neural crest cells), the right and left bulbar ridges, and the AV cushion form the interventricular septum.

II. Arterial vessels
A. Aortic arches (pharyngeal arch arteries): Initially, there are six paired aortic arches. Arches 3, 4, and 6 play a significant role in the adult. Arch 5 degenerates early in fetal development.
   1. Arches 1 and 2 give rise to the maxillary artery and stapedial artery, respectively.
   2. Arch 3 helps form the adult common carotid arteries bilaterally.
   3. Arch 4 helps form the aorta on the left and the proximal subclavian artery on the right.
   4. Arch 6 helps form the ductus arteriosus and part of the pulmonary trunk.
B. Paired dorsal aortae are paired vessels that run along the length of the embryo. They coalesce to form the descending aorta.

III. Venous vessels
A. The paired vitelline, umbilical, and cardinal veins form the definitive adult structures.
B. The vitelline veins help form the ductus venosus and hepatic sinusoids, the inferior vena cava, the portal vein, and the superior and inferior mesenteric veins.
C. Umbilical veins
   1. No adult vascular structures are formed by these veins.
   2. The left umbilical vein connects to the ductus venosus and carries oxygenated blood from the placenta to the fetus.
   3. Left umbilical vein gives rise to ligamentum teres hepatitis.
   4. Right umbilical vein regresses.
D. Cardinal veins
   1. The anterior cardinal veins help form the internal jugular vein and the superior vena cava.
   2. The posterior cardinal veins help form the inferior vena cava, common iliac veins, azygos vein, and renal veins.

IV. Fetal circulation (Figure 3-2)

V. Congenital defects of the heart and great vessels (Table 3-1)

PHYSIOLOGY AND PATHOLOGY OF HEART FUNCTION

Properly timed and integrated myocyte contraction is essential to normal heart function. Cardiac myocytes have gap junctions that allow for rapid relay of electrical signals between them. Electrical impulses are transmitted via the electrical conduction system composed of the sinoatrial (SA) node, atrioventricular (AV) node, and His–Purkinje cells (Figure 3-3). Normally, the SA node is the pacemaker of the heart. The node exhibits automaticity, in which spontaneous phase 4 depolarization generates rhythmic action potentials (APs). These electrical signals propagate from the SA node through the atrial tissue and cause it to contract. Further propagation leads to excitation of the AV node, the ventricular bundles, and, lastly, the ventricular tissue. The nodal tissues are dependent on Ca\(^{2+}\) for their phase 0 depolarization, whereas the cardiac muscular tissue uses Na\(^{+}\) for phase 0 depolarization. The AV node transmits APs more slowly than do the other cardiac tissues. This feature allows the atria to contract before the ventricles, with time for the ventricles to repolarize, fill with blood, and prepare to receive their next electrical signal. Furthermore, it also prevents excessively rapid beats from reaching and damaging the ventricular tissue. The conduction system of the heart can best be visualized on an
Multiple mechanisms can affect the intrinsic mechanical properties of the heart. Chronotropic effects on the heart cause a change in heart rate by affecting the rate of depolarization of the SA node. Inotropic effects cause a change in contractility of the heart. Greater contractility allows the heart to squeeze harder and increase cardiac output. Increased intracellular Ca\(^{2+}\), either drug mediated (e.g., cardiac glycosides) or as a result of sympathetic β-receptor stimulation, allows for an increased inotropic effect. The preload and afterload also affect the function of the heart. Increased preload as a result of increased filling of the ventricles lengths the myocytes, which induces stronger contraction, up to a certain point, after which the myocytes are too stretched to contract effectively. Afterload of the left ventricle is equivalent to aortic pressure. It is influenced by the total peripheral resistance. A higher afterload means the left ventricle must work harder or cardiac output will fall. The cardiovascular system is constantly working to maintain homeostatic equilibrium.

Electrocardiogram (ECG). ECG plots can determine disturbances, such as arrhythmias, along the cardiac conduction path.

Congenital cardiac defects with the letter D are initially left-to-right shunts (PDA, VSD, AVSD, and ASD), whereas those cardiac defects without the letter D are right-to-left shunts.

The ductus arteriosus closes in the first days of life. Exposure to oxygenated blood alters the production of prostaglandins (PGs). Indomethacin (PG synthesis inhibitor) induces closure of a patent ductus arteriosus (PDA), whereas alprostadil (PGE1) therapy maintains patency.

The umbilical circulation is one of the only places in the body (along with the pulmonary circulation) where an artery does not carry oxygenated blood. The paired umbilical arteries carry deoxygenated blood to the placenta, whereas the umbilical vein brings oxygenated blood back to the fetus.

The baroreceptor reflex greatly affects total peripheral resistance. The carotid sinus baroreceptors, located at the bifurcation of the carotid arteries, sense arterial pressure. Afferent signals via cranial nerve (CN) IX induce efferent signals via CN X to influence heart rate. Increased arterial pressure causes an increase in vagal output and a reduction of heart rate and blood pressure. A decrease in arterial pressure causes a decrease in vagal output, resulting in an increase in heart rate and blood pressure.
The most common type of atrial septal defect (ASD) is a patent foramen ovale.

Eisenmenger syndrome is the change from a left-to-right shunt to a right-to-left shunt, secondary to increasing pulmonary hypertension; it usually occurs as a result of a chronic, adaptive response to preexisting left-to-right shunts, such as a VSD.

Cyanosis occurs in right-to-left shunts: tetralogy of Fallot and transposition of the great vessels (TGV). Cyanosis can lead to clubbing, hypertrophic osteoarthropathy, and polycythemia. Initial left-to-right shunts are not cyanotic: ASD, VSD, PDA, and atrioventricular septal defect (AVSD).

### TABLE 3-1 Congenital Defects of the Heart and the Great Vessels

<table>
<thead>
<tr>
<th>Anomaly</th>
<th>Pathology</th>
<th>Clinical Presentation</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atrial septal defect (ASD)</td>
<td>Secundum ASD (defect of septum primum or septum secundum)</td>
<td>Left-to-right shunt, asymptomatic into the fourth decade, murmur, right ventricular hypertrophy</td>
<td>Much higher incidence in females (3:1); 75%–80% are secundum type</td>
</tr>
<tr>
<td></td>
<td>Primum ASD (low), sinus venosus ASD (high)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Coarctation of the aorta</td>
<td>Infantile (proximal to PDA); adult (constriction at closed ductus arteriosus, distal to the origin of left subclavian artery)</td>
<td>Symptoms depend on the extent of narrowing: infant presents with lower limb cyanosis and right heart failure at birth; adult asymptomatic with upper limb hypertension, rib notching on radiograph from collateral circulation through intercostal arteries, and weak pulses in lower limbs</td>
<td>Much higher incidence in males (3:1) and females with Turner syndrome</td>
</tr>
<tr>
<td>Patellar ductus arteriosus (PDA)</td>
<td>Failure of closure of the ductus arteriosus; may be caused by premature birth with hypoxemia or structural defects</td>
<td>Continuous machinery murmur</td>
<td>Second most common congenital heart defect</td>
</tr>
<tr>
<td>Tetralogy of Fallot</td>
<td>Defective development of the infundibular septum; results in overriding aorta, VSD, pulmonary stenosis, and hypertrophy of the right ventricle</td>
<td>Cyanosis (may not be present at birth), right-to-left shunt, &quot;boot-shaped heart&quot;</td>
<td>Survival to adulthood possible; patient assumes squatting position to relieve symptoms</td>
</tr>
<tr>
<td>Transposition of the great vessels</td>
<td>Aorta drains right ventricle; pulmonary artery from left ventricle; separate pulmonary and systemic circuits</td>
<td>Incompatible with life unless shunt present; cyanosis (present at birth)</td>
<td>Mother with diabetes</td>
</tr>
<tr>
<td>Ventricular septal defect (VSD)</td>
<td>Membranous VSD, Single muscular VSD</td>
<td>Left-to-right shunt; loud holosystolic murmur means small defect, large defects can present as heart failure at birth; small defects can close spontaneously</td>
<td>Much higher incidence in males; most common congenital heart defect (33%); 90% are membranous type</td>
</tr>
</tbody>
</table>
Hormonal systems also respond to changes in homeostasis. A major influence on the cardiovascular system is exerted by the renin-angiotensin-aldosterone (RAA) axis. Whereas the baroreceptors attempt to maintain adequate pressures in the vascular system over a short-term period, the RAA system helps to regulate pressure over a longer period of time. The RAA axis responds to changes in arterial pressure by altering salt and water retention by the kidneys. Low blood pressure causes an increased release of renin, which converts angiotensinogen from the liver to angiotensin I. Angiotensin I travels to the lung, where it is cleaved to angiotensin II (Ang II) by angiotensin-converting enzyme (ACE). Ang II stimulates constriction of arterioles and increases release of aldosterone (salt and water retention; see Chapter 6), both of which increase blood pressure. Atrial natriuretic peptide (ANP) also responds to blood pressure changes. An increase in blood pressure causes stretch of atrial myocytes, which then release ANP. ANP lowers blood pressure by relaxing smooth muscle, increasing salt and water excretion, and inhibiting renin release. Antidiuretic hormone (ADH), also known as arginine vasopressin (AVP), is involved in the response to changes in blood pressure. When released from the pituitary, it acts on the kidney to reduce urine output and retain water while simultaneously constricting arterioles to increase total peripheral resistance (Figure 3-4).

The physiologic function of the heart can be represented in several ways (e.g., pressure–volume loops and the cardiac cycle) (Figure 3-5). The effects of cardiac output, total peripheral resistance, contractility, preload, and afterload are represented on the Frank-Starling curve. Cardiac output is measured using the Fick principle (Figure 3-6), and normal output is approximately 5 L/min.
1. **Isovolumetric contraction**: time between mitral valve closure and aortic valve opening; time of highest oxygen consumption

2. **Systolic ejection**: time between aortic valve opening and closing

3. **Isovolumetric relaxation**: time between aortic valve closing and mitral valve opening

4. **Rapid filling**: time after mitral valve opening

5. **Reduced filling**: time right before mitral valve closing

C. **Progression of the action potential through cardiac muscle cells**

SA node → Action potential

Atrial muscle

AV node

Common bundle

Bundle branches

Purkinje fibers

Ventricular muscle

ECG

D. **Frank–Starling relationship**

Cardiac output

Venous return (L/min)

Mean systemic pressure

Right atrial pressure (mm Hg)

End-diastolic volume (L)

AV, atrioventricular; ECG, electrocardiogram; EDV, end-diastolic volume; ESV, end-systolic volume; SA, sinoatrial; TPR, total peripheral resistance.
The Cardiovascular System

Arrhythmias can be organized into tachycardias and bradycardias. The ECGs of important arrhythmias can be seen in Figure 3-7, and features of the heart blocks are described in Table 3-2.

Antiarrhythmics work to change different phases of depolarization and repolarization. They also alter the conduction velocity, change the effective refractory period (ERP), and alter the AP duration. The treatment options for arrhythmias are as follows:

I. Atrial fibrillation
   A. Rate control (with β-blockers, diltiazem, verapamil, or digoxin) is generally preferred over rhythm control.
**B. Conversion to sinus rhythm (if indicated) may be achieved with electrical cardioversion or antiarrhythmic drugs (most commonly, amiodarone), although reversion to atrial fibrillation is common.**

**II. Supraventricular tachycardia**
A. Adenosine (diagnostic purposes)
B. Verapamil (long-term control)

**III. Ventricular fibrillation**
A. Lidocaine or amiodarone

**IV. Ventricular tachycardia**
A. Digoxin

**V. Digitalis toxicity**
A. Activated charcoal in repeated doses (every 4 to 6 hours for 24 hours)
B. Digoxin immune Fab (only if one of the following is present):
   1. Hemodynamic instability
   2. Life-threatening arrhythmias or severe bradycardia (even if responsive to atropine)
   3. Plasma potassium level $>$ 5 mEq/L in an acute overdose
   4. Plasma digoxin level $>$ 10 ng/mL
   5. Ingestion of $>$ 10 mg of digoxin in adults (or $>$ 4 mg in children)
   6. Presence of a digoxin-toxic rhythm in the setting of an elevated digoxin level
C. Treat hyperkalemia only if it is causing ECG disturbances and avoid calcium, which can worsen intracellular hyperkalemia in these particular patients.
D. Atropine, if bradycardia is present

**VI. Torsades de pointes**
A. Intravenous (IV) Mg$^{2+}$

---

**Important cardiovascular equations**

<table>
<thead>
<tr>
<th>Equation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>$CO = O_2$ consumption</td>
<td>(O$<em>2$)$</em>{pulmonary artery}$ - (O$<em>2$)$</em>{pulmonary vein}$</td>
</tr>
<tr>
<td>$CO = SV \times HR$</td>
<td>$CO$ = cardiac output, $SV$ = stroke volume, $HR$ = heart rate</td>
</tr>
<tr>
<td>$R \alpha \frac{1}{r^4}$</td>
<td>This relationship shows how arteriolar diameter can effectively control systemic resistance. For instance, if the radius (r) is increased by 2, the resistance (R) drops 16-fold.</td>
</tr>
<tr>
<td>$Q = \frac{\Delta P}{R}$</td>
<td>$Q$ = flow, $\Delta P$ = Aortic pressure-right atrial pressure or pressure difference, $R$ = resistance</td>
</tr>
<tr>
<td>$MBP = CO \times TPR$</td>
<td>$MBP$ = mean blood pressure (equivalent to $\Delta P$), $CO$ = cardiac output (equivalent to $Q$), $TPR$ = total peripheral resistance (equivalent to $R$)</td>
</tr>
<tr>
<td>Series resistance: $R_{total} = R_1 + R_2 + R_3 + R_4 \ldots$</td>
<td>This relationship lowers resistance when the body recruits unused parallel vessels (especially in capillary beds)</td>
</tr>
<tr>
<td>Parallel resistance: $\frac{1}{R_{total}} = \frac{1}{R_1} + \frac{1}{R_2} + \frac{1}{R_3} + \frac{1}{R_4} \ldots$</td>
<td></td>
</tr>
</tbody>
</table>

**QUICK HIT**

Of the antiarrhythmics, class II and class III agents decrease mortality, whereas other antiarrhythmics can be proarrhythmics, so carefully monitor a patient.

**QUICK HIT**

Class II agents (β-blockers) work at nodal tissue, so use these to control ventricular rate affected by atrial fibrillation, atrial flutter, and excess catecholamines.
The Cardiovascular System

Sustained ventricular tachycardia

- Constant QRS morphology and fairly regular cycle length
- Initiating beat morphology may differ from ongoing VT
- AV dissociation is a hallmark but not always present nor easy to identify when present

Ventricular fibrillation

- Undulating baseline, no organized electrical activity
- Incompatible with life
- Atria may be dissociated, still in sinus rhythm

Atrial flutter

- A regular, saw-toothed pattern of atrial activity, usually very near 300/min
- Discrete, organized atrial activity on intracardiac electrograms
- Usually even-numbered AV conduction ratio (2:1, 4:1)

Atrial fibrillation

- Undulating, low amplitude atrial activity on ECG
- Intracardiac electrogram shows chaotic rapid spikes
- Variable conduction pattern as AV node is constantly bombarded with impulses; “long-short” sequences yield wide QRS complexes (aberrant, “Ashman” beats)

Wolff–Parkinson–White syndrome

- Accessory atrioventricular conductions
- Anterograde or retrograde conduction
- Tachyarrhythmias
- Blurred QRS (referred to as δ-wave)

AV, atrioventricular; ECG, electrocardiogram; VT, ventricular tachycardia.
The Cardiovascular System

Class IA (Na\(^+\) channel blockers)
- Disopyramide
- Procainamide
- Quinidine

Class IB (Na\(^+\) channel blockers)
- Lidocaine
- Tocaainide
- Mexilitine

Class IC (Na\(^+\) channel blockers)
- Flecainide
- Propafenone

Class II (\(\beta\)-blockers)
- Esmolol
- Metoprolol
- Propranolol

Class III (K\(^+\) channel blockers)
- Amiodarone
- Bretylum
- Sotalol

Class IV (Ca\(^{2+}\) channel blockers)
- Diltiazem
- Verapamil

Class IA (slows phase 0, prolongs phase 3); class IB (shortens phase 3); class IC (markedly slows phase 0); class II (suppresses phase 4 depolarization rate); class III (prolongs phase 3); class IV (slows the action potential).

Table 3-2 Conduction Anomalies

<table>
<thead>
<tr>
<th>Anomaly</th>
<th>Pathology</th>
<th>Notes</th>
<th>ECG</th>
</tr>
</thead>
<tbody>
<tr>
<td>First-degree heart block</td>
<td>Atrioventricular nodal length-ens PR interval</td>
<td>May be caused by drugs (e.g., (\beta)-blockers, digi-talis, and calcium channel blockers)</td>
<td></td>
</tr>
<tr>
<td>Second-degree heart block: Mobitz type 1 (Wenckebach)</td>
<td>Defect in atrioventricular node; progressively increasing PR interval until QRS wave is lost</td>
<td>Relatively common; usually does not require treatment</td>
<td></td>
</tr>
<tr>
<td>Second-degree heart block: Mobitz type 2</td>
<td>Defect in His–Purkinje system; constant PR interval with random dropped QRS complexes</td>
<td>Less common and more dangerous than Mobitz type 1; pacemaker</td>
<td></td>
</tr>
<tr>
<td>Third-degree heart block</td>
<td>No electrical connection between atria and ventricles; atria and ventricles contract independently</td>
<td>His–Purkinje system sets the rate of ventricular contraction; pacemaker may be necessary</td>
<td></td>
</tr>
</tbody>
</table>
Drugs that are used to treat arrhythmias may also cause them, especially when their use is stopped suddenly. This is an important consideration for digoxin, class IA (quinidine, disopyramide, and procainamide), class IC (propafenone, flecainide, and encainide), and class II (propranolol) drugs.

<table>
<thead>
<tr>
<th>Therapeutic Agent</th>
<th>Class–Pharmacology and Pharmacokinetics</th>
<th>Indications</th>
<th>Side Effects or Adverse Effects</th>
<th>Contraindications or Precautions to Consider, Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Digoxin</td>
<td>Inotropic agent—cardiac glycoside; inhibits Na/K/ATPase → indirect inhibition of Na⁺/Ca²⁺ exchanger → increases Ca²⁺ → increases cardiac contractility</td>
<td>Severe left ventricular systolic dysfunction (increases contractility), atrial fibrillation (decreases conduction at AV node and depresses SA node)</td>
<td>Progressive dysrhythmia, anorexia, nausea, vomiting, headache, fatigue, confusion, blurred vision, altered color perception, halos around dark objects</td>
<td>Contraindicated in patients with right-sided heart failure and diastolic failure; ECG changes: increases PR, decreases QT, depresses ST, and inverts T; toxicities of digoxin are increased by renal failure (decreases excretion), hypokalemia (potentiates the drug’s effects), and quinidine (decreases clearance and displaces digoxin)</td>
</tr>
</tbody>
</table>

**Sodium channel blockers (Class I)**

- **Quinidine, procaainamide, disopyramide**
  - Class IA—sodium channel blocker; increases AP duration, ERP, QT interval
  - Atrial and ventricular arrhythmia (especially reentrant and ectopic supraventricular and ventricular tachycardia)
  - Torsades de pointes; reversible lupus-like syndrome (procaainamide); Cinchonism—headache, tinnitus, thrombocytopenia (quinidine)

- **Lidocaine, mexiletine, tocainide**
  - Class IB—sodium channel blocker; decreases AP duration
  - Acute ventricular arrhythmias (especially post-MI), digitalis-induced arrhythmia; local anesthesia
  - CNS stimulation and depression, cardiovascular depression

- **Flecainide, propafenone**
  - Class IC—sodium channel blocker; no effect on AP duration
  - Ventricular tachycardia progressing to ventricular fibrillation, intractable supraventricular tachycardia, last resort in ventricular arrhythmias
  - Proarrhythmic (especially post-MI), prolongs refractory period in AV node

Hyperkalemia increases toxicity

(continued)
<table>
<thead>
<tr>
<th>Therapeutic Agent (common name, if relevant) [trade name, where appropriate]</th>
<th>Class—Pharmacology and Pharmacokinetics</th>
<th>Indications</th>
<th>Side Effects or Adverse Effects</th>
<th>Contraindications or Precautions to Consider; Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>β-Blockers (Class II)</strong> Propranolol, esmolol, metoprolol, atenolol, timolol</td>
<td>β-blocker—decreases cAMP and calcium currents → increases PR interval, suppresses abnormal pacemakers, especially in AV node</td>
<td>Ventricular tachycardia, supraventricular tachycardia, slowing the ventricular rate during atrial fibrillation and atrial flutter</td>
<td>Impotence, exacerbation of asthma, bradycardia, AV block, CHF, sedation, sleep alteration, dyslipidemia (metoprolol)</td>
<td>Esmolol (very short acting)</td>
</tr>
<tr>
<td><strong>Potassium channel blocker (Class III)</strong> Sotalol, ibutilide, bretylium, amiodarone</td>
<td>Potassium channel blocker—increases AP duration, ERP, and QT interval</td>
<td>Wolff–Parkinson–White syndrome; used when other antiarrhythmics fail</td>
<td>Torsades de pointes, excessive beta block, and hypotension; amiodarone—pulmonary fibrosis, corneal deposits, hepatotoxicity, skin deposits, photodermatitis, neurologic effects, constipation, bradycardia, CHF, heart block, and hypothyroidism/hyperthyroidism</td>
<td></td>
</tr>
<tr>
<td><strong>Calcium channel blockers (Class IV)</strong> Verapamil, diltiazem</td>
<td>Calcium channel blocker—decreases conduction velocity of AV nodal cells, increases ERP, PR interval</td>
<td>Prevent nodal arrhythmias (supraventricular tachycardia)</td>
<td>Constipation, flushing, edema, CHF, AV block, sinus node depression, torsades de pointes</td>
<td></td>
</tr>
<tr>
<td><strong>Other</strong> Adenosine</td>
<td>Increases potassium efflux → hyperpolarizes the cell</td>
<td>Diagnosis and treatment of AV nodal arrhythmias</td>
<td>Flushing, hypotension, and chest pain</td>
<td>Very short acting</td>
</tr>
<tr>
<td>Potassium</td>
<td>Depresses ectopic pacemaker in hypokalemia</td>
<td>Digoxin toxicity</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

AP, action potential; ATPase, adenosine triphosphatase; AV, atrioventricular; cAMP, cyclic adenosine monophosphate; CHF, congestive heart failure; CNS, central nervous system; ECG, electrocardiogram; ERP, effective refractory period; MI, myocardial infarction; SA, sinoatrial.
ATHEROSESCLEROSIS

I. Atherosclerosis is a disease of large and medium-sized vessels, characterized by the formation of atheromas (i.e., lesions that have a central lipid-rich core surrounded by fibrous tissue) deposited in the intima of arteries. It is the leading cause of mortality in the United States.

II. Risk factors
A. Major risk factors
   1. Dyslipidemia: high blood cholesterol, high low-density lipoproteins (LDLs), high triglycerides, and decreased high-density lipoproteins (HDLs; <45 mg/dL) (Table 3-4)
   2. Diabetes mellitus
   3. Cigarette smoking
   4. Hypertension
   5. Obesity
B. Minor risk factors
   1. Lack of physical activity
   2. Male sex
   3. Increased age
   4. Family history
   5. Oral contraceptives, decreased estrogens, or premature menopause
   6. Type A personality
   7. Elevated homocysteine level

III. Pathogenesis
A. Atheroma formation
   1. Monocytes adhere to vessel walls, enter tissue, and become macrophages.
   2. Macrophages are transformed into foam cells after engulfing oxidized LDLs.
   3. Foam cells accumulate in the intima.
   4. Foam cells release factors that cause the aggregation of platelets, the release of fibroblast growth factor, and the accumulation of smooth muscle.
   5. After formation of plaque, calcification occurs.
   6. The central core of the plaque consists mainly of cholesterol.
B. Complications
   1. Plaque rupture
   2. Ischemic heart disease or myocardial infarction (MI)
   3. Stroke
   4. Renal arterial ischemia
   5. Death

FAMILIAL DYSLIPIDEMIAS (Table 3-4)

<table>
<thead>
<tr>
<th>Familial Dyslipidemias</th>
<th>Elevated Blood Lipid Levels</th>
<th>Pathology (see Chapter 5)</th>
<th>Clinical Picture</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypercholesterolemia IIa</td>
<td>LDL ▲ Cholesterol</td>
<td>Decreased LDL receptors</td>
<td>Greatly increased vascular and heart disease; xanthomas</td>
<td>Cholestyramine/colestipol, lovastatin (and niacin for homozygotes)</td>
</tr>
</tbody>
</table>

(continued)
### TABLE 3-4  Selected Familial Dyslipidemia (Continued)

<table>
<thead>
<tr>
<th>Familial Dyslipidemias</th>
<th>Elevated Blood Lipid Levels</th>
<th>Pathology (see Chapter 5)</th>
<th>Clinical Picture</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dybetalipoproteinemia III</td>
<td>VLDL</td>
<td>TG, cholesterol</td>
<td>Altered apolipoprotein E</td>
<td>Increased vascular and heart disease; xanthomas</td>
</tr>
<tr>
<td>Hypertriglyceridemia IV</td>
<td>VLDL</td>
<td>TG, normal to cholesterol</td>
<td>Hepatic overproduction (with possible decreased clearance) of VLDL</td>
<td>Increased vascular and heart disease; obese, diabetic, pregnant, and alcoholic patients</td>
</tr>
</tbody>
</table>

LDL, low-density lipoproteins; TG, triglycerides; VLDL, very low-density lipoproteins.

---

### TABLE 3-5 Lipid-Lowering Agents (Table 3-5)

<table>
<thead>
<tr>
<th>Therapeutic Agent (common name, if relevant) [trade name, where appropriate]</th>
<th>Class–Pharmacology and Pharmacokinetics</th>
<th>Indications</th>
<th>Side Effects or Adverse Effects</th>
<th>Contraindications or Precautions to Consider; Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lovastatin, pravastatin, simvastatin, atorvastatin</td>
<td>HMG-CoA reductase inhibitors— inhibits the synthesis of cholesterol precursor mevalonate; decreases LDL, increases HDL, and decreases TG</td>
<td>High LDL, preventative after thrombotic event (e.g., MI, stroke)</td>
<td>Reversible increase in LFTs, myositis</td>
<td></td>
</tr>
<tr>
<td>Niacin</td>
<td>Inhibits lipolysis in fat tissue, reduces hepatic VLDL secretion into circulation; decreases LDL, increases HDL, and decreases TG</td>
<td>Increased LDL, decreased HDL</td>
<td>flushing (decreased by aspirin or long-term use)</td>
<td></td>
</tr>
<tr>
<td>Cholestyramine, colestipol</td>
<td>Bile acid resin/cholesterol absorption blocker—binds bile acids → prevents intestinal reabsorption of bile acid and therefore cholesterol; decreases LDL and increases HDL</td>
<td>Increased LDL</td>
<td>Tastes like sand, GI irritation, and decreased absorption of fat-soluble vitamins</td>
<td></td>
</tr>
<tr>
<td>Ezetimibe</td>
<td>Cholesterol absorption blocker—prevents cholesterol reabsorption at brush border in the small intestine; decreases LDL; no effect on HDL or TG</td>
<td>Increased LDL</td>
<td>Increased LFT (rarely)</td>
<td>No proven clinical benefit; may increase plaque thickness</td>
</tr>
<tr>
<td>Gemfibrozil, clofibrate, bezafibrate, fenofibrate</td>
<td>Uregulates lipoprotein lipase (peripheral) → increases TG clearance; decreases LDL, increases HDL, and decreases TG</td>
<td>Increased TG, increased LDL</td>
<td>Myositis, increased LFTs</td>
<td>Reduces TG more than other agents</td>
</tr>
</tbody>
</table>

GI, gastrointestinal; HDL, high-density lipoprotein; HMG-CoA, 3-hydroxy-3-methylglutaryl-coenzyme A; LDL, low-density lipoprotein; LFT, liver function test; MI, myocardial infarction; TG, triglyceride; VLDL, very low-density lipoprotein.
HYPERTENSION

I. Essential
   A. Most common type (95% of cases)
   B. Unknown etiology
   C. Risk factors
      1. Family history
      2. Race (more common in Blacks)
      3. Obesity
      4. Cigarette smoking
      5. Physical inactivity
   D. Characteristics
      1. Blood pressure greater than 140/90 mm Hg on three separate occasions, with the patient comfortably sitting and arm at the level of the patient’s heart.
   E. Chronic complications
      1. Hypertrophy of left ventricle
      2. Onion skinning of vessel walls
      3. Retinal hemorrhages
   F. Essential hypertension predisposes to ischemic heart disease (see next section).

II. Secondary hypertension refers to elevated systemic arterial pressure associated with a condition known to cause hypertension
   A. Renal diseases are the most common cause of secondary hypertension.
      1. Renal parenchymal disorders (chronic kidney disease)
      2. Unilateral renal artery stenosis
         a. Atherosclerosis (more common in Black males and older individuals)
         b. Fibromuscular dysplasia (more common in White females and younger individuals)
      3. Renin–angiotensin axis activated
   B. Endocrine causes
      1. Primary aldosteronism
      2. Pheochromocytoma
      3. Hyperthyroidism
      4. Acromegaly
      5. Cushing syndrome
   C. Coarctation of the aorta

III. Malignant hypertension
   A. Hypertensive urgency is blood pressure ≥180/120 mm Hg without symptoms and without evidence of end-organ damage.
   B. Hypertensive emergency (malignant hypertension) is blood pressure ≥180/120 mm Hg with evidence of end-organ damage.
      1. Cardiovascular—vascular damage, aortic dissection
      2. Pulmonary—pulmonary edema
      3. Renal—“flea-bitten kidneys,” azotemia
      4. Ocular—fundal hemorrhages, papilledema
      5. Central nervous system—encephalopathy, seizures, coma
   C. This type of hypertension causes early death because of cerebrovascular accident (CVA).
   D. Young Black males are the usual victims of this type of hypertension.

ANTIHYPERTENSIVE AGENTS (Table 3-6)

I. α-Blockers
   A. α-Adrenergic receptors are the primary controllers of vascular tone, blockers are used primarily to lower blood pressure.
      1. α₂-Selective agents commonly used in the treatment of hypertension include prazosin, doxazosin, and terazosin.
## TABLE 3-6 Antihypertensive Agents

<table>
<thead>
<tr>
<th>Therapeutic Agent (common name, if relevant) [trade name, where appropriate]</th>
<th>Class—Pharmacology and Pharmacokinetics</th>
<th>Indications</th>
<th>Side Effects or Adverse Effects</th>
<th>Contraindications or Precautions to Consider; Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Diuretics</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hydrochlorothiazide</td>
<td>Thiazide diuretic—impairs transport of Na⁺ and Cl⁻ into the cells of DCT</td>
<td>Hypertension, CHF, idiopathic hypercalciuria, nephrogenic diabetes insipidus</td>
<td>Hypokalemia, metabolic alkalosis, mild hyperlipidemia, hyperuricemia, nephrocalcinosis, hyperglycemia, hypotension</td>
<td>Do not give in patients with sulfa drug allergy</td>
</tr>
<tr>
<td>Furosemide</td>
<td>Loop diuretic—prevents cotransport of Na⁺, K⁺, and Cl⁻ in thick ascending limb</td>
<td>Hypertension, CHF, cirrhosis, nephrotic syndrome, pulmonary edema, and hypercalcemia</td>
<td>Potassium wasting, metabolic alkalosis, hypotension, dehydration, ototoxicity, nephritis, and gout</td>
<td>Do not give in patients with sulfa drug allergy</td>
</tr>
<tr>
<td><strong>RAA system</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Captopril, enalapril, fosinopril, lisinopril, quinapril</td>
<td>ACE inhibitor → inhibits conversion of angiotensin (Ang) I to II → decreases Ang II levels → prevents vasoconstriction from Ang II</td>
<td>Hypertension, CHF, post-MI agent, prevention/treatment of diabetic nephropathy</td>
<td>Cough, angioedema, hyperkalemia</td>
<td>Contraindicated in pregnancy (fetal renal malformation)</td>
</tr>
<tr>
<td>Losartan, valsartan, irbesartan, olmesartan, candesartan</td>
<td>ARBs → prevents vasoconstriction from Ang II</td>
<td>Hypertension</td>
<td>Fetal renal toxicity, hyperkalemia</td>
<td></td>
</tr>
<tr>
<td><strong>Sympathoplegics</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Metoprolol, atenolol, acebutolol, esmolol, propranolol, timolol, carvedilol, labetalol</td>
<td>β₁-Blocker (metoprolol, atenolol, acebutolol, esmolol), β₂-blocker (propranolol, timolol), carvedilol, and labetalol (α₁- and β-blocker)</td>
<td>Hypertension, angina, MI, antiarrhythmic</td>
<td>Bronchospasm, bradycardia, AV block, heart failure, sedation, and sleep alterations</td>
<td></td>
</tr>
<tr>
<td>Prazosin, terazosin, doxazosin</td>
<td>α₁-Blocker → vasodilation → decreases total peripheral resistance</td>
<td>Pheochromocytoma, hypertension, benign prostatic hyperplasia</td>
<td>Orthostatic hypotension, dizziness, and headache</td>
<td>First-dose orthostatic hypotension</td>
</tr>
<tr>
<td>Clonidine</td>
<td>Centrally acting sympatholytic agent (α₂-agonist) → decreases sympathetic outflow from CNS → decreases peripheral resistance</td>
<td>Hypertension, heroin, and cocaine withdrawal</td>
<td>Drowsiness, dry mouth, and rebound hypertension after abrupt withdrawal</td>
<td></td>
</tr>
<tr>
<td>Methylpredisophamide</td>
<td>Centrally acting sympatholytic agent (α-agonist) → decreases sympathetic outflow from CNS</td>
<td>Hypertension</td>
<td>Sedation and hemolytic anemia</td>
<td>Positive Coombs test</td>
</tr>
<tr>
<td>Hexamethonium</td>
<td>Nicotinic ganglionic blocker</td>
<td>Hypertensive emergency</td>
<td>Severe orthostatic hypotension, blurred vision, constipation, and sexual dysfunction</td>
<td></td>
</tr>
<tr>
<td>Reserpine</td>
<td>Prevents the storage of monoamines in synaptic vesicle</td>
<td>Hypertension</td>
<td>Mental depression, sedation, nasal stuffiness, and diarrhea</td>
<td></td>
</tr>
</tbody>
</table>

(continued)
2. They have little impact on the heart, but they do have selective effects that allow them to have other clinical uses (such as treatment for benign prostatic hypertrophy).

B. Side effects
   1. Postural hypotension with reflex tachycardia (most common)
   2. Nasal congestion and headache
   3. Rebound hypertension if stopped abruptly

C. Phenoxycbenzamine and phentolamine are nonselective α-blockers that can be used in the diagnosis and treatment of the symptoms of pheochromocytoma.

II. β-Blockers
   A. β-Blockers can be divided into four subgroups:
      1. Nonselective β-blockers (β₁ and β₂): propranolol, timolol, and nadolol
      2. β₁-Selective agents: metoprolol, atenolol, acebutolol, and esmolol

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### TABLE 3-6 Antihypertensive Agents (Continued)

<table>
<thead>
<tr>
<th>Therapeutic Agent (common name, if relevant) [trade name, where appropriate]</th>
<th>Class—Pharmacology and Pharmacokinetics</th>
<th>Indications</th>
<th>Side Effects or Adverse Effects</th>
<th>Contraindications or Precautions to Consider; Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Guanethidine</td>
<td>Interferes with norepinephrine release</td>
<td>Severe hypertension</td>
<td>Orthostatic hypotension, exercise hypotension, impotence, and diarrhea</td>
<td>Contraindicated in patients taking TCAs</td>
</tr>
<tr>
<td>Vasodilators</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hydralazine</td>
<td>Increases cGMP → smooth muscle relaxation → vasodilates arterioles → afterload reduction</td>
<td>Severe hypertension, CHF</td>
<td>Compensatory tachycardia, fluid retention, and lupus-like syndrome</td>
<td>First-line therapy for hypertension in pregnancy, used with methyldopa; contraindicated in angina/CAD because of compensatory tachycardia</td>
</tr>
<tr>
<td>Minoxidil</td>
<td>K⁺ channel opener → hyperpolarizes and relaxes vascular smooth muscle</td>
<td>Severe hypertension</td>
<td>Hypertrichosis and pericardial effusion</td>
<td></td>
</tr>
<tr>
<td>Nifedipine, felodipine, amlodipine</td>
<td>Dihydropyridine Ca²⁺ channel blockers block voltage-gated Ca²⁺ channels of vascular smooth muscle</td>
<td>Hypertension, angina pectoris, Prinzmetal angina, Raynaud phenomenon</td>
<td>Peripheral edema, flushing, dizziness, and constipation</td>
<td></td>
</tr>
<tr>
<td>Diltiazem, verapamil</td>
<td>Non-dihydropyridine Ca²⁺ channel blockers—block voltage-gated Ca²⁺ channels of cardiac smooth muscle</td>
<td>Hypertension, angina pectoris, arrhythmia</td>
<td>Cardiac depression, peripheral edema, flushing, dizziness, and constipation</td>
<td></td>
</tr>
<tr>
<td>Nitroprusside</td>
<td>Direct release of NO → increases cGMP → vasodilator (arterial dilation)</td>
<td>Hypertensive emergency, CHF, and angina</td>
<td>Cyanide toxicity, hypotension</td>
<td>Short acting</td>
</tr>
<tr>
<td>Diazoxide</td>
<td>K⁺ channel opener—hyperpolarizes and relaxes vascular smooth muscle</td>
<td>Hypertension</td>
<td>Hypoglycemia (reduces insulin release) and hypotension</td>
<td></td>
</tr>
</tbody>
</table>

ACE, angiotension-converting enzyme; ARB, angiotensin II receptor blocker; AV, atrioventricular; CAD, coronary artery disease; cGMP, cyclic guanosine monophosphate; CHF, congestive heart failure; CNS, central nervous system; DCT, distal convoluted tubule; MI, myocardial infarction; NO, nitric oxide; RAA, renin-angiotensin-aldosterone; TCA, tricyclic antidepressant.
3. \( \beta_2 \)-Selective agents (discussed in Chapter 4)
4. \( \alpha/\beta \)-Blockers (carvedilol, labetalol)

B. This important class of drugs has many clinical uses:
1. Cardiac uses (most common)
   a. Hypertension
   b. Stable angina
   c. Prophylaxis after an MI
2. Less common uses
   a. Symptomatic treatment of hyperthyroidism
   b. Prophylaxis against migraine headaches
   c. Anxiety disorder

C. Therapeutic effects of \( \beta \)-blockers on various organ systems are listed in Table 3-7.

D. Adverse effects
1. Sexual dysfunction in males
2. Arrhythmias if the drug is stopped abruptly
3. Bronchoconstriction
4. Blocking hypoglycemic response in a diabetic

III. Calcium channel blockers
A. Second-line antihypertensive agents
B. Act by binding to the \( L \)-type calcium channel of vascular smooth muscle cells and myocytes
C. Block the entry of calcium into these cells
D. These agents affect both vascular tone and the heart itself. Effects on the heart include negative inotropy and slowing of the conduction system.
E. Calcium channel blockers are often divided into two groups:
1. Dihydropyridines
   a. Examples: nifedipine and amlodipine
   b. Greater effect on vascular smooth muscle than on the heart
2. Non-dihydropyridines
   a. Examples: diltiazem and verapamil
   b. Increasingly greater effects on the myocardium
F. Adverse effects include hypotension, headache, constipation, peripheral edema, and exacerbation of gastroesophageal reflux and bradycardia.

IV. Other antihypertensive agents
A. Clonidine
1. Along with \( \alpha \)-methyldopa, a centrally acting antihypertensive agent
2. This agent acts as an agonist at presynaptic \( \alpha_2 \) receptors, thereby decreasing central sympathetic tone.

<table>
<thead>
<tr>
<th>Organ System</th>
<th>Effect</th>
<th>Clinical Implication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiac (( \beta_1 ))</td>
<td>Negative inotropic and chronotropic effects; slowing of SA and atrioventricular nodes</td>
<td>Decreases cardiac output; bradycardia can limit dosing; atrioventricular nodal slowing is useful in supraventricular tachycardia</td>
</tr>
<tr>
<td>Pulmonary (( \beta_2 ))</td>
<td>Constriction of airway smooth muscle</td>
<td>( \beta )-Blockers are contraindicated in patients with chronic obstructive pulmonary disease</td>
</tr>
<tr>
<td>Endocrine</td>
<td>Decreased glycogenolysis, decreased glucagon release</td>
<td>( \beta )-Blockers must be used with caution in patients with diabetes taking insulin who are at risk for hypoglycemia</td>
</tr>
<tr>
<td>Ocular</td>
<td>Decreased aqueous humor production by processes of ciliary body</td>
<td>( \beta )-Blockers, such as timolol, can be used topically for glaucoma</td>
</tr>
</tbody>
</table>

Note: Those effects known to be predominantly caused by either \( \beta_1 \) or \( \beta_2 \)-blockers are listed as such. SA, sinoatrial.
3. Adverse effects include sedation and rebound hypertension if the drug is stopped abruptly.
B. Sodium nitroprusside
1. Given intravenously, this agent is the drug of choice for hypertensive emergencies.
2. Given orally, this drug is toxic because it results in cyanide production.
3. It affects both arterial and venous smooth muscle.
C. Vasodilators (hydralazine, minoxidil)
1. Dilate both arteries and veins (predominantly arteries), lowering blood pressure
   a. Reflex tachycardia that results can actually precipitate attacks of angina.
   b. These agents are not first-line agents for hypertension.
   c. These are often used along with β-blockers and diuretics.
2. Adverse reactions to hydralazine include headache, arrhythmias, and a lupus-like reaction.
3. Adverse effects of minoxidil include sodium retention and hypertrichosis.

ANEURYSMS (Table 3-8)

<table>
<thead>
<tr>
<th>Type of Aneurysm</th>
<th>Etiology</th>
<th>Characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arteriovenous fistula</td>
<td>Abnormal communication between arteries and veins; usually secondary to trauma</td>
<td>Ischemic changes, aneurysm formation, high-output cardiac failure</td>
</tr>
<tr>
<td>Atherosclerotic</td>
<td>Atherosclerotic disease, coronary artery disease</td>
<td>Usually in the abdominal aorta; located between renal arteries and iliac bifurcation</td>
</tr>
<tr>
<td>Berry</td>
<td>Congenital medial weakness at the bifurcations of the cerebral arteries</td>
<td>Saccular lesions in cerebral vessels (especially at the circle of Willis), hemorrhage into the subarachnoid space</td>
</tr>
<tr>
<td>Dissecting</td>
<td>Hypertension, cystic medial necrosis, Marfan syndrome</td>
<td>Tearing pain, longitudinal separation of tunica media of aortic wall</td>
</tr>
<tr>
<td>Syphilitic</td>
<td>Tertiary syphilis, obliteration of the vasa vasaorum, necrosis of the media</td>
<td>Involves ascending aorta and aortic root; aortic valve insufficiency</td>
</tr>
<tr>
<td>Mycotic (infectious)</td>
<td>Inflammation secondary to bacterial infection; usually salmonella</td>
<td>Involves abdominal aorta</td>
</tr>
</tbody>
</table>

I. Abdominal aortic aneurysm (AAA)

A. Focal dilation of the aorta, generally thought to be due to atherosclerosis
B. The most common location is the infrarenal aorta. Therefore, an AAA may be palpated superior to the umbilicus because the aorta bifurcates at the level of the umbilicus.
C. Presentation
1. Usually asymptomatic until late in the course. May cause some abdominal pain.
2. The most common diagnosis mistaken for AAA in the emergency setting is kidney stones.
3. The most dangerous complication is rupture, which presents as a triad of hypotension, abdominal pain, and pulsatile mass in the abdomen. Hypertension increases the risk of rupture of an AAA.
D. All men aged 65 to 75 years with any history of smoking should be screened for AAA with a one-time abdominal sonogram.
E. Treatment is surgical repair for any of the following:
1. Aneurysm diameter ≥ 5.5 cm
2. Diameter increasing ≥ 0.5 cm in a 6-month interval
3. Any symptomatic AAA
Clinical Vignette 3-1

**CLINICAL PRESENTATION:** A 59-year-old male presents to the emergency room with sudden, severe, and constant low back pain. Past medical history is significant for hypertension, hyperlipidemia, emphysema, coronary artery disease, stable angina, and a 25-pack-year history of smoking. The patient was hospitalized for a cerebrovascular accident 7 years ago. Physical examination revealed a 5.8 cm pulsatile mass superior to the umbilicus in the abdomen. Temperature = 98.5°F; blood pressure = 150/90 mm Hg; heart rate = 80 bpm; and respiration rate = 23 breaths/min.

**DIFFERENTIALS:** Abdominal aortic aneurysm (AAA), aortic dissection, pyelonephritis/nephrolithiasis, prostatitis, and pancreatitis. Given that this pain developed suddenly and the presence of an abdominal pulsatile mass, this patient most likely has an AAA.

**LABORATORY STUDIES:** Proper follow-up for this patient would include an abdominal ultrasound and/or computerized tomography (CT) scan with contrast. The typical diameter for abdominal aorta is 2 cm; therefore, any size greater than this indicates presence of an aneurysm. Advantages of an ultrasound are that it is quick, easy, and inexpensive; however, it is very operator dependent, less useful in obese individuals, and does not provide information about the iliac arteries, which could also be aneurysmal. CT angiogram can also be helpful in describing the anatomy of the aorta prior to surgery, but it is not commonly done in clinical practice. All patients with AAA should also undergo cardiac evaluation because patients with AAA often have underlying vascular pathology. In these patients, cardiac catheterization should also be performed to assess cardiac risk and potentially revascularize the patients prior to operation.

**MANAGEMENT:** As an aneurysm becomes larger than 5.5 cm, the risk of rupture increases exponentially; an aneurysm smaller than 5.5 cm in diameter is less likely to rupture, and risk-to-benefit ratio of surgery is less supportive. Therefore, if an AAA is smaller than 5.5 cm in diameter and asymptomatic, the patient can be followed with ultrasound or CT surveillance every 6 months. If the aneurysm is larger than 5.5 cm in diameter and symptomatic, the patient should be taken to the operating room. A patient with a ruptured AAA is taken to the operating room.

II. Thoracic aortic dissection

A. A tear in the intima of the aorta, with blood forcing its way into the media and forming a false lumen

B. The most common risk factor is hypertension. Other risk factors can include trauma, syphilis aortitis, Marfan syndrome, and Ehlers–Danlos syndrome.

C. Most commonly found in the thoracic aorta
   1. Stanford A dissection involves any part of the ascending aorta and is treated surgically.
   2. Stanford B dissection is confined to the descending aorta (distal to the left subclavian artery).

D. Presentation
   1. Acute, “tearing” chest pain, radiating through to the back
   2. Widened mediastinum on chest x-ray
   3. Dissections that involve other vessels may cause MI, stroke symptoms or syncope, or decreased peripheral pulses.

E. Management
   1. First, stabilize the blood pressure with β-blockers (labetalol) or nitroprusside.
   2. Surgical repair for Stanford A dissections or Stanford B dissections with rupture or other complications

**ISCHEMIC HEART DISEASE**

I. It is defined as an inadequate supply of oxygen relative to demand.

II. Ischemic heart disease is most often caused by atherosclerosis.
III. There are four types of ischemic heart diseases.

A. Angina pectoris

1. Paroxysmal attacks of retrosternal pain, heaviness, and pressure-like or squeezing chest pain occur and may radiate to the neck, jaw, left shoulder, or arm. Angina pectoris is often associated with diaphoresis and nausea.
2. Imbalance between cardiac perfusion and cardiac demand is characteristic. Ninety percent occlusion of coronary vessel produces symptoms.
3. Three types of angina pectoris:
   a. Stable angina
      i. Most common form
      ii. Induced by exercise
      iii. Relieved by rest
      iv. Results from chronic stenosis of coronary arteries
   b. Prinzmetal (variant) angina
      i. Episodic pain occurs at rest.
      ii. Attacks are unrelated to activity, blood pressure, or heart rate but are related to coronary artery vasospasm.
      iii. Significant artery stenosis is often present.
   c. Unstable angina
      i. This type occurs at both rest and activity.
      ii. It is usually preceded by decreasing physical activity or gradual increase in stable anginal symptoms.
      iii. It produces pain of increasing duration.
      iv. It is induced by ruptured atherosclerotic plaque with subsequent platelet-mediated thrombosis, which partially occludes the vessel. This results in ischemia and angina, but there is no myocardial necrosis.

4. Treatment of stable angina
   a. Nitrates
      i. These drugs are converted within the cell to nitric oxide, a smooth muscle relaxant.
         a) The relaxation of vascular smooth muscle causes widespread venous dilation.
         b) This lowers preload and therefore reduces the workload and oxygen demand of the heart.
         c) To a lesser extent, the relaxation of coronary arteries provides ischemic myocardium with increased oxygen.
      ii. Sublingual nitroglycerin is the treatment of choice for acute episodes of angina.
      iii. A long-acting nitrate such as isosorbide dinitrate can be used for angina prophylaxis.
      iv. Unwanted side effects of nitrate therapy include headache and tachyphylaxis, postural hypotension, and facial flushing.
   b. Calcium channel blockers
   c. β-Blockers

B. MI

1. Lack of adequate perfusion to cardiac tissue leads to myocyte death in affected area.
2. MI is most often caused by atherosclerosis with plaque rupture and thrombus.
3. The subendocardium is most vulnerable to ischemia (because of decreased blood flow during systole) and thus most likely to infarct.
4. In a transmural infarct (see following text), the full thickness of the ventricular wall is affected within 35 hours.
5. Two types of MI are possible:
   a. Non-ST elevation MI (NSTEMI)
      i. Formerly called “nontransmural” or “non–Q-wave” infarct
      ii. As in unstable angina, atherosclerotic plaques rupture.
      iii. Platelet-mediated thrombosis completely occludes the vessel, resulting in loss of perfusion to inner one-third of muscular wall of ventricle occurs. Clot lysis limits the depth of infarction.
   b. ST elevation MI
      i. Formerly called “transmural” or “Q-wave” infarct
      ii. Cardiac stunned, resulting in rapid rise in cardiac enzymes.
      iii. Unlabeled necrosis occurs, which manifests as infarct size.

QUICK HIT

- Angina pectoris causes ST depression on ECGs, but this is only observed during the attack, which lasts 2 to 5 minutes.
- Anticoagulants (heparin, low-molecular-weight heparin, and aspirin), nitrates, and β-blockers can be used to treat unstable angina. Do not use calcium channel blockers or tissue plasminogen activator to treat unstable angina.
- Cocaine use can also result in coronary vasospasm resulting in myocardial ischemia. In general, cocaine works by inhibiting the reuptake of endogenous catecholamines (dopamine, norepinephrine, epinephrine, and serotonin). Conversely, amphetamines stimulate the release of endogenous catecholamines.
- When remembering the sequence of histopathologic changes after an MI, think of the 1-3-1-3 rule: 1 day (neutrophils dominate), 3 days (macrophages infiltrate), 1 week (fibroblasts infiltrate), and 3 weeks (granulation tissue most prominent).
iv. Tissue infarction and myocardial necrosis lead to release of cardiac enzymes (Figure 3-9).

v. ST-segment depression (but no ST elevation) is seen on ECG. Q waves do not develop.

b. ST elevation MI (STEMI)

i. Formerly called “transmural” or “Q-wave” infarct

ii. As in NSTEMI, atherosclerotic plaques rupture, and platelet-mediated thrombosis completely occludes the vessel. There is no clot lysis, so the infarction extends to the entire muscular wall.

iii. Tissue infarction and myocardial necrosis lead to release of cardiac enzymes (Figure 3-9).

iv. ST-segment elevation is seen on ECG, and Q waves eventually develop.

6. Complications

a. Arrhythmia—especially ventricular fibrillation (the primary cause of death in the first hour post-MI) heart block

b. Papillary muscle rupture—presents as acute mitral regurgitation 2 to 7 days post-MI

c. Myocardial rupture—rare, occurs most commonly 2 to 7 days post-MI

d. Dressler syndrome—pericardial inflammation occurring 2 to 6 weeks post-MI; presents with fever, malaise, pleuritic chest pain, pericardial friction rub, and elevated erythrocyte sedimentation rate (ESR)

e. Ventricular aneurysm—usually due to anterior wall MI

Because of state-dependent block, lidocaine works on slightly depolarized or ischemic tissue more than normal tissue. Therefore, use lidocaine (IV) to suppress acute MI-associated ventricular arrhythmias.
The Cardiovascular System

Clinical Vignette 3-2

CLINICAL PRESENTATION: A 45-year-old male was brought to the emergency department complaining of crushing chest pain of 1-hour duration, which he described as “a belt closed tightly around my chest.” He indicated the location of the pain with a closed fist in the substernal region. The morning of admission, the patient was feeling ill and then experienced pain in the chest, which radiated to his jaw, left shoulder, and down the left arm. The pain was associated with nausea; the patient denied conditions that improved or worsened the pain. The patient’s past medical history was significant for hyperlipidemia and hypertension. The patient stated that his father recently underwent coronary artery bypass. Past social history was significant for a 35-pack-year history of smoking and social drinking. On physical examination, the patient was found to be in acute distress and diaphoretic. Temperature = 97.6°F; blood pressure = 145/90 mm Hg; heart rate = 101 bpm; and respiration rate = 23 breaths/min.

DIFFERENTIALS: Acute myocardial infarction (MI), angina pectoris, aortic dissection, gastroesophageal reflux disease (GERD), pancreatitis and biliary tract disease, pericarditis, and pulmonary embolism (PE). Given the patient’s description of pain and family history of coronary artery disease, he most likely has suffered from an acute MI.

LABORATORY STUDIES: An acute MI would be diagnosed via (a) blood chemistry showing elevated cardiac enzymes or (b) ECG showing ST elevation if transmural or ST depression if subendocardial. With these changes, aortic dissection, GERD, and PE can be ruled out. In an aortic dissection, we would expect a widened mediastinum on chest radiograph, confirmed by CT scan; also, an aortogram showing a double lumen would be diagnostic. Stable angina can be ruled out because it typically lasts a few minutes, and although it can precede an MI, this pain is characteristically relieved by rest or nitroglycerin. Other laboratory studies that would be done in this patient include amylase, lipase, alkaline phosphatase (elevated in pancreatitis), and echocardiography (to rule out pericarditis). Interestingly, pericarditis presents with chest pain that radiates to the trapezoid region, worsens with inspiration, and is relieved by sitting up/leaning forward.

MANAGEMENT: Revascularization, if done early, is beneficial via thrombolytics or angioplasty. Patients should also receive morphine (reduces pain and is a vasodilator), heparin (to prevent formation of thrombus), and nitrates. This patient should be started and maintained on aspirin (shown to decrease mortality), β-blockers (prevent remodeling), ACE inhibitors (prevent remodeling), and statins (lower cholesterol and decrease risk of future coronary events).

CONGESTIVE HEART FAILURE (Table 3-9 and Figures 3-10 and 3-11)

CHF is a clinical diagnosis in which the heart is unable to pump an adequate amount of blood to meet the metabolic needs of the body. A number of factors play a role in CHF, including hormonal changes (RAA and sympathetic activation), peripheral vasoconstriction, and myocardial dysfunction. One of the final common pathways in CHF is

f. Mural thrombus with possible embolization

g. Progressive ischemic cardiomyopathy and congestive heart failure (CHF)

7. Remodeling and scar formation occur over a period of 36 months after an infarct (Figure 3-9).

C. Chronic ischemic heart disease (CIHD)

1. CHF that results from ischemic cardiac damage leads to CIHD.

2. Hypertrophy of the heart and cardiac decompensation occur as a result of infarction.

3. CIHD is most often found in the elderly.

D. Sudden cardiac death

1. This is an unexpected death from cardiac failure occurring within 2-hour post-MI.

2. This is caused less commonly by a congenital anomaly.

3. Marked atherosclerosis is usually present.

4. The mechanism of death is almost always because of arrhythmia.

QUICK HIT

Cor pulmonale is right-sided heart failure secondary to lung disorders that lead to pulmonary arterial hypertension.

QUICK HIT

Idiopathic dilated cardiomyopathy is the most common form of cardiomyopathy. Treatment includes digoxin, ACE inhibitors, heart transplant, and sometimes chronic anticoagulation.
TABLE 3-9 Congestive Heart Failure

<table>
<thead>
<tr>
<th>Etiology</th>
<th>Clinical Manifestations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Left-sided congestive heart failure (CHF)</td>
<td>Pulmonary edema</td>
</tr>
<tr>
<td>Ischemia (coronary artery disease)</td>
<td>Dyspnea on exertion/fatigue</td>
</tr>
<tr>
<td>Systemic hypertension</td>
<td>Orthopnea</td>
</tr>
<tr>
<td>Left-sided valvular disease</td>
<td>Paroxysmal nocturnal dyspnea</td>
</tr>
<tr>
<td>Myocarditis</td>
<td>Hyperventilation</td>
</tr>
<tr>
<td>Cardiomyopathy</td>
<td>Reduction in renal perfusion (activates renin-angiotensin-aldosterone axis)</td>
</tr>
<tr>
<td>Congenital heart disease</td>
<td></td>
</tr>
<tr>
<td>Pericardial disease</td>
<td></td>
</tr>
<tr>
<td>Right-sided CHF</td>
<td>Hepatomegaly/ascites (nutmeg liver)</td>
</tr>
<tr>
<td>Left-sided heart failure</td>
<td>Splenomegaly</td>
</tr>
<tr>
<td>Left-sided lesions</td>
<td>Peripheral edema (especially pitting edema of the ankles)</td>
</tr>
<tr>
<td>Coronary artery</td>
<td>Distention of neck veins</td>
</tr>
<tr>
<td>Myocarditis</td>
<td>Renal hypoxia</td>
</tr>
<tr>
<td>Cardiomyopathy</td>
<td></td>
</tr>
<tr>
<td>Right-sided valvular disease</td>
<td></td>
</tr>
</tbody>
</table>

hypoperfusion of the kidneys and activation of the RAA axis, which leads to sodium and water retention. Treatment is directed at either blocking the RAA axis or increasing the cardiac performance and, therefore, renal perfusion. Therapeutic agents in CHF treatment include ACE inhibitors, angiotensin II receptor blockers (ARBs), digitalis, diuretics, and dobutamine.

I. ACE inhibitors
   A. First-line treatment for CHF
   B. ACE inhibitors are able to lower blood pressure (lower afterload), improve cardiac performance, and prevent the aldosterone-mediated salt and water retention typical of CHF.
   C. Specific agents:
      1. Enalapril decreases mortality in CHF
      2. Other ACE inhibitors include captopril and lisinopril.
   D. Adverse effects of ACE inhibitors:
      1. Reversible renal failure
      2. Angioedema, hyperkalemia, dry cough, and orthostatic hypotension
      3. ACE inhibitors are fetotoxic and contraindicated in pregnancy.

II. ARBs
   A. These agents block the RAA axis at the Ang II receptor, producing the same benefits as ACE inhibitors.
   B. Examples of ARBs are losartan and valsartan.
   C. These drugs have all the same effects as the ACE inhibitors except that, unlike the ACE inhibitors, they do not increase levels of bradykinin and hence do not cause cough as a side effect.

III. Digitalis
   A. Treats CHF by increasing cardiac performance; digitalis treats CHF by increasing the intracellular concentration of calcium in cardiac myocytes, thus increasing contractility.
   B. Blocks sodium–potassium pump:
      1. This increases the intracellular sodium concentration.
      2. Activity of a sodium–calcium antiporter is decreased.
      3. Decreased activity of this antiporter raises intracellular calcium levels.
   C. Digitalis improves the symptoms of CHF, but unlike ACE inhibitors, it has not been shown to decrease mortality.
   D. Digitalis also has a low therapeutic index, which means that the toxic dose is closer to the therapeutic dose.
The Cardiovascular System

**Figure 3-10**
Congestive heart failure

- ↓ Myocardial contractility
- ↓ Cardiac output
- ↓ Effective blood volume
- ↑ Sympathetic nervous system
- ↑ Venous pressure

- → Maintain blood pressure
- → Renin release
- → Angiotensin ||
- → Aldosterone

- → Renal vasoconstriction
- ↓ Glomerular filtration rate
- ↓ Urinary excretion of Na+/H₂O

- ↓ Total body Na+/H₂O

→ EDEMA

**Figure 3-11**
A chest radiograph showing congestive heart failure and pulmonary edema

(A) Reproduced with permission from Daffner RH. Clinical Radiology: The Essentials. 2nd ed. Baltimore, MD: Lippincott Williams & Wilkins; 1999.)
Clinical Vignette 3-3

CLINICAL PRESENTATION: A 67-year-old female complains to her primary care physician of easy fatigue and that each night, she has to wake up to urinate (nocturia). She also mentions that each night, her ankles swell, and she sleeps with her head elevated on two to three pillows (orthopnea); otherwise, she finds herself waking to catch her breath (paroxysmal nocturnal dyspnea). Her past medical history is significant for hypertension; however, the patient has been noncompliant with medication. Physical examination reveals congestion; 1+ pitting edema, an enlarged liver, and elevated jugular venous pressure (JVP). Other findings include cold and clammy skin and S3 and S4 heart sounds. Temperature = 98.5°F; blood pressure = 165/100 mm Hg; heart rate = 92 bpm; and respiration rate = 34 breaths/min.

DIFFERENTIALS: CHF and renal failure. Given the patient’s history and classic presentation, this patient likely has CHF secondary to chronic hypertension.

LABORATORY STUDIES: Proper follow-up for suspect CHF would be (a) chest radiograph showing cardiomegaly (Figure 3-11), interstitial edema in the lungs, and pleural effusion; (b) echocardiogram (determines the cause of CHF, whether systolic or diastolic; quantifies ejection fraction [EF]); (c) ECG showing evidence of chamber enlargement or presence of ischemic disease; (d) radionuclide ventriculography using Tc (quantifies EF when echo suboptimal as in chronic obstructive pulmonary disease [COPD]); (e) cardiac catheterization; (f) stress testing; (g) urine analysis (elevated protein would suggest renal failure); and (h) blood chemistry (blood urea nitrogen [BUN] and creatinine [Cr] slightly elevated in CHF and markedly elevated in renal failure).

MANAGEMENT: Diastolic dysfunction is treated symptomatically. Systolic dysfunction should be managed by (a) sodium restriction, (b) diuretics (congestive symptoms), (c) ACE inhibitors (decrease preload, afterload, decrease mortality), and (d) digitalis (symptomatic relief; use in severe CHF). Note: If the patient cannot tolerate ACE inhibitors, use ARBs, hydralazine, and isosorbide dinitrates. Also, α-blockers have been proven to decrease mortality in post-MI CHF.

E. Common adverse reactions:
1. Nausea and headache
2. Arrhythmias (more serious)

IV. Diuretics, the other major treatment modality for CHF, are not discussed here [see Chapter 6].

INTRINSIC DISEASES OF THE HEART

I. Myocarditis
A. This is defined as inflammation of the cardiac muscle.
B. Etiology
1. Viral etiology is the most common cause (usually coxsackie B virus, parvovirus B19, and human herpes virus [HHV]-6).
2. HIV (via toxoplasmosis and metastasis of Kaposi sarcoma) may cause myocarditis.
3. Bacterial causes include Staphylococcus aureus, Corynebacterium diphtheriae, and tuberculosis.
4. Chagas disease
5. Lyme disease
6. Hypersensitivity reactions
7. Sarcoidosis
C. Physical examination
1. Muffled S1
2. Audible S3 heart sound
3. Murmur of mitral regurgitation
4. Cardiomegaly

Borrelia burgdorferi, a spirochete, causes Lyme disease and is transmitted by the Ixodes tick. Stage 1 is marked by erythema chronicum migrans. Stage 2 is marked by cardiac and neurologic involvement. Stage 3 involves arthritis.

Coxsackievirus B is the number one cause of neonatal myocarditis.

Trypanosoma cruzi causes Chagas disease and is transmitted by the reduvid bug (kissing bug).
II. Endocarditis
   A. Inflammation of the heart lining and connective tissue
   B. Causes
      1. Rheumatic heart disease—endocarditis may be caused by rheumatic fever (see below).
      2. Infective endocarditis
         a. Etiology
            i. Gram-positive cocci are the most common cause. Rarely, the cause is fungi (Aspergillus and Candida) or gram-negative bacteria.
            ii. Damage, surgical repair, prosthetic heart valves, or congenital abnormalities are predisposing conditions.
            iii. Vegetative growth (usually on atrial surface of valves) can throw septic thrombi to brain or peripheral circulation.
            iv. Endocarditis is complicated by perivalvular abscesses or rupture of chordae tendineae.
         b. Clinical features
            i. Mucosal petechiae
            ii. Janeway lesions (peripheral hemorrhages with slight nodular character)
            iii. Osler nodes (small, tender nodules on fingers and toe pads)
            iv. Splinter hemorrhages (subungual linear streaks)
            v. Roth spots (retinal hemorrhages)
            vi. Splenomegaly
            vii. The mitral and aortic valves are frequently involved.
            viii. Right-sided valvular lesions (usually of the tricuspid) suggest IV drug abuse and are associated with septic pulmonary emboli.
   C. Types
      1. Acute endocarditis
         a. The cause is most often S. aureus.
         b. Onset is rapid.
         c. Clinical features include fever, anemia, embolic events, and heart murmur.
         d. Treatment is with IV antibiotics.
      2. Subacute endocarditis
         a. The cause is most often the viridans streptococci.
         b. It results from poor dentition or oral surgery in patients with preexisting heart disease (and preexisting damage to heart valves).
         c. Onset is over a period of 6 months.
         d. Treatment is with IV antibiotics.
      3. Nonbacterial (marantic) endocarditis
         a. This type is associated with metastatic cancer.
         b. Sterile fibrin deposits appear on valves.
         c. Sterile emboli can cause cerebral infarct.
      4. Libman–Sacks endocarditis
         a. This is a manifestation of systemic lupus erythematosus (SLE).
         b. It is caused by autoantibody damage to valves.
         c. Vegetations form on both sides of the valve.
      5. Carcinoid syndrome
         a. This syndrome is characterized by increased serotonin and other secretory products from a carcinoid tumor.
         b. Plaque builds on right-sided valves of the heart.

III. Rheumatic heart disease
   A. This is a systemic inflammatory disorder with cardiac manifestations.
   B. Pathogenesis
      1. Acute rheumatic heart disease usually occurs 2 to 4 weeks after a bout of pharyngitis caused by group A β-hemolytic streptococci.
2. Antigenic mimicry occurs between streptococcal antigens and human antigens in the heart.
3. This results in immunologic origin for rheumatic heart disease.

C. Epidemiology
1. Children 5 to 15 years of age have the highest incidence of rheumatic fever.
2. Incidence is decreasing since the advent of penicillin.

D. Cardiac manifestations of rheumatic fever include the following conditions:
1. Pancarditis—inflammation of all structures of the heart
2. Pericarditis with effusions
3. Myocarditis
   a. Leads to cardiac failure
   b. Most common cause of early death in rheumatic fever
4. Endocarditis
   a. Usually afflicts the mitral and aortic valves (areas of high stress and turbulent flow)
   b. Mitral—aortic—tricuspid—pulmonary shows the order in which the valves become involved.
   c. Early nonembolic vegetations occur.
   d. With fibrosis and calcification, valvular damage leads to chronic rheumatic heart disease.

E. Other manifestations of rheumatic fever include:
1. Migratory polyarthritis
2. Sydenham chorea
3. Subcutaneous nodules
4. Erythema marginatum
5. Recent infection by group A streptococci (indicated by elevated antistreptolysin-O titers)
6. Aschoff body
   a. Lesion characterized by focal interstitial myocardial inflammation
   b. Fragmented collagen/fibrinoid material
   c. Anitschkow myocytes: large activated histiocytes
   d. Aschoff cells: granuloma with giant cells

IV. Cardiomyopathies (Table 3-10)

<table>
<thead>
<tr>
<th>Pathology</th>
<th>Etiology</th>
<th>Clinical Manifestations</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dilated (systolic or contractile dysfunction)</td>
<td><strong>Idiopathic</strong>, alcoholics, thiamine deficiency, peripartum, <em>coxsackievirus B</em>, <em>Trypanosoma cruzi</em>, tricyclic antidepressants, lithium, doxorubicin, pregnancy associated</td>
<td>Premature ventricular contractions, decreased ejection fraction, JVP, cardiomegaly, hepatomegaly</td>
<td>Most common form</td>
</tr>
</tbody>
</table>
### TABLE 3-10 Cardiomyopathies (Continued)

<table>
<thead>
<tr>
<th>Pathology</th>
<th>Etiology</th>
<th>Clinical Manifestations</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Restrictive (diastolic dysfunction or loss of compliance)</td>
<td>Stiffened heart muscle; may result in right and left heart failure; tricuspid regurgitation</td>
<td>Peripheral edema, ascites, jugular venous distention</td>
<td>Differentiate from hypertrophic cardiomyopathy</td>
</tr>
<tr>
<td>Hypertrophic (diastolic dysfunction or loss of compliance)</td>
<td>Ventricular and ventricular septal hypertrophy, mitral regurgitation</td>
<td>Dyspnea, syncope, S4, systolic murmur, cardiomegaly on chest radiograph</td>
<td>Relieved by squatting, worsened by Valsalva, exacerbated by physical exertion, sudden death</td>
</tr>
</tbody>
</table>

JVP: jugular venous pressure.

### V. Valvular heart diseases (Table 3-11)

### TABLE 3-11 Valvular Heart Disease and Murmurs

<table>
<thead>
<tr>
<th>Valvular Disease</th>
<th>Etiology</th>
<th>Physical Examination</th>
<th>Clinical Manifestations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systolic murmurs</td>
<td>Aortic stenosis</td>
<td>Delayed pulses, carotid thrill, crescendo-decrescendo systolic ejection murmur at right upper sternal border, decreased intensity with Valsalva</td>
<td>Syncpe, angina, dyspnea/CHF, death, treat symptomatic patients with valve replacement</td>
</tr>
<tr>
<td></td>
<td>Bicuspid aortic valves, degenerative calcification, RHD, unicuspid aortic valve, syphilis</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>RHD (50% of cases), LV dilation, ischemic heart disease, endocarditis, MVP, papillary muscle dysfunction (secondary to myocardial infarction)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mitral regurgitation</td>
<td>RHD</td>
<td>Splitting of S2; S3, holosystolic murmur at apex, radiating to the left axilla, increased intensity with squatting or handgrip</td>
<td>Anhythmias, dilated left atrium, holosystolic murmur</td>
</tr>
<tr>
<td>Mitral valve prolapse (MVP)</td>
<td>Myxomatous degeneration of mitral valve leaflets, such that leaflets Billow into the left atrium during systole</td>
<td>Midsystolic click, often followed by a late systolic murmur; decreased intensity with squatting</td>
<td>Can be associated with chest pain, palpitations, light-headedness, panic attacks</td>
</tr>
<tr>
<td>Ventricular septal defect</td>
<td>Congenital defect</td>
<td>Harsh, holosystolic murmur</td>
<td></td>
</tr>
<tr>
<td>Diastolic murmurs</td>
<td>Aortic regurgitation</td>
<td>Wide pulse pressure, water-hammer-pulse, S3, blowing, decrescendo diastolic murmur</td>
<td>Left ventricular enlargement, dyspnea, early diastolic murmur</td>
</tr>
<tr>
<td></td>
<td>Rheumatic heart disease, syphilitic aortitis, nondissecting aortic aneurysm, Marfan syndrome</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mitral stenosis</td>
<td>Usually rheumatic heart disease</td>
<td>Cyanosis, opening snap, diastolic rumbling murmur</td>
<td>Dyspnea, orthopnea, left atrial enlargement, mid to late diastolic murmur</td>
</tr>
</tbody>
</table>

CHF: congestive heart failure; LV: left ventricular; RHD, rheumatic heart disease.

Mitral valve prolapse (MVP) is the most frequently occurring valvular lesion, often found in young women and in patients with Marfan syndrome and related to tissue laxity. Characteristics of the heart sound in MVP include midsystolic click, followed by late systolic murmur.
### Peripheral Vascular Diseases (Table 3-12)

<table>
<thead>
<tr>
<th>Disease</th>
<th>Pathology</th>
<th>Vessels Affected</th>
<th>Clinical Manifestations</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Churg–Strauss</td>
<td>Eosinophils, vasculitis, perinuclear antineutrophil cytoplasmic antibody (p-ANCA)</td>
<td>Small and medium-sized arteries</td>
<td>Asthma, elevated plasma eosinophils, heart disease</td>
<td>May be associated with p-ANCA</td>
</tr>
<tr>
<td>Henoch–Schönlein purpura</td>
<td>IgA immune complex-mediated acute vasculitis, renal deposits in mesangium</td>
<td>Arterioles, capillaries, venules</td>
<td>Hemorrhagic urticaria, palpable purpura, fever, red blood cell casts in urine, atopic patient</td>
<td>Often associated with an upper respiratory infection, affects children</td>
</tr>
<tr>
<td>Kaposi sarcoma</td>
<td>Viral origin, common malignancy in patients with AIDS</td>
<td>Cutaneous and visceral vasculature</td>
<td>Malignant vascular tumor, especially in homosexual men</td>
<td>Probably results from reactivation of latent human herpesvirus B (HHV-8) infection</td>
</tr>
<tr>
<td>Kawasaki disease</td>
<td>Acute necrotizing inflammation</td>
<td>Large, medium, and small vessels</td>
<td>Fever, conjunctival lesions, lymphadenitis, coronary artery aneurysms</td>
<td>Affects young children</td>
</tr>
<tr>
<td>Rendu–Osler–Weber syndrome</td>
<td>Autosomal dominant, hereditary hemorrhagic telangiectasia</td>
<td>Dilation of venules and capillaries</td>
<td>Epistaxis, gastrointestinal (GI) bleeding</td>
<td>Increased occurrence in Mormon population</td>
</tr>
<tr>
<td>Polyarteritis nodosa (PAN)</td>
<td>Necrotizing degeneration of tunica media, aneurysms</td>
<td>Small and medium-sized arteries</td>
<td>Fever, weight loss, abdominal pain (GI), hypertension (renal)</td>
<td>Associated with hepatitis B infection</td>
</tr>
<tr>
<td>Takayasu arteritis (pulseless disease)</td>
<td>Inflammation leading to stenosis; aortic arch and the origins of great vessels</td>
<td>Medium and large arteries</td>
<td>Loss of carotid, radial, and ulnar pulses; fever, night sweats; deficits arthritis; visual; low blood pressure in upper extremities; claudication caused by lack of blood reaching extremities</td>
<td>Pathology referred to as “aortic arch syndrome”; young Asian females; corkscrew, widened aorta on angiogram</td>
</tr>
<tr>
<td>Temporal arteritis (giant cell arteritis)</td>
<td>Nodular inflammation of branches of carotid (especially temporal)</td>
<td>Medium and large arteries</td>
<td>Headache, absence of pulse in affected vessels, visual deficits, polymyalgia rheumatica</td>
<td>Significant elevation of sedimentation rate; affects the elderly</td>
</tr>
<tr>
<td>Thromboangiitis obliterans (Buerger disease)</td>
<td>Acute, full-thickness inflammation of vessels; may extend to nerves; occlusive lesions in extremities</td>
<td>Small and medium arteries and veins</td>
<td>Cold, pale limb; pain; Raynaud phenomenon; gangrene</td>
<td>Typical patient is a young Jewish man who smokes heavily</td>
</tr>
<tr>
<td>Wegener granulomatosis</td>
<td>Antineutrophil antibodies (cytoplasmic antineutrophil cytoplasmic antibody [c-ANCA]) causes necrotizing, granulomatous lesions in kidney, lung, and upper respiratory tract</td>
<td>Small arteries, small veins of kidneys and respiratory tract</td>
<td>Cough, ulcers of sinuses and nasal septum, red blood cell casts in urine, classic triad: (a) necrotizing vasculitis (b) necrotizing granulomas of respiratory tract (c) necrotizing glomerulitis</td>
<td>More common in males</td>
</tr>
</tbody>
</table>
CARDBIC NEOPLASMS

I. Metastatic tumors to the heart are more common than primary tumors

II. Primary tumors
A. Myxomas
   1. 90% found in atria
   2. Left atrium > right atrium
   3. Cause ball-valve obstruction, embolism, and fever
B. Rhabdomyoma
   1. Most common primary cardiac tumor found in children
   2. Often seen with tuberous sclerosis
   3. Composed of “spider cells” and glycogen vacuoles

DISEASES OF THE PERICARDIUM

I. Cardiac tamponade
   A. This is an accumulation of fluid in the pericardial sac, which causes cardiac filling defects because of compression of the heart.
      1. Blood is usually indicative of a traumatic perforation of the heart or aorta or rupture as a consequence of an MI.
      2. Serous transudate may accumulate as a result of edema or CHF.
   B. The most common causes are neoplasms, idiopathic pericarditis, and uremia.
   C. Principal features of cardiac tamponade include:
      1. Intracardiac pressure is elevated.
      2. Ventricular filling is limited.
      3. Cardiac output is reduced.
      4. Decreased or absent heart sounds on auscultation
   D. Pulsus paradoxus is a greater than normal (10 mm Hg) decline in systolic arterial pressure on inspiration.
   E. Treatment involves pericardiocentesis (removal of fluid from the pericardial cavity).

II. Pericarditis
   A. Pericarditis is defined as an inflammation of the pericardium (fibroserous membrane) covering the heart.
   B. Causes
      1. Usually idiopathic
      2. Coxsackievirus A or B (serous pericarditis)
      3. Tuberculosis (hemorrhagic pericarditis)
      4. Uremia (serofibrinous pericarditis)
      5. SLE (serous pericarditis)
      6. Scleroderma (serous pericarditis)
      7. Post-MI (Dressler syndrome; fibrinous pericarditis)
   C. Physical examination
      1. Jugular venous distention (JVD)
      2. Increase of JVP with inspiration (Kussmaul sign)
      3. Pericardial friction rub
      4. Distant heart sounds
   D. Characteristics
      1. Pain exacerbated by inspiration
      2. Pain relieved by sitting
      3. Cardiomegaly
      4. Hypotension
      5. Diffuse ST elevation on ECG
   E. Persistent, acute pericarditis leads to chronic, constrictive pericarditis.
      1. Both acute and chronic pericarditis mimic right-sided heart failure.
      2. Both acute and chronic pericarditis lead to obliteration of pericardial cavity.
      3. Fibrous tissue proliferation and calcification result.

QUICK HIT

The needle for a pericardiocentesis passes through the skin, superficial fascia, pectoralis major muscle, external intercostal membrane, internal intercostal membrane, fibrous pericardium, and parietal layer of serous pericardium.

An MI also produces ST elevation. However, in an MI, ST elevation is limited to certain leads (corresponding to anatomical regions) and associated with possible QRS changes.

Temporal arteritis is the most common vasculitis in the United States.
SHOCK

I. Shock is defined as a metabolic state in which oxygen delivery is inadequate to meet the oxygen demand.

II. Signs and symptoms
   A. Tachycardia
   B. Hypotension
   C. Oliguria
   D. Mental status changes
   E. Weak pulses
   F. Cool extremities

III. Types of shock (Table 3-13)

<table>
<thead>
<tr>
<th>Type of Shock</th>
<th>SVR</th>
<th>HR</th>
<th>PCWP</th>
<th>PCWP After Fluid Challenge</th>
<th>Mechanism</th>
<th>Clinical Causes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiogenic</td>
<td>High</td>
<td>Varies</td>
<td>High</td>
<td>Very high</td>
<td>Pump failure</td>
<td>Arrhythmias, heart failure, myocardial infarction</td>
</tr>
<tr>
<td>Hypovolemic</td>
<td>High</td>
<td>High</td>
<td>Low</td>
<td>Unchanged or high</td>
<td>Volume loss</td>
<td>Blood/ fluid/ plasma loss, burns, severe vomiting or diarrhea</td>
</tr>
<tr>
<td>Obstructive (tension pneumothorax, massive hemothorax)</td>
<td>High</td>
<td>High</td>
<td>Low or normal</td>
<td>Unchanged or increased</td>
<td>Extracardiac obstruction of blood flow</td>
<td>Tension pneumothorax, massive hemothorax</td>
</tr>
<tr>
<td>Obstructive (cardiac tamponade)</td>
<td>High</td>
<td>High</td>
<td>High</td>
<td>High or very high</td>
<td>Extracardiac obstruction of blood flow</td>
<td>Cardiac tamponade</td>
</tr>
<tr>
<td>Septic</td>
<td>Low</td>
<td>Low</td>
<td>Low or normal</td>
<td>High</td>
<td>Increased venous capacitance</td>
<td>Gram-negative endotoxemia, direct toxic injury</td>
</tr>
<tr>
<td>Neurogenic</td>
<td>Low</td>
<td>Low</td>
<td>Low or normal</td>
<td>High</td>
<td>Massive peripheral vasodilation</td>
<td>Severe cerebral, brain stem, or spinal cord injury</td>
</tr>
<tr>
<td>Anaphylactic</td>
<td>Low</td>
<td>High</td>
<td>Low</td>
<td>High</td>
<td>Increased venous capacitance due to histamine release</td>
<td>Type I hypersensitivity reaction to allergen</td>
</tr>
</tbody>
</table>

HR, heart rate; PCWP, pulmonary capillary wedge pressure; SVR, systemic vascular resistance.

QUICK HIT

Autoregulation of blood flow in the heart is altered to meet the demands of tissue metabolism via nitric oxide and adenosine. Autoregulation also occurs in the kidney and brain.

QUICK HIT

Septic shock is associated with vasodilation, hypotension, and warm extremities.

The Cardiovascular System

Septic shock is associated with vasodilation, hypotension, and warm extremities.
IV. Clinical manifestations of shock
   A. Acute tubular necrosis
   B. Necrosis in the brain
   C. Fatty change in the heart and liver
   D. Patchy hemorrhages in the colon
   E. Pulmonary edema due to acute lung injury

DRUGS THAT CAUSE ADVERSE EFFECTS TO THE CARDIOVASCULAR SYSTEM

I. Thrombotic complications: oral contraceptives (estrogen and progestins)

II. Cardiac toxicity: doxorubicin (antineoplastic), daunorubicin (antineoplastic),
    anthracyclines, tricyclic antidepressants, and lithium

III. Torsades de pointes: class IA (quinidine), class III (sotalol) antiarrhythmics, and
    tricyclic antidepressants
**DEVELOPMENT**

I. The lung bud forms from the foregut during week 4 of embryologic development.

II. The lining of the lower respiratory tract is derived from endoderm, whereas the connective tissue cartilage and muscle are derived from mesoderm.

III. Normal development causes the lung bud to completely separate from the esophagus at the level of the larynx.

IV. Incomplete separation causes a tracheoesophageal (TE) fistula (Figure 4-1).

A. In the most common form of TE fistula, the esophagus ends in a blind pouch (esophageal atresia) and air enters the stomach (gastric bubble on radiograph).

B. Signs and symptoms of esophageal atresia with a TE fistula
   1. Feeding difficulties within the first few days of life
   2. Possible aspiration pneumonia with respiratory distress
   3. Inability to pass nasogastric tube
   4. Copious secretions

![Figure 4-1: Tracheoesophageal fistula](image)
V. Diaphragm muscle
   A. This is the primary muscle used for breathing.
   B. The diaphragm muscle separates the pleural and peritoneal cavities.
   C. It is formed from fusion of the following structures:
      1. Septum transversum
      2. Paired pleuroperitoneal membranes
      3. Dorsal mesentery of the esophagus
      4. Body wall
   D. It is innervated by the phrenic nerves (C3, C4, and C5).
   E. Improper formation of the pleuroperitoneal membrane or its failure to fuse with
      the other three parts of the diaphragm can lead to a congenital diaphragmatic hernia (CDH), a condition
      with serious complications.
      1. Abdominal contents are forced into the pleural cavity.
      2. Lung hypoplasia results from compression by abdominal viscera.
      3. Hernias appear most often on the left side (posterolateral).
      4. Diaphragmatic hernia is associated with polyhydramnios.
      5. Diaphragmatic hernia presents at birth as a flattened abdomen, cyanosis, and
         inability to breathe.

PHYSICS AND FUNCTION OF THE LUNG

I. Lung volumes
   A. Capacities and volumes in the normal lung (Figure 4-2)
   B. Volumes and pressure during the breathing cycle (Figure 4-3)
   C. Spirometry tracing—normal versus diseased (Figure 4-4)
   D. Pulmonary function tests—obstructive versus restrictive (Figure 4-5)

II. Compliance
   A. Defined as $\frac{\Delta V}{\Delta P}$, where $V$ is volume and $P$ is pressure, compliance describes the
      ability of the chest wall and lung to expand when stretched.
      1. At functional residual capacity (FRC), the lungs have a tendency to collapse.
      2. This force is exactly balanced by the chest wall, which has a tendency to
         expand.
      3. Because these forces are in balance at FRC, the airway pressure is 0 mm Hg.
      Lung volumes above FRC create a positive airway pressure, whereas volumes
      below FRC create a negative airway pressure.
4. Low compliance implies a stiff chest wall or lung as seen in:
   a. Pulmonary fibrosis due to asbestosis, sarcoidosis, and adult respiratory
distress syndrome (ARDS)
   b. Pulmonary edema
   c. Paralysis of the respiratory muscles
5. High compliance implies a flaccid lung as a result of:
   a. Decreased elastic recoil as seen in emphysema and old age
   b. Bronchospasm as in asthma (Figure 4-4)
B. Surfactant plays an important role in lung compliance.
   1. Alveoli have a tendency to collapse.
   2. An alveolus with a small radius has more collapsing pressure than an alveolus
      with a large radius, according to Laplace law:
      \[ P \propto T/r \]
      where \( P \) is pressure required to prevent alveolar collapse, \( T \) is surface tension,
      and \( r \) is alveolar radius.
   3. Surfactant reduces the pressure and prevents collapse by reducing the intermo-
lolecular forces between water molecules lining the alveoli.
   4. Surfactant increases compliance and allows the alveoli to expand
      more easily.
   5. Neonatal respiratory distress syndrome (NRDS) occurs in premature infants
      (<37 weeks' gestation) because type II (surfactant-producing) pneumocytes
      are not yet fully developed and fail to produce sufficient surfactant.
   6. Atelectasis (collapsed alveoli) can result from NRDS.

III. Airway resistance
A. Airway resistance \((R)\) is inversely proportional to the fourth power of the radius
   \((r)\) (formula: \( R \propto 1/r^4 \)); thus, any mechanism that decreases the radius of the
   bronchi will greatly affect the airway resistance.
B. The **airway radius** is under the control of the parasympathetic and sympathetic nervous systems.

1. **Parasympathetic nervous system**
   a. Causes constriction of the airways
   b. Mediated by direct stimulation, airway irritation, and slow-reacting substance of anaphylaxis (SRS-A)
   c. Stimulates mucus secretion

2. **Sympathetic nervous system**
   a. Causes dilation of airways
   b. Used as treatment for allergy and asthma (β2-agonists)
   c. Functions in fight-or-flight autonomic reflexes; dilates airways to help provide oxygen in times of stress

---

**QUICK HIT:**

SRS-A is a combination of the leukotrienes C4, D4, and E4 (LTC4, LTD4, and LTE4). In the treatment of asthma, zileuton blocks production of leukotrienes by inhibiting the lipooxygenase enzyme, whereas zafirlukast blocks leukotriene receptors.

Leukotriene A4 (LTA4) is a precursor to leukotriene B4 (LTB4), LTC4, and LTD4.

LTE4, LTB4, is responsible for chemotaxis of neutrophils and adhesion of white blood cells.
3. Airway radius is also affected by the lung parenchyma, which is bound to the airway and exerts radial traction on it.

a. In restrictive disorders such as interstitial fibrosis, radial traction of the airway increases → increasing airway diameter → decreasing airway resistance → increasing expiratory airflow. Despite the increased expiratory airflow, the reduced lung compliance will decrease both forced vital capacity (FVC) and forced expiratory volume at 1 second (FEV\textsubscript{1}). Therefore, the FEV\textsubscript{1}/FVC ratio is normal or increased.

b. In obstructive disorders such as emphysema, destruction of elastic fibers → decreases radial traction → decreasing airway diameter → increasing resistance → decreasing expiratory airflow and FEV\textsubscript{1}/FVC ratios.

IV. Ventilation and perfusion

A. Ventilation/perfusion (V/Q) ratio: the ratio of the rate of alveolar ventilation to the rate of pulmonary blood flow

B. Varies over the entire lung (higher in the apices, lower in the bases in an upright patient), but is 0.8 on average

C. Dead space

1. Anatomic dead space is regions of the lung, such as the conducting airways, which are incapable of exchanging oxygen (O\textsubscript{2}) and carbon dioxide (CO\textsubscript{2}).

2. Physiologic dead space is the volume of the lungs that does not participate in the elimination of CO\textsubscript{2}.

   \[ V_D = V_T \times [(P_{ACO_2} - P_{ECO_2})/P_{ACO_2}] \]
The Respiratory System

V_d, physiologic dead space (mL); V_T, tidal volume (mL); PaCO_2, partial pressure of carbon dioxide, arterial blood (mm Hg); P(a)CO_2, partial pressure of carbon dioxide in expired air (mm Hg).

3. It causes a reduction in ventilation.
4. V/Q is reduced to 0 in complete airway occlusion.
5. A V/Q of 0 is considered a shunt and no gas exchange will occur (areas are perfused but not ventilated).

D. Blood flow obstruction
1. Blockage of a pulmonary artery or smaller vessel causes a reduction in perfusion.
2. A perfusion value of 0 yields an infinite V/Q ratio.
3. A V/Q of infinity is considered physiologic dead space.

E. Pulmonary embolism results in increased V/Q ratio (Table 4-1).
F. Blood flow and ventilation vary over the regions of the lung (Figure 4-6) due primarily to gravity.

<table>
<thead>
<tr>
<th>TABLE 4-1 Causes of Hypoxemia</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cause</strong></td>
</tr>
<tr>
<td>Right-to-left shunt</td>
</tr>
<tr>
<td>Ventilation/perfusion mismatch</td>
</tr>
<tr>
<td>Decreased diffusion capacity</td>
</tr>
<tr>
<td>Decreased P_0_2 in inspired air</td>
</tr>
<tr>
<td>Hypoventilation of central origin</td>
</tr>
<tr>
<td>Hypoventilation of peripheral origin</td>
</tr>
</tbody>
</table>

A–a gradient, alveolar–arterial gradient; COPD, chronic obstructive pulmonary disease; D_LCO, diffusing capacity of lung for carbon monoxide; PE, pulmonary embolus.

In determining the cause of hypoxemia in a patient, use a three-tier approach: (1) Check whether the A–a gradient is elevated, (2) check whether O_2 administration improved the condition and if the A–a gradient was corrected, and (3) look for other lab findings or associated conditions.
Administering high fraction of inspired oxygen (F\textsubscript{IO\textsubscript{2}}) to patients with chronic hypercapnia (e.g., COPD patients) can lead to respiratory failure because hypoxia is the only stimulus for respiration.

Hyperventilation associated with states of anxiety leads to decreased arterial \(\text{PaO}_2\), which causes constriction of cerebral vasculature, decreasing blood flow to the brain and producing feelings of faintness, suffocation, blurred vision, and chest tightness.

During exercise, pulmonary vascular resistance decreases as a result of dilation of the lung arterioles by metabolic products. The V/Q ratio becomes uniform over the entire lung. Conversely, during hypoxia, lack of oxygen constrains local lung vasculature, thus increasing pulmonary vascular resistance; this is the opposite of what takes place in the systemic circulation, wherein lack of oxygen results in vasodilation.

### CONTROL OF BREATHING

I. **Medulla**
   
   A. Mediates inspiration and expiration
   B. Generates the basic breathing rhythm
   C. Receives input via the vagus and glossopharyngeal nerves
   D. Sends output via the phrenic nerve to the diaphragm and via the spinal nerve to the intercostals and abdominal wall
   E. The cerebral cortex can override the medulla and provide voluntary control of breathing if desired

II. The central nervous system (CNS) seeks to keep \(\text{PaCO}_2\) within a narrow range. On the other hand, in the case of oxygen, the nervous system responds only to very low levels of \(\text{PaO}_2\).

III. **Depth and rate of respiration control these variables.**

   A. **Central control**
      
      1. Chemoreceptors in the **medulla** sense the pH of the cerebrospinal fluid (CSF).
      2. \(\text{CO}_2\) crosses the blood–brain barrier, where it binds with \(\text{H}_2\text{O}\) to form carbonic acid (\(\text{H}_2\text{CO}_3\)). \(\text{H}_2\text{CO}_3\) dissociates to hydrogen ion (\(\text{H}^+\)) and bicarbonate (\(\text{HCO}_3^-\)), causing an increase in \(\text{H}^+\) (decreasing the pH of the CSF).
      3. Increases in \([\text{H}^+]\) (hydrogen ion concentration) directly stimulate the central chemoreceptors, which stimulate breathing.
      4. Decreases in \([\text{H}^+]\) reduce stimulation of the receptors and slow respiration.

   B. **Peripheral control**
      
      1. Chemoreceptors in the **carotid bodies** and at the aortic arch bifurcation sense changes in \(\text{PaO}_2\), \(\text{PaCO}_2\), and \([\text{H}^+]\).
      2. Decreases in \(\text{PaO}_2\) below 60 mm Hg stimulate the peripheral chemoreceptors to increase rate and depth of breathing (in the absence of lung disease, decreased \(\text{PaO}_2\) is rarely the driving force for respiration).
      3. Increases in \(\text{PaCO}_2\) potentiate peripheral chemoreceptor response to \(\text{PaO}_2\) (major direct effect of changes in \(\text{PaCO}_2\) is on the central chemoreceptors).

### PULMONARY CIRCULATION

- **Zone 1**
  - Lowest blood flow
  - Alveolar pressure > arterial pressure > venous pressure
  - Capillaries collapse due to high alveolar pressure
  - Ventilation (\(V\)) is increased less than blood flow [also called perfusion (\(Q\))]
  - \(\frac{V}{Q} \approx 1\) (Ventilation in excess of perfusion)

- **Zone 2**
  - Blood flow is higher than Zone 1 but lower than Zone 3
  - Arterial pressure > alveolar pressure > venous pressure
  - Capillaries remain open because arterial pressure is greater than alveolar pressure
  - Ventilation (\(V\)) is approximately equivalent to perfusion (\(Q\))
  - \(\frac{V}{Q} = 1\) (Ventilation in excess of perfusion)

- **Zone 3**
  - Highest blood flow
  - Arterial pressure > venous pressure > alveolar pressure
  - Capillaries remain open because arterial pressure is higher than both alveolar and venous pressure
  - Ventilation (\(V\)) is increased less than perfusion (\(Q\))
  - \(\frac{V}{Q} \approx 1\) (Perfusion in excess of ventilation)
4. Increases in arterial \([H^+]\) directly stimulate the chemoreceptors, independent of the \(P_{aCO_2}\) (causes increased respiration in metabolic acidosis).
5. Stimulation of irritant receptors in large airways and stretch receptors in small airways inhibits inspiration.

C. Abnormal breathing
1. Cheyne–Stokes breathing
   a. Tidal volumes variably increase and decrease and are separated by a period of apnea.
   b. This breathing abnormality is a result of pontine dysfunction and is associated with drug overdose, hypoxia, CNS depression, congestive heart failure (CHF), and increased intracerebral pressure.
2. Kussmaul breathing
   a. Deep, labored breathing pattern associated with severe metabolic acidosis (e.g., diabetic ketoacidosis)
   b. Can be either fast or slow
3. Sleep apnea
   a. Obstructive sleep apnea
      i. Risk factors: middle age, male sex, obesity, smoking, hypertension, pharyngeal malformations, use of alcohol and other drugs
      ii. Characteristics
         a) Ventilatory effort exists.
         b) Airway is obstructed.
         c) Apnea is terminated by self-arousal.
         d) Apnea usually occurs in the nasopharynx or oropharynx when muscles relax during rapid eye movement (REM) sleep.
   b. Central sleep apnea
      i. Ventilatory effort does not exist.
      ii. Airway is not obstructed.
      iii. Patient does not arouse self.
      iv. Central sleep apnea, like obstructive sleep apnea, occurs in the REM stage of sleep.
      v. It is \(CO_2\) threshold–dependent; that is, there is decreased chemoreceptor sensitivity to \(O_2\) and \(CO_2\) concentrations.
   c. Therapy includes weight loss (for obstructive sleep apnea) and continuous positive airway pressure (CPAP); multiple drugs have been used in treatment, but none is as effective as CPAP.

IV. Gas exchange
A. Diffusion of gas depends on the partial pressure difference between the gas in the alveolus and the gas in the blood (i.e., the difference in pressure across the blood–air barrier).
B. Partial pressure
1. The alveolar partial pressure of oxygen \(P_{aO_2}\) can be calculated as follows:
   \[
P_{aO_2} = (760 - 47 \text{ mm Hg}) F_{O_2} - (P_{aCO_2}/0.8)
   \]
   where 760 mm Hg = total atmospheric pressure (at sea level);
   47 mm Hg = partial pressure of completely humidified air as found in the alveoli;
   \(F_{O_2}\) = percentage of air that is oxygen (normally 0.21);
   \(P_{aCO_2}\) = partial pressure of \(CO_2\) in the alveoli (normally 40);
   and 0.8 = the ratio of volume of \(CO_2\) produced to the volume of \(O_2\) consumed (respiratory quotient).
2. For \(O_2\), higher pressures will force more oxygen into the blood and allow it to equilibrate more readily.
3. For \(CO_2\), higher partial pressures in the blood (or lower in the alveoli) will force more \(CO_2\) out of the blood and into the lungs, where it can be expired.
4. The amount of \(O_2\) delivered to the tissues is also determined by hemoglobin concentration and red blood cell number (hematocrit) (see Chapter 10).
C. Disease affects diffusion capacity of the lung.
   1. Fibrosis causes a thickening of the interstitium, which hinders diffusion across the blood–air barrier.
   2. Emphysema destroys the alveolar walls and decreases the area available for gas exchange.

**LUNG DEFENSES**

I. Anatomic barriers
   A. Impaction
      1. Large particles (greater than 10 μm in diameter) fail to turn the corners of the respiratory tract.
      2. Common site: nasopharynx
   B. Sedimentation
      1. Medium particles (between 2 and 10 μm in diameter) settle as a result of weight.
      2. Common site: small airways
   C. Diffusion
      1. Small particles (between 0.5 and 2 μm in diameter) are engulfed by alveolar macrophages (dust cells).
      2. Common site: alveoli
   D. Suspension: particles less than 0.5 μm in diameter remain suspended in air.

II. Nonspecific
   A. Mucociliary escalator
      1. Particles are trapped in the gel layer of the upper airway.
      2. Ciliary motion removes particles.
   B. Cough
      1. Cough is a bronchoconstriction that occurs to prevent penetration of particles.
      2. It is also defined as deep inspiration followed by forced expiration.
      3. The cough reflex can be suppressed by antitussive agents such as opioids (see Chapter 9).
      4. Specific mechanisms include secretory immunoglobulin A (IgA) and complement.

**ADULT RESPIRATORY DISTRESS SYNDROME AND NEONATAL RESPIRATORY DISTRESS SYNDROME**

This group of diseases often leads to respiratory failure and death (Table 4-2).

| TABLE 4-2 Adult Respiratory Distress Syndrome (ARDS) and Neonatal Respiratory Distress Syndrome (NRDS) |
|-------------------------------------------------|-------------------------------------------------|
| **ARDS (Diffuse Alveolar Damage)**              | **NRDS (Hyaline Membrane Disease)**              |
| **Age group**                                   | **Premature infants**                            |
| **Causes**                                      | **Lack of surfactant production**                |
| Shock, infection, trauma, or aspiration         |                                                 |
| resulting in neutrophil recruitment and free   |                                                 |
| radical production (oxygen toxicity)            |                                                 |
| **Pathophysiology**                             | **Increased work to expand lungs; infant can**  |
| Impaired gas exchange caused by pulmonary      | **clear lungs of fluids but cannot fill**       |
| hemorrhage, pulmonary edema, or atelectasis     | **lungs with air; atelectasis**                  |
| **Features**                                    | **Respiratory insufficiency; cyanosis; hypoxemia;**|
| Respiratory insufficiency; cyanosis; hypoxemia; | **heavy, wet lungs; diffuse pulmonary infiltrates**|
| heavy, wet lungs; diffuse pulmonary infiltrates | **on radiograph; hyaline membranes in alveoli**  |
| on radiograph; hyaline membranes in alveoli     |                                                 |
| Pneumothorax may result—may be rapid and fatal  |                                                 |

**QUICK HIT**

Hyaline membrane disease is associated with diabetes of the mother.

Kartagener syndrome is an autosomal recessive disorder causing a defect in the dynein arms of cilia, resulting in infertility, situs inversus, chronic sinusitis, and bronchiectasis.

Hyaline membranes are characteristic of both ARDS and NRDS but are caused by distinctly different pathologic mechanisms.

Neutrophils are implicated in the pathogenesis of ARDS. Essentially, injury promotes neutrophil recruitment. Neutrophils release cytokines, ultimately leading to production of oxygen radicals, prostaglandins, and proteases and resulting in damage to the alveolar epithelium.
THE RESPIRATORY SYSTEM

PNEUMOTHORAX

I. Simple pneumothorax
   A. May be caused by spontaneous rupture of a bleb (congenital or secondary to paraseptal emphysema) or penetrating trauma causing a loss of negative intrathoracic pressure
   B. Is most commonly seen in tall, slender men 20 to 40 years of age
   C. Presents as sudden chest pain, shortness of breath (SOB), cough, hyperresonance, and decreased breath sounds over affected lung; chest radiograph shows radiolucency and in the case of a tension pneumothorax, the trachea deviates to the side of the pneumothorax
   D. Has a 50% recurrence rate
   E. Treatment includes the insertion of a chest tube with suction to create a vacuum for larger defects as well as monitoring for small defects such as air leaks.

II. Tension pneumothorax
   A. A flap of tissue allows air to enter pleural space but not to escape, causing an increase in pleural cavity pressure.
   B. Pressure builds, the mediastinum is displaced, the trachea deviates away from the lesion, jugular venous distention (JVD) occurs, and breath sounds are uneven.
   C. Cardiovascular and respiratory compromise may be rapidly fatal.

III. Open sucking chest wound
   A. Penetrating trauma to the chest wall and pleura can cause this condition.
   B. If the diameter of the lesion approaches the diameter of the trachea, air will preferentially enter through the defect.

PULMONARY VASCULAR DISEASES

A variety of diseases primarily affect the vasculature of the lungs (Table 4-3).

<table>
<thead>
<tr>
<th>Disease</th>
<th>Etiology</th>
<th>Features</th>
<th>Complications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pulmonary</td>
<td>Primary—may be associated with proliferation of vascular smooth muscle</td>
<td>Loud S2</td>
<td>Leads to cor pulmonale</td>
</tr>
<tr>
<td>hypertension</td>
<td>Secondary—owing to COPD or increased pulmonary blood flow (as seen with a left-to-right shunt)</td>
<td>Left parasternal heave due to right ventricular hypertrophy</td>
<td></td>
</tr>
<tr>
<td>Pulmonary</td>
<td>Commonly from proximal deep vein thrombosis (usually lower limb such as femoral veins) as a result of Virchow triad: blood stasis, endothelial damage (fat, infection, trauma), and hypercoagulable states</td>
<td>Respiratory alkalosis; increased A–a gradient; hemorrhagic, red, wedge-shaped infarct</td>
<td>Can lead to cardiovascular collapse and sudden death</td>
</tr>
<tr>
<td>embolism</td>
<td></td>
<td>Acute-onset dyspnea, chest pain, tachycardia, hypotension</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>V/Q ratio approaches infinity</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Saddle embolus—an embolus lodged at the pulmonary artery bifurcation, often fatal</td>
<td></td>
</tr>
</tbody>
</table>

(continued)
Chronic obstructive pulmonary disease (COPD) is characterized by airflow obstruction. This is in contrast to restrictive pulmonary diseases, which demonstrate defective lung expansion. Obstructive disorders have increased TLC, decreased FEV₁, and decreased FEV₁/FVC. Restrictive disorders show reduced lung volumes and normal or increased FEV₁/FVC. Normal FEV₁/FVC ratio is approximately 80%.

**Quick Hit**

Reid index: Ratio (normally < 0.4) between the thickness of the submucosal mucus-secreting glands and the thickness between the epithelium and cartilage overlying the bronchus.

**Quick Hit**

“Blue bloater”: Blue refers to cyanosis; bloater refers to the peripheral edema in these patients from pulmonary hypertension and right ventricular overload.

**Quick Hit**

Status asthmatics is a prolonged asthmatic attack that does not respond to therapy and can be fatal.

**Quick Hit**

There are many types of asthma, including extrinsic (children), intrinsic (adults), exercise induced, and cold air induced.

**Quick Hit**

Pulmonary edema caused by heart failure is characterized histologically by hemosiderin-laden macrophages (“heart failure cells”) and congested alveolar capillaries.

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**Quick Hit**

Chronic obstructive pulmonary disease (COPD) is characterized by airflow obstruction. This is in contrast to restrictive pulmonary diseases, which demonstrate defective lung expansion. Obstructive disorders have increased TLC, decreased FEV₁, and decreased FEV₁/FVC. Restrictive disorders show reduced lung volumes and normal or increased FEV₁/FVC. Normal FEV₁/FVC ratio is approximately 80%.

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### II. Therapeutic agents used in asthma and COPD (Table 4-5)

#### A. Inhaled agents

1. **β₂-Agonists**
   - **β₂-Agonists** are useful for treatment of an acute asthma attack characterized by SOB, chest tightness, wheezing, and cough as a result of bronchoconstriction.
   - The β₂-agonists stimulate adenylyl cyclase, resulting in the conversion of adenosine triphosphate (ATP) to cyclic adenosine monophosphate (cAMP); the increased levels of cAMP result in myriad effects, depending on the cell type in question.
   - **β₂-Agonists** are potent dilators of the bronchi. They act by relaxing smooth muscle in the airways.
   - Systemic activation of β₂-specific receptors (which is minimal with inhaled β₂-agonists) may result in vasodilation, a slight decrease in peripheral resistance, bronchodilation, increased glycogenolysis in muscle and in the liver, increased release of glucagons, and relaxation of uterine smooth muscle.
   - **Side effects** include tachycardia, hyperglycemia, hypokalemia, and hypomagnesemia.
   - **β₂-Agonists** have no effect on the inflammation associated with asthma.
   - **Selected β₂-agonists**:
     - Albuterol or terbutaline provides immediate relief of acute attacks without β₁-adrenoceptor stimulation.
     - Salmeterol has a longer duration of action and a slower onset of action.

2. **Corticosteroids**
   - In cases of moderate asthma, corticosteroids (inhaled or systemic) can be used to decrease the associated inflammation.
   - **inhaled corticosteroids** such as beclomethasone, triamcinolone, and flunisolide decrease the effect that inflammatory cells (mast cells, eosinophils, macrophages) have on the airway.

#### TABLE 4-4 Types of Chronic Obstructive Pulmonary Disease (Continued)

<table>
<thead>
<tr>
<th>Disease</th>
<th>Pathophysiology</th>
<th>Clinical Features and Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Emphysema</td>
<td>Dilated alveoli; damaged alveolar walls; damaged alveolar septae leads to enlarged alveolar airspaces; destruction of structural support to lymphatic vessels leads to heavy pigment deposition; decreased elastic recoil; centrilocular (associated with smoking), panacinar (α₁-antitrypsin deficiency), paraseptal (associated with scarred tissue, may lead to spontaneous pneumothorax in young patients), and irregular forms</td>
<td>&quot;Pink puffer&quot;**: paraseptal type may lead to pneumothorax; anteroposterior diameter increased (&quot;barrel chested&quot;); hypertrophy of accessory respiratory muscles; episodes of nonproductive cough; smoking cessation</td>
</tr>
<tr>
<td>Bronchiectasis</td>
<td>Chronic infection leads to irreversible bronchial dilation; destruction of bronchial wall; commonly caused by bronchial obstruction (e.g., tumor)</td>
<td>Copious amounts of purulent sputum; hemoptysis; possible lung abscess; associated with CF and Kartagener syndrome</td>
</tr>
</tbody>
</table>

CF, cystic fibrosis; CO₂, carbon dioxide; COPD, chronic obstructive pulmonary disease.
## TABLE 4-5 Therapeutic Agents for Asthma and Chronic Obstructive Pulmonary Disease

<table>
<thead>
<tr>
<th>Therapeutic Agent (common name, if relevant) [trade name, where appropriate]</th>
<th>Class–Pharmacology and Pharmacokinetics</th>
<th>Indications</th>
<th>Side Effects or Adverse Effects</th>
<th>Contraindications or Precautions to Consider; Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Epinephrine [Primatene Mist]</td>
<td>Adrenergic agonist (nonselective)—relaxes bronchial smooth muscle through β₂-receptor activity</td>
<td>Asthma</td>
<td>Tachycardia (β₁-receptor activity)</td>
<td></td>
</tr>
<tr>
<td>Isoproterenol [Isuprel]</td>
<td>β₁-agonist (nonselective)—relaxes bronchial smooth muscle through β₁-receptor activity</td>
<td>Asthma</td>
<td>Tachycardia (β₁-receptor activity)</td>
<td></td>
</tr>
<tr>
<td><strong>Albuterol</strong> [Proventil, Ventolin], <strong>levalbuterol</strong> [Xopenex]</td>
<td>β₂-agonist—leads to relaxation of smooth muscle</td>
<td>Asthma, COPD, bronchitis</td>
<td>Tremor, tachycardia, arrhythmia, headache, nausea, vomiting</td>
<td></td>
</tr>
<tr>
<td>Albuterol [Proventil, Ventolin], levalbuterol [Xopenex]</td>
<td>Long-acting β₂-agonist—leads to relaxation of smooth muscle</td>
<td>Asthma prophylaxis</td>
<td>Hand tremor, headache, nervousness, dizziness, cough, stuffy nose, runny nose, muscle pain/cramps, sore throat</td>
<td>Not for acute asthmatic attacks</td>
</tr>
<tr>
<td>Theophylline [Aerolate, Theo-24, Theo-Dur, Theolair, Uniphyl]</td>
<td>Methylxanthines—unknown mechanism; may inhibit phosphodiesterase → decreases cAMP hydrolysis → promotes bronchodilation; stimulates CNS, cardiac muscle; relaxes smooth muscle; promotes diuresis; increases cerebral vascular resistance</td>
<td>Asthma</td>
<td>Cardiotoxicity, neurotoxicity</td>
<td>Metabolized by cytochrome P450. Narrow therapeutic window</td>
</tr>
<tr>
<td>Ipratropium [Atrovent]</td>
<td>Muscarinic antagonist—competitively blocks muscarinic receptors → prevents bronchoconstriction</td>
<td>Asthma, COPD</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Beclomethasone, dexamethasone, prednisone</strong></td>
<td>Corticosteroids—inhibits leukotriene synthesis → reduces inflammation and leads to bronchodilation</td>
<td>Asthma, COPD</td>
<td>Osteoporosis, Cushingoid reaction, psychosis, glucose intolerance, infection, hypertension, cataracts, acne</td>
<td></td>
</tr>
<tr>
<td>Zilouton</td>
<td>Antileukotriene—5-lipoxygenase inhibitor → inhibits conversion of arachidonic acid to leukotriene → prevents bronchoconstricttion and inflammatory cell infiltration</td>
<td>Asthma</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Zafirlukast [Accolate], montelukast [Singulair]</td>
<td>Antileukotriene—blocks leukotriene receptors → prevents bronchoconstriction and inflammatory cell infiltration</td>
<td>Asthma (especially Aspirin-induced asthma)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cromolyn</td>
<td>Prevents release of mediators from mast cells → prevents bronchoconstriction and inflammation</td>
<td>Asthma prophylaxis</td>
<td></td>
<td>Not for acute asthmatic attacks</td>
</tr>
<tr>
<td>Nedocromil [Tilade]</td>
<td>Stabilizes membranes of mast cells and prevents mediator release</td>
<td>Asthma</td>
<td>Unpleasant taste</td>
<td>Not for acute asthmatic attacks</td>
</tr>
</tbody>
</table>

cAMP, cyclic adenosine monophosphate; CNS, central nervous system; COPD, chronic obstructive pulmonary disease.
A 59-year-old woman presents with a chief complaint of shortness of breath (SOB). Patient states she has been experiencing worsening SOB with minimal physical exertion. She has been experiencing bouts of productive cough every morning for the past 2 years. She has smoked two packs of cigarettes a day for the past 35 years. Patient denies any fevers or bloody sputum. Physical exam reveals an increased anteroposterior diameter of the chest wall and wheezes and rhonchi on inspiration. Temperature = 98.3°F; blood pressure = 142/92 mm Hg; heart rate = 93 bpm; respiration rate = 23 breaths/min.

Differentials: COPD, asthma, CHF. Given the patient’s presentation and long-standing history of smoking, this patient most likely has COPD.

Laboratory studies: Proper follow-up management would include an arterial blood gas to provide information regarding the patient’s O2 status because hypoxemia and hypercapnia may be present. Spirometry is the next best step in the evaluation process. Flow volume loops will assist in identifying restrictive from obstructive pulmonary disease. A forced expiratory volume at 1 second/forced vital capacity ratio in obstructive pulmonary diseases will be below the normal ratio of 0.8.

Management: Initial step in management is smoking cessation. β-Agonists and anticholinergic agents provide bronchodilation via nebulizers. Administration of oxygen is necessary to correct hypoxemia. Corticosteroids can be used in acute exacerbations along with antibiotics if there is suspicion of an underlying infection.

In cases of severe asthma, intravenous methylprednisolone or oral prednisone may be necessary for a short period.

d. The side effects of inhaled steroids are minimal when compared with systemic steroid use. However, adverse reactions can occur and include oral candidiasis, and, with long-term use, osteoporosis.

B. Other asthma medications
1. Cromolyn, a prophylactic anti-inflammatory agent
2. Ipratropium, a derivative of atropine that blocks the vagal aspect of airway smooth muscle contraction and mucus secretion
3. Theophylline, a bronchodilator, which may result in seizures and arrhythmias
4. Newer agents
   a. Zileuton, a 5-lipoxygenase inhibitor, blocks the conversion of arachidonic acid into leukotrienes, which are responsible for chemotaxis, increased secretion, and bronchospasm.
   b. Zafirlukast prevents the chemotactic and bronchospastic effects of leukotrienes C4, D4, and E4 by blocking their receptors.

Interstitial lung disease (ILD) is a noninfectious, nonmalignant condition characterized by inflammation and pathologic changes of the alveolar wall. Differentiation and diagnosis often require histologic evaluation of the lung. It is characterized as having decreased lung volumes and a normal to increased FEV1/FVC ratio.

<table>
<thead>
<tr>
<th>Disease</th>
<th>Pathophysiology</th>
<th>Population Most at Risk</th>
<th>Clinical Features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eosinophilic granuloma</td>
<td>Presence of Langerhans-like cells and Birbeck granules; subset of histiocytosis X</td>
<td>Former smokers</td>
<td>Lesions in lung or ribs, pneumothorax</td>
</tr>
<tr>
<td>Goodpasture syndrome</td>
<td>Pulmonary hemorrhage, anemia, glomerulonephritis, antibasement membrane antibodies</td>
<td>Men, middle-aged people</td>
<td>Hemoptysis, hematuria</td>
</tr>
</tbody>
</table>

(continued)
Environmental Lung Diseases (Pneumoconiosis) (Table 4-7)

This group of diseases is often caused by workplace exposure to various organic and chemical irritants. A careful history and pulmonary function testing are often important for diagnosis.

Approximately 70% to 80% of newly diagnosed pulmonary tuberculosis (TB) cases in adults are actually a result of reactivation of a clinically unsuspected infection acquired years to decades previously.

TABLE 4-7 Environmental Lung Diseases (Pneumoconiosis)

<table>
<thead>
<tr>
<th>Disease</th>
<th>Pathophysiology</th>
<th>Clinical Features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anthracosis</td>
<td>Carbon dust ingested by alveolar macrophages, visible black deposits seen on gross lung tissue samples</td>
<td>Usually asymptomatic</td>
</tr>
<tr>
<td>Asbestosis</td>
<td>Asbestos fibers ingested by alveolar macrophages, fibroblast proliferation, interstitial fibrosis (lower lobes), asbestos bodies and ferruginous bodies (hemosiderin laden asbestos fibers), pleural plaques and effusions</td>
<td>Increased risk of bronchogenic carcinoma and malignant mesothelioma, synergistic effect of asbestos and tobacco in causing bronchogenic carcinoma</td>
</tr>
<tr>
<td>Coal worker’s pneumoconiosis</td>
<td>Carbon dust ingested by alveolar macrophages forms bronchiolar macules; may progress to fibrosis</td>
<td>Plaques are asymptomatic; often benign, may progress to fibrosis; may be fatal owing to pulmonary hypertension and cor pulmonale, no evidence of increased risk for TB or lung cancer</td>
</tr>
<tr>
<td>Silicosis</td>
<td>Silica dust ingested by alveolar macrophages causing release of harmful enzymes; silicotic nodules (of collagen that may calcify) and thick pleural scars</td>
<td>Nodules may obstruct air or blood flow; concurrent TB common (silicotuberculosis)</td>
</tr>
<tr>
<td>Berylliosis</td>
<td>Induction of cell-mediated immunity leads to non-caseating granulomas, several organ systems affected; histologically identical to sarcoidosis</td>
<td>Increases lung cancer</td>
</tr>
</tbody>
</table>

TB, tuberculosis.
**RESPIRATORY INFECTIONS**

I. **Pneumonia**

A. **Pathogenesis**
1. Most commonly, pneumonia is caused by microaspiration from the oropharynx or inhalation of infectious droplets or particles.
2. Alcoholism, nasogastric tubes, and obtunded states increase risk of contracting pneumonia.
3. Normal oral flora consists of gram-positive cocci.
4. Hospitalized patients may be colonized by gram-negative rods (nosocomial infections).
5. Other portals of entry include respiratory droplets, hematogenous spread, contiguous spread, and traumatic inoculation.

B. **Clinical manifestations**
1. **Typical pneumonia** presents with acute fever, purulent sputum, pleuritic pain, and lobar “whited out” infiltrate on chest radiograph (e.g., *Streptococcus pneumoniae*).
2. **Atypical pneumonia** is characterized by slow onset of nonproductive cough, headache, gastrointestinal (GI) symptoms, and diffuse patchy infiltrate on chest radiograph (e.g., *Mycoplasma pneumoniae*).
3. **Nosocomial pneumonia** commonly occurs in the setting of an underlying disease, immunosuppression, or use of a ventilator (e.g., *Pseudomonas aeruginosa, Escherichia coli*).

C. **Location of pathology and typical organisms**
1. **Lobar** (intra-alveolar infiltrate): *S. pneumoniae*
2. **Bronchopneumonia** (bronchiolar infiltrate): *Staphylococcus aureus, Haemophilus influenzae, Streptococcus pneumoniae*, viral
3. **Interstitial** (diffuse infiltrate in alveolar wall): *M. pneumoniae, Legionella, Pneumocystis jiroveci*, viral

D. **Etiology**
1. Bacterial and mycoplasmal pneumonias (Table 4-8)
2. Viral pneumonia (Table 4-9)
3. Fungal pneumonia (Table 4-10)
4. Clinical diagnosis of pneumonia (Tables 4-11 and 4-12)

---

**TABLE 4-8 Bacterial and Mycoplasmal Pneumonia**

<table>
<thead>
<tr>
<th>Bacteria</th>
<th>Presentation</th>
<th>Population Most at Risk</th>
<th>Clinical Features</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Streptococcus pneumoniae</em></td>
<td>Typical</td>
<td>Adults</td>
<td>Most common cause of community-acquired pneumonia</td>
</tr>
<tr>
<td><em>Haemophilus influenzae</em></td>
<td>Typical</td>
<td>Elderly</td>
<td>Complicates viral infection, chronic respiratory disease</td>
</tr>
<tr>
<td><em>Staphylococcus aureus</em></td>
<td>Typical</td>
<td>Can cause typical community-acquired pneumonia but also infects immunocompromised and hospitalized patients</td>
<td>Abscesses, complicates viral infection, especially influenza</td>
</tr>
<tr>
<td><em>Streptococcus agalactiae</em></td>
<td>Typical</td>
<td>Neonates</td>
<td>Similar to <em>Streptococcus pneumoniae</em></td>
</tr>
<tr>
<td><em>Klobsiella pneumoniae</em></td>
<td>Typical</td>
<td>Patients with alcoholism</td>
<td>Aspiration of gastric contents</td>
</tr>
<tr>
<td><em>Mycoplasma pneumoniae</em></td>
<td>Atypical</td>
<td>Young adults</td>
<td>Most common cause of atypical pneumonia; positive cold agglutinin test</td>
</tr>
<tr>
<td><em>Legionella pneumophila</em></td>
<td>Atypical</td>
<td>Immunocompromised patients</td>
<td>Found in drinking water and air conditioners</td>
</tr>
<tr>
<td><em>Chlamydia pneumoniae</em></td>
<td>Atypical</td>
<td>Young adults</td>
<td>Upper and lower pulmonary tract infection</td>
</tr>
<tr>
<td><em>Chlamydia psittaci</em></td>
<td>Atypical</td>
<td>Pet bird owners</td>
<td>Bradycardia, splenomegaly</td>
</tr>
<tr>
<td><em>Chlamydia trachomatis</em></td>
<td>Atypical</td>
<td>Neonates</td>
<td>Also causes trachoma (chlamydial conjunctivitis leading to blindness)</td>
</tr>
</tbody>
</table>
### TABLE 4-9 Viral Pneumonia

<table>
<thead>
<tr>
<th>Virus</th>
<th>Pathophysiology</th>
<th>Clinical Features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Respiratory syncytial virus (types 1 and 2)</td>
<td>Atypical</td>
<td>Also causes bronchiolitis; more common in winter months; can cause serious respiratory distress in infants</td>
</tr>
<tr>
<td>Influenza</td>
<td>Atypical</td>
<td>Often complicated by secondary bacterial infection</td>
</tr>
</tbody>
</table>

### TABLE 4-10 Fungal Pneumonia

<table>
<thead>
<tr>
<th>Etiology</th>
<th>Pathophysiology</th>
<th>Clinical Features</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Histoplasma capsulatum</em></td>
<td>Atypical</td>
<td>Most infections are subclinical; tiny yeast forms in macrophages; found in Ohio, Mississippi, and Missouri River Valleys; yeast with a thin cell wall but no true capsule</td>
</tr>
<tr>
<td><em>Coccidioides immitis</em></td>
<td>Atypical</td>
<td>Most infections are subclinical; nonbudding spherules filled with endospores; &quot;valley fever&quot; found in southwestern deserts of United States</td>
</tr>
<tr>
<td><em>Pneumocystis jiroveci</em></td>
<td>Atypical</td>
<td>Often fatal common opportunistic infection in immunocompromised patients (such as patients with HIV)</td>
</tr>
<tr>
<td><em>Paracoccidioides brasiliensis</em></td>
<td>Atypical</td>
<td>Budding yeast resemble spokes of a &quot;captain’s wheel&quot;; found in Central and South Americas; yeast with multiple budding</td>
</tr>
<tr>
<td><em>Sporotrichosis</em></td>
<td>Atypical</td>
<td>Skin nodules that occur along lymphatics in the arms of rose gardeners</td>
</tr>
<tr>
<td><em>Aspergillus</em></td>
<td>Atypical</td>
<td>Fungal ball of hyphae (aspergilloma) in preexisting lung cavities or invasive pulmonary disease in immunocompromised patients</td>
</tr>
<tr>
<td><em>Blastomyces dermatitidis</em></td>
<td>Atypical</td>
<td>Yeast forms in body; 5–25-mm yeast with thick refractile wall and broad-based budding; found in Mississippi–Ohio River basins and around the Great Lakes</td>
</tr>
<tr>
<td><em>Candida albicans</em></td>
<td>Atypical</td>
<td>Yeast and hyphae</td>
</tr>
<tr>
<td><em>Cryptococcus neoformans</em></td>
<td>Atypical</td>
<td>Yeast with broad capsule</td>
</tr>
</tbody>
</table>

### TABLE 4-11 Clinical Diagnosis of Pneumonia

<table>
<thead>
<tr>
<th></th>
<th>Bacterial</th>
<th>Viral</th>
<th>Mycoplasma</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>Any; often younger than 2 years old</td>
<td>Any</td>
<td>Young adults (teenagers)</td>
</tr>
<tr>
<td>Fever</td>
<td>&gt;102.2°F</td>
<td>&lt;102.2°F</td>
<td>&lt;102.2°F</td>
</tr>
<tr>
<td>Onset</td>
<td>Abrupt</td>
<td>Gradual</td>
<td>Gradual fever, gradual cough</td>
</tr>
<tr>
<td>Relatives</td>
<td>Healthy</td>
<td>Sick (concurrent)</td>
<td>Sick (2–3 weeks previous)</td>
</tr>
<tr>
<td>Cough</td>
<td>Productive</td>
<td>Dry</td>
<td>Paroxysmal</td>
</tr>
<tr>
<td>Pleuritic chest pain</td>
<td>Yes (splitting)</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Physical examination</td>
<td>Tubular breath sounds; dull to percussion</td>
<td>Bilateral, diffuse rales</td>
<td>Rales in one or two segments</td>
</tr>
<tr>
<td>Radiographic findings</td>
<td>Consolidated &quot;whited out&quot; lobe</td>
<td>Diffuse, patchy, bilateral</td>
<td>Patchy; one or two lobes; no consolidation</td>
</tr>
</tbody>
</table>
II. Tuberculosis and its treatment (Figure 4-7)

A. Multiple drug therapy is used for the treatment of TB in an effort to combat drug resistance.

B. A common therapeutic regimen includes isoniazid (INH), rifampin, ethambutol, and pyrazinamide for a period of 2 months, followed by INH and rifampin for a period of 4 to 7 months.

1. INH
   a. INH, which diffuses into all body fluids, including breast milk, targets the outer layer of the mycobacteria.
   b. A common side effect of INH therapy is paresthesia, which can be corrected by the administration of pyridoxine (vitamin B₆).

2. Rifampin
   a. Rifampin inhibits RNA synthesis by blocking the β subunit of bacterial DNA-dependent RNA polymerase.
   b. Rifampin also induces cytochrome P450 enzymes in the liver and can decrease the half-lives of other agents in this way.
   c. One side effect of rifampin is the orange-red color of bodily fluids.

Miliary TB—think millet seed to remember multiple seedlike, white-gray lesions.

**QUICK HIT**
Mycobacterium tuberculosis are acid-fast bacteria because they have an envelope that contains large amounts of lipid and even true waxes that prevent the acid-fast stain (carbol-fuchsin) from leaking out.

**QUICK HIT**
Primary TB occurs in the upper part of the lower lobe or lower part of the upper lobe. However, secondary TB occurs in the apical area.

**QUICK HIT**
Rifampin decreases the half-lives of oral contraceptives as well as warfarin, digitoxin, ketoconazole, propranolol, and prednisone. Consequently, higher doses of these medications may be required to achieve the same therapeutic effect.

**MNEMONIC**

\[
\text{Ghon complex} = \text{Ghon focus and hilar lymph nodes}
\]

**TABLE 4-12 Most Common Causative Agents of Pneumonia by Age**

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Neonates (Birth–4 weeks)</th>
<th>Children (1 month–20 years)</th>
<th>Young Adults (20–40 years)</th>
<th>Adults (40–60 years)</th>
<th>Elderly (≥60 years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group B streptococcus</td>
<td>Viral: RSV, parainfluenza, influenza</td>
<td>Mycoplasma pneumoniae</td>
<td>Streptococcus pneumoniae</td>
<td>S. pneumoniae</td>
<td></td>
</tr>
<tr>
<td>Escherichia coli</td>
<td>S. pneumoniae</td>
<td>M. pneumoniae</td>
<td>Anaerobes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>M. pneumoniae</td>
<td>Chlamydia pneumoniae</td>
<td>Haemophilus influenza</td>
<td>H. influenza</td>
<td></td>
<td></td>
</tr>
<tr>
<td>C. pneumoniae</td>
<td>Viruses</td>
<td>Gram-negative rods</td>
<td>Anaerobes</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

RSV, respiratory syncytial virus.

**Figure 4-7**

**Tuberculosis**

- Secondary tuberculosis (TB)
  - Reactivation of primary TB, hematogenously spread
  - Clinical presentation includes weakness, hemoptysis, weight loss
  - Usually located in upper lobe
  - Large, cavitary lesions may rupture into bronchi
  - May extend beyond lung (miliary TB): common sites include meninges, spine (Pott disease) and psoas major muscle

- Primary tuberculosis (TB)
  - Subpleural and hilar lymph node granulomas (tubercles) = Ghon complex
  - Caseating necrosis with Langerhans giant cells
  - Usually does not become clinically symptomatic
  - Heals with calcification seen on chest radiograph
III. Upper respiratory infections

A. Otitis externa—most common cause is *P. aeruginosa*
B. Otitis media—most pathogens involved are *S. pneumoniae* and nontypable *H. influenzae*
C. Sinusitis
   1. Results from obstructed drainage outlets of the sinuses
   2. Caused by *S. pneumoniae, H. influenzae*, and *Moraxella*
D. Rhinitis
   1. Viral rhinitis
      a. Most commonly caused by rhinoviruses and coronaviruses, also by adenoviruses and parainfluenza viruses
      b. Common cold
   2. Bacterial rhinitis
      a. Often secondary to viral infection
      b. Commonly caused by *Streptococcus, Staphylococcus*, and *H. influenzae*
   3. Allergic rhinitis
      a. Type I hypersensitivity reactions
      b. Characterized by eosinophilia
E. Laryngitis
   1. Characterized by edema and inflammation of the vocal cords
   2. Caused by infection (*M. pneumoniae, parainfluenza virus*) or overuse
F. Croup versus epiglottitis (Table 4-13)

IV. Therapeutic agents (Table 4-14)

### TABLE 4-13 Croup versus Epiglottitis

<table>
<thead>
<tr>
<th></th>
<th>Croup</th>
<th>Epiglottitis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Organism</td>
<td>Parainfluenza virus (type 1 or 2)</td>
<td><em>Haemophilus influenzae</em> type B</td>
</tr>
<tr>
<td>Pathology</td>
<td>Inflammation of subglottic trachea</td>
<td>Inflamed epiglottis</td>
</tr>
<tr>
<td>Age</td>
<td>6 months to 2 years</td>
<td>1–5 years</td>
</tr>
<tr>
<td>Fever</td>
<td>&lt;102°F</td>
<td>&gt;102°F</td>
</tr>
<tr>
<td>Onset</td>
<td>Gradual (barking cough to stridor)</td>
<td>Abrupt; stridor</td>
</tr>
<tr>
<td>Associated symptoms</td>
<td>Rhinorrhea, hoarseness, conjunctivitis</td>
<td>None</td>
</tr>
<tr>
<td>Degree of illness</td>
<td>Not toxic, degree of symptoms greater than degree of illness</td>
<td>Toxic</td>
</tr>
<tr>
<td>Physical examination</td>
<td>Writhing, anxious, subglottic edema and “steeple sign” on radiograph</td>
<td>Quiet, “sniffing position,” drooling, “thumbnail” epiglottis on radiograph</td>
</tr>
<tr>
<td>Outcome</td>
<td>Self-limiting</td>
<td>Medical emergency; 90% of patients require surgery to reestablish airway</td>
</tr>
</tbody>
</table>

### TABLE 4-14 Therapeutic Agents for Allergy, Cough, and Cold

<table>
<thead>
<tr>
<th>Therapeutic Agent (common name, if relevant) (trade name, where appropriate)</th>
<th>Class-Pharmacology and Pharmacokinetics</th>
<th>Indications</th>
<th>Side Effects or Adverse Effects</th>
<th>Contraindications or Precautions to Consider; Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diphenhydramine, dimenhydrinate, chlorpheniramine</td>
<td>H₁ blocker (first generation)</td>
<td>Allergy, motion sickness, insomnia</td>
<td>Sedation, anti-muscarinic, anti-α adrenergic</td>
<td></td>
</tr>
<tr>
<td>Loratadine, fexofenadine, desloratadine, cetirizine</td>
<td>H₁ blocker (second generation)</td>
<td>Allergy</td>
<td>Sedating</td>
<td>Less sedating than first-generation H₁ blocker due to decreased CNS entry</td>
</tr>
</tbody>
</table>

(continued)
CYSTIC FIBROSIS

I. Cystic fibrosis (CF) is the most common lethal genetic disease in Caucasians.

II. Autosomal recessive mutation occurs on chromosome 7, the CF transmembrane conductance regulator (CFTR) gene. This leads to:
   A. Deletion of phenylalanine at position 508 in 90% of patients with CF in the United States
   B. Altered chloride and water transport in epithelial cells
   C. High sodium and chloride concentrations on sweat test
   D. Increased mucosal viscosity obstructs exocrine glands, which leads to organ failure
   E. An abnormally high rate of sodium absorption from luminal secretions and a decreased rate of chloride secretion into luminal secretions reduce the salt and water content of bronchiolar secretions.

III. Chronic pulmonary disease
   A. Most serious complication and leading cause of death in patients with CF
   B. P. aeruginosa infections are the most common in adults, followed by S. aureus and H. influenzae. In children, S. aureus is the most common infection.
   C. Increased residual volume (RV) and increased total lung capacity (TLC) are characteristics of COPD.
   D. Atelectasis
   E. Bronchiectasis

IV. Pancreatic insufficiency
   A. Nutritional deficiencies (especially of fat-soluble vitamins A, D, E, and K)
   B. Steatorrhea
   C. β-Cells are initially spared but become functionally inactive with age, leading to an increased need for insulin.

V. Meconium ileus
   A. Usually presents in infant with abdominal distention, small bowel obstruction, and emesis
LUNG NEOPLASMS (Tables 4-15 to 4-17)

I. Lung neoplasms are the leading cause of cancer death for both men and women in the United States.

II. Lung cancer is the second most common type of cancer (with the first being prostate cancer in men and breast cancer in women).

III. Lung cancer deaths among women are rising rapidly as a result of increased smoking in this population.

IV. Symptoms include cough, hemoptysis, airway obstruction, weight loss, and paraneoplastic syndromes.

### TABLE 4-15  Lung Neoplasms

<table>
<thead>
<tr>
<th>Tumor</th>
<th>Location and Histology</th>
<th>Clinical Features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adenocarcinoma</td>
<td>Peripheral, subpleural; usually on pre-existing parenchymal scars, glandular</td>
<td>Most common type; may be related to smoking; CEA-positive; K-ras oncogenes</td>
</tr>
<tr>
<td>Bronchioalveolar</td>
<td>Peripheral, subtype of adenocarcinoma; tumor cells line alveolar walls</td>
<td>Less strongly associated with smoking; autoantibodies to surfactant may exist</td>
</tr>
<tr>
<td>Carcinoid</td>
<td>Major bronchi; spread by direct extension</td>
<td>Increased secretion of 5-HT, flushing, wheezing, recurrent diarrhea, heart disease, low malignancy</td>
</tr>
<tr>
<td>Large cell</td>
<td>Peripheral, undifferentiated; giant cells with pleomorphism</td>
<td>Poor prognosis; metastasis to the brain; smoking</td>
</tr>
<tr>
<td>Metastasis</td>
<td>Cannonball lesions</td>
<td>Higher incidence than primary lung cancer</td>
</tr>
<tr>
<td>Small cell (oat cell)</td>
<td>Central, undifferentiated; most aggressive; small, dark blue cells; arise from neuroendocrine (Kulchitsky) cells</td>
<td>Poor prognosis; strongly associated with smoking; ectopic ACTH; ADH secretion</td>
</tr>
<tr>
<td>Squamous cell</td>
<td>Central; mass from bronchus; keratin pearls; cavitation</td>
<td>Strongly associated with smoking; secretion of PTH-like peptide</td>
</tr>
</tbody>
</table>

5-HT, serotonin; ACTH, adrenocorticotropic hormone; ADH, antidiuretic hormone; CEA, carcinoembryonic antigen; PTH, parathyroid hormone.

### TABLE 4-16  Other Respiratory Carcinomas

<table>
<thead>
<tr>
<th>Tumor</th>
<th>Histology</th>
<th>Risk Factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nasopharyngeal</td>
<td>Lymphoepithelioma (rich in lymphocytes)</td>
<td>Epstein–Barr virus infection; common in Southeast Asia (adult) and East Africa (childhood)</td>
</tr>
<tr>
<td>Laryngeal carcinoma</td>
<td>Squamous cell carcinoma</td>
<td>Smoking</td>
</tr>
</tbody>
</table>
THE RESPIRATORY SYSTEM

DRUGS THAT CAUSE ADVERSE EFFECTS TO THE RESPIRATORY SYSTEM

I. Pulmonary fibrosis: bleomycin (antineoplastic), amiodarone (antiarrhythmic), busulfan (antineoplastic)

II. Cough: angiotensin-converting enzyme inhibitors (versus angiotensin II receptor blockers = no cough)

TABLE 4-17 Paraneoplastic Syndromes of Lung Cancer

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Causes and Clinical Presentation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Horner syndrome</td>
<td>Superior sulcus tumors (Pancoast tumors); ptosis, miosis, anhidrosis</td>
</tr>
<tr>
<td>Superior vena cava (SVC) syndrome</td>
<td>Insidious compression or obstruction of the SVC; facial cyanosis, facial swelling, headache, venous distention of the neck, upper chest, and arms</td>
</tr>
<tr>
<td>Cushing syndrome</td>
<td>ACTH secretion; associated with small cell carcinoma; fat deposition of the face (moon faces), upper back (buffalo hump), truncal obesity, muscle weakness, purple striae</td>
</tr>
<tr>
<td>Hypercalcemia</td>
<td>Secretion of PTH-related protein (PTHrP); associated with squamous cell lung cancer</td>
</tr>
<tr>
<td>SIADH</td>
<td>Ectopic antidiuretic hormone (ADH) production; hyponatremia (Na⁺ below 120 mEq/L)</td>
</tr>
<tr>
<td>Lambert–Eaton myasthenic syndrome</td>
<td>Proximal muscle weakness with autonomic dysfunction; antibodies produced against presynaptic calcium channels of the neuromuscular junction, no improvement with administration of anticholinesterase agents</td>
</tr>
</tbody>
</table>

ACTH, adrenocorticotropic hormone; PTH, parathyroid hormone; SIADH, syndrome of inappropriate antidiuretic hormone.

Clinical Vignette 4-2

CLINICAL PRESENTATION: A 74-year-old man presents with shortness of breath, a chronic bloody cough, increased fatigue, and a weight loss of 20 lb over a 3-month period. Past medical history is significant for hypertension, emphysema, coronary artery disease, and a 26-pack-year history of smoking. Physical examination reveals wheezing in the right upper lobe. Temperature = 98.7° F; blood pressure = 140/92 mm Hg; heart rate = 80 bpm; and respiration rate = 25 breaths/min.

DIFFERENTIALS: Lung cancer, TB, pneumonia, left heart failure. Given the patient’s presentation and long-standing history of smoking, this patient most likely has lung cancer. The two most common causes of hemoptysis in the United States are bronchitis and lung cancer.

LABORATORY STUDIES: Proper follow-up for this patient would include imaging, such as a chest CT scan or a chest x-ray. If imaging reveals a mass, bronchoscopy can be performed to obtain cells via brushings, bronchoalveolar lavage, or biopsy. CT-guided fine needle biopsy can also be performed to gather cells.

MANAGEMENT: Treatments include surgical resection and chemotherapy independently or in combination with radiation. Non–small cell lung cancer should be staged using the TNM (tumor, node, metastasis) system. Patients with stage I or II non–small cell lung cancers can be cured with surgical resection and radiotherapy. Small cell lung cancer often has metastasized at the time of diagnosis, making surgical resection futile and limiting radiotherapy and chemotherapy as the only treatment options.

QUICK HIT

Paraneoplastic syndrome is a clinical and biochemical disturbance caused by a neoplasm that is not directly related to the primary tumor or metastases. Secretion of parathyroid hormone (PTH)–like hormone results in hypercalcemia. Ectopic antidiuretic hormone (ADH) production leads to syndrome of inappropriate antidiuretic hormone (SIADH) secretion with urinary retention and high urine osmolality. Adrenocorticotropic hormone (ACTH)–producing tumors lead to Cushing syndrome.

Mnemonic

To remember the symptoms of Horner syndrome, think “PAM is Horny.” P is ptosis, A is anhydrosis, M is miosis.

