FIRST AID FOR THE®

INTERNAL MEDICINE BOARDS

SECOND EDITION

- Resident-to-resident strategies for passing the ABIM exam
- Summaries of high-yield topics perfect for last-minute review
- Board-proven mnemonics and clinical pearls
- 20-page full-color insert of must-know clinical images

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FIRST AID FOR THE®

INTERNAL MEDICINE BOARDS

Second Edition

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DEDICATION

To the contributors to this and future editions, who took time to share their knowledge, insight, and humor for the benefit of residents and clinicians.

and

To our families, friends, and loved ones, who endured and assisted in the task of assembling this guide.

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CONTENTS

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PREFACE

With this revised and expanded edition of *First Aid for the® Internal Medicine Boards*, we hope to provide residents and clinicians with the most useful and up-to-date preparation guide for the American Board of Internal Medicine (ABIM) certification and recertification exams. This edition represents an outstanding effort by a talented group of authors and includes the following:

- A practical exam preparation guide with proven test-taking and study strategies
- Updated summaries of thousands of board-testable topics
- Hundreds of revised high-yield tables, diagrams, and illustrations
- Key facts in the margins highlighting "must know" information for the boards
- Mnemonics throughout, making learning memorable and fun

We invite you to share your thoughts and ideas to help us improve *First Aid for the® Internal Medicine Boards*. See How to Contribute, p. xiii.

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Thanks to our publisher, McGraw-Hill, for the valuable assistance of their staff. For enthusiasm, support, and commitment to this challenging project, thanks to our editor, Catherine Johnson. For outstanding editorial support, we thank Andrea Fellows. A special thanks to Rainbow Graphics, especially David Hommel and Susan Cooper, for remarkable editorial and production work.

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HOW TO CONTRIBUTE

To continue to produce a high-yield review source for the ABIM exam, you are invited to submit any suggestions or corrections. We also offer **paid internships** in medical education and publishing ranging from three months to one year (see below for details). Please send us your suggestions for

- Study and test-taking strategies for the ABIM
- New facts, mnemonics, diagrams, and illustrations
- Low-yield topics to remove

For each entry incorporated into the next edition, you will receive a **$10 gift certificate**, as well as personal acknowledgment in the next edition. Diagrams, tables, partial entries, updates, corrections, and study hints are also appreciated, and significant contributions will be compensated at the discretion of the authors. Also let us know about material in this edition that you feel is low yield and should be deleted.

The preferred way to submit entries, suggestions, or corrections is via our blog at **www.firstaidteam.com** or e-mail at **firstaidteam@yahoo.com**. Please include name, address, institutional affiliation, phone number, and e-mail address (if different from the address of origin).

NOTE TO CONTRIBUTORS

All entries become property of the authors and are subject to editing and reviewing. Please verify all data and spellings carefully. In the event that similar or duplicate entries are received, only the first entry received will be used. Include a reference to a standard textbook to facilitate verification of the fact. Please follow the style, punctuation, and format of this edition if possible.

INTERNSHIP OPPORTUNITIES

The author team is pleased to offer part-time and full-time paid internships in medical education and publishing to motivated physicians. Internships may range from three months (e.g., a summer) up to a full year. Participants will have an opportunity to author, edit, and earn academic credit on a wide variety of projects, including the popular *First Aid* series. Writing/editing experience, familiarity with Microsoft Word, and Internet access are desired. For more information, e-mail a résumé or a short description of your experience along with a cover letter to **firstaidteam@yahoo.com**.

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Introduction: Guide to the ABIM

INTRODUCTION

For house officers, the ABIM is the culmination of three years of hard work. For practicing physicians, it becomes part of their maintenance of certificate. However, the certification and recertification process does not simply represent yet another set of exams in a series of expensive tests. To your patients, it means that you have the level of clinical knowledge and competency required to provide good clinical care. In fact, according to a poll conducted for the ABIM, about 72% of adult patients are aware of their physicians' board-certification status.

The majority of your patients will be aware of your certification status.

In this chapter we talk more about the ABIM and provide you with proven approaches to conquering the exam. For a detailed description of the ABIM, visit **www.abim.org** or refer to the *Certification Examination in Internal Medicine Information Booklet*, which can also be found on the ABIM Web site.

ABIM—THE BASICS

How Do I Register to Take the Exam?

Register early to avoid an extra $400 late fee.

You can register for the exam online by going to "On-Line Services" at www.abim.org. The registration fee is currently about $1135. If you miss the application deadline, a $400 nonrefundable late fee is tacked on. Check the ABIM Web site for the latest registration deadlines, fees, and policies.

What If I Need to Cancel the Exam or Change Test Centers?

The ABIM currently provides partial refunds if a written cancellation is received before certain deadlines. You can also change your test center with a written request for a specific deadline. Check the ABIM Web site for the latest information on its refund and cancellation policy as well as procedures.

How Is the ABIM Test Structured?

As of August 2006, the ABIM exam is a one-day computer-based test (CBT). The exam is divided into four two-hour sections with 60 questions in each section, for a total of 240 questions. Images (blood smears, x-rays, ECGs, patient photos) are embedded in certain questions. During the time allotted for each block, examinees can answer test questions in any order as well as review responses and change answers. However, examinees cannot go back and change answers from previous blocks. The CBT format (see Figure 1) allows you to make your own notes on each question using a pop-up box, and it also permits you to click a box to designate which questions you might wish to review before the end of the session (time permitting).

Please check the ABIM Web site to check for Web demos, updates, and details about the new format, as well as to identify testing centers nearest to you.

What Types of Questions Are Asked?

All questions are **single-best-answer** types only. You will be presented with a scenario and a question followed by four to six options. Virtually all questions on the ABIM are vignette based. A substantial amount of extraneous informa-

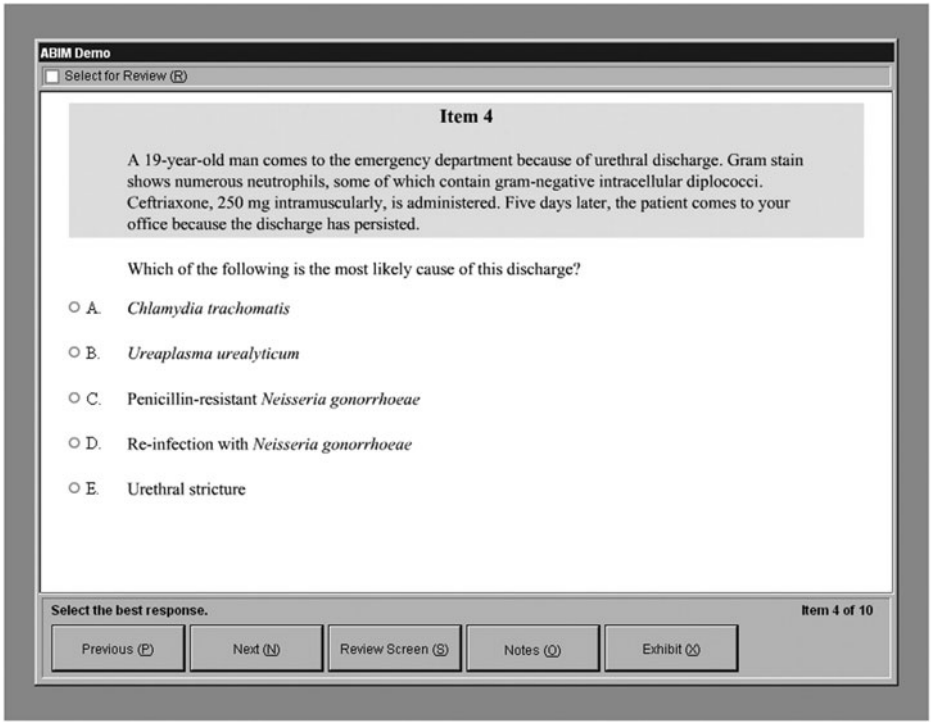

FIGURE 1. ABIM CBT format.

tion may be given, or a clinical scenario may be followed by a question that could be answered without actually requiring that you read the case. Some questions require interpretation of photomicrographs, radiology studies, photographs of physical findings, and the like. It is your job to determine which information is superfluous and which is pertinent to the case at hand.

Virtually all questions are case based.

Question content is based on a content "blueprint" developed by the ABIM (see Table 1). This blueprint may change from year to year, so check the ABIM Web site for the latest. About **75%** of the **primary content** focuses on traditional subspecialties such as cardiology and gastroenterology. The remaining **25%** pertains to certain outpatient or related specialties and subspecialties such as allergy/immunology, dermatology, and psychiatry. There are also **cross-content** questions that may integrate information from multiple primary content areas.

How Are the Scores Reported?

The passing scores are set before the exam administration, so your passing is not influenced by the relative performance of others taking the test with you. Scoring and reporting of test results may take up to **three months.** In addition, your pass/fail status will be available to you on the ABIM Web site through the "On-Line Services" within a day of the results being mailed to you. Note that you need to register to access this feature.

TABLE 1. ABIM Certification Blueprint

Primary Content Areas	Relative Proportions
Cardiovascular Disease	14%
Gastroenterology	9%
Pulmonary Disease	10%
Infectious Disease	9%
Rheumatology/Orthopedics	8%
Endocrinology/Metabolism	8%
Oncology	7%
Hematology	6%
Nephrology/Urology	6%
Allergy/Immunology	3%
Psychiatry	4%
Neurology	4%
Dermatology	4%
Obstetrics/Gynecology	3%
Ophthalmology	2%
Miscellaneous	3%
Total	100%

Cross-Content Areas	Relative Proportions
Critical Care Medicine	10%
Geriatric Medicine	10%
Prevention	6%
Women's Health	6%
Clinical Epidemiology	3%
Ethics	3%
Nutrition	3%
Palliative/End-of-Life Care	3%
Adolescent Medicine	2%
Occupational Medicine	2%
Substance Abuse	2%

Source: www.abim.org, 2007.

Your score report will give you a "pass/fail" decision, the overall number of questions you answered correctly with a corresponding percentile, and the number of questions you answered correctly with a corresponding percentile for the primary and cross-content subject areas noted in the blueprint. Each year, between **20 and 40 questions** on the exam do not count toward your final score. Again, these may be "experimental" questions or questions that are later disqualified. Historically, between **85% and 90%** of first-time examinees pass on the first attempt (see Table 2). About 90% of examinees who are recertifying pass on the first attempt, and about 97% are ultimately successful with multiple attempts. There is no limit on the number of retakes if an examinee fails.

TABLE 2. First-Time Test Taker Performance

Year	Number Taking	Percentage Passed
2006	7006	91%
2005	7051	91%
2004	7056	92%
2003	6751	92%
2002	7074	87%

Source: www.abim.org, 2007.

THE RECERTIFCATION EXAM

The recertification exam is given twice per year, typically in the spring (April or May) and in the fall (October). It is a one-day exam that consists of three modules lasting two hours each. Each module has 60 questions, for a total of 180 questions. You get two minutes per question. The recertification exam is currently administered as a CBT at a Pearson VUE testing site. Performance on the recertification exam is similar to that of the certification exam; however, pass rates have been trending downward over the last few years (see Table 3).

Check the ABIM Web site for the latest passing requirements.

TEST PREPARATION ADVICE

The good news about the ABIM is that it tends to focus on the diagnosis and management of diseases and conditions that you have likely seen as a resident and that you should expect to see as an internal medicine specialist. Assuming that you have performed well as a resident, *First Aid* and a good source of practice questions may be all you need. However, consider using *First Aid* as a **guide** and using multiple resources, including a standard textbook, journal review articles, MKSAP, or a concise electronic text such as *UpToDate*, as part

TABLE 3. Recertification Performance

Year	Percent Passed
2002	91%
2003	85%
2004	86%
2005	84%
2006	79%

The ABIM tends to focus on the horses, not the zebras.

Use a combination of First Aid, *textbooks, journal reviews, and practice questions.*

of your studies. Original research articles are low yield, and very new research (i.e., research done less than one to two years before the exam) will not be tested. In addition, there are a number of high-quality board review courses offered around the country. Board review courses are very expensive but can help those who need some focus and discipline.

Ideally, you should start your preparation early in your **last year of residency,** especially if you are starting a demanding job or fellowship right after residency. Cramming in the period between end of residency and the exam is **not advisable.**

As you study, concentrate on the **nuances of management,** especially for difficult or complicated cases. For **common diseases,** learn both common and **uncommon presentations;** for **uncommon diseases,** focus on the **classic presentations** and manifestations. Draw on the experiences of your residency training to anchor some of your learning. When you take the exam, you will realize that you've seen most of the clinical scenarios in your three years of wards, clinics, morning reports, case conferences, or grand rounds.

Other High-Yield Areas

Focus on topic areas that are typically not emphasized during residency training but are board favorites. These include the following:

- Topics in outpatient specialties (e.g., allergy, dermatology, ENT, ophthalmology)
- Formulas that are needed for quick recall (e.g., alveolar gas, anion gap, creatinine clearance)
- Basic biostatistics (e.g., sensitivity, specificity, positive predictive value, negative predictive value)
- Adverse effects of drugs

TEST-TAKING ADVICE

By this point in your life, you have probably gained more test-taking expertise than you care to admit. Nevertheless, here are a few tips to keep in mind when taking the exam:

- For long vignette questions, read the question stem and scan the options; **then** go back and read the case. You may get your answer without having to read through the whole case.
- There's no penalty for guessing, so you should **never** leave a question blank.
- Good pacing is key. You need to leave adequate time to get to all the questions. Even though you have two minutes per question on average, you should aim for a pace of 90 to 100 seconds per question. If you don't know the answer within a short period, make an educated guess and move on.
- It's okay to **second guess** yourself. Research shows that our "second hunches" tend to be better than our first guesses.
- Don't panic with "impossible" questions. They may be **experimental questions** that won't count. Again, take your best guess and move on.
- Note the age and race of the patient in each clinical scenario. When ethnicity is given, it is often relevant. Know these well, especially for more common diagnoses.

Never, ever leave a question blank! There's no penalty for guessing.

- Questions often describe clinical findings instead of naming eponyms (e.g., they cite "tender, erythematous bumps in the pads of the finger" instead of "Osler's nodes").

TESTING AND LICENSING AGENCIES

American Board of Internal Medicine
510 Walnut Street, Suite 1700
Philadelphia, PA 19106-3699
215-446-3500 or 800-441-2246
Fax: 215-446-3633
www.abim.org

Educational Commission for Foreign Medical Graduates (ECFMG)
3624 Market Street
Philadelphia, PA 19104-2685
215-386-5900
Fax: 215-386-9196
www.ecfmg.org

Federation of State Medical Boards (FSMB)
P.O. Box 619850
Dallas, TX 75261-9850
817-868-4000
Fax: 817-868-4099
www.fsmb.org

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CHAPTER 1

Allergy and Immunology

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DIAGNOSTIC TESTING IN ALLERGY

Allergy Skin Testing

- A confirmatory test for the presence of **allergen-specific IgE antibody.**
  - **Prick-puncture skin testing:** Adequate for most purposes. A drop of allergen extract is placed on the skin surface, and epidermal puncture is performed with a specialized needle.
  - **Intradermal skin testing:** Used for venom and penicillin testing; 0.02 mL of allergen is injected intracutaneously using a 26- to 27-gauge needle.
- All skin testing should use ⊕ (histamine) and ⊖ (saline) controls.
- Skin-testing **wheal-and-flare reactions** are measured 15–20 minutes after placement.

Laboratory Allergy Testing

- Radioallergosorbent (**RAST**) serologic testing is performed to confirm the presence of **allergen-specific IgE antibody.**
- Results are comparable to skin testing for pollen- and food-specific IgE.
- Recommended when the subject has anaphylactic sensitivity to the antigen; useful when skin testing is either not available or not possible owing to skin conditions or interfering medications (e.g., antihistamine use).
- RAST testing alone is generally **not** adequate for **venom or drug allergy** testing.

Delayed-Type Hypersensitivity Skin Testing

- An effective screening test for functional **cell-mediated immunity.**
- Involves **intradermal injection of 0.1 mL of purified antigen.** The standard panel includes ***Candida*, mumps, tetanus toxoid,** and **PPD.**
- The injection site is examined for **induration 48 hours** after injection.
- Approximately 95% of normal subjects will respond to one of the above-mentioned antigens.
- The absence of a response suggests deficient cell-mediated immunity or anergy.

Allergen Patch Testing

- The appropriate diagnostic test for **allergic contact dermatitis.**
- Suspected substances are applied to the skin with adhesive test strips for 48 hours.
- The skin site is examined 48 and 72 hours after application for evidence of erythema, edema, and vesiculation (reproduction of contact dermatitis).

DIAGNOSTIC TESTING IN IMMUNOLOGY

Complement Deficiency Testing

- **The complement pathway** consists of the **classic, alternative, and mannose-binding lectin pathways** (see Figure 1.1).
- **CH50** is a **screening** test for the **classic complement pathway.**
- All nine elements of **C1–C9** are required to produce a normal CH50.
- A normal CH50 does not exclude the possibility of low C3 or C4.

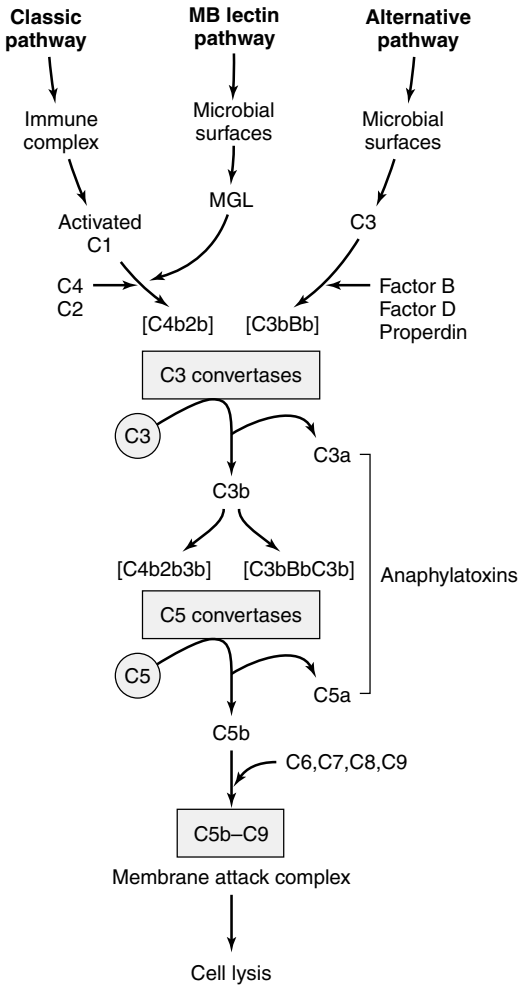

FIGURE 1.1. The complement reaction sequence.

(Reproduced, with permission, from Brooks GF et al. *Jawetz, Melnick, & Adelberg's Medical Microbiology*, 24th ed. New York: McGraw-Hill, 2004, Fig. 8-9.)

- **Deficiencies that lead to disease** include the following:
  - **CH50:** Any C1–C9.
  - **C1-INH:** Hereditary angioedema.
  - **C1, C2, C4:** Recurrent sinopulmonary infections (encapsulated bacteria).
  - **C2:** SLE.
  - **C3:** Pyogenic bacterial infections.
  - **C5–C9:** Neisserial infections.

Think of terminal complement deficiency (C5–C9) in an otherwise healthy patient presenting with recurrent Neisseria *meningitis.*

Humoral (B-Cell) and Cellular (T-Cell) Deficiency Testing

Testing for B- and T-cell deficiency is as follows:

- **CD19:** For **B-cell** immunity.
- **IgG, IgM, IgA, IgD, IgE:** For antibody.
- **CD3, CD4, CD8:** For **T-cell** immunity.
- **CD16, CD56:** For **natural killer cell** immunity.

GELL AND COOMBS CLASSIFICATION OF IMMUNOLOGIC REACTIONS

Gell-Coombs classification system—

ACID

Anaphylactic: type I
Cytotoxic: type II
Immune complex: type III
Delayed hypersensitivity: type IV

The traditional framework that is used to describe immune-mediated reactions. It is not inclusive of all complex immune processes.

Type I: Immediate Reactions (IgE Mediated)

- Specific antigen exposure causes **cross-linking of IgE on mast cell/basophil surfaces,** leading to the release of histamine, leukotrienes, prostaglandins, and **tryptase.**
- Mediator release leads to symptoms of **urticaria, rhinitis, wheezing, diarrhea, vomiting, hypotension,** and **anaphylaxis,** usually within **minutes** of antigen exposure.
- **Late-phase** type I reactions may cause **recurrent symptoms 4–8 hours** after exposure.

Type II: Cytotoxic Reactions

- Mediated by **antibodies,** primarily IgG and IgM, **directed at cell surface or tissue antigens.** Antigens may be native, foreign, or haptens (small foreign particles attached to larger native molecules).
- Antibodies **destroy cells** by **opsonization** (coating for phagocytosis), **complement-mediated lysis,** or **antibody-dependent cellular cytotoxicity.**
- Clinical examples include penicillin-induced autoimmune **hemolytic anemia** and certain forms of **autoimmune thyroiditis.**

Type III: Immune Complex Reactions

- Exposure to antigen in genetically predisposed individuals causes **antigen-antibody complex** formation.
- Antigen-antibody complexes **activate complement and neutrophil** infiltration, leading to tissue inflammation that most commonly affects the **skin, kidneys, joints,** and **lymphoreticular system.**
- Clinically presents with symptoms of "**serum sickness**" **10–14 days after exposure;** most frequently caused by **β-lactam antibiotics** or nonhuman antiserum (antithymocyte globulin, antivenoms).

Type IV: Delayed Hypersensitivity Reactions (T-Cell Mediated)

- Exposure to antigen causes direct activation of **sensitized T cells,** usually CD4+ cells.
- T-cell activation causes tissue **inflammation 48–96 hours after exposure.**
- The most common clinical reaction is **allergic contact dermatitis** such as that resulting from **poison ivy.**

ASTHMA

A **chronic inflammatory disorder** of the airway resulting in **airway hyperresponsiveness, airflow limitation,** and **respiratory symptoms.** Often begins in childhood, but may have adult onset. **Atopy** is a strong identifiable **risk fac-**

tor for the development of asthma. Subtypes include exercise-induced, occupational, aspirin-sensitive, and cough-variant asthma.

Symptoms

Symptoms include **dyspnea** (at rest or with exertion), **cough, wheezing,** mucus hypersecretion, chest tightness, and nocturnal awakenings with respiratory symptoms. Symptoms may have identifiable **triggers** (e.g., exercise, exposure to cat dander, NSAIDs, exposure to cold).

Exam

- **Acute exacerbations: Expiratory wheezing;** a prolonged expiratory phase; ↑ respiratory rate.
- **Severe exacerbations: Pulsus paradoxus,** cyanosis, lethargy, use of accessory muscles of respiration, silent chest (absence of wheezing due to lack of air movement).
- **Chronic asthma without exacerbation:** Presents with minimal to no wheezing. Signs of allergic rhinosinusitis (boggy nasal mucosa, posterior oropharynx cobblestoning, suborbital edema) are commonly found. **Exam may be normal** between exacerbations.

Differential

- **Upper airway obstruction:** Foreign body, tracheal compression, tracheal stenosis, vocal cord dysfunction.
- **Other lung disease:** Emphysema, chronic bronchitis, CF, allergic bronchopulmonary aspergillosis, Churg-Strauss syndrome, chronic eosinophilic pneumonia, obstructive sleep apnea, restrictive lung disease, pulmonary embolism.
- **Cardiovascular disease:** CHF, ischemic heart disease.
- **Respiratory infection:** Bacterial or viral pneumonia, bronchiectasis, sinusitis.

Diagnosis

Diagnosed by the history and objective evidence of **obstructive lung disease.**

- **PFTs:** Show a ↓ **FEV_1/FVC ratio** with **reversible obstruction** (> 12% ↑ in FEV_1 after bronchodilator use) and **normal diffusing capacity.**
- **Methacholine challenge:** Useful if baseline lung function is normal but clinical symptoms are suggestive of asthma. A ⊕ methacholine challenge test is not diagnostic of asthma, but a ⊖ test indicates that asthma is unlikely **(high sensitivity; lower specificity).**

*The role of a methacholine challenge is to **exclude** the diagnosis of asthma. A ⊕ challenge can be 2° to numerous etiologies and thus may not be definitive.*

Treatment

Acute exacerbations are treated as follows:

- **Initial treatment: Inhaled rapid-acting β_2-agonists** (albuterol), one dose q 20 min × 1 hour; **O_2** to keep saturation > 90%.
  - **Good response:** With a peak expiratory flow (PEF) > 80% of predicted or personal best after albuterol, continue albuterol q 3–4 h and institute appropriate chronic therapy (see below).
  - **Incomplete response:** With a PEF 60–80% of predicted or personal best, consider systemic corticosteroids; continue inhaled albuterol q 60 min × 1–3 hours if continued improvement is seen.

  - **Poor response or severe episode:** With a PEF < 60% of predicted or personal best, give systemic corticosteroids and consider systemic epinephrine (preferably IM), IV theophylline, and/or IV magnesium.
- Patients with improved symptoms, a PEF > 70%, and O_2 saturation > 90% for 60 minutes after the last treatment may be discharged home with appropriate outpatient therapy and follow-up. Oral corticosteroids are appropriate in most cases.
- Patients with **incomplete responses** after the initial two hours of treatment (persistent moderate symptoms, PEF < 70%, O_2 saturation < 90%) should be admitted for **inpatient therapy** and monitoring with inhaled **albuterol, O_2,** and **systemic corticosteroids.**
- Patients with a **poor response** to initial therapy (severe symptoms, lethargy, confusion, PEF < 30%, P_{O_2} < 60, P_{CO_2} > 45) should be admitted to the **ICU** for treatment with **inhaled albuterol, O_2, IV corticosteroids,** and **possible intubation** and mechanical ventilation.

Chronic asthma therapy is based on asthma severity as defined by the National Asthma Education and Prevention Program (NAEPP) guidelines (see Table 1.1). The treatment regimen should be **reviewed every 1–6 months,** with changes made depending on symptom severity and clinical course.

TABLE 1.1. NAEPP Guidelines for the Treatment of Chronic Asthma

Asthma Classification	Symptoms[a]	Pulmonary Function	Recommended Treatment
Mild intermittent	≤ 2 days per week, ≤ 2 nights per month.	PEF ≥ 80%	Bronchodilator 2–4 puffs q 4 h as needed. No daily medications necessary.
Mild persistent	> 2 days per week but < 1 time per day or > 2 nights per month.	PEF ≥ 80%	Add low-dose inhaled corticosteroids. Leukotriene modifiers, theophylline, and cromolyn may also be added.
Moderate persistent	Daily symptoms or > 1 night per week.	PEF 60–80%	↑ to medium-dose inhaled corticosteroids and add a long-acting inhaled β_2-agonist. Leukotriene modifiers or theophylline may also be added.
Severe persistent	Continuous symptoms.	PEF < 60%	↑ to high-dose inhaled corticosteroids. Daily oral corticosteroids may be added if necessary (60 mg QD).

[a] Dyspnea (at rest or with exertion), cough, wheezing, mucus hypersecretion, chest tightness, and nocturnal awakenings with respiratory symptoms.

- All asthma patients should use **2–4 puffs** of a **short-acting bronchodilator as needed for symptoms. Use of a short-acting bronchodilator ≥ 2 times per week** may indicate the need for ↑ control therapy.
- **Mild intermittent asthma (symptoms ≤ 2 days per week and ≤ 2 nights per month; PEF ≥ 80%): No daily medication** is needed.
- **Mild persistent asthma (symptoms > 2 days per week but < 1 time per day or > 2 nights per month; PEF ≥ 80%):**
  - **Low-dose inhaled corticosteroids** are preferred.
  - Other medications include leukotriene modifiers, theophylline, and cromolyn.
- **Moderate persistent asthma (daily symptoms or > 1 night per week and PEF 60–80%):**
  - **Low- to medium-dose inhaled corticosteroids** and **long-acting inhaled β_2-agonists** are preferred.
  - Alternative therapy involves inhaled corticosteroids and leukotriene modifiers or theophylline.
- **Severe persistent asthma (continuous symptoms; PEF < 60%):**
  - **High-dose inhaled corticosteroids and long-acting inhaled β_2-agonists.**
  - **Oral corticosteroids** at a dosage of up to 60 mg QD may be necessary.

Asthma symptoms that occur more than twice weekly generally indicate the need for inhaled corticosteroid therapy.

Additional treatment considerations include the following:

- Recognize the exacerbating effects of **environmental factors** such as allergens, air pollution, smoking, and weather (cold and humidity).
- Use potentially **exacerbating medications with caution** (aspirin, NSAIDs, β-blockers).
- Always consider **medication compliance and technique** as possible complicating factors in poorly controlled asthma.
- Treatment of **coexisting conditions** (e.g., **rhinitis, sinusitis, GERD**) may improve asthma.

Complications

- Hypoxemia, respiratory failure, pneumothorax or pneumomediastinum.
- Frequent hospitalization and previous intubation are warning signs of potentially fatal asthma.
- A subset of patients with chronic asthma develop **airway remodeling,** leading to accelerated, irreversible loss of lung function.

ALLERGIC RHINITIS

The **most common cause** of chronic rhinitis. Allergic factors are present in 75% of rhinitis cases. May be **seasonal or perennial;** incidence is greatest in adolescence and ↓ with advancing age. Usually persistent, with occasional spontaneous remission.

Symptoms

- Sneezing, nasal itching, rhinorrhea, nasal congestion, sore throat, throat clearing, itching of the throat and palate.
- Sleep disturbance; association with obstructive sleep apnea.
- Concomitant conjunctivitis with ocular itching, lacrimation, and puffiness.

Intranasal steroids are the most effective treatment for allergic rhinitis.

Exam

Patients present with swollen nasal turbinates with pale or bluish mucosa, clear nasal discharge, clear to white secretions along the posterior wall of the oropharynx, infraorbital darkening, conjunctival erythema, and lacrimation.

Differential

- **Nonallergic rhinitis:** Vasomotor or gustatory rhinitis.
- **Rhinitis medicamentosa:** Overuse of vasoconstricting nasal sprays, leading to rebound nasal congestion and associated symptoms.
- **Hormonal rhinitis:** Associated with pregnancy, use of OCPs, and hypothyroidism.
- **Drug-induced rhinitis:** Common causes include β-blockers, α-blockers, and cocaine.
- **Atrophic rhinitis:** Develops in elderly patients with atrophy of the nasal mucosa.
- **Infectious rhinosinusitis:** Acute viral syndromes lasting 7–10 days; bacterial sinusitis.
- **Nasal obstruction due to a structural abnormality:** Septal deviation, nasal polyposis, nasal tumor, foreign body.

Diagnosis

Based on the history and ⊕ **skin testing** to common aeroallergens (e.g., grass/tree/weed pollen, house dust mites, cockroaches, dog and cat dander, mold).

Treatment

- **Allergen avoidance measures:** Most effective for house dust mites (involves the use of allergen-impermeable bed and pillow casings and washing of bedding in hot water). Indoor pollen exposure can be reduced by keeping windows closed and using air conditioners.
- **Antihistamines:** Reduce sneezing, rhinorrhea, and pruritus. Less effective for nasal congestion; most effective if used regularly. Not effective for nonallergic rhinitis. Nonsedating antihistamines are preferable.
- **Oral decongestants:** Effectively reduce nasal congestion in allergic and nonallergic rhinitis. May cause insomnia and exacerbate hypertension or arrhythmia.
- **Intranasal steroids:** The most effective medication for allergic and nonallergic rhinitis. Have no significant systemic side effects; most beneficial when used regularly.
- **Allergen immunotherapy:** Indicated as an alternative or adjunct to medications. The only effective therapy that has been demonstrated to modify the long-term course of the disease.

Complications

Chronic sinusitis and otitis; exacerbation of asthma.

HYPERSENSITIVITY PNEUMONITIS

A complex immune-mediated lung disease resulting from repeated inhalational exposure to a wide variety of **organic dusts** (see Table 1.2). Presents in acute, subacute, and chronic forms.

TABLE 1.2. Selected Causes of Hypersensitivity Pneumonitis

Disease	Antigen	Source
Farmer's lung	*Micropolyspora faeni, Thermoactinomyces vulgaris.*	Moldy hay.
"Humidifier lung"	Thermophilic actinomycetes.	Contaminated humidifiers, heating systems, or air conditioners.
Bird-fancier's lung ("pigeon breeder's disease")	Avian proteins.	Bird serum and excreta.
Bagassosis	*Thermoactinomyces sacchari* and *T. vulgaris.*	Moldy sugar-cane fiber (bagasse).
Sequoiosis	*Graphium, Aureobasidium,* and other fungi.	Moldy redwood sawdust.
Maple bark stripper's disease	*Cryptostroma (Coniosporium) corticale.*	Rotting maple tree logs or bark.
Mushroom picker's disease	Same as farmer's lung.	Moldy compost.
Suberosis	*Penicillium frequentans.*	Moldy cork dust.
Detergent worker's lung	*Bacillus subtilis* enzyme.	Enzyme additives.

Reproduced, with permission, from Tierney LM et al. *Current Medical Diagnosis & Treatment,* 44th ed. New York: McGraw-Hill, 2005: 293.

Symptoms

- **Acute:** Nonproductive cough, shortness of breath, fever, diaphoresis, myalgias occurring 6–12 hours after intense antigen exposure.
- **Chronic:** Insidious onset of dyspnea, productive cough, fatigue, anorexia, weight loss.

Exam

- **Acute:** Patients are ill-appearing with fever, respiratory distress, and dry rales (wheezing is **not** a prominent symptom). Exam may be normal in asymptomatic patients between episodes of acute hypersensitivity pneumonitis.
- **Chronic:** Dry rales, ↓ breath sounds, digital clubbing.

Differential

- **Acute:**
  - **Pneumonia:** Bacterial, viral, or atypical.
  - **Toxic fume bronchiolitis:** Sulfur dioxide, ammonia, chlorine.
  - **Organic dust toxic syndrome:** Inhalation of dusts contaminated with bacteria and fungi.
- **Subacute or chronic:** Chronic bronchitis, idiopathic pulmonary fibrosis, chronic eosinophilic pneumonia, collagen vascular disease, sarcoidosis, 1° pulmonary histiocytosis, alveolar proteinosis.

Diagnosis

- **PFTs:**
  - **Acute: Restrictive pattern** with ↓ FVC and FEV_1. ↓ $\mathbf{DL_{CO}}$ is common.
  - **Chronic:** Combined obstructive and restrictive pattern.
- **Imaging:**
  - **Acute:** CXR shows transient patchy, peripheral, bilateral interstitial infiltrates. CT typically shows ground-glass opacifications and diffuse consolidation.
  - **Subacute:** CXR shows nodular, patchy infiltrates and fibrosis; CT shows centrilobular nodules with areas of ground-glass opacity.
  - **Chronic:** CXR shows fibrotic changes with honeycombing and areas of emphysema; CT shows honeycombing, fibrosis, traction bronchiectasis, ground-glass opacities, and small nodules.
- **Labs:**
  - **Acute:** Elevated WBC count; elevated ESR.
  - **Acute or chronic: High titers of precipitating IgG** against the offending antigen (indicates exposure, not necessarily disease). Double-gel immunodiffusion is preferred, as ELISA may be too sensitive.
- **Bronchoalveolar lavage:** Lymphocytosis with a predominance of CD8+ T cells.
- **Lung biopsy:** Interstitial and alveolar noncaseating granulomas; "foamy" macrophages; predominance of lymphocytes.
- **Inhalational challenge:** Not required or recommended for diagnosis; helpful when data are lacking or diagnosis is unclear. Performed only with careful medical monitoring.

Treatment

- Avoidance of the offending antigen.
- Oral corticosteroids at a dosage of 40–80 mg QD with tapering after clinical improvement has been achieved.

Complications

- Irreversible loss of lung function.
- Death is uncommon but has been reported.

ALLERGIC BRONCHOPULMONARY ASPERGILLOSIS (ABPA)

An immunologic reaction to antigens of *Aspergillus* present in the bronchial tree.

Symptoms

Asthma (may be cough variant or exercise induced); expectoration of golden brown mucous plugs; fever with acute flare.

Exam

Wheezing, rales, or bronchial breath sounds; digital clubbing and cyanosis (late-stage disease).

Differential

Asthma without ABPA, pneumonia (bacterial, viral, fungal, acid-fast bacilli), Churg-Strauss syndrome, eosinophilic pneumonias, CF.

Diagnosis

- **Essential criteria** for ABPA-S (seropositive ABPA) are as follows:
  - The presence of **asthma.**
  - ⊕ immediate **skin tests to *Aspergillus*.**
  - Elevated total serum **IgE (> 1000 ng/mL).**
  - Elevated serum ***Aspergillus*-specific IgE and/or IgG.**
- Other features include the following:
  - The above plus central bronchiectasis = ABPA-CB (ABPA with central bronchiectasis).
  - Precipitating antibodies to *Aspergillus*.
  - Peripheral blood eosinophilia (> 1000/mm^3).
  - CXR showing infiltrates (transient or fixed).
  - Sputum culture that is ⊕ for *Aspergillus* or that contains *Aspergillus* hyphae.

ABPA should be considered in any patient with poorly controlled asthma, particularly in the presence of CXR infiltrates.

Treatment

- **Prednisone;** itraconazole may be used as an adjunctive medication.
- Chronic inhaled corticosteroids to control asthma.

Complications

Corticosteroid-dependent asthma, irreversible loss of pulmonary function, chronic bronchitis, pulmonary fibrosis, death due to respiratory failure or cor pulmonale.

ALLERGIC FUNGAL SINUSITIS

An immunologic reaction to fungal aeroallergens (*Aspergillus, Bipolaris, Curvularia, Alternaria, Fusarium*) that causes chronic, refractory sinus disease.

Symptoms

Sinus congestion and obstruction that are refractory to antibiotics; thick mucoid **secretions** (**"peanut butter"** appearance); nasal polyposis; proptosis; asthma.

Exam

Presents with thickening of the sinus mucosa, allergic mucin on rhinoscopy, and nasal polyps.

Differential

- **Chronic rhinosinusitis:** Bacterial, allergic (nonfungal).
- Nasal polyposis without allergic fungal sinusitis.
- **Invasive fungal disease:** Seen in immunocompromised patients (HIV, diabetes).
- Mycetoma (fungus ball).

Diagnosis

- **Diagnostic criteria** include the following:
  - Chronic sinusitis for > 6 months.
  - **Allergic mucin** containing many eosinophils and fungal hyphae.

- **Sinus CT** showing opacification of the sinus (often unilateral) with **hyperattenuated,** expansile material.
- Absence of invasive fungal disease.

- **Other supportive findings** include peripheral blood eosinophilia and immediate skin tests ⊕ to fungus.

Treatment

- **Surgical** removal of allergic mucin.
- **Prednisone** 0.5–1.0 mg/kg for weeks with slow tapering.
- Intranasal corticosteroids; nasal irrigation.

Complications

Bony erosions from expansion of allergic mucin; surgical complications; high recurrence rate despite therapy.

URTICARIA AND ANGIOEDEMA

When used regularly at adequate doses, antihistamines successfully treat most cases of urticaria.

Localized edema in the skin or mucous membranes. Individual wheals (hives) typically last < 24 hours. May be acute (< 6 weeks of symptoms) or chronic (> 6 weeks).

Symptoms

Presents with pruritic hives and painful soft tissue swelling on the lips, oral mucosa, periorbital area, hands, and feet. **Individual skin lesions** resolve in < 24 hours without residual scarring. Angioedema may take longer to fully resolve.

*Think of hereditary angioedema in a patient presenting with recurrent episodes of angioedema **without** pruritus or urticaria. Check a C1 inhibitor (C1-INH) assay, which will be low.*

Exam

Erythematous, blanching skin wheals; soft tissue swelling as described above. No scarring or pigmentary changes can be seen at previously affected sites. Exam may be normal between symptomatic flares.

Differential

- **IgE-mediated allergic reaction:** Food, medication, insect stings.
- **Non-IgE reactions:** Aspirin, narcotics, radiocontrast media.
- **Physical urticaria:** Pressure, vibratory, solar, cholinergic, local heat and cold.
- **Autoimmunity:** Vasculitis, associated thyroiditis.
- **Infections:** Mononucleosis, viral hepatitis, fungal and parasitic disease.
- **Idiopathic:** Accounts for the majority of chronic urticaria cases.
- **Isolated angioedema:** Consider hereditary angioedema or acquired angioedema (associated with vasculitis and neoplasms).
- **Other:** Dermatographism; cutaneous mastocytosis.

*In contrast to angioedema associated with anaphylaxis, hereditary angioedema does **not** respond to epinephrine. Treat with fresh frozen plasma.*

Diagnosis

- The clinical history suggests diagnostic testing.
- Provocative testing for physical urticarias.
- Labs include ESR, ANA, skin biopsy (if necessary to exclude vasculitis), and antithyroid antibodies if autoimmunity is suspected.
- Order a CBC, viral hepatitis panel, and stool O&P if the history is suggestive of infection.
- In the setting of angioedema alone, obtain a C1 inhibitor assay to exclude

hereditary angioedema; determine the C1q level to exclude acquired angioedema.

The vast majority of chronic urticaria cases are idiopathic. Extensive laboratory evaluation in the absence of systemic symptoms or unusual features is generally not beneficial.

Treatment

- Avoid inciting exposure or treat the underlying condition if it is identified.
- **Antihistamines:** Regular use of nonsedating H_1 antagonists is preferred. Sedating H_1 antagonists may also be used QHS; H_2 antagonists may be helpful adjunctive medication.
- **Other:**
  - Ephedrine (OTC) is helpful for acute flares.
  - Leukotriene modifiers are beneficial in some cases.
  - Oral corticosteroids for severe, refractory cases.
  - Epinephrine for life-threatening laryngeal edema.
  - Danazol or stanozolol for chronic treatment of hereditary angioedema.

Complications

Laryngeal edema.

A patient with angioedema and well-controlled hypertension? Think ACEIs.

ATOPIC DERMATITIS

A chronic inflammatory skin disease that is often associated with a personal or family **history of atopy.** Usually begins in childhood.

Symptoms

Characterized by intense **pruritus** and an erythematous papular rash typically occurring in the flexural areas of the elbows, knees, ankles, and neck. Pruritus precedes the rash (**"an itch that rashes").** Chronic atopic dermatitis manifests as thickened nonerythematous plaques of skin (lichenification).

Exam

Presents with an erythematous papular rash in **flexural areas** as well as with excoriations, serous exudate, lichenification (if chronic), and other findings of atopic disease (boggy nasal mucosa, conjunctival erythema, expiratory wheezing).

Differential

- **Other dermatitis:** Seborrheic, irritant, contact, psoriasis.
- **Neoplasia:** Cutaneous T-cell lymphoma.
- **Infectious:** Scabies, candidiasis, tinea versicolor.
- **Hyper-IgE syndrome:** Usually diagnosed in childhood.

Diagnosis

Diagnosis is readily made through the history and physical. Consider skin biopsy to rule out cutaneous T-cell lymphoma in new-onset eczema in an adult.

Treatment

- **Skin hydration:** Lotions, emollients.
- **Topical corticosteroids.**
- **Antihistamines** to reduce pruritus.

- Avoid skin irritants (e.g., abrasive clothing, temperature extremes, harsh soaps).
- Avoid allergic triggers if identified (food, aeroallergens; more common in children).
- Treat bacterial, fungal, and viral **superinfection** as necessary.
- Topical **tacrolimus/pimecrolimus** and oral corticosteroids for severe disease.

COMPLICATIONS

- **Chronic skin changes:** Scarring, hyperpigmentation.
- **Cutaneous infection:** Bacterial (primarily *S. aureus*), viral (primarily HSV); risk of eczema vaccinatum with smallpox vaccine.

ALLERGIC CONTACT DERMATITIS

A lymphocyte-mediated delayed hypersensitivity reaction causing a skin rash on an antigen-exposed area.

SYMPTOMS

Characterized by a **pruritic** rash that typically appears 5–21 days after the initial exposure or 12–96 hours after reexposure in sensitized individuals. The typical pattern is **erythema** leading to **papules** and then **vesicles.** The rash precedes pruritus and appears in the distribution of antigen exposure (see Figure 1.2).

EXAM

- **Acute stage:** Skin erythema, papules, vesicles.
- **Subacute or chronic stage:** Crusting, scaling, lichenification, and thickening of the skin.

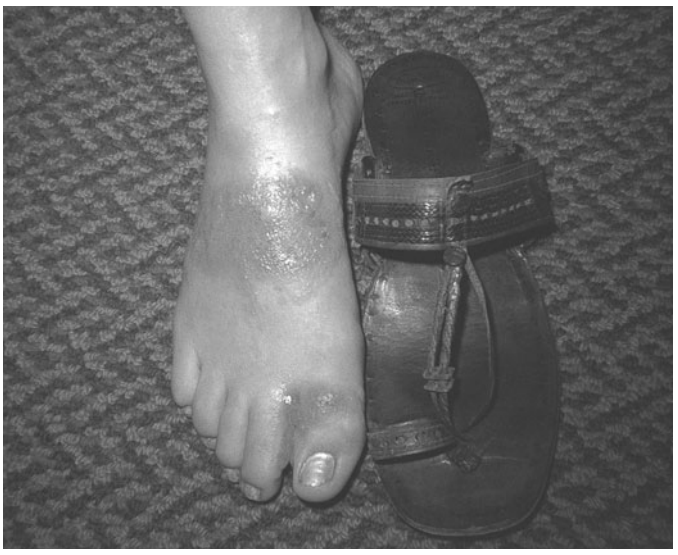

FIGURE 1.2. Contact dermatitis.

Erythematous papules, vesicles, and serous weeping localized to areas of contact with the offending agent are characteristic. (Reproduced, with permission, from Hurwitz RM. *Pathology of the Skin: Atlas of Clinical-Pathological Correlation.* Stamford, CT: Appleton & Lange, 1991: 3.)

Differential

Atopic dermatitis, seborrheic dermatitis, irritant dermatitis (antigen-nonspecific irritation, usually due to chemicals or detergents), psoriasis.

Diagnosis

- **Location of the rash:** Suggests the cause—e.g., feet (shoes), neck/ears (jewelry), face (cosmetics/hair products).
- **Allergy patch testing:** See above.

Treatment

Antigen avoidance, topical corticosteroids, antihistamines for pruritus, oral prednisone in severe or extensive cases.

Complications

2° infection from scratching affected skin.

ANAPHYLAXIS

A systemic type I (IgE-mediated) hypersensitivity reaction that is often life-threatening. Requires **previous exposure** (known or unknown) for sensitization. Risk factors include parenteral antigen exposure and repeated interrupted antigen exposure. Common causes are **foods** (especially peanuts and shellfish), **drugs** (especially penicillin), **latex, stinging insects,** and **blood products.**

Symptoms

- Symptoms include skin erythema, pruritus, urticaria, angioedema, laryngeal edema, wheezing, chest tightness, cramping abdominal pain, nausea, vomiting, diarrhea, diaphoresis, dizziness, a sense of "impending doom," hypotension, syncope, and shock.
- Symptoms most frequently appear **seconds to minutes after exposure** but may be delayed several hours for ingested agents.

Exam

Urticaria, angioedema, flushing, wheezing, stridor, diaphoresis, hypotension, tachycardia.

Differential

- **Other types of shock:** Cardiogenic, endotoxic, hemorrhagic.
- **Cardiovascular disease:** Arrhythmia, MI.
- **Scombroid:** Histamine poisoning from spoiled fish.
- **Anaphylactoid reaction:** Nonspecific mast cell activation (**not** IgE).
- **Other:** Carcinoid syndrome, pheochromocytoma, severe cold urticaria, vasovagal reaction, systemic mastocytosis, panic attack.

Diagnosis

- Elevated **serum tryptase** drawn 30 minutes to three hours after onset can help confirm the diagnosis.
- **Presence of allergen-specific IgE antibody** by skin or RAST testing (best performed one month after event).

The treatment of anaphylaxis consists of the prompt administration of epinephrine. Mortality is strongly associated with delays in epinephrine administration.

Treatment

- **Epinephrine** 1:1000 0.3 mL IM: Repeat every 15 minutes as needed.
- **Maintain airway:** O_2; inhaled bronchodilators; intubation if necessary.
- Rapid IV fluids if the patient is hypotensive.
- **Diphenhydramine:** Give 50 mg IV/IM/PO.
- **Corticosteroids** (prednisone 60 mg or equivalent) IV/IM/PO: Reduce late-phase recurrence of symptoms 4–8 hours later.
- Vasopressor medications in the presence of persistent hypotension.
- IV epinephrine 1:10,000 0.3 mL should be given only in terminal patients.
- Consider **glucagon and/or atropine for patients on β-blockers** whose symptoms are refractory to therapy.
- Monitor patients for 8–12 hours after reaction.
- Ensure that patients have access to injectable epinephrine and antihistamines on discharge.

The ABCs of anaphylaxis treatment:

Airway
Breathing
Circulation
Drugs
Exposure
Note: Epinephrine should be administered as soon as anaphylaxis is suspected.

Complications

Respiratory obstruction, cardiovascular collapse, death.

ANAPHYLACTOID REACTIONS

Clinically indistinguishable from anaphylactic reactions, but caused by nonspecific mast cell activation **(not IgE mediated).** May occur with initial exposure to medication. Common causes include radiocontrast media, vancomycin, amphotericin, opiates, and general anesthetics (induction agents and muscle relaxants).

Diagnosis

- Elevated **serum tryptase** drawn 30 minutes to three hours after onset helps confirm mast cell release.
- **Absence of allergen-specific IgE** antibody to suspected antigens by skin or RAST testing (best performed one month after event).

Treatment

- The same as that for anaphylaxis.
  - **Vancomycin:** Slow infusion rate.
  - **Radiocontrast media:** Use low-osmolality forms.
- Anaphylactoid reactions are **generally preventable with pretreatment** through use of corticosteroids and antihistamines. Pretreatment is recommended for patients with a history of reactions to radiocontrast media.

FOOD ALLERGY

True (IgE-mediated) food allergy in adults is most commonly caused by **peanuts, crustaceans, tree nuts,** and **fish.** Sensitivities to these foods tend to be lifelong. Multiple food allergies are rare in adults. Anaphylactic signs and symptoms occur **minutes to two hours after ingestion.**

Differential

- Nonallergic food intolerance (lactase deficiency, celiac disease, symptoms due to vasoactive amines).

- Food poisoning, including scombroid.
- Anaphylaxis due to other causes.
- Eosinophilic gastroenteritis.

Diagnosis

- Anaphylaxis may be confirmed with **elevated serum tryptase** if the test is conducted 30 minutes to three hours after the reaction.
- ⊕ **allergy skin or RAST tests** to food antigen.
- Conduct a double-blind placebo-controlled food challenge if the diagnosis is unclear.

Treatment

- Treat anaphylaxis in an acute setting (see above).
- Eliminate implicated foods from the diet.
- Ensure patient access to injectable epinephrine.

STINGING INSECT ALLERGY

Allergic reactions occur to three major stinging insect families: **vespids** (yellow jackets, hornets, wasps), **apids** (honeybees and bumblebees), and **fire ants.** Reactions are classified into **local** (symptoms at the sting site) and **systemic** (anaphylactic).

Symptoms/Exam

- **Local reaction:** Swelling and erythema; pain at the sting site lasting several hours.
- **Large local reaction:** Extensive swelling and erythema at the sting site lasting up to one week; nausea and malaise.
- **Systemic reaction:** Anaphylactic symptoms occurring within 15 minutes of sting.

Any adult who reacts systemically to an insect sting, regardless of reaction severity, should be evaluated for venom immunotherapy.

Differential

- **Toxic venom reaction:** Results from large venom burden delivery by **multiple simultaneous stings.** The pharmacologic properties of venom may cause hypotension and shock.
- Anaphylaxis due to other causes.

Diagnosis

- Systemic reactions may be confirmed by an **elevated serum tryptase** if drawn 30 minutes to three hours after reaction.
- Any systemic reaction should be confirmed with **venom-specific IgE by allergy skin or RAST testing** given the risk of recurrence with repeat stings. Testing should be performed several weeks after the reaction in view of mast cell depletion.

People who have an anaphylactic reaction to insect stings should be educated about their venom sensitivity and provided with self-administered injectable epinephrine (EpiPen)

Treatment

- **Large local:** Antihistamines; analgesics; a short prednisone course for severe or disabling local reactions.
- **Systemic:** Treatment is the same as that for anaphylaxis (see above).
- **Venom immunotherapy:** Recommended for patients with a history of systemic reaction and ⊕ venom-specific IgE tests. Immunotherapy is 98% effective in preventing systemic allergic reactions on resting.

- Insect avoidance.
- Ensure patient access to antihistamines and injectable epinephrine.

DRUG ALLERGY

Only a small portion of adverse drug reactions are drug hypersensitivity reactions (immune mediated), of which a small subset represents true drug allergy (IgE mediated).

Symptoms

Immunologic drug reactions may present with a wide range of symptoms. Common symptoms include urticaria, angioedema, morbilliform rash, blistering mucocutaneous lesions, cough, dyspnea, wheezing, anaphylaxis, arthralgias, fever, and lymphadenopathy.

Exam

- **Dermatologic findings:** Urticaria, angioedema, morbilliform rash, purpura, petechiae, exfoliative dermatitis, bullous skin lesions.
- **Other:** Wheezing, lymphadenopathy, jaundice, fever.

Differential

The vast majority of adverse drug reactions are due to predictable drug effects and do not represent true drug allergy.

- **Nonimmunologic adverse drug reaction:** Dose-related toxicity, pharmacologic side effects, drug-drug interactions.
- **Pseudoallergic reaction:** Direct mast cell release (opiates, vancomycin, radiocontrast media).
- Nondrug causes of presenting symptoms

Diagnosis

Diagnostic drug allergy skin testing is standardized and predictive only for penicillin.

- Diagnosed on the basis of clinical judgment using the following **general criteria:**
  - The patient's symptoms are consistent with an immunologic drug reaction.
  - The patient was administered a drug known to cause the symptoms.
  - The temporal sequence of drug administration and the appearance of symptoms are consistent with a drug reaction.
  - Other causes of the symptoms have effectively been excluded.
  - Laboratory data are supportive of an immunologic mechanism to explain the drug reaction (see below).
- When available, **diagnostic testing** supportive of an immunologic mechanism to explain the drug reaction (see Table 1.3).
- The drug challenge procedure is the definitive diagnostic test but should be performed only by an experienced clinician if an absolute indication exists for the drug.

Treatment

- **Discontinuation of drug:** In most instances, symptoms promptly resolve if the diagnosis is correct.
- If the drug is absolutely indicated, refer the patient for **graded challenge/desensitization.**
- **Symptomatic treatment for specific symptoms:** Antihistamines, topical corticosteroids, bronchodilators; oral corticosteroids in severe cases.

- **Patient education:** Educate patients with regard to the risk of future reaction, drug avoidance, and cross-reactive medications.

Complications

- **Fatal drug hypersensitivity:** Anaphylaxis, toxic epidermal necrolysis.
- **"Multiple drug allergy syndrome":** Lack of patient/physician understanding of adverse drug reactions can lead to multiple medication avoidance and restrictive, ineffective medical therapy.

MASTOCYTOSIS

A disease characterized by **excessive numbers of mast cells** in the skin, internal organs, and bone marrow. Caused by a somatic ***kit* gene mutation.** Has variable severity ranging from the isolated cutaneous form to indolent systemic disease to aggressive lymphoma-like disease or mast cell leukemia.

*Mastocytosis should be suspected when an **urticarial rash** is accompanied by abdominal (e.g., diarrhea), lymphatic (e.g., splenomegaly) or anaphylactic signs and symptoms.*

Symptoms

Pruritus, flushing, urticaria, diarrhea, nausea, vomiting, abdominal pain, headache, hypotension, anaphylaxis.

Exam

Presents with **urticaria pigmentosa** (a pigmented macular skin rash that urticates with stroking) as well as with lymphadenopathy, hepatomegaly, and splenomegaly.

TABLE 1.3. Diagnostic Testing and Therapy for Drug Hypersensitivity

Immunologic Reaction	Clinical Manifestations	Laboratory Tests	Therapeutic Considerations
Type I	Anaphylaxis, angioedema, urticaria, bronchospasm.	Skin testing, RAST testing, serum tryptase.	Discontinue drug; epinephrine, antihistamines, systemic corticosteroids, bronchodilators; inpatient monitoring if severe.
Type II	Hemolytic anemia, thrombocytopenia, neutropenia.	Direct/indirect Coombs' test.	Discontinue drug; consider systemic corticosteroids; transfusion in severe cases.
Type III	Serum sickness, vasculitis, glomerulonephritis.	Immune complexes, ESR, complement studies, ANA/ANCA, C-reactive protein, tissue biopsy for immunofluorescence studies.	Discontinue drug; NSAIDs, antihistamines; systemic corticosteroids or plasmapheresis if severe.
Type IV	Allergic contact dermatitis; maculopapular drug rash.[a]	Patch testing; lymphocyte proliferation assay.[b]	Discontinue drug; topical corticosteroids, antihistamines; systemic corticosteroids if severe.

[a] Suspected type IV reaction; mechanism not fully elucidated.

[b] Investigational test.

Differential

- **Anaphylaxis:** Drugs, foods, venoms, exercise induced, idiopathic.
- **Flushing syndromes:** Scombroid, carcinoid, VIPoma, pheochromocytoma.
- **Shock:** Cardiogenic, hemorrhagic, endotoxic.
- **Angioedema:** Hereditary or acquired.
- **Other:** Panic attack.

Diagnosis

Diagnosed by the presence of one major plus one minor or three minor criteria.

- **Major criteria:** Characteristic multifocal dense **infiltrates of mast cells on bone marrow** biopsy.
- **Minor criteria:**
  - Spindle-shaped morphology of mast cells on **tissue biopsy.**
  - Detection of the **c-*kit* mutation.**
  - **Flow cytometry** of bone marrow mast cells coexpressing CD117, CD2, and CD25.
  - **Serum tryptase** levels > 20 ng/mL.

Treatment

- H_1 and H_2 antagonists.
- Epinephrine for episodes of anaphylaxis.
- Topical steroids for skin lesions; oral corticosteroids for advanced disease.
- Bone marrow transplantation for patients with aggressive disease or associated hematologic disorders.

1° IMMUNODEFICIENCY IN ADULTS

Adult 1° immunodeficiencies (non-HIV) generally present in the second or third decade of life with **recurrent respiratory infections** due to antibody deficiency (hypogammaglobulinemia). Conditions include **common variable immunodeficiency** (CVID), **selective IgA deficiency** (most common, with an incidence of 1:500), IgG subclass deficiency, and selective antibody deficiency with normal immunoglobulins (SADNI).

Symptoms

- Presents with frequent **respiratory tract infections** (sinusitis, otitis, pneumonia); a need for IV or prolonged oral antibiotic courses to clear infections; and **chronic GI symptoms** such as diarrhea, cramping abdominal pain, or malabsorption.
- IgG subclass deficiency and selective IgA deficiency are often asymptomatic.

Exam

Nasal congestion and discharge; respiratory wheezing or rales; digital clubbing 2° to chronic lung disease; lymphadenopathy; splenomegaly.

Differential

- Hypogammaglobulinemia due to loss (GI, renal).
- Hypogammaglobulinemia due to medications (immunosuppressants, anticonvulsants).
- HIV, CF, allergic respiratory disease.

Diagnosis

- A **history** of recurrent infection.
- **Antibody deficiency by laboratory testing:** Order quantitative immunoglobulins initially, after which IgG subclasses may be obtained.
  - **CVID: Low IgG** (< 500), usually with low IgA and/or IgM.
  - **Selective IgA deficiency: Absence of IgA** (< 7) **with normal IgG** and IgM (the most common 1° immunodeficiency).
  - **IgG subclass deficiency:** Low levels of one or more IgG subclasses (IgG1, IgG2, IgG3, IgG4). Clinical significance is unclear.
  - **SADNI:** Normal immunoglobulin levels with failure to produce protective antibody levels against specific immunizations (most commonly pneumococcus; rarely tetanus).
- **Exclude other causes** of hypogammaglobulinemia (antibody loss due to protein-losing enteropathy or nephropathy, medication, lymphopenia).

Treatment

- **CVID:**
  - **IVIG** 400–500 mg/kg monthly.
  - Aggressive treatment of infection.
  - Monitor lung function; pulmonary hygiene for bronchiectasis.
- **Selective IgA deficiency:**
  - **Antibiotic therapy and/or prophylaxis** as necessary.
  - **IVIG is contraindicated** owing to possible anti-IgA IgE antibody.
  - Patients should receive only **washed blood products** in view of the **risk of anaphylaxis** with exposure to IgA.
- **IgG subclass deficiency and SADNI:**
  - Antibiotic therapy as needed.
  - IVIG is reserved for rare patients with significant infection despite preventive antibiotics.

Suspect IgA deficiency in a patient with an anaphylactic reaction that occurs seconds to minutes after a blood transfusion. Treat by immediately administering epinephrine and discontinuing the transfusion.

Complications

- **CVID:** Variable T-cell deficiency, GI **malignancy** (gastric cancer, small bowel lymphoma), **bronchiectasis, lymphoproliferative** disease, noncaseating granulomas of internal organs, **autoimmune disease.**
- **Selective IgA deficiency: Celiac disease, lymphoproliferative** disease, GI **malignancy** (gastric cancer, small bowel lymphoma), **autoimmune** disease.

NOTES

CHAPTER 2

Ambulatory Medicine

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Screening for Hyperlipidemia

Hyperlipidemia is a risk factor for CAD, stroke, and peripheral vascular disease. Other major risk factors for CAD are as follows:

- Age (men > 45, women > 55), cigarette smoking, hypertension, a family history of premature CAD, HDL < 40 (HDL > 60 is protective), elevated LDL.
- Risk factor equivalents to CAD include DM and symptomatic noncoronary atherosclerotic disease (e.g., carotid artery disease, peripheral arterial disease, abdominal aortic aneurysm).

Diagnosis

- Obtain fasting total cholesterol, LDL, HDL, and triglycerides (TG).
- If there are no risk factors for CAD, screening recommendations are as follows:
  - The United States Preventive Services Task Force (USPSTF) recommends that men ≥ 35 years of age and women ≥ 45 years of age be screened. Younger adults aged 20 and over should be screened if other major cardiovascular risk factors are present.
  - The National Cholesterol Education Program Adult Treatment Panel III (ATP III) recommends that adults ≥ 20 years of age be screened at least once every five years.
  - The optimal age to stop screening is unknown. There is insufficient evidence to support the screening of patients > 65 years of age unless multiple cardiovascular risk factors are present.

Treatment

- Therapeutic lifestyle changes (TLC) are indicated for all patients with an LDL above the goal. Such changes include the following:
  - A low-saturated-fat, low-cholesterol, high-fiber diet.
  - Consider plant stanols/sterols (2 g/day).
  - Weight management.
  - ↑ physical activity.
- For most patients requiring cholesterol-lowering medication, statins are first-line therapy because of their demonstrated impact on cardiovascular outcomes. The effects of and indications for the major classes of cholesterol-lowering agents are listed in Table 2.1.
- Table 2.2 identifies risk categories that determine LDL cholesterol goals.

Combining statins and fibrates ↑ the risk of myositis and rhabdomyolysis. Muscle toxicity may occur in 1–5% of patients treated with both a statin and gemfibrozil.

Myalgias occur in a minority of patients who take statins, but myositis with elevated CK and rhabdomyolysis with renal failure are very rare. Treat by stopping the statin and providing supportive care.

Screening for Diabetes Mellitus (DM)

- The American Diabetes Association (ADA) recommends screening for DM every three years starting at age 45 or earlier in the presence of risk factors. The USPSTF states that evidence is insufficient to recommend for or against DM screening in the general population, but it recommends screening for those with hypertension or hyperlipidemia.
- The ADA's diagnostic criteria include any of the following (on more than one occasion):
  - A **fasting blood glucose ≥ 126 mg/dL.**
  - **Symptoms of DM** (polyuria, polydipsia, weight loss) and a random blood glucose ≥ 200 mg/dL.

TABLE 2.1. Drugs for the Treatment of Hyperlipidemia

Drug Class	Examples/ Comments	LDL	HDL	TG	Applications	Adverse Effects
HMG-CoA reductase inhibitors	"Statins" (e.g., atorvastatin, simvastatin, pravastatin).	↓↓	↑	↓	**First-line** medications for lowering the risk of clinical cardiovascular events in most patients requiring lipid-lowering medication. Primarily lower LDL.	Elevated LFTs, myositis. **Myositis is more common when fibrates, and possibly niacin, are used with a statin.** Monitor LFTs and CK.
Niacin (nicotinic acid)		↓	↑↑	↓↓	Raise HDL; lower TG and LDL **(near-ideal effects on lipid profile).**	**Flushing** limits use (affects > 50% of patients). Can exacerbate gout and PUD; can cause elevated liver enzymes and blood glucose.
Fibrates	Gemfibrozil, fenofibrate.	↓	↑	↓↓	Hypertriglyceridemia.	Gallstones, hepatitis, myositis (especially when used with statins).
Bile acid–binding resins	Cholestyramine.	↓↓	↑	↑	Used to treat elevated LDL only. The only lipid-lowering medication that is **safe in pregnancy.**	GI upset (bloating/gas, constipation); impaired absorption of fat-soluble vitamins and some medications; worsening of high TG.
Ezetimibe	Inhibitor of intestinal cholesterol transporter.	↓	↑	↓	Used to treat elevated LDL. Often **used with a statin** when LDL goal is not reached with a statin alone.	Elevated transaminases when used in combination with statins.

- A two-hour blood glucose ≥ **200 mg/dL during an oral glucose tolerance test.**
- "Impaired fasting glucose" is defined as a fasting blood glucose of 110–126 mg/dL.
- Hemoglobin A_{1c} (HbA_{1c}) is **not** included in the ADA's diagnostic criteria because of standardization difficulties.

CANCER SCREENING

Refer to Table 2.3 for an overview of USPSTF cancer screening guidelines.

Breast Cancer

Risk factors for breast cancer include the following:

- A family history, particularly of premenopausal breast cancer, in one or more first-degree relatives.

TABLE 2.2. LDL Goals and Treatment Thresholds[a]

Risk Category	Definition	LDL Goal	Initiate TLC[b]	Consider Drug Therapy
High risk	CAD or CAD risk equivalents (10-year risk > 20%)	< 100 mg/dL (optional goal < 70 mg/dL)	≥ 100 mg/dL	≥ 100 mg/dL (< 100 mg/dL: consider drug options)
Moderately high risk	Two or more risk factors (10-year risk 10–20%)	< 130 mg/dL	≥ 130 mg/dL	≥ 130 mg/dL (100–130 mg/dL: consider drug options)
Moderate risk	Two or more risk factors (10-year risk < 10%)	< 130 mg/dL	≥ 130 mg/dL	≥ 160 mg/dL
Lower risk	0–1 risk factor	< 160 mg/dL	≥ 160 mg/dL	≥ 190 mg/dL (160–189 mg/dL: LDL-lowering drug optional)

[a] Derived from recommendations from the ATP III, 2004.

[b] Therapeutic lifestyle changes (TLC) include a low-fat, low-cholesterol, high-fiber diet; weight control; and exercise.

- ⊕ mutations of BRCA1 or BRCA2.
- Age > 40.
- Current or prior use of HRT (> 5 years).
- Age at menarche < 12; age at first birth > 30; age at menopause > 55.
- Heavy alcohol use.
- Obesity.
- A history of proliferative fibrocystic changes or atypical hyperplasia on breast biopsy.
- OCP use is probably not a risk factor in average-risk women but may be in those with a ⊕ family history.

Screening

Screening recommendations (based on USPSTF guidelines) are as follows:

- **Breast self-examination (BSE):** Not standardized, and **not shown to have benefit.**
- **Clinical breast examination (CBE):** Not standardized, and has a sensitivity of approximately 50%. Factors associated with a more sensitive exam include longer duration (> 3 minutes per breast) and a systematic search pattern (vertical strips). The USPSTF finds insufficient evidence to recommend for or against CBE as part of routine screening.
- **Mammography:** Screening should start at age 40 and should continue until age or comorbidities limit life expectancy.
  - Sensitivity is approximately 90% and is higher in older than in younger women.
  - The USPSTF recommends screening women of all ages every 1–2 years.
  - Some experts recommend no screening for women < 50 years of age because the benefits are likely small and the risks (false ⊕s) significant.

TABLE 2.3. USPSTF Cancer Screening Guidelines

	Breast	Colon	Cervix	Prostate	Lung
Target population	All women.	All women and men.	All women who have ever had sex and who have a cervix.	All men.	Smokers, other high-risk persons (e.g., COPD, asbestos exposure, IPF).
Strength of recommendation[a]	B	A	A	I	I
Age to start	40	50	Within three years of onset of sexual activity or age 21, whichever comes first.	The men most likely to benefit are those over age 50.	No recommendations.
Age to stop	No specific age. Women > 70 years of age may still benefit if they do not have significant comorbid disease.	No specific age. Consider stopping when comorbid conditions limit life expectancy (< 5 years).	Age 65 if a woman has had regular screening with normal results and is not otherwise at high risk.	Men > 70 years of age and those with a life expectancy of < 10 years are unlikely to benefit.	No recommendations.
Screening modality	Mammography with or without CBE.	Fecal occult blood testing (FOBT) or flexible sigmoidoscopy (+/– FOBT) or colonoscopy or double-contrast barium enema (DCBE). Each has different risks and advantages; there is no clear best test.	Pap smear. There is insufficient evidence to recommend for or against newer modalities, including HPV testing.	PSA and/or DRE.	Low-dose CT, CXR, and sputum cytology have all been proposed. Ongoing randomized trials will presumably help clarify the risks and benefits of each.
Frequency of screening	Every 1–2 years.	**FOBT:** Annual. **Flexible sigmoidoscopy, DCBE:** Every 5 years. **Colonoscopy:** Every 10 years.	At least every three years.	If screening has benefit, every 1–2 years.	No recommendations.

[a] **Strength of recommendations: A**—The USPSTF strongly recommends that clinicians provide the service to eligible patients. The USPSTF found good evidence that the service improves important health outcomes and concludes that benefits substantially outweigh harms. **B**—The USPSTF recommends that clinicians provide the service to eligible patients. The USPSTF found at least fair evidence that the service improves important health outcomes and concludes that benefits outweigh harms. **C**—The USPSTF makes no recommendation for or against routine provision of the service. The USPSTF found at least fair evidence that the service can improve health outcomes but concludes that the balance of benefits and harms is too close to justify a general recommendation. **D**—The USPSTF recommends against routinely providing the service to asymptomatic patients. The USPSTF found at least fair evidence that the service is ineffective or that harms outweigh benefits. **I**—The USPSTF concludes that the evidence is insufficient to recommend for or against routinely providing the service. Evidence that the service is effective is lacking, of poor quality, or conflicting, and the balance of benefits and harms cannot be determined.

- Others recommend annual screening because breast cancer in younger women tends to be more aggressive.
- **Genetic counseling** and consideration of BRCA1/BRCA2 mutation testing are recommended for those with the following risk factors:
  - A family history of breast cancer in two or more first-degree relatives (at least one premenopausal) or three or more first- or second-degree relatives.
  - Breast and ovarian cancer in the same patient or in any first- and second-degree relatives in the patient's family.
  - A family history of male breast cancer or women with bilateral breast cancer.
  - Ashkenazi Jewish heritage plus any first-degree relative (or two second-degree relatives) with breast or ovarian cancer.

Testing for BRCA1 and BRCA2 mutations should not be performed without prior genetic counseling. It should be considered only for women with family histories highly suggestive of a genetic susceptibility to breast and/or ovarian cancer.

Prevention

- Women with mutations of BRCA1 or BRCA2 should undergo intensive surveillance and may consider prophylactic mastectomy and/or oophorectomy.
- Tamoxifen therapy may be considered for 1° prevention in other women at high risk for breast cancer. Five years of tamoxifen therapy in high-risk women ↓ the risk of breast cancer by approximately 50%.
- Raloxifene is probably also effective for the 1° prevention of breast cancer, but evidence to support its use is weaker than that for tamoxifen.

Cervical Cancer

Cervical cancer screening with Pap smears was introduced in the 1960s and has led to a significant decline in the incidence of cervical cancer in the United States. Nonetheless, cervical cancer remains the second most common cancer among women worldwide and the sixth most common cancer in the United States. It is caused by the human papillomavirus, a common STD (HPV-16 and -18 are considered high-risk types). **Risk factors** include the following:

- Multiple sexual partners
- Early onset of intercourse
- Other STDs
- Smoking
- Low socioeconomic status
- HIV/immunosuppression

Screening

USPSTF guidelines for Pap screening are as follows:

- Sexually active women should be screened at least every three years starting at age 21 or within three years of the onset of sexual activity, whichever comes first. Those with known risk factors or a history of abnormal Pap smears should be screened annually.
- Screening may be stopped at approximately age 65 in women who have had adequate prior screening with normal results, and who are otherwise at low risk. **Older women who have not had a recent Pap test merit screening.**

- No further screening is indicated for those who have undergone a total hysterectomy for benign reasons.
- Evidence is insufficient to recommend for or against new technologies such as liquid-based Pap smears and HPV testing as part of routine screening.