To remember the location, risk factors, and hormone-producing properties for small cell and squamous cell carcinoma, think s with c, s, smoking, and s, secretions.
INNERVATION AND BLOOD SUPPLY OF THE GASTROINTESTINAL TRACT (Figure 5-1)

1) Foregut
- Derivatives
  - Esophagus
  - Stomach
  - First part of duodenum
  - Liver
  - Gallbladder
  - Pancreas (formed from fusion of dorsal and ventral buds)
- Supplied by celiac trunk
- Vagal parasympathetic nerve, thoracic nerve, and splanchnic sympathetic nerve

2) Midgut
- Derivatives
  - Second, third, and fourth parts of duodenum
  - Jejunum
  - Ileum
  - Appendix
  - Proximal two-thirds of colon (up to splenic flexure)
- Supplied by superior mesenteric artery
- Vagal parasympathetic nerve, thoracic splanchnic sympathetic nerve

3) Hindgut
- Derivatives
  - Distal one-third of colon including sigmoid colon and rectum to pectinate line
- Supplied by inferior mesenteric artery
- Pelvic splanchnic (S2–S4) parasympathetic nerve and lumbar splanchnic sympathetic nerve

4) Ectoderm
- Derivatives
  - Oropharynx (anterior two-thirds of tongue, lips, parotid glands, tooth enamel)
  - Anus, distal rectum (from pectinate line outward)
Hormones of the gastrointestinal system

**Figure 5-2**

- **Glucagon**: Secreted by cells of the pancreatic islets to promote glycogenolysis and gluconeogenesis.
- **Cholecystokinin (CCK)**: From cells in duodenum and jejunum and neurons of ileum and colon; secreted in response to amino acids and fatty acids entering the duodenum; causes contraction of gallbladder and pancreatic secretion of enzymes and \( \text{HCO}_3^- \).
- **Somatostatin**: Produced by D cells of stomach and duodenum and \( \delta \) cells of pancreatic islets to inhibit gastric \( \text{H}^+ \) secretion, pancreatic secretion, and lower bile flow and to promote intestinal SMC contraction.
- **Parasympathetic (ACh)**: Increases production of saliva; increased gastric \( \text{H}^+ \) secretion; increases pancreatic enzyme and \( \text{HCO}_3^- \) secretion; causes gallbladder contraction; allows for gastric receptive relaxation; stimulates enteric nervous system to create intestinal peristalsis; relaxes sphincters.
- **Nitric oxide**: Causes smooth muscle relaxation (e.g., lower esophageal sphincter [LES] relaxation).
- **Peptide YY**: Secreted by endocrine cells of ileum and colon to inhibit gastric \( \text{H}^+ \) secretion.
- **Motilin**: Secreted in upper GI tract to increase smooth muscle contraction in esophageal sphincter, stomach, and duodenum.
- **Vasoactive intestinal peptide (VIP)**: Secreted by smooth muscle and nerves of intestines; relaxes intestinal smooth muscle, causes pancreatic \( \text{HCO}_3^- \) secretion, and inhibits gastric \( \text{H}^+ \) secretion; enteric nervous system (ENS) peptide neurotransmitter, also relaxes lower esophageal sphincter, possibly as part of NO response.
- **Sympathetic (NE)**: Increases production of saliva; decreases splanchnic blood flow in fight-or-flight response; decreases motility; constricts sphincters.
- **Gastrin**: From antrum of stomach; secreted in response to \( \text{H}^+ \) and fatty acids entering the stomach; causes gastric \( \text{H}^+ \) secretion.
- **Somatostatin**: Produced by D cells of stomach and duodenum and \( \delta \) cells of pancreatic islets to inhibit gastric \( \text{H}^+ \) secretion, pancreatic secretion, and lower bile flow and to promote intestinal SMC contraction.
- **Secretin**: From S cells of small intestines; secreted in response to \( \text{H}^+ \) and fatty acids entering the duodenum; causes pancreatic secretion of \( \text{HCO}_3^- \) and inhibits gastric \( \text{H}^+ \) secretion.
- **Cholecystokinin (CCK)**: From cells in duodenum and jejunum and neurons of ileum and colon; secreted in response to amino acids and fatty acids entering the duodenum; causes contraction of gallbladder and pancreatic secretion of enzymes and \( \text{HCO}_3^- \).
- **Gastrin**: From antrum of stomach; secreted in response to \( \text{H}^+ \) and fatty acids entering the stomach; causes gastric \( \text{H}^+ \) secretion.
- **Vasoactive intestinal peptide (VIP)**: Secreted by smooth muscle and nerves of intestines; relaxes intestinal smooth muscle, causes pancreatic \( \text{HCO}_3^- \) secretion, and inhibits gastric \( \text{H}^+ \) secretion; enteric nervous system (ENS) peptide neurotransmitter, also relaxes lower esophageal sphincter, possibly as part of NO response.
- **Sympathetic (NE)**: Increases production of saliva; decreases splanchnic blood flow in fight-or-flight response; decreases motility; constricts sphincters.

ACo, acetylcholine; GI, gastrointestinal; \( \text{HCO}_3^- \), bicarbonate; NE, norepinephrine; NO, nitric oxide; SMC, smooth muscle cells.
**The Gastrointestinal System**

**Table 5-1** Important Congenital Malformations of the Gastrointestinal System

<table>
<thead>
<tr>
<th>Malformation</th>
<th>Clinical Features</th>
</tr>
</thead>
</table>
| Hypertrophic pyloric stenosis       | Thickening of the pylorus musculature  
  **Projectile vomiting**  
  Palpable knot “olive” in the pyloric region |
| Extrahepatic biliary atresia        | Incomplete recanalization of the bile duct during development  
  Presents shortly after birth  
  Dark urine  
  Clay-colored stool  
  Jaundice |
| Annular pancreas                    | Abnormal fusion of ventral and dorsal pancreatic buds, forming a constricting ring around the duodenum  
  Duodenal obstruction (bilious vomiting); presents shortly after birth |
| Meckel diverticulum                 | Persistent remnant of the vitelline duct  
  Forms an outpouching (true diverticulum) in the ileum  
  Ulceration and bleeding  
  Fifty percent contain either gastric or pancreatic tissue when symptomatic |
| Malrotation of the midgut           | Normal 270-degree rotation is not completed  
  Cecum and appendix lie in upper abdomen  
  Associated with volvulus (twisting of intestine), causing an obstruction |
| Intestinal stenosis or atresia      | Results from failure of the normal recanalization of the lumen  
  May produce failure to thrive |
| Hirschsprung disease (congenital or toxic megacolon) | Failure of neural crest cells to migrate to colon  
  No peristalsis  
  Constipation and abdominal distention in newborn  
  Bowel movement precipitated by digital rectal examination |
| Anal agenesis                       | Lack of anal opening as a result of improper formation of the urorectal septum  
  May cause rectovesical (anus to bladder), rectovaginal, or rectourethral fistula |

**Rule of 2s for Meckel diverticulum:**
- 2 feet from ileocecal junction;
- 2 inches long; 2% of the population affected; 2 times more common in men; and 2 types of ectopic tissue involved (gastric or pancreatic).
- Remember Meckel diverticulum as the disease associated with 2 because “di-” means “2.”

**Quick Hit:**
- The boundaries of the epiploic foramen of Winslow (opening of the lesser sac) are the hepatoduodenal ligament (containing the common bile duct [CBD], the proper hepatic artery, and the portal vein), located anteriorly; the caudate lobe of the liver, located superiorly; the duodenum, located inferiorly; and the inferior vena cava, located posteriorly.

**Quick Hit:**
- Duodenal atresia is associated with Down syndrome and demonstrates a characteristic “double-bubble” sign on radiograph and ultrasound.

**Quick Hit:**
- Many GI disorders present with abdominal pain—use the quality of pain to help you: sharp, stabbing epigastric pain that radiates to the back suggests pancreatitis; burning epigastric pain suggests a gastric or duodenal ulcer; and pain that shifts from the epigastrium to the right lower quadrant suggests appendicitis.

**Quick Hit:**
- The oropharynx, esophagus, and stomach
  1. The digestion of food begins in the oral cavity with salivary enzymes.
  2. The esophagus transports food to the stomach.
     A. The upper third of the esophagus is skeletal muscle.
     B. The middle third is both skeletal and smooth muscle.
     C. The lower third is smooth muscle.
     D. The lower esophageal sphincter (LES) relaxes in preparation for the passage of food into the stomach.
  3. The stomach receives and stores food.
     A. Receptive relaxation—the stomach relaxes to accommodate the entering food (a vagovagal reflex).
B. Three phases of gastric secretion
1. Cephalic phase—the sight, smell, taste, or thought of food stimulates secretion.
2. Gastric phase—secretion is caused by the entry of food into the stomach.
3. Intestinal phase—food entering the intestine causes a feedback stimulation of gastric secretion.

C. Important gastric secretions
1. Hydrochloric acid (HCl) is secreted by parietal cells of the fundus.
   a. Stimulated by gastrin, histamine, and vagal stimulation
   b. Inhibited by omeprazole (proton pump inhibitor), cimetidine (H₂ blocker), chyme in small intestine via gastric inhibitory peptide (GIP), and secretin
2. Intrinsic factor is secreted by parietal cells of the fundus.
   a. Binds to vitamin B₁₂ (extrinsic factor)
   b. Vitamin B₁₂–intrinsic factor complex absorbed in terminal ileum
3. Pepsinogen is secreted by chief cells.
   a. Pepsinogen is converted to pepsin by the low pH of the stomach.
   b. Pepsin begins the digestion of protein.
4. Gastrin secreted by the G cells of the antrum and pylorus stimulates the release of HCl from parietal cells.
5. Somatostatin is secreted by a variety of cells throughout the GI tract and has a global inhibitory effect.

D. The stomach grinds food into small particles and forces it into the duodenum.
1. Grinding (trituration) takes place in peristaltic waves occurring at a rate of three to five waves per minute.
2. Migrating motor complexes (MMCs), stimulated by motilin, occur in the interdigestive period and serve to flush undigested food through the GI system.

IV. Nonneoplastic disorders of the oropharynx, esophagus, and stomach (Table 5-2)

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Etiology and Pathology</th>
<th>Clinical Features</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sialolithiasis</td>
<td>Blockage of salivary gland duct preventing release of saliva; follows chronic sialadenitis (inflammation of the salivary glands)</td>
<td>Acute pain; usually in submandibular gland or Stensen duct of the parotid gland</td>
<td>Passage of stone can be induced by stimulating the secretion of saliva (e.g., by sucking on a lemon)</td>
</tr>
<tr>
<td>Pleomorphic adenoma</td>
<td>Increased risk with radiation exposure</td>
<td>Benign, recurring, mixed cell tumor of the parotid; may lead to facial nerve injury</td>
<td>Most frequent salivary gland tumor; more common in women 20–40 years of age</td>
</tr>
<tr>
<td>Esophageal variceal bleeding</td>
<td>Bleeding from esophageal varices owing to portal HTN</td>
<td>Hematemesis, signs of portal HTN (i.e., caput medusae, ascites)</td>
<td>Usually treated with vasoconstrictors (vasopressin); endoscopy required for diagnosis (to rule out bleeding ulcers)</td>
</tr>
<tr>
<td>Boerhaave syndrome</td>
<td>Complete rupture of the esophagus (all layers); caused by severe retching</td>
<td>Often presents as left pneumothorax; surgical correction necessary</td>
<td>Esophageal reflux disease predisposes to this condition</td>
</tr>
<tr>
<td>Mallory–Weiss tear</td>
<td>Laceration of the esophageal junction; usually caused by severe retching</td>
<td>Poststretching hematemesis</td>
<td>Alcoholics and bulimics are at an increased risk</td>
</tr>
</tbody>
</table>

(continued)
### TABLE 5-3 Neoplastic Disorders of the Oropharynx, Esophagus, and Stomach

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Etiology and Pathology</th>
<th>Clinical Features</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral cancer</td>
<td>Smoking, chewing tobacco, alcohol</td>
<td>Squamous cell carcinoma; may involve tongue</td>
<td>Leukoplakia (white patch on the mucous membrane that cannot be wiped off) is a common precursor lesion</td>
</tr>
<tr>
<td>Esophageal adenocarcinoma</td>
<td>Barrett esophagus, complication of GERD</td>
<td>Columnar metaplasia of esophageal squamous epithelium; distal third of the esophagus</td>
<td>More common in Whites</td>
</tr>
<tr>
<td>Esophageal squamous cell carcinoma</td>
<td>Alcohol and tobacco use; esophagitis</td>
<td>Dysphagia, anorexia, pain</td>
<td>More common in Blacks</td>
</tr>
<tr>
<td>Gastric carcinoma</td>
<td><em>Helicobacter pylori</em>, gastritis; low-fiber diet, nitrates; blood group A; high-salt diet; increased incidence in Japan owing to greater consumption of smoked foods</td>
<td>Aggressive spread from antrum to nodes and liver; Virchow node (enlarged left-sided supraclavicular lymph node); Krukenberg tumor (metastatic disease to the ovaries from the stomach characterized by mucinous, signet ring cells)</td>
<td>More common in men older than 50 years; infiltration of stomach walls with tumor cells and subsequent fibrosis leads to linitis plastica (leather-bottle stomach)</td>
</tr>
</tbody>
</table>

**Helicobacter pylori** infection is pharmacologically treated with “triple therapy.” The therapeutic regimen typically includes a proton pump inhibitor (omeprazole) and clarithromycin plus either amoxicillin or metronidazole.

**Helio**myoma is the most common benign tumor of the stomach.

V. Neoplastic disorders of the oropharynx, esophagus, and stomach (Table 5-3 and Figure 5-3)

Nonneoplastic and neoplastic disorders originating proximal to the pyloric sphincter often present with hematemesis and dysphagia as a result of alcohol and tobacco abuse.
To remember one cause and treatment of achalasia, think CHAgas disease and calcium-CHAannel blocker.

Various emetic substances in the blood stimulate the chemoreceptor trigger zone and area postrema to produce feelings of nausea and vomiting. Remember the extraintestinal causes of vomiting as part of your differential:

- Vestibular disturbance/Vagal
- Opiates
- Migraine/Metabolic (diabetic ketoacidosis, gastroparesis, hypercalcemia)
- Infections
- Toxicity
- Increased intracranial pressure (ICP)/Ingested alcohol
- Neurogenic, psychogenic
- Gestation

To remember one cause and treatment of achalasia, think CHAgas disease and calcium-CHAannel blocker.

Clinical Vignette 5-1

**CLINICAL PRESENTATION:** During a visit to her primary care physician, a 39-year-old woman complains of difficulty swallowing. She also reports some heartburn and weight loss but denies pain on swallowing. She is an otherwise healthy female with no medical problems. Physical examination shows intact cranial nerves, swallowing mechanisms, and motor function of extremities. Vital signs are stable. Barium-swallow radiograph is shown previously.

**DIFFERENTIALS:** Mechanical obstruction—cancer, strictures, and rings; oropharyngeal motility disorders—multiple sclerosis, stroke, poliomyelitis, Parkinson disease, and myasthenia gravis; esophageal motility disorders—achalasia, scleroderma, and diffuse esophageal spasm.

To remember the differentials for dysphagia, group them according to the phase of swallowing that has been disturbed and the type of pathology present (obstruction or motility disorder).

To sort through the differentials, look for three symptoms specific to esophageal pathology: dysphagia (difficulty swallowing), odynophagia (pain on swallowing), and heartburn. Odynophagia would suggest diffuse esophageal spasm, whereas heartburn would suggest gastroesophageal reflux disease (GERD). Determine the type of dysphagia: difficulty with solids indicates mechanical obstruction; trouble with both solids and liquids suggests esophageal motility disorders; and problems in transferring food from the oral cavity suggest oropharyngeal disorders. For oropharyngeal disorders, look for details in the history and physical examination such as aspiration pneumonia, nasal regurgitation, and cranial nerve pathology.

**LABORATORY STUDIES:** In this case, the barium-swallow chest radiograph shows dilation of the esophagus with narrowing at the LES confirming a diagnosis of achalasia. Other significant findings on chest radiograph include pneumonia, thickened esophageal folds, ulcerations, and strictures. Manometry is also helpful in esophageal motility disorders, and, in achalasia,

(continued)
Clinical Vignette 5-1 (Continued)

it would classically show a lack of ordered peristalsis, increased LES pressures, and failure of LES relaxation after swallowing. Esophagoscopy is helpful in visualizing and qualifying obstruction and mucosal wall integrity and is important to rule out cancer. Esophageal pH monitoring would also be done in this case to rule out GERD. If an oropharyngeal disorder is suspected, a swallowing electromyography is indicated and electromyelograms would be abnormal.

MANAGEMENT: Achalasia is treated by calcium channel blockers and nitrates to decrease LES pressure. Patients refractory to medical treatment can undergo endoscopic injection of botulinum toxin at the LES to block the release of acetylcholine locally. Surgical management options include myotomy of the gastroesophageal junction to relieve LES pressure with partial fundoplication to prevent reflux.

THE SMALL INTESTINE, LARGE INTESTINE, AND RECTUM

I. Muscular layers of the GI tract is shown in Figure 5-4.

II. The small intestine digests and absorbs the food.

A. Digestion is mediated by a variety of GI hormones, including cholecystokinin (CCK), secretin, somatostatin, and others (Figure 5-2).

B. Carbohydrates

1. Pancreatic amylase hydrolyzes glycogen, starch, and most other complex carbohydrates to disaccharides.
2. Disaccharides are broken down to monosaccharides by intestinal brush border enzymes and absorbed.
3. Monosaccharides are absorbed by a variety of mechanisms:
   a. Glucose and galactose are absorbed by sodium (Na+)−dependent transport.
   b. Fructose is absorbed by facilitated diffusion.
C. Protein
1. It is degraded to amino acids, dipeptides, and tripeptides by proteases produced by the pancreas.
   a. Activation of trypsinogen to trypsin
      i. Autoactivated
      ii. Activated by intestinal brush border enterokinases
   b. Trypsin degrades the peptide bonds of arginine or lysine.
   c. Trypsin also activates the other proteolytic pancreatic enzymes.
2. Proteins are absorbed by an Na\(^+\)/H\(^+\)-dependent transport.
   a. There are separate carriers for acidic, basic, and neutral amino acids.
   b. Dipeptides and tripeptides are absorbed faster than single amino acids.

D. Fats
1. Lipids are broken into droplets by the mixing action of the stomach.
2. Pancreatic lipase (and to a lesser extent salivary lipase) hydrolyzes triacylglycerol to fatty acids and 2-monoacylglycerol. Chronic pancreatitis decreases fat digestion and absorption due to decreased lipase release from the exocrine pancreas.
3. Bile salts (amphipathic molecules) emulsify the hydrolyzed products and form micelles.
4. Micelles allow for fat absorption (Figure 5-5).
5. A variety of familial and acquired disorders may disrupt lipid metabolism, resulting in hyperlipidemia.
   a. Hyperlipidemia, especially high levels of low-density lipoproteins (LDLs), is associated with coronary artery disease (CAD).
   b. Typically, treatment first involves dietary intervention and then drug therapy, regardless of the cause of the hyperlipidemia.
      i. 3-Hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors, also known as “statins,” such as atorvastatin, lovastatin, and pravastatin, are an effective and widely used means of lowering LDL.

**QUICK HIT**
Although the statins work well as cholesterol-lowering agents, they can be hepatotoxic. Consequently, patients who take them should undergo routine liver function tests.

**QUICK HIT**
Often, the amino acid transporter found in the intestines is identical to the amino acid transporter found in the renal tubules. As such, diseases that affect these transporters have multiorgan system effects. One of these diseases is Hartnup disease, which is a defect in the intestinal and renal tubular absorption of neutral amino acids leading to excretion of tryptophan derivatives and causing pellagra-like symptoms.

---

**Figure 5-5**
Absorption and digestion of fats (lipid metabolism)

CETP, cholesterol ester transfer protein; FFA, free fatty acid; HDL, high-density lipoprotein; IDL, intermediate-density lipoprotein; LCAT, lecithin-cholesterol acyltransferase; LDL, low-density lipoprotein; LRP, lipoprotein receptor-related protein; SRB1, scavenger receptor class B1; VLDL, very low-density lipoprotein.
The sweetener sucralose, a chloride derivative of sucrose, is absorbed at a level only 11% to 27% of intake, and most of it is excreted, unmetabolized, in feces.

ii. Bile acid-binding resins such as cholestyramine and colestipol work by binding bile acids in the intestine and promoting their subsequent loss in the stool, which ultimately lowers LDL levels.

iii. Nicotinic acid (niacin) inhibits the release of lipoproteins from the liver, lowering very low-density lipoproteins (VLDLs) and LDL.

III. The large intestine stores and excretes nondigestible material.
   A. Absorbs 2 to 3 L per day of water
   B. Secretes potassium (K⁺)
   C. Mediates defecation of undigested material through both voluntary and involuntary (rectosphincteric reflex) mechanisms

LOCATION OF ABSORPTION OF VITAMINS, MINERALS, AND NUTRIENTS (Figure 5-6)
Common clinical disorders of the GI tract, distal to the pyloric sphincter, will usually present as vague abdominal pain as a result of stimulation of the visceral afferent nerves. If the parietal peritoneum (the abdominal wall), innervated by the somatic afferent nerves, is irritated by the lesion, the pain will become more localized (as is seen in acute appendicitis).

**TABLE 5-4 Common Clinical Disorders of the Small Intestine, Large Intestine, and Rectum** (Table 5-4)

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Etiology and Pathology</th>
<th>Clinical Features</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hiatal hernia</td>
<td>Saddle herniation of stomach through diaphragm; smoking; obesity</td>
<td>Retrosternal pain (worse in supine position); can lead to GERD</td>
<td>Usually occurs in the sliding (versus rolling) form</td>
</tr>
<tr>
<td>Duodenal ulcers</td>
<td><em>Helicobacter pylori</em> (90% of cases); hypersecretion of acid; smokers; Zollinger–Ellison syndrome; blood group 0; associated with NSAID use</td>
<td>Coffee-ground vomiting; smooth border; clean base; black stools; pain at night or 2 h postprandial; perforation may result in acute pancreatitis</td>
<td>Not precancerous</td>
</tr>
<tr>
<td>Ischemic bowel disease</td>
<td>Atherosclerosis of celiac artery or mesenteric artery</td>
<td>Abdominal pain, nausea, vomiting, stool positive for blood test</td>
<td>Usually affects watershed areas (splenic flexure or rectosigmoid junction)</td>
</tr>
<tr>
<td>Diverticulitis</td>
<td>Outpouchings of the colon obstructed with fecalith leading to inflammation or infection; low-fiber diet</td>
<td>Usually involves the sigmoid colon; fever; leukocytosis; colicky pain; usually multiple in number and causes increased risk of perforation</td>
<td>False diverticula: pockets of mucosa and submucosa herniated through muscular layer (not all layers)</td>
</tr>
<tr>
<td>Appendicitis</td>
<td>Obstruction (usually fecalith or lymphoid hyperplasia); bacterial proliferation and mucosal invasion</td>
<td>Nausea, vomiting, anorexia, abdominal pain that migrates from epigastrium to right lower quadrant, pain at McBurney point, psoas sign or obturator sign, increased WBCs in blood</td>
<td>Differential diagnosis in females includes ectopic pregnancy, ovarian torsion, ruptured ovarian cyst, and pelvic inflammatory disease</td>
</tr>
<tr>
<td>Adenocarcinoma</td>
<td>Chronic IBD, low-fiber diet, older age, hereditary polyposis or adenomatous disorders</td>
<td>Increased CEA (not diagnostic; used to assess treatment); rectosigmoid tumors present in an annular manner producing early obstruction and constipation; left-sided tumors present with blood in the stool, whereas right-sided tumors typically present with anemia as a result of occult blood loss</td>
<td>Screen for occult blood in stool and flexible sigmoidoscopy; screening colonoscopy with a positive family history; third most common cause of cancer death (after lung and prostate/breast)</td>
</tr>
<tr>
<td>Carcinoid tumor</td>
<td>Arises from neuroendocrine cells (Kulchitsky cells); releases vasoactive peptides such as histamine, serotonin, and prostaglandins</td>
<td>Increased 5-HIAA in urine, diarrhea, flushing, right-sided heart valve lesions, hypotension, bronchospasm</td>
<td>Most common tumor of the appendix but also found in the ileum, rectum, and bronchus</td>
</tr>
</tbody>
</table>

5-HIAA, 5-hydroxyindoleacetic acid; CEA, carcinoembryonic antigen; GERD, gastroesophageal reflux disease; IBD, inflammatory bowel disease; NSAID, nonsteroidal anti-inflammatory drug; WBC, white blood cell.
Clinical Vignette 5-2

**CLINICAL PRESENTATION:** A 21-year-old woman presents to the emergency department with right lower quadrant pain of several hours’ duration. She reports that the pain began in the epigastrium and has since moved to the right lower quadrant. Since the onset of the pain, she reports no appetite and nausea. She is otherwise a healthy young female. Physical examination reveals tenderness at McBurney point. No peritoneal signs, psoas sign, or obturator sign. Rectal examination gives a negative result. Temperature = 100.3°F; blood pressure = 120/80 mm Hg; heart rate = 95 bpm; and respiration = 20 breaths/min.

**DIFFERENTIALS:** Appendicitis, mittelschmerz, ovarian cyst rupture, pelvic inflammatory disease, ectopic pregnancy, kidney stones, and Meckel diverticulum. The shift in pain described previously is classic for appendicitis. Also, anorexia, nausea, and vomiting beginning after the onset of pain are typical for appendicitis. Further, gynecologic history is needed on this patient to determine if midcycle pain associated with ovulation (mittelschmerz) was occurring. Also, a pelvic examination is indicated in this patient to further determine the pelvic pathology.

**LABORATORY STUDIES:** If this were a young man, the history and physical examination would be sufficient to indicate surgery for appendicitis. In a young woman, however, there is a longer differential list and a computerized tomography (CT) scan would be helpful in determining the cause of the pain. A complete blood count (CBC) often shows a mildly elevated white blood cell (WBC) count, but this is not a consistent finding. A human chorionic gonadotropin (hCG) pregnancy test and pelvic ultrasound should also be performed on this patient to rule out pelvic pathology.

**MANAGEMENT:** Laparoscopic or open appendectomy should be performed emergently because of the risk of rupture.

Diarrhea, the passage of abnormal amounts of fluid or semisolid fecal matter, can be mediated by a number of mechanisms. Osmotic diarrhea results when unabsorbed solutes increase intraluminal oncotic pressure, causing an outpouring of water. Surgical resection can lead to an inadequate surface for absorption of nutrients, resulting in a form of osmotic diarrhea. Active ion secretion causing obligatory water loss is termed secretory diarrhea. Altered intestinal motility, in which there is an alteration of the normally

Clinical Vignette 5-3

**CLINICAL PRESENTATION:** A 54-year-old woman presents to the emergency department with severe abdominal pain of 36 hours’ duration. Her past medical history is significant for CAD, hypertension (HTN), and diabetes. Physical examination reveals a soft, nondistended, tender abdomen with normal bowel sounds and no palpable masses. Temperature = 98.9°F; blood pressure = 140/90 mm Hg; heart rate = 99 bpm; and respiration rate = 21 breaths/min.

**DIFFERENTIALS:** Acute mesenteric ischemia, appendicitis, diverticulitis, colon adenocarcinoma, IBD, and pseudomembranous colitis. Pain disproportionate to the physical findings is strongly suggestive of mesenteric ischemia. As the ischemia progresses, peritonitis, sepsis, and shock may occur.

**LABORATORY STUDIES:** Mesenteric angiogram is the definitive diagnostic test for mesenteric ischemia. Plain abdominal radiographs are obtained to rule out other causes of acute abdominal pain. Abdominal radiographs with barium enema often show “thumbprinting” as a result of thickened edematous mucosal folds.

**MANAGEMENT:** Supportive therapy with intravenous (IV) fluids and broad-spectrum antibiotics should be started. Further treatment depends on the cause of the ischemia. Given the history of CAD in this patient, this is most likely thrombotic in nature, and direct intra-arterial injection of papaverine (a vasodilator) into the superior mesenteric system during arteriography will relieve the occlusion and vasospasm. An embolic occlusion indicates direct intra-arterial infusion of thrombolitics or embolectomy. If it is a venous thrombosis, heparin anticoagulation should be started. If signs of peritonitis develop, the nonviable bowel should be resected.
coordinated control of intestinal propulsion, may also result in diarrhea (often alternating with constipation). Finally, sloughing of colonic mucosa, caused by inflammation and necrosis, often as a result of infection, causes an **exudative form of diarrhea**.

**I. Bacterial causes of diarrhea** (Table 5-5)

**II. Viral causes of diarrhea** (Table 5-6)

**III. Protozoal causes of diarrhea** (Table 5-7)

<table>
<thead>
<tr>
<th><strong>TABLE 5-5</strong> Bacterial Causes of Diarrhea</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Infectious Agent</strong></td>
</tr>
<tr>
<td>Shigella</td>
</tr>
<tr>
<td>Salmonella</td>
</tr>
<tr>
<td>Campylobacter jejuni</td>
</tr>
<tr>
<td>Vibrio cholerae</td>
</tr>
<tr>
<td>Clostridium difficile</td>
</tr>
<tr>
<td>Enterotoxigenic <em>Escherichia coli</em> (traveler’s diarrhea)</td>
</tr>
<tr>
<td>Enterohemorrhagic <em>E. coli</em> (0157:H7)</td>
</tr>
<tr>
<td>Yersinia enterocolitica</td>
</tr>
</tbody>
</table>

**QUICK HIT**

*Salmonella* requires at least 100,000 organisms to be infectious; *Shigella*, however, requires only 100.

**QUICK HIT**

*Vibrio cholerae* produces an exotoxin that activates adenylate cyclase in the crypt cells. The increase in cyclic adenosine monophosphate (cAMP) activates chloride secretory channels. Consequently, sodium and water accompany chloride into the lumen, which results in an osmotic diarrhea.
### Table 5-7 Protozoal Causes of Diarrhea

<table>
<thead>
<tr>
<th>Infectious Agent</th>
<th>Clinical Features</th>
<th>Treatment</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Entamoeba histolytica</td>
<td>Bloody diarrhea, lower abdominal pain, may lead to dysentery with 10–12 bloody and mucous stools per day</td>
<td>Metronidazole</td>
<td>Caused by ingestion of viable cysts via fecal–oral route</td>
</tr>
<tr>
<td>Giardia lamblia</td>
<td>Watery, foul-smelling diarrhea; nausea; anorexia; cramps lasting weeks to months</td>
<td>Metronidazole</td>
<td>Fecal–oral transmission; often contracted while camping</td>
</tr>
<tr>
<td>Cryptosporidium</td>
<td>Watery diarrhea with large fluid loss; symptoms persist in immunocompromised patients; self-limited in healthy individuals</td>
<td>Supportive therapy</td>
<td>Immunocompromised patients (especially patients with AIDS); fecal–oral transmission of oocysts</td>
</tr>
</tbody>
</table>

### Table 5-6 Viral Causes of Diarrhea

<table>
<thead>
<tr>
<th>Infectious Agent</th>
<th>Clinical Features</th>
<th>Treatment</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rotavirus</td>
<td>Severe, dehydrating diarrhea; vomiting; low-grade fever</td>
<td>Supportive therapy only</td>
<td>Usually occurs during winter months; mainly affects infants</td>
</tr>
<tr>
<td>Norwalk virus</td>
<td>Mild diarrhea and vomiting</td>
<td>Supportive therapy only</td>
<td>Epidemics in underdeveloped countries; affects both children and adults</td>
</tr>
<tr>
<td>Adenovirus (serotypes 40 and 41)</td>
<td>Diarrhea and moderate vomiting</td>
<td>Supportive therapy only</td>
<td>Second to rotavirus as the cause of gastroenteritis in children</td>
</tr>
</tbody>
</table>

### Table 5-8 Comparison of Inflammatory Bowel Conditions

<table>
<thead>
<tr>
<th></th>
<th>Crohn Disease</th>
<th>Ulcerative Colitis</th>
</tr>
</thead>
</table>
| Typical patient | - Young person of Jewish descent  
- Bimodal age distribution: 25–40 years of age and 50–65 years of age  
- Female > male | - Person of Jewish descent  
- Recently quit smoking  
- Bimodal age distribution: 20–35 years of age and 65+ years of age  
- Male > female |
| Clinical findings | - Diarrhea  
- Abdominal pain  
- Fever  
- Malabsorption  
- Obstruction | - Bloody, mucous diarrhea  
- Abdominal pain  
- Fever  
- Weight loss  
- Toxic megacolon |

(continued)
THE GASTROINTESTINAL SYSTEM

QUICK HIT
Celiac disease (nontropical sprue) causes decreased absorption of fat and fat-soluble vitamins, leading to skeletal and hematologic conditions due to decreased vitamins D and K.

MALABSORPTION SYNDROMES OF THE SMALL INTESTINE
(Table 5-9)
Malabsorption may produce a variety of symptoms ranging from diarrhea to steatorrhea to specific nutrient deficiencies. For example, iron, vitamin B₁₂, fat-soluble vitamins (A, D, E, and K), or protein may be poorly absorbed and lead to systemic manifestations.

TABLE 5-9 Malabsorption Syndromes of the Small Intestine

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Pathology</th>
<th>Clinical Features</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abetalipoproteinemia</td>
<td>Lack of apolipoprotein B; defective chylomicron assembly; enterocytes congested with lipid</td>
<td>Acanthocytes (“burr” cells) in blood; no chylomicrons, VLDL, or LDL in blood; retinitis pigmentosa; peripheral neuropathy; mental retardation; ataxia</td>
<td>Autosomal recessive; vitamin E supplements may improve the retinopathy and neuropathy</td>
</tr>
</tbody>
</table>

(continued)
Malabsorption Syndromes of the Small Intestine (Continued)

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Pathology</th>
<th>Clinical Features</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Celiac disease (non-tropical sprue)</td>
<td>Gluten sensitivity</td>
<td>Foul-smelling, pale stool; villi of small intestine blunted; stunted growth; symptoms disappear when gluten is removed from diet</td>
<td>Associated with HLA-B8 and HLA-DQW2; predisposes to T-cell lymphoma and GI and breast cancer; if unmanaged, causes vitamin deficiency resulting in skeletal, hematologic, and neurologic symptoms</td>
</tr>
<tr>
<td>Disaccharidase deficiency</td>
<td>Enzyme deficiency; bacterial digestion of unabsorbed disaccharide</td>
<td>Diarrhea, bloating</td>
<td>Most commonly lactase deficiency</td>
</tr>
<tr>
<td>Tropical sprue</td>
<td>Etiology unclear</td>
<td>Affects small intestine; may cause vitamin deficiencies and megaloblastic anemia</td>
<td>Possible infectious cause; does not improve with gluten removal</td>
</tr>
<tr>
<td>Whipple disease</td>
<td>Systemic disease caused by Tropheryma whippiei</td>
<td>Diarrhea, weight loss, lymphadenopathy; hyperpigmentation, macrophages laden with T. whippiei</td>
<td>Older White males</td>
</tr>
<tr>
<td>Bacterial overgrowth</td>
<td>Bacterial overpopulation of small intestine owing to stasis, raised pH, impaired immunity, or clindamycin or ampicillin therapy</td>
<td>Inflammatory infiltrate in bowel wall</td>
<td>Treat with antibiotics, metronidazole, or oral vancomycin</td>
</tr>
</tbody>
</table>

GI, gastrointestinal; HLA-B8, human leukocyte antigen-B8; LDL, low-density lipoprotein; VLDL, very low-density lipoprotein.

NEOPLASTIC POLYPS (Table 5-10)

GI polyps can be very diverse in their presentation. Individuals can be asymptomatic, as is usually the case with tubular adenomas, or can present with serious systemic manifestations such as anemia secondary to invasive cancer.

I. Comparison of polyposis conditions (Table 5-11)

<table>
<thead>
<tr>
<th>Tubular Adenoma</th>
<th>Tubulovillous Adenoma</th>
<th>Villous Adenoma</th>
</tr>
</thead>
<tbody>
<tr>
<td>Usually benign</td>
<td>Greater potential of malignancy than tubular adenoma</td>
<td>Highly malignant</td>
</tr>
<tr>
<td>Multiple</td>
<td>Morphologically, shares features of both tubular and villous adenomas</td>
<td>Sessile tumors</td>
</tr>
<tr>
<td>Pedunculated</td>
<td>Greater chance of malignancy if genetically predisposed</td>
<td>Fingerlike projections</td>
</tr>
</tbody>
</table>
THE GASTROINTESTINAL SYSTEM

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The Gastrointestinal System

I. Microscopic organization of the liver (Figure 5-7)

II. Enterohepatic cycling and the excretion of bilirubin (Figure 5-8)

TABLE 5-11 Comparison of Polyposis Conditions

<table>
<thead>
<tr>
<th>Disease</th>
<th>Inheritance</th>
<th>Clinical Features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Familial adenomatous polyposis</td>
<td>Autosomal dominant</td>
<td>Colon lined with hundreds of polyps; potential for malignancy approaches 100%</td>
</tr>
<tr>
<td>Turcot syndrome</td>
<td>Autosomal dominant</td>
<td>Colonic polyps and central nervous system (CNS) tumors; potential for malignancy</td>
</tr>
<tr>
<td></td>
<td></td>
<td>approaches 100%</td>
</tr>
<tr>
<td>Gardner syndrome</td>
<td>Autosomal dominant</td>
<td>Colonic polyps; soft-tissue and bone tumors; potential for malignancy approaches</td>
</tr>
<tr>
<td></td>
<td></td>
<td>100%</td>
</tr>
<tr>
<td>Peutz–Jeghers syndrome</td>
<td>Autosomal dominant</td>
<td>Benign hamartomatous polyps of the gastrointestinal tract (especially the small</td>
</tr>
<tr>
<td></td>
<td></td>
<td>intestine); hyperpigmented mouth, hands, and genitalia; increased incidence of</td>
</tr>
<tr>
<td></td>
<td></td>
<td>tumors of the uterus, breast, ovaries, lung, stomach, and pancreas</td>
</tr>
<tr>
<td>Familial nonpolyposis syndrome</td>
<td>Autosomal dominant</td>
<td>Defect in DNA repair causing large number of colonic lesions (especially proximal);</td>
</tr>
<tr>
<td></td>
<td></td>
<td>potential for malignancy approaches 50%</td>
</tr>
</tbody>
</table>

Remember the drugs that cause hepatic necrosis by the phrase “Very Angry Hepatocytes”: Valproic acid, Acetaminophen, and Halothane.
### The Gastrointestinal System

#### The Gastrointestinal System

**Sources of Jaundice**

<table>
<thead>
<tr>
<th>Unconjugated</th>
<th>Conjugated</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gilbert syndrome</td>
<td>Dubin–Johnson syndrome</td>
</tr>
<tr>
<td>Crigler–Najjar syndrome</td>
<td>Obstruction of the common bile duct</td>
</tr>
<tr>
<td>Physiologic jaundice of newborn</td>
<td>Hepatitis</td>
</tr>
</tbody>
</table>

---

**FIGURE 5-3** Enterohepatic cycling and the excretion of bilirubin

- **Bilirubin**: Physiologic disease of the newborn
  - Crigler–Najjar Syndrome
  - Gilbert Syndrome

- **Cholesterol**: Portal circulation
- **Gallbladder**: Sphincter of Oddi
- **Duodenum**: Sources of Jaundice
- **Jejunum**: Terminal ileum
- **Colon**: 5% of bile salts in feces
- **5-8 %**: Enterohepatic cycling and the excretion of bilirubin

---

**Sources of Jaundice**

<table>
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<td>Gilbert syndrome</td>
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</tr>
<tr>
<td>Physiologic jaundice of newborn</td>
<td>Hepatitis</td>
</tr>
</tbody>
</table>

---

**Notes**

- 1° bile acids
- 2° bile acids
- 7-α-hydroxylase
- Conjugated
- Unconjugated

---

**Diagrams**

- **Gallbladder**: Sphincter of Oddi
- **Duodenum**: Sources of Jaundice
- **Jejunum**: Terminal ileum
- **Colon**: 5% of bile salts in feces
- **5-8 %**: Enterohepatic cycling and the excretion of bilirubin

---

**Legends**

- ➡️ = Direction of bile salt circulation
- = Bile salt active transport system
III. Viral hepatitis (Table 5-12 and Figure 5-9)

Viral hepatitis can lead to direct hyperbilirubinemia, elevated serum transaminases, icterus, or hepatomegaly, but not ascites. Morphologically, changes range from multifocal hepatocellular necrosis (hepatitis A and hepatitis B) to ballooning degeneration (hepatitis B and hepatitis C) to piecemeal necrosis (hepatitis C).

**TABLE 5-12 Viral Hepatitis**

<table>
<thead>
<tr>
<th></th>
<th>Hepatitis A</th>
<th>Hepatitis B</th>
<th>Hepatitis C</th>
<th>Hepatitis D</th>
<th>Hepatitis E</th>
</tr>
</thead>
<tbody>
<tr>
<td>Virus family</td>
<td>Picornavirus</td>
<td>Hepadnavirus</td>
<td>Flavivirus</td>
<td>Delta agent</td>
<td>Calicivirus</td>
</tr>
<tr>
<td>Viral morphology</td>
<td>Single-stranded RNA</td>
<td>Circular, double-stranded DNA</td>
<td>Single-stranded RNA</td>
<td>Incomplete genome of single-stranded RNA</td>
<td>Single-stranded RNA</td>
</tr>
<tr>
<td>Mode of transmission</td>
<td>Fecal–oral</td>
<td>Sexual and parenteral, transplacental</td>
<td>Parenteral; limited sexual; transplacental</td>
<td>Sexual and parenteral, transplacental</td>
<td>Fecal–oral</td>
</tr>
<tr>
<td>Diagnostic test</td>
<td>IgM anti-HAV</td>
<td>HBsAg; anti-HBcAg; HBeAg, HBV DNA; IgM anti-HBcAg</td>
<td>Anti-HCV</td>
<td>Anti-sag</td>
<td>None</td>
</tr>
<tr>
<td>Severity</td>
<td>Mild</td>
<td>Moderate</td>
<td>Mild</td>
<td>Severe</td>
<td>Mild</td>
</tr>
<tr>
<td>Chronic infection</td>
<td>No</td>
<td>10% of adults, 80%–90% of infants, and immunocompromised patients</td>
<td>80%–90%</td>
<td>No increase over hepatitis B alone</td>
<td>No</td>
</tr>
<tr>
<td>Carrier state</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Hepatocellular carcinoma</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Prophylaxis and treatment</td>
<td>Immune globulin; vaccine</td>
<td>Hepatitis B immune globulin; vaccine</td>
<td>Interferon and ribavirin</td>
<td>Hepatitis B immune globulin; vaccine</td>
<td>None</td>
</tr>
<tr>
<td>Notes</td>
<td>Incubation period of 14–15 days</td>
<td><strong>Dane particle:</strong> viral DNA genome, DNA polymerase, HBcAg, HBeAg, HBsAg; has <strong>reverse transcriptase</strong>; incubation period 60–90 days</td>
<td><strong>Most frequent cause of transfusion-mediated hepatitis</strong></td>
<td>Defective in replication; requires coinfection with hepatitis B</td>
<td>Hepatitis infection in third-world nations; mortality in pregnant females</td>
</tr>
</tbody>
</table>

HAV, hepatitis A virus; HBcAg, hepatitis B core antigen; HBeAg, hepatitis B envelope antigen; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; HCV, hepatitis C virus; IgM, immunoglobulin M.
Hepatitis B viral DNA, hepatitis B surface antigen (HBsAg), and hepatitis B envelope antigen (HBeAg) are indicators of virus replication. Antibody to hepatitis B surface antigen (HBsAb) is indicative of recovery and immunity; HBsAb is also positive following vaccination. Antibody to hepatitis B core antigen (HBcAb) is positive in early infection; in addition, HBcAb acts as a marker for hepatitis infection during the “window” period, which is the period during acute infection when HBsAg is undetectable and HBsAb has not yet appeared. During the window period, equivalent amounts of surface antigen and antibody neutralize each other and thus are not detectable by testing.

**QUICK HIT**

Hepatitis B viral DNA, hepatitis B surface antigen (HBsAg), and hepatitis B envelope antigen (HBeAg) are indicators of virus replication. Antibody to hepatitis B surface antigen (HBsAb) is indicative of recovery and immunity; HBsAb is also positive following vaccination. Antibody to hepatitis B core antigen (HBcAb) is positive in early infection; in addition, HBcAb acts as a marker for hepatitis infection during the “window” period, which is the period during acute infection when HBsAg is undetectable and HBsAb has not yet appeared. During the window period, equivalent amounts of surface antigen and antibody neutralize each other and thus are not detectable by testing.

**IV. Cirrhosis** (Table 5-13)

Cirrhosis is a disease of the liver characterized by fibrosis and disorganization of the lobular and vascular structure owing to the destruction and regeneration of hepatocytes.

**TABLE 5-13  Cirrhosis**

<table>
<thead>
<tr>
<th>Etiology</th>
<th>Pathology</th>
<th>Clinical Manifestation</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chronic alcohol abuse</td>
<td>Micronodular fatty liver; decreased metabolism of estrogen; decreased synthesis of coagulation factors</td>
<td>Jaundice, bleeding, gynecomastia, testicular atrophy, edema, asterixis, portal HTN (esophageal varices, spider angioma, and splenomegaly), encephalopathy</td>
<td>Most common cause of cirrhosis in the United States</td>
</tr>
<tr>
<td>Wilson disease</td>
<td>Decreased ceruloplasmin</td>
<td>Copper deposits in liver, basal ganglia (causing extrapyramidal signs), and Descomet membrane of cornea (Kayser–Fleischer ring)</td>
<td>Autosomal recessive</td>
</tr>
<tr>
<td>Hemochromatosis</td>
<td>Familial; increased total iron; decreased TIBC; increased ferritin; increased transferrin saturation</td>
<td>Iron deposits in liver, diabetes mellitus, increased skin pigmentation, cardiomyopathy</td>
<td>Bronze diabetes; increased risk of hepatocellular carcinoma</td>
</tr>
</tbody>
</table>

(continued)
### TABLE 5-13  Cirrhosis (Continued)

<table>
<thead>
<tr>
<th>Etiology</th>
<th>Pathology</th>
<th>Clinical Manifestation</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Posthepatic cirrhosis</td>
<td>Chronic active hepatitis caused by HBV and HCV infection</td>
<td>Jaundice, pruritus</td>
<td>Most likely cause of cirrhosis to lead to hepatocellular carcinoma</td>
</tr>
<tr>
<td>α₁-Antitrypsin deficiency</td>
<td>Autosomal recessive; defective α₁-antitrypsin accumulates in hepatocytes</td>
<td>Jaundice, panacinar emphysema, pancreatic manifestations</td>
<td>More severe in homozygous form (P*ZZ alleles)</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>Passive congestion</td>
<td>Nutmeg liver</td>
<td>Most often a result of right heart failure</td>
</tr>
</tbody>
</table>

ERCP, endoscopic retrograde cholangiopancreatography; HBV, hepatitis B virus; HCV, hepatitis C virus; HTN, hypertension; TIBC, total iron-binding capacity.

### TABLE 5-14  Common Clinical Disorders of the Hepatobiliary System

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Etiology and Pathology</th>
<th>Clinical Features</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cholelithiasis (gallstones)</td>
<td>Very common disease; women older than 40 years of age; obesity; multiparity</td>
<td>Steatorrhea, nausea, vomiting, bile duct obstruction, jaundice, may lead to cholangitis or cholecystitis, malignancy, positive Murphy sign</td>
<td>Cholesterol stones (large); pigment stones (seen in hemolytic anemia or excess bilirubin production); mixed stones (majority)</td>
</tr>
<tr>
<td>Primary biliary cirrhosis</td>
<td>Autoimmune disease leading to the destruction of intrahepatic bile ducts; middle-aged women</td>
<td>Pruritus, jaundice, hypercholesterolemia, RUQ discomfort, portal HTN</td>
<td>Positive antimitochondrial antibodies; associated with other autoimmune diseases</td>
</tr>
<tr>
<td>Primary sclerosing cholangitis</td>
<td>Fibrosis and stenosis of intrahepatic or extrahepatic bile ducts</td>
<td>Jaundice, pruritus, weight loss</td>
<td>Strong association with ulcerative colitis; increased incidence of cholangiocarcinoma</td>
</tr>
<tr>
<td>Adenocarcinoma of the gallbladder</td>
<td>Gallstones</td>
<td>Obstructive jaundice, enlarged gallbladder</td>
<td>Courvoisier law: obstruction of CBD enlarges the gallbladder, whereas obstructing stones do not; caused by scarring of the gallbladder</td>
</tr>
<tr>
<td>Hepatocellular adenoma (hepatoma)</td>
<td>Benign tumor; women 20–30 years of age taking oral contraceptives</td>
<td>Usually found incidentally; may cause pain or hemorrhage</td>
<td>10% may become malignant; oral contraceptive use should be stopped, lesion regresses with the cessation of contraceptive</td>
</tr>
<tr>
<td>Hepatocellular carcinoma</td>
<td>Cirrhosis, hepatitis B, hepatitis C, aflatoxin B (carcinogen in contaminated peanuts)</td>
<td>Increased α-fetoprotein, jaundice, abdominal distention, ascites</td>
<td>Hematogenous spread</td>
</tr>
</tbody>
</table>

CBD, common bile duct; HTN, hypertension; RUQ, right upper quadrant.

**QUICK HIT**

Pigment gallstones occurring in children or young adults with no history of pregnancy may be a result of a congenital hemoglobinopathy (e.g., sickle cell disease or thalassemia).

**QUICK HIT**

Murphy sign: Cessation of inspiration as a result of deep palpation of RUQ by examiner during inspiration; Charcot triad: Fever, RUQ pain, and jaundice; Reynold pentad: Charcot triad plus hypotension and mental status changes.

Metastatic disease is the most common source of malignancy in the liver.
**The Gastrointestinal System**

**Diseases of the gallbladder and biliary tract**

- **Cholelithiasis**
  - stone in GB
- **Acute cholecystitis**
  - inflammation of GB
- **Biliary colic**
  - pain from transient obstruction of cystic duct by stone
- **Choledocholithiasis**
  - stone in CBD
- **Acute cholangitis**
  - inflammation of CBD
- **Gallstone-induced pancreatitis**
- **Gallstone ileus**

**CBD,** common bile duct; **GB,** gallbladder.
The Gastrointestinal System

Clinical Vignette 5-4

CLINICAL PRESENTATION: A 6-year-old boy presents to the emergency department with multiple episodes of nausea and vomiting of 2 days' duration, and today his "stomach hurts." The worried mother reports finding the Tylenol bottle half empty this morning. On physical examination, the patient is jaundiced and diaphoretic, with right upper quadrant (RUQ) tenderness. Temperature = 98.6°F; blood pressure = 110/70 mm Hg; heart rate = 103 bpm; and respiration rate = 22 breaths/min.

DIFFERENTIALS: Acetaminophen-induced liver toxicity and gastroenteritis. The chemical structure of acetaminophen is N-acetyl-p-aminophenol (APAP). APAP itself is nontoxic but it is metabolized primarily in the liver by cytochrome P450 to a toxic metabolite, N-acetyl-p-benzoquinoneimine (NAPQI). Glutathione can bind NAPQI and lead to the excretion of nontoxic mercapturate conjugates in the urine. As the glutathione stores are diminished, NAPQI accumulates and covalently binds to the hepatocyte lipid bilayer, causing centrilobular necrosis. Inducers of cytochrome P450, such as ethanol, isoniazid, rifampin, phenytoin, barbiturates, and carbamazepine, can lead to an increased production of NAPQI.

LABORATORY STUDIES: Elevated serum APAP levels and transaminase levels greater than 1,000 U/L support the diagnosis of APAP hepatotoxicity. Coagulation studies should also be obtained to monitor the liver function.

MANAGEMENT: Glutathione stores can be replaced orally or intravenously by sulfhydryl-containing compounds like N-acetylcysteine. N-acetylcysteine also directly detoxifies NAPQI to nontoxic metabolites by acting as a substrate for sulfation. In addition to N-acetylcysteine, if the patient presents within hours of the incident, gastric lavage and oral charcoal could also be performed.
Clinical Vignette 5-5

CLINICAL PRESENTATION: During a visit to her primary care physician, a 42-year-old woman complains of intermittent right upper quadrant (RUQ) pain of several months’ duration that is worse after large and fatty meals. Pain is steady and lasts 1 to 4 hours and is sometimes associated with nausea and vomiting. Physical exam reveals a soft, nondistended abdomen with mild tenderness in the RUQ, normal bowel sounds, and no palpable masses. No cough tenderness, rebound tenderness, or tenderness to percussion. Temperature = 98.7°F; blood pressure = 130/80 mm Hg; heart rate = 85 bpm; and respiration rate = 20 breaths/min.

DIFFERENTIALS: Biliary colic/cholelithiasis, acute cholecystitis, choledocholithiasis, and acute cholangitis. When differentiating between the various causes of RUQ pain, use these findings to guide your approach: (a) when obstructive symptoms (jaundice, pruritus, light-colored stools, tea-colored urine, etc.) are present, consider a stone in the common bile duct (CBD) (e.g., choledocholithiasis or acute cholangitis); (b) inflammation of the parietal peritoneum elicited by cough tenderness, rebound tenderness, tenderness to percussion, and still posture indicates an inflammatory condition (e.g., acute cholecystitis or acute cholangitis); and (c) look for specific signs: Murphy sign (acute cholecystitis), Charcot triad (acute cholangitis), and Reynold pentad (acute suppurative cholangitis).

LABORATORY STUDIES: Ultrasound is the most effective imaging study for diagnosing cholelithiasis and is superior to CT and radiography. Relevant findings include stones, a thickened gallbladder wall, and pericholecystic fluid. Dilation of the CBD suggests obstruction. To sort through the differentials, look for an obstructive pattern on fractionate bilirubin and liver enzyme studies to support choledocholithiasis and acute cholangitis: elevated direct bilirubin and marked increases in alkaline phosphatase in comparison to mild increases in aspartate aminotransferase (AST) and alanine aminotransferase (ALT). Complete blood count studies showing an increase in white blood cells with a left shift would support an inflammatory condition (acute cholecystitis or cholangitis).

MANAGEMENT: Uncomplicated cholelithiasis and acute cholecystitis are treated surgically with a cholecystectomy. Choledocholithiasis and acute cholangitis are treated by endoscopic retrograde cholangiopancreatography (ERCP); if this fails, surgical exploration of the CBD is attempted. In acute cholecystitis and cholangitis, antibiotics are also given to resolve the underlying infection.

I. Common clinical disorders of the pancreas (Table 5-15)

In the United States, alcohol is the most common cause of pancreatic pathology.

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Etiology and Pathology</th>
<th>Clinical Features</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute pancreatitis</td>
<td>Gallstones (obstructing the ampulla of Vater); alcohol abuse</td>
<td>Midepigastric pain radiating to the back; increased serum amylase and lipase; hemorrhage may lead to Cullen or Grey Turner sign; hypocalcemia</td>
<td>Activation of pancreatic enzymes leads to autodigestion</td>
</tr>
<tr>
<td>Chronic pancreatitis</td>
<td>Alcoholism in adults; cystic fibrosis in children</td>
<td>Increased serum amylase and lipase, pancreatic calcifications, epigastric calcifications, steatorrhea</td>
<td>Irreversible; leads to organ atrophy; may lead to formation of pancreatic pseudocyst</td>
</tr>
<tr>
<td>Adenocarcinoma of the exocrine pancreas</td>
<td>More common in smokers</td>
<td>Invasive: Trousseau syndrome (migratory thrombophlebitis); radiating abdominal pain; obstructive jaundice; increased carcinoembryonic antigen</td>
<td>Poor prognosis; over 50% in the head of the pancreas; more common in Blacks, males, patients with diabetes, and people older than 60 years</td>
</tr>
</tbody>
</table>

(continued)
The presence of C-peptide in the blood distinguishes endogenous insulin secretion (as in an insulinoma) from exogenous insulin administration (as seen in Munchausen syndrome).

TABLE 5-15  Common Clinical Disorders of the Pancreas (Continued)

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Etiology and Pathology</th>
<th>Clinical Features</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Insulinoma (endocrine pancreas)</td>
<td>Originate in β cells</td>
<td>Whipple triad: hypoglycemia, CNS dysfunction, and reversal of CNS abnormalities with glucose</td>
<td>Most common islet cell tumor</td>
</tr>
<tr>
<td>Gastrinoma (Zollinger–Ellison syndrome)</td>
<td>Gastrin-secreting tumor (most commonly, islet cell origin)</td>
<td>Recurrent peptic ulcers</td>
<td>Part of multiple endocrine neoplasia type 1</td>
</tr>
</tbody>
</table>

CNS, central nervous system.

PATHOGENS OF THE GASTROINTESTINAL TRACT

I. Bacterial
   - Enterobacteriaceae
     - Vibrio cholerae
     - Clostridium botulinum
   - Salmonella
   - Shigella
   - Escherichia coli
     - Campylobacter jejuni
     - Helicobacter pylori
   - Staphylococcus aureus
   - Bacillus fragilis
   - Salmonella
   - Campylobacter jejuni
   - Helicobacter pylori

II. Parasitic
   - Entamoeba histolytica
   - Cryptosporidium
   - Ascaris lumbricoides
   - Giardia lamblia
   - Trichuris trichiura
   - Strongyloides stercoralis

III. Viral
   - Adenovirus
   - Norwalk agent
   - Echovirus
   - Reovirus
   - Coronavirus

THERAPEUTIC AGENTS FOR THE GASTROINTESTINAL SYSTEM

Various therapeutic agents have been designed to treat GI diseases such as heartburn (Table 5-16), diarrhea (Table 5-17), nausea (Table 5-18), and constipation (Table 5-19).

TABLE 5-16  Therapeutic Agents for Heartburn

<table>
<thead>
<tr>
<th>Therapeutic Agent (common name, if relevant) [trade name, where appropriate]</th>
<th>Class—Pharmacology and Pharmacokinetics</th>
<th>Indications</th>
<th>Side Effects or Adverse Effects</th>
<th>Contraindications or Precautions to Consider; Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cimetidine [Tagamet]</td>
<td>H₂ blocker—blocks histamine H₂ receptors; reversibly decreases proton secretion by parietal cells</td>
<td>Peptic ulcer disease, gastritis, esophageal reflux</td>
<td>Gynecomastia, impotence, and decreased libido in males; dizziness, headaches, and thrombocytopenia</td>
<td>Crosses placenta; decreases renal excretion of creatinine; cytochrome P450 inhibitor</td>
</tr>
<tr>
<td>Famotidine [Pepcid], ranitidine [Zantac], nizatidine</td>
<td>H₂ blocker—blocks histamine H₂ receptors; reversibly decreases proton secretion by parietal cells</td>
<td>Peptic ulcer disease, gastritis, esophageal reflux</td>
<td>Confusion, dizziness, headaches, and thrombocytopenia</td>
<td>Crosses placenta: milder side effect profile than cimetidine</td>
</tr>
</tbody>
</table>

(continued)
### Table 5.16 Therapeutic Agents for Heartburn (Continued)

<table>
<thead>
<tr>
<th>Therapeutic Agent (common name, if relevant) [trade name, where appropriate]</th>
<th>Class—Pharmacology and Pharmacokinetics</th>
<th>Indications</th>
<th>Side Effects or Adverse Effects</th>
<th>Contraindications or Precautions to Consider; Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Omeprazole [Prilosec], lansoprazole, esomeprazole</td>
<td>Proton pump inhibitor—irreversibly inhibits H⁺/K⁺-ATPase in gastric parietal cells → decreases proton secretion by parietal cells</td>
<td>Peptic ulcer disease, gastritis, esophageal reflux, and Zollinger–Ellison syndrome</td>
<td>Inhibits cytochrome P450, given with clarithromycin and amoxicillin or <em>Helicobacter pylori</em></td>
<td></td>
</tr>
<tr>
<td>Bismuth [Pepto-Bismol], sucralfate</td>
<td>Cytoprotectant—binds to ulcer base → protection; allows bicarbonate ion secretion to reestablish pH gradient in the mucus layer</td>
<td>Traveler’s diarrhea, peptic ulcer disease</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Misoprostol</td>
<td>Cytoprotectant—PGE₁ analog → increased production and secretion of gastric mucosa barrier; decreased acid production</td>
<td>Prevents NSAID-induced peptic ulcers; maintains patent ductus arteriosus</td>
<td>Diarrhea</td>
<td>Abortion-inducing drug, contraindicated in women of childbearing age</td>
</tr>
<tr>
<td>Pirenzepine, propantheline</td>
<td>Muscarinic antagonist—blocks M₁ receptors on ECL cells → decreases histamine secretion; blocks M₃ receptors on parietal cells → decreases acid secretion</td>
<td>Peptic ulcer</td>
<td>Tachycardia, dry mouth, blurry vision (difficulty accommodating)</td>
<td></td>
</tr>
<tr>
<td>Aluminum hydroxide</td>
<td>Antacid—buffers gastric acid by raising pH</td>
<td>Peptic ulcer, gas-tritis, esophageal reflux, and diarrhea</td>
<td>Constipation, hypophosphatemia, muscle weakness, osteodystrophy, seizures, and hypokalemia</td>
<td>Can affect the absorption, bioavailability, or urinary excretion of drugs by changing the gastric pH, urinary pH, or gastric emptying</td>
</tr>
<tr>
<td>Magnesium hydroxide (milk of magnesia)</td>
<td>Antacid—buffers gastric acid by raising pH</td>
<td>Peptic ulcer, gas-tritis, esophageal reflux, and constipation</td>
<td>Diarrhea, hyporeflexia, hypotension, cardiac arrest, hypokalemia</td>
<td>Can affect the absorption, bioavailability, or urinary excretion of drugs by changing the gastric pH, urinary pH, or gastric emptying</td>
</tr>
<tr>
<td>Calcium carbonate [TUMS, Caltrate]</td>
<td>Antacid—buffers gastric acid by raising pH</td>
<td>Peptic ulcer, gas-tritis, esophageal reflux, and calcium deficiency</td>
<td>Hypercalcemia, rebound acid increase, and hypokalemia</td>
<td>Can affect the absorption, bioavailability, or urinary excretion of drugs by changing the gastric pH, urinary pH, or gastric emptying</td>
</tr>
</tbody>
</table>

ATPase, adenosine triphosphatase; ECL, enterochromaffin-like; PGE₁, prostaglandin E₁.
### TABLE 5-17 Therapeutic Agents for Diarrhea, Ulcerative Colitis, and Crohn Disease

<table>
<thead>
<tr>
<th>Therapeutic Agent (common name, if relevant) [trade name, where appropriate]</th>
<th>Class—Pharmacology and Pharmacokinetics</th>
<th>Indications</th>
<th>Side Effects or Adverse Effects</th>
<th>Contraindications or Precautions to Consider; Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Loperamide [Imodium]</td>
<td>Antidiarrheal—similar to opioid agonist</td>
<td>Oral antidiarrheal</td>
<td>Malaise, nausea, sulfonamide toxicity, reversible oligospermia</td>
<td>Activated by colonic bacteria</td>
</tr>
<tr>
<td>Sulfasalazine</td>
<td>Anti-inflammatory—sulfapyridine (antibacterial) and mesalamine (anti-inflammatory)</td>
<td>Ulcerative colitis, Crohn disease</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Infliximab</td>
<td>Anti-inflammatory—monoclonal antibody that binds TNF → inhibits proinflammatory effects of TNF</td>
<td>Crohn disease, rheumatoid arthritis</td>
<td>Respiratory infection, fever, and hypotension</td>
<td></td>
</tr>
</tbody>
</table>

TNF, tumor necrosis factor.

### TABLE 5-18 Therapeutic Agents for Nausea

<table>
<thead>
<tr>
<th>Therapeutic Agent (common name, if relevant) [trade name, where appropriate]</th>
<th>Class—Pharmacology and Pharmacokinetics</th>
<th>Indications</th>
<th>Side Effects or Adverse Effects</th>
<th>Contraindications or Precautions to Consider; Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Scopolamine [Phenergan]</td>
<td>Anticholinergic—M₁-muscarinic receptor antagonist</td>
<td>Motion sickness; prophylaxis</td>
<td>Dry mouth, drowsiness, and vision disturbances</td>
<td>Delivered transdermally</td>
</tr>
<tr>
<td>Promethazine</td>
<td>Antihistamine—D₂-receptor antagonist; H₁ blocker</td>
<td>Counteracts nausea of migraine; allergies; motion sickness</td>
<td>Sedation, CNS depression, atropine-like effects, allergic dermatitis, blood dyscrasias, teratogenicity, acute antihistamine poisoning</td>
<td></td>
</tr>
<tr>
<td>Prochlorperazine [Compazine]</td>
<td>Dopamine antagonist—D₂-receptor antagonist</td>
<td>Nausea; counteracts nausea of migraine</td>
<td>Teratogenic</td>
<td></td>
</tr>
<tr>
<td>Metoclopramide [Reglan]</td>
<td>Dopamine antagonist—central and peripheral D₂, antagonism at low doses and weak 5-HT₃ antagonism at high doses; enhances acetylcholine release, prokinetic</td>
<td>Nausea; counteracts nausea of migraine; increases stomach motility</td>
<td>Sleepiness, fatigue, headache, insomnia, dizziness, nausea, akathisia, dystonia, and tardive dyskinesia</td>
<td></td>
</tr>
<tr>
<td>Ondansetron [Zofran]</td>
<td>Serotonin antagonist—5-HT₃ blocker</td>
<td>Nausea (caused by cancer therapy or postoperative state)</td>
<td>Headache, constipation, and dizziness</td>
<td></td>
</tr>
</tbody>
</table>

5-HT, serotonin; CNS, central nervous system.
<table>
<thead>
<tr>
<th>Therapeutic Agent (common name, if relevant) [trade name, where appropriate]</th>
<th>Class—Pharmacology and Pharmacokinetics</th>
<th>Indications</th>
<th>Side Effects or Adverse Effects</th>
<th>Contraindications or Precautions to Consider; Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methylcellulose [Citrucel] Psyllium [Perdiem Fiber]</td>
<td>Bulk-forming laxative—dietary fiber</td>
<td>Constipation</td>
<td>Impaction above strictures, fluid overload, gas, and bloating</td>
<td></td>
</tr>
<tr>
<td>Lactulose</td>
<td>Osmotic laxative</td>
<td>Decreases ammonia in hepatic encephalopathy; constipation</td>
<td>Abdominal bloating and flatulence</td>
<td>Lowers colon pH so that ammonia is trapped and then excreted</td>
</tr>
<tr>
<td>Magnesium hydroxide [milk of magnesia]</td>
<td>Osmotic laxative</td>
<td>Constipation, peptic ulcer, gastritis, and esophageal reflux</td>
<td>Diarrhea</td>
<td></td>
</tr>
<tr>
<td>Magnesium sulfate, Magnesium citrate</td>
<td>Osmotic laxative</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Docusate</td>
<td>Stool softener; by emulsifying stool, it makes the passage of stool easier</td>
<td>Constipation</td>
<td>Skin rash</td>
<td></td>
</tr>
<tr>
<td>Bisacodyl [Dulcolax]</td>
<td>Stimulant laxative; increases peristalsis</td>
<td>Constipation</td>
<td>Electrolyte imbalances (chronic use); gastric irritation</td>
<td></td>
</tr>
<tr>
<td>Senna [Senokot]</td>
<td>Stimulant laxative; increases peristalsis</td>
<td>Constipation</td>
<td>Electrolyte imbalances (chronic use); melanosis coli</td>
<td></td>
</tr>
<tr>
<td>Phenolphthalein [Ex-Lax]</td>
<td>Stimulant laxative—reduces the absorption of electrolytes and water from the gut</td>
<td>Constipation</td>
<td>Tumorigenic</td>
<td></td>
</tr>
<tr>
<td>Anthraquinones</td>
<td>Stimulant laxative—reduces the absorption of electrolytes and water from the gut</td>
<td>Constipation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Castor oil</td>
<td>Stimulant laxative—reduces the absorption of electrolytes and water from the gut; active component is ricinoleic acid</td>
<td>Constipation, labor induction</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mineral oil [Fleet Mineral Oil Enema]</td>
<td>Hyperosmolar agent—draws water into the gut lumen → gut distension → promotes peristalsis and evacuation of bowel</td>
<td>Preoperative patients; short-term treatment of constipation</td>
<td>May interfere with the absorption of fat-soluble vitamins</td>
<td></td>
</tr>
<tr>
<td>Metoclopramide [Reglan]</td>
<td>Prokinetic agent—D₂ receptor antagonist, increases resting tone, contractility, LES tone, and motility (does not affect colon transit time)</td>
<td>Diabetic and postoperative gastroparesis</td>
<td>Sleepiness, fatigue, headache, insomnia, dizziness, nausea, akathisia, dystonia, and tardive dyskinesia</td>
<td>Interacts with digoxin and diabetic agents; contraindicated in small bowel obstruction</td>
</tr>
</tbody>
</table>

LES, lower esophageal sphincter.
DEVELOPMENT

I. Intermediate mesoderm
   A. This forms the urogenital ridges on each side of the aorta.
   B. The nephrogenic cord arises from the urogenital ridge and gives rise, wholly or in part, to the pronephros, the mesonephros, and the metanephros.

II. Pronephros
   A. Forms in the fourth week
   B. Quickly regresses by the fifth week
   C. Nonfunctional

III. Mesonephros
   A. Forms late in the fourth week and is functional until the permanent kidney is able to develop
   B. The mesonephric duct forms from the mesonephros.
      1. Forms the ductus deferens, epididymis, ejaculatory duct, and seminal vesicle in the male
      2. Forms the ureteric bud from which the ureter, renal pelvis, calyces, and collecting tubules in both the male and female are derived
      3. No important genital or reproductive derivatives of the mesonephric duct specific to females are formed.

IV. Metanephros
   A. Develops into the adult kidney
   B. Formed during the fifth week from the ureteric bud and the metanephric mass (which is induced to form by contact with the ureteric bud) and begins to function in the ninth week
   C. Metanephric mesoderm forms the nephrons.
   D. “Ascends” from sacral levels to low thoracic levels during its development because of longitudinal growth of the fetus
   E. Urogenital sinus forms the bladder, which is continuous with allantois. Allantois is equivalent to the median umbilical ligament in the adult.
   F. Urethra
      1. Formed from endoderm and urogenital sinus
      2. Distal portion formed from ectoderm

V. Congenital anomalies of the renal system (Table 6-1)
The Renal System

GROSS DESCRIPTION OF THE KIDNEY

I. Paired adult kidneys weigh approximately 150 g each.

II. They are located posterior to the peritoneum and at approximately the level of the first lumbar vertebra.

III. The right kidney is slightly lower than the left, owing to downward displacement by the liver.

IV. The left renal vein lies posterior to the superior mesenteric artery and anterior to the abdominal aorta.

V. The kidney is highly vascularized; it filters more than 1,700 L of blood per day to produce about 1 L of urine.

VI. Kidney and urinary tract (Figure 6-1)

VII. Distribution of body water (Figure 6-2)

TABLE 6-1 Congenital Anomalies

<table>
<thead>
<tr>
<th>Anomaly</th>
<th>Characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bilateral renal agenesis (Potter sequence)</td>
<td>• Occurs when the ureteric bud does not form</td>
</tr>
<tr>
<td></td>
<td>• Oligohydramnios</td>
</tr>
<tr>
<td></td>
<td>• Limb deformities</td>
</tr>
<tr>
<td></td>
<td>• Facial deformities</td>
</tr>
<tr>
<td></td>
<td>• Pulmonary hypoplasia</td>
</tr>
<tr>
<td></td>
<td>• Bilateral agenesis is not compatible with life</td>
</tr>
<tr>
<td>Accessory renal arteries</td>
<td>• Arise from the aorta</td>
</tr>
<tr>
<td></td>
<td>• Feed a particular section of the kidney</td>
</tr>
<tr>
<td></td>
<td>• Are end arteries</td>
</tr>
<tr>
<td></td>
<td>• Cutting will produce ischemic infarct in the area they supply</td>
</tr>
<tr>
<td>Congenital polycystic kidney disease</td>
<td>• Multiple small and large cysts causing renal insufficiency</td>
</tr>
<tr>
<td></td>
<td>• Cysts are “closed”—not continuous with collecting system</td>
</tr>
<tr>
<td></td>
<td>• Enlarged kidneys palpable on newborn examination</td>
</tr>
<tr>
<td></td>
<td>• Death within days to weeks</td>
</tr>
<tr>
<td>Horseshoe kidney</td>
<td>• Inferior poles of the kidneys are fused</td>
</tr>
<tr>
<td></td>
<td>• Ascent is arrested at the level of the inferior mesenteric artery</td>
</tr>
<tr>
<td></td>
<td>• Increases probability of Wilms tumor</td>
</tr>
</tbody>
</table>

QUICK HIT

In the adult male, the ureter passes posterior to the ductus deferens; in the adult female, the ureter passes posterior to the uterine artery.

To remember the relationship of the arteries to the ureter, think “water under the bridge”; the ureters (which carry water) are posterior to the ovarian/testicular artery and uterine artery.

The left gonadal (testicular or ovarian) vein drains into the left renal vein; the right gonadal vein drains directly into the inferior vena cava.

QUICK HIT

In the adult male, the ureter passes posterior to the ductus deferens; in the adult female, the ureter passes posterior to the uterine artery.
THE RENAL SYSTEM

The Renal System

Ureter
Glomerular capillary tufts
Bowman capsule
Urinary space
Parietal epithelial (capsular cells)
Basement membrane
Mesangial cell
Mesangial matrix
Endothelial cell
Foot processes
Capillary lumen
Epithelial cell
Collecting duct
Loop of Henle

Kidney
Urethra

Bladder

F I G U R E  6-1
The kidney and urinary tract

F I G U R E  6-2
Distribution of body water

Total body water (TBW)

Men = 60% of body weight
Women = 50% of body weight
measured by tritiated H₂O
or D₂O

Intracellular fluid (ICF)
2/3 of TBW
• Cations = K⁺ and Mg²⁺
• Anions = proteins
and organic phosphates
• Measured by TBW – ECF
• Adipose tissue
devoid of H₂O

Extracellular fluid (ECF)
1/3 of TBW
• Cation = Na⁺
• Anions = Cl⁻ and
HCO₃⁻
• Measured by
insulin,
mannitol,
sulfate

Plasma
1/4 of ECF
• Measured by
Evans blue

Interstitial
3/4 of ECF
• Measured by
ECF – plasma
volume

Cl⁻, chloride; D₂O, heavy water; HCO₃⁻, bicarbonate; H₂O, water; K⁺, potassium; Mg²⁺, magnesium; Na⁺, sodium.

(Adapted with permission from Damjanov I. A Color Atlas and Textbook of Histopathology. Baltimore, MD: Lippincott Williams & Wilkins; 1996.)
NORMAL KIDNEY FUNCTION

I. Renal blood flow (RBF)
   A. 25% of cardiac output
   B. \[ \text{RBF} = \frac{\text{renal plasma flow (RPF)}}{[1 - \text{hematocrit (Hct)}]} \]
   C. Renal vasculature autoregulates RBF, keeping it constant even when arterial pressure varies from 100 to 200 mm Hg.

II. Renal plasma flow
   A. Effective RPF is measured by clearance of para-aminohippuric acid (PAH), which is filtered and secreted.
   B. This measurement underestimates by 10%.

III. Glomerular filtration rate (GFR)
   A. Normal GFR is 90 to 125 mL/min based on creatinine.
   B. It is measured by inulin clearance. Inulin is an ideal marker for the measurement of GFR because it is a substance that is filtered by the kidney but not reabsorbed or secreted. Therefore, urine levels of inulin vary directly with GFR. However, inulin clearance is not practical for clinical use.
   C. GFR is clinically measured with creatinine clearance. Endogenous creatinine is the most common clinical marker because it is filtered, minimally secreted, and not reabsorbed by the kidneys. Although creatinine excretion is generally 10% to 20% greater than filtration, this discrepancy is cancelled by the overestimation of plasma creatinine. Therefore, creatinine is relatively accurate for GFR calculation.
      1. Decreases in GFR cause a rise in blood urea nitrogen (BUN) and creatinine levels.
      2. GFR decreases with age.
   D. GFR is driven by Starling forces (filtration is always favored) (Figure 6-3).
   E. Renal clearance
      1. Removal of a substance from the blood by renal excretion
      2. Determined by the following equation:
         \[ \text{Clearance} = \frac{[U \times V]}{P} \text{ (in mL/min)} \]
         where \[ U = \text{concentration of substance in urine in mg/mL} \]
         \[ V = \text{urine volume (urine flow rate) in mL/min} \]
         \[ P = \text{plasma concentration of substance in mg/mL} \]

The Starling forces influence the glomerular filtration rate (GFR)
\[ \text{GFR} = K_f \times [(P_{GC} - P_{BS}) - (\pi_{GC} - \pi_{BS})] \]
where \( K_f \): The filtration coefficient of the glomerular capillaries
\( P_{GC} \): The hydrostatic pressure exerted by the fluid in the glomerular capillary. A dilated afferent arteriole increases \( P_{GC} \), as does a constricted efferent arteriole.
\( P_{BS} \): The hydrostatic pressure exerted by the fluid in Bowman space. Blockage or constriction of the ureters increases \( P_{BS} \).
\( \pi_{GC} \): The oncotic pressure of the glomerular capillary. The value of \( \pi_{GC} \) increases along the length of the capillary because the protein concentration in the capillary increases as water is forced into Bowman space.
\( \pi_{BS} \): The oncotic pressure in Bowman space. This value is usually zero.
Note: One common pitfall to using creatinine is muscle mass. Plasma creatinine varies directly with muscle mass, so individuals with lower muscle mass (e.g., emaciated, elderly) may have an artificially higher GFR and individuals with high muscle mass (e.g., bodybuilders) may have an artificially lower GFR. Similarly, with age and loss of muscle mass, GFR may remain stable when in fact there is a decline in glomerular function and a decrease in GFR.

3. Factors that determine clearance
   a. Highly cleared substances (e.g., PAH) are those that are filtered and secreted and not reabsorbed.
   b. Poorly cleared substances are those that are either not filtered (e.g., protein) or are completely reabsorbed (e.g., glucose).
   c. Reabsorption
      • Limited by the number of transporters for certain compounds (e.g., glucose) in various segments of tubule
      • Transport maximum ($T_m$) is the maximum rate of reabsorption at which the transporters are saturated.
      • At concentrations above $T_m$, excess is excreted.

IV. Filtration fraction (FF)
A. $FF = \frac{GFR}{RPF}$
B. The normal FF is 20%.
C. Variables that change FF:
   1. Ureteral obstruction decreases FF.
   2. Increased plasma proteins decrease FF (e.g., multiple myeloma).
   3. Decreased plasma proteins increase FF (e.g., liver failure).
   4. Constriction of efferent arteriole increases FF (e.g., angiotensin II).
   5. Dilatation of efferent arteriole decreases FF (e.g., ACE inhibitors).
   6. Constriction of afferent arteriole (e.g., nonsteroidal anti-inflammatory drugs [NSAIDs]) and dilatation of afferent arteriole (e.g., prostaglandins) changes GFR and RPF, but the FF remains constant.

V. Innervation and hormones
A. Juxtaglomerular apparatus (JGA) produces renin and is stimulated by the β-sympathetic adrenergics in the kidney and by a fall in pressure of the afferent arteriole.
B. Renin cleaves angiotensinogen to angiotensin I.
C. Angiotensin I is cleaved to angiotensin II by angiotensin-converting enzyme (ACE) in the lung.
   1. Functions of angiotensin II
      a. Stimulates aldosterone release from the zona glomerulosa
      b. Stimulates secretion of antidiuretic hormone (ADH, also known as arginine vasopressin [AVP]) and adrenocorticotropic hormone (ACTH) from the pituitary
      c. Acts as a potent local vasoconstrictor of the renal arterioles at low plasma levels
      d. Acts as a general systemic vasoconstrictor at high plasma levels
      e. Stimulates thirst
      f. Stimulates epinephrine and norepinephrine release from adrenal medulla
   2. Angiotensin II is inactivated to angiotensin III, a potent stimulator of aldosterone secretion but not an effective vasoconstrictor.

VI. Hormones and the nephron (Figure 6-4)

VII. Effects of volume change on fluid levels (Table 6-2)
A variety of hormones, such as ADH, aldosterone, and atrial natriuretic factor, regulate extracellular and intracellular volumes. Intake and output, as well as hormonal imbalance, can significantly alter the homeostatic fluid balance in the body.

QUICK HIT
ACE inhibitors, such as captopril and enalapril, reduce hypertension by inhibiting the conversion of angiotensin I to angiotensin II, thereby decreasing the release of aldosterone. Angiotensin II receptor blockers, such as losartan and valsartan, prevent angiotensin II from interacting with its receptor. This prevents angiotensin II from causing constriction of efferent arterioles.

QUICK HIT
The $T_m$ for glucose is reached at approximately 350 mg/dL. Greater concentrations result in an osmotic diuresis, such as that seen in diabetics with hyperglycemia.

QUICK HIT
Fanconi syndrome is a hereditary or acquired dysfunction of the proximal renal tubules. As a result of impaired glucose, amino acid, phosphate, and bicarbonate reabsorption, it manifests clinically as glycosuria, hyperphosphaturia, aminoaciduria, and acidosis.
### TABLE 6-2  **Effects of Volume Change on Fluid Levels**

<table>
<thead>
<tr>
<th>Type</th>
<th>Key Examples</th>
<th>ECF Volume</th>
<th>ICF Volume</th>
<th>ECF Osmolarity</th>
<th>Hct and Serum [Na⁺]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Isosmotic volume expansion</td>
<td>Isotonic fluid infusion (e.g., normal saline or lactated Ringer solution)</td>
<td>↑</td>
<td>No change</td>
<td>No change</td>
<td>↓ Hct — [Na⁺]</td>
</tr>
<tr>
<td>Isosmotic volume contraction</td>
<td>Diarrhea</td>
<td>↓</td>
<td>No change</td>
<td>No change</td>
<td>↑ Hct — [Na⁺]</td>
</tr>
<tr>
<td>Hypersmotic volume expansion</td>
<td>High NaCl intake</td>
<td>↑</td>
<td>↓</td>
<td>↑</td>
<td>↓ Hct ↑ [Na⁺]</td>
</tr>
<tr>
<td>Hypersmotic volume contraction</td>
<td>Sweating, fever, diabetes insipidus</td>
<td>↓</td>
<td>↓</td>
<td>↑</td>
<td>– Hct ≠ [Na⁺]</td>
</tr>
<tr>
<td>Hypopsmotic volume expansion</td>
<td>SIADH</td>
<td>↑</td>
<td>↑</td>
<td>↓</td>
<td>– Hct ↓ [Na⁺]</td>
</tr>
<tr>
<td>Hypopsmotic volume contraction</td>
<td>Adrenal insufficiency</td>
<td>↓</td>
<td>↑</td>
<td>↑</td>
<td>↑ Hct ↓ [Na⁺]</td>
</tr>
</tbody>
</table>

—, no change; ECF, extracellular fluid; Hct, hematocrit; ICF, intracellular fluid; Na⁺, sodium; SIADH, syndrome of inappropriate secretion of antidiuretic hormone. Reproduced with permission from Costanzo LS: *BRS Physiology*. 2nd ed. Baltimore, MD: Lippincott Williams & Wilkins; 1998.
VIII. Electrolyte balance in the nephron (Figure 6-5)
Acidosis or alkalosis is determined by evaluating blood pH, arterial partial pressure of carbon dioxide (\(\text{P} \text{CO}_2\)), and bicarbonate (\(\text{HCO}_3^-\)) concentration. Anion gap (AG) is calculated using the following equation: \(\text{AG} = \text{Na}^+ - (\text{Cl}^- + \text{HCO}_3^-)\). A normal AG is between 10 and 16 mEq/L. Certain acidic conditions result in an elevated AG by altering the concentration of anions not considered in the above formula (lactate, \(\beta\)-hydroxybutyrate, formate). Table 6-3 compares acidosis with alkalosis. Table 6-4 outlines the effects of metabolic and respiratory acid-base disturbances.
TABLE 6-3 Acidosis and Alkalosis

<table>
<thead>
<tr>
<th>Metabolic Disturbance</th>
<th>Presentation</th>
<th>Causes</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Metabolic acidosis</strong></td>
<td>Fatigue</td>
<td>Chronic renal failure</td>
</tr>
<tr>
<td></td>
<td>Shortness of breath</td>
<td>Lactic acidosis</td>
</tr>
<tr>
<td></td>
<td>Abdominal pain</td>
<td>Uremia</td>
</tr>
<tr>
<td></td>
<td>Vomiting</td>
<td><strong>Ketoacidosis</strong></td>
</tr>
<tr>
<td></td>
<td>Kussmaul respirations</td>
<td>Intoxication (aspirin, methanol, ethylene glycol)</td>
</tr>
<tr>
<td></td>
<td>Hypotension</td>
<td>Diarrhea$^a$</td>
</tr>
<tr>
<td></td>
<td>Tachycardia</td>
<td>Renal tubular acidosis$^a$</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Acetazolamide$^a$</td>
</tr>
<tr>
<td><strong>Respiratory acidosis</strong></td>
<td>Hypercapnia</td>
<td>Respiratory depression by drugs</td>
</tr>
<tr>
<td></td>
<td>Confusion</td>
<td>Cerebral disease</td>
</tr>
<tr>
<td></td>
<td>Blunted sensation and pain</td>
<td>Cardiopulmonary arrest response</td>
</tr>
<tr>
<td></td>
<td>Asterixis</td>
<td>Neuromuscular disease (e.g., myasthenia gravis)</td>
</tr>
<tr>
<td></td>
<td>Papilledema</td>
<td>Poor ventilation secondary to disease (e.g., asthma, pneumonia, bronchitis, emphysema)</td>
</tr>
<tr>
<td><strong>Metabolic alkalosis</strong></td>
<td>No specific signs or symptoms</td>
<td>Diuretics (loop and thiazide)</td>
</tr>
<tr>
<td></td>
<td>Can cause apathy, stupor, and confusion</td>
<td>Vomiting</td>
</tr>
<tr>
<td></td>
<td>If coupled with low calcium, can cause tetany</td>
<td>Milk alkali syndrome</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Large intake of alkaline substance</td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>Cushing syndrome</strong></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Primary aldosteronism</td>
</tr>
<tr>
<td><strong>Respiratory alkalosis</strong></td>
<td>Hyperventilation</td>
<td>Asthma</td>
</tr>
<tr>
<td></td>
<td>Numbness</td>
<td>Pneumonia</td>
</tr>
<tr>
<td></td>
<td>Tingling</td>
<td>Pulmonary edema</td>
</tr>
<tr>
<td></td>
<td>Paresthesia</td>
<td>Heart disease with cyanosis</td>
</tr>
<tr>
<td></td>
<td>Tetany, if severe</td>
<td>Pulmonary fibrosis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Aspirin intoxication</td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>Gram-negative sepsis</strong></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Fever</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Anxiety</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Pregnancy</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Drugs</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Conditions that stimulate the medullary respiratory center (e.g., altitude)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Aspirin intoxication (via stimulation of respiratory center)</td>
</tr>
</tbody>
</table>

$^a$Normal anion gap acidosis (other acidosis items have an increased anion gap).

To remember the causes of increased anion gap metabolic acidosis, think **MUDPILES**: Methanol, Uremia, Diabetic ketoacidosis, Paraldehyde, Isoniazid or iron tablets, Lactic acidosis, Ethylene glycol, Salicylates.

Renal tubular acidosis (RTA) is characterized by a normal anion gap. Type 1 (distal) RTA is caused by failure to excrete titratable acid and NH$_4^+$. Type 2 RTA is caused by renal loss of HCO$_3^-$, Type 4 RTA is caused by hypoaldosteronism, which leads to poor excretion of NH$_4^+$ and hyperkalemia.

Emphysema and bronchitis often cause chronic respiratory acidosis.

A patient’s respiratory status affects and is affected by his or her acid–base status. This is because of the reversible conversion of CO$_2$ to H$^+$ in the following way: H$_2$O + CO$_2$ $\leftrightarrow$ H$^+$ + H$_2$CO$_3$. The first reaction is catalyzed by the enzyme carbonic anhydrase.

Salicylate (aspirin) overdose causes respiratory alkalosis initially, followed by an increased anion gap metabolic acidosis.
A 24-year-old male medical student is brought to the emergency department after being found unconscious in his apartment by his roommate. It is unknown whether he suffered any trauma, but the roommate tells you that they just finished exam week at the medical school. There are no signs of injury on examination. The roommate tells you that the patient has no other medical problems. The patient cannot be aroused in the emergency department but does respond to pain. Vital signs: temperature 100.8°F; respiration rate (RR) 35 breaths/min; blood pressure 150/90 mm Hg; heart rate 104 bpm. Pupils are round and reactive to light bilaterally.

Laboratory tests reveal the following: WBC 8.4; Hgb 14.2; Hct 30.9; Na 140; K 3.8; Cl 102; HCO$_3^-$ 13; BUN = 16; Cr = 0.8; Gluc = 110. Arterial blood gasses are obtained and reveal the following: pH 7.19; PaCO$_2$ 26; PaO$_2$ 95.

DIFFERENTIAL: This patient has metabolic acidosis. In approaching a patient with metabolic acidosis, the first step is the calculation of the AG:

\[ \text{AG} = \text{Na}^+ - (\text{Cl}^- + \text{HCO}_3^-) \]

This patient has an increased AG metabolic acidosis (AG > 15) for which differentials are diabetic ketoacidosis (DKA), alcoholic ketoacidosis, lactic acidosis, starvation, renal failure, and overdose of salicylate, methanol, or ethylene glycol. Given that the patient is not diabetic and has a glucose of 114 mg/dL, DKA is unlikely. Also, renal function is not impaired. Because the cause is unclear, further testing is necessary.

LABORATORY STUDIES: To determine the cause of the AG metabolic acidosis in this patient, serum ketone, salicylate, lactate, blood alcohol, methanol, and ethylene glycol levels should be obtained. Next, determine whether this is a primary acid–base disorder or mixed disorder. Using Winter’s formula [1.5 (measured HCO$_3^-$) + 8 ± 2], the expected PaCO$_2$ level in this patient is 25.5 to 29.5 mm Hg. With a PaCO$_2$ of 26 mm Hg, this patient has an appropriate respiratory compensation response (RR of 35 breaths/min). If actual PaCO$_2$ is higher than expected, there is an additional acidotic process occurring. If actual PaCO$_2$ is lower than expected, then there is an additional alkalotic process occurring.

MANAGEMENT: Management depends on the cause of metabolic acidosis. Sodium bicarbonate may be needed in cases of severe acidemia, and mechanical ventilation may be required if patient is fatigued from hyperventilation.
GLOMERULAR DISEASES

I. Nephrotic syndrome

A. Features
   1. **Proteinuria** of >3.5 g of protein per 24 hours
   2. **Hypoalbuminemia**
   3. **Edema**
   4. **Hyperlipidemia**

B. Etiology
   1. Idiopathic—75%
   2. Systemic disease—25%

C. Common types (Table 6-5)

II. Nephritic syndrome

A. Features
   1. **Hematuria**
   2. **Hypertension**
   3. **Oliguria**
   4. **Azotemia**

B. Common types of nephritic glomerular diseases (Table 6-6)

III. Glomerular deposits in disease (Figure 6-9)

### TABLE 6-5 Nephrotic Glomerular Diseases

<table>
<thead>
<tr>
<th>Glomerular Disease</th>
<th>Etiology</th>
<th>Clinical Features</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Minimal change disease (lipoid nephrosis)</td>
<td>Fusion of foot processes on the basement membrane leads to loss of negative charge and changes in the protein selectivity; altered appearance of villi on epithelial cells</td>
<td>Electron microscopy shows <strong>fusion of podocyte foot processes</strong> (Figure 6-8) and lipid-laden renal cortices</td>
<td>Common in young children (usually younger than 5 years of age); responds well to steroids; albumin usually selectively secreted</td>
</tr>
<tr>
<td>Membranous nephropathy</td>
<td>Idiopathic; secondarily caused by SLE, hepatitis B, syphilis, gold, penicillamine, malignancy</td>
<td>Basement membrane thickening; <strong>“spike and dome” with subepithelial IgG and C3 deposits</strong></td>
<td>Common in young adults</td>
</tr>
<tr>
<td>Diabetic nephropathy</td>
<td>Microangiopathy leading to thickening of basement membrane</td>
<td>Basement membrane thickening</td>
<td>Two types: diffuse and nodular glomerulosclerosis; nodular glomerulosclerosis has <strong>Kimmelstiel-Wilson nodules</strong> (Figure 6-7); usually leads to renal failure</td>
</tr>
<tr>
<td>Renal amyloidosis</td>
<td>Subendothelial or mesangial amyloid deposits; associated with multiple myeloma</td>
<td>Stains: periodic acid-Schiff (PAS) {−}; Congo Red (+)</td>
<td>Increasing severity leads to renal failure</td>
</tr>
<tr>
<td>Focal and segmental glomerulosclerosis</td>
<td>Has four possible etiologies: idiopathic; superimposed on preexisting pathology; associated with loss of renal mass; secondary to other disorders (e.g., heroin abuse or HIV)</td>
<td>Sclerosis of some glomeruli; only capillary tuft is involved in affected glomeruli</td>
<td>Clinically similar to minimal change disease but affects older population</td>
</tr>
</tbody>
</table>

C3, third component of complement; IgG, immunoglobulin G; SLE, systemic lupus erythematosus.
**FIGURE 6-6** Minimal change disease

Electron micrograph showing effacement of the podocyte foot processes. BM, basement membrane; EC, endothelial cell; US, urinary space; V, vacuole. (Reproduced with permission from Rubin E, Farber JL. Pathology. 3rd ed. Philadelphia, PA: Lippincott Williams & Wilkins; 1999.)

**FIGURE 6-7** Diabetic nodular glomerulosclerosis

A periodic acid-Schiff stain demonstrates nodular Kimmelstiel-Wilson lesions at the periphery of the glomerulus, which are pathognomonic of diabetic glomerulosclerosis. (Reproduced with permission from Rubin E, Farber JL. Pathology. 3rd ed. Philadelphia, PA: Lippincott Williams & Wilkins; 1999.)
### TABLE 6-6 Nephritic Glomerular Diseases

<table>
<thead>
<tr>
<th>Disease</th>
<th>Etiology</th>
<th>Special Features</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Poststreptococcal glomerulonephritis</td>
<td>Poststreptococcal pharyngitis or impetigo, hepatitis B, high ASO titer, low C3, type III hypersensitivity</td>
<td>“Lumpy bumpy” deposits of antigen-antibody-C3 complexes, subepithelial humps on electron microscopy</td>
<td>Common in children, self-resolving, most common organisms are group A hemolytic streptococci, red cell casts in urine</td>
</tr>
<tr>
<td>Rapidly progressive (crescentic) glomerulonephritis</td>
<td>ANCA positive, poststreptococcal etiology 50%, renal failure within weeks or months</td>
<td>Accumulation of fibrin, macrophages, and PMNs in Bowman capsule; wrinkling of basement membrane on electron microscopy (crescents)</td>
<td>If it also involves upper respiratory system, then it is termed Wegener granulomatosis</td>
</tr>
<tr>
<td>Goodpasture syndrome</td>
<td>Antiglomerular basement membrane and alveolar basement membrane antibodies (type II hypersensitivity)</td>
<td>Linear pattern of IgG on fluorescence microscopy; may be associated with hemoptysis and pulmonary hemorrhage</td>
<td>Usually males in their mid-20s</td>
</tr>
<tr>
<td>Alport syndrome</td>
<td>Hereditary structural defect in collagen IV leads to leaky basement membrane</td>
<td>Glomerular basement membrane splitting on electron microscopy</td>
<td>Appears before age 20 years; associated with deafness and ocular problems</td>
</tr>
<tr>
<td>Lupus nephropathy</td>
<td>Anti-dsDNA</td>
<td>WHO classifications: <em>WHO I: normal</em> <em>WHO II: mesangial proliferation, little clinical relevance</em> <em>WHO III (focal proliferative): &lt;50% of glomeruli affected</em> <em>WHO IV (diffuse proliferative): worst prognosis; wire-loop lesions (Figure 6-B) (subendothelial immune complex deposition of IgM and IgG + C3)</em> <em>WHO V: membranous glomerulonephritis</em></td>
<td>Degree of kidney involvement correlates to SLE prognosis; may have nephritic qualities</td>
</tr>
<tr>
<td>IgA nephropathy (Berger disease)</td>
<td>IgA deposits in mesangium; hematuria usually follows infection</td>
<td>Mesangial cell proliferation on electron microscopy</td>
<td>Minimal clinical significance; common</td>
</tr>
<tr>
<td>Membranoproliferative glomerulonephritis</td>
<td>Type 2 has IgG autoantibody; C3 is reduced in all three types</td>
<td>Basement membrane thickens and appears as two layers, “train-track” appearance on electron microscopy</td>
<td>Three types: type 1, type 2 (dense deposit disease), and type 3; may lead to either nephrotic or nephritic syndromes</td>
</tr>
</tbody>
</table>

ANCA, antineutrophil cytoplasmic antibody; ASO, antistreptolysin-O; C3, third component of complement; dsDNA, double-stranded DNA; Ig, immunoglobulin; PMN, polymorphonuclear leukocyte; SLE, systemic lupus erythematosus; WHO, World Health Organization.
URINARY TRACT INFECTIONS

I. Cystitis
   A. Characteristic clinical features
      1. Dysuria
      2. Frequency
      3. Urgency
      4. Suprapubic pain
   B. Etiology and pathogenesis
      1. Bacteria gain access to the urinary tract via the urethra.
      2. Cystitis most frequently involves normal colonic flora.
         a. Escherichia coli is the most common cause (approximately 80%).
         b. Proteus, Klebsiella, and Enterobacter are also implicated.
         c. Staphylococcus saprophyticus causes 10% to 15% of infections in young women.
         d. Nosocomial cystitis is frequently caused by Pseudomonas or Staphylococcus aureus.
      3. Women have a higher incidence of infection because they have shorter urethras.
      4. Other risk factors include sexual activity, pregnancy, urinary obstruction, neurogenic bladder, and vesicoureteral reflux.
A 6-year-old girl presents to her pediatrician with puffy eyes of 2 weeks’ duration. The mother tells you that the patient has been taking more naps than usual and that the pants they had bought recently no longer fit her around the waist. The parents deny any recent upper respiratory infections (URIs). Physical examination shows periorbital edema, pedal edema, ascites, and weight gain. Cardiothoracic and pulmonary exam is negative, and vital signs are normal.

**DIFFERENTIALS:**
- Nephrotic syndrome, glomerulonephritis, congestive heart failure, sinusitis, allergic reaction, hepatic failure. Generalized edema and fatigue are expected in nephrotic syndrome, glomerulonephritis, congestive heart failure (CHF), and hepatic failure. The absence of murmur/gallops/crackles makes CHF less likely. The absence of jaundice makes hepatic failure less likely. A recent URI would suggest glomerulonephritis. Sinusitis is more likely to produce edema localized to periorbital region. Abrupt onset periorbital edema along with conjunctivitis, urticarial rash, wheezing, and rhinorrhea is expected in an allergic reaction. Minimal change disease is the most common cause of nephrotic syndrome in the patient’s age group.
- Diabetic nephropathy (mesangial growth and thickened basement membrane)
- Poststreptococcal glomerulonephritis (‘lumpy bumpy’ subepithelial IgG and C3)
- Membranous glomerulonephritis (Spike and dome IgG and C3)
- Membranoproliferative glomerulonephritis (Mesangial interposition of intramembranous deposits ‘train-track’ appearance)
- Goodpasture disease (Linear basement membrane deposits of IgG and C3)
- Rapidly progressive glomerulonephritis (Wrinkled BM (IgG and C3) discontinuous basement membrane)
- Minimal change disease and focal segmental glomerular sclerosis

**LABORATORY STUDIES:**
- Urinalysis shows proteinuria in both nephrotic and nephritic syndromes but is more severe in nephrotic syndrome. Hematuria is seen in nephritic syndrome. Blood studies would reveal hypoalbuminemia and hyperlipidemia in nephrotic syndrome and azotemia in nephritic syndrome.

**MANAGEMENT:**
- Nephrotic syndrome is best treated by albumin infusion followed by diuretics and corticosteroids. Many children grow out of minimal change disease.
THE RENAL SYSTEM

C. Diagnostic findings
1. Characteristic clinical features are present.
2. Pyuria (more than 8 leukocytes/high-power field)
3. Bacterial culture yields $>10^5$ organisms/mL.

D. Treatment
1. Cystitis is treated with antibiotics.
2. Recurrent cystitis may require prophylactic antibiotics.

II. Acute pyelonephritis
A. Characteristic clinical features
   1. Flank pain or costovertebral angle tenderness
   2. Dysuria
   3. Fever
   4. Chills
   5. Nausea and vomiting
   6. Diarrhea
B. Etiology and pathogenesis
   1. Bacteria ascend from an infected urinary bladder to the kidney via the vesicoureteral reflux.
   2. Infection may also spread hematogenously to the kidney (may not necessarily be preceded by acute cystitis).
   3. Causative organism is usually E. coli
C. Diagnostic findings
   1. Characteristic clinical features are present.
   2. Bacteriuria, pyuria, and white blood cell casts are seen on urine microscopy.
   3. Urine and blood cultures are performed to determine infection.
D. Treatment
   1. Treatment is with antibiotics, often intravenously.
   2. Recurrent infection can lead to chronic pyelonephritis. This condition has several complications:
      a. Scarring and deformity of the renal pelvis and calyces
      b. Interstitial fibrosis and tubular atrophy
      c. Ischemia of the tubules leading to microscopic “thyroidization” of the kidney

MAJOR CAUSES OF ACUTE RENAL FAILURE (Figure 6-10)

I. Prerenal failure is defined as oliguria and an increase in BUN and creatinine with inherently normal renal function.
A. Hypovolemic states
   1. Hemorrhage
   2. Burns
   3. Dehydration
   4. Vomiting
   5. Diarrhea
   6. Diuretics
   7. Pancreatitis
B. Low cardiac output states
   1. Arrhythmias
   2. Pulmonary embolus
   3. Myocardial or valvular disease
   4. Cardiac tamponade
   5. Pulmonary hypertension
C. Renal vasoconstrictive states resulting in ischemia may be caused by the following:
   1. Cirrhosis with ascites
   2. Vasoconstrictive drugs: epinephrine, norepinephrine, cyclosporine, amphotericin B
D. Intrinsic decrease of renal perfusion
   1. Cyclooxygenase (COX) inhibitors, NSAIDs
   2. ACE inhibitors

To remember the most common pathogens of UTIs, think KEEPS: Klebsiella, Enterobacter, E. coli, Proteus, S. saprophyticus.

Quick Hit
Cyclooxygenase is inhibited by aspirin and other nonsteroidal anti-inflammatory drugs (NSAIDs).
The Renal System

Prerenal causes
- Hypovolemia
- Low cardiac output
- Increased systemic vascular resistance
- Drugs: NSAIDs, COX inhibitors, ACE inhibitors

Renal (intrinsic) causes
- Renovesicular obstruction
- Glomerulonephritis
- Hemolytic uremic syndrome (HUS)
- Thrombotic thrombocytopenic purpura (TTP)
- Disseminated intravascular coagulation (DIC)
- Systemic lupus erythematosus (SLE)
- Scleroderma
- Acute tubular necrosis (ATN)
- Interstitial nephritis

Postrenal causes
- Ureteric obstruction (bilateral)
- Prostatic hyperplasia
- Bladder neck obstruction
- Stricture
- Phimosis

ACE, angiotensin-converting enzyme; COX, cyclooxygenase; NSAIDs, nonsteroidal anti-inflammatory drugs.
II. Acute intrinsic renal failure is the inherent malfunction of the renal tissue. It may be glomerular, tubular, or interstitial. Table 6-7 compares prerenal failure with intrinsic renal failure.

A. Acute tubular necrosis (ATN)
   1. Drugs that may lead to ATN are exogenous toxins (contrast, cyclosporine, aminoglycosides, ethylene glycol, acetaminophen, heavy metals) or endogenous toxins (myoglobin, uric acid, oxalate).
   2. Ischemia can result in ATN via causes related to prerenal failure.

B. Obstruction of renal vasculature from atherosclerosis, vasculitis, or other factors may also cause acute intrinsic renal failure.

C. Diseases that affect the glomeruli or microvasculature
   1. Disseminated intravascular coagulation (DIC)
   2. Glomerulonephritis
   3. Hemolytic uremic syndrome (HUS)
   4. Thrombotic thrombocytopenic purpura (TTP)
   5. Pregnancy
   6. Scleroderma
   7. Systemic lupus erythematosus (SLE)

D. Interstitial nephritis can have many causes.
   1. β-Lactams
   2. Sulfonamides
   3. Trimethoprim (TMP)
   4. Rifampin
   5. COX inhibitors
   6. Diuretics
   7. Captopril
   8. Infection
   9. Idiopathic

E. Acute renal transplant rejection is a cause of ATN.

III. Postrenal failure is bilateral obstruction of the ureters or obstruction of the urethra. It accounts for less than 5% of acute renal failure (ARF) and has a variety of causes.

A. Urolithiasis (see section on stone formation)
B. Prostatic hyperplasia
C. Tumor obstructing the bladder or the ureters bilaterally
D. Neurogenic bladder

CHRONIC RENAL FAILURE AND UREMIA (Figure 6-11)

I. Major causes of chronic renal failure (CRF)
   A. Hypertension
   B. Diabetes mellitus
II. Profound loss of renal function leads to uremia.
A. GFR is reduced to 50% to 65% of normal.
B. By-products of amino acid and protein metabolism (especially urea) cause a variety of signs and symptoms.
   1. Endocrine and electrolyte findings
      a. Hyperkalemia
      b. Hyperphosphatemia
      c. Hypertriglyceridemia
      d. Hyperuricemia
      e. Hypocalcemia and osteomalacia as a result of decreased 1,25-dihydroxycholecalciferol levels
      f. Impaired growth and development
      g. Infertility and sexual dysfunction
      h. Metabolic acidosis
   2. Gastrointestinal findings
      a. Anorexia
      b. Nausea
      c. Peptic ulcer
      d. Vomiting
   3. Renal findings: azotemia
   4. Cardiovascular and pulmonary findings
      a. Arterial hypertension
      b. Congestive heart failure
      c. Pericarditis
5. Dermatologic findings
   a. Pallor
   b. Pruritus
   c. “Uremic frost” (crystallized urea on the skin)

6. Neuromuscular findings
   a. Asterixis
   b. Headache and fatigue
   c. Peripheral neuropathy

7. Hematologic findings
   a. Increased susceptibility to infection
   b. Lymphocytopenia and leukopenia
   c. Normocytic, normochromic anemia

Clinical Vignette 6-3

**CLINICAL PRESENTATION:** A 55-year-old woman presents to her primary care physician with the chief complaint of nausea, vomiting, and feeling “out of it” over the past 2 days. She also reports urinating less frequently and weight gain, although she does not have much of an appetite. Her past medical history is significant for CHF. Physical examination reveals generalized edema and a 10-lb weight gain since her last visit 1 month ago.

**DIFFERENTIALS:** Acute renal failure (ARF), chronic renal failure (CRF), acute tubular necrosis. ARF is defined as rapid, progressive decrease in renal function characterized by elevation in blood urea nitrogen/creatinine (BUN/Cr) and possibly oliguria. Renal failure can be pre-renal, intrinsic renal, or postrenal. Prerenal failure is caused by insufficient renal perfusion as in CHF, whereas postrenal failure is caused by obstructed renal outflow. Intrinsic renal failure is caused by parenchymal damage to the glomerulus, tubules, interstitium, or vasculature. There are a number of causes for each type of renal failure (Figure 6-10). In this patient, hypovolemia from CHF is the cause of insufficient renal perfusion. Acute tubular necrosis causes 85% of intrinsic renal failure, but we would expect some history of renal ischemia or toxin exposure (see Quick Hit). CRF has lab findings in common with ARF, but we would expect clinical manifestations of uremia and multiple instances of abnormal BUN, Cr, and urinalysis.

**LABORATORY STUDIES:** A urinalysis would be obtained looking for the presence of casts. Presence of muddy brown casts (seen in acute tubular necrosis), red blood cell (RBC) casts (glomerular disease), or white blood cell (WBC) casts (pyelonephritis, acute interstitial nephritis) would not be expected in ARF. Urine chemistry consisting of BUN/Cr, fractional excretion of sodium (FENa\(^+\)), and urine osmolality would also be obtained. In prerenal and postrenal failure, the BUN/Cr ratio is typically greater than 20:1 because of increased urea absorption as compared to intrinsic renal failure. In prerenal failure, the FENa\(^+\) is less than 1% because the decreased glomerular filtration rate causes massive reabsorption of sodium and water, whereas in intrinsic renal failure, the FENa\(^+\) is greater than 2% to 3% because Na is poorly reabsorbed. Similarly, we expect increased urine osmolality in prerenal failure because the kidney is able to reabsorb water, whereas we see decreased urine osmolality in intrinsic renal failure because renal water reabsorption is impaired. Also, renal ultrasound would be obtained to rule out obstruction. Renal ultrasound showing small, echogenic kidneys are pathognomonic of CRF.

**MANAGEMENT:** The most important part of therapy is to follow urinary output: Patients with ARF first experience an oliguric phase followed by a diuretic phase. Approximately 40% of patients go on to a recovery phase with normalization of urine output. Correct fluid imbalance—some patients with ARF are dehydrated, whereas others are volume overloaded. Correct any electrolyte abnormalities and optimize cardiac output. Order dialysis if symptomatic uremia, acidemia, hyperkalemia, or volume overload develops.
**KIDNEY STONE FORMATION** (Figure 6-12)

**Calcium stones**
- A. Calcium oxalate (CO)
- B. Calcium phosphate (CP)
- 80% of stones
- Men
- 20–30 years of age
- Multiple (every 2–3 years)
- Familial predisposition
- Radiopaque
- May be caused by primary hyperthyroidism
- CP stones form more readily in alkaline urine pH > 6

**Struvite**
- 12% of stones
- Women
- Risk factors: Catheter, UTIs (especially *Proteus*)
- May fill renal pelvis and calyces (“staghorn”)
- Radiopaque

**Uric acid**
- 7% of stones
- Men
- Risk factors: 50% have gout
- Strong negative birefringence
- Radiolucent
- Associated with cell lysis (e.g., chemotherapy, leukemia)
- Uric acid increases urine acidity to pH < 5.5

**Cystine**
- 1% of stones
- Uncommon
- Hereditary
- Radiopaque (because of sulfur component)
- Natural inhibitors of stone formation are (1) citrate, (2) nephrocalcin, (3) Tamm-Horsfall protein (aka uromodulin), and (4) uropontin.

Clinical manifestations of kidney stones include hematuria and flank pain. UTI, urinary tract infection.

**AUTOSOMAL DOMINANT POLYCYSTIC KIDNEY DISEASE** (Figure 6-13)

**Autosomal dominant polycystic kidney disease (ADPKD) versus normal kidney**

Normal kidney  
Kidney with ADPKD
I. Etiology of autosomal dominant polycystic kidney disease (ADPKD)
A. Autosomal dominant
B. Occurs in midlife

II. Clinical features of ADPKD
A. Bilateral
B. Kidney parenchyma is partially replaced with cysts
C. Hematuria
D. Hypertension
E. Large palpable kidneys
F. Progressively worsening renal function leading to renal failure

III. ADPKD is associated with berry aneurysms of circle of Willis and cystic disease in other organs, especially the liver.

RENNAL CANCERS (Table 6-8)

I. The classic triad of hematuria, flank pain, and a flank mass is seen only in 10% to 20% of patients with renal cancer. Most are sporadic; however, smoking accounts for 20% to 30% of the cases.

<table>
<thead>
<tr>
<th>Malignancy</th>
<th>Etiology</th>
<th>Clinical Features</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Renal cell carcinoma</td>
<td>Smoking; alteration of chromosome 3 (as seen in von Hippel-Lindau disease)</td>
<td>Afflicts men 45–65 years of age; hematuria; mass; pain; fever, secondary polycythemia; paraneoplastic syndrome; usually extends from renal poles, with clear cells</td>
<td>Most common renal malignancy; may be associated with increased erythropoietin (EPO)</td>
</tr>
<tr>
<td>Wilms tumor (nephroblastoma)</td>
<td>Chromosome 11 abnormality, WAGR</td>
<td>Palpable flank mass in children 2–5 years old; hematuria</td>
<td>Most common renal malignancy of childhood (see following)</td>
</tr>
<tr>
<td>Transitional cell carcinoma</td>
<td>Cyclophosphamide treatment, smoking, aniline dye exposure</td>
<td>Hematuria</td>
<td>Most common tumor of the collecting system</td>
</tr>
</tbody>
</table>

WAGR, Wilms tumor, aniridia, genitourinary abnormalities, and mental retardation.

II. Nephroblastoma (Wilms tumor)
A. Most common malignant renal tumor in children
B. Malignant tissue is derived from embryonic nephrogenic tissue.
C. Peak incidence is between 2 and 4 years of age.
D. The two-hit theory of oncogenesis, which explains the etiology of Wilms tumor, requires a mutation of both copies of the Wilms tumor-1 (WT-1) tumor-suppressor gene on chromosome 11p.
E. Characteristic clinical features
   1. Hematuria
   2. Hypertension
   3. Large abdominal mass
   4. Intestinal obstruction
F. Part of WAGR syndrome (Wilms tumor, Aniridia, Genital anomalies, mental Retardation)
DIURETICS AND FLUID BALANCE

I. Diuretics

A. The diuretics in Figure 6-14 can be grouped into five main categories, each with a different mechanism of action (Table 6-9). The side effects of each type of diuretic are also different, which means that certain diuretics are better suited for certain patients.

**QUICK HIT**

In altitude sickness, in order to get enough oxygen, hyperventilation occurs, which causes respiratory alkalosis. Carbonic anhydrase inhibitors speed metabolic compensation by increasing urinary excretion of $\text{HCO}_3^-$, causing metabolic acidosis.

**QUICK HIT**

Mannitol and other osmotic diuretics also “pull” fluid into the bloodstream, thus decreasing pressure in glaucoma, in cases of increased intracranial pressure, and in surgery.

**QUICK HIT**

Loop diuretics, which have direct pulmonary vasodilatory properties, are particularly useful in the treatment of pulmonary edema.

**QUICK HIT**

Thiazide diuretics are sulfaph derivatives and should be used with caution in patients with sulfaph drug allergies.

![Effects of diuretics on the nephron](image)

**FIGURE 6-14**

Effects of diuretics on the nephron

- **Thiazides**
  - Hydrochlorothiazide
  - Chlorothiazide
    - (inhibit NaCl cotransporter)
    - Hyperkalemia
    - Hypocalcemia

- **Carbonic anhydrase inhibitors**
  - Acetazolamide
    - (HCO$_3^-$ retained in lumen)
    - Urine pH
    - Hypokalemia
    - Hypocalcemia
    - Hypernatremia

- **Potassium-sparing diuretics**
  - Triamterene
  - Amiloride
    - (block Na$^+$/K$^+$ channels)
    - Hyperkalemia

- **Loop diuretics**
  - Furosemide
  - Ethacrynic acid
  - Bumetanide
    - (inhibit Na$^+$/K$^+$/Cl$^-$ cotransporter)
    - Hypokalemic/hypochloremic alkalosis may develop

- **Osmotic diuretics**
  - Mannitol
  - Loop of Henle

- **Osmotic diuretics**
  - Glu, chloride; DCT, distal convoluted tubule; HCO$_3^-$, bicarbonate; JGA, juxtaglomerular apparatus; K$^+$, potassium; Na$^+$, sodium; PCT, proximal convoluted tubule.
### TABLE 6-9 Diuretics

<table>
<thead>
<tr>
<th>Therapeutic Agent</th>
<th>Mechanism of Action</th>
<th>Electrolytes Lost in Urine</th>
<th>Indications</th>
<th>Side Effects</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acetazolamide</td>
<td>Carbonic anhydrase inhibitors—inhibit carbonic anhydrase in PCT, which prevents HCO$_3^-$ reabsorption</td>
<td>Na$^+$, HCO$_3^-$, K$^+$</td>
<td>Glaucoma, urinary alkalization, metabolic alkalosis, altitude sickness</td>
<td>Hyperchloremic metabolic acidosis, sulfa drug allergy, neuropathy, ammonium toxicity</td>
<td>Causes decreased secretion of HCO$_3^-$ in aqueous humor</td>
</tr>
<tr>
<td><strong>Loop diuretics</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Furosemide, torsemide, bumetanide, ethacrynic acid</td>
<td>Prevents cotransport of Na$^+$, K$^+$, and Cl$^-$ in thick ascending limb of loop of Henle</td>
<td>Na$^+$, Cl$^-$, Ca$^{2+}$, K$^+$</td>
<td>Congestive heart failure, cirrhosis, nephrotic syndrome, pulmonary edema, hypertension, hypercalcemia</td>
<td>Ototoxicity, hypokalemic metabolic alkalosis, dehydration, sulfa drug allergy (not ethacrynic acid), nephritis, gout</td>
<td>Has rapid onset and short duration of action, which is ideal for relieving acute edema</td>
</tr>
<tr>
<td>Mannitol</td>
<td>Osmotic diuretic—prevents isosmotic reabsorption of filtrate in PCT, loop of Henle, and collecting tubule</td>
<td>Na$^+$ and all other filtered solutes</td>
<td>Shock, drug overdose, decrease intracranial or intraocular pressure; maintenance of urine flow in rhabdomyolysis</td>
<td>Pulmonary edema, dehydration; contraindicated in anuria and congestive heart failure</td>
<td>Results in increased urine volume; readily filtered and not reabsorbed</td>
</tr>
<tr>
<td><strong>Potassium-sparing diuretics</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Spironolactone, eplerenone</td>
<td>Binds to intracellular aldosterone steroid receptors in collecting tubules</td>
<td>Na$^+$, Cl$^-$</td>
<td>Hyperaldosteronism, potassium depletion, congestive heart failure, post-MI</td>
<td>Hyperkalemic metabolic acidosis, gynecomastia, and antiandrogen effects (spironolactone only)</td>
<td>Results in decreased secretion of K$^+$ and H$^+$, which can lead to hyperkalemic metabolic acidosis</td>
</tr>
<tr>
<td>Triamterene, amiloride</td>
<td>Blocks Na$^+$ channels in collecting tubules</td>
<td>Na$^+$, Cl$^-$</td>
<td>Hypertension, potassium depletion</td>
<td>Hyperkalemic metabolic acidosis</td>
<td>Often given in combination with a thiazide</td>
</tr>
<tr>
<td><strong>Thiazides</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hydrochlorothiazide (HCTZ), chlorthalidone,</td>
<td>Inhibit transport of Na$^+$ and Cl$^-$ into cells of the DCT</td>
<td>Na$^+$, Cl$^-$, K$^+$</td>
<td>Hypertension, idiopathic hypercalcuria, nephrogenic diabetes insipidus</td>
<td>Hypokalemic metabolic alkalosis, hypernatremia, hyperglycemia, hyperlipidemia, hyperuricemia, hypercalcemia, sulfa drug allergy</td>
<td>Causes decreased Ca$^{2+}$ excretion, can lead to K$^+$ wasting with chronic therapy</td>
</tr>
</tbody>
</table>

Ca$^{2+}$: calcium; Cl$^-$: chloride; DCT, distal convoluted tubule; HCO$_3^-$: bicarbonate; K$^+$: potassium; MI, myocardial infarction; Na$^+$: sodium; PCT, proximal convoluted tubule.
II. Antidiuretic hormone
   A. ADH causes an increase in the expression of water channels in the collecting tubule, which results in an increase in the reabsorption of water. Urine output drops, and concentration increases.
   B. In the syndrome of inappropriate secretion of antidiuretic hormone (SIADH), lithium or demeclocycline, which blocks the effects of ADH, can be administered to prevent excessive water retention.
   C. In central diabetes insipidus, either desmopressin (an ADH analog) or ADH can be given to prevent the excessive loss of dilute urine. These drugs are not useful in the nephrogenic (also known as the peripheral) form of diabetes insipidus, in which the kidneys do not respond to ADH.
DEVELOPMENT

I. Hypothalamus
   A. A division of the diencephalon
   B. Forms from the embryologic forebrain (see Chapter 2)

II. Pituitary gland consists of two lobes
   A. Anterior lobe: forms from Rathke pouch, an ectodermal diverticulum of the primitive mouth that invaginates upward
   B. Posterior lobe: forms from an evagination of the hypothalamus

III. Thyroid gland
   A. It forms from the endoderm of the floor of the pharynx.
   B. It begins as a diverticulum that migrates caudally.
   C. Thyroid follicular cells are derived from endoderm.

IV. Parathyroid glands
   A. Inferior parathyroid glands develop from the third pharyngeal pouch.
   B. Superior parathyroid glands develop from the fourth pharyngeal pouch.
   C. The parathyroid glands migrate caudally and come to lie on the dorsal surface of the thyroid gland.

V. Adrenal glands
   A. Gross description
      1. Paired adult adrenal glands weigh 4 g each.
      2. They are located immediately anterosuperior to the superior renal poles.
      3. They are enclosed in renal fascia.
   B. Adrenal cortex
      1. Forms from the mesoderm
      2. Includes three major parts
         a. Zona glomerulosa and zona fasciculata are present at birth.
         b. Zona reticularis is not completely formed until 3 years of age.
   C. Medulla of adrenal gland
      1. Chromaffin cells form from neural crest cells that invade the adrenal glands during development.
      2. These cells are in essence postganglionic neurons of the sympathetic nervous system.

VI. Pancreas
   A. It forms from a ventral and dorsal bud of endoderm from the foregut.
      1. The ventral bud forms the uncinate process and part of the pancreatic head.
      2. The dorsal bud forms part of the head, body, and tail.

QUICK HIT

DiGeorge syndrome is a malformation of the third and fourth pharyngeal pouches caused by a mutation of 22q11, leading to a spectrum of disorders including thymic hypoplasia, T-cell deficiency, absent parathyroids, and hypocalcemia.

Thyroglossal duct cysts are midline cysts of the neck. Branchial cleft cysts lie laterally anywhere along the anterior border of the sternocleidomastoid muscle.
B. Exocrine pancreas: Acinar cells and ducts form from endoderm surrounded by mesoderm.
C. Endocrine pancreas: Mesodermal cells aggregate to form pancreatic islet cells.

VII. Gonads (see Chapter 8)

**CONGENITAL MALFORMATIONS** *(Table 7-1)*

There is a wide spectrum of developmental abnormalities involving the endocrine system. Some of these malformations are anatomic, whereas others are biochemical.

<table>
<thead>
<tr>
<th>Malformation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Craniopharyngioma</td>
<td>Cystic tumor of the pituitary that forms from the remnants of the Rathke pouch; may cause diabetes insipidus</td>
</tr>
<tr>
<td>Thyroglossal duct cysts</td>
<td>A remnant of the descending migratory path of the thyroid that persists into adult life. Most are asymptomatic, but an infection may cause swelling and produce a progressively enlarging movable mass</td>
</tr>
<tr>
<td>Absence of parathyroid glands</td>
<td>Occurs in DiGeorge syndrome (thymic aplasia) (see Chapter 10). Inability to produce parathyroid hormone leads to hypoparathyroidism and hypocalcemia</td>
</tr>
<tr>
<td>Congenital adrenal hyperplasia</td>
<td>Figure 7-9</td>
</tr>
<tr>
<td>Annular pancreas</td>
<td>Ventral and dorsal pancreatic buds form a ring around the duodenum; may cause duodenal obstruction</td>
</tr>
<tr>
<td>Accessory pancreatic tissue</td>
<td>Normal pancreatic tissue found within the wall of the stomach; most common type of choristoma (normal tissue found misplaced within another organ)</td>
</tr>
</tbody>
</table>

**HORMONES** *(Table 7-2)*

Hormones are biologically active chemicals formed in an organ and carried through the blood to act on adjacent cells of the same organ or on a different body part. Hormone function can be localized or systemic. Hormones can alter the activity or structure of the target organ(s) depending on the specificity of the hormone’s effects. Hormones play an essential role in homeostasis, reproductive function, and metabolism, and they are vital in nearly every other body system as well.
### TABLE 7-2 Hormones

<table>
<thead>
<tr>
<th>Hormone</th>
<th>Secreted by</th>
<th>End-Organ Effects of Hormones</th>
<th>Stimulated by</th>
<th>Inhibited by</th>
</tr>
</thead>
<tbody>
<tr>
<td>GnRH</td>
<td>Hypothalamus</td>
<td>LH/FSH secretion</td>
<td>Puberty</td>
<td>Progesterone, testosterone</td>
</tr>
<tr>
<td>FSH</td>
<td>Anterior pituitary gland</td>
<td>Growth of follicles and estrogen secretion (acts on granulosa cells); maturation of sperm (acts on Sertoli cells)</td>
<td>Pulsatile release of GnRH</td>
<td>Constant GnRH release; inhibin</td>
</tr>
<tr>
<td>LH</td>
<td>Anterior pituitary gland (basophils)</td>
<td>Ovulation; formation of corpus luteum; estrogen/progesterone synthesis (acts on theca lutein cells); synthesis/secretion of testosterone (acts on Leydig cells)</td>
<td>Pulsatile release of GnRH</td>
<td>Constant GnRH release; progesterone, testosterone</td>
</tr>
<tr>
<td>Estrogen</td>
<td>Ovary (granulosa cells)</td>
<td>Proliferative phase of menstrual cycle; development of female reproductive organs</td>
<td>FSH</td>
<td>Estrogen</td>
</tr>
<tr>
<td>Progesterone</td>
<td>Ovary (granulosa lutein cells)</td>
<td>Breast development; secretory activity during luteal phase</td>
<td>LH</td>
<td>Progesterone</td>
</tr>
<tr>
<td>Testosterone</td>
<td>Testes (Leydig cells)</td>
<td>Spermatogenesis; conversion of testosterone to dihydrotestosterone via 5α-reductase stimulates development of secondary male sex characteristics</td>
<td>LH</td>
<td>Testosterone</td>
</tr>
<tr>
<td>hCG</td>
<td>Placenta (syncytiotrophoblast)</td>
<td>Increased estrogen/progesterone synthesis; maintains corpus luteum secretion of estrogen and progesterone</td>
<td>Trophoblast differentiation after implantation of fertilized egg</td>
<td></td>
</tr>
<tr>
<td>ACTH</td>
<td>Anterior pituitary</td>
<td>Synthesis and secretion of adrenal cortical hormones</td>
<td>CRH, stress</td>
<td>Cortisol</td>
</tr>
<tr>
<td>Cortisol (glucocorticoids)</td>
<td>Adrenal cortex (zona fasciculata)</td>
<td>Anti-inflammatory effects (via inhibition of phospholipase A2); immunosuppressive effects; stimulation of gluconeogenesis; increased blood sugar</td>
<td>ACTH</td>
<td>Cortisol</td>
</tr>
<tr>
<td>Aldosterone</td>
<td>Adrenal cortex (zona glomerulosa)</td>
<td>Increased renal sodium reabsorption and potassium secretion; increase in blood volume</td>
<td>Decrease in blood volume; angiotensin II; hyperkalemia; hyponatremia</td>
<td>Hypernatremia, hypokalemia, fluid overload</td>
</tr>
<tr>
<td>TSH</td>
<td>Anterior pituitary</td>
<td>Synthesis and secretion of thyroid hormone (T&lt;sub&gt;4&lt;/sub&gt;, T&lt;sub&gt;3&lt;/sub&gt;)</td>
<td>TRH</td>
<td>T&lt;sub&gt;4&lt;/sub&gt;, T&lt;sub&gt;3&lt;/sub&gt;</td>
</tr>
</tbody>
</table>

(continued)
<table>
<thead>
<tr>
<th>Hormone</th>
<th>Secreted by</th>
<th>End-Organ Effects of Hormones</th>
<th>Stimulated by</th>
<th>Inhibited by</th>
</tr>
</thead>
<tbody>
<tr>
<td>T&lt;sub&gt;4&lt;/sub&gt;, T&lt;sub&gt;3&lt;/sub&gt;</td>
<td>Thyroid</td>
<td>Growth; maturation of CNS; increased basal metabolic rate, cardiac output, and nutrient use</td>
<td>TSH, estrogen</td>
<td>Somatostatin, dopamine</td>
</tr>
<tr>
<td>Somatostatin (somatotropin-inhibiting hormone)</td>
<td>Hypothalamus</td>
<td>Inhibited secretion of growth hormone</td>
<td>Growth hormone, somatomedins (IGF)</td>
<td></td>
</tr>
<tr>
<td>GH (somatotropin)</td>
<td>Anterior pituitary (acidophils)</td>
<td>Decreased glucose uptake; increased protein synthesis, growth, organ size, and lean body mass</td>
<td>GHRH, exercise, sleep, puberty, hypoglycemia, estrogen, stress, endogenous opiates</td>
<td>Somatomedins (IGF), somatostatin, obesity, pregnancy, hyperglycemia</td>
</tr>
<tr>
<td>Prolactin</td>
<td>Anterior pituitary (acidophils)</td>
<td>Stimulation of milk production and secretion, breast development, inhibition of ovulation</td>
<td>Prolactin-stimulating factor, TRH</td>
<td>Prolactin-inhibiting factor (dopamine)</td>
</tr>
<tr>
<td>Oxytocin</td>
<td>Hypothalamus via posterior pituitary</td>
<td>Milk ejection from breast (milk letdown), uterine contraction</td>
<td>Suckling, sex, dilation of the cervix</td>
<td>Alcohol, stress</td>
</tr>
<tr>
<td>PTH</td>
<td>Parathyroid gland (chief cells)</td>
<td>Increased serum calcium, increased renal calcium absorption, inhibition of phosphate reabsorption, activates vitamin D to increase intestinal calcium absorption</td>
<td>Decreased serum calcium, mild decreased serum magnesium</td>
<td>Severe decrease in serum magnesium</td>
</tr>
<tr>
<td>Vitamin D 1,25-dihydroxycholecalciferol</td>
<td>Kidney (active form produced by activity of 1α-hydroxylase), sun-exposed skin</td>
<td>Increased intestinal calcium and phosphorus absorption, increased bone calcium resorption, increased kidney phosphate and calcium reabsorption</td>
<td>Decreased serum calcium, increased PTH, decreased serum phosphate</td>
<td></td>
</tr>
<tr>
<td>ADH (vasopressin)</td>
<td>Hypothalamus via posterior pituitary</td>
<td>Increased water permeability in distal tubules and collecting duct to regulate osmolarity (V2 receptor), constriction of vascular smooth muscle (V1 receptor)</td>
<td>Volume contraction, nicotine, opiates, increased serum osmolality</td>
<td>Ethanol, ANF, decreased serum osmolality</td>
</tr>
<tr>
<td>ANF</td>
<td>Atrial myocytes</td>
<td>Vasodilation to decrease systemic BP, increase urinary Na&lt;sup&gt;+&lt;/sup&gt; and H&lt;sub&gt;2&lt;/sub&gt;O excretion</td>
<td>Atrial stretch due to blood volume increase</td>
<td>ANF</td>
</tr>
<tr>
<td>Glucagon</td>
<td>Pancreatic islet cells (α cells)</td>
<td>Increased blood glucose, increased glycolysis and gluconeogenesis in the liver, increased lipolysis and ketone production</td>
<td>Decreased blood glucose; increased amino acids, ACh</td>
<td>Increased blood glucose; insulin; somatostatin</td>
</tr>
<tr>
<td>Insulin</td>
<td>Pancreatic islet cells (β cells)</td>
<td>Decreased blood glucose caused by increased uptake into muscle and fat, decreased glycolysis and gluconeogenesis, increased protein synthesis, increased fat deposition, inhibition of lipolysis</td>
<td>Increased blood glucose, amino acids; glucagon; ACh</td>
<td>Decreased blood glucose; somatostatin</td>
</tr>
<tr>
<td>Leptin</td>
<td>Fat cells</td>
<td>Reduced food intake (satiety); inhibits the arcuate nucleus and lateral nucleus of the hypothalamus, stimulates the ventromedial nucleus of the hypothalamus</td>
<td>Obesity, overeating, pregnancy</td>
<td>Fasting</td>
</tr>
</tbody>
</table>

ACh, acetylcholine; ACTH, adrenocorticotropic hormone; ADH, antiuretic hormone; ANF, atrial natriuretic factor; BP, blood pressure; CNS, central nervous system; CRH, corticotropin-releasing hormone; FSH, follicle-stimulating hormone; GH, growth hormone; GHRH, growth hormone-releasing hormone; GnRH, gonadotropin-releasing hormone; hCG, human chorionic gonadotropin; IGF, insulin-like growth factor; LH, luteinizing hormone; PTH, parathyroid hormone; T<sub>3</sub>, triiodothyronine; T<sub>4</sub>, thyroxine; TRH, thyrotropin-releasing hormone; TSH, thyroid-stimulating hormone.
I. Hormones of the hypothalamic–pituitary axis (Figure 7-1)

II. Hormones of the adrenal gland (Figure 7-2)

III. Hormone second-messenger system

The second-messenger system is the process by which extracellular signals are translated into cellular responses. Biologically active chemicals, such as hormones, bind to receptor sites on the cell membrane, resulting in phosphorylation of intracellular proteins or changes in ion channel conductivity and subsequent cellular modulation (Table 7-3 and Figure 7-3).

ACTH, adrenocorticotropic hormone; ADH, antidiuretic hormone; CRH, corticotropin-releasing hormone; FSH, follicle-stimulating hormone; GH, growth hormone; GnRH, gonadotropin-releasing hormone; LH, luteinizing hormone; T₃, triiodothyronine; T₄, thyroxine; TRH, thyrotropin-releasing hormone; TSH, thyroid-stimulating hormone.
Hormones of the adrenal gland

To remember the anatomic layers of the adrenal cortex, think **GFR**: Glomerulosa, Fasciculata, and Reticularis. To remember the hormones produced by each layer, think “the deeper you go, the sweeter it gets”: aldosterone (salt hormone), glucocorticoid (sugar hormone), and androgens (sex hormone).

**TABLE 7-3 Hormone Second-messenger Systems**

<table>
<thead>
<tr>
<th>cAMP</th>
<th>cGMP</th>
<th>IP$_3$</th>
<th>Steroid</th>
<th>Tyrosine Kinase</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\beta_1$-agonists</td>
<td>ANF</td>
<td>$\alpha_1$-agonists</td>
<td>Aldosterone</td>
<td>Insulin</td>
</tr>
<tr>
<td>$\beta_2$-agonists</td>
<td>EDRF</td>
<td>GnRH</td>
<td>Estrogen</td>
<td>IGF-1</td>
</tr>
<tr>
<td>LH</td>
<td>TRH</td>
<td>Glucocorticoids</td>
<td>Prolactin</td>
<td></td>
</tr>
<tr>
<td>FSH</td>
<td>GHRH</td>
<td>Testosterone</td>
<td>GH</td>
<td></td>
</tr>
<tr>
<td>TSH</td>
<td>Angiotensin II</td>
<td>Progesterone</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ADH ($V_1^+$)</td>
<td>ADH ($V_2$)</td>
<td>Thyroid</td>
<td></td>
<td></td>
</tr>
<tr>
<td>hCG</td>
<td>Oxytocin</td>
<td>Vitamin D</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CRH</td>
<td>PTH</td>
<td>Calcitonin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PTH</td>
<td>Glucagon</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

ADH, antidiuretic hormone; ANF, atrial natriuretic factor (also known as ANP, atrial natriuretic peptide); cAMP, cyclic adenosine monophosphate; cGMP, cyclic guanosine monophosphate; CRH, corticotropin-releasing hormone; EDRF, endothelium-derived relaxing factor; FSH, follicle-stimulating hormone; GH, growth hormone; GHRH, growth hormone–releasing hormone; GnRH, gonadotropin-releasing hormone; hCG, human chorionic gonadotropin; IGF, insulin-like growth factor; IP$_3$, inositol triphosphate; LH, luteinizing hormone; PTH, parathyroid hormone; TRH, thyrotropin-releasing hormone; TSH, thyroid-stimulating hormone.
The Endocrine System

G-Protein

Class | Action | Examples
--- | --- | ---
G<sub>q</sub> | Activates phospholipase C → cleaves phospholipids to form PIP<sub>2</sub>, which is subsequently cleaved into DAG and IP<sub>3</sub>. DAG activates protein kinase C. IP<sub>3</sub> increases intracellular calcium, which also has downstream effects (including activating protein kinase C). | H<sub>1</sub>, α<sub>y</sub>, V<sub>1</sub>, M<sub>1</sub>, M<sub>3</sub>
G<sub>i</sub> | Stimulates adenyl cyclase → converts ATP to cAMP, which activates protein kinase A | β<sub>1</sub>, β<sub>2</sub>, D<sub>1</sub>, H<sub>1</sub>, V<sub>2</sub>
G<sub>i</sub> | Inhibits adenyl cyclase → decreased cAMP production → decreased activity of protein kinase A | M<sub>2</sub>, α<sub>2</sub>, D<sub>2</sub>

ATP, adenosine triphosphate; cAMP, cyclic adenosine monophosphate; cGMP, cyclic guanosine monophosphate; DAG, diacylglycerol; ER, endoplasmic reticulum; GDP, guanosine 5’-diphosphate; GMP, guanosine monophosphate; GTP, guanosine triphosphate; IP<sub>3</sub>, inositol triphosphate; PIP<sub>2</sub>, phosphatidylinositol 4,5-bisphosphate; PKC, protein kinase C.
CALCIUM HOMEOSTASIS (Figure 7-4)

**Quick Hit**

Somatostatin is also secreted in the brain, gastrointestinal (GI) tract, and β cells of the pancreas. It functions to decrease systemic secretion of insulin, glucagon, and gastrin.

**Quick Hit**

Glucose enters cells through facilitated transporters designated glucose transporter (GLUT)-1 through GLUT-5. These transporters have the following locations:

- GLUT 1: erythrocytes, blood–brain barrier
- GLUT 2: liver, kidney, pancreatic β cell, intestinal mucosa
- GLUT 3: neurons
- GLUT 4*: adipose tissue, skeletal and cardiac muscle
- GLUT 5: intestinal epithelium

*insulin-responsive transport to membrane

**Insulin and Glucagon**

Insulin is a polypeptide hormone that serves to regulate several physiologic processes. Its primary role, in conjunction with the polypeptide hormone glucagon, is to maintain blood glucose levels. When blood glucose levels rise after a meal, insulin is released from the β cells of the pancreatic islets of Langerhans in proportion to the glucose concentration of blood. Innervation of pancreatic islets by a branch of the vagus nerve helps coordinate insulin release with digestion. Insulin interacts with surface receptors on muscle and adipose tissue and stimulates glucose absorption and triacylglycerol synthesis. In the liver, insulin inhibits gluconeogenesis and glycogen breakdown.

Insulin is formed by two polypeptides linked by disulfide bridges (Figure 7-5). The insulin receptor is tyrosine kinase linked; binding of insulin to the α subunit causes phosphorylation of the tyrosine kinase connected to the β subunit. This stimulates recruitment of glucose transporters (GLUTs) to the cell membrane (GLUT-4 in skeletal muscle) and increases the uptake of glucose (Figure 7-6). Glucagon counteracts the actions of insulin. It is a single polypeptide secreted by the α cells of the islets of Langerhans. Glucagon is secreted in response to low blood glucose, increased amino acids in the blood, and epinephrine. Glucagon secretion leads to a rise in blood glucose concentration via gluconeogenesis and glycogenolysis. Release of glucagon is inhibited by insulin. Glucagon is also responsible for the formation of ketone bodies, and increased uptake of amino acids by the liver muscle is not responsive to glucagon.

- **Blood Levels of Glucose, Insulin, and Glucagon after a High-Carbohydrate Meal** (Figure 7-7)
**FIGURE 7-5** Formation of insulin

Preproinsulin → Signal sequence → Endoplasmic reticulum → Proinsulin → Signal sequence → Golgi apparatus → Insulin + C-peptide

Insulin is stored in vesicles of pancreatic β cells.

**FIGURE 7-6** Insulin recruitment of glucose transporters

1. Activated receptor promotes recruitment of glucose transporters from intracellular pool to cell membrane.
2. Insulin binds to its receptor in the cell membrane.
3. Glucose transporters increase insulin-mediated uptake of glucose into cell.
4. Vesicles fuse to form an organelle called the endosome.
5. When insulin levels decrease, glucose transporters move from cell membrane to intracellular storage pool, where they can be recycled.

(Adapted with permission from Champe PC, Harvey RA. Lippincott's Illustrated Reviews: Biochemistry. 2nd ed. Philadelphia, PA: Lippincott-Raven, 1994.)
The Endocrine System

Blood Glucose Levels

I. Hypoglycemia

A. Causes
1. Excess insulin administration (in a patient with diabetes)
2. Sulfonylurea administration
3. Alcohol ingestion
4. Insulinoma
5. Factitious hyperinsulinism

B. Symptoms
1. Sweating
2. Palpitations
3. Anxiety
4. Tremor

C. Whipple triad (required for diagnosis)
1. Low blood glucose
2. Hypoglycemic symptoms
3. Improvement of symptoms with glucose administration

D. In patients with diabetes, these symptoms may not be present, and blood glucose may be allowed to drop to dangerous levels; coma or death may result.

E. Therapy
1. Glucose or intravenous (IV) dextrose should be given after measuring blood glucose levels.
2. Glucagon should be administered.
3. Epinephrine is sometimes appropriate therapy.

Quick Hit
In factitious hyperinsulinism, C-peptide levels will be low.

Quick Hit
Hypoglycemia triggers the release of anti-insulin hormones such as glucagon, cortisol, growth hormone, epinephrine, and norepinephrine to help maintain blood glucose levels. Epinephrine and norepinephrine also turn on the adrenergic response, resulting in symptoms of sweating, anxiety, palpitations, and tremor. Decreased availability of glucose to the central nervous system (CNS) eventually results in neuroglycopenic symptoms of lethargy, confusion, slurred speech, coma, and death.