Abnormalities on Pap smear are followed up with diagnostic colposcopy and biopsy.

PREVENTION

- Safer sexual practices (barrier contraceptives, fewer sexual partners) may help prevent cervical cancer.
- A vaccine against HPV strains 6, 11, 16, and 18 has been developed and is recommended for all women and girls aged 9–26 (see the discussion of immunizations below). Pap smear screening should proceed as per the guidelines outlined above in women who have been vaccinated.

Colorectal Cancer

- For most patients, screening for colorectal cancer should begin at age 50.
  - Screening should consist of annual FOBT, either alone or in combination with flexible sigmoidoscopy every 3–5 years **or** colonoscopy every 10 years.
  - There is no clear "best" method of screening, as each alternative has different risks, benefits, and costs, and direct comparative trials with clinical outcomes are lacking.
- Air-contrast barium enema is an alternative screening method, but little direct evidence exists that it ↓ mortality. There is insufficient evidence to recommend newer screening technologies such as CT colography ("virtual colonoscopy").
- Individuals at ↑ **risk** for colorectal cancer include those with a personal or strong family history of colorectal cancer or adenomatous polyps as well as those with a family history of hereditary colon cancer syndromes (familial adenomatous polyposis, hereditary nonpolyposis colon cancer).
  - High-risk patients should begin colonoscopy screening at age 40, or 10 years before the youngest affected relative was diagnosed.
  - Those with affected first-degree relatives should have colonoscopy every five years.

Because there is no direct evidence that screening for prostate cancer improves mortality, the USPSTF and other expert groups recommend routinely discussing the pros and cons of screening with at-risk men rather than routinely ordering a PSA or performing a DRE.

Prostate Cancer

- Prostate cancer screening with serum PSA testing and DRE are controversial because of their **lack of proven effectiveness in improving health outcomes.** The USPSTF gives prostate cancer screening an "I" rating, meaning that there is insufficient evidence to recommend for or against PSA and/or DRE.
- Most groups recommend that physicians **discuss both the potential advantages of PSA screening (early detection of possibly harmful cancers) and its disadvantages** (false-⊕ and false-⊖ results, overdiagnosis of highly indolent cancers, more biopsies, anxiety, morbidity associated with prostate cancer treatment).
- Consider screening in men ≥ 50 years of age if the patient is expected to live at least 10 years. Begin at a younger age (40–45 years of age) if patients

are at ↑ risk (e.g., African-American men or those with a first-degree relative with prostate cancer).

Lung Cancer

- Lung cancer is the leading cause of cancer death among men and women in the United States.
- Randomized trials evaluating CXR with or without sputum cytology have found ↑ detection of early-stage lung cancers but no improvement in either disease-specific mortality or overall mortality with screening.
- Low-dose helical CT (LDCT) is currently under investigation as a screening modality. Thus far, it would appear that LDCT is more sensitive than CXR but may be associated with an ↑ incidence of false ⊕s. Its mortality benefit has not yet been established.
- Several randomized clinical trials (RCTs) are currently being conducted to study the impact of screening LDCT on mortality, and various new technologies (e.g., molecular testing of sputum) are under investigation.
- At present, the USPSTF concludes that evidence is insufficient to recommend for or against screening for lung cancer in any group, including asymptomatic older smokers.

IMMUNIZATIONS

Table 2.4 describes the indications for and uses of some common vaccines. Several new vaccines became available in 2005–2006 (Tdap, HPV, varicella zoster).

*Live attenuated vaccines are contraindicated in pregnancy. Do **not** give MMR, varicella, or oral polio vaccines to women who are pregnant or who may become pregnant within four weeks of vaccination.*

OBESITY AND METABOLIC SYNDROME

Obesity

Currently, 65% of Americans are overweight and 30.4% are obese. Obesity ↑ morbidity and mortality, particularly from hypertension, type 2 DM, hyperlipidemia, CAD, degenerative joint disease, sleep apnea, steatohepatitis, breast/colorectal/prostate/uterine cancer, and psychosocial disorders.

Differential

- Hypothyroidism, Cushing's syndrome, medications (steroids, insulin, atypical antipsychotics).
- Fewer than 1% of obese patients have an identifiable, nonpsychiatric cause of obesity.

Diagnosis

The **body mass index (BMI)** reflects excess adipose tissue and is calculated by dividing measured body weight (kg) by height (meters squared):

$$\text{BMI} = \text{weight (kg)} / \text{height (m)}^2$$

The NIH defines a normal BMI as 18.5–24.9. Overweight is defined as a BMI of 25.0–29.9. Class I obesity is defined as 30.0–34.9, class II obesity as 35.0–39.9, and class III (extreme) obesity as ≥ 40.

TABLE 2.4. Adult Immunization Recommendations[a]

Vaccine	Indications	Schedule	Special Considerations
Tetanus, diphtheria, acellular pertussis (Td/Tdap)	All adults.	Td booster every 10 years. A 1° series of three doses for adults with an uncertain history of 1° vaccination. **A single dose of Tdap should be given once, in place of Td, to adults < 65 years of age.**	Give Tdap as soon as two years after the last Td for adults in close contact with infants < 12 months of age (e.g., immediately postpartum) as well as to all health care workers.
Human papillomavirus (HPV)	Women and girls 9–26 years of age regardless of any prior history of HPV infection, genital warts, or cervical dysplasia.	Three doses at 0, 2, and 6 months.	Ideally, should be administered before the onset of sexual activity. Not recommended during pregnancy.
Varicella-zoster	Adults over age 60, regardless of whether they have had a prior episode of VZV.	One dose.	Contraindicated in severely immunocompromised patients (e.g., those with advanced HIV, with a hematologic malignancy, or on high-dose chronic steroids).
Measles, mumps, rubella (MMR)	Adults born after 1957 without documentation of prior vaccination. Particular targets for vaccination include college students, health care workers, international travelers, and women of childbearing age.	One or two doses. A second dose is recommended for those at risk for measles or mumps (e.g., students, health care workers, travelers).	Contraindicated in pregnancy and in immunodeficiency states (e.g., HIV with severe immunosuppression, hematologic malignancy, long-term corticosteroid use [prednisone > 20 mg/day]).
Varicella	Adults without a clinical history of varicella, ⊕ titers, or a history of vaccination. Target those with close contact with immunocompromised patients or those who are at high risk of exposure/ transmission (health care/ child care workers, institutional staff and residents, college students, women of childbearing age).	Two doses 1–2 months apart.	Contraindicated during pregnancy and in the setting of immunosuppression (including all HIV-infected patients).

TABLE 2.4. Adult Immunization Recommendations[a] *(continued)*

Vaccine	Indications	Schedule	Special Considerations
Influenza	All adults. During shortages, priority should be given to those with cardiopulmonary disease, residents of chronic care facilities, those with chronic diseases (DM, renal insufficiency, HIV, other immunosuppression), health care workers, and pregnant women.	One dose annually.	Healthy, nonpregnant persons 5–49 years of age who are not in contact with immunocompromised patients may receive either **intranasal vaccine** or inactivated vaccine. All others should receive inactivated vaccine only.
Pneumococcal (polysaccharide)	All adults ≥ 65 years of age. Adults < 65 years of age with chronic pulmonary disorders (excluding asthma), cardiovascular disease, DM, chronic liver or renal disease, asplenia, or immunosuppression as well as those who are nursing home residents.	One dose for those ≥ 65 years of age at initial vaccination. A second dose at five years is recommended for patients with renal failure, asplenia, or immunosuppression. Give a second dose at 65 years of age (or five years after the first dose) if the first dose was given at < 65 years of age.	The vaccine should be given at least two weeks before elective splenectomy.
Hepatitis A	Those with chronic liver disease, recipients of clotting factor concentrates, men who have sex with men (MSM), illicit drug users, health care workers in contact with infected individuals, travelers to endemic areas.	Two doses 6–12 months apart.	
Hepatitis B	Renal failure/dialysis, HIV, chronic liver disease, those at risk for STDs (MSM, those not in a long-term, mutually monogamous relationship), health care workers, IV drug users, recipients of factor concentrates, household contacts of HBV-infected individuals.	Three doses (0, 1–2 months, 4–6 months).	Should be offered to any adult seeking protection against HBV.
Meningococcal	Those with asplenia (anatomic or functional) or terminal complement deficiency; college students living in dorms, travelers to endemic areas.	One dose. Consider a second dose at five years for those given polysaccharide vaccine.	

[a] Derived from guidelines established by the Centers for Disease Control and Prevention, 2006.

TREATMENT

- Weight loss improves type 2 DM, hypertension, cardiovascular risk, and hyperlipidemia (HDL, TG).
- A multidisciplinary approach combining a reduction in caloric intake, ↑ aerobic exercise, and social support optimizes the maintenance of weight loss. Diets include very low calorie diets (< 800 kcal/day) and low-carbohydrate diets (e.g., Atkins). Dietary interventions should be coordinated with a nutritionist to circumvent the pitfalls of problematic "fad" diets. Low-carbohydrate and low-fat diets are no more effective than calorie-restricted diets.
- The long-term effectiveness of weight loss diets is generally poor.
- Although pharmacotherapy leads to short-term weight loss, surgery is the only proven method for achieving long-term weight loss.
- In recent years, several obesity medications (**fenfluramine, dexfenfluramine**) have been removed from the market following reports of **valvular heart disease** and **pulmonary hypertension.**
- Indications for pharmacotherapy are as follows (see also Table 2.5):
  - Consider in patients with a BMI > 30 or in those with a BMI > 27 and obesity-related medical complications.
  - A course of medication for 6–12 months in conjunction with dietary modification leads to ↑ weight loss when compared to a placebo, but the long-term efficacy of such treatment has not been established.
- The long-term efficacy of **surgery** for weight reduction and improvement of comorbidities (DM, hypertension, hyperlipidemia, sleep apnea) has been established. Surgical procedures include gastric banding, gastric bypass (Roux-en-Y), gastroplasty, and duodenal switch procedures. Indications for bariatric surgery are as follows:
  - BMI > 40 (severe obesity).
  - BMI > 35 and obesity-related medical complications.
- Perioperative mortality ranges from 0.1% to 1.1% depending on the surgical procedure.
- Long-term complications of surgery include dumping syndrome, anastomotic stenosis, vitamin B_{12}/iron/vitamin D deficiencies, cholecystitis, and gastritis.

Consider surgery for patients with a BMI > 40 or a BMI > 35 plus obesity-related medical complications.

Metabolic Syndrome

Present in approximately 60% of obese individuals; confers a threefold risk of CAD. Insulin resistance ↑ the risk of type 2 DM in these patients.

TABLE 2.5. Commonly Used FDA-Approved Obesity Medications

DRUG	MECHANISM OF ACTION	SIDE EFFECTS
Sibutramine	Inhibits the uptake of serotonin and norepinephrine in the CNS (catecholaminergic).	Hypertension, ↑ heart rate, dry mouth, anorexia, constipation, insomnia, dizziness.
Orlistat	Inhibits intestinal lipase; ↓ fat absorption.	Fatty stools, gas, cramping.

Diagnosis

The diagnosis of metabolic syndrome requires three or more of the following:

- Elevated abdominal circumference (≥ 102 cm [40 inches] in men, ≥ 88 cm [35 inches] in women).
- Elevated BP (≥ 130/80 mmHg).
- Elevated TG (≥ 150 mg/dL or on drug treatment to lower TG).
- Elevated fasting blood glucose (≥ 100 mg/dL).
- Low HDL cholesterol (< 40 mg/dL in men, < 50 mg/dL in women).

Intensive lifestyle change, including weight loss, exercise, and a healthy diet, is key to managing metabolic syndrome and preventing clinical atherosclerosis and type 2 DM.

Treatment

- The goals for treatment of metabolic syndrome are to lower the risk of clinical atherosclerotic disease and to prevent the onset of type 2 DM.
- Intensive lifestyle change is effective at reducing the rates and complications of metabolic syndrome.
- Cardiovascular risk factors (lipids, blood glucose, BP) should be closely monitored and well controlled in these patients.

NUTRITIONAL AND HERBAL SUPPLEMENTS

- Vitamin and other nutritional deficiencies are discussed at length in the Hematology chapter.
- Table 2.6 lists the potential benefits of some common nutritional supplements. Table 2.7 outlines some common herbal supplements along with their clinical uses and side effects.
- In general, the level of evidence to support the efficacy of any of the commonly used herbal treatments is poor to fair, and none are currently recommended over FDA-approved medications.
- Because herbs and supplements are not regulated in the same way as prescription drugs, their purity and potency are highly variable.

ATHLETIC SCREENING FOR ADOLESCENTS

Although rare, sudden death may occur in competitive athletes as a result of **hypertrophic cardiomyopathy** (36%), **coronary anomalies** (19%), LVH, a ruptured aorta (Marfan's syndrome), and other rare congenital or acquired cardiac diseases. It is therefore recommended that students be evaluated prior to participation in high school and college athletics as well as every two years during competition. Evaluation should include the following:

- A careful history and physical exam focusing on cardiovascular risk factors, symptoms, and findings.
- An ECG and an echocardiogram in the presence of the following:
  - A family history of premature sudden death or cardiovascular disease.
  - Symptoms of chest pain, syncope, or near-syncope.
  - Elevated BP or abnormalities on cardiac examination.
  - A Marfan-like appearance (tall stature with long arms/legs/fingers).

Hypertrophic cardiomyopathy is the leading cause of sudden cardiac death in young athletes.

Commotio cordis, or sudden death due to direct blunt trauma to the chest wall and myocardium, is more common in children and is caused by precipitation of a PVC initiating a tachyarrhythmia.

TABLE 2.6. Effects of Selected Dietary Supplements

SUPPLEMENT	CLINICAL USES	EFFICACY
Glucosamine and chondroitin	Osteoarthritis (OA).	Several meta-analyses have shown benefit for symptoms of knee OA, but a recent RCT showed no benefit. The role of these supplements in the prevention of OA is unclear.
Calcium and vitamin D	Prevention and treatment of osteoporosis; prevention of colorectal cancer.	A recent RCT calls into question the efficacy of calcium supplementation for preventing osteoporosis. Vitamin D (800 IU/day) ↓ fracture risk, and adequate dietary or supplemental calcium is recommended. The benefits for colorectal cancer are unclear.
Vitamin E	Antioxidant; prevention of atherosclerosis, Alzheimer's disease, and cancer.	Ineffective for vascular disease prevention.
Omega-3 fatty acids	Cholesterol lowering; prevention of atherosclerotic disease.	There is no clear benefit derived from dietary or supplemental omega-3 fatty acids in the prevention of cardiovascular disease, cancer, or overall mortality.
Folic acid	Prevention of neural tube defects; prevention of atherosclerotic disease (via lowering homocysteine levels).	Doses of 0.4 mg/day or higher are clearly effective in preventing neural tube defects and should be recommended to all women who may become pregnant. Dosages of 4 mg/day are recommended for women taking antiepileptic medications during pregnancy. Several trials have shown no benefit in reducing the rate of clinical atherosclerotic disease despite lowered homocysteine levels.
Fiber supplements	Prevention of diverticulosis and colon cancer; cholesterol and blood sugar lowering.	Epidemiologic studies suggest a benefit from high-fiber diets for the conditions listed. However, randomized trials to prove this are lacking.
Soy protein	Relief of menopausal symptoms.	Possibly effective at high doses (50 g/day), especially from dietary sources rather than concentrated supplements.

OCCUPATIONAL MEDICINE

Occupational health problems include injuries or illness directly caused by work (e.g., a fall at work leading to wrist fracture) as well as those that are influenced by work (e.g., asthma in someone working with aerosolized chemicals) or that influence work (e.g., sleep apnea in an airline pilot). Some of the more common or serious occupational illnesses include the following:

- Cancers (e.g., mesothelioma and lung cancer in asbestos workers).
- Respiratory disorders (e.g., asthma, hypersensitivity pneumonitis, interstitial lung disease).

TABLE 2.7. Common Herbal Supplements

Herb	Condition	Efficacy	Side Effects
Ginkgo biloba	Dementia, claudication.	Has possible benefit in memory among demented patients compared to a placebo. A meta-analysis shows a small benefit over placebo in claudication symptoms. Its benefit for other conditions is unclear.	May have an anticoagulant effect. Stop this herb one week before surgery.
Echinacea	Prevention and treatment of the common cold.	Possibly effective for the treatment of URI, but there is no clear evidence of benefit in preventing URIs.	Rash, pruritus, nausea.
Saw palmetto	BPH.	Possibly improved urinary symptoms and flow.	Mild GI upset, headaches (rare).
St. John's wort	Depression.	Improved symptoms in mild to moderate depression. Ineffective for more severe depression.	**Induces cytochrome P-450,** thus decreasing some drug levels (e.g., warfarin, digoxin, OCPs, antiretrovirals). Cannot be combined with prescription antidepressants because of the risk of serotonin syndrome.
Kava	Anxiety, stress, insomnia.	Several meta-analyses show some benefit for relieving anxiety symptoms.	Sedation, especially in combination with alcohol. There have been several cases of severe hepatotoxicity.
Black cohosh	Menopausal symptoms.	Randomized trials have shown little if any benefit.	May have estrogenic effects.
Red clover	Menopausal symptoms.	An RCT found no evidence that red clover is effective in treating menopausal symptoms.	As with other phytoestrogens, red clover should be avoided in patients at ↑ risk for breast cancer.

- Contact dermatitis.
- Musculoskeletal injuries from acute trauma.
- Overuse injuries such as carpal tunnel syndrome.
- Neurologic disorders such as organophosphate or heavy metal poisoning.
- Health care–related illnesses such as hepatitis or HIV acquired via needlestick.

Patients should routinely be asked about the nature of their work and about any association between symptoms and work.

Health Care Workers and Disease Exposure/Prevention

- TB is commonly transmitted in a health care setting. All health care workers should thus have annual PPD testing and screening for symptoms of active TB.

- Vaccines routinely recommended for health care workers include hepatitis B, MMR, varicella (if not immune from natural infection), influenza, and Tdap.
- Needlestick injuries and other infectious body fluid exposures are of concern for all health care workers who are in direct contact with patients.
- Blood-borne viruses—particularly hepatitis B, hepatitis C, and HIV—are the most common infections acquired by needlestick injuries.
- In the event of a needlestick or other percutaneous exposure, urgent assessment is warranted and includes the following measures:
  - Clean the wound thoroughly.
  - Test the exposed worker for hepatitis B (infection and immunity), hepatitis C, and HIV.
  - Obtain a history that includes exposure type, the infection status of the source patient (by history and/or laboratory testing), and the vaccination history of the exposed worker.
  - Counsel the worker about the risk of infection and about the risks and benefits of postexposure prophylaxis with antiretrovirals to prevent HIV and/or hepatitis B vaccination/HBIG to prevent hepatitis B.
  - Arrange follow-up visits for monitoring the side effects of any prophylactic medications and for retesting several months later to rule out infection.

Remember the "rule of 3's" for occupational needlestick exposure—the likelihood of needlestick transmission for hepatitis B is 30%, for hepatitis C 3%, and for HIV 0.3%.

OPHTHALMOLOGY

Red Eye

Table 2.8 outlines common causes of red eye, including the following:

- **Conjunctivitis:** The three main etiologies are bacterial, viral, and allergic (see Figures 2.1 through 2.3).
- **Uveitis:** Often associated with systemic disease. The presence of eye pain or ↓ visual acuity should raise suspicion for uveitis in patients presenting with red eye. "Ciliary flush" on exam (see Figure 2.4) distinguishes this condition from conjunctivitis. See the discussion below for further details.
- **Acute angle-closure glaucoma:** Acute onset of pain and vision loss, often associated with headache, nausea, and vomiting. On exam, the pupil is midsized and does not react to light, and the cornea is "steamy" (see Figure 2.5).
- **Keratitis:** The most commonly tested etiology of red eye on the Boards is **HSV keratitis,** which is usually unilateral and suggested by ↓ vision. Branching (dendritic) ulcers on fluorescein stain test are diagnostic (see Figure 2.6).

All patients with a red eye and any of the following should be referred to an ophthalmologist emergently:

- *Moderate to severe eye pain*
- *↓ visual acuity*
- *Photophobia*
- *Pupillary abnormalities*
- *Ciliary flush (circumcorneal erythema)*

Additional etiologies of red eye include the following:

- **Foreign body:** Characterized by a sharp superficial pain. Perform a fluorescein test to rule out corneal abrasion.
- **Gonorrheal conjunctivitis:** Presents with abrupt onset of redness and purulent discharge in sexually active adults.
- **Chlamydial conjunctivitis:** Associated with chronic red eye in sexually active adults.
- **Subconjunctival hemorrhage:** Spares the limbus (see Figure 2.7); common with trauma, prolonged coughing or vomiting, and anticoagulant use. Resolves spontaneously in 2–3 weeks.

TABLE 2.8. Common Causes of Red Eye

	Viral Conjunctivitis	Allergic Conjunctivitis	Bacterial Conjunctivitis	Uveitis	Keratitis	Acute Angle-Closure Glaucoma
Incidence	Extremely common, especially after URI (adenovirus).	Common.	Common.	Common.	Common.	Uncommon.
Conjunctival injection and discharge	Unilateral or bilateral redness; watery discharge.	Bilateral redness, itching, and tearing; ropy discharge.	Unilateral redness; purulent discharge.	Circumcorneal redness (ciliary flush); no discharge.	Circumcorneal erythema.	Circumcorneal redness (ciliary flush); no discharge.
Pain, photophobia, vision changes	None.	None.	None.	Moderate pain, photophobia, blurred vision.	Pain, tearing, photophobia and ↓ vision. Purulent discharge in bacterial keratitis.	Severe pain, nausea, vomiting, ↓ visual acuity. Systemic symptoms include nausea and headache.
Cornea	Clear.	Clear.	Clear.	Usually clear. Hypopyon or hyphema may be present.	Hazy. Dendritic ulcer in HSV keratitis; punctate corneal lesions in bacterial keratitis.	Steamy.
Pupil	Normal.	Normal.	Normal.	Constricted; possibly irregular; poor light response.	Normal or constricted.	Moderately dilated and fixed; no light response.
Intraocular pressure	Normal.	Normal.	Normal.	Normal.	Normal.	High.
Therapy	Symptomatic; cold compresses.	Cold compresses, antihistamine drops, topical ketorolac (NSAID), topical mast cell stabilizer.	Erythromycin ointment; polymyxin-trimethoprim drops.	An emergency; refer to an ophthalmologist.	Urgent (viral, HSV) or emergent (bacterial) ophthalmology referral.	An emergency; refer to an ophthalmologist for laser iridectomy. Pupillary constriction (topical pilocarpine), pressure reduction (topical β-blockers, acetazolamide).

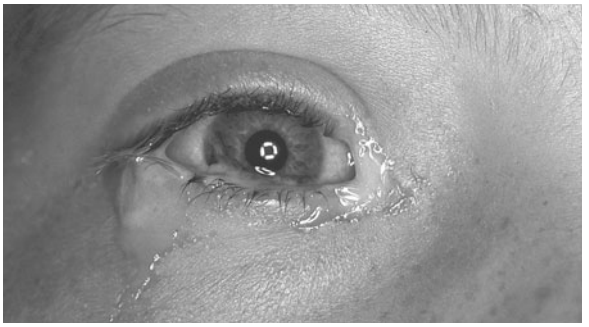


FIGURE 2.1. Bacterial conjunctivitis.

Note the conjunctival injection and purulent discharge. (Reproduced, with permission, from Frank Birinyi, MD, as printed in Knoop KJ et al. *Atlas of Emergency Medicine*, 2nd ed. New York: McGraw-Hill, 2002: 30.)

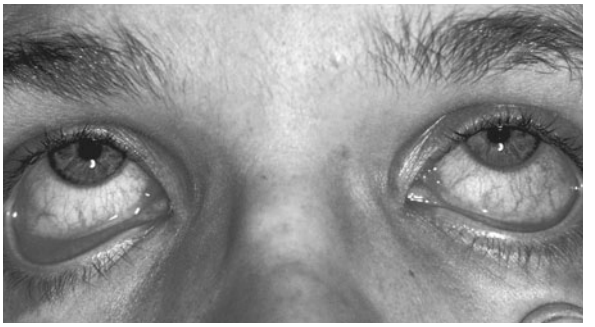


FIGURE 2.2. Viral conjunctivitis.

Note the conjunctival injection and watery discharge. (Reproduced, with permission, from Knoop KJ et al. *Atlas of Emergency Medicine*, 2nd ed. New York: McGraw-Hill, 2002: 31.)

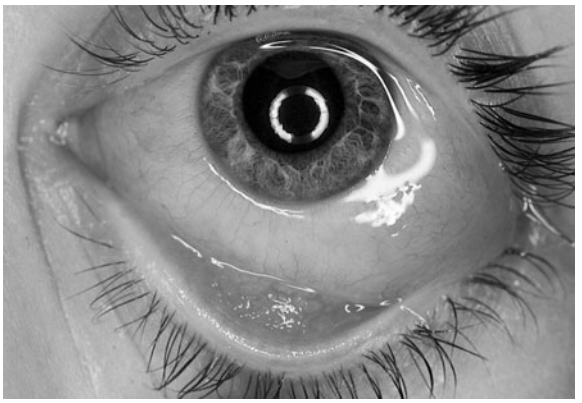


FIGURE 2.3. Allergic conjunctivitis.

Note the edematous, boggy conjunctiva. (Courtesy of Timothy D. McGuirk, DO.)

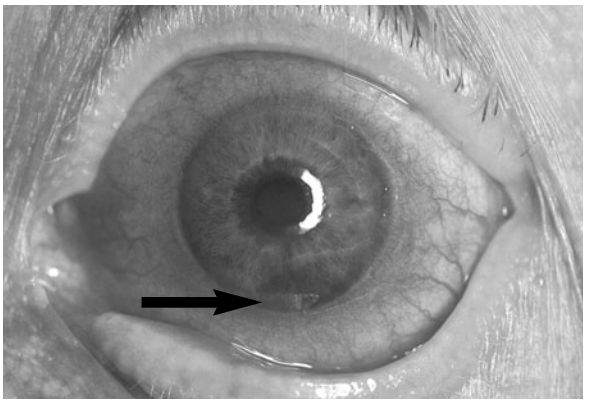


FIGURE 2.4. Anterior uveitis.

Note the conjunctival injection with ciliary flush (circumcorneal erythema) and hypopyon (pus pooling in front of the iris; see arrow). (Reproduced, with permission, from Knoop KJ et al. *Atlas of Emergency Medicine*, 2nd ed. New York: McGraw-Hill, 2002: 52.)

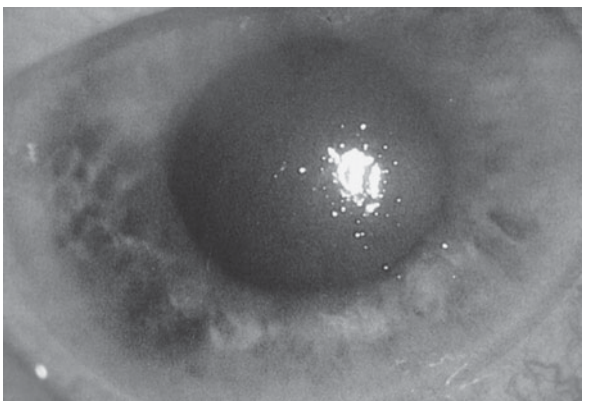


FIGURE 2.5. Acute angle-closure glaucoma.

Note the fixed, dilated pupil with cloudy cornea. (Reproduced, with permission, from Tintinalli JE, Kelen GD, Stapczynski JS. *Tintinalli's Emergency Medicine: A Comprehensive Study Guide*, 6th ed. New York: McGraw-Hill, 2004: 1460.)

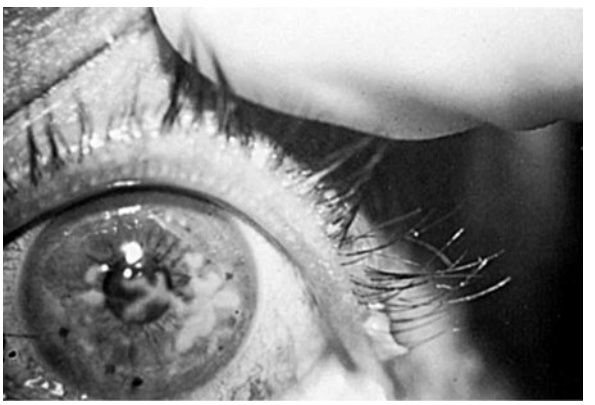


FIGURE 2.6. Herpes keratitis with dendritic ulcer.

(Reproduced, with permission, from Vaughan DG et al. *General Ophthalmology*, 15th ed. Stamford, CT: Appleton & Lange, 1999.)

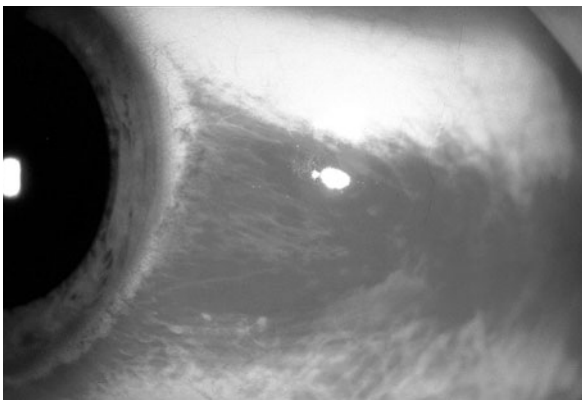


FIGURE 2.7. Subconjunctival hemorrhage.

Although the sudden appearance of diffuse bright red discoloration is alarming to patients, this condition is benign. (Reproduced with permission, from Riordan-Eva P, Whitcher JP. *Vaughan & Asbury's General Ophthalmology*, 17th ed. New York: McGraw-Hill, 2008.)

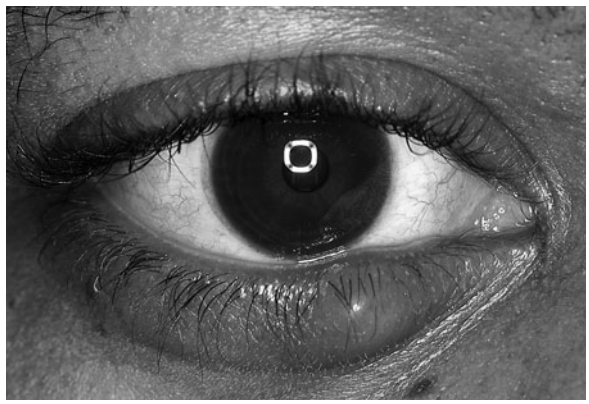


FIGURE 2.8. Hordeolum.

Focal swelling and erythema at the lid margin are seen. (Reproduced, with permission, from Frank Birinyi, MD, as printed in Knoop KJ et al. *Atlas of Emergency Medicine*, 2nd ed. New York: McGraw-Hill, 2002: 38.)

- **Blepharitis:** Chronic, bilateral inflammation of the lid margins. Presents with irritation, burning, and itching along with findings of red lids and scale in the lashes. May also cause conjunctival injection. Associated with rosacea and seborrheic dermatitis. Treat by removing scale with warm compresses and topical antibiotics.
- **Hordeolum (stye):** Infection of Moll's glands along the lash line. Presents with localized erythema, tenderness, and swelling (see Figure 2.8). Treat with warm compresses and topical antibiotics.
- **Chalazion:** Chronic, granulomatous inflammation of the meibomian gland. Presents with hard, nontender swelling on the upper or lower lid (see Figure 2.9). Treatment by an ophthalmologist consists of incision and curettage or corticosteroid injection.

Bacterial keratitis is an important complication of corneal abrasions in contact lens wearers. It is commonly caused by Pseudomonas *species and has an aggressive course. Contact lens wearers with corneal abrasions should receive prophylactic topical antibiotics and close follow-up.*

Loss of Vision

Categorized as either acute or chronic. Etiologies of **acute loss of vision** include the following:

- **Retinal artery occlusion:** Commonly due to an embolus; associated with giant cell arteritis. Characterized by sudden, **painless,** unilateral blindness and by a "**cherry-red spot**" in the macula (see Figure 2.10). Constitutes an emergency.
- **Retinal vein occlusion:** Commonly due to hypertension, hyperviscosity syndromes, hypercoagulable diseases, or Behçet's disease. Onset is sudden and painless with varying degrees of visual loss (see Figure 2.11). There is no effective acute treatment, so referral is urgent (but not emergent).
- **Vitreous hemorrhage:** Due to vitreous detachment, proliferative diabetic retinopathy, or retinal tears (see Figure 2.12). Visual acuity may be normal or reduced. Warrants urgent referral.
- **Retinal detachment:** May be spontaneous or due to trauma (see Figure 2.13). Presents with unilateral blurred vision that progressively worsens **(floaters or lights in peripheral vision).** Considered an emergency.
- **Amaurosis fugax ("fleeting blindness"):** Due to retinal emboli from ipsilateral carotid disease. Patients complain that "a curtain came down over

Causes of red eye—

GO SUCK

Glaucoma
Orbital disease
Scleritis
Uveitis
Conjunctivitis (viral, bacterial, allergic)
Keratitis (HSV)

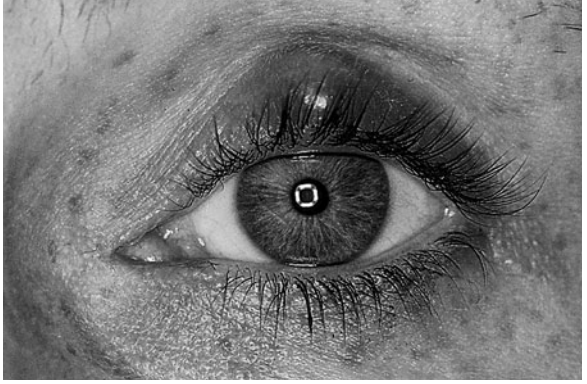


FIGURE 2.9. Chalazion.

Note the nodular focal swelling and erythema. (Reproduced, with permission, from Frank Birinyi, MD, as printed in Knoop KJ et al. *Atlas of Emergency Medicine*, 2nd ed. New York: McGraw-Hill, 2002: 39.)

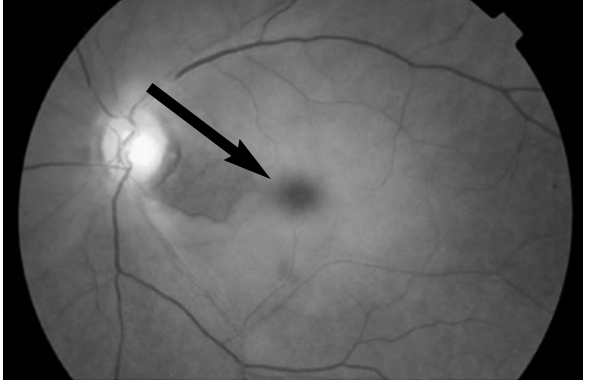


FIGURE 2.10. Retinal artery occlusion.

Acute central retinal artery occlusion is seen with an opaque white retina and attenuated vessels. A characteristic "cherry-red spot" is seen in the macula (see arrow). (Reproduced, with permission, from Riordan-Eva P. *Ophthalmology*. In: McPhee SJ et al. *Current Medical Diagnosis & Treatment:* 2008 online edition. New York: McGraw-Hill, 2008 online at www.AccessMedicine.com.)

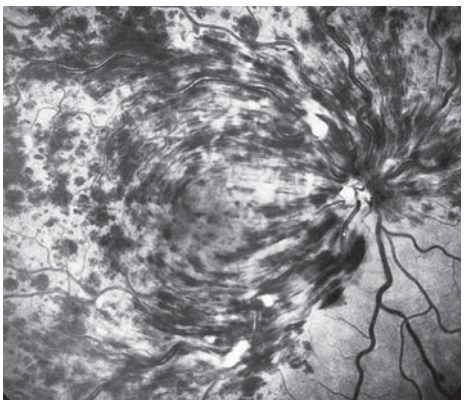


FIGURE 2.11. Retinal vein occlusion.

Central retinal vein occlusion with extensive superficial retinal hemorrhage obscuring macular and optic nerve detail. (Reproduced, with permission, from Riordan-Eva P, Whitcher JP. *Vaughan & Asbury's General Ophthalmology*, 16th ed. New York: McGraw-Hill, 2004: 207.)

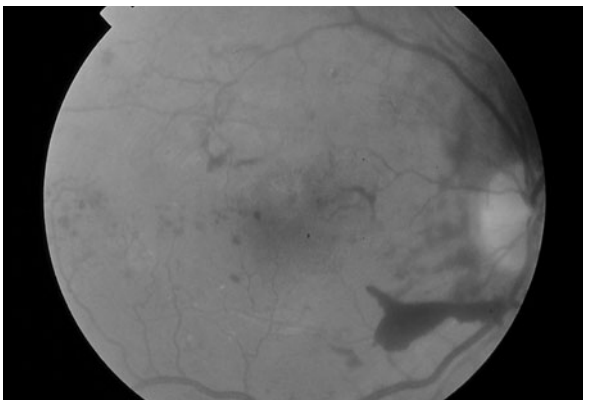


FIGURE 2.12. Vitreous hemorrhage.

The effect of gravity on the vitreous blood creates the appearance of a flat meniscus (keel-shaped blood) in a patient with vitreous hemorrhage associated with proliferative diabetic retinopathy. (Courtesy of Richard E. Wyszynski, MD.)

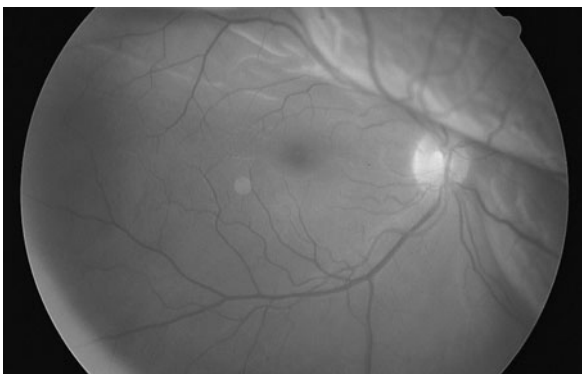


FIGURE 2.13. Retinal detachment.

Note the elevated sheet of retinal tissue with folds. In this patient, the fovea was spared, so acuity was normal but a superior detachment produced an inferior scotoma. (Reproduced, with permission, from Kasper DL et al. *Harrison's Principles of Internal Medicine*, 16th ed. New York: McGraw-Hill, 2004.)

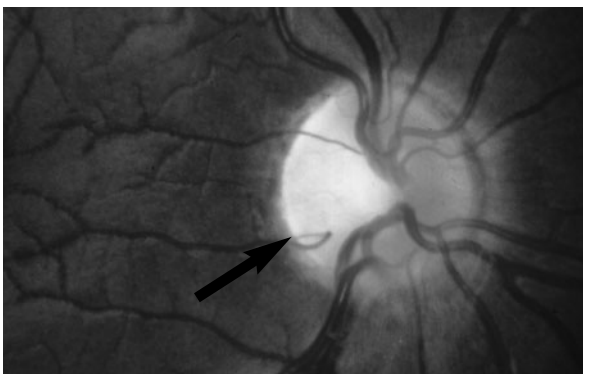


FIGURE 2.14. Optic neuritis.

Optic nerve pallor, either segmental (as in this case; see arrow) or generalized, is a nonspecific change that may be associated with a previous episode of optic neuritis or other insults to the optic nerve. (Courtesy of Richard E. Wyszynski, MD.)

my eye" for **only a few minutes.** Evaluate with carotid duplex ultrasonography or MRA and ESR +/– echocardiography. High-grade carotid stenoses may benefit from carotid endarterectomy; lower-grade stenoses benefit from antiplatelet drugs.

- **Optic neuritis:** Unilateral visual loss develops over several days, often accompanied by pain that improves within 2–3 weeks (see Figure 2.14). Associated with demyelinating diseases, especially MS.

The etiologies of **chronic loss of vision** include the following:

- **Age-related macular degeneration (AMD):** The most common cause of permanent visual loss in the elderly. Characterized by loss of **central** vision only. "Dry" AMD is characterized by drusen (yellow deposits in the macula; see Figure 2.15); "wet" AMD is marked by retinal neovascularization.
- **Open-angle glaucoma:** Loss of **peripheral** vision ("tunnel vision") over a period of years. Characterized by ↑ intraocular pressure and an ↑ cup-to-disk ratio (**"cupping"**). **Treatment includes a combination of topical β-blockers,** α_2-agonists, and prostaglandin analogs.
- **Cataracts:** Visible lens opacities. Blurred vision occurs over months or years. Treatment consists of lens replacement.
- **Nonproliferative diabetic retinopathy:** The most common cause of legal blindness in adult-onset diabetes. Characterized by dilation of veins, microaneurysms, hard exudates, and retinal hemorrhages (see Figure 2.16). Treat with intensive blood glucose control and laser photocoagulation.
- **Proliferative diabetic retinopathy:** Presents with neovascularization; vitreous hemorrhage is a common complication (see Figure 2.17). Treat with laser photocoagulation.

Cataract causes—

ABCD

Aging
Bang (trauma)
Congenital
Diabetes and other metabolic diseases (steroids)

Eye Findings in Systemic Diseases

Uveitis

Inflammation of the uveal tract, which is made up of the iris, ciliary body, and choroid (see Figure 2.4). May be seen in the following conditions:

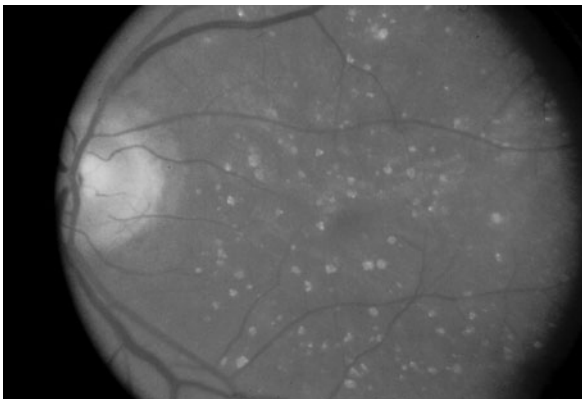


FIGURE 2.15. Age-related macular degeneration.

Note the macular drusen and retinal pigment epithelial atrophy (scalloped pigment loss) that are typical of age-related macular degeneration. (Courtesy of Richard E. Wyszynski, MD.)

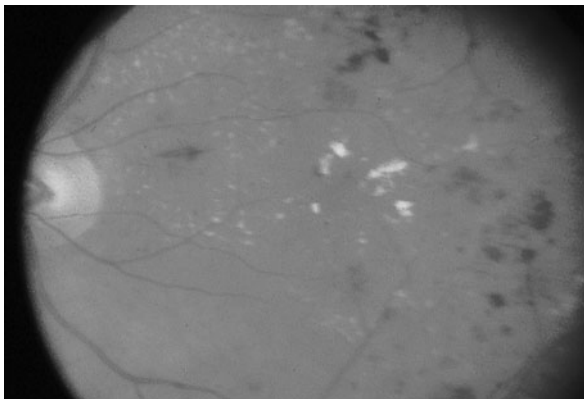


FIGURE 2.16. Nonproliferative diabetic retinopathy.

Hard exudates, dot hemorrhages, blot hemorrhages, flame hemorrhages, and microaneurysms are present. (Courtesy of Richard E. Wyszynski, MD.)

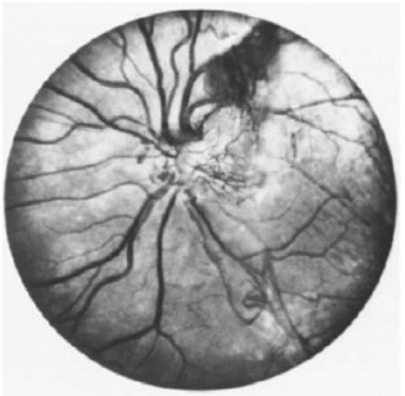


FIGURE 2.17. Proliferative diabetic retinopathy.

There is extensive neovascularization of the disk with an associated small intravitreal hemorrhage that obscures the upper temporal vessels. Along the inferior temporal arcade is another area of neovascularization. (Reproduced, with permission, from Fuster V et al. *Hurst's the Heart*, 11th ed. New York: McGraw-Hill, 2004: Fig. 12-46.)

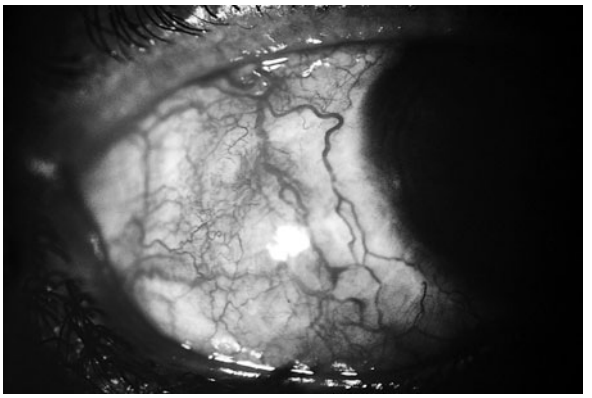


FIGURE 2.18. Scleritis.

A prominent generalized vascular injection is present. These vessels do not move when the overlying conjunctiva is moved with a cotton-tipped applicator. (Courtesy of Thomas F. Mauger, MD as printed in Knoop KJ et al. *Atlas of Emergency Medicine*, 2nd ed. New York: McGraw-Hill, 2002.)

- **HLA-B27-related conditions:** Reactive arthritis, ankylosing spondylitis, psoriasis, ulcerative colitis, Crohn's disease.
- Behçet's disease.
- **Granulomatous disease:** Wegener's granulomatosis, sarcoidosis.
- **Herpesvirus infections:** HSV, herpes zoster.
- **Syphilis:** Characterized by a "salt and pepper" fundus.
- **HIV-associated diseases:** Toxoplasmosis, CMV, HSV, herpes zoster, *Mycobacterium*, *Cryptococcus*, *Candida*.

Scleritis

- Localized or diffuse injection of the sclera (connective tissue just below conjunctival epithelium; see Figure 2.18). Seen in a number of autoimmune, granulomatous, and infectious diseases.
- **Sx/Exam:** Presents with eye pain and impaired vision.
- **Tx:** Urgent ophthalmology referral is indicated.

Keratoconjunctivitis Sicca

- A common condition, especially in older women. Hypofunctioning of the lacrimal glands ↓ the aqueous component of tears and thus leads to dry eyes. Often idiopathic, but may be associated with **Sjögren's syndrome** and certain drugs (e.g., antihistamines, topical β-blockers).
- **Sx/Exam:** Presents with dryness, redness, or a "scratchy" feeling in the eyes.
- **Tx:** Artificial tears or methylcellulose solutions. Lacrimal (punctal) occlusion is useful in refractory cases.

Bacterial Sinusitis

Eighty percent of sinusitis cases are due to viruses. Bacterial sinusitis results from impaired mucociliary clearance and obstruction of the osteomeatal complex. Viral and allergic rhinitis predispose to acute bacterial sinusitis. Causative organisms of acute sinusitis include *Streptococcus pneumoniae*, other streptococci, *Haemophilus influenzae*, and, less commonly, *S. aureus* and *Moraxella catarrhalis*. Chronic sinusitis may also be caused by *Pseudomonas aeruginosa* and anaerobes.

Symptoms/Exam

- Presents as unilateral or bilateral pain over the maxillary or frontal sinus or as a toothache. Acute sinusitis lasts > 1 week and up to 4 weeks. Chronic sinusitis lasts > 4 weeks.
- Exam reveals purulent nasal discharge and tenderness over the affected sinus.

Differential

- **Mucormycosis:**
  - A rare but dangerous fungal disease that spreads through the blood vessels and primarily affects **immunocompromised** patients, including those with DM, end-stage renal disease, bone marrow transplant, lymphoma, and AIDS.
  - Presents as sinusitis with more extreme facial pain accompanied by **necrotic eschar** of the nasal mucosa and cranial neuropathies in the late stages. Early diagnosis is key.
  - Treat emergently with amphotericin B and ENT surgical debridement.
- **Other:** If sinusitis is chronic and resistant to treatment, consider anatomical sinus obstruction, common variable immunodeficiency, a CF variant, or Wegener's granulomatosis.

Diagnosis

- Generally made through a history and clinical exam.
- Features suggesting bacterial rather than viral sinusitis include the following:
  - Symptom duration > 1 week.
  - Persistent fever.
  - Purulent nasal secretion.
  - Maxillary toothache or unilateral maxillary pain.
  - Poor response to decongestants.
  - Pain with bending forward.
  - Abnormal transillumination.
  - Symptoms that worsen after initial improvement.
- Imaging is not indicated for uncomplicated acute sinusitis. In cases of chronic sinusitis, refractory sinusitis, or suspected intracranial or orbital complications, a CT scan is more sensitive and cost-effective than x-ray imaging and may identify air-fluid levels or bony abnormalities.

Treatment

- Oral and/or nasal decongestants (e.g., oral pseudoephedrine, nasal oxymetazoline).

When used for more than a few days, nasal decongestants can cause rebound nasal congestion and discharge, a condition is known as rhinitis medicamentosa. *Patients with persistent rhinitis should be asked about nasal decongestant use, and these medications should never be prescribed for more than 2–3 days at a time.*

- **Acute sinusitis:** Amoxicillin or TMP-SMX × 10 days; amoxicillin-clavulanate in the presence of risk factors for anaerobes or resistant β-lactamase organisms (some strains of *H. influenzae* and *M. catarrhalis*). Risk factors include DM, immunocompromised states, and recent antibiotic use.
- **Chronic sinusitis: Amoxicillin-clavulanate for at least 3–4 weeks along with intranasal glucocorticoids.**

Acute Otitis Media

Common causative organisms include *S. pneumoniae*, *H. influenzae*, *M. catarrhalis*, *S. pyogenes*, and viruses.

Symptoms/Exam

Presents with ear pain, ear fullness, ↓ hearing, and an erythematous, bulging tympanic membrane (see Figure 2.19).

Differential

Distinguish on exam from serous otitis media, which is characterized by a normal or dull, nonerythematous tympanic membrane with nonpurulent fluid behind it.

Treatment

- Amoxicillin × 10–14 days.
- For penicillin-allergic patients, give TMP-SMX or a macrolide (erythromycin, azithromycin, clarithromycin).

Otitis Externa

Predisposing factors include water exposure or mechanical trauma (e.g., Q-tips). Often caused by gram-⊖ rods (e.g., *Pseudomonas*, *Proteus*) or by a fungus (e.g., *Aspergillus*).

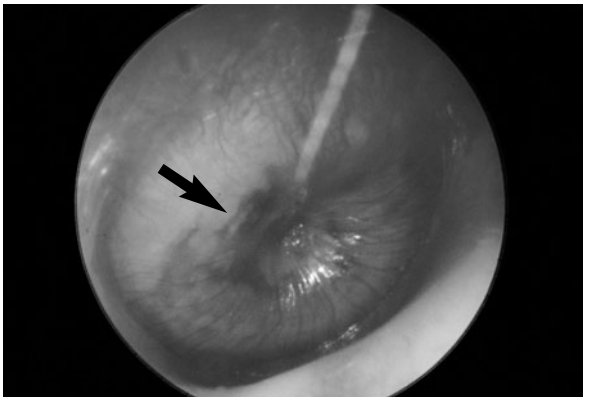


FIGURE 2.19. Acute otitis media.

Note the bulging, dull, erythematous tympanic membrane with pus behind it (see arrow). (Courtesy of Richard A. Chole, MD, PhD.)

Symptoms/Exam

Presents with ear pain that is often accompanied by pruritus and a purulent discharge. Erythema and edema of the ear canal with exudate may also be seen. Pain is elicited on manipulation of the ear.

Differential

Malignant external otitis is seen in **diabetics** and other immunocompromised patients. Persistent external otitis, usually caused by ***P. aeruginosa***, evolves into osteomyelitis. Presents with severe ear pain, foul-smelling discharge, and cranial nerve palsies. Diagnose by CT scan; treat with prolonged antipseudomonal antibiotics.

Treatment

- Avoid moisture and mechanical trauma.
- Give otic drops combining an antibiotic (e.g., neomycin sulfate, polymyxin B sulfate) or acetic acid and a corticosteroid.
- Clear the canal of cerumen and debris with a curette or hydrogen peroxide; use a cotton wick if blockage is severe.
- Add oral antibiotics to topical solutions if there is evidence of systemic spread (fever, regional lymphadenopathy).

Hearing Loss (HL)

Categorized as **conductive** (middle or external ear damage) or **sensorineural** (inner ear—cochlea or auditory nerve).

Exam

- Differentiate between conductive and sensorineural HL in the following manner:
  - **Weber test:** With the tuning fork on the forehead, sound normally stays in the middle of the forehead. **In conductive HL, the sound localizes to (i.e., is perceived as louder on) the affected side; in sensorineural HL, it localizes to the contralateral side.**
  - **Rinne test:** The tuning fork is first held on the mastoid. This sound (bone conduction) is then compared to that elicited with the tuning fork held near the ipsilateral ear (air conduction). Normally, air-conducted sound is louder than bone-conducted sound, but with **conductive HL, bone conduction is louder.**
- Conduct an audiology test.

Differential

Table 2.9 outlines the differential diagnosis of HL.

Treatment

- Prevention is the best treatment. Avoid excessive noise.
- Treat the underlying cause with antibiotics, removal of middle or outer ear blockages, repair of the tympanic membrane, or replacement of ossicles (in otosclerosis).
- For persistent sensorineural or conductive HL, consider hearing aids or, in cases of profound HL, cochlear implants.

TABLE 2.9. Differential Diagnosis of Hearing Loss

	SENSORINEURAL	CONDUCTIVE
Areas of damage	Inner ear: cochlea or nerve (CN VIII).	Middle or external ear.
Rinne test	Normal (air louder).	Abnormal (bone louder).
Weber test	Sound lateralizes to (is louder in) the good ear.	Sound lateralizes to the bad ear.
Causes	Age (presbycusis), excessive noise exposure, ototoxic drugs, Ménière's disease, acoustic neuroma.	Otitis media, otosclerosis, eustachian tube blockage, perforated tympanic membrane, cerumen.

Tinnitus

Perception of abnormal ear noises, usually due to HL. Although bothersome, it is benign in the absence of other symptoms.

DIFFERENTIAL

- **Ménière's disease** (episodic vertigo, sensorineural HL, tinnitus, and ear pressure).
- Vascular abnormalities such as carotid stenosis, AVMs, and vascular tumors cause **pulsatile tinnitus,** which can often be heard by the examiner.

TREATMENT

- Avoid exposure to excessive noise (e.g., rock concerts) and ototoxic drugs (aminoglycosides, salicylates, loop diuretics, cisplatin).
- Background noise (music, white noise) can be used to mask the tinnitus.

Pharyngitis

The main concern lies in identifying group A β-hemolytic streptococcal infection (GABHS). Adequate antibiotic treatment of GABHS usually prevents the complications of rheumatic fever and local abscess formation.

SYMPTOMS/EXAM

- The four classic features of GABHS (**Centor criteria**) are as follows:
  - Fever > 38°C.
  - Tender anterior cervical lymphadenopathy.
  - The absence of cough.
  - Pharyngotonsillar exudate.
- The presence of cough, hoarseness, and rhinorrhea makes GABHS less likely.

DIFFERENTIAL

- **Mononucleosis:** Occurs primarily in young adults, accounting for 5–10% of sore throats; characterized by the triad of lymphadenopathy, fever, and tonsillar exudates. Symptoms also include severe fatigue, headache, and malaise.

- EBV, the etiologic virus, can be transmitted through saliva (kissing) up to 18 months after 1° infection but is not very contagious.
- Diagnose with a ⊕ heterophile antibody (Monospot) test or a high anti-EBV titer.
- Complications include hepatitis, a morbilliform rash after **ampicillin** administration, and splenomegaly occurring within the first three weeks.
- To ↓ the risk of splenic rupture, noncontact sports must be avoided for 3–4 weeks and contact sports for 4–6 weeks after symptom onset.

- **Diphtheria:** Rare in the United States. Presents as sore throat, fever, and malaise with gray pseudomembranes on the tonsils. May be complicated by myocarditis and cranial neuropathies.
- **Viruses:** Viral infection is suggested by rhinorrhea and cough, other upper respiratory tract symptoms, and the absence of tonsillar exudate.
- **STIs:** Gonorrheal and chlamydial pharyngitis should be considered in sexually active patients.

Diagnosis

- **GABHS rapid antigen test:** The **test of choice;** has > 90% sensitivity. Routine cultures are not needed.
- **Clinical algorithm: Count the number of Centor criteria present.**
  - **4 of 4:** Treat empirically without a rapid antigen test.
  - **2–3 of 4:** Test and treat patients with ⊕ results.
  - **0–1 of 4:** No test and no antibiotic treatment.

Treatment

- Penicillin V potassium or cefuroxime × 10 days.
- Erythromycin for penicillin-allergic patients.
- **All cases (bacterial, viral):** Acetaminophen or NSAIDs and salt-water gargling.
- **Viral pharyngitis:** Patients may return to work when fever resolves and they are well enough to participate in normal activities.
- **Strep throat:** Patients may return to work after 24 hours of antibiotics.

Acute Bronchitis

A nonspecific term used to describe patients with normal underlying lungs who develop an acute cough with no clinical evidence of pneumonia. The most common causative organisms are respiratory **viruses** (coronavirus, rhinovirus, influenza, parainfluenza) and, to a lesser extent, atypical bacteria (*Mycoplasma pneumoniae, Chlamydia pneumoniae, Bordetella pertussis*).

Symptoms/Exam

- Presents with cough (productive or not) that may persist for 1–3 weeks, often with initial URI symptoms (rhinorrhea, sore throat).
- Exam findings range from clear to wheezes or rhonchi (from bronchospasm).

Differential

- It is important to rule out community-acquired pneumonia.
- Consider other URIs.
- *B. pertussis* infection (whooping cough) presents as a persistent "barking" or paroxysmal cough following typical URI symptoms. A high WBC count

with striking lymphocytosis is typical. Throat swab for PCR testing or culture are the diagnostic tests of choice, although sensitivity is low at the time of usual presentation.

Diagnosis

Diagnosis is made clinically. CXR is not routinely indicated.

Treatment

- **In patients without underlying pulmonary disease, antibiotics are not indicated** given the common viral etiology.
- Decongestants, expectorants, bronchodilators, and humidified air are used for symptomatic treatment.

Oral Lesions

Tables 2.10 and 2.11 outline the differential diagnosis of common oral lesions. See Figures 2.20 through 2.22 for images of oral thrush, aphthous stomatitis, and HSV gingivostomatitis, respectively.

UROLOGY

Urinary Incontinence

See the Geriatrics chapter for a complete discussion of urinary incontinence, including subtypes, clinical presentation, and treatment.

TABLE 2.10. Differential of White Oral Lesions

	Thrush	Leukoplakia	Lichen Planus
Definition/ epidemiology	Oral candidiasis, often in immunocompromised patients (diabetes, chemotherapy, local radiation, steroids, antibiotics).	Hyperkeratoses due to chronic irritation (dentures, tobacco), but ~2–6% represent dysplasia or early invasive squamous cell carcinoma (SCC).	Common; chronic inflammatory autoimmune disease.
Symptoms	Pain.	None.	Discomfort; often confused with candidiasis, leukoplakia, or SCC.
Exam	Creamy white patches over red mucosa (see Figure 2.20).	White lesions cannot be rubbed off.	Reticular or erosive.
Diagnosis	Clinical; can do KOH wet prep (spores).	Biopsy.	Biopsy.
Treatment	Fluconazole × 7–14 days; clotrimazole troches five times a day.	Treat if cancer.	Steroids (oral or topical).

TABLE 2.11. Differential Diagnosis of Common Mouth Ulcers

	Aphthous Ulcer (Canker Sore)	Herpes Stomatitis
Cause	Common; unknown cause (possible association with HHV-6).	Common; HSV.
Symptoms	Pain up to one week; heals within a few weeks.	Initial burning followed by small vesicles and then scabs.
Exam	Small ulcerations with yellow centers surrounded by red halos on nonkeratinized mucosa (buccal and lip mucosa; see Figure 2.21).	Vesicles, scabs. Usually on keratinized epithelium of the lips (see Figure 2.22).
Differential	If large or persistent, consider erythema multiforme, HSV, pemphigus, Behçet's disease, IBD, or SCC.	Aphthous ulcer, erythema multiforme, syphilis, cancer.
Treatment	Anti-inflammatory: topical steroids.	Not needed, but oral acyclovir × 7–14 days may shorten the course and mitigate postherpetic pain.
Prognosis	Recurrent.	Resolves quickly; frequent reactivation occurs in immunocompromised patients.

Benign Prostatic Hyperplasia (BPH)

Prevalence ↑ with age; > 90% of men > 80 years of age have an enlarged prostate.

Symptoms

- **Obstructive** symptoms include difficulty initiating a stream, terminal dribbling, and a weak stream.
- **Irritative** symptoms include urgency, frequency, and nocturia.

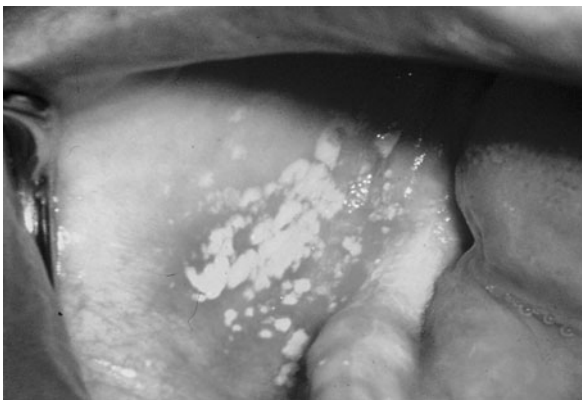


FIGURE 2.20. Thrush on the buccal mucosa.

Note the adherent white patches that are easily rubbed off with a tongue depressor (as opposed to leukoplakia, in which lesions cannot be removed with a tongue depressor). (Courtesy of James F. Steiner, DDS.)

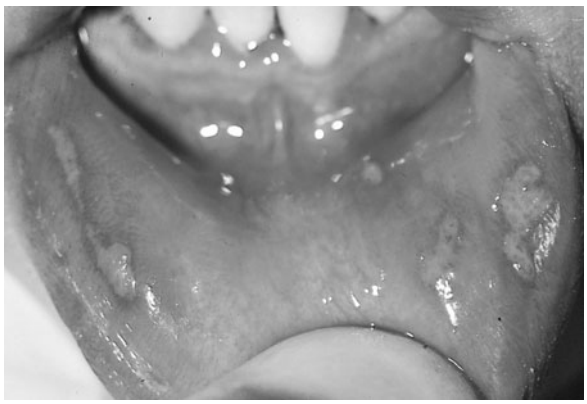


FIGURE 2.21. Aphthous ulcers on the lip and gingival mucosa.

Note the round, white, shallow ulcers. (Courtesy of James F. Steiner, DDS.)

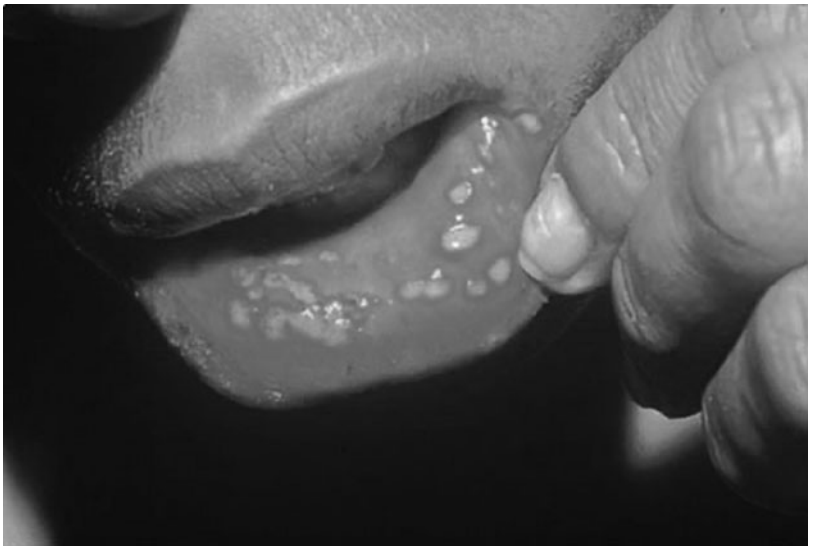


FIGURE 2.22. HSV 1° gingivostomatitis.

Multiple oral ulcerations are seen. (Reproduced, with permission, from Bondi EE et al. *Dermatology: Diagnosis & Treatment.* Stamford, CT: Appleton & Lange, 1991.)

- DRE may reveal an enlarged, symmetrically firm prostate, but the **size of the prostate correlates poorly with symptom severity.**

α-blockers are more effective than finasteride in improving BPH symptoms. Surgery is most effective in patients with severe symptoms.

DIFFERENTIAL

Prostate cancer, bladder cancer, bladder stones, UTI, interstitial cystitis, prostatitis, prostatodynia, neurogenic bladder.

DIAGNOSIS

- Diagnosed mainly by the history and exam. The American Urological Association symptom score can be useful in evaluating patients and in monitoring response to therapy.
- Obtain a UA and serum creatinine.
- PSA may be elevated in BPH but is not needed for diagnosis and is optional for prostate cancer screening (see the cancer screening discussion above).

Finasteride can lower PSA levels by 50%. In men who are being screened for prostate cancer and are taking finasteride, the biopsy threshold should be lowered accordingly.

TREATMENT

Depending on the severity of symptoms, treatment options include watchful waiting, pharmacologic therapy, and surgery (see also Tables 2.12 and 2.13):

- **Mild:** Watchful waiting only, as some men may have resolution of symptoms.
- **Moderate to severe:** Medications or surgery.
  - Dual therapy with α-blockers plus finasteride ↓ the risk of symptom progression and complications more effectively than either drug alone. Patients with severe symptoms or complications of BPH (see Table 2.13) benefit most from surgery, particularly after medication failure.
  - Minimally invasive procedures have fewer complications than TURP but are also less effective.

TABLE 2.12. Medications for BPH

	α_1-BLOCKERS	5α-REDUCTASE INHIBITORS
Drugs	Prazosin, doxazosin, terazosin, tamsulosin.	Finasteride.
Mechanism	↓ contractility of the prostate and bladder neck.	Block testosterone conversion to the more potent dihydrotestosterone.
Results	Improve symptoms and urinary flow rates; more effective than 5α-reductase inhibitors for symptom relief.	Improve symptoms; ↓ prostate size and PSA, especially in men with larger prostates.
Side effects	**Orthostatic hypotension,** nasal congestion, dizziness, fatigue.	↓ libido, ejaculatory dysfunction, impotence.

Erectile Dysfunction (ED)

Defined as an inability to acquire or maintain an erection sufficient for sexual intercourse in > 75% of attempts. Evaluation is directed at distinguishing organic from psychogenic causes (see Table 2.14).

DIAGNOSIS

- **Rule out an organic etiology:** Look for a history of medical conditions associated with ED with a physical exam focusing on evidence of endocrine abnormality (gynecomastia, testicle size), GU abnormalities (Peyronie's, prostate size), and peripheral neurovascular abnormalities. Screening labs should include glucose, cholesterol, TSH, testosterone, and prolactin.
- If testosterone or prolactin is abnormal, check FSH and LH to rule out a pituitary abnormality.

Up to one-quarter of all cases of ED may be related to drug or medication use.

TREATMENT

- Correct the underlying disorder (testosterone replacement for hypogonadism); eliminate medication- and drug-related causes.

TABLE 2.13. Urology Referral and Surgical Options for BPH

INDICATIONS FOR UROLOGY REFERRAL AND SURGERY	SURGICAL OPTIONS
Acute retention	Transurethral resection of the prostate (TURP)[a]
Hydronephrosis	Transurethral incision of the prostate (TUIP)
Recurrent UTIs	Open prostatectomy (gold standard)
Recurrent or refractory gross hematuria	Minimally invasive therapies
Renal insufficiency due to BPH	
Bladder stones	
Persistent severe symptoms despite maximal medical therapy	

[a] Side effects of TURP include the need for transfusion, retrograde ejaculation, impotence (10–40%, operator dependent), urinary incontinence, and hypervolemic hyponatremia.

TABLE 2.14. Medical Conditions Associated with ED

Condition	Examples/Comments
Psychogenic disorders	Performance anxiety, depression, mental stress.
Obesity, physical inactivity	
Diabetes mellitus	ED is seen in up to 50% of cases.
Peripheral vascular disease	
Endocrine disorders	Hypogonadism, hyperprolactinemia, thyroid abnormalities.
Pelvic surgery	
Spinal cord injury	
Drugs of abuse	Amphetamines, cocaine, marijuana, alcohol, tobacco.
Medications	**Antihypertensives:** Thiazides, β-blockers, clonidine, methyldopa. **Antiandrogens:** Spironolactone, H_2 blockers, finasteride. **Antidepressants:** TCAs, SSRIs. **Other:** Antipsychotics, benzodiazepines, opiates.

Rapid onset of ED suggests psychogenic causes or medication side effects. More gradual onset is associated with medical conditions. Low libido along with ED suggests a psychogenic, medication-related, or hormonal cause.

- Empiric therapy is often indicated in the absence of a suspected organic etiology. **Oral phosphodiesterase inhibitors (sildenafil, vardenafil, tadalafil)** are first-line therapy but are **contraindicated with nitrates or active cardiac disease** (can cause hypotension and sudden death).
- Psychosexual counseling is first-line therapy for psychogenic ED.
- Second-line therapies include intraurethral alprostadil suppositories, vacuum constrictive pumps, and penile prostheses.

Prostatitis

The differential includes acute bacterial prostatitis, chronic bacterial prostatitis, nonbacterial prostatitis, and prostatodynia. See Table 2.15 for key features of each.

Symptoms/Exam

Presents with irritative voiding symptoms and perineal or suprapubic pain. Acute bacterial prostatitis is notable for the presence of fever and an exquisitely tender prostate.

All patients with genital lesions should be screened for syphilis (serology).

Treatment

Table 2.15 outlines the treatment of prostatitis and prostatodynia.

Genital Lesions

Table 2.16 outlines the differential diagnosis and treatment of STIs that present as genital lesions. Figures 2.23 through 2.26 illustrate genital HSV le-

TABLE 2.15. Treatment of Prostatitis and Prostatodynia

	Acute Bacterial Prostatitis	Chronic Bacterial Prostatitis	Nonbacterial Prostatitis	Prostatodynia
Fever	+	–	–	–
UA	+	–	–	–
Expressed prostatic secretions	Contraindicated.	+	+	–
Bacterial culture	+	+	–	–
Prostate exam	Very tender.	Normal, boggy, or indurated.	Normal, boggy, or indurated.	Usually normal.
Etiology	Gram-⊖ rods (*E. coli*); less commonly gram-⊕ organisms (enterococcus).	Gram-⊖ rods; less commonly enterococcus.	Unknown; perhaps *Ureaplasma, Mycoplasma, Chlamydia.*	Varies; includes voiding dysfunction and pelvic floor musculature dysfunction.
Treatment	IV ampicillin and aminoglycosides until organism sensitivities are obtained; then switch to fluoroquinolones × 4–6 weeks.	TMP-SMX; fluoroquinolones × 6–12 weeks.	Erythromycin × 3–6 weeks if response at two weeks.	α-blocking drugs (e.g., terazosin) for bladder neck and urethral spasms; benzodiazepine and biofeedback for pelvic floor dysfunction.

Adapted, with permission, from Tierney LM et al. *Current Medical Diagnosis & Treatment,* 43rd ed. New York: McGraw-Hill, 2003: 914.

sions, genital warts, syphilitic chancre, and chancroid, respectively. Refer to the Women's Health chapter for a detailed discussion of gonorrheal and chlamydial infections (cervicitis, PID). The diagnosis and treatment of urethritis in men follow the same principles as those of cervicitis in women.

ORTHOPEDICS

Rotator Cuff Tendinitis or Tear

The spectrum of pathology ranges from subacromial bursitis and rotator cuff tendinitis to partial or full rotator cuff tear. Due to excessive overhead motion (e.g., baseball players).

Symptoms

Presents with nonspecific pain in the shoulder with occasional radiation down the lateral arm that worsens at night or with overhead movement. Motor weakness with abduction is seen in the presence of a tear.

TABLE 2.16. Differential Diagnosis of Genital Lesions

	HSV	Genital Warts (Condylomata Acuminata)	1° Syphilis	Chancroid
Cause	HSV-2 > HSV-1.	HPV.	*Treponema pallidum.*	*Haemophilus ducreyi.*
Incubation period/ triggers	**1°:** +/– asymptomatic; prodrome consists of malaise, genital paresthesias, and fever. **Reactivation:** Most commonly occurs with symptoms; triggers include stress, fever, and infection.	1–6 months; triggers include pregnancy and immunosuppression.	2–6 weeks.	3–5 days.
Symptoms	Painful, grouped vesicles; tingling, dysesthesia. Asymptomatic shedding is common.	Warty "cauliflower" growths or none.	Painless, clean-based ulcer ("chancre").	Pustule or pustules erode to form a painful ulcer with a necrotic base.
Exam	Groups of multiple, small vesicles.	Warty growths or none.	Ulcer on genitalia; nontender regional lymph nodes.	Usually unilateral, tender, fluctuant, matted nodes with overlying erythema.
Diagnosis	Mostly clinical; ⊕ viral culture or DFA or Tzanck smear with ⊕ intranuclear inclusions and multinucleated giant cells.	Clinical if wartlike; 4% acetic acid applied to the lesion turns tissue white with papillae.	**Serology:** RPR ⊕ 1–2 weeks after the 1° lesion is first seen. Immunofluorescence or darkfield microscopy of fluid with treponemes.	Culture of lesion on special media.
Treatment	**Acute episodes:** Acyclovir 400 mg TID, famciclovir 250 mg TID, valacyclovir 1000 mg BID × 10 days (first episode) or × 5 days (recurrence). **Suppression:** Acyclovir 400 mg BID or famciclovir 250 mg BID or valacyclovir 500 mg BID or 1 g QD.	Trichloroacetic acid; podophyllin (contraindicated in pregnancy); imiquimod.	Benzathine penicillin G IM × 1; in penicillin-allergic patients, doxycycline or tetracycline PO × 2 weeks.	Azithromycin 1 g PO × 1 or ceftriaxone 250 mg IM × 1.

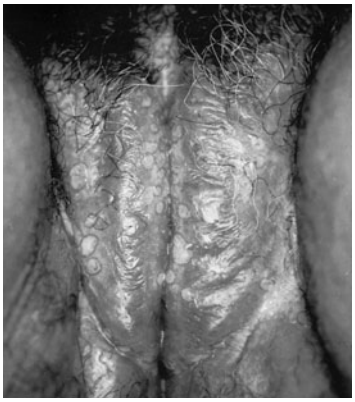


FIGURE 2.23. 1° HSV infection in a female.

Note the multiple, painful, grouped vesicles. (Reproduced, with permission, from Wendel GD, Cunningham FG: Sexually transmitted diseases in pregnancy. In *Williams Obstetrics*, 18th ed. (Suppl 13). Norwalk, CT: Appleton & Lange, August/September 1991.)

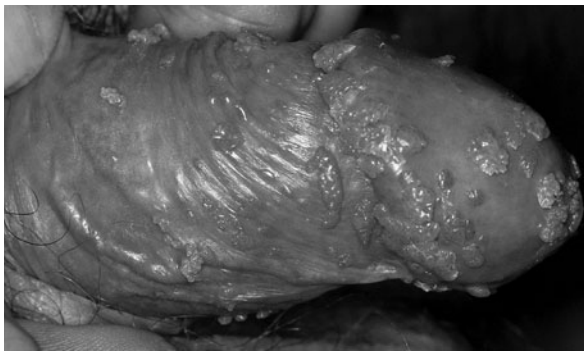


FIGURE 2.24. Penile warts.

Note the multiple soft, filiform papules on the glans penis and prepuce. (Reproduced, with permission, from Wolff K et al. *Fitzpatrick's Color Atlas & Synopsis of Clinical Dermatology*, 5th ed. New York: McGraw-Hill, 2005: 888.)

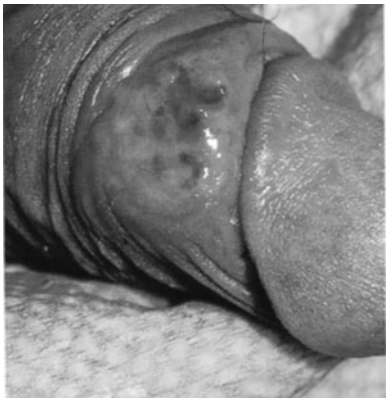


FIGURE 2.25. Syphilitic chancre.

This dry-based, painless ulcer with indurated borders is typical for a 1° chancre in a male patient. (Reproduced, with permission, from Bondi EE et al. *Dermatology: Diagnosis & Treatment.* Stamford, CT: Appleton & Lange, 1991: 394.)

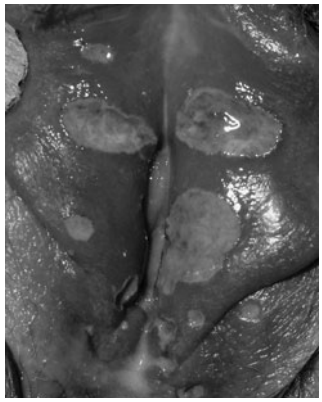


FIGURE 2.26. Chancroid.

Note the multiple painful, punched-out ulcers with undermined borders on the labia. (Reproduced, with permission, from Kasper DL et al. *Harrison's Principles of Internal Medicine*, 16th ed. New York: McGraw-Hill, 2004.)

Exam

- Exam reveals pain with abduction between 60 and 120 degrees. Tears lead to weakness on abduction ("drop arm test").
- Pain elicited by 60–120 degrees of passive abduction (**impingement sign**) suggests impingement or trapping of an **inflamed rotator cuff** on the overlying acromion.

Differential

- **Bicipital tendinitis:** Due to repetitive overhead motion (e.g., throwing, swimming). Exam reveals tenderness along the biceps tendon or muscle.
- **Degenerative joint disease.**
- **Systemic arthritis:** RA, pseudogout.

- **Referred pain:** May be derived from a pulmonary process (e.g., pulmonary embolism, pleural effusion), a subdiaphragmatic process, cervical spine disease, or brachial plexopathy.
- **Adhesive capsulitis (frozen shoulder):** Presents with progressive loss of range of motion (ROM), usually more from stiffness than from pain. Can follow rotator cuff tendinitis; more common in diabetics and older patients.

Knee swelling immediately post-trauma suggests a ligamentous tear (with hemarthrosis). Swelling occurring hours to days after trauma suggests meniscal injury.

Diagnosis

- Diagnosis is made by the history and exam.
- An MRI can be obtained if a complete tear is suspected or if no improvement is seen despite conservative therapy and the patient is a surgical candidate.

Treatment

- ↓ exacerbating activities; NSAIDs.
- Steroid injection is a common treatment but is no more effective than NSAID therapy.
- **ROM exercises** and rotator cuff strengthening can be initiated once acute pain has resolved.
- Refer to orthopedics for possible surgery if there is a complete tear or if no improvement is seen with conservative therapy after several months.

The thin female teenager who is an "exercise nut" is particularly prone to stress fractures.

Knee Pain

Table 2.17 outlines the etiologies and clinical characteristics of common knee injuries.

Diagnosis

- In a patient who presents after **acute trauma,** the **Ottawa Knee Rules** identify situations in which x-ray imaging is necessary to rule out a knee fracture. These guidelines recommend that an x-ray be obtained if any of the following is present:
  - Patient age ≥ 55 years.
  - Tenderness at the head of the fibula.
  - Isolated patellar tenderness.
  - Inability to bear weight both immediately after trauma and on exam.
  - Inability to flex the knee to 90 degrees.
- **MRI** is most sensitive for soft tissue injuries (e.g., meniscal and ligament tears).

Foot and Ankle Pain

A common reason for 1° care visits; may be acute or chronic.

Differential

See Table 2.18 for common causes of foot pain.

Diagnosis

In acute ankle or foot pain after trauma, use the **Ottawa Ankle Rules** to determine the need for x-ray imaging (see Figure 2.27).

TABLE 2.17. Common Knee Injuries

	Iliotibial Band Syndrome	Anserine Bursitis	Patellofemoral Pain Syndrome	Medial Meniscus Tear	ACL Tear
Those affected/ mechanism	Runners; deconditioned patients.	Runners, obese or deconditioned patients, people who work on their knees.	Runners/ deconditioned patients, often with chondromalacia of the patella. More common in women.	Twisting of the knee while the foot is firmly planted on the ground (soccer, football).	Twisting trauma, often in noncontact sports (e.g., skiing).
Symptoms	Lateral knee pain that is gradual; tightness after running.	Pain medial and inferior to the knee joint.	Anterior knee pain; often exacerbated by walking up and down stairs/hills.	Pop or tear at time of injury; severe pain with "locking," "catching," and **swelling that peaks the next day.**	Audible "pop" and giving way; **immediate swelling.**
Exam	Tenderness over the lateral femoral epicondyle.	Localized tenderness.	Pain on patellar compression while the patient contracts the quadriceps. Exam is often nonspecific.	Medial joint line tenderness; pain on hyperflexion and hyperextension; effusion; ⊕ McMurray's test.	⊕ anterior drawer sign, ⊕ Lachman's test, effusion.
Treatment	Rest and abstain from running until symptoms subside. Then resume gentle stretching, especially before running.	Avoid exacerbating activities. Hamstring stretches and quadriceps strengthening.	Quadriceps strengthening, avoid flexion loads, bicycling may be well tolerated.	Treat conservatively: RICE (rest, ice, compression, elevation); quadriceps strengthening with physical therapy; surgery only if symptoms persist.	Conservative; ACL reconstruction if the patient has a high activity level.

Lower Back Pain (LBP)

Extremely common, with up to 80% of the population affected at some time. Three-quarters of LBP patients improve within one month. Most have self-limited, nonspecific mechanical causes of LBP.

New-onset back pain in a patient with a previous diagnosis of cancer represents metastasis until proven otherwise. Spinal cord compression is a neurosurgical emergency.

Exam

- A 1° goal of initial evaluation is to rule out serious conditions as indicated by neurologic or systemic findings (see below).
- A **straight-leg raise** test is ⊕ and indicates nerve root irritation if passively straightening the leg in the supine or seated position causes radicular pain at less than a 60-degree angle. Has poor specificity (40%) but excellent sensitivity (80%) for lumbar disk herniation.

TABLE 2.18. Common Causes of Foot and Ankle Pain

Cause	Seen In/Etiology	Symptoms	Diagnosis	Treatment
Plantar fasciitis	Obese patients, prolonged standing, runners.	Plantar pain, especially with **first steps in morning.**	Tenderness over insertion of the plantar fascia at the medial heel. **Bone spurs on x-ray are neither sensitive nor specific for plantar fasciitis.**	↓ prolonged standing; arch supports; NSAIDs; stretches. In 80% of cases, symptoms resolve within one year.
Stress fracture	Runners, especially women.	Foot pain that worsens with weight bearing.	**X-ray may miss early fractures.** Obtain bone scan or MRI in the presence of high suspicion and when x-ray is ⊖.	**Hard-soled shoe** or walking cast for 3–4 weeks. Avoid exacerbating activities until fully healed.
Metatarsalgia	Seen in those with prolonged pressure on the anterior feet, especially from high heels.	Pain in the area of the metatarsal heads (one or multiple).	Clinical diagnosis; exclude other etiologies.	Avoid offending shoes; NSAIDs.
Morton's neuroma	Entrapment of the interdigital nerve. Affects women more than men.	**Forefoot pain and paresthesias radiating to toes;** the third web space is classic. Patients feel pain while wearing shoes but not when barefoot.	Usually a clinical diagnosis (tenderness in affected web space); MRI can confirm when surgery is a consideration.	Broad-toed shoes, orthotics, corticosteroid injections. Surgery should be reserved for refractory cases.
Bunions (hallux valgus)	Those who use ill-fitting footwear. **Women are affected more than men.**	Foot pain in the area of the first metatarsal.	**Deformity** of the first MTP joint with valgus deviation of the great toe.	Pain control and well-fitting shoes for early bunions; surgical correction (osteotomy) when pain/functional impairment are severe.
Gout	Those with risk factors for gout. **Men are affected more than women.**	**Sudden onset of exquisite pain in the first MTP** with redness/swelling. Can also present as **midfoot or Achilles tenosynovitis.**	**Inflammatory signs** at the first MTP. Other joints or risk factors for gout may be present.	NSAIDs, colchicine, oral or intra-articular corticosteroids.

TABLE 2.18. Common Causes of Foot and Ankle Pain *(continued)*

Cause	Seen In/Etiology	Symptoms	Diagnosis	Treatment
Achilles tendinitis	Athletes. Consider Achilles tendon tear and spondyloarthropathies in the differential.	Pain with running or jumping that **worsens with dorsiflexion** of the foot.	Tenderness at the Achilles insertion on the calcaneus. Consider an MRI if Achilles tendon tear is suspected.	NSAIDs, stretches, avoidance of offending activity.
Tarsal tunnel syndrome	Entrapment of the posterior tibial nerve under the medial flexor retinaculum. Can be post-traumatic or from chronic overuse.	**Heel/plantar foot pain and paresthesias.** Pain at night and after prolonged weight bearing.	**Tinel's sign**—reproduction of symptoms by tapping the tibial nerve posterior and inferior to the medial malleolus. X-ray is indicated to rule out associated bony abnormalities.	NSAIDs, corticosteroid injections, orthotics.

- A wide-based gait and a ⊕ Romberg sign are specific signs of spinal stenosis.
- Exam may also localize the origin of the nerve root syndrome (see Table 2.19).

Differential

- **Serious causes** of back pain can be distinguished as follows:
  - **Cancer:** Age > 50, a previous cancer history, unexplained weight loss.
  - **Compression fracture:** Age > 50, significant trauma, a history of osteoporosis, corticosteroid use.
  - **Infection (epidural abscess, diskitis, osteomyelitis, or endocarditis):** Fever, recent skin or urinary infection, immunosuppression, **IV drug use.**
  - **Cauda equina syndrome:** Bilateral leg weakness, bowel or bladder incontinence, saddle anesthesia.
- **Less urgent causes of back pain** include herniated disk; spinal stenosis; sciatica; musculoskeletal strain; and referred pain from a kidney stone, an intra-abdominal process, or herpes zoster. Table 2.20 outlines the distinguishing features of herniated disk and spinal stenosis.

Back pain causes—

DISC MASS

Degeneration (DJD, osteoporosis, spondylosis)
Infection/**I**njury
Spondylitis
Compression fracture
Multiple myeloma/**M**ets (cancer of the breast, kidney, lung, prostate, or thyroid)
Abdominal pain/**A**neurysm
Skin (herpes zoster), **S**train, **S**coliosis, and lordosis
Slipped disk/ **S**pondylolisthesis

Diagnosis

- The history and clinical exam are helpful in identifying the cause.
- A plain x-ray is indicated only if fracture, osteomyelitis, or cancer is being considered. Plain films are insensitive for metastasis, infection, and disk disease.
- MRI (or CT) is indicated urgently in cases of suspected cauda equina syndrome, cancer, or infection. For patients with suspected disk disease, imaging is not indicated unless symptoms persist for > 6 weeks or significant neurologic findings are present, particularly if surgery is being considered.
- The specificity of MRI is low, and care should be taken to intervene only when symptoms and physical findings can clearly be attributed to the abnormalities found on imaging.

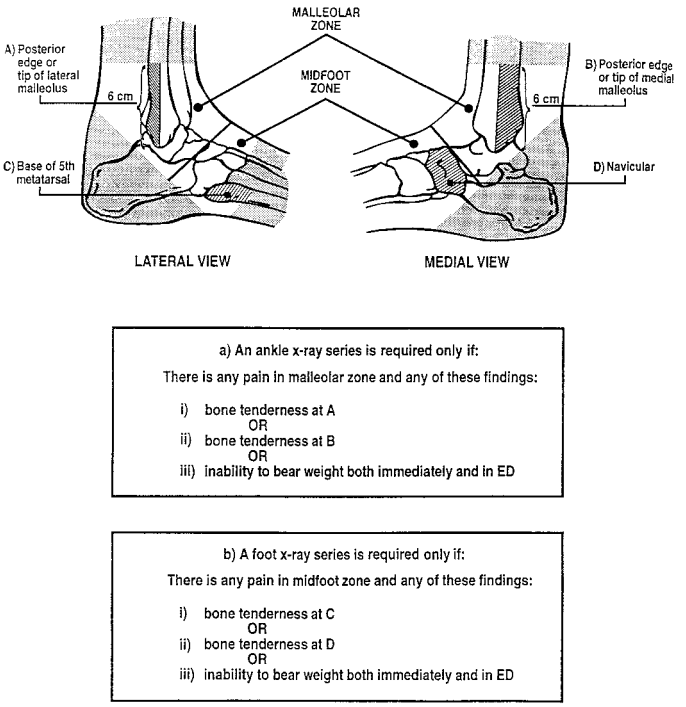


FIGURE 2.27. Ottawa Ankle Rules for x-rays in ankle/foot trauma.

(Reproduced, with permission, from Tintinalli JE et al. *Tintinalli's Emergency Medicine: A Comprehensive Study Guide*, 6th ed. New York: McGraw-Hill, 2004.)

"Red flags" in the history of a patient with new-onset back pain:

- *Age > 50*
- *History of cancer*
- *Fever*
- *Weight loss*
- *IV drug use*
- *Osteoporosis*
- *Lower extremity weakness*
- *Bowel or bladder dysfunction*

TREATMENT

- For mechanical causes of acute LBP, conservative therapy with NSAIDs and muscle relaxants, education, and **early return to ordinary activity** are indicated in the absence of major neurologic deficits or other alarm symptoms, as most cases of LBP resolve within 1–3 months. Bed rest is ineffective.
- Massage and manipulation by a chiropractor or physical therapist are safe and effective for benign, mechanical causes of LBP.
- Spinal stenosis can be treated with exercises to ↓ lumbar lordosis. Epidural corticosteroid injections provide some relief. Decompressive laminectomy may provide at least short-term symptom improvement for a majority of patients. Surgery for lumbar disk herniation is reserved for refractory radicular symptoms (duration > 6 weeks) or severe motor deficits.

TABLE 2.19. Nerve Root Syndromes (Sciatica)

NERVE ROOT	STRENGTH	SENSORY	REFLEXES
S1	Ankle plantar flexion (toe walking).	Lateral foot.	Achilles.
L5	Great toe dorsiflexion.	Medial forefoot.	None.
L4 (less common)	Ankle dorsiflexion (heel walking).	Medial calf.	Knee jerk.

TABLE 2.20. Herniated Disk vs. Spinal Stenosis

	Herniated Disk	Spinal Stenosis
Etiology	Degeneration of ligaments leads to disk prolapse, leading in turn to compression or inflammation of the nerve root. Nearly all involve the L4–L5 or L5–S1 interspace.	Narrowing of the spinal canal from osteophytes at facet joints, bulging disks, or a hypertrophied ligamentum flavum.
Symptoms	"Sciatica"—pain and paresthesias in the dermatome from the buttock radiating down to below the knee. **Worsens with sitting (lumbar flexion).**	"Neurogenic claudication"/"pseudoclaudication"—pain radiating to the buttocks, thighs, or lower legs. **Worsens with prolonged standing or walking (extension of spine); improves with sitting or walking uphill (flexion of the spine).**
Exam/diagnosis	See Table 2.19. A ⊕ straight-leg raise (pain at 60 degrees or less) is seen.	May have a ⊕ Romberg sign or wide-based gait. Exam is often unremarkable. MRI confirms the diagnosis.
Treatment	Limited bed rest < 2 days; ordinary activity; NSAIDs; chiropractic for benign, mechanical LBP is as effective as therapy prescribed by physicians.	Exercise to reduce lumbar lordosis; decompressive laminectomy.

CARDIOVASCULAR DISEASE

Hypertension

Hypertension is diagnosed when systolic BP is persistently ≥ 140 **OR** diastolic BP is ≥ 90 (see Table 2.21). Hypertension is associated with an ↑ risk of MI, heart failure, stroke, and kidney disease. The control of hypertension ↓ the risk of stroke, MI, and heart failure.

Diagnosis

- BP should be checked at least every two years starting at age 18.
- Unless acute end-organ damage is present or BP is above 220/115, the diagnosis of hypertension requires multiple BP readings above 140/90 on at least two different occasions.
- The Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7) identifies three goals of evaluation: (1) assess lifestyle and other cardiovascular risk factors or other disease that will affect management (diabetes, hyperlipidemia, smoking); (2) identify 2° causes of hypertension; and (3) assess for the presence of target-organ damage and cardiovascular disease (heart, brain, kidney, peripheral vascular disease, retinopathy).
- Identifiable causes of hypertension include the following:
  - Sleep apnea
  - Drug-induced hypertension (e.g., NSAIDs, OCPs, cyclosporine, decongestants, cocaine)
  - Chronic kidney disease (most common)
  - 1° aldosteronism

TABLE 2.21. Blood Pressure Classification

BP Category	Systolic BP (mmHg)	Diastolic BP (mmHg)
Normal	< 120	and < 80
Prehypertension	120–139	or 80–89
Stage 1 HTN	140–159	or 90–99
Stage 2 HTN	≥ 160	or ≥ 100

- Renovascular disease
- Cushing's syndrome
- Pheochromocytoma
- Coarctation of the aorta
- Thyroid or parathyroid disease

For most hypertensive patients, thiazide diuretics are the first-line agent of choice.

- Laboratory workup for patients diagnosed with hypertension should include UA, blood glucose, hematocrit, a lipid panel, potassium/creatinine/calcium levels, and an ECG. Urine albumin/creatinine level is optional.

Treatment

- The goal of BP management is **< 140/90,** or **< 130/80** in patients with **diabetes, renal disease,** or **cardiovascular disease.**
- All patients with prehypertension and stages 1 and 2 hypertension should be counseled about lifestyle modification (see Table 2.22). If a brief trial of nonpharmacologic therapy fails, medications should be added for those with stage 1 or 2 hypertension (see Table 2.23).
- Other modifiable cardiovascular risk factors (diabetes, hyperlipidemia, smoking) should be screened for and treated in hypertensive individuals.

TABLE 2.22. Lifestyle Modifications for Hypertension

Measure	Comments
Sodium restriction	No added salt or low-sodium diet.
DASH diet (Dietary Approaches to Stop Hypertension)	A diet rich in fruits, vegetables, and low-fat dairy products with ↓ saturated and unsaturated fat.
Weight reduction	If over the ideal BMI.
Aerobic physical activity	
Limitation of alcohol consumption	Limit to < 2 drinks per day for men and < 1 drink per day for women.

Smoking and Smoking Cessation

Smoking is the leading cause of preventable death in the United States. Treat as follows:

- Apply the **"5 A's" approach** advocated by the National Cancer Institute:
  - **A**sk (about smoking).
  - **A**dvise (all smokers to quit).
  - **A**ssess (readiness to quit).
  - **A**ssist (with pharmacologic and nonpharmacologic measures).
  - **A**rrange (follow-up and support).
- Physician intervention, even if as brief as 1–2 minutes, can ↑ the rate of smoking cessation.
- Offer all patients **pharmacotherapy,** which is **twice as effective** in promoting cessation as behavioral counseling alone (see Table 2.24).
  - Bupropion may be used in combination with nicotine replacement with additive benefits. Bupropion alone is more effective than a nicotine patch alone.
  - Varenicline, which was approved by the FDA in 2006, has not been studied in combination with either bupropion or nicotine replacement.

A combination of pharmacotherapy and behavioral counseling is most effective in promoting smoking cessation.

COMMON SYMPTOMS

Vertigo

An illusion of motion (a sensation that one's "head is spinning" or that the "room is whirling") can originate in the peripheral (labyrinth/inner ear) or central vestibular system. Other forms of dizziness include the following:

- **Presyncope:** A feeling of impending loss of consciousness ("I'm going to faint"). Usually due to postural changes rather than to arrhythmia or structural heart disease. See the Cardiology chapter for further details.
- **Disequilibrium:** Unsteadiness with standing or walking (patients complain that "my balance is off" or that "I feel as if I'm going to fall"). Common in older patients; often multifactorial.
- **Lightheadedness:** Anxiety ("I'm just dizzy").

Symptoms

- Presents with a sensation of exaggerated motion when there is little or no motion.
- Peripheral vertigo is often accompanied by nausea and vomiting; central vertigo often occurs in conjunction with other posterior circulation findings.
- Ipsilateral facial numbness or weakness or limb ataxia suggests a lesion of the cerebellopontine angle.

Exam

- Orthostatics.
- **Dix-Hallpike maneuver (positional testing):** Used to diagnose benign positional vertigo (BPV). Quickly bring the patient from a sitting to a supine position with one ear turned toward the table; repeat on the other side. A ⊕ test is defined as the presence of fatigable (10- to 20-second) nystagmus with or without vertigo. ⊕ in approximately 50% of patients with BPV.

Vertical nystagmus is always abnormal and almost always central.

TABLE 2.23. Antihypertensive Medications

	Thiazides	β-Blockers	ACEIs	Angiotensin II Receptor Blockers (ARBs)	Calcium Channel Blockers
Examples	HCTZ, chlorthalidone.	Atenolol, metoprolol.	Captopril, enalapril, ramipril.	Irbesartan, losartan, valsartan.	**Nondihydropyridines:** Diltiazem, verapamil. **Dihydropyridines:** Amlodipine, felodipine, nifedipine.
Side effects	Hypokalemia, ED, ↑ insulin resistance, hyperuricemia, ↑ TG. Metabolic side effects are more prominent at doses of > 25 mg/day.	Bronchospasm, bradycardia/AV node blockade, depression, fatigue, ED, ↑ insulin resistance.	Cough (10%), hyperkalemia, renal failure, angioedema.	No cough. Less hyperkalemia, renal failure, angioedema.	Conduction defects (nondihydropyridines); lower extremity edema (dihydropyridines).
Indications as first-line drug	Used in most patients as mono- or combination therapy (stage 1 or 2 hypertension), including isolated systolic hypertension in the elderly.	MI, high CAD risk.	DM with microalbuminuria/proteinuria; MI with systolic dysfunction or anterior infarct; non-DM-related proteinuria.	ACEI cough in patients who would otherwise have indications for ACEI.	Systolic hypertension, advanced age, CAD.
Other indications	Recurrent stroke prevention. May mitigate osteoporosis.	CHF, tachyarrhythmias, migraine.	CHF.	CHF, DM, chronic renal failure.	Atrial arrhythmias (nondihydropyridines), isolated systolic hypertension in elderly (dihydropyridines).
Contraindications	Gout.	Bronchospasm; high-degree (type II second- or third-degree) heart block.	Pregnancy.	Pregnancy.	High-degree heart block.

TABLE 2.24. Smoking Cessation Methods

Method	Mechanism/Use	Side Effects	Contraindications
Nicotine replacement (patch, gum, inhaler, nasal spray)	Apply patch daily. Chew gum or use nasal spray/inhaler PRN cravings.	Skin irritation (patch); mucosal irritation (nasal spray); cough (inhaler).	Recent MI, unstable angina, life-threatening arrhythmia, pregnancy (although nicotine replacement may be preferable to continued smoking).
Sustained-release bupropion	Atypical antidepressant. Begin one week prior to quit date; continue three or more months after quitting.	Restlessness/anxiety, tremor, insomnia, GI upset.	Seizures, head trauma, heavy alcohol use, history of eating disorders.
Varenicline	Nicotine agonist. Start one week prior to quit date; continue for 12 weeks.	Nausea/vomiting, constipation, altered dreams.	Not studied in combination with other pharmacotherapies.
Behavioral counseling	Individual, group, telephone hotlines.		

Diagnosis/Treatment

Differentiate between central and peripheral vertigo as indicated in Tables 2.25 and 2.26.

Peripheral vertigo is often more severe than central vertigo but should not have any associated neurologic symptoms.

Unintentional Weight Loss

Defined as an unintended weight loss of > 5% of usual body weight over 6–12 months. Unintentional weight loss is associated with excess morbidity and

TABLE 2.25. Causes of Central Vertigo

	Acoustic Neuroma (CN VIII Schwannoma)	Brain Stem Ischemia	Basilar Migraine	Multiple Sclerosis
Symptoms	**Unilateral** hearing loss.	**Symptoms of vertebrobasilar insufficiency: diplopia, dysarthria,** numbness.	Occipital **headache, visual disturbances,** sensory symptoms.	Chronic imbalance.
Duration	Continuous.	Varies.	Varies.	Fluctuating.
Signs/diagnosis	MRI.	MRI/CT, angiogram.	Diagnosis of exclusion.	MRI/CT.
Treatment	Surgery.	Stroke treatment.	β-blockers, ergots.	See the Neurology chapter.

TABLE 2.26. Causes of Peripheral Vertigo

	Benign Positional Vertigo (BPV)	Ménière's Syndrome	Vestibular Neuronitis/ Acute Labyrinthitis	Post-Traumatic
Symptoms	Onset is a few seconds **following head motion;** nausea/vomiting.	Has four classic symptoms: episodic vertigo, **sensorineural hearing loss, tinnitus, and ear fullness.**	May be preceded by URI; **sudden, continuous.**	
Duration	**Up to one minute.**	One to several hours.	A few days to one week.	A few days to one month.
Diagnosis	⊕ **Dix-Hallpike.**	**Clinical; MRI to rule out acoustic neuroma.**	Clinical.	Clinical. Rule out basilar skull fracture.
Etiology	Dislodging of otolith into the semicircular canal.	Distention of the endolymphatic compartment of the inner ear.	Unknown; often occurs after URI.	Post–head trauma.
Treatment	**Epley maneuver** (canalith repositioning); **habituation exercises.**	Bed rest; **low-salt diet** +/– **diuretics;** symptomatic treatment with antihistamines, anticholinergics, and benzodiazepines.	Symptomatic (meclizine or benzodiazepines).	Symptomatic.

mortality. It is idiopathic in up to one-third of cases. Other etiologies are as follows:

- **Cancer** and **GI disorders** (malabsorption, pancreatic insufficiency) and **psychiatric disorders** (depression, anxiety, dementia, anorexia nervosa) account for up to two-thirds of cases.
- Other causes include hyperthyroidism, DM, chronic diseases, and infections. Difficulty with food preparation or intake from any cause (social isolation with inability to shop/cook, ill-fitting dentures, dysphagia) should always be considered.

Diagnosis

- The history and exam often provide clues. Document the actual amount of weight lost.
- The initial evaluation should include CBC, TSH, electrolytes, UA, CXR, and age-appropriate cancer screening tests.
- The second evaluation (if the initial evaluation is ⊖) should consist of observation or, if the symptoms/exam are suggestive, further cancer screening or GI evaluation.

Treatment

- Treat the underlying disorder.
- Set caloric intake goals; give caloric supplementation.

- Appetite stimulants (megestrol acetate, dronabinol) are sometimes used in the presence of low appetite.

Fatigue

A common symptom that is most often due to stress, sleep disturbance, viral infection, or other illnesses. Causes include the following:

- Thyroid abnormalities (hypo- and hyperthyroidism)
- Infections (hepatitis, endocarditis)
- COPD
- CHF
- Anemia
- Sleep apnea
- Restless leg syndrome (RLS)
- Psychiatric disorders (depression, alcoholism)
- Drugs (β-blockers, sedatives)
- Autoimmune disorders

Chronic fatigue syndrome is defined as fatigue lasting at least six months that is not alleviated by rest and that interferes with daily activities, in combination with four or more of the following: impaired memory or concentration, sore throat, tender cervical or axillary lymph nodes, muscle pain, multijoint pain, new headaches, unrefreshing sleep, and postexertion malaise.

Treatment

The treatment of chronic fatigue syndrome should center on a **multidisciplinary approach** involving the following:

- Continuing psychiatric treatment.
- Cognitive-behavioral therapy (promotes self-help).
- Graded exercise (improves physical function).
- A supportive patient-physician relationship.

Chronic Cough

Defined as a cough lasting > 6 weeks. Three common causes are as follows:

- **Postnasal drip.**
- **Cough-variant asthma:** Exacerbated by seasonal allergies, exercise, and cold.
- **GERD:** Otherwise asymptomatic in 75% of cases.
- Other causes include post-URI cough (may persist for two months), *Bordetella pertussis*, chronic bronchitis, and ACEI use (may last for a few weeks after cessation).

Causes of chronic cough—

GASPS AND COUgh

GERD
Asthma
Smoking, chronic bronchitis
Postinfection
Sinusitis, postnasal drip
ACEIs
Neoplasm
Diverticulum
CHF
Outer ear disease
Upper airway obstruction

Diagnosis

- Findings suggesting specific etiologies of chronic cough include nasal bogginess, a "cobblestone" oropharynx, wheezes, a prolonged expiratory phase, and rales.
- Once benign, self-limited causes such as postviral cough have been ruled out, a CXR should be obtained before prolonged courses of empiric therapy are initiated.
- If the CXR is normal, a trial of empiric therapy for the most likely cause is appropriate (see below).

- If empiric therapy fails, consider PFTs (+/– methacholine challenge) for suspected asthma. Esophageal pH monitoring is definitive for GERD. ENT referral or a sinus CT may be appropriate for suspected postnasal drip.

Treatment

- Empirically treat the most likely causes (e.g., nasal corticosteroids, bronchodilators +/– inhaled steroids, acid suppressants).
- Maximal therapy for the suspected condition for 2–4 weeks is recommended prior to further diagnostic testing.

Insomnia

The most common of all sleep disorders, affecting roughly 15% of patients at some point. **Chronic insomnia** is defined as > 3 weeks of difficulty falling or staying asleep, frequent awakenings during the night, and a feeling of insufficient sleep (daytime fatigue, forgetfulness, irritability). Exacerbating factors include stress, pain, caffeine, daytime napping, early bedtimes, drug withdrawal (alcohol, benzodiazepines, opiates), and alcoholism.

Differential

RLS, periodic limb movement disorder (PLMD). See Table 2.27 for further details.

Diagnosis

- Diagnosis is mainly clinical.
- Rule out psychiatric and medical conditions—e.g., depression, PTSD, delirium, chronic pain, medication side effects, GERD, and nocturia from BPH or DM.
- Labs for RLS include CBC, ferritin, and BUN/creatinine.
- Polysomnography may help diagnose PLMD and RLS and may also rule out other sleep disorders, such as sleep apnea.

Treatment

- Treat the underlying disorder.
- Sleep hygiene and relaxation techniques are effective treatments for chronic insomnia.
- Benzodiazepines and benzodiazepine receptor agonists (zolpidem, zaleplon) are FDA approved for the treatment of short-term insomnia (7–10 days). Only eszopiclone is FDA approved for the chronic treatment of insomnia. Antidepressants such as trazodone and antihistamines are commonly used off-label for this indication despite a lack of evidence for their safety or efficacy.

Chronic Lower Extremity Edema

The differential for chronic bilateral lower extremity edema includes the following (see also Table 2.28):

- **Venous insufficiency:** Risk factors include obesity and a history of pregnancy. Varicose veins may be the only finding in the early stages. Edema, skin changes, and ulcerations (medial ankle) are later findings.

TABLE 2.27. Differential Diagnosis of Insomnia

	Restless Leg Syndrome	Periodic Limb Movement Disorder	Insomnia
Symptoms	A painless, "creepy-crawling" sensation that is relieved by leg movement but worsens at night and at rest.	Intermittent limb movements during non-REM sleep; seen in > 75% of patients with RLS.	Difficulty going to sleep without "physical" symptoms to explain the problem.
Disease associations	**Iron deficiency** (even in the absence of anemia), uremia, DM; idiopathic in most cases.	Uremia, TCAs, MAOIs.	Depression, anxiety, stimulants, chronic pain, alcohol.
Pathophysiology	Unknown; may involve abnormal dopamine transmission.		Unknown or disease specific.
Treatment	Correct the underlying disorder (e.g., iron supplementation); give dopaminergic agonists (carbidopa/levodopa, pramipexole) or benzodiazepines if dopaminergic agonists fail.	Same as that for RLS.	Correct the underlying disorder; sleep hygiene; medications.

- **Lymphedema:** Can be idiopathic (due to a congenital abnormality of the lymphatic system) or 2° to lymphatic obstruction (e.g., from tumor, filariasis, lymph node dissection, or radiation). The dorsum of the foot is commonly affected. Late changes include a nonpitting "peau d'orange" appearance.
- **Varicose veins:** May occur with or without chronic venous insufficiency.
- **Right-sided heart failure.**
- **Low albumin states:** Nephrotic syndrome; protein-losing enteropathy.
- **Inferior vena cava obstruction.**

TABLE 2.28. Causes of Chronic Bilateral Lower Extremity Edema

Mechanism	Causes
Elevated capillary hydrostatic pressure	**Venous insufficiency:** A heavy, achy feeling that worsens as the day progresses; "brawny" edema. CHF, constrictive pericarditis. **IVC compression:** Tumor, clot, lymph nodes. Pregnancy. **Filariasis:** Lymph node obstruction by *Wuchereria bancrofti* and *Brugia malayi.* **Drugs:** NSAIDs, glucocorticoids, estrogen.
↑ capillary permeability	Hypothyroid myxedema, drugs (calcium channel blockers, hydralazine), vasculitis.
↓ oncotic pressure	Nephrotic syndrome, protein-losing enteropathy, cirrhosis, malnutrition.

The differential for **unilateral lower extremity edema** is as follows:

- **Venous insufficiency:** Post–vein graft for CABG, prior DVT, leg injury.
- **Reflex sympathetic dystrophy:** Hyperesthesia and hyperhidrosis that occur a few weeks after trauma; trophic skin changes and pain out of proportion to the exam (see the discussion of complex regional pain syndrome below).
- **DVT:** Usually acute edema.
- **Infection:** Cellulitis or fasciitis.
- **Inflammation:** Gout; ruptured Baker's cyst (posterior knee).

Diagnosis

- The etiology can often be determined without diagnostic testing.
- Depending on the history and physical exam, consider ordering an echocardiogram, a UA for protein, liver enzymes, and abdominal/pelvic imaging to rule out systemic causes of edema or venous obstruction.
- Lower extremity ultrasound with Dopplers can rule out DVT and demonstrate venous incompetence.
- Radionuclide lymphoscintigraphy is the gold-standard test for lymphedema.

Treatment

- Treat the underlying causes, including discontinuation of contributing medications.
- Support stockings.
- Lifestyle modification (↓ salt) and leg elevation.
- Surgery or sclerotherapy are options for advanced varicosities.
- Meticulous skin care, gradient pressure stockings, massage therapy, and external pneumatic compression are modalities used to treat lymphedema.

Complex Regional Pain Syndrome (CRPS)

A rare condition characterized by autonomic and vasomotor instability in the affected extremity. Also known as reflex sympathetic dystrophy, the syndrome is usually preceded by direct physical trauma, which may be minor. Surgery on the affected limb may also precede the development of CRPS. Most commonly affects the hand.

Symptoms

- Presents as follows:
  - Diffuse pain of the affected extremity that is often burning, intense, and worsened by light touch.
  - Swelling.
  - Disturbances of color and temperature.
  - Dystrophic changes of affected skin and nails.
  - Limited ROM.
- The shoulder-hand variant presents with hand symptoms along with limited ROM at the ipsilateral shoulder. May occur after MI or neck/shoulder injury.

Diagnosis

- **Bone scan** is sensitive and reveals ↑ uptake in the affected extremity.
- Later in the course, radiographs reveal generalized **osteopenia.**

TREATMENT/PREVENTION

- Early mobilization after injury/surgery/MI reduces the chance of developing CRPS and improves the prognosis once it has occurred.
- Physical therapy is the mainstay of treatment and should focus on optimizing function of the affected limb.
- TCAs are first-line pharmacologic therapy, but other neuropathic pain medications (e.g., gabapentin, topical lidocaine) may also be tried. Prednisone (40 mg × 2 weeks, tapered over 2 weeks) is sometimes used in resistant cases. Bisphosphonates appear to be effective as well.
- Regional nerve blocks and dorsal column stimulation are also helpful.

MEDICAL ETHICS

Based on a group of fundamental principles that should guide the best practice (see Table 2.29).

Decision Making

- Decisions about medical care should be **shared** between the patient (or surrogate) and the provider.
- **Informed consent** can be verbal but should be put in writing for high-risk treatments.
- Patients can give informed consent provided that they demonstrate **decision-making capacity** by:
  - Understanding their medical condition and the treatment being proposed.
  - Communicating their understanding about risks, benefits, and alternatives to the proposed treatment.
  - Making decisions that are rational and consistent over time and with their values.
  - Demonstrating that they are not influenced by delirium.

Exceptions to the requirement for informed consent include life-threatening emergencies or circumstances in which patients waive their right to participate in the decision-making process.

TABLE 2.29. Guiding Principles in Biomedical Ethics

Ethical Principle	Explanation	Example
Beneficence	Be of benefit to your patient.	Physician counsels hyperlipidemic patient on lifestyle modifications.
Nonmaleficence	Do no harm to your patient.	Physician advises against epidural steroid injection for chronic back pain due to spinal stenosis because it is unlikely to benefit patient.
Justice	The equitable distribution of resources within a population.	Organ transplantation.
Autonomy	The right of patients to make their own decisions about their health care.	Patient gives informed consent (or refusal) to surgery.
Fidelity	Truthful disclosure to patients.	Physician informs patient that pneumothorax occurred during thoracentesis.

A diagnosis of dementia does not necessarily imply that the patient lacks capacity to make decisions, as long as the patient can satisfy the requirements of decision-making capacity.

- If a patient lacks capacity to make decisions, their advance directive or assigned surrogate guides decisions.

Confidentiality

- **HIPAA,** the Health Insurance Portability and Accountability Act of 1996, provides specific guidelines governing when and how the sharing of confidential patient information is acceptable.
- Exceptions to the rule of confidentiality:
  - Child or elder abuse or domestic violence.
  - Reportable diseases (e.g., STDs, conditions that could impair driving).
  - Threats by the patient to others' lives.
- When confidentiality must be broken, physicians should, when possible, discuss the need for disclosure with the patient in advance.

Error Reporting

Patients who have been injured, even if no error occurred, should be informed promptly and completely about what has happened.

Impaired Physicians

- Physicians who are impaired must not take on patient care responsibilities that they may not be able to perform safely and effectively.
- Causes of physician impairment include substance use (alcohol, other drugs), psychiatric illness, advanced dementia, or physical illness that interferes with the cognitive and/or motor skills needed to deliver care.
- Physicians have an ethical responsibility to protect patients from other physicians they know to be impaired. Legal reporting requirements vary.

Futile Care

- Physicians are not obliged to provide care they believe is futile.
- Futility is hard to define quantitatively, but generally accepted futile conditions are:
  - CPR in a patient who fails maximal life-support measures (e.g., a patient who suffers cardiac arrest due to hypotension refractory to multiple vasopressors).
  - An intervention that has already been tried and failed in the patient (e.g., if cancer worsened despite a complete course of chemotherapy, there would be no obligation to provide another course of the same therapy).
  - Treatment with no physiologic basis (e.g., plasmapheresis for septic shock).
- Ethical "gray zones" in futility include withdrawing care because the chance of success is small or because the patient's best outcome would be a low quality of life. Ethics consultations are often required to sort through these complex situations.

Resource Allocation

- Physicians should use health resources judiciously and appropriately (i.e., they should avoid unnecessary tests, medicines, procedures, and consults).

- A physician's primary responsibility is to his/her patient, and larger resource allocation decisions should be made at the societal, policy level.

GAY AND LESBIAN HEALTH

Sexual practices, not orientation, determine the risk of infections and cancers. Patients in homosexual relationships may have had heterosexual relationships in the past (and vice versa), and specific high-risk practices (e.g., receptive anal intercourse) may occur in patients who self-identify as either "gay" or "straight."

Risks

- There is an ↑ risk of anal cancer (caused by HPV) in men who have sex with men (MSM), particularly in those who are HIV ⊕.
- There may be a somewhat ↓ risk of cervical cancer and HPV among women who have sex with women; however, many women who self-identify as lesbian have had sex with men, and rates of HPV infection are significant in this population.
- There is a ↓ risk of gonorrhea, syphilis, and chlamydia among women not having sex with men.
- HIV, gonorrhea, chlamydia, syphilis, HAV, and HBV are ↑ among MSM.

Screening

- **In MSM:**
  - Screen for HIV and HBV.
  - **Urethritis:** Screen for *Neisseria gonorrhoeae* and *Chlamydia trachomatis* urethritis.
  - **Proctitis:** Screen for *N. gonorrhoeae*, *C. trachomatis*, HSV, and syphilis.
  - Offer HBV and HAV vaccines.
  - **Anal Pap smear:** In HIV-⊕ MSM, this test has characteristics similar to those of the cervical Pap.
- **In women who have sex with women,** cervical cancer screening should proceed according to standard guidelines (see the discussion of cancer screening above) even if patients have never had heterosexual contact.

*A highly **Sen**sitive test, when **N**egative, rules **out** the disease **(SnNout).***

*A highly **Sp**ecific test, when **P**ositive, rules* **in** *the disease **(SpPin).***

EVIDENCE-BASED MEDICINE

Major Study Types

Table 2.30 outlines the major types of studies seen in the medical literature.

Test Parameters

Test parameters measure the clinical usefulness of a test. These include the following:

- **Sensitivity (Sn)—"PID" (Positive in Disease):** The probability that a given test will be ⊕ in someone who has the disease in question.
- **Specificity of a test (Sp)—"NIH" (Negative in Health):** The probability that a given test will be ⊖ in someone who does not have the disease in question.

Sensitivity and specificity are characteristics of the diagnostic test itself. They do not depend on the population being tested or on disease prevalence.

TABLE 2.30. Statistical Study Types

Study Type	Explanation	Example	Advantages	Disadvantages
Randomized controlled trial	Intervenes by assigning exposure to subjects and observing disease outcome.	Assigning patients with hypertension to receive one of two treatments: diuretics or ACEIs.	True experiment erases unforeseen confounders. The optimal study type for assessing the effects of a particular intervention/exposure.	Expensive. The study population may be homogeneous, limiting the generalizability of results to the overall population. Small sample sizes limit the power to detect small but potentially important differences between groups.
Cohort study	Identifies exposure subjects and then follows for disease outcomes.	Identifying obese adults and following them for the development of hypertension.	The most robust observational study type; evaluates multiple exposures.	May take a long time to develop disease. Confounding and unmeasured variables may lead to incorrect conclusions.
Case-control study	Identifies cases and noncases of the disease outcome before determining exposure.	Identifying children born with a rare birth defect and looking at possible in utero exposures.	Cheap; fast; good for rare diseases and for generating hypotheses to subject to more rigorous study.	Prone to biases.
Cross-sectional study	Identifies exposure and outcome at the same time for each subject within a specified population.	Checking for hypertension and concurrently obtaining data on obesity in all persons seen in San Francisco county clinics.	Often survey data.	No ability to detect temporal relationship between exposure and outcome.
Systematic review	Summarizes the results of multiple individual trials addressing the same (or similar) research questions.	Qualitative review of all trials of omega-3 fatty acids for the prevention of cardiovascular disease.	Sets forth rigorous criteria to determine which studies will be included or excluded from the review. This helps limit bias in the summary conclusions.	Studies are often too small or too heterogeneous to apply rigorous statistical methods to the summary analysis. Qualitative summary conclusions are substituted for numeric data.
Meta-analysis	A subset of systematic reviews. Quantitative compilation of data from multiple small studies to generate a pooled result.	Cochrane review of all randomized trials comparing glucosamine with placebo or other treatments for patients with OA.	Provides an estimate of treatment effect, including magnitude of effect, when individual studies are too small to derive robust conclusions.	Uses a variety of statistical methods. Different meta-analyses of the same data can produce different results. When component studies are heterogeneous, it is difficult to interpret/use a pooled result.

- **Positive predictive value (PPV):** The probability that a disease is actually present in a person with a ⊕ test result.
- **Negative predictive value (NPV):** The probability that a disease is actually absent in a person with a ⊖ test result.
- **Likelihood ratio (LR):** The proportion of patients **with** a disease who have a certain test result divided by the proportion of patients **without** the disease in question who have the same test result ("**WOWO**"—**W**ith **O**ver **W**ithout).
  - **Example:** A high-probability V/Q scan has an LR of 14. This means that a high-probability V/Q scan is 14 times more likely to be seen in patients **with** pulmonary embolism than in patients **without** pulmonary embolism.

Unlike sensitivity and specificity, the PPV and NPV of a test vary depending on the prevalence of the disease in the population being tested.

Calculating Positive and Negative Predictive Values (PPV and NPV), Likelihood Ratios

Creating a 2 × 2 table of test results and disease status allows one to calculate PPV and NPV, as well as ⊕ and ⊖ LRs, when sensitivity and specificity are known (see Table 2.31).

- Sensitivity = a / a + c.
- Specificity = d / b + d.
- PPV = a / a + b.
- NPV = d / c + d.
- LR (⊕) = (sensitivity) / (1 − specificity).
- LR (−) = (1 − sensitivity) / (specificity).

Although there is no formal cutoff point, a ⊕ LR between 1 and 3 indicates a diagnostic test that is not very useful in ruling in disease. A ⊕ LR > 10 is generally accepted as a highly valuable diagnostic test.

An illustrative example of how to calculate PPV, NPV, and LRs, and how they depend upon disease prevalence, is outlined below.

- For a given disease, the diagnostic test under consideration has the following characteristics:
  - Sensitivity = 90%.
  - Specificity = 95%.
- For this test, then, the **likelihood ratios** of ⊕ and ⊖ results are as follows:
  - LR (+) = 0.90 / (1 − 0.95) = 18.
  - LR (−) = (1 − 0.90) / 0.95 = 0.105.
- Note that because the LRs are far from 1, this test appears to be useful both for ruling disease in and for ruling it out. However, disease prevalence in the population has a crucial effect on test performance, as seen below.
- Suppose the disease prevalence in the population in question is 20%. Given a total population of 1000 individuals, the 2 × 2 table of disease status/test result can be constructed as shown in Table 2.32.

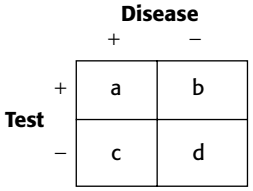
LRs are applied to pretest probabilities (the likelihood, before performing a diagnostic test, that the patient has the disease in question) to either ↑ (⊕ test) or ↓ (⊖ test) the likelihood that disease is present.

TABLE 2.31. Calculating PPV and NPV

	Disease Present	Disease Absent
Test ⊕	True ⊕ **a**	False ⊕ **b**
Test ⊖	**c** False ⊖	**d** True ⊖

TABLE 2.32. 2 × 2 Table, Assuming 20% Disease Prevalence

	Disease Present	Disease Absent	Totals
Test ⊕	180 a	40 b	220
Test ⊖	c 20	d 760	780
Totals	200	800	1000



$$Sn = \frac{a}{a+c}$$

$$Sp = \frac{d}{b+d}$$

- From this table, one can calculate PPV and NPV:
  - PPV = a / a + b = 180/220 = 81.8%.
  - NPV = d / c + d = 760/780 = 97.4%.
- In this population, 81.8% of ⊕ results occur in people who truly do have the disease (true ⊕s), while 97.4% of ⊖ results occur in people who truly do not have the disease (true ⊖s).
- For the same diagnostic test with the same sensitivity and specificity, **if the disease prevalence were 2%, the values in the 2 × 2 table would change** (see Table 2.33). In this population, the PPV and NPV are different:
  - PPV = a / a + b = 18/67 = 26.9%.
  - NPV = d / c + d = 931/933 = 99.8%.
- In this population, only 26.9% of ⊕ results occur in people who truly have the disease; 99.8% of ⊖ results occur in people who truly do not have the disease.
- This example illustrates the fact that when a disease is rare (2% prevalence) in the population being tested, even a fairly sensitive and specific test will have a low PPV. False ⊕s will be far more common than true ⊕s in this population.

$$PPV = \frac{a}{a+b}$$

$$NPV = \frac{d}{d+c}$$

Number Needed to Treat (NNT)

Defined as the number of patients who must receive the treatment in question in order to achieve one additional favorable outcome (or avoid one additional adverse outcome) compared to the control treatment. The lower the NNT, the more effective the treatment. **NNT = 1 / absolute risk reduction.** An example is as follows:

TABLE 2.33. 2 × 2 Table, Assuming 2% Disease Prevalence

	Disease Present	Disease Absent	Totals
Test ⊕	18 a	49 b	867
Test ⊖	c 2	d 931	933
Totals	20	980	1000

- A randomized trial finds that subjects treated with a placebo have a 25% incidence of adverse outcome X. Subjects treated with drug A have a 14% incidence of the same adverse outcome.
- The absolute reduction in risk for adverse outcome X with drug A vs. placebo is 25% – 14% = 11%. Thus, NNT = 1/0.11 = 9.09.
- This means that approximately nine patients would have to be treated with drug A instead of the placebo to prevent one case of adverse outcome X.

Threats to Validity

Table 2.34 and the discussion below delineate factors that can adversely affect the outcome of a statistical study.

- **Lead-time bias:** The time by which a screening test advances the date of diagnosis from the usual symptomatic phase to an earlier, presymptomatic phase. It occurs because the time between diagnosis and death will always ↑ by the amount of lead time (see Figure 2.28).

TABLE 2.34. Threats to the Validity of Statistical Studies

	Explanation	Examples
Confounding	Another variable (confounding factor) is associated with the predictor variable and the outcome variable without being in the causal pathway.	Coffee drinking is associated with a risk of MI. This does not mean that coffee causes MI; rather, coffee drinking (the confounder) is associated with smoking (the true predictor variable), and smoking causes MI.
Measurement (misclassification) biases	When the method of measuring an exposure or outcome misclassifies subjects either at random or in a systematic way. **Random misclassification:** When participants are placed in the wrong group (either with or without exposure/disease) in a random fashion. This biases the results to the null. **Nonrandom misclassification:** When placement into the correct vs. incorrect exposure group is dependent upon disease status. Recall bias is a common type of nonrandom misclassification. **Recall bias:** Self-reporting by study subjects is influenced by knowledge of the study hypothesis, or knowledge of subjects' own disease status.	Misclassification bias occurs if subjects provide inaccurate information. For example, subjects may underreport behaviors perceived as socially unacceptable, such as heavy alcohol use. If the likelihood of underreporting alcohol intake is independent of disease status, random misclassification of subjects occurs. Recall bias: In a case-control study, cancer patients may think harder than healthy controls about past toxic exposures, are more likely to recall them, and are thus more likely to be categorized as "exposed."
Selection bias	Study subjects are selected into (or drop out of) a study in a way that misleadingly changes the degree of association.	Subjects recruited into a study from a subspecialty referral center are more likely to have severe forms of illness than those from a broader community-based sample. Subjects who drop out of a study after recruitment may have different disease characteristics or associations than those who continue the study.

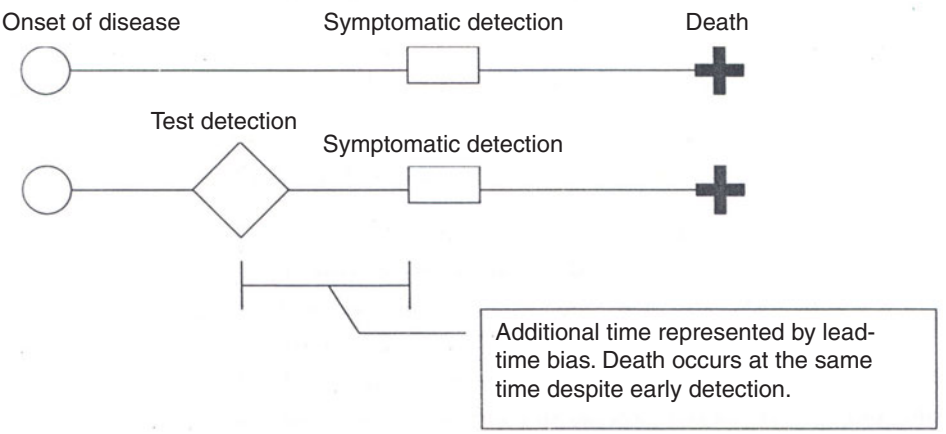


FIGURE 2.28. Lead-time bias.

- **Example:** A new screening test for pancreatic cancer is able to detect disease in a presymptomatic stage.
- Unfortunately, the poor overall prognosis for the disease remains the same. Screened patients know about their diagnosis sooner and live with the disease longer because of this knowledge, but their death is not truly postponed because no treatment exists to alter the outcome for patients diagnosed earlier in the course of illness.

Screen-detected patients will always live longer than clinically detected patients even if early detection and treatment confer no benefit because of lead-time and length-time biases.

- **Length-time bias:** Because cases vary in the lengths of their presymptomatic phase, screening will overdetect cases of slowly progressing disease (longer duration in the asymptomatic phase) and will miss rapidly progressing cases.
  - **Example:** In Figure 2.29, mammography is able to detect two cases of slowly growing breast cancer because of the long period between disease onset and symptoms, but two cases with rapid progression from onset to symptoms are missed. This type of bias occurs with every screening test.
  - Because more slowly progressive cases are more likely to be detected by the screening test, patients with screen-detected disease appear to have better outcomes than those with inherently aggressive disease diagnosed because of symptoms.

Hypothesis Testing

- **p-value:** A quantitative estimate of the probability that a particular study result could occur by chance alone if in fact there is no difference between groups or no treatment effect.
  - A result with a $p < 0.05$ signifies that the probability of the results occurring by chance is < 1 in 20 and is thus considered to be "statistically significant."
  - **Example:** A study finds that treatment A, compared to placebo, causes a 20% reduction in the chance of outcome B, with a p-value < 0.05. This means that if in fact treatment A is no different from a placebo, one would expect to find a treatment effect size of at least 20% in < 5% of trials due to chance alone.

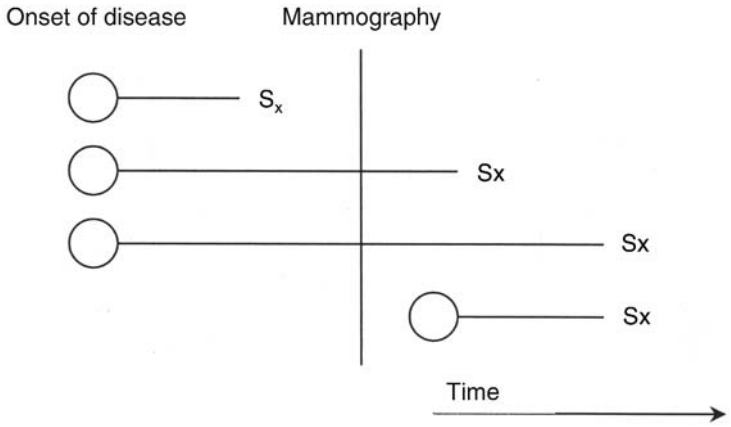


FIGURE 2.29. Length-time bias.

Two cases of breast cancer with brief time between disease onset and symptom appeareance (top and bottom cases) are missed by routine mammography. Two other cases, with longer presymptomatic phases, are detected by mammography.

- **Confidence interval (CI):** If a given study were repeated 100 times, the range into which results would be expected to fall in *x*% of trials is the *x*% CI. In the medical literature, the 95% CI is generally used (i.e., the range into which results would fall in 95 out of 100 repeats of the study in question).
  - **Example:** A study finds that the LR of a diagnostic test is 6.7.
  - The 95% confidence interval for this result is 5.0 – 8.2. This finding is abbreviated as LR = 6.7 (95% CI, 5.0 – 8.2).

A narrower CI around a result indicates a more precise result. Larger studies generally produce narrower CIs.

NOTES

CHAPTER 3

Cardiovascular Disease

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The Physical Exam

Arterial Pulsations

The following are examples of abnormal arterial pulsations and the disorders with which they are associated (see also Figure 3.1):

- **Diminished/exaggerated/asymmetric pulses:**
  - **Diminished pulses:** Atherosclerotic peripheral vascular disease (listen for bruits); conditions associated with low cardiac output (e.g., heart failure, cardiac tamponade, critical aortic stenosis).
  - **Exaggerated pulses:** Aortic regurgitation, coarctation (upper extremities only), patent ductus arteriosus (PDA), hyperthyroidism, arteriovenous fistulas.
  - **Asymmetric pulses:** Severe atherosclerotic vascular disease, aortic dissection, Takayasu's arteritis, coarctation of the aorta (palpate for femoral pulses that are delayed when compared with radial pulses).
- **Carotid pulsations:**
  - **Delayed upstroke:** Aortic stenosis.
  - **Bisferiens pulse:** Two palpable peaks during systole; occurs in mixed aortic stenosis, aortic regurgitation, and hypertrophic cardiomyopathy.
  - **Dicrotic pulse:** Two palpable peaks—one in systole and one in diastole. Most commonly occurs in young patients with severe heart failure and a very low ejection fraction (EF)—e.g., dilated cardiomyopathy 2° to alcoholism.
- **Peripheral pulses:**
  - **Corrigan (water-hammer) pulse:** Occurs in chronic, hemodynamically significant aortic regurgitation. Characterized by a rapid rise and fall of the radial pulse accentuated by wrist elevation.
  - **Pulsus paradoxus:** Defined as a **↓ in BP of > 10 mmHg** during normal inspiration. Occurs in cardiac tamponade, constrictive pericarditis, severe asthma, and COPD.
  - **Pulsus alternans:** Alternation of amplitude with every other heartbeat. Occurs in severe systolic heart failure.

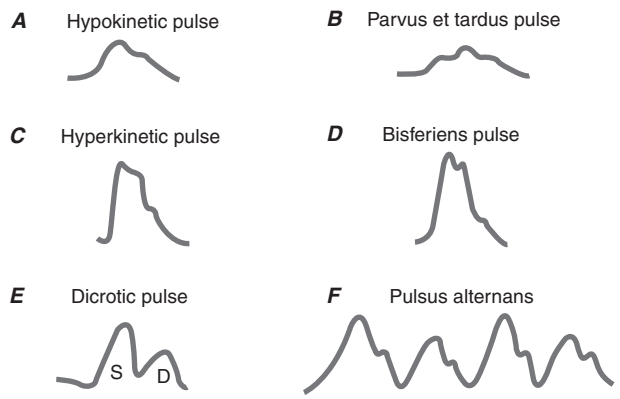


FIGURE 3.1. Arterial pulse waveforms.

(Adapted, with permission, from Fuster V et al. *Hurst's the Heart,* 10th ed. New York: McGraw-Hill, 2001.)

Venous Pulsations

The following are examples of **normal jugular venous pulsations** (see also Figure 3.2):

- **a wave:** Right atrial contraction.
- **c wave:** Closure of the tricuspid valve.
- **x descent:** Atrial relaxation.
- **v wave:** Ventricular systole (with passive venous filling of the atrium).
- **y descent:** Opening of the tricuspid valve with rapid emptying of the right atrium.
- **Jugular venous pressure (JVP):** During inspiration, the JVP declines.

Abnormal patterns of jugular venous pulsations include the following (see also Figure 3.3):

- **Cannon a waves:** Atrioventricular (AV) dissociation (the atrium contracts against a closed tricuspid valve).
- **Large a wave:** Tricuspid stenosis, pulmonary hypertension, pulmonary stenosis.
- **Absent a waves:** Atrial fibrillation (AF).
- **Large c-v wave:** Tricuspid regurgitation.
- **Prominent x descent:** Cardiac tamponade; constrictive pericarditis
- **Rapid y descent:** Constrictive pericarditis; restrictive cardiomyopathy.
- **Blunted y descent:** Tricuspid stenosis; right atrial myxoma (obstruction of right atrial emptying).
- **Absent y descent:** Cardiac tamponade.
- **Kussmaul's sign:** An ↑ in JVP during inspiration. Seen in chronic constrictive pericarditis; occasionally seen in tricuspid stenosis and CHF.

Inspiration (↑ venous return to the right atrium) increases right-sided murmurs but decreases left-sided murmurs.

Heart Murmurs

Table 3.1 illustrates the differential diagnosis of valvular heart disease. Table 3.2 differentiates systolic murmurs on the basis of their response to various physiologic maneuvers.

Heart Sounds

The following are examples of abnormal and normal heart sounds:

- S1:
  - Denotes closure of the mitral and tricuspid valves.
  - Diminished with severe left ventricular systolic dysfunction, mitral regurgitation, and long PR interval.
  - Accentuated with mitral stenosis, short PR interval, and atrial myxoma.
- S2:
  - Denotes closure of the aortic and pulmonic valves.

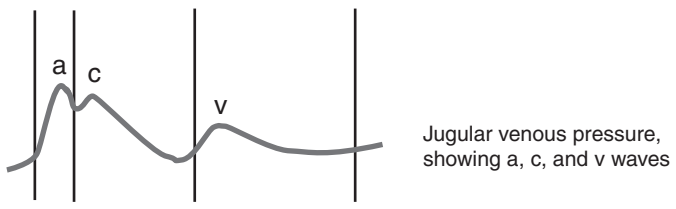


FIGURE 3.2. Normal jugular venous pulse waveforms.

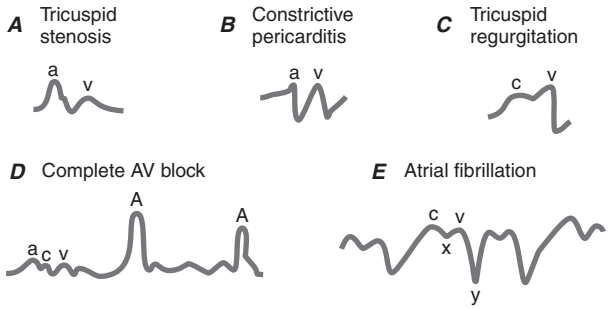


FIGURE 3.3. Abnormal jugular venous pulse waveforms.

a—a positive wave due to contraction of the right atrium. **c**—a positive deflection due to bulging of the tricuspid valve toward the atria at the onset of ventricular contraction. **x**—a negative deflection due to atrial relaxation. **v**—a positive deflection due to filling of the right atrium against the closed tricuspid valve during ventricular contraction. **y**—a negative deflection due to emptying of the right atrium upon ventricular relaxation. (Adapted, with permission, from Fuster V et al. *Hurst's the Heart*, 10th ed. New York: McGraw-Hill, 2001.)

- In normal hearts, the aortic component (A2) comes before the pulmonic component (P2).
- A2 is diminished in severe aortic stenosis.
- **Physiologic splitting:** The time between A2 and P2 widens during inspiration.
- **Normal splitting with loud P2:** Pulmonary hypertension.
- **Fixed splitting:** Atrial septal defect (ASD).
- **Variable/wide splitting:** All causes of right ventricular overload—e.g., pulmonic stenosis, ventricular septal defect (VSD), mitral regurgitation, and right bundle branch block (RBBB)
- **Paradoxical splitting:** ↑ splitting **with expiration.** Etiologies include aortic stenosis, left bundle branch block (LBBB), paced rhythm, and left ventricular systolic dysfunction.

- **S3:**
  - A low-pitched sound heard in diastole just after S2. Usually best heard at the apex.
  - Occurs as a result of sudden limitation of blood flow during ventricular filling.
  - Can be a normal finding in healthy young adults.
  - Abnormal in older adults; suggests elevated filling pressures in early diastole. Associated with enlargement of the ventricle and is typically due to left ventricular systolic dysfunction (but can be seen in diastolic dysfunction). Hemodynamically significant mitral regurgitation is another cause.
  - **A strong predictor of perioperative cardiovascular events.**
- **S4:**
  - A low-pitched sound heard in diastole just before S1.
  - Coincides with atrial systole ("atrial kick").
  - Occurs as a result of a stiff left ventricle with ↑ ventricular filling during atrial systole.
  - A normal finding with advancing age due to loss of ventricular compliance.
  - Pathologic causes include long-standing hypertension, aortic stenosis, hypertrophic cardiomyopathy, and other causes of a stiff left ventricle.
  - **Absent in AF.**

TABLE 3.1. Differential Diagnosis of Valvular Heart Disease

	Mitral Stenosis	Mitral Regurgitation	Aortic Stenosis	Aortic Regurgitation	Tricuspid Stenosis	Tricuspid Regurgitation
Inspection	Malar flush, precordial bulge, and diffuse pulsation in young patients.	Usually prominent and hyperdynamic apical impulse to the left of the midclavicular line (MCL).	Sustained point of maximal impulse (PMI); prominent atrial filling wave.	Hyperdynamic PMI to the left of the MCL and down. Visible carotid pulsations.	Giant a wave in jugular pulse with sinus rhythm. Often olive-colored skin (mixed jaundice and local cyanosis).	Large v wave in jugular pulse.
Palpation	"Tapping" sensation over the area of expected PMI. Mid-diastolic or presystolic thrill at the apex. Small pulse. Right ventricular pulsation in the left third to fifth intercostal space (ICS) parasternally when pulmonary hypertension is present.	Forceful, brisk PMI; systolic thrill over PMI. Pulse normal, small, or slightly collapsing.	Powerful, heaving PMI to the left and slightly below the MCL. Systolic thrill over the aortic area, sternal notch, or carotids. Small and slowly rising carotid pulse.	Apical impulse forceful and displaced significantly to the left and down. Prominent carotid pulses. Rapidly rising and collapsing pulses.	Mid-diastolic thrill between the lower left sternal border and PMI. Presystolic pulsation of the liver (sinus rhythm only).	Right ventricular pulsation. Occasionally systolic thrill at the lower left sternal edge. Systolic pulsation of the liver.
Heart sounds, rhythm, and blood pressure	Loud, snapping M1. Opening snap following S2 along the left sternal border or at the apex. AF is common. BP is normal.	M1 is normal or buried in murmur. Prominent third heart sound. AF is common. BP is normal. Midsystolic clicks may be present.	A2 is normal, soft, or absent. Paradoxic splitting of S2 if A2 is audible. Prominent S4. BP is normal, or systolic pressure is normal with high diastolic.	S1 is normal or reduced; A2 is loud. Wide pulse pressure with diastolic pressure < 60 mmHg.	S1 is often loud.	AF is usually present.

TABLE 3.1. Differential Diagnosis of Valvular Heart Disease *(continued)*

	Mitral Stenosis	Mitral Regurgitation	Aortic Stenosis	Aortic Regurgitation	Tricuspid Stenosis	Tricuspid Regurgitation
Murmurs	Low-pitched, rumbling; presystolic murmur merges with loud M1 and ends at or after A2. Onset at the opening snap ("mid-diastolic") with presystolic accentuation if in sinus rhythm. Localized at or near the apex. Rarely, short diastolic (Graham Steell) murmur along the lower left sternal border.	Blowing, high pitched; occasionally harsh or musical murmur that is pansystolic: begins with M1 and ends at or after A2. Loudest over PMI; transmitted to the left axilla and left infrascapular area.	Harsh, rough-sounding murmur that is classically midsystolic. Begins after M1, ends before A2, and reaches maximum intensity in midsystole. Best heard at the right second ICS parasternally or at the apex; heard in the carotids and occasionally in the upper interscapular area.	Blowing, often faint diastolic murmur that begins immediately after the aortic second sound and ends before the first sound. Louder along the left sternal border in the third to fourth ICS. Heard over the aortic area and apex. May be associated with a low-pitched mid-diastolic murmur at the apex (Austin Flint).	Blowing, high-pitched, occasionally harsh or musical murmur whose onset is mid-diastolic with presystolic accentuation if in sinus rhythm. Best heard at the third to fifth ICS along the left sternal border out to the apex.	Blowing, coarse, or musical murmur that is pansystolic. Begins with M1 and ends at or after A2. Best heard at the third to fifth ICS along the left sternal border out to the apex.
Optimum auscultatory conditions	After exercise, left lateral recumbency.	After exercise. In prolapse, findings are most prominent while standing.	Patient resting, leaning forward; breath held in full expiration.	Patient leaning forward; breath held in expiration.	Murmur is usually louder and at a peak during inspiration. Patient is recumbent.	Murmur usually becomes louder during inspiration.

TABLE 3.1. Differential Diagnosis of Valvular Heart Disease *(continued)*

	Mitral Stenosis	Mitral Regurgitation	Aortic Stenosis	Aortic Regurgitation	Tricuspid Stenosis	Tricuspid Regurgitation
X-ray	Straight left heart border. Large left atrium sharply indenting the esophagus. Elevation of the left main stem bronchus. Large right ventricle and pulmonary artery if pulmonary hypertension is present.	Enlarged left ventricle and left atrium.	Prominent ascending aorta; small knob. Calcified valve is common.	Moderate to severe left ventricular enlargement. Prominent aortic knob.	Enlarged right atrium only.	Enlarged right atrium and ventricle.
ECG	Broad P waves in standard leads; broad ⊖ phase of diphasic P in V_1. If pulmonary hypertension is present, tall, peaked P waves, right axis deviation, or RVH appears. RBBB.	Left axis deviation or frank LVH. P waves are broad, tall, or notched in standard leads. Broad ⊖ phase of diphasic P in V_1.	LVH.	LVH.	Tall, peaked P waves. Normal axis.	Right axis usual.