Blood levels of glucose, insulin, and glucagon after a high-carbohydrate meal

(Adapted with permission from Champe PC, Harvey RA. Lippincott’s Illustrated Reviews: Biochemistry. 2nd ed. Philadelphia, PA: Lippincott-Raven; 1994.)
Clinical Vignette 7-1

**CLINICAL PRESENTATION:** A 4-year-old boy presents to the emergency department having woken up this morning feeling lethargic and confused. The child’s past medical history is significant for two prior episodes of hypoglycemia. The patient’s parents also report resting tremor. Mother denies seizure activity, loss of consciousness, and recent trauma. Mother did urine dipstick, which showed glucose level of 42 mg/dL (low). Parents administered glucose orally and brought the patient to the emergency department. Physical examination revealed an anxious, diaphoretic child with slurred speech. No hepatomegaly. Vital signs: Temperature = 97.5°F; heart rate = 119 bpm; respiration rate = 30 breaths/min; blood pressure = 109/55 mm Hg; oxygen saturation = 99% on room air.

**DIFFERENTIALS:** Hyperinsulinism, fatty acid oxidation defect, glycogen storage disease, glyco- gen synthesis defect, gluconeogenesis defect, glucagon deficiency, cortisol deficiency, and growth hormone deficiency. Figure 7-8 groups the various causes of hypoglycemia in the child by pathophysiology.

**LABORATORY STUDIES:** Urine ketones should be assessed via urinalysis. If urine ketones are low, it indicates the presence of a hyperinsulinemic state or a defect in fatty acid oxidation (resulting in an inability to produce ketones). These are best differentiated by obtaining an insulin level. If urine ketones are high, further workup is necessary to differentiate liver metabolism from endocrine defects. Consequently, serum lactate, pyruvate, liver function tests, and uric acid levels should be obtained to help rule out possibilities such as maple syrup urine disease, glycojenolysis defect, glycogen storage disease, and gluconeogenesis defect. Also, serum cortisol levels should be obtained to rule out cortisol deficiency. Eventually, the patient should be screened for growth hormone and pituitary hormones.

**MANAGEMENT:** Key point is to treat first and evaluate lab studies later. After blood samples are drawn, a quick bedside glucose reading should be done. If hypoglycemia is mild and the patient is able to tolerate oral dosing, treat with oral glucose. If severe hypoglycemia occurs and/or if the patient is unable to tolerate oral dosing, provide dextrose bolus followed by appropriate maintenance infusion.

---

**FIGURE 7-8 Causes of hypoglycemia**

1. Decreased intake
   - Fasting
   - Malnutrition

2. Decreased absorption
   - Acute diarrhea

3. Decreased glycogen reserves
   - Defect in enzymes of glycogen synthesis pathway

4. Inability to mobilize glycogen
   - Glucagon deficiency

5. Ineffective glycogenolysis
   - Defect in enzyme of glucogenolytic pathway

6. Decreased or absent fat stores

7. Ineffective gluconeogenesis
   - Enzymatic defect in gluconeogenic pathway
   - Enzymatic defect in fatty acid oxidation

8. Hyperinsulinism
   - Islet cell adenoma
   - Oral hypoglycemic agents
   - Insulin therapy

9. Anti-insulin deficiency
   - Cortisol deficiency
   - Growth hormone deficiency
   - Hypopituitarism

10. Increased catabolic states
    - Large tumors
    - Illness
II. Hyperglycemia
A. Causes
1. Diabetes mellitus
2. Chronic pancreatitis
3. Acromegaly
4. Cushing syndrome
5. Adverse drug reactions
   a. Furosemide
   b. Glucocorticoids
   c. Growth hormone
   d. Oral contraceptives
   e. Thiazides
B. Acute symptoms
1. Ketoacidosis or hyperosmolar hyperglycemic state (see Table 7-6)
2. Polyuria
3. Polydipsia
4. Polyphagia
5. Weight loss
6. Encephalopathy
   a. Tremulousness
   b. Convulsions
   c. Coma

The chronic symptoms of hyperglycemia mimic the chronic complications of diabetes (see Table 7-7).

---

**DIABETES MELLITUS**

Diabetes mellitus (or, simply, diabetes) refers to a group of disorders that are characterized by hyperglycemia and affect 1% to 2% of the U.S. population. Although the pathogenesis of these disorders is varied, individuals with diabetes lack the ability to produce sufficient insulin or respond to secreted insulin in order to meet their metabolic needs. Furthermore, all patients with diabetes are vulnerable to complications such as nephropathy, neuropathy, and retinopathy. Monitoring and control of blood sugar, insulin replacement, proper diet, and exercise can significantly reduce the morbidity and mortality of this disease.

I. Diagnosis of diabetes mellitus (Table 7-4)
II. Type 1 versus type 2 diabetes mellitus (Table 7-5)

<table>
<thead>
<tr>
<th>TABLE 7-5 Type 1 versus Type 2 Diabetes Mellitus</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Type 1 Diabetes (15%)</strong></td>
</tr>
<tr>
<td>Cause</td>
</tr>
<tr>
<td>Chromosomal association</td>
</tr>
<tr>
<td>Family history</td>
</tr>
<tr>
<td>Age of onset</td>
</tr>
<tr>
<td>Body habitus</td>
</tr>
<tr>
<td>Plasma insulin</td>
</tr>
<tr>
<td>Plasma glucagon</td>
</tr>
<tr>
<td>Pancreas morphology</td>
</tr>
<tr>
<td>Acute complication (Table 7-6)</td>
</tr>
<tr>
<td>Common symptoms</td>
</tr>
<tr>
<td>Response to insulin therapy</td>
</tr>
<tr>
<td>Response to oral therapy</td>
</tr>
</tbody>
</table>

HLA-DQ, human leukocyte antigen-DQ.

III. Diabetic ketoacidosis and hyperosmolar hyperglycemic state (Table 7-6)

<table>
<thead>
<tr>
<th>TABLE 7-6 Diabetic Ketoacidosis and Hyperosmolar Hyperglycemic State</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>DKA</strong></td>
</tr>
<tr>
<td>Pathology</td>
</tr>
<tr>
<td>Patient</td>
</tr>
<tr>
<td>Precipitating event</td>
</tr>
<tr>
<td>Clinical presentation</td>
</tr>
<tr>
<td>Mortality</td>
</tr>
<tr>
<td>Treatment</td>
</tr>
</tbody>
</table>

DKA, diabetic ketoacidosis; HHS, hyperosmolar hyperglycemic state; MI, myocardial infarction.

QUICK HIT
Rubella, mumps, and coxsackie are viral agents that can trigger the autoimmune response of the body to pancreatic β cells and cause type 1 diabetes (also called juvenile-onset diabetes).

Individuals with insulin resistance often have elevated fibrinogen and plasminogen activator inhibitors, making them susceptible to thrombosis.

Type 1 diabetes can be distinguished from type 2 by low C-peptide levels, which also indicates the need for treatment with insulin.

The ketone bodies (acetoacetate, β-hydroxybutyrate) are produced by the liver from acetyl coenzyme A (CoA) in the fasting state. The body (including the brain after 4 to 5 days) uses the ketone bodies for energy instead of glucose and amino acids. Red blood cells (RBCs), however, can only use glucose.

In DKA, there is insufficient insulin to inhibit lipolysis at the adipocytes, which liberate stored fatty acids that are subsequently taken up by the liver and converted to ketones to meet the body’s energy demands. In HHS, however, there tends to be minimal ketosis because there is sufficient insulin to inhibit lipolysis and production of ketones.
IV. Chronic symptoms of diabetes (Table 7-7)

**Table 7-7 Chronic Symptoms of Diabetes Mellitus**

<table>
<thead>
<tr>
<th>Anatomic Location</th>
<th>Clinical Features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Red blood cells</td>
<td>Glycation (HbA(_1c)), measure of long-term control of diabetes (reflects past 3 months)</td>
</tr>
<tr>
<td>Blood vessels/cardiovascular system</td>
<td>Atherosclerosis, dyslipidemia, coronary artery disease, gangrene, peripheral vascular disease</td>
</tr>
<tr>
<td>Eyes</td>
<td>Retinopathy, hemorrhage, hard exudates, cotton-wool spots, cataracts, glaucoma</td>
</tr>
<tr>
<td>GI tract</td>
<td>Constipation, gastroparesis</td>
</tr>
<tr>
<td>Kidneys</td>
<td>Nephropathy, nodular sclerosis, Kimmelstiel–Wilson nodules, chronic renal failure, azotemia</td>
</tr>
<tr>
<td>Penis</td>
<td>Erectile dysfunction as a result of autonomic neuropathy</td>
</tr>
<tr>
<td>Extremities</td>
<td>Stocking-glove peripheral neuropathy, nonhealing ulcers</td>
</tr>
</tbody>
</table>

**GI**, gastrointestinal; HbA\(_1c\), hemoglobin A1c.

V. Treatment of diabetes mellitus (Tables 7-8 and 7-9)

The goal of treatment of both type 1 and type 2 diabetes mellitus is steady control of blood glucose levels. However, because the pathogenesis underlying these two disease processes is different, the therapy is also different.

Type 1 diabetes mellitus, which can be viewed simply as a total deficiency of insulin, may be treated with careful administration of exogenous insulin. This agent has been the only treatment option for type 1 diabetes mellitus for many years and remains so today. However, advances have been made in both the type of insulin and the method of delivery. To maintain steady glucose levels, different preparations of human insulin have been designed, each with a characteristic rate of onset and duration of action (Table 7-8). Insulin, a peptide hormone, cannot be given orally. It is typically administered subcutaneously and, in emergencies, intravenously.

Some combination of these types of insulin usually can be found that provides adequate glucose control during both the fed and fasting states. Treatment of type 1 diabetes mellitus is essentially a balancing act—too much insulin causes hypoglycemia, and too little leads to hyperglycemia, which, over time, leads to the long-term complications of diabetes mellitus.

**Table 7-8 Commonly Used Insulin Preparations**

<table>
<thead>
<tr>
<th>Insulin Preparation</th>
<th>Onset of Activity</th>
<th>Time of Peak Activity</th>
<th>Duration of Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Insulin lispro</td>
<td>5–15 min</td>
<td>1–2 h</td>
<td>3–4 h</td>
</tr>
<tr>
<td>Insulin aspart</td>
<td>5–15 min</td>
<td>1–2 h</td>
<td>3–4 h</td>
</tr>
<tr>
<td>Insulin glulisine</td>
<td>5–15 min</td>
<td>1–2 h</td>
<td>3–4 h</td>
</tr>
<tr>
<td>Regular insulin</td>
<td>30 min</td>
<td>2–4 h</td>
<td>6–8 h</td>
</tr>
<tr>
<td>NPH (neutral protamine Hagedorn) insulin</td>
<td>1–2 h</td>
<td>4–12 h</td>
<td>18–24 h</td>
</tr>
<tr>
<td>Insulin detemir</td>
<td>3–4 h</td>
<td>3–9 h</td>
<td>6–24 h</td>
</tr>
<tr>
<td>Insulin glargine</td>
<td>3–4 h</td>
<td>No peak</td>
<td>24 h or longer</td>
</tr>
<tr>
<td>Therapeutic Agent (common name, if relevant) [trade name, where appropriate]</td>
<td>Class—Pharmacology and Pharmacokinetics</td>
<td>Indications</td>
<td>Side Effects or Adverse Effects</td>
</tr>
<tr>
<td>---</td>
<td>---</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td><strong>Insulin</strong></td>
<td>Rapid-acting insulin—see mechanism for regular insulin</td>
<td>Diabetes mellitus (typically type 1), hyperkalemia, stress-induced hyperglycemia</td>
<td>Insulin allergy, insulin antibodies, lipodystrophy</td>
</tr>
<tr>
<td>Lispro [Humalog], aspart [Novolog], glulisine [Apidra]</td>
<td></td>
<td></td>
<td>Hypoglycemia (diaphoresis, vertigo, tachycardia), insulin allergy, insulin antibodies, lipodystrophy</td>
</tr>
<tr>
<td><strong>Regular insulin</strong> [Humulin R, Novolin R]</td>
<td>Short-acting insulin—liver: promotes glucose storage as glycogen, increases triglyceride synthesis Muscle: facilitates protein and glycogen synthesis Adipose tissue: improves triglyceride storage by activating plasma lipoprotein lipase, reduces circulating free fatty acids</td>
<td>Diabetes mellitus (typically type 1), hyperkalemia, stress-induced hyperglycemia</td>
<td>Hypoglycemia (diaphoresis, vertigo, tachycardia), insulin allergy, insulin antibodies, lipodystrophy</td>
</tr>
<tr>
<td><strong>NPH</strong> [Humulin N, Novolin N]</td>
<td>Intermediate-acting insulin—see mechanism for insulin</td>
<td>Diabetes mellitus (typically type 1)</td>
<td>Hypoglycemia (diaphoresis, vertigo, tachycardia), insulin allergy, insulin antibodies, lipodystrophy</td>
</tr>
<tr>
<td>Glargine [Lantus], detemir [Levemir]</td>
<td>Long-acting insulin—see mechanism for regular insulin</td>
<td>Diabetes mellitus (typically type 1)</td>
<td>Hypoglycemia (diaphoresis, vertigo, tachycardia), insulin allergy, insulin antibodies, lipodystrophy</td>
</tr>
<tr>
<td><strong>Sulfonylureas</strong></td>
<td>First-generation sulfonylureas—closes potassium channel in β-cell membrane → reduces K⁺ efflux, increases Ca²⁺ influx → increases secretion of insulin</td>
<td>Oral treatment for type 2 diabetes</td>
<td>Hypoglycemia, GI disturbances, muscle weakness, mental confusion</td>
</tr>
<tr>
<td>Tolbutamide, chlorpropamide</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glyburide [DiaBeta, Micronase], glimepiride [Amaryl], glipizide [Glucotrol]</td>
<td>Second generation sulfonylureas—closes potassium channel in pancreatic β-islet cell membrane → reduces K⁺ efflux, increases Ca²⁺ influx → increases secretion of insulin</td>
<td>Oral treatment for type 2 diabetes</td>
<td>Hypoglycemia, GI disturbances, muscle weakness, mental confusion, weight gain</td>
</tr>
<tr>
<td><strong>Biguanides</strong></td>
<td>Biguanide—decreases hepatic gluconeogenesis, increases glycolysis → decreases serum glucose levels</td>
<td>First-line oral treatment for type 2 diabetes</td>
<td>Lactic acidosis, GI upset (diarrhea, nausea, abdominal pain), metallic taste; decreased vitamin B₁₂ absorption</td>
</tr>
<tr>
<td>Metformin [Glucophage]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Thiazolidinediones</strong></td>
<td>Glitazones—bind PPARγ receptors; improve target cell sensitivity to insulin</td>
<td>Oral treatment for type 2 diabetes</td>
<td>Weight gain, edema, rare hepatotoxicity, increases LDL and triglycerides; rosiglitazone may increase the risk of MI</td>
</tr>
<tr>
<td>Pioglitazone [Actos], rosiglitazone [Avandia]</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Type 2 diabetes mellitus, which is more complex than type 1 disease, is characterized primarily by insulin resistance. In some cases, a strict regimen of diet and exercise completely reverses the course of the disease. In many cases, however, drugs are required to control blood sugar levels. The most commonly used drugs in type 2 diabetes mellitus are metformin and the insulin sensitizers. **Metformin**, in the biguanide class of agents, is considered by many to be the first-line drug of choice in type 2 diabetes mellitus and acts primarily by decreasing hepatic glucose production. Advantages include the very low risk of hypoglycemia as well as the weight loss and improvement in lipid profiles in many patients. The one feared adverse reaction is lactic acidosis, a rare but serious complication. Also, nausea and diarrhea are side effects of this medication.

**Pioglitazone** and **rosiglitazone**, of the thiazolidinedione class, are the two most common insulin sensitizers. Like metformin, these agents can be used alone or as part of a multidrug regimen for diabetic blood sugar control. Both drugs have a low risk of hypoglycemia. However, they have been known to exacerbate congestive heart failure, and frequent monitoring of liver function is required. Rosiglitazone may increase the risk of myocardial infarction (MI) and cardiovascular events.

Sulfonlureas were once the mainstay of treatment for type 2 diabetes, but they are used less frequently today. These drugs, which include agents such as glipizide and glyburide, act by increasing the release of insulin from the pancreas. To a lesser extent, these agents also decrease glucagon levels and increase insulin binding at target sites in the periphery. The primary side effect of these drugs is hypoglycemia.

### TABLE 7-9  Therapeutic Agents for Diabetes (Continued)

<table>
<thead>
<tr>
<th>Therapeutic Agent (common name, if relevant) [trade name, where appropriate]</th>
<th>Class—Pharmacology and Pharmacokinetics</th>
<th>Indications</th>
<th>Side Effects or Adverse Effects</th>
<th>Contraindications or Precautions to Consider; Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Other</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sitagliptin [Januvia], saxagliptin [Onglyza], linagliptin [Tradjenta]</td>
<td>DPP-IV inhibitors—prevents degradation of incretin hormones → decreased glucagon, increased insulin, delays gastric emptying</td>
<td>Oral treatment for type 2 diabetes</td>
<td>Diarrhea, constipation, edema</td>
<td></td>
</tr>
<tr>
<td>Exenatide [Byetta]</td>
<td>Incretin mimetic—agonizes GLP-1 receptors → decreases glucagon, increases insulin, delays gastric emptying</td>
<td>Injectable treatment for type 2 diabetes</td>
<td>Mild weight loss, nausea, hypoglycemia, constipation, slight risk of pancreatitis</td>
<td>Derived from exendin, a hormone found in Gila monster saliva</td>
</tr>
<tr>
<td>Liraglutide [Victoza]</td>
<td>Incretin mimetic—synthetic GLP-1 analog → decreases glucagon, increases insulin, delays gastric emptying</td>
<td>Injectable treatment for type 2 diabetes</td>
<td>Mild weight loss, nausea, vomiting, diarrhea, slight risk of pancreatitis</td>
<td>Increased incidence of medullary thyroid cancer in animal models</td>
</tr>
<tr>
<td>Pramlintide [Symlin]</td>
<td>Analog of amylin, a pancreatic hormone secreted with insulin that decreases glucagon and delays gastric emptying</td>
<td>Injectable treatment for type 2 diabetes</td>
<td>Nausea, vomiting, hypoglycemia</td>
<td></td>
</tr>
<tr>
<td><strong>α-Glucosidase inhibitors</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acarbose [Precose] miglitol</td>
<td><em>α-Glucosidase inhibitor</em>—inhibit intestinal brush border enzyme <em>α</em>-glucosidase → delays sugar hydrolysis and glucose absorption from gut → decreases postprandial hyperglycemia</td>
<td>Oral treatment for type 2 diabetes postprandially</td>
<td>GI effects (flatulence, cramps, diarrhea); may reduce absorption of iron</td>
<td></td>
</tr>
</tbody>
</table>

CHF, congestive heart failure; DPP-IV, dipeptidyl peptidase-IV; GI, gastrointestinal; GLP-1, glucagon-like peptide-1; LDL, low-density lipoprotein; NPH, neutral protamine Hagedorn; PPARγ, peroxisome proliferator-activated receptor gamma.
Clinical Vignette 7-2

CLINICAL PRESENTATION: An 8-year-old female child presents to the emergency department with complaints of several days of vomiting and thirst. The mother also reports that the patient has not been acting like herself lately and has been urinating more than usual. The patient recently recovered from an upper respiratory infection with high fevers. On examination, the patient is breathing rapidly and deeply (Kussmaul respirations), and a sweet smell is noticed on her breath. Her skin and oral mucosa are dry.

DIFFERENTIALS: Diabetic ketoacidosis (DKA), hyperosmolar hyperglycemic state (HHS), gastroenteritis, hypoglycemic coma, metabolic acidosis (from causes other than DKA).

LABORATORY STUDIES: A urinalysis should be obtained with interest in glucose and ketone levels—high glucose and ketone levels suggest DKA. In HHS, the glucose levels are elevated but there is no ketosis. HHS is more often seen in patients with type 2 diabetes, and DKA is more often seen in patients with type 1 diabetes. A blood chemistry would also be key in differentiating causes; in DKA, it would show high glucose, high ketones, and an acidic profile with low pH, low bicarbonate, and elevated anion gap from the ketones (organic acids). Also in DKA, serum potassium is high because the acidosis causes a shift of serum hydrogen ions into cells in exchange for intracellular potassium ions. Serum sodium appears decreased because hyperglycemia increases serum osmolality shifting water out of cells. Blood glucose and serum osmolality are significantly higher in HHS than in DKA, and ketones are not found because there are sufficient levels of insulin to prevent lipolysis, thereby preventing ketogenesis. HHS usually presents with a nonacidotic profile. Metabolic acidosis can also cause vomiting, Kussmaul respirations, a low blood pH, and bicarbonate. Causes of metabolic acidosis with a normal anion gap include diarrhea, renal tubular acidosis, or acetazolamide overdose. Causes of metabolic acidosis with an elevated anion gap include chronic renal failure, lactic acidosis, DKA, uremia, salicylate overdose, methanol ingestion, and ethylene glycol ingestion. To determine the cause of the metabolic acidosis in this patient, salicylate, lactate, blood alcohol, methanol, and ethylene glycol levels should be obtained. Finally, in gastroenteritis, a metabolic alkalosis from the vomiting is expected. In hypoglycemic coma, the glucose levels are low.

MANAGEMENT: Three-tiered approach: (1) Rehydration—a fluid bolus is indicated because the patient is severely dehydrated. Monitor rehydration status by noting resolution of mental status changes. The most common complication of this treatment is cerebral edema from too rapid a change in serum osmolality. (2) Insulin—to facilitate peripheral uptake of glucose, decrease ketone body formation. (3) Potassium replacement—although blood studies show high serum potassium levels that is misleading because the acidosis caused the potassium to shift out of cells and the body is actually potassium starved.

Obesity

Obesity is a multifactorial disease with a variable genetic component and is associated with diet, lifestyle, drugs, and endocrine disorders. Multiple therapeutic strategies including diet, exercise, bariatric surgery, and drugs can be attempted. Table 7-10 summarizes pharmacologic agents available in treating obesity.

<table>
<thead>
<tr>
<th>Therapeutic Agent (common name, if relevant) [trade name, where appropriate]</th>
<th>Class—Pharmacology and Pharmacokinetics</th>
<th>Indications</th>
<th>Side Effects or Adverse Effects</th>
<th>Contraindications or Precautions to Consider; Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Orlistat</td>
<td>Inhibits pancreatic lipases → alters fat metabolism</td>
<td>Obesity (long term)</td>
<td>Steatorrhea, GI irritation, reduced absorption of fat-soluble vitamins, and headache</td>
<td>Used in conjunction with modified diet</td>
</tr>
<tr>
<td>Phentermine</td>
<td>Sympathomimetic—stimulates the release of norepinephrine</td>
<td>Obesity (short term)</td>
<td>Hypertension, tachycardia, euphoria, tremor</td>
<td>Contraindicated in patients with cardiovascular disease or with history of drug abuse</td>
</tr>
</tbody>
</table>

GI, gastrointestinal.
The pituitary gland sits in the sella turcica. The anterior portion is regulated by the hypothalamus. The posterior portion contains extensions of hypothalamic neurons. Excess prolactin can result from estrogen therapy or drugs, such as antipsychotics, that interfere with dopamine (prolactin-inhibiting hormone).

### TABLE 7-11 Pituitary Disorders

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Etiology</th>
<th>Clinical Features</th>
<th>Laboratory Diagnosis</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prolactinoma</td>
<td>Lactotrophic (chromophobic) anterior pituitary tumor; most common pituitary tumor</td>
<td>Decreased libido, vision changes, amenorrhea, gynecomastia, galactorrhea, virilization</td>
<td>Minimal or no increase in serum prolactin after TRH given</td>
<td>Bromocriptine or surgery</td>
</tr>
<tr>
<td>Acromegaly (adults)/gigantism (children)</td>
<td>Somatotrophic (acidophilic) anterior pituitary adenoma</td>
<td>Prominent forehead, jaw, large hands, feet, enlargement of visceras; hyperglycemia; renal failure; hypertension; mental disturbances</td>
<td>Excess growth hormones and somatomedins (IGF-1)</td>
<td>Transsphenoidal surgery, bromocriptine, radiation, or octreotide</td>
</tr>
<tr>
<td>Cushing disease</td>
<td>Hypersecretion of ACTH from basophilic adenoma of pituitary</td>
<td>(Table 7-13) Suppression of ACTH secretion during high-dose dexamethasone test</td>
<td>Surgery or pituitary irradiation</td>
<td></td>
</tr>
<tr>
<td>Panhypopituitarism (Simmonds disease, Sheehan syndrome)</td>
<td>Pituitary tumors, ischemia, trauma; DIC, sickle cell anemia</td>
<td>Marked wasting, panhypopituitarism, headache, vomiting</td>
<td>Decreased levels of FSH, LH, ACTH, TSH</td>
<td>Hormone replacement</td>
</tr>
<tr>
<td>SIADH</td>
<td>Pituitary hypersecretion; ectopic production of ADH (small cell lung cancer)</td>
<td>Decreased urinary output, fatigue, mental disturbances</td>
<td>Hyponatremia, high urine osmolality</td>
<td>Fluid restriction</td>
</tr>
<tr>
<td>Diabetes insipidus</td>
<td>Central (neurogenic): ADH insufficiency Nephrogenic: lack of end-organ (kidney) response</td>
<td>Dehydration, thirst, polyuria, recent trauma to the head or anoxia</td>
<td>(Table 7-12), hyponatremia</td>
<td>Central: desmopressin (DDAVP) replaces ADH Nephrogenic: fluid restriction and thiazide response diuretics (works by a paradoxical effect)</td>
</tr>
</tbody>
</table>

ACTH, adrenocorticotropic hormone; ADH, antidiuretic hormone (vasopressin); DDAVP, 1-deamino-8-D-arginine vasopressin; DIC, disseminated intravascular coagulation; FSH, follicle-stimulating hormone; IGF-1, insulin-like growth factor 1; LH, luteinizing hormone; SIADH, syndrome of inappropriate secretion of antidiuretic hormone; TRH, thyrotropin-releasing hormone; TSH, thyroid-stimulating hormone.
DIABETES INSIPIDUS (Table 7-12)

Diabetes insipidus is a disease characterized by excessive low-osmolality urine output. There are two forms: central and nephrogenic.

<table>
<thead>
<tr>
<th>Urine Osmolality Greater than 280 mOsm/kg with Dehydration</th>
<th>Response to Antidiuretic Hormone after Dehydration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>+</td>
</tr>
<tr>
<td>Central diabetes insipidian</td>
<td>−</td>
</tr>
<tr>
<td>Partial diabetes insipidian</td>
<td>+</td>
</tr>
<tr>
<td>Nephrogenic diabetes insipidian</td>
<td>−</td>
</tr>
<tr>
<td>Primary polydipsia</td>
<td>+</td>
</tr>
</tbody>
</table>

THE ADRENAL GLANDS

I. Congenital adrenal hyperplasia (Figure 7-9)
The adrenal glands are anatomically divided into a medulla and a cortex. The cortex itself is divided into three anatomic layers. The four anatomic layers of the adrenal glands are responsible for various metabolic functions in the body.

II. Adrenal cortex pathology (Table 7-13)

<table>
<thead>
<tr>
<th>Disease</th>
<th>Etiology</th>
<th>Clinical Features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cushing syndrome</td>
<td>Excess cortisol as a result of iatrogenic corticosteroid therapy (most common cause), adrenal adenoma (more common than carcinoma); ectopic ACTH from neoplasm (especially small cell lung carcinoma)</td>
<td>Peripheral muscle wasting and weakness; central obesity with round facies and increased fat deposition at upper back, easy bruising with abdominal striae; bone demineralization, osteoporosis, psychosis, acne; hirsutism; hyperglycemia; hypertension</td>
</tr>
<tr>
<td>Cushing disease</td>
<td>Excess cortisol as a result of pituitary hypersecretion of ACTH; bilateral hyperplasia of adrenal cortex</td>
<td>Identical to Cushing syndrome</td>
</tr>
<tr>
<td>Conn syndrome (primary hyperaldosteronism)</td>
<td>Adrenal cortex adenoma (more common than hyperplasia, which is more common than carcinoma), sodium retention, low plasma renin</td>
<td>Hypertension, hypokalemic alkalosis</td>
</tr>
<tr>
<td>Secondary hyperaldosteronism</td>
<td>Renal tumors, renal ischemia, edematous conditions (cineasis, nephrotic syndromes, congestive heart failure), increased plasma renin</td>
<td>Hypertension, hypokalemic alkalosis</td>
</tr>
</tbody>
</table>

(continued)
The Endocrine System

**TABLE 7-13 Adrenal Cortex Pathology (Continued)**

<table>
<thead>
<tr>
<th>Disease</th>
<th>Etiology</th>
<th>Clinical Features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Addison disease</td>
<td>Most commonly idiopathic cortisol deficiency; possibly autoimmune; may be caused by tumor, infections (i.e., tuberculosis)</td>
<td>Hypotension, low serum sodium, hyperpigmentation, increased serum potassium</td>
</tr>
<tr>
<td>Neisseria meningitidis infection</td>
<td>leads to disseminated intravascular coagulation (DIC), hemorrhagic adrenal necrosis and circulation collapse</td>
<td>Acute hypotension and salt wasting, shock, more common in children; death within hours if not treated</td>
</tr>
</tbody>
</table>

ACTH, adrenocorticotropic hormone.

**QUICK HIT**

Hyperpigmentation in Addison disease is caused by increased production of proopiomelanocortin (POMC) by the pituitary. POMC is enzymatically split to yield adrenocorticotropic hormone (ACTH) and melanocyte-stimulating hormone (MSH).

**FIGURE 7-9** Congenital adrenal hyperplasia

**Steroid hormone synthesis**

- **17-α-Hydroxylase deficiency**
  - Sex hormones and cortisol not produced
  - Increased production of mineralocorticoids causes sodium and fluid retention and, therefore, hypertension.
  - Patient is phenotypically female but is unable to mature (amenorrhea and lack of secondary sexual characteristics).

- **21-α-Hydroxylase deficiency**
  - Most common form of CAH
  - Usually a partial deficiency
  - ACTH levels elevated, causing an increased flux to sex hormones and, therefore, masculinization.
  - Lack of mineralocorticoid production leads to inadequate Na⁺+ retention and, therefore, hypotension.

- **11-β-Hydroxylase deficiency**
  - Decrease in serum cortisol, aldosterone, and corticosterone
  - Increased production of deoxycorticosterone causes fluid retention and hypertension.
  - Masculinization as with 21-α-hydroxylase deficiency

ACTH, adrenocorticotropic hormone; NADPH, reduced nicotinamide adenine dinucleotide phosphate.
III. Adrenal medulla pathology (Table 7-14)

<table>
<thead>
<tr>
<th>Tumor</th>
<th>Pathology</th>
<th>Clinical Manifestation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neuroblastoma</td>
<td>Malignant; excess catecholamine secretion; N-myc (oncogene) amplification</td>
<td>Children: degree of N-myc amplification related to prognosis; abdominal pain, constipation, possibly some hypertension</td>
</tr>
<tr>
<td>Pheochromocytoma</td>
<td>Benign (10% malignant); tumor of chromaffin cells; seen in MEN 2a and 2b</td>
<td>Adults: hypertension (usually paroxysmal); palpitations, sweating, and headache; increased urinary vanillylmandelic acid (VMA)</td>
</tr>
</tbody>
</table>

Clinical Vignette 7-3

**CLINICAL PRESENTATION:** A 37-year-old woman presents to her primary care physician with a chief complaint of weight gain, fatigue, acne, and hirsutism. After further questions, the patient reports that she has not had her period for 3 months. Her past medical history is significant for a bone marrow transplantation, for which the patient is currently on medication. Patient denies a family history of diabetes or hypertension. Physical examination reveals central obesity, abdominal striae, bruising on thighs and buttocks, and muscle weakness. Vital signs: temperature = 97.5°F; heart rate = 80 bpm; respiration rate = 20 breaths/min; blood pressure = 140/90 mm Hg.

**DIFFERENTIAL:** Iatrogenic Cushing syndrome, adrenocorticotropic hormone (ACTH)–producing pituitary adenoma (Cushing disease), adrenal adenoma, ectopic ACTH production, and obesity. This patient is exhibiting signs and symptoms of high cortisol termed Cushing syndrome. Some findings (i.e., obesity, hypertension, osteoporosis, diabetes mellitus) are nonspecific and less helpful in diagnosis of Cushing syndrome. Easy bruising, striae, virilization, and myopathy are more helpful in the diagnosis. Also, patients with Cushing disease can have hyperpigmentation as a result of elevated ACTH levels, whereas patients with Cushing syndrome due to other causes will not have hyperpigmentation. The most common cause of Cushing syndrome is an unfavorable response to prescribed steroids; patient's recent transplantation history suggests the possibility that she received immunosuppressive steroids.

**LABORATORY STUDIES:** Figure 7-10 outlines the approach. The first step is to determine whether cortisol levels are elevated in this patient, which can be done via a urine 24-hour free cortisol level or an overnight dexamethasone suppression test. In this latter test, dexamethasone is given at night, and serum cortisol levels are measured in the morning. In normal individuals, dexamethasone should suppress the pituitary–adrenal axis, resulting in decreased cortisol in the morning. In Cushing syndrome, the serum cortisol remains elevated. The next step is to determine the cause of the cortisol elevation, which could be from (a) increased ACTH production at the level of the pituitary or ectopically, (b) increased cortisol production at the level of the adrenal gland, or (c) exogenous cortisol in the form of prednisone. To determine the cause, measure ACTH levels, which would be low in the case of exogenous cortisol and adrenal adenoma, because cortisol feedback inhibits the pituitary from secreting ACTH. Knowing which medications the patient is using helps in differentiating these causes. ACTH levels are high in patients with obesity, patients with ectopic ACTH production, or pituitary ACTH adenoma. The key differentiating factor is that low-dose dexamethasone will suppress ACTH production in obese individuals, high-dose dexamethasone will suppress ACTH production in pituitary adenoma cases, and nothing will suppress ACTH levels in the patients with ectopic ACTH production.

**MANAGEMENT:** This patient most likely has iatrogenic Cushing syndrome, which is remedied by tapering of the glucocorticoid. Pituitary or adrenal adenoma requires surgical removal of the neoplasm.
Approach to Cushing syndrome

1. Suspect Cushing syndrome
2. Overnight dexamethasone suppression test
   - Serum cortisol > 5 (abnormal)
   - Measure ACTH level
     - Low: Adrenal adenoma
     - High: Administer dexamethasone low dose
6. Cortisol/ACTH remains high
   - Administer dexamethasone high dose
     - Cortisol/ACTH remains high: Ectopic ACTH production
     - Cortisol/ACTH suppressed (low): ACTH secreting pituitary adenoma
   - Cortisol/ACTH suppressed (low)
     - Normal (obesity)

ACTH, adrenocorticotropic hormone; CT, computed tomography; MRI, magnetic resonance imaging.
### Table 7-15: Therapeutic Agents for Hypothalamic, Pituitary, and Adrenal Conditions

<table>
<thead>
<tr>
<th>Therapeutic Agent (common name, if relevant) [trade name, where appropriate]</th>
<th>Class—Pharmacology and Pharmacokinetics</th>
<th>Indications</th>
<th>Side Effects or Adverse Effects</th>
<th>Contraindications or Precautions to Consider; Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Growth hormone [somatropin, somatrem]</td>
<td>Synthetic analog of growth hormone—causes liver to produce insulin-like growth factors (somatomedins)</td>
<td>Replacement therapy in children with growth hormone deficiency, Turner syndrome; burn victims</td>
<td></td>
<td>Should not be used in patients with closed epiphyses</td>
</tr>
<tr>
<td>Growth hormone—releasing hormone (GHRH)</td>
<td>Synthetic analog of GHRH—stimulates release of GH</td>
<td>Dwarfism</td>
<td>Pain at injection</td>
<td></td>
</tr>
<tr>
<td>Octreotide [Sandostatin]</td>
<td>Synthetic analog of somatostatin—decreases release of GH, gastrin, secretin, VIP, CCK, glucagon, insulin</td>
<td>Acromegaly, glucagonoma, insulinoma, carcinoid syndrome</td>
<td>Nausea, cramps, gallstones</td>
<td></td>
</tr>
<tr>
<td>Oxytocin [Pitocin, Syntocinon]</td>
<td>Synthetic analog of oxytocin—stimulates uterine contraction and contraction of breast myoepithelial cells; milk letdown reflex</td>
<td>Induces labor; control uterine hemorrhage</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Desmopressin (DDAVP)</td>
<td>Synthetic analog of ADH—recruits water channels to luminal membrane in collecting duct</td>
<td>Central diabetes insipidus, nocturnal enuresis, von Willebrand disease</td>
<td>Overhydration; allergic reaction; larger doses result in pallor, diarrhea, hypertension; coronary constriction; chronic rhinopharyngitis</td>
<td>Synthetic analog to vasopressin; intranasal administration</td>
</tr>
<tr>
<td>Prednisone, hydrocortisone, triamcinolone, dexamethasone, beclomethasone</td>
<td>Glucocorticoid—inhibits protein synthesis; reduces lymph node and spleen size; inhibits cell cycle activity of lymphoid cells; lyses T cells; suppresses antibody, prostaglandin, and leukotriene synthesis; blocks monocyte production of IL-1</td>
<td>Addison disease, rheumatic arthritis, autoimmune disorders, allergic reaction, asthma, organ transplantation (especially during rejection crisis)</td>
<td>Osteoporosis, Cushingoid reaction, acne, psychosis, glucose intolerance, infection, hypertension, cataracts, peptic ulcers</td>
<td></td>
</tr>
</tbody>
</table>

ADH, antidiuretic hormone; CCK, cholecystokinin; GH, growth hormone; IL-1, interleukin 1; VIP, vasoactive intestinal peptide.
II. Myxedema
A. Can be described as hypothyroidism of the adult
B. Causes
1. Hashimoto thyroiditis (see the following)
2. Idiopathic causes
3. Iodine deficiency
   a. A problem in geographic areas with poor nutrition
   b. Deficiency in pregnant women can lead to cretinism in the child (see the following).
4. Paradoxically, high doses of iodine lead to a decrease in thyroid hormone production.
5. Overirradiation of the thyroid using iodine-131 for treatment of hyperthyroidism.
C. Clinical features of the hypothyroid state
1. Cold intolerance
2. Weight gain
3. Constipation
4. Lowering of voice
5. Menorrhagia
6. Slowed mental and physical function
7. Dry skin with coarse and brittle hair
8. Reflexes showing slow return phase ("hung reflex")
D. Treatment is usually with levothyroxine (T₄)

**QUICK HIT**
Because of its long half-life, T₄ is ideal as a hormone replacement in patients with hypothyroidism. Even with once-a-day dosing, steady serum levels of T₄ and T₃ can be achieved.

**THYROID**

I. Formation of thyroid hormone (Figure 7-11)

**Formation of thyroid hormone**

1. Oxidation of I⁻ by peroxidase followed by iodination of thyroglobulin
2. Condensation
3. Proteolytic release of hormone from follicle
   * Inhibited by propylthiouracil and methimazole
   † Inhibited by propylthiouracil

T₃, triiodothyronine; T₄, thyroxine.
III. Cretinism
A. Can be described as hypothyroidism of the fetus or child
B. Causes
   1. Iodine-deficient diet in the mother or during the early life of the child
   2. Thyroid-related enzyme deficiency
   3. Thyroid developmental defect
   4. Failure of thyroid descent during development
   5. Transfer of antithyroid antibodies from the mother with an autoimmune disease to the fetus
C. Clinical features
   1. Impaired physical growth
   2. Mental retardation
   3. Enlarged tongue
   4. Enlarged, distended abdomen

IV. Hashimoto thyroiditis
A. An autoimmune disorder causing hypothyroidism and a painless goiter
   1. Dense infiltrate of lymphocytes into the thyroid gland
   2. Antithyroglobulin and antithyroid peroxidase (formerly antithyro microsomal) antibodies
   3. 5:1 female predominance
   4. Incidence increases with age.
   5. Associated with human leukocyte antigen-DR3 (HLA-DR3) and HLA-B5
B. Is the most common form of hypothyroidism in those with adequate iodine intake
C. Clinical features
   1. Slowly progressing course with stages of euthyroid state, hyperthyroid state, and hypothyroid state
   2. May lead to a scarred and shrunken gland in hypothyroid state
   3. Microscopically, thyroid resembles lymph node
D. Associated with other autoimmune disorders
   1. Diabetes mellitus
   2. Pernicious anemia
   3. Sjogren syndrome

V. Subacute (de Quervain) thyroiditis
A. Transient hyperthyroidism with painful goiter
   1. Focal destruction of thyroid
   2. Granulomatous inflammation
   3. 3:1 female predominance
   4. Associated with HLA-B35
B. Causes—possibly as a result of recent viral infection with coxsackie virus, echovirus, adenovirus, measles, or mumps
C. Clinical features
   1. Acute febrile state
   2. Rapid, painful enlargement of the thyroid
   3. Transient hyperthyroidism owing to gland destruction
D. Self-limited disease

VI. Graves disease
A. Autoimmune disorder causing hyperthyroidism and goiter
   1. Thyroid-stimulating immunoglobulin (TSI) is an immunoglobulin G (IgG) antibody to the thyroid-stimulating hormone (TSH) receptor.
   2. Binding of TSI to the TSH receptor stimulates thyroid hormone production and hyperplasia of the thyroid gland.
   3. It is associated with HLA-DR3 and HLA-B8.
   4. It has a 4:1 female predominance.
TABLE 7-16 Therapeutic Agents for Thyroid Disorders

<table>
<thead>
<tr>
<th>Therapeutic Agent (common name, if relevant) [trade name, where appropriate]</th>
<th>Class—Pharmacology and Pharmacokinetics</th>
<th>Indications</th>
<th>Side Effects or Adverse Effects</th>
<th>Contraindications or Precautions to Consider; Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Propylthiouracil (PTU)</td>
<td>Antithyroid agent—inhbits peroxidase enzyme in thyroid [\rightarrow \text{decreases synthesis of thyroid hormone; also blocks peripheral conversion of } T_4 \text{ to } T_3]</td>
<td>Hyperthyroidism</td>
<td>Agranulocytosis</td>
<td>Crosses the placenta and can cause fetal goiter and hypothyroidism; preferred to methimazole in treating pregnant females with moderate to severe hyperthyroidism</td>
</tr>
<tr>
<td>Methimazole [Tapazole]</td>
<td>Antithyroid agent—inhbits peroxidase enzyme in thyroid [\rightarrow \text{decreases synthesis of thyroid hormone}]</td>
<td>Hyperthyroidism</td>
<td>Agranulocytosis</td>
<td>Crosses the placenta; can cause fetal goiter, hypothyroidism, and aplasia cutis (fetal scalp defect).</td>
</tr>
<tr>
<td>Levothyroxine (T_4) [Synthroid, Levothroid]</td>
<td>Synthetic analog of thyroxine (T_4)</td>
<td>Hypothyroidism</td>
<td>Tachycardia, heat intolerance, tremors, arrhythmia</td>
<td></td>
</tr>
<tr>
<td>Triiodothyronine (T_3) [Triostat]</td>
<td>Synthetic analog of thyroid hormone (T_3)</td>
<td>Hypothyroidism</td>
<td>Tachycardia, heat intolerance, tremors, arrhythmia</td>
<td></td>
</tr>
</tbody>
</table>

B. Clinical features of Graves disease

1. Hyperthyroidism and goiter caused by autoimmune immunoglobulins
   a. Increased total thyroxine (T\(_4\))
   b. Increased triiodothyronine (T\(_3\))
   c. Decreased TSH level
   d. Increased resin radioactive T\(_4\) uptake
   e. Increased radioactive iodine

2. Exophthalmos, proptosis
3. Warm, moist, and flushed skin
4. Thin, fine hair
5. Cardiovascular system
   a. Increased heart rate and cardiac output
   b. Palpitations and fibrillations
6. Muscle atrophy
   a. Weakening of skeletal muscles occurs.
   b. Vital capacity of lungs decreases owing to weakened respiratory muscles.
7. Weight loss occurs despite an increased appetite.
8. Diarrhea is common.
9. Menstrual flow may decrease or stop.

C. Treatment (Table 7-16)

1. Antithyroid drugs (e.g., propylthiouracil or methimazole)
2. A \(\beta\)-blocker to reduce the cardiac effects
3. Radioactive iodine (iodine-131)
4. Surgery
**Clinical Vignette 7-4**

**CLINICAL PRESENTATION:** A 40-year-old woman presents to your office with a 20-lb weight loss over the past 2 months despite eating more. She also reports irregular menses, diarrhea, and difficulty sleeping and concentrating. She denies chest pain and palpitations. Physical examination reveals warm, moist skin and resting hand tremor. Neck examination shows a diffusely enlarged, nontender thyroid gland. Vital signs: temperature = 99.0°F; respiration rate = 20 breaths/min; heart rate = 99 bpm; blood pressure = 140/90 mm Hg.

**DIFFERENTIALS:** Hyperthyroidism (Graves disease, factitious hyperthyroidism, subacute thyroiditis, multinodular goiter, thyroid adenoma), Hashimoto thyroiditis, menopause, panic disorder, and pheochromocytoma. The patient's symptoms are indicative of thyrotoxicosis. Of all the causes of thyrotoxicosis listed previously, exophthalmos and thyroid bruit occur only in Graves disease. Also, although Hashimoto thyroiditis eventually results in hypothyroidism, early findings in the disease are consistent with hyperthyroidism.

**LABORATORY STUDIES:** Figure 7-12 outlines the approach to determining a cause of hyperthyroidism in a patient. Serum thyroid-stimulating hormone (TSH) and triiodothyronine (T₃)/thyroxine (T₄) should be obtained. These tests would show elevated T₃/T₄ and suppressed TSH in hyperthyroidism and would be normal in menopause, panic disorder, and pheochromocytoma. A thyroid scan with radioactive iodide uptake is useful for distinguishing between the various causes of hyperthyroidism listed previously. A negative scan would be expected for subacute thyroiditis and factitious hyperthyroidism. These can be further differentiated by a thorough history and physical examination. The patient with subacute thyroiditis has a tender thyroid, systemic flulike symptoms, and possible history of recent viral infection. Factitious hyperthyroidism is more often seen in healthcare workers with access to T₃/T₄ who are abusing it for weight loss purposes. A positive scan of different types would be observed in Graves disease, multinodular goiter, and thyroid adenoma. In Graves disease, a diffuse hot scan would be seen, whereas in multinodular goiter, several nodules—both hot and cold—would be visualized. In thyroid adenoma, only one such hot nodule would be seen. Graves disease can be further supported by presence of thyroid-stimulating immunoglobulin G, which binds to thyrotropin receptors on the thyroid gland. These lab studies would be normal in menopause and panic disorder. Normal urine metanephrines and vanillylmandelic acid would rule out pheochromocytoma.

**THE ENDOCRINE SYSTEM**

**Quick Hit**

Thyrotoxicosis factitia is a factitious disorder in which the patient intentionally self-administers excess thyroid hormone (levothyroxine) to simulate the symptoms of hyperthyroidism.
### Table 7-18 Parathyroid Disorders

<table>
<thead>
<tr>
<th>Condition</th>
<th>Etiology</th>
<th>Clinical Features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary hyperparathyroidism</td>
<td>Adenoma (most common); hyperplasia more common than carcinoma; seen in MEN 1 and MEN 2a; excess parathyroid hormone (PTH); hypercalcemia</td>
<td>Osteitis fibrosa cystica (cystic “brown tumors” of bone); renal calculi and nephrocalcinosis; duodenal ulcers</td>
</tr>
<tr>
<td>Secondary hyperparathyroidism</td>
<td>Hypocalcemia caused by chronic renal failure (loss of vitamin D activation); parathyroid hyperplasia; excess PTH; high alkaline phosphatase</td>
<td>Cystic bone lesions; metastatic calcification of organs</td>
</tr>
<tr>
<td>Hyoparathyroidism</td>
<td>Most commonly secondary to thyroidectomy; seen in DiGeorge syndrome; hypocalcemia</td>
<td>Tetany; positive Chvostek and Trousseau signs</td>
</tr>
<tr>
<td>Pseudohypoparathyroidism</td>
<td>Autosomal recessive; deficient organ response to PTH</td>
<td>Short stature; underdeveloped fourth and fifth digits</td>
</tr>
</tbody>
</table>

MEN 1 and 2a, multiple endoplasmic neoplasia types 1 and 2a.

To remember the symptoms of hypercalcemia, think:
- **Bones**: pain in bones
- **Stones**: renal stones
- **Groans**: abdominal pain
- **Psychiatric overtones**: confused state
### Multiple Endocrine Neoplasia Syndromes

**Table 7-19**

<table>
<thead>
<tr>
<th>Type 1 (Wermer)</th>
<th>Type 2a (Sipple)</th>
<th>Type 2b</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parathyroid hyperplasia, pituitary adenomas, pancreatic tumors, angiofibromas</td>
<td>Medullary thyroid carcinoma, parathyroid hyperplasia, pheochromocytoma</td>
<td>Mucosal neuromas (particularly of the GI tract), medullary thyroid carcinoma, pheochromocytoma, marfanoid body habitus</td>
</tr>
</tbody>
</table>

**Quick Hit**
The multiple endocrine neoplasia (MEN) syndromes are autosomal dominant conditions in which more than one endocrine organ is affected by either hyperplasia or neoplasia.

**MEN 1** is a disease of 3 Ps: Pituitary, Parathyroid, and Pancreas.

**MEN 2a** is a disease of 1 M and 2 Ps: Medullary thyroid carcinoma, Parathyroid, and Pheochromocytoma.

**MEN 2b** is a disease of 2 Ms and 1 P: Mucosal neuromas, Medullary thyroid carcinoma, and Pheochromocytoma.

*GI, gastrointestinal.*
DETERMINATION OF SEX

Before the seventh week of gestation, the fetal gonads are not differentiated into either the male or female genotype. Primordial germ cells migrate into the genital ridge mesoderm to form testes and ovaries. The presence or absence of the Y chromosome and the sex-determining region of the Y chromosome (SRY) determine gonadal differentiation. Therefore, the “default” gender is female if there is no SRY region on an active Y chromosome. Gender determination, which occurs after the seventh week, depends on the type of gonads present.

FEMALE REPRODUCTIVE SYSTEM DEVELOPMENT

I. Ovaries and other female reproductive structures
   A. Primordial follicles contain primary oocytes (XX genotype) and follicular (granulosa) cells, which form the ovaries.
   B. As the upper abdomen grows, the ovaries “descend” toward the perineum.
   C. The gubernaculum assists in this descent and then becomes the ovarian ligament and the round ligament of the uterus.
   D. The paramesonephric ducts develop into the fallopian tubes and eventually into the uterus.

II. Vagina and uterus (Figure 8-1)

III. Breasts
   A. Only the main lactiferous ducts develop during the fetal life.
   B. Glands enlarge during puberty owing to the increased levels of estrogens, progestins, prolactin, and growth hormone.
The Reproductive System

A. Reproductive system of the newborn female

- Ovary (after descent)
- Uterine tube
- Round ligament of uterus
- Inguinal canal
- Vagina
- Labium majus
- Labium minora
- Labioscrotal swellings
- Urogenital sinus
- Mesonephric duct
- Gartner's duct
- Ovarian ligament

Structures arising from:
- Paramesonephric duct
- Urogenital sinus
- Mesonephric duct

B. Stages of development of the female external genitalia

- Indifferent stage: ♀ and ♂ identical
- Urogenital membrane
- Urogenital fold
- Labioscrotal swellings
- Mons pubis
- Glans clitoris
- Urethral orifice
- Hymen
- Vestibule of vagina
- Developing glans clitoris
- Fused labioscrotal swellings
- Phallus
- Urethral groove

(Adapted with permission from Moore KL, Persaud TVN. The Developing Human: Clinically Oriented Embryology. 6th ed. Philadelphia, PA: WB Saunders; 1998.)
MALE REPRODUCTIVE SYSTEM DEVELOPMENT

I. Testes and other male reproductive organs
A. Primary sex cords contain primordial germ cells of XY genotype. The Y chromosome codes for the testes-determining factor that allows for male gonadal differentiation (i.e., formation of medullary cords and seminiferous tubules).
B. Müllerian-inhibiting factor (MIF) is secreted by Sertoli cells. MIF causes regression of the müllerian (paramesonephric) ducts and their associated female genital structures (uterine tubes and uterus).
C. The mesonephric ducts, under the influence of testosterone, become the ductus deferens, the seminal vesicles, and the ejaculatory ducts in the adult male.

II. The prostate gland forms from the urogenital sinus (Figure 8-2)

(Adapted with permission from Moore KL, Persaud TVN. The Developing Human: Clinically Oriented Embryology. 6th ed. Philadelphia, PA: WB Saunders; 1998.)
III. External genitalia
A. Dihydrotestosterone (DHT) is responsible for the masculinization of genitalia.
B. The genital tubercle enlarges to become the glans penis.
C. The urogenital fold becomes the shaft of the penis.
D. The labioscrotal swellings fuse in the midline and become the scrotum.

- Spermatogenesis versus Oogenesis (Figure 8-3)
- Important Anatomic Features of the Perineum (Figure 8-4)
The Reproductive System

**Quick Hit**

Puberty in males, usually occurring at age 15 years, is marked by an increased testosterone, leading to greater hair distribution, growth of genitalia, nocturnal emissions, deepening of the voice, and increased muscle mass. Precocious puberty in males has a similar pathology to that in females, with the exception that it has a later age of onset.

**Mnemonic**

To remember the path of the sperm through the male reproductive system, think of the phrase “SEVEN UP”: Seminiferous tubules, Epididymis, Vas deferens, Ejaculatory duct, Nothing, Urethra, Penis.

**Figure 8-4**

**Important anatomic features of the perineum**

**A. Male perineum**
- Bladder
- Prostate gland
- Superior fascia of urogenital diaphragm
- Muscles within deep perineal space
- Inferior fascia of urogenital diaphragm
- Corpus cavernosum
- Urethra
- Corpus spongiosum
- Bulbospongious muscle
- Membranous layer of superficial fascia of urogenital region (Colles')

**B. Female perineum**
- Bladder
- Uterus
- Rectum
- External anal sphincter muscle
- Contents of superficial perineal space near midsagittal plane

**To remember the path of the sperm through the male reproductive system, think of the phrase “SEVEN UP”**: Seminiferous tubules, Epididymis, Vas deferens, Ejaculatory duct, Nothing, Urethra, Penis.
Congenital malformations are most often caused by exposure to teratogens during the third to eighth weeks of pregnancy, which is the period of organogenesis (Table 8-1).

**Table 8-1 Congenital Malformations**

<table>
<thead>
<tr>
<th>Malformation</th>
<th>Clinical Features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypospadias</td>
<td>• Urethra opens on the <strong>ventral</strong> side of the penis</td>
</tr>
<tr>
<td></td>
<td>• Spongy urethra does not form properly or the <strong>urogenital folds</strong> do not fuse</td>
</tr>
<tr>
<td></td>
<td>• Paucity of hormone receptors or too little hormone produced from the testes may play a role</td>
</tr>
<tr>
<td></td>
<td>• More common than epispadias</td>
</tr>
<tr>
<td>Epispadias</td>
<td>• Urethra opens on the <strong>dorsum</strong> of the penis</td>
</tr>
<tr>
<td>Undescended testis (cryptorchidism)</td>
<td>• Most are of unknown cause</td>
</tr>
<tr>
<td></td>
<td>• May be unilateral or bilateral</td>
</tr>
<tr>
<td></td>
<td>• Most testes descend before 1 year of life</td>
</tr>
<tr>
<td></td>
<td>• If testes remain undescended, <strong>sterility or testicular cancer</strong> can result</td>
</tr>
<tr>
<td>Congenital inguinal hernia (indirect hernia)</td>
<td>• A communication is formed between the <strong>tunica vaginalis</strong> (adjacent to the testis) and the peritoneal cavity</td>
</tr>
<tr>
<td></td>
<td>• A loop of intestine may herniate into the opening and become entrapped, resulting in obstruction</td>
</tr>
<tr>
<td>True hermaphroditism</td>
<td>• Both testicular and ovarian tissue are present</td>
</tr>
<tr>
<td></td>
<td>• External genitalia are ambiguous</td>
</tr>
<tr>
<td></td>
<td>• Usually 46,XX</td>
</tr>
<tr>
<td>Female pseudohermaphroditism</td>
<td>• XX genotype with <strong>virilization</strong> of the external genitalia is present</td>
</tr>
<tr>
<td></td>
<td>• The cause is <strong>excess androgen exposure</strong></td>
</tr>
<tr>
<td></td>
<td>• This malformation is most often caused by congenital adrenal hyperplasia, a <strong>21-hydroxylase deficiency</strong> (autosomal recessive disease with low cortisol and high ACTH)</td>
</tr>
<tr>
<td>Male pseudohermaphroditism</td>
<td>• XY genotype with varying ambiguities of the external genitalia</td>
</tr>
<tr>
<td></td>
<td>• The cause is a <strong>lack of MIF and testosterone</strong></td>
</tr>
<tr>
<td>Androgen insensitivity syndrome (testicular feminization)</td>
<td>• XY genotype with female phenotype</td>
</tr>
<tr>
<td></td>
<td>• Caused by a <strong>defective androgen receptor</strong></td>
</tr>
<tr>
<td></td>
<td>• Vagina ends blindly (no uterus)</td>
</tr>
<tr>
<td></td>
<td>• Normal female pubertal development occurs but pubic hair is scant and there are no menses</td>
</tr>
<tr>
<td>Double uterus completely</td>
<td>• The cause is failure of the <strong>paramesonephric ducts</strong> to fuse</td>
</tr>
<tr>
<td></td>
<td>• The condition may appear in two forms: uterus divided internally by a thin septum or a division of only the superior part of the uterus (bicornuate uterus)</td>
</tr>
<tr>
<td>Kallmann syndrome</td>
<td>• A deficiency of GnRH results in decreased FSH and LH</td>
</tr>
<tr>
<td></td>
<td>• No secondary sexual characteristics are present</td>
</tr>
<tr>
<td></td>
<td>• Associated with hypoplasia of the olfactory bulbs (<strong>anosmia</strong>)</td>
</tr>
</tbody>
</table>

ACTH, adrenocorticotropic hormone; FSH, follicle-stimulating hormone; GnRH, gonadotropin-releasing hormone; LH, luteinizing hormone; MIF, müllerian-inhibiting factor.
GENETIC ABNORMALITIES

The incidence of genetic abnormalities as a result of aberrant chromosomes significantly increases when the mother is older than 35 years of age. In these patients, additional consideration should be given to genetic testing.

- Genetic Abnormalities Caused by Abnormal Somatic Chromosomes (Table 8-2)
- Genetic Abnormalities Caused by Abnormal Sex Chromosomes (Table 8-3)

### TABLE 8-2 Genetic Abnormalities Caused by Abnormal Somatic Chromosomes

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Genotype</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Down syndrome</td>
<td>Trisomy 21 (95%) or Robertsonian translocation of 14 and 21</td>
<td>- Mental retardation</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Epicanthal folds</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Large tongue</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Brushfield spots on iris</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Simian crease in hands</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Increased incidence of congenital heart disease, acute leukemia, and dementia of the Alzheimer type later in life</td>
</tr>
<tr>
<td>Edwards syndrome</td>
<td>Trisomy 18</td>
<td>- Duodenal atresia</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Mental retardation</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Micronathia</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Rocker bottom feet</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Second digit overlaps third and fourth</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Increased incidence of congenital heart disease</td>
</tr>
<tr>
<td>Patau syndrome</td>
<td>Trisomy 13</td>
<td>- Mental retardation</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Microphthalmia</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Polydactyly</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Cleft lip and palate</td>
</tr>
<tr>
<td>Cri du chat syndrome</td>
<td>Deletion of 5p (5p−)</td>
<td>- Catlike cry</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Mental retardation</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Microcephaly</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Hypertelorism</td>
</tr>
</tbody>
</table>

### TABLE 8-3 Genetic Abnormalities Caused by Abnormal Sex Chromosomes

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Genotype</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Turner syndrome</td>
<td>45,XO</td>
<td>- Monosomy of the X chromosome</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Absence of Barr body</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Short stature</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Webbed neck</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Widely spaced nipples</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Wide, “shield-like” chest</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Wido carrying angle of arms</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Lack of sexual maturity</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Amenorrhea</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Coarctation of the aorta</td>
</tr>
<tr>
<td>Klinefelter syndrome</td>
<td>47,XXY</td>
<td>- Tall with long limbs</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Often presents with gynecomastia</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Hyalinization of seminiferous tubules</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Hypogonadism, lack of spermatogenesis leading to sterility</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- One Barr body</td>
</tr>
</tbody>
</table>

(continued)
### TABLE 8-3 Genetic Abnormalities Caused by Abnormal Sex Chromosomes (Continued)

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Genotype</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>XYY syndrome</td>
<td>47,XYY</td>
<td>• Normal-appearing male, often tall&lt;br&gt;• Often associated with <strong>aggressive</strong> behavior&lt;br&gt;• May be overrepresented in the population of incarcerated males</td>
</tr>
<tr>
<td>XXX syndrome</td>
<td>47,XXX</td>
<td>• Usually asymptomatic&lt;br&gt;• Rarely associated with <strong>menstrual irregularities</strong> and mild mental retardation&lt;br&gt;• Two Barr bodies</td>
</tr>
<tr>
<td>Fragile X syndrome</td>
<td>46,XY</td>
<td>• The end of the X chromosome appears delicate&lt;br&gt;• <strong>Macroorchidism</strong>&lt;br&gt;• Common cause of <strong>mental retardation</strong>&lt;br&gt;• Long face&lt;br&gt;• Low-set, large ears</td>
</tr>
<tr>
<td>Prader–Willi syndrome</td>
<td>−15q12 (no paternal contribution, imprinting disorder)</td>
<td>• Obesity&lt;br&gt;• <strong>Hyperphagia</strong>&lt;br&gt;• Hypogonadism&lt;br&gt;• Short stature&lt;br&gt;• Mental retardation</td>
</tr>
<tr>
<td>Angelman syndrome</td>
<td>−15q12 (no maternal contribution, imprinting disorder)</td>
<td>• Ataxia&lt;br&gt;• Mental retardation&lt;br&gt;• <strong>Inappropriate laughter</strong>&lt;br&gt;• Patient appears to act like a “happy puppet”</td>
</tr>
</tbody>
</table>

### MENARCHE, MENSTRUATION, AND MENOPAUSE

I. Menarche

A. First menstruation; usually occurs between **11 and 14 years** of age
B. Follows thelarche (development of breast buds) by 2 years
C. Precocious puberty
   1. Pubertal changes before 9 years of age in boys and 8 years of age in girls
   2. True precocious puberty
      a. Early but normal pubertal development
      b. Precocious puberty is **usually familial and not pathologic**.
      c. May cause emotional and social adjustment problems
   3. Incomplete precocious puberty
      a. Premature development of a single pubertal characteristic
      b. Types
         • Premature thelarche: breast budding before 8 years of age
         • Premature adrenarche: growth of axillary hair
         • Premature pubarche: growth of pubic hair
      c. Generally self-limited
   4. Etiology
      a. Central—increased follicle-stimulating hormone (FSH) and luteinizing hormone (LH) (from the pituitary) lead to sex steroid production by the gonads.
      b. Peripheral—caused by increased sex steroids not driven by pituitary gonadotropins (gonadal tumors, adrenal pathology, exogenous estrogens, etc.)

---

**QUICK HIT**: Breast surgery should not be performed in girls with precocious puberty because the excision of a “lump” in premature thelarche leads to the loss of an entire breast.
II. Menstruation and fertilization

Quick Hit

In understanding müllerian duct agenesis and androgen insensitivity syndrome, it is important to remember that the ovaries and the lower vagina are not derived from the müllerian system. The ovaries are derived from germ cells that migrate from the primitive yolk sac into the mesenchyme of the peritoneal cavity and subsequently develop into ova and supporting cells. The lower one-third of the vagina arises from the sionovaginal bulb, which fuses with the müllerian-derived upper two-thirds to form the complete vagina.

Quick Hit

There are four causes of primary amenorrhea in the female: Turner syndrome (XO), müllerian duct agenesis (XX), outflow obstruction (imperforate hymen, transverse vaginal septum) (XX), and androgen insensitivity syndrome (XY).

Quick Hit

Remember the function of luteinizing hormone (LH) and follicle-stimulating hormone (FSH) in the male; LH stimulates Leydig cells to produce testosterone and FSH stimulates spermatogenesis.

A. Hormone formation and function (Figure 8-5)
1. Ovarian steroids are synthesized from cholesterol.
2. LH from the pituitary regulates the conversion of cholesterol to pregnenolone (the first step in estrogen synthesis) in the theca cells.
3. FSH from the pituitary regulates the final step in estrogen synthesis in the granulosa cells.
4. Estrogen
   a. Secreted by the follicular cells of the ovary
   b. Induces development of the secondary sex characteristics
      • Binds to the estrogen receptor
      • Activated estrogen-receptor complex interacts with nuclear chromatin.
      • Initiates hormone-specific RNA synthesis
      • Results in protein synthesis
   c. Stimulates uterine growth and development
   d. Induces proliferation of endometrium
   e. Causes thickening of the vaginal mucosa
The Reproductive System

1. Corpus luteum synthesizes progesterone and estrogen (progestational phase).
2. Endometrial glands grow and become tortuous (secretory phase) creating spiral arteries.
3. Endometrium ready for possible implantation
4. Occurs after LH surge.
5. Oocyte expelled from ovary and likely enters fallopian tube.
6. Cervical mucus increased and thinned.
7. Body temperature increases by approximately 1° C.

Menses (days 1–4)
Without fertilization, endometrium is sloughed.

Follicular phase (days 5–14)
1. After menses, FSH levels fall and estrogen levels rise (estrogenic phase).
2. By days 6–8 of the cycle, one of the recruited follicles is selected and the rest degenerate.
3. Meiosis resumes and the oocyte progresses from prophase of meiosis I to metaphase of meiosis II.
4. The first polar body is formed.
5. The uterine endometrium proliferates (proliferative phase).
6. Rising estrogen levels induce LH surge.

Ovulation (day 15)
1. Occurs after LH surge.
2. Oocyte expelled from ovary and likely enters fallopian tube.
3. Cervical mucus increased and thinned.
4. Body temperature increases by approximately 1° C.

Luteal phase (days 15–28)
1. Corpus luteum synthesizes progesterone and estrogen (progestational phase).
2. Endometrial glands grow and become tortuous (secretory phase) creating spiral arteries.
3. Endometrium ready for possible implantation

Fertilization (days 16–21)
1. One sperm penetrates the oocyte.
2. The oocyte completes meiosis II.
3. Spermatocyte and oocyte fuse to form zygote.

Implantation (days 20–26)
1. Zygote embeds in endometrium.
2. Endometrial blood vessels infiltrate the theca interna over 14-day period.

Menses (days 1–4)
Without fertilization, endometrium is sloughed.

Pregnancy
Corpus luteum persists under the influence of hCG secreted by the rapidly developing placenta.

FSH, follicle-stimulating hormone; hCG, human chorionic gonadotropin; LH, luteinizing hormone.

B. Menstrual cycle (Figure 8-6)
1. One cycle is defined as the time from the onset of one menses to the next, with an average of 28 days.
2. Characteristic changes in the ovary lead to ovulation and hormone production (Figure 8-7).
C. Disorders

1. Abnormal uterine bleeding
   a. Functional menstrual disorders, characterized as excessive bleeding either during (“menorrhagia”) or between (“metrorrhagia”) menstrual periods
   b. Most common gynecologic problem during reproductive years
   c. Causes
      • Organic lesions (polyps, fibroids)
      • Hormonal dysregulation (anovulatory cycles, polycystic ovary syndrome, functional ovarian cysts)
      • Neoplasia (endometrial hyperplasia, cancer)
      • Abnormal pregnancy (ectopic pregnancy, abortion)

2. Polycystic ovary syndrome (Stein–Leventhal syndrome)
   a. Triad of
      • Androgen excess (hirsutism, acne)
      • Ovulatory dysfunction or anovulation (causing secondary amenorrhea)
      • Characteristic appearance of the ovaries on ultrasound (stromal fibrosis and small follicular cysts)
   b. Also associated with obesity and insulin resistance
   c. Increased LH and testosterone, increased estrogen (from aromatization of testosterone in adipose tissue), decreased FSH
   d. Endometrial hyperplasia is common; increased risk of endometrial adenocarcinoma
   e. Treat with weight loss; clomiphene or metformin for infertility/anovulation; oral contraceptives or progesterone; spironolactone for androgen excess

3. Endometriosis
   a. Nonneoplastic endometrial tissue located outside the uterus
   b. Responds to hormonal variations of menstrual cycle
   c. Most commonly occurs on the ovaries (bilateral)
   d. Presents as pain before and during menstruation
The reproductive system

- Multiple, small, hemosiderin-filled endometrial implants; “powder burns”; scarring; adhesions; endometriomas (large, blood-filled sacs called “chocolate cysts”)
- May result in infertility
- Treat with oral contraceptive pills (OCPs), leuprolide, and/or surgical excision. Danazol, a mild androgen, is rarely used anymore because of side effects.

4. Amenorrhea (Figures 8-8 and 8-9)
   a. Primary amenorrhea: absence of menarche in a woman by age 16 years
      - Genetic (Turner syndrome, androgen insensitivity syndrome)
      - Structural (imperforate hymen, müllerian duct agenesis)
      - Delayed puberty
   b. Secondary amenorrhea: cessation of menstruation for >3 months in a woman of reproductive age with cyclic periods or >6 months in a woman with irregular periods
      - Pregnancy
      - Ovarian failure
      - Polycystic ovary syndrome
      - Thyroid disorders
      - Athleticism
      - Anorexia
      - Stress

In approaching the various causes of amenorrhea, it is easiest to conceptualize them within the hypothalamic-pituitary-ovarian-uterine framework. It is postulated that stress, exercise, and anorexia act at the level of the hypothalamus to stop the menstrual cycle. Prolactin tumors at the pituitary level disrupt the neuroendocrine regulation of gonadotropin-releasing hormone, resulting in an abnormal menstrual function. At the ovarian level, ovarian failure, polycystic ovary syndrome (PCOS), and streak gonads of Turner syndrome result in menstrual dysfunction. Müllerian duct agenesis, imperforate hymen, and androgen insensitivity syndrome are abnormalities at the uterine and vaginal level.
III. Menopause

A. Last physiologic menstrual cycle usually occurs in the early 50s (mean age is 51½ years).

B. Estrogen levels fall (because of the reduced ovarian function) and FSH levels increase.

C. Early signs
   1. Anxiety
   2. Mood swings
   3. Irritability
   4. Depression
   5. Hot flashes: bouts of flushing and sweating

D. Late signs
   1. Vaginal dryness
   2. Painful intercourse
   3. Urinary tract infections
   4. Atrophy of breast tissue because of lack of estrogen stimulation
   5. Osteoporosis
   6. Decreased high-density lipoprotein (HDL), leading to an increased risk of coronary artery disease

E. Management of patients who are menopausal or postmenopausal may involve estrogen replacement therapy.
   1. Effects
      a. Decreases sleep disturbances
      b. Increases HDL and decreases low-density lipoprotein (LDL)
      c. Decreases postmenopausal vaginal atrophy
d. Decreases bone resorption and osteoporosis
e. Decreases frequency of “hot flashes” by reestablishing hypothalamic control of norepinephrine secretion

2. Risks and contraindications
   a. History of estrogen-dependent cancer
   b. Increased risk of breast and endometrial cancer
   c. In women with an intact uterus, estrogen increases the risk of developing endometrial carcinoma. Therefore, estrogen is combined with progestin to decrease the effects of unopposed estrogen.
   d. Women’s Health Initiative showed that estrogen increased the absolute risk of stroke by 0.13% when compared to placebo.

IV. Oral contraceptives
   A. Agents that interfere with ovulation to prevent pregnancy
   B. Combination pills contain progestin and estrogen.
      1. The estrogen component suppresses ovulation.
      2. The progestin component thickens the cervical mucus, reducing the passage of sperm.
   C. Other agents
      1. Progestin-only
         a. Available as pills, intramuscular (IM) injection, or progestin implants
         b. Progestin-only pills have higher failure rates; injections and implant devices have lower failure rates than combination oral contraceptives.
         c. Increased rate of menstrual irregularities
   2. Mifepristone (RU-486), a progestin antagonist
      a. Results in fetal abortion when given early in pregnancy (within first 6 weeks)
      b. Interferes with progesterone and decreases human chorionic gonadotropin (hCG)

D. Side effects
   1. Cardiovascular disease
      a. Women older than 35 years of age who smoke are at greatest risk from thromboembolism.
      b. Progestin-predominant preparations can lead to an increase in the LDL:HDL ratio.
   2. Benign liver hepatomas and hemangiomas
   3. Gallbladder disease
   4. Emotional changes

PREGNANCY AND ITS ASSOCIATED COMPLICATIONS

I. Normal pregnancy
   A. For clinical purposes, assume that a woman of childbearing age is pregnant unless proven otherwise.
   B. Normal gestation is 40 weeks.
   C. Clinical signs include missed periods, swollen breasts, fatigue, nausea, and elevated β-human chorionic gonadotropin (β-hCG) (serum).
   D. Hormonal regulation
      1. During fertilization, β-hCG produced by the placenta prevents corpus luteum regression.
      2. During the first trimester, the corpus luteum produces estrogen and progesterone.
      3. Second and third trimesters
         a. Progesterone is produced by the placenta.
         b. Estrogen production is regulated by the interplay among the fetal adrenal gland, fetal liver, and placenta.
      4. The initiating event in parturition is unknown, but delivery can be induced by oxytocin.
210 ● STEP-UP TO USMLE STEP 1

The Reproductive System

Clinical Vignette 8-1

CLINICAL PRESENTATION: A 17-year-old girl presents to her primary care physician with the chief complaint that she has not had her period for several months. She previously had fairly regular menses, with menarche at age 13 years. She is the daughter of a middle class family, an excellent student, and active in track outside of class. Physical examination shows a well-developed female with normal external female genitalia. Pelvic examination is deferred. Differentials: Pregnancy, anorexia nervosa, exercise, pituitary prolactinoma, polycystic ovary syndrome, ovarian failure, Turner syndrome, and hypothyroidism. Any female who reports missing her period should be evaluated for pregnancy. The first step in approaching amenorrhea is to determine whether the patient has had periods in the past (secondary amenorrhea) or has never experienced menstruation (primary amenorrhea). There are four diagnoses unique to primary amenorrhea: Turner syndrome, müllerian duct agenesis, imperforate hymen, and androgen insensitivity syndrome. These disorders can be ruled out in this case because the patient has a history of periods. (Note: Mosaic Turner syndrome can have some menstrual bleeding prior to the cessation of periods.) Figure 8-8 shows the various causes of amenorrhea. On the USMLE, look for certain symptoms that suggest some disorders over others: hirsutism (polycystic ovary syndrome [PCOS]), obesity (PCOS), galactorrhea (prolactinoma), webbed neck (Turner), widely spaced nipples (Turner), presence of abdominal masses (testes in androgen insensitivity syndrome), and renal anomalies (müllerian duct agenesis). Pelvic examination would be helpful in assessing imperforate hymen, androgen insensitivity syndrome (blind-ending short vaginal canal and absence of uterus and ovaries), and müllerian duct agenesis (blind-ending short vaginal canal and absence of uterus).

LABORATORY STUDIES: In approaching secondary amenorrhea (Figure 8-9), first obtain a pregnancy test. If negative, a battery of tests would be performed, including follicle-stimulating hormone (FSH), luteinizing hormone (LH), thyroid-stimulating hormone (TSH)/triiodothyronine (T3)/levothyroxine (T4), and prolactin levels to rule out hypothyroidism and prolactinoma, respectively. FSH and LH levels are expected to be high in cases of ovarian defects (Turner syndrome, ovarian failure, and PCOS) and low to normal in defects at the hypothalamic/pituitary level (pituitary tumors, anorexia, and athleticism). To further differentiate among these, if LH/FSH >2, it suggests PCOS, and testosterone and dehydroepiandrosterone sulfate (DHEAS) levels should be measured (will likely be elevated). Also, progesterin challenge should induce withdrawal from menstrual bleeding. Turner syndrome with ovarian failure can be distinguished by karyotype. In cases of suspected anatomical abnormalities, a pelvic ultrasound should be performed.

MANAGEMENT: Most treatments of secondary amenorrhea are directed to correct the underlying disease process via surgery or restore ovulatory cycle via estrogen–progestin therapy. PCOS is treated based on the reproductive desire of the female—spironolactone with clomiphene citrate is used if the patient is interested in conceiving; otherwise, oral contraception may be used.

5. Lactation
   a. Estrogen and progesterone block the effect of prolactin on the breast.
   b. Prolactin levels rise throughout pregnancy and suppress ovulation.
   c. Estrogen/progesterone levels fall after delivery.

E. Prenatal diagnostic procedures
1. Amniocentesis is an aspiration of fluid from the amniotic sac at ≥15 weeks’ gestation.
   a. α-Fetoprotein (AFP) assay for neural tube defects
   b. Spectrophotometry to determine hemolytic disease of the newborn (see Chapter 10)
   c. Sex chromatin studies for X-linked disease
   d. Cell culture studies for chromosomal abnormalities
   e. Enzyme and DNA analysis
   f. Infection testing (cytomegalovirus [CMV] or Toxoplasma DNA)
2. Maternal serum AFP
   a. Elevated in neural tube defects
   b. Reduced in Down syndrome

MNEMONIC
Remember the causes of Increased Maternal Serum Alpha FetoProtein: Intestinal obstruction, Multiple gestation/Myeloschisis, Spina bifida cystica, Anencephaly/Abdominal wall defects, Fetal deaths, and Placental abruption.
3. Chorionic villus sampling
   a. It can be performed at 10 weeks of pregnancy.
   b. Cells are aspirated from the chorionic villus.
   c. Cells are evaluated for genetic abnormalities.
4. Ultrasound
   a. Measures fetal size, determines sex, and diagnoses fetal malformations
F. Apgar score
   1. It is used for physical assessment of child 1 minute and 5 minutes after birth.
   2. Five categories are scored 0, 1, or 2, with 2 being indicative of better performance.
      a. Color (blue = 0, trunk pink = 1, all pink = 2)
      b. Heart rate (0 = 0, <100 = 1, 100+ = 2)
      c. Reflexes (none = 0, grimace = 1, grimace and irritable = 2)
      d. Muscle tone (none = 0, some = 1, active = 2)
      e. Respiration (none = 0, irregular = 1, regular = 2)
II. Abnormal placental attachment
   A. Abruptio placentae
      1. Placenta separates from the uterine wall before parturition.
      2. It is associated with painful bleeding in the third trimester.
      3. It usually leads to fetal death.
      4. It may result in hemorrhage and disseminated intravascular coagulation (DIC) in mother.
   B. Placenta accreta
      1. Direct connection of the myometrium to placenta after loss of decidua basalis
      2. Caused by prior surgery or trauma during pregnancy
      3. Improper separation results in massive hemorrhage
   C. Placenta previa
      1. Placenta attaches to the lower uterus and blocks the cervical os.
      2. It is associated with painless bleeding in the third trimester.
III. Ectopic pregnancy
   A. Risk factors
      1. Pelvic inflammatory disease (PID) (e.g., chronic salpingitis)
      2. Previous surgery
      3. Endometriosis
      4. Previous ectopic pregnancy
   B. Clinical features
      1. Amenorrhea
      2. Pelvic pain and cervical tenderness
      3. Tissue mass (usually in the fallopian tubes)
      4. Elevated β-hCG levels without intrauterine pregnancy
IV. Preeclampsia
   A. Diagnosis requires only hypertension and any proteinuria during pregnancy. It is often associated with edema.
   B. Most common in the last trimester of first pregnancy
   C. May result in eclampsia if untreated
      1. Eclampsia has manifestations similar to preeclampsia, but it also includes seizures and possibly DIC.
      2. HELLP syndrome is a severe, atypical variant of eclampsia, characterized by Hypertension, Elevated Liver enzymes, and Low Platelets.
V. Hydatidiform mole
   A. A benign placental tumor resembling a “cluster of grapes,” with a marked increase in β-hCG
   B. Manifests as vaginal bleeding and an increase in uterine size
   C. “Snowstorm” pattern seen on ultrasound

To remember the 5 parts of the Apgar score, think APGAR: Appearance, Pulse, Grimace, Activity, Respiration.

QUICK HIT

Eclampsia may be treated with magnesium sulfate. However, the treatment of choice for a complete cure is the delivery of the fetus, if feasible.

QUICK HIT

Hydatidiform moles are the most common precursors of gestational choriocarcinoma (a malignant neoplasm of trophoblastic cells).
D. Two types
   1. Complete mole
      a. Diploid XX karyotype
      b. No embryo present
      c. Completely paternal in origin
   2. Partial mole
      a. Triploid karyotype (XXX, XXY, or XYY)
      b. Embryonic parts may be present

VI. Gestational diabetes
A. Insulin resistance occurs in normal pregnancy.
B. The diagnosis is made using a 3-hour 100-g oral glucose tolerance test, if the patient’s serum glucose exceeds two of the four following criteria (exact cutoffs may vary by institution):
   1. Fasting >105 mg/dL
   2. 1 hour >190 mg/dL
   3. 2 hours >165 mg/dL
   4. 3 hours >145 mg/dL
C. High blood glucose leads to hyperglycemia in the fetus, macrosomia (enlarged body), increased risk of birth trauma, and increased likelihood of cesarean section because of the large size of fetus.
D. Neonatal hypoglycemia can occur because the infant's increased insulin production is too great.

VII. Infections causing birth defects (TORCHES)
A. The TORCHES are Toxoplasmosis, Other infections, Rubella, Cytomegalovirus infection, HIerpes simplex, and Syphilis.
B. This group of infectious organisms can cause birth defects if the mother is infected during pregnancy, especially in the first trimester.
   1. Infection with herpes simplex more commonly occurs during the passage through the birth canal.
C. Important agents in the “other” category are HIV, hepatitis B, and parvovirus B19.

GYNECOLOGIC DIAGNOSTIC TESTS

I. Wet mount
   A. Vaginal epithelial scrapings placed on a glass slide with a drop of saline
   B. Microbes detected
      1. Trichomonas appears as a pear-shaped, flagellated organism with sporadic movement.
      2. Bacterial vaginosis appears as vaginal epithelium with spotting and stippling (clue cells).

II. Potassium hydroxide (KOH) preparation
   A. KOH is added to a microscope slide prepared with vaginal epithelial scrapings.
   B. Epithelium is dissolved with KOH.
   C. Microbes detected
      1. Candida, which is resistant to KOH, remains on the slide and is identified by its budding cells with short hyphae.
      2. KOH reacts with bacterial amines, producing a “fishy odor” characteristic of bacterial vaginosis (whiff test).

III. Papanicolaou (Pap) smear
   A. Cells from the cervix are scraped and fixed onto a glass slide.
   B. Human papillomavirus (HPV) is characterized by koilocytes (large epithelial cells with perinuclear clearing).
   C. Precancerous lesions detected: cervical intraepithelial neoplasia (CIN) 1, 2, and 3
D. Cancers detected
1. Invasive squamous cell carcinoma (most common)
2. Cervical adenocarcinoma

SEXUALLY TRANSMITTED DISEASES

Between 20% and 50% of those patients with one sexually transmitted disease (STD) will have a coexisting infection with another. The sexual partners of those diagnosed with an STD should be treated. Physicians should encourage their patients to make partners aware of potential STD risk and urge them to seek diagnosis and treatment (Table 8-4).

TABLE 8-4 Sexually Transmitted Diseases

<table>
<thead>
<tr>
<th>Microbe</th>
<th>Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Klebsiella granulomatis</td>
<td>Granuloma inguinale; biopsy shows Donovan bodies</td>
</tr>
<tr>
<td>Chlamydia trachomatis</td>
<td>Urethritis; acute pelvic inflammatory disease; cervicitis; serotypes L1, L2, and L3 cause lymphogranuloma venereum, with ulcerative lesions of the genitalia</td>
</tr>
<tr>
<td>Haemophilus ducreyi</td>
<td>Chancroid, painful ulcerative lesions of the genitalia</td>
</tr>
<tr>
<td>Herpes simplex virus-2</td>
<td>Genital herpes, urethritis, painful ulcerative lesions of the genitalia</td>
</tr>
<tr>
<td>HIV types 1 and 2</td>
<td>AIDS</td>
</tr>
<tr>
<td>Human papillomavirus (especially serotypes 6 and 11)</td>
<td>Genital or anal warts (condyloma acuminatum) of vulva</td>
</tr>
<tr>
<td>Human papillomavirus (especially serotypes 16, 18, 31, and 45)</td>
<td>Squamous cell carcinoma of cervix, vagina, anus, or penis; CIN</td>
</tr>
<tr>
<td>Neisseria gonorrhoeae</td>
<td>Urethritis, acute pelvic inflammatory disease, cervicitis, pharyngitis, monarticular arthritis</td>
</tr>
<tr>
<td>Treponema pallidum</td>
<td>Syphilis: Primary syphilis—chancres (painless ulcerative lesions of the genitalia) Secondary syphilis—gray, wartlike lesions on the genitalia (condyloma lata); rash on palms and soles Tertiary syphilis—neurologic manifestations such as tabes dorsalis and ascending aortic aneurysm</td>
</tr>
<tr>
<td>Trichomonas vaginalis</td>
<td>Vulvovaginitis, male urethritis</td>
</tr>
</tbody>
</table>

CIN, cervical intraepithelial neoplasia.

FEMALE GYNECOLOGIC NEOPLASMS

Tumors of the gynecologic organs may manifest themselves as abnormal uterine bleeding and, as such, a heightened level of suspicion must be maintained with this presentation. Many of these neoplasms can be detected, and even prevented (as is the case with cervical cancer), by routine gynecologic examinations.

I. Ovarian neoplasms of epithelial cell origin (Table 8-5)
II. Ovarian neoplasms of germ cell origin (Table 8-6)
III. Tumors of the uterus (cervix and body) (Table 8-7)
IV. Tumors of the vulva and vagina (Table 8-8)
### TABLE 8-5 Ovarian Neoplasms of Epithelial Cell Origin

<table>
<thead>
<tr>
<th>Neoplasm</th>
<th>Morphology</th>
<th>Clinical Presentation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serous cystadenoma</td>
<td>Cystic</td>
<td>Benign; frequently bilateral</td>
</tr>
<tr>
<td>Serous cystadenocarcinoma</td>
<td>Cystic</td>
<td>Malignant; frequently bilateral; most common (50% of ovarian neoplasms)</td>
</tr>
<tr>
<td>Mucinous cystadenoma</td>
<td>Mucin-filled cysts</td>
<td>Benign</td>
</tr>
<tr>
<td>Mucinous cystadenocarcinoma</td>
<td>Mucin-filled cysts</td>
<td>Malignant; pseudomyxoma peritonei (diffuse peritoneal metastasis secreting mucin)</td>
</tr>
<tr>
<td>Endometrioid adenocarcinoma</td>
<td>Resembles endometrium</td>
<td>Malignant</td>
</tr>
<tr>
<td>Brenner tumor</td>
<td>Resembles transitional epithelium</td>
<td>Benign; rare tumor</td>
</tr>
<tr>
<td>Clear cell cancer</td>
<td>Abundant clear cytoplasm</td>
<td>Usually unilateral; rare</td>
</tr>
</tbody>
</table>

### QUICK HIT

Of ovarian neoplasms, 75% are epithelial in origin. These tumors are usually seen in middle-aged to elderly women.

### TABLE 8-6 Ovarian Neoplasms of Germ Cell Origin

<table>
<thead>
<tr>
<th>Neoplasm</th>
<th>Morphology</th>
<th>Clinical Features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dysgerminoma</td>
<td>Large cells with clear cytoplasm</td>
<td>Malignant; equivalent of seminoma; occurs in children</td>
</tr>
<tr>
<td>Endodermal sinus (yolk sac)</td>
<td>Resembles yolk sac</td>
<td>Malignant; produces AFP</td>
</tr>
<tr>
<td>Immature teratoma</td>
<td>Elements from multiple embryonic layers; poorly differentiated; resembles fetal or embryonic tissue</td>
<td>Malignant</td>
</tr>
<tr>
<td>Mature teratoma (dermoid cyst)</td>
<td>Elements from multiple embryonic layers, including hair, bone, tooth, and nervous tissue; duplication of maternal genetics; resembles adult tissue</td>
<td>Most common germ cell neoplasm (90%); benign (versus malignant in males)</td>
</tr>
<tr>
<td>Monodermal teratoma</td>
<td>Elements from multiple embryonic layers; one tissue type develops, most commonly thyroid tissue (struma ovarii)</td>
<td>Benign; hyperthyroidism</td>
</tr>
<tr>
<td>Choriocarcinoma</td>
<td>Usually seen in combination with other germ cell tumors</td>
<td>Malignant; produces (β-hCG)</td>
</tr>
<tr>
<td>Granulosa-theca tumor</td>
<td>Lipid-laden cells; fibroblast proliferation; cuboidal cells in cords; eosinophilic follicles (Call–Exner bodies)</td>
<td>Benign; may secrete estrogen, leading to precocious puberty or endometrial hyperplasia or carcinoma</td>
</tr>
<tr>
<td>Thecoma fibroma</td>
<td>Fibroblast proliferation</td>
<td>Benign; rare; in combination with ascites and hydrothorax, referred to as Meigs syndrome</td>
</tr>
<tr>
<td>Sertoli–Leydig cell tumor</td>
<td>Tubules containing Sertoli and Leydig cells</td>
<td>Produces testosterone; virilization</td>
</tr>
<tr>
<td>Metastasis</td>
<td>Most commonly from gastrointestinal tract, breast, or ovary; Krukenberg tumor, primary from stomach with signet-ring cells bilaterally</td>
<td>Only 5% of ovarian neoplasms</td>
</tr>
</tbody>
</table>

**QUICK HIT**

Germ cell tumors account for only 25% of ovarian neoplasms, but they are the most common ovarian tumors found in women younger than 20 years of age.

**QUICK HIT**

Cancer antigen 125 (CA-125) is elevated in more than 80% of ovarian carcinomas.

**QUICK HIT**

Toxic shock syndrome can result from bacterial (S. aureus) overgrowth on tampons. The enterotoxin involved acts as a superantigen, causing excess activation of T-helper cells, resulting in an increased cytokine production and septic shock.

**QUICK HIT**

AFP, α-fetoprotein; hCG, human chorionic gonadotropin.
## TABLE 8-7 Tumors of the Uterus (Cervix and Body)

<table>
<thead>
<tr>
<th>Neoplasm</th>
<th>Clinical Features</th>
</tr>
</thead>
</table>
| Cervical intraepithelial neoplasia (CIN)   | • May be classified as CIN I, CIN II, or CIN III  
• Neoplastic changes in the endometrium beginning at the squamocolumnar junction  
• CIN I: mild dysplasia extending less than one-third the thickness of the epithelium  
• CIN II: cells appear more malignant with increased mitotic figures and variation in nuclear size; approximately two-thirds of the epithelium involved  
• CIN III: also called carcinoma in situ; involves the full thickness of the cervical epithelium  
• Associated with HPV 16, 18, 31, 33, and 45 infection |
| Squamous cell carcinoma of the cervix      | • Evolves from a progression of CIN  
• Increased incidence is associated with early sexual activity and multiple sex partners, smoking, and immunosuppression |
| Leiomyoma                                  | • Benign tumor of the uterine body  
• The most common tumor of women (the most common malignancy in women is breast cancer)  
• Often multiple  
• Size increases with pregnancy and decreases with menopause |
| Leiomyosarcoma                             | • Uncommon  
• Does not arise from a preexisting dysplastic or neoplastic condition (fibroids) |
| Endometrial carcinoma                      | • The most common malignancy of the female genital tract  
• Associated with nulliparity  
• More often found in older women  
• Exogenous estrogens administration or estrogen-producing tumors may be the predisposing factors  
• Other risk factors are diabetes, tamoxifen, hypertension, and obesity  
• Usually presents as vaginal bleeding |

HPV, human papillomavirus.

## TABLE 8-8 Tumors of the Vulva and Vagina

<table>
<thead>
<tr>
<th>Tumor</th>
<th>Description</th>
</tr>
</thead>
</table>
| Papillary hidradenoma                | • Most common benign tumor of the vulva  
• Often presents as an ulcerated and bleeding nodule  
• Originates from apocrine sweat glands  
• Can easily be surgically removed |
| Squamous cell carcinoma of the vulva | • Similar to squamous cell carcinoma of the cervix  
• Highest occurrence in older women  
• Vulvar dystrophy precedes carcinoma  
• Associated with the infections of HPV 16, 18, 31, 33, and 45 |
| Paget disease of the vulva           | • Noninvasive intraepithelial adenocarcinoma, similar to Paget disease of the breast  
• Not always associated with underlying adenocarcinoma (unlike Paget disease of the breast) |
| Malignant melanoma                   | • Similar to malignant melanoma of the skin  
• 10% of malignant tumors of the vulva |
| Squamous cell carcinoma of the vagina| • The vagina is rarely a primary site of cancer formation  
• Usually an extension of squamous cell carcinoma of the cervix |
| Clear cell adenocarcinoma            | • A rare malignant tumor  
• Occurs in the daughters of women given diethylstilbestrol (DES) during pregnancy |
| Sarcoma botryoides                   | • A type of rhabdomyosarcoma  
• Usually occurs in girls younger than 5 years of age  
• “Bunch of grapes” that protrude from the vagina |

HPV, human papillomavirus.

---

**QUICK HIT**

Estrogens can be synthesized by adipose tissue. This may be partially responsible for predisposing obese women to endometrial carcinoma.
Breast pathology

Risk factors for breast cancer include being older than 45 years of age, nulliparity, early menarche, late menopause, high-fat diet, HER-2/neu oncogene activation, first-degree relative with positive history, and a history of breast cancer in the contralateral breast (Table 8-9).

<table>
<thead>
<tr>
<th>Condition</th>
<th>Pathology</th>
<th>Clinical Features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute mastitis</td>
<td>Entry of <em>Staphylococcus aureus</em> through nipple; focal cellulitis versus abscess</td>
<td>Most often occurs during nursing, may be caused by eczema</td>
</tr>
<tr>
<td>Fibrocystic changes</td>
<td>Breast mass; tender during menstruation; usually bilateral; “blue-domed” cysts</td>
<td>Most common breast disorder, nonneoplastic hypertrophy of breast tissue that is hormonally mediated; predisposition to cancer only if there is evidence of cellular atypia</td>
</tr>
<tr>
<td>Fibroadenoma</td>
<td>Painless; rubbery mass</td>
<td>Benign; most common tumor in patients younger than 25 years of age; not a precursor to malignancy</td>
</tr>
<tr>
<td>Intraductal papilloma</td>
<td>Tumor of the lactiferous ducts</td>
<td>May present as serous discharge or bloody discharge; benign, small risk of cancer</td>
</tr>
<tr>
<td>Phyllodes tumor</td>
<td>Large, bulky mass; cysts; leaflike projections; ulceration of the skin</td>
<td>Malignant potential, although most are benign; may recur</td>
</tr>
<tr>
<td>Ductal carcinoma in situ (DCIS)</td>
<td>Tumor cells fill the ducts but do not penetrate basement membrane; comedocarcinoma associated with caseous necrosis and cheesy discharge</td>
<td>Malignant; may progress to invasive</td>
</tr>
<tr>
<td>Lobular carcinoma in situ (LCIS)</td>
<td>Tumor cells do not penetrate basement membrane; estrogen-receptor (ER) and progesterone-receptor (PR) positive</td>
<td>Malignant; no palpable lesion—usually found incidentally on breast biopsy; associated with infiltrating ductal cancers arising from other lesions</td>
</tr>
<tr>
<td>Infiltrating ductal carcinoma</td>
<td>Firm mass; cells may form glands; fibrous stroma</td>
<td>Malignant; most common carcinoma of the breast; may be progression of ductal carcinoma in situ</td>
</tr>
<tr>
<td>Infiltrating lobular carcinoma</td>
<td>Cells line up “single file”, inactivation of E-cadherin</td>
<td>Malignant; often multiple and bilateral; bloody discharge</td>
</tr>
<tr>
<td>Paget disease</td>
<td>Superficial lesion of nipple or areola; Paget cells in epidermis (large cell with marginal clearing seen)</td>
<td>Malignant; indicative of underlying ductal carcinoma</td>
</tr>
<tr>
<td>Medullary carcinoma</td>
<td>Soft, fleshy tumor; characterized by lymphocytic infiltrate</td>
<td>Malignant</td>
</tr>
<tr>
<td>Inflammatory breast cancer</td>
<td>Inflammatory changes superimposed on any histologic type of breast cancer</td>
<td>Findings may include peau d’orange, dimpling of the breast, nipple retraction</td>
</tr>
</tbody>
</table>
**Clinical Vignette 8-2**

**CLINICAL PRESENTATION:** A 55-year-old man presents to his primary care physician with the chief complaint of frequent urination that has increased over the past few months. Although he feels an urgent need to urinate immediately, the patient finds that he has a weak urinary stream with intermittent flow and that he is straining to urinate, with resulting feeling of incomplete emptying. Also, the patient reports waking to urinate at night and has noted some blood in his urine lately. Rectal examination deferred reveals an enlarged prostate with no nodules palpable. Otherwise, the physical examination is benign and the vital signs are stable.

**DIFFERENTIAL:** Benign prostatic hyperplasia (BPH), urethral strictures, urinary tract infection, bladder cancer, bladder stone, and bladder trauma. Lower urinary tract symptoms can be best remembered by the mnemonic **WISE FUN**. **WISE** refers to the obstructive symptoms: Weak urinary stream, Intermittent flow, Straining to urinate, and Incomplete Emptying. **FUN** refers to the irritative symptoms: Frequency, Urgency, and Nocturia. BPH can present with any of these lower urinary tract symptoms and also hematuria. Urethral strictures can also result in obstructive symptoms, urinary tract infection (UTI) in irritative symptoms, and bladder cancer/stones/trauma in hematuria.

**LABORATORY STUDIES:** Urinalysis and urine culture should be obtained to rule out urinary tract infection. Also, **ultrasound** is useful for determining the bladder and prostate size but is not commonly used in initial evaluation of uncomplicated cases. More precise measurements of prostate can be made via **transrectal ultrasound**, which is indicated in select patients.

**MANAGEMENT:** An **α-blocker** relaxes the prostatic smooth muscle and is the first-line treatment for BPH. The most common side effect is dizziness. A **5α-reductase** inhibitor (finasteride) reduces symptoms by reducing the volume of the prostate. If pharmacologic therapy is unsuccessful, **transurethral resection of the prostate** is the gold standard surgical procedure for the treatment of BPH. Open radical prostatectomy is a cancer operation and is **not** indicated for benign prostatic obstruction.
TESTICULAR PATHOLOGY

Anatomic disorders of the testis occur more often in young children, whereas the infectious and neoplastic diseases are more likely to occur in the young adult, sexually active population. Routine testicular examinations can often prevent and detect serious complications. When detected early, testicular neoplasms are one of the most curable cancers.

I. Testicular disorders (Table 8-10)

II. Testicular neoplasms (Table 8-11)

### TABLE 8-10 Testicular Disorders

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Clinical Features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hydrocele</td>
<td>• Serous fluid collects in the tunica vaginalis</td>
</tr>
<tr>
<td></td>
<td>• Caused by patency between the peritoneal cavity and the tunica vaginalis</td>
</tr>
<tr>
<td>Hematocele</td>
<td>• Blood collects in the tunica vaginalis</td>
</tr>
<tr>
<td></td>
<td>• Usually caused by trauma</td>
</tr>
<tr>
<td>Varicocele</td>
<td>• Engorgement of the veins of the spermatic cord</td>
</tr>
<tr>
<td></td>
<td>• Most noticeable when patient is standing</td>
</tr>
<tr>
<td>Spermatocele</td>
<td>• Epididymal cyst containing sperm</td>
</tr>
<tr>
<td>Cryptorchidism</td>
<td>• Failure of one or both of the testes to descend</td>
</tr>
<tr>
<td></td>
<td>• Increased incidence of germ cell testicular cancer such as seminoma and</td>
</tr>
<tr>
<td></td>
<td>embryonal carcinoma (see testicular neoplasms [Table 8-11])</td>
</tr>
<tr>
<td></td>
<td>• Failure of descent leads to testicular atrophy, sterility, and increased risk of</td>
</tr>
<tr>
<td></td>
<td>germ cell neoplasia</td>
</tr>
<tr>
<td>Testicular torsion</td>
<td>• Twisting of the spermatic cord</td>
</tr>
<tr>
<td></td>
<td>• If untreated, will result in testicular necrosis</td>
</tr>
<tr>
<td>Orchitis</td>
<td>• Testicular infection and inflammation</td>
</tr>
<tr>
<td></td>
<td>• May be viral or bacterial in origin</td>
</tr>
<tr>
<td></td>
<td>• Can lead to sterility if bilateral</td>
</tr>
<tr>
<td>Epididymitis</td>
<td>• Inflammation and infection of the epididymis</td>
</tr>
<tr>
<td></td>
<td>• Most often caused by Neisseria gonorrhoeae, Chlamydia trachomatis,</td>
</tr>
<tr>
<td></td>
<td>Escherichia coli, and Mycobacterium tuberculosis</td>
</tr>
</tbody>
</table>
TABLE 8-11 Testicular Neoplasms

<table>
<thead>
<tr>
<th>Neoplasm</th>
<th>Site of Origin; Morphology</th>
<th>Clinical Features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Seminoma</td>
<td>Germ cell; arranged in lobules or nests</td>
<td>Malignant; incidence highest in 35–40-year-olds; painless enlargement of testis;</td>
</tr>
<tr>
<td></td>
<td></td>
<td>most common germ cell tumor; similar to dysgerminoma of the ovary; radiosensitive</td>
</tr>
<tr>
<td></td>
<td></td>
<td>and curable</td>
</tr>
<tr>
<td>Embryonal carcinoma</td>
<td>Germ cell; variable morphology with papillary convolutions</td>
<td>Malignant; highest incidence in men in their 20s; more aggressive than seminomas;</td>
</tr>
<tr>
<td></td>
<td></td>
<td>very common in mixed tumors</td>
</tr>
<tr>
<td>Yolk sac tumor</td>
<td>Germ cell; anastomosing cords; malignant; presents with pain or metastasis; similar to</td>
<td>Malignant; presents with pain or metastasis; similar to ovarian tumor; peak</td>
</tr>
<tr>
<td>(endodermal sinus tumor)</td>
<td>ovarian tumor; peak incidence in childhood (infants to 3 years of age); increased <strong>AFP</strong></td>
<td>incidence in childhood (infants to 3 years of age); increased <strong>AFP</strong></td>
</tr>
<tr>
<td>Teratoma</td>
<td>Two or more embryonic layers; <strong>multiple tissue types</strong> such as cartilage, epithelium,</td>
<td>Malignant; occurs at any age but more common in children; mature: heterogeneous</td>
</tr>
<tr>
<td></td>
<td>liver, and muscle</td>
<td>tissue in organoid fashion; immature: incompletely differentiated</td>
</tr>
<tr>
<td>Mixed germ cell tumor</td>
<td>Variable</td>
<td>Malignant; aggressive; more than one neoplastic pattern; <strong>most common</strong></td>
</tr>
<tr>
<td>Leydig cell tumor</td>
<td>Testicular stroma; intracytoplasmic <strong>Reinke crystals</strong></td>
<td>Benign; produces androgens, estrogens, or corticosteroids; often seen with</td>
</tr>
<tr>
<td>(interstitial)</td>
<td></td>
<td>precocious puberty or gynecomastia; similar to ovarian Sertoli–Leydig cell tumor</td>
</tr>
<tr>
<td>Sertoli cell tumor</td>
<td>Testicular stroma; forms cordlike structures</td>
<td>Benign; minor endocrine abnormalities; similar to ovarian Sertoli–Leydig cell</td>
</tr>
<tr>
<td>Choriocarcinoma</td>
<td>Trophoblastic cells; villous structures resembling placenta</td>
<td>Malignant; hemorrhagic; <strong>hCG</strong> elevated; peaks in early adulthood</td>
</tr>
</tbody>
</table>

**AFP**, α-fetoprotein; **hCG**, human chorionic gonadotropin.

PSYCHOSOCIAL DEVELOPMENT (Figure 8-11)

**F I G U R E 8-11** Stages of development

<table>
<thead>
<tr>
<th>Infancy (0–1 year old)</th>
<th>Toddler (1–3 years old)</th>
<th>School age (3–11 years old)</th>
<th>Adolescence (11–20 years old)</th>
<th>Early adulthood (20–40 years old)</th>
<th>Middle adulthood (40–60 years old)</th>
<th>Late adulthood (60–80 years old)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Freud</td>
<td>Oral</td>
<td>Anal</td>
<td>Phallic-oedipal (3–6 years old)</td>
<td>Genital</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Erikson</td>
<td>Trust versus mistrust</td>
<td>Autonomy versus shame and doubt</td>
<td>Initiative versus guilt (3–6 years old), industry versus inferiority</td>
<td>Identity versus role confusion</td>
<td>Intimacy versus isolation</td>
<td>Generativity versus stagnation</td>
</tr>
<tr>
<td>Piaget</td>
<td>Sensorimotor (0–2 years old)</td>
<td>Preoperational (2–7 years old)</td>
<td>Concrete operations (7–11 years old)</td>
<td>Formal operations</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Characteristics</td>
<td>Reflexes:</td>
<td></td>
<td>Terrible two’s (&quot;no&quot;); band-aid, parallel play</td>
<td>Cooperative play (4–7 years old); conservation of mass</td>
<td>First menstruation (11 years old), first ejaculation (13 years old), peer pressure</td>
<td>New family, children, role in society solidified, period of reassessment</td>
</tr>
<tr>
<td></td>
<td>• Palmar grasp</td>
<td></td>
<td>(2–4 years old); balance on one foot (2 years old); climb stairs (3 years old)</td>
<td>(7–11 years old); button clothes; throw a ball (4 years old)</td>
<td>(45–55 years old)</td>
<td>(45–55 years old)</td>
</tr>
<tr>
<td></td>
<td>(0–2 months old)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Rooting</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>(0–3 months old)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Babiński</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>(0–12 months old)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Milestones:</td>
<td>• Turn over</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>(5 months old)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Sit (6 months old)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Walk (12 months old)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

ECT, electroconvulsive therapy.
I. Postpartum depression
A. Up to 50% of all women develop a short-lived depression after giving birth (postpartum blues).
B. Etiology
   1. Change in hormone levels
   2. Increased responsibility
   3. Fatigue
C. Major depression is seen in 5% to 10% of all women after childbirth.

II. Attachment of the child to the mother
A. Anachistic depression: sustained absence of mother when child is between 6 and 12 months of age leads to a withdrawn and unresponsive infant.
B. Harlow showed that monkeys raised in isolation do not develop normally.
   1. Males are more affected than females.
   2. Recovery is not possible if isolation lasts longer than 6 months.
C. Bowlby showed that physical contact between the mother and the child is crucial to development.
D. Spitz observed that children without proper mothering are slow to develop and have a greater number of medical problems.
E. Mahler documented the development as a process in which the infant separates from the mother.
   1. Normal autistic phase (0 to 1 month): infant has little interaction
   2. Symbiotic phase (15 months): infant is close to mother
   3. Separation–individuation phase (5 to 16 months): child realizes individuality and begins to explore the environment.

III. Child abuse
A. It includes physical abuse, sexual abuse, and emotional neglect.
B. Risk factors
   1. Substance abuse by parents
   2. Poverty
   3. Marital problems or single-parent home
C. Physical abuse is marked by numerous fractures, bruises, subdural hematomas, or burns (at various stages of healing).
D. Sexual abuse of children is marked by trauma to the genitalia, STDs, or urinary tract infections.
E. Abuse predisposes the child to posttraumatic stress disorder (PTSD), dissociative disorders, depression, anorexia, phobias, and personality disorders.
F. Physician intervention is necessary and obligatory.

IV. Family therapy
A. Involves all members of a family even though only one person might have a problem
B. Identifies dysfunctional behavior and encourages communication and problem solving
C. Based on the concept that the family system is composed of subsystems in which boundaries are established and mutual accommodation occurs
SEXUALITY

I. Gender
A. Gender identity is an individual’s sense of being male or female, whereas gender role is the expression of one’s gender.
B. Sexual orientation is a physical preference for one or both genders (heterosexual, homosexual, and bisexual).
C. Psychological factors play a role in gender identity and sexual orientation.
1. Transsexual: a person who has the sense of being in the wrong-sex body and has a strong desire to correct it
2. Homosexual: a person who has a sexual preference for same-sex individuals
3. Transvestite: a man who dresses in women’s clothing for pleasure, usually heterosexual

II. Sexual dysfunction
A. Premature ejaculation (early climax without reaching plateau phase) is the most common male sexual disorder.
B. The most common sexual dysfunction in women is sexual arousal disorder, in which lubrication cannot be maintained throughout the sexual act.
C. Impotence (in men)
1. Failure to achieve erection or ejaculation
2. Usually has an organic component but may be psychogenic (e.g., caused by stress or anxiety)
   a. It is often related to alcohol abuse.
   b. It may also result from medical problems such as diabetes or illicit drug use.
   c. Psychogenic cause can be confirmed by observing erections during rapid eye movement (REM) sleep.
D. Vaginismus (in women)
1. Spasm in the outer third of the vagina
2. Difficulty during intercourse or pelvic examination
3. Often results from rape, incest, or abuse
E. Paraphilias (Table 8-12)

<table>
<thead>
<tr>
<th>Category</th>
<th>Description (How Sexual Pleasure Is Derived)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exhibitionism</td>
<td>Exposing one’s genitalia</td>
</tr>
<tr>
<td>Fetishism</td>
<td>Inanimate objects (e.g., women’s high-heeled shoes or undergarments)</td>
</tr>
<tr>
<td>Frotteurism</td>
<td>Furtively rubbing genitalia against a woman (e.g., pushing up against a woman in</td>
</tr>
<tr>
<td></td>
<td>a crowded subway)</td>
</tr>
<tr>
<td>Necrophilia</td>
<td>Corpses</td>
</tr>
<tr>
<td>Pedophilia</td>
<td>Children</td>
</tr>
<tr>
<td>Masochism</td>
<td>Receiving physical or psychological pain and humiliation</td>
</tr>
<tr>
<td>Sadism</td>
<td>Inducing physical or psychological pain and humiliation in others</td>
</tr>
<tr>
<td>Transvestic fetishism</td>
<td>Wearing women’s clothing (such men are still attracted to women)</td>
</tr>
<tr>
<td>Voyeurism</td>
<td>Furtively watching individuals engaged in intercourse or seductive activities</td>
</tr>
<tr>
<td>Zoophilia</td>
<td>Animals</td>
</tr>
</tbody>
</table>

To remember the four phases of normal sexual response, think EXPLORE: EXcitation, PLateau, Orgasm, and REsolution.

Quick Hit
Penile erection is achieved via two crucial steps: (a) parasympathetic-mediated relaxation of arterioles to the penis and (b) mechanical compression of the venous outflow channels.

Quick Hit
Pedophilia is the most common paraphilia and needs to be reported to the authorities on discovery by the physician if the patient acts on this desire.
Clinical Vignette 8-3

CLINICAL PRESENTATION: A 45-year-old man presents to his primary care physician for his yearly physical examination. His past medical history is significant for diabetes, hypertension, and hypercholesterolemia. He has been keeping physically fit with lengthy bike rides. He has not cut back on his tobacco usage and smokes 0.5 pack per day for 5 years. As you review the systems, he tells you that he has had increasing difficulty achieving a firm erection. He denies any recent penile or perineal trauma, surgery, or radiation. Vital signs: temperature = 97.4° F; respiration rate = 20 breaths/min; blood pressure = 150/90 mm Hg; and heart rate = 85 bpm.

DIFFERENTIALS: Erectile dysfunction (ED) from vascular, neurologic, iatrogenic, traumatic, or psychogenic origin. It is important to note that the bolded items in this patient’s history are the risk factors for ED.

LABORATORY STUDIES: Direct injection of prostaglandin E₁ into the corpora should result in a normal erection within minutes if the penile vasculature is normal. Nocturnal penile tumescence testing is useful in distinguishing psychogenic from organic impotence. Inadequate nocturnal erections suggest organic dysfunction, whereas normal erection during rapid eye movement (REM) sleep suggests psychogenic etiology. Given his diabetic history, formal neurologic testing may be needed.

MANAGEMENT: All patients with ED should be given an empiric trial of sildenafil as long as they do not have any contraindications. Contraindications include use of nitrates, active cardiac disease, or hypertension. Phosphodiesterase inhibitors such as sildenafil increase cyclic guanosine monophosphate (cGMP), which relaxes the smooth muscle surrounding the penile arterioles with resulting dilation of vasculature and erection. Patients with ED refractory to therapy with oral phosphodiesterase inhibitors should be referred to urology for other therapies such as vacuum constriction device, prostaglandin E₁ injections, and surgical placement of a penile prosthesis.
### Table 8-13  Therapeutic Agents for the Reproductive System

<table>
<thead>
<tr>
<th>Therapeutic Agent (common name, if relevant)</th>
<th>Class—Pharmacology and Pharmacokinetics</th>
<th>Indications</th>
<th>Side Effects or Adverse Effects</th>
<th>Contraindications or Precautions to Consider; Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Hormone antagonists</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Finasteride [Proscar]</td>
<td>Antiandrogen—5α-reductase inhibitor → decreases the conversion of testosterone to dihydrotestosterone</td>
<td>Benign prostatic hyperplasia, male-pattern baldness</td>
<td>Decreased libido, decreased ejaculate volume</td>
<td></td>
</tr>
<tr>
<td>Flutamide [Eulexin]</td>
<td>Antiandrogen—nonsteroidal, competitive androgen receptor blocker</td>
<td>Metastatic prostate cancer</td>
<td>Nausea, vomiting, diarrhea, rash, headache, anorexia, thrombocytopenia, gynecomastia, hepatotoxic</td>
<td>Inhibits cytochrome P450</td>
</tr>
<tr>
<td>Ketoconazole [Nizoral]</td>
<td>Antiandrogen—inhibits androstenedione (steroid) synthesis → inhibits adrenal and gonadal steroid synthesis; also prevents cell membrane formation</td>
<td>Prostate carcinoma, fungal infections</td>
<td>Nausea, vomiting, diarrhea, rash, headache, anorexia, thrombocytopenia, gynecomastia, hepatotoxic</td>
<td>Inhibits cytochrome P450</td>
</tr>
<tr>
<td>Spironolactone [Aldactone]</td>
<td>Antiandrogen—inhibits steroid binding</td>
<td>Hirsutism in women, acne in women, hyperaldosteronism, hypokalemia, hypertension, edema, and CHF</td>
<td>Gynecomastia, breast pain, hyperkalemia, impotence, menstrual irregularities</td>
<td></td>
</tr>
<tr>
<td>Mifepristone (RU-486)</td>
<td>Antiprogestrone—synthetic steroid, progesterone receptor blocker → blocks the effects of progesterone → myometrium contraction</td>
<td>Termination of intrauterine pregnancy</td>
<td>Heavy bleeding, uterine cramping, GI effects (nausea, vomiting, and anorexia)</td>
<td>Controversial “morning after” drug</td>
</tr>
<tr>
<td>Anastrozole [Arimidex]</td>
<td>Aromatase inhibitor</td>
<td>Breast cancer in postmenopausal women; endometriosis</td>
<td>Hot flashes, nausea, vomiting</td>
<td>Can be used in ER-positive or hormone receptor–unknown breast cancer</td>
</tr>
<tr>
<td><strong>Hormone agonists</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Methyltestosterone [Android, Virilon]</td>
<td>Androgen—anandrogen receptor agonist</td>
<td>In males: hypogonadism, delayed puberty (promotes secondary sex characteristics), impotence; In females: estrogen receptor-positive breast cancer</td>
<td>Masculinization (hirsutism), testicular atrophy, prostate hyperplasia, prostate cancer, impotence, stunted growth (premature epiphyseal plate closure), hyperlipidemia</td>
<td>Decreased testicular testosterone leading to Leydig cell inhibition and gonadal atrophy</td>
</tr>
</tbody>
</table>

(continued)
### TABLE 8-13 Therapeutic Agents for the Reproductive System (Continued)

<table>
<thead>
<tr>
<th>Therapeutic Agent (common name, if relevant) [trade name, where appropriate]</th>
<th>Class—Pharmacology and Pharmacokinetics</th>
<th>Indications</th>
<th>Side Effects or Adverse Effects</th>
<th>Contraindications or Precautions to Consider; Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ethinyl estradiol, diethylstilbestrol (DES), mestranol</td>
<td>Estrogen—bind estrogen receptor</td>
<td>In women: hypogonadism, ovarian failure, menstrual abnormalities; contraception In men: androgen-dependent prostate cancer</td>
<td>Endometrial cancer, endometrial bleeding, hypertension, thrombosis (stroke, cardiovascular disease)</td>
<td>Used in combination with progestin in patients with intact uterus; increased risk of endometrial cancer with unopposed estrogen therapy; females exposed to DES in utero have an increased risk of vaginal clear cell adenocarcinoma</td>
</tr>
<tr>
<td>Progesterone, norethindrone, levonorgestrel [Plan B], norgestimate, desogestrel, gestodene</td>
<td>Progesterone—bind progesterone receptors</td>
<td>Endometrial cancer, amenorrhea, abnormal uterine bleeding, prevention of pregnancy</td>
<td>Also used to prevent endometrial hyperplasia in postmenopausal women taking estrogen</td>
<td></td>
</tr>
<tr>
<td>Partial agonists and antagonists</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clomiphene [Clomid]</td>
<td>Selective estrogen receptor modulator—binds estrogen receptors in pituitary → prevents normal feedback inhibition, increases LH and FSH release from the pituitary → stimulates ovulation</td>
<td>Infertility—stimulates ovulation; PCOS</td>
<td>Hot flashes, ovarian enlargement, multiple gestation pregnancy, visual disturbances</td>
<td></td>
</tr>
<tr>
<td>Tamoxifen</td>
<td>Selective estrogen receptor modulator—competitively binds estrogen receptors; breast (estrogen antagonist): prevents proliferation of estrogen receptor positive tumor cells; endometrium (partial agonist); bone (agonist): decreases bone turnover, increases bone density</td>
<td>Treats estrogen-dependent breast cancer in postmenopausal women; reduces contralateral breast cancer</td>
<td>May increase the risk of endometrial cancer; hot flashes; flushing; increased risk of blood clots</td>
<td></td>
</tr>
<tr>
<td>Raloxifene [Evista]</td>
<td>Selective estrogen receptor modulator—breast (estrogen antagonist); endometrium (estrogen antagonist): prevents the proliferation of endometrium; bone (estrogen agonist): decreases bone turnover, increases bone density; cardiovascular (estrogen agonist): decreases LDL</td>
<td>Osteoporosis, breast cancer</td>
<td>Hot flashes, sinusitis, weight gain, muscle pain, leg cramps, increased risk of blood clots</td>
<td>Unlike estrogen, raloxifene does not decrease HDL</td>
</tr>
</tbody>
</table>
### TABLE 8-13 Therapeutic Agents for the Reproductive System (Continued)

<table>
<thead>
<tr>
<th>Therapeutic Agent (common name, if relevant) [trade name, where appropriate]</th>
<th>Class—Pharmacology and Pharmacokinetics</th>
<th>Indications</th>
<th>Side Effects or Adverse Effects</th>
<th>Contraindications or Precautions to Consider; Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Other</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Leuprolide [Lupron]</td>
<td>GnRH analog—agonist (when given pulsatile), antagonist (when given continuously)</td>
<td>Infertility (given pulsatile), prostate cancer (given continuous), uterine fibroids, endometriosis, precocious puberty</td>
<td>Nausea, vomiting, antiandrogen effects (testicular atrophy), menopausal symptoms</td>
<td></td>
</tr>
<tr>
<td>Sildenafil [Viagra], vardenafil [Levitra], tadalafil [Cialis]</td>
<td>Phosphodiesterase type 5 inhibitor (cGMP-specific) increased cGMP → smooth muscle relaxation → increased blood flow in the corpus cavernosum → penile erection</td>
<td>Erectile dysfunction</td>
<td>Abnormal vision (impaired blue-green color vision), UTIs, cardiovascular events, priapism, dyspepsia, headache, flushing</td>
<td>Risk of hypotension (fatal) in a patient taking nitrates</td>
</tr>
<tr>
<td><strong>Misoprostol [Cytotec]</strong></td>
<td>Prostaglandin—PGE analog → cervical dilation, uterine contractions</td>
<td>Induction of labor, termination of pregnancy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dinoprostone</td>
<td>Prostaglandin—PGE analog → cervical dilation, uterine contraction</td>
<td>Induction of labor, termination of pregnancy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ritodrine, terbutaline</td>
<td>β-agonist → uterine relaxation</td>
<td>Inhibits preterm labor; used to treat uterine hyperstimulation in labor</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Combination oral contraceptives</strong></td>
<td>Combination of estrogen and progesterone—estrogen → inhibits midcycle surge of gonadotropin secretion → prevents ovulation; progesterone → alters endometrium cervical mucus, tube motility, and peristalsis → less suitable for sperm penetration and implantation</td>
<td>Contraception, acne, hirsutism, PCOS</td>
<td></td>
<td>Contraindicated in patients with stroke or prior thromboembolic event, estrogen-dependent tumor, pregnancy, hypertriglyceridemia, heavy smokers; avoid use in women with migraines with aura and poorly controlled hypertension</td>
</tr>
<tr>
<td><strong>Hormone replacement therapy</strong></td>
<td>Combination of estrogen and progesterone</td>
<td>Menopause [relief of symptoms], osteoporosis, vulvar/vaginal atrophy, hypoestrogenism (hypogonadism)</td>
<td>Possible increased risk of stroke</td>
<td>Combination of progesterone and estrogen is used because unopposed estrogen increases the risk of endometrial cancer</td>
</tr>
</tbody>
</table>

**cGMP**, cyclic guanosine monophosphate; CHF, congestive heart failure; ER, estrogen receptor; FSH, follicle-stimulating hormone; GI, gastrointestinal; GnRH, gonadotropin-releasing hormone; HDL, high-density lipoprotein; LDL, low-density lipoprotein; LH, luteinizing hormone; PCOS, polycystic ovary syndrome; PGE, prostaglandin E; UTI, urinary tract infection.
The Musculoskeletal System

DEVELOPMENT

I. Bone formation
   A. Endochondral bone
      1. Forms over a cartilage frame
      2. Becomes the long bones of the skeleton (e.g., femur)
   B. Membranous bone
      1. Forms without a cartilage frame
      2. Becomes the flat bones of the skeleton (e.g., bones of the cranium)

II. Skeletal muscle
   A. It derives from somites.
   B. Each somite produces its own myotome.
   C. Each somite produces its own dermatome.

III. Pharyngeal arches
    Begin to develop in the fourth week and originate from neural crest cells.
    A. Arch 1
       1. Innervated by the mandibular branch of the trigeminal nerve (cranial nerve [CN] V)
       2. Gives rise to the following muscles:
          a. Muscles of mastication (temporalis, masseter, lateral pterygoid, medial pterygoid)
          b. Two tensor muscles (tensor veli palatini, tensor tympani)
          c. Two other muscles (mylohyoid, anterior belly of the digastric)
       3. Gives rise to the following skeletal structures:
          a. Malleus
          b. Incus
       4. Gives rise to the following ligamentous structures:
          a. Anterior ligament of malleus
          b. Sphenomandibular ligament
    B. Arch 2
       1. Innervated by the facial nerve (CN VII)
       2. Gives rise to the following muscles:
          a. Muscles of facial expression (orbicularis oculi, orbicularis oris, buccinator)
          b. Three other muscles (stylohyoid, stapedius, and the posterior belly of the digastric)
       3. Gives rise to the following skeletal structures:
          a. Greater cornu of hyoid bone
          b. Inferior portion of the body of hyoid bone
    C. Arch 3
       1. Innervated by the glossopharyngeal nerve (CN IX)
       2. Gives rise to the stylopharyngeus muscle
       3. Gives rise to the following skeletal structures:
          a. Greater cornu of the hyoid bone
          b. Lower portion of the body of hyoid bone
The Musculoskeletal System

QUICK HIT

All the intrinsic muscles of the pharynx, except the cricothyroid, are innervated by the recurrent laryngeal branches of the vagus nerve. Consequently, bilateral injury to the recurrent laryngeal nerves leaves the cricothyroid unopposed, and the vocal cords become tense and adducted.

QUICK HIT

Of all the intrinsic muscles of the larynx (posterior cricoarytenoid, lateral cricoarytenoid, arytenoid, thyroarytenoid, cricothyroid, transverse arytenoid, oblique arytenoid, and vocal muscle), the posterior cricoarytenoid muscle is the only muscle that abducts the vocal cords.

Exogenous estrogen administration (hormone replacement therapy) slows the rate of bone loss that occurs after menopause by stimulating osteoblasts via estrogen receptors.

D. Arch 4
1. Innervated by the vagus nerve (pharyngeal and superior laryngeal branches of CN X)
2. Gives rise to the following muscles:
   a. Cricothyroid muscle
   b. All the muscles of the soft palate and pharynx except the stylopharyngeus muscle (arch 3) and tensor veli palatini (arch 1)

E. Arch 6
1. Innervated by the vagus nerve (recurrent laryngeal branch of CN X)
2. Gives rise to the intrinsic muscles of the larynx except the cricothyroid

F. Arch 4 and arch 6 fuse to give rise to the thyroid, cricoids, arytenoids, corniculate, and cuneiform cartilages.

BONE FUNCTION AND METABOLISM (Figure 9-1)

I. Osteoblasts
A. They synthesize type I collagen and bone matrix proteins to form an unmineralized osteoid.
The Musculoskeletal System

B. Calcium ($Ca^{2+}$) and phosphate ($PO_{4}^{3-}$) are deposited on the cartilaginous matrix to form mineralized bone.

C. Blood supply goes to osteoblasts via vessels within the haversian canals.

D. When osteoblasts become surrounded by bone matrix, they become osteocytes.

II. Osteocytes

A. Occupy a space called lacuna

B. Communicate with other osteocytes via cytoplasmic extensions called canaliculi

C. Are influenced by parathyroid hormone (PTH) to stimulate osteoclastic bone resorption

D. Resorption allows $Ca^{2+}$ to be transferred rapidly into the blood.

E. Are not directly involved in bone resorption

III. Osteoclasts

A. Multinucleated cells formed from monocytes, which are responsible for bone resorption

B. Contain acid phosphatase

C. Resorb bone under influence of PTH

IV. Hormonal control (also see Chapter 7)

A. PTH

1. Release is stimulated by hypocalcemia and hypophosphatemia

2. Stimulates osteoclastic activity causing osteolysis and release of $Ca^{2+}$ from bone

3. Promotes the reabsorption of $Ca^{2+}$ in the distal tubule of the kidney

4. Inhibits $PO_{4}^{3-}$ reabsorption in the proximal tubule of the kidney

5. Converts vitamin D to its active form, 1,25-dihydroxycholecalciferol

6. Raises blood $Ca^{2+}$ and lowers blood $PO_{4}^{3-}$

B. Calcitonin

1. Inhibits osteoclasts, which inhibits bone resorption

2. Lowers blood $Ca^{2+}$

C. Vitamin D

1. Assists PTH in the resorption of bone

2. Increases $Ca^{2+}$ absorption from the intestine

3. Increases $Ca^{2+}$ reabsorption from the kidney

4. Increases $PO_{4}^{3-}$ reabsorption from the kidney

5. Raises blood $Ca^{2+}$ and $PO_{4}^{3-}$

6. Has net effect on bone growth

BONE, CARTILAGE, AND JOINT DISEASE

In the healthy adult, bone mass peaks between 20 and 25 years of age. Peak bone mass is typically higher in males and blacks. Bone diseases can adversely affect the mass and strength of the skeleton, predisposing the patient to fractures.

- Diseases that Affect Bone Formation (Table 9-1)

<table>
<thead>
<tr>
<th>Disease</th>
<th>Etiology</th>
<th>Clinical Features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Osteitis fibrosa cystica (von Recklinghausen disease of bone)</td>
<td>Caused by increased levels of PTH: primary or secondary hyperparathyroidism</td>
<td>Cystic spaces in the bone that are lined with osteoclasts; often colored brown owing to hemorrhage, hence the name “brown tumor of bone”</td>
</tr>
<tr>
<td>Achondroplasia (dwarfism)</td>
<td>Caused by failure of long bones to elongate because of narrow epiphyseal plates and sealing of these plates with the metaphysis; autosomal dominant disease; most common cause of dwarfism; linked to activating mutation in gene for fibroblast growth factor-3 receptor</td>
<td>Short limbs; normal-size head and trunk</td>
</tr>
</tbody>
</table>

(continued)
A 4-year-old child with the chief complaint of “belly pain” is brought to the emergency department by his mother. As you begin his physical examination, you note that the child is short for his age and that there are multiple ecchymoses on his lower extremities. The mother reports that her son bruises easily. A head, ear, eye, nose, and throat examination shows multiple dental caries and blue sclera. Physical examination shows that the abdomen is soft, nontender, and nondistended. There are normoactive bowel sounds. The patient is without organomegaly or masses. Temperature: 98.6°F; heart rate: 80 bpm; respiration rate: 18 breaths/min; blood pressure: 100/80 mm Hg.

Differentials: Osteogenesis imperfecta (OI), child abuse, child neglect. Short stature, multiple ecchymoses, and dental caries can be seen in each of the listed differentials. However, blue sclera is a characteristic finding of OI. Also, child abuse can be differentiated from OI based on nonskeletal manifestations such as retinal hemorrhage, intracranial bleeding, and splenic trauma.

Diagnostic Workup: Radiographs should be obtained of the skull, chest, long bones, and pelvis, looking for type of fracture as well as osteopenia (seen in OI). Diaphyseal fractures (break in the midshaft of long bone) and metaphyseal fractures (appear as corner chip of bone edge) suggest child abuse. In addition to multiple fractures, osteopenia would be seen on radiograph in OI. In child abuse, serial plain films should show healing and remineralization. In OI, fractures continue to occur in protective custody. In difficult cases, collagen synthesis analysis would show abnormal findings in OI.

Management: Medical therapy of OI is supportive, and in some cases, surgical interventions are done to improve weight bearing.
Table 9-2 Metabolic and Infectious Bone Disease

<table>
<thead>
<tr>
<th>Disease</th>
<th>Etiology</th>
<th>Clinical Features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Osteoporosis</td>
<td>Primary:</td>
<td>Bone mineral density is 2.5 or more standard deviations below normal; decrease in bone mass leads to fractures (especially of the weight-bearing bones of the spine); radiolucent bone seen on radiograph; DEXA scan positive</td>
</tr>
<tr>
<td></td>
<td>Type I: postmenopausal, with excess loss of trabecular bone</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Type II: men and women &gt;70 years of age, with loss of trabecular and cortical bone</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Secondary:</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Physical inactivity, increased parathyroid levels, hypercortisolism, hyperthyroidism, vitamin D deficiency, hypocalcemia</td>
<td></td>
</tr>
<tr>
<td>Scurvy</td>
<td>Lack of vitamin C intake; defective proline and lysine hydroxylation in collagen synthesis</td>
<td>Impaired bone formation and lesions result; painful subperiosteal hemorrhage; osteoporosis; bleeding gums; poor wound healing</td>
</tr>
<tr>
<td>Rickets (children); osteomalacia (adults)</td>
<td>Impaired calcification of bone because of deficiency of vitamin D; if caused by renal disease, termed &quot;renal osteodystrophy&quot;</td>
<td>Children: Skeletal malformations; Cranioptases (thinned and softened bones of the skull); Late fontanelle closure; Decreased height; Rachitic rosary (costochondral junction thickening resembling string of beads); Pigeon breast owing to a protruding sternum; Adults: Fractures; Radiolucency on radiography</td>
</tr>
<tr>
<td>Avascular necrosis</td>
<td>Death of osteocytes and fat necrosis via the following mechanisms: vascular compression, vascular interruption (fracture), thrombosis (sickle cell disease, caisson disease), vessel injury</td>
<td>Joint pain; osteoarthrosis; sites include head of the femur, shoulder, knee</td>
</tr>
<tr>
<td>Pyogenic osteomyelitis</td>
<td>Infection of bone most often caused by <em>Staphylococcus aureus</em>; routes of infection include hematogenous extension from adjacent infection, open fracture, or surgery</td>
<td>Acute febrile illness; pain; tenderness; usually affects metaphysis of distal femur, proximal tibia, and proximal humerus; forms sequestrum and involucrum</td>
</tr>
<tr>
<td>Tuberculous osteomyelitis</td>
<td>Tuberculoc infection spreads to bone from elsewhere in body</td>
<td>Seen in hips, long bones, hands, feet, and vertebrae (Pott disease)</td>
</tr>
</tbody>
</table>

DEXA, dual-energy x-ray absorptiometry.

I. Bisphosphonates

The bisphosphonates, which include alendronate, risedronate, ibandronate, pamidronate, and etidronate, inhibit osteoclast-mediated bone resorption by binding to hydroxyapatite. The bisphosphonates are most commonly used to prevent or treat postmenopausal osteoporosis but can also be used for Paget disease and steroid-induced osteoporosis.
II. Tumors of bone and cartilage (Table 9-3)

Tumors of the bone and cartilage, although rare, occur most commonly in the lower extremities of young males. Metastases are more common than primary tumors of the bone. Tumors of the prostate, breast, and lung account for 80% of bone metastases.

<table>
<thead>
<tr>
<th>Tumor</th>
<th>Morphology</th>
<th>Clinical Features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Osteochondroma</td>
<td>Benign bone tumor; most common benign tumor, originates in metaphysis of long bones; growth of mature bone (exostosis) with a cartilaginous cap</td>
<td>Most common in men younger than 25 years of age; usually occurs on the lower end of the femur or upper end of the tibia</td>
</tr>
<tr>
<td>Giant cell tumor</td>
<td>Benign bone tumor; spindle-shaped cells with multinucleated giant cells; most commonly occur in the epiphysis of the distal femur or proximal tibia</td>
<td>Most common in women 20–55 years of age; has &quot;soap bubble&quot; appearance on radiograph; usually occurs on the lower end of the femur or upper end of the tibia</td>
</tr>
<tr>
<td>Osteoma</td>
<td>Benign bone tumor; mature bone (dense tissue)</td>
<td>Most common in men; affects skull or facial bones; protrudes from surface; associated with Gardner syndrome</td>
</tr>
<tr>
<td>Osteoid osteoma</td>
<td>Benign bone tumor; nidus rimmed by osteoblasts and surrounded by vascular, spindled stroma; &lt;2 cm in diameter</td>
<td>Most common in men 20–30 years of age; occurs near the ends of the tibia and femur; painful due to excess prostaglandin E₂ production; radiolucent nidus is seen on radiograph</td>
</tr>
<tr>
<td>Osteosarcoma</td>
<td>Malignant mesenchymal bone tumor; malignant cells produce bone matrix; origin usually in metaphyseal long bones; destructive masses with hemorrhage and necrosis; retinoblastoma, Paget disease, radiation exposure are risk factors</td>
<td>Bimodal distribution, most common in boys in their teenage years and in elderly; usually occurs in tibia or femur near the knee; local pain; tenderness; swelling; metastasizes to lung first; growth under bone results in the Codman triangle and a &quot;sunburst&quot; appearance on radiograph</td>
</tr>
<tr>
<td>Chondrosarcoma</td>
<td>Malignant cartilage tumor; lobulated translucent tumors; necrosis; calcification</td>
<td>Most common in men usually 40 years of age or older; central skeleton is affected such as the pelvis, ribs, shoulders, spine; radiograph shows localized area of bone destruction</td>
</tr>
<tr>
<td>Ewing sarcoma</td>
<td>Malignant small round cell tumors of bone and soft tissue; t(11;22); sheets of small round cells producing Homer-Wright pseudorosettes; histologically similar to lymphoma, small cell carcinoma, rhabdomyosarcoma</td>
<td>Most common in boys 10–15 years of age; occurs in long bones, ribs, pelvis, scapula; early metastasis; responds to chemotherapy; painful, warm, swollen mass; &quot;onion skin&quot; appearance on radiograph</td>
</tr>
<tr>
<td>Fibrous dysplasia</td>
<td>Benign; bone replaced haphazardly by fibrous tissue</td>
<td>&quot;Chinese figures&quot; configuration on radiograph. Three types: Single bone involvement Several bones involved Several bones involved, along with precocious puberty and café au lait spots</td>
</tr>
<tr>
<td>Metastasis</td>
<td>Malignant; usually lytic lesions unless arising from prostate or breast</td>
<td>Originate from prostate, breast, kidney, lung; ectopic hormone production (parathyroid hormone-related protein [PTHrP])</td>
</tr>
</tbody>
</table>

Osteochondromas generally do not undergo malignant transformation to chondrosarcoma, except in the familial variety, which is characterized by multiple lesions.

Gardner syndrome is an autosomal dominant disorder characterized by multiple colonic polyps associated with other tumors such as osteomas of the skull, fibromas, thyroid cancer, epidermoid cysts, and sebaceous cysts.

In osteosarcoma, a "sunburst" appearance on radiography is due to calcified streaks that radiate from a tumor. Codman triangle is due to periosteum lifting away from the bone due to an underlying tumor.

The most common bone sarcoma in children is an osteosarcoma, followed by Ewing sarcoma.

Predisposing factors for osteosarcoma include Paget disease of the bone, mutations of the p53 gene on chromosome 17 (Li–Fraumeni syndrome), familial retinoblastoma, radiation, and bone infarcts.

The most common malignancy of the skeleton is metastatic tumors.
III. Arthritic joint disease (Table 9-4)
The etiology of arthritic joint diseases is not well understood. For this reason, treatment is often palliative rather than curative.

Two factors to consider in the differential diagnosis of an acutely painful joint include infection and urate deposition. These two entities may be distinguished from each other, in part, by aspiration of the joint fluid with evaluation for white blood cells (WBCs), bacteria on Gram stain, or crystals.

<table>
<thead>
<tr>
<th>Disease</th>
<th>Etiology</th>
<th>Clinical Features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Osteoarthritis (degenerative joint disease)</td>
<td>Degeneration of joint articular cartilage followed by growth of surrounding bone; the most common type of arthritis; primary type has no specific risk factor; secondary type related to trauma, metabolic disorder, or inflammatory arthropathy; knee is the most common site</td>
<td>Pain in joint after use, improves with rest, stiffness in the morning or after a period of immobility; “Joint mice” form from pieces of torn and frayed joint cartilage and broken pieces of osteophytes; erosion of cartilage results in eburnation (polishing) of the underlying bone; cysts visible in bone on radiograph; Heberden nodes are osteophytes at the DIP joint; Bouchard nodes are osteophytes of the PIP joints</td>
</tr>
<tr>
<td>Rheumatoid arthritis</td>
<td>Symmetrical, chronic inflammation of the synovium with edema and cellular infiltrate, leading to the destruction of articular cartilage of joints, most likely because of autoimmune reaction; synovial hypertrophy and hyperplasia; granulation tissue (pannus) over articular cartilage; rheumatoid factor—IgM autoantibody against the Fc receptor located on IgG; more common in women; associated with HLA-DR4</td>
<td>Ulnar deviation of MCP joints, swan-neck, and boutonnière deformity develop owing to inflammation, muscle atrophy, and contracture; DIP joints are spared; morning stiffness that improves throughout the day; subcutaneous rheumatoid nodules; systemic symptoms such as fever, weight loss, fatigue</td>
</tr>
<tr>
<td>Ankylosing spondylitis</td>
<td>Unknown cause; high association with HLA-B27; negative rheumatoid factor; males are more commonly affected</td>
<td>Bilateral sacroiliitis (inflammation of the sacroiliac joint) noted; chronic low back pain and stiffness; improves with movement; calcification of spinal ligaments and fusion of the facet joints produces a “bamboo spine”; may produce extraskeletal manifestations of apical lung fibrosis, aortic insufficiency, or cauda equina syndrome</td>
</tr>
<tr>
<td>Psoriatic arthritis</td>
<td>Unknown cause; may present similar to rheumatoid arthritis; HLA-B27 association; no rheumatoid factor; no male or female preponderance</td>
<td>Asymmetric involvement of DIP joints,PIP joints, feet, ankles, and knees; “pencil-in-a-cup” deformity of the proximal phalanges</td>
</tr>
<tr>
<td>Reiter syndrome</td>
<td>Caused by reaction to systemic illness that originated either enteropathically or urogenitally; HLA-B27 association; most common in males, usually 20–40 years of age</td>
<td>Classic triad of genitourinary inflammation (urethritis), ocular inflammation (conjunctivitis), and acute asymmetric arthritis</td>
</tr>
</tbody>
</table>

Table 9-4 Arthritic Joint Disease

To remember Reiter syndrome: “Can’t see” (uveitis), “can’t pee” (urethritis), “can’t climb a tree” (arthritis).
The Musculoskeletal System

### TABLE 9-4 Arthritic Joint Disease (Continued)

<table>
<thead>
<tr>
<th>Disease</th>
<th>Etiology</th>
<th>Clinical Features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gout</td>
<td>Inflammatory reaction in joints caused by monosodium urate crystal deposition; IgG opsonization of the crystals followed by phagocytosis stimulates inflammation; pathogenesis includes increased uric acid production such as Lesch–Nyhan syndrome (hypoxanthine-guanine phosphoribosyltransferase deficiency), increased activity of phosphoribosyl pyrophosphate (PRPP) synthetase, and decreased uric acid secretion such as diuretics; acidosis; often precipitated by a large, high-protein meal or by drinking excessive amounts of alcohol</td>
<td>First MTP joint involvement is called podagra; tophi (nodules of fibrous tissue and crystals) occur near the joints, on the ear, and on the Achilles tendon; renal damage may occur when crystals deposit in collecting tubules; urate crystals have strong negative birefringence under polarized light and are needle shaped. For treatment, see Table 9-5.</td>
</tr>
</tbody>
</table>

DIP, distal interphalangeal; HLA, human leukocyte antigen; Ig, immunoglobulin; MCP, metacarpophalangeal; MTP, metatarsophalangeal; PIP, proximal interphalangeal.