Adapted, with permission, from Tierney LM et al. *Current Medical Diagnosis & Treatment,* 44th ed. New York: McGraw-Hill, 2005: 318–320.

- **Systolic clicks:**
  - **Aortic ejection click:** A high-frequency sound in early systole. Occurs in the setting of aortic stenosis, aortic regurgitation, and aortic root dilatation (e.g., aneurysm of the ascending aorta, long-standing systemic hypertension).
  - **Pulmonic ejection click:** A high-frequency sound in early systole. ↓ in intensity during inspiration; occurs in the setting of pulmonary stenosis and pulmonary hypertension.
  - **Midsystolic click:** A high-frequency sound that occurs in the middle of systole. Most often due to mitral valve prolapse; may not be associated with a systolic murmur.

TABLE 3.2. Differential Diagnosis of Systolic Murmurs Based on Response to Various Maneuvers[a]

Maneuver	Innocent Flow Murmur	Tricuspid Regurgitation	Aortic Stenosis	Mitral Regurgitation/ VSD	Mitral Valve Prolapse	Hypertrophic Obstructive Cardiomyopathy
Inspiration	– or ↑	↑	–	–	–	–
Standing	↓	–	–	–	↑	↑
Squatting	↑	–	–	–	↓	↓
Valsalva	↓	↓	↓	↓	↑	↑
Handgrip/transient arterial occlusion	↓	–	–	↑	↑	↓
Post-PVC	↑	–	↑	–	–	↑

[a] ↑ or ↓ = change in intensity of murmur; – = no consistent change.

Reproduced, with permission, from Crawford MH. *Current Diagnosis & Treatment in Cardiology,* 2nd ed. New York: McGraw-Hill, 2003: Table 1-2.

- **Additional diastolic sounds:**
  - **Opening snap:** A high-frequency, early diastolic sound most frequently caused by mitral stenosis.
  - **Pericardial knock:** A low-frequency sound due to abrupt termination of ventricular filling in early diastole in the setting of constrictive pericarditis.
  - **Tumor plop:** Occasionally heard in patients with atrial myxoma.

Noninvasive Cardiac Testing

Electrocardiography (ECG)

The following are fundamentals of ECG interpretation:

- **Dimensions (one small box):** Height: 0.1 mV = 1 mm; duration: 40 msec = 1 mm.
- **Rate:** The normal heart rate is 60–100 bpm (300 ÷ number of large boxes = rate).
- **QRS axis:** A normal axis is −30° to +90°. An axis < −30° is left axis deviation; an axis > +90° is right axis deviation. Use QRS in leads I and II to determine axis. Upright in I and II = normal axis; upright in I and downward in II = left axis deviation; downward in I and upright in II = right axis deviation; downward in I and II = extreme axis deviation. **The differential diagnosis of axis deviations (in order of likelihood)** is outlined in Table 3.3.
- **Intervals:**
  - **PR:** Normal 120–200 msec (3–5 small boxes).
  - **QRS:** Abnormal > 120 msec (> 3 small boxes).
  - **QT:** Normal < 1/2 RR interval (rule of thumb).
  - **QTc:** Abnormal > 440 msec.

- **Right atrial abnormality (only one criterion needed):**
  - **Lead II:** P > 2.5 mm (P-wave height > 2.5 small boxes).
  - **Lead V_1:** P > 1.5 mm (P-wave height > 1.5 small boxes).
- **Left atrial abnormality (only one criterion needed):**
  - **Lead II:** P > 120 msec with notches separated by at least one small box.
  - **Lead V_1:** P wave has a ⊖ terminal deflection that is ≥ 40 msec by 1 mm (one small box by one small box).
- **Left ventricular hypertrophy (LVH):** There are numerous criteria for LVH, three of which are listed below. All are specific but insensitive, so fulfillment of one criterion is sufficient for LVH in patients > 35 years of age. ↓ specificity in younger patients (those < 35 years of age).
  - RaVL > 9 mm in women and > 11 mm in men.
  - RaVL + SV_3 > 20 mm in women and > 25 mm in men.
  - SV_1 + (RV_5 or RV_6) > 35 mm.
- **Right ventricular hypertrophy (RVH):** The following findings suggest RVH (there are several others):
  - Right axis deviation.
  - RV_1 + SV_6 > 11 mm (or simply look for a deep S wave in V_6).
  - R:S ratio > 1 in V_1 (in the absence of RBBB or posterior MI).
- **RBBB** (see Figure 3.4):
  - QRS > 120 msec.
  - Wide S wave in I, V_5, and V_6.
  - Second R wave (R′) in right precordial leads, with R′ greater than the initial R (look for "rabbit ears" in V_1 and V_2).
- **LBBB** (see Figure 3.4):
  - QRS > 120 msec, broad R wave in I and V_6, broad S wave in V_1, and a normal axis **or**
  - QRS > 120 msec, broad R wave in I, broad S wave in V_1, RS in V_6, and left axis deviation.
- **Left anterior fascicular block:** There are several sets of criteria for left anterior fascicular block:
  - The axis is more ⊖ than –45°.
  - Q in aVL, and time from onset of QRS to the peak of the R wave is > 0.05 sec.
  - Also look for Q in lead I and S in lead III.
- **Left posterior fascicular block: Must exclude anterolateral MI, RVH, and RBBB:** Axis > 100° and Q in lead III; S in lead I.
- Figure 3.5 illustrates the appearance on ECG of a range of medical conditions and drug effects. Figure 3.6 illustrates wide-complex tachycardia.

TABLE 3.3. Differential Diagnosis of Axis Deviations

Right Axis	Left Axis
RVH	Left anterior fascicular block
Lateral or anterolateral MI	Inferior MI
Wolff-Parkinson-White (WPW) syndrome with left-lateral free wall pathway	WPW with posteroseptal pathway
Left posterior fascicular block	COPD

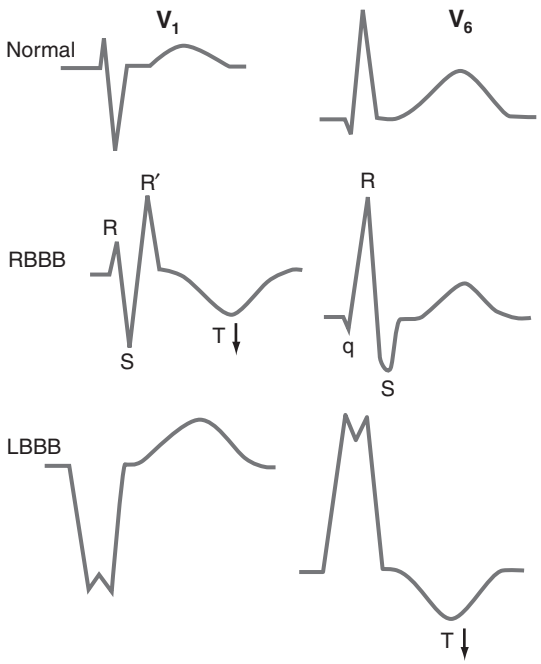


FIGURE 3.4. Bundle branch blocks.

(Reproduced, with permission, from Kasper DL et al. *Harrison's Principles of Internal Medicine*, 16th ed. New York: McGraw-Hill, 2005: 1315.)

Exercise Treadmill Testing

- A screening test for patients with symptoms suggestive of CAD **who have a normal resting ECG** and the ability to undergo vigorous exercise testing.
- Exercise ↑ myocardial O_2 demand and unmasks ↓ coronary flow reserve in patients with hemodynamically significant coronary stenoses.
- ST-segment depression (especially if horizontal or downsloping > 0.1 mV and lasting > 0.08 sec) has very high sensitivity and specificity for CAD if peak heart rate is at least **85%** of the maximum predicted rate (220 – age).
- **False positives** are more common in women and in those with atypical chest pain, no chest pain, and anemia.
- **False negatives** are more common in patients with preexisting CAD.
- An abnormal resting ECG (e.g., digoxin or LVH) may also ↓ the sensitivity and specificity of results.

Exercise treadmill testing (without imaging) in women, especially in premenopausal women, is less specific in predicting CAD compared to tests in men (many false positives). Imaging (e.g., dobutamine echocardiography or nuclear stress testing) is preferred for women.

Echocardiography

- A noninvasive ultrasound imaging modality used to identify anatomic abnormalities of the heart and great vessels; to assess the size and function of cardiac chambers; and to evaluate valvular function.
- **Resting** regional left ventricular wall motion abnormalities (hypokinesis, akinesis) are highly suggestive of ischemic heart disease but can be seen in nonischemic dilated cardiomyopathy. The distribution of wall motion abnormalities suggests the culprit coronary artery.
- **Stress echocardiography:** Used to determine regional wall motion abnormalities in patients with a relatively normal resting echocardiogram and signs or symptoms of ischemic heart disease. Stress with exercise or dobuta-

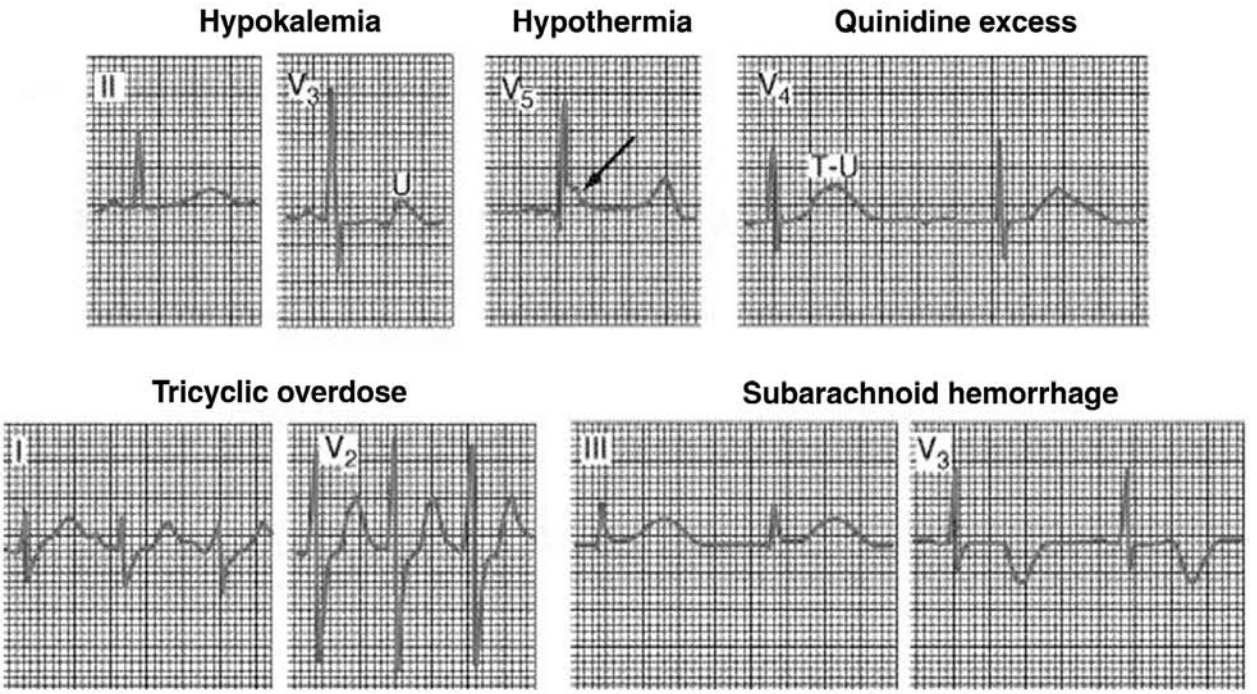


FIGURE 3.5. ECG manifestations of various of medical conditions and drug effects.

(Reproduced, with permission, from Kasper DL et al. *Harrison's Principles of Internal Medicine*, 16th ed. New York: McGraw-Hill, 2005: 1445, as adapted from Braunwald E et al. *Heart Disease: A Textbook of Cardiovascular Medicine*, 6th ed. Philadelphia, PA: Saunders, 2001, with permission from Elsevier.)

mine. **Contraindications** for using dobutamine include uncontrolled hypertension or recent clinically significant arrhythmia.

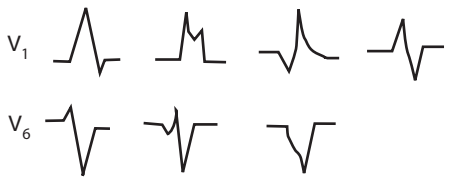
- **Doppler:** Used to investigate blood flow in the heart and great vessels. Very useful for detecting stenotic or regurgitant blood flow across the valves as well as any abnormal communications within the heart. Doppler velocities across a valve can be converted to pressure gradients. Cardiac output and pressure gradient data can be used to calculate stenotic valve areas.
- **Bubble study:** Injection of agitated normal saline to diagnose right-to-left shunts. Consider patent foramen ovale if bubbles flow directly from the right to the left atrium; consider intrapulmonary shunt with delayed appearance of bubbles in the left atrium.
- **Transesophageal echocardiography (TEE):** A small ultrasound probe placed into the esophagus that allows for higher-resolution images, especially of **posterior** cardiac structures (because the esophagus is just posterior to the heart). Common indications include the detection of left atrial thrombi, valvular vegetations, and thoracic aortic dissection.

Myocardial Perfusion Imaging

- A nuclear medicine study that looks for the presence and distribution of areas of myocardial ischemia on the basis of differences in myocardial perfusion.
- Exercise or pharmacologic stress (dipyridamole or adenosine) is used to induce coronary vasodilation, which ↑ flow to the myocardium perfused by

ECG criteria that favor ventricular tachycardia:

1. AV dissociation
2. QRS width: > 0.14 sec with RBBB configuration
   > 0.16 sec with LBBB configuration
3. QRS axis: Left axis deviation with RBBB morphology
   Extreme left axis deviation (northwest axis) with LBBB morphology
4. Concordance of QRS in precordial leads
5. Morphologic patterns of the QRS complex
   RBBB: Mono- or biphasic complex in V_1
   RS (*only with left axis deviation*) or QS in V_6



LBBB: Broad R wave in V_1 or $V_2 \geq 0.04$ sec
Onset of QRS to nadir of S wave in V_1 or V_2 of ≥ 0.07 sec
Notched downslope of S wave in V_1 and V_2
Q wave in V_6

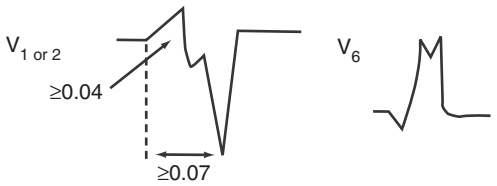


FIGURE 3.6. Wide-complex tachycardia.

(Reproduced, with permission, from Kasper DL et al. *Harrison's Principles of Internal Medicine*, 16th ed. New York: McGraw-Hill, 2005: 1352.)

healthy coronary arteries but fails to ↑ flow in the distribution of a hemodynamically significant stenosis. A **contraindication** to the use of either dipyridamole (Persantine) or adenosine is COPD, as both agents cause bronchoconstriction.

- Perfusion images show defects in areas where blood flow is relatively reduced. If a perfusion defect on the initial (stress) imaging improves on repeat (rest) imaging after 3–24 hours, the area is presumably still viable (i.e., it is a reversible defect).
- A fixed defect suggests myocardial scar tissue. Redistribution images can be performed after 24 hours to look for additional areas of viable myocardium.

Cardiac Catheterization and Coronary Angiography

Cardiac Catheterization Indications

Indications for cardiac catheterization include heart failure, pulmonary hypertension, suspected valvular disease, and congenital heart disease. It is also per-

formed to assess the severity of disease and guide further therapy. Table 3.4 lists contraindications to cardiac catheterization; Table 3.5 outlines patient characteristics associated with ↑ mortality from the procedure.

Coronary Angiography Indications

- **Elective (diagnostic):** For patients with known or suspected CAD who are candidates for coronary revascularization.
- **1°:** Initial reperfusion therapy for acute ST-segment-elevation MI (STEMI).
- **Rescue:** After failed thrombolysis (if there is ongoing chest pain and/or a < 50% ↓ in ST-segment elevation 60–90 minutes after thrombolysis).

Coronary Stents

- Patients treated with coronary stents must be treated with aspirin and **clopidogrel** for at least four weeks for bare-metal stents and for at least six months for drug-eluting stents (newer guidelines suggest treating with clopidogrel for > 1 year to prevent life-threatening stent thrombosis). If there are no contraindications, continuing clopidogrel for one year following stenting ↓ the risk of death and MI.
- Some believe that preprocedural loading with clopidogrel should be avoided if there is a chance that the patient will undergo coronary artery bypass grafting (CABG) in the next 5–7 days (associated with ↑ bleeding complications).
- Drug-eluting stents ↓ the incidence of restenosis with the use of antiproliferative agents (e.g., sirolimus and paclitaxel) but require more prolonged treatment with clopidogrel.

TABLE 3.4. Contraindications to Cardiac Catheterization and Angiography

Contraindication	Comments
Uncontrolled ventricular irritability	↑ risk of ventricular tachycardia and fibrillation during catheterization.
Uncorrected hypokalemia or digitalis toxicity	
Uncorrected hypertension	Predisposes to myocardial ischemia and/or heart failure during angiography.
Intercurrent febrile illness	
Decompensated heart failure	Especially acute pulmonary edema, unless catheterization can be performed with the patient sitting up.
Anticoagulated state	PT > 18 sec.
Severe allergy to radiocontrast agent	
Severe renal insufficiency and/or anuria	Unless dialysis is planned to remove fluid and radiographic contrast load.

Adapted, with permission, from Kasper DL et al. *Harrison's Principles of Internal Medicine,* 16th ed. New York: McGraw-Hill, 2005: 1328.

TABLE 3.5. Characteristics Associated with Increased Mortality from Cardiac Catheterization

VARIABLE	COMMENTS
Age	Infants (< 1 month) and the elderly (> 85 years) are at ↑ risk of death during cardiac catheterization. Elderly women appear to be at higher risk than elderly men.
Functional class	Mortality in class IV patients is > 10 times greater than that of class I–II.
Severity of coronary obstruction	Mortality for patients with left main coronary artery disease is > 10 times greater than that of patients with one- or two-vessel disease.
Valvular heart disease	Especially when severe and combined with coronary disease, associated with a higher risk of death at cardiac catheterization than CAD alone.
Left ventricular dysfunction	Mortality in patients with a left ventricular EF < 30% is > 10 times greater than that of patients with an EF of 50%.
Severe noncardiac disease	Patients with renal insufficiency, insulin-requiring diabetes, advanced cerebrovascular and/or peripheral vascular disease, or severe pulmonary insufficiency have an ↑ incidence of death and other major complications from cardiac catheterization.

Adapted, with permission, from Kasper DL et al. *Harrison's Principles of Internal Medicine,* 16th ed. New York: McGraw-Hill, 2005: 1328.

INDICATIONS FOR CABG

- Left main stenosis.
- Symptomatic two-vessel disease with proximal LAD disease and ↓ EF or ischemia on noninvasive imaging.
- Symptomatic three-vessel CAD.

COMPLICATIONS DURING PERCUTANEOUS CORONARY INTERVENTION (PCI)

- **Coronary arterial complications** include the following:
  - Distal microembolization of the coronary artery (5%).
  - Vessel perforation or dissection (1%).
  - **Abrupt closure (< 1% with stenting):** Of all cases, 75% occur within minutes of angioplasty and 25% within 24 hours. Usually due to dissection or thrombosis. One-third have major ischemic complications requiring emergent revascularization.
  - **Subacute thrombotic occlusion of coronary stent (1–4%) within 2–14 days:** Often results in MI or death.
  - **Gradual restenosis:** Defined as ≥ 50% narrowing of the luminal diameter within 1–6 months. There is a ↓ risk of in-stent restenosis with drug-eluting stents.
- **Other complications** are as follows:
  - Retroperitoneal bleeding.
  - Femoral artery hematoma, pseudoaneurysm, or fistula formation
  - **Contrast nephropathy:** Usually occurs 24–48 hours after contrast load. Diabetes and preexisting renal insufficiency are the most important risk factors. Prevent with pre- and postprocedural hydration. Acetylcys-

teine, ↓ volume of contrast, and low osmolar contrast are other preventive measures.

- **Atheroembolic kidney disease:** Look for eosinophilia, eosinophiluria, hypocomplementemia, and distal embolic complications ("blue toes").
- **Anaphylaxis or allergic reaction to contrast media:** In the presence of known contrast allergy, premedicate with diphenhydramine and steroids.
- **Hyperthyroidism in patients with known (or unknown) Graves' disease or toxic thyroid nodule:** Can present weeks to months after iodinated contrast load.

Cardiac Hemodynamics

Table 3.6 lists the normal values for cardiac hemodynamic parameters.

TABLE 3.6. Normal Values for Cardiac Hemodynamic Parameters

Parameter	Variable	Values
Pressures (mmHg)	**Systemic arterial:**	
	Peak systolic/end-diastolic	100–140/60–90
	Mean	70–105
	Left ventricle:	
	Peak systolic/end-diastolic	100–140/3–12
	Left atrium (or pulmonary capillary wedge):	
	Mean	2–10
	a wave	3–15
	v wave	3–15
	Pulmonary artery:	
	Peak systolic/end-diastolic	15–30/4–12
	Mean	9–18
	Right ventricle:	
	Peak systolic/end-diastolic	15–30/2–8
	Right atrium:	
	Mean	2–8
	a wave	2–10
	v wave	2–10
Resistances ([dyne • s]/cm^5)	Systemic vascular resistance	700–1600
	Pulmonary vascular resistance	20–130
Other measurements	Cardiac index ([L/min]/m^2)	2.6–4.2
	O_2 consumption index ([L/min]/m^2)	110–150
	Arteriovenous oxygen difference (mL/L)	30–50

Adapted, with permission, from Kasper DL et al. *Harrison's Principles of Internal Medicine,* 16th ed. New York: McGraw-Hill, 2005: 1329.

Acute Coronary Syndromes

Acute coronary syndromes encompass STEMI, non-ST-segment-elevation MI (NSTEMI), and unstable angina. Etiologies include unstable plaques with nonocclusive thrombosis (unstable angina and NSTEMI) and thrombotic occlusion of an epicardial coronary artery (STEMI).

Symptoms

Ischemic chest pain is often described as dull or squeezing substernal or left-sided discomfort associated with dyspnea and diaphoresis, with radiation down the left arm or into the neck.

Exam

Acute ischemia may be associated with an S4. Ischemic systolic dysfunction can cause pulmonary edema and an S3. Elevation of jugular venous pulsation is uncommon in the absence of right ventricular involvement.

Differential

Aortic dissection, pulmonary embolism, acute pericarditis, tension pneumothorax.

Diagnosis

- Based primarily on **risk factors** and **initial ECG during chest pain** (see Figure 3.7).
- In patients with chest pain, the initial goal is to rule out STEMI that requires immediate reperfusion therapy.
- In patients without ST-segment elevation, cardiac enzymes will determine if patients have NSTEMI or unstable angina.

Treatment

- **Immediate reperfusion is the goal for STEMI.**
  - 1° PCI is generally preferred if available.
  - Pharmacologic thrombolysis is also considered first-line therapy if administered **within 12 hours** of chest pain onset (especially at medical centers that do not have access to 24-hour PCI).
- Absolute contraindications to thrombolysis are as follows:
  - Active internal bleeding.
  - A history of hemorrhagic stroke.
  - Other strokes within the past year.
  - Known CNS neoplasm.
  - BP > 180/110 despite antihypertensive therapy.
  - Suspected aortic dissection.
- **Medical therapy for NSTEMI and unstable angina** includes the following:
  - Aspirin, β-blockers, ACEIs, and low-molecular-weight or unfractionated heparin. The addition of clopidogrel and glycoprotein IIB/IIIA inhibitors should be considered for high-risk patients.
  - If pain persists despite medical therapy or there is elevation in the troponin level, the patient is at higher risk of an event within six weeks and should proceed to coronary angiography.

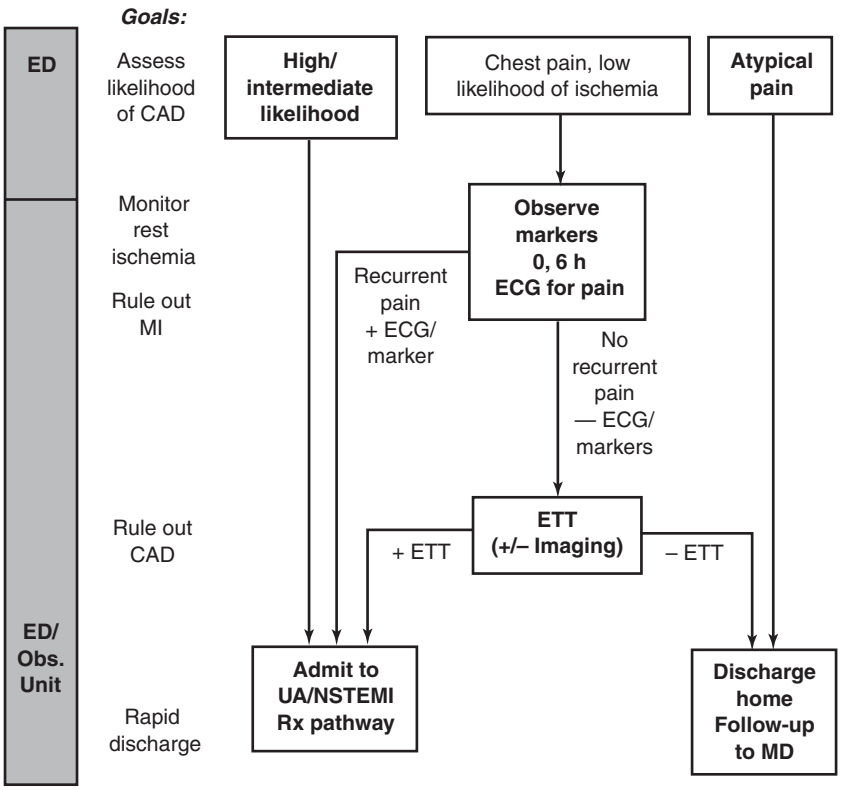


FIGURE 3.7. Evaluation of patients presenting with suspected unstable angina/NSTEMI.

ETT = exercise tolerance test. (Reproduced, with permission, from Kasper DL et al. *Harrison's Principles of Internal Medicine*, 16th ed. New York: McGraw-Hill, 2005.)

- Increasing evidence supports an early aggressive strategy (cardiac catheterization within 48 hours) for moderate- to high-risk patients who present with acute coronary syndromes. Patients with recurrent angina, elevated cardiac biomarkers, or ST-segment depression should be considered for early coronary angiography.

COMPLICATIONS

- **Delayed therapy:** Ischemic arrhythmias (VT/VF); extension of infarction resulting in chronic heart failure.
- **Complications of thrombolysis and aggressive anticoagulation/antiplatelet regimens:** Hemorrhagic stroke, GI bleeding, spontaneous retroperitoneal bleeding.
- **Hemodynamic complications of acute MI:** See Table 3.7.

Complications of Acute Myocardial Infarction

VENTRICULAR SEPTAL DEFECT (VSD)

- Affects 1–2% of patients with acute MI; occurs 3–7 days after MI.
- Presents as acute CHF symptoms with a new systolic murmur and thrill.
- Risk factors include large infarcts, single-vessel disease, poor collateral cir-

TABLE 3.7. Hemodynamic Complications of Acute MI

Condition	Cardiac Index ([L/min]/m²)	PCWP[a] (mmHg)	Systolic BP (mmHg)	Treatment
Uncomplicated	> 2.5	≤ 18	> 100	—
Hypovolemia	< 2.5	< 15	< 100	Successive boluses of normal saline. In the setting of inferior wall MI, consider right ventricular infarction (especially if right atrial pressure > 10).
Volume overload	> 2.5	> 20	> 100	Diuretic (e.g., furosemide 10–20 mg IV). Nitroglycerin, topical paste or IV.
Left ventricular failure	< 2.5	> 20	> 100	Diuretic (e.g., furosemide 10–20 mg IV). IV nitroglycerin (or if hypertensive, use IV nitroprusside).
Severe left venticular failure	< 2.5	> 20	< 100	**If BP ≥ 90:** IV dobutamine +/– IV nitroglycerin or sodium nitroprusside. **If BP < 90:** IV dopamine. **If accompanied by pulmonary edema:** Attempt diuresis with IV furosemide; may be limited by hypotension. If new systolic murmur is present, consider acute VSD or mitral regurgitation.
Cardiogenic shock	< 1.8	> 20	< 90 with oliguria and confusion	IV dopamine. Intra-aortic balloon pump. Coronary angiography may be life-saving.

[a]PCWP = pulmonary capillary wedge pressure.

Reproduced, with permission, from Kasper DL et al. *Harrison's Manual of Medicine,* 16th ed. New York: McGraw-Hill, 2005: 628.

culation, first infarct, and diabetes. Older women are also at ↑ risk.

- **Exam:** Presents as a holosystolic murmur that radiates from left to right over the precordium, heard loudest over the left lower sternal border.
- **Dx:** Echocardiography; right heart catheterization (with a Swan-Ganz catheter) to look for an ↑ in O_2 saturation in the right ventricle compared with the right atrium, IVC, and SVC.
- **Tx:** Vasodilators and surgical correction. If the patient is hypotensive, an intra-aortic balloon pump (IABP) can serve as a bridge until surgical intervention can be performed.

Papillary Muscle Rupture

- Affects 1% of patients with acute MI; occurs 2–7 days after MI. Presents as sudden acute pulmonary edema.
- Risk factors include inferior MI and VSD.
- **Exam:** Presents as a new systolic murmur, heard loudest at the apex, that

radiates to the axilla. The intensity of the murmur does not correlate with the severity of mitral regurgitation.
- **Dx:** Echocardiography; right heart catheterization.
- **Tx:** Vasodilators and surgical correction. If the patient is hypotensive, an IABP can serve as a bridge until surgical intervention can be performed.

Left Ventricular Free Wall Rupture

- **Affects** < 1% of patients with acute MI; accounts for up to 15% of early MI deaths. Occurs 5–14 days after MI or earlier in patients who receive thrombolysis.
- The classic presentation is that of nausea followed by hypotension, shock, and death.
- Risk factors include transmural MI, first MI, single-vessel disease, lack of collaterals, and female gender.
- **Exam:** Presents as acute decompensation related to cardiac tamponade (elevated JVP, pulsus paradoxus, diminished heart sounds).
- **Dx:** Echocardiography; right heart catheterization.
- **Tx:** Urgent pericardiocentesis and thoracotomy. **Cardiac rupture is a true cardiothoracic surgical emergency.**

Cardiogenic Shock

- Risk factors include anterior MI, diabetes, and older age.
- **Exam:** Look for signs of heart failure with associated hypotension. ↓ urine output is common.
- **Dx:** CXR, echocardiography, right heart catheterization.
- **Tx:** Revascularization, IABP, ventilatory support, dopamine/dobutamine.

Left Ventricular Aneurysm

- Affects 10–30% of patients after acute MI; incidence is decreasing in the era of PCI. Can occur acutely, but most are chronic and persist for > 6 weeks after MI. Anterior MI is a risk factor.
- **Exam:** Exam reveals a large, diffuse PMI; S3 may be present.
- **Dx:** ECG (Q waves in V_{1-3} with persistent ST-segment elevation), echocardiography, cardiac MRI.
- **Tx:**
  - **Acute:** Treat associated cardiogenic shock.
  - **Chronic:** Anticoagulate with heparin/warfarin if mural thrombus is present; consider a defibrillator if the left ventricular EF is < 35% or there are documented ventricular arrhythmias.
- **Prevention:** Early revascularization.

Early Pericarditis

- Affects 10% of patients with acute MI; occurs 1–4 days after MI. Transmural MI is a risk factor.
- **Sx:** Pain worsens when patients are supine and radiates to the trapezius ridge.
- **Exam:** Presents with a pericardial friction rub.
- **Dx:** ECG may show evidence of pericarditis; echocardiography may reveal pericardial effusion.

- **Tx:** Aspirin. Avoid NSAIDs and corticosteroids, which may interfere with the healing of infarcted myocardium. Avoid heparin to ↓ the risk of pericardial hemorrhagic transformation.

Late Pericarditis (Dressler's Syndrome)

- Affects 1–3% of patients with acute MI; thought to be 2° to immune-mediated injury. Occurs 1–8 weeks after MI.
- **Exam:** Presents with a pericardial rub and with fever.
- **Dx:** ECG may show evidence of pericarditis; echocardiography may show pericardial effusion.
- **Tx:** Aspirin. If > 4 weeks after MI, NSAIDs and/or corticosteroids can be used.

Arrhythmias

- Can occur at any time post-MI. Reperfusion arrhythmias within 24–48 hours of MI generally do not mandate aggressive therapy.
- **Dx:** ECG, telemetry. **Routine electrophysiologic or signal-average ECG testing is not recommended.**
- **Tx:** If ventricular arrhythmias persist > 48 hours post-MI and are symptomatic or hemodynamically significant, implantation of a defibrillator is more effective than antiarrhythmics.

Ischemic Complications

- Infarct extension, postinfarction angina, or reinfarction.
- **Dx/Tx:** Cardiac catheterization with PCI when indicated.

Embolic Complications

- Nonhemorrhagic stroke occurs in approximately 1% of patients post-MI. Occurs within 10 days after MI.
- Risk factors include anterior MI, large MI, and left ventricular aneurysm.
- **Exam:** Depends on the site of embolization. Look for signs of stroke or signs of limb or intestinal ischemia.
- **Tx:** Anticoagulation with heparin/warfarin.

Cardiogenic Shock

Occurs in approximately 5–7% of patients with acute MI and is the **leading cause of death related to acute MI.** See Figure 3.8 for the approach to hypotensive patients with acute MI. Etiologies are as follows:

- **Left ventricular systolic dysfunction:** The most common cause of cardiogenic shock (75% of patients).
- **STEMI:** Causes cardiogenic shock more frequently than does NSTEMI.
- **Acute, severe valvular insufficiency:** Most often due to acute mitral regurgitation.
- Isolated right ventricular MI.
- Cardiac tamponade.
- Left ventricular free wall rupture.
- Ventricular septal rupture.

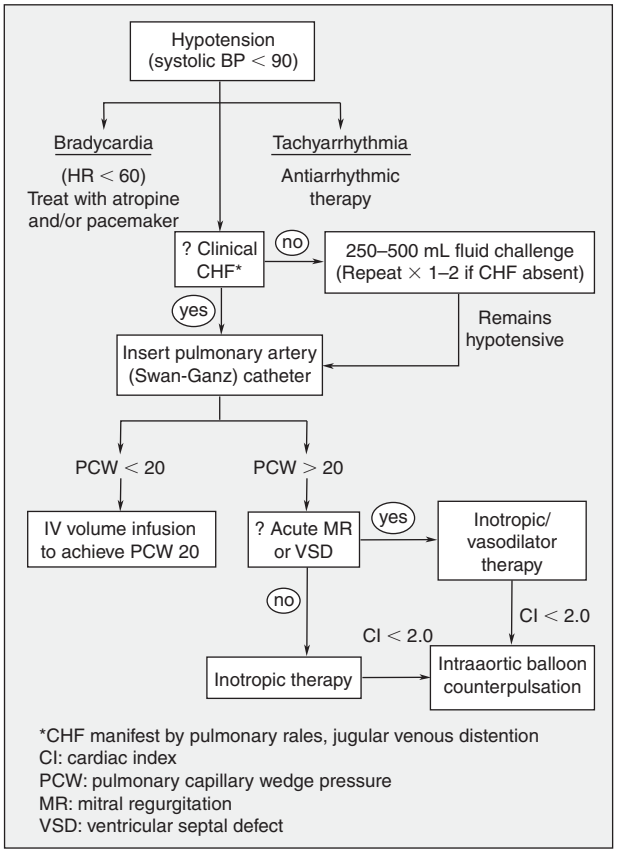


FIGURE 3.8. Approach to hypotensive patients with acute MI.

(Reproduced, with permission, from Braunwald E et al. *Harrison's Principles of Internal Medicine*, 15th ed. New York: McGraw-Hill, 2001.)

- **Left ventricular outflow tract obstruction:** Aortic stenosis; hypertrophic cardiomyopathy.
- **Obstruction to left ventricular filling:** Mitral stenosis; left atrial myxoma.

Symptoms/Exam

- Hypotension (systolic BP < 90 mmHg) or relative hypotension (a ↓ in systolic BP > 30 mmHg in a chronically hypertensive patient). Note that some patients with severe end-stage heart failure will have chronically low BP; look for evidence of hypoperfusion in these patients.
- Tachycardia.
- Hypoperfusion (cyanosis, poor peripheral pulses) despite adequate filling pressures.
- Dyspnea.
- Altered mental status (acute delirium).
- ↓ urine output.

Treatment

- If the underlying etiology is ischemic, proceed immediately to revascularization (PCI or CABG).

- Urgent revascularization is superior to medical management (thrombolysis) alone.
- **Supportive care** includes vasopressors, mechanical ventilation, and IABP counterpulsation.
  - Vasopressor therapy usually consists of dopamine and dobutamine. Norepinephrine can also be used in cases of refractory hypotension.
  - Placement of an IABP ↓ afterload and improves coronary perfusion in diastole. It is contraindicated in patients with severe peripheral vascular disease and hemodynamically significant aortic insufficiency.
- For ischemia-induced cardiogenic shock, nitrates and nitroprusside can be used, but only with extreme caution. IABP is a more effective therapy for coronary ischemia in these patients.
- Ventricular assist devices can serve as a bridge to cardiac transplantation.

Chronic Stable Angina

The hallmark is chronic, reproducible, exercise-induced chest discomfort that is relieved by rest and nitroglycerin. Unlike unstable angina and MI, stable angina is thought to involve a **fixed** coronary stenosis that limits myocardial O_2 delivery; angina results when demand outstrips supply. The most important CAD risk factors are diabetes, smoking, hyperlipidemia, hypertension, age, and a family history of premature CAD.

Symptoms

Ischemic chest pain is often described as dull or squeezing substernal or left-sided discomfort associated with dyspnea and diaphoresis, with radiation down the left arm or into the neck.

Exam

No specific exam findings can rule in or rule out CAD as a cause of chest pain.

Differential

GERD, esophageal spasm, herpes zoster, chest wall pain, costochondritis, coronary vasospasm.

Diagnosis

- Noninvasive stress testing with or without imaging (nuclear imaging or echocardiography).
- Invasive cardiac catheterization (angiography) is the gold standard.

Treatment

- **Risk factor reduction:** Includes smoking cessation and aggressive treatment of hypertension, hyperlipidemia, and diabetes (see the Ambulatory Medicine chapter).
- **Antianginal medical therapy:** Nitrates, β-blockers, calcium channel blockers.
- **2° prevention:** Aspirin, statins, and ACEIs have been shown to reduce cardiovascular events in patients with chronic CAD.
- **Revascularization:** PCI or CABG.

Flow-limiting stenoses that are responsible for stable angina are less likely to rupture and cause acute coronary syndromes than nonocclusive unstable plaques.

- **Enhanced external counterpulsation (EECP):** Used in patients whose angina is refractory to medical therapy and in whom revascularization is not possible.

Complications

Reduction in quality of life; limitation of activities of daily living.

Diagnostic Strategies and Risk Stratification for Chest Pain

Evaluation of Patients with Chest Pain

- The most important single test in the initial evaluation of patients with chest pain is the **ECG,** which should be obtained and interpreted within the first five minutes of presentation.
- The history, physical exam, and initial laboratory and radiographic assessment should focus on **excluding life-threatening causes of chest pain** (acute ischemic heart disease, aortic dissection, acute pericarditis, pulmonary embolism, tension pneumothorax, esophageal rupture).
- Troponins and CK-MB biomarkers typically become elevated **6–8 hours** after the onset of chest pain. Troponins remain elevated for several days; therefore, in patients with a recent MI, checking CK-MB can be useful to look for recurrent MI.

Acute Treatment

- All patients with chest pain should receive O_2, and an IV should be placed.
- Unless contraindicated, all patients with chest pain presumed to be ischemic in etiology should receive aspirin, β-blockers, nitrates, and heparin during the initial evaluation.

Risk Stratification

- All patients who present with chest pain should be risk stratified according to the presence or absence of coronary **risk factors** (e.g., older age, hypertension, DM, hyperlipidemia, smoking, a family history of premature CAD, chronic renal insufficiency).
- As the number of risk factors ↑, the likelihood that the patient's chest pain is ischemic in origin ↑ as well (even if the chest pain is atypical).
- Guidelines for stress testing are as follows:
  - High-risk patients with chest pain (e.g., ST-segment elevation on ECG or the presence of heart failure in the setting of ischemia or ⊕ biomarkers) should proceed directly to cardiac catheterization.
  - Lower-risk patients with a high likelihood of ischemia (as determined primarily by the presence of coronary risk factors, a history of CAD, ECG findings, or a ⊕ troponin result) should undergo future cardiac stress testing (ideally prior to discharge from the hospital).
  - Patients with an elevated troponin level and two or more high-risk prognostic variables (age ≥ 65 years, three or more traditional CAD risk factors, documented CAD with ≥ 50% stenosis, ST-segment deviation, two or more anginal episodes within the last 24 hours, ⊕ biomarkers, or aspirin use within the last week) should undergo cardiac catheterization within 24 hours.

Management of Coronary Artery Disease

Risk Factor Reduction

- **Modifiable CAD risk factors** such as DM, hypertension, hyperlipidemia, and smoking should be aggressively treated.
- Other risk factors (e.g., chronic renal insufficiency, cocaine use) should also be addressed.

Diabetes mellitus is now considered a CAD equivalent.

Pharmacologic Therapy

- **Aspirin:** ↓ mortality. Give 81 mg daily. If aspirin is absolutely contraindicated, clopidogrel can be used effectively.
- **Clopidogrel:** ↓ mortality in patients who have had recent acute coronary syndromes or who have had a coronary stent placed.
- **Statins:** ↓ mortality and the risk of acute cardiac events. Recent guidelines state that LDL should be < 100 mg/dL in patients with a history of CAD. However, recent trials indicate that patients may have better outcomes with even lower LDL levels (the newest guidelines indicate that LDL should be < 70 mg/dL in patients with a history of CAD).
- **β-blockers:** ↓ mortality. **All patients with CAD** should be on β-blockers unless absolutely contraindicated. In patients with reactive airway disease, cardioselective β-blockers should be tried and discontinued only if bronchospasm occurs. **DM is not a contraindication to β-blocker use.**
- **ACEIs:** ↓ mortality and the risk of MI and stroke. If not tolerated, an angiotensin receptor blocker should be prescribed.

Indications for Elective Revascularization

- Chronic stable angina with three-vessel disease.
- Two-vessel disease with proximal left anterior descending artery involvement.
- One- or two-vessel disease with high-risk features on noninvasive testing.
- Significant left main CAD (> 50% stenosis).
- Refractory symptoms of chronic angina.

CONGESTIVE HEART FAILURE (CHF)

Table 3.8 and the discussion that follows outline the stages, types, and clinical characteristics of CHF.

Systolic vs. Diastolic Dysfunction

Most patients with heart failure have a combination of systolic and diastolic dysfunction of the left ventricle.

Heart Failure with Systolic Dysfunction

- Clinically defined as evidence of a ↓ EF (by physical exam or echocardiogram) in the setting of symptoms and signs of heart failure.
- Affects all ages; more common in males. CAD is present in approximately 70% of patients with reduced systolic dysfunction.
- **Exam:** S3 is present.

TABLE 3.8. Stages of Heart Failure

Stage	Description
Stage A	Patients who are at risk of developing heart failure because of comorbid conditions that are strongly associated with the development of heart failure. Such patients have no signs or symptoms of heart failure and have never manifested signs or symptoms of heart failure. There are no structural or functional abnormalities of the valves or ventricles. Examples include systemic hypertension, CAD, and DM.
Stage B	Patients who have developed structural heart disease that is strongly associated with the development of heart failure but have no symptoms of heart failure and have never manifested signs or symptoms of heart failure. Examples include LVH; enlarged, dilated ventricles; asymptomatic valvular heart disease; and previous MI.
Stage C	Patients who have current or prior symptoms of heart failure associated with underlying structural heart disease. Represents the largest group of patients with clinical evidence of heart failure.
Stage D	Patients who have marked symptoms of heart failure at rest despite maximal medical therapy and who require specialized interventions. Examples include patients who cannot be safely discharged from the hospital, are repeatedly hospitalized, are in the hospital awaiting heart transplantation, are residing in a hospice setting, are living at home and receiving continuous IV support for symptom relief, or are being supported with a mechanical circulatory assist device.

Derived from the 2001 American College of Cardiology/American Heart Association (ACC/AHA) guidelines. Adapted, with permission, from Fuster V et al. *Hurst's the Heart,* 11th ed. New York: McGraw-Hill, 2004.

- **Dx:** Echocardiogram shows ↓ EF (≤ 40%) with an enlarged, dilated left ventricle.

Heart Failure with Diastolic Dysfunction

- Clinically defined as a normal EF (by echocardiogram) in the setting of symptoms and signs of heart failure.
- Affects elderly patients; occurs more often in females. Comorbidities include hypertension, DM, obesity, obstructive sleep apnea, and chronic kidney disease.
- Most patients will have diastolic dysfunction as the primary underlying pathophysiology.
- **Exam:** S4 is present (S3 may be present in patients with significantly elevated left ventricular filling pressures).
- **Dx:** Echocardiogram shows a normal or near-normal EF (> 50%); LVH is common.

Diastolic Dysfunction

Very common. Often coexists with systolic dysfunction; frequently associated with hypertension and ischemic heart disease. Diastolic dysfunction (based on echocardiographic findings) does not equal diastolic heart failure. Many patients have asymptomatic diastolic dysfunction (which is a risk factor for future morbidity and mortality), but diastolic heart failure denotes symptomatic heart failure in the setting of diastolic dysfunction. Etiologies are as follows:

- **Myocardial:** Impaired relaxation (ischemia, hypertrophy, cardiomyopathies, hypothyroidism, aging); ↑ passive stiffness (diffuse fibrosis, scarring, hypertrophy, infiltrative).
- **Endocardial:** Fibrosis; mitral stenosis.
- **Pericardial:** Constrictive pericarditis; cardiac tamponade.
- **Other:** Volume overload of the right ventricle; extrinsic compression (e.g., tumor).

In patients with isolated diastolic dysfunction, always consider underlying myocardial or pericardial causes of a stiff left ventricle (e.g., infiltrative diseases, constrictive pericarditis, restrictive cardiomyopathies).

Symptoms

Indistinguishable from systolic dysfunction on the basis of symptoms. May be asymptomatic, although patients have higher mortality when compared to controls.

Exam

- Look for evidence of heart failure (elevated jugular venous pulsations, crackles on lung exam, lower extremity edema).
- On cardiac exam, listen for an S4. **An S3 can be present when left ventricular filling pressures are severely elevated** (the presence or absence of S3 and/or S4 cannot be used to distinguish systolic from diastolic dysfunction).

Diagnosis

- There is no gold standard for diagnosis.
- **Echocardiography:** Shows a **normal EF** in the setting of signs and symptoms of heart failure. Also look for other clues of diastolic dysfunction (abnormal mitral inflow pattern, LVH, RVH/enlargement, left atrial enlargement) or causes of diastolic dysfunction (pericarditis, infiltrative diseases).
- **Cardiac catheterization:** Demonstrates an elevated A wave in left ventricular pressure tracing (represents left atrial contraction) and elevated left ventricular end-diastolic pressure (≥ 15 mmHg).

Treatment

- **No treatment has been convincingly shown to reduce mortality in patients with diastolic heart failure. Only one trial showed a ↓ in morbidity with angiotensin receptor blockers.**
- **Avoid exacerbating factors:** AF, tachycardia, ischemia, hypertension, fluid overload, anemia. **Aggressively control hypertension.**
- ACEIs and angiotensin receptor blockers may aid in cardiac remodeling.
- **Diuresis and slowing the heart rate:** β-blockers; nondihydropyridine calcium channel blockers (e.g., diltiazem, verapamil) may help symptoms but have not been proven to ↓ mortality. Use caution in patients with advanced diastolic heart failure, who may need preload and/or chronotropy to maintain cardiac output.

Treatment of Congestive Heart Failure

Systolic Dysfunction

- **Diuretics:** Acutely used to reduce symptoms of pulmonary edema; confer **no mortality benefit.** Maintenance doses of diuretics may need to be weight adjusted.

Even with maximal medical therapy (e.g. ACEIs, β-blockers), patients with an EF < 30% still have a ↓ in sudden death with placement of an implantable cardioverter-defibrillator (ICD).

- **ACEIs:** Have a proven **mortality benefit.** If ACEIs are not tolerated because of cough, substitute an angiotensin receptor blocker.
- **Hydralazine with nitrates:** Useful in an acute setting to reduce pulmonary edema by decreasing preload. Associated with a **mortality benefit** when used, but confers less benefit than ACEIs.
- **Spironolactone:** Yields a **mortality benefit** in class III–IV heart failure.
- **β-blockers:** Confer a **mortality benefit** in all classes of heart failure. However, do not start in the setting of acutely decompensated heart failure. Proven benefit is limited to carvedilol, bisoprolol, and long-acting metoprolol.
- **B-type natriuretic peptide (nesiritide):** Acts primarily as a vasodilator. Can be considered in severe heart failure requiring vasodilator therapy when nitroprusside or nitroglycerin are contraindicated. May provide additional improvement in symptoms, but may be associated with ↑ renal dysfunction and possibly ↑ mortality.
- **Mechanical therapy:** For severe heart failure due to ischemia, consider an IABP. For very poor cardiac output, consider a ventricular assist device as a bridge to cardiac transplantation.
- **Cardiac resynchronization: Mortality benefit.** Pacemaker-based therapy (with leads in the right atrium, the right ventricle, and a branch of the coronary sinus to pace the left ventricle) is used in patients with severe systolic heart failure (NYHA Class III–IV), EF < 35%, and a wide QRS (> 120 msec) on ECG. Improves ventricular synchrony and cardiac output.
- **Cardiac transplantation:** See Table 3.9.

TABLE 3.9. Indications and Contraindications for Cardiac Transplantation

VARIABLE	CRITERIA
Indications	1. End-stage heart disease that limits the prognosis for survival > 2 years or severely limits daily quality of life despite optimal medical and other surgical therapy. 2. No 2° exclusion criteria. 3. Suitable psychosocial profile and social support system. 4. Suitable physiologic/chronologic age.
Exclusion criteria	1. Active infectious process. 2. Recent pulmonary infarction. 3. Insulin-requiring diabetes with evidence of end-organ damage. 4. Irreversible pulmonary hypertension (pulmonary vascular resistance [PVR] poorly responsive to nitroprusside with PVR > 2 or pulmonary systolic pressure > 50 mmHg at peak dose or at mean arterial pressure of 65–70 mmHg). 5. Presence of circulating cytotoxic antibodies. 6. Presence of active PUD. 7. Active or recent malignancy. 8. Presence of severe COPD or chronic bronchitis. 9. Substance or alcohol abuse. 10. Presence of peripheral or cerebrovascular disease. 11. Other systemic diseases that would jeopardize rehabilitation post-transplant.

Adapted, with permission, from Braunwald E et al. *Harrison's Principles of Internal Medicine,* 15th ed. New York: McGraw-Hill, 2001.

See the discussion of systolic vs. diastolic function above.

CARDIOMYOPATHIES AND MYOCARDITIS

Tables 3.10 through 3.12 and the discussion below outline the etiologies, classification, and evaluation of cardiomyopathies.

Restrictive Cardiomyopathy

Infiltration or fibrosis of the myocardium causing impaired ventricular filling with preserved systolic function. In end-stage disease, systolic dysfunction may develop. Causes include amyloidosis, sarcoidosis, hemochromatosis, scleroderma, radiation, and fibrosis following cardiac surgery.

SYMPTOMS

Patients present with dyspnea, fatigue, and peripheral edema.

EXAM

Exam reveals an elevated JVP that ↑ with inspiration (**Kussmaul's sign**) and a normal left ventricular impulse; hepatosplenomegaly and ascites are seen in advanced disease.

DIFFERENTIAL

- **Hypertrophic cardiomyopathy.**
- **Dilated cardiomyopathy.**
- **Constrictive pericarditis:** Clinical presentation and physical exam may yield findings identical to those of restrictive cardiomyopathy. MRI shows pericardial thickening (> 5 mm), and right heart catheterization demonstrates equalization of diastolic pressures in constrictive pericarditis. See Table 3.13 for differentiating features of constrictive pericarditis and restrictive cardiomyopathy.

Restrictive cardiomyopathy causes severe diastolic dysfunction with preserved ejection fraction.

DIAGNOSIS

- **ECG:** Shows conduction system disease, low QRS voltage, and nonspecific ST-T-wave changes.
- **Echocardiography:** Demonstrates a restrictive filling pattern with preserved systolic function and biatrial enlargement. Infiltrative causes can present with the characteristic granular appearance of myocardium.
- **Right heart catheterization:** Dip-and-plateau ventricular filling pressure ("**square root sign**"), pulmonary hypertension, respiratory concordance of the right and left ventricles.
- **Myocardial biopsy:** Detects infiltrative diseases such as amyloidosis and sarcoidosis.

TREATMENT

- **Treat the underlying disease process** (e.g., amyloidosis, sarcoidosis).
- **Diuretics:** Reduce symptoms from venous congestion, but **overdiuresis leads to ↓ cardiac output due to preload dependence.**
- **β-blockers/calcium channel blockers:** May improve diastolic function early in disease process by slowing heart rate and increasing ventricular fill-

TABLE 3.10. Etiologic Classification of Cardiomyopathies[a]

1° Myocardial Involvement	2° Myocardial Involvement
Idiopathic (D, R, H)	Infective (D):
Familial (D, R, H)	Viral, bacterial, fungal, protozoal, metazoal myocarditis
Eosinophilic endomyocardial disease (R)	Spirochetal disease
	Rickettsial disease
Endomyocardial fibrosis (R)	Metabolic (D)
	Familial storage disease (D, R):
	Glycogen storage disease (D, R)
	Mucopolysaccharidoses
	Hemochromatosis
	Fabry's disease
	Deficiency (D):
	Electrolytes
	Nutritional
	Connective tissue disorders (D):
	SLE
	Polyarteritis nodosa
	RA
	Progressive systemic sclerosis
	Dermatomyositis
	Infiltrations and granulomas (R, D):
	Amyloidosis
	Sarcoidosis
	Malignancy
	Neuromuscular (D):
	Muscular dystrophy
	Myotonic dystrophy
	Friedreich's ataxia (H, D)
	Sensitivity and toxic reactions (D):
	Alcohol
	Radiation
	Drugs
	Peripartum heart disease (D)

[a] The principal clinical manifestations of each etiologic grouping are denoted by D (dilated), R (restrictive), or H (hypertrophic) cardiomyopathy.

Adapted, with permission, from Kasper DL et al. *Harrison's Principles of Internal Medicine,* 16th ed. New York: McGraw-Hill, 2005: 1408. As adapted from the WHO/ISFC task force report on the definition and classification of cardiomyopathies, 1980.

ing time. Caution should be used in administration, as this may result in a fall in cardiac output. **Avoid use of calcium channel blockers in amyloid heart disease because they can cause significant negative chronotropy.**

- **Cardiac transplantation:** Remains an option for patients with intractable heart failure without severe systemic disease.

TABLE 3.11. Clinical Classification of Cardiomyopathies

CATEGORY	CHARACTERISTICS
Dilated	Left and/or right ventricular enlargement, impaired systolic function, CHF, arrhythmias, emboli.
Restrictive	Endomyocardial scarring or myocardial infiltration resulting in restriction to left and/or right ventricular filling.
Hypertrophic	Disproportionate LVH, typically involving the septum more than the free wall, with or without an intraventricular systolic pressure gradient; usually of a nondilated left ventricular cavity.

Adapted, with permission, from Kasper DL et al. *Harrison's Principles of Internal Medicine,* 16th ed. New York: McGraw-Hill, 2005: 1408.

Hypertrophic Cardiomyopathy (HCM)

An autosomal-dominant disorder of myocardial structural proteins that causes premature, severe LVH. A subset of hypertrophic cardiomyopathy cases may have asymmetric septal hypertrophy and dynamic outflow tract obstruction.

TABLE 3.12. Evaluation of Cardiomyopathies

	DILATED	RESTRICTIVE	HYPERTROPHIC
CXR	Moderate to marked cardiac silhouette enlargement; pulmonary venous hypertension.	Mild cardiac silhouette enlargement.	Mild to moderate cardiac silhouette enlargement.
ECG	ST-segment and T-wave abnormalities.	Low voltage, conduction defects.	ST-segment and T-wave abnormalities; LVH; abnormal Q waves.
Echocardiogram	Left ventricular dilatation and dysfunction.	↑ left ventricular wall thickness; normal or mildly reduced systolic function.	Asymmetric septal hypertrophy; systolic anterior motion of the mitral valve.
Radionuclide studies	Left ventricular dilatation and dysfunction (RVG).[a]	Normal or mildly reduced systolic function (RVG).	Vigorous systolic function (RVG); perfusion defect (^{201}Tl).[a]
Cardiac catheterization	Left ventricular dilatation and dysfunction; elevated left- and often right-sided filling pressures; diminished cardiac output.	Normal or mildly reduced systolic function; elevated left- and right-sided filling pressures.	Vigorous systolic function; dynamic left ventricular outflow obstruction; elevated left- and right-sided filling pressures.

[a] RVG = radionuclide ventriculogram; ^{201}Tl = thallium 201.

Reproduced, with permission, from Kasper DL et al. *Harrison's Principles of Internal Medicine,* 16th ed. New York: McGraw-Hill, 2005: 1409.

TABLE 3.13. Constrictive Pericarditis vs. Restrictive Cardiomyopathy and Cardiac Tamponade

	Constrictive Pericarditis	Restrictive Cardiomyopathy	Cardiac Tamponade
History	TB, cardiac surgery, radiation therapy, collagen vascular disease, trauma, prior pericarditis.	Amyloidosis, hemochromatosis, sarcoidosis.	Prior pericardial effusion, cardiac surgery, malignancy (e.g., breast cancer), recent MI.
Physical exam			
Pulsus paradoxus	May be present.	Rare.	Frequent.
JVP	Prominent x and y descents; Kussmaul's sign may be present.	Prominent x and y descents; Kussmaul's sign may be present.	Absent or diminished y descent.
Heart sounds	Pericardial knock.	Prominent S4.	Muffled.
Murmurs	Not typically present.	Mitral and tricuspid regurgitation often present.	Not typically present.
ECG	Nonspecific.	Right or left atrial enlargement; AV conduction delay; bundle branch block.	Low voltage; electrical alternans.
CXR	Pericardial calcification.	Nonspecific.	Cardiomegaly.
Echocardiography	Pericardial thickening; pericardial effusion may be present; ventricular septal flattening with inspiration.	Atrial enlargement; moderate or severe diastolic dysfunction.	Pericardial effusion present; right ventricular collapse during diastole.
Hemodynamics			
Equalization of diastolic pressures	Present.	Left-sided pressures often higher than right-sided pressures.	Present.
Dip-and-plateau sign ("square root sign")	Present.	Present.	Not typically present.
Respiratory variation in left/right ventricular pressure tracings	Discordant peak right and left ventricular pressures.	Concordant peak right and left ventricular pressures.	Variable.

Symptoms

Presents with dyspnea, chest pain, and syncope.

Exam

- The obstructive form presents with a systolic crescendo-decrescendo murmur that **intensifies with a reduction in left ventricular volume** (e.g.,

standing, Valsalva maneuver) and **diminishes with an ↑ in left ventricular volume** (e.g., **hand grip** or **raising the legs when the patient is in a supine position**).
- An S4 and a sustained apical impulse are characteristic.
- Carotid upstrokes are **bifid** owing to midsystolic obstruction.

The following HCM patients should undergo risk stratification (electrophysiologic testing) and possible ICD placement: those with a family history of sudden death, syncope (especially if recurrent or exertional), nonsustained VT on Holter monitoring, > 3 cm thickness of interventricular septum, or decreased BP with exercise.

Differential

- **Valvular aortic stenosis:** The murmur of aortic stenosis radiates to the neck. Aortic stenosis also has weak and delayed carotid upstrokes (parvus et tardus).
- **Hypertensive heart disease:** Not typically associated with asymmetric septal hypertrophy or outflow tract obstruction.

Diagnosis

- **ECG:** Shows LVH and left atrial enlargement along with a broad, deep Q wave in leads I and II and in the left precordial leads (pseudoinfarction pattern). The apical form of the disease can have giant anterior T-wave inversions.
- **Echocardiogram:** Demonstrates LVH with systolic anterior motion of the mitral valve and left ventricular outflow tract obstruction. The pattern of hypertrophy varies. In the classic obstructive phenotype, the septum is asymmetrically hypertrophied. The left ventricular cavity is small and hypercontractile, often with diastolic dysfunction.
- **Holter monitor:** Detects ventricular arrhythmias as the cause of syncope.
- **Genetic testing:** Not routinely done, but has the potential to identify the genotype (which has prognostic value) and screen family members.

Agents that ↓ left ventricular volume, such as nitrates and diuretics, ↑ the outflow tract gradient, ↑ murmur intensity, and are contraindicated in patients with hypertrophic cardiomyopathy.

Treatment

- **Avoid strenuous exercise.**
- **β-blockers or verapamil:** Improve symptoms by negative inotropy, which ↓ the outflow tract gradient and slows heart rate to ↑ filling time.
- **Electrophysiologic study and implantable cardioverter-defibrillator (ICD) placement:** Indicated for patients with syncope or a family history of sudden cardiac death.
- **Surgical myectomy:** Removes tissue from hypertrophic septum and relieves outflow tract obstruction. Improves symptoms but does not ↓ the rate of sudden cardiac death.
- **Percutaneous alcohol septal ablation:** Has the same objective as surgical myectomy by injection of alcohol into hypertrophic septum, causing local infarction.
- **Endocarditis prophylaxis:** Patients with dynamic outflow obstruction or mitral regurgitation should receive endocarditis prophylaxis.

Dilated Cardiomyopathy

Most commonly occurs in the setting of ischemic heart disease. *Idiopathic dilated cardiomyopathy* is a term used to describe a dilated left ventricle with a ↓ EF in the absence of systemic hypertension, CAD, chronic alcoholism, congenital heart disease, or other systemic diseases known to cause dilated cardiomyopathy. Etiologies are as follows:

- **Idiopathic:** A genetic predisposition may exist.
- **2° to a known etiologic agent:**
  - **Acute myocarditis:** Infectious, toxic, or immune mediated.
  - **Drugs/toxins:** Anthracyclines, cocaine, amphetamines, alcohol.
  - **Nutritional:** Thiamine, carnitine deficiency.
  - **Collagen vascular disease** (e.g., Churg-Strauss syndrome).
  - **Chronic viral infections:** HIV, HCV.
  - **Endocrine:** Thyroid disorders, hypocalcemia, hypophosphatemia.
  - **Late-stage hemochromatosis.**
  - **X-linked muscular dystrophies.**

Symptoms

Presents with exertional dyspnea, fatigue, syncope, ↓ exercise tolerance, and edema.

Exam

Exam reveals an elevated JVP, diffuse PMI, S3, S4, a holosystolic murmur of mitral regurgitation, evidence of fluid overload (e.g., crackles on lung exam, lower extremity edema, ascites), and evidence of AF or other arrhythmias.

Diagnosis

- **ECG:** Can be normal. If abnormal, look for evidence of left ventricular enlargement, conduction disorders (wide QRS, LBBB), or arrhythmias (AF, nonsustained VT).
- **Echocardiogram:** ↓ EF; dilated left ventricle.
- **Laboratory evaluation:** Can be helpful in diagnosing specific etiologies (e.g., HIV).
- **Coronary angiography:** Excludes ischemic heart disease.
- **Endomyocardial biopsy: Not routinely recommended and generally low yield.**

Treatment

- Similar to that of systolic heart failure.
- **Revascularization:** Appropriate for patients with ischemic dilated cardiomyopathy.
- **Neurohormonal blockade: β-blockers, ACEIs** (or angiotensin receptor blockers), spironolactone (for patients with stage III or IV heart failure).
- **Symptom control:** Diuretics, nitrates.
- **Anticoagulation: Controversial;** generally used only in patients with a history of systemic thromboembolism, AF, or evidence of an intracardiac thrombus.
- **Other:** Hemofiltration (for patients with oliguria or renal dysfunction), cardiac resynchronization, ventricular assist devices, cardiac transplantation, ICD for malignant arrhythmias (e.g., VT).

Acute Myocarditis

A common cause of "idiopathic" dilated cardiomyopathy. Patients are typically young and healthy, and many present after a viral upper respiratory illness. Can be a cause of sudden cardiac death. Etiologies are as follows:

- **Infectious: Most commonly viral** (coxsackievirus, HIV), but can be caused by numerous pathogens, including *Trypanosoma cruzi* (Chagas' disease).

- **Immune mediated:** Allergic reaction to medications, sarcoidosis, scleroderma, SLE, and others.
- **Toxic:** Medications (anthracyclines), alcohol, heavy metals, and others.

Symptoms

Can be nonspecific. Look for flulike symptoms, fever, arthralgias, and malaise. In more severe cases, patients can present with chest pain, dyspnea, and symptoms of heart failure (e.g., orthopnea, edema, ↓ exercise tolerance).

Exam

Exam can be normal. If abnormal, look for evidence of heart failure.

Differential

CAD, aortic dissection, pericarditis, pulmonary embolism, pulmonary and GI illnesses.

Consider the diagnosis of myocarditis in young patients who present after a viral illness. They commonly have no coronary risk factors and have ⊕ cardiac enzymes but normal coronary arteries on cardiac catheterization.

Diagnosis

- The gold standard is **endomyocardial biopsy,** but because of patchy involvement of the myocardium, yield is not great and the test can be insensitive. By the time most patients seek medical care, fibrosis is the only finding on biopsy.
- **ECG:** Can be abnormal but is neither sensitive nor specific.
- **Cardiac biomarkers:** Elevated in the acute phase.
- **Echocardiography:** Can be helpful to look for focal wall motion abnormalities and ↓ EF, but findings are nonspecific.
- **Cardiac catheterization:** To exclude CAD.

Treatment

- No specific therapy. Steroids have not been shown to be helpful.
- Treat heart failure.
- Cardiac transplantation for severe cases.

PERICARDIAL DISEASE

Acute Pericarditis

Pericardial inflammation that results in chest pain, pericardial friction rub, and diffuse ST-segment elevation. Common etiologies are viral illness, connective tissue disease, and post-MI. May also be idiopathic.

Symptoms

- Classically described as sharp, pleuritic chest discomfort that **worsens while supine and eases while leaning forward.** Dull pain similar in quality to angina pectoris is also possible.
- A prodrome of flulike symptoms with fever and myalgias is often present in patients with viral pericarditis.

Exam

A pericardial **friction rub** is the hallmark. Classically described as having three components: atrial contraction, ventricular contraction, and ventricular filling.

Differential

- **Acute myocardial ischemia/infarction:** Reciprocal ST-segment depressions are key in distinguishing the ECG changes of STEMI from those of pericarditis.
- **Aortic dissection.**
- **Pneumothorax.**
- **Early repolarization:** A normal variant pattern of ST-segment elevation, usually with a "fishhook" configuration of the J point.
- **Costochondritis:** A diagnosis of exclusion.

In acute pericarditis, the atrial current of injury is reflected in aVR as PR-segment elevation, also known as the "knuckle sign" (the PR segment appears as if a knuckle is pushing it up).

Diagnosis

- Diagnosed by the following:
  - A consistent history of chest pain typical of acute pericarditis.
  - The presence of friction rub on exam (may not have the classic three components described above).
  - The presence of typical ECG changes (diffuse ST-segment elevation, PR-segment depression) **not compatible with a single coronary distribution** (see Figure 3.9 and Table 3.14); PR-segment elevation in aVR.
- Echocardiography is useful for excluding a large pericardial effusion, but many patients will have only a small effusion or a normal echocardiogram.

Treatment

- NSAIDs.
- Colchicine can be useful for patients with multiple recurrent episodes.
- Steroids are often used as a last resort when patients do not respond to other therapies.

Complications

- Anticoagulation should be avoided, but conversion to hemorrhagic pericarditis is rare.
- Echocardiography to rule out tamponade in patients with hypotension and elevated JVP.

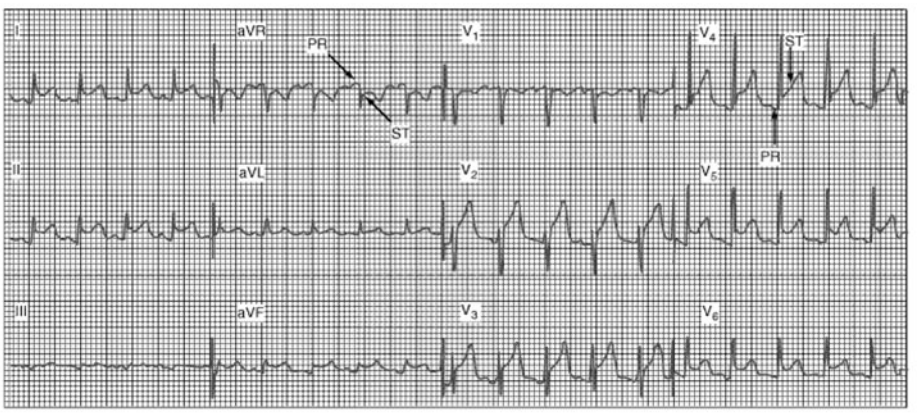


FIGURE 3.9. Acute pericarditis on ECG.

(Reproduced, with permission, from Kasper DL et al. *Harrison's Principles of Internal Medicine*, 16th ed. New York: McGraw-Hill, 2005: 1318.)

TABLE 3.14. ECG in Acute Pericarditis vs. Acute (Q-Wave) MI

	ST-Segment Elevation	ECG Lead Involvement	Evolution of ST and T Waves	PR-Segment Depression
Pericarditis	Concave upward	All leads involved except aVR and V_1.	ST remains elevated for several days; after ST returns to baseline, T waves invert.	Yes, in majority.
Acute MI	Convex upward	ST elevation over the infarcted region only; reciprocal ST depression in opposite leads.	T waves invert within hours, while ST is still elevated; followed by Q-wave development.	No.

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Pericardial Effusion

Slowly developing effusions can be asymptomatic. Rapidly developing effusions can lead to tamponade, causing severe chest pain and dyspnea. Etiologies include pericarditis, infections, uremia, malignancy, myxedema, nephrotic syndrome, cirrhosis, post–cardiac surgery, and medications.

Exam

A pericardial friction rub may be present. However, there may be a lack of findings in small effusions. Larger effusions can cause muffled heart sounds and elevated jugular venous pulsations. Rapidly evolving effusions can cause symptoms of cardiac tamponade.

Diagnosis

- **ECG:** Low voltage; electrical alternans (beat-to-beat variation in the height of the QRS complex).
- **CXR:** Cardiomegaly with a characteristic "boot-shaped heart."
- **Echocardiography:** Useful for visually detecting the effusion as well as for ruling out tamponade physiology.
- **Pericardiocentesis:** Can help diagnose the underlying cause of the effusion (e.g., transudate vs. exudate).

Treatment

- If unstable, follow guidelines for the treatment of **cardiac tamponade.**
- Drainage of fluid via pericardiocentesis or pericardial window may be necessary in slowly evolving effusions that become symptomatic.

If fluid from a bloody pericardial effusion clots on drainage, the fluid is likely coming from an acute or subacute ruptured myocardium or blood vessel. In other forms of bloody pericardial fluid (e.g., renal failure or malignancy), the fluid does not clot.

Constrictive Pericarditis

Impaired ventricular filling due to thickening and scarring of pericardium. Commonly associated with recurrent episodes of acute pericarditis, prior radiation therapy, neoplasm, collagen vascular disease, and post–cardiac surgery.

Symptoms

Presents with insidious onset of pulmonary and systemic venous congestion and ↓ cardiac output (fatigue, dyspnea, peripheral edema).

Exam

- Elevated JVP with prominent y descent and **Kussmaul's sign** (absence of normal fall in JVP during inspiration).
- There are prominent x and y descents on jugular venous pulsation exam, leading to an M-shaped contour. Pulsus paradoxus may be present.
- A pericardial knock (a high-pitched third heart sound heard 0.1 second after A2) may be heard following S2, representing rapid cessation of early diastolic filling.

Differential

- **Restrictive cardiomyopathy:** A similar presentation that may require MRI and/or myocardial biopsy to distinguish. On hemodynamic study, right and left ventricular pressures are concordant with respiration in restriction and discordant in constriction.
- **Cardiac tamponade:** Blunted y descent on right atrial pressure tracing, absence of Kussmaul's sign, and more frequent presence of pulsus paradoxus. Right heart catheterization shows diastolic equalization of pressures in both disorders, but a dip-and-plateau pattern is seen only in constriction (and restriction). Table 3.13 further outlines the distinctions between tamponade and pericardial restriction.
- **Cirrhosis:** Patients with hepatic congestion and ascites due to constriction can be incorrectly diagnosed as having cryptogenic cirrhosis.