**Quick Hit**

Lesch–Nyhan syndrome is an X-linked deficiency of hypoxanthine-guanine phosphoribosyl transferase (HGPRT) that results in elevated levels of uric acid and manifests as mental retardation, gout, and self-mutilation. It can be treated with allopurinol, which blocks xanthine oxidase, an important enzyme in the formation of uric acid.

Pseudogout, caused by calcium pyrophosphate crystals, resembles gout in its presentation. However, calcium pyrophosphate crystals have weak positive birefringence under polarized light.

### TABLE 9-5 Drugs Used to Treat Gout

<table>
<thead>
<tr>
<th>Therapeutic Agent</th>
<th>Mechanism of Action</th>
<th>Indications</th>
<th>Side Effects</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Allopurinol</td>
<td>Inhibition of uric acid production—competitive inhibitor of xanthine oxidase, decreases conversion of xanthine to uric acid</td>
<td>Chronic gout therapy; lymphoma, leukemia (prevents tumor lysis associated urate nephropathy), uric acid stones</td>
<td>Rash, fever, diarrhea, occasional peripheral neuritis; enhances effect of azathioprine</td>
<td>Should not be used to treat acute gout</td>
</tr>
<tr>
<td>Probenecid</td>
<td>Increased secretion of uric acid (uricosuric)—small dose inhibits uric acid secretion; large dose inhibits uric acid reabsorption (i.e., promotes excretion)</td>
<td>Chronic gout therapy</td>
<td>Caution: should not be used in patients with sulfa allergies</td>
<td>Should not be used to treat acute gout or patients with uric acid stones</td>
</tr>
<tr>
<td>Colchicine</td>
<td>Anti-inflammatory—inhibits microtubule formation, thereby interfering with normal mitosis and inhibiting WBC migration and phagocytosis</td>
<td>Acute gout therapy</td>
<td>Diarrhea (common)</td>
<td></td>
</tr>
</tbody>
</table>

(continued)
A 45-year-old man presents to the emergency department with severe pain in his left great toe that began suddenly yesterday evening. He reports exquisite tenderness, saying “even the bed sheet touching my toe was intolerable.” The patient also reports that yesterday afternoon, he had “gone out with the boys” and estimates drinking five to six beers. Patient denies both pain in other joints and having felt pain like this before. Physical examination shows swelling, erythema, rubor, and tenderness of the left great toe. His past medical history is significant for osteoarthritis of the left knee for which he takes ibuprofen. Temperature = 98.5°F; blood pressure = 135/70 mm Hg; heart rate = 85 bpm; respiration rate = 21 breaths/min.

**Differentials:** Septic arthritis, cellulitis, gout, pseudogout. Osteoarthritis and rheumatoid arthritis are ruled out in this case because they typically present as pain in multiple joints. Polyarticular pain should be thought of as inflammatory (showing signs of rubor, swelling, and erythema as in rheumatoid arthritis) and noninflammatory (as in osteoarthritis). Septic arthritis is unlikely in this case because of the location of the pain and the lack of fever. Based on the location of the pain, occurrence after a diet rich in purines, and the examination, this patient most likely is experiencing an acute gouty attack.

**Management:** Acute gout is treated by nonsteroidal anti-inflammatory drugs (NSAIDs; indomethacin is traditionally used, aspirin aggravates the problem), colchicines (if the patient did not respond to NSAIDs), and corticosteroids (if patient cannot tolerate NSAIDs or colchicine). Prophylactic therapy would not be initiated in this patient because this is his first acute gouty attack. Prophylactic therapy is indicated after two gouty attacks and consists of uricosuric drugs or allopurinol, depending on the amount of uric acid excreted in urine over 24 hours. Never give allopurinol for acute gout; it makes it worse.

### TABLE 9-5 Drugs Used to Treat Gout (Continued)

<table>
<thead>
<tr>
<th>Therapeutic Agent</th>
<th>Mechanism of Action</th>
<th>Indications</th>
<th>Side Effects</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>NSAIDs (e.g., indomethacin)</td>
<td>Decrease prostaglandin production, thereby interrupting the inflammatory process</td>
<td>Acute therapy</td>
<td>Bone marrow suppression and renal damage (indomethacin); GI distress and ulceration</td>
<td></td>
</tr>
<tr>
<td>Celecoxib</td>
<td>Selectively inhibits cyclooxygenase-2 (COX-2)</td>
<td>Acute therapy</td>
<td>Sulfur allergy; renal damage</td>
<td>Less toxic to GI mucosa than NSAIDs</td>
</tr>
<tr>
<td>Glucocorticoids (prednisone)</td>
<td>Suppresses prostaglandin and leukotriene synthesis</td>
<td>Acute therapy</td>
<td>Osteoporosis, Cushingoid reaction, psychosis, glucose intolerance, infection, hypertension, cataracts</td>
<td></td>
</tr>
</tbody>
</table>

GI, gastrointestinal; NSAID, nonsteroidal anti-inflammatory drug; WBC, white blood cell.
V. Infectious joint disease (Table 9-6)

<table>
<thead>
<tr>
<th>Disease</th>
<th>Etiology</th>
<th>Clinical Features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nongonococcal septic arthritis</td>
<td>Inflammation of joints; most commonly <em>Staphylococcus aureus</em> and <em>Streptococcus</em> species</td>
<td>Monoarticular arthritis, usually affecting the knee; chills and fever; positive Gram stain and cultures of synovial fluid</td>
</tr>
<tr>
<td>Gonococcal septic arthritis</td>
<td>Inflammation of joints and other systemic effects secondary to dissemination of sexually acquired gonococcal infection; most common form of arthritis in sexually active adults</td>
<td>Polyarticular arthritis, usually affects the knee; chills and fever, rash (including papules and pustules); Gram stain and synovial fluid cultures often negative</td>
</tr>
<tr>
<td>Lyme disease</td>
<td>Infection with <em>Borrelia burgdorferi</em>, which is transmitted by the tick <em>Ixodes dammini</em>; arthritis occurs late in the disease</td>
<td>Erythema chronicum migrans, a characteristic expanding bull’s-eye rash; knees are most common site of arthritis; may cause myocardial, pericardial, and neurologic manifestations</td>
</tr>
</tbody>
</table>

**SYSTEMIC LUPUS ERYTHEMATOSUS**

I. Prototypical connective tissue disorder that more frequently affects women

II. Clinical features
   A. Fever, lymphadenopathy, weight loss, and general malaise
   B. Immune complex deposition in the vessels of almost all organs
   C. Pulmonary fibrosis characterized by interstitial fibrosis or diffuse alveolitis
   D. Libman–Sacks endocarditis
      1. Mitral valve affected
      2. Sterile verrucous lesions seen on both sides of the leaflets
   E. Pericarditis and pleuritis
   F. Glomerular disease
      1. May range from mild to diffuse proliferative change
      2. Subendothelial and mesangial immune complex deposits
      3. Endothelial proliferation (wire loops) and thickened basement membranes (membranous glomerulonephritis)
   G. Arthralgia and arthritis
   H. Vasospasm of small vessels, especially of the fingers (Raynaud phenomenon)
   I. Cotton-wool spot lesions in fundus of eye
   J. Skin rash
      1. Characteristic butterfly rash over the malar eminences of the face
      2. Rashes can also be prevalent elsewhere on the body
      3. Rashes associated with exposure to sunlight (photosensitivity)

III. Laboratory findings
   A. Antinuclear antibodies (ANAs) are seen in almost all cases.
      1. ANA is a sensitive marker, but it is not specific for systemic lupus erythematosus (SLE).
      2. Presence of antibodies to double-stranded DNA is highly specific for SLE.
      3. Antibodies to Smith (Sm) antigen are also specific for SLE.

   QUICK HIT
   SLE has a female-to-male ratio of 2:1 and is more common in African-American women.

   QUICK HIT
   Presence of antibodies against double-stranded DNA antibodies and Smith (Sm) antigen is practically diagnostic of SLE.

   QUICK HIT
   Antihistone antibodies are associated with drug-induced lupus. Common drugs that cause drug-induced lupus: hydralazine, procainamide, isoniazid, chlorpromazine, methyldopa, and quinidine.
### Other Connective Tissue Disorders (Table 9-7)

Inherited disorders of the bone, skin, cartilage, and blood vessels are some of the most common genetic conditions in humans. These diseases are characterized by widespread manifestations.

<table>
<thead>
<tr>
<th>Disease</th>
<th>Etiology</th>
<th>Clinical Features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Marfan syndrome</td>
<td>Abnormality of fibrillin (a glycoprotein in microfibrils) due to mutations in the FBN1 gene on chromosome 15; results in skeletal, visual, and cardiovascular defects; autosomal dominant inheritance</td>
<td>Abnormally long fingers (arachnodactyly), arms, and legs; hyperextensible joints; tall and thin body habitus; high palate; ocular lens dislocation (ectopia lentis); cardiovascular defects including mitral valve prolapse, proximal aorta aneurysm, aortic valve insufficiency, and aortic dissection</td>
</tr>
<tr>
<td>Ehlers–Danlos syndrome</td>
<td>Genetic defect in type I and type III collagen and elastin formation</td>
<td>Frequent hemorrhage, hyperextensibility of joints and skin, fragility of tissue, poor wound healing</td>
</tr>
<tr>
<td>Progressive systemic sclerosis</td>
<td>Diffuse fibrosis and degeneration of almost every organ owing to autoimmune reaction; anti-scl70 (ANA); anticientromere antibody present in CREST (calcinosis cutis, Raynaud phenomenon, esophageal dysfunction, sclerodactyly, and telangiectasia); occurs more frequently in women</td>
<td>Hypertrophy of subcutaneous collagen leads to thickened skin, fixed facial expression, clawlike hand (sclerodactyly); Raynaud phenomenon; fibrosis of esophagus, GI tract, lungs, heart, and kidney</td>
</tr>
</tbody>
</table>
| Sjögren syndrome                     | Autoimmune reaction; anti-SSA (anti-Ro) and anti-SSB (anti-La) antibodies; anti-SSB antibody is highly specific; occurs more often in women Enlarged parotid glands as a consequence of lymphocytic infiltration; hypergammaglobulinemia | Classic triad:  
  - Dry eyes (xerophthalmia)  
  - Dry mouth (xerostomia)  
  - Presence of other connective tissue or autoimmune disease (often rheumatoid arthritis) |
| Polymyositis                          | Autoimmune inflammatory disorder; occurs more frequently in women; often associated with malignancy | Weakness in the proximal muscles of the extremities; high level of creatine kinase in serum; termed dermatomyositis when skin is involved |
| Mixed connective tissue disease      | Autoimmune disorder; occurs more frequently in women; renal involvement is rare (as opposed to other connective tissue diseases); antinuclear ribonucleic protein (anti-nRNP) is a highly specific ANA | Raynaud phenomenon, arthralgia, muscle inflammation, esophageal dysmotility |

**QUICK HIT**

In vitro, the hypocoagulable state is caused by antibodies that react with the cardiolipin test substrate. However, this reaction does not occur in vivo because the SLE patient is prone to excessive clotting, not excessive bleeding.
Clinical Vignette 9-3

CLINICAL PRESENTATION: A 35-year-old woman presents to her primary care physician complaining of joint pain in her wrist, ankle, and knee for the past several months. She also reports a painful intermittent rash of the same duration on her face that worsens in the sun. The patient also tells you that she has noted that her fingers oddly become very pale, turn blue, and then bright red while in the cold outdoors. Review of systems is positive for fatigue and weight loss. A head, eye, nose, and throat (HEENT) examination shows an erythematous rash over the cheeks and nasal bridge, sparing the nasolabial folds, hair thinning along the crown, and ulceration of the oral mucosa. Examination of the forearm shows a raised erythematous patch with some scaling. Temperature = 100.2° F; blood pressure = 145/90 mm Hg; heart rate = 75 bpm; respiration rate = 20 breaths/min.

DIFFERENTIALS: SLE, drug-induced lupus, discoid lupus, mixed connective tissue disease (MCTD), scleroderma. The arthralgia, malar rash, discoid lesions on sun-exposed arms, alopecia, weight loss, oral ulcers, and mild fever all suggest SLE. Drug-induced lupus could be ruled out from a detailed medication history (see Quick Hit for list of drugs). Although Raynaud phenomenon is observed in SLE, it also occurs in scleroderma. MCTD is a disorder in which features of SLE, systemic sclerosis, dermatomyositis, polymyositis, and Sjögren syndrome can coexist and overlap. Serologic studies should be performed to differentiate these further.

LABORATORY STUDIES: When given serologic studies on the USMLE, look for the following results: A positive antinuclear antibody (ANA) screening test occurs in SLE, rheumatoid arthritis, scleroderma, Sjögren syndrome, MCTD, polymyositis, dermatomyositis, and drug-induced lupus. A negative ANA screening test suggests that the diagnosis is likely not SLE. Presence of either anti–double-stranded DNA (dsDNA) or anti-Sm antibody is diagnostic of SLE. Antihistone antibodies are present in 100% of cases of drug-induced lupus. If negative, drug-induced lupus can be excluded. Ribonucleoprotein (RNP) antibodies are a specific marker of MCTD. Positive anti-scl70 indicates scleroderma, and positive anticentromere antibody specifically indicates CREST (calcinosis cutis, Raynaud phenomenon, esophageal motility disorder, sclerodactyly, and telangiectasia) syndrome. Complete blood count studies show anemia, leukopenia, lymphopenia, or thrombocytopenia in SLE. Also, serum electrolytes with blood urea nitrogen (BUN) and creatinine should be ordered to detect renal disease. In SLE, a urinalysis should also be performed, looking for proteinuria (evaluate further for nephrotic syndrome), cellular casts, and hematuria (evaluate further for glomerulonephritis).

MANAGEMENT: Depends on severity and type of symptoms: mild symptoms—NSAIDS; acute exacerbations—local/systemic corticosteroids; constitutional, cutaneous, articular symptoms—antimalarial agents (hydroxychloroquine); active glomerulonephritis—cytotoxic agents cyclophosphamide). Monitor for renal disease and hypertension.
The Musculoskeletal System

Brachial plexus

Lesions of the brachial plexus and its branches (Table 9-8)

Nerve damage and regeneration (Figure 9-3)

TABLE 9-8 Lesions of the Brachial Plexus and Its Branches

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Lesion</th>
<th>Cause</th>
<th>Clinical Features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Erb–Duchenne palsy</td>
<td>Upper brachial plexus</td>
<td>Hyperabduction of the arm (such as trauma, shoulder dystocia during delivery)</td>
<td>“Waiter’s tip” position (arm extended and adducted, forearm pronated)</td>
</tr>
<tr>
<td>Klumpke palsy</td>
<td>Lower brachial plexus (C8–T1)</td>
<td>Hyperabduction of the arm (shoulder dystocia during delivery)</td>
<td>Claw hand from ulnar nerve involvement; wrist and hand dysfunction; associated with Horner syndrome</td>
</tr>
<tr>
<td>Claw hand</td>
<td>Ulnar nerve</td>
<td>Occurs in children with epiphyseal separation of the medial epicondyle of the humerus</td>
<td>Weak finger adduction; medial hand numbness; dysfunction of fourth and fifth digit flexion</td>
</tr>
<tr>
<td>Radial nerve palsy</td>
<td>Radial nerve</td>
<td>Fracture of midhumerus</td>
<td>Wrist drop: inability to extend wrist or fingers; loss of sensation from dorsum of hand</td>
</tr>
<tr>
<td>Carpal tunnel syndrome</td>
<td>Median nerve</td>
<td>Repetitive motion (swelling within the flexor retinaculum compresses the median nerve)</td>
<td>Wrist flexion elicits pain; wrist extension relieves pain; symptoms worse at night</td>
</tr>
</tbody>
</table>

(continued)
The Musculoskeletal System

Nerve cell body

Nerve damage causes some degeneration of the distal segment. The nerve cell body undergoes chromatolysis (dispersion of Nissl substance).

The muscle continues to atrophy for 3 weeks. In the PNS, Schwann cells proliferate and help direct the regenerating neuron. In the CNS, astrocyte proliferation forms a scar, which prohibits nerve regeneration.

If the nerve fibers do not find the degenerating segment, a neuroma is formed.

Successful nerve regeneration allows the muscle fiber to return to its original size.

CNS, central nervous system; PNS, peripheral nervous system.

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Lesion</th>
<th>Cause</th>
<th>Clinical Features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medial winging of the scapula</td>
<td>Long thoracic nerve</td>
<td>Surgery (e.g., mastectomy)</td>
<td>Limited arm abduction and flexion; serratus anterior paralysis, medial scapula protrudes if patient pushes against a wall</td>
</tr>
<tr>
<td>Shoulder dislocation</td>
<td>Axillary nerve</td>
<td>Anterior dislocation (owing to forced abduction and extension)</td>
<td>Loss of innervation to deltoid; compromised shoulder flexion and extension; palpable depression under acromion</td>
</tr>
<tr>
<td>Surgical neck fracture of the humerus</td>
<td>Axillary nerve</td>
<td>A fall landing on the elbow</td>
<td>Loss of innervation to deltoid; compromised shoulder flexion and extension; palpable depression under acromion</td>
</tr>
</tbody>
</table>

**FIGURE 9-3** Nerve damage and regeneration

**QUICK HIT**

The median nerve can also be damaged in fractures of the distal third of the humerus and elbow (causing total loss of thumb opposition) or slashing of the wrist.

**MNEMONIC**

To remember the nerves affected by humerus fracture location, think ARM fracture from superior to inferior: Axillary-head of humerus; Radial-midshaft of humerus; Median-supracondylar/distal third of humerus.

**TABLE 9-8 Lesions of the Brachial Plexus and Its Branches (Continued)**
LUMBOSACRAL PLEXUS (Figure 9-4)

I. The lumbosacral plexus, which consists of the ventral rami of L1–S4, supplies the lower extremity.

II. Motor and sensory functions of the lumbosacral plexus

Sacral plexus lesions are commonly caused by locally invading or metastasizing carcinoma from pelvic organs (e.g., bladder, prostate, ovaries). Knowledge of the motor and sensory functions of the sacral plexus can assist in determining the deficits resulting from complications of these tumors (Tables 9-9 and 9-10).
### TABLE 9-9 Segmental Nerve Functions of the Lumbosacral Plexus

<table>
<thead>
<tr>
<th>Spinal Nerve</th>
<th>Muscle Innervation</th>
<th>Muscle Test</th>
<th>Sensory Function</th>
</tr>
</thead>
<tbody>
<tr>
<td>L1</td>
<td>Cremaster</td>
<td>Cremasteric reflex</td>
<td>Inguinal region</td>
</tr>
<tr>
<td>L2</td>
<td>Iliopsoas</td>
<td>Hip flexion</td>
<td>Upper anteromedial thigh</td>
</tr>
<tr>
<td>L3</td>
<td>Medial thigh</td>
<td>Hip adduction</td>
<td>Lower anteromedial thigh</td>
</tr>
<tr>
<td></td>
<td>Quadriceps femoris</td>
<td>Knee extension</td>
<td></td>
</tr>
<tr>
<td>L4</td>
<td>Tibialis anterior</td>
<td>Ankle dorsiflexion</td>
<td>Anteromedial leg</td>
</tr>
<tr>
<td>L5</td>
<td>Extensor hallucis longus</td>
<td>Great toe extension</td>
<td>Anterolateral leg, medial dorsal foot, plantar region of great toe</td>
</tr>
<tr>
<td>S1</td>
<td>Gastrocnemius, soleus, Posterior thigh</td>
<td>Ankle plantarflexion</td>
<td>Heel region, plantar foot, lateral dorsal foot</td>
</tr>
<tr>
<td></td>
<td>Gluteus maximus</td>
<td>Hip extension, knee flexion Power hip extension, external rotation</td>
<td></td>
</tr>
<tr>
<td>S2</td>
<td>Gastrocnemius, soleus, Foot intrinsics</td>
<td>Ankle plantarflexion Abduction and adduction of toes</td>
<td>Posterior upper thigh and leg</td>
</tr>
<tr>
<td>S3–S4</td>
<td>External anal sphincter Bulbospongiosus</td>
<td>External anal sphincter tone Bulbospongiosus reflex</td>
<td>Circumanal and perineal region</td>
</tr>
</tbody>
</table>

### TABLE 9-10 Peripheral Nerve Functions of the Sacral Plexus

<table>
<thead>
<tr>
<th>Nerve</th>
<th>Muscle Innervation</th>
<th>Muscle Test</th>
<th>Sensory Function</th>
</tr>
</thead>
<tbody>
<tr>
<td>Genitofemoral</td>
<td>Cremaster</td>
<td>Cremasteric reflex</td>
<td>Skin below middle of inguinal ligament</td>
</tr>
<tr>
<td>Lateral femoral cutaneous</td>
<td>None</td>
<td>None</td>
<td>Skin of lateral thigh</td>
</tr>
<tr>
<td>Femoral</td>
<td>Anterior thigh (quadriceps)</td>
<td>Knee extension</td>
<td>Skin of anteromedial thigh and leg</td>
</tr>
<tr>
<td>Obturator</td>
<td>Medial thigh</td>
<td>Hip adduction</td>
<td>Hip joint and medial skin of knee</td>
</tr>
<tr>
<td>Superior gluteal</td>
<td>Gluteus medius, gluteus minimus</td>
<td>Hip abduction and internal rotation</td>
<td>None</td>
</tr>
<tr>
<td>Inferior gluteal</td>
<td>Gluteus maximus</td>
<td>Power hip extension and external rotation</td>
<td>None</td>
</tr>
<tr>
<td>Posterior femoral cutaneous</td>
<td>None</td>
<td>None</td>
<td>Skin of posterior thigh and upper leg</td>
</tr>
<tr>
<td>Superficial peroneal</td>
<td>Lateral leg</td>
<td>Foot eversion</td>
<td>Skin of anterolateral leg and dorsum of foot</td>
</tr>
<tr>
<td>Deep peroneal</td>
<td>Anterior leg</td>
<td>Ankle dorsiflexion, foot inversion, metatarsophalangeal joint extension</td>
<td>Skin of dorsum of web space between great and second toes</td>
</tr>
<tr>
<td>Tibial</td>
<td>Posterior thigh, gastrocnemius, soleus, deep posterior leg, planar muscles</td>
<td>Hip extensions, knee flexion, foot inversion, toe flexion</td>
<td>Skin of posterior leg and plantar foot</td>
</tr>
</tbody>
</table>
Musculoskeletal dysfunction can be caused by rearrangement of bone, nerve, musculature, or any combination of these elements. Insult to the body can result in problems that are acute (e.g., a torn anterior cruciate ligament) or chronic (e.g., tennis elbow).

### TABLE 9-11 Other Traumatic Injuries

<table>
<thead>
<tr>
<th>Injury</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anterior cruciate ligament (ACL) tear</td>
<td>Positive anterior drawer sign (lower leg pulled forward with knee flexed); often manifests as “terrible triad” (i.e., torn medial collateral ligament, lateral meniscus damage, and torn ACL), which occurs due to a force to the knee directed laterally to medially</td>
</tr>
<tr>
<td>Clavicle fracture</td>
<td>Middle third of clavicle; upward displacement of proximal fragment due to the sternocleidomastoid muscle; downward displacement of distal fragment; severe pain</td>
</tr>
<tr>
<td>Compartment syndrome</td>
<td>Fascial sheets separate the limbs into anterior and posterior compartments; hemorrhage into these compartments owing to crush injury or fracture, results in compression of neurovascular structures and further complications, emergent fasciotomy is needed</td>
</tr>
<tr>
<td>Inversion sprain of ankle</td>
<td>Most common ankle injury; results from forced inversion; stretches or tears lateral ligaments (especially the anterior talofibular)</td>
</tr>
<tr>
<td>Scaphoid fracture</td>
<td>Tenderness in the anatomical snuffbox; may lead to avascular necrosis if left untreated; easily missed on radiographs</td>
</tr>
<tr>
<td>Scoliosis</td>
<td>Complex lateral deviation and torsion of the spine; may be idiopathic or congenital or may result from a short leg, hip displacement, or polio</td>
</tr>
<tr>
<td>Shoulder separation</td>
<td>Downward displacement of the clavicle as a result of laxity of the acromioclavicular and coracoclavicular ligaments</td>
</tr>
<tr>
<td>Subacromial bursitis</td>
<td>Inflammation of the subacromial bursa</td>
</tr>
<tr>
<td>Tennis elbow (lateral epicondyliitis)</td>
<td>Sprain of radial collateral ligament (lateral epicondyliitis); pain on wrist extension and forearm supination</td>
</tr>
<tr>
<td>Golfer’s elbow (medial epicondyliitis)</td>
<td>Overuse of the pronator teres, palmaris longus, and flexor carpi radialis; causes sprain of their tendinous insertion on the anterior medial epicondyliitis; pain on wrist flexion</td>
</tr>
</tbody>
</table>

(continued)
The Musculoskeletal System

Cell membrane damage (e.g., from trauma)

Phospholipid (cell membrane)

Phospholipids

Arachidonic acid

Lipoxygenase

Leukotrienes (chemotaxis, increased secretion, bronchospasm)

Cyclooxygenase (COX)-1

PGH₂

ASA

NSAIDs

TXA₂
(normal platelet function, vasoconstriction)

PGI₂ (gastric acid) († gastric mucus) († renal blood flow)

ASA, aspirin; NSAIDs, nonsteroidal anti-inflammatory drugs; PG, prostaglandin; TX, thromboxane.

**QUICK HIT**

It is believed that prostaglandin E₂ (PGE₂) sensitizes the nerve endings to the action of bradykinin, histamine, and other chemical mediators.

**QUICK HIT**

The Trendelenburg sign results in downward tilting of the pelvis to the side opposite that of injury when standing on the foot of the injured side secondary to weakness or paralysis of the gluteus muscle. It can also be seen in a hip dislocation or a fracture of the neck of the femur.

**QUICK HIT**

Drugs such as carbamazepine, rifampin, and isoniazid can increase the action of liver enzymes, thus increasing the metabolism and reducing the effectiveness of acetaminophen.

**QUICK HIT**

Administration of aspirin to children with fever increases the risk of Reye syndrome. Acetaminophen, ibuprofen, and other NSAIDs are viable alternatives for pain and fever in children.

**TABLE 9-11 Other Traumatic Injuries (Continued)**

<table>
<thead>
<tr>
<th>Injury</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Waddling gait</td>
<td>Limp caused by superior gluteal nerve injury affecting gluteus medius and gluteus minimus; inability to abduct thigh; results in Trendelenburg sign</td>
</tr>
</tbody>
</table>

**PAIN MANAGEMENT** *(Figure 9-5) (Table 9-12)*

I. Musculoskeletal conditions, such as fractures and soft-tissue injuries, can result in significant disability, pain, and inflammation. Medical management of this pain and discomfort involves the use of nonnarcotic and narcotic preparations.

II. Acetaminophen

Acetaminophen (Tylenol) is a nonnarcotic analgesic with antipyretic and analgesic properties. It has little anti-inflammatory action. After acetaminophen is absorbed by the gastrointestinal (GI) tract, it is metabolized in the liver. In therapeutic doses, acetaminophen has minimal significant adverse effects. However, in large doses, depletion of liver glutathione levels may occur, resulting in hepatic necrosis as a result of the excess N-acetyl-p-benzoquinoneimine (NAPQI). Treatment for acetaminophen overdose is aerosolized N-acetylcysteine, which regenerates the depleted levels of glutathione.

III. Nonsteroidal anti-inflammatory drugs (NSAIDs)

NSAIDs are similar to acetaminophen in that they have antipyretic and analgesic properties. In addition, these agents have anti-inflammatory effects. NSAIDs act by inhibiting cyclooxygenase (COX) enzymes (Figure 9-5).
A. Aspirin, the most common NSAID, blocks prostaglandin synthesis from arachidonic acid in the hypothalamus and in peripheral tissue, which provides its anti-inflammatory, antiplatelet, analgesic, and anti-inflammatory benefits. Unlike other NSAIDs, its inhibitory effect on COX enzymes is irreversible.

B. A major adverse effect of aspirin and NSAIDs (e.g., ibuprofen, indomethacin, naproxen, diclofenac, ketorolac) is increased risk of GI bleeding. By blocking prostaglandin synthesis, NSAIDs may result in GI ulcers and hemorrhage. Prostacyclin (PGI₂) inhibits gastric acid secretion, whereas prostaglandin (PG) E₂ and PGF₂α help synthesize protective mucus in the stomach and small intestine. COX-2 inhibitors such as celecoxib may be indicated in patients who have a history of GI conditions; these NSAIDs are more specific for the inflammatory mediators (Figure 9-3).

IV. Opioids

Opioids are useful for severe pain that is uncontrolled by NSAIDs. Opioids exert their effects by interacting with protein receptors in the central nervous system (CNS) and by inhibiting G proteins and adenylyl cyclase in the peripheral nervous system. Each family of opioid receptors—µ, κ, σ, and δ—has its own set of properties and binding potency, which correlates with the amount of analgesia provided. The µ receptors primarily mediate analgesia.

The strong agonists of the various receptor families are morphine, meperidine, methadone, fentanyl, and heroin. Moderate agonists include codeine and propoxyphene. Some of these agents can produce extreme states of euphoria and become drugs of abuse because of their binding affinity and their intrinsic effects on the CNS. Methadone, which induces less euphoria and has a longer duration of action, is often used to provide controlled withdrawal to agents such as morphine and heroin.

Opioid overdose can lead to respiratory depression, depression of the cough reflex, pinpoint pupils, constipation, bronchoconstriction, diaphoresis, and urinary retention. Naloxone and naltrexone reverse the adverse effects of opioids. A rapid-acting drug, naloxone, displaces the receptor-bound opioid agents. Its effects are short-lived (approximately 2 hours). However, naltrexone works for up to 48 hours.

### TABLE 9-12 Therapeutic Agents for Pain

<table>
<thead>
<tr>
<th>Therapeutic Agent (common name, if relevant) [trade name, where appropriate]</th>
<th>Class—Pharmacology and Pharmacokinetics</th>
<th>Indications</th>
<th>Side Effects or Adverse Effects</th>
<th>Contraindications or Precautions to Consider; Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acetaminophen [Tylenol]</td>
<td>Analgesic, antipyretic—reversibly inhibits COX centrally (inactivated peripherally); prostaglandin inhibitor, not anti-inflammatory</td>
<td>Pain, fever</td>
<td>Liver toxicity in high doses (high levels deplete glutathione)</td>
<td>Overdose treated with N-acetylcysteine (regenerates glutathione); unlike aspirin, can be used in children, gout, peptic ulcer, and patients with platelet dysfunction</td>
</tr>
<tr>
<td>Acetylsalicylic acid (aspirin)</td>
<td>Anti-inflammatory, antipyretic, analgesic—acetylates COX irreversibly</td>
<td>Articular, musculoskeletal pain; chronic pain; maintenance therapy for preventing clot formation</td>
<td>GI distress, GI ulcers, inhibits platelet aggregation; causes hypersensitivity reactions (rash); reversible hepatic dysfunction</td>
<td>Contraindicated for children with the flu or chicken pox (leads to Reye syndrome), patients with gout</td>
</tr>
<tr>
<td>Ibuprofen [Advil, Motrin]</td>
<td>NSAID—reversibly inhibits COX (both COX-1 and COX-2) decreases prostaglandin synthesis</td>
<td>Inflammation, pain</td>
<td>GI distress, GI ulcers, coagulation disorders, aplastic anemia, metabolic abnormalities, hypersensitivity, renal damage</td>
<td>(continued)</td>
</tr>
</tbody>
</table>
### TABLE 9.12 Therapeutic Agents for Pain (Continued)

<table>
<thead>
<tr>
<th>Therapeutic Agent (common name, if relevant) [trade name, where appropriate]</th>
<th>Class—Pharmacology and Pharmacokinetics</th>
<th>Indications</th>
<th>Side Effects or Adverse Effects</th>
<th>Contraindications or Precautions to Consider; Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Naproxen [Naprosyn, Aleve]</strong></td>
<td>NSAID—reversibly inhibits COX (both COX-1 and COX-2) → decreases prostaglandin synthesis</td>
<td>Inflammation, pain</td>
<td>GI distress, GI ulcers, coagulation disorders, aplastic anemia, metabolic abnormalities, hypersensitivity, renal damage</td>
<td></td>
</tr>
<tr>
<td><strong>Indomethacin [Indocin]</strong></td>
<td>NSAID—reversibly inhibits COX (both COX-1 and COX-2) → decreases prostaglandin synthesis</td>
<td>Acute gout; closes patent ductus arteriosus</td>
<td>GI distress, GI ulcers, coagulation disorders, aplastic anemia, metabolic abnormalities, hypersensitivity, renal damage</td>
<td></td>
</tr>
<tr>
<td><strong>Ketorolac [Toradol]</strong></td>
<td>NSAID—reversibly inhibits COX (both COX-1 and COX-2) → decreases prostaglandin synthesis; relieves pain and reduces swelling</td>
<td>Postoperative pain, severe pain</td>
<td>GI distress, GI ulcers, coagulation disorders, aplastic anemia, metabolic abnormalities, hypersensitivity, renal damage</td>
<td></td>
</tr>
<tr>
<td><strong>Celecoxib [Celebrex]</strong></td>
<td>NSAID—selectively inhibits COX-2</td>
<td>Rheumatoid arthritis, osteoarthritis, pain, inflammation</td>
<td>Increased risk of thrombosis; sulfa allergy; less toxic to GI mucosa</td>
<td>CDX-2 selectivity reduces inflammation while minimizing GI adverse effects (ulcers)</td>
</tr>
<tr>
<td><strong>Morphine [MS Contin, MSIR, Roxanol]</strong></td>
<td>Opioid agonist—converted to more potent morphine-6-glucose</td>
<td>Severe pain; general anesthetic; antitussive; antidiarrheal</td>
<td>Respiratory depression; histamine release; constipation; nausea; miosis</td>
<td></td>
</tr>
<tr>
<td><strong>Meperidine [Demerol]</strong></td>
<td>Opioid agonist</td>
<td>Pain, acute migraine attacks</td>
<td>CNS excitation at high doses; histamine release</td>
<td>Contraindicated in patients with MAOI (results in hyperpyrexia)</td>
</tr>
<tr>
<td><strong>Fentanyl</strong></td>
<td>Opioid agonist</td>
<td>Pain; general anesthetic</td>
<td>Prolonged recovery, nausea</td>
<td></td>
</tr>
<tr>
<td><strong>Codeine</strong></td>
<td>Opioid agonist</td>
<td>Pain; antitussive</td>
<td>Constipation</td>
<td></td>
</tr>
<tr>
<td><strong>Oxycodone [Roxicodone]</strong></td>
<td>Opioid agonist</td>
<td>Severe pain; general anesthetic</td>
<td>Respiratory depression, constipation, nausea</td>
<td></td>
</tr>
<tr>
<td><strong>Hydromorphone [Dilaudid]</strong></td>
<td>Opioid agonist</td>
<td>Pain; antitussive</td>
<td>Respiratory depression, constipation, nausea</td>
<td></td>
</tr>
<tr>
<td><strong>Methadone</strong></td>
<td>Opioid agonist—synthetic</td>
<td>Maintenance therapy for heroin addiction</td>
<td>Respiratory depression; histamine release; constipation; nausea; miosis</td>
<td></td>
</tr>
<tr>
<td><strong>Tramadol [Ultram]</strong></td>
<td>Analgesic—similar to opioid agonist</td>
<td>Chronic pain of osteoarthritis</td>
<td>Nausea, vomiting, constipation, drowsiness</td>
<td></td>
</tr>
</tbody>
</table>

CNS, central nervous system; COX, cyclooxygenase; GI, gastrointestinal; MAOI, monoamine oxidase inhibitor; MSIR, morphine sulfate instant release; NSAID, nonsteroidal anti-inflammatory drug.
MUSCLE FUNCTION AND DYSFUNCTION (Figure 9-6)

The cross-bridge cycle of skeletal muscle

**MNEMONIC**

Remember the number of nuclei in muscle cells by simply noting one heart in the body and one nucleus per heart muscle cell; many skeletal muscles, so many nuclei per skeletal muscle fiber. Also, location of nucleus mirrors location in human body. The heart is in the center of the body and the nucleus is centrally located. Skeletal muscles predominate in the periphery of the body and the nuclei are at the periphery.

I. Comparison of muscle fibers (Table 9-13) (Figure 9-7)

Muscle can be divided into three subtypes with differing physiologic roles.

A. **Smooth muscle** plays a significant role in the maintenance of the lumens of the respiratory and GI tracts and blood vessels.

B. **Cardiac muscle** contracts the heart and propels blood through the vasculature.

<table>
<thead>
<tr>
<th>Category</th>
<th>Smooth Muscle Fiber</th>
<th>Cardiac Muscle Fiber</th>
<th>Skeletal Muscle Fiber</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nuclei</td>
<td>Centrally located single nucleus</td>
<td>Centrally located single nucleus</td>
<td>Peripheral located multiple nuclei</td>
</tr>
<tr>
<td>Banding</td>
<td>No distinct bands</td>
<td>Distinct bands</td>
<td>Distinct bands</td>
</tr>
<tr>
<td>Z line (convergence actin filaments)</td>
<td>None; dense bodies present</td>
<td>Present</td>
<td>Present</td>
</tr>
</tbody>
</table>

(continued)
TABLE 9-13 Comparison of Muscle Fibers (Continued)

<table>
<thead>
<tr>
<th>Category</th>
<th>Smooth Muscle Fiber</th>
<th>Cardiac Muscle Fiber</th>
<th>Skeletal Muscle Fiber</th>
</tr>
</thead>
<tbody>
<tr>
<td>Transverse (T) tubules (membrane invaginations)</td>
<td>None</td>
<td>At Z line; diads</td>
<td>At A-I junction; triads</td>
</tr>
<tr>
<td>Junctional communication</td>
<td>Gap junctions</td>
<td>Intercalated discs</td>
<td>None</td>
</tr>
<tr>
<td>Neuromuscular junction</td>
<td>None</td>
<td>None</td>
<td>Present</td>
</tr>
<tr>
<td>Regeneration</td>
<td>High</td>
<td>None</td>
<td>Some</td>
</tr>
<tr>
<td>Calcium source</td>
<td>Sarcoplasmic reticulum; extracellular</td>
<td>Sarcoplasmic reticulum; extracellular</td>
<td>Sarcoplasmic reticulum</td>
</tr>
<tr>
<td>Mechanism of calcium release</td>
<td>IP$_3$ (inositol-1,4,5-triphosphate)</td>
<td>Calcium induced</td>
<td>Depolarization of T tubule</td>
</tr>
<tr>
<td>Calcium-binding protein</td>
<td>Calmodulin</td>
<td>Troponin</td>
<td>Troponin</td>
</tr>
</tbody>
</table>

FIGURE 9-7 Gross, histologic, microscopic anatomy of skeletal muscle
C. Skeletal muscle maintains posture and produces movement. There are two types of skeletal muscle fibers (Table 9-14).

II. Muscle tumors (Table 9-15)
Pathology of muscles can take many forms. Metabolic dyscrasias, which can be induced or inherited, are far more common than neoplasms.

III. Other neuromuscular disorders (Table 9-16)

IV. Neuromuscular blocking agents
Neuromuscular blocking agents, which are most often encountered in the operating room, are used to produce the flaccid paralysis that is essential for many procedures, such as abdominal operations and joint replacements. These drugs affect the muscles of the body in a typical order. The small, fast-twitch muscles of the face and eyes are the first to be paralyzed, followed by the muscles of the hand, limbs, and trunk. The intercostal muscles and the diaphragm are the last to be affected. As the effects of neuromuscular blockers wear off, the muscles regain function in the reverse order.
Neuromuscular blocking agents can be categorized in several ways. The most useful system divides them into central-acting and neuromuscular endplate (NMEP) blockers. The NMEP blockers can be further divided into depolarizing and nondepolarizing agents.

Centrally acting neuromuscular blocking drugs include diazepam and baclofen. **Diazepam**, a benzodiazepine, acts at γ-aminobutyric acid (GABA) receptors in the CNS. **Baclofen**, another GABA mimetic, also acts in the CNS to decrease muscle tone. Peripherally acting drugs include curare, succinylcholine, and dantrolene.

**Curare** acts as a nicotinic antagonist at the motor endplate to produce muscle relaxation. At low doses, this agent binds to and blocks the nicotinic receptor, a competitive blockade that can be overcome by increasing the concentration of acetylcholine. At higher doses, curare and the curare-like agents actually block ion channels at the NMEP (non-competitive block).

**Succinylcholine**, the only depolarizing neuromuscular blocking agent, acts by binding to and activating the nicotinic receptor of the NMEP. In phase 1 block, a wave of fasciculations rapidly passes over the patient as the drug is administered. The drug then remains attached to the nicotinic receptor and is not broken down by acetylcholinesterase. In phase 2 block, the membrane of the NMEP repolarizes, the muscles relax, and the succinylcholine continues to block the nicotinic receptor. Plasma cholinesterase quickly breaks down the drug, and its duration of action is only a few minutes. The rapid onset and short duration of action of succinylcholine make it ideal for use during rapid-sequence endotracheal intubation and electroconvulsive therapy.

### Table 9-16 Other Neuromuscular Disorders

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Etiology</th>
<th>Clinical Features</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lactic acidosis</td>
<td>Shock, sepsis, methanol poisoning, metformin toxicity, liver failure, diabetic ketoadidasosis</td>
<td>Increased serum lactate; <strong>metabolic acidosis</strong>; increased anion gap</td>
<td>May lead to coma or death</td>
</tr>
<tr>
<td>Myasthenia gravis</td>
<td>Acetylcholine receptor autoantibodies at the neuromuscular junction; linked to HLA-DR3; associated with thymus disorders</td>
<td>Muscle weakness with use; ptosis; manifests itself in facial, ocular, and limb muscles; proximal muscles affected first</td>
<td>Four times more common in women; diagnosis includes the edrophonium (Tensilon) test; anticholinesterase (e.g., edrophonium) improves condition</td>
</tr>
<tr>
<td>Duchenne muscular dystrophy</td>
<td>X-linked recessive; deficiency in dystrophin leading to lack of actin stabilization</td>
<td>Progressive, proximal muscle weaknesses, beginning with the pelvic girdle and extending to the shoulder girdle; <strong>pseudohypertrophy</strong> of muscles (e.g., calf); positive Gowers maneuver; leads to death via respiratory or cardiac failure</td>
<td>Increased serum creatine kinase and lactate dehydrogenase; clinical symptoms usually appear by age 5 years with wheelchair dependence by the end of the first decade of life and death in the 20s</td>
</tr>
<tr>
<td>Mitochondrial myopathy</td>
<td>Transmitted via mitochondrial DNA (mtDNA); non-Mendelian inheritance</td>
<td><strong>Ragged red fibers</strong> seen on muscle biopsy; proximal muscle weakness</td>
<td>Maternal mode of transmission</td>
</tr>
</tbody>
</table>

*HLA, human leukocyte antigen.*

### QUICK HIT
- Abnormality of the thymus is seen in 85% of patients with myasthenia gravis, 15% being a thymoma, requiring a thymectomy.
- Pseudohypertrophy is initially caused by muscle hyper trophy. Then as atrophy ensues, an increase in fat and connective tissue deposition occurs.
- **Becker muscular dystrophy** is a less common and less severe variant of Duchenne muscular dystrophy that involves the same gene (Xp21) and the dystrophin protein.
- When succinylcholine is used in combination with halothane, it can cause malignant hyperthermia in certain predisposed individuals. Treatment of this condition, which is characterized by severe, prolonged muscle contractions, involves the use of dantrolene and cooling blankets.
THE INGUINAL CANAL

I. The inguinal canal (Figure 9-8) (Table 9-17)

The inguinal canal contains the ilioinguinal nerve (sensory to the anterior aspect of labia or scrotum), spermatic cord in males (vas deferens, testicular artery, pampiniform plexus, genital branch of the genitofemoral nerve), and the round ligament of the uterus in females.

Hesselbach triangle is formed from the border of the rectus abdominis medially, inferior epigastric artery laterally, and the inguinal ligament inferiorly.

Hernias may cause small bowel obstruction. However, small bowel obstructions are most commonly caused by adhesions.

Hernia complications include small bowel entrapment (incarceration) and bowel ischemia (strangulation).

Hernias may cause small bowel obstruction. However, small bowel obstructions are most commonly caused by adhesions.

Hernia complications include small bowel entrapment (incarceration) and bowel ischemia (strangulation).

**TABLE 9-17 The Inguinal Canal**

<table>
<thead>
<tr>
<th>Border</th>
<th>Anatomic Composition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Superior</td>
<td>Falx inguinalis: internal abdominal oblique (IAO) and transversus abdominis muscles</td>
</tr>
<tr>
<td>Inferior</td>
<td>Inguinal ligament</td>
</tr>
<tr>
<td>Anterior</td>
<td>External abdominal oblique (EAO) aponeurosis; IAO and transversus abdominis muscles laterally</td>
</tr>
<tr>
<td>Posterior</td>
<td>Transversalis fascia; falx inguinalis medially</td>
</tr>
</tbody>
</table>
Dermatology

II. Hernias (Table 9-18)

<table>
<thead>
<tr>
<th>Hernia</th>
<th>Pathology</th>
<th>Clinical Features</th>
<th>Diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Direct inguinal</td>
<td>Parietal peritoneum passes directly through the abdominal wall (through the Hesselbach triangle)</td>
<td>More common in older males</td>
<td>Medial to inferior epigastric artery; located above pubic tubercle</td>
</tr>
<tr>
<td>Indirect inguinal</td>
<td>Parietal peritoneum passes through the internal inguinal ring and follows the inguinal canal; failure of the processus vaginalis to close properly</td>
<td>Most common type; occurs in young adult males more frequently than in females</td>
<td>Lateral to inferior epigastric artery; located above and medial to pubic tubercle; hernia sac may enter the scrotum in males</td>
</tr>
<tr>
<td>Femoral hernia</td>
<td>Parietal peritoneum passes through the femoral canal</td>
<td>More common in older females</td>
<td>Located below and lateral to pubic tubercle</td>
</tr>
</tbody>
</table>

A lack of pigment, such as in albinism, predisposes one to a variety of skin disorders, including actinic keratosis, basal cell carcinoma, squamous cell carcinoma, and malignant melanoma.

I. Skin (Figure 9-9)

A. Stratum basale is actively mitotic and gives rise to the other four layers.
B. Epidermis forms from ectoderm and dermis forms from mesoderm.
C. Melanocytes contain melanin pigment and are derived from neural crest.
D. Skin renews every 2 to 3 weeks.
E. Function
   1. Barrier to infection
   2. Thermoregulation
   3. Protection from desiccation
F. Two types of skin
   1. Thick skin (e.g., palms and soles of feet)
      a. Stratum basale (deepest layer)
      b. Stratum spinosum
      c. Stratum granulosum
      d. Stratum lucidum
      e. Stratum corneum (most superficial layer)
   2. Thin skin (e.g., face, genitalia, and back of hands): stratum lucidum is absent in thin skin (although it has all the other layers).
II. Skin disorders (Table 9-19)

Skin disorders are often characterized by pruritus, inflammation, and irritability. Skin lesions that are suggestive of malignancy demonstrate asymmetry, irregular borders, variations in color, and increasing size.

- Skin Cancers (Table 9-20)

<table>
<thead>
<tr>
<th>TABLE 9-19 Skin Disorders</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Disorder</strong></td>
</tr>
<tr>
<td>Keloid scarring</td>
</tr>
<tr>
<td></td>
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<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Xanthomas</td>
</tr>
<tr>
<td></td>
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<tr>
<td></td>
</tr>
<tr>
<td>Verrucae</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Seborrhoeic keratosis</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Actinic keratosis</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Albinism</td>
</tr>
<tr>
<td></td>
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<tr>
<td></td>
</tr>
<tr>
<td>Vitiligo</td>
</tr>
<tr>
<td>Melasma</td>
</tr>
<tr>
<td>Acanthosis nigricans</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Hemangiomas</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Psoriasis</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Atopic dermatitis (eczema)</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Disorder</td>
</tr>
<tr>
<td>--------------------------</td>
</tr>
</tbody>
</table>
| Squamous cell carcinoma  | - Malignant tumor of the skin associated with excessive exposure to sunlight (UV rays) leading to DNA damage, immunosuppression, or xeroderma pigmentosum  
|                          | - Rarely metastasizes  
|                          | - Characterized by ulcerated, scaling nodules  
|                          | - Appears microscopically as islands of neoplastic cells with *whorls of keratin* ("pearls") and cells with atypical nuclei at all levels of the epidermis |
| Basal cell carcinoma     | - *Most common skin tumor*  
|                          | - Appears grossly as a pearl-like papule on sun-exposed areas  
|                          | - Appears histologically as a dark cluster with *palisading peripheral cells*  
|                          | - Almost never metastasizes but can cause local invasive tissue destruction |
| Malignant melanoma       | - Aggressive tumor that arises from melanocytes (neural crest origin)  
|                          | - Associated with excess exposure to sunlight, immunosuppression, and xeroderma pigmentosum  
|                          | - Associated with the S-100 tumor marker  
|                          | - Two growth patterns:  
|                          |   - *Benign radial manner* (growth within skin layer)  
|                          |   - *Aggressive vertical manner* (growth through deeper layers) |

UV, ultraviolet.

USE ABCDE to identify nevi at higher risk for melanoma:  
**A** symmetry, **B** order irregular, **C**olor irregular, **D**iameter greater than 0.5 cm, **E**levation irregular.

**Mnemonic**  
*ME*lanoma is more likely to *ME*tastasize. Basal and squamous cell carcinoma hardly ever metastasize.
I. Red blood cell basics

A. Red blood cell (RBC) structure
   1. Lack a nucleus and organelles (more room for hemoglobin)
   2. Biconcave disc shape increases surface area (more efficient gas exchange)
   3. Spectrin: cytoskeletal protein that provides flexibility and maintains biconcavity
      a. High flexibility allows for easier movement through narrow vessels.
      b. Loss of biconcavity (e.g., sickle cell, spherocytosis) can result in hyperviscosity of blood or fragility of RBCs.

B. RBC respiration
   1. Glycolysis is the sole source of energy for RBCs because they lack mitochondria.
   2. 90% of glucose in RBCs enters glycolysis, whereas the remaining 10% enters the hexose monophosphate shunt.
   3. A deficiency of glycolytic enzymes (e.g., pyruvate kinase deficiency) leads to hemolysis and anemia.

C. Blood groups
   1. ABO: Defined by the presence or absence of A and B surface antigens (Table 10-1).
   2. Rh: Another RBC surface antigen. Blood is classified as Rh positive (Rh+) or Rh negative (Rh−).
   3. Erythroblastosis fetalis: Occurs when maternal anti-Rh IgG antibodies cross the placenta and bind Rh expressed on the fetal RBCs, leading to fetal hemolysis, jaundice, kernicterus, hydrops fetalis, and intrauterine death.
      a. Only occurs in an Rh− mother carrying an Rh+ fetus, when exposure to fetal Rh leads to the development of anti-Rh antibodies.
      b. Small numbers of RBCs may enter maternal circulation during pregnancy. More commonly, fetal RBCs enter maternal circulation during birth, when the placenta separates from the uterine wall.

<table>
<thead>
<tr>
<th>Group</th>
<th>Surface Antigen</th>
<th>Plasma Antibodies</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>A</td>
<td>Anti-B</td>
<td></td>
</tr>
<tr>
<td>B</td>
<td>B</td>
<td>Anti-A</td>
<td></td>
</tr>
<tr>
<td>AB</td>
<td>A and B</td>
<td>Neither anti-A nor anti-B</td>
<td>“Universal recipient” of RBCs</td>
</tr>
<tr>
<td>O</td>
<td>Neither A nor B</td>
<td>Anti-A and anti-B</td>
<td>“Universal donor” of RBCs</td>
</tr>
</tbody>
</table>

QUICK HIT
There are more than 50 different Rh antigens. The classification of blood as Rh+ or Rh− is always in reference to Rh0, which is the most immunogenic of the Rh factors.

QUICK HIT
Antibodies against A or B antigen develop from an immune response to cross-reactive bacterial antigens in the gut. Immune mechanisms of tolerance prevent the development of these antibodies if the corresponding human antigen is expressed on RBCs.

QUICK HIT
RBCs have an average life span of 120 days.

QUICK HIT
There are more than 50 different Rh antigens. The classification of blood as Rh+ or Rh− is always in reference to Rh0, which is the most immunogenic of the Rh factors.
<table>
<thead>
<tr>
<th>Form</th>
<th>Seen in</th>
</tr>
</thead>
</table>
| Acanthocytes (spur cells): RBCs with irregular spikes | • Liver disease  
• Abetalipoproteinemia |
| Echinocytes (burr cells): RBCs with smaller, regular spikes | • Uremia  
• Asplenia |
| Elliptocytes: Elliptical-shaped RBCs | Hereditary elliptocytosis |
| Macro-ovalocytes: Very large RBCs | Megaloblastic anemia |
| Ringed sideroblasts: RBC precursors with rings of iron granules around the nuclei (visible with Prussian blue stain), found in the bone marrow, not peripheral blood | Sideroblastic anemia (defect in heme synthesis that inhibits the use of iron) |
| Schistocytes (helmet cells): Fragmented RBCs | Microangiopathic and macroangiopathic hemolysis |

(continued)
<table>
<thead>
<tr>
<th>Form</th>
<th>Seen in</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sickle cells:</strong> Sickle-shaped RBCs</td>
<td>Sickle cell disease</td>
</tr>
</tbody>
</table>
| **Spherocytes:** Small, spherical RBCs with no central pallor | • Hereditary spherocytosis  
• Warm autoimmune hemolytic anemia |
| **Degmacytes:** Teardrop-shaped RBCs | Myelofibrosis                                |
| **Target cells:** RBCs resemble targets. Hemoglobin is seen in the center, surrounded by an area of pallor. | • Thalassemia  
• Hemoglobin C disease  
• Asplenia  
• Liver disease  
Caused by decreased ratio of hemoglobin to cell volume (may be due to either a decrease in hemoglobin or an increase in cell volume) |
| **Degmacytes (bite cells):** RBC appears to have a bite taken out of it, resulting from macrophage digestion of part of the RBC in the spleen. | May be seen in G6PD deficiency, when splenic macrophages remove Heinz bodies from RBCs |
| **Heinz bodies:** Aggregates of precipitated hemoglobin in the cytoplasm due to oxidation of iron (visible only using a special Heinz body preparation) | Seen in G6PD deficiency, in which cells cannot generate reducing agents through the HMP shunt, rendering heme susceptible to oxidation |
TABLE 10-2  Pathologic Red Blood Cell Forms (Continued)

<table>
<thead>
<tr>
<th>Form</th>
<th>Seen in</th>
</tr>
</thead>
<tbody>
<tr>
<td>Basophilic stippling: Small clumps of denatured RNA visible in RBC cytoplasm</td>
<td>Thalassemia, Anemia of chronic disease, Iron deficiency, Lead poisoning</td>
</tr>
<tr>
<td>Howell-Jolly bodies: Remnants of the nucleus that are still present in RBCs. Normally removed by macrophages in the spleen.</td>
<td>Asplenia</td>
</tr>
</tbody>
</table>

- Howell-Jolly bodies: Remnants of the nucleus that are still present in RBCs. Normally removed by macrophages in the spleen seen in Asplenia.

G6PD, glucose-6-phosphate dehydrogenase; HMP, hexose monophosphate; RBC, red blood cell.


II. Erythropoiesis

A. Prenatal erythropoiesis
   1. Hematopoiesis begins in the yolk sac (gestational age 3 to 8 weeks).
   2. Hematopoiesis then continues in the liver and spleen throughout much of fetal development.
   3. Hematopoiesis shifts to the bone marrow beginning at 28 weeks.

B. Postnatal erythropoiesis
   1. In infancy and childhood, hematopoiesis occurs in both flat bones (sternum, pelvis, cranium, vertebrae) and the long bones of the leg (tibia and femur).
2. In adulthood, hematopoiesis occurs mainly in the flat bones of the axial skeleton (vertebrae, sternum, ribs, pelvis).

C. Hemoglobin
1. Hemoglobin is made up of four globin peptide chains with an iron-containing heme molecule attached to each globin chain.
2. Hemoglobin variants are made up of different pairings of globin chains (Table 10-3).
   a. Hemoglobin A is made up of two α chains and two β chains, whereas fetal hemoglobin (hemoglobin F) is made up of two α chains and two γ chains.
   b. The γ chains have lower affinity for 2,3-diphosphoglycerol (2,3-DPG) and a higher affinity for O₂ compared to β chains. This allows for oxygen exchange from maternal hemoglobin to fetal hemoglobin across the placenta.

D. Heme synthesis (Figure 10-1)
1. The rate-limiting step is the conversion of glycine and succinyl CoA to δ-aminolevulinic acid (ALA) by ALA synthase, a reaction that requires vitamin B₆.
2. Deficiencies in enzymes in the heme synthesis pathway can result in specific diseases.
   a. Acute intermittent porphyria
      i. Deficiency of uroporphyrinogen I synthase (also known as porphobilinogen deaminase) resulting in ineffective heme synthesis and accumulation of porphobilinogen in the cytoplasm.
      ii. May be due to genetic factors or triggered by drugs (e.g., barbiturates, antiepileptic medications, rifampin, or metoclopramide).
      iii. Presentation: Neuropathic abdominal pain, dark red urine (“port wine urine”), polyneuropathy, psychological disturbances.
      iv. Labs: elevated urine porphobilinogen, elevated urine porphyrins
      v. Treatment: Give glucose and hematin to inhibit ALA synthase.
   b. Porphyria cutanea tarda
      i. Deficiency of uroporphyrinogen decarboxylase, resulting in ineffective heme synthesis and accumulation of proporphyrinogen in the cytoplasm.
      ii. This is the most common form of porphyria and is strongly associated with hepatitis C and alcoholism.
      iii. Presentation: Blistering (Figure 10-2), photosensitivity, facial hyperpigmentation, hypertrichosis, tea-colored urine
      iv. Labs: Elevated urine porphyrin, elevated aminotransferases
      v. Treatment: Avoidance of sunlight, cessation of alcohol and tobacco, phlebotomy, low-dose chloroquine phosphate
c. Lead poisoning
   i. Lead interferes with ALA dehydratase and ferrochelatase. Thus, lead poisoning mimics many symptoms of porphyria.
   ii. Lead poisoning is common in children exposed to lead dust from lead paint and adults with occupational lead exposure.
iii. **Presentation:** Global encephalopathy (learning disabilities, memory loss, delirium), peripheral neuropathy (foot drop, wrist drop), gingival lead lines, abdominal colic, renal failure.

iv. **Studies:** Microcytic anemia, basophilic stippling of RBCs, lead lines on x-rays of long bones.

v. **Treatment:** If chelation therapy is needed, ethylenediaminetetraacetic acid (EDTA) or succimer may be used in children or adults. In children with severe lead toxicity, use dimercaprol plus succimer.

### ANEMIA

#### I. Microcytic anemias

A. **Classification**

1. **Microcytes** are defined as RBCs with a mean corpuscular volume (MCV) less than 80 femtoliters (fL) in adults.
2. Microcytic anemias are the result of a deficit of hemoglobin.
3. **Microcytosis** is thought to result from increased division of RBC precursors in the bone marrow in order to reach a specific intracellular hemoglobin concentration.

B. **Iron deficiency anemia**

1. **Causes:**
   a. In U.S. adults and adolescents, **chronic blood loss** is the most common cause. (In U.S. children, excess intake of cow's milk with poor intake of iron-rich foods is most common.)
   b. In underdeveloped countries, poor iron intake is often the cause.
   c. In pregnancy, maternal iron stores may be inadequate for both the mother and the fetus, resulting in iron deficiency anemia.
2. **Presentation:** Fatigue, weakness, pallor, dyspnea, pica (desire to consume nonnutritive materials, especially ice), koilonychia (spooning of the nails)
3. **Labs:** Microcytic hypochromic anemia, decreased serum iron, decreased ferritin, increased transferrin, decreased percent transferrin saturation
4. **Treatment:** Iron supplementation, treatment of underlying etiology

C. **α-Thalassemia**

1. Autosomal recessive deficiency of α-globin chains that results in impaired hemoglobin production and abnormal hemoglobin forms.
   a. More prevalent among persons of African and Asian descent
   b. The severity of clinical presentation depends on the number of functional copies of the α-globin gene. There are four α-globin genes: two on each copy of chromosome 16 (Table 10-4).
2. **Presentation:** Fatigue, weakness, pallor, dyspnea, jaundice, hepatosplenomegaly (rare)
3. **Labs:** Microcytic anemia, increased reticulocytes, target cells
4. **Treatment:** Folate supplementation, transfusion (severe cases), bone marrow transplantation (severe cases)

D. **β-Thalassemia**

1. Deficiency of the β-globin chains that results in impaired hemoglobin production and abnormal hemoglobin forms.
   a. More prevalent among persons of Mediterranean and southern Asian descent
   b. The severity of clinical presentation depends on the number of functional copies of the β-globin gene. There are two β-globin genes: one on each copy of chromosome 11 (see Table 10-4).
2. **Presentation:** Minor—often asymptomatic; major—fatigue, weakness, pallor, jaundice, facial anomalies (“chipmunk facies”), hepatosplenomegaly
3. **Labs:** Microcytic anemia, increased reticulocytes, target cells, increased hemoglobin F, hemosiderosis, “hair-on-end” appearance on cranial x-ray (due to marrow expansion) (Figure 10-3)
4. **Treatment:** Transfusion, iron chelation, stem cell transplantation, splenectomy
TABLE 10-4  Variants of α- and β-Thalassemias

<table>
<thead>
<tr>
<th>Thalassemia Type</th>
<th>Variant</th>
<th>Number of Abnormal Genes</th>
<th>Characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>α</td>
<td>α-Thalassemia minima (silent carriers)</td>
<td>1</td>
<td>Generally asymptomatic; children of carriers at increased risk for thalassemia, pending genotype of other parent</td>
</tr>
<tr>
<td></td>
<td>α-Thalassemia trait</td>
<td>2</td>
<td>Reduced α-globin production; mild anemia; microcytic RBCs and target cells on blood smear</td>
</tr>
<tr>
<td></td>
<td>Hemoglobin H disease</td>
<td>3</td>
<td>Minimal α-globin production; chronic hemolytic anemia, pallor, splenomegaly; microcytic RBCs on blood smear; hemoglobin H in blood</td>
</tr>
<tr>
<td></td>
<td>Hydrops fetalis</td>
<td>4</td>
<td>Hemoglobin Bart’s (no α-globin production); fetal death occurs</td>
</tr>
<tr>
<td>β</td>
<td>β-Thalassemia minor</td>
<td>1</td>
<td>Reduced β-globin production, mild anemia, increase in hemoglobin A2, patients can lead normal lives; transfusions may be needed during periods of stress</td>
</tr>
<tr>
<td></td>
<td>β-Thalassemia major</td>
<td>2</td>
<td>No β-globin production; asymptomatic until decline of fetal hemoglobin; growth retardation, developmental delays, bony abnormalities, hepatosplenomegaly, anemia; increase in hemoglobin A2 and F; microcytic RBCs on blood smear; patients die in childhood without transfusions</td>
</tr>
</tbody>
</table>

RBCs, red blood cells.

E. Sideroblastic anemia
1. Microcytic anemia due to a defect of heme synthesis that leads to accumulation of iron in RBC precursors called “ringed sideroblasts.”
2. Ringed sideroblasts are nucleated RBC precursors in which the nucleus is surrounded by a ring of iron granules, seen on Prussian blue stain. These are found in the bone marrow but not in the peripheral blood.

FIGURE 10-3  β-Thalassemia

Lateral skull. Note the hair-on-end appearance that is the result of diploic erythroid hyperplasia. (From Yochum TR, Rowe LJ. Yochum and Rowe’s Essentials of Skeletal Radiology, 3rd ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2004. Used by permission of Wolters Kluwer Health/Lippincott Williams & Wilkins.)
3. Sideroblastic anemia may be due to one of several genetic defects (most commonly X-linked), alcohol abuse, or various drugs (isoniazid, chloramphenicol, linezolid).

4. Labs: Microcytic anemia, elevated serum iron, elevated ferritin, decreased transferrin, elevated transferrin saturation

5. Treatment: Treatment of underlying disease; vitamin B₆ supplementation (cofactor for ALA synthase)

F. Anemia of chronic disease (AOCĐ) (see p. 263) typically results in normocytic anemia but may cause microcytic hypochromic anemia if allowed to continue long enough. AOCĐ may be distinguished from iron deficiency using iron studies (Table 10-5).

II. Macrocytic anemias

A. Classification

1. Macrocytes are defined as RBCs with an MCV greater than 100 fl.

2. Megaloblastic anemia: Macrocytic anemia due to impaired DNA synthesis (most commonly due to vitamin B₁₂ or folate deficiency), which increases the time needed for RBCs to mature, allowing RBCs to grow larger before leaving the marrow.

3. Nonmegaloblastic anemia: Macrocytic anemia due to causes other than impaired DNA synthesis (e.g., liver disease, alcoholism, 5-fluorouracil, zidovudine, hydroxyurea)

B. Folate deficiency

1. Folate is normally converted to tetrahydrofolate, a carbon donor in purine synthesis. Folate deficiency impairs DNA synthesis and results in megaloblastic anemia.

2. Folate deficiency can result from malnutrition (especially in alcoholism), malabsorption, and drugs that interfere with folic acid metabolism (e.g., methotrexate, trimethoprim). Chronic hemolytic anemia (e.g., liver disease, alcoholism, 5-fluorouracil, zidovudine, hydroxyurea) and pregnancy increase folate requirements and may lead to folate deficiency.

3. Presentation: Fatigue, weakness, pallor, glossitis, peripheral neuropathy, dementia

C. Vitamin B₁₂ deficiency

1. Vitamin B₁₂ is normally used to regenerate tetrahydrofolate, which is required for purine synthesis.

2. Vitamin B₁₂ deficiency can result from malnutrition, alcoholism, malabsorption, pernicious anemia, Crohn disease, and rarely *Diphyllolobothrium latum* (fish tape worm) infection.

3. Presentation: Fatigue, weakness, pallor, glossitis, peripheral neuropathy, dementia

### Table 10-5 Interpretation of Iron Studies

<table>
<thead>
<tr>
<th></th>
<th>Iron-deiciency Anemia</th>
<th>Anemia of Chronic Disease</th>
<th>Sideroblastic Anemia</th>
<th>Hemochromatosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum iron</td>
<td>Low</td>
<td>Low</td>
<td>High</td>
<td>High</td>
</tr>
<tr>
<td>Serum ferritin</td>
<td>Low</td>
<td>High</td>
<td>High</td>
<td>High</td>
</tr>
<tr>
<td>TIBC</td>
<td>High</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
</tr>
<tr>
<td>% Transferrin saturation</td>
<td>Low (&lt;12%)</td>
<td>Normal (&gt;18%)</td>
<td>High</td>
<td>High</td>
</tr>
</tbody>
</table>

TIBC, total iron binding capacity.
4. Labs: Macrocytic anemia, hypersegmented neutrophils, elevated homocysteine, elevated methylmalonic acid
5. Treatment: Vitamin B₁₂ supplementation

D. Orotic aciduria is caused by a genetic defect of UMP synthase, an enzyme involved in pyrimidine biosynthesis, resulting in megaloblastic anemia. (See p. 280, Chapter 11)
E. Nonmegaloblastic macrocytosis (with or without anemia) may result from alcohol use or liver disease.
1. Alcohol is directly toxic to bone marrow. (Alcohol abuse can also lead to folate and vitamin B₁₂ deficiency and the resultant megaloblastic anemia.)
2. Liver disease may lead RBCs to absorb circulating phospholipids and cholesterol, leading to macrocytosis and the formation of target cells.

III. Nonhemolytic normocytic anemias
A. Anemia of chronic disease
1. Anemia seen with a concurrent inflammatory state. Chronic inflammation causes production of hepcidin from the liver, which inhibits ferroportin and prevents release of iron stores from macrophages.
2. Labs: Normocytic anemia (microcytic, hypochromic anemia in advanced cases), decreased serum iron, normal or elevated ferritin, decreased transferrin
3. Treatment: Treat underlying chronic disease
4. Nonhemolytic anemia: Failure or destruction of the bone marrow results in a decrease in RBCs.
B. Aplastic anemia
1. Failure or destruction of the bone marrow, normally accompanied by fatty infiltration.
2. Causes include exposures (radiation, anticancer drugs, chloramphenicol), viral infection, and congenital marrow failure syndromes such as Fanconi anemia. Idiopathic aplastic anemia is among the most commonly identified.
3. Presentation: Fatigue, weakness, pallor, malaise, purpura, mucosal bleeding, petechiae, and infections
4. Labs: Leukopenia, thrombocytopenia, neutropenia. Bone marrow space may be infiltrated with adipocytes (Figure 10-4).

**Figure 10-4** Aplastic Anemia

A. Normal bone marrow. B. Bone marrow in aplastic anemia. Few bone marrow cells are present. Most of the tissue shown is fat. (From McConnell TH. The Nature of Disease Pathology for the Health Professions. Philadelphia, PA: Wolters Kluwer Health | Lippincott Williams & Wilkins; 2007. Used with permission.)
5. **Treatment:** Treatments differ depending on the underlying etiology and may include removal of the offending agent, immunosuppressants, transfusions, or granulocyte colony-stimulating factor (G-CSF)/granulocyte-macrophage colony-stimulating factor (GM-CSF) to stimulate bone marrow. In severe cases, bone marrow transplant is indicated.

### IV. Hemolytic normocytic anemias

#### A. Classification

1. **Hemolytic anemia** is the result of premature destruction or death of the RBCs themselves.

2. Hemolytic anemias can be further classified based on the site of RBC destruction and the nature of the underlying cause:
   - **Intravascular versus extravascular hemolysis:** RBCs may be lysed within the blood vessels, causing hemoglobinuria and a decrease in free haptoglobin, or at a site other than the blood vessels (e.g., the spleen), causing an increase in unconjugated bilirubin.
   - **Intrinsic versus extrinsic hemolysis:** RBC lysis may either be due to a defect intrinsic to the RBCs themselves or due to something external to the RBCs.

#### B. Extrinsic hemolysis

1. **Microangiopathic anemia**—Mechanical destruction of RBCs as they pass through the lumina of obstructed/narrowed vessels. Commonly due to inappropriate intravascular activation of the coagulation system, forming intraluminal fibrin strands that rupture RBCs as they pass through the partially occluded vessels.
   - May be seen in disseminated intravascular coagulation (DIC), thrombotic thrombocytopenic purpura (TTP), hemolytic uremic syndrome (HUS), malignant hypertension
   - Labs: Schistocytes (fragmented RBCs) seen on peripheral smear
2. **Macroangiopathic anemia**—Mechanical destruction of RBCs in larger vessels due to shear forces from mechanical heart valves or rarely aortic stenosis
3. **Infections** such as malaria (*Plasmodium* species) or babesiosis (*Babesia* species) results in rupture of infected RBCs.
4. **Autoimmune hemolytic anemia**—Autoantibodies bind to red cells and trigger hemolysis through activation of complement
   - **Cold agglutinins**—IgM antibodies, which bind to RBCs more readily at lower temperatures, leading to aggregation (agglutination) of RBCs at lower temperatures. (See Figure 10-4.) RBCs are then hemolyzed by complement or destroyed in the spleen.
     - Associated with *Mycoplasma pneumoniae* infection, infectious mononucleosis, and certain malignancies (e.g., chronic lymphocytic leukemia [CLL])
     - **Presentation:** Fatigue, pallor, pain in fingers and toes, acrocyanosis, purple discoloration of extremities
     - **Labs:** Positive Coombs’ test, hemoglobinuria, ↑ reticulocytes, ↑ IgM (possibly), spherocytes (rare)
     - **Treatment:** Avoidance of cold temperatures, folic acid supplementation, treatment of underlying cause
   - **Warm agglutinins**—IgG antibodies, which bind to RBCs and normal body temperature, leading to agglutination of RBCs and hemolysis (similar to cold agglutinins)
     - More common than cold agglutinins
     - Associated with Epstein-Barr virus (EBV), HIV, systemic lupus erythematosus, CLL, non-Hodgkin lymphoma, and certain congenital immune abnormalities
     - Coombs’ test gives a positive result.
     - **Presentation:** Fatigue, weakness, pallor, jaundice, fever, abdominal pain, splenomegaly
     - **Labs:** Positive Coombs’ test, ↑ reticulocytes, spherocytes, Howell-Jolly bodies, hemoglobinuria

#### QUICK HIT

Haptoglobin binds free hemoglobin in circulation for the purpose of recycling. In intravascular hemolysis, haptoglobin will bind free hemoglobin from the lysed RBCs. These haptoglobin-hemoglobin complexes are removed from circulation, leading to the characteristic drop in circulating haptoglobin.
vi. **Treatment:** Folic acid supplementation, steroids, splenectomy, transfusion, treatment of underlying cause

C. Intrinsic hemolysis (Table 10-6)

### TABLE 10-6 Intrinsic Causes of Hemolytic Anemia

<table>
<thead>
<tr>
<th>Condition</th>
<th>Etiology</th>
<th>Clinical Features</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hereditary spherocytosis</td>
<td>Deficiency of RBC cytoskeletal proteins (e.g., ankyrin, spectrin) causes loss of biconcavity and formation of spherocytes, which are then destroyed by the spleen.</td>
<td>Spherocytosis, anisocytosis, splenomegaly, ↑ MCHC, ↑ RDW. Parvovirus B19 infection can cause aplastic crisis.</td>
<td>Splenectomy</td>
</tr>
<tr>
<td>Paroxysmal nocturnal</td>
<td>RBCs lack CD55 and CD59, which normally inhibit the function of the alternative complement attack complex on the surface of the RBC. Lack of CD55 and CD59 results in complement-mediated lysis of RBCs.</td>
<td>Triad of hemolytic anemia, pancytopenia, and venous thrombosis. Fever, abdominal pain, hemoglobinuria, ↓ leukocyte alkaline phosphatase. Diagnosed by flow cytometry.</td>
<td>Eculizumab (inhibits alternative complement complex), steroids, iron supplementation, stem cell transplantation</td>
</tr>
<tr>
<td>hemoglobinuria</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sickle cell disease</td>
<td>Mutation in /β-globin genes leads to glutamic acid → valine substitution, and formation of hemoglobin S, which can polymerize within the RBC. This distorts the RBCs into a sickle shape and decreases flexibility. Hypoxia, dehydration, and physiologic stress may exacerbate sickling and may trigger acute pain crises. Individuals who are homozygous for the hemoglobin S mutation have sickle cell anemia, as described here. Heterozygotes are said to have “sickle trait,” a benign, subclinical condition seen in about 8% of African Americans.</td>
<td>• Jaundice, fever, dactylitis, acute abdomen, vaso-occlusive disease, renal papillary necrosis • Autosplenectomy generally occurs by age 3–4. • Increased susceptibility to Salmonella osteomyelitis • Parvovirus B19 can lead to aplastic crisis. • ↑ Reticulocytes, ↑ hemoglobin F, “hair-on-end” appearance on x-ray of the skull</td>
<td>Hydroxyurea stimulates the production of hemoglobin F. Hematopoietic stem cell transplantation may be indicated in severe cases.</td>
</tr>
<tr>
<td>Hemoglobin C disease</td>
<td>Mutation in /β-globin causes intracellular hemoglobin polymerization into hexagonal crystals</td>
<td>Homozygotes have mild microcytic hemolytic anemia, splenomegaly, and gallstones; heterozygotes are asymptomatic.</td>
<td>Iron and/or folate supplementation</td>
</tr>
<tr>
<td>G6PD deficiency</td>
<td>Impairment in HMP shunt decreases reduction of glutathione, sensitizing cells to oxidative damage</td>
<td>Oxidized hemoglobin forms Heinz bodies within the RBCs. Macrophages in the spleen detect these abnormal RBCs and phagocytose the Heinz bodies, resulting in formation of degmacytes (“bite cells”).</td>
<td>Avoidance of foods/drugs that cause oxidative stress (dapsone, primaquine, fava beans, etc.)</td>
</tr>
<tr>
<td>Pyruvate kinase deficiency</td>
<td>Impairment of glycolysis prevents ATP production and inability to operate ATP-dependent ion pumps. Swelling of RBCs and loss of biconcavity leads to destruction in spleen.</td>
<td></td>
<td>Transfusion, vitamin B12, and folate supplementation, splenectomy</td>
</tr>
</tbody>
</table>

**Notes:**
- ATP, adenosine triphosphate; G6PD, glucose-6-phosphate dehydrogenase; HMP, hexose monophosphate; MCHC, mean corpuscular hemoglobin concentration; RBCs, red blood cells; RDW, red cell distribution width

---

I. **Normal hemostasis**

A. Overview

1. Hemostasis halts blood loss following an injury.
2. Hemostasis can be divided into two phases: formation of a **platelet plug** (primary hemostasis), followed by formation of a **fibrin clot** by the coagulation cascade (secondary hemostasis).
3. After the underlying tissue is repaired, the clot is broken down.
B. Platelets

1. Platelet basics
   a. Tiny, anucleate cells with a variety of organelles and surface receptors, with a life span of 7 to 10 days
   b. Formed by budding off of megakaryocytes in the bone marrow
   c. The normal concentration of platelets is 150,000 to 450,000 cells/μL of blood.

2. Platelet stimulation—Vascular endothelial injury leads to a three-step process of platelet adhesion, followed by platelet activation, followed by platelet aggregation to form a platelet plug (Figure 10-5).
   a. Adhesion: Endothelial cells secrete von Willebrand factor (vWF) into the subendothelium. Damage to the endothelium exposes vWF, which binds to subendothelial collagen and then to glycoprotein Ib (GpIb) on platelets.
   b. Activation: The binding of vWF signals platelets to change shape and form pseudopods (long, fingerlike extensions that assist in aggregation) and to secrete a number of factors, including:
      - Thromboxane A2
      - Platelet-derived growth factor
      - Serotonin
      - Fibrinogen
      - Lysosomal enzymes
      - ADP
      - Calcium
      - Thrombin
   c. Aggregation: Thromboxane A2 and ADP trigger expression of glycoprotein IIb/IIIa (GpIIb/IIIa) on the surface of the platelets. GpIIb/IIIa then binds circulating fibrinogen, forming cross-links between neighboring platelets and resulting in the platelet plug.

3. Platelet promotion of thrombogenesis—Several platelet-secreted factors are important for subsequent formation of the fibrin clot:
   a. Fibrinogen from platelets is converted to fibrin by the coagulation cascade.
   b. Thrombin converts fibrinogen to fibrin and also activates factors V, VIII, and XI.
   c. Calcium is an important cofactor for many steps in the coagulation cascade.

C. Coagulation cascade (Figure 10-6)

1. Coagulation pathways
   a. The tissue factor pathway is the main pathway for initiation of coagulation.
   b. The contact activation pathway then amplifies and maintains coagulation (although it can potentially initiate coagulation).
HEMATOLOGY

The two pathways subsequently converge into a single common pathway, resulting in formation of a fibrin clot.

2. Tissue factor pathway (extrinsic pathway)
   a. Tissue factor (thromboplastin) is found on the surface of subendothelial cells.
   b. Endothelial injury exposes subendothelial cells. Tissue factor then interacts with circulating factor VII.
   c. Factor VII is converted to its active form, factor VIIa, which converts factor X to its active form, factor Xa.
   d. Factor Xa initiates a signaling cascade that results in the cross-linking of fibrin, thus forming the fibrin clot via the common pathway.
   e. Prothrombin time (PT): A measure of the clotting time via the tissue factor pathway in a blood sample.
   f. International normalized ratio (INR): Ratio of the PT for a patient's sample to the PT for a reference sample, corrected for differences in reagents and testing systems. This is a standardized measure of the tissue factor pathway.

3. Contact activation pathway (intrinsic pathway)
   a. Circulating factor XII is activated to factor XIIa upon contact with negatively charged surfaces, such as subendothelial collagen (hence the name "contact activation pathway").
   b. Factor XIIa initiates a cascade that converts factor XI to factor Xa, followed by conversion of factor IX to factor IXa.
   c. Factor IXa, along with factor VIIIa, activates factor X to factor Xa.
   d. Factor Xa initiates a signaling cascade that results in the cross-linking of fibrin, thus forming the fibrin clot via the common pathway.
   e. Partial thromboplastin time (PTT): A measure of the clotting time via the contact activation pathway in a blood sample.

4. Regulation of coagulation
   a. The rate-limiting step occurs at factor X, where the tissue factor pathway and the contact activation pathway converge.
   b. Factor V and factor VIII are known as accelerating factors because they are part of a positive feedback loop along with thrombin (thrombin converts both factors V and VIII to their active forms, which leads to more thrombin, which converts more factors V and VIII, etc.)
c. **Protein C** and **protein S** are anticoagulants. Together, they inactivate **factor Va** and **factor VIIIa**.

d. **Antithrombin**: Inhibits **thrombin**, preventing the formation of fibrin monomers from fibrinogen. It is synthesized in the liver.

e. **Kallikrein**: Converted from **prekallikrein** by factor XIIa. Kallikrein converts **plasminogen** to **plasmin**, which is thrombolytic (breaks down clots).

5. **Coagulation and inflammation**
   a. Coagulation and inflammation promote each other.
   b. **Bradykinin**: Kallikrein converts high-molecular-weight kinin (HMWK) to **bradykinin**, which promotes inflammation by causing vasodilation and increasing vascular permeability.
   c. HMWK is also a cofactor for the conversion of factor XII to factor XIIa in the contact activation pathway.
   d. Inflammatory cytokines make blood vessels more thrombogenic (e.g., increasing the expression of tissue factor).
   e. Plasmin, in addition to breaking down clots, can also activate the complement cascade.

II. **Disorders of hemostasis**

A. **Classification**
   1. Bleeding disorders may involve the coagulation cascade, platelet plug formation, or both.

a. Platelet disorders are generally associated with microhemorrhages (e.g., petechiae, epistaxis, easy bruising). Bleeding time will generally be elevated because platelet plug formation is the first step in hemostasis (Table 10-7).

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Etiology</th>
<th>Presentation</th>
<th>Labs</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Immune thrombocytopenic purpura (ITP)</td>
<td>Autoantibodies against GpIIb/IIa leads to destruction of activated platelets.</td>
<td>Petechiae, purpura, gingival bleeding, GI bleeding, menorrhagia, epistaxis, easy bruising</td>
<td>↓ Platelet count, ↑ BT, ↑ megakaryocytes in bone marrow</td>
<td>Steroids, IVIG, splenectomy</td>
</tr>
<tr>
<td>Thrombotic thrombocytopenic purpura (TTP)</td>
<td>Deficiency of ADAMTS-13, an enzyme that aids in the breakdown of vWF; vWF remains active and promotes platelet activation, leading to platelet consumption.</td>
<td>Purpura, petechiae; classic pentad of: • Hemolysis (microangiopathic) • Renal insufficiency • Thrombocytopenia • Neurologic symptoms • Fever</td>
<td>↓ Platelet count, ↑ BT, schistocytes</td>
<td>Repeated plasma exchange</td>
</tr>
<tr>
<td>Hemolytic uremic syndrome (HUS)</td>
<td>Excessive activation of platelets, leading to platelet consumption, similar to TTP but clinically milder; often associated with <strong>E. coli 0157:H7</strong> infection in children</td>
<td>Abdominal pain, vomiting, diarrhea, fatigue, pallor; classic triad of: • Hemolysis (microangiopathic) • Renal insufficiency • Thrombocytopenia</td>
<td>↓ Platelet count, ↑ BT, schistocytes</td>
<td>Dialysis, supportive care, avoidance of platelet transfusions. Eculizumab used is some atypical forms of HUS.</td>
</tr>
<tr>
<td>Bernard-Soulier syndrome</td>
<td>AR defect in GpIIb that impairs the binding of platelets to vWF. Platelets are larger than normal and are removed from circulation by the spleen.</td>
<td>Epistaxis, easy bruising, menorrhagia, GI bleeding</td>
<td>↓ Platelet count, ↑ BT, enlarged platelets</td>
<td>Aminocaproic acid, desmopressin (to increase vWF release), platelet transfusion</td>
</tr>
<tr>
<td>Glanzmann thrombasthenia</td>
<td>AR defect in GpIIb/IIa that impairs platelet aggregation; platelet adhesion and activation are normal.</td>
<td>Petechiae, ecchymosis, menorrhagia, epistaxis</td>
<td>Normal platelet count, ↑ BT</td>
<td>Platelet transfusion, avoidance of drugs that affect platelet function</td>
</tr>
</tbody>
</table>

**ADAMTS-13, A Disintegrin And Metalloprotease with Thrombospondin-13; AR, autosomal recessive; BT, bleeding time; GI, gastrointestinal; Gp, glycoprotein; IVIG, intravenous immunoglobulin; vWF, von Willebrand factor**

**QUICK HITS**

- **Heparin** works by potentiating the action of antithrombin.
- **Bradykinin** is degraded by angiotensin-converting enzyme (ACE). This is why ACE inhibitors can lead to increased bradykinin and may cause angioedema.
QUICK HIT

b. Coagulation disorders (coagulopathies) are generally associated with macrohemorrhages (e.g., hemarthrosis, hematemesis, hematuria). Prothrombin time (PT) and/or partial thromboplastin time (PTT) will generally be elevated (Table 10-8).

c. Mixed disorders involve both platelets and coagulation cascades (see Table 10-8).

2. Clotting disorders (hypercoagulable states) involve only the coagulation cascade (Table 10-9). Hypercoagulability is usually due to genetic defects. The condition may not manifest unless there are additional factors (e.g., drugs, trauma, malignancy, prolonged immobilization).

### Table 10-8: Coagulation Disorders and Mixed Disorders

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Etiology</th>
<th>Presentation</th>
<th>Labs</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemophilia</td>
<td>X-linked recessive deficiency in factor VII (hemophilia A) or factor IX (hemophilia B)</td>
<td>Bleeding, hemarthrosis, easy bruising</td>
<td>↑PTT, no change in PT or INR</td>
<td>Transfusion of factor VIII or IX; desmopressin (to increase vWF release) may increase the life span of factor VIII in mild hemophilia A</td>
</tr>
<tr>
<td>Vitamin K deficiency</td>
<td>Lack of vitamin K results in decreased synthesis of factors II, VII, IX, and X (as well as proteins C and S); may be seen in neonates and patients with advanced liver disease</td>
<td>Bleeding, hemarthrosis, easy bruising</td>
<td>↑PT, ↑PTT, ↑INR</td>
<td>Vitamin K supplementation</td>
</tr>
<tr>
<td>Von Willebrand disease (mixed disorder)</td>
<td>Group of diseases involving inadequate production or decreased function of vWF, resulting in ↓stability of factor VIII and ↓platelet adherence</td>
<td>Easy bruising, bleeding, menorrhagia</td>
<td>↑Bleeding time, ↑PTT, positive ristocetin cofactor assay (tests vWF function)</td>
<td>Desmopressin (increases the release of vWF from the endothelium); vWF concentrates</td>
</tr>
<tr>
<td>Disseminated intravascular coagulation (mixed disorder)</td>
<td>Widespread activation of clotting results in hypocoagulability, due to the consumption of both platelets and coagulation factors</td>
<td>Bleeding, jaundice, hematemesis, shock, multiorgan failure (liver, kidneys) respiratory failure</td>
<td>Schistocytes, ↓platelet count, ↑BT, ↑PT, ↑PTT, ↑D-dimer (fibrin split products), ↓fibrinogen (late)</td>
<td>Treatment of underlying condition, anticoagulants, plasma infusion, platelet transfusion</td>
</tr>
</tbody>
</table>

BT, bleeding time; INR, international normalized ratio; PT, prothrombin time; PTT, partial thromboplastin time; vWF, von Willebrand factor.

### Table 10-9: Hypercoagulable States

<table>
<thead>
<tr>
<th>Disease</th>
<th>Cause</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Factor V Leiden</td>
<td>Mutation in factor V, making it resistant to protein C degradation</td>
<td>Also known as activated protein C resistance (APCR)</td>
</tr>
<tr>
<td>Prothrombin G20210A mutation</td>
<td>Mutation in prothrombin, leading to its overproduction</td>
<td>Due to guanine → alanine substitution</td>
</tr>
<tr>
<td>Antithrombin deficiency</td>
<td>Decrease in functional antithrombin</td>
<td>Inability to inactivate thrombin and other coagulation factors (VIIa, IXa, Xa, XIa)</td>
</tr>
<tr>
<td>Protein C deficiency, Protein S deficiency</td>
<td>Decrease in functional protein C or S</td>
<td>Inability to degrade factors Va and Vill a</td>
</tr>
</tbody>
</table>
### III. Drug affecting hemostasis (Tables 10-10 and 10-11)

#### TABLE 10-10 Antiplatelet Drugs

<table>
<thead>
<tr>
<th>Drug</th>
<th>Mechanism of Action</th>
<th>Uses</th>
<th>Adverse Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aspirin</td>
<td>Inhibits primarily COX-1, preventing conversion of arachidonic acid into prostaglandin H₂ (a precursor of thromboxane A₂)</td>
<td>Antipyretic, analgesic, anti-inflammatory; acute MI or ACS, PCI, acute thrombotic stroke; MI prevention</td>
<td>Hemorrhage; nausea, vomiting, gastric ulceration; tinnitus; hyperventilation, respiratory alkalosis; Reye syndrome (hepatoencephalopathy, hypoglycemia)</td>
</tr>
<tr>
<td>ADP receptor inhibitors (clopidogrel, ticlopidine, ticagrelor, prasugrel)</td>
<td>Block ADP receptor on platelets, preventing GpIIb/IIIa expression</td>
<td>ACS, MI, PCI, stroke</td>
<td>Hemorrhage, diarrhea, nausea, dyspepsia, increased infection risk, chest pain, headache</td>
</tr>
<tr>
<td>GpIIb/IIIa inhibitors (abciximab, eptifibatide, tirofiban)</td>
<td>Directly inhibits GpIIb/IIIa, preventing platelet aggregation</td>
<td>ACS, PCI</td>
<td>Hemorrhage, hypotension, back pain, nausea, chest pain, vomiting</td>
</tr>
</tbody>
</table>

ACS, acute coronary syndrome; ADP, adenosine diphosphate; COX, cyclooxygenase; GpIIb/IIIa, glycoprotein IIb/IIIa; MI, myocardial infarction; PCI, percutaneous coronary intervention.

#### TABLE 10-11 Anticoagulant Drugs

<table>
<thead>
<tr>
<th>Drug</th>
<th>Mechanism of Action</th>
<th>Uses</th>
<th>Adverse Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heparin</td>
<td>Activates antithrombin, inhibiting thrombin</td>
<td>DVT, MI, PE, acute stroke; safe in pregnancy, see Table 10-12</td>
<td>Hemorrhage, bone loss, decreased bone formation, osteoporosis, HIT</td>
</tr>
<tr>
<td>Low-molecular-weight heparin (enoxaparin, dalteparin, etc.)</td>
<td>Activates antithrombin, inhibiting factor Xa</td>
<td>DVT, MI, PCI, prevention of thrombosis</td>
<td>Hemorrhage, HIT</td>
</tr>
<tr>
<td>Direct thrombin inhibitors (bivalirudin, desirudin)</td>
<td>Derivatives of hirudin, an enzyme that inhibits thrombin</td>
<td>Angioplasty, HIT</td>
<td>Hemorrhage, back pain, nausea, headache, hypotension</td>
</tr>
<tr>
<td>Direct thrombin inhibitors (argatobran, dabigatran)</td>
<td>Inhibits thrombin (not hirudin derivatives)</td>
<td>AF, angioplasty</td>
<td>GI bleeding, hematuria, chest pain, hypotension, dyspepsia, gastritis</td>
</tr>
<tr>
<td>Direct factor Xa inhibitors (rivaroxaban, apixaban)</td>
<td>Inhibits factor Xa</td>
<td>AF, DVT, PE, post-op prophylaxis in knee or hip replacement</td>
<td>Hemorrhage, GI bleeding</td>
</tr>
<tr>
<td>Warfarin</td>
<td>Inhibits epoxide reductase, which is required for vitamin K recycling; thus, warfarin inhibits the synthesis of vitamin K-dependent coagulation factors (II, VII, IV, X, protein C, protein S)</td>
<td>Chronic anticoagulation for AF, DVT, PE; contraindicated in pregnancy, see Table 10-12</td>
<td>Hemorrhage, teratogenic, transient hypercoagulability when initiated, may lead to skin necrosis</td>
</tr>
<tr>
<td>Thrombolitics (streptokinase, urokinase, alteplase)</td>
<td>Activates plasmin, thus stimulating fibrinolysis</td>
<td>ST elevation MI, acute stroke</td>
<td>Hemorrhage, hypotension, GI bleeding, fever, nausea</td>
</tr>
</tbody>
</table>

AF, atrial fibrillation; DVT, deep vein thrombosis; HIT, heparin-induced thrombocytopenia; MI, myocardial infarction; PE, pulmonary embolism.
TABLE 10-12 Comparison of Heparin and Warfarin

<table>
<thead>
<tr>
<th></th>
<th>Heparin</th>
<th>Warfarin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Route of administration</td>
<td>IV, SC</td>
<td>Oral</td>
</tr>
<tr>
<td>Pharmacokinetics</td>
<td>Rapid onset; short half-life</td>
<td>Slow onset; long half-life</td>
</tr>
<tr>
<td>Use</td>
<td>Acute/short-term anticoagulation</td>
<td>Long-term anticoagulation</td>
</tr>
<tr>
<td>Contraindicated in pregnancy?</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Test for monitoring</td>
<td>PTT</td>
<td>PT, INR</td>
</tr>
<tr>
<td>Treatment of overdose</td>
<td>Protamine sulfate</td>
<td>Oral or IV vitamin K, fresh frozen plasma</td>
</tr>
</tbody>
</table>

INR, international normalized ratio; IV, intravenous; PT, prothrombin time; PTT, partial thromboplastin time; SC, subcutaneous.

LEUKOCYTE DISORDERS

I. Lymphoma

A. Hodgkin lymphoma

1. Malignancy of lymphocytes (mainly B cells), characterized by the presence of Reed-Sternberg cells (Figure 10-7), which are rare multinucleated or multi-lobed cells with prominent nucleoli (“owl eyes”). Reed-Sternberg cells also shrink on the slide, leaving a clear area around them.

   a. Age distribution is bimodal, with peak incidences at around 20 years and again at around 65 years.
   b. 50% of all Hodgkin lymphoma is associated with EBV.
   c. Hodgkin lymphoma is typically confined lymph nodes. Extranodal involvement is rare.
   d. Four histologic subtypes (Table 10-13)

2. Presentation: Nontender lymphadenopathy (especially in cervical lymphadenopathy), mediastinal lymphadenopathy, constitutional symptoms (“B” symptoms: low-grade fever, night sweats, weight loss), pruritus, and hepatosplenomegaly

3. Treatment: Radiation, chemotherapy, stem cell transplantation

B. Non-Hodgkin lymphoma

1. This is a large, heterogeneous group of lymphomas, all of which lack Reed-Sternberg cells. More than 35 subtypes (Table 10-14)

2. May occur at many sites where Hodgkin lymphoma is not normally seen.

FIGURE 10-7 Reed-Sternberg cell

Classic Reed-Sternberg cell. Mirror image nuclei contain large eosinophilic nucleoli. Reed-Sternberg cells also shrink on the slide, leaving a clear area around them. (From Rubin E, Farber JL. Pathology. 3rd ed. Philadelphia, PA: Lippincott Williams & Wilkins; 1999. Used with permission.)
### TABLE 10-13 Subtypes of Hodgkin Lymphoma

<table>
<thead>
<tr>
<th>Subtype</th>
<th>Epidemiology</th>
<th>Features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nodular sclerosing</td>
<td><strong>Most common subtype</strong>, mainly occurs in young adults; men = women</td>
<td>Biopsy shows cellular nodules separated by sclerosing bands of collagen; low occurrence of R-S cells; favorable prognosis</td>
</tr>
<tr>
<td>Mixed cellularity</td>
<td><strong>Second most common subtype</strong>, predominantly affects men.</td>
<td>High occurrence of R-S cells; less favorable (but still excellent) prognosis</td>
</tr>
<tr>
<td>Lymphocyte-predominant</td>
<td>Predominantly affects young men.</td>
<td>Low occurrence of R-S cells; favorable prognosis</td>
</tr>
<tr>
<td>Lymphocyte-depleted</td>
<td>Rare</td>
<td>High occurrence of R-S cells and low numbers of lymphocytes; high ratio of R-S cells to lymphocytes; very poor prognosis</td>
</tr>
</tbody>
</table>

R-S, Reed-Sternberg.

3. Can affect individuals of all ages, although certain subtypes predominate in specific age groups.

4. **Presentation:** Fatigue, weakness, peripheral lymphadenopathy, splenomegaly, skin lesions, and constitutional **B symptoms** are common.

5. **Labs:** Lymphocytosis and thrombocytosis are common. Anemia, thrombocytopenia, and leukopenia may indicate bone marrow involvement.

6. **Treatment:** Radiation, chemotherapy, bone marrow transplantation, stem cell transplantation.

### TABLE 10-14 Subtypes of Non-Hodgkin Lymphoma

<table>
<thead>
<tr>
<th>Subtype</th>
<th>Epidemiology</th>
<th>Features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diffuse large B-cell lymphoma</td>
<td><strong>Most common adult NHL</strong> (roughly 25% of all cases of NHL); 80% occur in adults (especially the elderly)</td>
<td>Associated with <strong>t(14;18)</strong></td>
</tr>
<tr>
<td>Lymphoblastic lymphoma</td>
<td><strong>Most common NHL in children</strong></td>
<td>Mediastinal mass</td>
</tr>
</tbody>
</table>
| Burkitt lymphoma            | • **Endemic** form is associated with EBV and usually involves the mandible. This is mainly seen in Africa.  
    • **Sporadic** form is usually found in the pelvis or the abdomen.  
    • **Immunodeficiency-associated** form is seen with HIV.                  | **t(8;14)** constitutively activates the c-Myc oncogene.  
    "Starry sky" appearance on biopsy (densely packed lymphocytes, with occasional lighter colored macrophages that have ingested tumor cells) (Figure 10-8) |
| Mantle cell lymphoma        | Rare B-cell lymphoma; affects older adults, especially males; poor prognosis                   | **t(11;14)** causes overexpression of cyclin D1, so that cells progress quickly to S phase                                        |
| Follicular lymphoma         | Good prognosis, but high rate of recurrence                                                      | **t(14;18)** causes over-expression of the antiapoptotic protein **bcl-2**                                                       |
| Small lymphocytic lymphoma  | Prognosis is fair to poor.                                                                       | Identical to chronic lymphocytic leukemia, except it occurs in the lymph nodes rather than the bone marrow                        |
| Marginal cell MALToma       | B-cell lymphoma found in the marginal zone of mucosa-associated lymphoid tissue (MALT); good prognosis | Associated with Sjögren syndrome, Hashimoto thyroiditis, and **Helicobacter pylori** infection                                  |
| Adult T-cell lymphoma       | Rare T-cell lymphoma; poor prognosis                                                              | Associated with HTLV-1 infection; presents with skin lesions                                                                       |
| Intestinal T-cell lymphoma  | Rare T-cell lymphoma; poor prognosis                                                              | Associated with celiac disease                                                                                                    |

EBV, Epstein-Barr virus; HIV, human immunodeficiency virus; HTLV, human T lymphocyte virus; NHL, non-Hodgkin lymphoma.
II. Leukemia

A. Acute lymphoblastic leukemia (ALL)

1. Normally occurs in children and young adults. The peak incidence is 2 to 5 years of age.
   a. It is most commonly associated with t(12;21) translocation (25% of cases), although multiple translocations have been identified.

2. Presentation: Fever, fatigue, pallor, dizziness, palpitations, dyspnea, bleeding, lymphadenopathy, bone pain, splenomegaly.

3. Labs: ↑ Lymphoblasts, neutropenia, thrombocytopenia, ↑ PT, ↓ fibrinogen, ↑ D-dimer, schistocytes, positive for terminal deoxynucleotidyl transferase (TdT) and periodic acid Schiff (PAS) stain.

4. Treatment: Radiation, chemotherapy, bone marrow transplantation.

5. Prognosis is favorable in children, but fair to poor in adults.

B. Acute myelogenous leukemia (AML)

1. Generally affects people over age 50 (median age is 65 years).
   a. Numerous chromosomal translocations and genetic mutations can cause different subtypes.
   b. AML is also associated with radiation, benzene, alkylating agents, myelodysplastic syndromes, and trisomy 21.

2. Presentation: Fatigue, weakness, dizziness, dyspnea, fever, anemia, splenomegaly, skin lesions.

3. Labs: Auer rods (thin, reddish-pink rods in the cytoplasm of myeloblasts, especially common in the M3 subtype of AML) (Figure 10-9). Negative PAS stain; neutropenia, thrombocytopenia, schistocytes, and disseminated intravascular coagulation (DIC) are also common in AML.

4. Treatment: Chemotherapy, bone marrow transplantation; all-trans retinoic acid (ATRA) in acute promyelocytic (M3) variant.

5. Prognosis is fair to poor, although this is heavily dependent on etiology and age.

C. Chronic lymphocytic leukemia

1. Affects elderly adults (usually over the age of 70).
   a. Due to its tendency to be indolent, older patients with CLL often die from other causes before CLL manifests.

2. Presentation: Often asymptomatic (25% to 50% of patients), although it may present with lymphadenopathy, mucocutaneous bleeding, petechiae, fatigue, splenomegaly, and hepatomegaly.
3. Labs: Smudge cells (lymphocytes with large, irregular nuclei and a smeared appearance of cytoplasm on the slide) (Figure 10-10), lymphocytosis, cytopenia, hypogammaglobulinemia, autoimmune hemolytic anemia (warm and/or cold agglutinins)
4. Treatment: Chemotherapy, bone marrow transplantation, splenectomy
5. Prognosis varies widely. It can be difficult to assess given the advanced age of CLL patients.

D. Chronic myelogenous leukemia (CML)
1. Occurs in adults ages 25 to 60, with an average age of 55.
   a. CML is always associated with a t(9;22) translocation (known as the Philadelphia chromosome).
2. Presentation: Fatigue, abdominal pain, weight loss, fever, splenomegaly, and hepatomegaly
3. Labs: ↑ Neutrophils and immature neutrophil precursors (bands, metamyelocytes, myelocytes), ↑ leukocytes, ↓ leukocyte alkaline phosphatase (LAP)
   t(9;22) creates an oncogene called bcr-abl, which encodes a constitutively activated tyrosine kinase. The drug imatinib targets this mutant protein and can be used to treat t(9;22)-positive malignancies.

QUICK HIT

• t(9;22) is always present in CML, sometimes in ALL, and rarely in AML.

• t(9;22) creates an oncogene called bcr-abl, which encodes a constitutively activated tyrosine kinase. The drug imatinib targets this mutant protein and can be used to treat t(9;22)-positive malignancies.

QUICK HIT

• t(9;22) is always present in CML, sometimes in ALL, and rarely in AML.

• t(9;22) creates an oncogene called bcr-abl, which encodes a constitutively activated tyrosine kinase. The drug imatinib targets this mutant protein and can be used to treat t(9;22)-positive malignancies.

Acute myelogenous leukemia

FIGURE 10-9
Prominent Auer rods (arrow) are seen in this specimen from a patient with the M3 variant of AML, which is also known as acute promyelocytic leukemia. (From Rubin R, Strayer DS. Rubin’s Pathology: Clinicopathologic Foundations of Medicine. 5th ed. Philadelphia, PA: Wolters Kluwer Health | Lippincott Williams & Wilkins; 2008. Used with permission.)

Chronic lymphocytic leukemia

FIGURE 10-10
A smear of peripheral blood shows numerous small- to medium-sized lymphocytes. A smudge cell is seen (arrow). (Image from Rubin E, Farber JL. Pathology. 3rd ed. Philadelphia, PA: Lippincott Williams & Wilkins; 1999. Used with permission.)
4. Treatment: Imatinib (inhibits the enzyme product of the bcr-abl gene found on the Philadelphia chromosome), hydroxyurea, bone marrow transplantation, splenectomy

5. Prognosis was historically poor but appears to have improved with imatinib. CML may progress to AML, which is known as blast crisis and carries a very poor prognosis.

III. Chronic myeloproliferative disorders

A. Polycythemia vera

1. Overproduction of red blood cells (RBCs) due to a benign neoplastic transformation of a myeloid precursor. Caused by a mutation of the Janus kinase 2 gene (JAK2), which increases hematopoietic stem cells’ sensitivity to growth factors.

2. Presentation: Plethora, headache, dizziness, pruritus, hypertension, splenomegaly, erythromelalgia

3. Labs: ↑ RBC mass, normal erythropoietin level and blood O₂ saturation, ↑ serum B₁₂, ↑ leukocytes, ↑ leukocyte alkaline phosphatase, hyperviscosity of blood

4. Treatment: Phlebotomy, hydroxyurea, splenectomy

B. Essential thrombocytosis

1. Overproduction of platelets due to JAK2 mutation and benign neoplastic transformation of a megakaryocyte precursor (similar to polycythemia vera but involving platelets rather than RBCs)

2. Presentation: Headache, digital pain, thrombosis or bleeding, neurologic symptoms, splenomegaly

3. Labs: ↑ Platelets, giant platelets and megakaryocytes, low to normal thrombopoietin level

4. Treatment: Hydroxyurea, aspirin, platelethresis

C. Myelofibrosis

1. Fibrotic obliteration of bone marrow space (Figure 10-11), resulting in pancytopenia.
   a. Generally affects patients over age 50
   b. There are numerous causes, including JAK2 mutation and certain malignancies.

2. Presentation: Fatigue, pallor, easy bruising, petechiae, bleeding, splenomegaly

3. Labs: Pancytopenia, anemia, teardrop cells, extramedullary hematopoiesis

4. Treatment: Ruxolitinib, hydroxyurea, thalidomide/prednisone, stem cell transplantation, splenectomy, radiation

A section of bone marrow shows collagenous fibrosis, osteosclerosis, and numerous abnormal megakaryocytes. (From Rubin E, Farber JL. Pathology. 3rd ed. Philadelphia, PA: Lippincott Williams & Wilkins; 1999. Used with permission.)
IV. Plasma cell dyscrasias

A. Multiple myeloma
1. Monoclonal plasma cell malignancy, resulting in overproduction of IgG (or less commonly IgA).
2. Presentation: Back pain, bone fractures, renal insufficiency, increased susceptibility to infection.
3. Labs: ↑ BUN and creatinine, hypercalcemia, anemia, Rouleaux formation on blood smear (Figure 10-12), ↑ serum gamma globulin, Bence-Jones proteins in urine, M spike on protein electrophoresis (Figure 10-13), amyloidosis, proliferation of plasma cells on bone marrow biopsy.
   a. Plasma cells produce cytokines that inhibit osteoblasts and stimulate osteoclasts, causing “punched-out” lytic bone lesions on X-ray (Figure 10-14).
4. Treatment: Chemotherapy, radiation, bone marrow transplantation.

B. Waldenstrom macroglobulinemia
1. A rare disease characterized by abnormal proliferation of IgM.
2. Presentation: Weakness, anorexia, peripheral neuropathy, fever, hepatomegaly, splenomegaly, lymphadenopathy.
3. Labs: ↑ IgM, Bence-Jones proteins in urine, amyloidosis, hyperviscosity of blood, PAS positive, lack of lytic bone lesions.
4. Treatment: Chemotherapy, bone marrow transplantation, thalidomide, plasmapheresis.

C. Plasmacytoma
1. Solid tumor of plasma cells.
2. Solitary plasmacytoma of bone
   a. Presentation: Compression fractures, back pain.
   b. Studies: M spike on protein electrophoresis, lytic bone lesion at tumor site, monoclonal plasma cell infiltration, rarely bone cysts and sclerotic lesions.
3. Extramedullary plasmacytoma
   a. Found outside of the bone, often found on mucosal surfaces in the head and neck.
   b. Presentation: Headache, epistaxis, sore throat, dysphagia, dyspnea, hemoptysis.
   c. Studies: M spike on protein electrophoresis (less common), local bone destruction.

(From Anderson SC, Poulsen KB. Anderson’s Atlas of Hematology. Baltimore, MD: Lippincott Williams & Wilkins; 2003. Used with permission.)
Abnormal serum protein electrophoretic patterns are contrasted with a normal pattern. In polyclonal hypergammaglobulinemia, which is characteristic of benign reactive processes, there is a broad-based increase in immunoglobulins due to immunoglobulin secretion by myriad discrete reactive plasma cells. In monoclonal gammopathy, which is characteristic of multiple myeloma, there is a narrow peak, or spike, due to the homogeneity of the immunoglobulin molecules secreted by a single clone of aberrant plasma cells. (From Rubin E, Farber JL. Pathology. 3rd ed. Philadelphia, PA: Lippincott Williams & Wilkins; 1999. Used with permission.)

A radiograph of the skull shows numerous punched-out radiolucent areas. (From Rubin E, Farber JL. Pathology. 3rd ed. Philadelphia, PA: Lippincott Williams & Wilkins; 1999. Used with permission.)
4. **Treatment:** Radiation, surgical resection
5. Plasmacytomas have a good prognosis but may eventually progress to multiple myeloma.

D. Monoclonal gammopathy of undetermined significance (MGUS)
1. Asymptomatic, abnormal proliferation of plasma cells with increased monoclonal immunoglobulin but is not necessarily malignant and does cause the systemic symptoms of multiple myeloma.
2. **Presentation:** Asymptomatic; usually discovered during routine evaluation or evaluation for an unrelated disorder.
3. **Studies:** M protein in serum (low levels), plasma cells in bone marrow (low levels), Bence-Jones protein in urine (sometimes); no lytic bone lesions, hypercalcemia, or anemia.
4. **Treatment:** No treatment necessary. Monitor for possible progression to multiple myeloma.
Biochemistry and Genetics

11

GENETICS

I. Nucleic acids

A. Purine synthesis
1. Overall reaction: Ribose-5-phosphate \( \rightarrow \) adenosine monophosphate (AMP) or guanosine monophosphate (GMP). This requires the amino acids glycine, aspartate, and glutamine. It also requires tetrahydrofolate.
2. Rate-limiting step: phosphoribosyl pyrophosphate (PRPP) \( \rightarrow \) \( \beta \)-5-phosphoribosyl-5-phosphoribosylamine (\( \beta \)-5-PRA) by glutamine PRPP amidotransferase. This step requires glutamine.
3. Initially, ribose-5-phosphate is converted to PRPP, which is then converted to \( \beta \)-5-PRA.
4. After several more steps, \( \beta \)-5-PRA is converted to inosine monophosphate (IMP).
5. IMP can then be converted to either GMP or AMP.
   a. The conversion of IMP to GMP is catalyzed by IMP dehydrogenase.
   b. This enzyme is inhibited by the drug mycophenolate.

B. Purine catabolism (Figure 11-1)
1. Overall reaction: AMP, IMP, GMP \( \rightarrow \) uric acid
2. GMP is converted to guanosine, which is then converted to guanine, followed by xanthine.
3. IMP is converted to inosine, which is then converted to hypoxanthine, followed by xanthine.
4. AMP is converted to adenosine. Adenosine is then converted to inosine by adenosine deaminase. Inosine is then converted to hypoxanthine, followed by xanthine.
5. Xanthine is converted to uric acid by xanthine oxidase. This enzyme is inhibited by the drug allopurinol.

C. Purine salvage
1. Overall reaction: Adenine \( \rightarrow \) AMP requires adenosine phosphoribosyl transferase (APRT). Hypoxanthine \( \rightarrow \) IMP and guanine \( \rightarrow \) GMP require hypoxanthine guanine phosphoribosyl transferase (HGPRT).
2. Lesch-Nyhan syndrome: X-linked recessive deficiency of HGPRT. The lack of purine salvage causes accumulation of uric acid. This causes mental retardation, self-mutilation, choreoathetosis, and gout. It is treated with allopurinol.

D. Pyrimidine synthesis
1. Overall reaction: Glutamine + bicarbonate \( \rightarrow \) uridine diphosphate (UDP), then UDP \( \rightarrow \) uridine triphosphate (UTP) \( \rightarrow \) cytosine triphosphate (CTP) (which requires glutamine) or UDP \( \rightarrow \) deoxyuridine monophosphate (dUMP) \( \rightarrow \) thymidine monophosphate (TMP) (which requires tetrahydrofolate). Both require aspartate and bicarbonate.
2. Rate-limiting step: Glutamine + bicarbonate \( \rightarrow \) carbamoyl phosphate by carbamoyl phosphate synthase II
3. Carbamoyl phosphate is converted to orotic acid.
4. Orotic acid is converted to UMP in a reaction that requires PRPP.
5. UMP is phosphorylated to UDP, which is then converted to dUMP. Alternatively, UDP is converted to deoxyuridine diphosphate (dUDP), then dUMP, and finally deoxothymidine monophosphate (dTMP).
   a. The conversion of UDP to dUDP is catalyzed by ribonucleotide reductase.
   b. Ribonucleotide reductase is inhibited by hydroxyurea.
6. Orotic aciduria: Deficiency of UMP due to an autosomal recessive defect in UMP synthase. This results in elevated orotic acid in the urine and megaloblastic anemia that is nonresponsive to vitamin B₁₂ or folate supplementation. Uridine supplementation is indicated instead.

The degradation of purine nucleotides to uric acid, illustrating some of the genetic diseases associated with this pathway. (Adapted with permission from Harvey RA, Ferrier DR. Lippincott's Illustrated Reviews: Biochemistry. 5th ed. Baltimore, MD: Wolters Kluwer Health | Lippincott Williams & Wilkins; 2011.)
II. DNA structure
A. DNA strand
1. Purines: Adenine, guanine
2. Pyrimidines: Thymine, cytosine, uracil
3. Adenine binds thymine (or uracil) through two hydrogen bonds.
4. Cytosine binds guanine through three hydrogen bonds.
5. Adjacent nucleotide pairings are linked by a phosphodiester backbone, which is what gives DNA its negative charge.

B. Chromosomes
1. DNA wraps twice around a core of histone proteins to form nucleosomes (Figure 11-2). Negatively charged DNA binds easily to the positively charged lysine and arginine residues in histone proteins.
2. The histone core is composed of four proteins: two each of H2A, H2B, H3, and H4.
   a. Prior to transcription, histones are acetylated, relaxing the DNA coiling.
   b. After transcription, histones are methylated, causing the DNA to coil more tightly.
3. H1 is the only histone protein that is not found in the histone core. It holds the DNA in place around the core and also interacts with linker DNA.
4. This combination of DNA and proteins is known as chromatin.
   a. Heterochromatin is condensed and transcriptionally inactive.
   b. Euchromatin is less condensed and transcriptionally active.
5. Supercoiling and packing of chromatin forms chromosomes.

III. DNA replication and repair
A. DNA replication (Figure 11-3)
1. Replication is started at the origin of replication by the pre-replication complex.
2. DNA helicase unwinds the DNA at the replication fork.
3. Topoisomerase relieves supercoiling at the other end of the DNA strand.
4. Single-strand binding proteins prevent the two strands from reannealing.
5. Each DNA strand is synthesized from the 5’ end to the 3’ end.
6. An RNA primer must be added to the DNA strand to allow replication by DNA polymerases.
   a. In eukaryotes, this function is carried out by DNA polymerase α.
   b. In prokaryotes, this function is carried out by primase.
7. Eukaryotic DNA replication
   a. DNA polymerase α synthesizes the initial RNA primer on the leading and lagging strands.
   b. DNA polymerase δ replicates the leading strand in a continuous fashion.
   c. DNA polymerase ε replicates the lagging strand in short, discontinuous segments called Okazaki fragments, which are later joined together by DNA ligase.
   d. DNA polymerase γ replicates mitochondrial DNA.

8. Prokaryotic DNA replication
   a. Primase synthesizes the initial RNA primers.
   b. DNA polymerase III replicates the leading strand in a continuous fashion and also synthesizes the Okazaki fragments on the lagging strand.
c. DNA polymerase I degrades the RNA primers and fills in gaps in the DNA.
d. DNA ligase joins the Okazaki fragments together.

9. Telomerase adds nucleotides to the 3’ ends of chromosomes to compensate for the loss of nucleotides during replication.
   a. In eukaryotes, DNA is linear, so the polymerase cannot reach the end of the strand. As a result, chromosomes get shorter with each replication.
   b. Germ cells express telomerase, which allows them to grow and divide for many generations.
   c. Somatic cells do not normally express telomerase. As they lose nucleotides from the ends of their chromosomes, they eventually reach a point where DNA replication is impaired and cells can no longer grow and divide.
   d. Somatic cancer cells often express telomerase, which is thought to be a major factor in their continued growth and division.

B. DNA mutations
1. Silent mutation: A mutation in the third position of a codon that does not change the resulting amino acid. This is due to transfer RNA (tRNA) wobble, which allows for tolerance of some of these mutations.
2. Missense mutation: A mutation that results in an amino acid substitution. This can cause a change in the folding and/or function of the resulting protein.
3. Nonsense mutation: A mutation that creates an early stop codon, resulting in termination of transcription and a shortened protein.
4. Frameshift mutation: Addition or deletion of a nucleotide shifts the reading frame, resulting in a completely different set of codons.
5. Pyrimidine dimer: Inappropriate binding of thymine to a neighboring thymine on the same DNA strand (or cytosine to cytosine, which is less common). This mutation is often caused by ultraviolet (UV) radiation.

C. DNA repair
1. Nucleotide excision repair: A segment of single-stranded DNA containing bulky, helix-distorting damage is removed by an endonuclease. The section is then filled in by DNA polymerases, and DNA ligase joins the ends. This is most commonly used to repair pyrimidine dimers.
2. Base excision repair: The damaged base is removed by a glycosylase, and the apurinic/apyrimidinic site is removed by an endonuclease. The gap is filled by a polymerase and sealed by ligase. This is most commonly used to remove uracil, hypoxanthine, or 3-methyladenine from DNA.
   a. Spontaneous deamination of cytosine forms uracil.
   b. Spontaneous deamination of adenine forms hypoxanthine.
   c. Methylation of adenine creates 3-methyladenine.
3. Mismatch repair: Mismatched nucleotides are removed by an endonuclease. This occurs immediately after the synthesis of the strand, just upstream of the DNA polymerase. The gap is filled by another polymerase and sealed by a ligase.
4. Nonhomologous end joining: Repair of double-stranded breaks by joining overhanging ends of DNA by a ligase. The gaps are filled in by polymerase and sealed by another ligase.

D. DNA repair defects
1. Xeroderma pigmentosum: Autosomal recessive deficiency in nucleotide excision repair. This causes extreme sensitivity to UV light, along with multiple skin malignancies. Patients must avoid all sunlight.
2. Ataxia telangiectasia: Autosomal recessive defect of the ATM protein, resulting in the inability to repair double-stranded DNA breaks. This causes many problems, including gait ataxia, immunodeficiency, telangiectasia, and an increased risk of cancer.
3. Bloom syndrome: Autosomal recessive defect of the BLM protein, which is a helicase that is important in both DNA repair and DNA replication. This causes hypersensitivity to UV light, short stature, immunodeficiency, and an increased risk of leukemia or lymphoma.
4. Hereditary nonpolyposis colorectal cancer (HNPPC): Autosomal dominant defect in mismatch repair. This greatly increases the risk of colorectal cancer as well as other cancers (especially endometrial cancer).
5. **BRCA1/BRCA2 mutation**: A defect in the proteins BRCA1 or BRCA2, which are involved in the repair of double-stranded DNA breaks. This greatly increases the risk of breast cancer as well as other cancers (especially ovarian cancer).

### IV. RNA transcription

A. **Important terms**

1. **Operon**: A region of DNA containing transcribed genes under the control of a single promoter region as well as structural DNA and operator sequences. Operons are generally found in prokaryotes, although they do occur less commonly in eukaryotes.
2. **Promoter**: The region of DNA to which RNA polymerase binds prior to the initiation of transcription.
3. **Operator**: A specialized region of DNA within the promoter of an inducible (lac operon) or repressible operon. This region binds inducer proteins or repressor proteins that either promote or prevent binding of RNA polymerase.
4. **Repressor**: A protein that binds to the operator region of a promoter and prevents transcription by RNA polymerase.
5. **Corepressor**: A substance that facilitates the binding of a repressor protein to an operator sequence.
6. **Inducer**: A substance that prevents the binding of a repressor protein to an operator sequence.
7. **Transcription factor**: Any protein that binds to DNA and regulates transcription.
8. **Response element**: Any region of DNA that is bound by a transcription factor.
9. **General transcription factor**: A protein that binds in or near the promoter region and facilitates the binding of RNA polymerase. General transcription factors are required for initiation of transcription. They bind to conserved sequences such as the CCAAT box (located about 75 base pairs upstream from the start site), the TATA box (about 25 base pairs upstream), and the Pribnow box (about 10 base pairs upstream).
10. **Enhancer**: A regulatory region of DNA that allows control of transcription through folding of the DNA. Enhancer regions are far more common in eukaryotes than in prokaryotes. They may be located near the promoter but are often thousands of base pairs upstream or downstream. Enhancer-bound proteins do not initiate or prevent transcription. They only affect the rate at which it occurs.
11. **Activator/repressor**: A protein that binds to an enhancer region and either stimulates or inhibits transcription, either through direct interactions with RNA polymerase or indirectly through interactions with transcription factors, other activators, or other repressors. Enhancer-bound repressors merely slow transcription, whereas operator-bound repressors prevent transcription.

B. **Transcription factors**

1. **Helix-loop-helix**: Characterized by two α helices connected by an amino acid loop. These generally form dimers when binding DNA. An example of a helix-loop-helix transcription factor is Myc, the mutated form of which is associated with Burkitt lymphoma.
2. **Helix-turn-helix**: Characterized by two α helices connected by a short strand of amino acids. Helix-turn-helix transcription factors bind DNA as monomers. The lac repressor contains a helix-turn-helix motif.
3. **Zinc finger**: These transcription factors have a DNA-binding domain containing an atom of zinc. GATA-3, a transcription factor that regulates many of the effects of cyclic adenosine monophosphate (cAMP) signaling, has a leucine zipper domain.
4. **Leucine zipper**: Transcription factors that bind DNA through two α helices that are held together by leucine residues. CREB, a transcription factor that regulates transcription, has a leucine zipper domain.

C. **RNA polymerases**

1. **Eukaryotic RNA polymerases**
   a. RNA Pol I: Transcribes ribosomal RNA (rRNA) in the nucleolus.
   b. RNA Pol II: Transcribes messenger RNA (mRNA) in the nucleoplasm.
   c. RNA Pol III: Transcribes tRNA in the nucleoplasm.
2. Prokaryotic RNA polymerase  
   a. Prokaryotes only have one RNA polymerase, and it transcribes rRNA, mRNA, and tRNA.

D. lac Operon
   1. Inducible operon that responds to an increase in levels of lactose by transcribing RNA that will then be translated to β-galactosidase
   2. Allolactose, a lactose derivative, binds the lac repressor that is bound to the operator region of the promoter, causing it to dissociate.
   3. Catabolite activator protein (CAP) complex, an activator that is required by RNA polymerase, only binds in the absence of glucose.
   4. Thus, β-galactosidase will only be synthesized in the presence of lactose and the absence of glucose.

E. Termination of prokaryotic transcription
   1. Rho factor uses its adenosine triphosphatase (ATPase) activity to dissociate RNA polymerase from the DNA strand.
   2. In intrinsic termination, the RNA polymerase encounters an RNA stem loop that forms in a region rich in guanine and cytosine. This stem loop is followed by a sequence of adenine-uracil base pairs between the nascent RNA strand and the template DNA. This promotes the release of RNA polymerase (the mechanism is unclear).

V. RNA translation
   A. Codons
      1. Sequences of mRNA, each three bases in length, that code for specific amino acids
      2. The start codon, AUG, codes for methionine in eukaryotes and N-formylmethionine in prokaryotes.
      3. The sequences UGA, UAA, and UAG are stop codons, each signaling the termination of translation.
   B. mRNA
      1. RNA within the nucleus is known as heterogeneous nuclear RNA (hnRNA).
      2. Precursor mRNA (pre-mRNA) is the term for transcribed RNA that has not yet undergone processing into mRNA.
         a. hnRNA and pre-mRNA are not synonymous. Pre-mRNA only makes up a small portion of hnRNA.
         b. Most hnRNA is composed of RNA transcripts that remain in the nucleus and regulate gene expression.
      3. Pre-mRNA is processed in the nucleus.
         a. Pre-mRNA is capped at the 5’ end with 7-methylguanosine. This requires S-adenosyl-methionine.
         b. The 3’ end is capped with a string of adenine residues known as the poly(A) tail. The site of this is determined by a polyadenylation signal sequence (5’-AAUAAA-3’).
         c. Introns are removed in a process known as RNA splicing.
      4. The processed mRNA then leaves the nucleus to enter translation.
   C. tRNA
      1. Transports amino acids to the ribosome, where they can be attached to the growing amino acid chain.
      2. The characteristic cloverleaf structure has an anticodon loop that attaches to the mRNA and a nucleic acid sequence of CCA at the 3’ end.
      3. The amino acid is attached to the 3’ end of the tRNA by an aminoacyl tRNA synthetase. This process is known as tRNA charging.
   D. Protein synthesis (Figure 11-4)
      1. Ribosomal subunits are synthesized in the nucleus and then transported into the cytosol.
         a. Eukaryotes have an 80s ribosome composed of a 40s and a 60s subunit.
         b. Prokaryotes have a 70s ribosome composed of a 30s and a 50s subunit.
      2. In initiation, initiation factors (IF) facilitate the attachment of the smaller ribosomal subunit (30s or 40s) to the mRNA strand just upstream of the start.
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A, adenine; Arg, arginine; C, cytosine; EF, elongation factor; fMET, formyl methionine; G, guanine; GDP, guanosine diphosphate; GTP, guanosine triphosphate; IF, initiation factor; Phe, phenylalanine; P\textsubscript{i}, inorganic phosphate; RF, release factor; T, thymine; tRNA, transfer RNA; U, uracil. (Adapted with permission from Harvey RA, Ferrier DR. Lippincott's Illustrated Reviews: Biochemistry. 5th ed. Baltimore, MD: Wolters Kluwer Health | Lippincott Williams & Wilkins; 2011.)

Protein synthesis

**INITIATION**

1. Initiation factors aid in the formation of the 30S initiation complex, in which the charged initiator tRNA is at the P site.

2. GTP on IF-2 is hydrolyzed and initiation factors are released when the 50S subunit arrives to form the 70S initiation complex.

**ELONGATION**

3. Elongation factors direct the binding of the appropriate tRNA to the codon in the empty A site. GTP on EF-Tu is hydrolyzed.

4. Peptidyltransferase, an activity of the rRNA of the 50S ribosomal subunit, catalyzes peptide bond formation, transferring the initiating amino acid (or peptide chain) from the P site onto the amino acid at the A site.

AMINOGLYCOSIDES

Bind to the 30S subunit and distort its structure, interfering with the initiation of protein synthesis.

TETRACYCLINES

Interact with 30S ribosomal subunits, blocking access of the aminoacyl-tRNA to the A site of the mRNA-ribosome complex.

CHLORAMPHENICOL

Inhibits prokaryotic peptidyltransferase. High levels may also inhibit mitochondrial protein synthesis.

Peptidyltransferase, an activity of the rRNA of the 50S ribosomal subunit, catalyzes peptide bond formation, transferring the initiating amino acid (or peptide chain) from the P site onto the amino acid at the A site.

Continued at top of next page
The ribosome moves a distance of three nucleotides along the mRNA in the 5' → 3' direction. What was in the P site is now in E; what was in the A site is now in P, and A is empty. GTP on EF-G is hydrolyzed.

Steps 3, 4, and 5 are repeated until a termination codon is encountered at the A site.

A termination codon is recognized by a release factor (RF), which results in release of the newly synthesized protein. The synthesizing complex dissociates. GTP on RF-3 is hydrolyzed.

MACROLIDES and CLINDAMYCIN and STREPTOGRAMINS
Bind irreversibly to a site on the 50S subunit of the bacterial ribosome, thus inhibiting translocation.

DIPHTHERIA TOXIN
Inactivates the eukaryotic elongation factor, EF-2, thus preventing translocation.

TERMINATION

Recycled
288  •  Step-Up to USMLE Step 1

codon (AUG). This positions the ribosomal subunit so that the P site can accept the aminoacyl tRNA containing methionine.
3. The aminoacyl tRNA binds, and the larger ribosomal subunit (50s or 60s) binds to the smaller ribosomal subunit. At the same time, the IFs are released from the complex through hydrolysis of guanosine triphosphate (GTP).
4. As elongation occurs, the incoming aminoacyl tRNAs bind to the A site of the ribosome.
5. A peptidyltransferase then attaches the amino acid from the aminoacyl tRNA at the P site to the amino acid at the A site.
   a. In prokaryotes, the peptidyltransferase is found in a 23s subunit that is part of the larger 50s subunit.
6. In translocation, the ribosome complex hydrolyzes GTP and moves three nucleotides down the mRNA strand. This requires elongation factor G (EF-G) in prokaryotes and elongation factor 2 (EF-2) in eukaryotes.
7. The newly uncharged tRNA moves to the E site, while the tRNA attached to the amino acid chain moves to the P site. As the incoming aminoacyl tRNA binds to the A site, the empty tRNA is ejected from the E site.
8. This process repeats until the stop codon is reached. Release factors then facilitate the release of the amino acid strand.
9. The amino acid must undergo posttranslational modifications prior to becoming a functional protein. This may include removal of N-terminal or C-terminal polypeptides, phosphorylation, glycosylation, hydroxylation, and many others.
E. Drugs that inhibit translation
   1. Aminoglycosides bind the 30s ribosomal subunit in prokaryotes and inhibit initiation.
   2. Linezolid binds the 50s subunit and prevents formation of the initiation complex.
   3. Tetracycline antibiotics bind to the A site of the 30s ribosome subunit and prevent the attachment of aminoacyl tRNAs.
   4. Chloramphenicol binds the 50s subunit and prevents the action of peptidyltransferase.
   5. Macrolides, lincosamides (including clindamycin and lincomycin), and streptogramins bind the 50s subunit and inhibit translocation of the ribosome complex.

VI. Inheritance
A. Modes of inheritance
   1. Autosomal dominant: Phenotype requires only one allele. Structural gene defects are often inherited in this pattern. Offspring with heterozygous parents have a 75% chance of inheriting the associated phenotype.
   2. Autosomal recessive: Phenotype requires two alleles. Enzyme defects are often inherited in this pattern. Offspring have a 75% chance of inheriting at least one allele from heterozygous parents but only a 25% chance of expressing the associated phenotype.
   3. X-linked dominant: Phenotype requires only one X-linked allele. Offspring from a heterozygous mother have a 50% chance of expressing the associated phenotype. If the father carries the allele, female offspring have a 100% chance of expressing the associated phenotype.
   4. X-linked recessive: Phenotype requires two X-linked alleles in women but only one X-linked allele in men. Offspring with a heterozygous mother have a 50% chance of inheriting the allele. Male offspring will then express the associated phenotype, while female offspring will only be carriers.
   5. Mitochondrial: Phenotype always manifests, and a mother will always pass mitochondria to both male and female offspring.
B. Important terms
   1. Codominance: Both alleles are expressed at the same time (e.g., ABO blood groupings).
2. **Variable expression**: The effect of the genes varies from one individual to another (e.g., neurofibromatosis, tuberous sclerosis).

3. **Pleiotropy**: A single gene has more than one effect on phenotype (e.g., phenylketonuria).

4. **Locus heterogeneity**: Several different genes can cause the same phenotype (e.g., genes related to Marfan syndrome and homocystinuria can both cause Marfanoid habitus).

5. **Mosaicism**: A condition when cells within the same individual differ in genetic makeup. This may result from mutations during development or genetic recombination during mitosis.

6. **Loss of heterozygosity**: Deletion or interruption of an allele, leaving only one functional allele. Loss of heterozygosity often has no effect because one functioning allele remains. However, in some cases (notably oncogenes), deletion of one allele is sufficient to cause a phenotypic change.

7. **Anticipation**: Phenotypes manifest earlier in the offspring than in the parents. This can continue through multiple generations. In the case of a disease, this may also manifest as an increase in severity in successive generations (e.g., Huntington disease).

8. **Incomplete penetrance**: Alleles do not always express the associated phenotype (e.g., BRCA1 and BRCA2 mutations do not always cause breast cancer).

9. **Imprinting**: Phenotypes resulting from the same alleles differ, depending on whether the allele came from the mother or the father (e.g., Prader–Willi syndrome, Angelman syndrome).
   a. **Prader–Willi syndrome**: Deletion of a paternal allele on chromosome 15 and inactivation of the corresponding maternal allele. It presents in infancy with hypotonia, poor feeding, and characteristic facial features. Later in life, it causes childhood osteoporosis, polyphagia and obesity, short stature, mental retardation, behavioral disorders, and incomplete sexual development.
   b. **Angelman syndrome**: Deletion of a maternal allele on chromosome 15 and inactivation of the corresponding paternal allele. It presents with mental retardation, seizures, ataxia, and inappropriate laughter.

10. **Dominant negative mutation**: A recessive allele in a heterozygous individual that interferes with the function of the normal, dominant allele. Transcription factors with a mutation that renders them nonfunctional may still bind DNA, preventing the binding of nonmutated transcription factors.

11. **Linkage disequilibrium**: The tendency for alleles at two or more loci to occur together more or less often than expected by random chance.

12. **Heteroplasmy**: The occurrence of both normal and mutated mitochondrial DNA. This causes variable expression of mitochondrial-associated diseases.

13. **Uniparental disomy**: The inheritance of two copies of a chromosome from one parent and no copies from the other parent rather than one copy from each parent.

C. Hardy–Weinberg population genetics

1. Assumptions
   a. p and q are the frequencies of two separate alleles in a population.
   b. Allelic frequencies are equally distributed among the sexes.
   c. The population is infinitely large.
   d. Everyone produces the same number of offspring.
   e. There are no mutations at the locus.
   f. There is no selective pressure for any of the genotypes.
   g. Mating is completely random.
   h. There is no net migration of alleles into or out of the population, that is, the population is closed.

2. Hardy–Weinberg equilibrium
   a. \( p + q = 1 \)
   b. \( p^2 + 2pq + q^2 = 1 \)
   c. \( p^2 = \text{frequency of individuals homozygous for the first allele} \)
   d. \( q^2 = \text{frequency of individuals homozygous for the second allele} \)
   e. \( 2pq = \text{frequency of heterozygous individuals} \)
f. For X-linked recessive alleles, the frequency of phenotypic expression is \( q \) for males and \( q^2 \) for females.
g. Evolution does not occur in Hardy–Weinberg equilibrium, and allelic frequencies do not change from generation to generation. Obviously, in reality, this never occurs.

VII. Genetics laboratory methods

A. Polymerase chain reaction (PCR)
   1. Used to create many copies of a segment of DNA
   2. DNA is mixed with DNA primers, heat-stable DNA polymerase, and deoxyribonucleotides.
   3. First, DNA is denatured by heating the solution to a high temperature. This separates the strands.
   4. Second, the solution is rapidly cooled to a relatively low temperature, allowing the primers to anneal to the DNA strands. The primers are designed so that they bind sequences that flank the DNA segment of interest.
   5. Third, the solution is heated to an intermediate temperature, which allows the polymerase to synthesize DNA using the primers as a starting point.
      a. PCR-denaturing temperatures will also denature most DNA polymerases. Therefore, PCR systems use Taq polymerase, a heat-stable DNA polymerase isolated from bacteria that live in hydrothermal vents.
   6. After the initial cycle, the primers will also bind the newly synthesized DNA. These three steps are repeated many times (typically 30 to 40 cycles), resulting in many copies of the region of interest.

B. Gel electrophoresis
   1. Used to separate segments of DNA (or RNA) according to size
   2. Samples are mixed with a fluorescent stain and loaded into wells at one end of a gel.
   3. The gel is covered with a buffer solution and a current is passed through it.
   4. Negatively charged DNA or RNA will migrate toward the positive pole.
   5. Migration will occur at different rates because smaller segments of DNA or RNA can move more quickly through the gel matrix.
   6. Samples are usually run alongside a control sample with segments of known size.
   7. This technique can reveal the size of a segment (may reveal insertions or deletions in genes) or allow for isolation of the DNA or RNA segment (can be cut out of the gel and analyzed further).
   8. Gel electrophoresis can also be used to separate proteins. Because proteins may be positive or negative, they are placed in wells in the middle of the gel, and they may migrate toward either end.

C. Blots
   1. Used to analyze DNA, RNA, or proteins through the use of labeled probes
   2. Samples are hybridized to a membrane or filter and treated with a labeled probe that is specific for a nucleotide sequence or an amino acid sequence.
   3. The probe is then detected by color change, fluorescence, or radioactivity.
   4. Southern blot: DNA is denatured in an alkaline solution and treated with a labeled DNA (or RNA) probe that is complementary to the sequence of interest.
   5. Northern blot: RNA is treated with a labeled RNA (or DNA) probe that is complementary to the sequence of interest. Normally, no denaturing solution is required because RNA is single stranded (except in the case of certain viruses).
   6. Western blot: Protein samples are treated with a labeled antibody that recognizes the protein of interest.
   7. Southwestern blot: Protein is treated with labeled oligonucleotides. This identifies proteins that bind specific DNA sequences, that is transcription factors.
   8. Blots are almost always paired with gel electrophoresis. DNA, RNA, or proteins that have been separated are transferred directly from the gel to the membrane or filter.
   9. Microarrays utilize these same techniques to analyze samples with thousands of probes at once. Special cartridges called chips contain tiny spots with very small amounts of probe material. The sample is added to the chip and analyzed using special equipment.
D. Enzyme-linked immunosorbent assay (ELISA)
   1. Uses antigen–antibody interactions to detect antigens or antigen-specific antibodies in a sample
   2. **Traditional ELISA (indirect):** Used to detect protein-specific antibodies in a serum sample. Serum is added to a well or vial coated with a protein of interest. Serum antibodies that recognize the protein will then bind. Unbound antibodies are washed away, and an enzyme-linked secondary antibody is added to bind the serum antibody.
   3. **Sandwich ELISA (direct):** Used to detect specific proteins in a serum sample. Serum is added to a well or vial coated with an antibody that recognizes the protein of interest. Surface-bound antibodies bind the proteins, and unbound proteins are washed away. An enzyme-linked antibody specific for the protein is then added.
   4. In both assays, a substrate for the enzyme is then added, resulting in a color change. The magnitude of the color change reflects either the concentration of protein or protein-specific antibodies in a sample.

E. Fluorescence in situ hybridization (FISH)
   1. Used to detect specific nucleic acid sequences within chromosomes or within cells
   2. Fluorescently labeled DNA or RNA probes are added to isolated chromosomes, where they will bind complementary sequences, revealing the location of the segment of interest.
   3. Probes can also be added to fixed cells or tissue sections to study gene expression. Because probes cannot access coiled DNA, they only bind segments that are being actively transcribed. In this way, they can reveal which cells or tissues are expressing certain genes. Alternatively, probes can be designed to bind mRNA.

F. Cloning
   1. Used to study DNA sequences for specific genes by using bacterial systems to make copies
   2. Reverse transcriptase is used to make complementary DNA (cDNA) from mRNA.
   3. The cDNA is then inserted into a bacterial plasmid, which is then taken up by bacterial cells.
   4. As the bacteria grow and divide, the plasmids are replicated. This creates many copies of the cDNA, which can then be isolated.
   5. cDNA is different from normal DNA because it lacks introns. This means that it contains only the coding sequences of the gene, and it can be studied without having to distinguish between the exons and introns.
   6. This system can also be used to manufacture bacterial proteins for study.

G. Modifications of gene expression
   1. **Knockout:** Deletion or disruption of a gene. The function of many genes can be determined by analyzing the effect of the loss of those genes. This technique is often used in bacteria and in mice, although it can theoretically be used in any animal model.
   2. **Knock-in:** The targeted insertion of a gene. Homologous recombination is used to replace one allele with another, ensuring that it is found in the same place and will be expressed as it normally would.
   3. **Transgenic animal:** A gene is inserted into the genome of an animal, but its insertion is random. Because the gene contains the promoter and many of the necessary response elements, it will often be transcribed normally. However, this method risks disruption of other genes if the gene of interest is inserted into another reading frame. In addition, multiple copies may insert at different sites, resulting in overexpression of the gene. This method is quicker and easier than knocking in, but it is less accurate.
   4. **Small interfering RNA (siRNA):** Short RNA strands that are complementary to mRNA from genes of interest are either inserted into cells or inserted into the genome so that they will be directly transcribed by the cells. These RNA molecules may bind to mRNA and prevent its translation or activate an RNA-induced silencing complex that targets the mRNA for degradation. The result is a knockdown of the protein.
5. Cre-Lox system: A system used for conditional deletions of specific DNA segments. Special recognition sequences, known as LoxP sequences, can be inserted into the genome flanking the DNA segment to be deleted. Cre recombinase, an enzyme that recognizes LoxP sites, can be inserted downstream from a specific promoter. Once Cre recombinase is synthesized, it will excise the portion of DNA between the LoxP sites. This allows for specific genes to be deleted only after the activation of another gene within the same cell.