Diagnosis

- **ECG:** No specific findings, but low voltage may be present.
- **CXR:** Shows pericardial calcifications (on lateral view) in approximately 25% of patients; bilateral pleural effusions are often present.
- **Echocardiogram:** Demonstrates pericardial thickening and adhesions, septal bounce, and a plethoric IVC without inspiratory collapse.
- **Right heart catheterization:** Equalization of diastolic pressures and dip-and-plateau pattern (**"square root sign"**) that reflects early diastolic filling followed by constraint from fixed pericardial volume. Interventricular discordance is specific for pericardial constriction.
- **MRI:** The most sensitive imaging modality for measuring abnormal pericardial thickness.

Treatment

Surgical pericardectomy is the treatment of choice, but mortality ranges from 5% to 12%, and symptom relief may not occur for several months following the procedure.

Cardiac Tamponade

An accumulation of pericardial fluid under pressure that impedes ventricular filling. Most commonly associated with malignancy, trauma, idiopathic factors, and ventricular rupture following MI.

Symptoms

Presents with dyspnea, chest pain, and lightheadedness.

Exam

Tachycardia and hypotension with diminished heart sounds and clear lungs; elevated JVP with blunting or absence of the y descent. Pulsus paradoxus is **> 10 mmHg.**

Differential

- **Constrictive pericarditis:** Has a slow, insidious onset. Kussmaul's sign is usually present. Echocardiogram shows pericardial thickening without large effusion.
- **Tension pneumothorax:** Can also present with tachycardia, hypotension, and elevated neck veins with **pulsus paradoxus.** ↑ ventilator pressures and loss of unilateral breath sounds are clues.

Diagnosis

- **ECG:** Low voltage and/or electrical alternans.
- **Echocardiogram:** Pericardial effusion with right atrial and right ventricular collapse; a plethoric IVC that does not collapse with inspiration. Respiratory variation of mitral and tricuspid inflow patterns (the echo equivalent of pulsus paradoxus) is also seen.
- **Cardiac catheterization:** Equalization of diastolic pressures (right atrial, right ventricular, pulmonary arterial, PCWP).

Cardiac tamponade is more closely related to the rate of pericardial fluid accumulation than to the size of the effusion. A small effusion may cause tamponade if it is acute.

Treatment

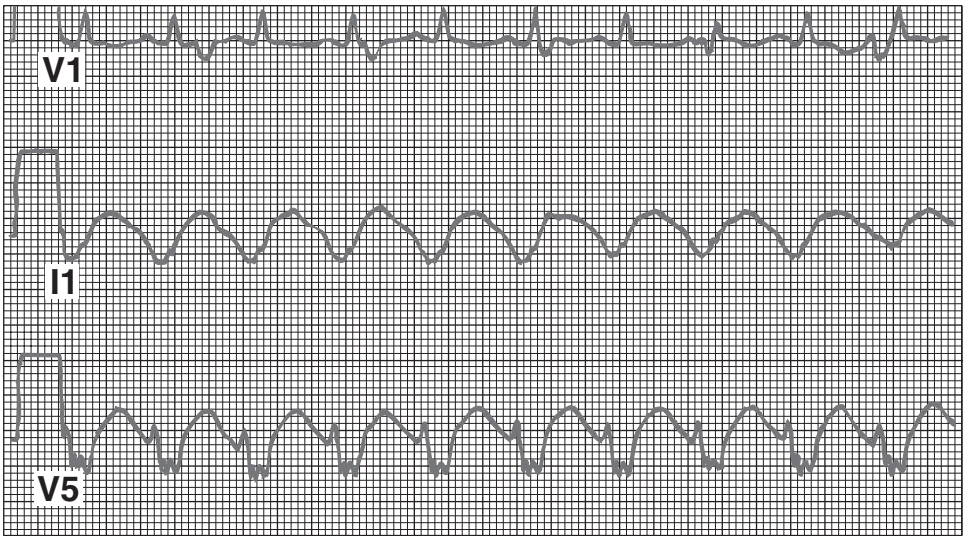
- **IV fluids:** ↑ preload and improve ventricular filling.
- **Dopamine:** Can improve cardiac output in preparation for pericardiocentesis.
- **Pericardiocentesis:** Usually performed with echocardiographic or fluoroscopic guidance to drain pericardial fluid.
- **Pericardial window:** Surgically placed or via balloon pericardiotomy to prevent reaccumulation of fluid.

ELECTROPHYSIOLOGY

Ventricular Tachycardia (VT) and Ventricular Fibrillation (VF)

Commonly caused by ischemia/infarction, cardiomyopathy, electrolytes, and drug toxicity. Types of VT are as follows (see also Figure 3.10):

- **Monomorphic:** Characterized by a uniform QRS pattern; most commonly associated with myocardial scar.
- **Polymorphic:** Bizarre and changing QRS morphology as seen in torsades de pointes; may be precipitated by myocardial ischemia. Torsades is most often associated with medications and electrolyte abnormalities that prolong the QT interval, such as type IC and type III antiarrhythmics, hypomagnesemia, hypocalcemia, and hypokalemia.



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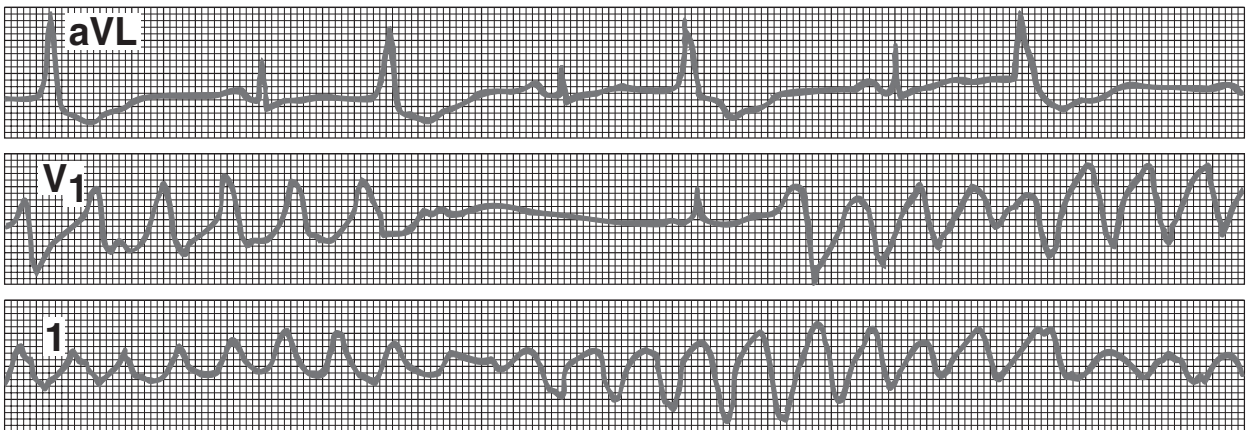

B

FIGURE 3.10. Ventricular tachycardia.

(A) Monomorphic VT with AV dissociation. P waves are dissociated from the underlying wide-complex rhythm (best seen on lead V_1). (B) Polymorphic VT associated with prolonged QT interval. (Reproduced, with permission, from Kasper DL et al. *Harrison's Principles of Internal Medicine*, 16th ed. New York: McGraw-Hill, 2005: 1352, 1353.)

Rule out myocardial ischemia in cases of polymorphic VT with a normal QT interval on baseline ECG.

Symptoms

Chest pain, dyspnea, and syncope due to poor systemic perfusion are common. The initial manifestation of VT/VF in many patients is sudden cardiac death.

Exam

Cannon A waves on jugular venous pulsation are seen during VT as a result of AV dissociation.

Differential

Supraventricular tachycardia (SVT) with aberrant conduction.

Diagnosis

- **For unstable patients, always assume VT until proven otherwise.**
- For stable patients, the Brugada criteria can be used to distinguish SVT with aberrancy from VT. Major criteria are as follows:
  - **AV dissociation is always VT.**
  - The absence of RS complexes in all precordial leads is VT.
  - Complexes not typical of LBBB or RBBB are usually VT.

Treatment

- **Electrical cardioversion** is the treatment of choice for unstable patients.
- IV therapy with amiodarone is now first-line therapy for stable VT.
- Polymorphic VT (including torsades de pointes) can be treated with rapid magnesium infusion and overdrive pacing.
- **ICD placement is indicated for causes that are not thought to be transient or reversible.**

Complications

Sudden cardiac death, hypoxic encephalopathy, demand cardiac ischemia/MI.

Atrial Fibrillation (AF)

The most common arrhythmia in the general population (0.5–1.0%). Prevalence ↑ with age (10% of individuals age > 80 years of age have AF). Etiologies are as follows:

- **Most common:** Hypertension, valvular heart disease, heart failure, CAD.
- **Other causes:** Pulmonary disease (COPD, pulmonary embolism), ischemia, rheumatic heart disease (rheumatic mitral stenosis), hyperthyroidism, sepsis, alcoholism, Wolff-Parkinson-White (WPW) syndrome, cardiac surgery.
- **Lone AF:** Normal echo; no risk factors (i.e., no hypertension, age < 65 years).

Symptoms/Exam

Can be asymptomatic or manifest as palpitations, fatigue, dyspnea, dizziness, diaphoresis, and/or symptoms of heart failure.

Differential

- **Irregular tachycardias:** AF, atrial flutter with variable block, multifocal atrial tachycardia, frequent premature atrial contractions.
- **Regular tachycardias:** Sinus tachycardia, atrial tachycardia (AT), AV nodal reentrant tachycardia (AVNRT), AV reentrant tachycardia (AVRT), accelerated junctional tachycardia.

Diagnosis

- **ECG: AF** is the most common cause of an irregularly irregular rhythm on ECG (see Figure 3.11). **Look for the absence of P waves.**
- **Echocardiogram:** Used to predict stroke risk (look for structural abnormalities such as left atrial enlargement, mitral stenosis, and ↓ EF). TEE can be used to visualize thrombus in the left atrium.

In patients > 65 years of age, maintaining sinus rhythm with antiarrhythmics is no more effective than rate control and anticoagulation in reducing the incidence of stroke or mortality.

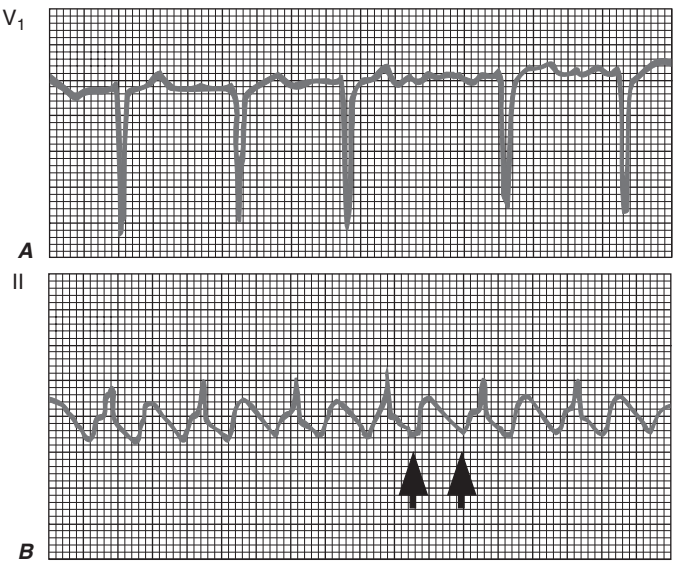

FIGURE 3.11. Atrial fibrillation and atrial flutter.

(A) Lead V_1 demonstrates an irregular ventricular rhythm associated with poorly defined irregular atrial activity consistent with AF. (B) Lead II demonstrates atrial flutter, identified by the regular "sawtooth-like" activity (arrows) at an atrial rate of 300 bpm with 2:1 ventricular response. (Reproduced, with permission, from Kasper DL et al. *Harrison's Principles of Internal Medicine*, 16th ed. New York: McGraw-Hill, 2005: 1345.)

TREATMENT

- **Unstable patients: Proceed directly to cardioversion (biphasic is preferable to monophasic).**
- **Rate control:** β-blockers or centrally acting nondihydropyridine calcium channel blockers (diltiazem, verapamil) are first line. For a reduced EF, use amiodarone or digoxin.
- **Rhythm control:** Guidelines suggest flecainide, propafenone, or sotalol as first-line therapy in patients without heart disease. Patients with CHF can be started on amiodarone or dofetilide; for those with CAD, sotalol is first line. Patients with hypertension and LVH should be started on amiodarone (those with hypertension and no LVH can be treated with flecainide or propafenone).
- **Anticoagulation:** Warfarin (with a goal INR of 2–3) or aspirin.
  - **Patients with a score of 2 or greater by the CHADS2 criteria** (1 point for **C**HF, **H**ypertension, **A**ge > 60, **D**iabetes; 2 points for prior **S**troke or TIA) should be anticoagulated with **warfarin** as opposed to aspirin alone to **prevent stroke.**
  - If the CHADS2 score is 1, warfarin or aspirin can be used.
  - **Lone AF** should be treated with **aspirin alone.**
  - Anticoagulation is unnecessary if AF is new onset and the duration is < 48 hours.
  - If AF is > 48 hours or if < 48 hours and associated with rheumatic mitral valve disease, anticoagulate with warfarin for 3–4 weeks prior to cardioversion (goal INR 2–3).
- **TEE-guided cardioversion:** Trials of TEE-guided cardioversion used anticoagulation for 24 hours prior to cardioversion and anticoagulated following cardioversion.

- **Postcardioversion:** Anticoagulate with warfarin for four weeks.
- **Rate control vs. rhythm control:** Studies have demonstrated that rate control with anticoagulation has the same outcome as rhythm control and may also be safer.
- **Post–cardiac surgery AF:** Most common with mitral valve surgery; occurs on postoperative days 2–3. Cardioversion is the most effective therapy. If AF recurs after cardioversion, treat with rate control and anticoagulation. Prophylaxis includes perioperative β-blockers or amiodarone.
- **WPW patients who present in AF with rapid ventricular response:** If baseline ECG shows a delta wave or if the current ECG shows wide, bizarre QRS complexes during AF, **avoid AV nodal blocking agents** (β-blockers, calcium channel blockers, adenosine, digoxin). The treatment of choice is IV procainamide, which slows conduction in the entire atrium. **If AV nodal blocking agents are given in this situation, the atrial impulses in rapid AF can proceed down the accessory pathway and cause VF and death.**

Atrial Flutter

After AF, atrial flutter is the most common atrial arrhythmia. It is usually caused by a macro-reentrant circuit within the **right atrium.**

Symptoms/Exam

May be asymptomatic. When symptoms occur, patients generally complain of palpitations, an irregular or fast heartbeat, lightheadedness, dyspnea, or ↓ exercise tolerance.

Diagnosis

Always consider the diagnosis of atrial flutter in patients who have a heart rate of ~150, since atrial flutter usually presents with a 2:1 AV block. May be typical or atypical.

- **Typical flutter:** The most common type of atrial flutter. ECG will generally show a **sawtooth pattern in the inferior leads** (II, III, aVF; see Figure 3.11). Look for discrete, upright, P-wave-like deflections in lead V_1 (the P-wave rate should be approximately 300 bpm).
- **Atypical flutter:** Look for continuous, regular atrial activity at a rate of 250–350 bpm without typical flutter morphology.

Treatment

- In the acute setting, three treatment options exist for the restoration of sinus rhythm:
  - **Antiarrhythmic drugs:** Ibutilide, flecainide, propafenone. Ibutilide is approximately 60% effective in restoring sinus rhythm but carries the risk of torsades de pointes due to QT prolongation.
  - **Cardioversion:** Useful in cases of hemodynamic instability.
  - **Rapid atrial pacing:** Overdrive pacing.
- Rate control can be achieved with centrally acting calcium channel blockers, β-blockers, or digoxin.
- **Long-term treatment:**
  - Radiofrequency ablation is highly effective.
  - Alternative treatments include antiarrhythmic drugs or antitachycardia pacemakers. These treatments generally require long-term anticoagulation with warfarin to lower the risk of thromboembolism.

When using ibutilide for chemical cardioversion of atrial flutter, monitor the QT interval closely. Torsades de pointes can occur, and treatment consists of IV magnesium and cardioversion.

Paroxysmal Supraventricular Tachycardia (PSVT)

The most common type of PSVT is AVNRT. Other forms are AT and AVRT. Mechanisms for PSVT are as follows:

- **AT:** Tachycardia arising from an ectopic atrial focus (↑ automaticity).
- **AVRT:** Reentry via an AV bypass tract (WPW syndrome if a delta wave is present on ECG).
- **AVNRT:** Reentry within the AV node.

Symptoms

Presents with palpitations, lightheadedness, and occasionally chest discomfort. Paroxysms usually begin in young adulthood and ↑ with age. Attacks begin and end suddenly and may last a few seconds or for hours.

Exam

Not usually associated with structural heart disease. There are no specific exam findings except for cannon A waves in the jugular venous pulsation during AVNRT due to atrial contraction against a closed tricuspid valve.

Differential

Based on the ECG:

- **If QRS is narrow:** AVRT, AVNRT.
- **If QRS is wide:** PSVT with aberrancy vs. VT.
- **If QRS is wide and the rhythm is irregular with bizarre QRS complexes:** AF conducting via an accessory pathway.

Diagnosis

- **ECG** (see Figure 3.12).
  - AVRT is a macro-reentrant circuit with retrograde P waves.
  - AVNRT is a micro-reentrant circuit with P waves buried in QRS.
  - AT has a "long RP" relationship, with P waves preceding each QRS.
- Holter or event monitoring is essential if episodes are not documented on a 12-lead ECG.
- An electrophysiologic study can be used for diagnosis and ablative therapy.

Treatment

- Acute termination can occur with carotid massage or rapid administration of adenosine.
- Medical management consists of AV nodal blocking agents (e.g., β-blockers).
- Curative therapy consists of catheter-based ablation.

Complications

- Rapid rates in older patients can cause demand ischemia and MI.
- The treatment of AF conducting via an accessory pathway with AV nodal blockade can cause rapid bypass tract conduction, leading to VF.

Wolff-Parkinson-White (WPW) Syndrome

In patients with WPW syndrome, an accessory pathway exists between the atria and ventricles as a result of a defect in the separation of the atria and ventricles during fetal development. WPW syndrome may be found inciden-

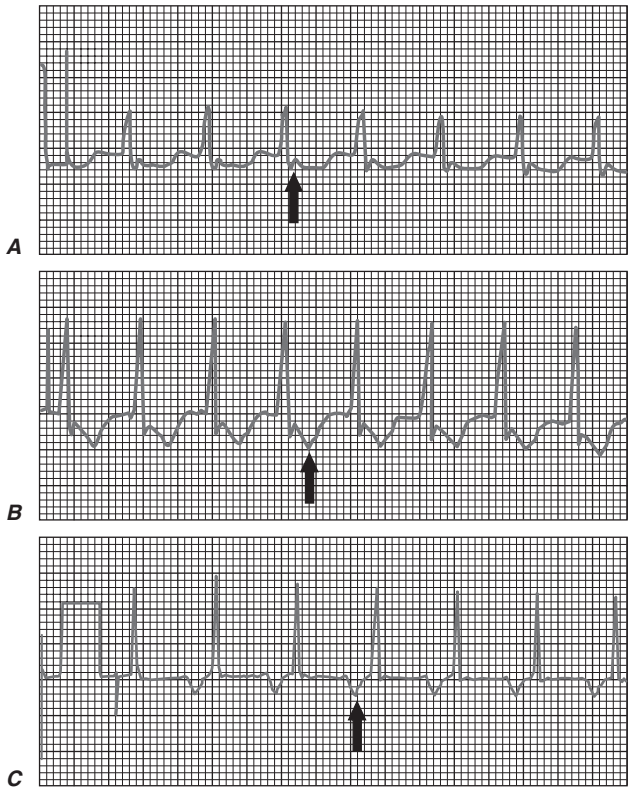

FIGURE 3.12. Examples of supraventricular tachycardia.

Arrows indicate P waves. (A) AV nodal reentry. Upright P waves are visible at the end of the QRS complex. (B) AV reentry using a concealed bypass tract. Inverted retrograde P waves are superimposed on the T waves. (C) Automatic atrial tachycardia. Inverted P waves follow the T waves and precede the QRS complex. (Reproduced, with permission, from Kasper DL et al. *Harrison's Principles of Internal Medicine,* 16th ed. New York: McGraw-Hill, 2005: 1349.)

tally on routine ECG. However, patients with WPW syndrome are at risk for tachyarrhythmias and even sudden cardiac death.

Diagnosis

- If the accessory pathway allows **anterograde conduction,** electrical impulses from the atria can conduct down the accessory pathway into the ventricles, causing ventricular preexcitation with a short PR interval and **classic delta waves on ECG** (slurring of the upstroke on the QRS, best seen in lead V_4; see Figure 3.13).
- Some patients with WPW syndrome have accessory pathways that allow only **retrograde conduction** from the ventricles to the atria. In these patients, the resting ECG will not show a delta wave. These patients have a so-called concealed bypass tract, and though they may have a normal resting ECG, they are still prone to the development of an AVNRT.

Treatment

Electrophysiologic study and catheter ablation of the bypass tracts is the treatment of choice for patients with WPW syndrome.

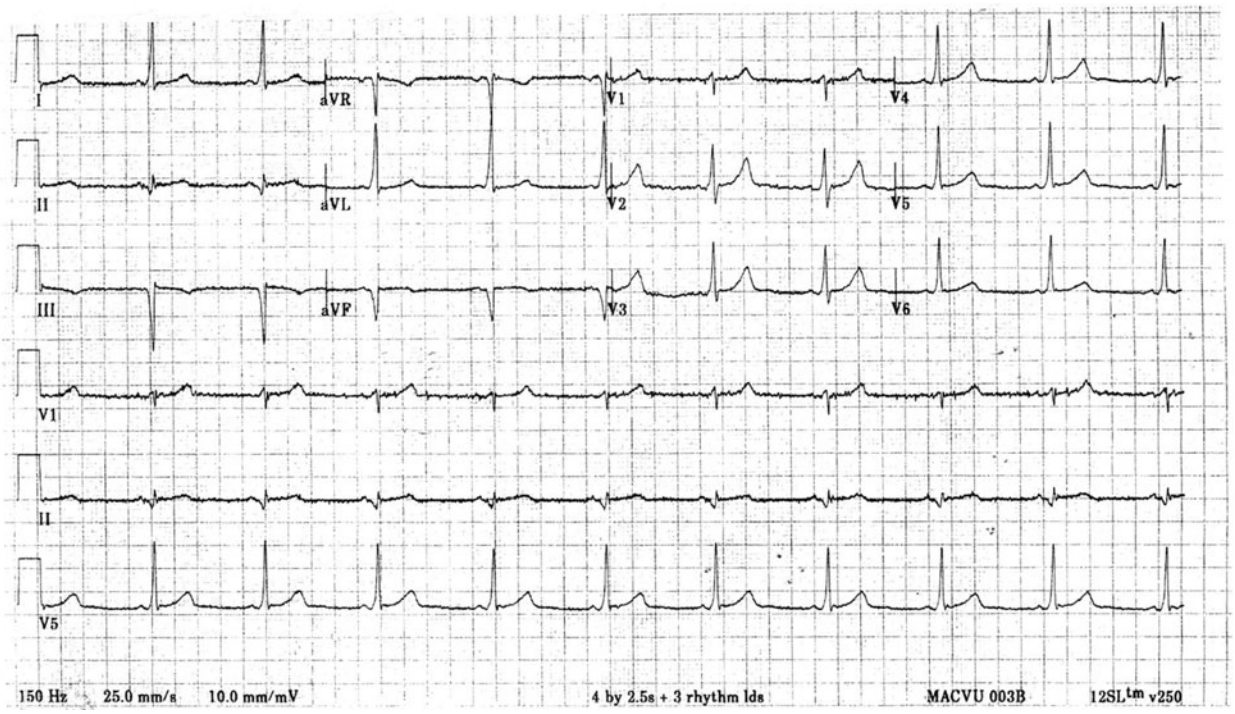

FIGURE 3.13. Classic Wolff-Parkinson-White ECG.

Note the short PR interval and classic delta waves on ECG (slurring of the upstroke of the QRS best seen in V_4).

COMPLICATIONS

- **AF** is the 1° complication of WPW syndrome.
- If the patient has a concealed bypass tract (i.e., no evidence of a delta wave or other evidence of WPW syndrome on baseline ECG), the standard treatment for AF (or any tachycardia) is safe.
- If the patient has evidence of a bypass tract on ECG (a delta wave) or if the patient is in AF with bizarre, aberrantly conducted complexes, this represents an emergency situation. **Do not give such patients AV nodal blocking agents,** since this can allow for 1:1 conduction of AF via the bypass tract, leading to VF and cardiac arrest. The treatment of choice for these patients is procainamide or cardioversion.

Cardiac Syncope

Cardiac syncope can be due to structural heart disease or arrhythmias. Cardiac syncope classically presents either with exertion (structural) or suddenly and without warning (arrhythmic). Overall causes are as follows:

- **Cardiac:** 18%.
- **Neurologic:** 10%.
- **Vasovagal:** 24%.
- **Orthostatic:** 8%.
- **Medications:** 3%.
- **Unknown:** 37%.

Symptoms/Exam

Causes may be structural or arrhythmic.

- **Common structural causes:**
  - **Aortic stenosis:** Usually occurs with exertion; look for associated angina or heart failure.
  - **Hypertrophic obstructive cardiomyopathy:** Can occur in all ages; may be dynamic in nature (i.e., may manifest in the setting of ↓ preload, such as postexercise). Syncope may also occur in a nonobstructive form as a result of ventricular arrhythmias.
- **Less common structural causes:** Pulmonary embolism, aortic dissection, cardiac tamponade.
- **Uncommon structural causes:** Pulmonary hypertension, atrial myxoma, subclavian steal.
- **Arrhythmic causes:**
  - **Bradycardia:**
    - **Sinus bradycardia:** Sick sinus syndrome, medications (e.g., β-blockers, calcium channel blockers).
    - **AV block (second, third degree):** Usually due to age-related conduction disease, medications, and/or ischemia.
    - **Carotid sinus hypersensitivity.**
  - **Tachycardia:**
    - **Supraventricular tachycardia:** A rare cause of syncope.
    - **VT:** Most often due to structural and/or ischemic heart disease.

Diagnosis

- **ECG:** Look for evidence of ischemia, arrhythmia, new bundle branch block, or a prolonged QT interval.
- **Echocardiogram:** Look for structural heart disease. Consider in patients with a history of heart disease, those with an abnormality on physical exam or ECG, or elderly patients.
- **Holter monitoring:** Use when the patient has symptoms that suggest arrhythmia (e.g., a cluster of spells, sudden loss of consciousness, palpitations, use of medications associated with arrhythmia, known heart disease, an abnormal ECG).
- **Tilt-table testing:** Use in patients with normal hearts and relatively infrequent syncope, nondiagnostic Holter monitoring, or symptoms that suggest vasovagal spells (e.g., warmth, nausea) but lack an obvious precipitating event.

Treatment

Guidelines for hospital admission are as follows:

- Evidence of MI, stroke, or arrhythmia.
- **Definite admission:** Chest pain; a history of CAD, heart failure, or ventricular arrhythmia; evidence of heart failure or valvular disease; focal neurologic deficits on physical exam; new ECG abnormalities.
- **Possible admission:** Patients > 70 years of age; those with exertional or frequent syncope, orthostasis, or injury due to a syncopal episode.

Bradycardia

If left untreated, Lyme disease can cause varying degrees of AV conduction block at any time in the course of the disease.

Incidence ↑ with age. Etiologies are as follows:

- **Intrinsic causes:** Idiopathic senile degeneration; ischemia (usually involving the inferior wall); infectious processes (endocarditis, Chagas' disease, Lyme disease); infiltrative diseases (sarcoidosis, amyloidosis, hemochromatosis); autoimmune disease (SLE, RA, scleroderma); iatrogenic factors (heart transplant, surgery); inherited/congenital disease (myotonic muscular dystrophy); conditioned heart (trained athletes).
- **Extrinsic causes:** Autonomic (neurocardiac, carotid sinus hypersensitivity, situational), medications (β-blockers, calcium channel blockers, clonidine, digoxin, antiarrhythmics), metabolic (electrolyte abnormalities, hypothyroidism, hypothermia), neurologic (↑ ICP, obstructive sleep apnea).

Symptoms

Patients may be asymptomatic or may present with dizziness, weakness, fatigue, heart failure, or loss of consciousness (syncope). Symptoms can also be related to the underlying cause of the bradycardia.

Exam

Look for evidence of ↓ pulse rate and evidence of the underlying cause of bradycardia. Look for **cannon A** waves in cases of complete AV dissociation (complete heart block).

Diagnosis

- **ECG:** Look for the origin of the rhythm and whether dropped beats or AV dissociation is present (evidence of AV block; see Table 3.15).
- **Telemetry,** event monitors, tilt-table testing, and electrophysiologic studies can also be helpful.

Treatment

- If the patient is **unstable,** follow ACLS protocols.
- If possible, treat the underlying cause (e.g., endocarditis).
- **Medications:** Atropine, **glucagon** (for β-blocker overdose), calcium (for

TABLE 3.15. ECG Findings with AV Block

Type of Block	ECG Findings
First degree	Prolonged PR interval (> 200 msec).
Second degree type I (Wenckebach)	Progressive prolongation of the PR interval until there is a dropped QRS. Progressive shortening of the RR interval and a constant PP interval are other signs.
Second degree type II	Regularly dropped QRS (e.g., every third QRS complex dropped). Constant PR interval (no prolongation). Usually associated with bundle branch blocks.
Third degree	Complete dissociation of P waves and QRS complexes (P-wave rate > QRS rate).

calcium channel blocker overdose). **Note:** Calcium is **contraindicated** in digoxin toxicity.
- **Transcutaneous or transvenous pacing:** Appropriate if medical therapy is ineffective.
- **Indication for permanent pacemakers:** Documented symptomatic bradycardia. If the patient is asymptomatic, pacemakers may be considered in patients with third-degree AV block with > 3 seconds of asystole or a heart rate < 40 bpm while the patient is awake. In second-degree type II AV block, pacemakers have a class II indication (there is conflicting evidence and opinion regarding the need for permanent pacing).

Indications for Permanent Pacing

Indications for permanent cardiac pacing, based on expert guidelines, are classified as follows: I (definite indications), II (indications with conflicting evidence or opinion), or III (not indicated or harmful). **All indications assume that transient causes such as drugs, electrolytes, and ischemia have been corrected or excluded.**

Class I

- **Third-degree AV block** and advanced second-degree AV block associated with the following:
  - Symptomatic bradycardia.
  - Arrhythmias or other conditions requiring medications that result in symptomatic bradycardia.
  - Documented asystole of > 3 seconds or escape rates < 40 bpm in **awake,** asymptomatic patients.
  - After AV junction ablation.
  - Post–cardiac surgery when AV block is not expected to resolve.
  - Neuromuscular diseases with AV block due to the unpredictable progression of AV conduction disease in these patients.
- **Second-degree AV block** (regardless of type) associated with symptomatic bradycardia.

Class IIA

- Asymptomatic third-degree AV block with **awake** escape rates of > 40 bpm.
- Asymptomatic type II second-degree block with narrow QRS (with wide QRS, it becomes a class I indication).
- Asymptomatic type I second-degree block with intra- or infra-His levels found on an electrophysiologic study done for another indication.
- First- and second-degree AV block with symptoms suggestive of pacemaker syndrome.

Class IIB

- Marked first-degree AV block (PR > 300 msec) in patients with left ventricular dysfunction.
- Neuromuscular diseases with any level of AV block due to the unpredictable progression of block in these patients.

Class III

- Asymptomatic first-degree AV block.
- Asymptomatic type I second-degree AV block not known to be due to a problem within or below the bundle of His.
- AV block that is expected to resolve and/or is not likely to recur.

Sudden Cardiac Death

Approximately 450,000 sudden cardiac deaths occur annually in the United States. Etiologies include CAD, MI, pulmonary embolism, aortic dissection, cardiac tamponade, and other acute cardiopulmonary insults. Seventy-five percent of patients do not survive cardiac arrest.

Causes in Young Athletes

- In young athletes, the causes of sudden cardiac death differ from those in the overall population. Causes in this population include the following (in order of decreasing incidence):
  - Hypertrophic cardiomyopathy.
  - Commotio cordis (a sudden blow to the precordium causing ventricular arrhythmia).
  - Coronary artery anomalies.
  - Myocarditis.
  - Ruptured aortic aneurysm (e.g., due to Marfan's syndrome or Ehlers-Danlos syndrome).
  - Arrhythmogenic right ventricular dysplasia, in which the right ventricle is replaced by fat and fibrosis, causing ↑ frequency of ventricular arrhythmias.
  - Aortic stenosis.
  - Myocardial bridge causing coronary ischemia during ventricular contraction.
  - Atherosclerotic CAD.
  - Coronary artery vasospasm.
  - Brugada syndrome, which is caused by a sodium channel defect that predisposes to VF. The baseline ECG shows incomplete RBBB and ST-segment elevation in the precordial leads.
  - Long QT syndrome.
- **Noncardiac precipitants** of sudden cardiac death in young athletes include asthma, illicit drug use (e.g., cocaine, ephedra, amphetamines), and heat stroke.

Screening in Young Athletes

- It is difficult to assess patients for risk factors of sudden cardiac death because these conditions are rare and because millions of young athletes need to be screened.
- Although screening usually involves history taking and physical examination, these measures alone lack the sensitivity to detect even the most common causes of sudden cardiac death in athletes (e.g., hypertrophic cardiomyopathy).
- In patients with a suggestive history or physical examination, further workup with ECG and echocardiography is warranted.

Implantable Cardioverter-Defibrillators (ICDs)

Risk Factors for Ventricular Arrhythmias

Include dilated cardiomyopathy (with a reduced EF), hypertension, hyperlipidemia, tobacco, diabetes, a family history of sudden cardiac death, myocardial ischemia and reperfusion, and toxins (e.g., cocaine).

2° Prevention

- **Goal:** To prevent recurrent sudden cardiac death in patients with a history of VT or VF.
- **Drugs:** Antiarrhythmic drugs have been disappointing in the 2° prevention of sudden cardiac death, especially in the large group of patients who are post-MI. Standard therapies for CAD alone (especially β-blockers) play a significant role in decreasing sudden cardiac death in these patients.
- **Devices: ICDs** are superior to amiodarone in patients with CAD who have survived cardiac arrest and have a **low** EF.
- There is no survival advantage of ICDs over amiodarone in patients who have an EF > 35%.

1° Prevention

- **Goal:** To prevent sudden cardiac death in patients who have no history of VT and/or VF.
- Studies have shown that in patients with a history of MI who have an EF < 30%, ICD therapy improves mortality and is superior to antiarrhythmic therapy.

Indications for ICD Use

- **Etiology of heart failure:** Recent studies indicate that ICD therapy appears effective for **both** ischemic and nonischemic cardiomyopathy.
- **Severity of heart failure:** Consider ICDs in patients with an EF < 30%.
- **Noninvasive testing:**
  - **T-wave alternans:** Microfluctuations in the morphology of T waves on ECG may indicate an ↑ risk of sudden cardiac death (requires specialized testing).
  - **Heart rate variability:** ↓ heart rate variability corresponds to worsening heart failure and may be associated with an ↑ risk of sudden cardiac death.

VALVULAR HEART DISEASE

Aortic Stenosis

The most common causes are senile calcific aortic stenosis and congenital bicuspid aortic valve. Rheumatic aortic stenosis is usually not hemodynamically significant and **almost always occurs in the presence of mitral valve disease.**

Aortic valve replacement should be performed as soon as symptoms develop in aortic stenosis to prevent cardiac death.

Symptoms

Presents with a long asymptomatic period followed by the development of the classic triad of **angina, syncope, and heart failure.** The normal valve area is 3 cm^2, and symptoms usually do not develop until the area is < 1 cm^2.

Aortic stenosis has been associated with an ↑ risk of GI bleeding, which is now thought to be due to acquired von Willebrand's disease from disruption of von Willebrand factor multimers as they pass through the stenotic aortic valve.

Exam

- A crescendo-decrescendo systolic murmur is heard at the base of the heart with radiation to the carotid arteries. Late-peaking murmurs signify more severe stenosis.
- Diminished carotid upstrokes (parvus et tardus) and a sustained PMI due to LVH may be present.
- A systolic ejection click can occur in patients with a bicuspid aortic valve. A2 diminishes in intensity, and S2 may be single.

Differential

- **Sub- or supravalvular stenosis:** Due to left ventricular outflow tract membrane or fibromuscular ring (rare).
- **Hypertrophic obstructive cardiomyopathy:** Murmur accentuated with Valsalva or standing and ↓ by hand grip.

Diagnosis

- **Echocardiography:** A modified Bernoulli equation is used to derive the pressure gradient across the aortic valve. The aortic valve area is derived by the continuity equation. The severity of aortic stenosis per the 2006 AHA/ACC guidelines can be classified as follows:
  - **Mild disease:** A valve area > 1.5 cm^2, mean gradient < 25 mmHg.
  - **Moderate disease:** A valve area 1–1.5 cm^2, mean gradient 25–40 mmHg.
  - **Severe disease:** A valve area < 1 cm^2, mean gradient > 40 mmHg.
  - Follow-up echocardiography is recommended every year for severe aortic stenosis; every 1–2 years for moderate aortic stenosis; and every 3–5 years for mild aortic stenosis.
- **Cardiac catheterization: Required to exclude significant coronary stenoses in symptomatic patients who are scheduled for surgery and are at risk for CAD.** Also needed to confirm the severity of aortic stenosis when there is a discrepancy between clinical and noninvasive data.
- **Dobutamine stress testing:** Used in cases of low-gradient aortic stenosis (severe aortic stenosis by valve area, but mean gradient < 40 mmHg) to distinguish true stenosis from pseudostenosis caused by ↓ systolic function. If true aortic stenosis is present, the gradient will ↑ and the valve area will remain unchanged. If pseudostenosis is present, the valve area will ↑.

Treatment

- **Aortic valve replacement:** The only therapy for **symptomatic** aortic stenosis. Older patients do quite well after aortic valve replacement and should not be disqualified by age alone. Patients who are unlikely to outlive a bioprothesis can be spared the lifelong anticoagulation that is required for mechanical valves.
- **Antibiotic prophylaxis against subacute bacterial endocarditis:** Indicated for **all patients.**
- **Aortic valvuloplasty:** May be effective in young adults with congenital aortic stenosis. **Less effective in patients with degenerative aortic stenosis,** and **should be considered palliative therapy or a bridge to surgery.**

Complications

- Sudden death occurs but is uncommon (< 1% per year) in patients with severe asymptomatic aortic stenosis.

- **If left untreated, the average time to death is as follows:**
  - **After onset of syncope:** 2.5–3 years.
  - **After onset of angina:** Three years.
  - **After onset of dyspnea:** Two years.
  - **After onset of CHF:** 1.5 years.

Aortic Regurgitation

Can be caused by destruction or malfunction of the valve leaflets (infective endocarditis, bicuspid aortic valve, rheumatic valve disease) or dilatation of the aortic root such that the leaflets no longer coapt (Marfan's syndrome, aortic dissection).

Symptoms

- **Acute aortic regurgitation:** Presents with rapid onset of cardiogenic shock.
- **Chronic aortic regurgitation:** A long asymptomatic period followed by progressive dyspnea on exertion and other signs of heart failure.

Exam

- Exam reveals a soft S1 (usually due to a long PR interval) and a soft or absent A2 with a decrescendo blowing diastolic murmur at the base.
- A wide pulse pressure with water-hammer peripheral pulses is also seen.
- Other peripheral signs include a bruit over the femoral artery (Duroziez's sign); nail-bed pulsations (Quincke's pulse); and a popliteal-brachial BP difference of > 20 mmHg (Hill's sign).
- In acute aortic regurgitation, these signs are usually not present, and the only clues may be ↓ intensity of S1 and a short, blowing diastolic murmur.
- In severe aortic regurgitation, the anterior mitral valve leaflet can vibrate in the aortic regurgitation jet, creating an apical diastolic rumble that mimics mitral stenosis (Flint murmur).

Indications for valve replacement in aortic regurgitation include the development of symptoms or left ventricular systolic failure even in the absence of symptoms.

Differential

Other causes of diastolic murmurs include mitral stenosis, tricuspid stenosis, pulmonic insufficiency, and atrial myxoma.

Diagnosis

- **Echocardiography:** Essential for determining left ventricular size and function as well as the structure of the aortic valve. TEE is often necessary to rule out endocarditis in acute aortic regurgitation.
- **Cardiac catheterization:** Aortography can be used to estimate the degree of regurgitation if noninvasive studies are inconclusive. Coronary angiography is indicated to exclude CAD in patients at risk prior to surgery.

Treatment

- In asymptomatic patients with normal left ventricular function, afterload reduction may be considered, but evidence for benefit is lacking. ACEIs or other vasodilators may ↓ left ventricular volume overload and progression to heart failure.
- **Aortic valve replacement:** Should be considered in symptomatic patients or in those without symptoms who develop worsening left ventricular dilatation and systolic failure.

- **Acute aortic regurgitation:** Surgery is the definitive therapy, since mortality is high in this setting. IV vasodilators may be used as a bridge to surgery.
- **Endocarditis prophylaxis:** Consider in all patients.

Complications

Irreversible left ventricular systolic dysfunction if valve replacement is delayed.

Mitral Stenosis

Almost exclusively due to **rheumatic heart disease,** with rare cases due to congenital lesions and calcification of the mitral annulus. The normal mitral valve area is 4–6 cm^2. Severe mitral stenosis occurs when the valve area is < 1 cm^2.

Symptoms

Characterized by a long asymptomatic period followed by gradual onset of dyspnea on exertion and findings of right heart failure and pulmonary hypertension. Hemoptysis and thromboembolic stroke are late findings.

Exam

- Exam reveals a loud S1 and an opening snap of stenotic leaflets after S2 followed by an apical diastolic rumble.
- Signs of pulmonary hypertension (a loud P2) and right heart failure (elevated JVP and hepatic congestion) are present in advanced disease.

Differential

- **Left atrial myxoma:** Causes obstruction of mitral inflow.
- **Cor triatriatum:** Left atrial septations cause postcapillary pulmonary hypertension.
- **Aortic insufficiency:** Can mimic the murmur of mitral stenosis (Flint murmur) due to restriction of mitral valve leaflet motion by regurgitant blood from the aortic valve, but no opening snap is present.

Diagnosis

- **Echocardiography:** Used to estimate valve area and to measure the transmitral pressure gradient. Mitral valve morphology on echocardiography determines a patient's suitability for percutaneous valvuloplasty.
- **TEE:** Indicated to exclude left atrial thrombus in patients scheduled for balloon valvotomy.
- **Cardiac catheterization:** Can be used to directly measure the valve gradient through simultaneous recording of PCWP and left ventricular diastolic pressure. Rarely needed for diagnosis; performed prior to percutaneous balloon valvotomy.

Treatment

- **Percutaneous mitral balloon valvotomy:** Unlike aortic valvuloplasty, balloon dilatation of the mitral valve has proven to be a successful strategy in patients without concomitant mitral regurgitation. Consider this intervention in symptomatic patients with isolated mitral stenosis and an effective valve area < 1.0 cm^2. This is the appropriate intervention in pregnant

women for whom medical therapy has failed. Severe annular calcification, severe mitral regurgitation, and atrial thrombus are all contraindications to balloon valvuloplasty.
- **Mitral valve replacement:** For patients who are not candidates for valvotomy or if the effective valve area is < 0.6 cm^2.
- Endocarditis prophylaxis is indicated for all patients.

Complications

- Left atrial enlargement and AF with resultant stasis is common and can result in left atrial thrombus formation and embolic stroke.
- Pulmonary hypertension and 2° tricuspid regurgitation.

Patients with rheumatic heart disease typically have involvement of the mitral valve. Isolated involvement of the aortic or tricuspid valve with sparing of the mitral valve is exceedingly rare in patients with rheumatic heart disease.

Mitral Regurgitation

Common causes of mitral regurgitation include mitral valve prolapse, myxomatous (degenerative) mitral valve disease, dilated cardiomyopathy (which causes functional mitral regurgitation due to dilatation of the mitral valve annulus), rheumatic heart disease (acute mitral valvulitis produces the Carey Coombs murmur of acute rheumatic fever), acute ischemia (due to rupture of a papillary muscle), mitral valve endocarditis, and trauma to the mitral valve.

Symptoms

- **Acute mitral regurgitation:** Abrupt onset of dyspnea due to pulmonary edema.
- **Chronic mitral regurgitation:** Can be asymptomatic. In severe cases, can present with dyspnea and symptoms of heart failure.

Exam

- Presents with a soft S1 and a holosystolic, blowing murmur heard best at the apex with radiation to the axilla. S3 can be due to mitral regurgitation alone (in the absence of systolic heart failure), and its presence suggests severe mitral regurgitation.
- Acute mitral regurgitation can be associated with hypotension and pulmonary edema; murmur may be early systolic.
- The intensity of the murmur does not generally correlate with mitral regurgitation severity as documented by echocardiogram.

Differential

- **Aortic stenosis:** Can mimic the murmur of mitral regurgitation (Gallavardin phenomenon).
- **Tricuspid regurgitation:** Characterized by a holosystolic murmur best heard at the left sternal border; ↑ in intensity with inspiration.

Diagnosis

- **Early detection of mitral regurgitation is essential because treatment should be initiated before symptoms occur.**
- **Exercise stress testing:** Document exercise limitation before symptoms occur at rest.
- **Echocardiography:** Transthoracic echocardiography (TTE) is important for diagnosis as well as for grading the severity of mitral regurgitation. TEE

In patients with mitral regurgitation, the intensity of the murmur on physical exam does not correlate with disease severity. In patients with acute myocardial ischemia, even a low-intensity murmur of mitral regurgitation should alert the physician to the possibility of papillary rupture.

is useful in patients who may need surgical repair or mitral valve replacement.
  - Echocardiography should be performed every 2–5 years in mild to moderate mitral regurgitation with a normal end-systolic diameter and an EF > 65%.
  - Echocardiography should be performed every 6–12 months in patients with severe mitral regurgitation, an end-systolic diameter > 4.0 cm, or an EF < 65%.
- **Catheterization:** To exclude CAD prior to surgery.

Treatment

- See Figure 3.14 for an overview of the treatment of advanced mitral regurgitation.
- **Medications:** ACEIs are useful only in patients with left ventricular dysfunction or hypertension. Medical therapy is generally the only option in patients with an EF < 30%.
- **Surgical intervention:**
  - **Indications for surgery** include symptoms related to mitral regurgitation, left ventricular dysfunction, AF, or pulmonary hypertension.
  - **Optimal timing of surgery is early in the course of the disease,** when patients progress from a chronic, compensated state to symptomatic mitral regurgitation.
  - Surgical outcomes are best in patients who have an EF > 60% and a left ventricular end-systolic diameter < 4.5 cm.

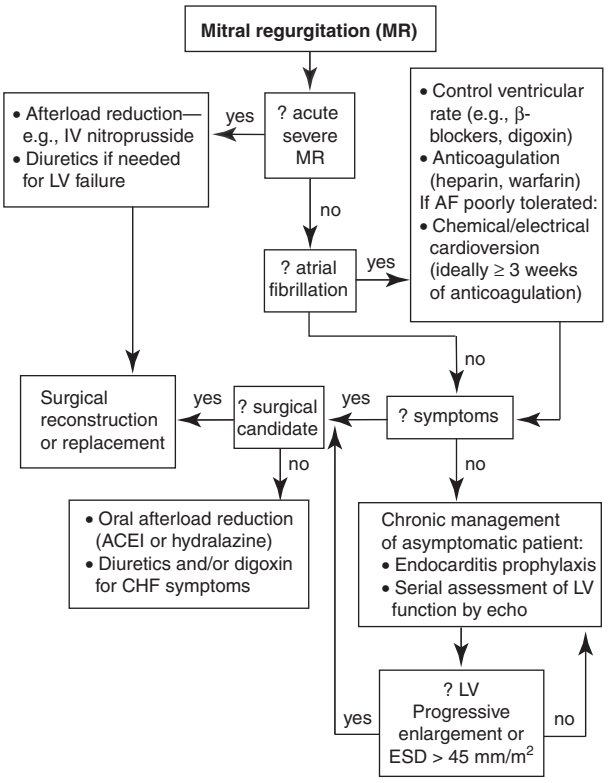

FIGURE 3.14. Management of advanced mitral regurgitation.

(Reproduced, with permission, from Braunwald E et al. *Harrison's Manual of Medicine,* 15th ed. New York: McGraw-Hill, 2001.)

- **Mitral valve repair:** Associated with better outcomes than mitral valve replacement. Repair is most successful when mitral regurgitation is due to prolapse of the posterior mitral valve leaflet.
- **Mitral valve replacement:** For symptomatic patients with an EF > 30% when the mitral valve is not technically repairable (can be predicted by echocardiography).

Mitral Valve Prolapse

Defined by a displaced and abnormally thickened, redundant mitral valve leaflet that projects into the left atrium during systole. Most recent studies demonstrate a prevalence of approximately 0.5–2.5% in the general population, with men and women affected equally. Mitral valve prolapse may be complicated by chordal rupture or endocarditis, both of which can lead to severe mitral regurgitation. Etiologies are as follows:

- **1°:** Familial, sporadic, Marfan's syndrome, connective tissue disease.
- **2°:** CAD, rheumatic heart disease, "flail leaflet," ↓ left ventricular dimension (hypertrophic cardiomyopathy, pulmonary hypertension, dehydration).

Symptoms

Most patients have no symptoms, and the diagnosis is often found incidentally on physical exam or echocardiography. However, some patients may present with atypical chest pain, palpitations, or TIAs.

Exam

Exam reveals a midsystolic click and midsystolic murmur with characteristic response to maneuvers. In more severe cases, listen for the holosystolic murmur of mitral regurgitation.

Endocarditis prophylaxis is not needed for patients with mitral valve prolapse unless they have evidence of mitral regurgitation, thickened mitral valves leaflets, or an audible systolic murmur associated with the midsystolic click.

Diagnosis

Echocardiography should be used for initial assessment; then follow every 3–5 years unless symptomatic or associated with mitral regurgitation (check echocardiogram yearly).

Treatment

- **Aspirin:** After a TIA and for patients < 65 years of age with lone AF.
- **Warfarin:** After a stroke and for those > 65 years of age with coexistent AF, hypertension, mitral regurgitation, or heart failure.
- β-blockers and electrophysiologic testing for control of arrhythmias.
- Surgery for cases of severe mitral regurgitation.

Prosthetic Valves

Indications for Placement

- **Bioprosthetic valves:** Older patients; patients with a life expectancy < 10–15 years; or those who cannot take long-term anticoagulant therapy (e.g., bleeding diathesis, high risk for trauma, poor compliance).
- **Mechanical valves:** Young patients; patients with a life expectancy > 10–15 years or with other indications for chronic anticoagulation (e.g., AF).

Repair vs. Replacement

- **Repair:** Mitral valve prolapse, ischemic mitral regurgitation, bicuspid aortic valve with prolapse, mitral or tricuspid annular dilatation with normal leaflets.
- **Replacement:** Rheumatic heart disease, endocarditis, heavily calcified valve, restricted leaflet motion, extensive leaflet destruction.

Anticoagulation

- No anticoagulation is needed for porcine valves after **three months** of warfarin therapy. Aspirin can be used in high-risk patients.
- For patients with mechanical valves, the level of anticoagulation depends on the location and type of valve (valves in the mitral and tricuspid position and older **caged-ball valves are most prone to thrombosis**).
- Risk factors for thromboembolic complications include AF, previous systemic emboli, left atrial thrombus, and severe left ventricular dysfunction.

Complications of Prosthetic Valves

- AF.
- Conduction disturbances.
- **Endocarditis:**
  - **Early prosthetic valve endocarditis:** Occurs during the first 60 days after valve replacement, most commonly due to *S. epidermidis;* often fulminant and associated with high mortality rates.
  - **Late prosthetic valve endocarditis:** Most often occurs in patients with multiple valves or bioprosthetic valves. Microbiology is similar to that of native valve endocarditis.
- **Hemolysis:** Look for schistocytes on peripheral smear. Usually occurs in the presence of perivalvular leak.
- **Thrombosis:**
  - At highest risk are those with mitral location of the valve and inadequate anticoagulation.
  - Presents clinically as heart failure, poor systemic perfusion, or systemic embolization.
  - Often presents acutely with hemodynamic instability.
  - Diagnose with echocardiogram.
  - For small thrombi (< 5 mm) that are nonobstructive, IV heparin should be tried initially. For large thrombi (> 5 mm), use more aggressive therapy such as fibrinolysis or valve replacement.
- **Perivalvular leak:** Rare. In severe cases, look for hemolytic anemia and valvular insufficiency causing heart failure.
- **Emboli:** Typically present as stroke, but can present as intestinal or limb ischemia.
- **1° valve failure:** Most common with bioprosthetic valves; usually occurs after 10 years.

ADULT CONGENITAL HEART DISEASE

Congenital heart disease comprises 2% of adult heart disease. Only the most common noncyanotic heart defects will be presented here. Table 3.16 out-

TABLE 3.16. Tolerance of Pregnancy by Patients with Congenital Cardiac Malformations

Well Tolerated	Intermediate Effect	Poorly Tolerated
NYHA class I	NYHA class II–III	NHYA class IV
Left-to-right shunts without pulmonary hypertension	Repaired transposition of the great arteries	Right-to-left shunt; unrepaired cyanotic heart disease
Aortic or mitral valvular regurgitation (mild to moderate)	Fontan repairs	Pulmonary hypertension and/or pulmonary vascular disease (e.g., Eisenmenger's, 1° pulmonary hypertension)
Pulmonic or tricuspid regurgitation (if low pressure, even severe)	Aortic or mitral stenosis (moderate)	Aortic or mitral stenosis (severe)
Pulmonic stenosis (mild to moderate)	Ebstein's anomaly	Pulmonic stenosis (severe)
Well-repaired tetralogy of Fallot		Marfan's or aortic coarctation

Reproduced, with permission, from Kasper DL et al. *Harrison's Principles of Internal Medicine,* 16th ed. New York: McGraw-Hill, 2005: 1383.

lines the extent to which patients with congenital cardiac malformations can tolerate pregnancy. Examples of adult congenital heart disease follow.

Atrial Septal Defect (ASD)

There are three major types: ostium secundum (most common), ostium primum, and sinus venosus.

Symptoms

Most cases are asymptomatic and are either diagnosed incidentally on echocardiography or found during workup of paradoxical emboli. Large shunts can cause dyspnea on exertion and orthopnea.

Exam

- Characterized by a **fixed wide splitting of S2** with a loud P2 as pulmonary hypertension develops.
- Exam reveals a systolic flow murmur (usually best heard at the left upper sternal border) and occasionally a diastolic rumble across the tricuspid valve due to ↑ flow.

Diagnosis

- **ECG:** Shows incomplete RBBB with right axis deviation in ostium secundum ASD. Left axis deviation suggests ostium primum ASD; RVH may be present in all forms
- **CXR:** Shows a prominent pulmonary artery, an enlarged right atrium, and an enlarged right ventricle.
- **Echocardiography with agitated saline bubble study:** Can be used to visualize the intracardiac shunt and to determine the ratio of pulmonary-to-systemic blood flow (Q_p/Q_s).
- **TEE:** Extremely useful for documenting the location and size of the defect and for excluding associated lesions.

Correction of ASD carries a long-term survival rate better than that of medical therapy alone and is recommended even for asymptomatic patients with significant shunts ($Q_p/Q_s > 1.5:1$).

- Cardiac catheterization documenting an increase in O_2 saturation between the SVC and the right atrium is the gold standard.

Treatment

- Percutaneous device closure is the treatment of choice for ostium secundum ASDs.
- Surgical correction is indicated for very large defects as well as for ostium primum and sinus venosus defects.
- Endocarditis prophylaxis is not indicated for isolated uncorrected ASDs but is indicated for six months after closure by device or surgery.

Complications

- Paradoxical embolization leading to TIAs and strokes.
- AF and atrial flutter.
- Pulmonary hypertension and **Eisenmenger's syndrome.**
- Endocarditis is rare in patients with secundum ASD but can occur in other types.

Coarctation of the Aorta

Proximal narrowing of the descending aorta just beyond the left subclavian artery with development of collateral circulation involving the internal mammary, intercostal, and axillary arteries. A bicuspid aortic valve is present in > 50% of patients with coarctation of the aorta. More common in males than in females.

Symptoms

Presents with headache, dyspnea, fatigue, and leg claudication.

Exam

Exam reveals diminished femoral pulses with a radial-to-femoral-pulse delay and a continuous scapular murmur due to collateral flow.

Differential

- Other causes of 2° hypertension, including renal artery stenosis.
- Peripheral arterial disease leads to diminished femoral pulses and claudication.

Diagnosis

- **CXR:** Reveals rib notching from enlarged collaterals.
- **ECG:** Shows LVH.
- **Cardiac catheterization with aortography:** To define stenosis and measure gradient.
- **MRI/MRA:** Offer excellent visualization of the location and extent of coarctation.

Treatment

- Medical treatment of hypertension.
- Surgical correction is appropriate for patients < 20 years of age and in older patients with upper extremity hypertension and a gradient of ≥ 20 mmHg.

- Balloon dilatation with or without stent placement is an alternative for native or recurrent coarctation.
- Requires prophylaxis for endocarditis during dental procedures where there may be perforation of the oral mucosa.

Coarctation of the aorta is commonly associated with congenital bicuspid aortic valve.

Complications

- LVH and dilatation due to ↑ afterload.
- Severe hypertension.
- Aortic dissection or rupture
- SAH due to rupture of aneurysms of the circle of Willis (rare).
- Premature CAD.

Patent Ductus Arteriosus (PDA)

Uncommon in adults. Risk factors include premature birth and exposure to rubella virus in the first trimester.

Symptoms

Usually asymptomatic, but moderate to large shunts can cause dyspnea, fatigue, and eventually signs and symptoms of pulmonary hypertension and right heart failure.

Exam

- Exam reveals a continuous "machinery-like" murmur at the left upper sternal border and bounding peripheral pulses due to rapid aortic runoff to the pulmonary artery.
- In the presence of pulmonary hypertension (Eisenmenger's syndrome), the murmur is absent or soft, and there is differential cyanosis involving the lower extremities and sparing the upper extremities.

Differential

Other shunts, including ASDs and VSDs.

Diagnosis

- **ECG:** Nonspecific; LVH and left atrial enlargement in the absence of pulmonary hypertension can be seen.
- **Echocardiography:** Can be used to calculate the shunt fraction and to estimate pulmonary artery systolic pressure. Abnormal ductal flow can be visualized in the pulmonary artery.
- **Cardiac catheterization:** Can be used to document an increase in O_2 saturation from the right ventricle to the pulmonary artery.

Differential cyanosis of the fingers (pink) and toes (blue and clubbed) is pathognomonic for Eisenmenger's syndrome caused by an uncorrected PDA.

Treatment

Endocarditis prophylaxis, transcatheter coil closure, surgical correction.

Complications

Eisenmenger's syndrome with pulmonary hypertension and shunt reversal; infective endocarditis.

Ventricular Septal Defect (VSD)

Most VSDs occur in close proximity to the membranous portion of the intraventricular septum, but muscular, supracristal, inlet, and outlet VSDs can also occur.

Symptoms

Most patients diagnosed in adulthood are asymptomatic, but insidious dyspnea on exertion and orthopnea may develop.

Surgical closure is contraindicated once Eisenmenger's syndrome develops because it can ↑ pulmonary hypertension and right heart failure.

Exam

- A holosystolic murmur is heard at the left lower sternal border with a right ventricular heave and prolonged splitting of S2.
- As pulmonary arterial pressure ↑, a loud P2 and tricuspid regurgitation can also be appreciated.
- Cyanosis, clubbing, and signs of right heart failure can appear with the development of Eisenmenger's syndrome.

Differential

Other shunts, including ASD and PDA.

Diagnosis

- Echocardiography with agitated saline bubble study can be used to visualize the intracardiac shunt, determine size, and ascertain Q_p/Q_s.
- Cardiac catheterization documenting an increase in O_2 saturation between the right atrium and right ventricle is the gold standard.
- **ECG:** Nonspecific; LVH and left atrial enlargement in the absence of pulmonary hypertension can be seen. Right atrial enlargement, RVH, and RBBB can develop with the development of pulmonary hypertension.
- **CXR:** Cardiomegaly and enlarged pulmonary arteries.

Treatment

- Endocarditis prophylaxis for a VSD of any size.
- Diuretics and vasodilators to ↓ left-to-right shunt and symptoms of right heart failure.
- Surgical correction is appropriate for patients with significant shunt ($Q_p/Q_s > 1.7:1$).
- Once pulmonary hypertension occurs (systolic pulmonary artery pressure > 85 mmHg), mortality is ~50%

Complications

- **Eisenmenger's syndrome:**
  - Long-standing left-to-right shunting causes pulmonary vascular hyperplasia, resulting in pulmonary arterial hypertension and shunt reversal (right-to-left shunt).
  - Symptoms include dyspnea, chest pain, syncope, and hemoptysis.
- Paradoxical embolism leading to TIAs or stroke.
- Infective endocarditis.

Aortic Dissection

Approximately 2000 cases are diagnosed each year in the United States. Aortic dissection is associated with uncontrolled hypertension, medial degeneration of the aorta (Marfan's syndrome, Ehlers-Danlos syndrome), cocaine use, coarctation, congenital bicuspid valve, trauma, cardiac surgery, pregnancy, and syphilitic aortitis. **Type A = proximal dissection; type B = distal dissection** (the dissection flap originates distal to the left subclavian artery).

Symptoms

- Classically presents as a sudden-onset "tearing" or "ripping" sensation originating in the chest and radiating to the back, but symptoms may not be classic.
- Unlike MI, pain is maximal at the onset and is not gradual in nature.
- Can present with organ hypoperfusion due to occlusion of arteries by the dissection flap (e.g., coronary ischemia, stroke, intestinal ischemia, renal failure, limb ischemia).
- Other presentations include cardiac tamponade and aortic insufficiency in cases of proximal aortic dissection.

Exam

- BP is elevated (although hypotension can be seen with proximal dissections associated with tamponade).
- In proximal dissection, listen for the diastolic murmur of aortic insufficiency.
- Exam reveals pulse deficits or unequal pulses between the right and left arms.
- Can present with focal neurologic deficits (from associated cerebrovascular infarct) or with paraplegia (from associated anterior spinal artery compromise).

Proximal (type A) aortic dissection can present as acute inferior or right-sided MI due to involvement of the right coronary artery (prone to occlusion by the dissection flap).

Differential

Acute MI, cardiac tamponade, thoracic or abdominal aortic aneurysm, pulmonary embolism, tension pneumothorax, esophageal rupture.

Diagnosis

- Three major clinical predictors are sudden, tearing chest pain; differential pulses or blood pressures between the right and left arms; and abnormal aortic or mediastinal contour on CXR. If all three are present, the positive likelihood ratio is 0.66. The negative likelihood ratio if all three are absent is 0.07.
- **CXR:** Look for a widened mediastinum (occurs in approximately 60% of all aortic dissections).
- **TEE:** The fastest and most portable method for unstable patients, but may not be available at all hospitals. Sensitivity is 98% and specificity 95%.
- **Chest CT:** Sensitivity is 94% and specificity 87%.
- **MRI:** Highly sensitive (98%) and specific (98%), but the test is slow and may not be available at many hospitals. Good for following patients with type B dissections.
- **Aortography:** Not ideal given the invasive nature of the test and the associated delay in initiating definitive surgical therapy.

Proximal (type A) aortic dissection can present as acute paraplegia due to occlusion of the anterior spinal artery.

Treatment

- **Type A:** Surgical repair.
- **Type B:** Admit to the ICU for medical management of hypertension. Treat first with β-blockers (esmolol, labetalol) and then with IV nitroprusside. Avoid anticoagulation. Surgery is indicated for complications of dissection, end-organ damage, or failure to control hypertension.

Complications

- Acute MI from occlusion of the right coronary artery by the dissection flap or dissection of the coronary artery.
- Acute aortic insufficiency, which can present as hemodynamic instability and heart failure.
- Cardiac tamponade due to dissection into the pericardium.
- Cardiac arrest.
- Cerebrovascular accident (due to concomitant carotid artery dissection).
- Occlusion of distal arteries can lead to end-organ damage (e.g., paraplegia, renal failure, intestinal ischemia, limb ischemia).

Peripheral Vascular Disease

Atherosclerosis of the peripheral arterial system is associated with the same clinical risk factors as coronary disease (smoking, diabetes, hypertension, and hyperlipidemia).

Symptoms

Intermittent claudication is reproducible pain in the lower extremity muscles that is brought on by exercise and relieved by rest; however, most peripheral vascular disease is asymptomatic.

Exam

Presents with poor distal pulses, femoral bruits, loss of hair in the legs and feet, slow capillary refill, and poor wound healing (chronic ulceration).

Differential

- Nearly all peripheral vascular disease is caused by atherosclerosis. Less common causes include coarctation, fibrodysplasia, retroperitoneal fibrosis, and radiation.
- Nonarterial causes of limb pain include spinal stenosis (pseudoclaudication), deep venous thrombosis, and peripheral neuropathy (often coexists with peripheral vascular disease in diabetics).

Diagnosis

- **Ankle-brachial index (ABI) < 0.90** (the highest ankle systolic pressure measured by Doppler divided by the highest brachial systolic pressure).
- **MRI** is a useful noninvasive diagnostic test.
- Lower extremity **angiography** is the gold standard.

Treatment

- Aggressive cardiac risk factor reduction, including control of smoking, hypertension, and hyperlipidemia.
- Initiate a structured exercise rehabilitation program.

- **Pharmacotherapy:**
  - **Antiplatelet agents:** Aspirin is first-line therapy for overall cardiovascular event reduction, but data also support the use of ticlopidine, clopidogrel, and dipyridamole in peripheral vascular disease.
  - **ACEIs.**
  - **Pentoxifylline:** ↑ RBC deformability to ↑ capillary flow.
  - **Cilostazol:** Inhibits platelet aggregation and promotes lower arterial vasodilation.
- **Surgery:**
  - Percutaneous transluminal angioplasty and lower extremity revascularization bypass surgery should be used only for severe symptoms.
  - Thrombolytic therapy is appropriate for acute limb ischemia.

If defined as ABI < 0.90, most peripheral vascular disease is asymptomatic but still confers a high risk of adverse cardiovascular events and death.

COMPLICATIONS

- Critical leg ischemia leading to limb amputation.
- Even asymptomatic peripheral vascular disease is a major risk factor for adverse cardiovascular events

NOTES

CHAPTER 4

Critical Care

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ACUTE RESPIRATORY DISTRESS SYNDROME (ARDS)

Acute-onset respiratory failure characterized by bilateral pulmonary infiltrates and hypoxemia in the setting of a pulmonary capillary occlusion pressure of ≤ 18 mmHg or in the absence of clinical evidence of left atrial hypertension. Thought to be due to both alveolar epithelial cell and vascular endothelial cell injury. Commonly associated with pneumonia, aspiration, sepsis, trauma, acute pancreatitis, cardiopulmonary bypass, transfusion of blood products, inhalational injury, and reperfusion injury after lung transplantation.

Symptoms/Exam

- Presents with rapid onset of dyspnea, tachypnea, and diffuse crackles.
- Approximately 25% of survivors have no pulmonary impairment at one year; 50% have mild impairment, 25% moderate impairment, and a small fraction severe impairment. Reduced single-breath DL_{CO} is the most common pulmonary function abnormality.

Differential

Cardiogenic pulmonary edema, pneumonia, diffuse alveolar hemorrhage.

To improve mortality in patients with ARDS, target a tidal volume of ≤ 6 cc/kg ***predicted*** *body weight.*

Diagnosis

Both acute lung injury (ALI) and ARDS are clinically defined by rapidity of symptom onset, oxygenation, hemodynamic criteria, and CXR findings (see Table 4.1). Additional findings are as follows:

- **CT of the thorax:** May demonstrate alveolar filling and consolidation in dependent lung zones with sparing of other areas.
- **Bronchoalveolar lavage (BAL):** May help differentiate the etiology (e.g., *Pneumocystis* in the immunocompromised patient).

Treatment

- Search for and treat the underlying cause of acute respiratory failure (ARF).
- Most patients with ARDS require mechanical ventilation during the course of the disease.
  - **Use of tidal volumes ≤ 6 cc/kg of predicted body weight has been shown to ↓ mortality.**
  - Positive end-expiratory pressure (PEEP) can help improve oxygenation and ↓ high levels of inspired O_2.
    - Plateau pressure must be kept at < 30 cm H_2O to prevent barotrauma (see the discussion of ventilator management).

TABLE 4.1. Diagnosis of ALI vs. ARDS

	Onset of Symptoms	Oxygenation	Hemodynamics	CXR
ALI	Acute	$Pao_2/Fio_2 \leq 300$	Low or normal left atrial pressure	Bilateral infiltrates
ARDS	Acute	$Pao_2/Fio_2 \leq 200$	Low or normal left atrial pressure	Bilateral infiltrates

    - There is no difference in mortality between high and low PEEP strategies; therefore a low PEEP strategy is recommended.
- Information from trials to guide fluid management in ALI and ARDS patients includes the following:
    - Pulmonary artery catheters should not routinely guide fluid management, as outcomes are equivalent to those associated with central venous catheters.
    - A conservative fluid management strategy (i.e., one involving less volume) is preferred over a liberal fluid strategy. In a recent randomized trial comparing such strategies, both techniques yielded similar 60-day mortality rates, but conservative management was found to be associated with shorter mechanical ventilation and ICU times.
- Corticosteroids have been given in the proliferative phase of ARDS, but their use in this context is still considered experimental. The use of inhaled vasodilators, exogenous surfactant, high-frequency ventilation, liquid ventilation, and antioxidant therapy have been studied with no proven benefit.

ACUTE RESPIRATORY FAILURE (ARF)

Consists of failure in oxygenation characterized by hypoxemia or failure in ventilation characterized by hypercarbia. Oxygenation and ventilatory failure can occur simultaneously. However, failure in oxygenation may occur despite adequate ventilation (pulmonary hypertension and a newly patent foramen ovale), and failure in ventilation may occur despite adequate oxygenation (neuromuscular weakness).

Symptoms/Exam

The clinical presentation varies with the underlying disease process. Whereas dyspnea, tachypnea, respiratory alkalosis, and hypoxemia suggest hypoxic respiratory failure, ↓ respiratory rate and unresponsiveness point to hypercarbic respiratory failure.

Differential

The differential of ARF is outlined in Tables 4.2 and 4.3.

Treatment

- Treatment depends on the etiology. In all cases, focus on providing sufficient O_2 through use of supplemental oxygen and maintenance of adequate ventilation.
- In patients with COPD and ARF, evidence suggests that noninvasive positive-pressure mechanical ventilation ↓ the need for intubation, shortens hospital stays, and ↓ in-hospital mortality.
- For patients with pulmonary edema and ARF, evidence strongly suggests that the use of continuous positive airway pressure (CPAP) greatly ↓ the need for intubation.
- Although noninvasive techniques have been studied in other causes of ARF, results have been controversial, and intubation with mechanical ventilation remains the standard of care.

TABLE 4.2. Etiologies of Hypoxemic Respiratory Failure

Cause	Mechanism	Disease States	Comments
↓ Fio_2 or low total O_2	O_2 is replaced by other gases (enclosed spaces, fire), or low O_2 from high altitudes and air travel results in reduced Pao_2.		
Diffusion abnormality	Reduction in diffusion capacity leads to low Pao_2.	Pulmonary alveolar proteinosis.	An uncommon cause of hypoxemic respiratory failure.
Hypoventilation	↓ minute ventilation results in ↑ $Paco_2$ and ↓ Pao_2 according to the alveolar gas equation.	See Table 4.3.	Normal alveolar-arterial (A-a) gradient.
Ventilation-perfusion (V/Q) mismatch	Results when there is an altered ratio of perfusion to ventilation.	Pulmonary embolus, pulmonary hypertension, COPD, asthma.	↑ A-a gradient; Pao_2 corrects with supplemental O_2.
Shunt	Occurs when there is perfusion to the nonventilated lung or a communication between the arterial and venous systems.	ARDS, pneumonia, pulmonary AVM, congenital heart disease, patent foramen ovale with right-to-left flow.	↑ A-a gradient; Pao_2 does not correct with supplemental O_2.

VENTILATOR MANAGEMENT

A ventilator is a machine designed to reduce the mechanical work of breathing and to improve gas exchange. Invasive ventilatory support is provided through an airway such as an endotracheal or tracheostomy tube. The main indication for mechanical ventilation is **ARF** of any cause. Patients with ARF and COPD or pulmonary edema may respond to noninvasive techniques. Other indications include surgery with general anesthesia and airway protection with drug overdose.