6. Karyotyping: Metaphase chromosomes are stained, paired, and ordered according to size, banding pattern, and morphology. This is useful in diagnosing chromosomal imbalances.

**PROTEIN**

I. Amino acids

A. Classifications

1. Essential amino acids: Phe, Val, Thr, Trp, Ile, Met, His, Arg, Leu, Lys
2. Acidic amino acids: Aspartic acid (Asp), glutamic acid (Glu). These carry a negative charge at normal body pH.
3. Basic amino acids: Lys, Arg, His. Lys and Arg carry a positive charge at normal body pH. His is neutral.

B. Important amino acid derivatives

1. Phenylalanine: Can be converted to tyrosine
2. Tyrosine: Dopamine, norepinephrine, epinephrine, melanin
3. Arginine: Urea, and nitric oxide. Arginine is also required for creatine synthesis.
4. Tryptophan: Niacin, nicotinamide adenine dinucleotide (NAD), nicotinamide adenine dinucleotide phosphate (NADP), serotonin, melatonin
5. Histidine: Histamine
6. Glycine: Porphyrin (part of heme synthesis)
7. Glutamate: γ-aminobutyric acid (GABA), glutathione
8. Methionine: S-adenosylmethionine (SAM; transfers methyl units in the synthesis of both epinephrine and creatine)

C. Amino acid disorders

1. Phenylketonuria
   a. Autosomal recessive deficiency of phenylalanine hydroxylase or tetrahydrobiopterin (less common)
   b. Phenylalanine cannot be converted to tyrosine. Phenylalanine then accumulates and is converted to phenylketones (i.e., phenylacetate, phenylpyruvate, phenyl-lactate).
   c. Presentation: Fair skin and hair, eczema, intellectual disability, musty or mousy odor, seizures, microcephaly
   d. Labs: ↑ Phenylalanine, cranial demyelination (in untreated, older patients)
   e. Treatment: Decreased dietary phenylalanine and/or increased dietary tyrosine. Tetrahydrobiopterin supplementation may also be indicated.
      i. Restriction of phenylalanine within the first few weeks of life prevents developmental abnormalities.
      ii. Patients remain largely asymptomatic as long as the diet is strictly followed.
   f. Maternal phenylketonuria: Phenylalanine intake in phenylketonuric mothers during pregnancy may result in fetal defects such as microcephaly, mental retardation, growth retardation, and congenital heart defects.

2. Alkaptonuria
   a. Autosomal recessive deficiency of homogentisic acid oxidase, an enzyme involved in tyrosine catabolism
   b. Alkaptonuria is a relatively benign condition, but it may manifest with moderate to severe arthralgia.
   c. Presentation: Grayish-brown sclera, ochronosis (darkened tissues), dark urine, decreased joint mobility (due to deposition of homogentisic acid in joints), calcifications in affected areas
   d. Labs: ↑ Homogentisic acid in urine, spinal disk degeneration and calcification
3. Albinism
   a. Autosomal recessive deficiency of tyrosinase or a defect of tyrosine transport into cells. Albinism may also result from a defect or deficiency of melanocytes (less common).
   b. This results in the inability to synthesize melanin, which increases the risk of skin cancer.
   c. **Presentation:** Hypopigmentation of the skin and hair, iris depigmentation, visual impairment, photosensitivity.
   d. **Labs:** ↓ Tyrosinase activity (in some cases). Genetic tests provide the most definitive diagnosis.
   e. **Treatment:** Treatment is normally not indicated.

4. Homocystinuria
   a. Autosomal recessive deficiency of cystathionine synthase, an enzyme involved in the synthesis of cysteine from homocysteine.
   b. Homocystinuria may also be due to a deficiency of cofactors in the synthesis of methionine from homocysteine.
   c. The result is the accumulation of homocysteine.
   d. **Presentation:** Mental retardation, subluxation of the lenses of the eyes, Marfanoid habitus (tall stature, long limbs, joint hypermobility, and long fingers [arachnodactyly]).
   e. **Labs:** ↑ Homocysteine, ↑ methionine (only in cystathionine synthase deficiency), osteoporosis, kyphosis, atherosclerosis.
   f. **Treatment:** Supplementation with vitamins B<sub>6</sub> and B<sub>12</sub> and folic acid, increased dietary cysteine, decreased dietary methionine.

5. Cystinuria
   a. Autosomal recessive defect of the renal tubular transporter of COLA (cysteine, ornithine, lysine, arginine).
   b. Cysteine reabsorption is impaired.
   c. **Presentation:** Recurrent urinary tract infections.
   d. **Labs:** The presence of hexagonal crystals in urine is considered pathognomonic for cystinuria. Bilateral renal calculi and renal colic are also common.
   e. **Treatment:** Hydration, potassium citrate (alkalinizes urine), penicillamine or /H<sub>9251</sub>-mercaptopropionylglycine (bind cystine and increase its solubility).

6. Maple syrup urine disease
   a. Autosomal recessive deficiency of branched-chain α-ketoacid dehydrogenase, an enzyme that breaks down branched-chain amino acids (i.e., Ile, Leu, Val).
   b. This causes accumulation of branched-chain amino acids and their corresponding α-ketoacids.
   c. **Presentation:** Urine that smells like maple syrup (Ile excretion), mental retardation, CNS defects (Leu accumulation).
   d. **Labs:** Serum alloisoleucine, ↑ urine organic acids.
   e. **Treatment:** Decreased dietary branched-chain amino acids, dialysis (severe cases).

7. Hartnup disease
   a. Autosomal recessive defect of neutral amino acid transporters in the kidneys and intestines.
   b. Causes malabsorption of tryptophan and lack of niacin synthesis.
   c. Hartnup disease is generally asymptomatic except in cases of poor diet.
   d. **Presentation:** Niacin deficiency causes dementia, dermatitis, and diarrhea (pellagra). Photosensitivity is also common.
   e. **Labs:** ↑ Neutral amino acids in urine.
   f. **Treatment:** High dietary protein, decreased exposure to sunlight, nicotinic acid or nicotinamide supplementation.
II. Collagen

A. Classification
1. Collagen is the most abundant protein in the body. It provides structure and substance to extracellular space.
2. Type I: Found in skin, bones, dentin, and scar tissue. This is the most common type of collagen.
3. Type II: Found in cartilage, vitreous body of the eye, and nucleus pulposus
4. Type III: Found in blood vessels, skin, uterus, fetal tissue, and granulation tissue
5. Type IV: Found in basement membrane

B. Synthesis and structure (Figure 11-5)
1. Collagen is composed of very long chains with a regular structure of Gly-Pro-X, or Gly-X-hydroxyproline.
2. Collagen synthesis begins inside fibroblasts, then finishes outside of the cells.
   a. Alpha chains (preprocollagen) are synthesized in the rough endoplasmic reticulum (RER) of fibroblasts.
   b. Lysine and proline residues are then hydroxylated in a reaction that requires vitamin C.
   c. Hydroxylated lysine residues are then glycosylated, and hydrogen and sulfide bonds are formed as alpha chains are linked into a triple helix (procollagen).
   d. Procollagen is exocytosed, and the terminal regions are cleaved (tropocollagen).
   e. Finally, tropocollagen chains are cross-linked through covalent bonds between lysine and hydroxylysine residues to form large collagen fibrils (collagen).

C. Osteogenesis imperfecta (OI)
1. Most commonly an autosomal dominant deficiency of collagen synthesis involving type I collagen
2. OI causes weak bones, hence its alternate name, “brittle bone disease.”
3. Subtypes
   a. Type I: Mildest and most common subtype. Type I collagen is normal but is synthesized at a low level. Alternatively, type I collagen may be abnormal, although this is less frequent.
   b. Type II: Collagen is deficient in both quantity and quality. This is a very severe condition that causes intrauterine death or early postnatal death.
   c. There are many other subtypes of OI with varying severity.
4. Presentation: Blue sclerae (the choroid is visible through the thin collagen mesh), skin and teeth deformities, hearing loss, scoliosis, limb deformities, frequent fractures from minimal trauma
5. Radiology: Fractures on X-ray, excessive callus formation, thoracic cage deformity, skull changes, low bone density
6. Treatment: Surgical correction; pamidronate (inhibits osteoclasts); increased dietary intake of calcium, phosphorus, and vitamin D

D. Ehlers–Danlos syndrome
1. May be either autosomal dominant or recessive. Ehlers–Danlos may be caused by varying defects in different types of collagen, but it affects connective tissue rather than bone.
2. Causes weakness of blood vessels, joint cartilage, and skin
3. Presentation: Muscle weakness, easy bruising, hemorrhages, hyperelastic skin, joint hypermobility. Aneurysms are also common.
4. Radiology: Opaque nodules on X-ray, disorderly dermal collagen fibers
5. Treatment: There is no treatment for Ehlers–Danlos syndrome. Only the symptoms can be managed.

E. Alport syndrome
1. Most commonly an X-linked dominant defect in type IV collagen, although it may also be autosomal dominant or recessive
2. This causes weakness of the basement membrane, which is most evident in the kidneys.
   a. Lenticous is a thinning of the capsule around the lens of the eye.
Collagen synthesis

1. Selected proline and lysine residues are hydroxylated
2. mRNA is translated into prepro-α polypeptide chains that are extruded into the endoplasmic reticulum where signal sequence is removed
3. mRNA is translated into prepro-α polypeptide chains that are extruded into the endoplasmic reticulum where signal sequence is removed
4. Genes for pro-α1- and pro-α2-chains are transcribed into mRNAs
5. Requires vitamin C

- Three pro-α-chains assemble
- Intrachain and interchain disulfide bonds form at C-terminal propeptide extension

6. Selected lysine residues are glycosylated with glucose (●) and galactose (○)

7. Procollagen molecule

8. Triple helix forms by zipper-like folding

9. N-terminal and C-terminal propeptides cleaved by procollagen peptidases

10. Procollagen molecule secreted from Golgi vacuole into extracellular matrix

11. Cross-linked fibrils

12. Self-assembly of collagen molecules into fibrils and subsequent cross-linking

4. **Labs:** Hematuria, proteinuria, nephritis, red blood cell (RBC) casts
5. **Treatment:** There is no definite treatment for Alport syndrome. Kidney transplantation is indicated for end-stage renal disease.

### III. Elastin

#### A. Structure
1. Elastin is an extracellular matrix protein. It is not as strong as collagen, but it stretches more.
2. Found in blood vessels (especially arteries) and alveoli of lungs, larynx, and ligamenta flava of the spine
3. Contains high amounts of proline and glycine. In contrast to collagen, these residues are nonhydroxylated.
4. Tropoelastins are held together by a matrix of fibrillin.

#### B. Marfan syndrome (Figure 11-6)
1. Autosomal dominant defect of fibrillin
2. This causes weakness of blood vessels, skeletal deformities, cardiovascular abnormalities (e.g., aortic dissection), and pulmonary difficulties.

---

**Figure 11-6**

**A.** Marfan syndrome in a 14-year-old boy. Note arachnodactyly, relatively long limbs (dolichostenomelia), pectus carinatum, sparse subcutaneous fat, unilateral genu valgum, and pes planus. The patient also had scoliosis. This patient died of aortic rupture at age 15 years.

**B.** A positive Steinberg thumb sign consists of protrusion of the distal phalanx of the thumb beyond the ulnar border of the clenched fist and reflects both longitudinal laxity of the hand and a long thumb. (Reproduced with permission from Koopman WJ, Moreland LW. *Arthritis and Allied Conditions A Textbook of Rheumatology*. 15th ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2005.)
3. **Presentation**: Pectus carinatum, pectus excavatum, genu valgum, subluxation of the lens of the eye, tall stature, long limbs, long fingers (arachnodactyly), joint hypermobility, positive Steinberg sign (Figure 11-6B), scoliosis
4. **Labs**: There are no specific lab tests for Marfan syndrome other than screening for genetic markers.
5. **Treatment**: β-blockers for heart conditions, surgical intervention

C. α1-Antitrypsin deficiency
1. Autosomal recessive deficiency of α1-antitrypsin, which inhibits elastase
2. The lack of elastase inhibition leads to the systemic breakdown of elastin.
3. Defective α1-antitrypsin proteins may also accumulate and polymerize in hepatocytes.
4. **Presentation**: Panacinar emphysema and associated dyspnea (most common), cirrhosis, hepatitis
   - Panacinar emphysema affects the entire alveolus at once. In contrast, centriacinar emphysema affects the bronchioles and spreads to the alveoli, whereas paraseptal emphysema affects only the distal alveolar ducts and sacs.
5. **Labs**: ↓ Serum α1-antitrypsin, ↑ AST, ↑ ALT, ↓ pulmonary function
6. **Treatment**: Prolastin (plasma proteins will replace missing enzymes), liver or lung transplantation

IV. **Nitrogen metabolism**

A. **Urea cycle** (Figure 11-7)
   1. **Overall reaction**: \( \text{NH}_3 \rightarrow \text{urea} \). This requires three adenosine triphosphate (ATP) and aspartate.
   2. **Rate-limiting step**: Ammonia + bicarbonate \( \rightarrow \) carbamoyl phosphate via carbamoyl phosphate synthase I
   3. This pathway excretes excess nitrogen from amino acid metabolism in the form of urea.

B. **Alanine cycle** (Figure 11-8)
   1. Pathway for the movement of nitrogen to the liver for conversion to uric acid
   2. Pyruvate and glutamate are converted to alanine and α-ketoglutarate in the cells via alanine aminotransferase (ALT). This requires vitamin B₆ (in the form of pyridoxal phosphate).
   3. Alanine is released into the blood, where it travels to the liver.
   4. Alanine and α-ketoglutarate are converted back to pyruvate and glutamate in the liver, also via ALT and vitamin B₆.
   5. Glutamate then undergoes deamination, donating its amino group to the urea cycle and regenerating α-ketoglutarate.
   6. **Transamination**: The exchange of an amine group for a keto group between two molecules. In this case, an amino acid (glutamate, alanine) exchanges an amine group for a keto group from an α-ketoacid (pyruvate, α-ketoglutarate).
C. Ornithine transcarbamoylase deficiency
   1. X-linked recessive. This is the most common disorder of the urea cycle.
   2. Ornithine transcarbamylase (OTC) deficiency results in an inability to synthesize citrulline from carbamoyl phosphate and ornithine. This causes the urea cycle to stall. Ammonia then accumulates, causing hyperammonemia.
   3. Presentation: Slurred speech, somnolence, vomiting, blurred vision
   4. Labs: Hematuria, orotic acid in the blood and urine, cerebral edema, decreased blood urea nitrogen (BUN) (due to decreased production of urea)
   5. Treatment: Phenylbutyrate, which binds glutamine and facilitates its excretion

D. Hyperammonemia
   1. Various causes. It may be hereditary or acquired.
   2. Excess ammonia depletes \( \alpha \)-ketoglutarate, which impairs the tricarboxylic acid (TCA) cycle.
   3. Presentation: Similar to OTC deficiency. Additional symptoms are associated with the underlying cause.
   4. Labs: Alkalosis of blood, ↑ serum glutamine, ↑ serum alanine
   5. Treatment: Treated with lactulose, a sugar that cannot be absorbed by enterocytes. It then travels to the intestines, where it is broken down by bacteria, creating an acidic environment. Ammonia in the blood diffuses through intestinal enterocytes, where it is protonated by hydrogen ions, becoming ammonium. Ammonium cannot reenter the blood and is excreted in the stool.

## CARBOHYDRATE METABOLISM

### I. Glucose uptake and processing

A. Glucose transporters
   1. Glucose enters the body through enterocytes in the gut. Once in circulation, it enters cells through glucose transporters (GLUT).
   2. GLUT-1: Found on RBCs and the endothelium of the blood–brain barrier, as well as many other tissues. Mediates basal (low-level) uptake of glucose.
   3. GLUT-2: Found on cells that regulate glucose (e.g., hepatocytes, pancreatic beta cells), although there is some evidence that beta cell GLUT-1 may be more important for stimulating insulin release
   4. GLUT-3: Found mainly on neurons and the placenta
   5. GLUT-4: Found on skeletal muscle and adipose tissue. This is the insulin-dependent glucose transporter.
B. Hexokinase and glucokinase
   1. Enzymes that phosphorylate glucose to glucose-6-phosphate, which confers a negative charge. It can no longer cross the membrane and thus remains inside the cell.
   2. **Glucokinase**: Found in hepatocytes and pancreatic beta cells. Induced by insulin.
      a. Very high $K_m$ (low affinity for glucose; high concentration to reach half of maximum reaction velocity)
      b. Very high $V_{max}$ (high capacity to phosphorylate glucose)
      c. Glucokinase activity is very low except when glucose concentration increases substantially.
   3. **Hexokinase**: Found in many cells of the body. Not induced by insulin.
      a. Low $K_m$ (high affinity for glucose), but low $V_{max}$ (low capacity for glucose phosphorylation)

II. **Glycolysis** *(Figure 11-9)*
   A. Overview
      1. **Overall reaction**: Glucose $\rightarrow$ 2 pyruvate + 2 ATP
      2. **Rate-limiting step**: Fructose-6-phosphate $\rightarrow$ fructose-1,6-bisphosphate via phosphofructokinase-1 (PFK-1)
      3. This process does not require oxygen.
      4. All cells of the body can break down glucose, but it occurs mainly in RBCs (other cells obtain most of their energy through aerobic respiration).
   B. Important steps
      1. Glucose $\rightarrow$ glucose-6-phosphate via hexokinase or glucokinase
      2. Fructose-6-phosphate $\rightarrow$ fructose-1,6-bisphosphate via PFK-1
         a. Promoted by AMP and fructose-2,6-bisphosphate
         b. Inhibited by ATP and citrate (feedback inhibition from TCA cycle)
      3. Fructose-1,6-bisphosphate $\rightarrow$ glyceraldehyde-3-phosphate and dihydroxyacetone phosphate (DHAP)
      4. DHAP $\rightarrow$ glyceraldehyde-3-phosphate

---

**QUICK HIT**
Because RBCs can only perform glycolysis, glycolytic enzyme deficiencies cause hemolytic anemia. **Pyruvate kinase** deficiency is the most common cause.
5. Glyceraldehyde-3-phosphate $\rightarrow$ 1,3-bisphosphoglycerate via glyceraldehyde-3-phosphate dehydrogenase (GAPDH).
6. Phosphoenolpyruvate (PEP) $\rightarrow$ pyruvate via pyruvate kinase
   a. Promoted by fructose-1,6-bisphosphate
   b. Inhibited by ATP and alanine
7. Phosphofructokinase-2/fructose bisphosphatase-2 (PFK-2/FBP-2) can promote either glycolysis or gluconeogenesis.
   a. Fed state: PFK-2 promotes glycolysis by converting glucose-6-phosphate to fructose-2,6-bisphosphate, which allosterically activates PFK-1.
   b. Fasting state: Glucagon binds cellular receptors, stimulating adenylyl cyclase to convert ATP to cAMP. cAMP activates protein kinase A, which phosphorylates PFK-2, inactivating it, and activating FBP-2. FBP-2 then converts fructose-1,6-bisphosphate to fructose-6-phosphate, which can then enter gluconeogenesis.

III. Gluconeogenesis (Figure 11-9)
A. Overview
1. Overall reaction: 2 pyruvate $\rightarrow$ glucose. This requires four ATP, two GTP, and two nicotinamide adenine dinucleotide (NADH).
2. Rate-limiting step: Fructose-1,6-bisphosphate $\rightarrow$ fructose-6-phosphate via fructose-1,6-bisphosphatase
3. The steps of gluconeogenesis are essentially the steps of glycolysis reversed, with a few exceptions (Table 11-1).
4. Whereas all cells can perform glycolysis, most cannot perform gluconeogenesis. This occurs mainly in the liver as well as the kidneys and small intestine under fasting conditions.
5. Nongluconeogenic cells lack glucose-6-phosphatase. These cells cannot convert glucose-6-phosphate (G6P) to glucose in the final step of gluconeogenesis. G6P is then shunted into the glycogenesis pathway.
6. Pyruvate may come from a number of sources, including TCA cycle intermediates and amino acids.
B. Important steps
1. Pyruvate $\rightarrow$ oxaloacetate via pyruvate carboxylase. This requires biotin and ATP.
   a. Promoted by acetyl-CoA
2. Oxaloacetate $\rightarrow$ malate, which requires NADH. Malate is then transported out of the mitochondrion into the cytosol. Malate $\rightarrow$ oxaloacetate, which requires NAD\(^+\).
   a. Gluconeogenesis mainly occurs in the cytosol, but oxaloacetate cannot cross the mitochondrial membrane. It must first be converted to malate, which can move across via transporter proteins. Once in the cytosol, malate is converted back into oxaloacetate.
3. Oxaloacetate $\rightarrow$ PEP via PEP carboxykinase. This requires GTP.
4. 3-phosphoglycerate $\rightarrow$ 1,3-bisphosphoglycerate. This requires ATP.
5. Fructose-1,6-bisphosphate $\rightarrow$ fructose-6-phosphate via fructose-1,6-bisphosphatase
   a. Promoted by ATP
   b. Inhibited by AMP and fructose-2,6-bisphosphate
6. Glucose-6-phosphate $\rightarrow$ glucose via glucose-6-phosphatase. Glucose can now exit the cell.
C. Cori cycle (Figure 11-10)
1. Overall reaction: Pyruvate $\rightarrow$ lactate $\rightarrow$ pyruvate
2. This is also known as the lactic acid cycle.
3. Pyruvate is converted to lactate via lactate dehydrogenase in cells.
4. Lactic acid is then released into the blood where it travels to the liver.
5. Lactate is converted to pyruvate in the liver, also via lactate dehydrogenase.
6. Pyruvate then enters gluconeogenesis and is converted to glucose.

IV. Glycogenesis
A. Overview
1. Overall reaction: Glucose $\rightarrow$ glycogen, requiring one ATP per glucose molecule
2. Rate-limiting step: UDP-glucose attachment to glycogen molecule via glycogen synthase
TABLE 11-1  Glycolysis versus Gluconeogenesis

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<th>Intermediates</th>
<th>Gluconeogenesis Enzymes</th>
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Cori cycle

**ANAEROBIC GLYCOLYSIS**

**GLUCONEOGENESIS**
3. Glucose is converted into chains and attached to existing glycogen molecules.
4. Glucose conversion to glucose-6-phosphate requires one ATP, but glycogenesis mainly begins with glucose-6-phosphate from gluconeogenesis.
5. Occurs in skeletal muscles and hepatocytes

B. Important steps
1. Glucose $\rightarrow$ glucose-6-phosphate via glucokinase or hexokinase. This requires ATP.
2. Glucose-6-phosphate $\rightarrow$ glucose-1-phosphate via phosphoglucomutase
3. Glucose-1-phosphate $\rightarrow$ UDP-glucose via UDP-glucose phosphorylase. This requires UTP.
4. UDP-glucose is attached to a glucose chain on the glycogen molecule through an $\alpha$-1,4 linkage via glycogen synthase.
5. Glucose chains are attached to other glucose chains midstrand through $\alpha$-1,6 linkages. This is catalyzed by branching enzyme.

V. Glycogenolysis (Figure 11-11)
A. Overview
1. Overall reaction: Glycogen $\rightarrow$ glucose. This does not consume ATP.
2. Rate-limiting step: Breakdown of $\alpha$-1,4 linkages by glycogen phosphorylase
3. Glucose monomers are sequentially removed from glycogen and processed into glucose.
4. Requires the breakdown of both the $\alpha$-1,4 and the $\alpha$-1,6 linkages.
B. Important steps
1. $\alpha$-1,4 linkages are broken down by glycogen phosphorylase to yield glucose-1-phosphate.
   a. Promoted by epinephrine and glucagon
   b. Inhibited by insulin
2. Glucose-1-phosphate $\rightarrow$ glucose-6-phosphate via phosphoglucomutase
3. Glucose-6-phosphate $\rightarrow$ glucose via glucose-6-phosphatase
   a. Because most cells cannot perform this step, glucose-6-phosphate is then used to generate ATP through glycolysis.
4. $\alpha$-1,6 linkages are broken down by $\alpha$-1,6 glucosidase. This reaction produces glucose directly.

VI. Glycogen storage diseases (Figure 11-11)
A. McArdle disease
1. Autosomal recessive deficiency of myophosphorylase (muscle isoform of glycogen phosphorylase). This is also known as type V glycogen storage disease.
2. Muscle cells are unable to break down the $\alpha$-1,4 linkages of glycogen.
3. Muscle cells then swell due to increased glycogen as well as osmotic influx of water.
4. Lysis of muscle cells releases myoglobin, which can interfere with kidney function (rhabdomyolysis).
5. Presentation: Muscle cramps, muscle weakness, fatigue, burgundy-colored urine
6. Labs: ↑ Creatine kinase, myoglobinuria
7. Treatment: Restriction of intense physical activity
B. Von Gierke disease
1. Autosomal recessive deficiency of glucose-6-phosphatase. It is also known as type I glycogen storage disease.
2. The inability to synthesize glucose (either from gluconeogenesis or glycogenolysis) affects hepatocytes, kidney cells, and small intestine cells.
3. Glucose-6-phosphate is shunted into glycogenesis, resulting in excess glycogen.
4. Presentation: Seizures (due to severe hypoglycemia), hepatomegaly, hypertension, xanthomas
5. Labs: ↑ Serum lactate, hyperlipidemia, nephropathy, gout
6. Treatment: Diet containing high protein and cornstarch (cornstarch takes longer to break down, resulting in a slow, steady release of glucose that can prevent hypoglycemia in glycogen storage diseases). Liver transplantation may be necessary in severe cases.
Glycogenolysis and glycogen storage disorders

**Type I: Von Gierke disease**
- Affects liver, kidney, and intestine
- Fasting hypoglycemia–severe
- Fatty liver, hepatomegaly
- Hyperlacticacidemia and hyperuricemia
- Normal glycogen structure, increased glycogen stored

**Type II: Pompe disease**
- Inborn lysosomal enzyme defect
- Generalized (liver, heart, muscle)
- Excessive glycogen concentrations found in abnormal vacuoles in the cytosol
- Normal blood sugar levels
- Severe cardiomegaly
- Early death usually occurs
- Normal glycogen structure

**Type IIIa: Cori disease**
- Defect in the muscle debranching enzyme versus type IIIb which involves the liver enzyme

**Type V: McArdle syndrome**
- Skeletal muscle affected, liver enzyme normal
- Inborn lysosomal enzyme defect
- Generalized (liver, heart, muscle)
- Hyperlacticacidemia and hyperuricemia
- Normal glycogen structure, increased glycogen stored

(Adapted with permission from Champe PC, Harvey RA, Ferrier DR. Lippincott’s Illustrated Reviews: Biochemistry. 2nd ed. Philadelphia, PA: Lippincott-Raven; 1994:41.)
C. Cori disease
1. Autosomal recessive deficiency of debranching enzyme. It is also known as type III glycogen storage disease.
2. Cells are unable to break down the α-1,6 linkages of glycogen (α-1,4 linkages can still be broken down by glycogen phosphorylase).
3. This is generally mild compared to McArdle disease.
4. Presentation: Seizures, hepatomegaly, splenomegaly, growth retardation
5. Labs: Hypoglycemia, myoglobinuria, hyperlipidemia, ↑ serum lactate (in some cases)
6. Treatment: Treatment is unnecessary in many cases. A diet containing high protein and cornstarch may be helpful.

D. Pompe disease
1. Autosomal recessive deficiency of lysosomal α-1,4 glucosidase (part of glycogenolysis in lysosomes)
2. Glycogen accumulates in lysosomes, disrupting many cellular functions.
   a. Incidental lysosomal uptake of glycogen from the cytosol is normal, and a small percentage of glycogen can be found in the lysosomes of most cells.
   b. The enzymes in lysosomal glycogenolysis must function at a lower pH and thus differ from enzymes in cytosolic glycogenolysis.
3. Presentation: Breathing difficulty, muscle weakness, macroglossia, hepatomegaly, depressed reflexes
4. Labs: Aneurysms, cardiomegaly, vacuolar myopathy
5. Treatment: Alglucosidase alfa (infants only), pulmonary hygiene, high-protein diet

VII. Other carbohydrates
A. Fructose metabolism
1. Essential fructosuria: Autosomal recessive deficiency of fructokinase, which converts fructose to fructose-1-phosphate. Fructose appears in the blood and urine and causes mild diuresis. This is a relatively benign condition.
   a. Essential fructosuria does not cause osmotic damage because unphosphorylated fructose simply diffuses back out of the cells.
2. Aldolase B deficiency: Autosomal recessive disease in which fructose metabolism stalls, resulting in the accumulation of fructose-1-phosphate. This trapping of phosphate impairs glycolysis and gluconeogenesis and causes hypoglycemia, vomiting, jaundice, and hepatomegaly. The treatment is decreased fructose/sucrose intake.

B. Galactose metabolism
1. Galactokinase deficiency: An autosomal recessive disease that causes the accumulation of galactitol. This causes cataracts because the lens of the eye is particularly sensitive to sugar accumulation.
   a. Galactose is reduced to galactitol by intracellular aldose reductase, an enzyme that is normally involved in the synthesis of fructose from glucose.
2. Galactosemia: An autosomal recessive deficiency of galactose-1-phosphate uridylyltransferase. This causes accumulation of galactose-1-phosphate, which causes more severe cataracts than in galactokinase deficiency. It also causes hepatomegaly, jaundice, failure to thrive, and mental retardation. The treatment is galactose and lactose restriction.

C. Lactose metabolism
1. Lactase deficiency: An autosomal recessive disease that causes lactose intolerance. Lactose is a dimer, so it does not get absorbed by enterocytes. It then moves into the intestine, where it is processed by bacteria. This causes gas, bloating, and osmotic diarrhea. This can be treated with lactase supplementation or dairy restriction.
   a. Temporary lactase deficiency can result from infections that erode microvilli, the main source of lactase.

D. Ethanol metabolism
1. Ethanol can be converted to acetaldehyde via alcohol dehydrogenase. This generates NADH.
   a. Alcohol dehydrogenase follows zero-order kinetics. This means that its rate is independent of the concentration of ethanol.
2. Acetaldehyde is further converted to acetate via **acetaldehyde dehydrogenase**. This also generates NADH.
   a. NADH made in this manner does not usually enter the electron transport chain because ethanol metabolism takes place in the liver.
   b. NADH builds up and must be reoxidized to \( \text{NAD}^+ \). The liver accomplishes this by converting pyruvate to lactate and oxaloacetate to malate. This impairs the TCA cycle and gluconeogenesis and causes hypoglycemia.
3. Acetate can then be converted to acetyl-CoA, resulting in more NADH and FADH\(_2\).
4. **Fomepizole**: Inhibits alcohol dehydrogenase. It is used as an antidote for methanol and ethylene glycol poisoning.
5. **Disulfiram**: Inhibits acetaldehyde dehydrogenase. Buildup of acetaldehyde causes vomiting and flushing. Thus, disulfiram is prescribed to recovering alcoholics to deter drinking.

### OXIDATIVE PROCESSES

#### I. Aerobic respiration (oxidative phosphorylation)

A. Electron transport chain (Figure 11-12)
   1. Occurs in the mitochondria. Electrons are transferred from NADH or FADH\(_2\) to membrane-bound protein complexes.
   2. Electrons move down chain through a series of redox reactions. This provides energy for each complex to pump protons from the mitochondrial matrix to the intermembranous space.

\[ \text{NAD} + \text{H}^+ + \text{NADH} \rightarrow 2\text{H}^+ + \text{NAD}^+ \]

\[ 1/2\text{O}_2 + 2\text{H}^+ \rightarrow \text{H}_2\text{O} \]

**NAD**, nicotinamide adenine dinucleotide; **e\(^-\)**, electron.

![Electron transport chain](image_url)
3. This creates an electrochemical gradient. Protons then flow down the gradient through ATP synthase, which uses the energy to synthesize ATP.

B. Important steps

1. **Complex I**: Also known as NADH dehydrogenase. It converts NADH to \( \text{NAD}^+ \).
2. **Complex II**: Also known as succinate dehydrogenase. It converts \( \text{FADH}_2 \) to FAD. This requires coenzyme Q.
   a. The transfer of electrons from \( \text{FADH}_2 \) to complex II occurs at a lower energy level than at complex I. This is why \( \text{FADH}_2 \) provides fewer ATP molecules than NADH.
3. **Complex III**: Contains cytochromes B and C1. This transfers electrons to cytochrome c.
4. **Complex IV**: Cytochromes A and A3. It accepts electrons from cytochrome c. Electrons join oxygen and hydrogen to form water.
5. **Complex V**: ATP synthase. Protons travel through this complex from the intermembranous space to the mitochondrial matrix. This powers the synthesis of ATP from ADP and \( \text{P}_i \).

C. Inhibitors of the electron transport chain

1. **Complex I**: Inhibited by amobarbital (barbiturate), rotenone, and methyl-phenyl-pyridinium (MPP)
   a. MPP comes from the in vivo processing of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), a neurotoxin that destroys dopaminergic neurons. MPTP is an impurity that can form during the attempted synthesis of 1-methyl-4-phenyl-4-propionoxypiperidine (MPPP), an opioid and meperidine analog.
2. **Complex III**: Inhibited by antimycin A
3. **Complex IV**: Inhibited by cyanide, sodium azide, carbon monoxide, hydrogen sulfide
4. Uncoupling agents: Allow protons to bypass ATP synthase when crossing the membrane. This wastes energy, generating heat.
   a. Thermogenin: Natural substance found in brown fat. It generates heat in cold temperatures.
   b. 2,4-Dinitrophenol: Found in wood-preserving agents
   c. Aspirin: Uncoupling action causes hyperthermia in aspirin overdose.

II. Other oxidative processes

A. Tricarboxylic acid cycle (Figure 11-13)

1. Overall reaction: Pyruvate → Oxaloacetate + 3 NADH + 1 FADH₂ + 1 GTP
2. Rate-limiting step: Isocitrate → α-ketoglutarate via isocitrate dehydrogenase
3. Replenishes reducing agents and provides precursors and intermediates for a number of reactions
4. Pyruvate is converted to acetyl-CoA via the **pyruvate dehydrogenase complex**. This reaction requires thiamine pyrophosphate (TPP), lipoic acid, coenzyme A (CoA), flavin adenine dinucleotide (FAD), and nicotinamide adenine dinucleotide (NAD⁺).
   a. Pyruvate dehydrogenase deficiency: Pyruvate is shunted into other pathways. Excess conversion of pyruvate to lactate causes lactic acidosis. Neurologic defects are common. Diets high in fat can provide other substrates for acetyl-CoA synthesis. Ketogenic amino acids (Lys, Leu) are also helpful.
   b. The most common form displays an X-linked dominant pattern of inheritance. Other forms are autosomal recessive.
   c. This may be an acquired deficiency, often due to arsenic poisoning or lack of thiamine (common in alcoholics).
5. Acetyl-CoA is converted to citrate via citrate synthase.
6. Isocitrate is converted to α-ketoglutarate via isocitrate dehydrogenase. This step produces NADH and requires the exact same cofactors as pyruvate dehydrogenase.
7. α-Ketoglutarate is then converted to succinyl-CoA via α-ketoglutarate dehydratase. This step produces NADH.

B. Hexose monophosphate (HMP) shunt (pentose phosphate pathway)

1. Overall reaction: Glucose-6-phosphate → nicotinamide adenine dinucleotide phosphate (NADPH) and ribulose-5-phosphate

**QUICK HIT**

Coenzyme Q supplementation may optimize this process. Heart attack patients receive coenzyme Q to maximize the capacity of cardiac myocytes to generate ATP.

**QUICK HIT**

Arsenic inhibits lipoic acid. Arsenic poisoning presents with garlic breath, rice-water stool, and vomiting.

**MNEMONIC**

Remember the cofactors for pyruvate dehydrogenase by the phrase, “Tender Loving Care For Nobody”:
TPP
Lipoic acid
CoA
FAD
NAD⁺
2. NADPH is required for fatty acid synthesis, cholesterol synthesis, oxygen free radical generation, protection from oxidative damage, and cytochrome p450 activities.

3. Ribulose-5-phosphate is used to generate PRPP, which is required for nucleotide synthesis.

C. Antioxidant functions
   1. Protects cells against oxidative damage
   2. RBCs convert $H_2O_2$ to $H_2O$ via glutathione peroxidase. This requires glutathione and NADPH.

3. Glucose-6-phosphate dehydrogenase deficiency: X-linked recessive disease, resulting in the inability to synthesize NADPH. RBCs are vulnerable to oxidative damage, resulting in hemolytic anemia. Heinz bodies and bite cells are seen on blood smear. Patients must avoid substances that cause oxidative damage, such as fava beans, sulfonamides, and antimalarial drugs.

### Table 11-2  Paths of Pyruvate

<table>
<thead>
<tr>
<th>Reaction</th>
<th>Enzyme</th>
<th>Subsequent Pathway</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pyruvate $\rightarrow$ Oxaloacetate</td>
<td>Pyruvate carboxylase</td>
<td>Gluconeogenesis</td>
</tr>
<tr>
<td>Pyruvate $\rightarrow$ Lactate</td>
<td>Lactate dehydrogenase</td>
<td>Cori cycle</td>
</tr>
<tr>
<td>Pyruvate $\rightarrow$ Alanine</td>
<td>Alanine transaminase</td>
<td>Alanine cycle</td>
</tr>
<tr>
<td>Pyruvate $\rightarrow$ Acetyl-CoA</td>
<td>Pyruvate dehydrogenase</td>
<td>TCA cycle</td>
</tr>
</tbody>
</table>

Pyruvate is extremely versatile and can enter a number of different pathways (Table 11-2).
D. Oxidative burst
1. There are two different reactive oxygen species that are used in the oxidative burst: superoxide and hydrogen peroxide. In addition, hydrogen peroxide can be used to create hypochlorous acid.
2. \( \text{O}_2^- + \text{NADPH} \rightarrow \text{NADP}^+ + \text{H}^+ + \text{O}_2 \) (superoxide) via NADPH oxidase
3. \( \text{O}_2^- + \text{H}^+ \rightarrow \text{O}_2 + \text{H}_2\text{O}_2 \) (hydrogen peroxide) via superoxide dismutase
4. \( \text{H}_2\text{O}_2 + \text{Cl}^- \rightarrow \text{H}_2\text{O} + \text{HOCl} \) (hypochlorous acid) via myeloperoxidase
5. Superoxide, hydrogen peroxide, and hypochlorous acid are all important in antibacterial immune functions.
6. Chronic granulomatous disease: X-linked recessive or autosomal recessive deficiency of NADPH oxidase. Macrophages cannot synthesize reactive oxygen species, although they can still utilize exogenous hydrogen peroxide. However, this is ineffective against catalase-positive organisms (e.g., \textit{Staphylococcus aureus}, \textit{Aspergillus}), making patients vulnerable to these infections.

**LIPID METABOLISM**

I. Lipoproteins (Table 11-3)

A. Transport
1. Triglycerides are broken down in the small intestine by pancreatic lipase.
2. Chylomicrons: Created from dietary fat by enterocytes and released into the lymph via ApoB48. Chylomicrons enter the blood, where peripheral cells pull triglycerides from them as they circulate. The remnants travel to the liver and are taken up by lipoprotein-related receptor protein (LRP).
   a. Peripheral cells take triglycerides from lipoproteins using the enzyme lipoprotein lipase.
3. VLDL: Very low-density lipoprotein (VLDL) is created from chylomicron remnants and is released into the blood via ApoB100.
4. IDL: Once VLDL has lost a significant amount of triglycerides, it is known as intermediate-density lipoprotein (IDL).
5. LDL: When IDL has lost most of its remaining triglycerides, it is known as low-density lipoprotein (LDL). It can serve as a cholesterol source for other cells (especially hepatocytes) via clathrin-mediated endocytosis or LRP.
6. HDL: High-density lipoprotein (HDL) is synthesized in the liver and can accept excess cholesterol from cells via lecithin cholesterol acyltransferase (LCAT). It may then donate cholesterol to VLDL or to LDL via cholesterol ester transfer protein (CETP) or to hepatocytes via scavenger receptor B1 (SRB1). For this reason, the cholesterol content of HDL varies widely.
7. Abetalipoproteinemia: Autosomal recessive mutation in microsomal triglyceride transfer protein (MTTP) that prevents synthesis of ApoB48 and ApoB100. Enterocytes cannot release chylomicrons into lymph. This causes steatorrhea in infancy and failure to thrive. Swollen enterocytes are seen on biopsy. Acanthocytes, night blindness, and ataxia are also common. This can be treated with vitamin E.

<table>
<thead>
<tr>
<th>Lipoprotein</th>
<th>% Triacylglycerols</th>
<th>% Cholesterol</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chylomicrons</td>
<td>84–86</td>
<td>5</td>
</tr>
<tr>
<td>VLDL</td>
<td>55</td>
<td>19–25</td>
</tr>
<tr>
<td>IDL</td>
<td>31</td>
<td>29–30</td>
</tr>
<tr>
<td>LDL</td>
<td>6–10</td>
<td>50</td>
</tr>
<tr>
<td>HDL</td>
<td>4–6</td>
<td>16–50 (highly variable)</td>
</tr>
</tbody>
</table>
B. Apolipoproteins
1. ApoB48: Mediates secretion of chylomicrons from intestine
2. ApoB100: Found on VLDL, IDL, and LDL
3. ApoE: Mediates extra remnant uptake
4. ApoA1: Activates LCAT. Found on HDL
5. ApoC2: Cofactor for lipoprotein lipase

C. Dyslipidemia
1. An abnormal amount of lipids in the blood. Most cases of dyslipidemia are classified as hyperlipidemia.
2. Type I hyperlipidemia: Autosomal recessive mutation of lipoprotein lipase or ApoC2 (activates lipoprotein lipase). This causes hyperchylomicronemia, which leads to acute pancreatitis, hepatosplenomegaly, and eruptive xanthomas.
3. Type IIa hyperlipidemia: Autosomal dominant mutation that causes a decrease or absence of LDL receptors. This leads to increased LDL causing familial hypercholesterolemia. The result is accelerated atherosclerosis, tendon xanthomas (especially the Achilles tendon), xanthomas around the eyelids, and corneal arcus (grayish-blue ring around the cornea) (Figure 11-14).
   a. Homozygosity in type IIa hyperlipidemia causes earlier onset of symptoms.
4. Type IV hyperlipidemia: Autosomal dominant defect in VLDL production in the liver. This leads to familial hypertriglyceridemia, which causes acute pancreatitis.

II. Cholesterol and fatty acids
A. Cholesterol synthesis
1. Overall reaction: Acetyl-CoA + acetoacetyl-CoA → cholesterol
2. Rate-limiting step: 3-Hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) → mevalonate via HMG-CoA reductase
3. Inhibited by statins

B. Fatty acid synthesis
1. Overall reaction: Acetyl-CoA → fatty acids
2. Rate-limiting step: Acetyl-CoA → malonyl-CoA via acetyl-CoA carboxylase
3. Occurs in the cytoplasm of hepatocytes
4. Citrate is transferred out of the mitochondria to the cytoplasm.
5. Citrate and CoA are then converted to oxaloacetate and acetyl-CoA.
6. Acetyl-CoA is then converted to malonyl-CoA, or to acetyl-ACP.
   a. Acyl carrier protein (ACP) is a specialized protein that binds acyl groups from acyl-CoA.
7. Malonyl-CoA is then converted to malonyl-ACP.
8. Malonyl-CoA and acetyl-CoA are converted to butyryl-ACP.
9. The reaction is repeated to elongate the chain into palmitoyl-ACP (a 16-carbon chain), which is then hydrolyzed to palmitate.

C. Fatty acid oxidation
1. Overall reaction: Fatty acid → acetyl-CoA
2. Rate-limiting step: Acyl-CoA + carnitine → acyl carnitine by carnitine acyl-transferase I. After the fatty acid chain is bound to a molecule of CoA, it is then
bound to carnitine for transfer from the cytoplasm through the mitochondrial membrane.
3. In the mitochondria, beta oxidation breaks down fatty acids into molecules of acetyl-CoA.
4. Carnitine acyltransferase deficiency: Accumulation of fatty acids in the cytoplasm causes weakness, hypotonia, and hypoketotic hypoglycemia.

D. Omega-3 fatty acids
1. Essential fatty acids (meaning they cannot be synthesized in the body). They are found in fish oils and flaxseed oil.
2. Omega-3 fatty acids are named for the position of the unsaturated bond at the third carbon.
3. Three forms: eicosapentanoic acid (EPA), docosahexanoic acid (DHA), and alpha linolenic acid (ALA)
4. Omega-3 fatty acids are supplemented in hypertriglyceridemia to lower serum triglyceride levels. They can reduce arrhythmias and may augment nerve and eye development in utero. Additionally, they also reduce inflammation in rheumatoid arthritis.

MALNUTRITION
A. Ketogenesis
1. Overall reaction: 2 acetyl-CoA → acetoacetate
2. Rate-limiting step: Acetoacetyl-CoA → HMG-CoA via HMG-CoA synthase
3. Synthesized in the liver. Fatty acids and amino acids are metabolized to acetoacetate.
4. Acetoacetate and NADH can then be converted to β-hydroxybutyrate. Acetoacetate and β-hydroxybutyrate are two of the three ketone bodies (the third is acetone).
5. Ketone bodies can be used by many cells but most importantly, muscle and brain cells.
6. Ketogenesis occurs when the oxidative capacity of the TCA cycle is exceeded due to excess acetyl-CoA from fatty acid breakdown or when oxaloacetate is depleted due to increased gluconeogenesis, as in starvation.
7. Ketone bodies are metabolized into 2 acetyl-CoA upon reaching other sites.
8. Acetoacetate can spontaneously lose a carbon dioxide (CO₂) to become acetone. This causes fruity-smelling breath, a hallmark of ketosis and diabetic ketoacidosis.

B. Fasting state
1. Postabsorptive period
   a. Glucose is produced in the liver through glycogenolysis and gluconeogenesis.
   b. Fatty acids are produced from adipocytes beginning 4 to 6 hours after the last meal.
   c. Glycogen stores are depleted 10 to 18 hours after the last meal.
2. Starvation mode
   a. Glycogenolysis is low because glycogen stores have been depleted.
   b. Gluconeogenesis is occurring at a high rate.
   c. Fatty acids are being released and broken down.
   d. The brain predominantly uses glucose at this point, whereas the muscles and other tissues mainly use fatty acids.
   e. Ketogenesis begins in intermediate starvation.

C. Malnutrition states
1. Kwashiorkor: Caused by protein malnutrition. The inability to maintain skin regeneration causes lesions. Patients develop fatty liver. Low serum protein creates an osmotic imbalance and causes edema.
   a. Fatty liver is due to an inability to synthesize ApoB100, which normally allows lipoproteins to leave the liver.
2. Marasmus: A condition resulting from total caloric malnutrition. This is characterized by tissue and muscle wasting, loss of subcutaneous fat, and variable edema.
3. **Refeeding syndrome**: The result of sudden food intake after prolonged starvation. During fasting, the body adapts by releasing osmotically active substances (e.g., potassium, phosphates) into the blood to maintain osmotic balance. A sudden increase in caloric intake causes all cells to shift from fasting to fed state at once, resulting in uptake of many nutrients in blood. This depletion of magnesium, phosphate, potassium, and so forth from the blood can cause arrhythmias and neurologic problems.

## ENZYMATIC CATALYSTS

### I. **Minerals**

#### A. Iron
1. Found in hemoglobin and myoglobin. Iron is stored in the liver, spleen, and bone marrow.
2. **Ferritin**: Binds iron and stores it within cells. Ferritin is found in high concentration in hepatocytes. It is also an acute-phase reactant (the liver releases ferritin to bind up free iron in order to sequester it from pathogens).
3. **Transferrin**: Binds free ferric molecules and transports them through the plasma. Transferrin is increased in cases of iron deficiency.
4. **Iron poisoning**: Causes peroxidation of lipid membranes and free radical generation. Iron poisoning initially results in gastric bleeding and hypovolemic shock. Metabolic acidosis follows, and gastrointestinal (GI) scarring can create obstructions weeks later.

#### B. Zinc
1. Common cofactor for many enzymatic reactions
2. Zinc is required for zinc-finger DNA transcription factors as well as lactate dehydrogenase, and carbonic anhydrase. Zinc is also required for optimal immune responses.
3. Zinc is supplemented in patients healing from wounds because these patients have a higher zinc requirement due to increased DNA transcription.
4. **Zinc deficiency**: Causes delayed wound healing, decreased immune response, acrodermatitis enteropathica (rash around eyes, mouth, nose, and anus), anorexia, diarrhea, growth retardation, depressed mental function, poor night vision, infertility

#### C. Calcium
1. Parathyroid hormone (PTH) regulates calcium metabolism. Excess PTH causes hypercalcemia and “stones, bones, groans, and psychiatric overtones.”
2. Hypocalcemia presents with Trousseau sign (carpal muscle spasm upon tightening of blood pressure cuff) and Chvostek sign (facial muscle spasm upon tapping the cheek).
3. Calcium is required for muscle contraction, neurotransmitter release, platelet function, coagulation cascades, and various intracellular processes including the utilization of ATP and glucose.

#### D. Lead
1. **Lead poisoning**: Decreased IQ, hearing problems, growth impairment, peripheral neuropathy, wrist drop, foot drop, lead lines in bone (Figure 11-15) and gingivae, anemia, nephropathy, encephalopathy
2. Children living in homes that were painted before 1978 are at greater risk of lead poisoning (lead paint was common before 1978).
3. The treatment is removal of exposure and chelation (succimer, EDTA, dimercaprol in severe cases).

#### E. Mercury
1. **Mercury poisoning**: Mercury accumulates in the kidneys and brain. This causes neurologic problems (e.g., tremor), neuropsychiatric problems (e.g., excitability, insomnia), acroodynia, and abdominal pain.
2. Poisoning can come from eating too much of certain fish. Mercury is also found in old thermometers and batteries.
II. Fat-soluble vitamins

A. Vitamin A

1. Forms
   a. Retinol is the form in which vitamin A is stored in the liver.
   b. Retinal is created from retinol and NAD\(^+\), and it is the active form of vitamin A.
   c. Beta carotene is cleaved in the intestine to yield two molecules of retinal.
   d. Retinoic acid is the irreversibly oxidized form of retinol.

2. Function
   a. Retinol and retinal are both required for vision as well as reproduction.
   b. Retinoic acid is required for various functions including maintenance of skin and epithelium (especially mucus-secreting cells) as well as growth.

3. Vitamin A deficiency
   a. Causes night blindness, xerophthalmia (failure to produce tears), and keratomalacia (wrinkling and clouding of the cornea)
   b. Vitamin A deficiency also presents with Bitot spots (dry, silver-gray plaques on the bulbar conjunctiva).

4. Vitamin A toxicity
   a. Results in headache, nausea, vomiting, stupor, dry skin, pruritus, and pseudotumor cerebri (increased intracranial pressure)
   b. Hepatomegaly and cirrhosis may also be seen along with bone and joint pain.
   c. Excess vitamin A can inhibit neural crest cell migration and is contraindicated in pregnant women.

5. Medical uses
   a. Topical retinoic acid is used to treat psoriasis and acne as well as to reduce wrinkles.
   b. Isotretinoin is an oral retinoic acid derivate used to treat acne. It is better known as Accutane.
   c. Vitamin A is also useful in the treatment of measles and acute myelogenous leukemia.

B. Vitamin D

1. Forms
   a. Vitamin D\(_2\), ergocalciferol
   b. Vitamin D\(_3\), cholecalciferol
   c. 1,25-dihydroxy-vitamin D, calcitriol (active form of vitamin D)
2. Function
   a. Affects gene expression through interactions with DNA
   b. Vitamin D also increases calcium and phosphate uptake in the intestines and the distal tubules.

3. Synthesis of active form
   a. Initially, vitamin D$_3$ is absorbed in the intestine.
   b. Alternatively, vitamin D$_3$ is synthesized from 7-dehydrocholesterol in the skin in a reaction that is stimulated by UV light.
   c. D$_2$ or D$_3$ binds to $\alpha_1$-globulin and is then transported to the liver.
   d. In the liver, vitamin D is converted to 25-hydroxy-vitamin D by 25-hydroxylase. This can also happen in macrophages.
   e. 25-hydroxy-vitamin D leaves the liver and travels to the kidney, where it is converted to 1,25-dihydroxy-vitamin D by $\alpha_1$-hydroxylase. This is the active form.

4. Vitamin D deficiency
   a. Known as osteomalacia in adults and rickets in children
   b. Deficiency of vitamin D causes hypocalcemia, which increases PTH. PTH then promotes bone resorption and decreases renal calcium excretion. PTH also promotes excretion of phosphate, leading to inhibition of bone mineralization because bone is mostly calcium phosphate.
   c. Symptoms include lumbar lordosis, pectus carinatum, bow-legged appearance, and rachitic rosary (overgrowth of the cartilage or osteoid tissue at the costochondral junctions).
   d. Dark-skinned individuals may be deficient in vitamin D. Increased melanin in the skin absorbs UV light that might otherwise be used for vitamin D production.

5. Vitamin D toxicity
   a. Excess vitamin D can cause hypercalcemia.
   b. Sarcoidosis can lead to excess vitamin D. Macrophages in granulomas may overproduce 25-hydroxy-vitamin D.

C. Vitamin E
   1. Forms
      a. The most common form is also known as gamma-tocopherol.
      b. $\alpha$-Tocopherol is the second most common and it is the most biologically active form.
   2. Function
      a. Important in the regulation of enzymatic reactions, gene expression, and platelet aggregation. Vitamin E is also important for neurologic function.
      b. Vitamin E is an important antioxidant, and it is incorporated into cell membranes to protect cells from oxidative damage.
   3. Vitamin E deficiency
      a. Results in peripheral neuropathy and muscle weakness
      b. Vitamin E deficiency also causes spinocerebellar degeneration, resulting in ataxia.

D. Vitamin K
   1. Forms
      a. Vitamin K$_1$, also known as phylloquinone, is found in green, leafy vegetables.
      b. Vitamin K$_2$ is the main form in animals.
   2. Function
      a. Involved in the synthesis of clotting factors as well as proteins C and S
   3. Vitamin K deficiency
      a. Results in hemorrhagic disease
      b. Newborns are particularly prone to this. They lack the commensal gut bacteria that synthesize vitamin K, and breast milk is very low in vitamin K.
      c. Warfarin, certain anticonvulsants, and antibiotics that kill off gut bacteria can all cause vitamin K deficiency.

III. Water-soluble vitamins
   A. Vitamin C
      1. Forms
         a. Also known as ascorbic acid. There is only one form of vitamin C.
2. Function
   a. Catalyzes the hydroxylation of proline and lysine residues during collagen synthesis
   b. Vitamin C is also required for the synthesis of norepinephrine from dopamine, and it serves as a circulating antioxidant in the blood.
   c. The absorption of iron is facilitated by vitamin C, which maintains iron in the reduced state.
3. Vitamin C deficiency
   a. Also known as scurvy
   b. Lack of vitamin C causes sore and spongy gums, loose teeth, hemorrhages due to fragile blood vessels, swollen joints, hemarthrosis, impaired wound healing, and anemia.

B. Vitamin B₁₂ and folic acid
1. Forms
   a. Vitamin B₁₂ is also known as cobalamin, named for the cobalt element at its center.
   b. Tetrahydrofolate is the biologically active form of folic acid.
   c. N-methyl folate is the intracellular storage form of folic acid.
2. Function
   a. Required for purine and pyrimidine synthesis
   b. B₁₂ is required for the regeneration of tetrahydrofolate and also for the synthesis of methionine.
   c. B₁₂ is also required for the conversion of methylmalonyl-CoA to succinyl-CoA, which can then enter the TCA cycle.
3. Biosynthesis
   a. Neither plants nor animals can synthesize vitamin B₁₂. Bacteria synthesize it effectively, and this is where all B₁₂ ultimately originates. Animals require B₁₂, which is why animal products in the diet are the main source of B₁₂. Plants do not require B₁₂ and thus are very poor sources.
   b. Animals cannot synthesize folate either, but plants can. Plants are thus an important dietary source of folate.
4. Vitamin B₁₂ and folic acid deficiencies
   a. Results in megaloblastic anemia
   b. B₁₂ and folic acid deficiencies can also cause neural tube defects in utero and growth failure in children.
   c. B₁₂ deficiency can cause a folic acid deficiency.
   d. B₁₂ deficiency can also cause homocystinuria, methylmalonic acid in urine, and myelin degeneration resulting in neurologic symptoms (B₁₂ neuropathy is also known as subacute combined degeneration).
   e. Pernicious anemia is the most common cause of B₁₂ deficiency.
   f. Crohn disease and celiac disease can also cause B₁₂ deficiency because both affect the distal ileum where B₁₂ is absorbed.

C. Vitamin B₆
1. Forms
   a. There are three natural forms: pyridoxamine, pyridoxine, and pyridoxal.
   b. Pyridoxal phosphate is the active form of B₆.
2. Function
   a. Cofactor for amino acid metabolism
   b. B₆, or rather pyridoxal phosphate, is also required for the synthesis of heme, niacin, histamine, GABA, dopamine, epinephrine, and norepinephrine.
3. Vitamin B₆ deficiency
   a. Causes angular cheilitis (Figure 11-16), glossitis, hyperirritability, and peripheral neuropathy
   b. B₆ deficiency also causes convulsions due to the lack of the inhibitory neurotransmitter GABA.
   c. Isoniazid can cause B₆ deficiency.
D. Thiamine
1. Forms
   a. Also known as vitamin B₁
   b. Thiamine pyrophosphate is the active form of thiamine.
2. Function
   a. TPP is required for the conversion of pyruvate to acetyl-CoA and the conversion of α-ketoglutarate to succinyl-CoA.
   b. TPP is also needed to convert ribose-5-phosphate to glyceraldehyde-3-phosphate.
3. Thiamine deficiency
   a. Thiamine deficiency causes beriberi. Dry beriberi affects the peripheral nervous system and presents with muscle weakness and peripheral neuropathy. Wet beriberi affects the cardiovascular system, leading to peripheral edema and heart failure.
   b. Thiamine deficiency also causes Wernicke–Korsakoff syndrome. This affects the CNS and presents with ocular disturbances, nystagmus, gait ataxia, and Korsakoff syndrome, which is characterized by retrograde recall problems, inability to acquire new information, and confabulations.

E. Riboflavin
1. Forms
   a. Also known as vitamin B₂
   b. The biologic forms are flavin mononucleotide (FMN) and flavin adenine dinucleotide (FAD).
2. Function
   a. FMN and FAD are cofactors for redox reactions.
3. Riboflavin deficiency
   a. Causes dermatitis, angular cheilitis, and glossitis.

F. Niacin
1. Forms
   a. Also known as vitamin B₃.
   b. The biologic forms of niacin are NAD and NADP.
2. Function
   a. NAD and NADP are important in both DNA repair and steroid hormone synthesis.
3. Niacin deficiency
   a. Also known as pellagra. This presents with dermatitis, diarrhea, and dementia (the three D’s of pellagra).
4. Medical uses
   a. Niacin is used to treat type IIb hyperlipoproteinemia (hypercholesterolemia). It inhibits lipolysis in adipose tissue, leading to decreased fatty acids. This decreases synthesis of VLDL and thus LDL.
   b. Niacin is normally administered with aspirin to avoid a flushing reaction.
G. Pantothenic acid
   1. Forms
      a. Also known as vitamin B₅
   2. Function
      a. Pantothenic acid is a component of CoA and is required for the creation of acetyl-CoA.
      b. Pantothenic acid is needed for the TCA cycle and for the synthesis and oxidation of fatty acids.

H. Biotin
   1. Forms
      a. Biotin is also known as vitamin B₇.
   2. Function
      a. Biotin is a cofactor for carboxylation reactions.
   3. Biotin deficiency
      a. Avidin, a glycoprotein found in raw egg whites, can impair absorption of biotin.
      b. Certain antibiotics can also cause biotin deficiency.
BACTERIA

I. Bacterial basics

A. Structure

1. Gram-positive bacteria possess a phospholipid membrane surrounded by a thick cell wall (Figure 12-1, Figure 12-2A).
2. Gram-negative bacteria possess an inner phospholipid membrane surrounded by a thin cell wall, which is further surrounded by an outer phospholipid membrane (Figure 12-1, Figure 12-2B).
3. Peptidoglycan: The main component of bacterial cell walls. It is a rigid sugar backbone with cross-linked side chains.
4. Teichoic acid: Provides rigidity to the cell walls of gram-positive bacteria. Teichoic acid also induces secretion of tumor necrosis factor alpha (TNF-α) and interleukin-1 by immune cells.
5. Periplasm: Also known as the periplasmic space, this is the area between the inner and outer membranes in gram-negative bacteria and contains the peptidoglycan cell wall layer. This is the location of β-lactamases.
   a. The space between the gram-positive membrane and the cell wall is also sometimes referred to as the periplasmic space.
6. Lipopolysaccharide (LPS): A type of endotoxin, LPS is typically found in the outer membrane of gram-negative bacteria and induces the secretion of TNF-α.

Quick Hit

Some bacteria, such as Mycoplasma, lack cell walls. Others, such as Chlamydia, have atypical cell walls and are not typically classified as gram positive or negative.
and interleukin-1 by immune cells. Specifically, the immune system responds to a component of LPS called Lipid A.

7. Glycocalyx: A polysaccharide layer that surrounds bacteria. When it is highly organized, it is referred to as the bacterial capsule. If it is diffuse and loosely attached, it is simply called a slime layer. It can protect cells from phagocytosis and mediate attachment to foreign surfaces (e.g., catheters, implanted devices).
   a. A capsule can be detected by the addition of antcapsular sera to a bacterial culture, which causes the cells to swell. This is called the quellung reaction.

8. Pili and fimbriae: Rigid structures extending from the surface of bacteria that mediate attachment to other bacteria or to host cells and tissues. Pili are present in low numbers and are generally used for bacterial conjugation (exchange of genetic material). Fimbriae are present in higher numbers and are used more commonly in biofilm formation.

9. Flagella: Long, filamentous structures that provide motility to bacteria

10. Plasmids: Circular DNA found in bacterial cytoplasm. Plasmids are separate from chromosomal DNA and tend to contain genes that code for toxins, antibiotic resistance, and certain enzymes. Plasmids are exchanged between bacteria during conjugation.

**B. Morphology**

1. **Bacilli**: Rod-shaped bacteria. Most genera of bacteria fall into this category, including *Clostridium*, *Salmonella*, *Pseudomonas*, *Bacillus*, *Yersinia*, *Legionella*, *Mycobacterium*, *Listeria*, *Shigella*, *Klebsiella*, *Enterobacter*, *Proteus*, and *Escherichia* (Figure 12-2B).
   a. A “bacillus” is any rod-shaped bacterium, whereas *Bacillus* is a specific genus of bacteria. To further complicate the matter, *Bacillus* is a taxonomic class that contains many non–rod-shaped bacteria, including *Streptococcus*.

2. **Coccii**: Spherical bacteria. Examples include *Streptococcus*, *Staphylococcus*, and *Neisseria* (Figure 12-2A).

3. **Cocacobacilli**: A bacterial shape between defined rods and defined spheres. Examples include *Garthnerella*, *Coxiella*, *Haemophilus*, and *Bordetella*.

4. **Spirilla**: Spiral-shaped bacteria. Examples include *Borrelia*, *Treponema*, *Leptospira*, and *Spriillum* (rat-bite fever).

5. **Branching filament**: Some bacteria, such as *Nocardia* and *Actinomyces*, grow in a pattern similar to that of fungi. These are called branching filamentous bacteria.

6. **Endospores**: Certain bacteria form endospores under stressful conditions (e.g., low nutrients, low moisture, temperature extremes). These are tough structures encompassing the bacterial DNA and part of the cytoplasm. Examples of endospore-forming bacteria include *Bacillus* and *Clostridium* species.

**C. Aerobes versus anaerobes**

1. **Obligate aerobes**: Require oxygen for growth. Obligate aerobic bacteria do not have fermentation mechanisms for energy production. Examples include *Pseudomonas*, *Nocardia*, *Mycobacterium tuberculosis*, and some strains of *Bacillus*.
   a. Certain strains of *Pseudomonas* can use nitrogen compounds instead of oxygen in the electron transport chain and are thus considered to be facultative anaerobes (see following).

2. **Obligate anaerobes**: Incapable of growth in the presence of oxygen. Obligate anaerobic bacteria often lack the enzymes catalase and superoxide dismutase, which would otherwise prevent damage from reactive oxygen species. They obtain energy through fermentation or through the use of alternate electron acceptors. Examples include *Clostridium*, *Bacteroides*, *Actinomyces*, and *Treponema*.
   a. Some obligate anaerobes express both catalase and superoxide dismutase, yet still cannot grow in the presence of oxygen. The reason for this is still under investigation.

3. **Facultative anaerobes**: Bacteria that can obtain energy through aerobic respiration or fermentation, depending on the environment. Examples include *Staphylococcus*, *Escherichia coli*, *Listeria*, *Vibrio*, *Salmonella*, *Shigella*, *Klebsiella*, and some strains of *Haemophilus influenzae*.
4. **Microaerophile**: A specific type of obligate aerobe that requires oxygen but at a lower concentration than is found in the atmosphere. If the oxygen concentration is too high or too low, they will either die or cease to thrive. Examples include *Streptococcus pyogenes*, *Helicobacter pylori*, *Borrelia burgdorferi*, and *Campylobacter*.

5. **Aerotolerance**: Anaerobic bacteria that can thrive in the presence of oxygen, although they cannot use it for energy production. These bacteria are rare, and aerotolerance is generally strain-specific.

D. **Bacterial genetics**

1. **Conjugation**: Bacteria connect with each other through pilus interaction. Plasmids can then be copied and transferred to other bacteria. Chromosomal bacteria can also be transferred through this process, but this is less common.

2. **Transposition**: “Jumping genes” can move from chromosomal DNA to plasmid DNA and vice versa. When coupled with conjugation, this is another method that chromosomal DNA can be transferred between bacteria.

3. **Transduction**: A bacteriophage (a virus that infects bacterial cells) may inadvertently package bacterial DNA into virions and then transfer them into other bacterial cells during subsequent infections.

E. **Bacterial staining techniques**

1. **Gram stain**: A staining method for identifying bacteria based on the characteristics of their cell walls (Figure 12-2)
   a. Bacteria are treated with crystal violet stain, which enters the cells.
   b. Iodine is added, forming a large complex with intracellular crystal violet.
   c. Cells are treated with alcohol or acetone. Gram-positive bacteria become dehydrated, and the thick peptidoglycan layer shrinks, closing the pores and trapping the crystal violet complexes inside. Gram-negative bacteria lose their outer membrane, and the thin peptidoglycan layer allows the stain to leak out of the cell.
   d. Cells are treated with a different stain to allow visualization of the gram-negative bacteria.
   e. **Poorly staining bacteria**: Treponema (too thin to be visualized), Mycobacteria (high lipid content in cell wall interferes with stain), Mycoplasma (lack a cell wall), *Legionella pneumophila* (high LPS content interferes with stain), Chlamydia (atypical cell wall, intracellular), and Rickettsia (primarily intracellular)

2. **Giemsa stain**: Binds phosphate groups of DNA. Used to identify intracellular parasites and bacteria (e.g., *Plasmodium*, *Trypanosoma*, *Histoplasma*, *Chlamydia*).

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**Figure 12-2** Gram stain

A. **Clusters of Gram-positive cocci**

   - **Neutrophils** (white blood cells)

B. **Gram-negative rods**

3. Periodic acid-Schiff (PAS) stain: Detects glycogen, glycoproteins, and proteoglycans. Used commonly to stain macrophages infected with *Tropheryma whippelii* (Whipple disease) because these bacteria have a high amount of glycoprotein in their cell membranes.

4. Ziehl-Neelsen stain: Allows differentiation between acid-fast and non–acid-fast organisms. Used to identify bacteria such as *Mycobacterium* and *Nocardia*. (It can also be used to identify *Cryptosporidium*.) Acid-fast organisms have cell walls that contain mycolic acid, which interferes with crystal violet uptake during Gram staining. In the Ziehl-Neelsen method, they are stained instead with carbol fuchsin, which has a high affinity for mycolic acid. When treated with acid or alcohol, they will retain the stain (hence the term “acid-fast”), while non–acid-fast organisms will not.

5. India ink: Used in negative staining, where encapsulated organisms are visualized by the empty spaces they form in the dark ink background. This is normally used to stain for *Cryptococcus neoformans*.

6. Silver stain: Used to identify fungi, as well as *Legionella*, which stains poorly with Gram stain. Treatment with chromic acid oxidizes polysaccharides in the organisms’ cell walls. Further treatment with a silver compound produces a deep black color.

**Culture and identification**

1. **Growth curve:** Used to determine the speed at which a bacterial strain reproduces (Figure 12-3)
   - **Lag phase:** Metabolic activity in preparation for cell division.
   - **Exponential phase:** Rapid cell division at which point the replication speed reaches its maximum. Also known as the “log phase.”
   - **Stationary phase:** As nutrients in the growth medium are depleted, replication slows to the point that it matches the rate of cell death.
   - **Death phase:** Nutrient depletion reaches a point where the medium can no longer sustain the bacteria, and they begin to die and break down.

2. **Special growth requirements:** Although most bacteria can grow effectively on standard media (i.e., LB broth/agar, tryptic soy broth/agar, MH broth/agar), others have specific requirements.
   - **Haemophilus influenzae:** Chocolate agar (MH agar with lysed red blood cells) fortified with V factor (NAD⁺) and X factor (hematin)
   - **Bordetella pertussis:** Bordet-Gengou agar (LB agar containing potato solids and blood)

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**Figure 12-3**

Bacterial growth curve

The growth of a bacterial culture. Bacteria in the inoculum sometimes resume growth slowly (lag phase, hours 0 to 5). They then enter the exponential phase of growth (hours 5 to 10). When foodstuff is exhausted or toxic material accumulates, they enter the stationary phase (hours 10 onward). During the stationary phase, bacterial cultures may lose their viability, as reflected in the viable count, often without losing cell integrity (maintaining a constant total count). (Reprinted with permission from Engleberg NC, Dermody T, DiRita V. *Schaefer’s Mechanisms of Microbial Disease*. 4th ed. Baltimore, MD: Wolters Kluwer Health | Lippincott Williams & Wilkins; 2007.)
c. \textit{Corynebacterium diphtheriae}: Grown on Loeffler serum medium (contains animal protein and dextrose) followed by growth on Hoyle agar (contains tellurite and beef extract)
d. \textit{Mycobacterium tuberculosis}: Lowenstein-Jensen agar (Bordet-Gengou agar with asparagine, penicillin, and nalidixic acid)
e. \textit{Mycoplasma pneumoniae}: Eaton agar (LB agar with animal protein, yeast extract, penicillin, and animal serum)
f. \textit{Legionella} species: Buffered charcoal yeast extract agar (charcoal, yeast extract, α-ketoglutarate, cysteine, and iron)

3. \textbf{Oxidase test}: The oxidase test determines if a bacterial strain possesses cytochrome c oxidase (complex IV of the electron transport chain).
   a. Oxidase-negative bacteria do not necessarily perform anaerobic respiration. They may simply use a different cytochrome other than cytochrome c for aerobic respiration.

4. \textbf{Catalase test}: Catalase degrades hydrogen peroxide into oxygen and water. Bacterial production of catalase is an adaptation that prevents hydrogen peroxide from being converted to reactive oxygen species by host myeloperoxidase. The catalase test simply involves mixing hydrogen peroxide with a sample of bacteria; frothing or bubbling indicates the degradation of the hydrogen peroxide.

5. \textbf{Coagulase test}: Coagulase converts fibrinogen to fibrin. The test involves mixing a sample of bacteria with plasma. If coagulase is present, clumping will be observed. This test is classically used to differentiate coagulase-positive \textit{Staphylococcus aureus} from other staphylococci, which are coagulase-negative.

6. \textbf{Hemolysis test}: The hemolytic capability of bacteria can be tested by plating samples onto agar containing blood (traditionally sheep or rabbit blood) (Figure 12-4).
   a. \textit{α-hemolysis}, sometimes referred to as partial hemolysis, is seen as a dark green area around the colonies. This is due to oxidation of the hemoglobin in the blood. The term is a misnomer, as no cell lysis actually takes place.

\textbf{QUICK HIT}

A third type of hemolysis, known as \textit{γ-hemolysis}, actually refers to the total absence of hemolytic activity.
In clinical microbiology, the classic α-hemolytic bacteria is *Streptococcus pneumoniae*, although viridans strep are also α-hemolytic.

b. **β-Hemolysis** is complete lysis of the red blood cells and appears on the agar as a cleared area around the colonies. Group A strep are commonly associated with β-hemolysis, although some group B strep, as well as *Listeria* and *Clostridium*, may also display β-hemolysis.

7. **Carbohydrate fermentation test**: Tests the ability of bacteria to ferment various carbohydrates by detecting gas bubbles and acidification of media. Most carbohydrates, such as lactose, maltose, glucose, etc., can be tested. This is generally used to differentiate gram-negative bacteria.
   a. MacConkey agar is a lactose-supplemented growth medium that can be used to differentiate gram-negative bacteria based on lactose fermentation. Lactose fermenters appear pink, whereas non-fermenters appear white.

II. **Bacterial toxins**

A. **Endotoxins**
   1. Endotoxin is a general term for any toxin found within a cell or attached to a cell membrane/wall.
   2. The only endotoxin relevant to human disease is LPS, and the two terms are often used interchangeably.
      a. Gram-negative bacteria are the only organisms that express LPS.
      b. LPS stimulates the secretion of the cytokines interleukin-1, interleukin-6, and TNF-α by immune cells, especially macrophages. This results in inflammation.
      c. LPS stimulates the secretion of nitric oxide by macrophages, which causes vasodilation. This is the chief mechanism behind septic shock in endotoxemia.
      d. LPS activates the complement pathway, which also causes inflammation as well as histamine release, further contributing to hypotension.
      e. Finally, LPS activates factor XII in the coagulation cascade, which can cause disseminated intravascular coagulation (DIC).
   3. Several other examples of endotoxins can be found in bacteria that infect plants and insects.

B. **Exotoxin basics**
   1. Toxins that are secreted are called exotoxins. Unlike endotoxins, there are many different types of exotoxins.
   2. Exotoxins are generally polypeptides and, as such, tend to be more antigenic than endotoxin (generate an antibody response).
      a. Antibodies are readily generated against protein antigens.
      b. Carbohydrate antigens (such as LPS) preferentially stimulate a T cell–independent antigen response, which produces lower affinity IgM rather than IgG. This, combined with the variability of the structure of LPS, makes LPS a relatively poor antigen.
   3. Unlike endotoxin, exotoxins can be directly damaging to cells and tissue. They may be encoded by chromosomal DNA, plasmid DNA, or even bacteriophage DNA or RNA. (In contrast, LPS is only encoded by chromosomal DNA.)
   4. **Superantigen**: A specialized exotoxin that binds T-cell receptors and major histocompatibility complex (MHC) class II cell surface molecules. This causes generalized, nonspecific T-cell activation, which can result in dangerous systemic inflammation.
      a. Normally, the interaction of a T-cell receptor with MHC class II on an antigen-presenting cell is transient. However, when the T-cell receptor recognizes the antigen, the interaction is stabilized long enough for T-cell activation to occur.
      b. Superantigens bind both the T-cell receptor and MHC class II outside of the binding groove, artificially stabilizing the interaction, resulting in T-cell activation in the absence of antigen recognition.
C. Common exotoxins

1. *Staphylococcus aureus*: Different Staph strains secrete various toxins that can cause a range of different symptoms through varying mechanisms of action:
   a. **α-Toxin**: Pore-forming toxin that breaks down red blood cells as well as endothelial and epithelial cells.
   b. **β-Toxin**: A two-component sphingomyelinase that may be important for iron scavenging. Its role in human disease is not clear.
   c. **γ-Toxin**: A two-component exotoxin that is formed from the combination of several different proteins. γ-Toxin preferentially lyases leukocytes, although its importance to pathogenesis is unclear.
   d. **Panton-Valentine leukocidin**: A two-component exotoxin common in methicillin-resistant *Staphylococcus aureus* (MRSA), which lyses a variety of cell types. This is the chief cause of necrotizing pneumonia in MRSA infections.
   e. **Enterotoxins**: A family of specialized exotoxins that disrupt the gut. These are the main cause of food poisoning symptoms.
   f. **Toxic shock syndrome toxin** (TSST): TSST is a superantigen that causes toxic shock syndrome. Staph strains expressing TSST often infect mucosal sites.
   g. **Exfoliating toxins**: Disrupt cell-to-cell interactions by breaking down desmoglein. This is the cause of scalded skin syndrome.

2. *Streptococcus pyogenes*: Also known as group A strep, this is the organism that causes scarlet fever. It produces several toxins:
   a. **Streptolysin O**: One of the main exotoxins of *S. pyogenes*, responsible for red blood cell lysis. Antibodies against streptolysin O are used to detect the infection in lab tests.
   b. **Streptolysin S**: A hemolytic cardiotoxin that is not immunogenic (no antibodies are produced against it).
   c. **Pyogenic exotoxins**: Streptococcal pyogenic exotoxins A, B, and C (also known as erythrogenic toxins) are superantigens that are responsible for the symptoms of scarlet fever.
      i. Pyogenic exotoxins are also responsible for the symptoms of streptococcal toxic shock syndrome.

3. *Shigella species*: Produce Shiga toxin, which cleaves 60s ribosomal RNA, thus inhibiting protein synthesis (this is the same mechanism as ricin). Shiga toxin also activates complement and induces signaling cascades that lead to cytokine release. This is the mechanism behind the symptoms of TTP-HUS.
   a. *E. coli* O157:H7 produces Shiga-like toxins, which are very similar to Shiga toxin. It is believed that the strain acquired Shiga toxin through genetic transfer at some point in the past.

4. *Escherichia coli*: In addition to Shiga-like toxin (which is rare), *E. coli* produces two other exotoxins of note, both of which cause the symptoms of traveler’s diarrhea:
   a. **Heat-labile enterotoxin**: Activates adenylate cyclase through ribosylation of G protein-coupled receptors. This raises intracellular cyclic adenosine monophosphate (cAMP) levels, leading to the secretion of chloride ions and water into the gut lumen, causing diarrhea.
   b. **Heat-stable enterotoxin**: Activates guanylate cyclase, which raises intracellular cyclic guanosine monophosphate (cGMP) levels, leading to ion secretion and diarrhea.

5. *Yersinia enterocolitica*: Produces Yersinia stable toxin, which activates guanylate cyclase. This raises intracellular cGMP levels, causing ion secretion and diarrhea (blood in the stool is from bacterial invasion of the intestinal wall).

6. *Bacillus anthracis*: The etiologic agent behind anthrax secretes an exotoxin called edema factor. It acts as an adenylate cyclase, which increases intracellular cAMP. This leads to ion release and edema.

7. *Vibrio cholerae*: Secretes cholera toxin, which stimulates G protein-coupled receptors. This activates adenylate cyclase, which increases intracellular cAMP.
This causes ion and water release into the gut lumen, leading to rice-water diarrhea.

8. *Bordetella pertussis*: Pertussis toxin inhibits Gi protein-coupled receptors (inhibitory G protein-coupled receptors), which leads to increased activation of adenylate cyclase. This raises intracellular cAMP, which leads to increased insulin release and hypoglycemia. This same mechanism is thought to be responsible for the characteristic whooping cough.

9. *Corynebacterium diphtheriae*: Diphtheria toxin catalyzes the transfer of NAD+ to eukaryotic elongation factor 2 (eEF2), which inactivates eEF2, inhibiting protein synthesis. This causes pseudomembranous pharyngitis and can damage nerves and cardiac cells.

10. *Pseudomonas aeruginosa*: Secretes exotoxin A, which adenosine diphosphate (ADP) ribosylates eEF2. This inactivates eEF2 and inhibits protein synthesis, resulting in cell death.

11. *Clostridium tetani*: Secretes tetanospasmin, which is a metalloproteinase.
   It binds to nerves and travels to the central nervous system (CNS), where it binds gangliosides. It then inhibits γ-aminobutyric acid (GABA) and glycine, which causes the characteristic muscle rigidity and spasms.

12. *Clostridium botulinum*: Botulinum toxin cleaves proteins required for the fusion of intracellular vesicles with membranes. This inhibits the release of acetylcholine from cholinergic neurons, leading to flaccid paralysis, urinary retention, and constipation.

13. *Clostridium perfringens*: Secretes an alpha toxin that hydrolyzes phospholipids and produces diacylglycerol. This activates a variety of signaling cascades leading to the production of inflammatory mediators. This also generates gaseous byproducts, causing gas gangrene.

### III. Gram-positive bacteria

A. *Staphylococcus* species

1. *Staphylococcus aureus*
   a. Coagulase-positive, catalase-positive cocci
   b. Normally found as a commensal organism in the nasal cavity and on the skin
   c. May cause infections involving skin, wounds, organs, respiratory tract, urinary tract, heart, meninges, joints, digestive tract, and bones
   d. *S. aureus* also causes scalded skin syndrome, toxic shock syndrome, and bacteremia, as well as necrotizing fasciitis.
   e. These infections can be much more difficult to treat if the infection involves MRSA.
   f. Produce protein A, which inhibits opsonin-mediated phagocytosis
   g. Certain strains also secrete TSST, alpha toxin, beta toxin, delta toxin, and Panton-Valentine leukocidin.
   h. Some strains produce staphyloxanthin, a golden pigment that acts as an antioxidant.

2. *Staphylococcus epidermidis*
   a. Coagulase-negative, catalase-positive cocci
   b. Normally found as a commensal organism on the skin
   c. Commonly forms biofilms on catheters on implanted devices

3. *Staphylococcus saprophyticus*
   a. Coagulase-negative, catalase-positive cocci
   b. Adheres readily to urogenital mucosa
   c. Responsible for 10%–20% of all urinary tract infections in females

B. *Streptococcus* species

1. *Streptococcus pneumoniae*
   a. Catalase-negative, α-hemolytic, encapsulated cocci
   b. Most common cause of meningitis, otitis media, pneumonia, and sinusitis
   c. May also cause conjunctivitis, bacteremia, septic arthritis, osteomyelitis, various soft tissue infections, endocarditis, and pericarditis
d. Secretes IgA protease, which allows it to more efficiently colonize mucosal surfaces

e. Asplenic patients are at higher risk for *S. pneumoniae* infection.

2. Viridans group strep
   a. Catalase-negative, α-hemolytic cocci
   b. Viridans group strep can be differentiated from *S. pneumoniae* through an optochin test. Viridans group strep are resistant to optochin, which is toxic to *S. pneumoniae*.
   c. Viridans group strep lack a polysaccharide capsule and can also be differentiated from *S. pneumoniae* through a quellung test.
   d. Commonly cause dental caries (especially *S. mutans*) and subacute bacterial endocarditis (especially *S. sanguinis*).
   e. *S. mutans* and *S. sanguinis* are both found in dental plaques and may enter the bloodstream during dental procedures. It may then cause endocarditis in patients with existing endothelial damage.

3. Group A streptococci
   a. Catalase-negative, β-hemolytic cocci. *Streptococcus pyogenes* is the most important member of this group.
   b. May cause pharyngitis, necrotizing fasciitis, or toxic shock syndrome.
   c. Group A strep may also cause some of the same conditions as *Staphylococcus* species, such as folliculitis, cellulitis, or impetigo.
   d. Group A strep infections can also lead to autoimmune disorders, such as acute glomerulonephritis and rheumatic fever.

4. Group B streptococci
   a. Catalase-negative, β-hemolytic, encapsulated cocci.
   b. *Streptococcus agalactiae* is the only member of this group.
   c. Generally found as commensal vaginal flora.
   d. Commonly causes pneumonia, sepsis, and meningitis in children, especially infants.

5. Group D streptococci
   a. Catalase-negative, γ-hemolytic (rarely α-hemolytic) cocci.
   b. Non-enterococcal group D strep still includes *Streptococcus bovis* and *Streptococcus equinus*.
   c. *S. bovis* can cause bacteremia and subacute bacterial endocarditis. It is also strongly associated with colon cancer (found in 15% of patients).
   d. *S. equinus* is extremely rare in humans, although it has been reported to cause endocarditis and peritonitis.

C. *Enterococcus* species
   1. Catalase-negative, nonhemolytic (γ-hemolytic) spherical bacteria. Certain strains are encapsulated.
   2. Normal gut flora that only cause disease when they invade a different environment.
   3. Previously considered group D strep, but now classified as a unique genus.
   5. Vancomycin-resistant *Enterococci* (VRE) are an emerging problem.

D. *Corynebacterium diphtheriae* infection (diphtheria)
   2. Cause diphtheria and secrete an exotoxin that inactivates eEF2.
   3. Progression of disease may lead to myocarditis and cranial nerve deficits.
   4. Generally affects children younger than 12 years.
   5. Diphtheria is rare in the United States today due to the widespread use of immunizations (DTaP and DPT). It is still a problem in developing countries.
   6. Presentation: Pseudomembranous pharyngitis, cervical lymphadenopathy, malaise, fever, headache, sore throat, dysphagia, cough.
   7. Labs: Positive throat and/or sinus cultures, positive Elek test (diphtheria toxin), leukocytosis, proteinuria.
   8. Treatment: Antibiotics, diphtheria antitoxin, supportive care.
E. *Clostridium tetani* infection (tetanus, lockjaw)

1. Gram-positive, spore-forming bacilli that cause tetanus
2. Secretes tetanospasmin (tetanus toxin), which enters motor neurons and travels to the spinal cord. It then inhibits the release of glycine and GABA from central inhibitor neurons. This causes muscle rigidity and lockjaw.
   a. This is an irreversible process. Antitoxin can only neutralize unbound tetanospasmin. Recovery requires new nerve terminals and formation of new synapses.
3. Commonly acquired through minor wounds
4. Primarily affects older, unvaccinated adults. Neonatal tetanus is a major cause of infant mortality in underdeveloped countries.
5. **Presentation:** Sore throat, dysphagia, local muscle rigidity, general muscle rigidity, lockjaw, stiffness, reflex spasms, positive spatula test
6. **Labs:** No specific laboratory tests exist for diagnosing tetanus, although they may be necessary to rule out strychnine poisoning.
7. **Treatment:** Tetanus immune globulin, wound debridement, anticonvulsants. Antibiotics have questionable efficacy.

F. *Clostridium botulinum* infection (botulism)

1. Gram-positive, spore-forming bacilli
2. Commonly acquired from improperly canned food. Most cases of botulism involve infants, typically after ingestion of honey.
3. Botulinum toxin binds irreversibly to nerves, blocking acetylcholine release. Respiratory muscle weakness may progress to respiratory failure. Low mortality, but high morbidity.
4. **Presentation:** Nausea, vomiting, dysphagia, diplopia, fixed and/or dilated pupils, dry mouth unrelieved by drinking fluids, descending paralysis
5. **Labs:** Laboratory tests are generally not helpful. Mouse neutralization bioassay can confirm the presence of botulinum toxin.
6. **Treatment:** Heptavalent botulism antitoxin, supportive care

G. *Clostridium perfringens* infection (gas gangrene)

1. Gram-positive, spore-forming bacilli
2. Most common cause of clostridial gas gangrene. Mortality is 20%–30% with treatment (100% without treatment).
3. **Presentation:** Acute pain, edema bullae, erythema with purplish-black discoloration, crepitant tissue
4. **Diagnostics:** Fine gas bubbles within soft tissues, sialidase in serum and wound discharge, gram-positive rods in wound discharge, possible hepatic dysfunction, possible azotemia, possible renal failure, possible metabolic acidosis
   a. Blood and wound discharge cultures can confirm the presence of *Clostridium* but require a minimum of 48 hours. Thus, they are rarely used for diagnosis because this delay will almost always result in the patient’s death.
5. **Treatment:** Supportive care, hyperbaric oxygen therapy, tissue debridement, amputation, antibiotics

H. *Clostridium difficile* infection (pseudomembranous colitis)

1. Gram-positive, oxidase-negative, spore-forming bacilli
2. Secretes toxin B, a cytotoxin that kills enterocytes, causing pseudomembranous colitis
3. **Presentation:** Watery diarrhea, abdominal pain, fever
4. **Diagnostics:** Leukocytosis (which can be very pronounced), hypoalbuminemia, leukocytosis and erythrocytes in stool, positive stool culture, positive glutamate dehydrogenase assay, positive stool cytotoxin test, positive *C. difficile* PCR on stool sample, pseudomembranes on colonoscopy
5. **Treatment:** Supportive care, cessation of the causative antibiotic, metronidazole, vancomycin, or fidaxomicin
I. Bacillus anthracis infection (anthrax)
1. Gram-positive, encapsulated bacilli that cause anthrax
2. Anthrax is generally a mild cutaneous infection, although it can be serious if it progresses to bacteremia.
   a. Inhalation anthrax is rare, but the mortality is extremely high. It is normally contracted from farm animals.
   b. B. anthracis secretes edema toxin, which increases intracellular cAMP, causing fluid to accumulate in tissues.
   c. B. anthracis also secretes lethal toxin, which causes cell death through a poorly understood mechanism.
3. Presentation: Black skin lesions, black eschar, necrosis surrounded by an edematous ring, flulike symptoms (inhalation anthrax), fever (inhalation anthrax), myalgias (inhalation anthrax), cyanosis (inhalation anthrax)
4. Diagnostics: Widening of the mediastinum, lung crackles, positive exudate/pleural fluid culture, pleural effusion, positive blood culture, hemorrhagic cerebrospinal fluid (CSF)
5. Treatment: Antibiotics, raxibacumab, supportive care

J. Listeria monocytogenes infection
1. Gram-positive bacilli that cause listeriosis
2. Contracted through ingestion of contaminated food, especially dairy products and deli meats
3. Generally affects infants and elderly patients as well as immunocompromised individuals
4. Maternal listeriosis can lead to chorioamnionitis, premature labor, spontaneous abortion, and stillbirth. It can also be transmitted to the infant during childbirth.
5. Mortality is relatively low, except in the case of early-onset neonatal listeriosis
6. Presentation: Flulike symptoms, headache, fever, diarrhea, cyanosis (neonatal listeriosis), tachypnea
7. Diagnostics: Positive culture of CSF or affected tissues, abscesses in brain
8. Treatment: Antibiotics, supportive care

K. Actinomyces infection
1. Gram-positive, filamentous bacilli that cause actinomycosis. Most species are facultative anaerobes, growing best in an anaerobic environment.
2. Cervicofacial actinomycosis is the most common form. It generally follows oral surgery and results in oral and facial abscesses that spread. These form sinuses that exude sulfurous fluid.
3. Presentation: Oral/facial nodules, sulfurous exudates, lockjaw (if the mastication muscles are affected)
4. Labs: Anemia, leukocytosis (mild), elevated C-reactive protein (CRP) and sedimentation rate, positive exudate culture
5. Treatment: Antibiotics, surgical excision of sinus tracts and fibrotic lesions, drainage of abscesses

L. Nocardia infection
1. Gram-positive, filamentous bacilli that are partially acid-fast that cause nocardiosis
2. Causes pulmonary symptoms in immunocompromised hosts
3. Presentation: Fever, productive cough
4. Diagnostics: Endobronchial masses, pulmonary abscesses, localized or diffuse pneumonia, cavitation, pleural effusion
5. Treatment: Antibiotics, surgical abscess removal

IV. Gram-negative bacteria
A. Shigella infection (shigellosis)
1. Common cause of bloody diarrhea due to secretion of Shiga toxin. Major public health problem in developing countries. Has a very low minimum infective dose (as few as 10 organisms)
2. Shigellosis is generally self-limiting in the United States, although it has a 20% mortality rate in underdeveloped countries.

Quick Hit
Bloody diarrhea often results from invasion and destruction of the intestinal wall by pathogens such as:
- E. coli O157:H7
- Shigella
- Campylobacter
- Salmonella
3. Spread through fecal–oral transmission, often in contaminated water or food. It is less commonly transmitted through sexual contact.
4. **Presentation:** Fever; dehydration; abdominal tenderness; emesis; large-volume, watery diarrhea
5. **Labs:** Stool with fecal blood, leukocytes, and *Shigella* organisms. Blood tests are normally inconclusive, although a left shift in the leukocyte count may be seen.
6. **Treatment:** Treatment is only indicated in severe cases. Penicillins, cephalosporins, fluoroquinolones, macrolides, sulfonamides, or tetracyclines may all be used. Antidiarrheals are contraindicated because they may exacerbate the infection. Zinc supplementation may also decrease the duration and severity of the disease in children.

**B. *Salmonella* infection**
1. Common cause of bloody diarrhea
2. Common foodborne pathogen found in beef, poultry, and eggs. It may also be found in contaminated fruits, vegetables, dairy products, and shellfish.
   a. *Salmonella* may also be contracted through contact with pet reptiles (turtles) and amphibians.
3. Generally a self-limited disease, although mortality is relatively high if the infection progresses to bacteremia (rare).
4. **Presentation:** Diarrhea (occasionally large volume), fever, abdominal cramping, headache, myalgias, rose spots on chest and abdomen (typhoid fever only)
5. **Labs:** Positive stool culture (except typhoid fever), positive bone marrow aspirate culture (more sensitive than blood culture in typhoid fever), positive urine culture (typhoid fever only), leukopenia, neutropenia, anemia
6. **Treatment:** Supportive care is normally indicated. Antibiotics are not recommended unless the patient is at risk for invasive disease because they do not shorten illness.

**C. *Escherichia coli***
1. **Enterotoxigenic *E. coli* (ETEC) infection**
   a. ETEC generally affects the small intestine and is a common cause of traveler's diarrhea (a self-limited infection).
   b. ETEC produces a heat-labile enterotoxin and a heat-stable enterotoxin.
   c. **Presentation:** Watery diarrhea, dehydration, abdominal cramps
      i. Because ETEC does not invade the intestinal wall, there is no fever and no blood in the stool.
   d. **Labs:** Not generally done. Diagnosis is made based on symptoms.
   e. **Treatment:** Antibiotics (fluoroquinolones or azithromycin) for moderate to severe disease, along with supportive care
2. **Enterohemorrhagic *E. coli* (EHEC) infection**
   a. Generally affects the large intestine, causing hemorrhagic colitis
   b. *E. coli* O157:H7 serotype can cause hemolytic uremic syndrome (HUS).
   c. EHEC secretes a Shiga toxin.
   d. **Presentation:** Bloody diarrhea, fever, dehydration, hemolysis, uremia, HUS symptoms (thrombocytopenia, anemia, acute renal failure)
   e. **Labs:** Stool cultures may test positive for O157:H7 (other serotypes are not generally tested).
   f. **Treatment:** Supportive care only (antibiotics are not known to be beneficial and may worsen the clinical course)
3. **Enteropathogenic *E. coli* (EPEC) infection**
   a. A common cause of diarrhea in children, especially in developing countries or nurseries
   b. EPEC generally affects the small intestine, where it adheres to intestinal wall and flattens the villi, prevents absorption.
   c. **Presentation:** Watery diarrhea (lower volume than ETEC infection), dehydration
   d. **Labs:** EPEC may be detected through adherence assays, serotyping, and DNA probes, although these tests are rarely performed.
   e. **Treatment:** Supportive care, antibiotic therapy in more severe cases
4. **Enteroinvasive *E. coli* (EIEC) infection**
   a. EIEC affects the large intestine and causes a *Shigella*-like dysentery, although infections are rare.
b. **Presentation:** Bloody diarrhea, fever, dehydration, abdominal cramps, tenesmus
c. **Labs:** Not normally done, but DNA probe and animal pathogenicity tests may be performed.
d. **Treatment:** Fluoroquinolones, along with supportive care. Antimotility agents are contraindicated.

D. **Campylobacter jejuni** infection
1. Gram-negative, oxidase-positive bacilli from the family *Campylobacteriaceae*
3. Fecal–oral transmission, or from contaminated poultry, meat, and unpasteurized milk
4. **Presentation:** Fever, headache, myalgias, abdominal pain, diarrhea (sometimes bloody), vomiting, tenesmus
5. **Labs:** Positive stool culture, fecal leukocytes and erythrocytes, peripheral blood leukocytosis
6. **Treatment:** Supportive care. Antibiotics only for those who have severe disease or at risk for severe disease. Antimotility agents are contraindicated because they may prolong disease.

E. **Yersinia enterocolitica** infection
1. Common cause of diarrhea in developing countries. May also cause enterocolitis, terminal ileitis, mesenteric lymphadenitis, and pseudoappendicitis.
2. Most often affects children. Self-limited and generally responsive to therapy. Mortality is high if disease progresses to bacteremia.
3. Commonly contracted from contaminated pork, milk, water, and tofu. Also rarely associated with household pets.
4. **Presentation:** Diarrhea (sometimes bloody), fever, abdominal pain, emesis, erythema nodosum
5. **Labs:** Leukocytosis, positive stool culture, positive blood culture
6. **Treatment:** Supportive care, antibiotics may be used in severe cases

F. **Vibrio cholerae** infection
1. Gram-negative, oxidase-positive bacilli in the family *Vibrionaceae*
2. Secretes cholera toxin, which causes rice-water diarrhea. High mortality in developing countries.
3. Usually transmitted through contaminated food and water (classically shellfish/oysters)
4. Increased free iron (as seen in hemolytic anemia or hemochromatosis) also increases the risk of disseminated infections, although more commonly associated with *Vibrio vulnificus* than *Vibrio cholerae*.
5. **Presentation:** Diarrhea, abdominal pain, nausea, vomiting, fever, headache, myalgias
6. **Labs:** Fecal leukocytes and erythrocytes, gram-negative bacteria in stool
7. **Treatment:** Supportive care, including urgent rehydration, and antibiotics

G. **Proteus** infection
1. Most human Proteus infections are caused by *Proteus mirabilis*. *Proteus vulgaris* and *Proteus penneri* can also cause disease.
2. Common cause of urinary tract infections. Proteus species are capable of producing urease, which converts urea into ammonia and CO$_2$. This results in the formation of struvite (magnesium-ammonium-phosphate). Struvite stones can enlarge to create **staghorn calculi** in the renal pelvis and calyces.
3. **Presentation:** Dysuria, increased frequency of urination, back pain, suprapubic pain, fever
4. **Labs:** Positive urine culture, alkaline urine, pyuria, hematuria, renal calculi. *Proteus* species demonstrate swarming motility, and it is difficult to isolate single colonies from culture plates.
5. **Treatment:** Antibiotics, surgical removal of renal calculi

H. **Klebsiella pneumoniae** infection
1. Common cause of lobar community-acquired pneumonia in patients with alcoholism or diabetes as well as health care–associated pneumonia and UTI
2. **Klebsiella** pneumonia, especially when complicated by bacteremia, has a high mortality rate.

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**QUICK HIT**

*Campylobacter jejuni* infection is often associated with Guillain-Barré syndrome and reactive arthritis.
3. Generally affects debilitated middle-aged men and older men with alcoholism. Nosocomial infections may also affect children or immunocompromised adults.
4. Presentation: Red “currant jelly” sputum, fever, chills, flulike symptoms, productive cough
5. Diagnostics: Leukocytosis, gram-negative bacteria in sputum, bulging fissure in affected lung lobes, cavitation, pleural effusion
6. Treatment: Antibiotics, surgical care for drainage or debridement as necessary

I. Neisseria gonorrhoeae infection
1. Gram-negative cocci that cause gonorrhea. Most commonly acquired through sexual contact.
2. Also a common cause of septic arthritis in young, sexually active individuals
3. May also cause neonatal conjunctivitis (contracted from the mother during birth), pelvic inflammatory disease, and Fitz-Hugh-Curtis syndrome
   a. Fitz-Hugh-Curtis syndrome is a rare complication of pelvic inflammatory disease. It occurs when the spread of the infection results in inflammation of the liver capsule.
4. Infections may become bloodborne and cause osteomyelitis, meningitis, endocarditis, acute respiratory distress syndrome (ARDS), or septic shock.
5. Presentation: Arthralgias (septic arthritis), rash (disseminated gonococcal infection), pharyngitis and cervical lymphadenopathy (oral–genital transmission), right upper quadrant pain (perihepatitis), purulent conjunctivitis (autoinoculation). Other symptoms differ between men and women as well as between adults and neonates.
   a. Women: Vaginal discharge, dysuria, intermenstrual bleeding, dyspareunia, abdominal pain, tenesmus
   b. Men: Urethritis, serous or purulent penile discharge, acute epididymitis, abnormal urine stream, tenesmus
   c. Neonates: Purulent conjunctivitis, eye pain, redness
6. Labs: Positive PCR on genital swab or urine, positive culture (specific to infected site), mildly elevated sed rate
7. Treatment: Antibiotics, drainage of infected joints

J. Neisseria meningitidis infection
1. Gram-negative, encapsulated cocci that cause meningococcal meningitis. It is naturally found on mucosal surfaces of the nasopharynx and, less commonly, the urogenital and anal mucosa.
2. Infections are likely the result of colonization with a new strain, in which the bacteria spread prior to the development of protective antibodies.
3. Risk factors include smoking, concurrent respiratory infection, and crowded living conditions.
4. Ten percent to 20% of infections progress to bacteremia, which can then progress to meningitis. Mortality is relatively high in underdeveloped countries.
5. Children may develop Waterhouse–Friderichsen syndrome, which occurs when a bacterial infection causes hemorrhage into the adrenal glands, resulting in adrenal insufficiency. This can lead to shock, DIC, and sepsis.
6. Presentation: Headache, fever, nausea, vomiting, photophobia, stiff neck, lethargy, petechial rash, seizures (mainly in children)
7. Diagnostics: Increased nuchal rigidity, increased CSF proteins, decreased CSF glucose, increased polymorphonuclear leukocytes in CSF, positive CSF culture, meningeal lesions, cerebral edema, cerebral ischemia
8. Treatment: Antibiotics, anti-inflammatories, surgical intervention for complications

K. Haemophilus influenzae infections
1. Gram-negative coccobacilli that cause a variety of infections
   a. H. influenzae most commonly causes epiglottitis, especially in children
   b. May also cause bacteremia, meningitis, otitis media, sinusitis, pneumonia, and empyema
   c. Mortality is very low, with the exception of H. influenzae meningitis in underdeveloped countries.
2. Certain strains are encapsulated.
3. Transmitted through direct contact or inhalation of respiratory droplets
4. **Epiglottitis presentation:** Fever, sore throat, dysphagia, drooling, “sniffing dog position,” progressive respiratory difficulty
   a. The “sniffing dog position” is seen when a patient lifts his or her head and extends his or her neck in an effort to open the airway as he or she attempts to breathe.
5. **Diagnostics:** Thumb sign on x-ray (dilation of the hypopharynx in epiglottitis) (Figure 12-5), straightened cervical spine, positive culture of fluid from infected site, positive blood culture
6. **Treatment:** Antibiotics, intubation as necessary, supportive care

**L. Legionella pneumophila infection**
1. Gram-negative bacilli that cause two notable clinical illnesses:
   a. Legionnaires disease (pneumonia with alveolitis and bronchiolitis)
   b. Pontiac fever (a self-limited, flu-like illness that presents without pneumonia)
2. Transmitted through aerosolized, contaminated water
3. Mortality rate is dependent on factors such as age, underlying conditions, and delay in treatment but may be anywhere between 9% and 80%.
4. **Presentation:** Fever, weakness, fatigue, malaise, myalgias, nonproductive cough progressing to productive cough, chest pain, headache, confusion, cerebellar ataxia
5. **Diagnostics:** Hypotension, proteinuria, hematuria, elevated sed rate, elevated CRP, hyponatremia, hypophosphatemia, elevated creatine kinase, positive sputum culture, positive urinary antigen, lung infiltrates on chest x-ray (CXR)
6. **Treatment:** Antibiotics, supportive care

**M. Pseudomonas aeruginosa infection**
1. Gram-negative bacilli that have many toxins and virulence factors, including exotoxin A, which inactivates eEF2
2. It is one of the most common causes of health care–associated pneumonia.
   a. May cause otitis externa, urinary tract infections, surgical site infections, and osteomyelitis. Progression to bacteremia is common.
   b. *P. aeruginosa* also commonly causes hot tub folliculitis.
3. *P. aeruginosa* rarely affects healthy individuals. Most patients are immunocompromised or have a disruption in physical barriers (e.g., burns, intravenous [IV] lines, catheters). Because of this, *Pseudomonas* infections have a high mortality rate.
4. **Diagnostics:** azotemia, leukocytosis, elevated erythrocyte sedimentation rate (ESR) and CRP, rapid progression of CXR findings

**QUICK HIT:**
Pseudomonas infections are especially common in cystic fibrosis and burn patients.
5. **Treatment**: Fluoroquinolones, cefepime, aztreonam, piperacillin-tazobactam, meropenem. Surgical drainage of abscesses and additional treatment based on specific site of infection may also be indicated.

N. *Helicobacter pylori* infection
   1. Gram-negative, spiral-shaped bacteria that causes gastritis
   2. Found in the gastrointestinal (GI) tract of more than 50% of the world population. Most common cause of duodenal ulcers (~90%). Increases the risk of gastric adenocarcinoma and lymphoma.
   3. **Presentation**: Generally asymptomatic. Symptoms may include nausea, vomiting, abdominal pain, diarrhea, heartburn, and halitosis.
   4. Labs: Positive fecal antigen test, positive carbon-13 urea breath test
   5. **Treatment**: Antibiotics combined with a proton pump inhibitor

V. Nonstaining bacteria
   A. *Mycobacterium tuberculosis* infection
      1. *M. tuberculosis* is considered to be gram-positive, although they do not stain properly due to a waxy outer layer and their intracellular life cycle.
      2. Transmitted in airborne particles
      3. Tuberculosis (TB) is a common cause of death worldwide. This is due to a combination of factors, including drug resistance, lack of public health infrastructure, and HIV co-infection.
         a. **Primary tuberculosis**: Infection in an individual who has not been previously exposed. Often asymptomatic. The patient recovers, often without any indications of the infection. However, the mycobacteria is not always cleared, and instead enters a dormant (latent) state.
         b. **Secondary tuberculosis**: Latent TB can reactivate and cause severe respiratory symptoms. This may also lead to extrapulmonary tuberculosis, which can cause CNS lesions and meningitis.
            i. TB in the vertebral bodies is known as Pott disease.
            ii. **Miliary tuberculosis** is caused by hematogenous spread of TB that causes many tiny lesions (1–5 mm) throughout the lung.
      4. **Presentation**: Cough, rales, weight loss, fever, night sweats, hemoptysis, chest pain, fatigue, lymphadenopathy
      5. **Diagnostics**: Positive tuberculin skin test, positive interferon gamma release assay, positive acid-fast bacilli (AFB) smear on sputum, cavitary lesions on CXR, hilar lymphadenopathy and Ghon focus on CXR (collectively called the Ghon complex) (Figure 12-6). Diagnostic culture of *M. tuberculosis* takes 2–6 weeks to grow on agar.

   ![Ghon complex](image-url)
6. **Treatment**: Rifampin, isoniazid, pyrazinamide, and ethambutol. Other antibiotics may be needed for multidrug-resistant strains. Surgical resection of infected lung tissue may be indicated in refractory cases.

B. *Mycobacterium leprae* infection

1. Causes Hansen disease (leprosy). There are two forms: lepromatous and tuberculoid.
   a. **Lepromatous leprosy** occurs when infected individuals mount a minimal cellular immune response. Manifests with extensive skin lesions and symmetric peripheral nerve involvement.
   b. **Tuberculoid leprosy** occurs when infected individuals mount a strong cellular immune response. Manifests with limited skin lesions and asymmetric peripheral nerve involvement.

2. Route of transmission may be through respiratory droplets. Also associated with direct contact with infected armadillos.

3. Although leprosy can be a debilitating disease due to nerve damage, it has low mortality and low infectivity. Most exposed individuals never develop the disease.

4. **Presentation**: Nodules and thick plaques on fingers, peripheral neuropathy, muscle weakness, clawed hands, foot drop, leonine facies (advanced leprosy)

5. **Labs**: Positive nasal smear or skin biopsy, positive anti-phenolic glycolipid-1 antibody test (less specific for tuberculoid leprosy), positive or negative lymphocyte migration inhibition test (tuberculoid or lepromatous leprosy respectively)

6. **Treatment**: Dapsone, clofazimine, and rifampin

C. *Leptospira interrogans* infection (leptospirosis)

1. *Leptospira interrogans* is a motile spirochete. It is one of the most common zoonotic organisms in the world, although it is most commonly seen in tropical climates.

2. Found in water contaminated with animal urine

3. It produces a range of clinical presentations:
   a. Subclinical infection without noticeable symptoms
   b. Self-limited, mild disease presenting with flulike symptoms
   c. Severe disease causing kidney and liver failure
   d. Can also present as pulmonary disease, with hemorrhage, acute respiratory distress syndrome, and multiorgan failure

4. Morbidity from leptospirosis can be high, although mortality is low. When death does occur, it is commonly due to pulmonary involvement.

5. **Presentation**: Flulike symptoms (fever, myalgias), headache, abdominal pain, jaundice, photophobia, conjunctivitis, tachycardia, hypotension, oliguria

6. **Diagnosis**: Elevated creatinine and blood urea nitrogen (BUN), pulmonary edema and/or myocarditis on CXR, alveolar lung disease, positive cultures, positive serology

7. **Treatment**: Antibiotics, supportive care in severe cases

D. *Borrelia burgdorferi* infection (Lyme disease)

1. *B. burgdorferi* is a motile spirochete that causes Lyme disease.

2. Most common tick-borne disease in the United States (specifically transmitted by ticks from the genus *Ixodes*).

3. Lyme disease can be divided into three stages:
   a. Stage 1: Localized infection. Nonspecific, flulike symptoms, accompanied by erythema migrans around the tick bite, occurring about 1 month after tick bite. Many patients will clear the infection during this stage, some without any symptoms.
   b. Stage 2: Disseminated infection. Occurs several weeks to several months after initial infection. Manifests with neurologic and cardiac symptoms.
   c. Stage 3: Chronic disease. May occur several months to several years after the initial infection. Debilitating arthritis and encephalitis are seen.

4. Diagnosis is problematic due to a number of factors:
   a. Early lyme disease occurs when the erythema migrans first appears. IgM and IgG may be negative at this early stage. If the patient has been in an endemic area recently and erythema migrans is present, the patient should be treated empirically.
b. When the patient has early disseminated disease, he or she may have multiple erythema migrans lesions on exam as well as possible meningitis, carditis, and facial palsy. Serology (IgM and IgG) should be positive at this point.
c. Lyme disease is difficult to diagnose if the erythema migrans lesion is not present or if it is hidden under hair.
5. Prognosis is favorable with timely treatment, but chronic musculoskeletal symptoms, neurologic impairment, and chronic fatigue may be seen if treatment is delayed for an extended period of time. Lyme disease is very rarely fatal.
6. Presentation: Varies depending on disease stage:
   a. Stage 1: Erythema migrans (Figure 12-7), fever, myalgias, fatigue, flulike symptoms
   b. Stage 2: Additional skin lesions, musculoskeletal and neurologic symptoms, inflammatory arthritis, Bell palsy
   c. Stage 3: Myalgias, hemiparesis, ataxia, seizures, cognitive impairment, acrodermatitis chronic atrophicans
7. Diagnostics: Varies depending on disease stage. Positive antibody titer, mononuclear cells in CSF; electrocardiogram (ECG) may reveal atrioventricular block or other cardiac abnormalities
8. Treatment: Doxycycline, amoxicillin, cefuroxime

**E. Treponema pallidum** infection (syphilis)
1. Treponema pallidum is a spirochete that causes syphilis. It is commonly transmitted through sexual contact with infected individuals. Also transmitted vertically from mother to fetus.
2. Syphilis is divided into four stages: primary, secondary, latent, and tertiary.
   a. **Primary syphilis:** Normally presents with a single, painless chancre 3–6 weeks after initial exposure. Few patients will seek treatment for this.
   b. **Secondary syphilis:** Develops 4–10 weeks after the appearance of the initial lesion. This coincides with the dissemination of Treponema throughout the body.
   c. **Latent syphilis:** During this period, patients are often asymptomatic although they still carry the bacteria. This period can last for a very long period of time (25 years in some cases).
   d. **Tertiary syphilis:** Relatively rare manifestation that may occur years after initial exposure. Three presentations include:
      i. Gummatous syphilis: Characterized by the appearance of gummas (granulomatous lesions). These are found on skin, in bones, and even in internal organs.
      ii. Cardiovascular syphilis: Commonly causes aortitis and predisposes to aneurysms of the ascending aorta, aortic dissection, and possibly aortic valve pathology
      iii. Neurosyphilis: May cause meningitis, hearing loss, tabes dorsalis, Argyll Robertson pupil, and various neurologic abnormalities
e. **Congenital syphilis:** Vertical transmission from mother to fetus can cause the child to develop abnormalities such as saber shins, saddle nose, Hutchinson teeth, mulberry molars, and frontal bossing.

3. **Presentation:** Varies according to stage:
   a. Primary syphilis: Painless chancre
   b. Secondary syphilis: Fever, malaise, chills, maculopapular rash that classically involves palms/soles, alopecia areata, condylomata lata
   c. Latent syphilis: Generally asymptomatic
   d. Tertiary syphilis: Gummas, positive Romberg sign, sensory ataxia, Argyll Robertson pupil, deafness, dementia, altered mental status

4. **Labs:** Positive rapid plasma reagin (RPR) or Venereal Disease Research Laboratory (VDRL) test, positive fluorescent treponemal antibody absorption (FTA-ABS) test. The FTA-ABS test is necessary to confirm the result of a positive RPR or VDRL, which can produce false positives.

5. **Treatment:** Penicillin is the antibiotic of choice. Doxycycline can be used in the case of penicillin allergy.

F. **Gardnerella vaginalis** infection
   1. *Gardnerella vaginalis* is a poorly staining, nonmotile coccobacillus that is associated with bacterial vaginosis (BV).
      a. BV is not considered a sexually transmitted disease. It is often spread through sexual contact but can also be acquired in other ways.
      b. Antibiotics, IUDs, douching, and low estrogen can also predispose to BV.
      c. Untreated infections may cause endometritis, salpingitis, pelvic inflammatory disease, and pregnancy/labor complications.
      d. BV also increases the chances of contracting HIV through sexual contact.
   2. Although *Gardnerella* is usually involved in cases of BV, evidence indicates that the disease is the result of synergism between *Gardnerella* and one or more additional bacteria.
   3. **Presentation:** Gray vaginal discharge, vaginal odor, vulvar irritation
   4. **Labs:** Clue cells in discharge, discharge pH > 4.5, positive whiff test. Cultures are not useful due to the polymicrobial nature of the infection.
   5. **Treatment:** Metronidazole or clindamycin

G. **Rickettsia** infection
   1. *Rickettsia* are obligate intracellular bacteria that stain poorly with Gram stain, although they do have gram-negative cell walls.
      a. *Rickettsia rickettsii* causes Rocky Mountain spotted fever.
      b. *Rickettsia typhi* causes endemic typhus, transmitted by rat fleas.
      c. *Rickettsia prowazekii* cause epidemic typhus, transmitted by lice.
      i. Infections with *Rickettsia prowazekii* have a high mortality rate in untreated, elderly patients.
   2. **Presentation:** Headache, fever, and rash (rickettsial triad); abdominal pain; diarrhea; conjunctivitis; mental confusion; delirium; rales
   3. **Labs:** No rapid tests are available for early diagnosis of rickettsial infections. Thrombocytopenia, elevated LFTs. Positive Weil-Felix agglutination test, positive anti-rickettsial antibodies on indirect fluorescent antibody (IFA) test.
   4. **Treatment:** Doxycycline is the treatment of choice. Chloramphenicol may be used as an alternative.

H. **Coxiella burnetii** infection (Q fever)
   1. *Coxiella burnetii* is an obligate intracellular bacterium that was originally classified as *Rickettsia*. It stains poorly with Gram stain, although it does have gram-negative cell walls.
   2. Transmitted in aerosolized form from urine, feces, milk, and birth products of animal hosts. *Coxiella* is extremely infective, requiring fewer than 10 organisms in some cases.
   3. Causes Q fever, which is generally a self-limited disease with an excellent prognosis, although it may progress to atypical pneumonia or hepatitis
   4. **Presentation:** Fever, headache, myalgias, chills, fatigue, sweating, crackles on chest auscultation, nonproductive cough
5. Diagnostics: Elevated liver enzymes, mild thrombocytopenia, elevated sed rate, negative Weil-Felix agglutination test, atypical pneumonia on CXR, hepatomegaly. Serologic tests are not useful in determining treatment because they require 3–4 weeks.

6. Treatment: Doxycycline or other antibiotics

I. *Chlamydia psittaci* infection (Psittacosis)
   1. *Chlamydia psittaci* is an intracellular bacterium that causes psittacosis. Infection normally manifests as pneumonia but may progress to a systemic disease that causes gastrointestinal, neurologic, and dermatologic sequelae.
   2. Transmitted to humans through aerosolized bird secretions or feces, especially those of exotic birds
   3. With antibiotic therapy, fatalities are extremely rare.
   4. Presentation: Fever, chills, malaise, nonproductive cough, dyspnea, pharyngitis, epistaxis, Horder spots (which resemble the rose spots of typhoid fever, but are found on the face), splenomegaly
   5. Labs: Mildly elevated liver enzymes, mild proteinuria, anti-*Chlamydia* antibodies
   6. Treatment: Antibiotics, supportive care as needed

J. *Chlamydia pneumoniae* infection
   1. *Chlamydia pneumoniae* is an intracellular bacterium that causes pneumonia.
   2. *Chlamydia pneumoniae* is responsible for 10%–20% of all cases of community-acquired pneumonia. It causes mild disease in adolescents and young adults but may cause more severe disease in older adults.
   3. Presentation: Nonproductive cough, malaise, fever, sinus percussion tenderness, pharyngeal erythema, rhonchi, rales
   5. Treatment: Tetracyclines, macrolides

K. *Chlamydia trachomatis* infection
   1. Intracellular bacteria that cause a variety of diseases depending on the serotype.
   2. Trachoma: Caused by serotypes A, B, Ba, and C
      a. The leading infectious cause of blindness
      b. Transmitted chiefly between children and caregivers
      c. Repeated reinfection can lead to conjunctival scarring.
      d. Untreated infections can cause blindness.
   3. Chlamydial genitourinary infection: Caused by serotypes D–K
      a. The most commonly reported sexually transmitted disease in the United States
      c. May also cause neonatal conjunctivitis and neonatal pneumonia due to exposure during passage through the birth canal
      d. Many infections can be subclinical, especially in women. Because these women do not seek treatment, this increases the risk of transmission as well as pregnancy complications.
   4. Lymphogranuloma venereum: Caused by serotypes L1, L2, and L3
      a. Rare infection that causes acute lymphadenitis and primary ulcers
      b. May cause rectal disease that is commonly mistaken for inflammatory bowel disease
      c. If left untreated, disfiguring ulcerations and genital enlargement can occur.
      d. Generally presents with self-limited ulcers or papules, followed by lymphadenopathy after 2–6 weeks. Proctocolitis may occur years later.
      e. Mortality is very low with proper treatment.
   5. Presentation: Varies by disease
      a. Trachoma: Self-epilation of eyelashes, blepharospasm, mucopurulent keratoconjunctivitis, corneal follicles, trichiasis, corneal opacity
b. **Chlamydial genitourinary infection:** Urethritis, cervicitis, salpingitis, epididymitis, proctitis, conjunctivitis, urethral or vaginal discharge, dysuria, dyspareunia

c. **Lymphogranuloma venereum:** Inguinal and/or femoral lymphadenopathy, genital ulcers, genital papules, rectal ulcerations, proctocolitis, fever, chills, malaise, myalgias, tenesmus

6. **Labs:** Positive polymerase chain reaction (PCR) test, peripheral eosinophilia, positive urine culture, positive anti-chlamydial antibodies

7. **Treatment:** Antibiotics

I. **Mycoplasma pneumoniae** infection

1. Non–gram-staining bacteria that lack a cell wall
2. A common cause of community-acquired pneumonia (“walking pneumonia”). Generally seen in patients under age 40 years and in military barracks and prisons. Only 5%–10% of infected patients actually develop pneumonia.
3. **Presentation:** Headache, nonproductive cough, fever, malaise, nontoxic appearance, rhonchi, rales
4. **Labs:** Atypical pneumonia on CXR, positive cold agglutinin test. Sputum cultures are not helpful due to the slow growth rate of *M. pneumoniae*.
5. **Treatment:** Antibiotics

### Antibiotics

#### I. Cell wall inhibitors

A. **Penicillins**

1. Inhibit the formation of bacterial cell walls by interfering with the enzyme transpeptidase, which normally catalyzes the cross-linking of peptidoglycan strands
2. Contain a β-lactam ring structure
3. Most penicillins are considered bactericidal.
4. Generally used in gram-positive infections (e.g., *Streptococcus*, *Actinomyces*, *Staphylococcus*) as well as certain spirochete infections (e.g., syphilis)
5. There are four different categories of penicillins:
   a. **Natural penicillins:** Include penicillin G (intravenous) and penicillin V (oral)
   b. **β-lactamase–resistant penicillins:** Include nafcillin, oxacillin, and dicloxacillin. Less susceptible to inactivation by penicillinase (β-lactamase). Sometimes referred to as anti-staphylococcal penicillins due to their efficacy in Staph infections.
   c. **Aminopenicillins:** Include amoxicillin and ampicillin. Have a wider spectrum than other categories of penicillins. Commonly used for urinary tract infections.
   d. **Extended-spectrum penicillins:** Include ticarcillin, carbenicillin, and piperacillin. Also known as antipseudomonal antibiotics, these are used for *Pseudomonas* infections. They are also effective against a number of gram-negative rods.
6. To protect against β-lactamase inactivation, some of these are administered along with β-lactamase inhibitors (i.e., clavulanic acid, tazobactam, sulbactam).
7. Commonly cause hypersensitivity reactions. Ampicillin and amoxicillin may also cause a full body rash when administered to mononucleosis patients.

B. **Cephalosporins**

1. Inhibit the formation of bacterial cell walls by interfering with the enzyme transpeptidase, which normally catalyzes the cross-linking of peptidoglycan strands
2. Contain a β-lactam ring structure
3. Most cephalosporins are bactericidal.
4. Generally less susceptible to penicillinases compared to penicillins
5. More effective against gram-negative bacteria compared to penicillins

**QUICK HIT**

The chief mechanism of β-lactam resistance is production of β-lactamase.

**QUICK HIT**

Methicillin resistance in *Staphylococcus* is determined in a laboratory setting. Methicillin is not used in humans.

**Mnemonic**

To remember the gram-negative bacteria that are susceptible to aminopenicillins, use **HELPSS**:

- *Haemophilus influenzae*
- *Escherichia coli*
- *Listeria monocytogenes*
- *Proteus mirabilis*
- *Salmonella*
- *Shigella*
6. Cephalosporins are divided into four generations. Each generation is more effective against gram-negative bacteria than the previous generation but generally less effective against gram-positive bacteria.
   a. **First generation**: Includes cefazolin, cefadroxil, and cephalexin. Effective against the gram-negatives *Proteus mirabilis*, *E. coli*, and *Klebsiella* as well as many gram-positive bacteria. Commonly used to treat urinary tract infections.
   b. **Second generation**: Includes cefoxitin, cefaclor, cefuroxime, cefotetan, andcefprozil. Effective against the same gram-negative bacteria as first generation cephalosporins, with the addition of *H. influenzae*, *Enterobacter*, *Neisseria*, and *Serratia*.
   c. **Third generation**: Includes ceftriaxone, cefotaxime, cefazidime, cefditoren, cefixime, cepodoxime, and cefdinir. Used against serious gram-negative infections and pneumococcal meningitis. Cefazidime in particular is effective against *Pseudomonas*.
   d. **Fourth generation**: Includes cefepime and ceftaroline. Broad-spectrum antibiotics that are effective against a wide range of gram-negative bacteria as well as many gram-positive bacteria.

7. Cephalosporins are generally ineffective against *Listeria*, MRSA, *Enterococcus*, *Mycoplasma*, and *Chlamydia*.

8. Fewer than 10% of individuals with type I, IgE-mediated penicillin allergies or hypersensitivities also react to cephalosporins.

9. Ceftriaxone increases the risk of nephrotoxicity when combined with aminoglycoside antibiotics.

C. **Aztreonam**

1. Aztreonam is the only monobactam (monocyclic β-lactam) antibiotic that is used in humans.
2. It inhibits cell wall synthesis by binding to the transpeptidase enzyme, although at a different site than penicillins and cephalosporins.
3. It works synergistically with aminoglycoside antibiotics to increase killing ability. Aztreonam has no cross-reactivity with penicillins and is safe to use in patients with penicillin allergies.
4. Effective against gram-negative rods. Ineffective against gram-positive bacteria and anaerobic bacteria.

D. **Carbapenems**

1. Imipenem/cilastatin, meropenem, ertapenem, doripenem
   a. Imipenem is always administered with cilastatin, which inhibits renal-dehydropeptidase. This prevents enzymatic inactivation of imipenem.
   b. Powerful, broad-spectrum antibiotics that are β-lactamase-resistant
   c. Effective against both gram-positive and gram-negative bacteria, including anaerobic bacteria and *Pseudomonas*
5. Generally used to treat life-threatening infections
6. Carbapenems have a number of potential side effects, including rash, GI distress, and CNS toxicity.

E. **Vancomycin**

1. A glycopeptide antibiotic that inhibits cell wall formation by binding to the peptidoglycan strands themselves rather than the transpeptidase enzyme
2. Vancomycin is effective against many gram-positive bacteria, including several drug-resistant species. These include MRSA, *Clostridium difficile*, and various enterococci.
3. Although vancomycin does have oral formulations, it has very poor oral bioavailability and is generally administered intravenously. Oral vancomycin is only indicated for the treatment of *C. difficile* colitis.
4. Generally used only in serious or refractory cases
5. Side effects include nephrotoxicity, ototoxicity, thrombophlebitis, and red man syndrome (a diffuse flushing of the entire body due to mast cell degranulation). Red man syndrome is a relatively common side effect of vancomycin and can often be prevented by slowing the infusion and pretreatment with an antihistamine.

The glycopeptide class also includes the less commonly used telavancin and teicoplanin antibiotics as well as the antineoplastic drug bleomycin.
II. Protein synthesis inhibitors

A. Aminoglycosides
   1. Gentamicin, neomycin, amikacin, tobramycin, kanamycin, streptomycin
   2. Bind the 30S ribosome, interfering with protein synthesis
   3. Aminoglycosides are generally bactericidal, but they require oxygen for uptake. This means they are ineffective against anaerobic bacteria.
   4. Used to treat severe gram-negative infections. Also work synergistically with β-lactam antibiotics for some infections.
   5. Side effects include nephrotoxicity and ototoxicity.
   6. Aminoglycosides are contraindicated in pregnancy.

B. Linezolid
   1. Binds the 50S ribosome, interfering with protein synthesis
   2. Linezolid may be either bactericidal or bacteriostatic depending on the infection.
   3. Mainly used to treat MRSA infections and VRE infections
   4. Good oral bioavailability allows for the treatment of these infections on an outpatient basis.
   5. Linezolid is not approved for the treatment of gram-negative bacterial infections.
   6. In patients who are taking antidepressants, linezolid increases the risk of serotonin syndrome (excess serotonin causes restlessness and agitation, diarrhea, tachycardia, hypertension, cognitive impairment, and loss of coordination).

C. Tetracyclines
   1. Tetracycline, doxycycline, demeclocycline, minocycline, tigecycline
   2. Bind the 30S ribosome, interfering with protein synthesis
   3. Tetracyclines are usually bacteriostatic.
   4. Due to the fact that they are chiefly excreted in the feces, tetracyclines are suitable for use in patients with renal failure.
   5. Used to treat Vibrio cholerae, Chlamydia, Ureaplasma urealyticum, Mycoplasma pneumoniae, H. pylori, B. burgdorferi, Rickettsia, and tularemia, as well as acne
   6. Tetracyclines should not be taken with milk, antacids, or iron-containing preparations. Calcium, iron, and magnesium will inhibit the absorption.
   7. Side effects include GI distress, discoloration of teeth and inhibition of bone growth in children, and photosensitivity. Minocycline in particular can cause patients to develop bluish-gray skin pigmentation with prolonged use.
   8. Tetracyclines are contraindicated in pregnancy.

D. Macrolides
   1. Erythromycin, azithromycin, clarithromycin
   2. Bind the 30S ribosome, interfering with protein synthesis
   3. Macrolides are usually bacteriostatic antibiotics.
   4. Used to treat atypical pneumonias (i.e., Mycoplasma, Chlamydia, Legionella), respiratory tract infections (sinusitis, bronchitis), and sexually transmitted diseases
   5. Side effects included prolonged QT interval (especially with erythromycin), GI distress, eosinophilia, and rashes.
   6. Macrolides inhibit the activity of hepatic enzymes and can thus increase the serum concentration of drugs such as theophylline and warfarin.

E. Chloramphenicol
   1. Inhibits the 30S ribosome, interfering with protein synthesis
   2. Chloramphenicol is bacteriostatic.
   3. Rarely used. Only indicated when a serious infection is refractory to other treatment.
   4. Effective against H. influenzae, N. meningitidis, and Streptococcus pneumoniae
   5. Side effects include dose-dependent anemia, aplastic anemia, and gray baby syndrome when administered to neonates.

F. Clindamycin
   1. Inhibits the 30S ribosome, interfering with protein synthesis
      a. Clindamycin belongs to a class of antibiotics called lincosamides.
      b. Lincomycin is the only other lincosamide approved for humans, and it is rarely used.
2. Clindamycin is bacteriostatic.
3. One of a small number of medications used to treat anaerobic infections
4. Also effective against C. perfringens and MRSA
5. Side effects include GI symptoms, pseudomembranous colitis, and Stevens-Johnson syndrome.

G. Streptogramins
1. Quinupristin, dalfopristin
2. Alone, each of the streptogramins is bacteriostatic. However, used together (which they always are), they can be bactericidal.
3. Dalfopristin binds the 50S ribosome, causing a conformational change that enhances the binding of quinupristin. Together they inhibit peptide transfer and protein chain elongation.
4. Used against gram-positive organisms. Notable for their effectiveness against MRSA and vancomycin-resistant enterococci.
5. Side effects include arthralgias and myalgias, which significantly limit their use. Also cause cytochrome P450 inhibition.

III. Antimycobacterial antibiotics
A. Isoniazid
1. Inhibits the synthesis of mycolic acid, which is a component of the mycobacterial cell wall
2. Isoniazid is generally bactericidal.
3. The only drug that is used for solo prophylaxis against tuberculosis
4. Commonly used together with rifampin, pyrazinamide, and ethambutol to treat active tuberculosis
5. Side effects include drug-induced lupus, hepatotoxicity, and neurotoxicity (which can be prevented with concomitant administration of pyridoxine).

B. Rifampin
1. Binds DNA-dependent RNA polymerase, preventing RNA transcription
2. Rifampin is bactericidal.
3. Rifampin is used to treat tuberculosis, usually in combination with isoniazid, pyrazinamide, and ethambutol.
   a. Rifampin should not be used as monotherapy because resistance can develop rapidly.
   b. May also be used in combination with dapsone and clofazimine to treat leprosy
4. Sometimes used for prophylaxis against meningitis from N. meningitidis and H. influenzae
5. Side effects include reddish-orange body fluids. Also promotes the upregulation of cytochrome P450.

C. Pyrazinamide
1. Inhibits the synthesis of mycolic acid
2. Generally bactericidal for intracellular organisms
3. Used exclusively to treat tuberculosis and almost always in combination with rifampin, isoniazid, and ethambutol
4. Side effects include hyperuricemia and hepatotoxicity.

D. Ethambutol
1. Inhibits arabinosyltransferase, preventing the attachment of mycolic acids to peptidoglycans in the cell wall
2. Ethambutol is bacteriostatic.
3. Used in combination with rifampin, pyrazinamide, and isoniazid to treat tuberculosis
4. Side effects include optic neuropathy leading to reversible red-green color blindness.

E. Dapsone
1. Inhibits the synthesis of folic acid by mycobacteria
2. Used in combination with rifampin and clofazimine to treat leprosy. Also used to treat dermatitis herpetiformis and acne vulgaris and as prophylaxis against Pneumocystis pneumonia.
3. May be either bactericidal or bacteriostatic depending on the bacterial strain.
4. Side effects include hemolysis and methemoglobinemia.

F. Clofazimine
1. Binds bacterial DNA, inhibiting replication and transcription.
2. Clofazimine is bactericidal.
3. Generally used in combination with dapsone and rifampin to treat leprosy.
4. Clofazimine has many side effects, including skin discoloration and ichthyosis.

IV. Other antibiotics
A. Fluoroquinolones
1. Ciprofloxacin, levofloxacin, moxifloxacin, gemifloxacin, norfloxacin, ofloxacin.
2. Inhibits topoisomerase and DNA gyrase, interfering with DNA replication.
3. Used mainly to treat gram-negative infections, although some gram-positive bacteria are also susceptible. Commonly used for respiratory tract and urinary tract infections.
4. Fluoroquinolones should not be taken with antacids or supplements that include calcium, iron, or magnesium because these can inhibit their absorption.
5. Side effects include GI distress and tendonitis.
   a. Fluoroquinolones are not absolutely contraindicated in pregnant women and children but are strongly recommended against due to the possibility of arthropathies related to developmental abnormalities and damage to articular cartilage.
   b. Fluoroquinolones are recommended for use in children with cystic fibrosis, although they require monitoring of the joints.

B. Sulfonamides
1. Sulfamethoxazole, sulfisoxazole, sulfadiazine.
2. Inhibit dihydropteroate synthetase, interfering with folic acid synthesis.
   a. Effective against some gram-negative and some gram-positive bacteria, although it is mainly used to treat urinary tract infections, Pneumocystis pneumonia, and sometimes MRSA infections.
   b. Also effective in shigellosis and salmonellosis.
3. Generally bacteriostatic when used alone. However, sulfonamide antibiotics are most commonly administered in conjunction with trimethoprim. This combination is bactericidal.
4. The most common side effect is hypersensitivity reactions because sulfonamides are common.
   a. Symptoms include fever, pruritic rash, hemolytic anemia, thrombocytopenia, agranulocytosis, and urticaria.
   b. Reactions to sulfonamides can be life-threatening.
5. Other side effects include nephrotoxicity, photosensitivity, hemolysis, keratitis in infants, and Stevens-Johnson syndrome.

C. Trimethoprim
1. Inhibits dihydrofolate reductase, interfering with folic acid synthesis.
2. Almost always used in conjunction with a sulfonamide antibiotic. The combination of the two is bactericidal.
3. Side effects are generally related to folic acid deficiency, such as megaloblastic anemia, leukopenia, and granulocytopenia. Folic acid supplementation reverses these.

D. Nitrofurantoïn
1. Undergoes reduction inside bacterial cells, producing reactive products that can inactivate ribosomes and other proteins as well as damage DNA.
2. Nitrofurantoïn is bactericidal.
3. Used almost exclusively to treat urinary tract infections.
4. Not used to treat pyelonephritis because its poor tissue availability makes it largely ineffective.
   a. Nitrofurantoïn is generally taken with food to improve its absorption.
5. Side effects include nausea, headaches, and diarrhea.

**QUICK HIT**

Early-generation quinolones (e.g., ofloxacin, ciprofloxacin) are less effective against gram-positive bacteria, but later-generation drugs (e.g., levofloxacin, moxifloxacin) have improved gram-positive coverage.

**Mnemonic**

To remember the antibiotics that are contraindicated during pregnancy, remember, "CountlessSAFe Moms Take Really Good Care":
- Clarithromycin
- Sulfonamides
- Aminoglycosides
- Fluoroquinolones
- Metronidazole
- Tetracyclines
- Ribavirin
- Griseofulvin
- Chloramphenicol
E. Metronidazole
   1. Selectively absorbed by anaerobic bacteria and certain protozoa, metronidazole is reduced intracellularly. The metabolites then inactivate enzymes and degrade DNA.
   2. Uses:
      a. Used against anaerobic bacteria and Gardnerella vaginalis
      b. Also indicated for Giardia, Entamoeba, and Trichomonas infections
      c. Also used in conjunction with tetracycline and bismuth subsalicylate in H. pylori infection (triple therapy)
   3. Side effects include a disulfiram-like reaction when alcohol is consumed.

F. Polymyxins
   1. Polymyxin B, colistin (polymyxin E)
   2. May be either bactericidal or bacteriostatic, depending on the infection
   3. Act as detergents, altering bacterial membranes and destabilizing them. Also bind and inactivate endotoxins.
   4. Used to treat gram-negative infections
   5. Side effects include acute renal tubular necrosis and neurotoxicity. Polymyxins are almost always used as topical treatments.

VIRUSES

I. Viral basics
   A. Viral structure
      1. Wide range of genome sizes, roughly 3 to 300 kb
      2. Repeating elements (e.g., capsid structure) simplify the genetic requirement because fewer genes are needed.
      3. Nucleocapsid contains either DNA or RNA.
      4. Surface proteins facilitate attachment to host cells.
      5. Some viruses are surrounded by a lipid envelope, usually acquired from a host cell. Viral envelopes may be derived from the cell membrane, the nuclear membrane, or even the endoplasmic reticulum (see Table 12-1).
         a. Enveloped viruses are more sensitive to desiccation and, thus, are generally transmitted through droplets, sexual contact, or parenteral invasion.
         b. Nonenveloped viruses can withstand much harsher conditions and are more likely to spread via the fecal–oral route.
   B. Viral genetics
      1. Reassortment: When two or more viruses infect the same cell, genetic material from one virion may be mistakenly packaged into a different virion. This can lead to the creation of viruses with properties that they would otherwise not possess.
         a. This only occurs when viruses have segmented genomes.
         b. In humans, reassortment only occurs with RNA viruses.
      2. Recombination: When two or more viruses infect the same cell, crossover between homologous regions of DNA (similar to homologous recombination in humans) can produce new viral progeny with different properties.
         a. This almost always involves DNA viruses, or retroviruses, due to their DNA phase.
      3. Complementation: When a virus has a mutation that prevents it from effectively replicating, it may be able to replicate by infecting a cell at the same time as a fully functional virus. Proteins from the functional virus may be able to participate in the replication of the mutated virus, thus temporarily overcoming the mutation.
         a. This is only effective for one generation because the virus will encounter the same problems upon infection of subsequent cells.
      4. Phenotypic mixing: When two viruses infect the same cell, progeny may be packaged with the proper genetic material, but with coat components from both parents. This can alter the tissue specificity of the virion, allowing to temporarily infect different cells.
<table>
<thead>
<tr>
<th>Genome</th>
<th>Family (**enveloped viruses)</th>
<th>Clinically Important Virus</th>
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<tbody>
<tr>
<td>DNA</td>
<td>dsDNA</td>
<td>Herpes simplex virus 1 (HSV-1)</td>
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<td>Human herpes virus 6 (HHV-6)</td>
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<td>Poxviridae**</td>
<td>Variola virus (small pox)</td>
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<td>Human T-cell leukemia virus (HTLV)</td>
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DNA, deoxyribonucleic acid; dsDNA, double-stranded DNA; dsRNA, double-stranded RNA; RNA, ribonucleic acid; RT, reverse transcriptase; ssDNA, single-stranded DNA; (+)ssRNA, positive-sense single-stranded RNA; (−)ssRNA, negative-sense single-stranded RNA.
5. **Naked viral genome infectivity**: Not all viruses require a capsid or an envelope to infect cells. The genetic material from viruses that only use host enzymes is often infectious on its own. Naked double-stranded viral DNA is infectious on its own (except poxvirus and hepatitis B), as is positive, single-stranded RNA.

   a. Negative single-stranded RNA and double-stranded RNA are not infectious.

C. **DNA versus RNA viruses** *(Table 12-1)*

1. **DNA viruses**
   a. Most DNA viruses contain double-stranded DNA. (Exception: Parvovirus is the only single-stranded DNA virus that infects humans.)
   b. DNA genomes are normally linear. (Exceptions: Papillomavirus and polyomavirus have circular genomes.)
   c. Replication of DNA viruses generally occurs in the nucleus because they must use host enzymes for translation. (Exception: Poxvirus possesses its own RNA polymerase, which allows it to replicate in the cytoplasm.)

2. **RNA viruses**
   a. Most RNA viruses contain single-stranded RNA. (Exception: Reoviruses and retroviruses contain double-stranded RNA.)
   b. Positive-sense RNA, which can be immediately translated into proteins, is more common (see Table 12-1).
   c. Replication of RNA viruses generally occurs in the cytoplasm because they do not require the host nuclear RNA polymerase. (Exceptions: Influenza virus uses an exonuclease to cleave the 5' end of methylated host RNA, which then acts as a primer for the synthesis of viral RNA. Retroviruses must enter the nucleus so that the DNA that is transcribed from viral RNA can then be inserted into the host genome.)

II. **DNA viruses**

A. **Herpesviruses**

1. **Herpes simplex virus 1** (HSV-1) *(human herpesvirus 1)*
   a. Causes oral herpes labialis (cold sores). Also causes gingivostomatitis, keratoconjunctivitis, and temporal lobe encephalitis. May less commonly cause genital herpes.
   b. It can be transmitted through any mucosal surface or through abraded skin.
   c. The virus lies dormant in the trigeminal ganglia, occasionally causing disease and then resolving again.

2. **Herpes simplex virus 2** (HSV-2) *(human herpesvirus 2)*
   a. Most common cause of genital herpes *(Figure 12-8)*
   b. The virus lies dormant in the sacral nerve root ganglia, occasionally causing disease and then resolving again.

---

**FIGURE 12-8** Herpes simplex virus

This herpes simplex outbreak on the buttock demonstrates the classic herpetic lesions: grouped vesicles on an erythematous base. *(Reprinted with permission from Goodheart HP. Goodheart’s Photoguide of Common Skin Disorders. 2nd ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2003.)*
c. Normally transmitted through sexual contact, although it can be transmitted through any mucosal surface or through abraded skin
i. Infants born to HSV-positive mothers often contract HSV as they pass through the birth canal, provided the mother is actively shedding the virus.
ii. If the mother has a primary infection (as opposed to a reactivation), transmission may occur in utero.

3. **Varicella zoster virus** (VZV) (human herpesvirus 3)
   a. Primary VZV infection causes chicken pox. Reactivation is known as herpes zoster (shingles).
   b. May cause encephalitis and pneumonia. This is rare in children but more common in adults (especially immunocompromised patients).
   c. VZV lies dormant in the dorsal ganglia. Reactivation causes vesicle formation only on the affected dermatome.
   d. Transmission of primary VZV may be through skin contact or through the respiratory route. In contrast, transmission of reactivated VZV requires direct contact with active lesions.
   e. Disseminated herpes zoster, which is almost entirely restricted to immunocompromised patients, can be transmitted through the respiratory route as well.

4. **Epstein–Barr virus** (EBV) (human herpesvirus 4)
   a. Causative agent in infectious mononucleosis
   b. Generally spread through oral secretions of infected individuals
   c. Infects B cells, which prompts a strong T-cell response. This results in the atypical lymphocytosis that is characteristic of EBV infection.
      i. These atypical lymphocytes (Downey cells) are large, basophilic cells with abundant cytoplasm.
   d. Infectious mononucleosis presents with malaise, fever, sore throat, and posterior cervical lymphadenopathy. Splenomegaly is common and requires restriction of physical activity.
   e. Diagnosis often uses a monospot test that detects heterophile antibodies.
      i. Heterophile antibodies are not specific for EBV. Rather, they are the result of nonspecific B cell activation by EBV and may bind antigens to which the body has never been exposed.
      ii. In the case of the monospot test, antibody-mediated agglutination of equine, ovine, or bovine red blood cells indicates a positive result.
   f. EBV is also associated with Hodgkin lymphoma, Burkitt lymphoma, nasopharyngeal carcinoma, diffuse large cell lymphoma, oral hairy leukoplakia, and various other lymphoproliferative disorders.

5. **Cytomegalovirus** (CMV) (human herpesvirus 5)
   a. Causes mononucleosis-like symptoms with a negative result on monospot
   b. Common perinatal infection. Also may be spread through infected bodily fluids, including saliva and breast milk.
   c. Infections can be severe in immunosuppressed (e.g., transplant recipients) or immunocompromised patients (e.g., AIDS).
      i. CMV may cause acute retinitis in AIDS patients that can blind them permanently in a matter of days.
      ii. CMV may also cause GI ulcerations in AIDS patients that is initially mistaken for *Candida* infection.
   d. CMV-infected cells can be identified by their characteristic “owl eye” appearance of inclusion bodies (Figure 12-9).

6. **Human herpesvirus 6** (HHV-6)
   a. Causes roseola in children (also known as exanthem subitum, and “sixth disease”)
   b. Most children are infected with HHV-6 by age 2 years.
   c. Roseola manifests with 3–5 days of high fever (>102°) without accompanying symptoms. This is followed by a maculopapular rash as the fever breaks. Roseola may also cause febrile seizures.
   d. Like all herpesviruses, HHV-6 causes a lifelong latent infection. However, there are few long-term consequences because reactivations are generally asymptomatic.
7. Human herpesvirus 7 (HHV-7)
   a. Almost all humans have been infected with HHV-7 by age 5 years.
   b. It may cause roseola-like symptoms, but this often occurs in older children as compared to HHV-6.
   c. HHV-7 may also reactivate later in life, although it is generally asymptomatic.
8. Kaposi sarcoma–associated herpesvirus (KSHV) (human herpesvirus 8)
   a. Only 5% of the U.S. population is infected with KSHV.
   b. It infects spindle cells from vascular and lymphatic endothelium. This results in the formation of vascular tumors (Kaposi sarcoma).
   c. KSHV generally causes symptoms only in HIV and AIDS patients or in some immunosuppressed patients.
   d. Kaposi sarcoma may also affect immunocompetent individuals, although this form produces slow-growing, benign tumors.

B. Human papillomavirus (HPV)
   1. There are more than 120 types of HPV.
   2. Types 1 and 2 are associated with common warts and plantar warts.
   3. Types 6 and 11 cause about 90% of all genital warts.
   4. Types 16 and 18 are responsible for 70% of all cases of invasive cervical cancer. They may also cause cancers of the vulva, vagina, anus, and penis.

C. Adenovirus
   1. Family of viruses that generally cause an upper respiratory infection followed by conjunctivitis. This is commonly accompanied by diarrhea.
   2. Various serotypes of adenovirus can also cause febrile pharyngitis, acute hemorrhagic cystitis, and pneumonia.

D. Poxvirus
   1. Smallpox is caused by an enveloped version of poxvirus called variola virus. It has been eradicated, although it remains of concern due to its potential as a bioterrorism agent.
   2. Cowpox is caused by a poxvirus called Vaccinia. It can cause “milkmaid’s blisters” in people who make contact with infected cow udders.
   3. Molluscum contagiosum is a type of poxvirus that causes flesh-colored dome lesions with a central dimple or umbilication (Figure 12-10). It is generally benign and usually resolves on its own in immunocompetent patients. In immunocompromised individuals, it can cause chronic skin lesions.

E. Polyomavirus
   1. The most common polyomavirus in humans is JC virus.
   2. JC virus causes progressive multifocal leukoencephalopathy (PML) in HIV patients.
F. Hepadnavirus
1. The most important hepadnavirus in humans is hepatitis B virus (see Chapter 5).
2. Transmitted sexually, parenterally, or perinatally.
3. Most patients are asymptomatic, although 10% will progress to chronic hepatitis (80%–90% of immunocompromised individuals).
4. Infants are vaccinated for hepatitis B shortly after birth.

G. Parvovirus B19
1. The smallest DNA virus in humans. It is also the only single-stranded DNA virus that infects humans.
2. Disease presentations
   a. Causes “fifth disease” in children, which manifests with a classic “slapped cheek” rash on the face.
   b. Infection in adults rarely results in a cheek rash but may cause acute inflammatory arthritis.
   c. Parvovirus can cause a transient aplastic crisis in sickle cell patients.
   d. In pregnancy, parvovirus can cause miscarriage or hydrops fetalis.

III. RNA viruses
A. Rotavirus
1. A virus of the Reoviridae family that is the primary cause of fatal diarrhea in children worldwide.
2. Severe diarrhea and vomiting cause dehydration and electrolyte abnormalities.
3. Outbreaks are less severe in the United States and generally occur in small children in day care centers or playgrounds.

B. Coltivirus
1. A virus of the Reoviridae family that causes Colorado tick fever.
2. Spread by wood ticks, which are found in mountainous regions of the western United States and Canada.
3. Causes an acute, self-limited, flulike illness.

C. Picornavirus
1. Picornaviridae is a family of small (“pico”) RNA viruses including hepatitis A virus and the genus Enterovirus.
   a. They are primarily spread through the fecal–oral route, although enteroviruses can also be transmitted in respiratory secretions.
   b. Human enteroviruses are further divided into Echovirus, Poliovirus, Rhinovirus, and Coxackievirus.
2. Hepatitis A
   a. A virus of the family Picornaviridae that is transmitted through the fecal–oral route, most commonly in contaminated food or water.
   b. Presents with fatigue, abdominal pain, nausea, and jaundice.
   c. Unlike hepatitis B, hepatitis A does not cause a latent infection and produces no chronic disease. Patients generally recover completely (see Chapter 5).
3. Echovirus
   a. An enterovirus that causes aseptic meningitis, myocarditis, and upper respiratory tract infections
   b. Echovirus-associated meningitis is less severe than bacterial meningitis and may not require hospital care.

4. Poliovirus
   a. An enterovirus that infects the gray matter of the anterior horn of the spinal cord and the motor neurons of the pons and medulla
   b. Causes paralysis and eventual death
   c. Polio vaccines have made cases rare in the United States, but they are common in other parts of the world.

5. Rhinovirus
   a. Rhinovirus is one of the top two causes of the common cold (along with coronavirus). There are more than 100 types of rhinovirus.
   b. Rhinovirus was once classified as its own genus but has recently been reclassified and is now considered to be part of the Enterovirus genus.

6. Coxsackievirus
   a. An enterovirus that also causes aseptic meningitis and myocarditis, along with pericarditis, herpangina, and hand, foot, and mouth disease
   b. Coxsackievirus is the most common cause of viral myocarditis in the United States.
   c. Hand, foot, and mouth disease presents with vesicular or papular lesions on posterior oropharynx as well as the palms and soles of the feet (Figure 12-11).

D. Norwalk virus
   1. A virus of the family *Caliciviridae* that causes gastroenteritis. This results in vomiting and diarrhea.
   2. Spread through fecal–oral route, although vomitus can also spread it
   3. Often seen in point-source outbreaks (e.g., cruise ships, nursing homes)

E. Yellow fever virus
   1. A virus in the family *Flaviviridae* that causes yellow fever
   2. It is an arbovirus that is transmitted by mosquitoes. Commonly seen in sub-Saharan Africa and South America. Fatal in up to 50% of cases.
   3. Presents with high fever, hemorrhagic disease, jaundice, and “coffee ground” emesis (due to the presence of dark brown, partially digested blood in the vomitus)

F. Dengue virus
   1. A virus of the family *Flaviviridae* that causes dengue fever. Classified as an arbovirus, although it can also be transmitted by nonhuman primates.
2. Dengue fever is possibly the most common mosquito-borne illness in the world, more than 50 million cases per year.
   a. Presents with severe headache (especially retro-orbital headache), myalgias, arthralgias, and rarely hemorrhagic fever (due to thrombocytopenia)
   b. Dengue fever is also known as “breakbone fever” due to the severe musculoskeletal pain it causes.

G. West Nile virus (WNV)
1. A virus of the family Flaviviridae. Also classified as an arbovirus, although birds are the natural host (mosquitoes only transfer it from birds to humans).
2. May cause symptoms in incidental human hosts but cannot be transmitted from one person to another
3. WNV infections generally present with flulike symptoms, including fever, headache, malaise, back pain, myalgias, and anorexia. Approximately 1 in 150 patients experiences severe neurologic problems, including meningitis, encephalitis, muscle weakness, and flaccid paralysis.
4. Diagnosis is usually made by identifying anti-WNV IgM antibodies in the CSF (IgM indicates acute disease. IgG against WNV is not diagnostic because it is likely that many people have been exposed to WNV at some point.)
5. Treatment is supportive only. There are currently no antivirals that are effective against WNV.

H. St. Louis encephalitis virus (SLEV)
1. A virus in the family Flaviviridae. Also classified as an arbovirus.
2. SLEV infection generally presents with flulike symptoms, along with confusion, disorientation, and tremors. In severe cases, meningitis, encephalitis, and convulsions are seen, along with cranial nerve palsies and coma.
3. SLEV-specific IgM in the CSF is used to diagnose the infection.
4. Supportive care is indicated because there are no antivirals that are effective.

I. Rubella virus
1. A virus in the family Togaviridae that causes rubella, also known as German measles
2. Presents with fever, lymphadenopathy, arthralgias, and rash
3. Causes congenital defects in utero, including patent ductus arteriosus and pulmonic stenosis

J. Coronavirus
1. Coronaviridae is a family of viruses that cause the common cold (along with rhinovirus).
2. Also the causative agent behind severe acute respiratory syndrome (SARS)

K. Influenza virus
1. An enveloped virus in the family Orthomyxoviridae
2. Contains hemagglutinin (promotes viral attachment) and neuraminidase (releases progeny virions from host cell)
3. Rapid genetic changes occur due to mutations (genetic drift) and reassortment (genetic shift).
4. Flu vaccines contain three different influenza viruses that are determined to be the most likely to cause infection based on data from flu cases in the previous year.
5. Presentation: Sudden onset of headache, fever, myalgias (especially back and body aches), malaise, and nonspecific upper respiratory symptoms (nasal discharge, sore throat, cough). Despite popular perception, gastrointestinal complaints are relatively uncommon.
   a. Influenza virus can cause severe complications, such as viral pneumonia.
   b. Influenza infection can also increase the risk of secondary bacterial infection, which is the most common cause of mortality.
6. H5N1 influenza: Also known as avian influenza (“bird flu”). It has a 60% mortality rate in humans but is currently only transmitted directly from birds to humans (no human-to-human transmission has been observed). Treatment is oseltamivir.
7. H1N1 influenza: Sometimes commonly called as “swine flu.” Derived from swine, avian, and human flu viruses. Presents with typical influenza symptoms, along with diarrhea and vomiting. Treatment is oseltamivir or zanamivir.
L. Parainfluenza virus
   1. An enveloped virus in the family *Paramyxoviridae* that causes croup (laryngotracheobronchitis)
   2. Presents with a barking seal cough, hoarseness, and stridor. Respiratory distress can occur.
   3. CXR may reveal the steeple sign (narrowing of the trachea proximal to the larynx) (Figure 12-12).
   4. Treatment involves cool mist, steam, or cool air. In severe cases, racemic epinephrine, steroids, and oxygen can be used.

M. Respiratory syncytial virus (RSV)
   1. RSV is an enveloped virus in the family *Paramyxoviridae* that causes bronchiolitis and pneumonia. Common in young children in winter months.
   2. RSV has a transmembrane protein called F protein that allows infected cells to fuse with uninfected cells (forming syncyta).
   3. Presents with fever, nasal congestion, cough, wheezing, and respiratory distress in severe cases
   4. Supportive care is the preferred treatment. Antivirals, bronchodilators, and corticosteroids are not recommended.

N. Rubeola virus (measles)
   1. An enveloped virus in the family *Paramyxoviridae* that causes measles
   2. Presents with coryza (runny nose), cough, and conjunctivitis, along with Koplik spots (bluish-gray specks on the buccal mucosa) (Figure 12-13) followed by generalized rash.
3. Rubeola virus can also cause acute and chronic encephalitis as well as fetal loss and premature birth in pregnant women.
   a. The chronic form is known as subacute sclerosing panencephalitis (SSPE) and may manifest years after the patient has seemingly recovered.
4. In immunocompromised patients, rubeola virus can cause giant cell pneumonia.

O. Mumps virus
1. An enveloped virus in the family Paramyxoviridae that causes inflammation of the parotid glands (parotitis), or, less commonly, viral meningitis
2. Mumps virus can also cause orchitis (inflammation of the testes) that may result in sterility.

P. Rabies virus
1. An enveloped virus with a bullet-shaped capsid in the family Rhabdoviridae
2. Mainly infects animals, although it can infect humans after contact with infected animals
3. Rabies virus travels along the peripheral nerves and infects the CNS. Infected tissues contain Negri bodies, which are eosinophilic cytoplasmic inclusions that contain the capsids (Figure 12-14).

IV. HIV
A. Structure (Figure 12-15)
1. Diploid genome (two RNA strands)
2. Conical capsid around RNA, composed of viral protein p24 (encoded by the gag gene)
3. Capsid surrounded by spherical viral envelope, a lipid bilayer into which are embedded glycoproteins gp120 and gp41. (The env gene codes for the protein gp160. Cleavage of this protein yields gp120 and gp41.)
4. Contains the enzymes reverse transcriptase and integrase (both encoded by the pol gene) as well as protease

B. Replication
1. gp120 recognizes and binds CD4 on the surface of T cells, macrophages, or dendritic cells.
2. gp120 then undergoes a conformational change, allowing it to bind a coreceptor molecule on the cell (either CCR5 or CXCR4).
   a. Tropism is the tendency for a virus to preferentially infect cells that express a specific receptor.
   b. HIV strains are differentiated based on whether they bind CXCR4 (called X4 strains) or CCR5 (called R5 strains).
3. Binding of the coreceptors allows gp41 to insert itself into the cell membrane. The virus then fuses with the host cell, and the viral capsid is internalized.
   a. Initial infections mostly involve macrophages and dendritic cells because these are found at mucosal surfaces. This requires viral recognition of CCR5.
   b. As the infection progresses, viruses that recognize CXCR4 begin to predominate, permitting infection of T cells. This is known as a tropism switch.
4. Reverse transcriptase synthesizes DNA from the RNA genome. When cells begin to divide, this DNA integrates into the cell's genome.
   a. Once integrated into the host DNA, the provirus can remain latent for years.
   b. In quiescent cells, the viral DNA may remain in the cytoplasm for an extended period of time until cell division occurs.
5. Viral DNA is then translated by the host cell polymerases into viral proteins.
6. Cells are killed through a combination of viral actions and immune responses (the chief mechanism of cell death in HIV infections is still uncertain).

C. Disease progression (Figure 12-16)
1. Patients are generally asymptomatic for at least the first month after exposure. These patients may also test negative for HIV during this time.
2. One to 2 months after exposure, patients may experience flulike or mononucleosis-like symptoms (acute retroviral syndrome). These symptoms resolve on their own after several weeks.
3. The patient then enters an asymptomatic period that corresponds with low-level viral reproduction (clinical latency). This phase may last for years.

QUICK HIT: Certain strains of HIV can effectively bind both CXCR4 and CCR5. This is known as dual tropism.

QUICK HIT: HIV displays clinical latency, which is the absence of symptoms despite continuous low-level viral reproduction. This is different from viral latency, which refers to a dormant period prior to the eventual onset of viral reproduction (e.g., herpesvirus).
4. As T cell levels decrease, the patient begins to experience opportunistic infections.

D. Diagnosis

1. Diagnosis of HIV
   a. Initial screening is conducted using an enzyme-linked immunosorbent assay (ELISA) test. This will detect anti-HIV antibodies in the patient’s serum. This test is highly sensitive but has some false-positive results.
   b. Positive results on the HIV ELISA screen are confirmed using a Western blot, which also detects anti-HIV antibodies. This test has a very high specificity.
   c. PCR tests are used to determine the viral load, and this may be used to confirm the diagnosis if the patient’s antibody titer is not high enough to yield positive results on the ELISA and/or Western blot screens (i.e., the initial 1–2 months postinfection). Viral load can also be used to monitor the effectiveness of drug therapy.

2. Diagnosis of AIDS
   a. A CD4 T-cell count <200 cells/µL is sufficient for a diagnosis of AIDS. (Healthy patients generally have CD4 counts between 500 and 1,500 cells/µL.)
   b. Alternatively, an AIDS diagnosis can be confirmed if the amount of CD4 T cells as a percentage of total lymphocytes drops below 14%. (A normal CD4 percentage is about 40%.)
   c. The presence of certain opportunistic infections that are seen almost exclusively in AIDS patients (e.g., *Pneumocystis jirovecii*) can also be considered diagnostic of AIDS.

E. Opportunistic infections and associated conditions

1. *Pneumocystis jirovecii*: Fungus that causes interstitial pneumonia
2. *Mycobacterium tuberculosis*: Generally occurs very early in the course of AIDS. May involve only the lungs or may spread to other organs, depending on the degree of immunodeficiency.
3. *Mycobacterium avium complex* (MAC): Also known as *Mycobacterium avium intracellulare* (MAI). Generally occurs after the CD4 count falls below 50 cells/µL.
4. *Histoplasma capsulatum*: Causes a systemic disease characterized by hepatosplenic, fever, and cough, especially with CD4 counts <100 cells/µL.
5. *Cryptococcus neoformans*: Eighty percent to 90% of cryptococcosis cases occur in patients with AIDS, often manifesting as meningitis.
6. *Cytomegalovirus*: CMV retinitis most commonly occurs when CD4 cell counts fall below 50 cells/µL. It may also cause esophagitis and/or colitis, although CMV can manifest as disseminated disease in rare cases.
7. *Toxoplasma gondii*: Toxoplasmosis is the cause of 50% of all CNS lesions in AIDS patients. These tend to manifest as ring-enhancing lesions.

**QUICK HIT**

PCR tests are also useful for diagnosing HIV infections in newborns from HIV-positive mothers.

**QUICK HIT**

*Pneumocystis pneumonia* is commonly referred to as “PCP.”
8. **JC virus**: PML is the result of reactivation of latent JC virus.
9. **Cryptosporidium**: Causes chronic diarrhea that can lead to significant wasting in AIDS patients. (The disease is self-limited in immunocompetent individuals.)
10. **Candida albicans**: Candidiasis is the most common fungal infection in AIDS patients. It generally affects the oral cavity and often occurs in asymptomatic individuals. Its appearance generally heralds the transition to AIDS. In individuals with CD4 counts <100 cells/μL, it can also affect the esophagus and the vagina.
11. **Herpes simplex virus**: HSV causes ulcers in most infected individuals, but AIDS patients have longer, more severe outbreaks.
12. **Epstein–Barr virus (EBV)**: Often causes oral hairy leukoplakia in AIDS patients
13. **Non-Hodgkin lymphoma**: AIDS patients are particularly susceptible to primary CNS lymphoma and large B-cell lymphoma, both of which are associated with EBV infection.
14. **Human papillomavirus**: May cause squamous cell carcinomas of the cervix or anus
15. **Kaposi sarcoma**: Common neoplasm in AIDS patients. Vascular tumors cause the appearance of cutaneous purple lesions (Figure 12-17). These lesions may also appear on mucous membranes or internal organs. This condition is associated with HHV-8.

**QUICK HIT**

Bacillary angiomatosis due to *Bartonella henselae* causes the formation of highly vascular cutaneous lesions, which may be mistaken for Kaposi sarcoma.

**QUICK HIT**

NRTIs must be activated (phosphorylated) by thymidine kinase before becoming functional.

**Microbiology**

**FIGURE 12-17** Kaposi sarcoma

Lesions of AIDS-related Kaposi sarcoma. Whereas some patients may have lesions that remain flat, others experience extensively disseminated, raised lesions with edema. (Reprinted with permission from DeVita VT, Hellaman S, Rosenberg S. *AIDS: Etiology, diagnosis, treatment, and prevention*. 4th ed. Philadelphia, PA: Lippincott-Raven; 1997.)

**F. Treatment**

1. **Antiretroviral therapy** (*Table 12-2*)
   - The standard regimen is called highly active antiretroviral therapy (HAART), a combination of three different drugs designed to inhibit viral replication as well as to avoid the development of resistance.
   - HAART generally involves two different nucleoside reverse transcriptase inhibitors (NRTI), known as the “NRTI backbone,” combined with a third drug from a different class.
   - Indicated for all patients with CD4 counts <350 cells/μL or a diagnosis of AIDS, although it is recommended for all HIV-positive patients
2. **Prophylaxis for opportunistic infections**
   - CD4 <200 cells/μL: Begin PCP prophylaxis with TMP-SMX, with or without aerosolized pentamidine. In sulfa-allergic patients, the drug of choice is dapsone, although patients must be evaluated for glucose-6-phosphate dehydrogenase (G6PD) deficiency.
<table>
<thead>
<tr>
<th>Therapeutic Agent (common name, if relevant)</th>
<th>Class—Pharmacology and Pharmacokinetics</th>
<th>Indications</th>
<th>Side or Adverse Effects</th>
<th>Contraindications or Precautions to Consider, Notes</th>
</tr>
</thead>
</table>
| Zidovudine (ZDV, formerly AZT) | NRTI—guanosine analog  
→ inhibits viral reverse transcriptase  
→ prevents integration of DNA copy of viral genome into host DNA | HAART; HIV pregnant women to reduce fetal transmission | Bone marrow suppression (neutropenia, anemia), peripheral neuropathy, pancreatitis, lactic acidosis | Effects of bone marrow suppression can be reduced by the addition of GM-CSF |
| Didanosine (ddI) | NRTI—guanosine analog;  
(similar to Zidovudine) | HAART | Bone marrow suppression, peripheral neuropathy, pancreatitis, lactic acidosis, hepatic steatosis | |
| Abacavir (ABC) | NRTI—guanosine analog  
(similar to Zidovudine) | HAART | Bone marrow suppression, peripheral neuropathy, pancreatitis, lactic acidosis, hypersensitivity reaction (can be fatal) | Check HLA-B*5701 test prior to starting ABC to avoid giving to patients at risk for hypersensitivity reactions |
| Lamivudine (3TC) | NRTI—cytidine analog  
→ inhibits viral reverse transcriptase  
→ prevents integration of DNA copy of viral genome into the host DNA | HAART | Bone marrow suppression, peripheral neuropathy, pancreatitis, and lactic acidosis | |
| Emtricitabine (FTC) | NRTI—cytidine analog  
(similar to Lamivudine) | HAART | Bone marrow suppression, peripheral neuropathy, pancreatitis, lactic acidosis | |
| Tenofovir (TDF) | Nucleotide reverse transcriptase inhibitor—adenosine analog  
→ inhibits viral reverse transcriptase | HAART | Nausea, vomiting, headache, renal dysfunction | Although it is often classified with the NRTIs, it is actually a nucleotide reverse transcriptase inhibitor. |
| Nevirapine, delavirdine, efavirenz, etravirine, rilpivirine | NNRTI—noncompetitively bind viral reverse transcriptase and inhibits the movement of protein domains  
→ terminates viral DNA synthesis  
→ prevents integration of viral genome into the host DNA | HAART | Rash, bone marrow suppression, peripheral neuropathy; *Efavirenz causes neuropsychiatric problems (nightmares, depression), and dizziness and is teratogenic* | |
| Saquinavir (SQV), ritonavir (RTV), indinavir (IDV), nefalinavir, fosamprenavir, lopinavir, tipranavir, atazanavir, darunavir | Protease inhibitors—HIV-1 protease is responsible for the final step of viral proliferation; inhibits protease in progeny virions  
→ assembly of nonfunctional viruses | HAART | GI intolerance (nausea, diarrhea), hyperglycemia, hyperlipidemia, lipodystrophy,  
*All protease inhibitors and in-ripravir; metabolized cytochrome P450 (many potential drug interactions)* | |
| Enfuvirtide | Fusion inhibitor—binds viral gp41 subunit  
→ inhibits conformation change (required for fusion with CD4 cell)  
→ blocks viral entry and replication | Patients with persistent viral replication on antiretroviral therapy | Hypersensitivity reactions and injection site reactions; increased risk of bacterial pneumonia | Used in combination with other antiretroviral drugs |
TABLE 12.2 Therapeutic Agents in HIV (Continued)

<table>
<thead>
<tr>
<th>Therapeutic Agent (common name, if relevant)</th>
<th>Class—Pharmacology and Pharmacokinetics</th>
<th>Indications</th>
<th>Side or Adverse Effects</th>
<th>Contraindications or Precautions to Consider; Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Raltegravir, elvitegravir</td>
<td>Integrase inhibitors— inhibit the final step in integration of viral DNA into host DNA</td>
<td>HAART</td>
<td>Hyperglycemia, hyperlipidemia, pancreatitis, hepatotoxicity</td>
<td></td>
</tr>
<tr>
<td>Maraviroc</td>
<td>CCR5 antagonist— inhibits viral CCR5 coreceptor [\rightarrow] blocks viral entry to host cell</td>
<td>HAART</td>
<td>Fever, cough, upper respiratory infections, peripheral neuropathy, dizziness</td>
<td></td>
</tr>
</tbody>
</table>

CCR5, C-C chemokine receptor type 5; CD4, cluster of differentiation 4; GI, gastrointestinal; GM-CSF, granulocyte-macrophage colony-stimulating factor; HAART, highly active antiretroviral therapy; NRTI, nucleoside reverse transcriptase inhibitor; NNRTI, non-nucleoside reverse transcriptase inhibitor.

b. CD4 <100 cells/µL: Begin prophylaxis against reactivation of toxoplasmosis with TMP-SMX. In sulfa-allergic patients, a combination of dapsone, pyrimethamine, and leucovorin is used.

c. CD4 <50 cells/µL: Begin MAC prophylaxis with azithromycin.

Fungi

I. Yeast infections

A. Candida albicans infection (candidiasis)
   1. Skin-resident yeast that causes candidiasis. Candida albicans is also found in the GI tract and in the female genital tract.
   2. Diseases
      a. Severe infections only affect immunocompromised patients, although C. albicans can cause superficial infections in immunocompetent individuals.
      b. Vaginal candidiasis is not uncommon in immunocompetent women, although the risk is increased in diabetics and women who have recently undergone treatment with antibiotics.
      c. Diaper rash in infants
      d. Intertrigo is a candidal rash in the skin folds of obese patients or underneath the breasts.
      e. Candida can enter the bloodstream of IV drug users or patients with central lines. It can then cause multiple organ conditions, including endocarditis, hepatosplenic candidiasis, or endophthalmitis. Disseminated candidiasis has a mortality rate of 30%–40%.
   3. Presentation: Oral thrush, esophagitis, painful swallowing, dysphagia, substernal chest pain, vulvovaginitis, vaginal itch, vaginal discharge, rash with satellite lesions, intertrigo
   4. Labs: Positive blood culture, positive urine culture, positive β-glucan detection assay
   5. Treatment: Nystatin, clotrimazole, fluconazole, amphotericin B, caspofungin, micafungin, anidulafungin

B. Cryptococcus neoformans infection
   1. Encapsulated yeast that causes cryptococcosis and cryptococcal meningitis
   2. Cryptococcus is found in soil and pigeon droppings and primarily transmitted via the respiratory route. Generally only affects immunocompromised individuals, particularly cryptococcal meningitis, which is often fatal.
   3. Presentation: Cough, pleuritic chest pain, fever, dyspnea, lymphadenopathy, altered mental status (cryptococcal meningitis)
4. **Diagnostics:** “Soap-bubble” brain lesion, positive blood culture, cryptococci in CSF; nodules and hilar lymphadenopathy on CXR, granulomas on biopsy
5. **Treatment:** Amphotericin B, flucytosine, fluconazole

C. **Pneumocystis jirovecii** infection
1. Yeast that causes *Pneumocystis* pneumonia (PCP). Generally only affects immunocompromised patients. It is the most common opportunistic infection in HIV-positive patients and has a mortality rate of 10%–20%.
2. *Pneumocystis jirovecii* is commonly found in the respiratory tract and is believed to be transmitted in an airborne manner.
3. **Presentation:** Dyspnea, nonproductive cough, fever, crackles on auscultation, tachypnea, tachycardia
4. **Diagnostics:** Atypical pneumonia on CXR, *Pneumocystis* in bronchial lavage, ground glass appearance of interstitial infiltrates on CXR, elevated LDH, positive β-glucan assay
5. **Treatment:** Trimethoprim/sulfamethoxazole, corticosteroids (only in severe cases)

D. **Malassezia furfur** infection (tinea versicolor)
1. *Malassezia furfur* is a yeast that causes tinea versicolor, a condition named for the hypopigmented and hyperpigmented skin patches that result from the infection.
2. Immunocompromised individuals and individuals on corticosteroid therapy have a mildly increased risk for tinea versicolor.
3. **Presentation:** Round, scaly, nonpruritic macules on the trunk and proximal limbs; papules; patches of hyperpigmentation or hypopigmentation (Figure 12-18)
4. **Labs:** “Spaghetti and meatball” appearance on KOH test. Cultures are rarely performed.
5. **Treatment:** Topical antifungals, high rate of recurrence

**QUICK HIT**

*P. jirovecii* was formerly called *P. carinii*. Thus, “PCP” stood for “*Pneumocystis carinii* pneumonia” but now stands for “*Pneumocystis pneumonia*.”

II. **Mold infections**
A. **Aspergillus** infection
1. Multiple species of *Aspergillus* cause human disease and are found ubiquitously in nature.
2. *Aspergillus fumigatus* and *Aspergillus flavus* are the most common causes in humans, although there are more than 200 different species of *Aspergillus*.
3. May cause allergic bronchopulmonary aspergillosis (ABPA) or necrotizing pneumonia or may form aspergillomas in the lungs
4. Immunocompromised patients are susceptible to disseminated aspergillosis, which has a very high mortality rate.
5. Rarely affects immunocompetent individuals
6. **Presentation:** Fever, productive cough, hemoptysis, dyspnea, pleuritic chest pain
7. **Diagnostics:** Acute-angled hyphae on plate culture, neutropenia, eosinophilia (ABPA), positive Aspergillus antigen skin test (ABPA), Aspergillus-specific serum antibodies, pulmonary infiltrates on CXR, positive sputum culture (invasive aspergillosis)
8. **Treatment:** Voriconazole, posaconazole, amphotericin B lipid formulation, corticosteroids (not recommended in immunocompromised patients), surgical care for refractory cases of necrotizing pneumonia

B. **Mucormycosis**
   1. *Rhizopus* and *Mucor* molds are the most common causes. Both are ubiquitous in the environment.
   2. Mucormycosis is a rare disease that generally occurs in immunocompromised individuals, especially patients with diabetic ketoacidosis.
   3. The most common form is rhinocerebral mucormycosis, although it may also be pulmonary, cutaneous, gastrointestinal, or disseminated.
      - a. The rhinocerebral form has a mortality rate of 50%–70%.
      - b. The disseminated form has a mortality rate of nearly 100%.
   4. **Presentation:** Headache, facial pain, numbness, fever, hyposmia, black nasal discharge, diplopia, vision loss, black eschars in the palate or the nose, orbital swelling, facial cellulitis
   5. **Diagnostics:** Right-angled hyphae on plate culture, *Mucoraceae* in tissue biopsy, mucosal thickening, bony erosions, sinusitis. Blood cultures are generally negative.
   6. **Treatment:** Amphotericin B lipid formulation, posaconazole. Surgical debridement of necrotic tissue is mandatory.

C. **Dermatophytosis**
   1. Caused by a group of molds known as dermatophytes. This includes *Trichophyton*, *Microsporum*, and *Epidermophyton*. These molds may be resident in human skin, soil, or animals, depending on the species.
   2. Dermatophytes cause a wide variety of superficial skin conditions.
      a. **Tinea pedis:** Affects the soles of the feet. Also known as athlete's foot. Most common presentation of dermatophytosis. *Trichophyton rubrum* is the most common cause.
      b. **Tinea cruris:** Affects the groin. Also known as jock itch. Second most common presentation of dermatophytosis. *Trichophyton rubrum* and *Epidermophyton floccosum* are the most common causes.
      c. **Tinea corporis:** Affects the glabrous (hairless) skin. Most commonly caused by *Trichophyton rubrum*.
      d. **Tinea capitis:** Affects the scalp. Most common dermatophytosis in children. *Trichophyton tonsurans* is the most common cause.
      e. **Tinea unguium:** Affects the fingernails and toenails. Also known as onychomycosis. Generally caused by *Trichophyton rubrum*, although it can also be caused by *Candida*.
      f. Other forms of tinea include tinea manuum (hands), tinea barbae (hairy facial skin), and tinea faciei (glabrous facial skin).
   3. **Presentation:** Dry scaly skin, rash, erythematous plaques, papules, pruritic lesions with central clearing (tinea capitis), thickened discolored nails (tinea unguium)
   4. **Labs:** Fungal hyphae on skin scrapings or hair samples, positive fungal culture
   5. **Treatment:** Topical terbinafine, topical clotrimazole, topical ketoconazole, topical econazole, oral itraconazole, griseofulvin (tinea capitis)

III. **Dimorphic fungi**

A. **Histoplasma capsulatum** infection
   1. *Histoplasma capsulatum* is a dimorphic fungus that causes histoplasmosis.
   2. It is endemic in the Mississippi, Missouri, and Ohio river valleys as well as numerous other river valleys around the world. It is found in soil as well as in bat droppings.
   3. It is transmitted through inhalation of airborne spores, which may remain dormant for years.
   4. Most infected individuals are asymptomatic. Symptomatic individuals are generally immunocompromised, or they have been exposed to a very high inoculum load.
5. In symptomatic patients, infection usually causes include mild pulmonary disease, which may progress to pericarditis or mediastinal fibrosis. Disseminated histoplasmosis is generally only seen in immunocompromised patients.

6. **Presentation**: Fever, headache, malaise, myalgias, abdominal pain, rales and wheezing.

7. **Diagnostics**: Positive skin antigen test, pulmonary infiltrates on CXR, mild anemia, pancytopenia, elevated alkaline phosphatase (ALP), positive blood and sputum cultures.

8. **Treatment**: Fluconazole, itraconazole, amphotericin B, corticosteroids.

B. **Blastomyces dermatitidis** infection

1. *Blastomyces dermatitidis* is a dimorphic fungus that cause blastomycosis.

2. Transmitted by inhalation of spores from soil. Incubation period is 20–40 days.

3. Fifty percent of patients will never develop symptoms.

4. Extrapulmonary dissemination is rare in immunocompetent individuals.

5. Blastomycosis is not normally fatal, unless a patient is immunocompromised or the untreated infection has progressed to acute respiratory distress syndrome.

6. **Presentation**: Fever, chills, myalgias, dyspnea, cough, skin lesions, arthralgias.

7. **Diagnostics**: Leukocytosis, hypoxemia, positive sputum KOH test, positive stain and culture. CXR findings are nonspecific.

8. **Treatment**: Itraconazole, amphotericin B.

C. **Coccidioides immitis** infection

1. *Coccidioides immitis* is a dimorphic fungus that causes coccidioidomycosis (also known as San Joaquin valley fever).

2. Transmission by inhalation of spores from soil. Normally seen in the southwestern United States.

3. Coccidioides actually forms spherules in vivo. Spherules are double-walled structures that are filled with many daughter endospores (Figure 12-19). These eventually burst, releasing the endospores into the surrounding tissue.

4. Most infected patients are asymptomatic or only mildly symptomatic.

5. Primary infection usually presents as pneumonia, with fatigue, cough, fever, and arthralgias (sometimes called desert rheumatism).

6. Immunocompromised individuals are more susceptible to disseminated infections, although it does occur in otherwise healthy individuals. Disseminated infection can involve the skin, CNS, bones, and joints.

7. **Presentation**: Fever, cough, chest pain, fatigue, dyspnea, erythema nodosum, arthralgias, rales, rhonchi. Headache, blurred vision, and altered mental status are associated with meningitis.

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![Coccidioides immitis spherules](image-url)

*Lung granuloma with Coccidioides spherule. (Reprinted with permission from McClatchey KD. *Clinical Laboratory Medicine*. 2nd ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2002.)*
8. **Diagnostics:** Elevated sed rate, positive IgM or IgG serum titer, positive fungal culture, positive antigen skin test, elevated CSF protein (meningitis), spherules on biopsy.

9. **Treatment:** Amphotericin B, fluconazole, ketoconazole, itraconazole

D. *Paracoccidioides brasiliensis* infection

1. *Paracoccidioides brasiliensis* is a dimorphic fungus that causes paracoccidioidomycosis when it is inhaled from the environment.
2. Endemic to Central and South America. Most cases of paracoccidioidomycosis in the United States are believed to be due to activation of latent infections that originated in Central or South America.
3. Paracoccidioidomycosis is usually asymptomatic, although it can progress to severe pulmonary infection. It may also cause fibrosis of mucous membranes, which can result in long-term sequelae.
4. Immunocompromised individuals do not have a significantly higher rate of infection, although they are at higher risk for disseminated disease once infected.
5. **Presentation:** Cough (dry or productive), dyspnea, malaise, fever, laryngeal and pharyngeal lesions, oral lesions, skin lesions, cervical lymphadenopathy
6. **Diagnostics:** “Captain’s wheel” spores in tissue or fluid samples (Figure 12-20), interstitial infiltrates on CXR
7. **Treatment:** Amphotericin B, itraconazole, ketoconazole, supportive care, reconstructive surgery for fibrotic sequelae

E. *Sporothrix schenckii* infection

1. *Sporothrix schenckii* is a dimorphic fungus that causes sporotrichosis. It is found in soil and on vegetation. It is commonly transmitted through skin wounds and is informally known as rose gardener's disease.
2. Generally begins as a skin lesion or subcutaneous nodule at the wound site. It then spreads, with more lesions and nodules appearing along the draining lymphatics.
3. Disseminated sporotrichosis is very rare and usually only occurs in immunocompromised patients.

**Figure 12-20 Paracoccidioides spores**

The lung contains *Paracoccidioides brasiliensis*, which displays many external buds arising circumferentially from the mother organism (“captain’s wheel” spores).
4. **Presentation:** Painless skin lesions or nodules, ulcerating lesions
5. **Diagnostics:** Positive fungal cultures, positive antibody titer, granulomatous inflammation in skin biopsy
6. **Treatment:** Itraconazole, fluconazole, amphotericin B lipid formulation, saturated solution of potassium iodide (SSKI)

### IV. Antifungal drugs (Table 12-3)

<table>
<thead>
<tr>
<th>Therapeutic Agent</th>
<th>Class—Pharmacology and Pharmacokinetics</th>
<th>Indications</th>
<th>Side or Adverse Effects</th>
<th>Contraindications or Precautions to Consider; Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amphotericin B</td>
<td>Polyene—binds ergosterol in fungal cell membrane, altering cell permeability</td>
<td>Used for severe systemic fungal infections or infections where first-line antifungals are failing</td>
<td>Nephrotoxicity, fever, chills, anemia, phlebitis, arhythmias, hypotension, hypokalemia</td>
<td>Administered intravenously; liposomal formulation has fewer side effects but is expensive</td>
</tr>
<tr>
<td>Nystatin</td>
<td>Polyene—binds ergosterol in fungal cell membrane, altering cell permeability</td>
<td>Topically for cutaneous or vulvovaginal candidiasis. “Swish and swallow” for oral thrush</td>
<td>Too toxic for systemic use; diarrhea, nausea, vomiting, and stomach pain from swallowing nystatin suspension</td>
<td>Topical nystatin is safe for use in pregnancy, but oral nystatin suspension is not recommended</td>
</tr>
<tr>
<td>Fluconazole</td>
<td>Triazole—interferes with synthesis of the fungal membrane by inhibiting lanosterol 14α-demethylase, which normally converts lanosterol to ergosterol</td>
<td>Oropharyngeal and esophageal candidiasis, cryptococcal meningitis, vulvovaginitis</td>
<td>Increased LFTs, headache, nausea, abdominal pain, diarrhea</td>
<td>Contraindicated in pregnancy</td>
</tr>
<tr>
<td>Itraconazole</td>
<td>Triazole—(same as fluconazole)</td>
<td>Life-threatening mycoses (blastomycosis, aspergillosis, histoplasmosis), oral candidiasis, onychomycosis</td>
<td>Increased LFTs, nausea, vomiting, rash, headache</td>
<td>Not recommended during pregnancy</td>
</tr>
<tr>
<td>Voriconazole</td>
<td>Triazole—(same as fluconazole)</td>
<td>Invasive aspergillosis, candidemia, candidiasis</td>
<td>Visual changes, hallucinations, increased LFTs</td>
<td>Contraindicated in pregnancy</td>
</tr>
<tr>
<td>Posaconazole</td>
<td>Triazole—(same as fluconazole)</td>
<td>Aspergillus prophylaxis in neutropenia, refractory candidiasis</td>
<td>Hypokalemia, hypomagnesemia, anemia, thrombocytopenia, vaginal hemorrhage, nausea, vomiting, diarrhea</td>
<td>May be used in pregnancy, although it is not recommended</td>
</tr>
<tr>
<td>Ketoconazole</td>
<td>Imidazole—(same mechanism as fluconazole)</td>
<td>Seborheic dermatitis, tinea versicolor, dermatophytoses, endemic mycoses. Largely replaced by newer antifungals.</td>
<td>Nausea, vomiting, skin irritation, hepatotoxicity, gynecomastia</td>
<td>May be used in pregnancy if necessary</td>
</tr>
<tr>
<td>Clotrimazole (Lotrimin, Mycelex)</td>
<td>Imidazole—(same mechanism as fluconazole)</td>
<td>Topical use for dermatophytoses and <em>Candida</em> vulvovaginitis</td>
<td>Abnormal LFTs as well as mild irritation at the application site</td>
<td>Safe for use in pregnancy</td>
</tr>
<tr>
<td>Miconazole (Desenex, Monistat)</td>
<td>Imidazole—(same mechanism as fluconazole)</td>
<td>Topical use for dermatophytoses and <em>Candida</em> vulvovaginitis. Oral use for oropharyngeal candidiasis.</td>
<td>Skin irritation at the topical application site; GI symptoms when taken orally</td>
<td>May be used in pregnancy, although it is not recommended</td>
</tr>
</tbody>
</table>
### TABLE 12-3 Antifungal Drugs (Continued)

<table>
<thead>
<tr>
<th>Therapeutic Agent</th>
<th>Class—Pharmacology and Pharmacokinetics</th>
<th>Indications</th>
<th>Side or Adverse Effects</th>
<th>Contraindications or Precautions to Consider; Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Terbinafine (Lamisil)</td>
<td>Allylamine—inhibits squalene epoxidase, which normally converts squalene to lanosterol → interferes with fungal membrane synthesis</td>
<td>Topically for dermatophytoses, orally for onychomycosis and tinea capitis</td>
<td>Skin irritation at the topical application site; GI symptoms and increased LFTs when taken orally</td>
<td>Safe for use in pregnancy</td>
</tr>
<tr>
<td>Caspofungin</td>
<td>Echinocandin—inhibits β-1,3-D-glucan synthase → interferes with cell wall synthesis</td>
<td>Candidemia, candidiasis, invasive aspergillosis</td>
<td>Phlebitis, fever, rash, increased LFTs</td>
<td>May be used in pregnancy but is not recommended</td>
</tr>
<tr>
<td>Flucytosine</td>
<td>Pyrimidine analog that inhibits DNA and protein synthesis</td>
<td>Candidiasis, <em>Cryptococcus</em> infections; combined with amphotericin B to treat systemic fungal infections, particularly cryptococcal meningitis</td>
<td>Bone marrow suppression, increased LFTs, some GI symptoms</td>
<td>May be used in pregnancy, although it is not recommended</td>
</tr>
<tr>
<td>Griseofulvin</td>
<td>Inhibits microtubule function, interfering with mitosis</td>
<td>Used orally to treat dermatophytoses</td>
<td>GI symptoms, headache, confusion</td>
<td>Induces cytochrome P450; contraindicated in pregnancy (teratogenic)</td>
</tr>
</tbody>
</table>

GI, gastrointestinal; LFTs, liver function tests.

### TABLE 12-4 Protozoa (Table 12-4)

<table>
<thead>
<tr>
<th>Organism</th>
<th>Clinical Features</th>
<th>Transmission</th>
<th>Labs</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cryptosporidium</td>
<td>Chronic diarrhea in HIV-positive patients, possible respiratory or biliary tract infections. (Immunocompetent patients have only mild, self-limited diarrhea)</td>
<td>Contaminated water or person-to-person contact</td>
<td>Cryptosporidium in stool, elevated ALP (biliary involvement), dilated biliary ducts and/or enlarged gallbladder (biliary involvement). CXR for respiratory involvement is nonspecific.</td>
<td>Nitazoxanide, paromomycin, antidiarrheals, supportive therapy</td>
</tr>
<tr>
<td>Giardia lamblia</td>
<td>Diarrhea, greasy stool flatulence, abdominal distention</td>
<td>Water contaminated with animal feces, commonly affects campers and hikers</td>
<td>Trophozoites (pear-shaped cysts with double nuclei) in stool (Figure 12-21), increased fecal fat.</td>
<td>Metronidazole, tinidazole, paromomycin</td>
</tr>
<tr>
<td>Entamoeba histolytica</td>
<td>Invasion of the colon causes bloody diarrhea. May also cause liver abscesses (RUQ abdominal pain)</td>
<td>Contaminated water or food</td>
<td>Leukocytosis, elevated ALP, RBCs in trophozoites, anti-<em>Entamoeba</em> Ab in serum</td>
<td>Metronidazole, nitazoxonide, tinidazole, paromomycin, surgical intervention if liver abscesses are refractory to medication</td>
</tr>
<tr>
<td>Trichomonas vaginalis</td>
<td>Vaginal irritation, malodorous green vaginal discharge, dyspareunia, dysuria. (Men may also be infected but are generally asymptomatic.)</td>
<td>Sexual contact</td>
<td>Low vaginal pH, flagellated protozoa in vaginal discharge</td>
<td>Metronidazole, tinidazole</td>
</tr>
</tbody>
</table>

(continued)
<table>
<thead>
<tr>
<th>Organism</th>
<th>Clinical Features</th>
<th>Transmission</th>
<th>Labs</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Toxoplasma gondii</em></td>
<td>Brain abscesses in HIV-positive patients. Crosses the placenta to cause fetal choriorhinits, hydrocephalus, and intracranial calcifications.</td>
<td>Normally contracted from cat feces</td>
<td>Ring-enhancing brain lesions on MRI, anti- <em>Toxoplasma</em> Ab in serum, tachyzoites or cysts in tissues or fluids.</td>
<td>Sulfadiazine, pyrimethamine, folic acid</td>
</tr>
<tr>
<td><em>Plasmodium species</em></td>
<td>Malaria: cyclical fever, sweats, chills, headache, cough, hemoglobinuria, arthralgias, myalgias, altered mental status (P. falciparum)</td>
<td>Anopheles mosquito</td>
<td>Hemolytic anemia, merozoites on blood smear, banana-shaped gametocyte (P. falciparum) (Figure 12-22)</td>
<td>Primaquine, chloroquine, quinine, mefloquine, atovaquone/proguanil, artesunate/lumefantrine</td>
</tr>
<tr>
<td><em>Naegleria fowleri</em></td>
<td>Flagellated protozoan that causes primary amebic meningoencephalitis: fever, ageusia, headache, stiff neck, mental status changes, seizures, cranial nerve palsies</td>
<td>Contracted from freshwater lakes.</td>
<td>Trophozoites in CSF or brain biopsy, positive CSF culture, elevated CSF protein</td>
<td>Intravenous and intrathecal amphotericin B. (Almost universally fatal. Death occurs within 5–10 days)</td>
</tr>
<tr>
<td><em>Trypanosoma brucei</em></td>
<td>African sleeping sickness; chance at bite site; early stage has mild symptoms like fever, malaise, rash appear; late stage CNS involvement, leading to headaches, somnolence, and seizures</td>
<td>Transmitted by the tsetse fly. Endemic to sub-Saharan Africa.</td>
<td><em>T. brucei</em> on smear, hypoalbuminemia, hypergammaglobulinemia, elevated ESR, anemia, thrombocytopenia, elevated CSF protein</td>
<td>Suramin, or melarsoprol or eflornithine for CNS involvement</td>
</tr>
<tr>
<td><em>Trypanosoma cruzi</em></td>
<td>Chagas disease: fever, lymphadenopathy, dilated cardiomyopathy, megasplasphagus, megacolon</td>
<td>Transmitted by reduviid bug (&quot;kissing bug&quot;). Endemic to North and South America.</td>
<td><em>T. cruzi</em> on blood smear</td>
<td>Nifurtimox, benznidazole</td>
</tr>
<tr>
<td><em>Leishmania donovani</em></td>
<td>Intracellular protozoa that cause cutaneous leishmaniasis (ulcerating papules, hyperpigmentation) and visceral leishmaniasis (spiking fever, night sweats, splenomegaly)</td>
<td>Transmitted by the female sandfly</td>
<td>Pancytopenia, anemia, macrophages containing amastigotes, positive tissue culture, positive PCR test</td>
<td>Amphotericin B lipid formulation for visceral leishmaniasis. Sodium stibogluconate for cutaneous leishmaniasis.</td>
</tr>
<tr>
<td><em>Babesia microti</em></td>
<td>Babesiosis, which is clinically similar to malaria, without cyclical fevers</td>
<td>Transmitted by <em>bodes</em> ticks</td>
<td>Anemia, hemoglobinuria, ring forms in red blood cells, cross-shaped tetrad merozoites in RBCs (Figure 12-23)</td>
<td>Atovaquone plus azithromycin, or quinine plus clindamycin</td>
</tr>
</tbody>
</table>

Ab, antibodies; ALP, alkaline phosphatase; CXR, chest x-ray; CNS, central nervous system; CSF, cerebrospinal fluid; ESR, erythrocyte sedimentation rate; PCR, polymerase chain reaction; RBCs, red blood cells; RUQ, right upper quadrant.
**Microbiology**

**FIGURE 12.22** Plasmodium stages


**FIGURE 12.23** Babesiosis

*Babesia microti*-infected erythrocytes from a case of transfusion-transmitted babesiosis. Note the ring form (open arrow) and the characteristic tetrad or “Maltese cross” (closed arrow). (Reprinted with permission from Gorbach SL, Bartlett JG, et al. *Infectious Diseases*. Philadelphia, PA: Lippincott Williams & Wilkins; 2004.)
## HELMINTHS (Tables 12-5, 12-6, 12-7)

### TABLE 12-5 Nematodes (Roundworms)

<table>
<thead>
<tr>
<th>Organism</th>
<th>Clinical Features</th>
<th>Transmission/ Life Cycle</th>
<th>Labs</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enterobius vermicularis (pinworm)</td>
<td>Anal pruritus</td>
<td>Fecal–oral transmission; worms reside in the colon and migrate to the rectum at night to lay eggs, which hatch in 6 hours</td>
<td>Worms in stool, positive &quot;tape test&quot; (place transparent tape over the anus at night, then examine for eggs)</td>
<td>Albendazole, mebendazole</td>
</tr>
<tr>
<td>Ascaris lumbricoides (giant roundworm)</td>
<td>Abdominal pain and distention, nausea, dizziness, Löffler syndrome (wheezing, cough, dyspnea, chest pain)</td>
<td>Fecal–oral transmission; eggs hatch in the small intestine, enter bloodstream, go to the lungs, move up into the oropharynx, then down into the GI tract and begin to lay eggs</td>
<td>Eggs in stool, larvae in sputum, peripheral eosinophilia, intraluminal worms on abdominal x-ray</td>
<td>Albendazole, mebendazole, pyrantel pamoate</td>
</tr>
<tr>
<td>Trichinella spiralis</td>
<td>Diarrhea (initially), fever, headache, fatigue, weakness, periorbital edema, myalgias, myositis</td>
<td>Contracted from consumption of undercooked pork or wild game; larvae migrate from the GI tract into the muscles</td>
<td>Eosinophilia, elevated CK and LDH, myoglobinuria, anti-Trichinella Ab in serum, larvae on muscle biopsy</td>
<td>Albendazole, mebendazole, corticosteroids</td>
</tr>
<tr>
<td>Strongyloides stercoralis</td>
<td>Pruritic rash at the entry site (&quot;ground itch&quot;), nonspecific GI symptoms, wheezing and mild cough; altered mental status and seizures only appear in patients with the disseminated form</td>
<td>Reside in soil, enter humans by penetrating the skin; enters bloodstream, travels to lungs, then migrates through oropharynx to the intestine to lay eggs; eggs hatch in the intestine, and larvae are excreted in the feces</td>
<td>Eosinophilia, Strongyloides larvae in stool, antibodies in serum</td>
<td>Ivermectin, albendazole, mebendazole</td>
</tr>
<tr>
<td>Ancylostoma duodenale and Necator americanus (hookworms)</td>
<td>Pruritic rash at the entry site (&quot;ground itch&quot;), diarrhea, abdominal pain, and symptoms of anemia</td>
<td>Reside in soil, enter humans by penetrating the skin; life cycle similar to Strongyloides</td>
<td>Anemia, hookworm eggs in stool, eosinophilia (acute phase)</td>
<td>Albendazole, mebendazole</td>
</tr>
<tr>
<td>Wuchereria bancrofti</td>
<td>Lymphatic filariasis and elephantiasis: fever, lymphadenopathy, testicular pain, edema, hydrocele, elephantiasis of limbs or genitals</td>
<td>Transmitted by mosquitoes; larvae migrate to the lymphatics, where they cause inflammation and lymphatic obstruction</td>
<td>Worms; blood or hydrocele fluid, antigen in peripheral blood, eosinophilia</td>
<td>Diethylcarbamazine, doxycycline, ivermectin, albendazole; surgical excision for large hydroceles and scrotal elephantiasis</td>
</tr>
</tbody>
</table>

Ab, antibodies; CK, creatine kinase; GI, gastrointestinal; LDH, lactate dehydrogenase.
### TABLE 12-6 Cestodes (Tapeworms)

<table>
<thead>
<tr>
<th>Organism</th>
<th>Clinical Features</th>
<th>Transmission/ Life Cycle</th>
<th>Labs</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Taenia solium</em></td>
<td>GI tract infection with the tape-worm causes abdominal pain, anorexia, weight loss; larval cyst formation in host organs or tissues (cysticercosis); CNS involvement (neurocysticercosis) can cause seizures and altered mental status</td>
<td>GI infection with the tapeworm results from eating undercooked pork containing larval cysts. Cysticercosis results from ingesting food/water containing tape-worm eggs.</td>
<td>Eosinophilia, <em>Taenia</em> eggs in stool; cysts on CT or MRI, abnormal CSF findings (neurocysticercosis)</td>
<td>Albendazole, praziquantel, dexamethasone. Surgical removal of cysts as needed.</td>
</tr>
<tr>
<td><em>Diphyllobothrium latum</em></td>
<td>Usually asymptomatic; may cause abdominal pain or indigestion may be seen; worms may absorb nutrients in the intestine (may lead to B$_{12}$ deficiency)</td>
<td>Contracted by eating undercooked fish, mature in the small intestine</td>
<td>Megaloblastic anemia, eosinophilia, decreased vitamin B$_{12}$, eggs or worm segments in stool</td>
<td>Praziquantel</td>
</tr>
<tr>
<td><em>Echinococcus granulosus</em></td>
<td>Pulmonary cystic echinococcosis (cough, chest pain, dyspnea); hepatic echinococcosis (RUQ abdominal pain, jaundice, hepatomegaly)</td>
<td>Contracted from ingestion of food or water contaminated with dog feces; eggs hatch in the GI tract and larvae form hydatid cysts throughout the body</td>
<td>Lymphopenia, thrombocytopenia, elevated LFTs, hydatid cysts on imaging</td>
<td>Albendazole, surgical removal of cysts, aspiration of cyst fluid and injection of a scolicidal agent</td>
</tr>
</tbody>
</table>

CNS, central nervous system; CSF, cerebrospinal fluid; CT, computed tomography; GI, gastrointestinal; LFT, liver function tests; MRI, magnetic resonance imaging; RUQ, right upper quadrant.

### TABLE 12-7 Trematodes (Flatworms)

<table>
<thead>
<tr>
<th>Organism</th>
<th>Clinical Features</th>
<th>Transmission/ Life Cycle</th>
<th>Labs</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Schistosoma mansoni</em>, <em>Schistosoma haematobium</em> (blood flukes)</td>
<td>Acute infection can present with fever, lethargy, myalgias, dysuria, abdominal pain, diarrhea, lymphadenopathy, hepatitisplenomegaly; squamous cell CA of the bladder (<em>S. haematobium</em>)</td>
<td>Eggs hatch in water; larvae are ingested by freshwater snails and mature into the infectious form (cercariae); cercariae penetrate the skin of a new human host; they mature in the lungs or the liver; mature flukes migrate to the mesenteric vessels (<em>S. mansoni</em>) or the urinary tract (<em>S. haematobium</em>).</td>
<td>Hematuria (<em>S. haematobium</em>), peripheral eosinophilia, elevated LFTs, <em>Schistosoma</em> eggs in urine or stool, serum antibodies, positive urine PCR test</td>
<td>Praziquantel</td>
</tr>
<tr>
<td><em>Paragonimus westermani</em> (lung fluke)</td>
<td>Resides in the lungs of the host, causing chronic bronchitis and hemoptysis; fever, cough, dyspnea, chest pain</td>
<td>Contracted from ingestion of undercooked crab meat, eggs expelled through coughing, or are swallowed and expelled in the stool</td>
<td>Eosinophilia, eggs in sputum and stool, ring shadows and nodules on CXR, pleural thickening</td>
<td>Praziquantel</td>
</tr>
<tr>
<td><em>Clonorchis sinensis</em> (liver fluke)</td>
<td>Clonorchis lives in the biliary tract and is associated with pigmented gallstones and cholangiocarcinoma; fever, RUQ abdominal pain, diarrhea</td>
<td>Contracted from ingestion of undercooked fish; endemic in Far East and Southeast Asia.</td>
<td>Eosinophilia, eggs in stool, anti-<em>Clonorchis</em> Ab in serum</td>
<td>Praziquantel, albendazole</td>
</tr>
</tbody>
</table>

Ab, antibodies; CA, carcinoma; CXR, chest x-ray; LFT, liver function test; PCR, polymerase chain reaction; RUQ, right upper quadrant.
COMPONENTS OF THE IMMUNE SYSTEM

I. Primary lymphoid organs
   A. Bone marrow
      1. All immune cells originate in the bone marrow.
      2. B lymphocytes (B cells) fully mature in the bone marrow.
      3. Most other leukocytes migrate to peripheral sites to fully mature.
   B. Thymus
      1. Derived from the third branch pouch; enlarges during childhood and then
         begins to atrophy in puberty
      2. Site of T-lymphocyte (T-cell) maturation

II. Secondary lymphoid organs
   A. Spleen
      1. The spleen filters the blood, constantly sampling it for antigens.
      2. Individuals without a functioning spleen are more susceptible to encapsulated
         bacteria.
      3. The spleen contains white pulp and red pulp, surrounded by a fibrous capsule
         (Figure 13-1).
         a. Red pulp contains large numbers of red blood cells.
         b. Macrophages and other antigen-presenting cells (APCs) phagocytose antigens
            found in the red pulp and bring them to the marginal zone surrounding the
            white pulp, where they present those antigens to lymphocytes in the white pulp.
         c. White pulp contains large numbers of white blood cells.
            i. Within the white pulp is a central artery, surrounded by a band of T cells
               called the periarterial lymphatic sheath (PALS).
            ii. White pulp also contains organized follicles of B cells.
      4. The spleen also sequesters roughly one-third of the body's platelets.
   B. Lymph nodes
      1. Found throughout the body, although they tend to be clustered in tissues that
         are exposed to the environment
      2. Lymph nodes sample the lymph draining from nearby tissues and facilitate the
         development of an immune response to any antigens found in those tissues.
         This lymph ultimately drains into the bloodstream (often after passing through
         other lymph nodes and lymphatic ducts).
      3. Each lymph node can be divided into zones (Figure 13-2):
         a. The cortex (outermost layer) contains B lymphocytes (B cells) arranged
            in follicles. Once activated, B cells will proliferate and secrete antibodies,
            which can then enter the bloodstream.
         b. The paracortex contains mainly T lymphocytes (T cells). When activated,
            T cells proliferate and secrete cytokines to facilitate the immune response.
            The paracortex also contains endothelial venules, which allow B cell and
            T cells to enter the lymph nodes from the blood.

Mnemonic

Remember the encapsulated bacteria with the mnemonic
“Even Some Pretty Nasty Killers Have Shiny Bodies”:
- Escherichia coli
- Streptococcus pneumoniae
- Pseudomonas aeruginosa
- Neisseria meningitidis
- Klebsiella pneumoniae
- Haemophilus influenzae type B
- Salmonella typhi
- Group B strep

Quick Hit

Splenomegaly often results in thrombocytopenia.

Lymph is the interstitial fluid that contains antigens, cells,
 cellular debris, cytokines, and other proteins.

During infection, T-cell proliferation causes enlarge-
 ment of the lymph node paracortex.
The spleen, the largest lymphoid organ, possesses a thick collagenous connective tissue capsule (Ca). Because it lies within the abdominal cavity, it is surrounded by a simple squamous epithelium (E). Connective tissue septa (SE), derived from the capsule, penetrate the substance of the spleen, conveying blood vessels (BV) into the interior of the organ. Histologically, the spleen is composed of white pulp (WP) and red pulp (RP). White pulp is arranged as a cylindrical, multilayered sheath of lymphocytes (Ly) surrounding a blood vessel known as the central artery (CA). The red pulp consists of sinusoids (S) meandering through a cellular tissue known as pulp cords (PC). The white pulp of the spleen is found in two different arrangements. The one represented in this photomicrograph is known as a periarterial lymphatic sheath (PALS), composed mostly of T lymphocytes. The zone of lymphocytes at the junction of the PALS and the red pulp is known as the marginal zone (MZ). (From Gartner LP, Hiatt, JL. Color Atlas and Text of Histology. Philadelphia: Wolters Kluwer Health | Lippincott Williams & Wilkins, 2013. Used with permission.)
c. The medulla (innermost layer) contains mostly macrophages and plasma cells. Activated plasma cells secrete antibodies directly into the bloodstream.

4. Lymphatic drainage (Table 13-1)

C. Mucosa-associated lymphoid tissue (MALT)
1. MALT is unencapsulated lymphoid tissue that lines the respiratory tract, digestive tract, and genitourinary tract.
   a. These are often divided into the gut-associated lymphoid tissue (GALT), the bronchus-associated lymphoid tissue (BALT), and the nasal-associated lymphoid tissue (NALT), as well as others.
2. GALT contains highly organized lymphoid tissue known as Peyer patches. These are found in the lamina propria and submucosa of the ileum and are separated from the intestinal lumen by a layer of flattened epithelial cells known as microfold cells (M cells).
   a. M cells constantly sample the intestinal lumen and transcytose antigens to the underlying Peyer patches. There, APCs phagocytose the antigens and present them to resident T cells and B cells.
3. Other forms of MALT are less organized and are often inducible (as opposed to Peyer patches, which are constitutive). The epithelial layer over these tissues may contain fewer M cells or no M cells at all. The role of these tissues, as well as their mechanisms, is still being elucidated.

III. Innate versus adaptive immune system (including complement)
A. Innate immune system
1. Responds rapidly to foreign antigens but is nonspecific
   a. Uses pattern recognition receptors, which recognize structures that are common to many bacteria, such as lipopolysaccharide, flagellin, and unmethylated DNA
   b. Receptors may also recognize viral components such as double-stranded RNA
   c. Also recognizes mutated or damaged host cells, allowing for the early elimination of many cancerous cells
   d. Cells with the appropriate receptors can also use existing antibodies to target infected cells through antibody-dependent cell-mediated cytotoxicity. This is still considered part of the innate immune response.
2. Components of the innate immune response
   a. Neutrophils are the first cells to appear at the site of damage or infection. They can phagocytose bacteria and promote inflammation through the secretion of cytokines.
b. Macrophages secrete cytokines and phagocytose pathogens and antigens. In fact, macrophage cytokine signaling often initiates the innate immune response, as they are resident in many tissues.

c. Natural killer (NK) cells recognize mutated or damaged cells through a complex combination of activating and inhibitory receptors on the target cell surface. They can also kill antibody-coated infected cells.

d. Dendritic cells phagocytose antigens and then secrete cytokines, which recruit and activate other immune cells, as well as promote inflammation.

e. Eosinophils also act to kill parasites during the innate immune response when necessary.

f. Antibacterial proteins can interfere with the membranes and the metabolic activity of many pathogens.

g. Complement

i. Complement is a specialized group of serum proteins that can directly lyse cells (host cells or pathogen cells), opsonize cells to facilitate phagocytosis, and promote inflammation.

ii. There are three specific pathways of complement activation (Figure 13-3):

a) Classical pathway: Begins with binding of C1 to IgG or IgM on the surface of a cell. C1 then cleaves C4 into C4a and C4b as well as C2 into C2a and C2b. C4b and C2b combine to form an enzyme that cleaves C3. This cascade continues through C5, C6, C7, C8, and multiple C9 molecules, which form the membrane attack complex (MAC). This creates a pore on the surface of the cell, leading to lysis.

b) Alternative pathway: Spontaneous hydrolysis of C3 produces C3a and C3b. C3b can then bind factor B, which is hydrolyzed to Ba and Bb. The complex of C3b and Bb can then cleave more C3. From this point on, the cascade is identical to the classical pathway.

c) Lectin pathway: Begins with the binding of mannose-binding lectin to mannose on the surface of a cell. It can then recruit serine proteases to cleave C4 and C2. From here, the cascade is identical to the classical pathway.

Figure 13-3
The complement pathway
Classical pathway

IgM or IgG

Activated C1

C4 and C2

C4b-C2a complex

(C3 convertase)

C4a

C2b

C3a

C3b

C3b-Bb (C3 alternate convertase)

Factor D

C3b-Factor B

C3b

C3b-Bb-C3b

(C3 alternate convertase)

C3b

C3a

C5

C4b-C2a-C3b

(C5 convertase)

or

C3b-Bb-C3b

(C5 alternate convertase)

C5a

C5b

C6

C7

C8

C9

C5b6789

(membrane attack complex)

(From Diallo AO, Chandrasekhara V. Microbiology Recall. Philadelphia: Lippincott Williams & Wilkins, 2004. Used with permission.)
iii. The “a” components that result from hydrolysis of complement are anaphylatoxins. They promote histamine release by mast cells and basophils as well as neutrophil infiltration. (C3a and C5a have the strongest anaphylactic activity.)

iv. C3b is important for opsonization, which is a process of coating pathogens with proteins so that they are more appealing to phagocytes.

v. Deficiency of C3 is associated with recurrent Streptococcus pneumoniae and Haemophilus influenzae infections.

vi. A circulating protein known as C1 esterase inhibitor is important for proper immune function. Deficiency of this protein is associated with hereditary angioedema, although the mechanism is not well understood.

vii. Deficiency of C5, C6, C7, C8, or C9 (all part of the MAC) is associated with Neisseria infections.

viii. Host cells express surface receptors that inhibit complement. Decay-accelerating factor (CD55) and MAC-inhibitory protein (CD59) are the most important ones. Deficiencies in these can lead to paroxysmal nocturnal hemoglobinuria.

B. Adaptive immune system

1. Responds slowly to foreign antigens but is antigen-specific.
2. Initial exposure to an antigen prompts the development of memory B and T cells. Upon subsequent exposure, these cells can respond much more quickly.
3. This memory function of the adaptive immune response allows for immunization.
4. Components of the adaptive immune response
   a. B cells secrete antibodies, which can serve many different functions.
   b. T cells secrete cytokines and interact with B cells to promote maturation and immunoglobulin (Ig) class switching.
   c. Macrophages and dendritic cells secrete cytokines that influence T-cell differentiation. They also continue to phagocytose pathogens and present antigen.
   d. Mast cell and basophil responses during allergic reactions are actually the result of IgE production during the adaptive immune response.

ANTIGEN PRESENTATION

I. Major histocompatibility complexes

A. Major histocompatibility complexes (MHC) class I
   1. Found on the surfaces of all nucleated cells in the human body
   2. CD8 surface proteins on cytotoxic T cells can recognize MHC class I on the surface of other cells.
      a. Virus-infected cells express viral proteins and bind them to MHC class I on their surfaces.
      b. Cancer cells express mutated cancer proteins and bind them to MHC class I on their surfaces.
      c. Cytotoxic T cells recognize these foreign antigens and initiate apoptosis in the diseased cells.
      d. Healthy cells express self-proteins on MHC class I. Due to tolerance mechanisms, these almost never elicit an immune response.
   3. Three genes code for MHC class I: HLA-A, HLA-B, and HLA-C.
      a. The HLA-B27 subtype is associated with several autoimmune diseases: psoriatic arthritis, ankylosing spondylitis, inflammatory bowel disease, and reactive arthritis.

B. MHC class II
   1. Found mainly on APCs (dendritic cells, macrophages, etc.)
   2. APCs phagocytose pathogens and bind those exogenous antigens to MHC class II on their surfaces.
3. CD4 surface proteins on T helper cells can recognize MHC class II on the surface of APCs, leading to activation and differentiation of the T helper cells.

4. Three genes code for MHC class II: HLA-DP, HLA-DQ, and HLA-DR.
   a. The HLA-DR3 and HLA-DR4 subtypes are strongly associated with type 1 diabetes.

IMMUNE CELL FUNCTION

I. Dendritic cells
   A. Dendritic cells serve as the chief APCs of the immune system. They are named for the membranous extensions that resemble the dendrites of a neuron.
   B. They reside in tissues until they encounter and capture antigen through one of three methods: phagocytosis, receptor-mediated endocytosis, and pinocytosis.
   C. Upon capturing antigen, the dendritic cells become activated and migrate to lymphoid tissue where they can present the antigen to T cells.
   D. Langerhans cell histiocytosis is a disease characterized by the excessive proliferation of Langerhans cells (a type of dendritic cells found in the epidermis), which can manifest as skin or bone lesions. These cells are identified by the presence of tennis racket-shaped organelles known as Birbeck granules (Figure 13-4).

II. T cells
   A. T-cell selection
      1. T cells undergo positive and negative selection in the thymus (Figure 13-5).
      2. Thymocytes (immature T-cell precursors) in the cortex of the thymus possess both CD4 and CD8 surface markers as well as T-cell receptors (TCRs) that can bind to specific antigens and MHC molecules.
      3. Positive selection takes place in the cortex of the thymus and ensures that all T cells released from the thymus will be able to recognize MHC molecules on APCs.
         a. APCs display a wide variety of antigens on MHC class I and class II molecules, allowing thymocytes to bind to these cells.
         b. Cortex cells feed a survival signal to thymocytes whose TCRs are capable of successfully binding to antigen and MHC.
c. Thymocytes are allowed to die if their TCRs are incapable of binding antigen and MHC.

d. If the thymocyte’s TCR and CD4 successfully bind to an MHC class II, it will lose its CD8 surface marker and become a CD4⁺ T helper cell.

e. If the thymocyte’s TCR and CD8 successfully bind to an MHC class I, it will lose its CD4 surface marker and become a CD8⁺ cytotoxic T cell.

4. Negative selection takes place at the corticomedullary junction of the thymus and ensures that no T cells released from the thymus will bind to self-peptides, which would result in autoimmunity.

a. APCs display a wide variety of self-peptides, allowing thymocytes to bind.

b. Thymocytes that interact too strongly with self-peptides receive a signal to undergo apoptosis.

c. Thymocytes that do not bind to these self-peptides receive no apoptosis signal and migrate to the medulla, where they are released from the thymus as mature T cells.

B. T helper cells (Tₜ cells)

1. Tₜ cells are the main effector cells of the adaptive immune response. They are characterized by the surface expression of CD3 (TCRs) and CD4. They can be further divided into type 1 (Tₜ₁) and type 2 (Tₜ₂).

a. Tₜ₁ cells stimulate macrophages and cytotoxic T cells.

b. Tₜ₂ cells stimulate B cells to become plasma cells, which produce antibodies.

2. Tₜ cell differentiation (Figure 13-6)

a. Naïve Tₜ cells leave the thymus as Tₜ₀ cells.

b. The cytokine interleukin-12 (IL-12) induces Tₜ₀ cells to become Tₜ₁ cells.

i. Tₜ₁ cells secrete interleukin-2 (IL-2), which stimulates proliferation of cytotoxic T cells more Tₜ₁ cells.
ii. T\(_h\)1 cells secrete interferon gamma (IFN-\(\gamma\)), which activates macrophages and suppresses proliferation of T\(_h\)2 cells.

c. The cytokine interleukin-4 (IL-4) induces T\(_h\)0 cells to become T\(_h\)2 cells.
   i. T\(_h\)2 cells secrete IL-4 and IL-5, which stimulate B-cell proliferation.
   ii. T\(_h\)2 cells secrete IL-10, which inhibits proliferation of T\(_h\)1 cells.

C. Cytotoxic T cells (T\(_c\) cells)
1. T\(_c\) cells are characterized by the surface expression of CD3 (TCR) and CD8. They induce apoptosis in:
   a. Host cells with intracellular infections (viral, bacterial, parasitic)
   b. Damaged, mutated, and cancerous host cells
   c. Donor cells from grafts or transplants
2. They induce apoptosis by one of two mechanisms:
   a. T\(_c\) cells may release cytotoxic granules containing perforin and granzymes, which stimulate apoptosis of the target cell.
   b. T\(_c\) cells may express a surface molecule called the Fas ligand (FasL), which interacts with a Fas receptor (FasR) on the target cell, triggering a series of downstream events, which lead to apoptosis.

D. T-cell activation
1. T cells require two signals for activation.
2. T\(_h\) cell activation
   a. The first signal involves binding of the TCR to MHC class II on an APC.
   b. The second signal (or co-stimulatory signal) commonly comes from the engagement of CD28 on the T cell with either CD80 or CD86 on the APC.
   c. Alternatively, the co-stimulatory signal may come from cytokines such as IL-2.
3. T\(_c\) cell activation
   a. The first signal involves binding of the TCR to MHC class I on infected/damaged cells.
   b. The co-stimulatory signal is the same as in T\(_h\) cell activation.

E. Regulatory T cells
1. A small, specialized subset of T\(_h\) cells that regulate the immune system by suppressing B cells, T\(_h\) cells, and T\(_c\) cells.
2. They produce IL-10 and other anti-inflammatory cytokines.
3. The role of regulatory T cells is to dampen the inflammatory response in order to control it and prevent damage to healthy tissue. Regulatory T cells may
also promote the cessation of the immune response once the target cells or pathogens have been cleared, although this is not well understood.

4. Dysfunction of regulatory T cells has been strongly implicated in many autoimmune disorders.

III. B cells

A. B-cell function
1. The main function of B cells is to produce antibodies to support the adaptive immune response.
2. B cells are defined by the surface expression of CD19, CD20, CD21, as well as IgM and IgD.
3. After encountering antigen and becoming activated, they transform into plasma cells, which produce large quantities of Ig against that antigen.
   a. B cells are mainly activated by cytokines produced by T\textsubscript{H}2 cells, such as IL-4, IL-5, and TGF-β.
4. Once activated, some B cells become memory B cells, which lie dormant until they encounter their cognate antigen again, at which point they can rapidly begin producing antibodies in response.
   a. Memory B cells decrease in number with age. This is why vaccine efficacy is decreased in the elderly.
5. B cells that produce Igs against self-antigens are signaled to undergo apoptosis in the bone marrow in a negative selection process similar to that seen in thymic T cells.

B. B-cell activation
1. B-cell activation begins when antigen binds to either IgM or IgD on the B-cell surface, which functions as a B-cell receptor, similar to the TCR.
2. The B cell then endocytoses the antigen and affixes it to MHC class II on the cell’s surface.
3. The B cell must then present the antigen to an activated T cell.
   a. The engagement of the TCR with the B cell’s MHC class II delivers the first activation signal to the B cell.
   b. The second (co-stimulatory) signal is typically mediated by engagement of CD40 on the B cell’s surface by a CD40 ligand (CD40L) on the T cell, although it may also come from CD28-B7 engagement.
4. T-independent B-cell activation: B cells may be fully activated by specific antigens without co-stimulatory signals from T cells. If a large antigen with repeating segments binds two B-cell receptors simultaneously, it may deliver a strong enough signal on its own to activate the B cell.
   a. Because there is no cytokine signal to stimulate class switching, B cells activated in this manner will secrete IgM. This is the only case in which IgM is produced by mature B cells.

IV. Other cell types

A. Natural killer (NK) cells
1. NK cells are lymphocytes of the innate immune response.
2. As part of the innate (rather than adaptive) immune response, NK cells do not recognize specific antigens. Rather, they are given activating and/or inhibitory signals by specific surface molecules on target cells (such as intracellularly infected cells and cancer cells, which exhibit upregulation of pro-apoptotic molecules). Generally, the ratio of activating-to-inhibitory signals determines whether or not the target cell is signaled to undergo apoptosis.
   a. Like T\textsubscript{c} cells, NK cells use perforin and granzymes or Fas-FasL interaction to induce apoptosis in target cells
   b. NK cells can also kill target cells coated with IgG antibodies, which is called antibody-dependent cell-mediated cytotoxicity (ADCC). CD16 on the surface of NK cells promotes ADCC by binding to the constant (Fc) region of antibodies.
3. IL-2, IL-12, IFN-α, and IFN-β can activate NK cells and enhance their activity.

\[ \text{B cells mature in the bone marrow, unlike T cells, which are formed in the bone marrow but which mature in the thymus.} \]
4. NK cells are the main source of IFN-γ during the early immune response and thus are the main activators of macrophages initially.

B. Monocytes and macrophages
1. Monocytes initially develop in the bone marrow. Once they leave the bone marrow, they circulate for 8 to 12 hours as they mature further. They then migrate into tissues where they fully mature and become resident macrophages.
2. Mature macrophages residing in specific tissues are sometimes given different names and often have different functions and display phenotypic differences.
   a. Skin/connective tissue—Histiocytes (may also refer to dendritic cells)
   b. Liver—Kupffer cells
   c. Joints—A cells
   d. Neural tissue—Microglia
   e. Bone—Osteoclasts
3. Macrophages are most commonly activated by IFN-γ secreted by NK cells or T cells.
4. Functions
   a. Macrophages are the second most important APCs behind dendritic cells.
   b. Activated macrophages secrete proinflammatory cytokines such as IL-1β, IL-6, and TNF-α.
   c. Phagocytosis—The expression of CD16 and CD32 (which bind to the Fc portion of IgG) allows macrophages to phagocytose antibody-coated cells or antigens. Macrophages also express receptors for complement components, which also facilitates phagocytosis.
   d. The main method of killing by macrophages is lysosomal digestion. In addition to lowering the pH, macrophages also produce damaging oxygen radicals using the intralysosomal enzyme NADPH oxidase. This is called the oxidative burst.

C. Granulocytes
1. Eosinophils are important in the host defense against parasites.
2. Neutrophils are the first cells to appear at the site of damage or infection. They can phagocytose bacteria and promote inflammation through the secretion of cytokines.
3. Basophils are coated with IgE so that when an antigen binds to the IgE, the basophil releases histamine and other chemicals, which mediate allergic reactions (type I hypersensitivity).
4. Mast cells are very similar to basophils but derived from a different cell lineage. Mast cells reside in tissues, whereas basophils are found in circulation.

### CYTOKINES

#### I. Interferons
A. There are two groups of interferons, classified as type I and type II.
B. Type I interferons include IFN-α and IFN-β. Both of these cytokines are important in viral immunity as they stimulate the antiviral functions of numerous cells, including NK cells. These interferons are also important for antitumor immunity.
   1. Recombinant IFN-α is used to treat certain forms of leukemia, lymphoma, and melanoma, as well as hepatitis C.
C. IFN-γ is the only type II interferon found in humans. It is the chief inflammatory cytokine and is mainly associated with T helper type 1 responses. IFN-γ is the cytokine that most commonly activates macrophages.
   1. Recombinant IFN-γ is used to treat chronic granulomatous disease and osteoporosis.

#### II. Interleukins (IL)
A. IL-1 and IL-6 are acute phase cytokines and can stimulate the secretion of acute phase reactants by wide variety of cell types. Both act as pyrogens (cause fever).
B. IL-2 is the classic T-cell stimulator, although it can also stimulate the growth and proliferation of other cell types, including B cells and NK cells.
1. Recombinant IL-2 (aldesleukin) is used to treat metastatic renal cell carcinoma and metastatic melanoma.
2. Basiliximab, which blocks the action of IL-2 by binding the IL-2 receptor on cells, is used to prevent transplant rejection.
C. IL-3 is a T cell–secreted cytokine that promotes growth of bone marrow stem cells.
D. IL-4 and IL-5 are associated mainly with B-cell activation.
E. IL-10 is associated with T_h2 responses. It is considered the classic anti-inflammatory cytokine, as it acts in direct opposition to IFN-γ. It also stimulates the production of IgA by B cells.
F. IL-11 stimulates the growth of megakaryocytes and granulocyte-macrophage progenitors in the bone marrow.
1. Oprelvekin is a recombinant form of IL-11 that is administered to patients after chemotherapy treatments to stimulate the bone marrow to produce platelets.
G. IL-12 is secreted by APCs and intracellularly infected cells. It is one of the main cytokines that stimulates the development of T helper type 1 responses.

III. Tumor necrosis factors (TNF)
A. TNF-α is the most important member of this family of cytokines. In addition to its proinflammatory role, it also promotes neutrophil infiltration. TNF-α is implicated in many autoimmune conditions as well as septic shock.
1. TNF-α is directly inhibited by the monoclonal antibodies infliximab, adalimumab, and golimumab as well as the fusion protein etanercept.
B. Additional members of this family include lymphotoxins α and β as well as FasL.
C. Most members of the TNF family are transmembrane proteins rather than secreted proteins.

IV. Other growth factors
A. Transforming growth factor β (TGF-β) inhibits the growth of a variety of cell types. It also stimulates B cell production of IgA.
B. Granulocyte macrophage colony-stimulating factor (GM-CSF) and granulocyte colony-stimulating factor (G-CSF) stimulate the growth and differentiation of monocytes and neutrophils, both at the bone marrow level and in the periphery.
1. Filgrastim and sargramostim are recombinant forms of G-CSF and GM-CSF, respectively. They are used to stimulate bone marrow granulocyte production after chemotherapy treatment.
C. Erythropoietin and thrombopoietin stimulate bone marrow production of erythrocytes and platelets, respectively.
1. Recombinant forms are used to treat anemia and thrombocytopenia.

IMMUNOGLOBULINS

I. Immunoglobulin structure (Figure 13-7)
A. Each antibody is composed of two heavy chains and two light chains held together with disulfide bonds. There are two types of light chain (κ, λ) and five types of heavy chains (α, δ, ε, γ, μ). The heavy chains dictate the Ig isotype (IgA, IgD, IgE, IgG, and IgM).
B. Antibodies are divided into two regions: the antigen-binding region (Fab) and the constant region (Fc).
1. The Fab region contains the variable segments, which determine antigen specificity (idiotype).
2. The Fc region is constant among all antibodies of a given isotype.
II. Antibody functions
A. Iggs have several general functions:
   1. Antigen neutralization, which is particularly important for toxins. In fact, antivenom consists of antibodies that bind up the toxins and prevent them from acting.
   2. Opsonization
   3. Antibody-dependent cell-mediated cytotoxicity
   4. Activation of complement
B. Specific Ig isotypes perform specific functions and capabilities (Table 13-2).

III. Antibody diversity
A. There are two mechanisms through which B cells create antibody diversity: V(J)D recombination and somatic hypermutation.
B. V(J)D recombination—the main mechanism by which a static genome can generate highly variable Fab regions to bind to a nearly infinite variety of antigens.
   1. Variable (V), joining (J), and diverse (D) segments in the DNA undergo genetic rearrangement during B-cell development.
   2. The recombinase-activating genes 1 and 2 (RAG1, RAG2) facilitate this process. Mutations in either of these genes results in severe combined immunodeficiency.
   3. V(J)D recombination is also responsible for generating diverse TCRs.
C. Somatic hypermutation is a process that introduces random point mutations into the antibody sequence, which can increase the affinity of antibodies for the target antigen. This occurs after a B cell recognizes an antigen and becomes activated.
   1. The resulting antibody will usually still recognize the target antigen, but, depending on the mutations, its affinity may be either increased or decreased.
### TABLE 13-2 Antibody Functions

<table>
<thead>
<tr>
<th>Isotype</th>
<th>Description</th>
</tr>
</thead>
</table>
| IgG     | - IgG comprises 80% of antibodies in human serum.  
          - Secreted by activated B cells  
          - IgG is the only isotype that can cross placenta.  
          - Capable of complement fixation and activation  
          - Most common antibody in opsonization of bacteria  
          - Neutralizes viruses and bacterial toxins |
| IgA     | - Primarily secreted by B cells in MALT (in the GI tract, etc.)  
          - Exists as a monomer in circulation  
          - "Secretory IgA" is a dimer of two IgA antibodies joined end-to-end. As secretory IgA transcytosis across the epithelium, it is bound to a glycoprotein called "secretory component" that protects the IgA from the harsh GI environment. |
| IgE     | - Bound by Fc receptors on the surface of mast cells, eosinophils, and basophils  
          - Associated with allergic responses  
          - Mediates immunity to parasites |
| IgM     | - Found almost exclusively on the surface of naive B cells and functions as the B-cell receptor  
          - Produced as part of the primary immune response before the B cell switches to produce a different Ig isotype  
          - Secreted as a pentamer in circulation  
          - The best activator of complement |
| IgD     | - Found almost exclusively on the surface of naive B cells  
          - Very small amounts can be found in circulation  
          - Function unknown |

2. B cells that produce antibodies with higher affinity will be preferentially activated as more antigen is encountered, causing them to proliferate.

**IV. Immunization**

A. **Passive immunity** involves the transfer of Igs into a patient to confer temporary immunity to a pathogen or toxin. These antibodies have a half-life of roughly 21 days. Examples:
   1. The transfer of IgA from mother to infant through breast milk
   2. **Palivizumab** is an IgG antibody against respiratory syncytial virus (RSV) that may be given to premature neonates who are at high risk of RSV infection and meet certain criteria.

B. **Active immunization** occurs as the result of either previous infection or vaccination. In these cases, the patient possesses memory B cells that can secrete pathogen-specific or toxin-specific antibodies in response to an infection or a toxin.
   1. Memory B cells eventually die. Booster vaccinations are given every few years to develop new memory B cells.

C. Vaccines may contain live attenuated pathogens, inactivated pathogens, or components of pathogens.
   1. **Live attenuated pathogens** are often capable of replication in the host. This allows for the development of a strong immune response and long-lasting immunity.
      a. Examples include vaccines against measles/mumps/rubella (MMR), smallpox, and the intranasal influenza vaccine.
   2. **Inactivated or killed pathogens** elicit a weaker immune response than live pathogens, largely due to their inability to replicate. These vaccines tend to stimulate an antibody response but are less effective at priming T cells. The immunity provided by inactivated vaccines does not last as long and often requires boosters. Most vaccines fall into this category.
3. **Subunit vaccines** contain only specific proteins, toxins, or capsular polysaccharides from a pathogen. These can only be used if the immunogenic factors from a pathogen have been identified. Examples:
   a. The *S. pneumoniae* vaccine contains 23 specific streptococcal proteins.
   b. The *Neisseria meningitidis* vaccine contains capsular polysaccharides.

### INAPPROPRIATE IMMUNE RESPONSES

#### I. Autoimmunity

A. Despite tolerance mechanisms, the immune system will occasionally respond to self-antigens as foreign, which can lead to a variety of clinical disorders (Table 13-3).

<table>
<thead>
<tr>
<th>Autoantibody</th>
<th>Associated Disorder</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anti-IgG antibodies (rheumatoid factor)</td>
<td>Rheumatoid arthritis</td>
</tr>
<tr>
<td>Anti-citrullinated protein antibodies (ACPA)</td>
<td>Rheumatoid arthritis</td>
</tr>
<tr>
<td>Anti-centromere</td>
<td>Limited cutaneous systemic sclerosis (CREST syndrome)</td>
</tr>
<tr>
<td>Anti-Scl-70 (anti-DNA topoisomerase I)</td>
<td>Diffuse cutaneous systemic sclerosis (scleroderma)</td>
</tr>
<tr>
<td>Anti-histone</td>
<td>Drug-induced lupus</td>
</tr>
<tr>
<td>Antinuclear antibodies (ANA)</td>
<td>Systemic lupus erythematosus</td>
</tr>
<tr>
<td>Anti-Smith</td>
<td>Systemic lupus erythematosus</td>
</tr>
<tr>
<td>Anti–double-stranded DNA (anti-dsDNA)</td>
<td>Lupus nephritis</td>
</tr>
<tr>
<td>Anti–Jo-1 (anti-histidyl tRNA synthetase)</td>
<td>Polymyositis and dermatoimmunositis</td>
</tr>
<tr>
<td>Anti-SSA (anti-Ro)</td>
<td>Sjögren syndrome</td>
</tr>
<tr>
<td>Anti-SSB (anti-La)</td>
<td>Sjögren syndrome</td>
</tr>
<tr>
<td>Anti–U1-ribonucleoprotein (anti–U1-RNP)</td>
<td>Mixed connective tissue disease</td>
</tr>
<tr>
<td>Anti-desmoglein</td>
<td>Pemphigus vulgaris</td>
</tr>
<tr>
<td>Anti-acetylcholine receptor</td>
<td>Myasthenia gravis</td>
</tr>
<tr>
<td>Anti-endomysial (anti-tissue transglutaminase)</td>
<td>Celiac disease</td>
</tr>
<tr>
<td>Anti-gliadin</td>
<td>Celiac disease</td>
</tr>
<tr>
<td>Anti-mitochondrial (AMA)</td>
<td>Primary biliary cirrhosis</td>
</tr>
<tr>
<td>Anti-Sp100</td>
<td>Primary biliary cirrhosis</td>
</tr>
<tr>
<td>Anti-smooth muscle (ASMA)</td>
<td>Autoimmune hepatitis</td>
</tr>
<tr>
<td>Anti–glutamate decarboxylase</td>
<td>Diabetes mellitus type 1</td>
</tr>
<tr>
<td>Anti-thyrotropin receptor</td>
<td>Graves disease</td>
</tr>
<tr>
<td>Anti–thyroid peroxidase (anti-TPO)</td>
<td>Hashimoto thyroiditis</td>
</tr>
<tr>
<td>Anti–thyroglobulin</td>
<td>• Hashimoto thyroiditis</td>
</tr>
<tr>
<td>Anti-thyroglobulin</td>
<td>• Graves disease</td>
</tr>
<tr>
<td>Anti-basement membrane</td>
<td>Goodpasture syndrome</td>
</tr>
<tr>
<td>Cytoplasmic antineutrophil cytoplasmic (c-ANCA)</td>
<td>Granulomatosis with polyangiitis (Wegener’s)</td>
</tr>
<tr>
<td>Perinuclear antineutrophil cytoplasmic (p-ANCA)</td>
<td>• Pauci-immune crescentic glomerulonephritis</td>
</tr>
<tr>
<td></td>
<td>• Eosinophilic granulomatosis with polyangiitis (Churg-Strauss)</td>
</tr>
<tr>
<td></td>
<td>• Microscopic polyangiitis</td>
</tr>
</tbody>
</table>
II. Hypersensitivity Reactions

<table>
<thead>
<tr>
<th>Mechanism</th>
<th>Time Course</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type I, Free antigen cross-links IgE bound to the surface of presensitized mast cells or basophils, resulting in degranulation and release of histamine and bradykinin. This leads to increased vascular permeability, tissue edema, and anaphylactic shock in severe cases.</td>
<td>May occur within a few seconds to a few minutes</td>
<td>Food and drug allergies, allergic rhinitis, asthma, wheal and flare (hives), reactions to bee/wasp stings, anaphylaxis</td>
</tr>
<tr>
<td>Type II, IgG or IgM autoantibodies bind to antigens on the surface of cells and promote cell destruction via activation of complement or ADCC</td>
<td>May develop over several hours to weeks</td>
<td>Transfusion reactions, erythroblastosis fetalis, drug-induced hemolytic anemia, pernicious anemia, Goodpasture syndrome, ITP, myasthenia gravis, acute rheumatic fever</td>
</tr>
<tr>
<td>Type III, IgG antibodies against soluble antigens form immune complexes that are deposited in tissues, resulting in complement activation and recruitment of neutrophils; causes damage to the surrounding tissue</td>
<td>May develop over several hours to weeks</td>
<td>Serum sickness, Arthus reaction, SLE, RA, PAN, poststreptococcal GN</td>
</tr>
<tr>
<td>Type IV, Previously sensitized T cells bind to antigen and release IL-2 and IFN-γ, causing inflammation and macrophage activation; also known as delayed-type hypersensitivity or cell-mediated hypersensitivity.</td>
<td>Typically manifests within 24–48 hours</td>
<td>Contact dermatitis (poison ivy, latex allergy, etc.), PPD skin test, Hashimoto thyroiditis, Guillain-Barré syndrome, multiple sclerosis, GVHD</td>
</tr>
</tbody>
</table>

ADCC, antibody-dependent cell-mediated cytotoxicity; GN, glomerulonephritis; GVHD, graft-versus-host disease; IFN, interferon; IL, interleukin; ITP, idiopathic thrombocytopenic purpura; PAN, polyarteritis nodosa; PPD, purified protein derivative; RA, rheumatoid arthritis; SLE, systemic lupus erythematosus

III. Immunodeficiencies

A. B-cell deficiencies
   1. Bruton agammaglobulinemia
      a. Also known as X-linked agammaglobulinemia
      b. A mutation in the gene for Bruton tyrosine kinase prevents B-cell maturation. These patients have extremely low levels of antibodies and have underdeveloped lymphoid organs.
      c. Recurrent infections begin after 6 months of age, once passive maternal immunity has disappeared.
      d. Prognosis is very good with proper therapy, likely due to the functional cell-mediated immune response.
      e. Presentation: Delayed growth (patients are often physically smaller than others their age), small or absent lymph nodes, recurrent sinopulmonary infections that respond poorly to antibiotics, pyoderma gangrenosum
      f. Labs: Undetectable IgA and IgM, IgG <100 mg/dL, low B-cell count
      g. Treatment: Intravenous immunoglobulins (IVIG), antibiotics as necessary
2. Selective IgA deficiency
   a. Patients are more susceptible to diseases of the respiratory tract and GI tract. IgA-deficient patients are more likely to suffer from asthma and allergies.
   b. Due to the lack of IgA, a significant percentage of patients will develop antibodies against IgA. This can cause type II hypersensitivity reactions against IgA-containing materials such as blood and plasma.
   c. Presentation: Recurrent sinus and lung infections, recurrent GI infections, chronic nasal discharge, cramps after eating
   d. Labs: Undetectable serum IgA, normal to elevated serum IgM
   e. Treatment: There is no specific treatment. Patients may be given antibiotics as necessary.

B. T-cell deficiencies

1. DiGeorge syndrome (thymic aplasia)
   a. Patients fail to develop a thymus due to defects of the third and fourth branchial pouches. Patients lack mature T cells.
   b. Congenital defects of the heart and the great vessels are very common.
   c. Presentation: Positive Chvostek sign, positive Trousseau sign; recurrent viral, fungal, and protozoal infections; characteristic facies (broad nasal bridge, long face, narrow palpebral fissures, micrognathia, asymmetric crying face)
   d. Diagnostics: Chromosome 22q11 deletion, hypocalcemia, lymphopenia, absent thymic silhouette on neonatal imaging
   e. Treatment: Patients may require prophylactic antibiotics and calcium supplementation. Surgical correction of cardiac and vascular defects may be indicated.

2. Chronic mucocutaneous candidiasis (CMC)
   a. Defects in T-cell–mediated immunity predispose patients to Candida infections
   b. These defects may be related to cytokines, signaling molecules, TCRs, and many other possible factors. As such, CMC is not a specific disease but rather a phenotypic presentation that may be indicative of a number of etiologies.
   c. Presentation: Recurrent candidal infections, oral thrush, skin lesions, thickened nails, angular cheilitis, hyperkeratotic plaques
   d. Labs: Candida in samples from affected area, lymphopenia
   e. Treatment: Antifungal therapy, surgical removal of hyperkeratotic plaques if indicated

3. Hyper-IgM syndrome
   a. Caused by mutations in CD40L on T cells. This prevents T cells from delivering a co-stimulatory signal to B cells, and as a result, class switching does not occur. B cells will produce high levels of IgM but will never fully mature to IgG-, IgA-, or IgE-producing plasma cells.
   i. Hyper-IgM syndrome may also result from mutations in CD40 on B cells, or mutations in activation-induced cytidine deaminase (AICDA), which is an important enzyme involved in class switching.
   b. Prognosis is relatively poor in these patients. Roughly 20% survive past age 20. Infectious pneumonia is the most common cause of death.
   c. Presentation: Recurrent infections, failure to thrive, lymphadenopathy, mucosal ulcerations
   d. Labs: Reduced IgG, IgE, and IgA in serum; elevated serum IgM, neutropenia
   e. Treatment: IVIG, antibiotics, antifungal prophylaxis, filgrastim in neutropenic patients

C. Combined B- and T-cell deficiencies

1. Severe combined immunodeficiency (SCID) syndrome
   a. Defects in stem cell differentiation result in a lack of functional B and T cells. As a result, these patients also lack a thymus. Most patients succumb to severe infection by age 2.
b. Most of these patients have a much higher level of NK cells due to compensatory immune mechanisms.

c. Presentation includes the classic triad of:
   i. **Severe recurrent infections** (candidiasis, fatal or recurrent viral infections, *Pneumocystis jiroveci* pneumonia)
   ii. **Chronic diarrhea**
   iii. **Failure to thrive**

d. **Diagnostics:** Lymphopenia, low serum Ig, small or absent thymus on imaging

e. **Treatment:** Bone marrow transplantation is the only chance that these patients have for survival. Antibiotic therapy is not generally helpful because most antibiotics require a functional immune system to be effective. IVIG therapy can often prolong patient survival until bone marrow transplant can be performed.

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2. Wiskott-Aldrich syndrome

a. This is an X-linked immunodeficiency, and as such, it affects males almost exclusively.

b. A defect in WASp (Wiskott-Aldrich syndrome protein) causes impaired actin mobilization. This has a wide variety of effects on the immune system as well as other functions.

c. These patients are at increased risk for infections, autoimmunity, and hematologic malignancies.

d. Most patients do not survive childhood. The average age of death is 8 years.

e. **Presentation:** Purpura, eczema, bloody diarrhea, prolonged bleeding, bruising

f. **Labs:** Thrombocytopenia, low serum IgM, elevated serum IgA and IgE, decreased platelet size

g. **Treatment:** Bone marrow transplant is the only cure. Splenectomy may be indicated to treat thrombocytopenia. Various drugs, including corticosteroids, antibiotics, chemotherapeutics, and IVIG may be indicated, depending on the patient’s clinical presentation.

---

3. Ataxia-telangiectasia

a. A defect in DNA repair mechanisms that causes a number of systemic problems

b. Patients are especially sensitive to radiation. This puts them at an increased risk for lymphoma and leukemia.

c. Telangiectasias do not normally appear until at least age 5, and there are no characteristic symptoms prior to this. Thus, many children may develop neoplasms due to the delay in diagnosis.

d. Prognosis is poor, with death occurring at an average age of 25 years.

e. **Presentation:** Cerebellar ataxia, poor smooth pursuit of moving target with the eyes, telangiectasias, recurrent sinopulmonary infections, choreoathetosis, intention tremor, peripheral neuropathy

f. **Labs:** Low serum IgA, lymphopenia, elevated α-fetoprotein.

g. **Treatment:** Antibiotic therapy is helpful, but most care is supportive.

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D. Phagocyte deficiencies

1. Chronic granulomatous disease

a. A defect in NADPH oxidase impairs intralysosomal killing by phagocytes (lack of oxidative burst).

b. Patients are especially sensitive to catalase-positive organisms.

c. Intracellular survival of phagocytesed bacteria leads to granuloma formation in lymph nodes, skin, lungs, liver, GI tract, and bones.

d. **Presentation:** Recurrent pyoderma, pyrexia, diarrhea, short stature, recurrent infections, gingival abscesses, hepatosplenomegaly

e. **Labs:** Positive nitroblue tetrazolium dye test (the classic test, seldom used in modern practice; flow cytometry is more commonly used), leukocytosis, microcytic anemia, elevated serum Ig

f. **Treatment:** Prophylactic TMP-SMX, intravenous IFN-γ, corticosteroids, surgical drainage of abscesses and granulomas resection if indicated
2. Chediak-Higashi syndrome  
   a. A defect in lysosomal transport proteins prevents the transport of enzymes into lysosomes.  
   b. Phagocytosed pathogens and other materials accumulate in lysosomes due to the inability of phagocytes to degrade them.  
   c. Prognosis is poor, with few patients surviving into adulthood.  
   d. Presentation includes the classic triad of:  
      i. Partial albinism  
      ii. Recurrent respiratory tract and skin infections  
      iii. Neurologic disorders  
   e. Diagnostics: Giant granules in phagocytes on blood smear, giant inclusion bodies on bone marrow smear, loss of alveolar bone on oral x-ray, brain and spinal cord atrophy on imaging  
   f. Treatment: Bone marrow transplants are the only cure. IVIG and microtubule inhibitors may assist in management of the disease. Colchicine can be used to treat systemic inflammation.  
3. Hyper-IgE syndrome (Job syndrome)  
   a. Deficiency of STAT3 intracellular signaling leads to a lack of IFN-γ, ultimately resulting in impaired neutrophil chemotaxis.  
   b. Class switching to IgG and IgA is impaired due to inadequate production of cytokines normally produced in response to STAT3-mediated signaling. Thus, B-cell activation almost always results in IgE production.  
   c. Patients often fail to lose primary teeth and may develop two rows of teeth during early adolescence.  
   d. Death normally results from infection in the late 20s to early 30s.  
   e. Presentation includes the classic triad of:  
      i. Eczema  
      ii. Recurrent cold Staphylococcus aureus abscesses  
      iii. Coarse facial features (broad nose, prominent forehead, deep-set eyes, doughy skin)  
   f. Labs: Elevated serum IgE, eosinophilia  
   g. Treatment: Antibiotics, surgical drainage of skin boils, surgical extraction of primary teeth  

**TRANSPLANTATION**

I. Transplant rejection  
   A. Overview  
      1. Transplant recipients must be matched for histocompatibility in order to avoid immune responses against the transplanted tissue.  
      2. Clinical histocompatibility is determined by MHC class I alleles. There are three genes that code for MHC class I (HLA-A, HLA-B, and HLA-C) and there are two alleles for each. In an ideal scenario, recipient alleles will match all six donor alleles, although this almost never occurs in practice.  
      3. Numerous additional antigens can impact histocompatibility, although to a much lower degree. These are known as minor histocompatibility antigens and are not typically screened for prior to transplantation.  
      4. Transplantation of tissue must be accompanied by immunosuppressive therapy for the rest of a patient’s life to avoid rejection.  
   B. Hyperacute rejection  
      1. Occurs within minutes to hours  
      2. Mediated by preformed anti-donor antibodies. These anti-donor antibodies may be the result of exposure to fetal tissue (i.e., pregnancy), transfused blood, or prior transplants.  
      3. Patients are normally screened for reactions to MHC class I antigens prior to transplantation. Thus, hyperacute transplant rejection is rare and is most commonly the result of human error.
C. Acute rejection
1. Occurs within weeks (usually within 3 months)
2. Normally mediated by T<sub>c</sub> cells. Transplanted cells display foreign antigens on MHC class I, which the host’s T<sub>c</sub> cells interpret as being host cells displaying foreign antigens.

D. Chronic rejection
1. Occurs gradually over several months to years due to the inability of immunosuppressive regimens to completely prevent the immune response to foreign tissue.
2. Over time, T<sub>c</sub> cells and antibody-mediated responses will damage the tissue, causing vascular damage, fibrosis, and other forms of organ-specific damage.
3. All transplanted tissue eventually succumbs to the host immune response. The realistic goal is to maintain it for 15 to 20 years.

E. Graft-versus-host disease (GVHD)
1. GVHD occurs when the transplanted tissue mounts an immune response against the host.
2. This is most commonly associated with bone marrow transplants due to the density of immune cells and immune cell precursors. These cells can recognize the host tissue as foreign and cause systemic problems such as rash, hemolysis, hepatosplenomegaly, abdominal pain, nausea/vomiting, and diarrhea.
3. Blood transfusions and solid organ transplants also carry a risk of GVHD, although this is extremely rare.

II. Immunosuppressants

A. Cyclosporine
1. Binds to cyclophilin in lymphocytes, inhibiting calcineurin. This inhibits activation and differentiation. This can affect any lymphocytes, but the effect is largely T-cell specific, where it inhibits the production of IL-2.
2. Indicated for the prevention of solid organ rejection after transplant
3. Side effects include nephrotoxicity, hypertension, hirsutism, tremor, viral infections, and lymphoma.

B. Macrolide immunosuppressants
1. Tacrolimus (FK506) and pimecrolimus are macrolides that inhibit activation and differentiation of T cells by forming a complex with enzymes called FK binding proteins (FKBP). This inhibits calcineurin and prevents IL-2 secretion.
   a. Tacrolimus is indicated for the prevention of solid organ transplant rejection. Side effects of tacrolimus include nephrotoxicity, hypertension, and neurotoxicity (headache, paresthesias).
   b. Pimecrolimus is used topically to treat eczema. Side effects include burning at the application site, pruritus, and rash.
2. Sirolimus (also known as rapamycin) is a macrolide that inhibits T-cell activation and differentiation by forming a complex with FKBP-12, leading to inhibition of an enzyme called mTOR (mammalian target of rapamycin), rendering the cell insensitive to the effects of IL-2.
   a. Used to prevent solid organ transplant rejection
   b. Side effects include thrombocytopenia and interstitial pneumonitis but no nephrotoxicity (unlike tacrolimus).

C. Azathioprine
1. A purine analog that is metabolized to 6-mercaptopurine (6-MP). It interferes with DNA synthesis, which inhibits cell proliferation.
2. Indicated for the prevention of solid organ transplant rejection as well as for the treatment of rheumatoid arthritis and certain cancers
3. Side effects include infections and leukopenia.

D. Mycophenolate
1. Inhibits inosine monophosphate (IMP) dehydrogenase, thus interfering with guanine synthesis and DNA synthesis. This in turn inhibits T- and B-cell proliferation.

**QUICK HIT**
6-MP is metabolized by xanthine oxidase, so concurrent administration of xanthine oxidase inhibitors such as allopurinol will increase the toxicity of azathioprine and 6-MP.
2. Indicated for the prevention of solid organ transplant rejection and the treatment of lupus nephritis
3. Side effects are numerous and include hyperglycemia, hypercholesterolemia, hypomagnesemia, leukopenia, infection, lymphoma, and hypertension.

E. Thalidomide
1. Suppresses TNF-α activity as well as the expression of cell surface adhesion molecules, which inhibits leukocyte migration
2. Indicated for the treatment of erythema nodosum leprosum and multiple myeloma
3. Side effects include somnolence, rash, and headache.
4. Thalidomide is highly teratogenic (causes limb anomalies known as phocomelia) and is contraindicated in pregnancy.

F. Glucocorticoids
1. Prednisone, prednisolone, methylprednisolone, dexamethasone, betamethasone, triamcinolone, etc.
2. May have a number of different effects, including suppression of leukocyte migration, inhibition of prostaglandin synthesis, inhibition of proinflammatory cytokine synthesis, suppression of lymphocyte proliferation
3. May be indicated for the treatment of inflammation, allergic reactions, asthma, rheumatoid arthritis, multiple sclerosis
4. Glucocorticoids have a wide spectrum of activity and may have any of a number of side effects, including infection, indigestion, insomnia, easy bruising, hyperglycemia, adrenal insufficiency, growth suppression, delayed puberty, and anovulation.

G. Anti–TNF-α drugs
1. Etanercept
   a. A fusion protein that contains the Fc portion of IgG and the extracellular portion of the TNF-α receptor. It functions as “decoy receptor,” which binds TNF-α in circulation, leading to inhibition of TNF-mediated inflammation and cell activation.
   b. Indicated for the treatment of plaque psoriasis, psoriatic arthritis, rheumatoid arthritis, and ankylosing spondylitis
   c. Side effects include infections, headache, rhinitis, and injection site reactions.
2. Anti–TNF-α antibodies
   a. Adalimumab, golimumab, and infliximab are monoclonal antibodies that bind TNF-α, inhibiting TNF-mediated inflammation and cell activation.
   c. Side effects include infection, headache, rash, sinusitis, and injection site reactions. Infliximab has also been associated with development of transient antinuclear antibodies. The mechanism for this is still under investigation.

H. Rituximab
1. Monoclonal antibody that binds CD20 on the surface of B cells, inducing complement-mediated lysis. This results in functional inhibition of antibody responses.
2. Indicated for the treatment of rheumatoid arthritis, granulomatosis with polyangiitis, microscopic polyangiitis, as well as B-cell neoplasms.
3. Side effects include hypertension, infection, rhinitis, nausea, and fever.
The following pages contain high-yield information designed for review in the days just preceding the Step 1 examination.

### Most Common

Often on the USMLE exam, the student finds two responses that could potentially answer a question. The National Board of Medical Examiners (NBME) is testing the student to identify the more common of the two responses; for example, the more common cause, site, or type. The following is a high-yield summary of the most common characteristics of the various disorders listed in this text.

#### Nervous System

<table>
<thead>
<tr>
<th>Most Common . . .</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Aneurysm of circle of Willis</td>
<td>Anterior communicating artery, bitemporal hemianopsia</td>
</tr>
<tr>
<td>Blindness</td>
<td>Diabetic retinopathy</td>
</tr>
<tr>
<td>Blindness—preventable</td>
<td><em>Chlamydia trachomatis</em></td>
</tr>
<tr>
<td>Bacterial meningitis—elderly</td>
<td><em>Streptococcus pneumoniae</em></td>
</tr>
<tr>
<td>Bacterial meningitis—newborns</td>
<td><em>Escherichia coli</em></td>
</tr>
<tr>
<td>Bacterial meningitis—toddlers</td>
<td><em>Haemophilus influenzae type b</em></td>
</tr>
<tr>
<td>Bacterial meningitis—young adults</td>
<td><em>Neisseria meningitidis</em></td>
</tr>
<tr>
<td>Primary cancer of the brain—child</td>
<td>Medulloblastoma (cerebellum)</td>
</tr>
<tr>
<td>Primary cancer of the brain—adult</td>
<td>Astrocytoma (specifically glioblastoma), meningioma, schwannoma</td>
</tr>
<tr>
<td>Dementia</td>
<td>1. Alzheimer</td>
</tr>
<tr>
<td></td>
<td>2. Multi-infarct dementia</td>
</tr>
<tr>
<td>Demyelinating disease</td>
<td>Multiple sclerosis</td>
</tr>
<tr>
<td>Location of adult brain tumors</td>
<td>Above tentorium</td>
</tr>
<tr>
<td>Location of childhood brain tumors</td>
<td>Below tentorium (Mnemonic: Children are short, they cannot reach above the tentorium.)</td>
</tr>
<tr>
<td>Mental retardation</td>
<td>1. <em>Fetal alcohol syndrome</em> (most common overall cause)</td>
</tr>
<tr>
<td></td>
<td>2. Down syndrome (females) or fragile X (in males) (most common genetic causes)</td>
</tr>
<tr>
<td>Motor neuron disease</td>
<td><em>Amyotrophic lateral sclerosis (ALS)</em></td>
</tr>
<tr>
<td>Viral encephalitis</td>
<td><em>Herpes simplex virus (HSV)</em></td>
</tr>
</tbody>
</table>
## Cardiovascular System

### Most Common . . .

<table>
<thead>
<tr>
<th>Condition</th>
<th>Cause/Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute mitral insufficiency—children</td>
<td>Kawasaki disease</td>
</tr>
<tr>
<td>Aneurysm</td>
<td>Abdominal aorta</td>
</tr>
<tr>
<td>AV fistula</td>
<td>Penetrating knife wound</td>
</tr>
<tr>
<td>Cancer of the heart—adults</td>
<td>Metastases</td>
</tr>
<tr>
<td>Cancer of the heart—primary—adults</td>
<td>Myxoma “ball valve”</td>
</tr>
<tr>
<td>Cancer of the heart—primary—kids</td>
<td>Rhabdomyoma</td>
</tr>
<tr>
<td>Cardiomyopathy</td>
<td>Dilated (congestive) cardiomyopathy</td>
</tr>
<tr>
<td>Cause of acute endocarditis</td>
<td><em>Staphylococcus aureus</em></td>
</tr>
<tr>
<td>Cause of subacute endocarditis</td>
<td><em>Viridans streptococci</em></td>
</tr>
<tr>
<td>Congenital cardiac anomaly</td>
<td>Ventricular septal defect (membranous &gt; muscular)</td>
</tr>
<tr>
<td>Congenital early cyanosis</td>
<td>Tetralogy of Fallot</td>
</tr>
<tr>
<td>Coronary artery thrombosis</td>
<td>Left anterior descending</td>
</tr>
<tr>
<td>Death in hypertension</td>
<td>1. Acute mitral insufficiency</td>
</tr>
<tr>
<td></td>
<td>2. Lenticulostriate stroke</td>
</tr>
<tr>
<td></td>
<td>3. Renal failure (benign nephrosclerosis)</td>
</tr>
<tr>
<td>Death in the United States</td>
<td>Ischemic heart disease</td>
</tr>
<tr>
<td>Heart murmur</td>
<td>Mitral valve prolapse</td>
</tr>
<tr>
<td>Heart valve in bacterial endocarditis</td>
<td>Mitral</td>
</tr>
<tr>
<td>Heart valve in bacterial endocarditis in IV drug users</td>
<td>Tricuspid</td>
</tr>
<tr>
<td>Heart valve involved in rheumatic fever</td>
<td>Mitral &gt; aortic</td>
</tr>
<tr>
<td>Hypertension</td>
<td>1. Essential (95%)</td>
</tr>
<tr>
<td></td>
<td>2. Renal disease</td>
</tr>
<tr>
<td>Hypertension—children</td>
<td>Renal disease, cystic disease, Wilms tumor</td>
</tr>
<tr>
<td>Hypertension—young women</td>
<td>Oral contraceptives</td>
</tr>
<tr>
<td>Myocarditis</td>
<td><em>Coxsackie B virus</em></td>
</tr>
<tr>
<td>Right heart failure</td>
<td>Left heart failure</td>
</tr>
<tr>
<td>Secondary hypertension</td>
<td>Renal disease</td>
</tr>
<tr>
<td>Sites of atherosclerosis</td>
<td>Abdominal aorta &gt; coronary &gt; popliteal &gt; carotid</td>
</tr>
<tr>
<td>Vasculitis (of medium and small arteries)</td>
<td>Temporal arteritis</td>
</tr>
</tbody>
</table>

AV, atrioventricular; IV, intravenous.
## Respiratory System

### Most Common . . .

<table>
<thead>
<tr>
<th>Condition</th>
<th>Cause</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cause of pneumonia in debilitated, hospitalized patient</td>
<td><strong>Klebsiella</strong></td>
</tr>
<tr>
<td>Cause of epiglottitis</td>
<td><strong>Haemophilus influenzae type b</strong></td>
</tr>
<tr>
<td>Cause of IV drug user bacteremia/pneumonia</td>
<td><strong>Staphylococcus aureus</strong></td>
</tr>
<tr>
<td>Cause of opportunistic infection of AIDS</td>
<td><strong>Pneumocystis jirovecii</strong> is most common overall.</td>
</tr>
<tr>
<td>Death in patients with Alzheimer disease</td>
<td><strong>Pneumonia</strong></td>
</tr>
<tr>
<td>Fatal genetic defect in Caucasians</td>
<td><strong>Cystic fibrosis</strong></td>
</tr>
</tbody>
</table>
| Pneumonia—community—atypical                                              | 1. **Mycoplasma**  
2. **Legionella**                                                      |
| Pneumonia—community—typical                                               | 1. **Streptococcus pneumoniae**                                       |
|                                                                           | 2. **H. influenzae**                                                  |
|                                                                           | 3. **Klebsiella**                                                     |
| Pneumonia—hospital acquired                                               | 1. **Klebsiella**  
2. **Pseudomonas**  
3. **Escherichia coli**                                                   |
| Pulmonary hypertension                                                    | **Chronic obstructive pulmonary disease (COPD)**                      |
| Cancer associated with syndrome of inappropriate secretion of antidiuretic hormone (SIADH) | **Small cell carcinoma of the lung**                                  |
| Tracheoesophageal fistula                                                  | **Lower esophagus communicates with trachea; upper esophagus ends in blind pouch.** |
### Gastrointestinal System

#### Most Common...

<table>
<thead>
<tr>
<th>Condition</th>
<th>Cause</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bug in food poisoning</td>
<td><em>Staphylococcus aureus</em></td>
</tr>
<tr>
<td>Bug in gastrointestinal (GI) tract</td>
<td>1. <em>Bacteroides</em></td>
</tr>
<tr>
<td></td>
<td>2. <em>Escherichia coli</em></td>
</tr>
<tr>
<td>Cancer of the appendix</td>
<td>Carcinoid—rarely metastasizes</td>
</tr>
<tr>
<td>Cancer of the esophagus—malignant</td>
<td><em>Adenocarcinoma</em> &gt; squamous cell carcinoma (in United States)</td>
</tr>
<tr>
<td>Cancer of the liver</td>
<td>Metastasis; lung &gt; GI</td>
</tr>
<tr>
<td>Tumor of the liver—primary, benign</td>
<td><em>Cavernous hemangioma</em></td>
</tr>
<tr>
<td>Cancer of the liver—primary</td>
<td><em>Hepatocellular carcinoma</em></td>
</tr>
<tr>
<td>Cancer of the mouth</td>
<td><em>Squamous cell carcinoma or mucoepidermoid carcinoma</em></td>
</tr>
<tr>
<td>Cancer of the mouth—upper lip</td>
<td><em>Basal cell carcinoma</em></td>
</tr>
<tr>
<td>Cancer of the nasal cavities</td>
<td><em>Squamous cell carcinoma</em></td>
</tr>
<tr>
<td>Cancer of the pancreas</td>
<td><em>Adenocarcinoma</em> (usually in the head of pancreas)</td>
</tr>
<tr>
<td>Cancer of the salivary glands</td>
<td><em>Pleomorphic adenoma</em></td>
</tr>
<tr>
<td>Cancer of the small bowel</td>
<td><em>Carcinoid</em>—frequent metastasis from ileum</td>
</tr>
<tr>
<td>Cancer of the spleen—benign</td>
<td><em>Cavernous hemangioma</em></td>
</tr>
<tr>
<td>Cancer of the stomach</td>
<td><em>Gastric adenocarcinoma</em> (intestinal type or diffuse type)</td>
</tr>
<tr>
<td>Cirrhosis</td>
<td>Alcohol</td>
</tr>
<tr>
<td>Congenital GI anomaly</td>
<td><em>Meckel diverticulum</em></td>
</tr>
<tr>
<td>Diarrhea—children</td>
<td><em>Rotavirus</em></td>
</tr>
<tr>
<td>Dietary deficiency</td>
<td><em>Iron</em></td>
</tr>
<tr>
<td>GI obstruction</td>
<td>1. <em>Adhesions</em></td>
</tr>
<tr>
<td></td>
<td>2. Indirect inguinal hernia</td>
</tr>
<tr>
<td>Intussusception</td>
<td><em>Terminal ileum into cecum</em></td>
</tr>
<tr>
<td>Liver disease</td>
<td><em>Alcoholic liver disease</em></td>
</tr>
<tr>
<td>Liver infection</td>
<td><em>Viral hepatitis (HAV and HBV)</em></td>
</tr>
<tr>
<td>Lysosomal storage disease</td>
<td><em>Gaucher disease</em></td>
</tr>
<tr>
<td>Portal hypertension</td>
<td><em>Cirrhosis</em></td>
</tr>
<tr>
<td>Protozoal diarrhea</td>
<td><em>Giardia</em></td>
</tr>
<tr>
<td>Site of diverticula</td>
<td><em>Sigmoid colon</em></td>
</tr>
<tr>
<td>Surgical emergency</td>
<td><em>Acute appendicitis</em></td>
</tr>
<tr>
<td>Worm infection in the United States</td>
<td>1. <em>Pinworm</em></td>
</tr>
<tr>
<td></td>
<td>2. <em>Ascaris</em></td>
</tr>
</tbody>
</table>

HAV, hepatitis A virus; HBV, hepatitis B virus.
## Renal System

### Most Common . . .

<table>
<thead>
<tr>
<th>Condition</th>
<th>Category</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amyloidosis</td>
<td>Immunologic (Bence Jones protein in multiple myeloma is also called the amyloid light chain.)</td>
</tr>
<tr>
<td>Death in patients with systemic lupus erythematosus (SLE)</td>
<td>Lupus nephropathy type IV (diffuse proliferative)</td>
</tr>
<tr>
<td>End-stage renal disease</td>
<td>Diabetes</td>
</tr>
<tr>
<td>Glomerulonephritis</td>
<td>IgA nephropathy (also known as Berger disease)</td>
</tr>
<tr>
<td>Nephrotic syndrome—adults</td>
<td>Focal segmental glomerulosclerosis</td>
</tr>
<tr>
<td>Nephrotic syndrome—kids</td>
<td>Minimal change disease</td>
</tr>
<tr>
<td>Renal failure</td>
<td>Acute tubular necrosis</td>
</tr>
</tbody>
</table>

Ig, immunoglobulin.

## Endocrine System

### Most Common . . .

<table>
<thead>
<tr>
<th>Condition</th>
<th>Category</th>
</tr>
</thead>
</table>
| Addison disease | 1. Autoimmune  
2. Infection |
| Cancer of the adrenal medulla—adults | Pheochromocytoma |
| Cancer of the adrenal medulla—kids | Neuroblastoma |
| Cancer of the pituitary | 1. Prolactinoma  
2. Somatotropic “acidophilic” adenoma |
| Cancer of the thyroid | Papillary carcinoma |
| Congenital adrenal hyperplasia | 1. 21-Hydroxylase deficiency  
2. 11-Hydroxylase deficiency |
| Cushing | 1. Exogenous steroid therapy  
2. Primary adrenocorticotropin hormone (ACTH) tumor  
3. Adrenal adenoma  
4. Ectopic ACTH tumor |
| Enzyme deficiency | 21-Hydroxylase—95% of congenital adrenal hyperplasia |
| Hypercalcemia | Hyperparathyroidism |
| Hyperparathyroidism—primary | 1. Solitary adenomas  
2. Parathyroid hyperplasia  
3. Parathyroid carcinoma |
| Hyperparathyroidism—secondary | Hypocalcemia due to chronic renal failure |
| Hyperthyroidism | Graves disease |
| Hypopituitarism—adults | Nonfunctioning pituitary adenoma |
| Hypopituitarism—kids | Craniopharyngioma |
| Hypothyroidism | Hashimoto thyroiditis |
| Peripheral neuropathy | Diabetes mellitus |
| Thyroid disease | Goiter |
### Reproductive System

**Most Common . . .**

<table>
<thead>
<tr>
<th>Condition</th>
<th>Diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breast mass (premenopausal)</td>
<td>Fibrocystic change (premenopausal)</td>
</tr>
<tr>
<td>Breast mass (postmenopausal)</td>
<td>Breast carcinoma</td>
</tr>
<tr>
<td>Cancer in gynecologic—malignancy</td>
<td>Endometrial carcinoma</td>
</tr>
<tr>
<td>Cancer in men</td>
<td>Prostate carcinoma</td>
</tr>
<tr>
<td>Cancer in women</td>
<td>Uterine leiomyoma (fibroids)</td>
</tr>
<tr>
<td>Cancer in women—malignant</td>
<td>Breast carcinoma</td>
</tr>
<tr>
<td>Cancer of the breast</td>
<td>Infiltrating ductal adenocarcinoma</td>
</tr>
<tr>
<td>Cancer of the ovary—benign</td>
<td>Serous cystadenoma</td>
</tr>
<tr>
<td>Cancer of the ovary—malignant</td>
<td>Serous cystadenocarcinoma</td>
</tr>
<tr>
<td>Cancer of the placenta—benign</td>
<td>Cavernous hemangioma</td>
</tr>
<tr>
<td>Cancer of the testicles</td>
<td>Seminoma</td>
</tr>
<tr>
<td>Cancer that invades the female genitourinary (GU) tract</td>
<td>Endometrial adenocarcinoma</td>
</tr>
<tr>
<td>Cause of pelvic inflammatory disease (PID)</td>
<td><em>Neisseria gonorrhoeae or Chlamydia trachomatis</em></td>
</tr>
<tr>
<td>Chromosomal disorder</td>
<td>Down syndrome</td>
</tr>
<tr>
<td>Hernia</td>
<td>Indirect</td>
</tr>
<tr>
<td>Opportunistic infection in AIDS</td>
<td><em>Pneumocystis jirovecii</em></td>
</tr>
<tr>
<td>Sexually transmitted disease</td>
<td><em>C. trachomatis</em></td>
</tr>
</tbody>
</table>

### Musculoskeletal System

**Most Common . . .**

<table>
<thead>
<tr>
<th>Condition</th>
<th>Diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bacterial arthritis in young adults</td>
<td><em>Neisseria gonorrhoeae</em></td>
</tr>
<tr>
<td>Cancer of the bone</td>
<td>Metastases from breast and prostate</td>
</tr>
<tr>
<td>Cancer of the bone—primary—adults</td>
<td>Multiple myeloma</td>
</tr>
<tr>
<td>Cancer of the connective tissue—benign</td>
<td>Lipoma</td>
</tr>
<tr>
<td>Cancer of the skin</td>
<td>Basal cell carcinoma</td>
</tr>
<tr>
<td>Carpal bone dislocation</td>
<td>Lunate</td>
</tr>
<tr>
<td>Carpal bone fracture</td>
<td>Scaphoid</td>
</tr>
<tr>
<td>Disk herniation</td>
<td>L4–L5</td>
</tr>
</tbody>
</table>
### The Hematopoietic and Lymphoreticular System

#### Most Common . . .

<table>
<thead>
<tr>
<th>Cancer Type</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leukemia—14-year-old</td>
<td>Acute lymphoblastic leukemia (ALL)</td>
</tr>
<tr>
<td>Leukemia—15–39-year-old</td>
<td>Acute myeloid leukemia (AML)</td>
</tr>
<tr>
<td>Leukemia—40–60-year-old</td>
<td>Chronic myelogenous leukemia (CML)</td>
</tr>
<tr>
<td>Leukemia—&gt;60-year-old</td>
<td>Chronic lymphocytic leukemia (CLL)</td>
</tr>
<tr>
<td>Cancer in infancy</td>
<td>Hemangioma</td>
</tr>
</tbody>
</table>
| Cancer in children | 1. Leukemia  
2. Medulloblastoma of cerebellum |
| Cancer; genetic alteration | p53 |
| Cancer; malignant lymphoma in children | Burkitt lymphoma |
| Cancer; site of metastasis | Regional lymph nodes |
| Cancer; site of metastasis (second most common) | Liver |
| Hereditary bleeding disorder | von Willebrand disease |
| Single-gene disorder | Thalassemia |
| Type of Hodgkin lymphoma | Nodular sclerosis Hodgkin lymphoma |
| Type of non-Hodgkin lymphoma | Diffuse large B-cell lymphoma |
### Quick Lists: Important Formulas

#### Physiology

<table>
<thead>
<tr>
<th>Formula</th>
<th>Notes</th>
</tr>
</thead>
</table>
| Cardiac output | \( \text{CO} = \text{Rate of } O_2 \text{ consumption} / \left(\text{arterial } O_2 \text{ content} - \text{venous } O_2 \text{ content}\right) \)
| \( \text{CO} = \text{SV} \times \text{HR} \) | \( \text{SV} = \text{Stroke volume} \)
| \( \text{HR} = \text{Heart rate} \) |
| Mean arterial pressure | \( \text{MAP} = \text{CO} \times \text{TPR} \)
| \( \text{MAP} = 1/3 \text{SBP} + 2/3 \text{DBP} \) | \( \text{CO} = \text{Cardiac output} \)
| \( \text{TPR} = \text{Total peripheral resistance} \)
| \( \text{SBP} = \text{Systolic blood pressure} \)
| \( \text{DBP} = \text{Diastolic blood pressure} \) |
| Stroke volume | \( \text{EDV} - \text{ESV} \)
| \( \text{EDV} = \text{End diastolic volume} \)
| \( \text{ESV} = \text{End systolic volume} \) |
| Ejection fraction | \( \text{SV} / \text{EDV} \times 100 \)
| \( \text{SV} = \text{Stroke volume} \)
| \( \text{EDV} = \text{End diastolic volume} \) |
| Resistance | \( 8\eta L / \pi r^4 \)
| \( \eta = \text{Viscosity} \)
| \( L = \text{Length} \)
| \( r = \text{Radius} \) |
| Net filtration pressure | \( (P_C - P) - (\pi_C - \pi) \)
| \( P_C = \text{Hydrostatic capillary pressure} \)
| \( P = \text{Hydrostatic pressure in Bowman space} \)
| \( \pi_C = \text{Osmotic capillary pressure} \)
| \( \pi = \text{Osmotic interstitial pressure} \) |
| Glomerular filtration rate | \( \text{GFR} = K_f (P_{GC} - P_{BS}) - (\pi_{GC} - \pi_{BS}) \)
| \( \text{GFR} = C_{\text{PAH}} U_{\text{PAH}} / P_{\text{PAH}} \)
| \( \text{GFR} = \text{Glomerular filtration rate} \)
| \( K_f = \text{Filtration constant} \)
| \( P_{GC} = \text{Hydrostatic pressure in glomerular capillaries} \)
| \( P_{BS} = \text{Hydrostatic pressure in Bowman space} \)
| \( \pi_{GC} = \text{Osmotic pressure in glomerular capillaries} \)
| \( \pi_{BS} = \text{Osmotic pressure in Bowman space} \)
| \( C_{\text{PAH}} = \text{Clearance of para-aminohippuric acid (PAH)} \)
| \( U_{\text{PAH}} = \text{Urine concentration of PAH} \)
| \( V = \text{Urine flow rate} \)
| \( P_{\text{PAH}} = \text{Plasma concentration of PAH} \) |
| Effective renal plasma flow | \( C_{\text{PAH}} = U_{\text{PAH}} / P_{\text{PAH}} \)
| \( C_{\text{PAH}} = \text{Clearance of PAH} \)
| \( U_{\text{PAH}} = \text{Urine concentration of PAH} \)
| \( V = \text{Urine flow rate} \)
| \( P_{\text{PAH}} = \text{Plasma concentration of PAH} \) |
| Renal blood flow | \( \text{RPF} / (1 - \text{Hct}) \)
| \( \text{RPF} = \text{Renal plasma flow} \)
| \( \text{Hct} = \text{Hematocrit} \) |
| Filtration fraction | \( \text{GFR} / \text{RPF} \)
| \( \text{GFR} = \text{Glomerular filtration rate} \)
| \( \text{RPF} = \text{Renal plasma flow} \) |
| Free water clearance | \( \text{CH}_2O = V - C_{\text{osm}} \times \text{where} \)
| \( C_{\text{osm}} = U_{\text{osm}} V / P_{\text{osm}} \)
| \( \text{CH}_2O = \text{Clearance of water} \)
| \( U_{\text{osm}} = \text{Urine osmolality} \)
| \( P_{\text{osm}} = \text{Plasma osmolality} \)
| \( V = \text{Urine flow rate} \) |
Biostatistics

**Quick List: Important Formulas**

<table>
<thead>
<tr>
<th>Disease</th>
<th>Formula</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensitivity</td>
<td>TP / (TP + FN)</td>
</tr>
<tr>
<td>Specificity</td>
<td>TN / (TN + FP)</td>
</tr>
<tr>
<td>Positive predictive value</td>
<td>TP / (TP + FP)</td>
</tr>
<tr>
<td>Negative predictive value</td>
<td>TN / (TN + FN)</td>
</tr>
<tr>
<td>Prevalence</td>
<td>TP + FN / (TP + FP + TN + FN) Generally calculated by incidence × duration of disease</td>
</tr>
<tr>
<td>Incidence</td>
<td>Generally calculated by number of new cases / susceptible population</td>
</tr>
<tr>
<td>Relative risk (RR)</td>
<td>RR = [TP / (TP + FP)] / [FN / (FN + TN)]</td>
</tr>
<tr>
<td>Attributable risk (AR)</td>
<td>AR = [TP / (TP + FP)] − [FN / (FN + TN)]</td>
</tr>
</tbody>
</table>

FN, false negative; FP, false positive; TN, true negative; TP, true positive.

Genetics

**Quick List: Inherited Diseases**

<table>
<thead>
<tr>
<th>Mode of Inheritance</th>
<th>Diseases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Autosomal dominant diseases</td>
<td>Adult polycystic kidney disease, familial hypercholesterolemia, Marfan syndrome, neurofibromatosis type 1, neurofibromatosis type 2, tuberous sclerosis, von Hippel–Lindau disease, Huntington disease, familial adenomatous polyposis, hereditary spherocytosis, achondroplasia</td>
</tr>
<tr>
<td>Autosomal recessive diseases</td>
<td>Cystic fibrosis, albinism, α1-antitrypsin deficiency, phenylketonuria, thalassemias, sickle cell anemia, glycogen storage disease, mucopolysaccharidosis (except Hunter syndrome), sphingolipidoses (except Fabry disease), infant polycystic kidney disease, hemochromatosis</td>
</tr>
<tr>
<td>X-linked dominant diseases</td>
<td>Hypophosphatemic rickets</td>
</tr>
<tr>
<td>X-linked recessive diseases</td>
<td>Bruton agammaglobulinemia, Wiskott–Aldrich syndrome, fragile X syndrome, GSD-P deficiency, ocular albinism, Lesch–Nyhan syndrome, Duchenne muscular dystrophy, hemophilia A and B, Fabry disease, Hunter syndrome</td>
</tr>
<tr>
<td>Mitochondrial diseases</td>
<td>Leber hereditary optic neuropathy, mitochondrial myopathies</td>
</tr>
<tr>
<td>Trisomies</td>
<td>Down syndrome (chromosome 21), Edward syndrome (chromosome 18), Patau syndrome (chromosome 13)</td>
</tr>
<tr>
<td>Trinucleotide repeat diseases</td>
<td>Huntington disease, myotonic dystrophy, Friedreich ataxia, fragile X syndrome</td>
</tr>
</tbody>
</table>

G6PD, glucose-6-phosphate dehydrogenase.

Pharmacology

**Quick List: Important Formulas**

<table>
<thead>
<tr>
<th>Disease</th>
<th>Formula</th>
</tr>
</thead>
<tbody>
<tr>
<td>Volume of distribution</td>
<td>Total drug in body / plasma concentration</td>
</tr>
<tr>
<td>Clearance</td>
<td>Rate of elimination of drug / plasma concentration</td>
</tr>
<tr>
<td>Half-life</td>
<td>0.7 × volume of distribution / clearance</td>
</tr>
<tr>
<td>Loading dose</td>
<td>Target plasma concentration × volume of distribution / bioavailability Bioavailability = 1, when medication given IV</td>
</tr>
<tr>
<td>Maintenance dose</td>
<td>Target plasma concentration × clearance / bioavailability Bioavailability = 1, when medication given IV</td>
</tr>
</tbody>
</table>

IV, intravenous.
Quick List: Important Drug Side Effects Based on Organ System (Figure 1)

SKIN
1. Photosensitivity—sulfonamides, amiodarone, tetracycline
2. Lupus-like syndrome—hydralazine, isoniazid, procainamide, phenytoin

VASCULAR
1. Facial flushing—niacin, verapamil, nifedipine, diltiazem, adenosine, vancomycin

CARDIAC
1. Coronary vasospasm—cocaine, sumatriptan
2. Dilated cardiomyopathy—doxorubicin, daunorubicin
3. Torsades de pointes—antiarrhythmics (sotalol, quinidine), cisapride

PULMONARY
1. Cough—ACE inhibitors
2. Pulmonary fibrosis—bleomycin, busulfan, amiodarone

HEPATOBILIARY
1. Hepatitis—isoniazid
2. Hepatic necrosis—halothane, valproic acid, acetaminophen
3. Acute cholestatic hepatitis—erythromycin, azithromycin, clarithromycin

HEMATOPOIETIC
1. Agranulocytosis—clozapine, carbamazepine, colchicine, propylthiouracil, methimazole
2. Aplastic anemia—chloramphenicol, benzene, NSAIDs, propylthiouracil, methimazole
3. Hemolytic anemia (direct Coombs-positive)—methyldopa
4. Hemolytic anemia in patients with G6PD deficiency—isoniazid, sulfonamide, Primaquine, aspirin, ibuprofen, nitrofurantoin
5. Gray baby syndrome—chloramphenicol
6. Thrombosis—oral contraceptives

GENITOURINARY
1. Interstitial nephritis—methicillin, NSAIDs
2. Hemorrhagic cystitis—cyclophosphamide, ifosfamide
3. Fanconi syndrome—expired tetracycline

INTESTINAL
1. Pseudomembrane colitis—clindamycin, ampicillin

MUSCULOSKELETAL
1. Osteoporosis—corticosteroids, heparin
2. Gout—furosemide, thiazide diuretic
3. Tendonitis, tendon rupture, cartilage damage—fluoroquinolones
4. Gingival hyperplasia—phenytoin

NERVOUS SYSTEM
1. Seizures—bupropion, imipenem/cilastatin
2. Tardive dyskinesia—antipsychotics
3. Reaction with alcohol intake (headache, nausea, vomiting, flushing)—metronidazole, specific cephalosporins, procarbazine, sulfonylureas (first generation)
4. Neurotoxicity/nephrotoxicity—polymyxins
5. Ototoxicity/nephrotoxicity—cisplatin, furosemide, bumetanide, ethacrynic acid, gentamicin, neomycin, tobramycin, amikacin

ENDOCRINE
1. Adrenocortical insufficiency—glucocorticoid withdrawal
2. Gynecomastia—spironolactone, digitalis, cimetidine, alcohol (chronic use), estrogens, ketoconazole
3. Hot flashes—tamoxifen, clomiphene
4. Diabetes insipidus—lithium, demeclocycline

ACE, angiotensin-converting enzyme; G6PD, glucose-6-phosphate dehydrogenase; NSAIDs, nonsteroidal anti-inflammatory drugs.
### Quick List: Drugs to Avoid in Pregnancy

<table>
<thead>
<tr>
<th>Drug</th>
<th>Reason</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACE inhibitors</td>
<td>Fetal renal malformations</td>
</tr>
<tr>
<td>Aminoglycosides</td>
<td>Ototoxicity</td>
</tr>
<tr>
<td>Atorvastatin</td>
<td>Congenital defects, termination of pregnancy</td>
</tr>
<tr>
<td>Fluoroquinolones</td>
<td>Cartilage damage</td>
</tr>
<tr>
<td>Griseofulvin</td>
<td>Teratogenic</td>
</tr>
<tr>
<td>Methysergide</td>
<td>Oxytocic effects</td>
</tr>
<tr>
<td>Metronidazole</td>
<td>Mutagenesis</td>
</tr>
<tr>
<td>Ribavirin</td>
<td>Teratogenic</td>
</tr>
<tr>
<td>Sulfonamides</td>
<td>Kernicterus</td>
</tr>
<tr>
<td>Tetracyclines</td>
<td>Discolored teeth, inhibition of bone growth</td>
</tr>
<tr>
<td>Warfarin</td>
<td>Teratogenic</td>
</tr>
</tbody>
</table>

ACE, angiotensin-converting enzyme.