Classification

Mechanical ventilation is categorized by the way in which the machine terminates an inspired breath:

- **Volume cycled (most common):** Terminates inspiration after a preset volume has been delivered.
- **Pressure cycled:** Ends inspiration when a preset pressure has been reached. The volume of the delivered breath will vary depending on lung/chest wall mechanics.
- **Flow cycled:** Stops inspiration when a flow rate has been reached. The ventilator delivers a breath with a preset pressure, and the cycle is terminated when the inspiratory flow rate falls to a predetermined level.
- **Time cycled:** Ceases inspiration after a preset inspiratory time has elapsed.

TABLE 4.3. Etiologies of Hypercarbic Respiratory Failure

Cause	Mechanism	Disease States
CNS disorders/↓ ventilatory drive	↓ minute ventilation leads to ↑ $Paco_2$.	Drug overdose, CNS lesion/infarction, central sleep apnea, hypothyroidism.
Peripheral nerve disorders	Same as above.	Guillain-Barré syndrome, ALS, poliomyelitis, West Nile virus, ICU-acquired paresis.
Neuromuscular junction disorders	Same as above.	Myasthenia gravis, botulism.
Muscle disorders	Same as above.	Muscular dystrophy, glycogen storage disease, ICU-acquired paresis.
Lung disorders	↓ alveolar ventilation due to obstructive lung disease leads to ↑ $Paco_2$.	COPD, asthma, CF.
Chest wall disorders	Chest wall mechanics are altered, leading to ↓ alveolar ventilation and ↑ $Paco_2$.	Kyphoscoliosis, massive obesity.

Mode

Full ventilatory support is provided using either conventional mechanical ventilation or alternative modes of ventilation.

- **Conventional modes:**
  - **Assist control:** Senses an inspiratory effort and delivers a preset tidal volume. The physician sets a mandatory minimum machine-triggered rate and the tidal volume. If the patient attempts to spontaneously breathe above the set rate, the additional breaths will be delivered at the same tidal volume as the mandatory breaths. Tidal volume is determined by the physician, whereas respiratory rate is patient dependent.
  - **Synchronized intermittent mandatory ventilation:** Delivers a breath of set tidal volume at a set rate (e.g., AC). Additionally, the patient may breathe spontaneously and will get the tidal volume he/she can pull spontaneously. The spontaneous breaths and mandatory breaths are synchronized to reduce breath stacking.
  - **Pressure support:** Delivers a breath with a set pressure; ends inspiration once flow rate has fallen to a percentage of its maximum value. Although many patients find this mode comfortable, it requires close monitoring, as tidal volume and respiratory rate are both determined by the patient. **Caution:** There is no set minute ventilation, so a non–spontaneously breathing patient will have apnea. Can be combined with synchronized intermittent mandatory ventilation.
- **Alternative modes:**
  - **Pressure control:** Delivers a breath until a preset pressure is reached. Evidence suggests that there is no clear-cut advantage to this mode in comparison to conventional mechanical ventilation.
  - **High-frequency oscillator ventilation:** Delivers rapid, low-tidal-volume breaths that oscillate around a mean airway pressure. The literature

suggests that this is an acceptable alternative to conventional ventilator modes in patients with ARDS. However, the need for specialized equipment and training limits its use. Moreover, a definitive demonstration of its benefit over conventional ventilation is still lacking.

- **Airway pressure release ventilation:** Provides continuous positive pressure to inflate the lungs. The pressure is cyclically **released** to allow for lung deflation and gas exchange. Remains an experimental mode of ventilation.

Settings and Measurements

After a patient has been intubated, a number of adjustments must be made and physiologic measurements obtained from the ventilator. Table 4.4 presents the differential for patients with ventilator crises.

- **Mode:** The initial choice should be based on physician and staff familiarity with the ventilator mode as well as on the patient-specific disease process. Assist control is a good first choice in most clinical situations and is the most common ventilator mode used in the ICU.
- **Respiratory rate:** The minute ventilation needs prior to intubation should be approximated. Respiratory rate multiplied by tidal volume will deter-

TABLE 4.4. Etiologies of Ventilator Crises

↑ Peak Airway Pressure/Normal Plateau Pressure	↑ Peak Airway Pressure/High Plateau Pressure	↓ O_2 Saturation	Rising Partial Pressure of CO_2	Patient Distress
■ Endotracheal tube obstruction, kink, or malposition ■ **Airway obstruction:** Bronchospasm, mucous plug ■ **Patient effort/agitation:** Coughing, biting, fighting	■ **Reduced lung compliance:** Pulmonary edema, pneumonia ■ **Reduced chest wall/abdominal compliance:** Pneumothorax, abdominal distention	■ Ventilator/mixer malfunction ■ Endotracheal tube malposition/leak ■ **New lung derangement:** Atelectasis, aspiration, edema ■ **New cardiovascular derangement:** Shock, pulmonary embolism, decreases in hemoglobin concentration ■ ↑ oxygen consumption ■ Changes in body position, increasing shunt	■ Ventilator malfunction ■ Endotracheal tube malfunction/leak ■ **New patient mechanical derangement:** Bronchospasm, edema ■ ↑ dead space ■ ↑ CO_2 production	■ Pain/discomfort unrelated to the ventilator or respiratory system (e.g., myocardial ischemia) ■ Endotracheal tube malposition ■ Increasing work of breathing ■ Rising partial pressure of CO_2 ■ Oxyhemoglobin desaturation ■ Shock/pulmonary embolism ■ Inadequate sedation ■ Alcohol or drug withdrawal

Adapted, with permission, from Hall JB et al. *Principles of Critical Care,* 3rd ed. New York: McGraw-Hill, 2005.

mine minute ventilation. If the patient is paralyzed, the rate should reflect the patient's entire needs. If the patient is very ill, one may wish to provide almost all breaths as mandatory breaths so that the work of triggering is removed. Rates up to 35 are generally acceptable unless the patient cannot fully exhale at such rapid rates (e.g., status asthmaticus). Slower rates should then be used even if hypercapnia occurs.

- **Tidal volume:** The use of tidal volumes of 6 cc/kg for ARDS patients has been shown to ↓ mortality when compared with higher tidal volumes. Evidence also suggests that lower tidal volumes may reduce the risk of ventilator-induced lung injury.
- **Fio_2:** In general, start with 100% Fio_2. Attempts should be made to ↓ O_2 to the lowest amount needed to keep arterial saturation > 90% or Pao_2 > 60 mmHg.
- **Flow rate:** Rates of 60 L/min are sufficient for most patients. Rates must often be ↑ in patients with ARF and COPD.
- **Sensitivity:** A sensitivity of −1 to −3 cm H_2O is often used. If the ventilator is too sensitive (a more positive number), breaths may be triggered simply by moving the patient or ventilator tubing. Flow triggering is also possible.
- **PEEP:** A small amount (5 cm H_2O) is typically used. ↑ levels are used in patients with ARDS to improve oxygenation and possibly to prevent further lung injury. Higher levels of PEEP may also be used in patients with cardiogenic pulmonary edema to improve oxygenation as well as to ↓ preload and afterload.
- **Plateau pressure:** Measured by occluding the expiratory port at end inspiration. Since flow is held at the end of a breath, this pressure reflects the static compliance of the lungs and chest wall. The peak-plateau difference helps determine the source of the high pressure.

$$\text{Static compliance} = V_T / (\text{PPL} - \text{PEEP})$$

where V_T = tidal volume and PPL = plateau pressure.

- **Peak pressure:** Measured directly by the ventilator. Reflects pressure due to flow resistance (ventilator circuit, endotracheal tube, proximal airways) and lung and chest wall compliance. Increases in peak pressure suggest either ↓ lung/chest wall compliance or ↑ airway resistance. If the peak pressure is elevated, examine the patient and measure plateau pressure (see Table 4.4).
- **Auto-PEEP:** Measured by covering the expiratory port on the ventilator at end expiration. Caused by delayed emptying of the lungs and subsequent initiation of a new breath before the lungs have fully emptied. Common in mechanically ventilated patients with COPD and asthma.

To prevent barotrauma (i.e., pneumothorax), target a plateau pressure, not peak pressure, below 30 cm H_2O, as the risk ↑ when plateau airway pressure exceeds 35 cm H_2O.

Sedation Management and Weaning

- Administer both anxiolytic and analgesic medications to patients while they are receiving mechanical ventilation through an endotracheal tube.
- Daily interruption of sedative infusions in critically ill patients improves outcomes in comparison to usual care.
- Twenty percent of mechanically ventilated patients fail their first attempt at weaning. Weigh the benefits of early extubation (preventing pneumonia, GI bleeding, and venous thromboembolism) against the effects of premature extubation (reintubation, which ↑ mortality).
- Once the patient is awake, attempt a spontaneous breathing trial if he/she passes a screen for readiness to wean.

Most patients with shock present with cold and clammy skin; however, distributive (i.e., septic) shock often presents with flushed, hyperemic skin.

Adrenal insufficiency and severe hypo- or hyperthyroidism may present clinically as shock. These diagnoses should be considered when patients are not responding to fluid resuscitation.

A physiologic state characterized by reduced tissue perfusion and subsequent tissue hypoxia. Prolonged tissue hypoxia often leads to cell death, organ damage, multiorgan system failure, and eventual death.

Symptoms/Exam

Most patients who present with shock are hypotensive. This ↓ in blood pressure is due to a fall in cardiac output and/or to a reduction in systemic vascular resistance (SVR). Regardless of the cause of shock, the majority of patients are also tachypneic and tachycardic and appear to be in distress. A narrowed pulse pressure, cool extremities, and delayed capillary refill suggest a cardiac cause with diminished cardiac output. By contrast, fever, a bounding pulse, warm extremities, and rapid capillary refill suggest an infectious cause with preserved or ↑ cardiac output and ↓ SVR. ↓ JVP might suggest hypovolemia, and the presence of an elevated JVP, pulsus paradoxus, and muffled heart sounds implies pericardial tamponade.

Diagnosis

Shock can be categorized into four different types, as indicated in Table 4.5. If the type of shock cannot be determined after careful physical examination, additional information can be obtained using invasive monitoring devices.

- **Echocardiography:** Useful for distinguishing poor cardiac function from hypovolemia; can also confirm pericardial tamponade or significant pulmonary hypertension.
- **Central venous catheter:** Use in the superior vena cava can provide an estimate of right heart filling pressures.
- **Pulmonary artery catheter:** Can help measure cardiac output, pulmonary capillary occlusion pressure (PCOP), and $S\bar{v}O_2$ and help calculate SVR to differentiate the type of shock. However, controversy exists over the use of pulmonary artery catheters in this setting, as they have not been shown to improve patient outcomes.

Treatment

Regardless of the cause, treatment should focus on resuscitation and improving end-organ perfusion.

TABLE 4.5. Categories of Shock

	Cardiac Output	SVR	PCOP	$S\bar{v}O_2$[a]	Examples
Distributive	↑	↓	↓	↔ or ↑	Sepsis, anaphylaxis.
Cardiogenic	↓	↑	↑ (except in RV infarct)	↓	Acute MI, CHF.
Hypovolemic	↓	↑	↓	↓	Trauma, bleeding.
Obstructive	↓	↑	↑ (tamponade) or ↓ (pulmonary embolism)	↓	Tamponade, pulmonary embolism, tension pneumothorax.

[a] SvO2 = mixed venous arterial saturation.

- Aggressive IV fluid hydration should be given to patients with hypovolemic or distributive shock. Blood products should be given in cases of trauma or acute bleeding.
- Broad-spectrum antibiotics should be given empirically if infection is suspected. If a patient remains in shock despite the restoration of intravascular volume, vasoactive drugs such as dopamine, norepinephrine, and phenylephrine should be considered.

SEPSIS

A clinical syndrome associated with severe infection that arises from systemic inflammation and uncontrolled release of proinflammatory mediators, leading to extensive tissue injury. Despite improvements in antibiotics and advances in critical care, mortality and morbidity remain high. Sepsis can be viewed as a spectrum of disease that includes systemic inflammatory response syndrome (SIRS), sepsis, severe sepsis, and septic shock. These conditions within the continuum of sepsis are defined in Table 4.6.

Symptoms/Exam

Patients in the early phases of sepsis are often anxious, febrile, tachycardic, and tachypneic. The physical exam is variable and may initially demonstrate bounding pulses, warm extremities, and rapid capillary refill in the patient with SIRS. However, signs may progress to showing weak pulses, cool extremities, and slow capillary refill in patients with severe sepsis and septic shock.

Treating patients with severe sepsis is as easy as ABCDE:

Antibiotics/**A**RDS—low tidal volume ventilation
Blood sugar control
Corticosteroids
Drotrecogin alfa (activated)
Early goal-directed therapy

Differential

Cardiogenic, obstructive, or hypovolemic shock; fulminant hepatic failure; drug overdose; adrenal insufficiency; pancreatitis.

Diagnosis/Treatment

- Always obtain appropriate cultures before initiating antibiotic therapy. These should include the following:

TABLE 4.6. Conditions Associated with Sepsis

Condition	Definition
SIRS	A clinical syndrome recognized by the presence of two or more of the following: ■ Temperature > 38°C or < 36°C ■ HR > 90 bpm ■ RR > 20 breaths per minute or $Paco_2$ < 32 mmHg ■ WBC > 12,000 cells/mm^3, < 4000 cells/mm^3, or > 10% bands.
Sepsis	SIRS with definitive evidence of infection.
Severe sepsis	Sepsis with organ dysfunction and hypoperfusion.
Septic shock	Sepsis with hypotension despite adequate fluid resuscitation combined with altered mental status, oliguria, and/or lactic acidosis.

- At least two sets of blood cultures, with at least one drawn percutaneously.
- Cultures of other sites, including urine, CSF, wounds, respiratory secretions, or other body fluids, as indicated by the clinical situation.

- IV antibiotic therapy should be initiated within the first hour of severe sepsis and should adhere to the following criteria:
  - Include at least one drug that penetrates into the suspected source of sepsis.
  - Reassess after 48–72 hours on the basis of clinical and microbiological information.
  - Continue for 7–10 days, guided by clinical response once a pathogen has been identified.
  - Include combination therapy for *Pseudomonas* infection in neutropenic patients.
- Initial resuscitation should begin as soon as the syndrome is recognized. In light of ongoing capillary leak and systemic venodilation, patients will often require up to 10 L of fluid within the first 24 hours. During the **first six hours** of resuscitation, goals should include the following:
  - **Central venous pressure (CVP):** 8–12 mmHg.
  - **Mean arterial pressure (MAP):** > 65 mmHg.
  - **Urine output:** ≥ 0.5 mL/kg/hr.
  - **Central venous or mixed venous saturation:** ≥ 70%.
- Start vasopressors if no sustained response is seen to fluid challenge.
  - Norepinephrine and dopamine are first-line agents.
  - Vasopressin may be considered after failure of fluids and conventional vasopressors.
  - Treatment should be guided by the placement of an arterial catheter in most patients.
  - Treatment should **not** include low-dose dopamine for renal protection.
- Corticosteroids have been shown to be effective in patients with **septic shock** who still require vasopressors despite adequate volume resuscitation. If plasma cortisol does not ↑ by at least 9 μg/dL after an **ACTH stimulation test,** continue treatment with hydrocortisone and fludrocortisone.
- Recombinant human activated protein C or drotrecogin alfa (activated) is recommended for patients with a high risk of death and with no absolute contraindication related to likelihood of bleeding. In a recent clinical trial, mortality was increased in patients with single-organ failure or an APACHE score of < 25.
- Consider the following interventions in all critically ill patients, including those with sepsis:
  - Catheter-related bloodstream infections can be significantly ↓ through a simple strategy of washing hands, cleaning the skin with chlorhexidine, avoiding the femoral vein, using full barrier precautions during catheter insertion, and removing unnecessary catheters.
  - Intensive insulin therapy targeting a blood glucose level of **80–110 mg/dL** has been shown to improve mortality in a surgical ICU setting. However, a similar trial in the medical ICU did not show an improvement in mortality, but patients were weaned from the ventilator and discharged from the medical ICU faster in comparison with liberal glycemic control.
  - Once hypoperfusion has resolved, blood transfusion should occur only at a hemoglobin level of ≤ 7 **g/dL** unless the patient is suffering from cardiac ischemia, lactic acidosis, or acute hemorrhage.

- Sepsis is one of the most common causes of ARDS, and low tidal volume ventilation (**6 cc/kg predicted body weight**) should be initiated if the patient develops this condition.
- All patients in the ICU should receive DVT and GI prophylaxis.

FEVER IN THE ICU

Fever is a common problem in the ICU and is defined as a temperature ≥ 38.3°C (≥ 101°F). Accurate and reproducible measurements are necessary to detect disease. Mixed venous blood in the pulmonary artery is the ideal site for measuring core body temperature. Ear thermometry is reproducible and is usually only a few tenths of a degree below core body temperature. Oral and axillary measurements are not recommended. A systematic and comprehensive diagnostic approach is necessary, as both infectious and noninfectious sources are common causes of fever in the ICU.

Symptoms/Exam

Patients in the ICU often cannot describe symptoms because of invasive devices and sedation. The patient's medical history and medications should thus be carefully reviewed. A thorough examination should follow, with particular attention paid to assessment of the sinuses, heart, lungs, skin, and intravascular device sites.

Differential

The etiologies of fever in the ICU are given in the mnemonics **PAID WOMAN** and **VW CARS.**

Diagnosis/Treatment

- Obtain blood cultures as well as other cultures (wound, urine, stool).
- If an obvious source of infection is identified, appropriate antibiotics should be started. If there is no obvious source of infection and fever is ≤ 39°C (≤ 102°F), evaluate for the noninfectious causes listed above. If fever is > 39°C (> 102°F), remove old central lines and culture the catheter tip at the same time as a peripheral blood culture.
- An NG tube should be removed and replaced with an orogastric tube, and a CXR should be reviewed for any new infiltrates. Empiric antibiotics are warranted if fever persists.
- If fever continues despite empiric broad-spectrum antibiotics, consider abdominal imaging and antifungal coverage.

Noninfectious causes of fever in the ICU—PAID WOMAN

Pancreatitis/**P**ulmonary embolism
Adrenal insufficiency
Ischemic bowel
Drug reaction/**D**VT
Withdrawal
Other
Myocardial infarction
Acalculous cholecystitis
Neoplasm

Infectious causes of fever in the ICU—VW CARS

Ventilator-associated pneumonia
Wound infection
C. difficile colitis
Abdominal abscess
Related to catheter
Sepsis/**S**inusitis

VENTILATOR-ASSOCIATED PNEUMONIA (VAP)

Ventilator-associated pneumonia (VAP) is the most common nosocomial infection in the ICU and has a higher mortality rate than other hospital-acquired infections. VAP is pneumonia that develops in a patient **48 hours** after being intubated. Approximately 20% of critically ill patients receiving mechanical ventilation will develop VAP, resulting in higher mortality, longer ICU stays, and ↑ use of resources. The most common etiologic agents are *S. aureus, Pseudomonas aeruginosa,* and Enterobacteriaceae (e.g., *E. cloacae*).

Symptoms/Exam

- Patients with VAP will frequently develop fever, worsening hypoxia, and an ↑ in purulent secretions from their endotracheal tube.

- The history should focus on presence of chronic lung disease, length of mechanical ventilation, aspiration, head-of-bed level, use of NG tubes, and delayed extubation, as all of these factors can ↑ the risk of VAP.

Diagnosis

Clinical, radiographic, and airway sampling are all frequently used, but controversy exists as to which diagnostic strategy is best.

- **Clinical criteria:** VAP is suggested by fever 48 hours after intubation, a new pulmonary infiltrate, leukocytosis, and ↑ secretions.
- **Radiographic criteria:** Have a high false-⊕ rate; however, the presence of an air bronchogram may predict VAP.
- **Airway sampling:** Can occur in the lower airways via bronchoscopy or a mini-BAL. Tracheal aspirates are also acceptable forms of culture. Randomized controlled trials have not demonstrated which sampling method is best. It is therefore recommended that individual hospitals use the method with which they have the most experience.

Treatment

Keep patients in the semirecumbent position (30–45 degrees) rather than supine as an easy intervention to prevent VAP.

Appropriate initial antibiotic coverage is the most important factor in determining patient outcomes from VAP. However, the need for broad-spectrum antibiotics must be balanced against the development of resistant bacteria. Therefore, changing antibiotics to a more narrow spectrum as cultures become available (deescalation) is vital. Guidelines are as follows:

- Patients should initially receive broad-spectrum antibiotics.
- Coverage should take into account the most common microbes: S. *aureus*, *Pseudomonas*, and Enterobacteriaceae.
- The exact antibiotics chosen should be based on local resistance patterns.
- Antibiotics should be deescalated (using the most narrow spectrum possible) based on the results of respiratory tract cultures.
- A **seven-day course** of antibiotic therapy is recommended for patients with uncomplicated VAP who have elicited a good clinical response, and in whom no *Pseudomonas* has been isolated

Prevention

There are numerous modifiable risk factors to help in the prevention of VAP. Four easy interventions include the following:

- Keep the head of the bed elevated to at least **30 degrees.**
- In ICU patients with multiple drug-resistant organisms, adhere strictly to universal and barrier precautions (e.g., wash hands and wear yellow gowns).
- ↓ the amount of mechanical ventilation time:
  - In the appropriate clinical setting, use noninvasive mechanical ventilation.
  - Interrupt sedation daily.
  - Use weaning protocols.
- Remove the NG tube and convert to orogastric tube placement.

CHAPTER 5

Dermatology

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COMMON SKIN DISORDERS

Acne

Due to excess sebum, abnormal follicular keratinization, and proliferation of *Propionibacterium acnes*. Medications that exacerbate acne include glucocorticoids, anabolic steroids, lithium, some antiepileptics, OCPs with androgenic potential, and iodides. **Dietary factors do not play a significant role.**

Symptoms/Exam

Presents with **noninflammatory** comedones ("blackheads and whiteheads") and **inflammatory** papules, pustules, nodules, or cysts.

Treatment

- Treatment is three-pronged:
  - **Regulation of follicular keratinization:** Topical retinoids.
  - **Treatment of *P. acnes* and inflammation:** Antibiotics (topical and systemic) and benzoyl peroxide.
  - **Decreasing sebum:** Antiandrogens, spironolactone, isotretinoin.
- Treatment further depends on **type and severity:**
  - Treatment for noninflammatory comedones focuses on retinoids; treatment for inflammatory lesions centers on antibiotics.
  - The therapeutic ladder is as follows:
    - **Topical:** Monotherapy is rare. Use a topical retinoid + benzoyl peroxide or a topical antibiotic.
    - **Systemic:** Systemic antibiotics, isotretinoin, antiandrogens, or spironolactone.

Isotretinoin is teratogenic and is contraindicated in pregnancy. Side effects include dry skin, cheilitis, transaminase elevation, and hypertriglyceridemia. Depression has also been associated with isotretinoin use.

In recalcitrant cases of acne, signs such as hirsutism and irregular menses may point to possible endocrine disorders (congenital adrenal hyperplasia, polycystic ovarian syndrome, Cushing's disease).

Rosacea

A chronic inflammatory **facial** disorder affecting middle-aged to older adults.

Symptoms

- Presents with episodic flushing and facial erythema.
- **Triggers** include hot liquids, spicy food, alcohol, sun, and heat.

Exam

- **No comedones are seen.** Exam reveals erythematous papules and pustules and telangiectasias (see Figure 5.1).
- Symmetric **central facial** involvement is also characteristic (malar cheeks, nose, chin, forehead).
- **Rhinophyma** is most often seen in men with long-standing disease.
- **Red eyes** (blepharitis, keratitis, conjunctivitis, iritis) may indicate ocular rosacea.

Facial steroid creams may cause a dermatitis that resembles rosacea.

Treatment

- **Avoid triggers.**
- Encourage sunscreen use.
- **Topical** therapy (metronidazole gel or cream; sodium sulfacetamide lotion).

Rosacea keratitis may lead to blindness.

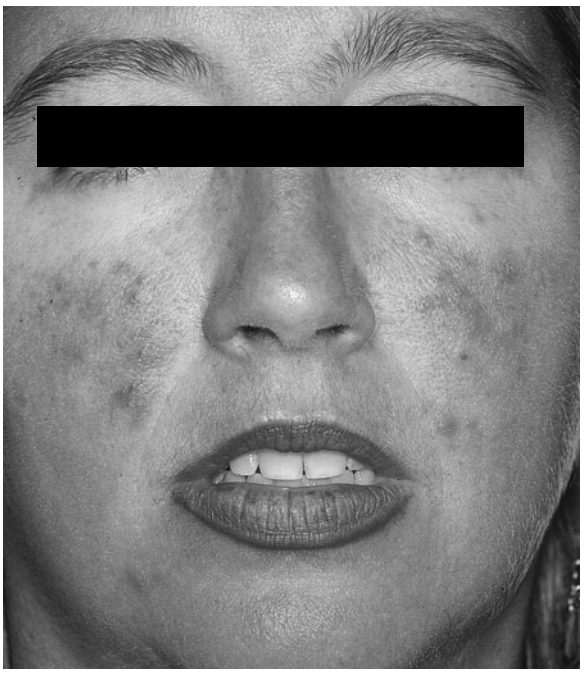

FIGURE 5.1. Rosacea.

Papules, pustules, and telangiectasias are seen on the central face. Note the lack of comedones. (Reproduced, with permission, from Wolff K et al. *Fitzpatrick's Color Atlas & Synopsis of Clinical Dermatology*, 5th ed. New York: McGraw-Hill, 2005: 9.)

- **Systemic** antibiotics are appropriate in the setting of ocular involvement or if topical therapy is ineffective.
- Oral isotretinoin for severe disease.

Seborrheic Dermatitis

Severe, recalcitrant seborrheic dermatitis may be a clue pointing to underlying HIV infection.

An inflammatory reaction to *Pityrosporum ovale* yeast. Disease associations include **AIDS, Parkinson's,** and **stroke.** Also seen in acutely ill patients.

Symptoms/Exam

- Exam reveals dry or "greasy," yellow, sharply demarcated scales on an erythematous base (see Figure 5.2)
- Crusts and fissures with bacterial superinfection may also be seen.
- Usually localized to the **scalp, postauricular region, central facial area** (especially the eyebrows and nasolabial folds), and flexural areas.

Treatment

To prevent medication-related complications, high-potency topical steroids should not be used on the face or groin.

- **Scalp:**
  - Shampoos containing tar, zinc pyrithione, or selenium.
  - Ketoconazole 2% shampoo lathered on the scalp and all affected areas.
  - Topical steroids are appropriate for more resistant disease.
- **Face: Ketoconazole 2% cream** +/– intermittent low-potency topical steroids or macrolactams (tacrolimus or pimecrolimus).
- **Intertriginous areas:** Low-potency steroid lotions or creams +/– ketoconazole 2% cream.

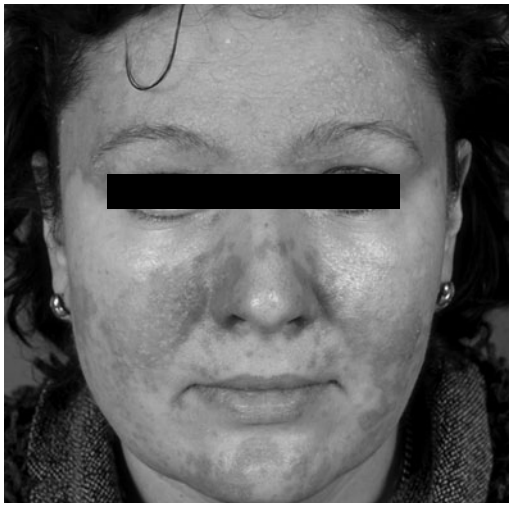

FIGURE 5.2. Seborrheic dermatitis.

Note the yellow, "greasy" scales on an erythematous base, localized to the central face. (Reproduced, with permission, from Wolff K et al. *Fitzpatrick's Color Atlas & Synopsis of Clinical Dermatology*, 5th ed. New York: McGraw-Hill, 2005: 51.)

Psoriasis

A T-cell immune-mediated inflammatory disease that has a genetic predisposition and is characterized by a bimodal peak incidence at 27 and 55 years of age. Has variable clinical presentations that include the following:

- **Localized plaque type:** Most common.
- **Guttate ("droplike"):** Occurs in young adults following strep throat.
- **Generalized pustular or erythrodermic:** Rare, life-threatening variants.

Symptoms

- Usually asymptomatic, although **itching** may be present.
- **Koebner's phenomenon** may be seen when psoriatic lesions are induced at sites of injury or irritation to normal skin.
- **Triggers** include trauma, stress, and **medications** (lithium, β-blockers, prednisone taper, antimalarials, ACEIs, interferons).
- A severe form is seen in **HIV** infection.

Exam

- **Localized plaque type:** Presents with sharply demarcated, erythematous plaques with **silvery-white scales, often symmetrically distributed on the elbows, knees, scalp, palms, and soles** (see Figure 5.3).
- **Guttate type:** Characterized by **numerous small, discrete papules and plaques that are widely distributed.**
- **Nail pitting:** Fine "ice-pick" stippling.
- The **inverse variant** involves the flexural surfaces (axillae, groin).

Diagnosis

- Diagnosed by clinical findings; biopsy is rarely performed.
- In **guttate psoriasis,** consider obtaining an ASO titer and/or a throat culture for group A β-hemolytic streptococcal infection.

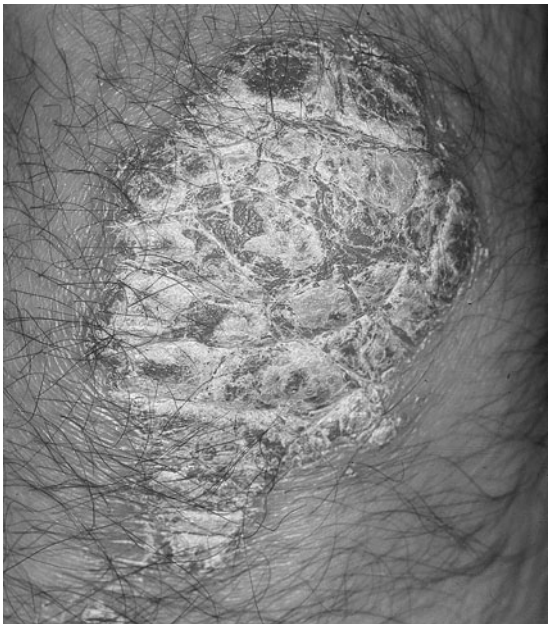

FIGURE 5.3. Psoriasis vulgaris (elbow).

Note the well-demarcated erythematous plaque with thick white scale. (Reproduced, with permission, from Wolff K et al. *Fitzpatrick's Color Atlas & Synopsis of Clinical Dermatology*, 5th ed. New York: McGraw-Hill, 2005: 57.)

Systemic corticosteroids are contraindicated in the treatment of psoriasis because of the risk of inducing pustular psoriasis and severe disease rebound on withdrawal of medication.

TREATMENT

- **Limited plaque disease: Topical therapies** such as potent topical steroids, vitamin D analogs (calcipotriene), retinoids, coal tar, and anthralin.
- **Generalized disease:** UVB light, oral retinoids, PUVA (psoralen and UVA light).
- **Refractory disease or psoriatic arthritis:** Methotrexate, cyclosporine, sulfasalazine, biologics (e.g., alefacept, efalizumab, etanercept).
- **Guttate psoriasis:** Penicillin VK or erythromycin to treat strep throat +/– topical therapies or UVB.
- Day treatment (aka Goeckerman therapy) with crude coal tar and UVB is associated with disease remission in > 80% of cases.

COMPLICATIONS

Psoriatic arthritis (< 10%), especially affecting the **DIP joints** of the hands, and **sacroiliitis.**

Pityriasis Rosea

Most often occurs in young adult **women.** Caused by human herpesvirus 6 and 7 (HHV-6, 7).

SYMPTOMS

- Presents with mild pruritus.
- A larger "**herald patch**" often precedes the generalized trunk eruption by 1–2 weeks.

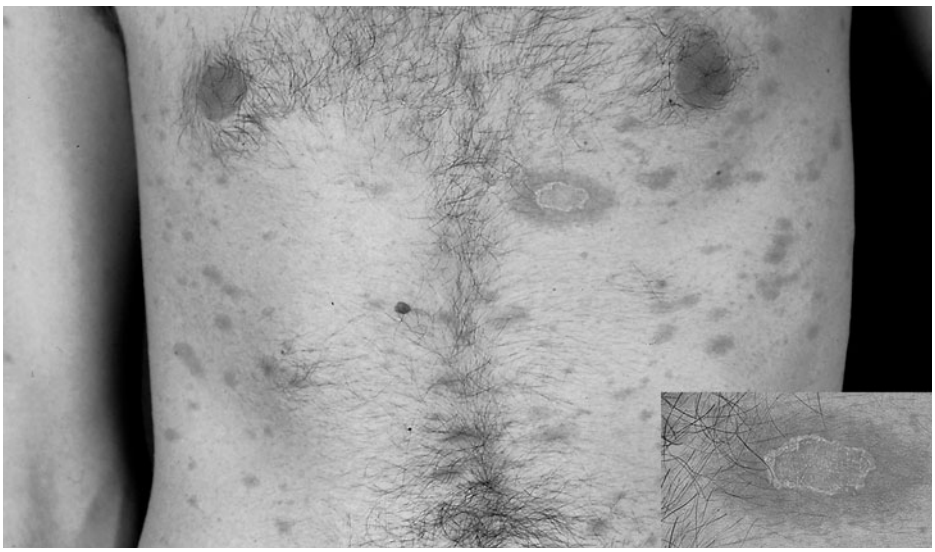

FIGURE 5.4. Pityriasis rosea.

Pink plaques with an oval configuration are seen that follow the lines of cleavage. Inset: Herald patch. The collarette of scale is more obvious on this magnification. (Reproduced, with permission, from Wolff K et al. *Fitzpatrick's Color Atlas & Synopsis of Clinical Dermatology*, 5th ed. New York: McGraw-Hill, 2005: 119.)

EXAM

- Exam reveals dull pink "salmon-colored" plaques up to 2 cm in diameter with a "cigarette paper" appearance, a silver **collarette of scale,** and a well-demarcated erythematous base (see Figure 5.4).
- Shows a "**Christmas tree**" distribution, with the long axis of lesions following lines of cleavage.
- Involves the trunk and proximal extremities; **spares the face.**
- An inverse pattern involving the axillae and groin may also be seen.

TREATMENT

A **self-limited** illness that shows spontaneous resolution within about two months.

CUTANEOUS INFECTIONS

Impetigo

A superficial infection of the epidermis that is **contagious** and **autoinoculable.** Caused by *Staphylococcus*, group A streptococcus, or both. Infection may occur as a 1° event or as a 2° superinfection of an underlying dermatitis.

Bullous impetigo is usually caused by S. aureus.

SYMPTOMS/EXAM

- 1° lesions are vesicles or pustules that most often affect the **face.**
- Vesicles or pustules rupture, forming erosions with an overlying **honey-colored crust.**

Recurrent impetigo suggests S. aureus *nasal carriage. Treat with intranasal mupirocin +/– oral rifampin plus another antistaphylococcal antibiotic.*

Diagnosis

Gram stain and culture can confirm clinical suspicion if the diagnosis is in doubt.

Treatment

Mupirocin ointment for limited disease; systemic antibiotics for more severe involvement.

Complications

Most cases resolve without scarring. When left untreated, lesions can progress to deeper infections and even to sepsis.

Erysipelas

Acute cellulitis usually affecting the **central face;** due to **group A streptococci.** Elderly and immunocompromised patients are at greater risk than the general population.

Symptoms

- Patients are **systemically ill** with fevers, chills, and malaise.
- Lesions are hot, painful, and **rapidly advancing.**

Exam

Exam reveals **brightly erythematous,** smooth, indurated edematous plaques with raised, **sharply demarcated** margins (see Figure 5.5)

Treatment

Prompt administration of **IV antibiotics** with activity against β-hemolytic streptococci.

Complications

If the condition is left untreated, bacteremia and sepsis may develop.

Anthrax

Caused by *Bacillus anthracis,* a gram-⊕, spore-forming aerobic rod; transmitted through the skin or mucous membranes or by inhalation via contaminated soil, animals, animal products, or **biological warfare.** Some **95% of anthrax cases worldwide are cutaneous.**

Symptoms

- Has three clinical manifestations: cutaneous, GI, and pulmonary (woolsorters' disease).
- A two- to seven-day incubation period is followed by the development of characteristically evolving lesions (see below).
- Systemic presentation includes fever, malaise, headache, nausea, and vomiting.

Exam

- The 1° lesion is a small, erythematous macule that evolves into a papule with **vesicles,** significant erythema, and **edema.**

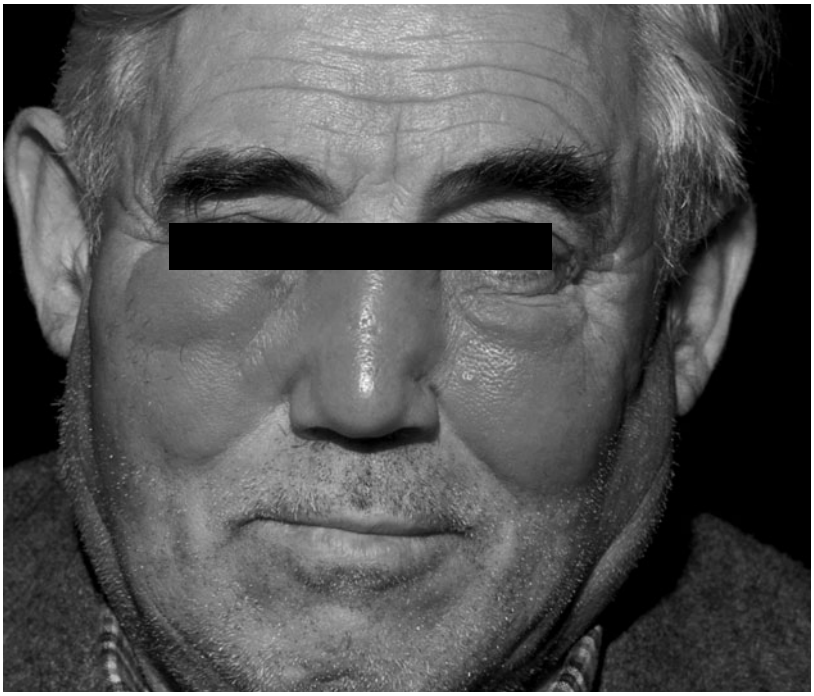

FIGURE 5.5. Erysipelas of the face.

Painful, well-defined, shiny, erythematous, edematous plaques caused by group A streptococcus. (Reproduced, with permission, from Wolff K et al. *Fitzpatrick's Color Atlas & Synopsis of Clinical Dermatology*, 5th ed. New York: McGraw-Hill, 2005: 605.)

- One to three days later, the papule ulcerates, leaving the characteristic black **necrotic eschar.**
- **No pain or tenderness** is seen.
- Suppurative regional adenopathy may develop.

Diagnosis

The causative organism is identified by smear (gram-⊕ encapsulated rods) or culture.

Treatment

- IV penicillin G is labeled for use for inhalational anthrax; however, the CDC recommends against penicillin or ampicillin as monotherapy in light of concerns about resistance.
- Oral ciprofloxacin or doxycycline may be effective for mild, localized cutaneous disease.
- IV ciprofloxacin or doxycycline and one or two additional antimicrobials are recommended for bioterrorism-associated anthrax. These can be tailored once sensitivities are known. Treatment duration is 60 days.
- Most cutaneous cases resolve spontaneously without significant sequelae, but 10–20% of untreated cutaneous cases may result in death.

Dermatophytosis (Tinea)

A superficial fungal infection of the skin, hair follicles, and/or nails that is transmitted from person to person via **fomites.** Scalp infection is seen mainly

Tinea pedis affecting the web spaces is the most common cause of cellulitis in otherwise healthy patients.

in children. Predisposing factors include atopic dermatitis, immunosuppression, sweating, and occlusion.

Symptoms/Exam

- **Tinea pedis:** Presents with dry scales, maceration, and/or fissuring of the web spaces; scaling in a "moccasin" or "ballet slipper" distribution; and vesicles and bullae.
- **Tinea cruris (groin):** Characterized by erythematous, well-demarcated plaques with **clear centers** and active, advancing, scaly, **sharp borders.**
- **Tinea unguium/onychomycosis:** Yellowing and thickening of the nail with subungual debris; frequently associated with chronic tinea pedis.

Dermatophytid (id reaction) is a hypersensitivity reaction to a tinea infection on a distant body site (e.g., a patient with tinea pedis develops pruritic vesicles on the hands)

Diagnosis

KOH of skin scraping to identify hyphae +/– fungal culture.

Treatment

- Maintain good hygiene; keep affected areas dry.
- Topical antifungals; oral antifungals in refractory cases.
- **Topical therapy is usually ineffective for onychomycosis.** The risks and benefits of oral antifungal therapy should be considered.
- Griseofulvin is the treatment of choice for tinea capitis.

A tinea patient with pain suggests a 2° bacterial infection.

Complications

Maceration and fissuring of skin may provide a portal of entry for bacteria, resulting in **cellulitis, especially if the patient has diabetes or is immunocompromised.**

Pityriasis (Tinea) Versicolor

A mild infection caused by a nondermatophyte fungus (***Malassezia globosa*, formerly named *Pityrosporum ovale***) and facilitated by high humidity and sebum production.

Symptoms/Exam

- Exam reveals numerous round or oval, sharply demarcated macules that may be tan, brown, pink, or white (see Figure 5.6).
- Scales are subtle.
- Often presents in a seborrheic distribution involving the upper trunk and shoulders.

Diagnosis

KOH of skin scraping to identify hyphae and budding spores ("**spaghetti and meatballs**" appearance).

Treatment

- Selenium sulfide lotion or ketoconazole shampoo lathered on the scalp and affected areas of the trunk.
- **A single oral dose of ketoconazole 400 mg results in short-term cure in 90% of cases.**

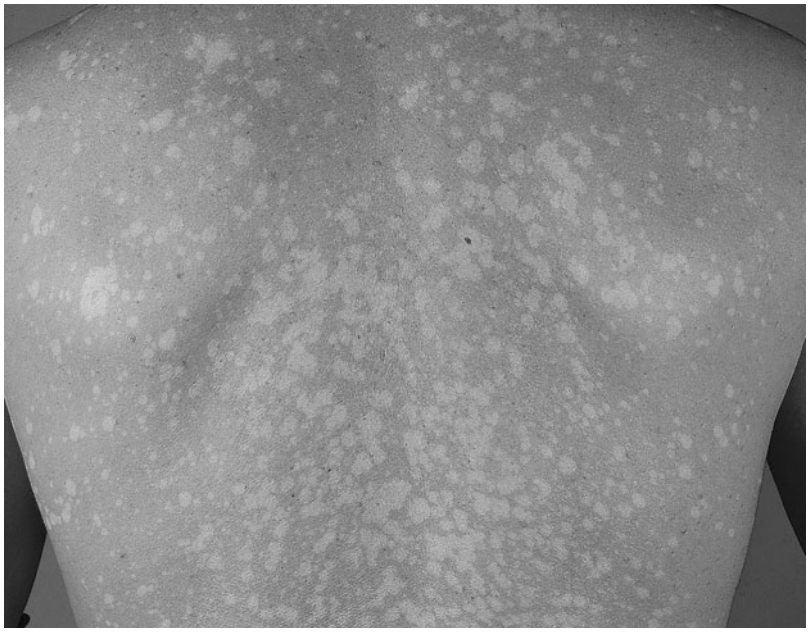

FIGURE 5.6. Tinea versicolor.

Note the multiple, well-demarcated hypopigmented macules. (Reproduced, with permission, from Wolff K et al. *Fitzpatrick's Color Atlas & Synopsis of Clinical Dermatology*, 5th ed. New York: McGraw-Hill, 2005: 731.)

Candidiasis

Risk factors include DM, obesity, sweating, heat, maceration, systemic and topical steroid use, and chronic debilitation. Antibiotics and OCP use may also be contributory.

Symptoms/Exam

- Favors moist intertriginous areas.
- Initial vesiculopustules enlarge and rupture, becoming eroded and confluent.
- **Brightly erythematous,** sharply demarcated plaques are seen with scalloped borders (see Figure 5.7).
- **Satellite lesions** (pustular lesions at the periphery) may coalesce and extend into larger lesions.

Diagnosis

Usually a clinical diagnosis, supported by KOH with pseudohyphae and yeast forms or culture.

Treatment

- Keep affected areas dry.
- Topical antifungals are highly effective.

HSV-2 infection accounts for the majority of genital herpes lesions.

Herpes Simplex (HSV)

HSV-1 and HSV-2 are double-stranded DNA viruses with the ability to invade, remain latent, and then replicate within the nerve cell ganglia. Morbidity

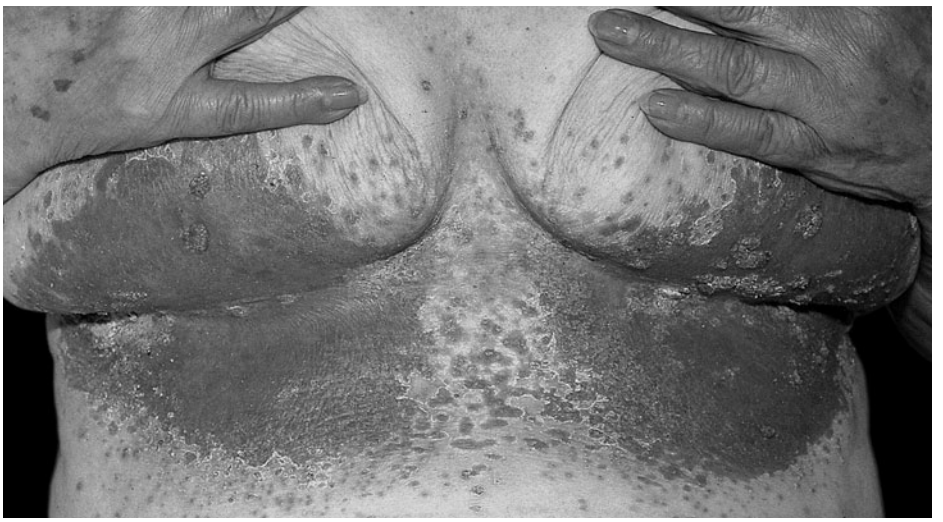

FIGURE 5.7. Cutaneous candidiasis: intertrigo.

Confluent bright red papules with "satellite" pustules are seen. (Reproduced, with permission, from Wolff K et al. *Fitzpatrick's Color Atlas & Synopsis of Clinical Dermatology*, 5th ed. New York: McGraw-Hill, 2005: 719.)

results from recurrent outbreaks. Transmission occurs through direct contact with mucosal surfaces. **Asymptomatic viral shedding** occurs in 60–80% of infected patients.

Symptoms/Exam

Presents with small, grouped vesicles on an erythematous base that crust, most commonly affecting the vermilion border of the lips, the genitals, and the buttocks.

Diagnosis

Direct fluorescent antibody, viral culture, PCR, or evidence of viropathic changes on biopsy.

HSV is the most common cause of recurrent erythema multiforme.

Treatment

- Lesions spontaneously heal within one week.
- Immediate treatment with oral antiviral agents may reduce the duration of the outbreak by 12–24 hours.
- Suppressive treatment should be considered in patients with frequent or severe outbreaks; such treatment can ↓ outbreaks by 85% and viral shedding by 90%.
- Potent topical steroids ↓ the pain, duration, and size of orolabial lesions.
- Immunosuppressed patients may require parenteral acyclovir.

Patients with atopic dermatitis are at risk for eczema herpeticum, a diffuse cutaneous HSV superinfection.

Complications

- Disseminated cutaneous disease in patients with underlying dermatitis (**eczema herpeticum;** see Figure 5.8).
- Immunosuppressed patients are at risk for potentially life-threatening **systemic disease** involving the lungs, liver, and CNS.

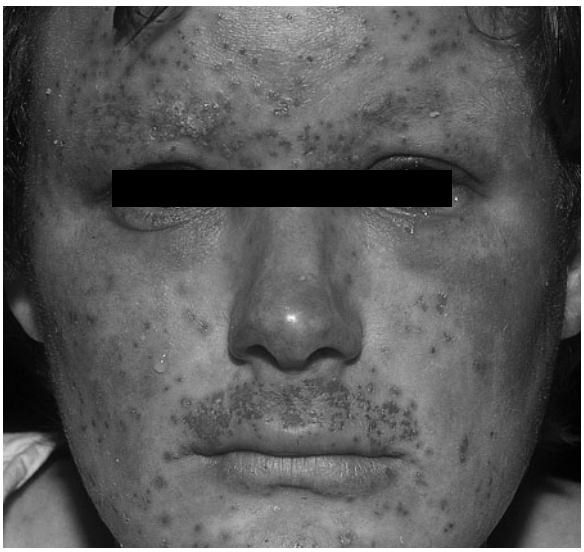

FIGURE 5.8. Eczema herpeticum on the face in a patient with HSV infection.

Confluent and discrete crusted erosions associated with erythema and edema are seen in a patient with atopic dermatitis. (Reproduced, with permission, from Wolff K et al. *Fitzpatrick's Color Atlas & Synopsis of Clinical Dermatology*, 5th ed. New York: McGraw-Hill, 2005: 809.)

Herpes Zoster

Varicella-zoster virus (VZV) is the agent of the 1° infection **varicella** (chickenpox) and is also responsible for its reactivation in the form of **herpes zoster** (shingles). The risk of zoster ↑ with age and is also greater in immunosuppressed adults (e.g., those with HIV infection and malignancy).

Symptoms

Presents with unilateral **dermatomal pain** followed by skin lesions.

Exam

- Exam reveals clustered vesicular lesions, most commonly on the trunk or face (see Figure 5.9).
- The presence of > 25 lesions in noncontiguous dermatomes suggests disseminated zoster.
- Herpes zoster ophthalmicus accounts for approximately 7–10% of all zoster cases.

Diagnosis

Direct fluorescent antibody, viral culture, PCR, or evidence of viropathic changes on biopsy.

Treatment

- Antivirals (e.g., acyclovir) are most effective when started within 48 hours of onset.
- Treatment is always indicated in the presence of ocular involvement as well as for immunosuppressed and debilitated patients with extensive cutaneous involvement.

Disseminated zoster or zoster in apparently healthy patients < 40 years of age should raise the suspicion of HIV disease.

The pain of zoster may precede skin lesions by several days and may mimic that of angina, pleurisy, cholecystitis, appendicitis, or hepatitis

Vesicles on the nasal tip or side indicate nasociliary branch involvement (Hutchinson's sign) and should prompt referral to an ophthalmologist to exclude orbital involvement.

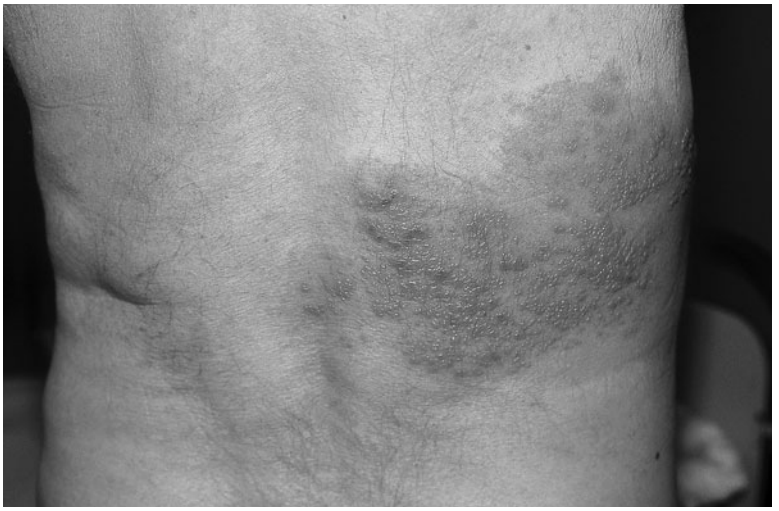

FIGURE 5.9. Herpes zoster in T8–T10 dermatomes in a patient with VZV infection.

Grouped vesicles and pustules are seen on a base of erythema and edema involving the posterior chest wall. (Reproduced, with permission, from Wolff K et al. *Fitzpatrick's Color Atlas & Synopsis of Clinical Dermatology,* 5th ed. New York: McGraw-Hill, 2005: 823.)

Antiviral therapy within 72 hours may ↓ the duration and severity of PHN. This is especially important in the elderly, a population that is at ↑ risk for the development of this complication.

COMPLICATIONS

- **Postherpetic neuralgia (PHN):**
  - There is an ↑ risk in the **elderly** and following **trigeminal** zoster.
  - Treatment of shingles within 72 hours may ↓ the duration and severity of PHN.
  - PHN treatment options include capsaicin, amitriptyline, gabapentin, and regional nerve blocks.

Smallpox

Caused by variola, a double-stranded DNA poxvirus transmitted via viral implantation on the oropharyngeal or respiratory mucosa.

SYMPTOMS

- A 12-day incubation period is followed by the **sudden onset** of fever, headache, malaise, and vomiting.
- A centrifugally spreading rash appears after the cessation of constitutional symptoms.

EXAM

- Erythematous macules evolve synchronously into vesicles and pustules.
- Lesions crust over in approximately two weeks, followed by separation of the crust.
- Heals with characteristic pitted scarring.

DIAGNOSIS

Electron microscopy (staining for poxvirus particles), PCR, IgM-specific antibody, or cell culture.

Treatment

- Supportive.
- Give antibiotics if 2° bacterial infection is suspected.
- **Vaccination is controversial** (see below).

In smallpox, lesions are synchronous (all in the same stage), whereas the lesions of varicella are in varying stages of development and healing.

Complications

- Complications of **smallpox vaccination** include the following:
  - **Generalized vaccinia:** Infection with vaccinia virus 4–10 days after vaccination; characterized by disseminated papulovesicles that evolve into pustules. Can be due to autoinoculation upon contact with the vaccination site.
  - **Eczema vaccinatum:** Vaccinia virus superinfects the skin of patients with dermatitis (usually atopic dermatitis). Lymphadenopathy, fever, malaise, encephalitis, neurologic symptoms, and even death may occur on rare occasions.
- **High-risk conditions for vaccine-related complications** include **eczema** or exfoliative dermatitis, malignancies necessitating chemotherapy, HIV infection, hereditary immune deficiency disorders, and pregnancy.
- Vaccinia immune globulin may be used for the treatment of progressive vaccinia, eczema vaccinatum, severe generalized vaccinia, and periocular autoinoculation.
- Additional complications include corneal opacity and ulceration, arthritis and synovitis, pneumonitis, and encephalitis.
- **The case fatality rate is 20–30%** and usually results from bacterial superinfection or severe inflammatory response.

Patients with smallpox are infectious from the time of rash onset until all crusts have separated.

Scabies

Skin infestation by the mite *Sarcoptes scabiei*. The female adult mite burrows and lays eggs in the stratum corneum. Highly **contagious;** spreads through prolonged contact with an infected host.

Symptoms

- Presents with intense pruritus, especially at night.
- Itching and rash result from a delayed type IV hypersensitivity reaction to the mites, their eggs, or their feces, resulting in a two- to four-week delay between infection and onset of symptoms.
- Crusted (or "Norwegian") scabies occurs in immunocompromised and institutionalized patients.

Exam

- Presents with small pruritic vesicles, pustules, and **burrows;** look in the **webbed spaces** of the fingers (see Figure 5.10), volar wrists, elbows, **axillae,** belt line, feet, scrotum, and areolae.
- **The face is usually spared.**
- A generalized **hypersensitivity rash** may develop at distant sites.
- In crusted scabies, lesions are hyperkeratotic and crusted, covering large areas. Associated scalp lesions and nail dystrophy are also seen.

Diagnosis

Examine **skin scrapings** with light microscopy to identify mites, ova, or fecal pellets.

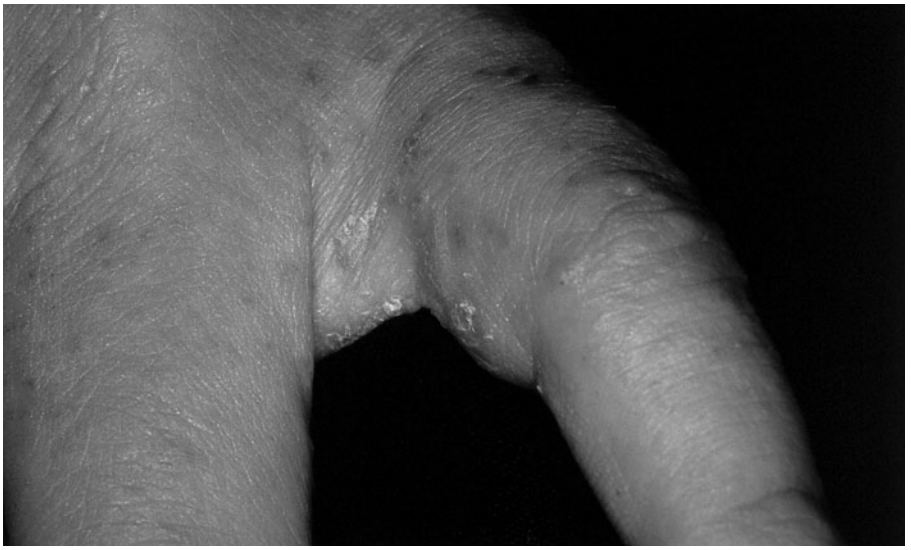

FIGURE 5.10. Scabies.

Papules and burrows are seen in typical locations on the finger web. (Reproduced, with permission, from Wolff K et al. *Fitzpatrick's Color Atlas & Synopsis of Clinical Dermatology*, 5th ed. New York: McGraw-Hill, 2005: 855.)

Itching and rash 2° to hypersensitivity reactions may persist for weeks or months despite effectively treated scabies infection.

TREATMENT

- Apply **permethrin 5%** below the neck; leave on for eight hours and shower off. Treatment may be repeated in one week. Wash linens and clothing in hot water.
- **Ivermectin** may be needed to treat crusted scabies, conventional cases refractory to topical therapy, epidemics in institutions, or superinfected scabies.
- Other STDs should be excluded.

DERMATOLOGIC MANIFESTATIONS OF SYSTEMIC DISEASES

Cardiovascular

Infective Endocarditis

Dermatologic findings associated with infective endocarditis are outlined in Table 5.1.

Livedo reticularis is a clinical reaction pattern resulting from vascular obstruction or hyperviscosity. Some cases may be caused by drugs such as corticosteroids, amantadine, or epinephrine.

Livedo Reticularis

Obstruction of arteriolar flow from vasospasm, obstruction, hyperviscosity, or obstruction of venous outflow. May be idiopathic. 2° etiologies include the following:

- Atheroemboli (postangiography) and cholesterol emboli syndrome (see the Rheumatology chapter)
- Antiphospholipid antibody syndrome
- SLE
- Cryoglobulins

TABLE 5.1. Dermatologic Manifestations of Infective Endocarditis

Clinical Findings	Characteristics
Petechiae	
Splinter hemorrhages	Subungual, dark red linear macules.
Roth's spots	Oval retinal hemorrhages with a clear, pale center.
Osler's nodes	Small, **tender** violaceous papules on the pads of the digits (**O**sler = **O**uch).
Janeway lesions	Small, slightly papular red/violaceous hemorrhages on the palmar and plantar surfaces. Most commonly seen in acute endocarditis.
Clubbing	
Peripheral emboli	

- Medications (e.g., prednisone, amantadine, epinephrine)
- Other hypercoagulable states

Symptoms/Exam

- Symmetric; involves the extremities. More prominent with exposure to cold.
- Presents with mottled or **netlike bluish** (livid) discoloration of the skin (see Figure 5.11).

Diagnosis

Tests for underlying disease include CBC, coagulation studies, ANA, RF, antiphospholipid antibodies, and cryoglobulins.

Treatment

- Treat the underlying disease.
- Pentoxifylline 400 mg PO TID and low-dose aspirin may be helpful.

Gastrointestinal

Table 5.2 outlines the dermatologic manifestations of common GI disorders, including porphyria cutanea tarda, cryoglobulinemia, lichen planus, and dermatitis herpetiformis.

The prognosis of cryoglobulinemia is often guarded and is dependent on underlying disease.

Hematologic

Table 5.3 outlines the dermatologic manifestations of hematologic disorders.

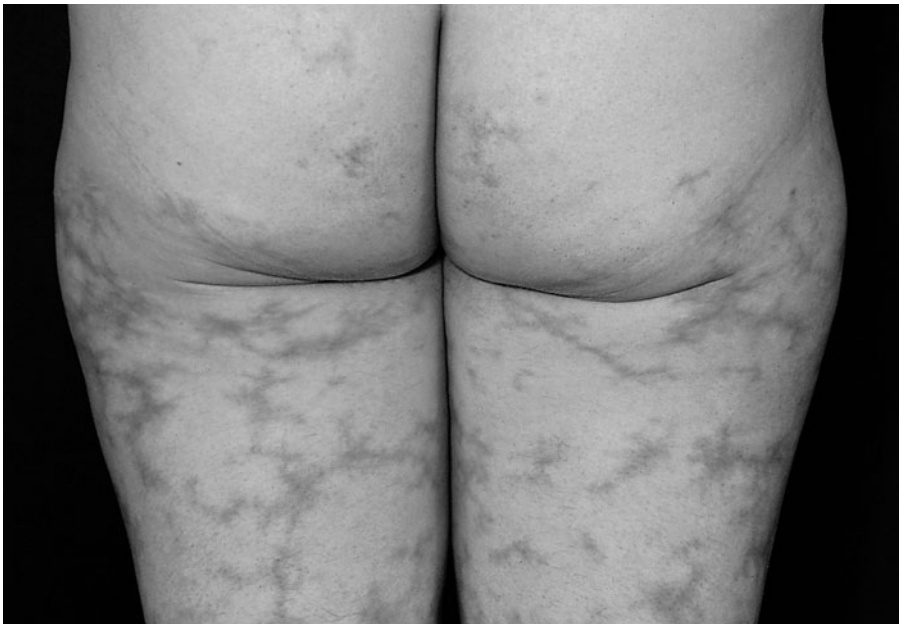

FIGURE 5.11. Symptomatic livedo reticularis.

A bluish, netlike, arborizing pattern is seen on the posterior thighs and buttocks. (Reproduced, with permission, from Wolff K et al. *Fitzpatrick's Color Atlas & Synopsis of Clinical Dermatology*, 5th ed. New York: McGraw-Hill, 2005: 381.)

Oncologic

Transplant recipients should be regularly examined for skin cancers because these patients are at higher risk for such cancers.

Post-transplant Skin Malignancy

- Squamous cell carcinomas (SCCs) are more common than basal cell carcinomas (BCCs) in post-transplant patients.
- The incidence of malignancy ↑ with the duration of immunosuppressive therapy.

Paraneoplastic Disease

Table 5.4 outlines the dermatologic manifestations of common paraneoplastic disorders.

Sweet's Syndrome

- A **neutrophilic dermatosis** that can be subdivided into five groups: paraneoplastic (most commonly associated with acute myeloid leukemia and lymphomas), drug induced, pregnancy related, associated with inflammatory or autoimmune disorders (e.g., RA), and idiopathic.
- **Dx:** Two major and two minor criteria are required for diagnosis:
  - **Major:**
    1. Abrupt onset of tender, erythematous plaques. Lesions are often described as "pseudovesicular"; they look like vesicles or bullae but are firm on palpation.
    2. Histopathology consistent with Sweet's syndrome.

TABLE 5.2. Dermatologic Manifestations of GI Disorders

Disorder	Etiology	Skin Manifestations	Most Common Disease Associations
Porphyria cutanea tarda	Reduced activity of uroporphyrinogen decarboxylase, an enzyme in the heme biosynthetic pathway. May be inherited or acquired.	**Painless** vesicles and bullae on the face and dorsa of the hands. Facial hypertrichosis.	HCV (85%). **Medications: NSAIDs, estrogens, tetracyclines.**
Cryoglobulinemia	Cryoglobulins are immunoglobulins that precipitate on cold exposure, causing vessel occlusion or immune complex vasculitis.	Vasculitis of the skin (palpable purpura, livedo), kidneys, GI tract, and CNS.	**HCV; lymphoproliferative disorders (lymphoma, myeloma).**
Lichen planus	Idiopathic.	Flat-topped purple, polygonal, pruritic papules (see Figure 5.12). Affect the flexor wrist, lumbar region, shins, and penis. Mucous membrane lesions are found in 40–50% of cases.	**Chronic HBV and HCV;** 1° biliary cirrhosis. **Medications:** Streptomycin, tetracycline, NSAIDs, HCTZ, antimalarials.
Dermatitis herpetiformis	Likely immune complexes of IgA and epidermal tissue transglutaminase. The cutaneous manifestation of gluten sensitivity.	**Extremely pruritic,** grouped vesicles symmetrically distributed over the elbows, forearms, back, buttocks, and knees.	**Gluten-sensitive enteropathy; celiac disease.** ↑ risk of GI lymphoma.
Pyoderma gangrenosum	Unknown; an underlying immunologic abnormality is favored.	Painful, rapidly advancing deep ulcer (see Figure 5.13).	**Ulcerative colitis** > **Crohn's disease.**

- **Minor:**
  1. Fever and constitutional symptoms.
  2. Leukocytosis.
  3. Preceded by associated infection (e.g., streptococcus or yersiniosis) or associated with malignancy, inflammatory disorder, or pregnancy.
  4. Excellent response to corticosteroids.
- **Tx:** First-line treatment is systemic corticosteroids. Alternative treatments are dapsone, colchicine, or potassium iodide.

Endocrine and Metabolic

Table 5.5 outlines the dermatologic manifestations of endocrine and metabolic disorders.

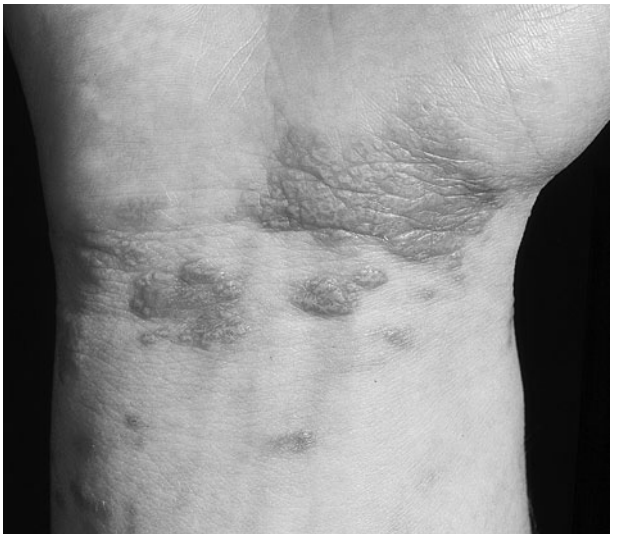

FIGURE 5.12. Lichen planus.

Flat-topped, polygonal, sharply defined, shiny, violaceous papules are seen. (Reproduced, with permission, from Wolff K et al. *Fitzpatrick's Color Atlas & Synopsis of Clinical Dermatology*, 5th ed. New York: McGraw-Hill, 2005: 125.)

Renal

Cutaneous signs associated with end-stage renal disease are as follows:

- Calcinosis cutis (metastatic).
- **Calciphylaxis:** Progressive calcification of vessels leading to ischemic necrosis of surrounding skin and soft tissues.
- **Pruritus:** Can be severe, leading to lichen simplex chronicus (hyperpigmented, leathery plaques) or prurigo nodularis (hard, keratotic, nodules) from chronic rubbing and scratching.

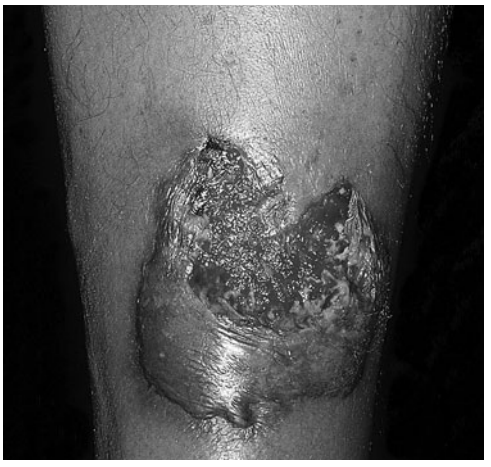

FIGURE 5.13. Pyoderma gangrenosum.

A painful ulcer is seen with a dusky-red peripheral rim and an undermined border. (Reproduced, with permission, from Wolff K et al. *Fitzpatrick's Color Atlas & Synopsis of Clinical Dermatology*, 5th ed. New York: McGraw-Hill, 2005: 153.)

TABLE 5.3. Dermatologic Manifestations of Hematologic Disease

Disorder	Skin Manifestations	Most Common Disease Associations
1° amyloidosis	Blood vessel fragility leads to "raccoon eyes" and pinch purpura (purpura due to mild trauma). Macroglossia.	Multiple myeloma; Waldenström's macroglobulinemia.
2° amyloidosis	Cutaneous signs are rare.	Chronic inflammatory diseases such as RA and infections such as leprosy, TB, and osteomyelitis.
Mastocytosis	Solitary mastocytoma or generalized urticaria. A ⊕ Darier's sign (pruritus and wheal) is elicited by stroking.	Symptoms include urticaria, GI symptoms, and flushing. Lymphoma, leukemia.

- **Uremic frost:** Very rare.
- **Xerosis:** Dry skin.

HIV Disease

In HIV-infected patients, **seborrheic dermatitis** is the **most common** cutaneous condition, usually developing early and increasing in severity with decreasing CD4+ count. Common mucocutaneous findings and skin disorders associated with HIV are outlined in Tables 5.6 and 5.7 and in the sections that follow.

TABLE 5.4. Dermatologic Manifestations of Neoplastic Disease

Disorder	Skin Manifestations	Commonly Associated Malignancy
Glucagonoma	Necrolytic migratory erythema, glossitis, angular cheilitis.	Glucagon-secreting tumors of the pancreas.
Dermatomyositis	Heliotrope rash, Gottron's papules (violaceous papules overlying the finger joints), photodistributed eruption (see Figure 5.14).	**Ovarian cancer;** other solid tumors.
Extramammary Paget's disease	Erythematous plaques with scales, erosion, and exudate. Affects the anogenital region.	Underlying vulvar or penile adenocarcinomas and regional internal malignancies.
Leukocytoclastic vasculitis	Small vessel vasculitis; palpable purpura.	Lymphoproliferative neoplasms; solid tumors.
Paraneoplastic pemphigus	Painful mucosal erosions. Pruritic; evolve into blisters.	**Non-Hodgkin's lymphoma;** chronic lymphocytic leukemia.
Sign of Leser-Trélat	Abrupt eruption of numerous pruritic seborrheic keratoses.	**Adenocarcinomas (60%), especially gastric.**

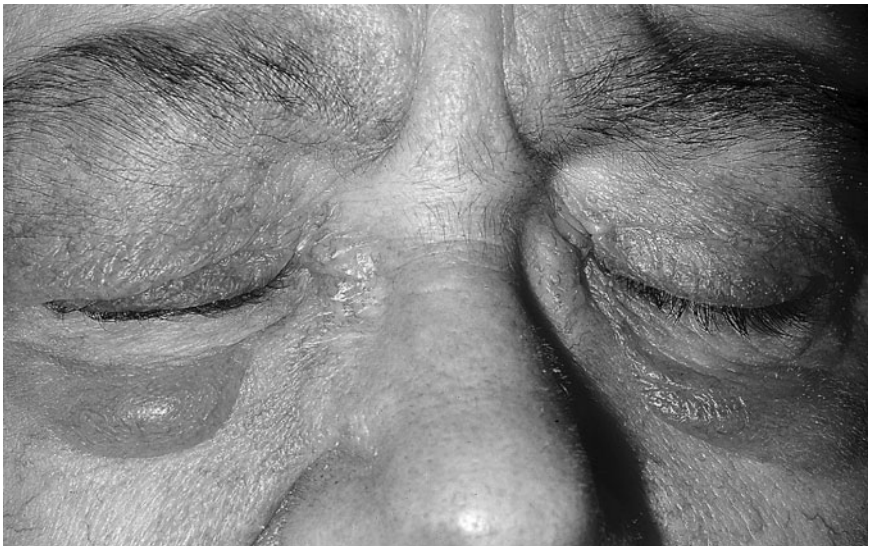

FIGURE 5.14. Dermatomyositis.

Heliotrope (reddish-purple) erythema of the upper eyelids can be seen along with edema of the lower lids. (Reproduced, with permission, from Wolff K et al. *Fitzpatrick's Color Atlas & Synopsis of Clinical Dermatology*, 5th ed. New York: McGraw-Hill, 2005: 373.)