### Quick List: Cytochrome P450 Interactions

<table>
<thead>
<tr>
<th>Effect</th>
<th>Agent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inhibitors</td>
<td>Cimetidine, ritonavir (protease inhibitors), amiodarone, ciprofloxacin, ketoconazole, acute alcohol use, macrolides, isoniazid, grapefruit juice, omeprazole, sulfonamides</td>
</tr>
<tr>
<td>Inducers</td>
<td>Phenytoin, rifampin, St. John’s wort, barbiturates, griseofulvin, carbamazepine</td>
</tr>
</tbody>
</table>
## Quick List: Antidotes

<table>
<thead>
<tr>
<th>Toxic agent</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acetaminophen</td>
<td>N-acetylcysteine</td>
</tr>
<tr>
<td>Amphetamine</td>
<td>Ammonium chloride (acidify urine)</td>
</tr>
<tr>
<td>Arsenic</td>
<td>Dimercaprol (BAL), succimer, penicillamine</td>
</tr>
<tr>
<td>Aspirin</td>
<td>Activated charcoal, sodium bicarbonate (alkalinize urine), dialysis</td>
</tr>
<tr>
<td>Atropine</td>
<td>Physostigmine</td>
</tr>
<tr>
<td>Benzodiazepines</td>
<td>Flumazenil</td>
</tr>
<tr>
<td>β-Blockers</td>
<td>Atropine, activated charcoal, glucagon, CaCl$_2$</td>
</tr>
<tr>
<td>Carbon monoxide</td>
<td>100% oxygen, hyperbaric oxygen</td>
</tr>
<tr>
<td>Cocaine</td>
<td>Supportive care, benzodiazepines, calcium channel blockers</td>
</tr>
<tr>
<td>Copper</td>
<td>Penicillamine</td>
</tr>
<tr>
<td>Cyanide</td>
<td>Sodium thiosulfate, amyl nitrate plus sodium nitrite</td>
</tr>
<tr>
<td>Digitalis</td>
<td>Activated charcoal, digoxin immune Fab, potassium (if serum K$^+$ level is low), possibly atropine</td>
</tr>
<tr>
<td>Ethylene glycol (antifreeze)</td>
<td>Fomepizole, ethanol, dialysis</td>
</tr>
<tr>
<td>Heparin</td>
<td>Protamine sulfate</td>
</tr>
<tr>
<td>Iron</td>
<td>Deferoxamine</td>
</tr>
<tr>
<td>Isoniazid</td>
<td>Vitamin B$_6$</td>
</tr>
<tr>
<td>Isopropyl alcohol</td>
<td>Supportive care</td>
</tr>
<tr>
<td>Lead</td>
<td>Succimer, EDTA, dimercaprol</td>
</tr>
<tr>
<td>Mercury</td>
<td>Dimercaprol</td>
</tr>
<tr>
<td>Methanol</td>
<td>Fomepizole, ethanol, dialysis</td>
</tr>
<tr>
<td>Methemoglobin</td>
<td>Methylene blue</td>
</tr>
<tr>
<td>Opioids</td>
<td>Naloxone, naltrexone</td>
</tr>
<tr>
<td>Organophosphates</td>
<td>Atropine, pralidoxime</td>
</tr>
<tr>
<td>Streptokinase</td>
<td>Aminocaproic acid</td>
</tr>
<tr>
<td>Sulfonylureas</td>
<td>Dextrose, octreotide</td>
</tr>
<tr>
<td>tPA</td>
<td>Aminocaproic acid</td>
</tr>
<tr>
<td>Tricyclic antidepressants</td>
<td>Gastric lavage, sodium bicarbonate (serum alkalinization), diazepam for seizures</td>
</tr>
<tr>
<td>Warfarin</td>
<td>Vitamin K, fresh frozen plasma</td>
</tr>
</tbody>
</table>

BAL, British anti-Lewisite; CaCl$_2$, calcium chloride; EDTA, ethylenediaminetetraacetic acid; tPA, tissue plasminogen activator.
**Microbiology**

### Quick List: Buzzwords for Microbiologic Infections

<table>
<thead>
<tr>
<th>Clinical Characteristics</th>
<th>Organism</th>
</tr>
</thead>
<tbody>
<tr>
<td>Branching rods in oral infections</td>
<td><em>Actinomyces israelii</em></td>
</tr>
<tr>
<td>Burn infections</td>
<td><em>Pseudomonas aeruginosa</em></td>
</tr>
<tr>
<td>Cat bite</td>
<td><em>Pasteurella multocida</em></td>
</tr>
<tr>
<td>Chancroid</td>
<td><em>Haemophilus ducreyi</em></td>
</tr>
<tr>
<td>Clue cells</td>
<td><em>Gardnerella vaginalis</em></td>
</tr>
<tr>
<td>Cold agglutinins</td>
<td><em>Mycoplasma pneumoniae</em></td>
</tr>
<tr>
<td>Currant jelly sputum</td>
<td><em>Klebsiella</em></td>
</tr>
<tr>
<td>Erythema chronicum migrans</td>
<td><em>Lyme disease</em></td>
</tr>
<tr>
<td>Ghon focus</td>
<td><em>Primary tuberculosis</em></td>
</tr>
<tr>
<td>Jarisch–Herxheimer reaction</td>
<td><em>Syphilis</em>—treatment of an asymptomatic patient results in rapid lysis leading to symptoms</td>
</tr>
<tr>
<td>Negri bodies</td>
<td><em>Rabies</em></td>
</tr>
<tr>
<td>Owl’s eye</td>
<td><em>CMV</em></td>
</tr>
<tr>
<td>Pediatric infection (in an unvaccinated patient)</td>
<td><em>Haemophilus influenzae</em></td>
</tr>
<tr>
<td>Pneumonia in cystic fibrosis</td>
<td><em>P. aeruginosa</em></td>
</tr>
<tr>
<td>Rash on palms or soles</td>
<td><em>Rocky Mountain spotted fever, secondary syphilis</em></td>
</tr>
<tr>
<td>Reactive arthritis (Reiter syndrome)</td>
<td><em>Urethritis, conjunctivitis, arthritis</em></td>
</tr>
<tr>
<td>Roth spots in retina</td>
<td><em>Endocarditis</em></td>
</tr>
<tr>
<td>Slapped cheeks</td>
<td><em>Parvovirus B19 (erythema infectiosum)</em></td>
</tr>
<tr>
<td>Splinter hemorrhages in fingernails</td>
<td><em>Endocarditis</em></td>
</tr>
<tr>
<td>Strawberry tongue</td>
<td><em>Scarlet fever</em></td>
</tr>
<tr>
<td>Suboccipital lymphadenopathy</td>
<td><em>Rubella</em></td>
</tr>
<tr>
<td>Sulfur granules</td>
<td><em>A. israelii</em></td>
</tr>
<tr>
<td>Tabes dorsalis</td>
<td><em>Tertiary syphilis</em></td>
</tr>
<tr>
<td>Thumb sign on lateral x-ray</td>
<td><em>Epiglottis</em> (usually with <em>H. influenzae</em>)</td>
</tr>
<tr>
<td>Traumatic open wound</td>
<td><em>Clostridium perfringens</em></td>
</tr>
</tbody>
</table>

CMV, cytomegalovirus.
<table>
<thead>
<tr>
<th>Gram Stain Characteristics</th>
<th>Organisms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gram-positive cocci</td>
<td><em>Staphylococcus</em> (catalase +), <em>Streptococcus</em> (catalase -), <em>Enterococcus</em> (catalase -)</td>
</tr>
<tr>
<td>Gram-positive rods</td>
<td><em>Clostridium</em> (anaerobe), <em>Corynebacterium</em>, <em>Listeria</em>, <em>Bacillus</em></td>
</tr>
<tr>
<td>Gram-negative cocci</td>
<td><em>Neisseria</em></td>
</tr>
<tr>
<td>Gram-negative coccoid rods</td>
<td><em>Haemophilus influenzae</em>, <em>Pasteurella</em>, <em>Brucella</em>, <em>Bordetella pertussis</em></td>
</tr>
</tbody>
</table>
| Gram-negative rods         | **Lactose fermenters**: *Klebsiella* (fast*), *Escherichia coli* (fast), *Enterobacter* (fast), *Citrobacter* (slow), *Serratia* (slow)  
**Lactose nonfermenters**: *Shigella* (oxidase -), *Salmonella* (oxidase -), *Proteus* (oxidase -), *Pseudomonas* (oxidase +) |

*Fast fermenter, slow fermenter.*
APPENDIX I: Drug Index

The therapeutic agents shown in boldface type are those that are often emphasized in the classroom and the clinic. Particular attention should be paid to the information about these agents.

<table>
<thead>
<tr>
<th>Therapeutic Agent (common name, if relevant) [trade name, where appropriate]</th>
<th>Class—Pharmacology and Pharmacokinetics</th>
<th>Indications</th>
<th>Side Effects or Adverse Effects</th>
<th>Contraindications or Precautions to Consider; Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Abacavir (ABC)</strong></td>
<td>Antiviral, nucleoside reverse transcriptase inhibitor—guanosine analog (\rightarrow) inhibits viral reverse transcriptase (\rightarrow) prevents integration of DNA copy of viral genome into host DNA</td>
<td>AIDS (used in HAART)</td>
<td>Neutropenia, anemia, peripheral neuropathy, pancreatitis, lactic acidosis, and hypersensitivity reaction (can be fatal)</td>
<td>Check HLA-B*5701 test prior to starting ABC to avoid giving to patients at risk for hypersensitivity reactions</td>
</tr>
<tr>
<td><strong>Acarbose [Precose]</strong></td>
<td>Hypoglycemic agent; (\alpha)-glucosidase inhibitor—inhbits intestinal brush border enzyme (\alpha)-glucosidase (\rightarrow) delays sugar hydrolysis and glucose absorption from gut (\rightarrow) decreases postprandial hyperglycemia</td>
<td>Oral treatment for type 2 diabetes postprandially</td>
<td>Flatulence, cramps, diarrhea; may reduce absorption of iron</td>
<td>Does not cause reactive hypoglycemia; decreases HbA1c</td>
</tr>
<tr>
<td><strong>Acebutolol [Sectral]</strong></td>
<td>Antiarrhythmic (class II)—antihypertensive; (\beta)-blocker</td>
<td>Hypertension, PVCs</td>
<td></td>
<td>Cardiodefective; intrinsic sympathomimetic activity (useful in treating patients with hypertension who also have bradycardia)</td>
</tr>
<tr>
<td><strong>Acetaminophen [Tylenol]</strong></td>
<td>Analgesic, antipyretic—reversibly inhibits COX centrally (inactivated peripherally); prostaglandin inhibitor, not anti-inflammatory</td>
<td>Pain, fever</td>
<td>Liver toxicity in high doses (high levels deplete glutathione)</td>
<td>Overdose treated with (N)-acetylcysteine (regenerates glutathione); unlike aspirin, can be used in children and patients with gout, peptic ulcer, and platelet dysfunction</td>
</tr>
</tbody>
</table>

(continued)
### APPENDIX I: **Drug Index**

<table>
<thead>
<tr>
<th>Therapeutic Agent (common name, if relevant) [trade name, where appropriate]</th>
<th>Class—Pharmacology and Pharmacokinetics</th>
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<th>Side Effects or Adverse Effects</th>
<th>Contraindications or Precautions to Consider; Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acetazolamide [Diamox]</td>
<td>Carbonic anhydrase inhibitor, diuretic—inhibits carbonic anhydrase on PCT and DCT, which prevents $\text{HCO}_3^-$ reabsorption; lose $\text{Na}^+$, $\text{HCO}_3^-$, and $\text{K}^+$ in urine</td>
<td>Glaucoma, high altitude, metabolic alkalosis, alkalization of urine, epilepsy</td>
<td>Hyperchloremic metabolic acidosis, sulfa drug allergy, neuropathy, and ammonium toxicity</td>
<td>Weak diuretic because other sites further downstream along the nephron can compensate for sodium loss; causes decreased secretion of $\text{HCO}_3^-$ in aqueous humor</td>
</tr>
<tr>
<td>Acetylcholine</td>
<td>Muscarinic and nicotinic agonist</td>
<td>Eye surgery (miotic)</td>
<td>Increased cholinergic stimulation (MNEMONIC: DUMBBELSS—Diarrhea, Urination, Miosis, Bronchoconstriction, Bradycardia, Excitation of skeletal muscle, Lacrimation, Salivation, Sweating)</td>
<td>Contraindicated for patients with peptic ulcer, asthma, hyperthyroidism, or parkinsonism</td>
</tr>
<tr>
<td>Acetylsalicylic acid (aspirin)</td>
<td>Anti-inflammatory, antipyretic, analgesic—acetylates COX irreversibly</td>
<td>Articular, musculoskeletal pain; chronic pain; maintenance therapy for preventing clot formation</td>
<td>GI distress, GI ulcers; inhibits platelet aggregation; causes hypersensitivity reactions (rash); reversible hepatic dysfunction</td>
<td>Contraindicated for children with flu or chicken pox (leads to Reye syndrome) and patients with gout</td>
</tr>
<tr>
<td>ACTH (corticotropin)</td>
<td>Increases production of steroids by the adrenal cortex</td>
<td>Test adrenal function in adrenocortical insufficiency</td>
<td>Increased cortisol indicates pituitary defect; unchanged cortisol indicates adrenal defect</td>
<td></td>
</tr>
<tr>
<td>Acyclovir [Zovirax]</td>
<td>Antiviral—guanosine analog, monophosphorylated by viral thymidine kinase; triphosphorylated form inhibits viral DNA polymerase</td>
<td>HSV, VZV, EBV, CMV (at high doses); HSV-induced mucocutaneous genital lesions and encephalitis</td>
<td>Side effects depend on the route of administration: IV—neurotoxicity, renal problems, tremor; oral—diarrhea, headache; topical—local skin irritation</td>
<td>Resistant forms lack thymidine kinase</td>
</tr>
<tr>
<td>Adenosine [Adenocard]</td>
<td>Antiarrhythmic—increases potassium efflux $\rightarrow$ hyperpolarizes cell</td>
<td>Diagnosis and treatment of AV nodal arrhythmias</td>
<td>Flushing, hypotension, and chest pain</td>
<td>Very short acting</td>
</tr>
<tr>
<td>Albendazole [Albenza]</td>
<td>Anthelmintic—blocks glucose uptake, resulting in eventual depletion of the parasite’s energy stores</td>
<td>Ascaris (roundworm), Ancylostoma (hookworm), Trichuris (whipworm), Strongyloides; cysticercosis, hydatid disease</td>
<td>Teratogenic; embryotoxic; mild nausea, vomiting, and dizziness</td>
<td>Contraindicated in pregnant patients</td>
</tr>
<tr>
<td>Drug</td>
<td>Action</td>
<td>Uses</td>
<td>Side Effects</td>
<td>Notes</td>
</tr>
<tr>
<td>-----------------------</td>
<td>------------------------------------------------------------------------</td>
<td>----------------------------------------------------------------------</td>
<td>----------------------------------------------------------------------------</td>
<td>-------------------------------------------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Albuterol [Proventil, Ventolin]</td>
<td>Bronchodilation—(\beta_2)-agonist, leads to relaxation of smooth muscle</td>
<td>Asthma, COPD, bronchitis</td>
<td>Tremor, tachycardia, arrhythmia, headache, nausea, and vomiting</td>
<td>Benzedrines used for withdrawal symptoms; intoxication treated by thiamine, glucose, folic acid, and multivitamins</td>
</tr>
</tbody>
</table>
| Alcohol (EtOH)        | Acts at \(\text{GABA}_A\) receptor                                      | Sedative; hypnotic; depressive action on brain; indicated for methanol and ethylene glycol overdose | Intoxication (in order of increasing BAL): fine motor, coordination, ataxia, lethargy, coma, and respiratory depression  | Withdrawal: nausea, diaphoresis, delirium tremens, and seizures  
Fetal alcohol syndrome: mental retardation, growth deficiencies, microcephaly, and smooth philtrum  
Chronic effects of alcoholism: decreased liver function; Wernicke–Korsakoff syndrome, dilated cardiomyopathy, gynecomastia, and testicular atrophy  |
| Aldesleukin [Proleukin] | Recombinant cytokine—human recombinant IL-2                           | Metastatic renal cell carcinoma, metastatic melanoma, AML           |                                                                                     |                                                                                                                                     |
| Alendronate [Fosamax] | Bone stabilizer—bisphosphonate; pyrophosphate analog; reduces hydroxyapatite crystal formation, growth, and dissolution, which reduces bone turnover | Hypercalcemia of malignancy, Paget disease, osteoporosis, hyperparathyroidism | Pill-induced esophagitis                                                   |                                                                                                                                     |
| Allopurinol [Zyloprim] | Antigout—competitive inhibitor of xanthine oxidase; converted to oxypurinol by xanthine oxidase, which also produces uric acid \(\rightarrow\) allopurinol and oxypurinol inhibit xanthine oxidase \(\rightarrow\) decreased uric acid production | Chronic gout therapy; lymphoma, leukemia (prevents tumor lysis—associated urate nephropathy), and uric acid stones; rheumatic arthritis | Rash; fever; GI problems, hepatotoxicity; inhibition of the metabolism of other drugs; enhances the effect of azathioprine | Should not be used to treat acute gout; inhibition of the metabolism of other drugs; enhances the effect of azathioprine                  |
| Alprazolam [Xanax]    | Antianxiety—intermediate-acting benzodiazepine                         | Panic attack; phobia; MNEMONIC: AL PRAYS when he’s in fear         | Sedation                                                                      | Respiratory depression if taken with alcohol                                                                                                                                               |
| Alprostadil [Vasopro] | Impotency therapy; PGE\(_1\) agonist                                  | Impotency; maintains PDA                                            | Penile pain; prolonged erection; flushing, bradycardia, tachycardia, hypotension, and apnea |                                                                                                                                     |
## APPENDIX I: Drug Index

<table>
<thead>
<tr>
<th>Therapeutic Agent (common name, if relevant) [trade name, where appropriate]</th>
<th>Class—Pharmacology and Pharmacokinetics</th>
<th>Indications</th>
<th>Side Effects or Adverse Effects</th>
<th>Contraindications or Precautions to Consider; Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Aluminum hydroxide</strong></td>
<td>Antacid—buffers gastric acid by raising the pH; <strong>antidiarrheal</strong>—delays gastric emptying</td>
<td>Peptic ulcer, gastritis, esophageal reflux, and diarrhea</td>
<td>Constipation, hypophosphatemia, muscle weakness, osteodystrophy, seizures, and hypokalemia</td>
<td>Can affect the absorption, bioavailability, or urinary excretion of drugs by changing gastric pH, urinary pH, or gastric emptying</td>
</tr>
<tr>
<td><strong>Amantadine [Symmetrel]</strong></td>
<td>Antiviral—antiparkinsonian; inhibits fusion of lysosomes; inhibits viral penetration and uncoating; increases release of endogenous dopamine</td>
<td>Influenza A (prophylaxis and treatment), Parkinson disease</td>
<td>CNS effects (ataxia, dizziness, slurred speech, nervousness, and seizure), anticholinergic, orthostatic hypotension, livedo reticularis</td>
<td>Mechanism of viral resistance is mutated M2 protein</td>
</tr>
<tr>
<td><strong>Amikacin [Amikin]</strong></td>
<td>Antibiotic—aminoglycoside, protein synthesis inhibitor; irreversibly binds 30S ribosome subunits; bacteriostatic at low concentration; bactericidal at high concentration</td>
<td>Broad spectrum: gram-negative rods; good for bone and eye infections; <em>Proteus</em>, <em>Pseudomonas</em>, <em>Enterobacter</em>, <em>Klebsiella</em>, and <em>Escherichia coli</em></td>
<td>Otototoxicity, renal toxicity, neuromuscular blockade, nausea, vomiting, vertigo, allergic rash</td>
<td>Does not cover anaerobes</td>
</tr>
<tr>
<td><strong>Amiloride [Midamor]</strong></td>
<td>Potassium-sparing diuretic—binds to intracellular aldosterone steroid receptors in collecting tubules; blocks induction of Na⁺ channels and Na⁺/ATPase synthesis and blocks Na⁺ channels directly; lose Na⁺ and Cl⁻ in urine</td>
<td>Hyperaldosteronism, potassium depletion, CHF</td>
<td>Hyperkalemic metabolic acidosis, gynecomasia (spironolactone), and antiandrogen effects</td>
<td>Results in decreased secretion of K⁺ and H⁺, which can lead to hyperkalemic metabolic acidosis; often given in combination with a thiazide</td>
</tr>
<tr>
<td><strong>Aminocaproic acid [Amicar]</strong></td>
<td>Competitive inhibition of plasminogen activation</td>
<td>Inhibits fibrinolysis; promotes thrombosis</td>
<td>Oral administration</td>
<td></td>
</tr>
<tr>
<td><strong>Aminoglutethimide [Cytadren]</strong></td>
<td>Antineoplastic—aromatase inhibitor; cytochrome P450 inhibitor that catalyzes the rate-limiting step of adrenal steroid synthesis</td>
<td>Breast cancer, Cushing syndrome</td>
<td>GI and neurologic side effects; transient maculopapular rash</td>
<td>Do not cover anaerobes because oxidative metabolism is required for uptake of these drugs</td>
</tr>
<tr>
<td><strong>Aminoglycosides</strong></td>
<td>Antibiotic—irreversibly binds 30S ribosome subunits; bacteriostatic at low concentration; bactericidal at high concentration</td>
<td>Broad spectrum: gram-negative rods; good for bone and eye infections; <em>Proteus</em>, <em>Pseudomonas</em>, <em>Enterobacter</em>, <em>Klebsiella</em>, and <em>Escherichia coli</em>; also used for tuberculosis</td>
<td>Otototoxicity, renal toxicity, neuromuscular blockade, nausea, vomiting, vertigo, allergic rash</td>
<td>Examples include gentamycin, neomycin, and streptomycin</td>
</tr>
<tr>
<td>Drug</td>
<td>Class/Action</td>
<td>Indications</td>
<td>Side Effects</td>
<td></td>
</tr>
<tr>
<td>--------------------------</td>
<td>--------------------------------------------</td>
<td>------------------------------------------------------------------------------</td>
<td>------------------------------------------------------------------------------</td>
<td></td>
</tr>
<tr>
<td>Amiodarone [Cordarone]</td>
<td>Antiarrhythmic (class III)—K⁺ channel blocker</td>
<td>Ventricular/supraventricular arrhythmias</td>
<td>Hepatotoxicity, thyroid toxicity, pulmonary fibrosis, photodermatitis</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Also functions as class IA, II, and IV antiarrhythmic</td>
<td></td>
</tr>
<tr>
<td>Amitriptyline [Elavil]</td>
<td>TCAs—inhibit reuptake of NE and 5-HT at neuronal synapses</td>
<td>Major depression, panic disorder, sedative, prophylaxis for migraines</td>
<td>Sedation, α-blocking effects (orthostatic hypotension), anticholinergic (tachycardia, dry mouth, and urinary retention), hallucinations (in elderly), and confusion (in elderly); overdose toxicity results in convulsions, coma, cardiotoxicity (arrhythmias), respiratory depression, and hyperpyrexia</td>
<td></td>
</tr>
<tr>
<td>Amlodipine [Norvasc]</td>
<td>Dihydropyridine Ca²⁺ channel blocker—block voltage-gated Ca²⁺ channels of vascular smooth muscle</td>
<td>Hypertension, angina pectoris, Prinzmetal angina, Raynaud phenomenon</td>
<td>Peripheral edema, flushing, dizziness, and constipation</td>
<td></td>
</tr>
<tr>
<td>Amobarbital [Amytal sodium]</td>
<td>Sedative-hypnotic; barbiturate; prolongs IPSP duration for GABA receptor</td>
<td>Antiepileptic, cerebral edema, anesthetic</td>
<td>Sedation, respiratory depression</td>
<td></td>
</tr>
<tr>
<td>Amodiaquine</td>
<td>Antimalarial—uncertain mechanism</td>
<td>Suppression and treatment of acute attacks</td>
<td>Headache; GI and visual disturbances; pruritus; prolonged therapy may lead to retinopathy</td>
<td></td>
</tr>
<tr>
<td>Amoxapine</td>
<td>TCAs—inhibit reuptake of NE and 5-HT at neuronal synapses</td>
<td>Major depression, panic disorder</td>
<td>Sedation, α-blocking effects (orthostatic hypotension), anticholinergic (tachycardia, dry mouth, and urinary retention), hallucinations (in elderly), and confusion (in elderly); overdose toxicity results in convulsions, coma, cardiotoxicity (arrhythmias), respiratory depression, and hyperpyrexia</td>
<td></td>
</tr>
<tr>
<td>Amoxicillin</td>
<td>Antibiotic—β-lactam, penicillin derivative, cell wall inhibitor; same mechanism as penicillin; distinguished by activity against gram-negative rods: bactericidal</td>
<td>Gram-positive cocci, gram-positive rods, gram-negative cocci, and gram-negative rods—extended spectrum: E. coli, Proteus, Salmonella, Shigella, and Haemophilus influenzae</td>
<td>Hypersensitivity reaction; rash when given to mononucleosis patients</td>
<td></td>
</tr>
<tr>
<td>Amoxicillin/clavulanic acid [Augmentin]</td>
<td>Antibiotic—clavulanic acid inhibits β-lactamase</td>
<td></td>
<td>Orally administered; not effective against penicillin-resistant Staphylococcus; can be combined with clavulanic acid (β-lactamase inhibitor) to enhance spectrum</td>
<td></td>
</tr>
</tbody>
</table>

(continued)
## APPENDIX I: Drug Index

<table>
<thead>
<tr>
<th>Therapeutic Agent (common name, if relevant) [trade name, where appropriate]</th>
<th>Class—Pharmacology and Pharmacokinetics</th>
<th>Indications</th>
<th>Side Effects or Adverse Effects</th>
<th>Contraindications or Precautions to Consider; Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amphetamine</td>
<td>Stimulant—releases NE, dopamine, and 5-HT</td>
<td>Narcolepsy, attention deficit disorder, weight reduction</td>
<td>Dilated pupils, psychosis, hallucinations, increased BP</td>
<td>Contraindicated with MAOI; metabolized by liver</td>
</tr>
<tr>
<td>Amphotericin B [Fungizone]</td>
<td>Antifungal—binds to cell membrane sterols (especially ergosterol), forms pores in membrane; fungicidal</td>
<td>Wide spectrum fungal coverage: Candida, Histoplasma, Cryptococcus, Blastomyces, Aspergillus, Coccidioides, Scurerthrax, and Mucor</td>
<td>Impairment of renal function, hypersensitivity, flushing, fever, shaking chills, hypotension, thrombophlebitis, anemia, arrhythmias, hypokalemia</td>
<td>Penetrates CNS poorly; poor GI absorption, so given IV</td>
</tr>
<tr>
<td>Ampicillin</td>
<td>Antibiotic—β-lactam, penicillin derivative, cell wall inhibitor; same mechanism as penicillin; distinguished by activity against gram-negative rods; bactericidal</td>
<td>Gram-positive cocci, gram-positive rods, gram-negative cocci, and gram-negatives rods—extended spectrum: E. coli, Proteus, Salmonella, Shigella, and H. influenzae</td>
<td>Hypersensitivity reaction; rash, when given to mononucleosis patients</td>
<td></td>
</tr>
<tr>
<td>Amprenavir</td>
<td>Antiviral, protease inhibitor—protease responsible for final step of viral proliferation; inhibits protease in progeny virions → assembly of nonfunctional viruses</td>
<td>AIDS (used in HAART)</td>
<td>GI irritation (nausea, diarrhea), hyperglycemia, hyperlipidemia, and lipodystrophy</td>
<td>All protease inhibitors end in -navir; metabolism occurs by cytochrome P450</td>
</tr>
<tr>
<td>Amrinone [Inocor]</td>
<td>Inotropic agent—phosphodiesterase inhibitor, increases contractility via increase in intracellular Ca²⁺</td>
<td>Acute CHF</td>
<td>Thrombocytopenia, arrhythmias, hepatotoxicity, and GI disturbances</td>
<td>Rarely used today because of the side effects</td>
</tr>
<tr>
<td>Anastrozole [Arimidex]</td>
<td>Aromatase inhibitor</td>
<td>Breast cancer in postmenopausal women, endometriosis</td>
<td>Hot flashes, nausea, and vomiting</td>
<td>Can be used in estrogen receptor–positive or hormone receptor–unknown breast cancer</td>
</tr>
<tr>
<td>Anistreplase (APSAC) [Eminase]</td>
<td>Thrombolytic—plasminogen activator</td>
<td>Lysis of clots</td>
<td>Hemorrhage</td>
<td>Active compound via deacylation by esterase</td>
</tr>
<tr>
<td>Anthraquinone</td>
<td>Stimulant laxative—reduces absorption of electrolytes and water from gut</td>
<td>Constipation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>α₂-Antiplasmin</td>
<td>Inhibits fibrinolysis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aprotinin [Trasylol]</td>
<td>Homestatic agent—antiplasmin activator</td>
<td>Inhibits fibrinolysis; promotes thrombosis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asparaginase [Elspar]</td>
<td>Antineoplastic—deprives cells of asparagines</td>
<td>Cancer</td>
<td>Fever, mental depression, coma, hepatotoxicity</td>
<td></td>
</tr>
<tr>
<td>Drug</td>
<td>Mechanism or Use</td>
<td>Side Effects</td>
<td>Contraindications/Additional Notes</td>
<td></td>
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<tr>
<td>Aspart [NovoLog]</td>
<td>Rapid-acting insulin—see mechanism for regular insulin</td>
<td>Diabetes mellitus (typically type 1), hyperkalemia, and stress-induced hyperglycemia</td>
<td>Hypoglycemia (diaphoresis, vertigo, and tachycardia), insulin allergy, insulin antibodies, lipodystrophy</td>
<td></td>
</tr>
<tr>
<td>Atenolol [Tenormin]</td>
<td>Antihypertensive—β₁-blocker</td>
<td>Hypertension, angina</td>
<td>Bradycardia, heart block, fatigue, impotence; masks signs of hypoglycemia in diabetics</td>
<td></td>
</tr>
<tr>
<td>Atorvastatin [Lipitor]</td>
<td>Lipid-lowering agent—HMG-CoA reductase inhibitor, inhibits synthesis of cholesterol precursor mevalonate; decreases LDL, increases HDL, and decreases TG</td>
<td>High LDL, preventative after thrombotic event (e.g., MI or stroke)</td>
<td>Reversible increase in LFTs; myositis</td>
<td></td>
</tr>
<tr>
<td>Atracurium [Tracrium injection]</td>
<td>Nondepolarizing neuromuscular blocker</td>
<td>Minimal histamine release</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atropine</td>
<td>Reversible cholinergic muscarinic blocker</td>
<td>Dries salivary secretions; Parkinson disease; peptic ulcer; diarrhea; GI spasm, bladder spasm; COPD; asthma; cholinomimetic poisoning; antiarrhythmic; high dose: vasodilation as a result of histamine release; mydriasis and cycloplegia (thorough fundus exam, accurate refraction)</td>
<td>Dry mouth, hyperthermia, mydriasis, tachycardia, hot and flushed skin, agitation, delirium; MNEMONIC: Dry as a bone (dry mouth), hot as a hare (inhibition of sweating), red as a beet (tachycardia, cutaneous vasodilation), blind as a bat (blurring vision), mad as a hatter (hallucinations and delirium)</td>
<td></td>
</tr>
<tr>
<td>Aurothioglucose [Solganal]</td>
<td>Antirheumatic—gold salt</td>
<td>Rheumatic arthritis</td>
<td>Skin eruption, itching, toxic nephritis, bone marrow suppression</td>
<td></td>
</tr>
<tr>
<td>Aurothioglycolate</td>
<td>Antirheumatic—gold salt</td>
<td>Rheumatic arthritis</td>
<td>Skin eruption, itching, toxic nephritis, bone marrow suppression</td>
<td></td>
</tr>
<tr>
<td>Azathioprine [Imuran]</td>
<td>Immunosuppressant—purine antagonist, inhibits nucleic acid metabolism, blocks both CMI and humoral response</td>
<td>Transplant (especially kidney), acute glomerulonephritis, renal component of lupus, rheumatoid arthritis</td>
<td>Bone marrow depression, rash, fever, nausea, vomiting, hepatotoxicity, malignancy, GI intolerance</td>
<td></td>
</tr>
<tr>
<td>Azithromycin [Zithromax]</td>
<td>Antibiotic—macrolide, protein synthesis inhibitor, binds to the 23S RNA of the 50S ribosome subunits → blocks translocation → prevents protein synthesis; bacteriostatic</td>
<td>First choice for cell wall–deficient bugs: <em>Mycoplasma, Rickettsia, Chlamydia, Legionella, Corynebacterium diphtheriae</em>, gram-positive cocci (Streptococcus)</td>
<td>GI discomfort, acute cholestatic hepatitis, rashes; increases the concentration of oral anticoagulants and theophyllines</td>
<td></td>
</tr>
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(continued)
<table>
<thead>
<tr>
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</tr>
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<tbody>
<tr>
<td>Aztreonam [Azactam]</td>
<td>Antibiotic—monocyclic ( \beta )-lactam, cell wall inhibitor; same mechanism as penicillin (binds to PBP3); bactericidal</td>
<td>Gram-negative bacteria, especially <em>Pseudomonas, Klebsiella, Serratia</em>, and <em>Enterobacteriaceae</em>; no activity against gram-positives or anaerobes</td>
<td>Rash, GI distress (nausea, vomiting, etc.)</td>
<td>Does not cross-react with penicillin; synergistic with aminoglycosides; can be used in patients with penicillin allergies and renal insufficiency who cannot take aminoglycosides</td>
</tr>
<tr>
<td>Bacitracin</td>
<td>Antibiotic—inhinders cell wall formation; bactericidal</td>
<td>Gram-positive bacteria</td>
<td>Nephrotoxic</td>
<td>Topical only</td>
</tr>
<tr>
<td>Baclofen [Lioresal]</td>
<td>Skeletal muscle relaxant—GABA mimetic; works at the GABA(_B) receptor</td>
<td>Muscle spasms, tetanus contractions, orthopedic manipulation</td>
<td></td>
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</tr>
<tr>
<td>BCNU [carmustine]</td>
<td>Antineoplastic—DNA alkylation</td>
<td>Cancer</td>
<td>Delayed bone marrow suppression, lung and kidney damage</td>
<td></td>
</tr>
<tr>
<td>Beclomethasone</td>
<td>Corticosteroids—inhibit leukotriene synthesis ( \rightarrow ) reduces inflammation and leads to bronchodilation</td>
<td>Asthma, COPD</td>
<td>Osteoporosis, cushingoid reaction, psychosis, glucose intolerance, infection, hypertension, cataracts</td>
<td></td>
</tr>
<tr>
<td>Benserazide</td>
<td>Antiparkinsonian—inhibits decarboxylase (L-dopa to dopamine) in periphery</td>
<td>Parkinson disease</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Benztropine [Cogentin]</td>
<td>Antiparkinsonian—muscarinic blocker; ( H), blocker</td>
<td>Parkinson disease</td>
<td>Sedation, urinary retention, dry mouth, constipation, and mental confusion</td>
<td>Less effective than levodopa in Parkinson disease</td>
</tr>
<tr>
<td>Bephenium hydroxynaphthoate</td>
<td>Anthelmintic—cholinergic agonist causing contraction, then relaxation in worm</td>
<td>Necator and Ancylostoma (hookworms)</td>
<td>Vomiting</td>
<td></td>
</tr>
<tr>
<td>Betamethasone</td>
<td>Glucocorticoid</td>
<td>Induction of surfactant synthesis in premature infants</td>
<td></td>
<td>One of two steroids to cross placenta</td>
</tr>
<tr>
<td>Bisacodyl [Dulcolax]</td>
<td>Stimulant laxative, increases peristalsis</td>
<td>Constipation</td>
<td>Electrolyte imbalances (chronic use), gastric irritation</td>
<td></td>
</tr>
<tr>
<td>Drug Name</td>
<td>Description</td>
<td>Indications</td>
<td>Side Effects</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Bischloroethylamines (nitrogen mustards) [Mustargen]</td>
<td>Antineoplastic—DNA alkylation and cross-linking</td>
<td>Cancer</td>
<td>Nausea, vomiting, bone marrow suppression, alopecia, teratogenicity, carcinogenicity</td>
<td></td>
</tr>
<tr>
<td>Bismuth [Pepto-Bismol]</td>
<td>Cytoprotectant—binds to ulcer base → protection; allows bicarbonate ion secretion to reestablish pH gradient in the mucous layer</td>
<td>Traveler’s diarrhea, peptic ulcer disease</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Black widow spider venom</td>
<td>Presynaptic neuromuscular junction blocker—overstimulates acetylcholine release</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bleomycin [Blenoxane]</td>
<td>Antineoplastic—generates free radicals that bind, intercalate, and cut DNA</td>
<td>Testicular cancer and Hodgkin lymphoma</td>
<td>Pulmonary fibrosis, fever, blistering, stomatitis, hypersensitivity reactions (anaphylaxis)</td>
<td></td>
</tr>
<tr>
<td>Botulinum [Botox, Dysport]</td>
<td>Neuromuscular blocker—presynaptic neuromuscular junction blocker; prevents acetylcholine release</td>
<td>Wrinkles, muscle spasm</td>
<td>Paralysis</td>
<td></td>
</tr>
<tr>
<td>Bretylium [Bretylol]</td>
<td>Antiarrhythmic (class III)—K⁺ channel blocker; prolongs ventricular action potential, effective refractory period, and blocks NE release</td>
<td>Arrhythmias; refractory ventricular fibrillation and ventricular tachycardia during cardiac arrest</td>
<td>Orthostatic hypotension, nausea, vomiting</td>
<td></td>
</tr>
<tr>
<td>Bromocriptine [Parlodel]</td>
<td>Antiparkinsonian—agonist at D₂; partial antagonist at D₁</td>
<td>Parkinson disease, hyperprolactinemia, acromegaly (paradoxical effect—releases growth hormone from normal pituitary)</td>
<td>Inhibits prolactin release; hallucination, delirium, nausea, vomiting, cardiac arrhythmia, postural hypotension, and erythromelalgia</td>
<td></td>
</tr>
<tr>
<td>Buclizine</td>
<td>Antiemetic</td>
<td>Sedation, parkinsonism</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Budesonide [Rhinocort]</td>
<td>Intranasal glucocorticoids—decrease cytokine synthesis; downregulate inflammatory response in the nasal mucosa</td>
<td>Nasal congestion, allergic rhinitis</td>
<td>Local irritation of nasal mucosa, epistaxis</td>
<td></td>
</tr>
<tr>
<td>Bumetanide [Bumex]</td>
<td>Loop diuretic—inhibits Na⁺/K⁺/2Cl⁻ reabsorption in the loop of Henle</td>
<td>CHF, diuresis, pulmonary edema, acute hypercalcemia, acute hyperkalemia, acute renal failure</td>
<td>Ototoxicity, interstitial nephritis, hyperuricemia, acute hypervolemia, hypokalemia, metabolic alkalosis, hyperglycemia, hypocalcemia, hypomagnesemia</td>
<td></td>
</tr>
<tr>
<td>α-Bungarotoxin</td>
<td>Postsynaptic neuromuscular junction blocker; irreversibly binds nicotinic receptor</td>
<td>Paralysis</td>
<td>Component of snake venom</td>
<td></td>
</tr>
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<td>Therapeutic Agent (common name, if relevant) [trade name, where appropriate]</td>
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<tr>
<td>Bupivacaine</td>
<td>Anesthetic—blocks Na⁺ channel intracellularly</td>
<td>Local anesthetic</td>
<td>Sleepiness, light-headedness, myocardial depression, hypotension, visual/audio disturbances, restlessness, nystagmus, shivering, tonic–clonic convulsions, death</td>
<td></td>
</tr>
<tr>
<td>Buprenorphine [Buprenex]</td>
<td>Opioid analog—mixed agonist/antagonist action</td>
<td>Treatment of opioid/cocaine dependence</td>
<td>Respiratory depression, sedation, and nausea/vomiting</td>
<td></td>
</tr>
<tr>
<td>Bupropion [Wellbutrin, Zyban]</td>
<td>Antidepressant—unknown mechanism; thought to be an agonist at D₂, 5-HT</td>
<td>Major depression, smoking cessation</td>
<td>Tachycardia, insomnia, headache, and seizure (especially patients with bulimia) Does not have sexual side effects such as those occurring with SSRIs</td>
<td></td>
</tr>
<tr>
<td>Buspirone [Buspar]</td>
<td>Antidepressant partial agonist at serotonin receptors</td>
<td>Generalized anxiety</td>
<td>2 weeks for effects to become apparent Avoid in patients with peptic ulcer because it stimulates gastric mucosal secretions</td>
<td></td>
</tr>
<tr>
<td>Caffeine [NoDoz]</td>
<td>Stimulant—adenosine receptor blocker; stimulates CNS and cardiac muscle; relaxes smooth muscle; produces diuresis; increases cerebrovascular resistance</td>
<td>Acute migraine attack</td>
<td>Crosses placenta and into breast milk</td>
<td></td>
</tr>
<tr>
<td>Calcitonin [Calcimar, Miacalcin]</td>
<td>Hypocalcemic agent—anti-osteoporotic agent; lowers plasma Ca²⁺ and phosphate; inhibits bone and kidney reabsorption</td>
<td>Hypercalcemia, Paget disease, osteoporosis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Calcium carbonate [TUMS, Caltrate]</td>
<td>Antacid—buffers gastric acid by raising pH</td>
<td>Peptic ulcer, gastritis, esophageal reflux, and calcium deficiency</td>
<td>Hypercalcemia, rebound acid increase, and hypokalemia Can affect the absorption, bioavailability, or urinary excretion of drugs by changing gastric pH, urinary pH, or gastric emptying</td>
<td></td>
</tr>
<tr>
<td>Calcium citrate</td>
<td>Dietary Ca²⁺ supplement</td>
<td>Ca²⁺ deficiency</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Calcium gluconate</td>
<td>Dietary Ca²⁺ supplement</td>
<td>Ca²⁺ deficiency</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Calcium lactate</td>
<td>Dietary Ca²⁺ supplement</td>
<td>Ca²⁺ deficiency</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Captopril [Capoten]</td>
<td>Antihypertensive—ACE inhibitor inhibits conversion of angiotensin I to II decreases angiotensin II (Ang II) levels prevents vasoconstriction from Ang II</td>
<td>Hypertension, CHF, post-MI; prevention/treatment of diabetic nephropathy</td>
<td>Cough, angioedema, hyperkalemia, renal insufficiency (especially in bilateral renal artery stenosis) Contraindicated in pregnancy (fetal renal malformation)</td>
<td></td>
</tr>
<tr>
<td>Drug Name</td>
<td>Class</td>
<td>Mechanism/Effect</td>
<td>Contraindications</td>
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</tr>
<tr>
<td>Carbachol (Isopto Carbachol)</td>
<td>Antiglaucoma agent</td>
<td>Muscarinic cholinergic agonist, works on both muscarinic and nicotinic receptors</td>
<td>DUMBBELSS (see Acetylcholine) Contraindicated in patients with peptic ulcer, asthma, hyperthyroidism, and Parkinson disease</td>
<td></td>
</tr>
<tr>
<td>Carbamazepine (Tegretol)</td>
<td>Antiepileptic</td>
<td>Prolongs inactivated state of Na⁺ channels; decreases release of glutamate and excitatory neurotransmitters</td>
<td>Agranulocytosis, liver toxicity (check LFTs), and aplastic anemia Induces cytochrome P450</td>
<td></td>
</tr>
<tr>
<td>Carbenicillin</td>
<td>Antibiotic</td>
<td>-lactam, penicillin derivative, cell wall inhibitor; same mechanism as penicillin; distinguished by activity against <em>Pseudomonas</em>, bacterialidal</td>
<td>Hypersensitivity reactions, decreased platelet function Not effective against penicillin-resistant <em>Staphylococcus</em>; can be combined with clavulanic acid (<em>β</em>-lactamase inhibitor) to enhance spectrum; administered IV</td>
<td></td>
</tr>
<tr>
<td>Carbidopa-levodopa (Sinemet)</td>
<td>Antiparkinsonian</td>
<td>Inhibits decarboxylase (L-dopa to dopamine) in periphery; does not cross BBB</td>
<td>Treatment efficacy declines with progression of disease due to a decrease in healthy dopaminergic neurons required for levodopa’s MOA</td>
<td></td>
</tr>
<tr>
<td>Carboplatin (Paraplatin)</td>
<td>Antineoplastic</td>
<td>Cross-links DNA</td>
<td>Ovarian cancer Bone marrow suppression and anemia Contains platinum</td>
<td></td>
</tr>
<tr>
<td>Carprofenol (Prostin)</td>
<td>Abortive agent</td>
<td>PGF₂α</td>
<td>Therapeutic abortion Nausea, vomiting, diarrhea</td>
<td></td>
</tr>
<tr>
<td>Carvedilol</td>
<td>Antihypertensive, antiarrhythmic</td>
<td>Class III—α- and β-blocker</td>
<td>Hypertension, angina, MI, and antiarrhythmic Impotence, asthma, bradycardia, AV block, heart failure, sedation, and sleep alterations</td>
<td></td>
</tr>
<tr>
<td>Carprofenol (Prostin)</td>
<td>Antiinflammatory</td>
<td>Inhibits cell wall synthesis</td>
<td>GI irritation, flushing Administrated IV</td>
<td></td>
</tr>
<tr>
<td>Castor oil</td>
<td>Stimulant laxative</td>
<td>Reduces absorption of electrolytes and water from gut; active component is ricinoleic acid</td>
<td>Constipation, labor induction</td>
<td></td>
</tr>
<tr>
<td>Celecoxib (Celebrex)</td>
<td>NSAID—selectively inhibits COX-2</td>
<td>Rheumatoid arthritis, osteoarthritis; pain, inflammation Increased risk of thrombosis, sulfia allergy, and less toxic to GI mucosa</td>
<td>COX-2 selectivity reduces inflammation while minimizing GI adverse effects (ulcers)</td>
<td></td>
</tr>
</tbody>
</table>
## APPENDIX I: Drug Index

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<tr>
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<tr>
<td><strong>Cephalosporins</strong></td>
<td>Antibiotic—β-lactam, cell wall inhibitor, same mechanism as penicillin, bactericidal, from first generation to third generation: a. Gram-positive coverage decreases b. Gram-negative coverage increases c. CNS penetration increases d. β-Lactamase resistance increases</td>
<td>First generation: Gram-positive cocci and <em>PEcK</em> (Proteus mirabilis, <em>Escherichia coli</em>, and <em>Klebsiella</em>); second generation: same as first generation + <em>HENPEcK</em> (<em>H. influenzae</em>, <em>Enterobacter</em>, and <em>Neisseria</em>); third generation: cephalosporins are used for meningitis, <em>Klebsiella</em>, Lyme disease, and gram-negative bacteria</td>
<td>Hypersensitivity reaction, pain at injection site, intolerance to alcohol (cefamandole, cefotetan, moxalactam, and cefoperazone), hypothrombinemia (cefamandole, cefoperazone, and moxalactam, due to vitamin K inhibition), thrombophlebitis, positive Coombs test</td>
<td>First generation: cefazolin, cephalexin; second generation: cefaclor, cefoxitin, and cefuroxime; third generation: ceftriaxone, cefotaxime, and ceftazidime; fourth generation: ceftazidime; <em>Pseudomonas</em> coverage: ceftazidime and ceftazidime; cross-hypersensitivity with penicillins occurs in 5%–10% of patients</td>
</tr>
<tr>
<td><strong>Chloral hydrate</strong></td>
<td>Anesthetic agent</td>
<td>Sedative (in children), hypnotic</td>
<td>Bitter taste, GI distress</td>
<td>Inexpensive</td>
</tr>
<tr>
<td><strong>Chlorambucil [Leukeran]</strong></td>
<td>Antineoplastic—DNA alkylation and cross-linking</td>
<td>Cancer</td>
<td>Nausea, vomiting, bone marrow suppression (mild), alopecia, teratogenicity, carcinogenicity, and pulmonary fibrosis</td>
<td></td>
</tr>
<tr>
<td><strong>Chloramphenicol [Chloromycetin]</strong></td>
<td>Antibiotic—protein synthesis inhibitor; inhibits 50S peptidyl transferase activity; bacteriostatic but bactericidal versus <em>H. influenzae</em> and <em>Neisseria meningitidis</em></td>
<td>Meningitis (<em>H. influenzae</em>, <em>N. meningitidis</em>, and <em>Streptococcus pneumoniae</em>), typhoid fever, <em>Salmonella</em>, <em>Rickettsia</em> (Rocky Mountain spotted fever in children), <em>Bacteroides</em></td>
<td>Fatal aplastic anemia, bone marrow suppression, gray baby syndrome (cyanosis, vomiting, green stools, and vasomotor collapse due to insufficient glucuronidase in neonatal liver)</td>
<td>Interactions with phenytoin, warfarin, or coumadin; inhibits cytochrome P450; used to treat serious infections after other antibiotics have failed given side effects</td>
</tr>
<tr>
<td><strong>Chlordiazepoxide [Librium]</strong></td>
<td>Long-acting benzodiazepine; antianxiety; enhances GABA; increases IPSP amplitude</td>
<td>Sedative, hypnotic, antianxiety, antiepileptic; alcohol withdrawal</td>
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</tr>
<tr>
<td><strong>Chloroquine phosphate [Aralen]</strong></td>
<td>Antimalarial—inhibits dihydrofolate reductase</td>
<td>Prophylaxis for falciparum malaria; suppression of vivax malaria</td>
<td>Minor GI upset</td>
<td></td>
</tr>
<tr>
<td><strong>Chloroquine phosphate [Aralen]</strong></td>
<td>Antimalarial—uncertain mechanism</td>
<td>Suppression of malaria and treatment of acute attack; amebiasis; clonorchis; rheumatoid arthritis; SLE</td>
<td>Headache, GI disturbances, visual disturbances, pruritus; prolonged therapy may lead to retinopathy</td>
<td></td>
</tr>
<tr>
<td><strong>Chloroprocaine</strong></td>
<td>Anesthetic—block Na+ channel intracellularly</td>
<td>Local anesthetic</td>
<td>Sleepiness, light-headedness, visual/audio disturbances, restlessness, nystagmus, shivering, tonic–clonic convulsions, death</td>
<td></td>
</tr>
<tr>
<td>Drug</td>
<td>Category</td>
<td>Actions</td>
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<tr>
<td>Chlorpheniramine</td>
<td>Antihistamine—H&lt;sub&gt;1&lt;/sub&gt; blocker</td>
<td>Allergies, motion sickness, Sedation, CNS depression, atropine-like effects, allergic dermatitis, blood dyscrasias, teratogenicity, acute antihistamine poisoning</td>
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<tr>
<td>Chlorpromazine</td>
<td>Antineuromuscular, antipsychotic—phenothiazines; blocks D&lt;sub&gt;2&lt;/sub&gt;, α&lt;sub&gt;1&lt;/sub&gt;, and H&lt;sub&gt;1&lt;/sub&gt; receptors</td>
<td>Antipsychotic, antiemetic, hiccups, Extrapyramidal (dystonia, akinesia, akathisia, and tardive dyskinesia), anticholinergic (dry mouth, constipation), alpha blockade (hypotension), histamine (sedation); toxicity results in neuroleptic malignant syndrome (rigidity, myoglobinuria, autonomic instability, and hyperpyrexia) Atropine-like effects fairly common</td>
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<tr>
<td>Chlorpropamide</td>
<td>Hypoglycemic agent, first-generation sulfonylurea—closes potassium channel in β-cell membrane, reduces K&lt;sup&gt;+&lt;/sup&gt; efflux, increases Ca&lt;sup&gt;2+&lt;/sup&gt; influx, increases secretion of insulin</td>
<td>Oral treatment for type 2 diabetes, Hypoglycemia, GI disturbances, muscle weakness, mental confusion, Rarely used due to toxicity</td>
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<tr>
<td>Cholestyramine</td>
<td>Lipid-lowering agent—bile acid resins act by binding bile acids in the small intestine, forming insoluble complexes that are excreted; decreased bile acids stimulate the liver to increase conversion of cholesterol to bile acids, increasing hepatic LDL receptors, decreasing serum LDL</td>
<td>Reduction of cholesterol, Steatorrhea, constipation, impairment of absorption of drugs/vitamins, Inhibits warfarin absorption</td>
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<tr>
<td>Chorionic gonadotropin</td>
<td>Infertility therapy—LH-like in action</td>
<td>Treats infertility, induces ovulation, induces masculinization in infertile men, diagnostic for cryptorchidism in young boys</td>
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<tr>
<td>Cimetidine</td>
<td>H&lt;sub&gt;2&lt;/sub&gt; blocker—blocks histamine H&lt;sub&gt;2&lt;/sub&gt; receptors reversibly, decreases proton secretion by parietal cells</td>
<td>Peptic ulcer disease, gastritis, esophageal reflux, Gynecomastia, impotence, decreased libido in males, confusion, dizziness, and headaches, Crosses placenta, decreases renal excretion of creatinine, CYP&lt;sub&gt;450&lt;/sub&gt; inhibitor</td>
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<tr>
<td>Ciprofloxacin</td>
<td>Antibiotic—quinolone, DNA synthesis inhibitor; inhibits DNA gyrase (topoisomerase II) and toposomerase IV, blocks DNA synthesis, bactericidal</td>
<td>Gram-negative infections (especially UTI and bone): Pseudomonas, Enterobacteriaceae, and Neisseria; gram-positive infections (staphylococci); intracellular: Legionella, GI disturbances, headache, dizziness, phototoxicity, cartilage damage (children, fetus), tendonitis and tendon rupture (adults), myalgias (children), May elevate theophylline to toxic levels, causing seizure; divalent cations inhibit gut absorption; therefore, quinolones cannot be taken with milk, iron-containing preparations, or antacids.</td>
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<thead>
<tr>
<th>Therapeutic Agent (common name, if relevant) [trade name, where appropriate]</th>
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<tr>
<td>Cisapride [Propulsid]</td>
<td>GI stimulant—prokinetic; increases acetylcholine release at myenteric plexus → increases esophageal tone, gastric/duodenal contractility (improves colon transit time)</td>
<td>Constipation</td>
<td>Torsades de pointes</td>
<td>Rarely used; interacts with erythromycin, ketoconazole, nefazodone, and fluconazole to produce torsades de pointes</td>
</tr>
<tr>
<td>Cisplatin [Platinol]</td>
<td>Antineoplastic—cross-links DNA</td>
<td>Cancer</td>
<td>Bone marrow and renal toxicity, cystitis, peripheral neuropathy, ototoxicity; alopecia (severe)</td>
<td></td>
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<tr>
<td>Citalopram</td>
<td>SSRIs—inhibit reuptake of 5-HT at neuronal synapses</td>
<td>Major depression, OCD, anorexia, and bulimia</td>
<td>Inhibits liver enzymes, nausea, agitation, sexual dysfunction (anorgasmia), and dystonic reactions</td>
<td>Contraindicated with MAOIs secondary to serotonin syndrome (hyperthermia, muscle rigidity, and cardiovascular collapse); allows time for antidepressant effect, usually takes 2–3 weeks</td>
</tr>
<tr>
<td>Clarithromycin [Biaxin]</td>
<td>Antibiotic—macrolide, protein synthesis inhibitor; binds to the 23S RNA of the 50S ribosome subunits → blocks translocation → prevents protein synthesis; bacteriostatic</td>
<td>First choice for cell wall–deficient bugs: <em>Mycoplasma, Rickettsia, Chlamydia, and Legionella; Corynebacterium diphtheriae;</em> gram-positive cocci (<em>Streptococcus</em>)</td>
<td>GI discomfort, acute cholestatic hepatitis, and rashes; increases concentration of oral anticoagulants and theophyllines</td>
<td>Can be used in patients with streptococcal infections and penicillin allergies</td>
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<tr>
<td>Clavulanic acid</td>
<td>β-Lactamase inhibitor; synergistic with penicillins</td>
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<tr>
<td>Clindamycin [Cleocin]</td>
<td>Antibiotic—protein synthesis inhibitor; binds to 50S subunits → blocks peptide bond formation; bacteriostatic or bactericidal depending on concentration, site, and organism</td>
<td>Gram-positive bacteria (<em>Streptococcus</em> and <em>Staphylococcus</em>); treats anaerobic infections</td>
<td>Severe diarrhea; potentially fatal pseudomembranous colitis caused by <em>Clostridium difficile</em></td>
<td></td>
</tr>
<tr>
<td>Clofazimine [Lamprene]</td>
<td>Antibiotic—antileprosy; unknown mechanism</td>
<td>Mycobacterium leprae</td>
<td>Turns skin red-brown or black</td>
<td></td>
</tr>
<tr>
<td>Clofibrate [Atromid-S]</td>
<td>Lipid-lowering agent—upregulates lipoprotein lipase (periphery) → increases TG clearance; decreases LDL, increases HDL, and decreases TG</td>
<td>Increased TG, increased LDL</td>
<td>Myositis, increased LFTs; increased risk of GI and liver cancer; potentiates anticoagulant drugs; gallstones; mild GI disturbances</td>
<td></td>
</tr>
<tr>
<td><strong>Clomiphene [Clomid]</strong></td>
<td><strong>Selective estrogen receptor modulator</strong>—binds estrogen receptors in pituitary → prevents normal feedback inhibition, increases LH and FSH release from pituitary → stimulates ovulation</td>
<td><strong>Stimulates ovulation in infertility, PCOS</strong></td>
<td><strong>Hot flashes, ovarian enlargement, multiple gestation pregnancy, and visual disturbances</strong></td>
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<tr>
<td><strong>Clomipramine</strong></td>
<td>TCAs—<strong>inhibit reuptake</strong> of NE and 5-HT at neuronal synapses</td>
<td><strong>Major depression, OCD, and panic disorder</strong></td>
<td><strong>Sedation, α-blocking effects (orthostatic hypotension), anticholinergic (tachycardia, dry mouth, and urinary retention), hallucinations (in elderly), and confusion (in elderly); overdose toxicity results in convulsions, coma, cardiotoxicity (arrhythmias), respiratory depression, and hyperpyrexia</strong></td>
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<tr>
<td><strong>Clonazepam [Klonopin]</strong></td>
<td><strong>Antiepileptic</strong>—benzodiazepine</td>
<td><strong>Epilepsy (absence of seizures)</strong></td>
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<tr>
<td><strong>Clonidine [Catapres]</strong></td>
<td><strong>Antihypertensive</strong>—centrally acting sympathetic agent (α₂-agonist) → decreases sympathetic outflow from CNS → decreases peripheral resistance</td>
<td><strong>Hypertension, smoking withdrawal, heroin and cocaine withdrawal</strong></td>
<td><strong>Drowsiness, dry mouth; rebound hypertension after abrupt withdrawal</strong></td>
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</tr>
<tr>
<td><strong>Clotrimazole [Lotrimin, Mycelex]</strong></td>
<td>Antifungal—<strong>inhibits ergosterol synthesis, preventing cell membrane formation</strong></td>
<td><strong>Topical use against yeasts, dermatophytes, ringworm, fungi, mold, and oral candidiasis in AIDS</strong></td>
<td><strong>Burning, itching, and redness when used topically</strong></td>
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</tr>
<tr>
<td><strong>Clozapine [Clozaril]</strong></td>
<td>Atypical antipsychotic—blocks D₄, α₁, 5-HT, muscarinic receptors</td>
<td><strong>Schizophrenia, useful for positive and negative symptoms</strong></td>
<td><strong>Agranulocytosis, extrapyramidal (occurs at a lower rate than typicals), anticholinergic (dry mouth, constipation), alpha blockade (hypotension), histamine (sedation); toxicity results in neuroleptic malignant syndrome (occurs at a lower rate than typicals)</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Cocaine</strong></td>
<td><strong>CNS stimulant</strong>—blocks NE, 5-HT, and dopamine reuptake</td>
<td><strong>Local anesthetic</strong></td>
<td><strong>Vasoconstriction, hypertension, nasal mucus ischemia</strong></td>
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<tr>
<td><strong>Codeine</strong></td>
<td><strong>Opioid agonist</strong></td>
<td><strong>Pain, antitussive</strong></td>
<td><strong>Constipation</strong></td>
<td></td>
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<tr>
<td><strong>Colchicine</strong></td>
<td>Anti-inflammatory—<strong>interrupts microtubule formation</strong>, thereby interfering with normal mitosis and inhibiting WBC migration and phagocytosis</td>
<td><strong>Acute gout therapy</strong></td>
<td><strong>Diarrhea (common)</strong></td>
<td></td>
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</tbody>
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<th>Therapeutic Agent (common name, if relevant) [trade name, where appropriate]</th>
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<tr>
<td>Colestipol [Colestid]</td>
<td>Lipid-lowering agent—bile acid resin, impedes fat absorption; lowers LDL, binds cholesterol metabolites</td>
<td>Reduction of cholesterol</td>
<td>Steatorrhea, constipation, impaired absorption of drugs and vitamins</td>
<td></td>
</tr>
<tr>
<td>Corticotropin-releasing hormone [CRH]</td>
<td>Increases ACTH production by anterior pituitary</td>
<td>Used in diagnosis of Cushing syndrome</td>
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</tr>
<tr>
<td>Cortisol (hydrocortisone) [Hydrocortone, Nutracort]</td>
<td>Glucocorticoid—induces new protein synthesis; increases gluconeogenesis and lipolysis; reduces peripheral glucose use; catabolic effect on muscle, bone, skin, fat, and lymph tissue; anti-inflammatory; immunosuppressant</td>
<td>Adrenal insufficiency, congenital adrenal hyperplasia, diagnosis of pituitary—adrenal disorder, reduces inflammation (especially chronic), leukemia, decreases hypercalcemia</td>
<td>Iatrogenic Cushing syndrome, redistribution of fat, acne, insomnia, weight gain, hypokalemia, decrease in skeletal muscle, osteoporosis, hyperglycemia, ulcers, psychosis, cataracts, increased susceptibility to infections, growth suppression in children</td>
<td></td>
</tr>
<tr>
<td>Cosyntropin [Cortrosyn]</td>
<td>ACTH analog—increases production of steroids by adrenal</td>
<td>Used in diagnosis of adenocortical insufficiency</td>
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<tr>
<td>Cromolyn [Nasalcrom, Gastrocrom]</td>
<td>Antiasthmatic—prevents release of mediators from mast cells → prevents bronchoconstriction and inflammation</td>
<td>Asthma prophylaxis</td>
<td>Laryngeal edema (rare) Not used during acute exacerbation</td>
<td></td>
</tr>
<tr>
<td>Cyanocobalamin [Anacobin]</td>
<td>Supplies vitamin B₁₂</td>
<td>B₁₂ deficiency</td>
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</tr>
<tr>
<td>Cyclobenzaprine [Flexeril]</td>
<td>Centrally acting muscle relaxant</td>
<td>Muscle spasms, tetanus contractions, orthopedic manipulation</td>
<td>Antimuscarinic effects</td>
<td></td>
</tr>
<tr>
<td>Cyclophosphamide [Cytoxan]</td>
<td>Immunosuppressant—alkylating agent; destroys proliferating lymphoid cells; alkylates resting cells</td>
<td>Transplant rejection, rheumatic arthritis</td>
<td>GI and bone marrow toxicity, hemorrhagic cystitis Coadministration of mesna will prevent hemorrhagic cystitis</td>
<td></td>
</tr>
<tr>
<td>Cycloserine [Seromycin]</td>
<td>Antibiotic—analog of o-alanine; interferes with cell wall synthesis</td>
<td>Mycobacterium</td>
<td>Psychotic reactions</td>
<td></td>
</tr>
<tr>
<td>Cyclosporine [Sandimmune]</td>
<td>Immunosuppressant—inhibits T-helper cell activity; inhibits IL-2, IL-3, and IFN-γ formation by T-helper cells</td>
<td>Transplant rejection</td>
<td>Nephrototoxic, hepatotoxic; hypertension; increased incidence of viral infection and lymphoma</td>
<td></td>
</tr>
<tr>
<td>Cyproheptadine [Periactin]</td>
<td>Antihistamine—antipruritic; 5-HT₂ agonist; histamine blocker</td>
<td>Decreases diarrhea in carcinoid tumors, decreases dumping syndrome</td>
<td>Weight gain</td>
<td></td>
</tr>
<tr>
<td>Drug Name</td>
<td>ATC Code</td>
<td>Pharmacological Action</td>
<td>Indications</td>
<td>Adverse Effects</td>
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<tr>
<td>Cytosine arabinoside</td>
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<td>Antineoplastic—inhibits DNA replication and RNA polymerization; competitive inhibitor of dCTP; inhibits chain elongation</td>
<td>Cancer, AML</td>
<td>Severe myelosuppression, stomatitis, alopecia</td>
</tr>
<tr>
<td>Dacarbazine (DTIC-Dome)</td>
<td></td>
<td>Antineoplastic—DNA alkylation; strand breakage; inhibits nucleic acid and protein synthesis</td>
<td>Cancer</td>
<td></td>
</tr>
<tr>
<td>Dactinomycin (Cosmegen)</td>
<td></td>
<td>Antineoplastic—intercalates into DNA</td>
<td>Cancer</td>
<td>Skin eruptions, hyperkeratosis</td>
</tr>
<tr>
<td>Danazol (Danocrine)</td>
<td></td>
<td>Testosterone derivative—weak agonist for androgen, progesterone, and glucocorticoid receptors</td>
<td>Endometriosis and fibrocystic disease</td>
<td>Masculinization in women, gynecomastia in men</td>
</tr>
<tr>
<td>Dantrolene (Dantrium)</td>
<td></td>
<td>Non–centrally acting muscle relaxant—decreases Ca$^{2+}$/H$^{1+}$ from sarcoplasmic reticulum</td>
<td>Malignant hyperthermia</td>
<td>Hepatotoxic</td>
</tr>
<tr>
<td>Dapsone (Dapsone)</td>
<td></td>
<td>Antibiotic—related to sulfonamides</td>
<td>Mycobacterium leprae</td>
<td>GI disturbances, hemolysis, methemoglobinemia</td>
</tr>
<tr>
<td>Daunorubicin (DaunoXome, Cerubidine)</td>
<td></td>
<td>Antineoplastic—oxidizes free radicals; intercalates into DNA; breaks DNA; affects plasma membrane</td>
<td>Cancer</td>
<td>Cardiac changes resulting in cumulative cardiotoxicity</td>
</tr>
<tr>
<td>Deferoxamine (Desferal)</td>
<td></td>
<td>Metal chelator</td>
<td>Acute toxicity of iron</td>
<td>Hypotensive shock; neurotoxic if long-term use</td>
</tr>
<tr>
<td>Delavirdine</td>
<td></td>
<td>Antiviral, nonnucleoside reverse transcriptase inhibitor—binds viral reverse transcriptase and inhibits movement of protein domains → terminates viral DNA synthesis → prevents integration of viral genome into host DNA</td>
<td>AIDS (used in HAART)</td>
<td>Neutropenia, anemia, peripheral neuropathy, and rash</td>
</tr>
<tr>
<td>Desipramine (Norpramin)</td>
<td></td>
<td>TCAs—inhibit reuptake of NE and 5-HT at neuronal synapses</td>
<td>Major depression, panic disorder, and anxiety</td>
<td>Sedation, α-blocking effects (orthostatic hypotension), anticholinergic (tachycardia, dry mouth, and urinary retention), hallucinations (in elderly), and confusion (in elderly); overdose toxicity results in convulsions, coma, cardiotoxicity (arrhythmias), respiratory depression, and hyperpyrexia</td>
</tr>
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Desipramine is the least sedating of the TCA
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<tr>
<td>Desmopressin [DDAVP]</td>
<td>Antidiuretic—synthetic analog of antidiuretic hormone, recruits water channels to luminal membrane in collecting duct</td>
<td>Antidiuresis, central (pituitary) diabetes insipidus</td>
<td>Overhydration; allergic reaction; larger doses result in pallor, diarrhea, and hypertension; coronary constriction; chronic rhinopharyngitis</td>
<td>Synthetic analog to vasopressin, intranasal administration</td>
</tr>
<tr>
<td>Desogestrel</td>
<td>Progestosterone—binds progesterone receptors</td>
<td>Endometrial cancer, amenorrhea, abnormal uterine bleeding, and prevention of pregnancy</td>
<td>Hypoglycemia (diaphoresis, vertigo, tachycardia), insulin allergy, insulin antibodies, lipodystrophy</td>
<td>Also used to prevent endometrial hyperplasia in postmenopausal women taking estrogen</td>
</tr>
<tr>
<td>Detemir [Levemir]</td>
<td>Long-acting insulin—see mechanism for regular insulin</td>
<td>Diabetes mellitus (typically type 1)</td>
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<tr>
<td>Dexamethasone [Decadron, Maxidex]</td>
<td>Corticosteroid—reduces lymph node and spleen size; inhibits cell cycle activity of lymphoid cells; lyses T cells; suppresses antibody, prostaglandin, and leukotriene synthesis; blocks monocyte production of IL-1</td>
<td>Antiemetic, autoimmune disorders, allergic reactions, asthma, organ transplantation (especially during rejection crisis), test for etiology of hypercortisolism</td>
<td>Insomnia, epigastric disturbances, cushingoid reaction, psychosis, glucose intolerance, infection, hypertension, cataracts</td>
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<tr>
<td>DHEA</td>
<td>Androgen and estrogen precursor</td>
<td>Acne, hair loss, hirsutism, deepening of voice</td>
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<tr>
<td>Diazepam [Valium]</td>
<td>Antianxiety, benzodiazepine—enhances GABA; increases IPSP amplitude</td>
<td>Sedative, hypnotic, antianxiety, antiepileptic (status epilepticus, grand mal)</td>
<td>Sedation</td>
<td></td>
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<tr>
<td>Diazepam-binding inhibitor (DBI)</td>
<td>Benzodiazepine receptor antagonist</td>
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<tr>
<td>Diclofenac [Cataflam, Voltaren]</td>
<td>K⁺ channel opener—hyperpolarizes and relaxes vascular smooth muscle</td>
<td>Hypertension</td>
<td>Hypoglycemia (reduces insulin release), hypotension</td>
<td></td>
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<tr>
<td>Dicloxacillin [Dynapen, Pathocil]</td>
<td>Antibiotic—β-lactam, penicillin derivative, cell wall inhibitor; same mechanism as penicillin; distinguished by activity against penicillinase-producing Staphylococcus; bactericidal</td>
<td>Staphylococcal infections (except MRSA)</td>
<td>Hypersensitivity reactions, interstitial nephritis (methicillin)</td>
<td>Penicillinase resistant; MRSA is resistant to methicillin because of altered penicillin-binding protein target site</td>
</tr>
<tr>
<td>Dicyclomine [Bentyl]</td>
<td>Antimuscarinic</td>
<td>Bladder/GI spasm, decreases acid in ulcer</td>
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<tr>
<td>Drug Name</td>
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<td>Side Effects</td>
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<tr>
<td>Didanosine (ddl) [Videx]</td>
<td>Nucleoside reverse transcriptase inhibitor—guanosine analog</td>
<td>Inhibits viral reverse transcriptase → prevents integration of DNA copy of viral genome into host DNA</td>
<td>AIDS (used in HAART)</td>
<td>Neutropenia, anemia, peripheral neuropathy, pancreatitis, and lactic acidosis</td>
</tr>
<tr>
<td>Diethycarbamazine [Hetrazan]</td>
<td>Anthelmintic—sensitizes helminths</td>
<td>Filariasis to phagocytosis by macrophages</td>
<td></td>
<td>Headache, malaise, joint pain, anorexia; death of filaria causes swelling and edema of skin, enlarged lymph nodes, hyperpyrexia, and tachycardia</td>
</tr>
<tr>
<td>Digitoxin [Crystodigin]</td>
<td>Inotropic agent—cardiac glycoside; increases cardiac contractility</td>
<td>Severe left ventricular systolic dysfunction, antiarhythmic</td>
<td>Progressive dysrhythmia, anorexia, nausea, vomiting, headache, fatigue, confusion, blurred vision, altered color perception, halos around dark objects</td>
<td></td>
</tr>
<tr>
<td>Diphenhydramine [Benadryl]</td>
<td>Antihistamine—antiemetic; muscarinic blocker; H₁ blocker (first generation)</td>
<td>Allergic reactions, asthma, motion sickness, anxiolytic, insomnia</td>
<td>Sedation, CNS depression, atropine-like effects, allergic dermatitis, blood dyscrasias, teratogenicity, acute antihistamine poisoning</td>
<td>Rarely used as antiparkinsonian agent</td>
</tr>
<tr>
<td>Therapeutic Agent (common name, if relevant) [trade name, where appropriate]</td>
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<tr>
<td>Disopyramide [Norpace]</td>
<td>Antiarrhythmic (class IA)—Na⁺ channel blocker</td>
<td>Wolff–Parkinson–White syndrome</td>
<td>Heart failure</td>
<td>Contraindicated in patients with sick sinus syndrome</td>
</tr>
<tr>
<td>Disulfiram [Antabuse]</td>
<td>Antialcoholic agent—inhibits aldehyde dehydrogenase</td>
<td>Alcoholism</td>
<td>Tachycardia, hyperventilation, nausea</td>
<td></td>
</tr>
<tr>
<td>Dobutamine [Dobutrex]</td>
<td>Inotropic agent—β-agonist; positive inotropic effects on the heart and vasodilation</td>
<td>Acute heart failure; increases cardiac output</td>
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<tr>
<td>Docusate</td>
<td>Stool softener; by emulsifying stool, makes passage of stool easier</td>
<td>Constipation</td>
<td>Rash</td>
<td></td>
</tr>
<tr>
<td>Doxazosin [Cardura]</td>
<td>Antihypertensive—α₁-blocker</td>
<td>Hypertension, BPH</td>
<td>Orthostatic hypotension, dizziness, and headache</td>
<td>First-dose orthostatic hypotension</td>
</tr>
<tr>
<td>Doxepin [Sinequan]</td>
<td>TCAs— inhibit reuptake of NE and 5-HT at neuronal synapses</td>
<td>Major depression, panic disorder, and potent antihistamine</td>
<td>Sedation, β-blocking effects (orthostatic hypotension), anti-cholinergic (tachycardia, dry mouth, and urinary retention), hallucinations (in elderly), and confusion (in elderly); overdose toxicity results in convulsions, coma, cardiotoxicity (arrhythmias), respiratory depression, and hyperpyrexia</td>
<td></td>
</tr>
<tr>
<td>Doxorubicin [Adriamycin]</td>
<td>Antineoplastic—oxidizes free radicals; intercalates into DNA; breaks DNA; affects plasma membrane</td>
<td>Cancer</td>
<td>Cardiac changes resulting in cumulative cardiotoxicity</td>
<td></td>
</tr>
<tr>
<td>Doxycycline</td>
<td>Tetracycline antibiotic—protein synthesis inhibitor; binds 30S ribosome subunits → prevents attachment of tRNA; bacteriostatic</td>
<td>Broad spectrum including atypical pathogens: Chlamydia, Rickettsia, Mycoplasma pneumoniae, Vibrio cholerae, Ureaplasma urealyticum, Francisella tularensis, Helicobacter pylori, and Borrelia burgdorferi (Lyme disease)</td>
<td>Liver toxicity, GI distress, depression of bone/teeth development (less than with tetracycline), photosensitivity (less than with tetracycline), Fanconi syndrome</td>
<td>Contraindicated in pregnancy and children; divalent cations inhibit gut absorption, therefore cannot take with milk, antacids, or iron-containing preparations; fecally eliminated</td>
</tr>
<tr>
<td>Dronabinol [Marinol]</td>
<td>Antiemetic—unknown mechanism; binds cannabinoid receptors and inhibits vomiting center in medulla</td>
<td>Antiemetic, appetite stimulant in patients with AIDS</td>
<td>Dry mouth, dizziness, inability to concentrate, disorientation, anxiety, tachycardia, depression, paranoia, psychosis</td>
<td>THC derivative</td>
</tr>
<tr>
<td>Echothiophate [Phospholine Iodide]</td>
<td>Antiglaucoma—inhibits cholinesterase; nicotinic receptor stimulator; irreversible</td>
<td>Closed-angle glaucoma</td>
<td>Open-angle glaucoma</td>
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<tr>
<td>Drug</td>
<td>Category</td>
<td>Effect</td>
<td>Side Effects</td>
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<tr>
<td>Edetate calcium disodium (calcium EDTA)</td>
<td>Metal chelator</td>
<td>Lead toxicity</td>
<td>Nephrotoxic</td>
<td></td>
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<tr>
<td>Edrophonium [Enlon, Tension]</td>
<td>Cholinesterase inhibitor</td>
<td>Diagnosis of myasthenia gravis, emergency anesthetic</td>
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<tr>
<td>Efavirenz</td>
<td>Antiviral, nonnucleoside reverse transcriptase inhibitor—binds viral reverse transcriptase and inhibits movement of protein domains → terminates viral DNA synthesis → prevents integration of viral genome into host DNA</td>
<td>AIDS (used in HAART)</td>
<td>Depression, dizziness, vivid dreams; teratogenic</td>
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<tr>
<td>Emetine</td>
<td>Antiprotozoal—causes degeneration of nucleus and reticulation of cytoplasm; directly lethal</td>
<td>Severe amebic infection</td>
<td>Diarrhea, nausea, vomiting, abdominal pain; cardiac effects: hypotension, precordial pain, ECG changes</td>
<td></td>
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<tr>
<td>Emtricitabine (FTC)</td>
<td>Antiviral, nucleoside reverse transcriptase inhibitor—cytidine analog → inhibits viral reverse transcriptase → prevents integration of DNA copy of the viral genome into the host DNA</td>
<td>AIDS (used in HAART)</td>
<td>Neutropenia, anemia, peripheral neuropathy, pancreatitis, and lactic acidosis</td>
<td></td>
</tr>
<tr>
<td>Enalapril [Vasotec]</td>
<td>Antihypertensive—ACE inhibitor → inhibits conversion of angiotensin I to II → decreases Ang II levels → prevents vasoconstriction from Ang II</td>
<td>Hypertension, CHF, post-MI; prevention/treatment of diabetic nephropathy</td>
<td>Cough, angioedema, hyperkalemia, renal insufficiency (especially in bilateral renal artery stenosis)</td>
<td></td>
</tr>
<tr>
<td>Encaainide</td>
<td>Antiarrhythmia (class IC)—Na⁺ channel blocker</td>
<td>Wolff–Parkinson–White syndrome</td>
<td>No antimuscarinic action; no effect on action potential</td>
<td></td>
</tr>
<tr>
<td>Enflurane [Ethrane]</td>
<td>Anesthetic agent</td>
<td>General anesthetic</td>
<td>Abnormal ECG or seizures</td>
<td></td>
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<tr>
<td>Enfuuvirtide</td>
<td>Antiviral, fusion inhibitor—binds viral gp41 subunit → inhibits conformation change (required for fusion with CD4 cell) → blocks viral entry and replication</td>
<td>AIDS (used in patients on antiretroviral therapy with persistent viral replication)</td>
<td>Hypersensitivity reactions, reaction at injection site, and bacterial pneumonia</td>
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</tbody>
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(continued)
<table>
<thead>
<tr>
<th>Therapeutic Agent (common name, if relevant) [trade name, where appropriate]</th>
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</thead>
<tbody>
<tr>
<td><strong>Enoxaparin</strong> [Lovenox]</td>
<td>Low-molecular-weight heparin; enhances inhibition of factor Xa and thrombin by increasing antithrombin activity (preferentially increases the inhibition of factor Xa)</td>
<td>Prophylaxis of thrombosis</td>
<td>Elevated AST/ALT (reversible), heparin-associated thrombocytopenia</td>
<td>Caution in recent surgery or active bleeding ulcers or internal hemorrhages; fewer bleeding complications, more bioavailable, and longer half-life than unfractionated heparin; no requirement for monitoring</td>
</tr>
<tr>
<td>Ephedrine</td>
<td>Bronchodilation—mixed adrenergic agonist</td>
<td>Stimulates NE release, antitussive, myasthenia gravis</td>
<td>Increases BP</td>
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<tr>
<td>Epinephrine</td>
<td>Adrenergic agonist</td>
<td>Acute asthma, anaphylactic shock</td>
<td></td>
<td>Activates both α- and β-receptors, but is preferential for β</td>
</tr>
<tr>
<td><strong>Eplerenone</strong></td>
<td>Potassium-sparing diuretic—binds to intracellular aldosterone steroid receptors in collecting tubules; blocks induction of Na+/ channels and Na+/ATPase synthesis; loss of Na+, Cl− in urine</td>
<td>Hyperaldosteronism, potassium depletion, and CHF</td>
<td>Hyperkalemic metabolic acidosis, gynecomastia (spironolactone), and antiandrogen effects</td>
<td>Like spironolactone but more selective for mineralocorticoid receptors; results in decreased secretion of K+ and H+, which can lead to hyperkalemic metabolic acidosis; often given in combination with a thiazide</td>
</tr>
<tr>
<td><strong>Epoetin alfa</strong> [Procrit, Epogen]</td>
<td>Colony-stimulating factor—erythropoietin produced via recombinant DNA technology</td>
<td>Anemia (especially in renal failure), AIDS</td>
<td>Hypertension</td>
<td></td>
</tr>
<tr>
<td><strong>Epoprostenol</strong> [Flolan]</td>
<td>Prostacyclin—increases cardiac index and stroke volume; decreases pulmonary vascular resistance and mean systemic pressure</td>
<td>Pulmonary hypertension</td>
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<tr>
<td><strong>Ergotamine</strong> [Ergomar]</td>
<td>Antimigraine—vasoconstriction</td>
<td>Acute attack of migraine</td>
<td>Gangrene as a result of vasoconstriction</td>
<td>Contraindicated in pregnant patients or patients with cardiovascular disease or coronary artery disease</td>
</tr>
<tr>
<td><strong>Erythromycin</strong></td>
<td>Antibiotic—macrolide, protein synthesis inhibitor; binds to the 23S RNA of the 50S ribosome subunits → blocks translocation → prevents protein synthesis; bacteriostatic</td>
<td>First choice for cell wall–deficient bugs: <em>Mycoplasma, Rickettsia, Chlamydia, and Legionella; Corynebacterium diphtheriae</em>; gram-positive cocci (<em>Streptococcus</em>)</td>
<td>GI discomfort, acute cholestatic hepatitis, and rashes; increases concentration of oral anticoagulants and theophyllines</td>
<td>Can be used in patients with streptococcal infections and penicillin allergies</td>
</tr>
<tr>
<td><strong>Esmolol</strong> [Brevibloc]</td>
<td>Antiarrhythmic (class II)—β₁-selective blocker</td>
<td>Blocks the effect of catecholamines on heart, decreases the activity of nodal tissue, slows sinus rate, depresses AV conduction</td>
<td>Asthma, negative inotropic agent</td>
<td>Short duration</td>
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<tr>
<td><strong>Estrogen</strong> [Estratab, Premarin]</td>
<td>Growth and development of female organs; linear bone growth; epiphyseal closure; endometrial growth; maintains responsiveness of breasts, uterus, and vagina; inhibits bone resorption; increases hepatic production of α₂-globulins, coagulation factors II, VII, IX, and X, and HDL; decreases antithrombin and cholesterol</td>
<td>Osteoporosis; contraception; can be used in combination with progesterone</td>
<td>Small increased incidence of breast and endometrial cancers; blood clots; may lead to sodium and water retention; nausea; breast tenderness; hyperpigmentation; increased risk of bleeding, gallbladder disease, migraines, hypertension</td>
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<tr>
<td><strong>Etanercept</strong></td>
<td>Recombinant form of human TNF receptor → binds TNF → decreases inflammatory response</td>
<td>Rheumatoid arthritis, psoriasis, and ankylosing spondylitis</td>
<td>Infections</td>
<td></td>
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<tr>
<td><strong>Ethacrynic acid</strong> [Edecrin]</td>
<td>Phenoxyacetic acid derivative diuretic—prevents cotransport of Na⁺, K⁺, and Cl⁻ in thick ascending limb; loss of Na⁺, Cl⁻, Ca²⁺, and K⁺ in urine</td>
<td>Diuresis in patients with sulfa drug allergy</td>
<td>Ototoxicity, hypokalemic metabolic alkalosis, and dehydration</td>
<td>Can be given to patients with sulfa drug allergy, hyperuricemia, and acute gout</td>
</tr>
<tr>
<td><strong>Ethambutol</strong> [Myambutol]</td>
<td>Antibiotic—unknown mechanism</td>
<td>Mycobacterium</td>
<td>Optic neuropathy (red-green color blindness), tolerance develops</td>
<td></td>
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<tr>
<td><strong>Ether</strong></td>
<td>Anesthetic agent</td>
<td>General anesthetic</td>
<td>Fire/explosion</td>
<td>No longer used</td>
</tr>
<tr>
<td><strong>Ethinyl estradiol</strong></td>
<td>Estrogen—binds estrogen receptor</td>
<td>In women: hypogonadism, ovarian failure, contraception, and menstrual abnormalities; in men: androgen-dependent prostate cancer</td>
<td>Endometrial cancer, bleeding, and thrombosis</td>
<td>Used in combination with progestin in patients with intact uterus; increased risk of endometrial cancer with unopposed estrogen therapy; females exposed to diethylstilbestrol in utero have an increased risk of vaginal clear cell adenocarcinoma</td>
</tr>
<tr>
<td><strong>Ethosuximide</strong></td>
<td>Antiepileptic—decreases Ca²⁺ conduction</td>
<td>Epilepsy (absence seizures)</td>
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<tr>
<td><strong>Etidocaine</strong> [Duranest]</td>
<td>Anesthetic agent—blocks Na⁺ intracellularly</td>
<td>Local anesthetic</td>
<td>Sleepiness, light-headedness, visual/audio disturbances, restlessness, nystagmus, shivering, tonic-clonic convulsions, death, greater toxicity than other local anesthetics</td>
<td></td>
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<tr>
<td>Etidronate [Didronel]</td>
<td>Bone stabilizer—pyrophosphate analog; reduces hydroxyapatite crystal formation, growth, and dissolution, which reduces bone turnover</td>
<td>Hypercalcemia of malignancy, Paget disease, osteoporosis, hyperparathyroidism</td>
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<tr>
<td>Etomidate [Amidate]</td>
<td>Anesthetic agent</td>
<td>Induces stage 3 anesthesia</td>
<td>Painful injection, myoclonic movements</td>
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<tr>
<td>Etoposide</td>
<td>Antineoplastic—G2 phase specific—inhibits topoisomerase II → increases DNA degradation</td>
<td>Small cell lung cancer, prostate and testicular carcinoma</td>
<td>Myelosuppression, nausea, vomiting, alopecia</td>
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<tr>
<td>Etretinate</td>
<td>Vitamin A analog</td>
<td>Severe acne, psoriasis</td>
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<tr>
<td>Exenatide [Byetta]</td>
<td>Hypoglycemic agent, incretin mimetic—agonizes GLP-1 receptors → decreases glucagon, increases insulin, delays gastric emptying</td>
<td>Injectable treatment for type 2 diabetes</td>
<td>Mild weight loss, nausea, hypoglycemia, constipation, slight risk of pancreatitis</td>
<td>Derived from exendin, a hormone found in Gila monster saliva</td>
</tr>
<tr>
<td>Ezetimibe [Zetia]</td>
<td>Antihyperlipidemia; cholesterol absorption blocker—prevents cholesterol reabsorption at brush border in small intestine; decreases LDL; no effect on HDL or TG</td>
<td>Increased LDL, hypertriglyceridemia, cardiac event risk reduction</td>
<td>Increases LFT (rarely); myopathy, hepatotoxicity, pancreatitis; abdominal symptoms</td>
<td>No proven clinical benefit; may increase plaque thickness</td>
</tr>
<tr>
<td>Famotidine [Pepcid]</td>
<td>H₂ blocker—reversibly blocks histamine H₂ receptors → reduces gastric acid secretion</td>
<td>Peptic ulcer disease, gastritis, and esophageal reflux</td>
<td>Gynecomastia, rare: confusion, dizziness, and headaches</td>
<td>Crosses placenta; milder side effect profile than cimetidine and ranitidine</td>
</tr>
<tr>
<td>Felodipine [Plendil]</td>
<td>Dihydropyridine Ca²⁺ channel blocker—block voltage-gated Ca²⁺ channels of vascular smooth muscle</td>
<td>Hypertension, angina pectoris, Prinzmetal angina, Raynaud phenomenon</td>
<td>Peripheral edema, flushing, dizziness, and constipation</td>
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<tr>
<td>Fenofibrate</td>
<td>Lipid-lowering agent—upregulates lipoprotein lipase (periphery) → increases TG clearance; decreases LDL, increases HDL, and decreases TG</td>
<td>Increased TG, increased LDL</td>
<td>Myositis, increased LFTs</td>
<td>Reduces TG more than other agents</td>
</tr>
<tr>
<td>Fentanyl</td>
<td>Opioid agonist</td>
<td>Pain, general anesthetic</td>
<td>Prolonged recovery, nausea</td>
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<tr>
<td>Fexofenadine hydrochloride [Allegra]</td>
<td>Antihistamine</td>
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<tr>
<td>Drug</td>
<td>Class/Actions</td>
<td>Side effects</td>
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<tr>
<td>Filgrastim [Neupogen]</td>
<td>Granulocyte-macrophage colony-stimulating factor</td>
<td>Recovery of bone marrow (e.g., chemotherapy-induced neutropenia)</td>
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<tr>
<td>Finasteride [Proscar]</td>
<td>Antiandrogen—5α-reductase inhibitor — decreases the conversion of testosterone to dihydrotestosterone</td>
<td>BPH, male pattern baldness</td>
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<td>Decreased libido, decreased ejaculate volume</td>
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<tr>
<td>Flecainide [Tambocor]</td>
<td>Antiarrhythmic (class IC)—Na⁺ channel blocker</td>
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<tr>
<td>Fluconazole [Diflucan]</td>
<td>Antifungal—inhibits ergosterol synthesis, preventing cell membrane formation</td>
<td>Cryptococcal meningitis, mucosal candidiasis, coccidioidomycosis</td>
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<td>Abdominal pain, nausea, hepatotoxicity</td>
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<tr>
<td>Flucytosine [Ancobon]</td>
<td>Antifungal—competitive inhibitor of thymidylate synthetase; impairs DNA synthesis</td>
<td>Candida, Cryptococcus</td>
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<td>Nausea, vomiting, diarrhea, rash, bone marrow and liver toxicity, enterocolitis</td>
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<td>Imported in the fungus via permease</td>
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<td>Fludrocortisone [Florinef]</td>
<td>Mineralocorticoid—aldosterone analog</td>
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<tr>
<td>Flumazenil [Romazicon]</td>
<td>Benzodiazepine receptor antagonist</td>
<td>Alcohol abuse, anxiety</td>
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<tr>
<td>Flunarizine [Sibelium]</td>
<td>Weak Ca²⁺ channel blocker</td>
<td>Prophylaxis for migraine</td>
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<tr>
<td>Fluoride</td>
<td>Stabilizes hydroxyapatite crystal structure; stimulates new growth of bone (unknown mechanism)</td>
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<td>Nausea, vomiting, neurológic symptoms, arthralgias, arthritis</td>
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<td>Stains teeth in toxic amounts</td>
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<tr>
<td>5-Fluorouracil (5-FU)</td>
<td>Antineoplastic—inhibits thymidylate synthetase; inhibits RNA synthesis</td>
<td>Colon and breast cancer</td>
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<td></td>
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<td>Delayed toxicity: nausea, oral and GI ulcers, and bone marrow depression</td>
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<tr>
<td>Fluoxetine [Prozac]</td>
<td>SSRIs—inhibit reuptake of 5-HT at neuronal synapses</td>
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<td>Major depression, OCD, anorexia, bulimia, anxiety</td>
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<td>Inhibits liver enzymes, nausea, agitation, sexual dysfunction (anorgasmia), and dystonic reactions</td>
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<td>Contraindicated with MAOIs secondary to serotonin syndrome (hyperthermia, muscle rigidity, and cardiovascular collapse); allows time for antidepressant effect, usually takes 2–3 weeks</td>
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<tr>
<td>Fluphenazine [Prolixin]</td>
<td>Antipsychotic—phenothiazine; blocks D₂, α₁, and H₁ receptors</td>
<td>Psychosis</td>
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<td>Extrapyramidal (dystonia, akinesia, akathisia, and tardive dyskinesia),</td>
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<td>anticholinergic (dry mouth, constipation), alpha blockade (hypotension), and histamine (sedation); toxicity results in neuroleptic malignant syndrome (rigidity, myoglobinuria, autonomic instability, and hyperpyrexia)</td>
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<td>Extrapyramidal side effects are more common</td>
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<tr>
<td>Flurazepam [Dalmane]</td>
<td>Benzodiazepine—enhances GABA; increases IPSP amplitude</td>
<td>Sedative, hypnotic, antianxiety, antiepileptic</td>
<td></td>
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<tr>
<td>Flutamide [Eulexin]</td>
<td>Antiandrogen—nonsteroidal, competitive androgen receptor blocker</td>
<td>Metastatic prostate cancer</td>
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<tr>
<td>Fluticasone [Flonase]</td>
<td>Intranasal glucocorticoids—decrease cytokine synthesis, downregulate inflammatory response in the nasal mucosa</td>
<td>Nasal congestion, allergic rhinitis</td>
<td>Local irritation of nasal mucosa, epistaxis</td>
<td></td>
</tr>
<tr>
<td>Fluvastatin [Lescol]</td>
<td>Lipid-lowering agent—inhibits HMG-CoA reductase; lowers LDL</td>
<td>Hyperlipidemia (especially type II)</td>
<td>Liver toxicity, myopathy, mild GI disturbances</td>
<td>Contraindicated in pregnant or lactating women and children</td>
</tr>
<tr>
<td>Folic acid [Folvite]</td>
<td>Vitamin—one carbon carrier; nucleic acid synthesis</td>
<td>Given to pregnant women to prevent neural tube defects in utero</td>
<td>Hypocalcemia; CNS, cardiac, and renal toxicity; anemia</td>
<td>Decreased in pregnancy or with the use of phenytoin and isoniazid</td>
</tr>
<tr>
<td>Foscarnet [Foscavir]</td>
<td>Antiviral—nonnucleoside inhibitor of DNA polymerase</td>
<td>CMV retinitis (resistant to ganciclovir), HSV (resistant to acyclovir)</td>
<td>Cough, angioedema, hyperkalemia, renal insufficiency (especially in bilateral renal artery stenosis)</td>
<td>Does not require activation by viral kinase</td>
</tr>
<tr>
<td>Fosinopril [Monopril]</td>
<td>Antihypertensive—ACE inhibitor → inhibits conversion of angiotensin I to II → decreases Ang II levels → prevents vasoconstriction from Ang II</td>
<td>Hypertension, CHF, post-MI; prevention/treatment of diabetic nephropathy</td>
<td>Cough, angioedema, hyperkalemia, renal insufficiency (especially in bilateral renal artery stenosis)</td>
<td>Contraindicated in pregnancy (fetal renal malformation)</td>
</tr>
<tr>
<td>Furosemide [Lasix]</td>
<td>Loop diuretic—prevents cotransport of Na⁺, K⁺, and Cl⁻ in thick ascending limb; loss of Na⁺, Cl⁻, Ca²⁺, and K⁺ in urine</td>
<td>Hypertension, CHF, cirrhosis, nephrotic syndrome, pulmonary edema, hypercalcemia</td>
<td>Potassium wasting, metabolic alkalosis, hypotension, dehydration, ototoxicity, nephritis, and gout</td>
<td>Do not give in patients with sulfa drug allergy; rapid onset and short duration of action, which is ideal for relieving acute edema</td>
</tr>
<tr>
<td>Gabapentin [Neurontin]</td>
<td>Antiepileptic—blocks Na⁺ channels</td>
<td>Add-on drug for epilepsy</td>
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<td></td>
</tr>
<tr>
<td>Ganciclovir [Cytovene]</td>
<td>Antiviral—guanosine analog, inhibits viral DNA polymerase</td>
<td>CMV (especially CMV retinitis in AIDS)</td>
<td>Bone marrow suppression (leukopenia, neutropenia, and thrombocytopenia), renal impairment, seizures</td>
<td>Resistance from lack of thymidine kinase or mutation of viral DNA polymerase; more toxic than acyclovir</td>
</tr>
<tr>
<td>Gemfibrozil</td>
<td>Lipid-lowering agent—upregulates lipoprotein lipase (periphery) → increases TG clearance; decreases LDL, increases HDL, and decreases TG</td>
<td>Increased TG, increased LDL</td>
<td>Myopathy, increased LFTs; potentiates anticoagulant drugs; gallstones; mild GI disturbances</td>
<td>Reduces TG more than other agents; contraindicated in patients with impaired renal or hepatic function and pregnant or lactating women</td>
</tr>
<tr>
<td><strong>Gentamicin</strong> [Garamycin]</td>
<td><strong>Antibiotic</strong>—<strong>aminoglycoside</strong>, protein synthesis inhibitor; irreversibly binds 30S ribosome subunits; <strong>bacteriostatic</strong> at low concentration; <strong>bactericidal</strong> at high concentration</td>
<td><strong>Broad spectrum</strong>: gram-negative rods; good for <strong>bone</strong> and <strong>eye</strong> infections; <strong>Proteus</strong>, <strong>Pseudomonas</strong>, <strong>Enterobacter</strong>, <strong>Klebsiella</strong>, and <strong>Escherichia coli</strong></td>
<td><strong>Otoxicity</strong>, <strong>renal toxicity</strong>, <strong>neuromuscular blockade</strong>, nausea, vomiting, vertigo, allergic rash</td>
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<tr>
<td><strong>Gestodene</strong></td>
<td><strong>Progestosterone</strong>—binds progesterone receptors</td>
<td><strong>Endometrial cancer</strong>, amenorrhea, abnormal uterine bleeding, and prevention of pregnancy</td>
<td>Also used to prevent endometrial hyperplasia in postmenopausal women taking estrogen</td>
<td></td>
</tr>
<tr>
<td><strong>Glargine</strong> [Lantus]</td>
<td><strong>Long-acting insulin</strong>—see mechanism for regular insulin</td>
<td><strong>Diabetes mellitus</strong> (typically <strong>type 1</strong>), <strong>Hypoglycemia</strong> (diaphoresis, vertigo, and tachycardia), insulin allergy, insulin antibodies, lipodystrophy</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Glimepiride</strong> [Amaryl]</td>
<td><strong>Hypoglycemic agent, second-generation sulfonylurea</strong>—closes potassium channel in pancreatic β-islet cell membrane → reduces K⁺ efflux, increases Ca²⁺ influx → increases secretion of insulin</td>
<td>Oral treatment for <strong>type 2 diabetes</strong></td>
<td>Not useful in type 1 diabetes mellitus because it requires some β-cell function</td>
<td></td>
</tr>
<tr>
<td><strong>Glipizide</strong> [Glucotrol]</td>
<td><strong>Hypoglycemic agent, second-generation sulfonylurea</strong>—closes potassium channel in pancreatic β-islet cell membrane → reduces K⁺ efflux, increases Ca²⁺ influx → increases secretion of insulin</td>
<td>Oral treatment for <strong>type 2 diabetes</strong></td>
<td>Not useful in type 1 diabetes mellitus because it requires some β-cell function</td>
<td></td>
</tr>
<tr>
<td><strong>Glyburide</strong> [DiaBeta, Micronase]</td>
<td><strong>Hypoglycemic agent, second-generation sulfonylurea</strong>—closes potassium channel in pancreatic β-islet cell membrane → reduces K⁺ efflux, increases Ca²⁺ influx → increases secretion of insulin</td>
<td>Oral treatment for <strong>type 2 diabetes</strong></td>
<td>Not useful in type 1 diabetes mellitus because it requires some β-cell function</td>
<td></td>
</tr>
<tr>
<td><strong>Glyceryl guaiacolate</strong> [Fenesin]</td>
<td><strong>Expectorant</strong>—increases bronchial secretions</td>
<td><strong>Promotes cough</strong></td>
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<td></td>
</tr>
<tr>
<td><strong>Glycopyrrolate</strong> [Robinul]</td>
<td><strong>Antimuscarinic</strong></td>
<td><strong>Bladder/GI spasm</strong>, decreases acid in ulcer</td>
<td>Quaternary amine</td>
<td></td>
</tr>
<tr>
<td><strong>GnRH</strong></td>
<td>Controls release of FSH, LH</td>
<td><strong>Stimulates pituitary function</strong></td>
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</tr>
<tr>
<td><strong>Gonadorelin</strong> [Lutrepulse]</td>
<td><strong>Analog of GnRH</strong>—controls release of FSH, LH</td>
<td><strong>Stimulates pituitary function</strong></td>
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</tr>
</tbody>
</table>

(continued)
## APPENDIX I: Drug Index

<table>
<thead>
<tr>
<th>Therapeutic Agent (common name, if relevant) [trade name, where appropriate]</th>
<th>Class—Pharmacology and Pharmacokinetics</th>
<th>Indications</th>
<th>Side Effects or Adverse Effects</th>
<th>Contraindications or Precautions to Consider; Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Griseofulvin</strong> [Fulvicin, Grifulvin, Grisactin]</td>
<td>Antifungal—inhbits cell mitosis by disrupting mitotic spindles; binds to tubulin</td>
<td>Dermatophytes (especially <em>Trichophyton rubrum</em>)</td>
<td>Headache, mental confusion, rash, GI irritation, hepatotoxic, photosensitivity, carcinogenic, teratogenic</td>
<td>Increases cytochrome P450 and warfarin metabolism</td>
</tr>
<tr>
<td><strong>Growth hormone</strong> (somatotropin, somatrem)</td>
<td>Synthetic analog of growth hormone—causes liver to produce insulin-like growth factors (somatomedins)</td>
<td>Replacement therapy in children with growth hormone deficiency, Turner syndrome; burn victims</td>
<td></td>
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</tr>
<tr>
<td><strong>Growth hormone—releasing hormone (GHRH)</strong></td>
<td>Synthetic analog of GHRH—stimulates the release of growth hormone</td>
<td>Dwarfism</td>
<td>Pain at injection site</td>
<td></td>
</tr>
<tr>
<td><strong>Guaifenesin</strong> [Robitussin]</td>
<td>Expectorant—thins mucus and lubricates irritated respiratory tract</td>
<td>Cough associated with common cold and minor upper respiratory tract infections</td>
<td>Orthostatic hypotension, exercise hypotension, impotence, and diarrhea</td>
<td>Does not suppress cough reflex</td>
</tr>
<tr>
<td><strong>Guanethidine</strong> [Ismelin]</td>
<td>Antihypertensive—interferes with NE release</td>
<td>Severe hypertension</td>
<td></td>
<td>Contraindicated in patients taking TCAs</td>
</tr>
<tr>
<td><strong>Haloperidol</strong> [Haldol]</td>
<td>Antipsychotic—butyrophenone; blocks D and α₁ receptors</td>
<td>Schizophrenia, psychosis, acute mania, and Tourette syndrome</td>
<td>Extrapyramidal [dystonia, akinesia, akathisia, and tardive dyskinesia], endocrine (galactorrhea), anticholinergic (dry mouth, constipation), alpha blockade (hypotension), and histamine (sedation); prolonged QT syndrome; toxicity results in neuroleptic malignant syndrome (rigidity, myoglobinuria, autonomic instability, and hyperpyrexia)</td>
<td>Extrapyramidal side effects are more common; neuroleptic malignant syndrome is treated with dantrolene and dopamine agonists</td>
</tr>
<tr>
<td><strong>Haloprogin</strong> [Halotex]</td>
<td>Antifungal—unknown mechanism; fungistatic</td>
<td>Topical for tinea pedis</td>
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<td></td>
</tr>
<tr>
<td><strong>Halothane</strong></td>
<td>Anesthetic agent</td>
<td>General anesthetic</td>
<td>Hepatotoxic, malignant hyperthermia (with succinylcholine), arrhythmia</td>
<td>Contraindicated in adults</td>
</tr>
<tr>
<td><strong>Heparin</strong></td>
<td>Anticoagulant—increases PTT by accelerating antithrombin</td>
<td>Deep vein thrombosis, pulmonary thrombosis, MI</td>
<td>Overdose reversed by IV protamine sulfate, osteoporosis</td>
<td>Fast acting; does not cross placenta</td>
</tr>
<tr>
<td><strong>Heroin</strong></td>
<td>Metabolized to morphine</td>
<td></td>
<td>More lipid soluble than morphine</td>
<td></td>
</tr>
<tr>
<td>Drug Name</td>
<td>Drug Class</td>
<td>Side Effects</td>
<td>Contraindications</td>
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<tr>
<td><strong>Hexamethonium</strong></td>
<td>Nicotinic ganglionic blocker</td>
<td>Hypertensive emergency</td>
<td>Severe orthostatic hypotension, blurred vision, constipation, and sexual dysfunction</td>
<td></td>
</tr>
<tr>
<td><strong>Hydralazine [Apresoline]</strong></td>
<td>Antihypertensive—increases cGMP smooth muscle relaxation → vasodilates arterioles → afterload reduction</td>
<td>Severe hypertension, CHF</td>
<td>Compensatory tachycardia, fluid retention, lupus-like syndrome</td>
<td>First-line therapy for hypertension in pregnancy, used with methyl-pseudoephedrine, contraindicated in angina/ coronary artery disease because of compensatory tachycardia</td>
</tr>
<tr>
<td><strong>Hydrochlorothiazide (HCTZ) [HydroDIURIL]</strong></td>
<td>Thiazide diuretic—inhibits transport of Na⁺ and Cl⁻ into the cells of DCT</td>
<td>Hypertension, CHF; idiopathic hypercalciuria, and nephrogenic diabetes insipidus</td>
<td>Hypokalemia, metabolic alkalosis, mild hyperlipidemia, hyperuricemia, malaise, hypercalcemia, hyperglycemia, and hyponatremia</td>
<td>Do not give in patients with sulfa drug allergy</td>
</tr>
<tr>
<td><strong>Hydrocodone and acetaminophen [Bancap-HC]</strong></td>
<td>Opioid agonist</td>
<td>Antitussive, analgesic</td>
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<td></td>
</tr>
<tr>
<td><strong>Hydromorphone [Dilaudid]</strong></td>
<td>Opioid agonist</td>
<td>Antitussive, analgesic</td>
<td>Respiratory depression, constipation, nausea</td>
<td></td>
</tr>
<tr>
<td><strong>Hydroxychloroquine [Plaquenil]</strong></td>
<td>Antiprotozoal―antiinflammatory</td>
<td>Rheumatic arthritis, malaria</td>
<td>Ocular toxicity (blurred vision)</td>
<td>Contraindicated in patients with psoriasis</td>
</tr>
<tr>
<td><strong>Hydroxyurea [Hydra]</strong></td>
<td>Antineoplastic—binds ribonucleotide reductase; inhibits formation of DNA</td>
<td>Melanoma, chronic myelogenous leukemia, sickle cell disease</td>
<td>Nausea, vomiting, bone marrow suppression</td>
<td></td>
</tr>
<tr>
<td><strong>Ibuprofen [Advil, Motrin]</strong></td>
<td>NSAID—reversibly inhibits COX (both COX-1 and COX-2) → decreases prostaglandin synthesis</td>
<td>Inflammation, pain</td>
<td>GI distress, GI ulcers, coagulation disorders, aplastic anemia, metabolic abnormalities, hypersensitivity, renal damage</td>
<td></td>
</tr>
<tr>
<td><strong>Ibutilide [Corvert]</strong></td>
<td>Antiarrhythmic (class III)—K⁺ channel blocker</td>
<td>Terminates atrial fibrillation and flutter</td>
<td>Prolongs QT interval</td>
<td></td>
</tr>
<tr>
<td><strong>Idazoxan</strong></td>
<td>Antihypertensive—α₂-blocker</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Idoxuridine [Herplex Liquifilm]</strong></td>
<td>Antiviral—thymidine analog; inhibits DNA polymerase; inhibits DNA synthesis</td>
<td>Topical for HSV keratitis</td>
<td>Local irritation, allergic contact keratitis</td>
<td></td>
</tr>
<tr>
<td><strong>Ifosfamide [Ifex]</strong></td>
<td>Antineoplastic—DNA alkylation and cross-linking</td>
<td>Cancer</td>
<td>Hemorrhagic cystitis, nephrotoxicity, nausea, vomiting, bone marrow suppression, alopecia, teratogenicity, carcinogenicity</td>
<td>Coadministration of mesna will prevent hemorrhagic cystitis</td>
</tr>
</tbody>
</table>

(continued)
<table>
<thead>
<tr>
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</tr>
</thead>
<tbody>
<tr>
<td><strong>Imipenem and cilastatin</strong> [Primaxin]</td>
<td>Antibiotic—<em>carbapenem</em>, cell wall inhibitor; same mechanism as penicillin; bactericidal</td>
<td>Broad spectrum—<em>gram-positive cocci</em> (MSSA and <em>Streptococcus</em>), <em>gram-negative rods</em> (<em>Pseudomonas</em> and <em>Enterobacter</em> spp.), <em>anaerobes</em></td>
<td>Hypersensitivity reaction, <strong>seizure</strong>, confusion state, and superinfection (pseudomembranous colitis)</td>
<td>Significant side effects limit use to when other drugs have failed or in the case of life-threatening infections; always administered with cilastatin (inhibits renal dehydropeptidase) to reduce inactivation in renal tubules</td>
</tr>
<tr>
<td><strong>Imipramine</strong> [Tofranil]</td>
<td>TCAs—inhibit reuptake of NE and 5-HT at neuronal synapses</td>
<td>Major depression, nocturnal enuresis, and panic disorder</td>
<td>Sedation, <strong>α-blocking effects</strong> (orthostatic hypotension), <strong>anticholinergic</strong> (tachycardia, dry mouth, and urinary retention), hallucinations (in elderly), and confusion (in elderly); overdose toxicity results in <strong>convulsions</strong>, <strong>coma</strong>, <strong>cardiotoxicity</strong> (arrhythmias), respiratory depression, and hyperpyrexia</td>
<td></td>
</tr>
<tr>
<td><strong>Indecainide</strong></td>
<td>Antiarrhythmic (class IC) Na⁺ channel blockers</td>
<td>No antimuscarinic action; no effect on action potential</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Indinavir</strong> [Crixivan]</td>
<td>Antiviral, protease inhibitor—protease responsible for final step of viral proliferation; inhibits protease in progeny virions → assembly of nonfunctional viruses</td>
<td>AIDS (used in HAART)</td>
<td>GI irritation (nausea, diarrhea), hyperglycemia, hyperlipidemia, lipodystrophy, thrombocytopenia</td>
<td>All protease inhibitors ending in -navir; metabolism occurs by cytochrome P450</td>
</tr>
<tr>
<td><strong>Indomethacin</strong> [Indocin]</td>
<td>Anti-inflammatory, NSAID—reversibly inhibits COX (both COX-1 and COX-2) → decreases prostaglandin synthesis</td>
<td>Acute gout therapy; closes PDA</td>
<td>GI distress, GI ulcers, coagulation disorders, aplastic anemia, metabolic abnormalities, hypersensitivity, renal damage</td>
<td></td>
</tr>
<tr>
<td><strong>Infliximab</strong></td>
<td>Anti-inflammatory—monoclonal antibody that binds TNF → inhibits proinflammatory effects of TNF</td>
<td>Crohn disease, rheumatoid arthritis, and ankylosing spondylitis</td>
<td>Infections, fever, hypotension, and reactivation of latent tuberculosis</td>
<td></td>
</tr>
</tbody>
</table>
### Insulin, regular [Humulin R, Novolin R]

**Short-acting insulin—Liver:** promotes glucose storage as glycogen; increases TG synthesis  
**Muscle:** facilitates protein and glycogen synthesis  
**Adipose tissue:** improves TG storage by activating plasma lipoprotein lipase; reduces circulating free fatty acids

**Diabetes mellitus** (typically type 1), hyperkalemia, and stress-induced hyperglycemia  
**Hypoglycemia** (diaphoresis, vertigo, and tachycardia), insulin allergy, insulin antibodies, lipodystrophy

### Interferon α-2a [Roferon A], α-2b [Intron A], and α-2c [Alferon-N]

**Antiviral—glycoproteins—block viral RNA, DNA, and protein synthesis**  
**Genital warts, chronic hepatitis B and C, AIDS-related Kaposi sarcoma, laryngeal papillomatosis, hairy cell leukemia**  
**Flulike symptoms, neutropenia, depression**

### Interferon β-1a [Avonex, Rebi]

**Antiviral—glycoproteins—block viral RNA, DNA, and protein synthesis**  
**Multiple sclerosis**  
**Flulike symptoms, neutropenia, depression**

### Interferon γ-1b [Actimmune]

**Antiviral—glycoproteins—block viral RNA, DNA, and protein synthesis**  
**Chronic granulomatous disease**  
**Flulike symptoms, neutropenia**

### Ipecac (syrup) [Quelidrine]

**Expectorant—increases bronchial secretions**  
**Promotes cough**

### Ipratropium [Atrovent]

**Bronchodilator—muscarinic antagonist; competitively blocks muscarinic receptors → prevents bronchoconstriction**  
**Asthma, COPD**

### Isocarboxazid [Marplan]

**MAOIs—inhibit degradation of NE and 5-HT at neuronal synapses**  
**Atypical depression** (with hypersomnia, anxiety, sensitivity to rejection, and hypochondriasis)  
**Hypertensive episodes** with ingestion of tyramine-containing foods or β-agonists, hyperthermia, and convulsions  
**Contraindicated with SSRIs and meperidine secondary to serotonin syndrome (hyperthermia, muscle rigidity, and cardiovascular collapse)**

### Isoflurane

**Anesthetic**  
**General anesthetic**  
**Best muscle relaxant, most widely used**

### Isoniazid (INH)

**Antibiotic—inhibits synthesis of mycolic acids**  
**Mycobacterium treatment** (*Mycobacterium tuberculosis* and *Mycobacterium kansasii*); *Mycobacterium tuberculosis prophylaxis*  
**Peripheral and CNS effects as a result of pyridoxine deficiency; liver damage, hemolytic anemia in G6PD deficiency, SLE-like syndromes**  
**Pyridoxine (vitamin B₆) can prevent neurotoxicity**

### Isoproterenol [Isuprel]

**Bronchodilator—β-agonist (non-selective); relaxes bronchial smooth muscle through β₁-receptor activity**  
**Asthma**  
**Tachycardia (β₁-receptor activity)**

### Isosorbide dinitrate [Isordil]

**Antiangular—stimulates the synthesis of cGMP, leading to muscle relaxation via NO formation; vasodilator**  
**Angina, CHF**  
**Headache, orthostatic hypotension, syncope**  
**Long acting**

### Isotretinoin [Accutane]

**Vitamin A analog**  
**Severe acne, psoriasis**  
**Keratinization, teratogenic**

(continued)
## APPENDIX I: Drug Index

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<th>Therapeutic Agent (common name, if relevant) [trade name, where appropriate]</th>
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<tr>
<td>Itraconazole [Sporanox]</td>
<td>Antifungal—inhibits ergosterol synthesis, preventing cell membrane formation</td>
<td>Oral for dermatophytoses and onychomycosis; drug of choice for histoplasmosis, blastomycosis, sporotrichosis, paracoccidiodomycosis</td>
<td>GI disturbances, hepatotoxicity</td>
<td></td>
</tr>
<tr>
<td>Ivermectin</td>
<td>Anthelmintic—binds to invertebrate chloride channels → hyperpolarizes parasite nerve and muscle cells → parasite paralysis</td>
<td>Onchocerciasis, strongyloidiasis</td>
<td>Mazzotti-like reaction</td>
<td>Contraindicated in pregnancy</td>
</tr>
<tr>
<td>Ketamine [Ketalar]</td>
<td>Anesthetic agent; blocks NMDA-type glutamate receptors</td>
<td>General anesthetic</td>
<td>Dissociative anesthesia, catatonia, hallucinations</td>
<td></td>
</tr>
<tr>
<td>Ketoconazole [Nizoral]</td>
<td>Antifungal—inhibits ergosterol synthesis, preventing cell membrane formation; inhibits adrenal and gonadal steroid synthesis</td>
<td>Chronic mucocutaneous candidiasis, blastomycosis, histoplasmosis, coccidioidomycosis, hypercortisolism, prostate carcinoma</td>
<td>GI irritation, gynecomastia, thrombocytopenia, hepatotoxic, rash, fever, chills</td>
<td>Inhibits cytochrome P450</td>
</tr>
<tr>
<td>Ketorolac [Toradol]</td>
<td>NSAID—reversibly inhibits COX (both COX-1 and COX-2) → decreases prostaglandin synthesis; relieves pain and reduces swelling</td>
<td>Postoperative pain, severe pain</td>
<td>GI distress, GI ulcers, coagulation disorders, aplastic anemia, metabolic abnormalities, hypersensitivity, renal damage</td>
<td></td>
</tr>
<tr>
<td>Labetalol [Normodyne, Trandate]</td>
<td>Antihypertensive—nonselective β- and α1-blocker</td>
<td>Hypertension</td>
<td>Bronchospasm, bradycardia, AV block, heart failure, sedation, and sleep alterations</td>
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</tr>
<tr>
<td>Lactulose</td>
<td>Osmotic laxative</td>
<td>Decreases ammonia in hepatic encephalopathy; constipation</td>
<td>Abdominal bloating, flatulence</td>
<td>Lowers colon pH so that ammonia is trapped and then excreted</td>
</tr>
<tr>
<td>Lamivudine (3TC) [Epivir]</td>
<td>Antiviral, nucleoside reverse transcriptase inhibitor—cytidine analog → inhibits viral reverse transcriptase → prevents integration of DNA copy of viral genome into host DNA</td>
<td>AIDS (used in HAART)</td>
<td>Neutropenia, anemia, peripheral neuropathy, pancreatitis, and lactic acidosis</td>
<td></td>
</tr>
<tr>
<td>Lamotrigine [Lamictal]</td>
<td>Antiepileptic—blocks Na+ channels</td>
<td>Add-on drug for epilepsy</td>
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<tr>
<td>Lansoprazole</td>
<td>Proton pump inhibitor—irreversibly inhibits H+/K+–ATPase in gastric parietal cells → decreases proton secretion by parietal cells</td>
<td>Peptic ulcer disease, gastritis, esophageal reflux, Zollinger–Ellison syndrome</td>
<td></td>
<td>Inhibits cytochrome P450; given with clarithromycin and amoxicillin for H. pylori</td>
</tr>
<tr>
<td>Drug</td>
<td>Action</td>
<td>Adverse Effects</td>
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<tr>
<td>Latanoprost</td>
<td>PGF₂₀</td>
<td>Glaucoma, Blurred vision, burning, hyperemia, itching, hyperpigmentation of iris, keratitis</td>
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<tr>
<td>Leucovorin</td>
<td>Allows stem cells to bypass the inhibition of dihydrofolate reductase caused by methotrexate</td>
<td>Treats acute toxicity of methotrexate</td>
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</tr>
<tr>
<td>Leuprolide</td>
<td>GnRH analog—agonist (when given pulsatile), antagonist (when given continuously)</td>
<td>Infertility (given pulsatile), prostate cancer (given continuous), uterine fibroids, endometriosis, precocious puberty</td>
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<tr>
<td>Levamisole</td>
<td>Anthelmintic—immunostimulatory to host; helps rid the host of parasite</td>
<td>Ascaris (roundworm), Ancylostoma (hookworm), therapy for immunodeficiency</td>
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</tr>
<tr>
<td>Levodopa</td>
<td>Antiparkinsonian agent—precursor of dopamine; administered with carbidopa (most often) or benserazide to inhibit carboxylase deactivation of levodopa in periphery</td>
<td>Parkinson disease</td>
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<td></td>
</tr>
<tr>
<td>Levothyroxine</td>
<td>Synthetic analog of thyroxine (T₄)</td>
<td>Hypothyroidism</td>
<td></td>
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</tr>
<tr>
<td>Levofloxacin</td>
<td>Antibiotic—quinolone; inhibits DNA gyrase (topoisomerase III) and topoisomerase IV → blocks DNA synthesis; bactericidal</td>
<td>Gram-negative infections (especially UTI and bone): Pseudomonas, Enterobacteriaceae, and Neisseria; gram-positive infections (Staphylococcus, Streptococcus); intracellular: Legionella</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Levonorgestrel</td>
<td>Progesterone—binds progesterone receptors</td>
<td>Endometrial cancer, amenorrhea, abnormal uterine bleeding, and prevention of pregnancy</td>
<td></td>
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</tr>
<tr>
<td>Levothyroxine</td>
<td>Synthetic analog of thyroxine (T₄)</td>
<td>Hypothyroidism</td>
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</tr>
<tr>
<td>Lidocaine</td>
<td>Antiarrhythmic (class IB), anesthetic agent—blocks Na⁺ channels intracellularly</td>
<td>Local anesthetic, ventricular tachycardia</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Sleepiness, light-headedness, visual/audio disturbances, restlessness, nystagmus, shivering, tonic–clonic convulsion, death</td>
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<th>Contraindications or Precautions to Consider; Notes</th>
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<tbody>
<tr>
<td>Linagliptin [Tradjenta]</td>
<td>Hypoglycemic agent, DPP-IV inhibitor—prevents degradation of incretin hormones → decreases glucagon, increased insulin</td>
<td>Oral treatment for type 2 diabetes</td>
<td>Diarrhea, constipation, edema</td>
<td></td>
</tr>
<tr>
<td>Liraglutide [Victoza]</td>
<td>Hypoglycemic agent, incretin mimetic—agonizes GLP-1 receptors → decreases glucagon, increases insulin, delays gastric emptying</td>
<td>Injectable treatment for type 2 diabetes</td>
<td>Mild weight loss, nausea, vomiting, diarrhea, slight risk of pancreatitis</td>
<td>Increased incidence of medullary thyroid cancer in animal models</td>
</tr>
<tr>
<td>Lisinopril [Prinivil, Zestril]</td>
<td>Antihypertensive—ACE inhibitor → inhibits conversion of angiotensin I to II → decreases Ang II levels → prevents vasoconstriction from Ang II</td>
<td>Hypertension, CHF, post-MI; prevention/treatment of diabetic nephropathy</td>
<td>Cough, angioedema, hyperkalemia, renal insufficiency (especially in bilateral renal artery stenosis)</td>
<td>Contraindicated in pregnancy (fetal renal malformation)</td>
</tr>
<tr>
<td>Lispro [Humalog]</td>
<td>Rapid-acting insulin—see mechanism for regular insulin</td>
<td>Diabetes mellitus (typically type 1), hyperkalemia, and stress-induced hyperglycemia</td>
<td>Hypoglycemia (diaphoresis, vertigo, and tachycardia), insulin allergy, insulin antibodies, lipodystrophy</td>
<td></td>
</tr>
<tr>
<td>Lithium [Eskalith, Lithobid, Lithotabs, Lithonate]</td>
<td>Antimanic—unclear mechanism; inhibits regeneration of IP3 and DAG; important for many second-messenger systems</td>
<td>Bipolar disorder, acute manic events</td>
<td>Tremor, hypothyroidism, polyuria, and teratogenesis</td>
<td>Close monitoring of serum levels required due to narrow therapeutic window</td>
</tr>
<tr>
<td>Loperamide [Imodium]</td>
<td>Antidiarrheal—similar to opioid agonist</td>
<td>Oral antidiarrheal</td>
<td></td>
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</tr>
<tr>
<td>Loratadine [Claritin]</td>
<td>Antihistamine—H1, blocker (second generation)</td>
<td>Seasonal allergies</td>
<td>Sedating; rare: headache, dizziness, fatigue, CNS, weak antiandrogenic effect, leukopenia, and reduced sperm count</td>
<td>Inhibits metabolism or absorption of some drugs; less sedating than first-generation H1, blocker due to decreased CNS entry</td>
</tr>
<tr>
<td>Lorazepam [Ativan]</td>
<td>Antianxiety—benzodiazepine, enhances GABA, increases IPSP amplitude</td>
<td>Sedative, hypnotic, antianxiety, antiepileptic; panic attack</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Losartan [Cozaar]</td>
<td>Antihypertensive—Ang II receptor blockers → prevents vasoconstriction from Ang II</td>
<td>Hypertension</td>
<td>Fetal renal toxicity, hyperkalemia</td>
<td></td>
</tr>
<tr>
<td>Lovastatin [Mevacor]</td>
<td>Lipid-lowering agent—HMG-CoA reductase inhibitors—inhibits synthesis of cholesterol precursor mevalonate; decreases LDL, increases HDL, and decreases TG</td>
<td>High LDL, preventative after thrombotic event (e.g., MI, stroke)</td>
<td>Reversible increase in LFTs; myositis</td>
<td>Contraindicated in pregnant or lactating women and children</td>
</tr>
<tr>
<td>Drug Name</td>
<td>Action</td>
<td>Effects</td>
<td>Comments</td>
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<tr>
<td>Magnesium hydroxide (milk of magnesia)</td>
<td>Antacid, osmotic laxative—buffers gastric acid by raising pH</td>
<td>Peptic ulcer, gastritis, esophageal reflux, and constipation</td>
<td>Diarrhea, hyporeflexia, hypotension, cardiac arrest, and hypokalemia; Can affect the absorption, bioavailability, or urinary excretion of drugs by changing the gastric pH, urinary pH, or gastric emptying</td>
<td></td>
</tr>
<tr>
<td>Magnesium sulfate, magnesium citrate</td>
<td>Osmotic laxative</td>
<td></td>
<td>Magnesium toxicity (in renal insufficiency)</td>
<td></td>
</tr>
<tr>
<td>Malathion</td>
<td>Organophosphate—reduces cholinesterase activity</td>
<td>Shock, drug overdose, decreased intracranial or intraocular pressure; maintenance of urine flow in rhabdomyolysis</td>
<td>Pulmonary edema, dehydration; contraindicated in anuria and CHF; Results in increased urine volume; readily filtered and not reabsorbed</td>
<td></td>
</tr>
<tr>
<td>Mannitol [Osmitrol]</td>
<td>Osmotic diuretic—prevents osmotic reabsorption of filtrate in PCT, loop of Henle, and collecting tubule; loss of Na+ and all other filtered solutes in urine</td>
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<tr>
<td>Maprotiline</td>
<td>Blocks NE uptake</td>
<td>Major depression</td>
<td>Sedation, orthostatic hypotension</td>
<td></td>
</tr>
<tr>
<td>Maraviroc</td>
<td>Antiretroviral, CCR5 antagonist—blocks viral entry to host cell</td>
<td>AIDS, patients on antiretroviral therapy with persistent viral replication</td>
<td>Fever, cough, upper respiratory infections, peripheral neuropathy, dizziness</td>
<td></td>
</tr>
<tr>
<td>Mebendazole [Vermox]</td>
<td>Anthelmintic—irreversible; inhibits glucose uptake</td>
<td>Hookworm, roundworm, threadworm, some cestodes</td>
<td></td>
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<tr>
<td>Mecamylamine [Inversine]</td>
<td>Antihypertensive—nicotinic ganglionic blocker</td>
<td>Hypertension emergency; smoking cessation</td>
<td>Decreases GI motility, cycloplegia, hypotension, xerostomia</td>
<td></td>
</tr>
<tr>
<td>Mechlorethamine (nitrogen mustard) [Mustargen]</td>
<td>Antineoplastic—DNA alkylation and cross-linking</td>
<td>Cancer</td>
<td>Nausea, vomiting, bone marrow suppression, alopecia, teratogenicity, carcinogenicity</td>
<td></td>
</tr>
<tr>
<td>Meclizine [Antivert, Bonine]</td>
<td>Antiemetic agent—H₁ receptor blocker</td>
<td>Emesis, vertigo</td>
<td>Teratogenic</td>
<td></td>
</tr>
<tr>
<td>Mefloquine [Lariam]</td>
<td>Antimalarial—uncertain mechanism</td>
<td>Treatment of acute attack of chloroquine-resistant organisms</td>
<td>CNS: dizziness, disorientation, hallucinations, seizure, and depression; GI disturbances; nausea; vomiting; abdominal pain</td>
<td></td>
</tr>
<tr>
<td>Melatonin</td>
<td>Promotes sleep</td>
<td>Clock shifting</td>
<td>Pineal hormone</td>
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<tr>
<td>Melphalan [Alkeran]</td>
<td>Antineoplastic—DNA alkylation and cross-linking</td>
<td>Cancer</td>
<td>Nausea, vomiting, bone marrow suppression (serious), alopecia, teratogenicity, carcinogenicity, pulmonary fibrosis, hypersensitivity</td>
<td></td>
</tr>
<tr>
<td>Menotropin [Pergonal]</td>
<td>Mixture of FSH and LH</td>
<td>Secondary hypogonadism with infertility</td>
<td></td>
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</tr>
<tr>
<td>Meperidine [Demerol]</td>
<td>Opioid agonist</td>
<td>Pain, acute migraine attacks</td>
<td>CNS excitation at high doses; histamine release; antimuscarinic effects</td>
<td>Contraindicated in patients with MAOI (results in hyperpyrexia)</td>
</tr>
<tr>
<td>Mephenesin</td>
<td>Centrally acting muscle relaxant</td>
<td>Muscle spasms, tetanus contractions, orthopedic manipulation</td>
<td>Sedation</td>
<td></td>
</tr>
<tr>
<td>Mepivacaine [Isocaine]</td>
<td>Anesthetic agent—blocks Na⁺ channels intracellularly</td>
<td>Local anesthetic</td>
<td>Sleepiness, light-headedness, visual/audio disturbances, restlessness, nystagmus, shivering, tonic–clonic convulsion, death</td>
<td></td>
</tr>
<tr>
<td>6-Mercaptopurine [Purinethol]</td>
<td>Antineoplastic—inhibits purine synthesis; disrupts DNA and RNA synthesis</td>
<td>Childhood leukemias</td>
<td>Myelosuppression</td>
<td></td>
</tr>
<tr>
<td>Meropenem [Merrem]</td>
<td>Carbapenem—cell wall inhibitor; same mechanism as penicillin; bactericidal</td>
<td>Broad spectrum—gram-positive cocci (MSSA and Streptococcus), gram-negative rods (Pseudomonas and Enterobacter spp.), anaerobes</td>
<td>Reduced risk of seizure compared to imipenem</td>
<td>Stable to dihydropeptidase I, unlike imipenem</td>
</tr>
<tr>
<td>Metformin [Glucophage]</td>
<td>Hypoglycemic agent, biguanide—decreases hepatic gluconeogenesis, increases glycolysis → decreases serum glucose levels</td>
<td>First-line oral treatment for type 2 diabetes</td>
<td>Lactic acidosis. GI upset (diarrhea, nausea, and abdominal pain), metallic taste; decreased vitamin B₁₂ absorption</td>
<td>Stop drug in patients undergoing studies or procedures involving contrast; contraindicated in patients with renal dysfunction</td>
</tr>
<tr>
<td>Methadone [Dolophine]</td>
<td>Opioid agonist—synthetic</td>
<td>Maintenance therapy for heroin addiction, pain</td>
<td>Respiratory depression, histamine release, constipation, nausea, miosis</td>
<td></td>
</tr>
<tr>
<td>Methicillin</td>
<td>Antibiotic—β-lactam, penicillin derivative, cell wall inhibitor; same mechanism as penicillin; distinguished by activity against penicillinase-producing Staphylococcus; bactericidal</td>
<td>Staphylococcal infections (except MRSA)</td>
<td>Hypersensitivity reactions; interstitial nephritis (methicillin)</td>
<td>Penicillinase resistant; MRSA is resistant to methicillin because of altered penicillin-binding protein target site</td>
</tr>
<tr>
<td>Drug Name [Brand]</td>
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<tr>
<td>Methimazole [Tapazole]</td>
<td>Antithyroid agent—inhibits peroxidase enzyme in thyroid → decreases synthesis of thyroid hormone</td>
<td>Hyperthyroidism</td>
<td>Agranulocytosis</td>
<td></td>
</tr>
<tr>
<td>Methohexital [Brevital]</td>
<td>Anesthetic agent—barbiturate; prolongs IPSP duration</td>
<td>Antiepileptic, cerebral edema, anesthetic (stage 3 anesthetic)</td>
<td>Ultrashort acting</td>
<td></td>
</tr>
<tr>
<td>Methotrexate [Rheumatrex]</td>
<td>Antineoplastic—folic acid analog (dihydrofolate reductase inhibitor); immunosuppressant</td>
<td>Rheumatoid arthritis, bone marrow transplant, acute lymphocytic and myelogenous leukemia, choriocarcinoma, lung cancer, ectopic pregnancy</td>
<td>Oral and GI ulceration, myelo-suppression, thrombocytopenia, leukopenia, hepatotoxicity, fibrotic lung disease</td>
<td></td>
</tr>
<tr>
<td>Methoxyflurane [Penthane]</td>
<td>Anesthetic agent</td>
<td>General anesthetic</td>
<td>Nephrotoxic</td>
<td></td>
</tr>
<tr>
<td>Methylcellulose [Citrucel]</td>
<td>Bulk-forming laxative—dietary fiber</td>
<td>Constipation</td>
<td>Impaction above strictures, fluid overload, gas, and bloating</td>
<td></td>
</tr>
<tr>
<td>Methyldopa [Aldomet]</td>
<td>Antihypertensive—centrally acting sympathetic agent (α-agonist) → decreases sympathetic outflow from CNS</td>
<td>Hypertension</td>
<td>Sedation, hemolytic anemia</td>
<td></td>
</tr>
<tr>
<td>Methylphenidate [Ritalin]</td>
<td>CNS stimulant—amphetamine; releases neurotransmitter from synapse</td>
<td>Stimulant; treatment of choice for attention deficit hyperactivity disorder</td>
<td>Positive Coombs test</td>
<td></td>
</tr>
<tr>
<td>Methyltestosterone [Android, Virilon]</td>
<td>Androgen—androgen receptor agonist</td>
<td>In men: hypogonadism, delayed puberty (promotes secondary sex characteristics), and impotence; in women: estrogen receptor-positive breast cancer</td>
<td>Masculinization (hirsutism), testicular atrophy, prostate hyperplasia, prostate cancer, impotence, stunted growth (premature epiphysial plate closure), and hyperlipidemia</td>
<td></td>
</tr>
<tr>
<td>Methysergide [Sansert]</td>
<td>Antimigraine—5-HT antagonist and weak vasoconstrictor</td>
<td>Prophylaxis of migraine</td>
<td>GI distress; inflammatory fibrosis of kidney, lung, and cardiac valves</td>
<td></td>
</tr>
<tr>
<td>Metoclopramide [Reglan]</td>
<td>GI stimulant—prokinetic agent; D₂-receptor antagonist; central and peripheral D₂ antagonism at low doses, weak 5-HT₂ antagonist, at high doses; enhances acetylcholine release, increases resting tone, contractility, lower esophageal sphincter tone, and motility (does not affect colon transit time)</td>
<td>Diabetic and postoperative gastroparesis, nausea, counteracts nausea of migraine, increases stomach motility</td>
<td>Sleepiness, fatigue, headache, insomnia, dizziness, nausea, akathisia, dystonia, and tardive dyskinesia</td>
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<td><strong>Metocurine [Metubine Iodide]</strong></td>
<td>Nondepolarizing neuromuscular blocker</td>
<td></td>
<td>Hypokalemia, hyperuricemia, hypovolemia, hyperglycemia (especially in diabetics), hypercalcaemia, hypersensitivity reaction, Na⁺ excretion in advanced renal failure</td>
<td></td>
</tr>
<tr>
<td><strong>Metolazone [Mykrox, Zaroxolyn]</strong></td>
<td>Diuretic—decreases Na⁺ reabsorption in the distal tubule by inhibiting the Na/Cl⁻ cotransporter; reduced peripheral resistance</td>
<td>Hypertension, CHF</td>
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</tr>
<tr>
<td><strong>Metoprolol [Lopressor, Toprol XL]</strong></td>
<td>Antihypertensive, antiarrhythmic (class II)—β₁-selective blocker</td>
<td>Hypertension, angina, MI, and antiarrhythmic</td>
<td>Impotence, asthma, bradycardia, AV block, heart failure, sedation, and sleep alterations</td>
<td></td>
</tr>
<tr>
<td><strong>Metronidazole [Flagyl]</strong></td>
<td>Antibiotic, antiprotozoal—penetrates cell membrane and gives off nitro moiety → forms toxic metabolites → reacts and damages DNA; bactericidal</td>
<td>Bacteroides fragilis (especially for endocarditis and CNS), pseudomembranous colitis (C. difficile); amebiasis; giardiasis; trichomoniasis, bacterial vaginosis (Gardinerella vaginalis); peptic ulcer disease (part of H. pylori triple therapy)</td>
<td>Nausea, vomiting, disulfiram-like reaction to alcohol, metallic taste, paresthesia, stomatitis, carcinogenic and mutagenic</td>
<td>Contraindicated in pregnancy</td>
</tr>
<tr>
<td><strong>Metyrapone [Metopirone]</strong></td>
<td>Inhibits cortisol synthesis</td>
<td>Diagnosis of pituitary dysfunction</td>
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<tr>
<td><strong>Mevastatin</strong></td>
<td>Lipid-lowering agent—inhibits HMG-CoA reductase; lowers LDL</td>
<td>Hyperlipidemia (especially type II)</td>
<td>Liver toxicity, myopathy, mild GI disturbances</td>
<td>Contraindicated in pregnant or lactating women or in children</td>
</tr>
<tr>
<td><strong>Metaxilene [Mexitil]</strong></td>
<td>Antiarrhythmic (class Ib)—Na⁺ channel blocker</td>
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<tr>
<td><strong>Midazolam [Versed]</strong></td>
<td>Benzodiazepine; short acting</td>
<td>Preanaesthetic medication; produces antegrade amnesia (loss of memory of events after administration) calming down the patient</td>
<td>Circulatory and respiratory depression</td>
<td>Flumazenil antagonizes CNS depression caused by benzodiazepines</td>
</tr>
<tr>
<td><strong>Mifepristone (RU-486)</strong></td>
<td>Antiprogestrone —synthetic steroid, progestrone receptor blocker → blocks the effects of progesterone → myometrium contraction</td>
<td>Termination of intrauterine pregnancy (emergency postcoital contraceptive)</td>
<td>Heavy bleeding, uterine cramping, GI effects (nausea, vomiting, and anorexia)</td>
<td>Controversial “morning after” drug</td>
</tr>
<tr>
<td><strong>Miglitol</strong></td>
<td>Hypoglycemic agent, α-glucosidase inhibitor—inhibits intestinal brush border enzyme α-glucosidase → delays sugar hydrolysis and glucose absorption → decreases postprandial hyperglycemia</td>
<td>Oral treatment for type 2 diabetes postprandially</td>
<td>Flatulence, cramps, and diarrhea; may reduce absorption of iron</td>
<td>Does not cause reactive hypoglycemia; decreases HbA₁c</td>
</tr>
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<tr>
<td>Milrinone [Primacor]</td>
<td>Inotropic agent—phosphodiesterase inhibitor; increases contractility via increase in intracellular Ca²⁺</td>
<td>CHF</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mineral oil [Fleet Mineral Oil Emema]</td>
<td>Laxative—hyperosmolar agent</td>
<td>Preoperative patients, short-term treatment of constipation</td>
<td>May interfere with the absorption of fat-soluble vitamins</td>
<td></td>
</tr>
<tr>
<td>Minoxidil [Loniten, Rogaine]</td>
<td>Antihypertensive—K⁺ channel opener</td>
<td>Severe hypertension</td>
<td>Hypertrichosis, pericardial effusion</td>
<td></td>
</tr>
<tr>
<td>Mirtazapine</td>
<td>α₂-Antagonist</td>
<td>Major depression (especially with insomnia)</td>
<td>Weight gain, dry mouth, increased appetite, and sedation</td>
<td></td>
</tr>
<tr>
<td>Misoprostol [Cytotec]</td>
<td>Cytoprotectant—PGE₁ analog</td>
<td>Prevents NSAID-induced peptic ulcers, maintains PDA, induction of labor, termination of pregnancy</td>
<td>Diarrhea</td>
<td>Abortion-inducing drug, contraindicated in women of childbearing age</td>
</tr>
<tr>
<td>Molindone [Moban]</td>
<td>Antipsychotic—blocks D₂ receptors</td>
<td>Psychosis</td>
<td>Parkinsonism, tardive dyskinesia</td>
<td></td>
</tr>
<tr>
<td>Montelukast [Singulair]</td>
<td>Leukotriene inhibitor, reduces inflammation</td>
<td>Asthma</td>
<td>Not for acute attacks</td>
<td></td>
</tr>
<tr>
<td>Moricizine [Ethmozine]</td>
<td>Antiarrhythmic (class IC)—Na⁺ channel blockers</td>
<td>Ventricular arrhythmia</td>
<td>Dizziness, nausea</td>
<td></td>
</tr>
<tr>
<td>Morphine [Astramorph, Duramorph, Infumorph, Kadian, MS Contin, Oramorph, MSIR, Roxanol]</td>
<td>Opioid agonist—chronic oral dose converted to more potent morphine-6-glucuronide</td>
<td>Severe pain, general anesthetic, antitussive, antidiarrheal</td>
<td>Respiratory depression, histamine release, constipation, nausea, miosis</td>
<td></td>
</tr>
<tr>
<td>Moxifloxacin [Avelox]</td>
<td>Antibiotic—quinolone; inhibits DNA gyrase (topoisomerase II) and topoisomerase IV → blocks DNA synthesis; bactericidal</td>
<td>Less activity against gram-negative infections than other fluoroquinolones; gram-positive infections (Staphylococcus, Streptococcus); intracellular: Legionella, anaerobes</td>
<td>GI disturbances, headache, dizziness, phototoxicity, cartilage damage (children, fetus), tendonitis and tendon rupture (adults), myalgias (children)</td>
<td>May elevate theophylline to toxic levels, causing seizure; contraindicated in pregnant women; divalent cations inhibit gut absorption, therefore cannot be taken with milk, antacids, or iron-containing preparations</td>
</tr>
<tr>
<td>Muromonab (OKT3)</td>
<td>Immunosuppressant—monoclonal antibody against CD3 on T lymphocytes</td>
<td>Acute rejection of renal transplants</td>
<td></td>
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<tr>
<td>Muscarine</td>
<td>Muscarinic agonist</td>
<td>Abdominal pain, diarrhea, bronchoconstriction</td>
<td>Contraindicated in patients with peptic ulcer, asthma, hyperthyroidism, and Parkinson disease</td>
<td></td>
</tr>
<tr>
<td>Nabilone [Cesamet]</td>
<td>Antiemetic—unknown mechanism; binds cannabinoid receptors and inhibits vomiting center in medulla</td>
<td>Emesis</td>
<td>Dry mouth, dizziness, inability to concentrate, disorientation, anxiety, tachycardia, depression, paranoia, psychosis</td>
<td></td>
</tr>
<tr>
<td>N-Acetylcysteine [Mucomyst]</td>
<td>Breaks disulfide bonds; mucolytic (loosens mucus plugs)—replenishes glutathione</td>
<td>Overdose of acetaminophen; liquefies sputum to assist expulsing</td>
<td>Unpleasant odor during administration</td>
<td></td>
</tr>
<tr>
<td>Nadolol [Corgard]</td>
<td>Antihypertensive—antianginal; blocker</td>
<td>Hypertension, angina, esophageal varices</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nafcillin</td>
<td>Antibiotic—β-lactam, penicillin derivative, cell wall inhibitor; same mechanism as penicillin; distinguished by activity against penicillinase-producing Staphylococcus; bactericidal</td>
<td>Staphylococcal infections (except MRSA)</td>
<td>Hypersensitivity reactions</td>
<td></td>
</tr>
<tr>
<td>Nalbuphine [Nubain]</td>
<td>Mixed agonist/antagonist of opioids</td>
<td>Similar to pentazocine</td>
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</tr>
<tr>
<td>Nalorphine</td>
<td>Mixed agonist/antagonist of opioids</td>
<td>Antagonizes the effects of morphine</td>
<td>Respiratory depression, analgesia</td>
<td></td>
</tr>
<tr>
<td>Naloxone [Narcan]</td>
<td>Antagonist of all opioids</td>
<td>Drug of choice for opioid antagonism</td>
<td>Ineffective to use against barbiturate overdose but safe</td>
<td></td>
</tr>
<tr>
<td>Naltrexone [RelVia]</td>
<td>Antagonist of all opioids</td>
<td>Longer action than naloxone; can be used orally</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Naproxen [Naprosyn, Aleve]</td>
<td>NSAID—reversibly inhibits COX (both COX-1 and COX-2) → decreases prostaglandin synthesis</td>
<td>Inflammation, pain</td>
<td>GI distress, GI ulcers, coagulation disorders, aplastic anemia, metabolic abnormalities, hypersensitivity, renal damage</td>
<td></td>
</tr>
<tr>
<td>Natamycin [Natacyn]</td>
<td>Antifungal—binds to cell membrane sterols (especially ergosterol); forms pores in membrane; fungicidal</td>
<td>Topical for fungal keratitis (eye)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nedocromil [Tilade]</td>
<td>Antiasthmatic; stabilizes membranes of mast cells and prevents mediator release</td>
<td>Asthma</td>
<td>Unpleasant taste</td>
<td></td>
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<td></td>
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<td></td>
<td>Not for acute asthmatic attacks</td>
</tr>
<tr>
<td>Drug</td>
<td>Category</td>
<td>Effect</td>
<td>Side Effects</td>
<td></td>
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<tr>
<td>Nefazodone [Serzone]</td>
<td>Antidepressant — postsynaptic 5-HT₂ antagonist</td>
<td>Depression</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nelfinavir</td>
<td>Antiviral, protease inhibitor — protease responsible for final step of viral proliferation; inhibits protease in progeny virions → assembly of nonfunctional viruses</td>
<td>AIDS (used in HAART)</td>
<td>GI irritation (nausea, diarrhea), hyperglycemia, hyperlipidemia, and lipodystrophy. All protease inhibitors end in -navir; metabolism occurs by cytochrome P450</td>
<td></td>
</tr>
<tr>
<td>Neomycin [Mycifradin, Neosporin]</td>
<td>Antibiotic — aminoglycoside; binds 30S ribosome subunits; bacteriostatic at low concentration; bactericidal at high concentration</td>
<td>Reduction of gut flora</td>
<td>Renal damage, deafness. Inhibits absorption of digitalis; topical use</td>
<td></td>
</tr>
<tr>
<td>Neostigmine [Prostigmin]</td>
<td>Inhibits cholinesterase</td>
<td>Paralytic ileus, neurogenic bladder, myasthenia gravis</td>
<td></td>
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</tr>
<tr>
<td>Nevirapine</td>
<td>Antiviral, nonnucleoside reverse transcriptase inhibitor — binds viral reverse transcriptase and inhibits movement of protein domains → terminates viral DNA synthesis → prevents integration of viral genome into the host DNA</td>
<td>AIDS (used in HAART)</td>
<td>Neutropenia, anemia, peripheral neuropathy, and rash</td>
<td></td>
</tr>
<tr>
<td>Niclosamide [Nicoclide]</td>
<td>Anthelmintic — inhibits anaerobic metabolism</td>
<td>Tapeworms: Taenia solium, Taenia saginata, Hymenolepis nana</td>
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</tr>
<tr>
<td>Nicotinic [Habitrol, NicoDerm, Nicotrol]</td>
<td>Nicotinic agonist</td>
<td>Stops smoking</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nifedipine [Adalat, Procardia]</td>
<td>Dihydropyridine Ca²⁺ channel blocker — blocks voltage-gated Ca²⁺ channels of vascular smooth muscle</td>
<td>Hypertension, angina pectoris, Prinzmetal angina, Raynaud phenomenon</td>
<td>Peripheral edema, flushing, dizziness, and constipation</td>
<td></td>
</tr>
<tr>
<td>Nitrofurantoin [Macrobid]</td>
<td>Antibiotic — urinary antiseptic; unknown mechanism of action</td>
<td>Gram-positive and gram-negative bacteria</td>
<td>Contraindicated in patients with renal insufficiency</td>
<td></td>
</tr>
<tr>
<td>Nitroglycerin</td>
<td>Antianginal — stimulates synthesis of cGMP, leading to muscle relaxation via NO formation</td>
<td>Angina</td>
<td>Headache, orthostatic hypotension, syncope. Monday disease; short acting</td>
<td></td>
</tr>
<tr>
<td>Nitrosoureas</td>
<td>Antineoplastic — alkylating agent; lipid soluble</td>
<td>CNS tumors</td>
<td></td>
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<tr>
<td>Nitrous oxide</td>
<td>Anesthetic agent</td>
<td>General anesthetic</td>
<td>Hypoxia</td>
<td></td>
</tr>
<tr>
<td>Therapeutic Agent (common name, if relevant) [trade name, where appropriate]</td>
<td>Class—Pharmacology and Pharmacokinetics</td>
<td>Indications</td>
<td>Side Effects or Adverse Effects</td>
<td>Contraindications or Precautions to Consider; Notes</td>
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<tr>
<td><strong>Nizatidine [Axid]</strong></td>
<td>H₂ blocker—reversibly blocks histamine H₂ receptors → reduces gastric acid secretion</td>
<td>Peptic ulcer disease, gastritis, and esophageal reflux</td>
<td>Gynecomastia; rare: confusion, dizziness, and headaches</td>
<td>Crosses placenta; milder side effect profile than cimetidine and ranitidine</td>
</tr>
<tr>
<td><strong>Norethindrone</strong></td>
<td>Progestosterone—binds progesterone receptors</td>
<td>Endometrial cancer, amenorrhea, abnormal uterine bleeding, and prevention of pregnancy</td>
<td></td>
<td>Also used to prevent endometrial hyperplasia in postmenopausal women taking estrogen</td>
</tr>
<tr>
<td><strong>Norfloxacin</strong></td>
<td>Antibiotic—quinolone; inhibits DNA gyrase (topoisomerase II) and topoisomerase IV → blocks DNA synthesis; bactericidal</td>
<td>Gram-negative infections (especially UTI and bone); <em>Pseudomonas, Enterobacteriaceae,</em> and <em>Neisseria;</em> gram-positive infections (staphylococci)</td>
<td>GI disturbances, headache, dizziness, phototoxicity, cartilage damage (children, fetus), tendonitis and tendon rupture (adults), myalgias (children)</td>
<td>May elevate theophylline to toxic levels, causing seizure; divalent cations inhibit gut absorption, therefore cannot be taken with milk, antacids, or iron-containing preparations</td>
</tr>
<tr>
<td><strong>Norgestimate</strong></td>
<td>Progestrone—binds progesterone receptors</td>
<td>Endometrial cancer, amenorrhea, abnormal uterine bleeding, and prevention of pregnancy</td>
<td></td>
<td>Also used to prevent endometrial hyperplasia in postmenopausal women taking estrogen</td>
</tr>
<tr>
<td><strong>Nortriptyline [Pamelor]</strong></td>
<td>TCAs—reuptake of NE and 5-HT at neuronal synapses</td>
<td>Major depression, panic disorder, and anxiety</td>
<td>Sedation, α-blocking effects (orthostatic hypotension), anticholinergic (tachycardia, dry mouth, and urinary retention), hallucinations (in elderly), and confusion (in elderly); overdose toxicity results in convulsions, coma, cardiotoxicity (arrhythmias), respiratory depression, and hyperpyrexia</td>
<td></td>
</tr>
<tr>
<td><strong>NPH [Humulin N, Novolin N]</strong></td>
<td>Intermediate-acting insulin—see mechanism for regular insulin</td>
<td>Diabetes mellitus (typically type 1)</td>
<td>Hypoglycemia (diaphoresis, vertigo, and tachycardia), insulin allergy, insulin antibodies, lipodystrophy</td>
<td></td>
</tr>
<tr>
<td><strong>Nystatin [Mycostatin]</strong></td>
<td>Antifungal—binds to cell membrane sterols (especially ergosterol) → disrupting fungal membranes; fungicidal</td>
<td>Mucosal candidal infections (skin, vaginal, and GI)</td>
<td>Few</td>
<td>Used topically or as mouth rinse; too toxic for systemic use</td>
</tr>
<tr>
<td><strong>Octreotide [Sandostatin]</strong></td>
<td>Synthetic analog of somatostatin—decreases release of growth hormone, gastrin, secretin, VIP, CCK, glucagon, and insulin</td>
<td>Acromegaly, glucagonoma, insulinoma carcinoid syndrome</td>
<td>Nausea, cramps, and gallstones</td>
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</tr>
<tr>
<td>Drug</td>
<td>Class Description</td>
<td>Indications</td>
<td>Side Effects / Precautions</td>
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<tr>
<td>Ofloxacin [Floxin]</td>
<td>Antibiotic—quinolone, DNA synthesis inhibitor; inhibits DNA gyrase (topoisomerase II) and topoisomerase IV → blocks DNA synthesis; bactericidal</td>
<td>Gram-negative infections (especially UTI and bone): <em>Pseudomonas</em>, Enterobacteriaceae, and <em>Neisseria</em>, gram-positive infections (staphylococci); intracellular: <em>Legionella</em></td>
<td>GI disturbances, headache, dizziness, phototoxicity, cartilage damage (children, fetus), tendonitis and tendon rupture (adults), myalgias (children) May elevate theophylline to toxic levels, causing seizure; divalent cations inhibit gut absorption, therefore cannot be taken with milk, antacids, or iron-containing preparations</td>
<td></td>
</tr>
<tr>
<td>Olanzapine [Zyprexa]</td>
<td>Atypical antipsychotic—blocks D₄, α₁, 5-HT, and muscarinic receptors</td>
<td>Schizophrenia, OCD, anxiety disorder, depression, mania, and Tourette syndrome</td>
<td>Agranulocytosis, weight gain, diabetes; extrapyramidal (occurs at a lower rate than typicals), anticholinergic (dry mouth, constipation), alpha blockade (hypotension), histamine (sedation); toxicity results in neuroleptic malignant syndrome (occurs at a lower rate than typicals)</td>
<td></td>
</tr>
<tr>
<td>Omeprazole [Prilosec]</td>
<td>Proton pump inhibitors—irreversibly inhibits H⁺/K⁺-ATPase in gastric parietal cells → decreases proton secretion by parietal cells</td>
<td>Peptic ulcer disease, gastritis, esophageal reflux, and Zollinger–Ellison syndrome</td>
<td>Inhibits cytochrome P450; given with clarithromycin and amoxicillin for <em>H. pylori</em></td>
<td></td>
</tr>
<tr>
<td>Ondansetron [Zofran]</td>
<td>Antiemetic—serotonin antagonist, 5-HT³ blocker</td>
<td>Nausea (caused by cancer therapy or postoperative state)</td>
<td>Headache, constipation, dizziness</td>
<td></td>
</tr>
<tr>
<td>Oprelvekin [Neumega]</td>
<td>IL-11 stimulates multiple stages of thrombopoiesis, increasing platelet production</td>
<td>Thrombocytopenia</td>
<td></td>
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</tr>
<tr>
<td>Orlistat [Xenical]</td>
<td>Inhibits pancreatic lipases → alters fat metabolism</td>
<td>Obesity (long term)</td>
<td>Steatorrhea, GI irritation, reduced absorption of fat-soluble vitamins, and headache Used in conjunction with modified diet</td>
<td></td>
</tr>
<tr>
<td>Oseltamivir [Tamiflu]</td>
<td>Antiviral—inhibits neuraminidase → decreases release of progeny viruses</td>
<td>Influenza A and B treatment and prophylaxis</td>
<td>Begin within 2 days of onset of flu symptoms to decrease the duration and intensity of symptoms</td>
<td></td>
</tr>
<tr>
<td>Oxacillin [Bactocill]</td>
<td>Antibiotic—β-lactam; penicillinase resistant</td>
<td>Staphylococcal infections</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oxaprozin [Daypro]</td>
<td>NSAID—mildly uricosuric</td>
<td>Acute gout</td>
<td>Contraindicated in patients with kidney stones</td>
<td></td>
</tr>
<tr>
<td>Oxazepam [Serax]</td>
<td>Antianxiety—benzodiazepine; enhances GABA; increases IPSP amplitude</td>
<td>Sedative, hypnotic, antiepileptic, anxiolytic</td>
<td>Recommended for use in elderly</td>
<td></td>
</tr>
<tr>
<td>Oxybutynin [Ditropan]</td>
<td>Antimuscarinic</td>
<td>Bladder/GI spasm, decreases acid in ulcer</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Therapeutic Agent (common name, if relevant) [trade name, where appropriate]</td>
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<tr>
<td><strong>Oxycodone</strong> [Roxicodone]</td>
<td>Partial opioid agonist at mu receptor</td>
<td>Severe pain, general anesthetic</td>
<td>Respiratory depression, constipation, nausea</td>
<td></td>
</tr>
<tr>
<td><strong>Oxytocin</strong> [Pitocin, Syntocinon]</td>
<td>Synthetic analog of oxytocin—stimulates uterine contraction and contraction of breast myoepithelial cells; milk letdown reflex</td>
<td>Induces labor, controls uterine hemorrhage</td>
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<tr>
<td><strong>Paclitaxel</strong> [Taxol]</td>
<td>Antineoplastic—stabilizes polymerization of microtubules</td>
<td>Ovarian and breast cancer</td>
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<tr>
<td><strong>Pamidronate</strong> [Aredia]</td>
<td>Bone stabilizer—pyrophosphate analog; reduces hydroxyapatite crystal formation, growth, and dissolution, which reduces bone turnover</td>
<td>Hypercalcemia of malignancy, Paget disease, osteoporosis, hyperparathyroidism</td>
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<tr>
<td><strong>Pancuronium</strong> [Pavulon]</td>
<td>Nondepolarizing neuromuscular blocker</td>
<td></td>
<td>Minimal histamine release</td>
<td></td>
</tr>
<tr>
<td><strong>Paroxetine</strong> [Paxil]</td>
<td>SSRIs—inhibit reuptake of 5-HT at neuronal synapses</td>
<td>Major depression, OCD, anorexia, and bulimia</td>
<td>Inhibits liver enzymes, nausea, agitation, sexual dysfunction (anorgasmia), and dystonic reactions</td>
<td></td>
</tr>
<tr>
<td><strong>Penicillamine</strong> [Cuprimine, Depen]</td>
<td>Antiarthritis—anti-gold medicine; not specific; unknown mechanism; arthritis relief</td>
<td>Rheumatic arthritis, copper poisoning, metal chelator</td>
<td>Decreases vitamin B&lt;sub&gt;6&lt;/sub&gt;, bone marrow suppression; proteinuria; autoimmune syndrome</td>
<td></td>
</tr>
<tr>
<td><strong>Penicillin</strong></td>
<td>Antibiotic—β-lactam, cell wall inhibitor; binds penicillin-binding protein → inhibits transpeptidase cross-linking of cell wall → inhibits bacterial cell wall synthesis → activates autolytic enzymes, bactericidal</td>
<td>Gram-positive cocci, gram-negative rods, gram-negative cocci, some anaerobes, enterococci, and spirochetes</td>
<td>Hypersensitivity reactions, neutropenia, thrombocytopenia, anemia, CNS effects, superinfection (pseudomembranous colitis)</td>
<td></td>
</tr>
<tr>
<td><strong>Pentazocine</strong> [Talwin]</td>
<td>Mixed agonist/antagonist of opioids</td>
<td>Analgesia</td>
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<tr>
<td><strong>Pentobarbital</strong> [Nembutal Sodium]</td>
<td>Barbiturate—prolongs IPSP duration</td>
<td>Cerebral edema, anesthetic</td>
<td>Only mixed agonist/antagonist available orally</td>
<td></td>
</tr>
<tr>
<td>Drug</td>
<td>Description</td>
<td>Common Uses</td>
<td>Side Effects/Interactions</td>
<td></td>
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<tr>
<td>Pergolide [Permax]</td>
<td>Antiparkinsonian—dopamine agonist; inhibits prolactin release</td>
<td>Treats breast engorgement, inhibits lactation</td>
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<tr>
<td>Phenazocine</td>
<td>Opioid agonist</td>
<td></td>
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</tr>
<tr>
<td>Phenelzine</td>
<td>Antidepressant, MAOIs—inhbits degradation of NE and 5-HT at neuronal synapses</td>
<td>Atypical depression (with hypopomnia, anxiety, sensitivity to rejection, and hypochondriasis)</td>
<td>Hypertensive episodes with ingestion of tyramine-containing foods or β-agonists, hyperthermia, and convulsions. Contraindicated with SSRIs and meperidine secondary to serotonin syndrome (hyperthermia, muscle rigidity, and cardiovascular collapse)</td>
<td></td>
</tr>
<tr>
<td>Phenobarbital</td>
<td>Barbiturate—prolongs IPSP duration</td>
<td>Antiepileptic (partial and tonic-clonic), cerebral edema, anesthetic</td>
<td>Sedation, Many drug interactions</td>
<td></td>
</tr>
<tr>
<td>Phenolphthalein [Ex-Lax]</td>
<td>Stimulant laxative—reduces absorption of electrolytes and water from gut</td>
<td>Constipation</td>
<td>Tumorigenic</td>
<td></td>
</tr>
<tr>
<td>Phenoxybenzamine [Dibenzyline]</td>
<td>Antihypertensive—α-blocker; long acting; irreversible</td>
<td>Phaeochromocytoma</td>
<td>Nasal congestion, miosis, orthostatic hypotension</td>
<td></td>
</tr>
<tr>
<td>Phentolamine [Regitine]</td>
<td>Antihypertensive—α-blocker</td>
<td>Diagnosis of pheochromocytoma; hypertension (especially tyrosine induced)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Phenylbutazone [Butazolidin]</td>
<td>NSAID</td>
<td>Rheumatic arthritis, acute gout</td>
<td>Agranulocytosis, aplastic anemia</td>
<td></td>
</tr>
<tr>
<td>Phenytoin [Dilantin]</td>
<td>Antiepileptic—decreases Na⁺ flux</td>
<td>Epilepsy (partial and tonic-clonic), digitalis-induced arrhythmia</td>
<td>Decreases folic acid, gingival hyperplasia, hirsutism, nystagmus</td>
<td></td>
</tr>
<tr>
<td>Phenytoin [Dilantin]</td>
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<td>Decreases folic acid, gingival hyperplasia, hirsutism, nystagmus</td>
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</tr>
<tr>
<td>Physostigmine [Eserine]</td>
<td>Inhibits cholinesterase</td>
<td>Intestinal or bladder atony, glaucoma</td>
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<tr>
<td>Pilocarpine [Ocusert]</td>
<td>Antiglaucoma—muscarinic agonist</td>
<td>Xerostomia, narrow- and open-angle glaucoma</td>
<td>Focusing problems, nausea, abdominal pain, sweating; high dose: bradycardia, hypotension</td>
<td></td>
</tr>
<tr>
<td>Pindolol [Visken]</td>
<td>Antihypertensive, antiarrhythmic (class III)—β-blocker</td>
<td>Hypertension</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### Therapeutic Agent (common name, if relevant) [trade name, where appropriate]

<table>
<thead>
<tr>
<th>Class—Pharmacology and Pharmacokinetics</th>
<th>Indications</th>
<th>Side Effects or Adverse Effects</th>
<th>Contraindications or Precautions to Consider; Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Pioglitazone [Actos]</strong></td>
<td>Hypoglycemic agent, thiazolidinedione — binds PPAR receptors; improves target cell response to insulin</td>
<td>Oral treatment for type 2 diabetes</td>
<td>Weight gain, edema, hepatotoxicity; increases LDL and TGs</td>
</tr>
<tr>
<td><strong>Piperacillin [Pipracil], piperacillin-tazobactam [Zosyn]</strong></td>
<td>Antibiotic—β-lactam, penicillin derivative, cell wall inhibitor; same mechanism as penicillin; distinguished by activity against <em>Pseudomonas</em>, bactericidal</td>
<td>Extended spectrum—<em>Pseudomonas</em>, <em>Proteus</em>, and <em>Enterobacter</em> species</td>
<td>Hypersensitivity reactions, decreased platelet function</td>
</tr>
<tr>
<td><strong>Pirenzepine</strong></td>
<td>Muscarinic antagonist—blocks M&lt;sub&gt;1&lt;/sub&gt; receptors on ECL cells → decreases histamine secretion; blocks M&lt;sub&gt;3&lt;/sub&gt; receptors on parietal cells → decreases acid secretion</td>
<td>Peptic ulcer</td>
<td>Tachycardia, dry mouth, and blurry vision (difficulty accommodating)</td>
</tr>
<tr>
<td><strong>Piroxicam [Feldene]</strong></td>
<td>NSAID</td>
<td></td>
<td>Long acting; contraindicated in the elderly</td>
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<tr>
<td><strong>Platelet-activating factor (PAF)</strong></td>
<td>Activation of platelets and PMN aggregation; increases vascular permeability</td>
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<tr>
<td><strong>Plicamycin [Mithracin]</strong></td>
<td>Antineoplastic—inhibits DNA-directed RNA synthesis; decreases protein synthesis needed for bone reabsorption</td>
<td>Paget disease, hypercalcemia</td>
<td></td>
</tr>
<tr>
<td><strong>Polymyxins (colistin)</strong></td>
<td>Antibiotic—binds to cell membranes → disrupt osmotic properties; bactericidal</td>
<td>Gram-negative bacteria: <em>Pseudomonas</em> and coliforms; usually topical; can be used IV or nebulized for difficult-to-treat gram-negative infections</td>
<td>Neurotoxic, nephrotoxic (acute renal tubular necrosis)</td>
</tr>
<tr>
<td><strong>Potassium</strong></td>
<td>Depresses ectopic pacemaker in hypokalemia</td>
<td>Digoxin toxicity</td>
<td></td>
</tr>
<tr>
<td><strong>Potassium iodide [Thyro-Block]</strong></td>
<td>Expectorant—increases bronchial secretions; high doses decrease release of thyroid hormone</td>
<td>Promotes cough; hyperthyroidism</td>
<td></td>
</tr>
<tr>
<td><strong>Pralidoxime (2-PAM) [Protopam]</strong></td>
<td>Acetylcholinesterase reactivator</td>
<td>Overdose of malathion/parathion organophosphates; must be used before aging occurs</td>
<td></td>
</tr>
<tr>
<td>Drug Name</td>
<td>Description</td>
<td>Indications</td>
<td>Side Effects</td>
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<tr>
<td><strong>Pramlintide [Symlin]</strong></td>
<td>Hypoglycemic agent, analog of amylin—a pancreatic hormone secreted with insulin that decreases glucagon and delays gastric emptying</td>
<td>Injectable treatment for type 2 diabetes</td>
<td>Nausea, vomiting, hypoglycemia</td>
</tr>
<tr>
<td><strong>Pravastatin [Pravachol]</strong></td>
<td>Lipid-lowering agent—HMG-CoA reductase inhibitor—inhibits synthesis of cholesterol precursor mevalonate; decreases LDL, increases HDL, and decreases TG</td>
<td>High LDL, preventative after thrombotic event (e.g., MI, stroke)</td>
<td>Reversible increase in LFTs; myositis; Contraindicated in pregnant or lactating women and children</td>
</tr>
<tr>
<td><strong>Praziquantel [Biltricide]</strong></td>
<td>Anthelmintic—increases membrane permeability causing loss of Ca&lt;sup&gt;2+&lt;/sup&gt;</td>
<td>Schistosomes, flukes</td>
<td>Gl disturbances, headache, fever, urticaria</td>
</tr>
<tr>
<td><strong>Prazosin [Minipress]</strong></td>
<td>Anti hypertensive—α&lt;sub&gt;1&lt;/sub&gt;-blocker → vasodilation → decreases total peripheral resistance</td>
<td>Pheochromocytoma, hypertension, BPH</td>
<td>Orthostatic hypotension, dizziness, headache</td>
</tr>
<tr>
<td><strong>Prednisone [Deltasone]</strong></td>
<td>Glucocorticoid—inhibits protein synthesis; reduces lymph node and spleen size; inhibits cell cycle activity of lymphoid cells; lyses T cells; suppresses antibody, prostaglandin, and leukotriene synthesis; blocks monocyte production of IL-1</td>
<td>Rheumatic arthritis, autoimmune disorders, allergic reaction, asthma, COPD, organ transplantation (especially during rejection crisis)</td>
<td>Osteoporosis, cushingoid reaction, psychosis, glucose intolerance, infection, hypertension, cataracts</td>
</tr>
<tr>
<td><strong>Prilocaine [Citanest]</strong></td>
<td>Anesthetic agent—blocks Na&lt;sup&gt;+&lt;/sup&gt; channels intracellularly</td>
<td>Local anesthetic</td>
<td>Sleepiness, light-headedness, visual/audio disturbances, restlessness, nystagmus, shivering, tonic-clonic convulsions, death</td>
</tr>
<tr>
<td><strong>Primaquine phosphate</strong></td>
<td>Antimalarial—unknown mechanism</td>
<td>Prevents relapse of <em>Plasmodium ovale</em> and <em>Plasmodium vivax</em> malaria; prophylaxis for <em>Plasmodium falciparum</em> malaria</td>
<td>GI disturbances, mild anemia; marked hemolysis in G6PD-deficient individuals; prolongs QT interval</td>
</tr>
<tr>
<td><strong>Probenecid [Benemid]</strong></td>
<td>Antigout—increased secretion of uric acid (uricosuric)—competes with uric acid for reabsorption in the kidney</td>
<td>Chronic gout therapy</td>
<td>Caution: should not be used in patients with sulfa allergies; rash; GI disturbances; drowsiness</td>
</tr>
<tr>
<td><strong>Probucol [Bifenabid, Lesterol]</strong></td>
<td>Lipid-lowering agent—lowers LDL and HDL; mechanism unknown</td>
<td>Hyperlipidemia</td>
<td>Prolongs QT interval; GI disturbances; Contraindicated in patients with heart disease</td>
</tr>
<tr>
<td><strong>Procainamide [Pronestyl, Procanbid]</strong></td>
<td>Antiarrhythmic (class IA)—Na&lt;sup&gt;+&lt;/sup&gt; channel blocker</td>
<td>Ventricular arrhythmia</td>
<td>Lupus-like syndrome</td>
</tr>
</tbody>
</table>

(continued)
<table>
<thead>
<tr>
<th>Therapeutic Agent (common name, if relevant) [trade name, where appropriate]</th>
<th>Class—Pharmacology and Pharmacokinetics</th>
<th>Indications</th>
<th>Side Effects or Adverse Effects</th>
<th>Contraindications or Precautions to Consider; Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Procaine [Novocain]</td>
<td>Anesthetic agent—blocks Na⁺ intracellularly</td>
<td>Local anesthetic</td>
<td>Sleepiness, light-headedness, visual/audio disturbances, restlessness, nystagmus, shivering, tonic-clonic convulsions, death</td>
<td></td>
</tr>
<tr>
<td>Procarbazine [Matulane]</td>
<td>Antineoplastic—DNA alkylation and strand breakage; inhibits nucleic acid and protein synthesis</td>
<td>Cancer</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prochlorperazine [Compazine]</td>
<td>Antiemetic—dopamine (D₂-receptor) antagonist</td>
<td>Nausea; counteracts nausea of migraine</td>
<td>Teratogenic</td>
<td></td>
</tr>
<tr>
<td>Progesterone [Progestasert]</td>
<td>Hormone—causes secretory changes in endometrium and breast; necessary to maintain pregnancy</td>
<td>Endometrial cancer, amenorrhea, abnormal uterine bleeding, and prevention of pregnancy</td>
<td>Long-lasting suppression of menses, endometriosis, hirsutism, bleeding disorders, nausea, breast tenderness, hyperpigmentation, gallbladder disease, migraines, hypertension</td>
<td>Also used to prevent endometrial hyperplasia in postmenopausal women taking estrogen</td>
</tr>
<tr>
<td>Prolactin</td>
<td>Hormone—stimulates lactation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Promethazine [Phenergan]</td>
<td>Antihistamine, antiemetic—D₂-receptor antagonist; H₁ blocker</td>
<td>Counteracts nausea of migraine; allergies, motion sickness</td>
<td>Sedation, CNS depression, atropine-like effects, allergic dermatitis, blood dyscrasias, teratogenicity, acute antihistamine poisoning</td>
<td></td>
</tr>
<tr>
<td>Propantheline</td>
<td>Muscarinic antagonist—blocks M₁ receptors on ECL cells → decreases histamine secretion; blocks M₃ receptors on parietal cells → decreases acid secretion</td>
<td>Peptic ulcer</td>
<td>Tachycardia, dry mouth, and blurry vision (difficulty accommodating)</td>
<td></td>
</tr>
<tr>
<td>Propofol [Diprivan]</td>
<td>Anesthetic agent</td>
<td>General anesthetic; fast acting for ambulatory or outpatients</td>
<td>Seizure</td>
<td></td>
</tr>
<tr>
<td>Drug</td>
<td>Class Description</td>
<td>Side Effects</td>
<td>Other Effects</td>
<td></td>
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<tr>
<td><strong>Propranolol</strong></td>
<td>β-Blocker, antimigraine—decreases cAMP and calcium currents → increases PR interval, suppresses abnormal pacemakers, especially in AV node</td>
<td>Ventricular tachycardia, supraventricular tachycardia, and slowing ventricular rate during atrial fibrillation and atrial flutter</td>
<td>Impotence, exacerbation of asthma, bradycardia, AV block, CHF, sedation, and sleep alteration</td>
<td></td>
</tr>
<tr>
<td><strong>Propylthiouracil</strong></td>
<td>Antithyroid agent—inhibits peroxidase enzyme in thyroid → decreases synthesis of thyroid hormone</td>
<td>Hyperthyroidism</td>
<td>Agranulocytosis</td>
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<td></td>
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<td></td>
<td>Crosses the placenta and can cause fetal goiter and hypothyroidism; preferred to methimazole in treating pregnant women with moderate to severe hyperthyroidism</td>
<td></td>
</tr>
<tr>
<td><strong>Protriptyline</strong></td>
<td>Antidepressant—TCA; blocks NE, 5-HT, muscarinic, α₂, and histamine receptors</td>
<td>Depression, anxiety</td>
<td>Tremors (NE block), anorexia (5-HT block), anticholinergic (muscarinic block), hypotension (α₁-block), drowsiness (histamine block)</td>
<td></td>
</tr>
<tr>
<td><strong>Pseudoephedrine</strong></td>
<td>α- and β-Adrenergic agonist; stimulates bronchial relaxation (β), increases heart rate (β), and vasoconstriction (α)</td>
<td>Nasal decongestant; sinusitis, upper respiratory tract infection</td>
<td>Tachycardia, increased BP, hypersensitivity</td>
<td></td>
</tr>
<tr>
<td><strong>Psyllium</strong></td>
<td>Bulk-forming laxative—dietary fiber</td>
<td>Constipation</td>
<td>Impaction above strictures, fluid overload, gas, and bloating</td>
<td></td>
</tr>
<tr>
<td><strong>PTH</strong></td>
<td>Increases plasma Ca²⁺ levels by increasing reabsorption in kidney; activates vitamin D, which aids in Ca²⁺ absorption from gut; resorbs Ca²⁺ from bone; decreases phosphate reabsorption by kidney</td>
<td></td>
<td>Used to distinguish between hypoparathyroidism and pseudohypoparathyroidism</td>
<td></td>
</tr>
<tr>
<td><strong>Pyrantel</strong></td>
<td>Anthelmintic—depolarizing neuromuscular blocker causing spastic paralysis in worms</td>
<td>Ascaris (roundworm), Ancylostoma (hookworm), threadworm</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Pyrazinamide</strong></td>
<td>Antibiotic—postulated mechanism involves inhibition of enzyme pyrazinamidase → inhibition of fatty acid synthesis</td>
<td>Mycobacterium</td>
<td>Impairs liver function</td>
<td></td>
</tr>
<tr>
<td><strong>Pyridostigmine</strong></td>
<td>Inhibits cholinesterase</td>
<td>Myasthenia gravis</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Pyrimethamine</strong></td>
<td>Antimalarial—inhibits dihydrofolate reductase</td>
<td>Malaria</td>
<td>Large doses causes megaloblastic anemia</td>
<td></td>
</tr>
</tbody>
</table>

(continued)
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<tbody>
<tr>
<td>Quetiapine [Seroquel]</td>
<td>Atypical antipsychotic—blocks D₂, 5-HT, α₁, and H₁ receptors</td>
<td>Schizophrenia, acute mania</td>
<td>Suicide attempt in major depression, arrhythmia, extrapyramidal (occurs at a lower rate than typicals), anticholinergic (occurs at lower rate than other agents), alpha blockade (hypotension), and histamine (sedation); toxicity results in neuroleptic malignant syndrome (occurs at a lower rate than typicals)</td>
<td></td>
</tr>
<tr>
<td>Quinapril [Accupril]</td>
<td>Antihypertensive—ACE inhibitor → inhibits conversion of angiotensin I to II → decreases Ang II levels → prevents vasoconstriction from Ang II</td>
<td>Hypertension, CHF, post-MI; prevention/treatment of diabetic nephropathy</td>
<td>Cough, angioedema, hyperkalemia, renal insufficiency (especially in bilateral renal artery stenosis)</td>
<td>Contraindicated in pregnancy (fetal renal malformation)</td>
</tr>
<tr>
<td>Quinidine [Quinaglute]</td>
<td>Antiarrhythmic (class IA)—Na⁺ channel blocker</td>
<td>Arrhythmias, acute malarial infection</td>
<td>May precipitate arrhythmias at high doses; nausea; vomiting; diarrhea; cinchonism: tinnitus, headache, nausea, disturbed vision; renal damage; hemolytic anemia; purpura; agranulocytosis</td>
<td>Torsades de pointes, inhibits cytochrome P450</td>
</tr>
<tr>
<td>Quinine</td>
<td>Antimalarial—unknown mechanism</td>
<td>Suppression and treatment of acute attack of chloroquine-resistant organism; leg cramps</td>
<td>Cinchonism: tinnitus, headache, nausea, disturbed vision; renal damage; hemolytic anemia; purpura; agranulocytosis</td>
<td></td>
</tr>
<tr>
<td>Quinolones</td>
<td>Antibiotic—blocks DNA synthesis by inhibiting DNA gyrase</td>
<td>Gram-negative infections (especially UTI and bone): Pseudomonas, Enterobacteriaceae, and Neisseria; gram-positive infections; intracellular: Legionella</td>
<td>GI disturbances, headache, diziness, phototoxicity, cartilage damage</td>
<td>May elevate theophylline to toxic levels, causing seizure; divalent cations inhibit gut absorption, therefore cannot be taken with milk antacids, or iron-containing preparations</td>
</tr>
<tr>
<td>Radioiodide (I-131)</td>
<td>Destroys thyroid gland</td>
<td>Hyperthyroidism</td>
<td>Hypothyroidism</td>
<td></td>
</tr>
<tr>
<td>Drug Name</td>
<td>Category</td>
<td>Effects</td>
<td>Side Effects</td>
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</tr>
<tr>
<td>Raloxifene [Evista]</td>
<td>Selective estrogen receptor modulator—breast (estrogen antagonist); endometrium (estrogen antagonist); prevents proliferation of endometrium; bone (estrogen agonist); decreases bone turnover, increases bone density; cardiovascular (estrogen agonist); decreases LDL</td>
<td>Osteoporosis, breast cancer</td>
<td>Hot flashes, sinusitis, weight gain, muscle pain, leg cramps, increased risk of blood clots</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Unlike estrogen, raloxifene does not decrease HDL</td>
<td></td>
</tr>
<tr>
<td>Raltegravir</td>
<td>Antiviral, integrase inhibitor— inhibits the final step in integration of viral DNA into host DNA</td>
<td>HAART</td>
<td>Neutropenia, pancreatitis, hepatotoxicity, hyperglycemia</td>
<td></td>
</tr>
<tr>
<td>Ranitidine [Zantac]</td>
<td>H&lt;sub&gt;2&lt;/sub&gt; blocker—blocks histamine H&lt;sub&gt;2&lt;/sub&gt; receptors reversibly → decreases proton secretion by parietal cells</td>
<td>Peptic ulcer disease, gastritis, and esophageal reflux</td>
<td>Gynecomastia, impotence, decreased libido in males, confusion, dizziness, and headaches</td>
<td></td>
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<td></td>
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<td></td>
<td>Crosses placenta, decreases renal excretion of creatinine, cytochrome P450 inhibitor</td>
<td></td>
</tr>
<tr>
<td>Repaglinide [Prandin]</td>
<td>Hypoglycemic agent— meglitinide; acts at pancreatic islet cell to reduce K&lt;sup&gt;+&lt;/sup&gt; efflux, increases Ca&lt;sup&gt;2+&lt;/sup&gt; influx, increases secretion of insulin</td>
<td>Oral treatment for type 2 diabetes</td>
<td>Hypoglycemia</td>
<td></td>
</tr>
<tr>
<td>Reserpine [Rauferia]</td>
<td>Antihypertensive—prevents storage of monoamines in synaptic vesicle</td>
<td>Hypertension</td>
<td>Mental depression, sedation, nasal stuffiness, and diarrhea</td>
<td></td>
</tr>
<tr>
<td>RhoGAM</td>
<td>Rh immunoglobulin</td>
<td>Prevents hemolytic disease of the newborn</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ribavirin</td>
<td>Antiviral—guanosine analog; inhibits IMP dehydrogenase → decreases synthesis of guanine nucleotides</td>
<td>Hepatitis C when given with interferon</td>
<td>Hemolytic anemia, elevated bilirubin; teratogen</td>
<td></td>
</tr>
<tr>
<td>Rifampin [Rifadin]</td>
<td>Antibiotic—inhibits DNA-dependent RNA polymerase</td>
<td>Mycobacterium; reduces resistance to dapsone when used in treatment of leprosy; prophylaxis in close contacts of people with N. meningitidis meningitis</td>
<td>Turns body fluid orange in color; liver damage</td>
<td></td>
</tr>
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<td></td>
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<td></td>
<td>Interferes with birth control pills by increasing estrogen metabolism; induces cytochrome P450</td>
<td></td>
</tr>
<tr>
<td>Risedronate [Actonel]</td>
<td>Bone stabilizer—bisphosphonate; pyrophosphate analog; reduces hydroxyapatite crystal formation, growth, and dissolution, which reduces bone turnover</td>
<td>Hypercalcemia of malignancy, Paget disease, osteoporosis, hyperparathyroidism</td>
<td>Pill-induced esophagitis</td>
<td></td>
</tr>
<tr>
<td>Therapeutic Agent (common name, if relevant) [trade name, where appropriate]</td>
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</tr>
<tr>
<td>Risperidone</td>
<td>Atypical antipsychotic—blocks D₂, 5-HT, α₁, and H₁ receptors</td>
<td>Schizophrenia, useful for positive and negative symptoms</td>
<td>Agranulocytosis, extrapyramidal (occurs at a lower rate than typicals), anticholinergic (occurs at lower rate than other agents), alpha blockade (hypotension), and histamine (sedation); toxicity results in neuroleptic malignant syndrome (occurs at a lower rate than typicals)</td>
<td>Second-line agent used for refractory schizophrenia</td>
</tr>
<tr>
<td>Ritodrine [Yutopar]</td>
<td>β₂-Agonist → uterine relaxation</td>
<td>Inhibits preterm labor</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ritonavir [Norvir]</td>
<td>Antiviral, protease inhibitor—protease responsible for final step of viral proliferation; inhibits protease in progeny virions → assembly of nonfunctional viruses</td>
<td>AIDS (used in HAART)</td>
<td>GI irritation (nausea, diarrhea), hyperglycemia, hyperlipidemia, and lipodystrophy</td>
<td>All protease inhibitors end in -navir; metabolism occurs by cytochrome P450</td>
</tr>
<tr>
<td>Rituximab</td>
<td>Monoclonal antibodies; binds to CD20 receptor on tumor cells, resulting in lysis</td>
<td>Non-Hodgkin lymphoma</td>
<td>Fever, rigor, chills; nausea, hypersensitivity; tumor lysis syndrome; irregular heart rhythms; infection; pancytopenia</td>
<td></td>
</tr>
<tr>
<td>Ropivacaine</td>
<td>Anesthetic agent—blocks Na⁺ intracellularly</td>
<td>Local anesthetic</td>
<td>Sleepiness, light-headedness, visual/audio disturbances, restlessness, nystagmus, shivering, tonic-clonic convolution, death</td>
<td></td>
</tr>
<tr>
<td>Rosiglitazone [Avandia]</td>
<td>Hypoglycemic agent, thiazolidinedione—binds PPARγ receptors, improves target cell response to insulin</td>
<td>Oral treatment for type 2 diabetes</td>
<td>Weight gain, edema, hepatotoxicity; increases LDL and TGs; may increase risk of MI</td>
<td>Contraindicated in CHF</td>
</tr>
<tr>
<td>Salmeterol [Serevent]</td>
<td>Antiasthmatic—long-acting β₂-agonist, leads to relaxation of smooth muscle</td>
<td>Asthma prophylaxis</td>
<td>Hand tremor, headache, nervousness, dizziness, cough, stuffed nose, runny nose, ear pain, muscle pain/cramps, sore throat</td>
<td>Not in acute asthmatic attack</td>
</tr>
<tr>
<td>Saquinavir [Invirase]</td>
<td>Antiviral, protease inhibitor—protease responsible for final step of viral proliferation; inhibits protease in progeny virions → assembly of nonfunctional viruses</td>
<td>AIDS (used in HAART)</td>
<td>GI irritation (nausea, diarrhea), hyperglycemia, hyperlipidemia, and lipodystrophy</td>
<td>All protease inhibitors end in -navir; metabolism occurs by cytochrome P450</td>
</tr>
<tr>
<td>Sargramostim [Leukine]</td>
<td>Granulocyte-macrophage colony-stimulating factor</td>
<td>Recovery of bone marrow (e.g., bone marrow transplant failure)</td>
<td>Hypertension</td>
<td></td>
</tr>
<tr>
<td>Drug</td>
<td>Class</td>
<td>Effect</td>
<td>Side Effects</td>
<td>Use</td>
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<tr>
<td><strong>Sarin/soman</strong></td>
<td></td>
<td></td>
<td>Irreversibly inhibits cholinesterase</td>
<td>Rapidly fatal</td>
</tr>
<tr>
<td><strong>Saxagliptin</strong> [Onglyza]</td>
<td>Hypoglycemic agent, DPP-IV inhibitor</td>
<td>Prevents degradation of incretin hormones ( \rightarrow ) decreased glucagon, increased insulin</td>
<td>Oral treatment for type 2 diabetes</td>
<td>Diarrhea, constipation, edema</td>
</tr>
<tr>
<td><strong>Scopolamine</strong></td>
<td>Anticholinergic</td>
<td>( \text{M}_1 )-muscarinic receptor antagonist</td>
<td>Motion sickness prophylaxis</td>
<td>Dry mouth, drowsiness, and vision disturbances</td>
</tr>
<tr>
<td><strong>Scorpion toxin</strong></td>
<td></td>
<td>Presynaptic neuromuscular junction blocker; overstimulates acetylcholine release</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Secobarbital [Seconal Sodium]</strong></td>
<td>Antiepileptic—anesthetic agent; barbiturate; prolongs IPSP duration</td>
<td>Epilepsy, cerebral edema</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Selegiline [Eldepryl]</strong></td>
<td>Antiparkinsonian</td>
<td>Increases dopamine by inhibiting MAO, irreversibly</td>
<td>Parkinson disease</td>
<td></td>
</tr>
<tr>
<td><strong>Senna [Senokot]</strong></td>
<td>Stimulant laxative; increases peristalsis</td>
<td>Constipation</td>
<td>Electrolyte imbalances (chronic use), melanosi coli</td>
<td></td>
</tr>
<tr>
<td><strong>Sertraline [Zoloft]</strong></td>
<td>SSRIs—inhibit reuptake of 5-HT at neuronal synapses</td>
<td>Major depression, OCD, anorexia, bulimia, and anxiety</td>
<td>Inhibits liver enzymes, nausea, agitation, sexual dysfunction (anorgasmia), and dystonic reactions</td>
<td>Contraindicated with MAOIs secondary to serotonin syndrome (hyperthermia, muscle rigidity, and cardiovascular collapse); allows time for antidepressant effect, usually takes 2–3 weeks</td>
</tr>
<tr>
<td><strong>Sevoflurane [Sevorane, Ultane]</strong></td>
<td>Anesthetic agent</td>
<td>General anesthetic</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Sibutramine [Meridia]</strong></td>
<td>Sympathomimetic serotonin and NE reuptake inhibitor</td>
<td>Obesity (short term and long term)</td>
<td>Hypertension, tachycardia</td>
<td></td>
</tr>
<tr>
<td><strong>Sildenafil</strong> [Viagra]</td>
<td>Phosphodiesterase type 5 inhibitor (cGMP-specific)—increased cGMP ( \rightarrow ) smooth muscle relaxation ( \rightarrow ) increased blood flow in the corpus cavernosum ( \rightarrow ) penile erection</td>
<td>Erectile dysfunction</td>
<td>Abnormal vision (impaired blue-green color vision), UTIs, cardiovascular events, priapism, dyspepsia, headache, and flushing</td>
<td>Risk of hypotension (fatal) in patient taking nitrates</td>
</tr>
<tr>
<td><strong>Simvastatin [Zocor]</strong></td>
<td>Lipid-lowering agent—HMG-CoA reductase inhibitors— inhibit synthesis of cholesterol precursor mevalonate; decreases LDL, increases HDL, and decreases TG</td>
<td>High LDL, preventative after thrombotic event (e.g., MI, stroke)</td>
<td>Reversible increase in LFTs; myositis</td>
<td>Contraindicated in pregnant and lactating women and children</td>
</tr>
</tbody>
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(continued)
## APPENDIX I: Drug Index

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<tr>
<th>Therapeutic Agent (common name, if relevant) [trade name, where appropriate]</th>
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<tr>
<td>Sitagliptin [Januvia]</td>
<td>Hypoglycemic agent, DPP-IV inhibitor—prevents degradation of incretin hormones → decreased glucagon, increased insulin</td>
<td>Oral treatment for type 2 diabetes</td>
<td>Diarrhea, constipation, edema</td>
<td></td>
</tr>
<tr>
<td>Sodium nitroprusside</td>
<td>Antianginal—direct release of NO → increases cGMP → vasodilator (arterial dilation)</td>
<td>Hypertensive emergency, CHF, and angina</td>
<td>Cyanide toxicity, hypotension</td>
<td>Short acting, given IV</td>
</tr>
<tr>
<td>Somatostatin [Zecnil]</td>
<td>Hormone—decreases release of growth hormone, gastrin, secretin, VIP, CCK, glucagon, and insulin</td>
<td>Acromegaly, glucagonoma, insulinoma</td>
<td>Nausea, cramps, gallstones</td>
<td></td>
</tr>
<tr>
<td>Sotalol [Betapace]</td>
<td>Antiarrhythmic (class III)—K⁺ channel blocker</td>
<td>Torsades de pointas</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Spectinomycin [Trobicin]</td>
<td>Aminoglycoside antibiotic—protein synthesis inhibitor; irreversibly binds 30S ribosome subunits; bacteriostatic at low concentration; bactericidal at high concentration</td>
<td>Broad spectrum: gram-negative rods; good for bone and eye infections; Proteus, Pseudomonas, Enterobacter, Klebsiella, and Escherichia coli</td>
<td>Ototoxicity, renal toxicity, neuromuscular blockade, nausea, vomiting, vertigo, allergic rash, superinfections</td>
<td>Used to treat gonorrhea in those allergic to penicillin</td>
</tr>
<tr>
<td>Spironolactone [Aldactone]</td>
<td>Potassium-sparing diuretic—binds to intracellular aldosterone steroid receptors in collecting tubules; blocks induction of Na⁺ channels and Na⁺/ATPase synthesis or blocks Na⁺ channels directly (amiloride, triamterene); loss of Na⁺, Cl⁻ in urine</td>
<td>Hyperaldosteronism, potassium depletion, and CHF</td>
<td>Hyperkalemic metabolic acidosis, gynecomastia (spironolactone), and antiandrogen effects</td>
<td>Results in decreased secretion of K⁺ and H⁺, which can lead to hyperkalemic metabolic acidosis; often given in combination with a thiazide</td>
</tr>
<tr>
<td>Streptokinase [Streptase]</td>
<td>Thrombolytic—plasminogen activator</td>
<td>Lysis of clots</td>
<td>Hemorrhage</td>
<td></td>
</tr>
<tr>
<td>Streptomycin</td>
<td>Aminoglycoside antibiotic—protein synthesis inhibitor; irreversibly binds 30S ribosome subunits; bacteriostatic at low concentration; bactericidal at high concentration</td>
<td>Broad spectrum: gram-negative rods; good for bone and eye infections; Proteus, Pseudomonas, Enterobacter, Klebsiella, and Escherichia coli; tuberculosis and other mycobacteria</td>
<td>Ototoxicity, renal toxicity, neuromuscular blockade, nausea, vomiting, vertigo, allergic rash, superinfections</td>
<td></td>
</tr>
<tr>
<td>Strychnine</td>
<td>Acts on the postsynaptic Renshaw cell; binds to glycine receptor (mimics effect of tetanus)</td>
<td>Depression</td>
<td>Fatal seizures</td>
<td>Rat poison</td>
</tr>
<tr>
<td>Drug Name</td>
<td>Category</td>
<td>Action</td>
<td>Side Effect</td>
<td>Contraindication</td>
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</tr>
<tr>
<td>Succinylcholine [Anectine]</td>
<td>Depolarizing neuromuscular blocker</td>
<td>Rapid-sequence intubation</td>
<td>Increases intraocular pressure; succinylcholine apnea in genetically defective pseudocholinesterase; malignant hyperthermia if given with halothane</td>
<td>Contraindicated in patients with glaucoma and patients taking antibiotics</td>
</tr>
<tr>
<td>Sucralfate [Carafate]</td>
<td>Antulcer—protective coating of GI lining</td>
<td>Reduces the effect of gastric acid on mucosa</td>
<td>Constipation</td>
<td></td>
</tr>
<tr>
<td>Sulfamethoxazole, sulfisoxazole, sulfadiazine</td>
<td>Antibiotic—sulfonamide, DNA synthesis inhibitor; competitive inhibitor of dihydropteroate synthetase (blocks folic acid synthesis); bacteriostatic</td>
<td>Broad spectrum: gram-positive UTI; chlamydial infection of genital tract and eye; treatment of nocardiosis</td>
<td>Forms crystals in kidney and bladder, causing damage; hypersensitivity reaction; photosensitivity; kernicterus (in infants); hemolysis (in G6PD deficiency)</td>
<td>Displaces other drugs such as warfarin from albumin</td>
</tr>
<tr>
<td>Sulfasalazine</td>
<td>Anti-inflammatory—sulfapyridine (antibacterial) and mesalamine (anti-inflammatory)</td>
<td>Ulcerative colitis, Crohn disease</td>
<td>Malaise, nausea, sulfonamide toxicity, and reversible oligospermia</td>
<td>Activated by colonic bacteria</td>
</tr>
<tr>
<td>Sulfapyrazone [Anturane]</td>
<td>Antigout—increased secretion of uric acid (uricosuric)—competes with uric acid for reabsorption in the kidney</td>
<td>Chronic gout therapy</td>
<td>Caution: should not be used in patients with sulf a allergies; GI irritation; hypersensitivity reaction; agranulocytosis</td>
<td>Should not be used to treat acute gout or patients with uric acid stones</td>
</tr>
<tr>
<td>Sulindac [Clinoril]</td>
<td>Anti-inflammatory—prodrug sulfide</td>
<td>Chronic inflammation (arthritis)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sumatriptan [Imitrex]</td>
<td>Antimigraine—agonist at 5-HT1d receptors</td>
<td>Acute attack of migraine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tacrolimus (FK506) [Prograf]</td>
<td>Immunosuppressant—blocks activation of T-cell transcription factors; involved in IL synthesis</td>
<td>Transplant rejection</td>
<td>Nephrotoxic; neurotoxic; hyperglycemia; GI disturbances</td>
<td></td>
</tr>
<tr>
<td>Tamoxifen [NoVadex]</td>
<td>Selective estrogen receptor modulator—competitively binds estrogen receptors; breast (estrogen antagonist); prevents proliferation of estrogen receptor-positive tumor cells; endometrium (partial agonist); bone (agonist); decreases bone turnover, increases bone density</td>
<td>Treats estrogen-dependent breast cancer in postmenopausal women; reduces contralateral breast cancer; osteoporosis prevention</td>
<td>May increase risk of endometrial cancer; increased risk of blood clots; hot flashes; flushing</td>
<td></td>
</tr>
<tr>
<td>Temazepam [Restoril]</td>
<td>Benzodiazepine—enhances GABA, increases IPSP amplitude</td>
<td>Sedative, hypnotic, antianxiety, antiepileptic</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
# APPENDIX I: Drug Index

<table>
<thead>
<tr>
<th>Therapeutic Agent (common name, if relevant) [trade name, where appropriate]</th>
<th>Class—Pharmacology and Pharmacokinetics</th>
<th>Indications</th>
<th>Side Effects or Adverse Effects</th>
<th>Contraindications or Precautions to Consider; Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tenofovir disoproxil fumarate (TDF)</td>
<td>Antiviral, nucleoside reverse transcriptase inhibitor—adenosine analog → inhibits viral reverse transcriptase</td>
<td>HAART</td>
<td>Nausea, vomiting, headache, renal dysfunction</td>
<td></td>
</tr>
<tr>
<td>Terazosin [Hytrin]</td>
<td>Antihypertensive—α₁-blocker</td>
<td>Pheochromocytoma, hypertension, BPH</td>
<td>Postural hypotension</td>
<td></td>
</tr>
<tr>
<td>Terbinafine [Lamisil]</td>
<td>Antifungal—inhibits squalene-2,3-epoxidase</td>
<td>Orally for onychomycosis, topically for dermatophytes</td>
<td>Hepatotoxicity</td>
<td></td>
</tr>
<tr>
<td>Terbutaline [Brethine, Bricanyl, Brethaire]</td>
<td>β₂-Agonist—bronchodilator; relaxes uterus</td>
<td>Bronchodilates to treat asthma; inhibits preterm labor; treatment of uterine hyperstimulation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tetanus toxin</td>
<td>Acts at the presynaptic Renshaw cell; prevents glycine release</td>
<td>Seizures</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tetracaine [Pontocaine]</td>
<td>Anesthetic agent—blocks Na⁺ channels intracellularly</td>
<td>Local anesthetic</td>
<td>Sleepiness, light-headedness, visual/audio disturbances, restlessness, nystagmus, shivering, tonic–clonic convulsions, death</td>
<td></td>
</tr>
<tr>
<td>Tetracycline [Achromycin, Sumycin, Topicycline]</td>
<td>Tetracycline antibiotic—protein synthesis inhibitor; binds 30S ribosome subunits → prevents attachment of tRNA; bacteriostatic</td>
<td>Broad-spectrum including atypical pathogens: <em>Chlamydia, Rickettsia, M. pneumoniae, V. cholerae, U. urealyticum, Francisella tularensis, H. pylori, and B. burgdorferi</em> (Lyme disease)</td>
<td>Liver toxicity, GI distress, depression of bone/teeth development, photosensitivity, Fanconi syndrome</td>
<td>Contraindicated in pregnancy and children; divalent cations inhibit gut absorption, therefore cannot take with milk, antacids, or iron-containing preparations; renally eliminated</td>
</tr>
<tr>
<td>THC (active ingredient in marijuana)</td>
<td>Unknown mechanism; binds cannabinoid receptors and inhibits vomiting center in medulla</td>
<td>Antiemetic</td>
<td>Dry mouth, dizziness, inability to concentrate, disorientation, anxiety, tachycardia, depression, paranoia, psychosis</td>
<td></td>
</tr>
<tr>
<td>Theophylline [Aerolate, Eliophyllin, Respid, Slo-bid, Slo-Phyllin, Theo-24, Theo-Dur, Theolair, Uniphyll]</td>
<td>Methylxanthines—unknown mechanism; postulated to inhibit phosphodiesterase → decreases cAMP hydrolysis → promotes bronchodilation; stimulates CNS, cardiac muscle; relaxes smooth muscle; produces diuresis; increases cerebral vascular resistance</td>
<td>Asthma</td>
<td>Cardiotoxicity, neurotoxicity</td>
<td>Metabolized by cytochrome P450; narrow therapeutic window; tolerance develops</td>
</tr>
</tbody>
</table>
## APPENDIX I: Drug Index

<table>
<thead>
<tr>
<th><strong>Thiabendazole [Mintezol]</strong></th>
<th><strong>Antihelmintic</strong></th>
<th><strong>Strongyloides, Ancylostoma</strong>&lt;br&gt;(hookworm), <strong>Enterobius</strong> [pinworm], <strong>Trichuris</strong> [whipworm]</th>
<th><strong>Vomiting, diarrhea, dizziness, bradycardia, hypotension, paresthesia, yellow vision, angioneurotic edema, perianal rashes</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>6-Thioguanine</td>
<td>Antineoplastic—inhibits purine synthesis; disrupts DNA and RNA synthesis</td>
<td>Adult leukemias</td>
<td>Bone marrow suppression</td>
</tr>
<tr>
<td>Thiopental [Pentothal]</td>
<td>Anesthetic agent—barbiturate; prolongs IPSP duration</td>
<td>Antiepileptic, cerebral edema, anesthetic (stage 3 anesthetic)</td>
<td>Laryngospasm during stage 3 induction</td>
</tr>
<tr>
<td>Thioridazine [Mellaril]</td>
<td>Antipsychotic—phenothiazines; muscarinic, blocks D&lt;sub&gt;2&lt;/sub&gt; and α&lt;sub&gt;1&lt;/sub&gt; receptors</td>
<td>Psychosis</td>
<td>Extrapyramidal (dystonia, akinesia, akathisia, and tardive dyskinesia), anticholinergic (dry mouth, constipation), alpha blockade (hypotension), and histamine (sedation); toxicity results in neuroleptic malignant syndrome (rigidity, myoglobinuria, autonomic instability, and hyperpyrexia)</td>
</tr>
<tr>
<td>Thiotepa [Thioplex]</td>
<td>Antineoplastic—unknown mechanism</td>
<td>Cancer</td>
<td>Cardiac toxicity (prolongs QT interval); atropine-like effects are very common; antimuscarinic effects exacerbate tardive dyskinesia; visual impairment has been reported</td>
</tr>
<tr>
<td>Thiothixene [Navane]</td>
<td>Antipsychotic—thioxanthene; blocks D&lt;sub&gt;2&lt;/sub&gt;, α&lt;sub&gt;1&lt;/sub&gt;, and H&lt;sub&gt;1&lt;/sub&gt; receptors</td>
<td>Psychosis</td>
<td>Anticholinergic effects</td>
</tr>
<tr>
<td>Thrombopoietin</td>
<td>Recombinant human thrombopoietin</td>
<td>Thrombocytopenia</td>
<td>Not effective against penicillin-resistant Staphylococcus; can be combined with clavulanic acid (β-lactamase inhibitor) to enhance spectrum; administered IV</td>
</tr>
<tr>
<td>Ticarcillin [Ticar], ticarcillin-clavulanate [Timentin]</td>
<td>Antibiotic—β-lactam, penicillin derivative, cell wall inhibitor; same mechanism as penicillin; distinguished by activity against <em>Pseudomonas</em>, bactericidal</td>
<td>Extended spectrum—<em>Pseudomonas</em>, Proteus, and Enterobacter spp.</td>
<td>Hypersensitivity reactions, decreased platelet function</td>
</tr>
<tr>
<td>Ticlopidine [Ticlid]</td>
<td>Inhibits ADP-induced platelet aggregation, acts on ADP receptor</td>
<td>Transient ischemic attack, stroke</td>
<td>Not effective against penicillin-resistant Staphylococcus; can be combined with clavulanic acid (β-lactamase inhibitor) to enhance spectrum; administered IV</td>
</tr>
<tr>
<td>Timolol [Betimol, Blocadren, Timoptic]</td>
<td>Antiglaucoma—antihypertensive; β-blocker</td>
<td>Hypertension, MI, glaucoma</td>
<td>Asthma, bradycardia</td>
</tr>
<tr>
<td>Tizanidine [Zanaflex]</td>
<td>Centrally acting muscle relaxant—presynaptic inhibition of motor neurons; acts like clonidine on α&lt;sub&gt;2&lt;/sub&gt; receptor</td>
<td>Muscle spasms from spinal cord injury; multiple sclerosis</td>
<td></td>
</tr>
<tr>
<td>Tocainide [Tonocard]</td>
<td>Antiarrhythmic (class IB)—Na&lt;sup&gt;+&lt;/sup&gt; channel blocker</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tolbutamide [Orinase]</td>
<td>Hypoglycemic agent, first-generation sulfonylurea—closes potassium channels located in β-cell membrane → reduces K&lt;sup&gt;+&lt;/sup&gt; efflux, increases Ca&lt;sup&gt;2+&lt;/sup&gt; influx → increases secretion of insulin</td>
<td>Oral treatment for type 2 diabetes</td>
<td>Hypoglycemia, GI disturbances, muscle weakness, mental confusion</td>
</tr>
</tbody>
</table>

(continued)
<table>
<thead>
<tr>
<th>Therapeutic Agent (common name, if relevant) [trade name, where appropriate]</th>
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<th>Indications</th>
<th>Side Effects or Adverse Effects</th>
<th>Contraindications or Precautions to Consider; Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tolnaftate [Tinactin, Desenex]</td>
<td>Antifungal—unknown mechanism; bactericidal</td>
<td>Topical against <em>Trichophyton rubrum</em>, <em>Trichophyton tonsurans</em>, and <em>Trichophyton mentagrophytes</em></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Topiramate [Topamax]</td>
<td>Antiepileptic—blocks Na⁺ channels</td>
<td>Add-on drug for epilepsy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Torsemide [Demadex]</td>
<td>Loop diuretic; inhibits Na⁺/K⁺/Cl⁻ channels</td>
<td>Diuresis</td>
<td>Ototoxicity, metabolic alkalosis, hypokalemia, hyperglycemia, hyperuricemia</td>
<td></td>
</tr>
<tr>
<td>tPA [alteplase] [Activase]</td>
<td>Thrombolytic—plasminogen activator</td>
<td>Lysis of clots</td>
<td>Hemorrhage</td>
<td></td>
</tr>
<tr>
<td>Tramadol [Ultram]</td>
<td>Analgesic—similar to opioid agonist</td>
<td>Chronic pain of osteoarthritis</td>
<td>Nausea, vomiting, constipation, and drowsiness</td>
<td></td>
</tr>
<tr>
<td>Tranexamic acid (AMCHA) [Cyklokapron]</td>
<td>Thrombotic agent—competitive inhibitor of plasminogen activation</td>
<td>Inhibits fibrinolysis; promotes thrombosis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tranylcypromine [Parnate]</td>
<td>Antidepressant—MAOI; inhibits degradation of NE and 5-HT at neuronal synapses; nonselective, but isoenzyme A most important; reversible</td>
<td>Atypical depression (with hypersomnia, anxiety, sensitivity to rejection, and hypochondriasis)</td>
<td>Hypertensive episodes with ingestion of tyramine-containing foods or β-agonists, hyperthermia, and convulsions</td>
<td>Contraindicated with SSRIs and meperidine secondary to serotonin syndrome (hyperthermia, muscle rigidity, and cardiovascular collapse); only reversible MAOI</td>
</tr>
<tr>
<td>Trazodone [Desyrel]</td>
<td>Atypical antidepressant—inhibits reuptake of serotonin</td>
<td>Major depression (especially with insomnia), insomnia</td>
<td>Sedation, nausea, priapism, and postural hypotension</td>
<td></td>
</tr>
<tr>
<td>Tretinoin [Retin-A]</td>
<td>Retinoids—inhibits microcomedo formation and existing lesions; makes keratinocytes in sebaceous follicles less adherent and easier to remove</td>
<td>Acne, skin cancer</td>
<td>Photosensitivity</td>
<td></td>
</tr>
<tr>
<td>TRH (prorelin) [Relefact TRH]</td>
<td>Stimulates TSH and prolactin release</td>
<td>Diagnosis of thyroid disease</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Triamcinolone</td>
<td>Glucocorticoid—inhibits protein synthesis; reduces lymph node and spleen size; inhibits cell cycle activity of lymphoid cells; lyases T cells; suppresses antibody, prostaglandin, and leukotriene synthesis; blocks monocyte production of IL-1</td>
<td>Addison disease, rheumatic arthritis, autoimmune disorders, allergic reaction, asthma, organ transplantation (especially during rejection crisis)</td>
<td>Osteoporosis, cushingoid reaction, psychosis, glucose intolerance, infection, hypertension, cataracts, peptic ulcers</td>
<td></td>
</tr>
<tr>
<td>Drug Name [Trade Name]</td>
<td>Description</td>
<td>Indications</td>
<td>Side Effects</td>
<td></td>
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</tr>
<tr>
<td>Triamterene [Dyrenium]</td>
<td>Potassium-sparing diuretic—binds to intracellular aldosterone steroid receptors in collecting tubules; blocks induction of Na+ channels and Na+/K+ ATPase synthesis and blocks Na channels directly; loss of Na+, Cl– in urine</td>
<td>Hyperaldosteronism, potassium depletion, and CHF</td>
<td>Hyperkalemic metabolic acidosis, gynecomastia (spironolactone), and antiandrogen effects. Results in decreased secretion of K+ and H+, which can lead to hyperkalemic metabolic acidosis; often given in combination with a thiazide</td>
<td></td>
</tr>
<tr>
<td>Triazolam [Halcion]</td>
<td>Benzodiazepine—enhances GABA; increases IPSP amplitude</td>
<td>Sedative, hypnotic, antianxiety</td>
<td>Paranoia, violent behavior, antiepileptic</td>
<td></td>
</tr>
<tr>
<td>Trientine</td>
<td>Metal chelator</td>
<td>Copper poisoning, Wilson disease</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Trifluridine ophthalmic [Viroptic]</td>
<td>Antiviral—thymidine derivative; inhibits DNA polymerase; inhibits DNA synthesis</td>
<td>DNA viruses</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Trihexyphenidyl [Artane]</td>
<td>Antiparkinsonian—muscarnic blocker</td>
<td>Parkinson disease</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Triiodothyronine (T3) [Thyrox]</td>
<td>Synthetic analog of thyroid hormone T3</td>
<td>Hypothyroidism</td>
<td>Tachycardia, heat intolerance, tremors, and arrhythmia</td>
<td></td>
</tr>
<tr>
<td>Trimethaphan [Arfonad]</td>
<td>Antihypertensive—nondepolarizing nicotinic blocker</td>
<td>Hypertension (short term)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Trimethoprim [Proloprim, Trimpex]</td>
<td>Antibiotic—DNA synthesis inhibitor; competitive inhibition of dihydrofolate reductase (blocks folic acid synthesis); bacteriostatic</td>
<td>Gram-negative UTI; combined with sulfonamides to treat UTI, otitis media, chronic bronchitis, shigellosis, Salmonella, and PCP</td>
<td>Megaloblastic anemia, leukopenia, and granulocytopenia. Supplementation with folic acid may help pancytopenia</td>
<td></td>
</tr>
<tr>
<td>TSH (thyrotropin) [Thyrogen]</td>
<td>Increases output of thyroid hormone</td>
<td>Assesses thyroid function; increases uptake of I-131 in thyroid carcinoma</td>
<td></td>
<td></td>
</tr>
<tr>
<td>d-Tubocurarine [Tubarine]</td>
<td>Nondepolarizing neuromuscular blocker</td>
<td>Topical for dermatophytes (especially tinea pedis)</td>
<td>Paralysis</td>
<td></td>
</tr>
<tr>
<td>Undecylenic acid [Desenex]</td>
<td>Antifungal—unknown mechanism; fungistatic</td>
<td></td>
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<tr>
<td>Urofollitropin [Metrodin]</td>
<td>FSH analog</td>
<td>Infertility</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urokinase [Abbokinase]</td>
<td>Thrombolytic agent—plasminogen activator</td>
<td>Lysis of clots</td>
<td>Hemorrhage</td>
<td></td>
</tr>
<tr>
<td>Valacyclovir [Valtrex]</td>
<td>Antiviral—guanosine analog, inhibits DNA polymerase</td>
<td>HSV, VZV, EBV, and CMV at high doses</td>
<td>GI disturbances, CNS and renal problems, headache, tremor, rash. Longer lasting than acyclovir</td>
<td></td>
</tr>
<tr>
<td>Valproic acid [Depakene]</td>
<td>Antiepileptic—blocks Na+ channels and increases GABA</td>
<td>Epilepsy: partial, absence, and tonic–clonic</td>
<td>Liver toxicity, pancreatitis; potentially fatal</td>
<td></td>
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</tbody>
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(continued)
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<tr>
<td><strong>Valsartan</strong> [Diovan]</td>
<td>Antihypertensive—Ang II receptor blockers → prevents vasoconstriction from Ang II</td>
<td>Hypertension</td>
<td>Fetal renal toxicity, hyperkalemia</td>
<td></td>
</tr>
<tr>
<td><strong>Vancomycin</strong> [Vancocin]</td>
<td>Antibiotic—cell wall inhibitor; binds to D-alanyl-D-alanine portion of cell wall → inhibits cell wall glycopeptide polymerization → stops bacterial cell wall synthesis; usually bactericidal</td>
<td>Serious infections by gram-positive bacteria: <em>Streptococcus, Staphylococcus, and some anaerobes (especially C. difficile)</em></td>
<td>Ototoxicity, nephrotoxicity, thrombophlebitis, and diffuse flushing—“red man syndrome” caused by histamine release</td>
<td>Can prevent red man syndrome by pretreatment with antihistamines and slow infusion; resistance occurs when bacteria change amino acid in cell wall to D-alanyl-D-lactate</td>
</tr>
<tr>
<td><strong>Vardenafil</strong></td>
<td>Phosphodiesterase type 5 inhibitor (cGMP-specific)—increased cGMP → smooth muscle relaxation → increased blood flow in the corpus cavernosum → penile erection</td>
<td>Erectile dysfunction</td>
<td>Abnormal vision (impaired blue-green color vision), UTIs, cardiovascular events, priapism, dyspepsia, headache, and flushing</td>
<td>Risk of hypotension (fatal) in patient taking nitrates</td>
</tr>
<tr>
<td><strong>Vasopressin</strong> [Pitressin]</td>
<td>Antidiuretic—recruits water channels to luminal membrane in collecting duct</td>
<td>Antidiuresis; treats central diabetes insipidus</td>
<td>Overhydration; allergic reaction; larger doses: pallor, diarrhea, and hypertension; coronary constriction; chronic rhinopharyngitis</td>
<td>Also known as antidiuretic hormone</td>
</tr>
<tr>
<td><strong>Vecuronium</strong> [Norcuron]</td>
<td>Nondepolarizing neuromuscular blocker</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Venlafaxine</strong> [Effexor]</td>
<td>Antidepressant, anti-anxiolytic—serotonin and NE reuptake inhibitor</td>
<td>Depression, generalized anxiety disorder, social phobia</td>
<td>Sweating, nausea, constipation, anorexia, somnolence, dry mouth, dizziness, insomnia, and hypertension; nervousness, abnormal dreams, tremor, abnormal vision, impotence, and anorgasmia</td>
<td></td>
</tr>
<tr>
<td><strong>Verapamil</strong> [Calan, Isoptin]</td>
<td>Non-dihydropyridine Ca²⁺ channel blockers—block voltage-gated Ca²⁺ channels of cardiac smooth muscle</td>
<td>Hypertension, angina pectoris, arrhythmia</td>
<td>Cardiac depression, peripheral edema, flushing, dizziness, and constipation</td>
<td></td>
</tr>
<tr>
<td><strong>Vidarabine</strong> [Vira-A]</td>
<td>Antiviral—adenosine analog; inhibits DNA polymerase</td>
<td>Herpes (also topical for HSV keratitis); varicella</td>
<td>GI disturbances; CNS, bone marrow suppression, liver and kidney dysfunction</td>
<td></td>
</tr>
<tr>
<td><strong>Vinblastine</strong> [Velban]</td>
<td>Antineoplastic—blocks polymerization of microtubules</td>
<td>Hodgkin disease</td>
<td>Peripheral neuritis</td>
<td></td>
</tr>
<tr>
<td>Drug</td>
<td>Category/Action</td>
<td>Indications</td>
<td>Adverse Effects</td>
<td></td>
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<td>-----------------------------</td>
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<tr>
<td><strong>Vincristine</strong> (Oncovin)</td>
<td>Antineoplastic—blocks polymerization of microtubules</td>
<td>Acute leukemia</td>
<td>Peripheral neuritis</td>
<td></td>
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<tr>
<td>Vitamin A (retinol) [Aquasol A]</td>
<td>Vitamin</td>
<td>Night blindness, xerophthalmia</td>
<td>Hyperkeratosis</td>
<td></td>
</tr>
<tr>
<td><strong>Vitamin B&lt;sub&gt;1&lt;/sub&gt; (thiamine)</strong></td>
<td>Vitamin</td>
<td>Alcoholics (prophylaxis for Wernicke–Korsakoff syndrome)</td>
<td>Decrease results in beriberi</td>
<td></td>
</tr>
<tr>
<td>Vitamin B&lt;sub&gt;2&lt;/sub&gt; (riboflavin)</td>
<td>Vitamin—component of flavin compounds: FMN, FAD</td>
<td></td>
<td>Inhibits chlorpromazine; decreased results in skin, oral, and ocular lesions</td>
<td></td>
</tr>
<tr>
<td>Vitamin B&lt;sub&gt;3&lt;/sub&gt; (nicotinic acid, niacin)</td>
<td>Vitamin—component of nicotinic compounds: NAD, NADH</td>
<td>Maintains integrity of skin, decreases VLDL and LDL, increases HDL</td>
<td>Flushing, pruritus, myopathy, hepatotoxicity</td>
<td></td>
</tr>
<tr>
<td>Vitamin B&lt;sub&gt;5&lt;/sub&gt; (pantothenic acid)</td>
<td>Vitamin—component of CoA</td>
<td></td>
<td>Decrease results in dermatitis, diarrhea, dementia, and death</td>
<td></td>
</tr>
<tr>
<td>Vitamin B&lt;sub&gt;6&lt;/sub&gt; (pyridoxine)</td>
<td>Vitamin</td>
<td>Protein metabolism, neurotransmitter synthesis</td>
<td>Neuritis, convulsions</td>
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<tr>
<td>Vitamin B&lt;sub&gt;12&lt;/sub&gt; (Cyanocobalamin)</td>
<td>Vitamin</td>
<td>Megaloblastic anemia</td>
<td>Isoniazid decreases amount</td>
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<td>Vitamin C (ascorbic acid)</td>
<td>Vitamin</td>
<td>Maintains collagen; oxidation-reduction reactions</td>
<td>Decrease results in scurvy</td>
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<td>Vitamin D (calcitriol) [Rocaltrol]</td>
<td>Vitamin—binds to receptors in cytoplasm; alters gene expression and protein synthesis; increases bone resorption of Ca&lt;sup&gt;2+&lt;/sup&gt;; increases renal and intestinal absorption of Ca&lt;sup&gt;2+&lt;/sup&gt; and phosphate</td>
<td>Rickets, osteomalacia, hypocalcemia, hypoparathyroidism, osteoporosis</td>
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<td>Vitamin E</td>
<td>Vitamin—antioxidant</td>
<td>Possible prophylaxis for heart disease</td>
<td>Decrease results in abortion, creatinuria, and ceroid pigment</td>
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<td>Vitamin K (phytonadione) [Mephyton]</td>
<td>Vitamin—enhances clotting factors</td>
<td>Bleeding disorders</td>
<td>Decreased in children of mothers taking phenytoin or phenobarbital</td>
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<td>Voriconazole [Vfend]</td>
<td>Antifungal—inhibits ergosterol synthesis, preventing cell membrane formation</td>
<td>Serious invasive fungal infections (invasive aspergillosis, invasive candidiasis)</td>
<td>Vision disturbances (blurred vision, light sensitivity). GI disturbances, hepatotoxicity</td>
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<tr>
<td>Warfarin [Coumadin]</td>
<td>Anticoagulant—inhibits potassium epoxide regeneration</td>
<td>Thrombosis</td>
<td>Bleeding</td>
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<td></td>
<td></td>
<td></td>
<td>Contraindicated in pregnancy, patients with liver, CNS, and hemostatic disease; 99% exists protein bound; extremely sensitive to cytochrome P450 system</td>
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<td>Therapeutic Agent (common name, if relevant) [trade name, where appropriate]</td>
<td>Class—Pharmacology and Pharmacokinetics</td>
<td>Indications</td>
<td>Side Effects or Adverse Effects</td>
<td>Contraindications or Precautions to Consider; Notes</td>
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<td>Yohimbine</td>
<td>Impotence therapy—α2 antagonist</td>
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<td>Zafirlukast (Accolate), montelukast (Singular)</td>
<td>Antiasthma agent—antileukotriene; blocks leukotriene receptors (leukotriene D&lt;sub&gt;2&lt;/sub&gt;, LTD&lt;sub&gt;2&lt;/sub&gt;) → prevents bronchoconstriction and inflammatory cell infiltrate</td>
<td>Asthma (especially aspirin-induced asthma)</td>
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<td>Zanamivir (Relenza)</td>
<td>Antiviral—inhibits neuraminidase → decreases release of progeny viruses</td>
<td>Influenza A and B treatment and prophylaxis</td>
<td>Begin within 2 days of onset of flu symptoms to decrease the duration and intensity of symptoms</td>
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<td>Zidovudine (ZDV; formerly azidothymidine [AZT]) (Retrovir)</td>
<td>Antiasthma, nucleoside reverse transcriptase inhibitor—inhibits viral reverse transcriptase → prevents integration of DNA copy of viral genome into the host DNA</td>
<td>AIDS (used in HAART); pregnant women with HIV to reduce fetal transmission</td>
<td>Neutropenia, anemia (megalo- blasts), peripheral neuropathy, pancreatitis, and lactic acidosis</td>
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<tr>
<td>Zileuton</td>
<td>Antiasthma agent—5-lipoxygenase inhibitor → inhibits conversion of arachidonic acid to leukotriene → prevents bronchoconstriction and inflammatory cell infiltrate</td>
<td>Improves asthma</td>
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<td>Zolpidem [Ambien]</td>
<td>Binds to benzodiazepine receptor but is not a benzodiazepine</td>
<td>Insomnia</td>
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5-HT, 5-hydroxytryptamine (serotonin); ACE, angiotensin-converting enzyme; ACTH, adrenocorticotropic hormone; ADP, adenosine diphosphate; AMCHA, 4-(aminomethyl) cyclohexane carboxylic acid; AML, acute myelocytic leukemia; ANP, atrial natriuretic peptide; AST/ALT, aspartate aminotransferase/alanine aminotransferase; ATPase, adenosine triphosphatase; AV, atrioventricular; BCNU, bischloroethyl nitrosourea; BP, blood pressure; BPH, benign prostatic hypertrophy; cAMP, cyclic adenosine monophosphate; CD4, cell-mediated immunity; CMS, central nervous system; CoA, coenzyme A; COPD, chronic obstructive pulmonary disease; COX, cyclooxygenase; DAG, diacylglycerol; DNA, deoxyribonucleic acid; DHEA, dehydroepiandrosterone; DPP-IV, dipeptidyl peptidase-IV; EBV, Epstein–Barr virus; ECL, enterochromaffin-like; EtOH, ethanol; FAD, flavin adenine dinucleotide; FMN, flavin mononucleotide; FSH, follicle-stimulating hormone; G6PD, glucose-6-phosphate dehydrogenase; GABA, γ-aminobutyric acid; GI, gastrointestinal; GLP-1, glucagon-like peptide-1; GnRH, gonadotropin-releasing hormone; HAART, highly active antiretroviral therapy; HDL, high-density lipoprotein; HLA, human leukocyte antigen; HMG-CoA, 3-hydroxy-3-methylglutaryl coenzyme A; HSV, herpes simplex virus; IGF-1, insulin-like growth factor-1; IL-1, interleukin-1; IL-6, interleukin-6; INN, international nonproprietary name; IP<sub>3</sub>, inositol triphosphate; IV, intravenous; LDL, low-density lipoprotein; LFT, liver function test; L-T, luteinizing hormone; MAO, monoamine oxidase; MAOI, monoamine oxidase inhibitor; MI, myocardial infarction; MPA, memantine; MRA, mechanistic action; MRSA, methicillin-resistant Staphylococcus aureus; MRSA, methicillin-resistant Staphylococcus aureus; NA, noradrenaline; NAD, nicotinamide adenine dinucleotide; NE, norepinephrine; NMDA, N-methyl-D-aspartate; NO, nitric oxide; NPH, neutral protamine Hagedorn; NSAID, nonsteroidal anti-inflammatory drug; OCD, obsessive-compulsive disorder; PCOS, polycystic ovary syndrome; PCT, peroxisome proliferator-activated receptor-γ; PDE, phosphodiesterase; PGE<sub>1</sub>, prostaglandin E<sub>1</sub>; PGE<sub>2</sub>, prostaglandin E<sub>2</sub>; PGF<sub>2</sub>, prostaglandin F<sub>2</sub>; PMN, polymorphonuclear; PPAR-γ, peroxisome proliferator-activated receptor-γ; PTH, parathyroid hormone; PTT, partial thromboplastin time; PVC, premature ventricular contraction; Rh, rhesus [factor]; SA, sinusoidal; SLE, systemic lupus erythematosus; SSRIs, selective serotonin reuptake inhibitors; TCA, tricyclic antidepressant; TDF, tenofovir disoproxil fumarate; TGF, tumor growth factor; Tg, thyroglobulin; TSH, thyroid-stimulating hormone; T2DM, type-2 diabetes mellitus; TNF, tumor necrosis factor; UP, upper respiratory tract; UTI, urinary tract infection; VIP, vasoactive intestinal peptide; VLDL, very low-density lipoprotein; VZV, varicella-zoster virus; WBC, white blood cell.
# APPENDIX II: Bug Index

## BACTERIA

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<tr>
<th>Name</th>
<th>Morphology</th>
<th>Pathogenesis</th>
<th>Description of Disease</th>
<th>Laboratory Findings, Notes</th>
<th>Transmission</th>
<th>Prevention and Therapy</th>
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<tbody>
<tr>
<td>Actinomyces israelii</td>
<td>Gram-positive; filamentous; anaerobic</td>
<td>Unknown</td>
<td>Actinomycosis—oral, thoracic, pelvic, or peritoneal abscesses with draining sinus tracts</td>
<td>Forms filaments; sulfur granules</td>
<td>Dental disease or trauma</td>
<td>Penicillin and drainage</td>
</tr>
<tr>
<td>Bacillus anthracis</td>
<td>Gram-positive; rod with square ends; capsule of D-glutamate (only protein capsule); non-motile; spore former; aerobic</td>
<td>Anthrax toxin—edema factor (exotoxin); protective antigen for cell entry; lethal factor (zinc MP increases TNF)</td>
<td>Anthrax—three clinical syndromes: cutaneous (black eschar), inhalational (respiratory symptoms and widened mediastinum), and GI (abdominal pain)</td>
<td>Medusa head colonies; catalase positive</td>
<td>Spores from animals (usually cattle)</td>
<td>Attenuated strain human vaccine; penicillin; ciprofloxacin; doxycycline</td>
</tr>
<tr>
<td>Bacillus cereus</td>
<td>Gram-positive; rod; spore former; aerobic</td>
<td>Spores germinate when rice is reheated; enterotoxins—emetic toxin (heat stable), diarrhea toxin (heat labile)</td>
<td>Food poisoning—early vomiting and late diarrhea</td>
<td></td>
<td>Enters through the GI tract via reheated rice</td>
<td>Avoid reheated rice and beans; treatment is symptomatic; cephalosporin</td>
</tr>
<tr>
<td>Bacteroides fragilis</td>
<td>Gram-negative; bacilli; anaerobic; capsulated; no exotoxin</td>
<td>Capsule; weak endotoxin</td>
<td>Infections below diaphragm; peritonitis; bacteremia; pelvic inflammatory disease; foul-smelling abscess; sepsis</td>
<td>Mixed infections; pleomorphic</td>
<td>Deep penetrating wounds; wound debridement</td>
<td>Metronidazole, clindamycin</td>
</tr>
<tr>
<td>Bordetella pertussis</td>
<td>Gram-negative; coccobacilli; capsule</td>
<td>Noninvasive infection of bronchial epithelium; pertussis toxin (two subunits)—A subunit ADP ribosylates adenylyl cyclase, increasing cAMP, whereas B subunit causes attachment; tracheal cytotoxin destroys ciliated epithelial cells, resulting in cough</td>
<td>Whooping cough; three stages of disease: catarhal, paroxysmal coughing, and convalescent</td>
<td>Culture nasopharynx onto 10%–15% blood agar (Bordet-Gengou agar); slide agglutination test</td>
<td>Droplet nuclei</td>
<td>Acellular pertussis vaccine (at 2, 4, and 6 months) or whole inactive cells; erythromycin (use in catarhal stage or prophylaxis for sick contacts); treatment in paroxysmal coughing stage is supportive</td>
</tr>
<tr>
<td>Borrelia burgdorferi</td>
<td>Spirochete; microaerophilic; flagella</td>
<td>Invasion and replication in the bloodstream; immune response to organism results in pathology</td>
<td>Lyme disease—erythema chronicum migrans with involvement of the heart, joints, and CNS</td>
<td>Common in the northeastern, midwestern, and western United States</td>
<td>Deer ticks; serology</td>
<td>Avoid ticks; wear long pants in wooded areas; doxycycline and penicillin</td>
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</tbody>
</table>

(continued)
## APPENDIX II: Bug Index

### BACTERIA (Continued)

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<td>Catalase; LPS; inhibits release of peroxidase in macrophages</td>
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<td>Campylobacter jejuni</td>
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<td>Obligate intracellular</td>
<td>Replicates within host lysosomes, using host’s cellular machinery</td>
<td>Strains A–C: blindness; strains D–K: nongonococcal urethritis, cervicitis; strains L1–L3: lymphogranuloma venereum</td>
<td>Leading cause of preventable blindness in the world; inactive form extracellular (elementary body) and metabolically active form intracellular (reticulate body)</td>
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<td>Gram-positive; rod; spore former; anaerobic</td>
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<td>Exotoxins A and B—A (cholera-like) causes fluid release and hemorrhagic necrosis; B (diphtheria-like) damages mucosa and causes pseudo-membrane formation</td>
<td>Antibiotic-associated pseudo-membranous colitis; bloody diarrhea</td>
<td>ELISA detects toxin B in the stool sample</td>
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<td>Clostridium difficile</td>
<td>Gram-positive; rod; spore former; anaerobic</td>
<td>Exotoxins A and B—A (cholera-like) causes fluid release and hemorrhagic necrosis; B (diphtheria-like) damages mucosa and causes pseudo-membrane formation</td>
<td>Antibiotic-associated pseudo-membranous colitis; bloody diarrhea</td>
<td>ELISA detects toxin B in the stool sample</td>
<td>Hospital workers</td>
<td>Withdraw causative antibiotics (classically clindamycin); oral metronidazole, oral vancomycin</td>
</tr>
<tr>
<td><strong>Clostridium perfringens</strong></td>
<td>Gram-positive; rod; spore former; anaerobic</td>
<td>α-Toxin (damages cell membranes); β-toxin (tissue necrosis and hemolysis); cholera-like heat-labile enterotoxin (food poisoning—watery diarrhea); spores establish in GI and produce enterotoxins</td>
<td>Gas gangrene; food poisoning; anaerobic cellulites</td>
<td>Large rods found in food; double zone of hemolysis</td>
<td>Grows in traumatized tissue (muscle); spores in food and soil germinate in reheated foods (stews, soups)</td>
<td>Clean and debride wounds; cook food well</td>
</tr>
<tr>
<td><strong>Clostridium tetani</strong></td>
<td>Gram-positive; rod; spore former (tennis racquet shaped); anaerobic</td>
<td>Tetanos toxin (exotoxin)—blocks release of inhibitory neurotransmitters</td>
<td>Tetanus: lockjaw (trismus), spastic paralysis (opisthotonos), and sardonic grin (risus sardonicus)</td>
<td>Usually not recovered by culture</td>
<td>Spore entry via wound (e.g., a rusty nail)</td>
<td>Tetanus toxoid vaccine (2, 4, 6, and 18 months); booster every 10 years; tetanus Ig (passive immunity); penicillin</td>
</tr>
<tr>
<td><strong>Corynebacterium diphtheriae</strong></td>
<td>Gram-positive; rod; club shaped; arranged in V or L form; not spore former</td>
<td>Exotoxin—A subunit ADP ribosylates EF-2, and B subunit binds toxin to the cell; phage conversion</td>
<td>Diphtheria—pseudomembrane forms in the throat; bull neck; systemic toxemia</td>
<td>Tellurite plate (Loffler medium) grows black colonies</td>
<td>Airborne droplets</td>
<td>Inactivated toxoid vaccine; antitoxin (neutralizes unbound toxin); penicillin; erythromycin</td>
</tr>
<tr>
<td><strong>Coxiella burnetii</strong></td>
<td>Obligate intracellular</td>
<td>Unknown</td>
<td>Q fever</td>
<td>Only rickettsia not transmitted to humans by an arthropod vector; occupational hazard for tanners, sheep shearers, and dairy farmers</td>
<td>Inhalation of aerosols of urine and feces; transplacental</td>
<td>Tetracycline</td>
</tr>
<tr>
<td><strong>Enterococcus faecalis</strong></td>
<td>Gram-positive; cocci</td>
<td>Lipoteichoic acid</td>
<td>Urinary, biliary, and cardiovascular infections; endocarditis</td>
<td>Catalase negative; bacitracin resistant; variable hemolysis; grows in 6.5% NaCl/Lancefield group D</td>
<td>Normal flora of gut gaining access to blood</td>
<td>Penicillin or amoxicillin and an aminoglycoside</td>
</tr>
<tr>
<td><strong>Escherichia coli</strong></td>
<td>Gram-negative; bacilli</td>
<td>Endotoxin—septic shock; heat-labile enterotoxin (LT): increased cAMP leads to diarrhea; heat-stable enterotoxin (ST) stimulates guanylate cyclase to cause diarrhea; pili: adhere to epithelium especially in UTIs; verotoxin (O157:H7); Shigella-like toxin in enterohemorrhagic E. coli (EHEC) that inhibits 28S rRNA to cause bloody diarrhea</td>
<td>UTI: sepsis; neonatal meningitis; enteropathogenic E. coli (EPEC): traveler’s diarrhea; enterotoxigenic E. coli (ETEC): watery diarrhea; enteroinvasive E. coli (EIEC): dysenter; HEC: bloody diarrhea, hemolytic uremic syndrome</td>
<td>Oxidase—cysteine agar</td>
<td>Transplacental; fecal–oral route; foodborne</td>
<td>UTIs: trimethoprim-sulfamethoxazole, ciprofloxacin; sepsis: cephalosporins; traveler’s diarrhea: rehydration</td>
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<tr>
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<tbody>
<tr>
<td>Francisella tularensis</td>
<td>Gram-negative; rod; intracellular</td>
<td>Capsule; intracellular within macrophages; granuloma formation</td>
<td>Painful lymph nodes; glandular and ocular ulcers</td>
<td>Serology</td>
<td>Zoonotic via rabbits and ticks</td>
<td>Live attenuated vaccine; streptomycin; thorough cooking of meat</td>
</tr>
<tr>
<td>Gardnerella vaginalis</td>
<td>Gram variable; bacillus; anaerobic</td>
<td>Unknown</td>
<td>Vaginosis—watery discharge, fishy odor</td>
<td>Clue cells (epithelial cells coated with bacteria); whiff test</td>
<td></td>
<td>Metronidazole</td>
</tr>
<tr>
<td>Haemophilus ducreyi</td>
<td>Gram-negative; bacilli</td>
<td>Virulence via pili</td>
<td>Chancroid with pain and purulent exudate</td>
<td>Lesions similar to those of syphilis; lymphadenopathy</td>
<td></td>
<td>Sexually transmitted</td>
</tr>
<tr>
<td>Haemophilus influenzae</td>
<td>Gram-negative; coccobacilli; polysaccharide capsule (polyribitol phosphate)</td>
<td>IgA protease degrades antibody and attaches to respiratory tract; capsule (type B) prevents phagocytosis</td>
<td>Infantile meningitis; epiglotitis; number 2 cause of otitis media and sinusitis</td>
<td>Needs heme (factor X) and NAD (factor V) to grow; chocolate agar; check CSF</td>
<td>Respiratory droplets</td>
<td>Hib vaccine (B-type capsule conjugated to diphtheria toxoid as a carrier protein); ceftriaxone</td>
</tr>
<tr>
<td>Helicobacter pylori</td>
<td>Gram-negative; bacilli; motile; flagella</td>
<td>Urease results in ammonia production and subsequent gastric damage</td>
<td>Peptic ulcers (type B gastritis)</td>
<td>Microaerophilic; Campy plate; urea breath test; urease positive; serology ELISA; biopsy</td>
<td>Ingestion</td>
<td>Triple therapy: amoxicillin, omeprazole, and clarithromycin; quadruple therapy: bismuth, tetracycline, metronidazole, and omeprazole</td>
</tr>
<tr>
<td>Klebsiella pneumoniae</td>
<td>Gram-negative; bacilli; capsule; positive quellung reaction</td>
<td>Large capsule hinders phagocytosis</td>
<td>Pneumonia, particularly in malnourished alcoholics; UTI; bacteremia</td>
<td>Currant jelly sputum (thick bloody sputum)</td>
<td>Aspiration of respiratory droplets</td>
<td>Cephalosporins</td>
</tr>
<tr>
<td>Legionella pneumophila</td>
<td>Gram-negative; bacilli</td>
<td>Endotoxin affects smokers, alcoholics, and those older than 55 years of age</td>
<td>Legionnaire disease (atypical pneumonia)</td>
<td>Dieterle silver stain; cysteine required for culture; urine test for Legionella antigen</td>
<td>Aerosol from environmental water sources and contaminated air conditioning system</td>
<td>Erythromycin, quinolones</td>
</tr>
<tr>
<td>Listeria monocytogenes</td>
<td>Gram-positive; rod; arranged in V or L form; tumbling motility; not spore former</td>
<td>Grows intracellularly in macrophages; listeriolysin-O cytotoxic</td>
<td>Meningitis and sepsis in newborns and immunocompromised individuals</td>
<td>Small, gray colonies; β-hemolysis; motility; serology</td>
<td>Transferred to humans by animals or their feces, unpasteurized milk; contaminated vegetables, cheese, and cabbage</td>
<td>Ampicillin and gentamicin; trimethoprim-sulfamethoxazole</td>
</tr>
<tr>
<td><strong>Moraxella catarrhalis</strong></td>
<td>Gram-negative; diplococcus</td>
<td>Upper respiratory tract infection; number 3 cause of otitis media and sinusitis</td>
<td>Transmitted by respiratory secretions</td>
<td>Azithromycin; penicillin resistant (100% strains make β-lactamase)</td>
<td></td>
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</tr>
<tr>
<td><strong>Mycobacterium avium-intracellulare (MAC)</strong></td>
<td>Acid-fast bacilli</td>
<td>Unknown</td>
<td>TB-like disease in immunocompromised individuals</td>
<td>From the soil and water to immunocompromised individuals</td>
<td>Azithromycin plus ethambutol plus rifampin</td>
<td></td>
</tr>
<tr>
<td><strong>Mycobacterium leprae</strong></td>
<td>Acid-fast bacilli; obligate intracellular</td>
<td>Tuberculoid: cell-mediated response causes damage; lepromatous: anergy of CD8 cells leads to uncontrolled replication</td>
<td>Leprosy—tuberculoid and lepromatous; lesions in cool parts of body</td>
<td>Cannot be grown in culture but is harvested in the footpads of armadillos; acid-fast stain of infected areas; lepra cells (modified mononuclear epithelioid cells containing acid-fast bacilli)</td>
<td>Prolonged contact, especially with the lepromatous form</td>
<td>Dapsone and rifampin for tuberculoid form (6-month treatment); clofazimine, dapsone, and rifampin for lepromatous form (2-year treatment)</td>
</tr>
<tr>
<td><strong>Mycobacterium tuberculosis</strong></td>
<td>Acid-fast bacilli; aerobic; high lipid cell walls (mycotic acids and wax D)</td>
<td>Cord factor; granulomas and caseation</td>
<td>Primary TB (chronic pneumonia), secondary TB (reactivation, hemoptysis), military TB (disseminated), latent TB</td>
<td>Ziehl-Neelsen stain; slow-growing (3–8 weeks) or Lowenstein-Jensen medium; niacin positive; PPD positive if &gt;10 cm after 48 h</td>
<td>Droplets from coughing</td>
<td>BCG vaccine with live attenuated organisms (rarely used in the United States); isoniazid, rifampin, ethambutol, pyrazinamide initially, then isoniazid plus rifampin to complete 6–9 months of therapy</td>
</tr>
<tr>
<td><strong>Mycoplasma pneumoniae</strong></td>
<td>Obligate intracellular; not seen on a Gram stain; smallest free-living organism; only bacteria with cholesterol in membrane (no cell wall)</td>
<td>Hydrogen peroxide and lytic enzymes resulting in damage to the respiratory tract</td>
<td>Walking pneumonia; bullous myringitis (inflamed tympanic membrane); common in young adults (college)</td>
<td>Positive cold agglutinin; highest incidence in 5- to 15-year-olds</td>
<td>Respiratory droplets</td>
<td>Erythromycin</td>
</tr>
<tr>
<td><strong>Neisseria gonorrhoeae</strong> (gonococcus)</td>
<td>Gram-negative; cocci; coffee bean–shaped pairs; no polysaccharide capsule</td>
<td>Endotoxin (lipid A); pili with variation; proteins I, II, III (porin, adhesion, autoagglutination); IgA protease penicillinase plasmid</td>
<td>Urethral and vaginal infections; discharge; salpingitis and PID; neonatal conjunctivitis; septic arthritis</td>
<td>Thayer-Martin agar; only glucose fermentation; oxidase positive; also check for chlamydia caused by common coinfection</td>
<td>Sexual contact; newborns; symptomatic in men but not usually in women</td>
<td>Condoms; erythromycin or silver nitrate in neonates; ceftriaxone; spectinomycin and tetracycline</td>
</tr>
<tr>
<td><strong>Neisseria meningitidis</strong> (meningococcus)</td>
<td>Gram-negative; diplococci; coffee bean–shaped pairs; polysaccharide capsule (antiphagocytic)</td>
<td>Endotoxin (LPS) contains lipid A; capsule; IgA protease; pili variation; deficiencies in late-acting complement components; asplenic patients</td>
<td>Meningitis; petechial rash; pharyngitis; Waterhouse–Friderichsen syndrome</td>
<td>Glucose and maltose fermentation; oxidase positive; lumbar puncture with high protein and low glucose; grows on Thayer-Martin agar</td>
<td>Respiratory droplets</td>
<td>Vaccine, rifampin, or ciprofloxacin (prophylaxis for close contacts); penicillin G or ceftriaxone</td>
</tr>
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### BACTERIA (Continued)

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<tr>
<td><strong>Nocardia asteroides</strong></td>
<td>Acid-fast; gram-positive branching bacillus; aerobic</td>
<td>Lysosome-phagosome fusion inhibited, immunocompromised individuals at risk</td>
<td>Nocardiosis—lung, heart, kidney, and brain abscesses</td>
<td>Forms filaments</td>
<td>Airborne particles from soil; noncommunicable</td>
<td>Sulfonamides</td>
</tr>
<tr>
<td><strong>Pasteurella multocida</strong></td>
<td>Gram-negative; cocccobacillus;</td>
<td></td>
<td></td>
<td></td>
<td>Bite/scratch of a dog or cat</td>
<td></td>
</tr>
<tr>
<td><strong>Proteus vulgaris and mirabilis</strong></td>
<td>Gram-negative; bacillus</td>
<td>Pili (adherence to renal pelvis); urease (alkalinization urine, increased precipitation, resulting in increased stone formation)</td>
<td>UTI</td>
<td>Urease positive; swarming motility colonies</td>
<td>GU flora</td>
<td>Ciprofloxacin, trimethoprim-sulfamethoxazole (TMP–SMX)</td>
</tr>
<tr>
<td><strong>Pseudomonas aeruginosa</strong></td>
<td>Gram-negative; cocccobacilli</td>
<td></td>
<td></td>
<td></td>
<td>Water; environment; opportunistic: patients with catheters, leukemia, burns, cystic fibrosis, ventilatory assistance, neutropenia, chronic lung disease</td>
<td>May express broad resistance to antibiotics</td>
</tr>
<tr>
<td><strong>Rickettsia prowazekii</strong></td>
<td>Obligate intracellular</td>
<td>Invasion of the endothelial lining; possible endotoxin</td>
<td>Epidemic typhus</td>
<td></td>
<td>Louse</td>
<td>Tetracycline</td>
</tr>
<tr>
<td><strong>Rickettsia rickettsii</strong></td>
<td>Obligate intracellular</td>
<td>Invasion of endothelial lining</td>
<td>Rocky Mountain spotted fever: vasculitis, rash spreads from periphery inward</td>
<td>Well-Felix reaction (agglutination when patient’s serum mixed with OX strain of Proteus vulgaris)</td>
<td>Dermacentor ticks</td>
<td>Tetracycline</td>
</tr>
<tr>
<td><strong>Rickettsia typhi</strong></td>
<td>Obligate intracellular</td>
<td>Invasion of endothelial lining</td>
<td>Endemic typhus—rash spreads from the trunk outward</td>
<td></td>
<td>Spread by fleas</td>
<td>Tetracycline</td>
</tr>
<tr>
<td><strong>Salmonella spp.</strong></td>
<td>Gram-negative; rod; multiple flagella</td>
<td>Invades mucosa of GI tract; penetration of layers and systemic infection (typhoid fever); flagellar proteins; endotoxin</td>
<td>Typhoid fever, gastroenteritis, sepsis</td>
<td>Lactose-negative; polysaccharide, somatic O antigens and protein flagellar H antigens; (usually poultry) encapsulated; Widal test</td>
<td>Fecal–oral; contaminated food</td>
<td>Fluoroquinolone, ceftriaxone, azithromycin</td>
</tr>
<tr>
<td><strong>Shigella spp.</strong></td>
<td>Gram-negative; rod; nonmotile; not spore former</td>
<td>Invades mucosal M cells; presented to macrophage, which increase TNF and IL-1; produces micro-abscesses and ulcers; begins in small intestine and invades lower colon, Shiga toxin (A/B toxin): works on 28S ribosome and removes the base; low infective dose; invasion into blood is rare.</td>
<td>Bacterial dysentry (shigellosis): ulcerative colitis of large intestine, fever, chills, cramps, tenesmus, bloody stool.</td>
<td>Rectal swab; three types: dysenteriae (rare, most severe), sonnei (most common, day care), flexneri (gay men).</td>
<td>Fecal–oral route.</td>
<td>Public health measures; significant resistance; fluoroquinolone, ceftriaxone, azithromycin.</td>
</tr>
<tr>
<td><strong>Staphylococcus aureus</strong></td>
<td>Gram-positive; cocci; capsule; protein A in the cell wall; yellow, creamy, grapelike clusters on culture. Rapid growth; protein A (antiphagocytic); enterotoxin (watery diarrhea); toxic shock syndrome toxin; exfoliation; α-toxin; coagulase.</td>
<td>Abscesses; pyogenic infections (endocarditis, osteomyelitis); food poisoning; toxic shock syndrome; scalded skin syndrome.</td>
<td>Coagulase positive; catalase positive; β-hemolytic; novo-biocin sensitive; ferment mannitol.</td>
<td>Via the hands from the skin, nasal mucosa; enterotoxin: ham, chicken salad, cottage cheese, processed food.</td>
<td>Hand washing; 80% penicillin resistant (make β-lactamase); vancomycin; first-generation cephalosporin; nafcillin, oxacillin.</td>
<td></td>
</tr>
<tr>
<td><strong>Staphylococcus epidermidis</strong></td>
<td>Gram-positive; cocci; white, creamy, grapelike clusters on culture. Surface glycocalyx.</td>
<td>Endocarditis; infection on catheters and implant sites; sepsis in neonates.</td>
<td>Coagulase negative; catalase positive, no hemolysis; novobiocin sensitive.</td>
<td>On skin; IV drug users.</td>
<td>Vancomycin.</td>
<td></td>
</tr>
<tr>
<td><strong>Staphylococcus saprophyticus</strong></td>
<td>Gram-positive; cocci; creamy, grapelike clusters. Selectively adheres to transitional epithelium.</td>
<td>UTI in young women.</td>
<td>Coagulase negative; catalase positive, no hemolysis; novobiocin resistant.</td>
<td>Many sexual partners.</td>
<td>Quinolones, oral cephalosporin.</td>
<td></td>
</tr>
<tr>
<td><strong>Streptococcus agalactiae</strong></td>
<td>Gram-positive; cocci; diploid; group B Streptococcus. Capsular antigen (contains sialic acid blocks opsonization).</td>
<td>Number 1 cause of neonatal sepsis and meningitis.</td>
<td>Catalase negative; bacitracin resistant; β-hemolysin; Lancefield group B; hippurate hydrolysis positive.</td>
<td>Genital tract of some women.</td>
<td>Ampicillin before delivery; penicillin G.</td>
<td></td>
</tr>
<tr>
<td><strong>Streptococcus pneumoniae</strong></td>
<td>Gram-positive; cocci; lancet shaped; in pairs; polysaccharide capsule (85 different types). Capsule prevents phagocytosis; IgA protease; adheres to mucosa.</td>
<td>Pneumonia; meningitis; bacteremia; upper respiratory infection; otitis media.</td>
<td>Catalase negative; α-hemolysin bile soluble; inhibited by optochin; quelling reaction (capsular swelling).</td>
<td>Inhalation of aerosols, which leads to colonization of oropharynx.</td>
<td>Polysaccharide capsular vaccine available for high-risk groups; penicillin and erythromycin.</td>
<td></td>
</tr>
<tr>
<td><strong>Streptococcus pyogenes</strong></td>
<td>Gram-positive; cocci; chains or pairs; rough or smooth hyaluronic acid capsule.</td>
<td>M protein (pili); streptokinase (dissolves fibrin); DNase; hyaluronidase; hemolysins: erythrogenic toxin (scarlet fever rash); streptolysin-O and streptolysin-S; exotoxin A (superantigen causing TSS-like syndrome).</td>
<td>Pharyngitis; cellulitis; rheumatic fever; acute glomerulonephritis; TSS-like syndrome.</td>
<td>Catalase negative; bacitracin (A disk) sensitive; (β-hemolytic; anti-streptolysin-O for serotyping; Lancefield group A; rapid antigen detection test.</td>
<td>May colonize skin, throat.</td>
<td>Penicillin G (increasing resistance to erythromycin). (continued)</td>
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<tr>
<td><em>Treponema pallidum</em></td>
<td>Spirochete</td>
<td>Multiplication followed by blood vessel involvement</td>
<td>Syphilis—primary with painless sores, purulent exudate, and induration; secondary with a rash; tertiary (rare) includes CNS involvement and aortitis</td>
<td>Dark field microscopy; screen with RPR or VDRL test for cardiolipin (nontreponemal tests); confirm with FTA-Abbs or MHA-tp (treponemal specific test); systemic illness can occur with treatment (Jarisch–Herrheimer reaction)</td>
<td>Sexually transmitted; transplacental</td>
<td>Penicillin</td>
</tr>
<tr>
<td><em>Tropheryma whippelii</em></td>
<td>Gram-positive; rod actinomycete</td>
<td>Foamy macrophages found in the lamina propria of the jejunum</td>
<td>Whipple disease—steatorrhea, lymphadenopathy, fever, and cough</td>
<td>Visualization of the organism in a biopsy of the small bowel</td>
<td>Unknown</td>
<td>Trimethoprim-sulfamethoxazole</td>
</tr>
<tr>
<td><em>Vibrio cholerae</em></td>
<td>Gram-negative; comma-shaped rod; polar flagella ADP ribosylates G protein</td>
<td>Pili adhere to gut mucosa; phage-coded cholera toxin; two A active subunits and five B-binding units (A subunit increasing cAMP and causing movement of ions and water out of the cell)</td>
<td>Rice-water stools</td>
<td>Fecal specimens culture; agglutination assays</td>
<td>Fecal–oral route via water and food</td>
<td>Vaccine not available in the United States; rehydration; tetracycline, fluoroquinolones, trimethoprim-sulfamethoxazole</td>
</tr>
<tr>
<td><em>Vibrio parahaemolyticus</em></td>
<td>Gram-negative; comma-shaped rod</td>
<td>Toxin</td>
<td>Explosive diarrhea, cramps, nausea</td>
<td>High-infective dose required</td>
<td>Shellfish; raw or undercooked seafood</td>
<td>Self-limited</td>
</tr>
<tr>
<td><em>Yersinia pestis</em></td>
<td>Gram-negative; bacillus; intracellular</td>
<td>V and W antigens (active within macrophages); fibrinolysin; F1 protein inhibits phagocytosis</td>
<td>Bubonic plague (with lymph node swelling and bubo); fever; conjunctivitis</td>
<td>Cultures are hazardous and precautions must be taken</td>
<td>Zoootic via rat fleas</td>
<td>Vaccine; gentamicin, doxycycline</td>
</tr>
</tbody>
</table>

ADP, adenosine diphosphate; BCG, bacille Calmette–Guerin; cAMP, cyclic adenosine monophosphate; CNS, central nervous system; CSF, cerebrospinal fluid; DNase, deoxyribonuclease; ELISA, enzyme-linked immunosorbent assay; FTA-abs, fluorescent treponemal antibody absorption test; GI, gastrointestinal; GU, genitourinary; Hb, *Haemophilus influenzae* type b; Ig, immunoglobulin; IL, interleukin; IV, intravenous; LPS, lipopolysaccharide; MHA-tp, microhemagglutination assay test; MP, metalloproteinase; NaCl, sodium chloride; NAD, nicotinamide adenine dinucleotide; PID, pelvic inflammatory disease; PPD, purified protein derivative; RPR, rapid plasma reagin; TB, tuberculosis; TNF, tumor necrosis factor; TSS, toxic shock syndrome; UTI, urinary tract infection; VDRL, Venereal Disease Research Laboratory.
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<tr>
<td>Adenovirus</td>
<td>Nonenveloped DNA virus; double stranded</td>
<td>Pharyngitis or pneumonia; acute gastroenteritis; conjunctivitis</td>
<td>Infects the epithelium of the eyes, respiratory tract, and GI tract</td>
<td>Complement fixation</td>
<td>Respiratory droplets; hand-to-eye; also fecal–oral</td>
<td>Live vaccine for military populations; no treatments</td>
</tr>
<tr>
<td>Coronavirus</td>
<td>Enveloped single-stranded positive RNA virus</td>
<td>Common cold</td>
<td>Infects upper respiratory tract</td>
<td>None</td>
<td>Respiratory secretions</td>
<td>None</td>
</tr>
<tr>
<td>Coxsackie B virus</td>
<td>Nonenveloped RNA virus; single stranded; linear; positive polarity</td>
<td>Myocarditis, pericarditis, spastic paralysis</td>
<td>Replicates in the pharynx and GI tract and spreads to other tissues</td>
<td>Isolating virus in cell culture; rise in convalescent antibody</td>
<td>Fecal–oral and respiratory</td>
<td>No therapy or prevention</td>
</tr>
<tr>
<td>Cytomegalovirus</td>
<td>Enveloped DNA virus; linear; double stranded</td>
<td>Pneumonia, retinitis, and hepatitis in immunocompromised patients; mononucleosis-like syndrome in immunocompromised patients; cytomegalic inclusion disease of fetus</td>
<td>Infects the oropharynx initially; involves lymphocytes</td>
<td>“Owl’s eye” nuclear inclusions</td>
<td>Human body fluids; transplacental, organ transplantation</td>
<td>Ganciclovir</td>
</tr>
<tr>
<td>Epstein–Barr virus</td>
<td>Enveloped DNA virus; linear; double stranded</td>
<td>Infectious mononucleosis; causes Burkitt lymphoma</td>
<td>Spreads via the lymph nodes and bloodstream to the liver and spleen from the pharyngeal epithelium</td>
<td>Atypical lymphocytes; positive heterophil antibody (Monospot test); common infection of college students</td>
<td>Saliva</td>
<td>None</td>
</tr>
<tr>
<td>Hantavirus</td>
<td>Enveloped RNA virus; single stranded; circular, segmented; negative polarity</td>
<td>Hanta pulmonary syndrome— influenza-like followed by acute respiratory failure</td>
<td>Invasion of the respiratory epithelium</td>
<td>PCR assay of viral RNA from lung tissue</td>
<td>Airborne (inhalation of rodent urine and feces); found in southwestern United States</td>
<td>None</td>
</tr>
<tr>
<td>Hepatitis A virus</td>
<td>Nonenveloped RNA virus; single stranded; positive polarity</td>
<td>Hepatitis A; causes acute hepatitis; no chronic infection</td>
<td>Replicates in the GI tract; spreads to the liver; hepatocellular injury via cytotoxic T-cell response</td>
<td>Detect IgM antibody</td>
<td>Fecal–oral route</td>
<td>Killed viral vaccine; immune globulin during the incubation period may hinder disease</td>
</tr>
</tbody>
</table>

(continued)
<table>
<thead>
<tr>
<th>Name</th>
<th>Morphology</th>
<th>Description of Disease</th>
<th>Pathogenesis</th>
<th>Laboratory Findings, Notes</th>
<th>Transmission</th>
<th>Prevention and Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hepatitis B virus (HBV)</td>
<td>Enveloped DNA virus; incomplete circular double stranded; polymerase in virion (virion called the Dane particle); surface antigen (HBsAg); core antigen (HBcAg)</td>
<td>Hepatitis B; arthritis; rash; glomerulonephritis; may result in hepatocellular carcinoma</td>
<td>Immune response (CD8 cells) to the virus results in hepatocellular injury; Ag–Ab complexes form</td>
<td>Serologic tests for HBsAg, HBsAb, HBeAb and HBcAb</td>
<td>Blood, perinatal, sexual</td>
<td>Vaccine; interferon-α, tenofovir, lamivudine inhibit HBV DNA synthesis</td>
</tr>
<tr>
<td>Hepatitis C virus (HCV)</td>
<td>Enveloped RNA virus; single stranded; positive polarity</td>
<td>Hepatitis C; possible predisposition to hepatocellular carcinoma</td>
<td>Cytotoxic T cells result in hepatocellular injury</td>
<td>HCV RNA or anti-HCV Ab; currently the most common cause of transfusion-related hepatitis</td>
<td>Blood, perinatal, sexual</td>
<td>Interferon-α, ribavirin</td>
</tr>
<tr>
<td>Hepatitis D virus (delta virus)</td>
<td>Enveloped defective RNA virus; single stranded; negative polarity; no polymerase</td>
<td>Hepatitis D</td>
<td>Cytotoxic T cells result in hepatocellular injury; uses HBsAg as a protein coat and can only replicate in hosts already infected with HBV</td>
<td>Serologic testing for delta antigen</td>
<td>Blood, perinatal, sexual</td>
<td>Interferon-α, prevention of hepatitis B</td>
</tr>
<tr>
<td>Hepatitis E virus (HEV)</td>
<td>Enveloped; single-stranded RNA virus; positive polarity</td>
<td>Hepatitis E; acute hepatitis no chronic disease</td>
<td>Anti-HEV IgM antibody by ELISA</td>
<td>Fecal–oral route</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Herpes simplex virus type 1</td>
<td>Enveloped DNA virus; linear; double stranded</td>
<td>Herpes labialis (fever blisters and cold sores); keratitis; encephalitis</td>
<td>Lesions on the mouth and face initially; travels retrograde and becomes latent in the trigeminal ganglion; recurrences induced by sunlight, stress, and fever</td>
<td>Multinucleated giant cells on Tzanck smear; immunofluorescence of infected cells; in situ hybridization defects; viral DNA</td>
<td>Saliva; direct contact with the lesion</td>
<td>Acyclovir, trifluorothymidine for keratitis</td>
</tr>
<tr>
<td>Herpes simplex virus type 2</td>
<td>Enveloped DNA virus; linear; double stranded</td>
<td>Herpes genitalis; meningitis</td>
<td>Vesicular lesions on the genitalia; retrograde passage through the axon and latency in the sacral ganglion; stress-induced recurrences</td>
<td>Multinucleated giant cells on Tzanck smear; immunofluorescence of infected cells; in situ hybridization defects; viral DNA</td>
<td>Sexual, transplacental</td>
<td>Acyclovir</td>
</tr>
<tr>
<td>Human herpes virus 6</td>
<td>Enveloped DNA virus; linear; double stranded</td>
<td>Roseola infantum (exanthem subitum)—common disease of children characterized by high fever and rash</td>
<td>Infects T and B cells</td>
<td>PCR or acute and convalescent antibody titers</td>
<td>Saliva</td>
<td>Symptomatic</td>
</tr>
<tr>
<td>Virus Type</td>
<td>Virus Characteristics</td>
<td>Disease</td>
<td>Diagnosis and Treatment</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>HIV</td>
<td>Enveloped RNA virus; diploid; single stranded; positive polarity; reverse transcriptase, retrovirus</td>
<td></td>
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</tr>
<tr>
<td>AIDS</td>
<td>Infects and kills helper T cells via the CD4 receptors and gp120 protein</td>
<td></td>
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</tr>
<tr>
<td>Screen with ELISA; Western blot test confirms</td>
<td>Sexual, body fluids, perinatal; blood products</td>
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</tr>
<tr>
<td>HIV-infected mothers and newborns; HAART; treat opportunistic infections such as pneumonia or Kaposi sarcoma</td>
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</tr>
<tr>
<td>Influenza virus</td>
<td>Enveloped RNA virus; segmented; single stranded; negative polarity; polymerase in virion</td>
<td></td>
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</tr>
<tr>
<td>Influenza</td>
<td>Infects the epithelium of the respiratory tract via hemagglutinin and neuraminidase on surface spikes; antigenic shift and drift of surface spikes lead to epidemics</td>
<td></td>
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</tr>
<tr>
<td>Cell culture; hemagglutination inhibition; complement fixation; H and N protein spikes</td>
<td>Respiratory droplets; vaccine composed of inactivated strains of current virus, which causes disease</td>
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<tr>
<td>Zanamivir and oseltamivir for both prevention and treatment; vaccine composed of inactivated strains of current virus, which causes disease</td>
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</tr>
<tr>
<td>Measles virus</td>
<td>Enveloped RNA virus; single stranded; negative polarity; polymerase in virion</td>
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</tr>
<tr>
<td>Measles, subacute sclerosing panencephalitis (SSPE)</td>
<td>Infection spreads via the bloodstream from the upper respiratory tract to the organs; maculopapular rash caused by an immune response (Koplik spots)</td>
<td></td>
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<tr>
<td>Usually not done</td>
<td>Respiratory droplets</td>
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<tr>
<td>Attenuated vaccine; no treatment</td>
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</tr>
<tr>
<td>Mumps virus</td>
<td>Enveloped RNA virus; single stranded; negative polarity; polymerase in virion</td>
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</tr>
<tr>
<td>Mumps; sterility owing to bilateral orchitis</td>
<td>Spreads from the upper respiratory tract to the organs (parotid glands, testes, ovaries, and CNS) via the bloodstream</td>
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</tr>
<tr>
<td>Cell culture and hemadsorption; rise in antiviral antibody</td>
<td>Respiratory droplets</td>
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<tr>
<td>Attenuated vaccine; no treatment</td>
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</tr>
<tr>
<td>Norwalk virus</td>
<td>Nonenveloped; RNA virus; single stranded; linear; positive polarity</td>
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<tr>
<td>Gastroenteritis</td>
<td>Binds to cells of intestinal brush border; prevents absorption of water and nutrients; blunted villi in jejunum; infiltration with mononuclear cells</td>
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<tr>
<td>Not performed; serology; ELISA for Ag; stool EM</td>
<td>Fecal-oral</td>
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<tr>
<td>Symptomatic treatment</td>
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<tr>
<td>Papillomavirus</td>
<td>Nonenveloped DNA virus; circular; double stranded</td>
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<tr>
<td>Papillomas (warts); condylomata acuminata; cervical and penile carcinoma</td>
<td>dsDNA incorporates into host DNA; E1 and E2 promote DNA replication; E6 and E7 early viral genes inhibit activity of p53 and Rb tumor suppressor genes, respectively</td>
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<tr>
<td>Koilocytes (squamous cell with perinuclear clearing) in lesions; to define type use in situ DNA hybridization</td>
<td></td>
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<tr>
<td>Sexual via direct contact with genital lesions</td>
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<tr>
<td>Interferon-α, liquid nitrogen for warts; vaccine; annual Pap smear for cervical cancer screening</td>
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<tr>
<td>Parainfluenza</td>
<td>Enveloped; single stranded–RNA virus</td>
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</tr>
<tr>
<td>Upper respiratory tract infection, croup (laryngotracheobronchitis), bronchitis, pneumonia</td>
<td>Two major surface glycoproteins fusion and HN; replication limited to respiratory epithelial cells</td>
<td></td>
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<tr>
<td>Direct person-to-person contact and large droplet aerosols</td>
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<tr>
<td>Supportive</td>
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</tbody>
</table>
### APPENDIX II: Bug Index

#### VIRUSES (Continued)

<table>
<thead>
<tr>
<th>Name</th>
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<th>Prevention and Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parvovirus B19</td>
<td>Nonenveloped; DNA virus; single stranded; linear</td>
<td>Erythema infectiosum (fifth disease) — characterized by “slapped cheek” appearance; may cause aplastic crisis in sickle cell disease</td>
<td>Erythema infectiosum — virus causes immune complex deposition; aplastic anemia. Virus infects immature RBCs and kills them</td>
<td>Parvovirus-specific IgG/IgM antibody levels; laboratory analysis for viral DNA</td>
<td>Unknown — may be respiratory or direct contact</td>
<td>Self-limited</td>
</tr>
<tr>
<td>Pelioirus</td>
<td>Nonenveloped RNA virus; single stranded; positive polarity</td>
<td>Abortive poliomyelitis, aseptic meningitis (more common), paralytic poliomyelitis, progressive postpoliomyelitis muscle atrophy (very rare)</td>
<td>Replicates in the pharynx and GI tract and spreads to the CNS; death of the anterior horn cells in the spinal cord; neurotropic for motor cortex</td>
<td>Isolation from CSF</td>
<td>Fecal–oral</td>
<td>Rabies</td>
</tr>
<tr>
<td>Rabies virus</td>
<td>Enveloped RNA virus; bullet shape; single stranded; negative polarity RNA; polymerase in virion</td>
<td>Rabies</td>
<td>ACh receptor of neuron binds virus; the virus follows the retrograde direction to invade the CNS and brain, resulting in encephalitis</td>
<td>Negri bodies (eosinophilic inclusion in nerve cell)</td>
<td>Animal (skunks, bats) bites; domestic dogs in developing countries</td>
<td>Before exposure: vaccine; after exposure: antirabies Ig plus inactivated vaccine from human cell culture; no treatment</td>
</tr>
<tr>
<td>Reovirus (Rotavirus)</td>
<td>Nonenveloped RNA virus; 11 segments; double stranded; RNA polymerase in virion</td>
<td>Gastroenteritis in children</td>
<td>Resistant to stomach acid, thus infects the small intestine</td>
<td>ELISA detects the virus in stool</td>
<td>Respiratory droplets; fecal–oral route</td>
<td>Rehydration with fluids and electrolytes</td>
</tr>
<tr>
<td>Respiratory syncytial virus</td>
<td>Enveloped RNA virus; single stranded; negative polarity; polymerase in virion</td>
<td>Pneumonia or bronchiolitis in children</td>
<td>Immune response to lower respiratory tract infection</td>
<td>Multinucleated giant cells</td>
<td>Direct person-to-person contact</td>
<td>Supportive; ribavirin no longer recommended for children</td>
</tr>
<tr>
<td>Virus</td>
<td>Classification</td>
<td>Disease(s)</td>
<td>Mode of transmission</td>
<td>Mode of infection</td>
<td>Treatment</td>
<td></td>
</tr>
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</tr>
<tr>
<td>Rhinovirus</td>
<td>Nonenveloped RNA virus; single stranded; positive polarity; numerous serotypes</td>
<td>Common cold</td>
<td>Upper respiratory tract mucosa and conjunctiva infected; replicates at temperatures &lt;37° C; killed by stomach acid</td>
<td>None</td>
<td>Aerosol droplets with hand-to-nose transmission</td>
<td>None</td>
</tr>
<tr>
<td>Rubella virus</td>
<td>Enveloped RNA virus; single stranded; positive polarity</td>
<td>Rubella; congenital; cardiovascular and neurologic malformations, especially if infection occurs during the first trimester</td>
<td>Spreads from the nasopharynx to the skin via the bloodstream; rash caused by replication and immune injury; German measles</td>
<td>Growth in cell culture via interference of Coxsackie virus; recent infection in the mother is detected by IgM, IgA</td>
<td>Respiratory droplets</td>
<td>Attenuated vaccine; no treatment</td>
</tr>
<tr>
<td>Varicella-zoster virus</td>
<td>Enveloped DNA virus; linear; double stranded</td>
<td>Chicken pox (varicella) in children; shingles (zoster) in adults</td>
<td>Infects respiratory tract and spreads to the liver and skin via the blood; an acute episode followed by latency in the sensory ganglia; numerous crop of vesicles in different stages at different times</td>
<td>Intranuclear inclusions; shingles is usually unilateral and generally follows the distribution of the dermatomes</td>
<td>Chicken pox: respiratory droplets; shingles: re-activation of the latent virus</td>
<td>Attenuated vaccine; famciclovir, valacyclovir</td>
</tr>
<tr>
<td>Variola virus</td>
<td>Double stranded; DNA</td>
<td>Smallpox (rare)</td>
<td>Respiratory infection; initially replicates in URT; systemic dissemination by lymphatics; replication in multiple organs; extensive rash to hemorrhage of small blood vessels; single crop of vesicles in one stage all at once</td>
<td>Vaccinia variola</td>
<td>Vaccinia variola</td>
<td></td>
</tr>
</tbody>
</table>

ACh, acetylcholine; Ag–Ab, antigen–antibody; AZT, azidothymidine; CD, cluster of differentiation; CNS, central nervous system; CSF, cerebrospinal fluid; dsDNA, double-stranded DNA; ELSA, enzyme-linked immunosorbent assay; EM, electron microscopy; GI, gastrointestinal; HAART, highly active antiretroviral therapy; HBeAb, hepatitis B e antibody; HBsAb, hepatitis B surface antibody; HN, hemagglutinin-neuraminidase; Ig, immunoglobulin; PCR, polymerase chain reaction; Rb, retinoblastoma; RBC, red blood cell; URT, upper respiratory tract.
# APPENDIX II: Bug Index

## FUNGI

<table>
<thead>
<tr>
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</tr>
</thead>
<tbody>
<tr>
<td>Aspergillus fumigatus</td>
<td>Filamentous; septate hyphae and dichotomous branching; mold only</td>
<td>Opportunistic; growth of Aspergillus in a preexisting cavitary lesion in the lung</td>
<td>Aspergilloma—hemoptysis; invasive aspergillosis in neutropenic individuals</td>
<td>Septate, branching hyphae; “fungus ball” seen on a radiograph</td>
<td>Airborne spores</td>
<td>Amphotericin B, voriconazole; surgery to remove a “fungus ball”</td>
</tr>
<tr>
<td>Blastomyces dermatitidis</td>
<td>Dimorphic fungus—mold in the soil but a yeast in tissue</td>
<td>Invades the respiratory tract and may invade the skin or bone</td>
<td>Blastomycosis—granulomatous and suppurative infection of the respiratory tract</td>
<td>Tissue biopsy showing circular yeast with a broad-based bud</td>
<td>Airborne; endemic to North America</td>
<td>Itraconazole; amphotericin B for serious infections</td>
</tr>
<tr>
<td>Candida albicans</td>
<td>Pseudohyphae and hyphae on invasion; yeast in normal flora; germ tubes at 37°C; yeast only</td>
<td>Opportunistic in immunosuppressed patients and those with foreign bodies (e.g., catheters); mucocutaneous lesions in children with a T-cell defect</td>
<td>Thrush, chronic mucocutaneous candidiasis, vaginal candidiasis</td>
<td>Colonies on Sabouraud agar; germ tube formation</td>
<td>Part of the normal flora</td>
<td>Oral form can be prevented by nystatin “swish and swallow”; treatment with nystatin, miconazole; amphotericin B, fluconazole, or caspofungin for bloodstream infection</td>
</tr>
<tr>
<td>Coccidioides immitis</td>
<td>Dimorphic—mold in the soil, spherule in tissue; barrel-shaped hyphae</td>
<td>Inhalation; spherules, releasing endospores within the respiratory tract</td>
<td>Coccidioidomycosis—an influenza-like illness with fever and cough</td>
<td>Tissue specimen showing spherules</td>
<td>Airborne; endemic to southwestern United States and Latin America</td>
<td>Amphotericin B, itraconazole, ketoconazole</td>
</tr>
<tr>
<td>Cryptococcus neoformans</td>
<td>Encapsulated; not dimorphic; yeast only</td>
<td>Usually immunocompromised patients; spreads via the bloodstream</td>
<td>Cryptococcosis, cryptococcal meningitis</td>
<td>Organism with a capsule seen on an India ink preparation; latex agglutination test</td>
<td>Inhalation of airborne yeast cells</td>
<td>Oral fluconazole as preventative in patients with AIDS; amphotericin B with flucytosine as initial therapy for cryptococcal meningitis</td>
</tr>
<tr>
<td>Histoplasma capsulatum</td>
<td>Dimorphic—a mold in the soil, a yeast in tissue; septate hyphae</td>
<td>Inhaled spores are engulfed by macrophages and develop into yeast forms intracellularly</td>
<td>Histoplasmosis—granulomas in the lung tissue</td>
<td>Tissue biopsy showing yeast cells visible in macrophages; radioimmunoassay for Histoplasma RNA and DNA</td>
<td>Airborne; endemic to Ohio and Mississippi River valleys; found in bird droppings</td>
<td>Amphotericin B, itraconazole</td>
</tr>
<tr>
<td>Mucor spp.</td>
<td>Nonseptate hyphae that branch at near right angles; mold only</td>
<td>Invades the nasal sinuses, lungs, and GI tract</td>
<td>Tissue necrosis</td>
<td>Nonseptate hyphae seen microscopically</td>
<td>Airborne</td>
<td>Amphotericin B; debridement of necrotic tissue</td>
</tr>
<tr>
<td>Pneumocystis jiroveci</td>
<td>Respiratory pathogen</td>
<td>Alveolar inflammation</td>
<td>Pneumonia</td>
<td>Silver stain</td>
<td>Inhalation by immunocompromised individual</td>
<td>Trimethoprim-sulfamethoxazole; pentamidine</td>
</tr>
<tr>
<td>Sporothrix schenckii</td>
<td>Thermally dimorphic fungus</td>
<td>Inflammation and swelling of the lymph nodes and vessels</td>
<td>Sporotrichosis (“rose gardener’s disease”)</td>
<td>Cigar-shaped budding cells</td>
<td>Thorn prick</td>
<td>Protection during gardening; potassium iodide; itraconazole</td>
</tr>
</tbody>
</table>

GI, gastrointestinal; IV, intravenous.
## Parasites and Protozoa

<table>
<thead>
<tr>
<th>Name</th>
<th>Morphology</th>
<th>Pathogenesis</th>
<th>Description of Disease</th>
<th>Laboratory Findings, Notes</th>
<th>Transmission</th>
<th>Prevention and Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ascaris lumbricoides</td>
<td>Intestinal parasite</td>
<td>Larvae in the lung and a heavy worm burden in gastrointestinal tract</td>
<td>Ascariasis—intestinal obstruction, abdominal pain, coughing, nausea</td>
<td>Eosinophilia; eggs in feces</td>
<td>Contaminated food or soil</td>
<td>Maintain sanitary conditions; ivermectin or mebendazole</td>
</tr>
<tr>
<td>Entamoeba histolytica</td>
<td>Intestinal protozoan; cigar-shaped cysts; four nuclei</td>
<td>Trophozoite form invades the colon</td>
<td>Amebic dysentery, liver abscess, flash-shaped ulcers</td>
<td>Trophozoites or cysts seen in stool</td>
<td>Fecal–oral</td>
<td>Maintain sanitary conditions; metronidazole with iodoquinol or paromomycin; steroids exacerbate</td>
</tr>
<tr>
<td>Enterobius vermicularis</td>
<td>Intestinal parasite</td>
<td>Worms migrate to anus at night to lay eggs; results in perianal pruritus</td>
<td>Pinworm infection—anal pruritus, vaginal irritation, and cystitis</td>
<td>Eggs on “Scotch tape” test (tape applied to the anus and then viewed under a microscope)</td>
<td>Fecal–oral</td>
<td>Reinfecion by self; fecal–oral contact; egg ingestion</td>
</tr>
<tr>
<td>Giardia lamblia</td>
<td>Intestinal protozoan; pear shaped; flagella; tumbling motility; two nuclei; four flagella</td>
<td>Interferes with fat and protein absorption</td>
<td>Giardiasis—acute diarrhea, flatulence, bloating</td>
<td>Trophozoites or cysts in stool</td>
<td>Fecal–oral</td>
<td>Do not drink untreated water from streams or rivers; metronidazole</td>
</tr>
<tr>
<td>Leishmania donovani</td>
<td>Protozoan</td>
<td>Organs of the reticuloendothelial system are destroyed by macrophages infected with the protozoan</td>
<td>Cutaneous leishmaniasis—ulcerating papules that heal slowly; visceral leishmaniasis (&quot;kala-azar&quot;)—hyperpigmentation of the skin, massive splenomegaly, fever, anemia, and malaise</td>
<td>Biopsy of reticuloendothelial tissue shows the infected macrophages</td>
<td>Female Phlebotomus sandfly transmits the disease from the infected host to a human</td>
<td>Protection from sandfly bites; sodium stibogluconate (antimony compound) for cutaneous form; lipoosomal amphotericin B for visceral form</td>
</tr>
<tr>
<td>Plasmodium spp.</td>
<td>Blood and tissue protozoan; signet ring trophozoites in RBCs; banana-shaped gametocytes (Plasmodium falciparum)</td>
<td>Sporozoites from bite enter the bloodstream and invade hepatocytes (exoerythrocytic phase); merozoites invade the RBCs (erythrocytic phase)</td>
<td>Malaria—fever, chills, hepatomegaly, splenomegaly; symptoms in cyclical pattern (3 days for P. malariae; 2 days for P. ovale, P. falciparum, P. vivax); tissue anoxia</td>
<td>Blood smear shows organisms; P. falciparum is acute and needs immediate treatment</td>
<td>Female Anopheles mosquito</td>
<td>Insecticides or protection from bites; chloroquine, quinine, atovaquone-proguanil, mefloquine, atriamether/lumefantrine</td>
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### PARASITES AND PROTOZOA (Continued)

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<tr>
<th>Name</th>
<th>Morphology</th>
<th>Pathogenesis</th>
<th>Description of Disease</th>
<th>Laboratory Findings, Notes</th>
<th>Transmission</th>
<th>Prevention and Therapy</th>
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<td><em>Schistosoma</em> spp.</td>
<td>Blood fluke; eggs have spine (<em>S. mansoni</em> has large lateral spine, <em>S. haematobium</em> has a terminal spine, <em>S. japonicum</em> has a small lateral spine); two sexes</td>
<td>Eggs lead to inflammation, fibrosis, and granuloma formation</td>
<td>Schistosomiasis—pipestem fibrosis of liver; <em>S. haematobium</em> affects the bladder; <em>S. mansoni</em> affects the mesenteric vessels</td>
<td>Eggs in the stool or urine</td>
<td>Penetration of the skin by cercariae</td>
<td>Maintain sanitary conditions; praziquantel</td>
</tr>
<tr>
<td><em>Taenia</em> sp.</td>
<td>Cestode: <em>T. solium</em>—pork tapeworm; <em>T. saginata</em>—beef; <em>Diphyllolobothrium latum</em>—fish; four suckers and circle of hooks; 5–10 uterine branches</td>
<td>Encyst in tissue (eyes, brain, muscle) resulting in mass lesions</td>
<td>Taeniasis and cysticercosis</td>
<td>Gravid proglottids in stool</td>
<td>Eating raw or undercooked meat (taeniasis), or fecal–oral (cysticercosis)</td>
<td>Cook meat and maintain sanitary conditions; albendazole or praziquantel</td>
</tr>
<tr>
<td><em>Toxoplasma gondii</em></td>
<td>Tissue protozoan</td>
<td>Infects macrophages; infects the brain, liver, eyes</td>
<td>Toxoplasmosis</td>
<td>Serologic; high morbidity and mortality</td>
<td>Ingestion of cysts; cat feces; transplacental</td>
<td>Cook meat and avoid cat feces; sulfadiazine positive, pyrimethamine</td>
</tr>
<tr>
<td><em>Trichinella spiralis</em></td>
<td>Intestinal parasite</td>
<td>Muscle inflammation</td>
<td>Trichinosis—peri orbital edema, myositis, fever, and diarrhea</td>
<td>Larvae on muscle biopsy; eosinophilia by 14th day; double-barreled egg</td>
<td>Eating raw or undercooked meat</td>
<td>Cook meat; thiabendazole</td>
</tr>
<tr>
<td><em>Trichomonas vaginalis</em></td>
<td>Urogenital protozoan; pear shaped; flagella; trophozoites</td>
<td>attaches to the wall of the vagina</td>
<td>Trichomoniasis—itching and burning with greenish discharge from the vagina (strawberry cervix)</td>
<td>Visible in secretions</td>
<td>Sexual transmission</td>
<td>Treat both partners; metronidazole</td>
</tr>
<tr>
<td><em>Trypanosoma brucei</em> (African)</td>
<td>Blood and tissue protozoan</td>
<td>Infects the brain and leads to encephalitis</td>
<td>Sleeping sickness—fever, enlarged lymph nodes, somnolence, coma, death</td>
<td>Visible in the blood</td>
<td>Tsetse fly (in Africa)</td>
<td>Protection from bites; insecticide; suramin</td>
</tr>
<tr>
<td><em>Trypanosoma cruzi</em> (American)</td>
<td>Blood and tissue protozoan</td>
<td>Amastigotes attack cells, especially cardiac muscle cells</td>
<td>Chagas disease—dilated cardiomyopathy, meg aesophagus, megacolon</td>
<td>Visible in the blood</td>
<td>Reduviid bugs (in Latin America) (also known as “kissing bugs”)</td>
<td>Protect from bites; insecticide; nifurtimox</td>
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