KAPOSI'S SARCOMA (KS)

A **vascular** neoplasm linked to infection with **HHV-8.** Often confused with skin lesions of *Bartonella* infection.

SYMPTOMS/EXAM

- Presents with asymptomatic mucocutaneous lesions that may bleed easily or ulcerate and cause pain.
- Less commonly involves the respiratory tract (nodules or hemoptysis) or the GI tract (GI bleed).

TABLE 5.5. Dermatologic Manifestations of Endocrine and Metabolic Disease

DISORDER	SKIN MANIFESTATIONS	MOST COMMON DISEASE ASSOCIATIONS
Acanthosis nigricans	Velvety, dirty hyperpigmentation; affects the axillae, groin, and neck (see Figure 5.15). Insidious, asymptomatic.	**Insulin resistance:** DM, obesity, Cushing's disease. **Medications:** Nicotinic acid, glucocorticoid therapy, OCPs, growth hormone therapy. **Paraneoplastic:** Gastric adenocarcinoma.
Necrobiosis lipoidica	Waxy plaques with an elevated border. Affects the lower legs (> 80% pretibial). Lesions have a brownish-red color and an atrophic yellow center.	DM.
Xanthoma	Crops of small, discrete, dome-shaped, yellow-orange papules. Affects the eyelids and tendons (classically involving the Achilles tendon).	Hyperlipidemia; familial combined hypertriglyceridemia (triglyceride level > 1000 mg/dL).

TABLE 5.6. Mucocutaneous Findings Associated with HIV Infection

Risk of HIV Infection	Mucocutaneous Finding
High—serotesting always indicated.	Acute retroviral syndrome KS Oral hairy leukoplakia (see Figure 5.16) Proximal subungual onychomycosis Bacillary angiomatosis Eosinophilic folliculitis Any STD Skin findings of IV drug use
Moderate—serotesting may be indicated.	Herpes zoster Molluscum contagiosum—multiple facial in an adult Candidiasis—oropharyngeal, esophageal, or recurrent vulvovaginal
Possible—serotesting may be indicated.	Generalized lymphadenopathy Seborrheic dermatitis Aphthous ulcers (recurrent, refractory to therapy)

Adapted, with permission, from Wolff K et al. *Fitzpatrick's Color Atlas & Synopsis of Clinical Dermatology,* 5th ed. New York: McGraw-Hill, 2005: 937.

Diagnosis

Diagnosed by skin biopsy of characteristic lesions (see Figure 5.17).

Treatment

- Highly active antiretroviral therapy (HAART).
- Local measures include intralesional chemotherapy, irradiation, laser surgery, and excision.

TABLE 5.7. Common Skin Disorders Found in HIV-Infected Patients

CD4 > 200	CD4 < 200	CD4 < 50
Seborrheic dermatitis	**Infection:**	**Unusual opportunistic infections:**
Psoriasis	■ Chronic HSV	■ Chronic HSV
Reiter's syndrome	■ Molluscum contagiosum	■ Refractory molluscum contagiosum
Atopic dermatitis	■ Bacillary angiomatosis	■ Chronic VZV
Herpes zoster	■ Systemic fungal infection	■ Atypical mycobacteria
Acne rosacea	■ Mycobacterial infection	■ Crusted scabies
Oral hairy leukoplakia	■ KS	■ KS
Warts	**Inflammatory:**	
S. aureus folliculitis	■ Eosinophilic folliculitis	
Mucocutaneous candidiasis	■ Drug reactions	
Kaposi's sarcoma (KS)	■ Photodermatitis	
	■ Prurigo nodularis	

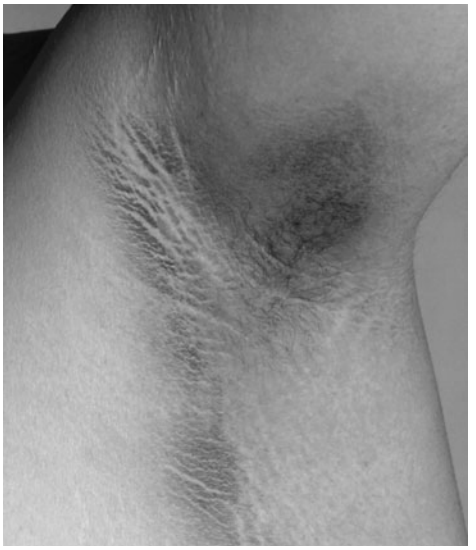

FIGURE 5.15. Acanthosis nigricans.

Note the velvety, dark brown epidermal thickening of the armpit. (Reproduced, with permission, from Wolff K et al. *Fitzpatrick's Color Atlas & Synopsis of Clinical Dermatology*, 5th ed. New York: McGraw-Hill, 2005: 87.)

More than 90% of patients with pulmonary KS will have mucocutaneous KS. Inspect the skin and hard palate!

COMPLICATIONS

Larger or ulcerated lesions may bleed, cause functional disturbance, or obstruct lymphatic drainage.

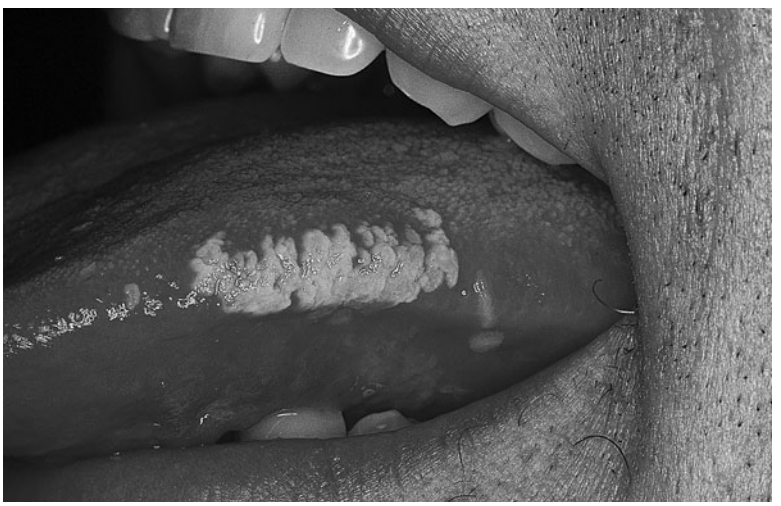

FIGURE 5.16. Oral hairy leukoplakia.

Note the corrugated white plaque on the lateral tongue. Essentially pathognomonic for HIV infection. (Reproduced, with permission, from Wolff K et al. *Fitzpatrick's Color Atlas & Synopsis of Clinical Dermatology*, 5th ed. New York: McGraw-Hill, 2005: 943.)

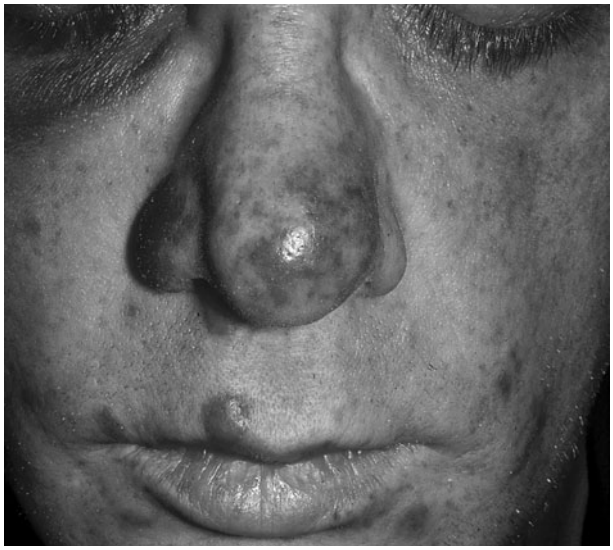

FIGURE 5.17. HIV-associated Kaposi's sarcoma.

Multiple bruise-like purplish and brownish macules, papules, and nodules can be seen. (Reproduced, with permission, from Wolff K et al. *Fitzpatrick's Color Atlas & Synopsis of Clinical Dermatology*, 5th ed. New York: McGraw-Hill, 2005: 539.)

HIV-Associated Lipodystrophy

Lipodystrophy is part of a metabolic syndrome that includes hyperlipidemia, insulin resistance, and type 2 DM. Protease inhibitors are frequently implicated, most commonly **ritonavir/saquinavir,** followed by indinavir and nelfinavir. However, lipodystrophy can also occur in HIV-infected patients who are not on protease inhibitors.

Cutaneous signs of HIV-associated lipodystrophy should alert the physician to possible associated hyperlipidemia, insulin resistance, and type 2 DM.

Symptoms/Exam

Clinical features include the following:

- Facial and peripheral fat wasting.
- Dorsothoracic fat pad hypertrophy.
- ↑ abdominal girth (**central adiposity**) 2° to accumulation of intra-abdominal fat.

Treatment

Substitution of a non–protease inhibitor may be beneficial.

Complications

Associated hyperlipidemia and impaired glucose tolerance lead to an ↑ risk of CAD.

AUTOIMMUNE DISEASES WITH PROMINENT CUTANEOUS FEATURES

Table 5.8 lists the dermatologic manifestations of common autoimmune disorders, including SLE, dermatomyositis, and scleroderma.

TABLE 5.8. Cutaneous Manifestations of Autoimmune Diseases

Disorder	Cutaneous Manifestations	Systemic Associations
SLE	**Acute cutaneous:** Malar ("butterfly") rash (see Figure 5.18); photodistribution. **Other:** Discoid plaques, periungual telangiectasias, alopecia, lupus panniculitis.	See the Rheumatology chapter for details on the diagnosis and management of SLE.
Dermatomyositis	Heliotrope rash (a violaceous rash over the eyelids) is nearly pathognomonic. Gottron's papules (flat-topped violaceous papules) over bony prominences, especially the MCP joints. "Shawl sign": erythema over the upper back and chest.	↑ **risk of malignancy: ovary; other solid tumors (breast, lung, stomach, colon, uterus).**
Scleroderma	**Extremities:** Raynaud's phenomenon, sclerodactyly, periungual telangiectasias, sclerosis (see Figure 5.19). **Face:** Telangiectasias; masklike facies. **Other:** Cutaneous calcification.	See the Rheumatology chapter for a discussion of the systemic manifestations of scleroderma.
Morphea (localized scleroderma of unknown etiology)	Asymptomatic, with violaceous and then ivory-colored plaques.	Associated with *Borrelia burgdorferi* infection in Europe only as well as with post–radiation therapy.

CUTANEOUS REACTION PATTERNS

Erythema Nodosum

An immunologic reaction in the panniculus (fat) triggered by infection, medications, and benign and malignant systemic diseases. The cause is often undetermined. Etiologies may include the following (see also Table 5.9):

- **Infection:** Streptococcal, tuberculosis, fungal (including tinea capitis) and viral infection.
- **Medications:** Sulfonamides and OCPs are most commonly implicated.
- **Systemic diseases: Sarcoidosis** (Löfgren's syndrome), especially if patients present with hilar adenopathy. Also associated with ulcerative colitis, Crohn's disease, Behçet's disease, leukemia, and lymphoma.

Symptoms/Exam

- Presents with erythematous, tender nodules that are most commonly located on the anterior shins.
- Fever, malaise, and arthralgias are seen with onset of new lesions.

Treatment

- Spontaneous resolution is seen in 3–6 weeks without scarring.
- NSAIDs, prednisone, potassium iodide.

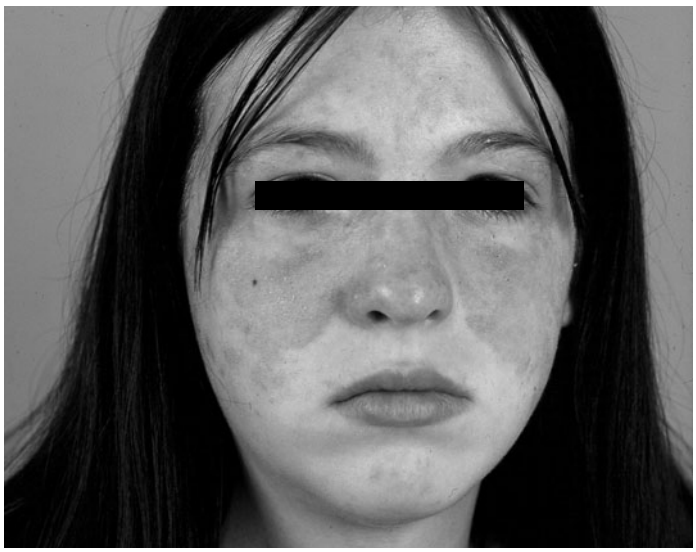

FIGURE 5.18. Acute systemic lupus erythematosus.

A typical "malar rash" is seen with red, sharply defined erythema in a "butterfly" pattern on the face. (Reproduced, with permission, from Wolff K et al. *Fitzpatrick's Color Atlas & Synopsis of Clinical Dermatology*, 5th ed. New York: McGraw-Hill, 2005: 385.)

Urticaria

A vascular reaction of the skin characterized by localized cutaneous edema (wheals) and severe itching or stinging. It is categorized as acute (resolution within six weeks of onset) and chronic (daily episodes lasting > 6 weeks.) Etiologies are numerous, and the **cause is often undetermined.** Common etiologies include the following (see also Table 5.9):

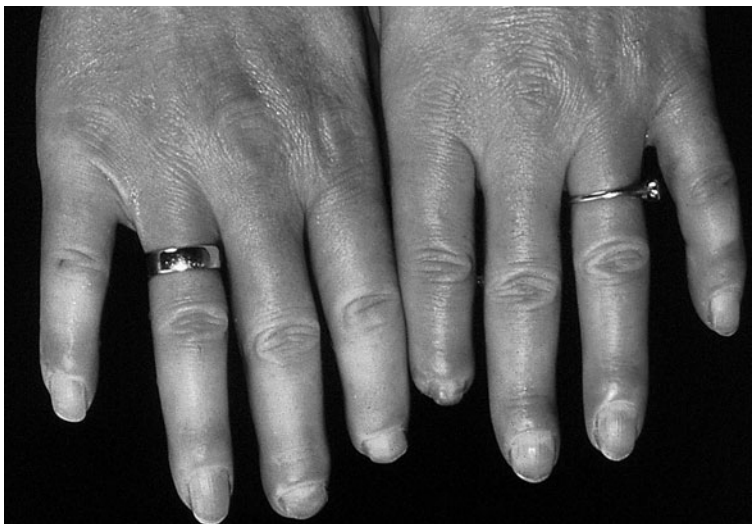

FIGURE 5.19. Raynaud's phenomenon and acrosclerosis in a patient with scleroderma.

(Reproduced, with permission, from Wolff K et al. *Fitzpatrick's Color Atlas & Synopsis of Clinical Dermatology*, 5th ed. New York: McGraw-Hill, 2005: 399.)

TABLE 5.9. Cutaneous Reaction Patterns and Their Associated Diseases

Reaction Pattern	Definition	Signs and Symptoms	Associated Diseases
Erythema nodosum	Inflammatory/immunologic reaction pattern of the panniculus.	**Tender bumps on the anterior shins.** Appear as red, ill-defined erythemas but palpated as deep-seated nodules. Fever, malaise, arthralgias (50%).	**Infection:** ■ Streptococcal ■ TB ■ Other bacteria, fungi, viruses **Medication:** ■ Sulfonamides ■ **OCPs** **Other:** ■ **Sarcoidosis** (Löfgren's syndrome) ■ Ulcerative colitis > Crohn's disease ■ Leukemia ■ Behçet's disease
Urticaria (see Figure 5.20)		Transient wheals, pruritus, dermatographism.	**Acute urticaria** (< 30 days): ■ Arthropod bites ■ Parasites ■ **Medications** **Chronic urticaria** (> 30 days): ■ **Idiopathic (80%)**
Erythema multiforme (EM) (see Figure 5.21)	Reaction pattern of dermal blood vessels and 2° epidermal changes.	**Target lesion:** ■ Palms and soles, face, genitals ■ Bilateral, symmetric **EM minor:** ■ Little or no mucous membrane involvement ■ No systemic symptoms **EM major:** ■ Positive **Nikolsky's sign** ■ Systemic: pulmonary, eyes	**Recurrent EM minor:** ■ **HSV is the cause in 90% of cases** **EM major:** ■ Medications: sulfonamides, NSAIDs, anticonvulsants (phenytoin) ■ *Mycoplasma pneumoniae* **Idiopathic: 50%**

- **Acute urticaria:** Medications (penicillin, aspirin), food, food additives, infection (streptococcal), arthropod bites, parasites.
- **Chronic urticaria:** Autoimmune conditions (e.g., thyroiditis, vitiligo, DM), infection, parasitosis, possible association with malignancy (e.g., carcinomas, Hodgkin's disease).

Symptoms/Exam

Presents with erythematous, pruritic wheals that remain for < 24 hours (see Figure 5.20). Individual lesions that persist for > 24 hours suggest urticarial vasculitis and require a biopsy.

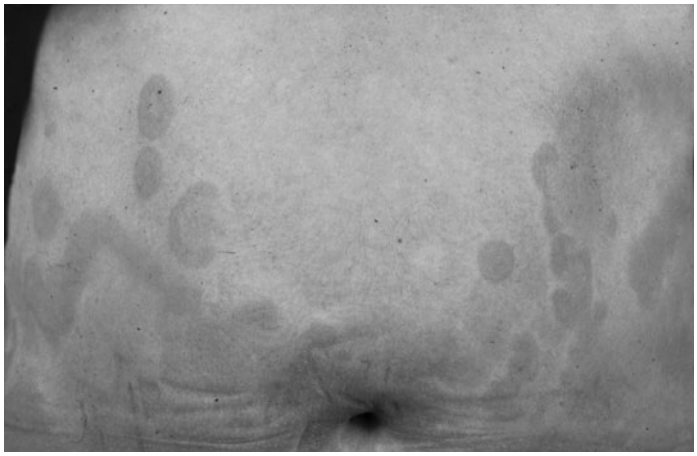

FIGURE 5.20. Urticaria.

Pruritic wheals have a white to light pink color centrally and are accompanied by peripheral erythema. (Reproduced, with permission, from Wolff K et al. *Fitzpatrick's Color Atlas & Synopsis of Clinical Dermatology*, 5th ed. New York: McGraw-Hill, 2005: 363.)

TREATMENT

Antihistamines are the mainstay of treatment.

Erythema Multiforme (EM)

Also known as erythema multiforme minor or herpes simplex–associated erythema multiforme (HAEM), EM is an immunologic reaction pattern of dermal blood vessels with 2° epidermal change. Ninety percent of cases of EM minor are associated with HSV infection. EM major, or Stevens-Johnson syndrome (SJS), is more commonly caused by *Mycoplasma pneumoniae* or medications (e.g., sulfonamides, NSAIDs, anticonvulsants).

SYMPTOMS/EXAM

- Target lesions present with a dusky purple central zone (or later with a crust, blister, or erosion) with an outer concentric red zone (see Figure 5.21).
- Symmetric and bilateral involvement of the palms, soles, faces, and genitalia is seen.
- Further distinguished as follows:
  - **EM minor:** No mucosal involvement; no systemic symptoms.
  - **EM major:** Presents with bullae; involves two mucosal surfaces; shows systemic involvement of the eyes and lungs.

TREATMENT

- **EM minor:** Self-limited; consider acyclovir prophylaxis for recurrent episodes.
- **EM major:** Hospitalization (often to a burn unit in light of fluid/electrolyte imbalances); stop the offending drug. Supportive care, ophthalmology consult, and physical therapy.

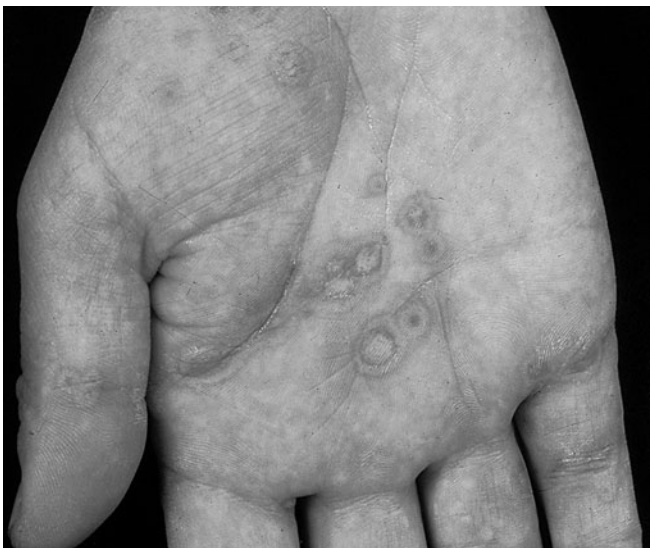

FIGURE 5.21. Erythema multiforme.

Targetoid lesions are seen on the palms. (Reproduced, with permission, from Wolff K et al. *Fitzpatrick's Color Atlas & Synopsis of Clinical Dermatology*, 5th ed. New York: McGraw-Hill, 2005: 141.)

Blistering Disorders

Bullous pemphigoid and **pemphigus vulgaris** are **autoimmune blistering disorders** of the skin and mucous membranes resulting from the loss of epidermal cell-to-cell adhesion (see Figures 5.22 and 5.23). Table 5.10 distinguishes these disorders in terms of their clinical presentation.

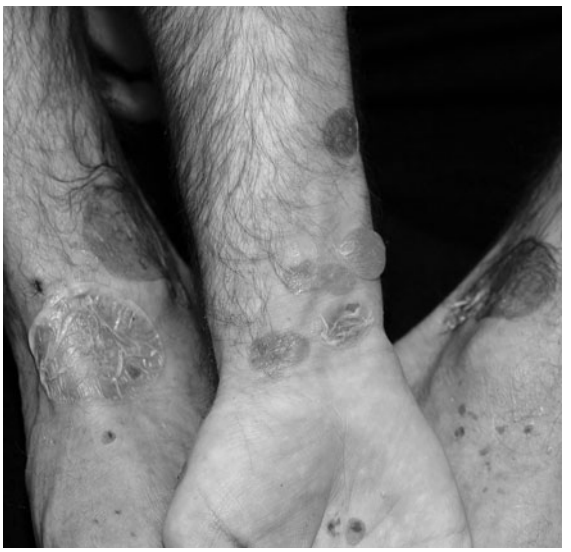

FIGURE 5.22. Bullous pemphigoid.

Tense bullae with serous fluid are seen. (Reproduced, with permission, from Wolff K et al. *Fitzpatrick's Color Atlas & Synopsis of Clinical Dermatology*, 5th ed. New York: McGraw-Hill, 2005: 108.)

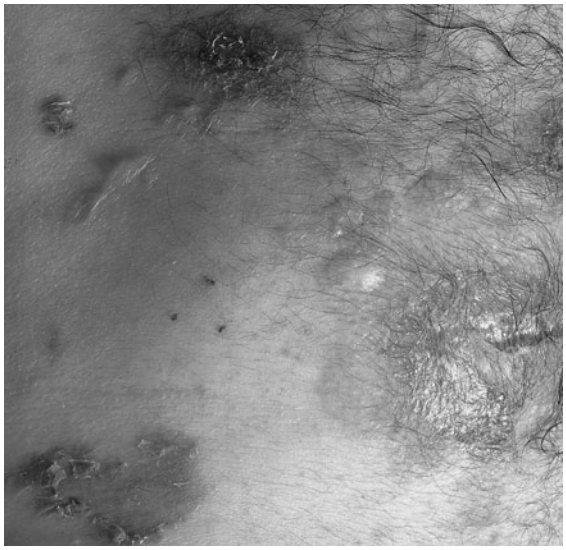

FIGURE 5.23. Pemphigus vulgaris.

Because of the fragility of the blisters, pemphigus vulgaris presents as erosions. (Reproduced, with permission, from Wolff K et al. *Fitzpatrick's Color Atlas & Synopsis of Clinical Dermatology*, 5th ed. New York: McGraw-Hill, 2005: 104.)

Diagnosis

- Submit skin biopsy for histology and direct immunofluorescence.
- In bullous pemphigoid, indirect immunofluorescence reveals circulating anti–basement membrane antibodies in the sera of 70% of patients.

Treatment

Topical high-potency steroids for localized disease; prednisone +/– other immunosuppressants for diffuse disease.

CUTANEOUS DRUG REACTIONS

Dermatologic drug reactions include the following:

- **Hospital: Penicillins, sulfonamides,** and **blood products** account for nearly two-thirds of all cutaneous reactions.
- **Ambulatory setting: Antibiotics, NSAIDs, anticonvulsants.**
- The most frequent drug eruptions are as follows:
  - **Morbilliform** drug eruption (30–50% of cases).
  - **Fixed drug eruptions.**
  - **Urticaria** +/– angioedema.

See Tables 5.11 through 5.13 and Figures 5.24 and 5.25 for the pathophysiology and clinical patterns of various drug eruptions.

Diagnosis

- Clinical features favoring medication as a cause of drug reactions are as follows:
  - Previous experience with a given drug.
  - Lack of alternative explanations (worsening of preexisting disease, infection).

TABLE 5.10. Bullous Pemphigoid vs. Pemphigus Vulgaris

	BULLOUS PEMPHIGOID	PEMPHIGUS VULGARIS
Site of blistering	Subepidermal.	Intraepidermal.
Epidemiology	Age > 60. The most common autoimmune blistering disease.	Age 40–60.
Pruritus	Severe.	Not prominent.
Nikolsky's sign (superficial separation of skin with pressure)	⊖	⊕
Oral mucosal lesions	Minority (< 30%).	Majority (> 50%).
Blisters and bullae	Intact, tense (see Figure 5.22).	Rupture easily; flaccid (see Figure 5.23).
Complications	Few.	Bacterial and viral superinfection. Has high mortality if left untreated owing to sepsis. Rare ocular involvement requires referral.
Systemic associations	None.	Rarely thymoma, myasthenia gravis.
Subtypes	None.	Drug induced (penicillamine and ACEIs), paraneoplastic.

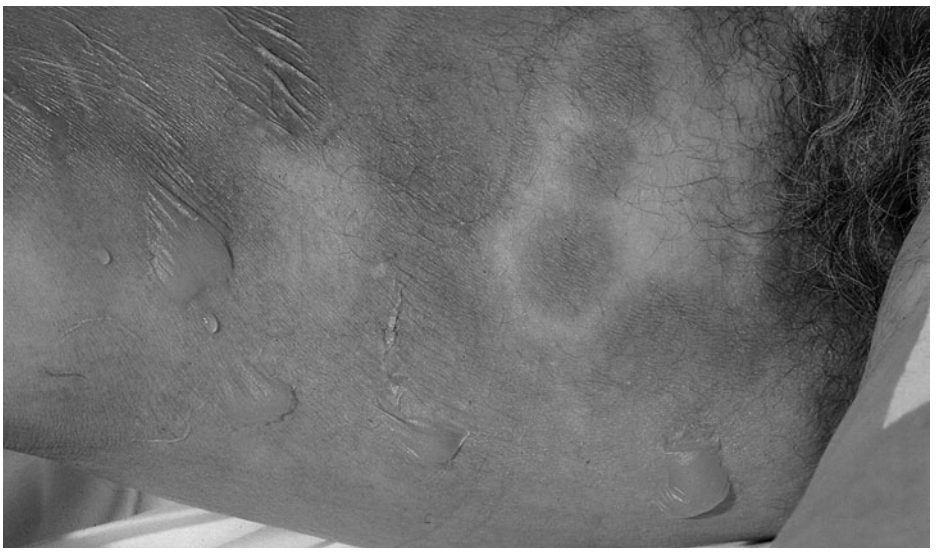

FIGURE 5.24. Stevens-Johnson syndrome.

Generalized eruption of initially targetlike lesions that become confluent, brightly erythematous, and bullous. (Reproduced, with permission, from Wolff K et al. *Fitzpatrick's Color Atlas & Synopsis of Clinical Dermatology,* 5th ed. New York: McGraw-Hill, 2005: 145.)

TABLE 5.11. Nonimmunologic Drug Reactions

Mechanism	Example
Expected adverse effects	Chemotherapy-induced alopecia.
Ecologic disturbance	Candidiasis and antibiotics.
Overdosage	Warfarin purpura.
Drug interaction	Barbiturates and warfarin (purpura).
Cumulative	Argyria (silver nitrate), antimalarial pigmentation.
Idiosyncratic causes	Drug-induced lupus in response to procainamide.
Altered metabolism	Warfarin necrosis and lack of protein C.
Exacerbation of underlying disorder	Lithium and psoriasis.
Phototoxicity	↑ sensitivity to sun caused by toxic photoproducts of different drugs (tetracyclines).
Direct release of mast cell mediators	Aspirin, NSAIDs, radiographic contrast material.
Jarisch-Herxheimer phenomenon	Penicillin therapy for syphilis; antifungal therapy for dermatophyte.

Adapted, with permission, from Kerdel FA, Jimenez-Acosta F. *Dermatology: Just the Facts.* New York: McGraw-Hill, 2003: 36.

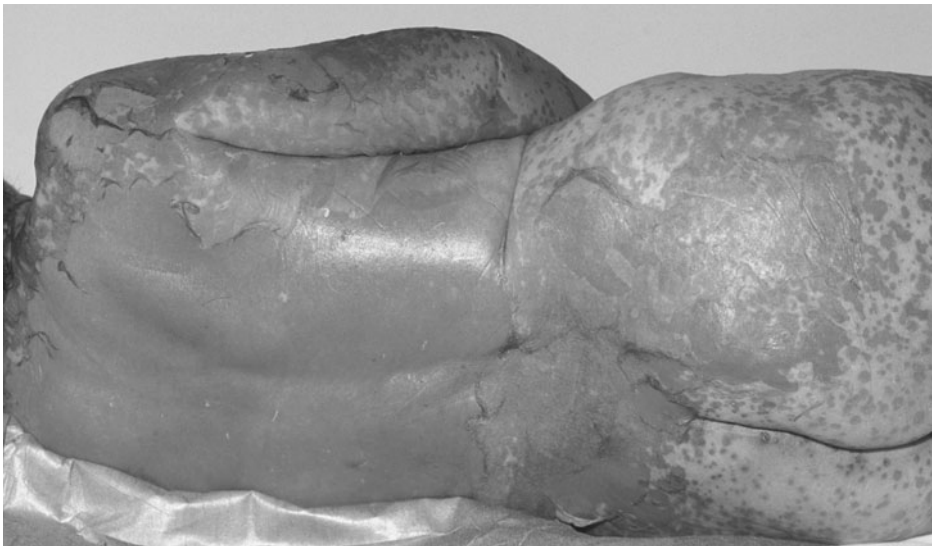

FIGURE 5.25. Toxic epidermal necrolysis.

Bulla formation with rapid desquamation. (Reproduced, with permission, from Wolff K et al. *Fitzpatrick's Color Atlas & Synopsis of Clinical Dermatology*, 5th ed. New York: McGraw-Hill, 2005: 147.)

TABLE 5.12. Immunologically Mediated Adverse Cutaneous Drug Reactions[a]

Type of Reaction	Pathogenesis	Examples of Causative Drugs	Clinical Patterns
Type I	IgE mediated; immediate-type immunologic reactions.	Penicillin.	Urticaria/angioedema of skin/mucosa; edema of other organs; anaphylactic shock.
Type II	Drug + cytotoxic antibodies cause lysis of cells such as platelets or leukocytes.	Penicillin, sulfonamides, quinidine, INH.	Petechiae due to thrombocytopenic purpura; drug-induced pemphigus.
Type III	IgG or IgM antibodies are formed to a drug; immune complexes deposited in small vessels activate complement and recruitment of granulocytes.	Immunoglobulins, antibiotics.	Vasculitis, urticaria, serum sickness.
Type IV	A cell-mediated immune reaction. Sensitized lymphocytes react with a drug, thereby liberating cytokines, which trigger a cutaneous inflammatory response.	Sulfamethoxazole, anticonvulsants, allopurinol.	Morbilliform exanthematous reactions, fixed drug eruption, lichenoid eruptions, SJS, toxic epidermal necrolysis.

[a] After the Gell and Coombs classification of immune reactions.

Reproduced, with permission, from Wolff K et al. *Fitzpatrick's Color Atlas & Synopsis of Clinical Dermatology,* 5th ed. New York: McGraw-Hill, 2005: 543.

- **Timing:** Most drug reactions occur **within two weeks. Hypersensitivity reactions may be delayed up to eight weeks.**
- **Discontinuation:** Reaction should abate within three weeks.
- **Rechallenge:** Allows for a definitive diagnosis, although usually impractical.

- Consider drug levels for dose-dependent reactions.
- Skin biopsy is helpful in determining the reaction pattern but cannot identify the specific agent.
- Peripheral **eosinophilia** is suggestive of drug sensitivity.

Treatment

The treatment of drug reactions is dependent on the cause.

CUTANEOUS ONCOLOGY

Atypical Nevi

Patients with numerous atypical nevi (atypical nevus syndrome or dysplastic nevus syndrome) and two first-degree relatives with a history of melanoma have a lifetime risk of melanoma approaching 100%.

Roughly 5–10% of individuals in the United States have one or more atypical nevi.

Symptoms/Exam

Lesions are > 6 mm with variegated hyperpigmentation and asymmetric, irregular, "fuzzy" borders (some with a "fried egg" appearance).

TABLE 5.13. Clinical Features of Severe Cutaneous Reactions Often Induced by Drugs

Diagnosis	Mucosal Lesions	Typical Skin Lesions	Common Signs and Symptoms	Other Causes Not Related	Drugs Most Often Implicated
Stevens-Johnson syndrome (SJS)	Erosions are usually seen at two or more sites.	Small blisters on dusky purpuric macules or atypical targets (see Figure 5.24). Rare areas of confluence. Detachment of ≤ 10% of body surface area.	Some 10–30% present with fever.	Postinfectious EM major rare (HSV or *Mycoplasma*).	NSAIDs, sulfa drugs, antiepileptics (phenytoin, carbamazepine), penicillin, allopurinol.
Toxic epidermal necrolysis	Erosions are usually at two or more sites.	Individual lesions are like those seen in SJS (see Figure 5.25).	Fever is nearly universal. "Acute skin failure"; leukopenia. Confluent erythema. The outer layer of the epidermis readily separates from the basal layer with lateral pressure (Nikolsky's sign). Large sheet of necrotic epidermis. Detachment of > 30% of body surface area.	Viral infections, immunization, chemicals, *Mycoplasma* pneumonia.	Same as above.
Anticonvulsant hypersensitivity syndrome	Infrequent.	Severe exanthem (may become purpuric). Exfoliative dermatitis.	Some 30–50% of cases present with fever, lymphadenopathy, hepatitis, nephritis, carditis, eosinophilia, and atypical lymphocytes.	Cutaneous lymphoma.	Anticonvulsants.
Serum sickness or reactions resembling serum sickness	Absent.	Morbilliform lesions, sometimes with urticaria.	Fever, arthralgias.	Infection.	

TABLE 5.13. Clinical Features of Severe Cutaneous Reactions Often Induced by Drugs *(continued)*

Diagnosis	Mucosal Lesions	Typical Skin Lesions	Common Signs and Symptoms	Other Causes Not Related	Drugs Most Often Implicated
Anticoagulant-induced necrosis	Infrequent.	Erythema; then purpura and necrosis, especially of fatty areas.	Pain in affected areas.	DIC.	Warfarin, especially in the setting of low protein C or S.
Angioedema	Often involved.	Urticaria or swelling of the central part of the face.	Respiratory distress, cardiovascular collapse.	Insect stings, foods.	NSAIDs, ACEIs, penicillin.

Adapted, with permission, from Kasper DL et al. *Harrison's Principles of Internal Medicine,* 16th ed. New York: McGraw-Hill, 2005: 323.

Diagnosis/Treatment

Excisional biopsy is warranted only when melanoma is suspected.

Complications

The incidence of melanoma is ↑ in patients with atypical nevi. A minority of melanomas arise from atypical nevi.

Malignant melanoma risk—MMRISK

Moles: atypical
Moles: total number > 50
Red hair and freckling
Inability to tan: skin phototypes I and II
Severe sunburn, especially in childhood
Kindred: first-degree relative

Melanoma

A malignancy of melanocytes that may occur on any skin or mucosal surface. It is the **sixth most common cancer** in the United States. Risk factors are expressed in the mnemonic **MMRISK.**

Symptoms

- A **changing mole** (see the mnemonic "**the ABCDEs**").
- **Superficial spreading** malignant melanomas are most common (responsible for 70% of all melanomas in Caucasians), arising on sun-exposed regions of older patients (see Figure 5.26).
- Other subtypes include nodular, lentigo maligna, and acral-lentiginous.

Melanoma—The ABCDEs

Asymmetry
Borders: irregular
Color: variegated
Diameter > 6 mm
Evolution: lesion changes over time

Exam

Physical findings are expressed in the mnemonic "**the ABCDEs.**"

Diagnosis

- **Tumor thickness** (Breslow's classification) and lymph node status are the most important prognostic factors. Melanomas **< 1 mm** in thickness are considered **lower risk,** and **staging workup is not indicated in these cases.**
- Additional significant prognostic indicators include site, specific histologic features, and gender (men are at higher risk than women).

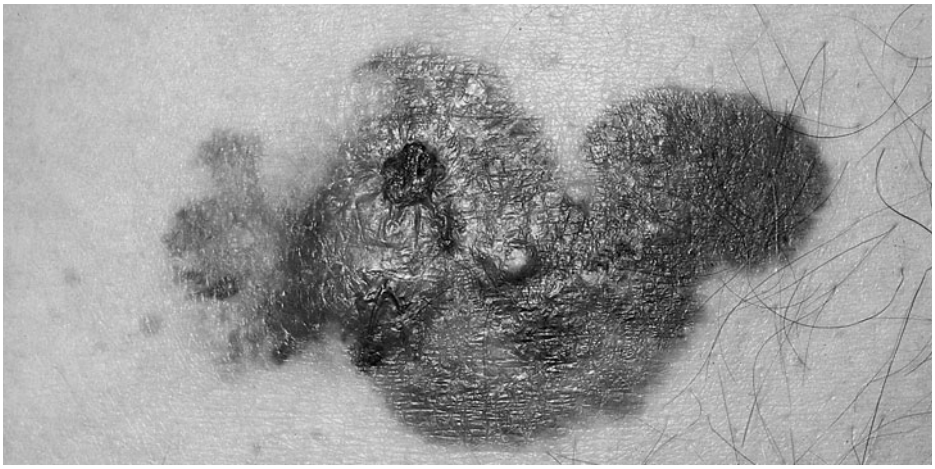

FIGURE 5.26. Superficial spreading melanoma.

A highly characteristic lesion is seen with an irregular pigmentary pattern and scalloped borders. (Reproduced, with permission, from Wolff K et al. *Fitzpatrick's Color Atlas & Synopsis of Clinical Dermatology*, 5th ed. New York: McGraw-Hill, 2005: 318.)

Treatment

Wide reexcision with appropriate margins. Sentinel lymph node biopsy is recommended for malignant melanomas > 1 mm thick and is also essential in medical decision making with regard to adjuvant therapy. Further information on the workup and treatment of melanoma is given in Table 5.14.

Complications

Metastasis usually occurs in the following sequence: local recurrence, regional lymph nodes, distant metastasis (liver, lung, bone, brain). Five-year survival rates with lymph node involvement and distant metastasis are 30% and 10%, respectively.

TABLE 5.14. Scheme for the Diagnostic Workup and Follow-up of Melanoma

Breslow Depth (mm)	Follow-up	
	Physical Exam	CXR and Labs[a]
Stage I	6 months × 2 years; 12 months thereafter.	Initial.
Stage IIa	4 months × 3 years; 12 months thereafter.	Yearly.
Stage IIb	4 months × 3 years; 6 months × 2 years; 12 months thereafter.	Yearly.
Regional (stage III) or distant (stage IV) disease	3–4 months × 5 years; 12 months thereafter.	Every other visit × 5 years; yearly thereafter; initial CT scans of head/chest/abdomen/pelvis or PET if available.

[a] LFTs and LDH.

Adapted, with permission, from Kerdel FA, Jimenez-Acosta F. *Dermatology: Just the Facts.* New York: McGraw-Hill, 2003: 271.

The central face and ears are high-risk areas for BCCs.

Basal Cell Carcinoma (BCC)

Represent **80% of all skin cancers.** Occur in sun-exposed areas. The mean age at diagnosis is 62 years.

Symptoms/Exam

- **Head and neck:** Presents with papules or nodules with telangiectasias and a "pearly" or translucent quality. A central erosion or crust (noduloulcerative type) is often seen (see Figure 5.27).
- **Chest, back, and extremities:** A scaly erythematous plaque (superficial type) is seen that may resemble a plaque of eczema.

Diagnosis

Shave biopsy.

Treatment

Treatment is dependent on the individual tumor and on patient characteristics. Both surgical and nonsurgical techniques are employed. Sun avoidance and patient education are key components of management.

Complications

Metastatic spread is uncommon (< 0.1%).

SCC is more common and more aggressive in solid organ transplant recipients, chronically immunosuppressed patients, and HIV-infected patients.

Squamous Cell Carcinoma (SCC)

Represent 20% of all skin cancers; typically affect patients > 55 years of age. SCC in situ, also known as Bowen's disease, is confined to the epidermis; invasive SCC invades into the dermis. SCCs may arise within **actinic keratoses** or within HPV-induced lesions (see Figure 5.28).

Diagnosis

Skin biopsy.

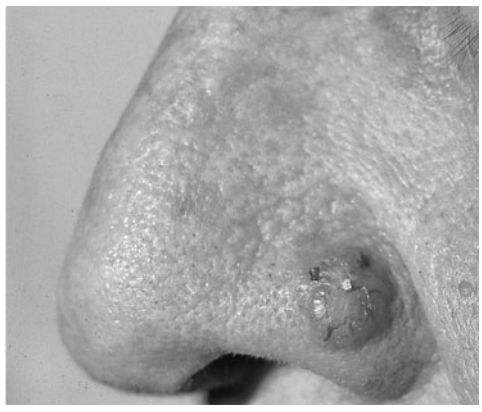

FIGURE 5.27. Nodular basal cell carcinoma.

Note the smooth, pearly nodule with telangiectasias. (Reproduced, with permission, from Wolff K et al. *Fitzpatrick's Color Atlas & Synopsis of Clinical Dermatology*, 5th ed. New York: McGraw-Hill, 2005: 283.)

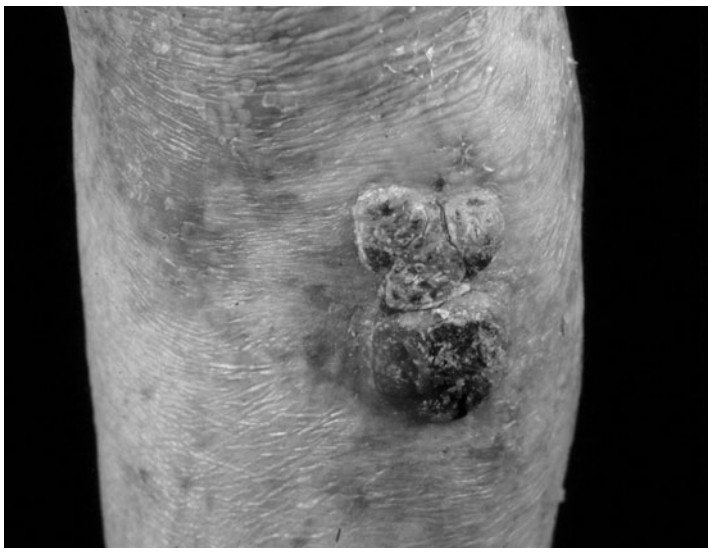

FIGURE 5.28. Squamous cell carcinoma.

A hyperkeratotic nodule with ulceration. (Reproduced, with permission, from Wolff K et al. *Fitzpatrick's Color Atlas & Synopsis of Clinical Dermatology*, 5th ed. New York: McGraw-Hill, 2005: 279.)

Treatment

- Because SCCs have a **higher metastatic and recurrence rate than BCCs,** treatment of invasive disease is primarily surgical.
- Prevention with sun avoidance and patient education are key components of disease management.

Complications

The overall five-year recurrence and metastatic rates are 8% and 5%, respectively.

In immunosuppressed patients, SCCs are more common than BCCs. These patients need to be followed more closely, as SCCs are more aggressive with higher metastatic potential.

Cutaneous T-Cell Lymphoma (CTCL)

Also known as mycosis fungoides, CTCL is an indolent malignancy of mature CD4+ helper T lymphocytes. Average age at onset is 50 years (range 5–70); men are affected twice as often as women. CTCL is divided into patch, plaque, and tumor stages.

Symptoms/Exam

- Presents with scaly, **pruritic, erythematous patches and plaques** most commonly located in a "bathing trunk" distribution.
- Erythroderma with Sézary syndrome is rare.

Treatment

Topical corticosteroids, UV light, or nitrogen mustard for patch/plaque stages. Systemic therapy for nonresponsive or more advanced disease.

Because of the nondescript appearance of CTCL lesions, delays in diagnosis often approach a decade. Survival is not affected in limited patch-stage disease.

COMPLICATIONS

Sézary syndrome is the leukemic form of CTCL and consists of erythroderma, lymphadenopathy, and circulating Sézary cells. Without therapy, its course is progressive, and patients succumb to opportunistic infections. Therapy includes treatment for CTCL as well as supportive measures for erythroderma.

MISCELLANEOUS

Photodermatitis

In patients with recurrent photodistributed eruptions, consider diseases characterized by photosensitivity, including SLE.

A group of inflammatory skin reactions attributable to the following:

- **UV radiation: Polymorphous light eruption** is a common photodermatitis, especially among Native Americans, that is due to **delayed-type hypersensitivity reaction** to an antigen induced by UV radiation (especially UVA).
- **Medications: NSAIDs, antibiotics** (some tetracyclines), phenothiazines, sulfones, chlorothiazides, sulfonylureas.
- **Hereditary disorders:** Porphyrias, phenylketonuria, xeroderma pigmentosum.

Pigmentary Disorders

Tables 5.15 and 5.16 outline disorders associated with hyper- and hypopigmentation.

Verruca and Condyloma

Distinguished as follows:

- HPV causes clinical lesions that vary according to subtype. More than 150 types of HPV have been identified.
- **Verruca vulgaris,** the common wart (70% of all warts), occurs primarily on the extremities.
- **Condylomata acuminata,** warts in the **anogenital** region, are the most commonly diagnosed STD.
- Genital HPV types (**types 16 and 18**) play an important role in the malignant transformation of benign verrucae into **cervical and anogenital cancer.**
- ↑ incidence and more widespread disease are seen in **immunocompromised** patients.

TABLE 5.15. Disorders of Hyperpigmentation

DISORDER	ASSOCIATED DISEASE
Pigmented nevi, ephelides (freckles), lentigines	
Melasma	Estrogen effect; often seen in pregnancy.
Café-au-lait spots, axillary freckling	Neurofibromatosis.

TABLE 5.16. Disorders of Hypopigmentation

Disorder	Associated Disease
Vitiligo (melanocytes destroyed)	Hypothyroidism, hyperthyroidism, pernicious anemia, DM, Addison's disease.
Albinism	Eye and vision are often affected.
Piebaldism	Autosomal dominant; neurologic dysfunction.

Treatment

- In immunocompetent patients, lesions usually **resolve spontaneously** over 1–2 years.
- Treatment modalities include mechanical destruction (cryotherapy, laser therapy) or stimulation of the immune system (topical imiquimod; application of sensitizing agents).

Complications

Malignant transformation to SCC may occur in certain subtypes.

Seborrheic Keratosis

- The most common benign epidermal growth; probably has an autosomal-dominant inheritance.
- **Sx/Exam:**
  - Asymptomatic; occasionally pruritic.
  - Has a "**stuck-on**" appearance.
- **Tx:** No treatment is necessary.

NOTES

CHAPTER 6

Endocrinology

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Under hypothalamic regulation, the anterior pituitary produces and releases ACTH, TSH, FSH, LH, GH, and prolactin (see Figure 6.1). The posterior pituitary stores and releases ADH and oxytocin. Tables 6.1 and 6.2 further describe the pituitary hormones and the factors that regulate secretion.

Pituitary Tumors

Microadenomas are < 1 cm; **macroadenomas** are > 1 cm. The risk of panhypopituitarism and visual loss ↑ with larger tumor size.

The most common functional pituitary tumor is prolactinoma, which can usually be treated medically with dopamine agonists (bromocriptine, cabergoline).

Symptoms/Exam

Characterized by the following:

- **Neurologic symptoms** (headache; visual field cuts, especially "tunnel vision"; nerve palsies).
- **Hormonal excess or deficiency** (see Tables 6.1 and 6.2).
- **Incidental discovery on imaging studies** (up to 10% of the general population have pituitary incidentalomas).

Differential

The differential diagnosis of sellar lesions is outlined in Table 6.3.

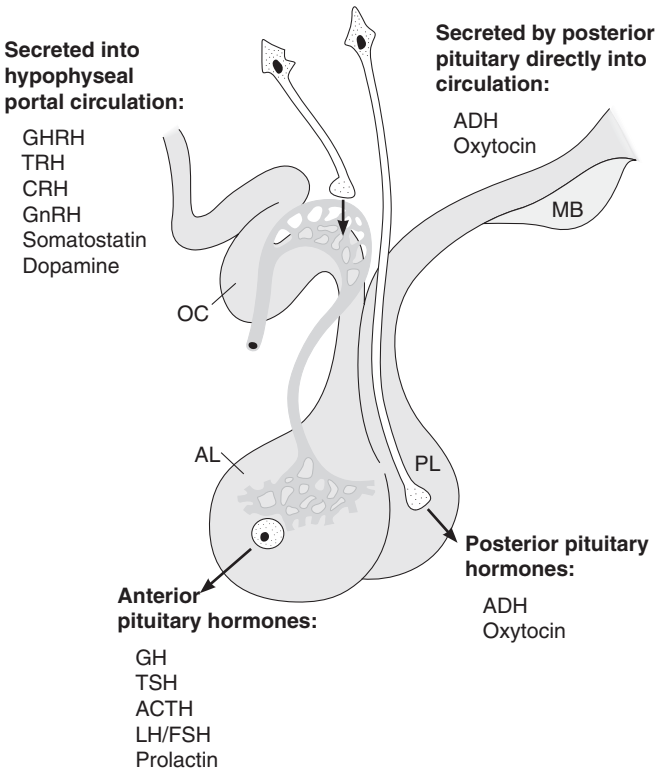

FIGURE 6.1. Secretion of hypothalamic and pituitary hormones.

AL, anterior lobe; MB, mammillary bodies; OC, optic chiasm; PL, posterior lobe. (Adapted, with permission, from Gardner DG, Shoback DM. *Greenspan's Basic & Clinical Endocrinology*, 8th ed. New York: McGraw-Hill, 2007: 106.)

TABLE 6.1. Anterior Pituitary Hormones and Their Function

Hormone	Increased by	Decreased by	Excess	Deficiency	Target Organ
ACTH	CRH, stress	High cortisol	Cushing's syndrome	Adrenal insufficiency	Adrenals
TSH	TRH	High T_4 and/or T_3	Hyperthyroidism	Hypothyroidism	Thyroid
LH/FSH	GnRH	Gonadal sex steroids		Hypogonadism	Gonads
GH	GHRH, hypoglycemia, dopamine	Somatostatin	**Childhood:** Gigantism **Adulthood:** Acromegaly	**Childhood:** Short stature **Adulthood:** Poor sense of well-being	Liver Multiple
Prolactin	Pregnancy, nursing, TRH, stress	Dopamine	Galactorrhea, hypogonadism	Inability to lactate	Breasts

In acute 2° adrenal insufficiency, or AI (e.g., pituitary apoplexy), a Cortrosyn stimulation test result is likely to be normal because the adrenal glands have not had time to atrophy. So if suspicion for AI is high, treat with steroids!

Diagnosis

- **Labs:** Once a tumor is identified, check TSH, free T_4, prolactin, ACTH, cortisol, LH, FSH, IGF-1, and testosterone (in men) or estradiol (in women with amenorrhea) to assess for hormonal excess or deficiency.
- **Pituitary imaging:** The best imaging of tumors is obtained with a **sellar-specific MRI. A regular MRI of the brain may miss these small tumors!**
- **Formal visual field testing:** For macroadenomas or tumors compressing the optic chiasm.

Treatment

- **Medical:** Some tumors shrink with hormonal manipulation. Prolactinomas are treated primarily with dopamine agonists (e.g., bromocriptine, cabergoline).
- **Surgical:** The **transsphenoidal** approach is successful in approximately 90% of patients with microadenomas.
- **Radiation:** Conventional radiotherapy or gamma-knife radiosurgery can be used postoperatively if there is residual tumor. It may take years to realize the full effect, and there is a high risk of hypopituitarism.

TABLE 6.2. Posterior Pituitary Hormones and Their Function

Hormone	Increased by	Decreased by	Excess	Deficiency	Target Organ
ADH	↑ osmolality; hypovolemia	↓ osmolality	SIADH	Diabetes insipidus (DI)	Kidneys, cardiovascular system
Oxytocin	Distention of the uterus, cervix, and vagina; nipple stimulation; estrogen enhances action			Not required for parturition	Uterus, breasts (causes contraction of smooth muscle)

TABLE 6.3. Differential Diagnosis of Sellar Lesions

- **Pituitary adenoma:**
  - Prolactinoma: Most common pituitary microadenoma
  - GH secreting: Often very large
  - Nonfunctioning: One-third of all pituitary tumors; most common macroadenoma
  - ACTH secreting: Most common cause of Cushing's syndrome
  - TSH secreting: Rare; < 1% of all pituitary tumors
  - Coscreting > 1 hormone (e.g., GH and prolactin): Rare
- **Physiologic enlargement of the pituitary gland:**
  - Lactotroph hyperplasia in pregnancy
  - Thyrotroph hyperplasia due to 1° hypothyroidism
  - Gonadotroph hyperplasia due to 1° hypogonadism
- **1° malignancies:**
  - Germ cell tumors
  - Sarcomas
  - Chordomas
  - Lymphomas
  - Pituitary carcinomas
- **Metastases:**
  - Breast cancer
  - Lung cancer
- **Cysts:**
  - Rathke's cleft cyst
  - Arachnoid cyst
  - Dermoid cyst
- **Infections in immunocompromised patients:**
  - Abscesses
  - Tuberculomas
- **Other:**
  - Craniopharyngioma
  - Meningioma
  - Lymphocytic hypophysitis—autoimmune destruction of the pituitary, often postpartum

COMPLICATIONS

- **Hypopituitarism**: See below.
- **Apoplexy:** Acute, spontaneous hemorrhagic infarction that is **life-threatening.** Has a fulminant presentation with severe headache, visual field defects, ophthalmoplegia, and hypotension +/– meningismus. Constitutes an emergency; treat with corticosteroids +/– transsphenoidal decompression.
- **Diabetes insipidus (DI) or SIADH** (especially postoperatively; patients may recover).
- **Visual field defects.**

Tumors cause DI (by affecting posterior pituitary function) only when they are large and invade the suprasellar space. 1° pituitary tumors rarely cause DI.

PROLACTINOMA

The **most common type of pituitary tumor.** The majority of lesions are microadenomas (< 1 cm).

Women typically present with prolactinomas earlier than men because of amenorrhea and galactorrhea. Therefore, women often have microprolactinomas (< 1 cm) at diagnosis, whereas men have macroprolactinomas.

When a woman presents with amenorrhea, hyperprolactinemia, and a homogeneously enlarged pituitary gland (up to two times normal), the first thing to rule out is pregnancy!

Symptoms/Exam

- **Women: Galactorrhea; amenorrhea;** oligomenorrhea with **anovulation** and infertility in 90%.
- **Men:** Impotence, ↓ libido, galactorrhea (very rare).
- **Both:** Symptoms due to a large tumor—headache, visual field cuts, and hypopituitarism.

Differential

The differential includes the following (see also Table 6.4):

- **Medications.**
- **Pregnancy, lactation:** Prolactin can reach 200 ng/mL in the second trimester.
- **Hypothalamic lesions; pituitary stalk compression or damage.**
- **Hypothyroidism:** TRH stimulates prolactin secretion.
- **Nontumoral hyperprolactinemia** (idiopathic).

Diagnosis

- **Labs:** Elevated prolactin with normal TFTs and a ⊖ **pregnancy test.**
- **Imaging:** Obtain an MRI if prolactin is elevated in the absence of pregnancy or the medications listed in Table 6.4.

Treatment

- **Medical: Dopamine agonists** such as **bromocriptine** or **cabergoline.** Once prolactin is normalized, repeat pituitary MRI to ensure tumor shrinkage.
  - Cabergoline has fewer side effects.
  - Bromocriptine is preferred for ovulation induction, since there is more experience with it in pregnancy.
  - Dopamine agonists (especially cabergoline at high doses) have been associated with cardiac valve abnormalities.
- **Surgery:** Transsphenoidal resection is curative in 85–90% of patients and is generally used if medical therapy is ineffective or if vision is threatened.
- **Radiation:** Conventional radiotherapy or gamma-knife radiosurgery if the tumor is refractory to medical and surgical therapy.

TABLE 6.4. Differential Diagnosis of Hyperprolactinemia

Physiologic	Pharmacologic	Pathologic
Pregnancy	TRH	Pituitary tumors
Nursing	Estrogen	Hypothalamic/pituitary stalk tumors
Nipple stimulation	Vasoactive intestinal peptide	Hypothyroidism
Exercise	Dopamine antagonists	Neuraxis irradiation
Stress (hypoglycemia)	(phenothiazines, haloperidol,	Chest wall lesions
Sleep	risperidone, metoclopramide,	Spinal cord lesions
Seizures	reserpine, methyldopa,	Chronic renal failure
Neonatal	amoxapine, opioids)	Severe liver disease
	MAOIs	
	Cimetidine (IV)	
	Verapamil	
	Licorice	

Adapted, with permission, from Gardner DG, Shoback DM. *Greenspan's Basic & Clinical Endocrinology,* 8th ed. New York: McGraw-Hill, 2007: 119.

Growth Hormone (GH) Excess

Childhood cases of GH excess are associated with gigantism (delayed epiphyseal closure leading to extremely tall stature); cases in adulthood are associated with acromegaly. Etiologies include the following:

- **Benign pituitary adenoma:** In > 99% of cases, GH excess states are due to a GH-secreting pituitary adenoma. Typically they are macroadenomas (> 1 cm), as diagnosis is often delayed by as much as 10 years.
- **Iatrogenic:** Treatment with human GH.
- **Ectopic GH or GHRH:** Extremely rare; seen with lung carcinoma, carcinoid, and pancreatic islet cell tumors.

Symptoms/Exam

- **Cardiac:** Hypertension (25%); cardiac hypertrophy.
- **Endocrine: Glucose intolerance** (50%) or overt DM; hypercalciuria with nephrolithiasis (10%); hypogonadism (60% in females, 45% in males).
- **Constitutional:** Heat intolerance, weight gain, fatigue.
- **Neurologic:** Visual field cuts and headaches.
- **GI:** ↑ colonic polyp frequency (order colonoscopy after diagnosis).
- **Other:**
  - Soft tissue proliferation (enlargement of the hands and feet); **coarsening of facial features.**
  - Sweaty palms and soles.
  - Paresthesias (**carpal tunnel syndrome** is found in 70% of cases).
  - An ↑ in shoe, ring, or glove size.
  - Skin tags.

In a patient with coarse facial features and new DM, check IGF-1 (not GH) to rule out acromegaly.

Diagnosis

- **Labs:** Random GH is not helpful. **Elevated IGF-1 levels** are the hallmark.
- **Glucose suppression:** A GH > 2 ng/mL 60 minutes after a 100-g oral glucose load is diagnostic.
- **Radiology:** MRI of the pituitary.

Treatment

- **Surgery:** Transsphenoidal resection is usually first-line therapy and is curative in 60–80% of cases.
- **Medical:** If GH excess persists after surgery, long-acting octreotide (a somatostatin analog) is usually added. If octreotide fails, pegvisomant, a GH receptor antagonist, will normalize IGF-1 levels in 80–90% of patients with acromegaly.
- **Radiotherapy:** Used in patients with inadequate responses to surgical and medical therapy.

Complications

Hypopituitarism and **cardiovascular** effects (hypertension, CHF, CAD).

In panhypopituitarism, ACTH is generally the last hormone to become deficient–and the most life-threatening.

Hypopituitarism

Diminished or absent secretion of one or more pituitary hormones. Etiologies are outlined below.

In a man with hypopituitarism and skin bronzing, think hemochromatosis.

Symptoms/Exam

Presentation depends on the particular hormone deficiency. In increasing order of importance, with **ACTH being preserved the longest,** pituitary hormones are lost as follows:

- **GH deficiency:** May be asymptomatic in adults. Has been associated with ↑ fat mass, bone loss, cardiovascular risk factors, and possibly reduced quality of life.
- **LH/FSH deficiency:** Hypogonadism. Manifested in men as lack of libido and impotence and in women as irregular menses/amenorrhea.
- **TSH deficiency:** Hypothyroidism.
- **ACTH deficiency:** AI (weakness, nausea, vomiting, anorexia, weight loss, fever, and hypotension). Hyperkalemia is generally present only in 1° AI.
- **ADH** deficiency (DI) is seen only if the posterior pituitary is also involved.

Differential

Remember the "**eight I's**": **I**nvasive, **I**nfiltrative, **I**nfarction, **I**njury, **I**mmunologic, **I**atrogenic, **I**nfectious, **I**diopathic.

- **Invasive causes:** Pituitary adenomas (usually nonproductive macroadenomas), craniopharyngioma, 1° CNS tumors, metastatic tumors, anatomic malformations (e.g., encephalocele and parasellar aneurysms).
- **Infiltrative causes:** Sarcoidosis, hemochromatosis, histiocytosis X.
- **Infarction:**
  - **Sheehan's syndrome:** Pituitary infarction associated with postpartum hemorrhage and vascular collapse. Typically presents with difficulty in lactation and failure to resume menses postpartum.
  - **Pituitary apoplexy:** Spontaneous hemorrhagic infarction of a preexisting pituitary tumor (see above).
- **Injury:** Severe head trauma can lead to anterior pituitary dysfunction and DI.
- **Immunologic causes: Lymphocytic hypophysitis.** During or just after pregnancy, 50% of patients have other autoimmune disease.
- **Iatrogenic:** Most likely after **pituitary surgery** or **radiation therapy.**
- **Infectious:** Rare; include TB, syphilis, and fungi.
- **Idiopathic: Empty sella syndrome.**
  - The subarachnoid space extends into the sella turcica, partially filling it with CSF and flattening the pituitary gland. Due to congenital incompetence of the diaphragma sellae (the **most common cause**) or to pituitary surgery, radiation therapy, or pituitary infarction.
  - Check for hormone deficiencies and hyperprolactinemia, but most patients who have a radiologic diagnosis have normal pituitary function and do not require treatment.

Diagnosis

Specific hormonal testing includes the following:

- **ACTH/adrenal axis:** Abnormal ACTH and cortisol. See the discussion of AI below for details on the **cosyntropin test.** Note that the test may be normal in acute pituitary dysfunction, since in this setting, the adrenals can still respond to a pharmacologic dose of ACTH.
- **Thyroid axis:** Low free T_4 (TSH levels are **not** reliable for this diagnosis, as levels may be low or normal) in 2° hypothyroidism.
- **Gonadotropins:** Low FSH/LH, testosterone, or estradiol.
- **GH:** Low IGF-1, GH provocative testing.
- **ADH:** If DI is suspected, test as described in Table 6.5.

TABLE 6.5. Diagnosis of Central DI, Nephrogenic DI, and Psychogenic Polydipsia

Test	Central DI	Nephrogenic DI	Psychogenic Polydipsia
Random plasma osmolality	↑	↑	↓
Random urine osmolality	↓	↓	↓
Urine osmolality during water deprivation	No change	No change	↑
Urine osmolality after IV DDAVP	↑	No change	↑
Plasma ADH	↓	Normal to ↑	↓

Treatment

Seventy-five percent or more of the pituitary must be destroyed before there is clinical evidence of hypopituitarism.

Treat the underlying cause. Medical treatment consists of correcting hormone deficiencies:

- **ACTH:** Hydrocortisone 10–30 mg/day, two-thirds in the morning and one-third in the afternoon/evening.
- **TSH:** Replace with levothyroxine (adjust to a goal of normal free T_4).
- **GnRH:**
  - **Men:** Replace testosterone by injection, patch, or gel.
  - **Women:** If premenopausal, OCPs or HRT.
- **GH:** Human GH is available.
- **ADH:** Intranasal DDAVP 10 μg QD-BID.

Diabetes Insipidus (DI)

Deficient ADH action resulting in copious amounts of extremely dilute urine. Subtypes are as follows:

- **Central DI:** Caused by destruction or dysfunction of the posterior pituitary by neurosurgery, infection, tumors, cysts, hypophysectomy, histiocytosis X, granulomatous disease, vascular disruption, autoimmune disease, trauma, or genetic diseases.
- **Nephrogenic DI:** Caused by chronic renal disease, congenital factors, hypercalcemia, hypokalemia, and **lithium.**

Symptoms/Exam

Keeping up with fluid losses from massive polyuria is a key component of DI treatment.

- **Polyuria,** polydipsia.
- The hallmark is inappropriately **dilute urine** in the setting of **elevated serum osmolality (urine osmolality < serum osmolality).**
- **Hypernatremia** occurs if the patient lacks access to free water or does not have an intact thirst mechanism.

Differential

Psychogenic polydipsia—polyuria due to ↑ drinking, usually > 5 L of water per day, leading to dilution of extracellular fluid and water diuresis.

Diagnosis

Diagnosed as follows (see also Table 6.5):

- **Plasma and urine osmolality.**
- **Water deprivation test:** If serum osmolality is not elevated, consider this test, in which the patient is denied access to water, and serum and plasma osmolalities are checked frequently until serum osmolality is elevated.
  - Urine specific gravity < 1.005 or urine osmolality < 200 mOsm/L indicates DI.
  - A rise in urine osmolality > plasma osmolality indicates psychogenic polydipsia.
- **DDAVP test** (synthetic vasopressin): Once the diagnosis of DI is established, perform to distinguish central from nephrogenic DI.

TREATMENT

- **Central DI:** DDAVP administration (IV, SQ, PO, or intranasally).
- **Nephrogenic DI:** Treat the underlying disorder if possible. Thiazide diuretics and amiloride may be helpful.

COMPLICATIONS

Hypernatremia, hydronephrosis.

The single best screening test for evaluating thyroid function is TSH. Low levels most commonly represent hyperthyroidism; high levels suggest hypothyroidism.

THYROID DISORDERS

Tests and Imaging

THYROID FUNCTION TESTS (TFTS)

Table 6.6 outlines the role of TFTs in diagnosing thyroid disorders. Figure 6.2 illustrates the hypothalamic-pituitary-thyroid axis.

- **Thyrotropin (TSH)** is the best screening test and is the most sensitive indicator of thyroid dysfunction. If there is 2° (pituitary) thyroid dysfunction, the TSH is unreliable, and FT_4 is used instead.

TABLE 6.6. TFTs in Thyroid Disease

	TSH	Free T_4	T_3/Free T_3
1° hypothyroidism	↑	↓	↓
2° (pituitary) hypothyroidism	↓/Normal	↓	↓
3° (hypothalamic) hypothyroidism	↓	↓	↓
1° hyperthyroidism	↓	↑	↑
2° hyperthyroidism (rare; TSH-secreting adenoma)	↑	↑	↑
Exogenous hyperthyroidism	↓	↑	Mild ↑
Euthyroid sick (acute)	↓/Normal[a]	Rare ↑/Normal/↓	↓
Euthyroid sick (recovery)	↑[b]	Normal	Normal

[a] ↓ (but not undetectable), especially if the patient has received dopamine, glucocorticoids, narcotics, or NSAIDs.

[b] Usually not > 20 mIU/L.

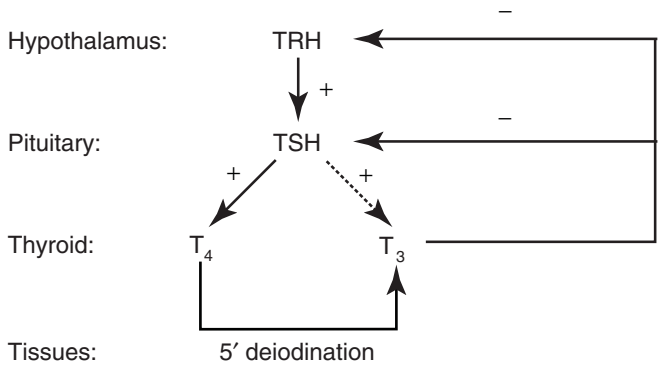

FIGURE 6.2. The hypothalamic-pituitary-thyroid axis.

TSH is produced by the pituitary in response to TRH. TSH stimulates the thyroid gland to secrete T_4 and low levels of T_3. T_4 is converted in the periphery by 5′ deiodinase to T_3, the active form of the hormone. T_3 is also primarily responsible for feedback inhibition on the hypothalamus and pituitary. Most T_4 is bound to TBG and is not accessible to conversion; therefore, free T_4 provides a more accurate assessment of thyroid hormone level.

- If TSH is abnormal, the next step is to check a FT_4.
- If TSH is low and FT_4 is normal, then check a **total or free T_3 (TT_3 or FT_3)** to rule out "T_3 thyrotoxicosis." TT_3 or FT_3 is often low in euthyroid sick syndrome and amiodarone-induced hypothyroidism. It is not necessary to check TT_3 or FT_3 in the evaluation of routine hypothyroidism.

Thyroid Antibodies

- **Thyroglobulin (Tg) antibodies:** Found in 50–60% of patients with Graves' disease and in 90% of those with early Hashimoto's thyroiditis. If present, thyroglobulin assay is not reliable.
- **Thyroid peroxidase (TPO) antibodies:** Antibodies to a thyroid-specific enzyme (TPO); present in 50–80% of Graves' disease patients and in > 90% of those with Hashimoto's thyroiditis.
- **Thyroid-stimulating immunoglobulin (TSI):** Stimulates the receptor to produce more thyroid hormone; present in 80–95% of Graves' patients.

Radionuclide Uptake and Scan of the Thyroid Gland

The test is performed as follows:

- ^{123}I is administered orally, and the **percent of radioiodine uptake** is obtained at 4–6 and 24 hours (see Table 6.7).
- The test is usually accompanied by a **scan** to determine the geographic distribution of its functional activity (i.e., to determine if hot or cold nodules are present).
  - A **hot** nodule implies overactivity of the nodule.
  - A **cold** nodule implies no activity of the nodule. Most malignant nodules are cold.
- Most often used to determine the etiology of hyperthyroidism; not useful in the evaluation of hypothyroidism.
- Also used to follow patients with thyroid cancer after thyroidectomy.
- Can be used to determine the dose for ^{131}I radioiodine thyroid ablation.

TABLE 6.7. Hyperthyroidism Differential Based on Radioiodine Uptake and Scan

Decreased Uptake	Diffusely Increased Uptake	Uneven Uptake
Thyroiditis	Graves' disease	Toxic multinodular goiter (multiple hot and cold nodules)
Exogenous thyroid hormone ingestion		Solitary toxic nodule (one hot nodule; the remainder of the thyroid appears cold)
Struma ovarii		Cancer (cold nodule)

Thyroid/Neck Ultrasound

Indications include the following:

- To confirm the clinical suspicion of a thyroid nodule, precisely measure size, and determine radiographic characteristics.
  - Colloid or "comet tail artifact" usually points to benign disease.
  - Microcalcifications or irregular shape/borders are suspicious for malignancy.
- To detect local recurrence in thyroid cancer.
- Not routinely done in the evaluation of hyper- or hypothyroidism.

Hypothyroidism

Affects 2% of adult women and 0.1–0.2% of adult men. Etiologies include the following:

- **Hashimoto's (autoimmune) thyroiditis:** The **most common cause in the United States.** Characterized by goiter in early disease and by a small, firm gland in late disease.
- **Late phase of thyroiditis:** After the acute phase of hyperthyroidism, hypothyroidism may occur but is usually transient (see below).
- **Drugs:** Amiodarone, lithium, interferon, iodide (kelp, radiocontrast dyes).
- **Iatrogenic:** Postsurgical or post–radioactive iodine (RAI) treatment.
- **Iodine deficiency:** Rare in the United States but common worldwide. Often associated with a grossly enlarged gland.
- **Rare causes:** 2° hypothyroidism due to hypopituitarism; 3° hypothyroidism due to hypothalamic dysfunction; peripheral resistance to thyroid hormone.

In iodine-sufficient areas such as the United States, amiodarone induces hypothyroidism more often than hyperthyroidism.

Symptoms/Exam

- **Symptoms are nonspecific** and include **fatigue, weight gain, cold intolerance, dry skin, menstrual irregularities, and constipation.**
- On exam, the thyroid is often small but can also be enlarged.
- May also present with periorbital edema; rough, dry skin; peripheral edema; bradycardia; hoarse voice; coarse hair; shortened eyebrows; and delayed relaxation phase of DTRs.
- ECG may demonstrate low voltage.

Diagnosis

- **Labs:** The most common findings are an **elevated TSH** (> 10 mIU/L) **and a ↓ FT_4.** In Hashimoto's, there may be ⊕ TPO and/or Tg **antibodies** (see above).
- **Radiology:** RAI scan and ultrasound are generally not indicated.

Treatment

- **Thyroid hormone replacement:** Levothyroxine (LT_4) is generally used. The replacement dose is usually 1.6 μg/kg/day.
- In elderly patients or those with heart disease, **start low and go slow** (12.5–25.0 μg/day; then slowly ↑ the dose by 25-μg increments every month until euthyroid).
- The decision as to whether to treat **subclinical hypothyroidism** (slightly elevated TSH, usually < 10 mU/L, with a normal FT_4) is controversial and depends on the patient's clinical profile and preference. Some clinicians favor treatment in the presence of a goiter, ⊕ thyroid antibodies, or hyperlipidemia.
- Additional treatment may be required depending on the cause.

Autoimmune thyroid disease may be associated with other endocrine autoimmune disorders, most prominently pernicious anemia and AI.

Complications

- **Myxedema coma:** Characterized by weakness, hypothermia, hypoventilation with hypercapnia, hypoglycemia, hyponatremia, water intoxication, shock, and death. Treatment is supportive therapy with rewarming, intubation, and IV LT_4. Often precipitated by infection or other forms of stress. Consider glucocorticoids for AI, which can coexist with thyroid disease.
- **Other complications:** Anemia (normocytic), CHF, depression, and lipid abnormalities (elevated LDL and TG).

Hyperthyroidism

Etiologies of hyperthyroidism include the following (see also Table 6.8):

- **Graves' disease (the most common cause):** Affects females more often than males in a ratio of 5:1. Peak incidence is at 20–40 years.
- **Solitary toxic nodule.**
- **Toxic multinodular goiter.**
- **Thyroiditis.**
- **Rare causes:** Exogenous thyroid hormone ingestion (thyrotoxicosis factitia), struma ovarii (ovarian tumor produces thyroid hormone), hydatidiform mole (hCG mimics TSH action), and productive follicular thyroid carcinoma.

Symptoms

May present with weight loss, anxiety, **palpitations,** fatigue, hyperdefecation, **heat intolerance,** sweating, and amenorrhea.

Exam

Findings include the following:

- **General:** Lid lag, tachycardia, ↑ pulse pressure, hyperreflexia, restlessness, goiter (smooth and homogeneous in Graves' disease; irregular in multinodular goiter).
- **Graves' disease only:** Ophthalmopathy (20–25% clinically obvious), dermopathy (2–3%; **pretibial myxedema**), thyroid bruit (due to ↑ vascularity), onycholysis (separation of the fingernails from the nail bed). Eye findings include **exophthalmos** (see Figure 6.3), proptosis, conjunctival inflammation, and periorbital edema.

Two physical findings are pathognomonic of Graves' disease: pretibial myxedema and exophthalmos.

TABLE 6.8. Causes and Treatment of Hyperthyroidism

Cause	Thyroid Exam	Unique Findings	RAI Uptake & Scan	Treatment
Graves' disease	Diffusely enlarged thyroid; bruit may be present.	Ophthalmopathy and dermopathy. TSI = TSH receptor antibody (⊕ in 80–95%); TPO antibody (⊕ in 50–80% but low specificity).	Diffusely ↑ uptake.	Meds (MMI, PTU), RAI, surgery for very large, obstructing goiter.
Solitary toxic nodule	Single palpable nodule.	Autoantibodies are usually absent. May have predominantly T_3 toxicosis.	Single focus of ↑ uptake.	Definitive therapy: RAI or surgery.
Multinodular goiter	"Lumpy-bumpy," enlarged thyroid.	Autoantibodies are usually absent. May have predominantly T_3 toxicosis.	Multiple hot and/or cold nodules.	Definitive therapy: RAI or surgery.
Thyroiditis	Tender, enlarged thyroid.	Possibly associated with fever or viral illness. Elevated ESR and thyroglobulin; autoantibodies are usually absent. A hypothyroid phase may follow. Can be caused by meds (e.g., amiodarone).	Diffusely ↓ uptake.	β-blockers, NSAIDs, steroids if indicated.
Exogenous hyperthyroidism	Normal or nonpalpable.	The patient may be taking weight loss medications or have psychiatric illness. Low thyroglobulin levels can distinguish from thyroiditis.	Diffusely ↓ uptake.	Discontinuation of thyroid hormone.

Diagnosis

Diagnosed as follows (see also Figure 6.4):

- **Labs:** TSH, FT_4, occasionally FT_3, thyroid antibodies (see above).
- **Radiology:** RAI uptake and scan if the type of hyperthyroidism is in question or if RAI therapy is planned. Antithyroid medications must be held at least seven days before RAI is administered.

Treatment

- **Medications:** Methimazole (MMI) and propylthiouracil (PTU) can be used to ↓ thyroid hormone production. **In pregnancy, PTU is the first choice.**

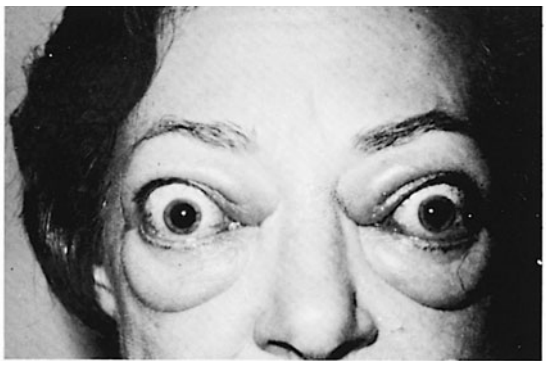

FIGURE 6.3. Graves' ophthalmopathy.

Characterized by periorbital edema, injection of corneal blood vessels, and proptosis. (Reproduced, with permission, from Greenspan FS, Gardner DG. *Basic & Clinical Endocrinology*, 7th ed. New York: McGraw-Hill, 2004: 263.)

Elderly patients may present with apathetic hyperthyroidism, which is characterized by depression, slow atrial fibrillation, weight loss, and a small goiter.

- In Graves' disease, treatment for 18 months can lead to complete remission in 50% of cases.
- β-blockers can be used in the acute phase to control tachycardia and other symptoms.

- **RAI:** The treatment of choice for solitary toxic nodules and toxic multinodular goiter, since these conditions generally do not spontaneously remit with medical therapy. Contraindicated in pregnancy. Yields a 90% cure rate for Graves' with a single dose.
- **Surgery:** Indicated in uncontrolled disease during pregnancy, for extremely

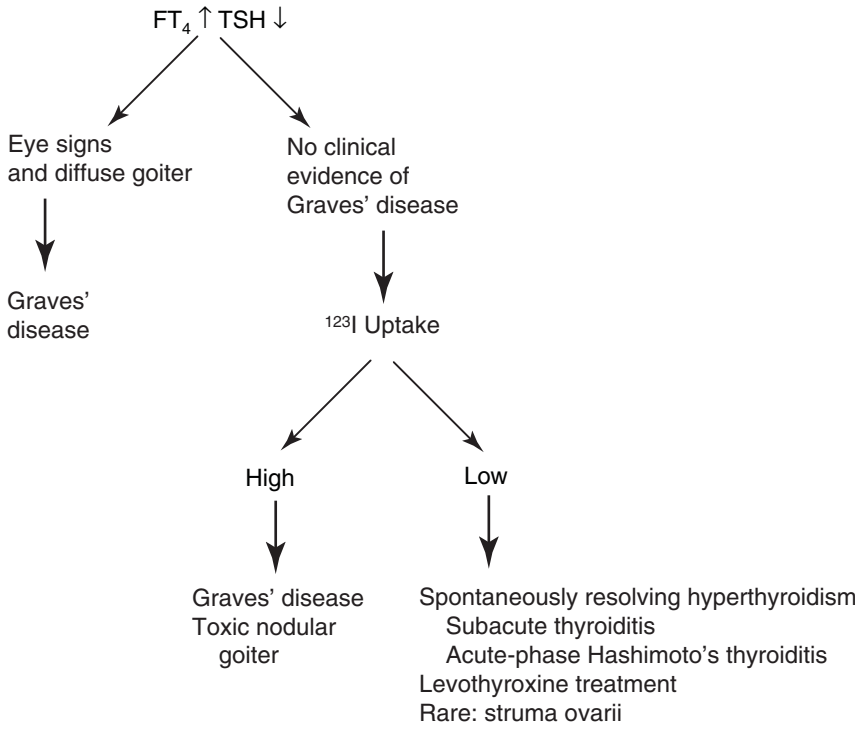

FIGURE 6.4. Algorithm for the diagnosis of hyperthyroidism.

large goiters causing obstruction, for amiodarone-induced thyroiditis that is refractory to medical management, or for patients who object to RAI and cannot tolerate antithyroid drugs. Risks include hypoparathyroidism and recurrent laryngeal nerve injury.

Complications

- **Atrial fibrillation (AF):** Particularly common in the elderly. Thyroid function should be checked in all cases of new AF. Associated with a higher risk of stroke than other causes of nonvalvular AF.
- **Ophthalmopathy:** Can lead to nerve or muscular entrapment (and thus to blindness or palsies). Can be precipitated or **worsened by RAI therapy,** especially in **smokers.** Treatment includes high-dose glucocorticoids and eye surgery.
- **Thyroid storm:** Characterized by **fever,** extreme tachycardia (HR > 120), delirium, agitation, diarrhea, vomiting, jaundice, and CHF. Treatment involves high-dose propranolol, PTU (600- to 1000-mg loading dose, then 200–250 mg q 4 h), glucocorticoids, and iodide (SSKI or Lugol's).

Thyroiditis

There are many different types of thyroiditis, all of which **can present with hyper-, hypo-, and/or euthyroid states** (see Table 6.9).

Symptoms/Exam

- **Early stage:** Characterized by thyroid inflammation (high ESR) and by the release of preformed thyroid hormone, which leads to clinical hyperthyroidism, suppressed TSH, and low RAI uptake.
- **Late stage:** Characterized by thyroid "burnout" and hypothyroidism.
- Most patients with acute thyroiditis eventually recover thyroid function.

Treatment

See Table 6.9.

Thyroid Disease in Pregnancy

See the discussion in the Women's Health chapter.

Thyroid medications are not indicated in euthyroid sick syndrome; treat the underlying illness.

Euthyroid Sick Syndrome

Seen in hospitalized or terminally ill patients, typically without symptoms. The **most common abnormality is a low T_3 level.** TSH levels vary, often rising during the recovery phase; this should not be confused with hypothyroidism.

Thyroid Nodules and Cancer

Nodules are more common in women but are more likely to be malignant in men. Radiation exposure (e.g., Chernobyl; treatment of childhood acne) is a major risk factor. The "**90%**" mnemonic applies:

- **90% of nodules are benign.**
- **90% of nodules are cold** on RAI uptake scan; 15–20% of these are malignant and 1% of hot nodules are malignant.

TABLE 6.9. Clinical Features and Differential Diagnosis of Thyroiditis

Type	Etiology	Clinical Findings	Tests	Treatment
Subacute thyroiditis (de Quervain's)	Viral.	Hyperthyroid early, then hypothyroid. Tender, large thyroid; fever.	Elevated ESR; no antithyroid antibodies; low RAI uptake.	β-blocker, NSAIDs, acetaminophen +/– steroids.
Hashimoto's thyroiditis	Autoimmune.	Usually hypothyroid; painless +/– goiter.	95% have ⊕ antibodies; anti-TPO most sensitive.	Levothyroxine.
Suppurative thyroiditis	Bacteria > other infectious agents.	Fever, neck pain, tender thyroid.	TFTs normal. No uptake on RAI scan; ⊕ cultures.	Antibiotics and drainage.
Amiodarone	Am**IOD**arone contains **IOD**ine.	Three changes due to amiodarone: 1. Asymptomatic TFT changes ($\downarrow T_4 \rightarrow T_3$ conversion) 2. Hypothyroidism 3. Hyperthyroidism	1. $\uparrow FT_4$ and total T_4; then low T_3 and high TSH. 2. High TSH; low FT_4 and T_3. 3. Low TSH; high FT_4 and T_3.	1. No treatment needed; will normalize eventually. 2. Gradual titration of levothyroxine. 3. As for other thyroiditis; stop amiodarone if possible.
Other medications	Lithium, α-interferon, interleukin-2.		Lithium typically causes hypothyroid profile.	Stop medication if possible.
Riedel's thyroiditis	Fibrosis; rare.	Compressive symptoms—stridor, dyspnea, SVC syndrome.	Approximately 67% have ⊕ antibodies.	Surgery to relieve obstruction.
Postpartum thyroiditis	Lymphocytic infiltration; seen after up to 10% of pregnancies.	Small, nontender thyroid.	May see hyper- or hypothyroidism. Antibodies often ⊕; RAI uptake low.	No treatment unless propranolol is needed for tachycardia. It is important to monitor TFTs in future pregnancies.

- **90% of thyroid malignancies present as a thyroid nodule or lump.**
- > 90% of cancers are either papillary or follicular, which carry the best prognoses.

Symptoms/Exam

- Present with a firm, palpable nodule.
- Cervical lymphadenopathy and hoarseness are concerning signs.
- Often found incidentally on radiologic studies done for other purposes.

The overall risk of thyroid cancer is the same whether a patient has a single nodule or multiple nodules.

Medullary thyroid cancer can produce elevated levels of calcitonin and is often associated with MEN 2A or 2B.

Differential

Thyroid nodules may be benign or represent one of four main types of cancer:

- **1° thyroid cancer:**
  - **Papillary: Most common;** spreads lymphatically. Has an **excellent prognosis overall,** with a > 95% five-year survival for all but metastatic disease.
  - **Follicular:** More aggressive; spreads locally and hematogenously. Can metastasize to the bone, lungs, and brain. Rarely produces thyroid hormone.
  - **Medullary:** A tumor of parafollicular C cells. May secrete calcitonin. Fifteen percent are familial or associated with multiple endocrine neoplasia (MEN) 2A or 2B.
  - **Anaplastic:** Undifferentiated. Has a **poor prognosis;** usually occurs in older patients.
- **Other:** Metastases to thyroid (breast, kidney, melanoma, lung); lymphoma (1° or metastatic).

Diagnosis

Diagnosed as follows (see also Figure 6.5):

- The first step is to check TSH.
- Thyroid/neck ultrasound is recommended to determine the size of the nodule as well as to detect other nodules and/or lymphadenopathy. The presence of irregular shape/borders and microcalcifications is associated with malignancy.

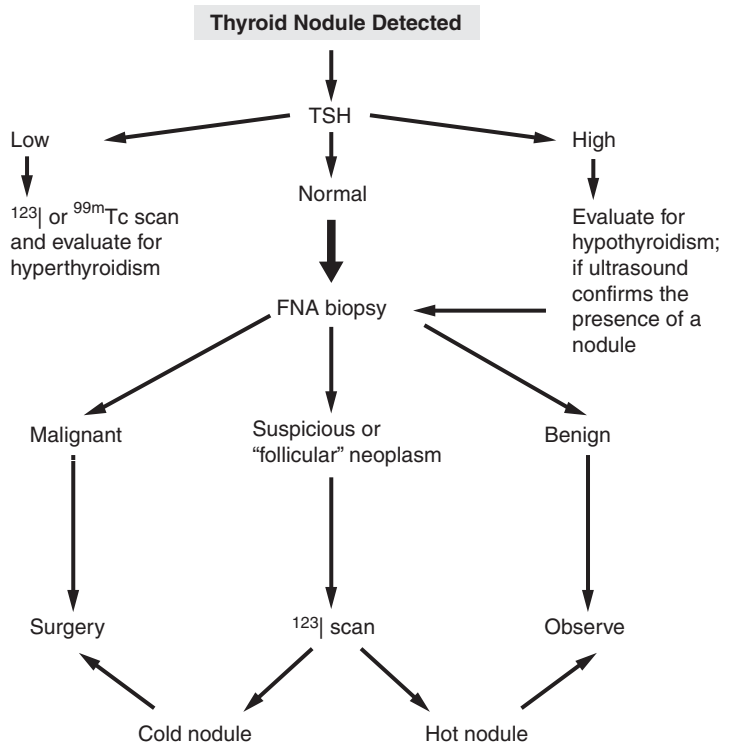

FIGURE 6.5. Evaluation of a thyroid mass.

(Adapted, with permission, from Gardner DG, Shoback DM. *Greenspan's Basic & Clinical Endocrinology*, 8th ed. New York: McGraw-Hill, 2007: 270.)

- **All euthyroid and hypothyroid nodules should be biopsied with fine-needle aspiration (FNA).** May be done under ultrasound guidance if not palpable. Four pathologic results are possible:
  - **Malignant:** Surgery.
  - **Benign:** Follow. The use of LT_4 to suppress the growth of benign nodules is no longer recommended, as it is often ineffective and may be associated with toxicity (especially in the elderly).
  - **Insufficient for diagnosis:** Repeat FNA after six weeks.
  - **Follicular neoplasm or "suspicious for malignancy":** Consider ^{123}I scan (functional nodules = low risk). Lobectomy is usually done for definitive diagnosis (~15% are malignant). Follicular adenoma cannot be distinguished from carcinoma by FNA.
- If a multinodular goiter is present, FNA of the most suspicious nodule (by radiologic features) or the dominant nodule (largest nodule > 1 cm) is acceptable, although it will not diagnose all cases of malignancy. Such patients should be followed, and nodules that ↑ in size should be considered for FNA.

Thyroglobulin is a good marker for the presence of thyroid tissue. If present after total thyroidectomy and RAI remnant ablation, it can indicate thyroid cancer recurrence.

TREATMENT

- **Nodules:** See Figure 6.5.
- **Papillary/follicular cancer:**
  - **First:** Surgical thyroidectomy.
  - **Second:** RAI remnant ablation.
  - **Third:** LT_4 to suppress TSH.

ADRENAL GLAND DISORDERS

The adrenal gland has two main portions and is under control of the hypothalamus and pituitary (see Figure 6.6):

- **Medulla:** Produces catecholamines (epinephrine, norepinephrine, and dopamine).
- **Cortex:** Composed of three zones—remember as **GFR:**
  - **G**lomerulosa: The 1° producer of mineralocorticoids **(aldosterone).**
  - **F**asciculata: The 1° producer of **cortisol** and androgens.
  - **R**eticularis: Also produces androgens and cortisol.
- ACTH and cortisol follow a circadian rhythm; levels are highest around 6:00 A.M.

The most common cause of AI is exogenous glucocorticoid use.

Adrenal Insufficiency (AI)

2° AI (ACTH deficiency) is much more common than 1° AI (adrenal failure). Etiologies are as follows (see also Table 6.10):

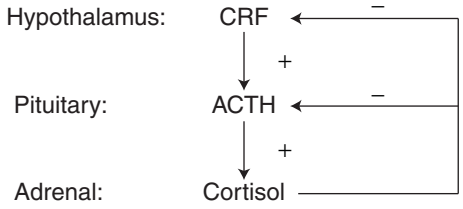

FIGURE 6.6. The hypothalamic-pituitary-adrenal axis.

TABLE 6.10. 1° vs. 2° Adrenal Insufficiency

	1°	2°
ACTH	High	Low
Cortisol	Low	Low
Hyperkalemia	Common	No
Hyponatremia	May be present	May be present
Eosinophilia	May be present	Absent
Hyperpigmentation	May be present	Absent
Mineralocorticoid replacement needed	Yes	No

Hyperpigmentation indicates 1° AI (most notable in the oral mucosa, palmar creases, and recent scars) due to compensatory high levels of ACTH that stimulate melanocytes to produce excess melanin.

- **1° AI (Addison's disease):** Because of high adrenal reserve, more than 90% of both adrenal cortices must fail to cause clinical AI.
  - **Autoimmune: The most common** etiology of 1° AI. Often accompanied by other autoimmune disorders.
  - **Metastatic malignancy** and **lymphoma.**
  - **Hemorrhage:** Seen in critically ill patients, pregnancy, anticoagulated patients, and **antiphospholipid antibody syndrome.**
  - **Infection:** TB, fungi (*Histoplasma*), CMV, HIV.
  - **Infiltrative disorders:** Amyloid, hemochromatosis.
  - **Congenital adrenal hyperplasia.**
  - **Adrenal leukodystrophy.**
  - **Drugs:** Ketoconazole, metyrapone, aminoglutethimide, trilostane, mitotane, etomidate.
- **2° AI:**
  - **Iatrogenic: Glucocorticoids;** anabolic steroids (e.g., megestrol).
  - **Pituitary or hypothalamic tumors.**

Symptoms/Exam

A poststimulation cortisol level of < 18 μg/dL suggests AI.

- Presents with weakness, fatigue, anorexia, weight loss, nausea, vomiting, diarrhea, unexplained abdominal pain, and postural lightheadedness.
- With 1° AI, **hyperpigmentation** of the oral mucosa and palmar creases is also found.
- Exam reveals orthostatic **hypotension.**

Diagnosis

- **Labs: Hyponatremia,** hyperkalemia (only in 1° AI), eosinophilia, azotemia due to volume depletion, mild metabolic acidosis and hypercalcemia.
- **Step 1: Confirm the diagnosis of AI.**
  - **Random cortisol: Any random cortisol ≥ 18 μg/dL** rules out AI. However, a low or normal value is not useful.
  - **Cosyntropin stimulation test:**
    - Obtain baseline ACTH and cortisol.

- Administer cosyntropin (synthetic ACTH) 250 μg IM or IV.
- Check cortisol level 30–60 minutes later. Values are normal if post-stimulation cortisol is ≥ 18–20 μg/dL.

- **Step 2: Distinguish 1°** from 2° AI. An elevated ACTH level in a patient with AI implies 1° AI.
- **Step 3: Further evaluate the cause** (often through anatomic imaging). Studies may include a CT of the adrenal glands (e.g., if infection, tumor, or hemorrhage is suspected) or a pituitary MRI (e.g., for 2° AI without an obvious cause).

If a patient presents with acute bilateral adrenal hemorrhage, remember to test for antiphospholipid antibody syndrome.

Treatment

- Hydrocortisone 10–30 mg/day, two-thirds in the morning and one-third in the afternoon/evening (prednisone 5 mg/day can also be used). Stress doses are as follows:
  - **Minor stress** (e.g., mild pneumonia): Double the usual dose.
  - **Major stress** (e.g., illness requiring hospitalization or surgery): Give 50 mg IV q 6–8 h; taper as illness improves.
- Fludrocortisone 0.05–0.10 mg/day. Note that this is needed **only in 1° AI, not in 2° AI.**

Complications

Adrenal crisis—acute deficiency of cortisol, usually due to major stress in a patient with preexisting AI. Characterized by headache, nausea, vomiting, confusion, fever, and significant hypotension. The condition is **fatal** if not treated with immediate steroid therapy.

Cushing's Syndrome

A syndrome due to excess cortisol. Etiologies are as follows:

- **Exogenous corticosteroids: The most common cause overall.**
- **Endogenous causes:**
  - **Cushing's disease** (70% of endogenous cases): Due to ACTH hypersecretion from a **pituitary** adenoma (80–90% are microadenomas). The female-to male ratio is 8:1.
  - **Ectopic ACTH** (15%): From nonpituitary neoplasms producing ACTH (e.g., small cell lung carcinoma, bronchial carcinoids). Rapid increases in ACTH levels lead to marked hyperpigmentation, metabolic alkalosis, and hypokalemia, sometimes without other cushingoid features. More common in men.
  - **Adrenal** (15%): Adenoma, carcinoma, or nodular adrenal hyperplasia.

Symptoms/Exam

Table 6.11 lists the clinical characteristics of Cushing's syndrome.

Diagnosis

- **Lab abnormalities:** Metabolic alkalosis, hypokalemia, hypercalciuria, leukocytosis with relative lymphopenia, hyperglycemia, and glucose intolerance.
- Principles of evaluation (see Figure 6.7) are as follows:
  - Confirm excess cortisol production.

TABLE 6.11. Clinical Features of Cushing's Syndrome

General	Dermatologic	Musculoskeletal	Neuropsychiatric	Gonadal Dysfunction	Metabolic
Obesity (90%) Hypertension (85%)	Plethora (70%) Hirsutism (75%) Striae (50%) Acne (35%) Bruising (35%)	Osteopenia (80%) Weakness (65%)	Emotional lability Euphoria Depression Psychosis	Menstrual disorders (70%) Impotence, ↓ libido (85%)	Glucose intolerance (75%) Diabetes (20%) Hyperlipidemia (70%) Polyuria (30%) Kidney stones (15%)

Adapted, with permission, from Greenspan FS, Gardner DG. *Greenspan's Basic & Clinical Endocrinology,* 7th ed. New York: McGraw-Hill, 2004: 401.

- Determine if ACTH dependent or independent.
- Use imaging to localize the source.

Treatment

- **Cushing's disease:** Transsphenoidal pituitary adenoma resection.
- **Ectopic ACTH:**
  - Treat the underlying neoplasm.
  - If the neoplasm is not identifiable or treatable, options are as follows:
    - Pharmacologic blockade of steroid synthesis (ketoconazole, metyrapone, aminoglutethimide).
    - Potassium replacement (consider spironolactone to aid potassium maintenance, as these patients require industrial doses of potassium replacement).
    - Bilateral adrenalectomy if all else fails.
- **Adrenal tumors:** Unilateral adrenalectomy.

Complications

Complications include all those associated with long-term glucocorticoid therapy—e.g., diabetes, hypertension, cardiovascular disease, obesity, osteoporosis, and susceptibility to infections such as *Nocardia*, PCP, and other opportunistic pathogens.

Hyperaldosteronism

May account for 0.5–10% of patients with hypertension. Etiologies are as follows:

- **Aldosterone-producing adenoma (Conn's disease):** Accounts for 60% of cases of 1° aldosteronism; three times more common in women.
- **Idiopathic hyperaldosteronism:** Responsible for one-third of cases of 1° aldosteronism; normal-appearing adrenals or bilateral hyperplasia is seen on CT scan.
- **Familial aldosteronism:** A rare autosomal-dominant condition; suspect if > 1 family member is affected.
  - **Type 1 (glucocorticoid-remediable aldosteronism):** Aldosterone secretion is stimulated by ACTH.

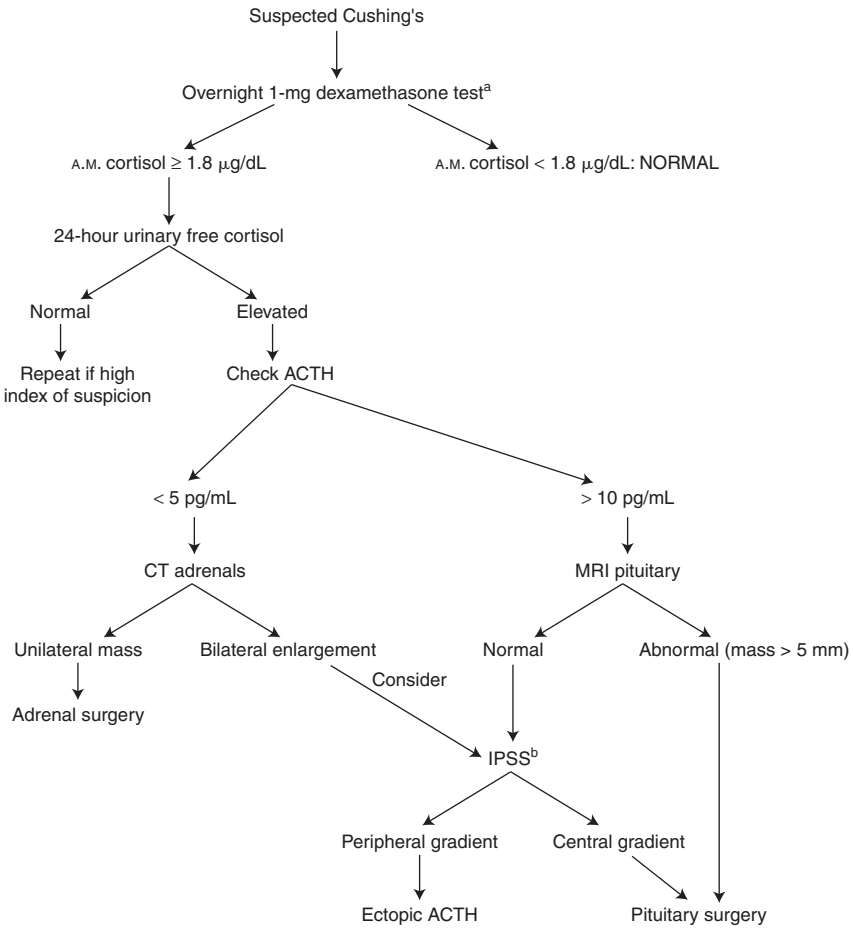

FIGURE 6.7. Evaluation and diagnosis of Cushing's syndrome.

[a] **Overnight 1-mg dexamethasone test:** Give the patient 1 mg dexamethasone PO to be taken at 11:00 P.M. The following morning, check cortisol between 7:00 and 9:00. If cortisol is < 1.8 μg/dL, normal; no Cushing's.

[b] IPSS = inferior petrosal sinus sampling. Catheters are used to measure levels of ACTH draining from the pituitary and periphery before and after CRH stimulation. If the gradient is greater from the pituitary, it suggests a central source. If greater from the periphery, the source is peripheral.

- **Type 2:** Can have either adenoma or idiopathic hyperaldosteronism.
- **Aldosterone-producing adrenocortical carcinoma:** Rare; responsible for < 1% of cases of 1° aldosteronism. **Hyperandrogenism** and/or **hypercortisolism** are clues to the diagnosis.

Symptoms/Exam

Hypertension and hypokalemia are classic features, although a low K^+ is not necessary for diagnosis. Most patients are asymptomatic, and there are no characteristic physical findings.

Diagnosis

- **Plasma aldosterone concentration (PAC) and plasma renin activity (PRA):** Best evaluated after the patient has been placed on a high-salt diet or after salt supplementation for one week (see Figure 6.8).

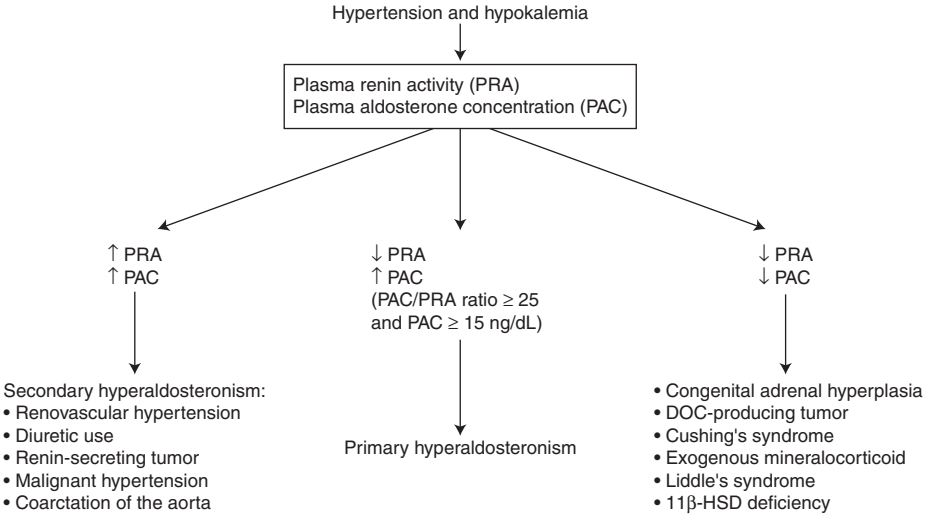

FIGURE 6.8. Evaluation of hypertension with hypokalemia.

A PAC/PRA ratio ≥ 25 and an absolute PAC ≥ 15 are characteristic of 1° aldosteronism.

- **24-hour urine collection for aldosterone, Na, and K:** Look for high aldosterone secretion in the setting of euvolemia and a high-sodium diet (manifested by a $U_{Na} > 50$ mEq/day) and potassium wasting.
- If the diagnosis is uncertain, **confirmatory testing with saline loading** (2 L of saline infused over 2–4 hours) will fail to suppress PAC into the normal range in patients with 1° aldosteronism (as opposed to low-renin essential hypertension).
- Once 1° aldosteronism is diagnosed, obtain an **adrenal CT** to distinguish between Conn's and idiopathic hyperaldosteronism.
- Some institutions perform **adrenal vein sampling** to localize the source in patients of older age, with less severe biochemical findings, and/or with equivocal CT findings (nodules < 1 cm or bilateral adrenal abnormalities).

TREATMENT

- **Spironolactone** (in high doses up to 400 mg/day) or **eplerenone** blocks the mineralocorticoid receptor and usually normalizes K^+. In men, the most common side effect of spironolactone is **gynecomastia,** but other side effects may occur (e.g., rash, impotence, epigastric discomfort).
- **Unilateral adrenalectomy** is recommended for patients with a single adenoma.

Pheochromocytoma

Pheochromocytoma rule of 10's:

10% are normotensive
10% occur in children
10% are familial
10% are bilateral
10% are malignant
10% are extra-adrenal (called paragangliomas)

Rare tumors (affecting < 0.1% of patients with hypertension and < 4% of patients with adrenal incidentalomas) that arise from chromaffin cells and **produce epinephrine and/or norepinephrine.** Subtypes are as follows:

- Adrenal tumor (90% of pheochromocytomas).
- Extra-adrenal locations (paragangliomas).

SYMPTOMS/EXAM

- Presents with **episodic attacks** of throbbing in the chest, trunk, and head, often precipitated by movements that compress the tumor.

- **Headaches, diaphoresis, palpitations,** tremor and anxiety, nausea, vomiting, fatigue, abdominal or chest pain, weight loss, cold hands and feet, and constipation may also be seen.
- Approximately 90–95% of patients have hypertension, but in 25% of cases, hypertension is episodic. Orthostasis is usually present.

*Patients with pheochromocytoma are usually thin—"**F**at **Ph**eos are **F**ew and **F**ar between."*

Diagnosis

- **Step 1:** Make a biochemical diagnosis.
  - **24-hour urinary metanephrines and catecholamines or plasma-free metanephrines:** Levels are usually at least 2–3 times higher in patients with pheochromocytomas.
- **Step 2:** Localize the tumor.
  - **CT** or **MRI** of the adrenals is used to find adrenal pheochromocytomas.
  - If the adrenals appear normal, a **^{123}I-MIBG** scan can localize extra-adrenal pheochromocytomas and metastases. It is approximately 85% sensitive and 99% specific.

Treatment

- **Pharmacologic preparation for surgery:**
  - **Phenoxybenzamine:** α-adrenergic blocker—a key first step.
  - **β-blockers:** Used to control heart rate, but only **after** BP is controlled and good α-blockade has been achieved.
  - Some centers prefer **calcium channel blockers.**
- **Hydration:** It is essential that patients be well hydrated before surgery.
- **Surgical resection** by an experienced surgeon is the definitive treatment for these tumors. Associated with a **90% cure rate.**
- **Postoperative complications include hypotension and hypoglycemia.** Always hang dextrose-containing IV fluids in the recovery room!
- **Follow-up:** Should include 24-hour urine for metanephrines and normetanephrines two weeks postoperatively. If levels are normal, surgical resection can be considered complete. Patients should then undergo yearly biochemical evaluation for at least 10 years.

Do not use β-blockers in patients with pheochromocytoma before adequate α-blockade has been achieved, as unopposed β-blockade can lead to paroxysmal worsening of the hypertension.

Complications

Hypertensive crises, MI, cerebrovascular accidents, arrhythmias, renal failure, dissecting aortic aneurysm.

Adrenal Incidentalomas

Adrenal lesions are found incidentally in approximately 2% of patients undergoing abdominal CT for unrelated reasons. Autopsy series indicate a prevalence of 6%.

Always rule out pheochromocytoma (since it can be life-threatening) and Cushing's syndrome (since subclinical disease is relatively common) in adrenal incidentaloma.

Exam

Depends on whether the lesion is functioning or nonfunctioning. If functioning, refer to the discussions above.

Differential

- **Functional adenoma:** Cushing's syndrome, pheochromocytoma, aldosteronoma.
- **Nonfunctional adenoma.**

- **Adrenal carcinoma:** Often large (> 4–5 cm) and high density on CT scan. Sixty percent are functional, usually secreting androgens or cortisol (or both hormones). **Virilization** in the presence of an adrenal mass suggests malignancy.
- **Metastases:** Most commonly arise from the lung, GI tract, kidney, or breast.
- **Other:** Myelolipoma (look for the presence of fat on CT scan), cysts, congenital adrenal hyperplasia, hemorrhage (usually bilateral).

DIAGNOSIS/TREATMENT

If a patient has a history of malignancy, the probability that an adrenal lesion is a metastasis is 25–30%. This is the only instance in which to consider needle biopsy of the lesion–but you must rule out pheochromocytoma first.

- **Step 1:** Rule out functional tumor.
  - 24-hour urine collection for catecholamines and metanephrines or plasma metanephrines to rule out pheochromocytoma.
  - 1-mg dexamethasone suppression test to rule out Cushing's.
  - Plasma renin activity and aldosterone level to screen for aldosteronoma in patients with hypertension or hypokalemia.
- **Step 2:** Rule out metastasis with percutaneous adrenal needle biopsy only in the setting of known 1° malignancy. The procedure plays no role in patients without a history of cancer, as it cannot distinguish between benign and malignant adrenal masses. Rule out pheochromocytoma first, as manipulation of tumor can precipitate crisis.
- **Step 3:** Treatment is based on the size and functional status of the mass:
  - If the lesion is < 4 cm and nonfunctional, repeat imaging at 6 and 12 months. Consider periodic endocrine evaluation, since hormonal excess can develop over time.
  - If the lesion is > 4 cm and nonfunctional, resect.
  - If functional, treat as you would for pheochromocytoma, Cushing's, or aldosteronoma.

DISORDERS OF LIPID AND CARBOHYDRATE METABOLISM

Diabetes Mellitus (DM)

*Hemoglobin A_{1c} is used to monitor treatment but is **not** an accepted way to make the initial diagnosis of diabetes.*

Table 6.12 shows the diagnostic criteria and Table 6.13 the screening criteria used by the American Diabetes Association (ADA) for DM. The diagnosis of DM should be confirmed on a subsequent day unless there are obvious signs of hyperglycemia. Three **autoantibodies** are commonly found in patients with type 1 DM:

- Anti–glutamic acid decarboxylase (GAD) antibody.
- Anti-ICA 512 antibody.

TABLE 6.12. Criteria for the Diagnosis of DM (ADA Guidelines, 2007)

The presence of any one of the following is diagnostic:
1. Symptoms of diabetes (polyuria, polydipsia, unexplained weight loss) plus a random glucose concentration ≥ 200 mg/dL (11.1 mmol/L).
2. Fasting (≥ 8 hours) plasma glucose ≥ 126 mg/dL (7 mmol/L).
3. Two-hour plasma glucose ≥ 200 mg/dL (11.1 mmol/L) during oral glucose tolerance test with a 75-g glucose load.

TABLE 6.13. Diabetes Screening Criteria (ADA Guidelines, 2007)

1. Testing should be considered in all individuals ≥ 45 years of age, particularly if BMI ≥ 25 kg/m², and if normal, it should be repeated every three years.

2. Testing should be considered at a younger age and carried out more frequently in the following individuals:
   - Overweight (body mass index [BMI] ≥ 25 kg/m²).
   - Physically inactive.
   - First-degree relative with diabetes.
   - Members of high-risk ethnic groups (African-American, Hispanic, Native American, Asian-American, Pacific Islander).
   - Delivered a baby weighing > 9 lb or diagnosed with gestational diabetes.
   - Hypertension (BP ≥ 140/90 mmHg).
   - Have an HDL < 35 mg/dL and/or a TG level > 250 mg/dL.
   - Impaired glucose tolerance or impaired fasting glucose on previous testing.
   - Clinical conditions associated with insulin resistance (e.g., PCOS or acanthosis nigricans).
   - Vascular disease.

- Anti-insulin antibody. Most people will develop anti-insulin antibodies with insulin treatment; therefore, these antibodies are useful only in the first 1–2 weeks after insulin therapy is initiated.

Age does not necessarily determine the type of DM; more children are being diagnosed with type 2 DM and more adults with type 1 DM.

Symptoms/Exam

- **Presents with the three "polys": polyuria, polydipsia,** and **polyphagia.**
- **Other:** Rapid weight loss, dehydration, blurry vision, neuropathy, altered consciousness, acanthosis nigricans (indicates insulin resistance), candidal vulvovaginitis.
- **Signs of DKA: Kussmaul respirations** (rapid deep breaths); **fruity breath odor** from acetone.

Differential

- **Type 1 DM:** Caused by autoimmune destruction of the pancreatic islet cells; associated with a genetic predisposition. The classic patient is young and thin and requires insulin **at all times** to avoid ketosis.
- **Type 2 DM:** Associated with obesity and insulin resistance; accounts for roughly 90% of DM cases in the United States. Shows a strong polygenic predisposition.
- **2° causes of DM:** Insulin deficiency or resistance from many causes, such as CF, pancreatitis, Cushing's syndrome, and medications (glucocorticoids, thiazides, pentamidine). May also be due to genetic defects in β-cell function (e.g., mature-onset diabetes of the young, or MODY).
- **Latent autoimmune diabetes in adults:** Generally considered a form of type 1 DM seen in adults. Patients have ⊕ autoantibodies, but the course is less severe than that in children.

First-line treatment of type 2 DM in an obese patient with normal renal function (Cr < 1.5) is metformin.

Treatment

- **Routine diabetic care:** See Table 6.14.
- **Glycemic control:** For therapeutic goals, see Table 6.15.
  - **Oral medications for type 2 DM:** See Table 6.16. Treatment is usually initiated with a single agent. Metformin is first-line therapy in type 2 DM (in the absence of contraindications such as Cr > 1.5 mg/dL). Of-

Hold metformin immediately before and after radiologic studies with IV contrast in light of the risk of lactic acidosis.

TABLE 6.14. Routine Diabetic Care

Element	Measures
Diet and exercise	Weight loss for overweight and obese individuals. Low-fat (~30% energy intake) diet, monitoring of carbohydrate intake, and regular exercise (150 minutes of moderate exercise or 90 minutes of vigorous exercise per week distributed over three or more days).
Hemoglobin A_{1c} (HbA_{1c})	Measure at least two times per year in stable patients; measure every three months during medication changes and until < 7%.
BP control	Goal BP is < 130/80 mmHg. First-line therapy is usually ACEIs or ARBs, but β-blockers and diuretics may also be used.
Lipids	Goal LDL < 100 mg/dL, TG < 150 mg/dL, and HDL > 40 mg/dL.
Aspirin therapy	Give 75–162 mg of aspirin per day in all adult patients with DM and cardiovascular disease. Consider use in patients ≥ 40 years of age and in younger patients (> 21 years) with cardiac risk factors (familial hypercholesterolemia, hypertension, smoking, dyslipidemia, albuminuria).
Smoking cessation	All patients should be advised not to smoke.
Nephropathy screening	Annual microalbumin screen in type 1 DM patients five years after the initial diagnosis and in all type 2 DM patients. Treat microalbuminuria with ACEIs or ARBs. Check creatinine at least annually in order to estimate GFR and stage level of CKD.
Neuropathy screening	Screen for distal symmetric polyneuropathy at diagnosis and annually. Screen for autonomic neuropathy at diagnosis for type 2 DM and five years after the diagnosis for type 1 DM. Electrophysiologic testing is rarely needed.
Foot care	A comprehensive foot examination and foot self-care education annually with visual inspection at each visit. Abnormality should trigger referral for special footwear or podiatry. Screen for peripheral arterial disease with history, exam for pedal pulses, and consider ankle-brachial index testing.
Retinopathy	Type 1 DM patients should have an initial eye exam within 3–5 years of onset and then annually. Type 2 DM patients should have an initial exam soon after diagnosis and annually thereafter. Laser therapy can reduce the risk of vision loss.
Immunizations	Annual influenza vaccine in patients > 6 months of age; at least one lifetime pneumococcal vaccine for adults.
Preconception care	HbA_{1c} should be normal or as close as possible to normal before conception; oral antidiabetic agents, statins, and ARBs/ACEIs should be discontinued before pregnancy.

ten, a second or third oral agent (usually a sulfonylurea or thiazolidinedione) or basal insulin is needed as the disease progresses.

- **Insulin:** For all type 1 DM and many type 2 DM patients (see Table 6.17). Potential insulin regimens include "**basal-bolus**" (**basal** coverage with intermediate- to long-acting insulin plus **bolus** short-acting before meals) and **continuous SQ insulin infusion** delivered via an SQ catheter ("insulin pump").

- **Pancreatic/islet cell transplant:** Experimental.

TABLE 6.15. Treatment Goals for Nonpregnant DM Patients (both type 1 and type 2)

	Normal	Goal	Additional Action Suggested
Preprandial capillary plasma glucose (mg/dL)	< 100	90–130	< 90 or > 150
Peak postprandial capillary plasma glucose (mg/dL)	< 140	< 180	Target only if preprandial glucose is at target and HbA_{1c} is still elevated.
Plasma average bedtime glucose (mg/dL)	< 120	110–150	< 110 or > 180
HbA_{1c} (%)	< 6	< 7[a]	> 8

[a] The HbA_{1c} goal for *patients in general* is < 7%, but for an *individual patient* is as close to normal (< 6%) as possible without significant hypoglycemia.

Acute Complications

Acute complications of DM can stem from ketoacidosis or from hyperosmolar coma (see Tables 6.18 and 6.19):

- **Ketoacidosis:** Can be the initial manifestation of type 1 DM, but may also occur in patients with type 1 or type 2 DM when a stressor is present (e.g., infection, infarction, surgery, medical noncompliance). Often presents with abdominal pain, vomiting, Kussmaul respirations, and a fruity breath odor. Mortality is just < 5%. Look for and treat a precipitating event when possible.
  - The first goal is to close the anion gap with an IV **insulin drip;** the glucose will ↓ as the gap closes. Once glucose levels are < 250 mg/dL, add dextrose to IV fluids. When the anion gap has closed, the insulin may be switched to SQ. Start SQ insulin **before** discontinuing the insulin drip to prevent "rebound" hyperglycemia.
  - **Fluids:** Start with NS. If the patient is not in shock, sodium is normal or elevated, and/or potassium must be repleted concurrently, switch to 1/2 NS or D5 1/2 NS.
  - **Potassium:** Usually falsely elevated due to acidosis, so when in the 4.0–4.5 range, start K^+ replacement (potassium levels will fall with treatment).
  - Bicarbonate, magnesium, and phosphate are usually not needed.
- **Hyperosmolar coma:**
  - Characterized by significant hyperglycemia (often > 600 mg/dL), hyperosmolality, and dehydration without ketosis. Mortality is 40–50%, as this often occurs in elderly patients with multiple comorbidities. There is often a precipitating event (infection, infarction, intoxication, medical noncompliance).
  - Presents with "polys," weakness, lethargy, and confusion (when osm > 310) or with coma (osm > 330). Treatment is similar to that for DKA; treat the underlying stressor and give fluids, insulin drip, and electrolyte replacement.
    - **Fluids:** Often need 6–10 L. Start with NS and then follow with 1/2 NS; add D5 when glucose levels are < 250. Watch for pulmonary edema and volume overload in elderly patients.
    - **Insulin drip:** See the DKA section above.
    - **Potassium:** See the DKA section above.

Continue an insulin drip until the anion gap closes even after glucose has normalized.

TABLE 6.16. Medication Classes Used in Type 2 DM

Class	Names	Mechanism	Adverse Effects	Comments
Sulfonylureas	Glimepiride, glipizide, glyburide, tolazamide, tolbutamide	Promote insulin secretion by pancreatic β cells.	Hypoglycemia.	Different medications have varying degrees of renal or liver metabolism.
Biguanides	Metformin	↓ hepatic glucose production; enhance peripheral insulin sensitivity.	GI effects (nausea, diarrhea, ↓ appetite). Lactic acidosis (rare).	Promote weight loss. Lactic acidosis risk is ↑ in patients with renal disease (Cr > 1.5 in men; Cr > 1.4 in women), CHF, severe respiratory disease, or liver disease; with use of IV radiocontrast agents; and in the elderly (> 80 years).
Meglitinides	Repaglinide, nateglinide	Acute insulin secretion by pancreatic β cells.	Hypoglycemia.	Dosed TID; short action for postprandial hyperglycemia. Marketed as carrying a lower risk of hypoglycemia than sulfonylureas.
Thiazolidinediones	Rosiglitazone, pioglitazone	↑ insulin sensitivity in muscle and fat.	Fluid retention, edema, weight gain.	Previous agents in this class caused liver disease; LFTs should be checked at baseline and then periodically. Should not be used in patients with heart failure or active liver disease.
α-glucosidase inhibitors	Miglitol, acarbose	Delay breakdown of ingested complex carbohydrates.	Gas, bloating, diarrhea.	Start low and gradually ↑ the dose. Should not be used in patients with GI problems.
Amylin analog	Pramlintide	Slows gastric emptying; prevents abnormal postprandial glucagon rise seen in diabetics.	Nausea, hypoglycemia.	Administered as mealtime SQ injections in both type 1 and type 2 diabetics taking prandial insulin.

TABLE 6.16. Medication Classes Used in Type 2 DM *(continued)*

Class	Names	Mechanism	Adverse Effects	Comments
Glucose-like peptide-1 (GLP-1) agonists	Exenatide	"Incretin" mimetic (incretins are gut hormones that stimulate endogenous insulin release).	GI effects (nausea, vomiting, diarrhea) and ↓ appetite.	Available in prefilled syringes for SQ injection BID. Promote weight loss; approved for use in combination with other oral agents. Resistant to degradation by DPP-IV (see below).
Dipeptidyl peptidase IV (DPP-IV) inhibitors	Sitagliptin, vildagliptin (coming soon)	Prevent rapid breakdown of incretin hormones (e.g., GLP-1).	URI, nasopharyngitis, headache.	Weight-neutral.

Chronic Complications

- **Microvascular complications:**
  - **Retinopathy:** Occurs after DM has been present for 3–5 years. Prevent with a yearly eye exam and laser therapy for retinal neovascularization.
  - **Nephropathy:** The first sign is usually microalbuminuria. Prevent with BP control, glucose control, and ACEIs or ARBs.
  - **Neuropathy:** Often progressive, involving the distal feet and hands. Prevent ulcers with foot care, careful inspection, and podiatry as needed. Also susceptible to autonomic neuropathy, mononeuropathies, and polyradiculopathies.
- **Macrovascular complications:** Associated with an ↑ risk of MI and stroke. Prevent with aspirin therapy in high-risk patients; maintain a low threshold for cardiac stress testing; and keep LDL < 100 mg/dL (or < 70 mg/dL in high-risk patients with known CAD).
- **Hypoglycemia:** Most often occurs in patients taking insulin, although oral medications can also cause this condition. See the discussion of hypoglycemia for details.

Two landmark trials show that lowering HbA_{1c} prevents microvascular complications: the Diabetes Control and Complications Trial for type 1 DM and the UK Prospective Diabetes Study for type 2 DM.

TABLE 6.17. Summary of Insulin Characteristics

	Insulin Type	Onset	Peak Action	Duration
Ultra-short-acting (SQ)	Lispro, aspart, glulisine	5–15 minutes	60–90 minutes	3–4 hours
Short-acting (SQ)	Regular	15–30 minutes	1–3 hours	5–7 hours
Intermediate-acting (SQ)	NPH	2–4 hours	8–10 hours	18–24 hours
Long-acting (SQ)	Glargine, detemir	3–4 hours	Glargine has virtually no peak; detemir peaks at 6–8 hours	Up to 24 hours

TABLE 6.18. DKA vs. Hyperosmolar Coma

	DKA	Hyperosmolar Coma
Serum HCO_3	Low (< 15 mEq/L)	Normal or slightly low
pH	< 7.3	> 7.3
Blood glucose	< 800 mg/dL and can be normal	Often > 800 mg/dL
Serum ketones	> 5 mmol/L	< 5 mmol/L
Urine ketones	Large	Small

- **Infections:** Diabetic patients are at ↑ risk of unusual infections such as necrotizing fasciitis or myositis, mucormycosis, emphysematous cholecystitis, and malignant otitis externa.
- Studies indicate that **tight glycemic control** can ↓ the incidence of chronic complications, especially microvascular disease.

Gestational Diabetes

See the section in the Women's Health chapter.

Metabolic Syndrome

Associated with insulin resistance.

Exam/Diagnosis

The diagnosis is based on the presence of any **three of the following** (per the Adult Treatment Panel III criteria):

- Abdominal obesity (waist circumference > 40 inches in men and > 35 inches in women).
- TG > 150 mg/dL.
- HDL < 40 mg/dL in men and < 50 mg/dL in women.
- BP > 130/85 mmHg.
- Fasting glucose > 110 mg/dL.

Treatment

Patients should be targeted for lifestyle changes and pharmacologic therapy as indicated for their individual risk factors.

TABLE 6.19. Formulas to Guide DKA and Hyperosmolar Coma Management

Anion gap = Na − (Cl + CO_2) (normal: usually 7–13; depends on lab; use measured Na)
Calculated osmolality = 2 × Na + glucose/18 + BUN/2.8 + ethanol/4.6
Corrected Na = measured Na + 1.5 (glucose − 150)/100 **OR** Corrected Na = measured Na + [(glucose − 100) × 1.6] / 100

Hypoglycemia

Although most hypoglycemic reactions occur in patients being treated with insulin, they may also be seen in those on sulfonylureas, meglitinides, and, rarely, metformin or thiazolidinediones (usually when used in combination with sulfonylureas or insulin).

Autonomic symptoms from hypoglycemia can be blunted in patients on β-blockers or in those who have hypoglycemia unawareness from repeated hypoglycemic episodes.

Symptoms/Exam

- **Neuroglycopenic symptoms** (low glucose delivery to the brain): Mental confusion, stupor, coma, focal neurologic findings mimicking stroke, death.
- **Autonomic symptoms:** Tachycardia, palpitations, sweating, tremulousness, nausea, hunger.

Differential

- **Insulin reaction:** Too much insulin, too little food, or too much exercise can cause hypoglycemia in patients on insulin.
- **Sulfonylurea overdose:** Especially problematic in elderly patients or in patients with renal failure causing ↓ medication clearance.
- **Factitious hypoglycemia:** A surreptitious or inadvertent (e.g., incorrect medication dispensed) hypoglycemic agent use in a nondiabetic patient.
- **Insulinomas:** Rare tumors of the pancreatic islets cells that secrete insulin. Usually single, benign tumors that can be surgically resected.
- **Reactive hypoglycemia:** Hypoglycemia after a meal may be seen in patients with "dumping syndrome" following bariatric surgery; otherwise rare.
- **Autoimmune hypoglycemia:** A rare condition with anti-insulin antibodies that cause hypoglycemia.

Diagnosis

Diagnosis should proceed as follows:

- **Step 1:** Check a glucose level at the time symptoms arise to confirm hypoglycemia.
- **Step 2:** Distinguish the causes of hypoglycemia in nondiabetic patients by performing a supervised fast up to 72 hours. When glucose levels are < 45 mg/dL and the patient experiences the characteristic symptoms of hypoglycemia, measure simultaneous glucose, insulin, C-peptide, proinsulin, and sulfonylurea levels (see Table 6.20).

Treatment

- **Conscious patients:** Glucose tablets; orange juice or other sugar-containing beverages.

TABLE 6.20. Diagnosis of Hypoglycemic Disorders[a]

	Insulin	C-Peptide	Sulfonylurea Screen
Insulinoma	High	High	–
Factitious insulin ingestion	High	Low	–
Sulfonylureas	High	High	+

[a] A 72-hour fast is necessary to rule out insulinoma. Insulin and C-peptide levels should be measured when glucose < 45 mg/dL accompanied by characteristic symptoms of hypoglycemia.

Hypertriglyceridemia can cause milky-appearing serum when TG > 350 mg/dL.

- **Unconscious patients:** Give 1 mg glucagon IM or 50% glucose solution IV. If these are not available, honey, syrup, or glucose gel may be rubbed into the buccal mucosa.

Familial Lipid Abnormalities

Table 6.21 outlines the presentation of various lipid abnormalities. For more detail, see the section in the Ambulatory Care chapter regarding routine hyperlipidemia management. Always consider 2° causes that can exacerbate lipid abnormalities in predisposed individuals:

Sodium can be falsely ↓ ("pseudohyponatremia") when TG levels are elevated.

- **Hypertriglyceridemia: Poor diabetes control,** alcohol, corticosteroid or estrogen therapy, uremia, HIV (especially in those treated with protease inhibitors), nephrotic syndrome (when albumin is < 1–2 g/dL), acromegaly, hypothyroidism (rarely), hypergammaglobulinemia.
- **Hypercholesterolemia:** Hypothyroidism, nephrotic syndrome, immunoglobulin disorders, anorexia nervosa, cholestasis.

Treatment

- Patients should be treated with low-fat diets and encouraged to maintain a normal body weight.
- Initial pharmacologic therapy depends upon the 1° lipid abnormality targeted.
  - **High TGs:** Fibrates (clofibrate, gemfibrozil, fenofibrate), niacin, and omega-3 fatty acids (used at high doses). Can use high-potency statins.
  - **High LDL:** Statins are generally first line; ezetimibe or a bile acid sequestrant can be added if needed.
  - **Low HDL:** A 2° goal of therapy, and often difficult to treat. May ↑ when TGs are lowered. Niacin is usually the most effective of the anti-TG medications at raising HDL.

Statins and gemfibrozil used together lead to an ↑ risk of rhabdomyolysis. In patients requiring both a statin and a fibrate, use fenofibrate instead of gemfibrozil, since it does not compete with statins for the glucuronidation elimination pathway.

MINERAL METABOLISM AND METABOLIC BONE DISEASE

Calcium Metabolism

Figure 6.9 delineates the hormonal control of calcium metabolism. Figure 6.10 graphically depicts the mechanisms of vitamin D metabolism. The **25-hydroxyvitamin D** (25-HD) level indicates body vitamin D stores, and **1,25-dihydroxyvitamin D** (1,25-DHD) is the biologically active hormone.

Hypercalcemia

Eighty percent of hospitalized hypercalcemia cases are due to malignancy. Eighty percent of outpatient hypercalcemia cases are due to 1° hyperparathyroidism.

Most commonly presents as an incidentally discovered laboratory abnormality in an asymptomatic patient. Can be classified as PTH-mediated hypercalcemia (1° hyperparathyroidism) vs. other causes (in which PTH is suppressed).

Symptoms/Exam

Best remembered by the mnemonic "**psychic moans, abdominal groans, stones, and bones**" (see Table 6.22).

Differential

- **1° hyperparathyroidism:** See the separate section below.
- **Malignancy-associated hypercalcemia:** Occurs in 10–15% of malignan-

TABLE 6.21. Common Familial Lipid Abnormalities

Disease[a]	Cholesterol	TG	LDL	HDL	Signs/Symptoms	Treatment
Isolated hypertriglyceridemia					Eruptive cutaneous xanthomas, lipemia retinalis, acute pancreatitis.	
Lipoprotein lipase deficiency (AR)	Normal	2000–25,000	Normal	Low	Childhood diagnosis. Hepatosplenomegaly.	Dietary; meds are not very effective.
Apo C-II deficiency (AR)–required cofactor for lipoprotein lipase	Normal	2000–25,000	Low	Low	Childhood diagnosis. Hepatosplenomegaly.	Dietary; meds are not very effective.
Familial hypertriglyceridemia (AD)	Normal	200–500	Normal	Low		Anti-TG meds.[b]
Isolated hypercholesterolemia					Tendon xanthomas.	
Familial hypercholesterolemia—deficiency or malfunction of LDL receptor (AD)	Heterozygous: 275–500 Homozygous: > 500	Normal	Very high	Normal	Premature CAD. Homozygous: CAD in first decade.	Statin, ezetimibe, niacin.
Familial defective Apo B-100—impaired LDL binding	275–500	Normal	Very high	Normal	Premature CAD.	Statin, ezetimibe, niacin.
Combined hypertriglyceridemia and hypercholesterolemia						
Familial combined hyperlipidemia (AD) —can be isolated ↑ TG, ↑ LDL, or both	250–500	250–750	High	Low	Premature CAD. Associated with insulin resistance.	Statin, ezetimibe, niacin.
Familial dysbetalipoproteinemia—APO E2 isoform (AR)	250–500	250–500	Low	Normal	Palmar and tubular xanthomas and xanthelasmas.	Statin; anti-TG medications.[b]

[a] AR = autosomal recessive; AD = autosomal dominant.

[b] Anti-TG medications = clofibrate, gemfibrozil, fenofibrate, niacin, and high-dose omega-3 fatty acids. Can use high-potency statins.

cies and portends a poor prognosis. In 98% of patients, the identity of the tumor is obvious at presentation. Has three mechanisms:

- **Tumor release of PTH-related peptide (PTHrP)—most common:** Homologous to PTH, but **not** detected by intact PTH serum assay, and does not ↑ 1,25-DHD production. Seen with solid tumors (e.g., breast, lung, renal cell, ovarian, and bladder carcinoma).

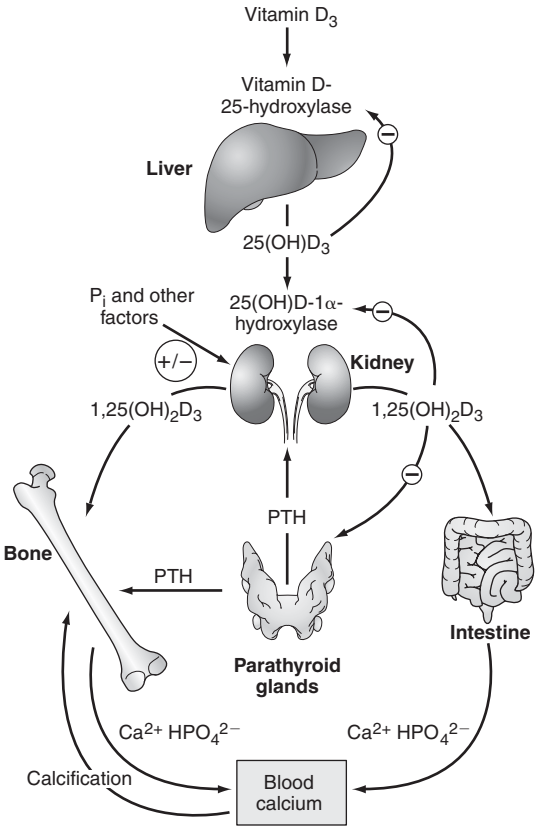

FIGURE 6.9. Hormonal control loop for calcium metabolism and function.

Low serum calcium levels prompt a proportional increase in PTH concentration, which mobilizes calcium from the bone. PTH also increases the synthesis of $1,25(OH)_2$ vitamin D in the kidney, which in turn stimulates the mobilization of calcium from bone, increases absorption of calcium in the intestine, and downregulates PTH synthesis. (Reproduced, with permission, from Kasper DL et al. *Harrison's Principles of Internal Medicine,* 16th ed. New York: McGraw-Hill, 2005: 2246.)

- **1,25-DHD production by tumor:** Due to 1α-hydroxylase activity; associated with lymphomas.
- **Local osteolysis from metastases or adjacent tumor mass:** Typically multiple myeloma and breast cancer.

- **Granulomatous disorders:** Include sarcoidosis and TB.
  - Granulomas contain 1α-hydroxylase, which allows them to make **1,25-DHD.**
  - Treatment with glucocorticoids is uniquely effective, directly suppressing the 1α-hydroxylase enzyme.
- **Endocrinopathies:**
  - Ten percent of **thyrotoxic** patients have mild hypercalcemia.
  - **Adrenal insufficiency.** Rare: pheochromocytoma, VIPoma.
- **Hypervitaminosis A and D:**
  - Vitamin A excess leads to bone resorption and associated hypercalcemia.
  - Vitamin D intoxication leads to elevated 25-HD levels, which stimulate ↑ intestinal absorption of calcium and ↓ renal excretion.
- **Drug induced:** Thiazides, lithium, calcium-based antacids, estrogens, androgens, teriparatide (PTH 1-84).

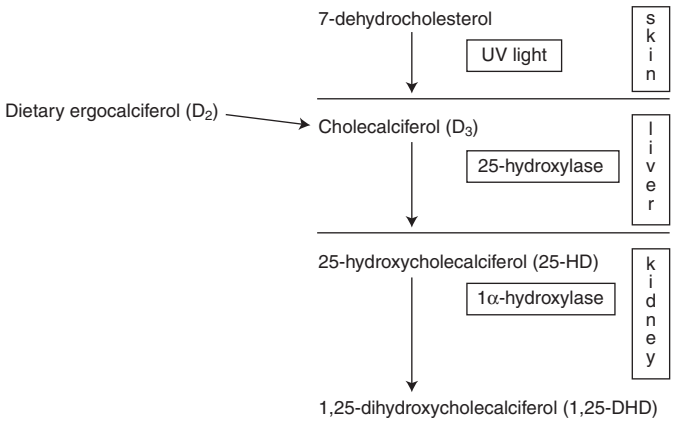

FIGURE 6.10. Vitamin D metabolism.

Vitamin D is derived when UV light from the sun hits the skin, converting 7-dehydrocholesterol into cholecalciferol (D_3), or when ergocalciferol (D_2) is ingested and then converted to D_3. D_3 is 25-hydroxylated to 25-hydroxycholecalciferol (25-HD) in the liver. 25-HD is the primary storage form. 25-HD is converted to 1,25-dihydroxycholecalciferol (1,25-DHD) in the kidney under PTH regulation. 1,25-DHD is the active form of the hormone.

- **Immobilization:** Usually seen in adolescents or others with high bone turnover states (Paget's, hyperthyroidism) due to marked ↑ in bone resorption. Associated with hypercalciuria.
- **Milk-alkali syndrome:** Occurs when large quantities of calcium are ingested with absorbable antacids and cause hypercalcemia, alkalosis, nephrocalcinosis, and kidney dysfunction.

DIAGNOSIS

- When an elevated serum calcium level is found, first check ionized calcium or correct for albumin level:

$$\text{Corrected } Ca^{++} = \text{serum Ca (mg/dL)} + [0.8 \times (4.0 - \text{albumin (g/dL)})]$$

  i.e., for each 1.0-mg/dL ↓ in albumin, add 0.8 mg/dL to measured total serum calcium.
- Next, obtain a PTH. If elevated, the differential should include PTH-mediated causes of hypercalcemia; if suppressed, a PTHrP, 25-HD, and 1,25-DHD should be obtained (see Table 6.23).

TABLE 6.22. Signs and Symptoms of Hypercalcemia

PSYCHIC MOANS	ABDOMINAL GROANS	STONES	BONES	OTHER
Lethargy	Nausea	Nephrolithiasis	Osteitis fibrosa	Weakness
Depression	Vomiting	Nephrocalcinosis	Arthritis	Hypertonia
Psychosis	Constipation	Nephrogenic DI	Fractures (depending	Bradycardia
Ataxia	Anorexia	(polyuria, polydipsia)	on the cause)	Shortened QT
Stupor		Uremia		Band keratopathy[a]
Coma				

[a] A mottled-looking band stretching horizontally across the cornea.

TABLE 6.23. Laboratory Findings Associated with Hypercalcemia

	Calcium	Phosphorus	PTH	PTHrP	Other
PTH mediated	↑	↓	↑	↓	
PTHrP mediated	↑	↓	↓	↑	
1,25-DHD mediated	↑	↑	↓	↓	↑ 1,25-DHD
Vitamin D intoxication	↑	↑	↓	↓	↑ 25-HD

Treatment

- **Hydration with NS is the essential element in treating acute hypercalcemia.** Often requires 2.5–4.0 L of NS per day; start at 300–500 cc/hr except in the setting of CHF.
- **Loop diuretics** are indicated **only after complete rehydration.**
- IV **bisphosphonates** (pamidronate or zoledronic acid):
  - The treatment of choice in suspected hypercalcemia of malignancy.
  - Its effect on serum calcium will be **delayed at least 24 hours,** and the calcium nadir will occur approximately 3–5 days after injection. Hypocalcemic effects will last 4–6 weeks.
  - Side effects include a mild ↑ in serum creatinine in approximately 15% of patients; transient fever and myalgia in 20% of patients; and hypophosphatemia.
- **Calcitonin (SQ):**
  - Use only in the presence of severe symptomatic hypercalcemia.
  - Works faster than bisphosphonates, but efficacy is lost after three days owing to tachyphylaxis.
- **Glucocorticoids:** First-line treatment in patients with vitamin D– or vitamin A–mediated hypercalcemia, especially owing to ↑ 1α-hydroxylase activity of lymphoma or granulomatous disease.

1° Hyperparathyroidism

Hyperparathyroidism causes the greatest bone loss at the forearm, followed by the hip (sites of cortical bone). The spine (trabecular bone) is least affected.

Incidence is 42 in 100,000, and the female-to-male ratio is 2:1. **Eighty percent are due to a single parathyroid adenoma;** the rest are due to multigland hyperplasia and cancer. Can be part of **MEN 1 or MEN 2A syndrome.**

Symptoms/Exam

- Like hypercalcemia, it presents with "**psychic moans, abdominal groans, stones, and bones.**"
- **Eighty-five percent of patients are asymptomatic and are diagnosed on screening labs.**
- **Musculoskeletal:** Osteoporosis.
- **Renal: Nephrolithiasis;** gradual onset of **renal insufficiency** from nephrocalcinosis and nephrogenic DI.
- **Osteitis fibrosa cystica:** ↑ bone turnover causing bone pain and pathologic fractures. Also characterized by elevated alkaline phosphatase. X-rays of phalanges and skull reveal subperiosteal resorption of cortical bone. Os-

teolytic lesions due to brown tumors (cystic bone lesions containing fibrous tissue) may also be apparent.

Differential

- **Familial benign hypocalciuric hypercalcemia (FBHH):** Autosomal dominant; a lifelong, asymptomatic, mild hypercalcemia. Differentiated from 1° hyperparathyroidism by normal/mildly elevated PTH and marked **hypocalciuria.** This syndrome **requires no therapy.**
- **MEN syndromes:** See the section on MEN below.
- **Lithium therapy:** Lithium shifts the set point for PTH secretion, resulting in hypercalcemia.

If the patient is asymptomatic, consider FBHH and check for hypocalciuria before sending the patient for a parathyroidectomy!

Diagnosis

Made by laboratory tests **showing ↑ PTH, ↑ Ca^{++}, and ↓ phosphorus.** Further evaluation should include the following:

- 24-hour urinary calcium and creatinine.
- Evaluation of renal function with creatinine.
- Bone mineral density (BMD) evaluation by dual-energy x-ray absorptiometry (DEXA).
- Measurement of 25-HD level. Low levels can cause 2° hyperparathyroidism and predispose to hungry bone syndrome (see below).
- Imaging studies of the parathyroid glands (neck ultrasound and parathyroid sestamibi scan) are **not useful for diagnosis** but may be helpful in preoperative planning.

Treatment

- **Parathyroidectomy** is the treatment of choice. The **cure rate is 95%,** and the complication rate (hypoparathyroidism, recurrent laryngeal nerve injury) is < 1%. **Surgery is recommended under the following conditions:**
  - Age < 50.
  - Serum calcium 1.0 mg/dL above the upper normal level.
  - 24-hour urine calcium > 400 mg.
  - Creatinine clearance reduced by 30%.
  - BMD with a T-score < −2.5 at any site.
  - Patient preference or inability to follow up.
- **Medical therapy:** Usually reserved for symptomatic patients who either refuse or are unsuitable candidates for surgery. Bisphosphonates can prevent bone loss. Cinacalcet, which ↓ PTH secretion, can reduce serum calcium, but it is currently FDA approved only for 2° hyperparathyroidism from chronic kidney failure or hypercalcemia from parathyroid carcinoma.

Complications

- Hypercalcemia.
- Nephrolithiasis.
- Nephrocalcinosis with renal insufficiency.
- Osteoporosis.
- **Hungry bone syndrome** rarely occurs after parathyroidectomy when rapid skeletal remineralization leads to hypocalcemia.

Hypocalcemia

Chronic hypocalcemia results from deficiency or failure to respond to either PTH or vitamin D. Acute hypocalcemia can occur even when PTH is high if adaptive mechanisms are overwhelmed.

Symptoms/Exam

- **Neuromuscular excitability:** Paresthesias, seizures, organic brain syndrome, or the hallmark, **tetany**—a state of spontaneous tonic muscular contraction. Often heralded by numbness and tingling of the fingertips and perioral zone, its classic component is carpopedal spasm.
  - **Chvostek's sign:** Contraction of facial muscles in response to tapping of the facial nerve. Note that 25% of normal individuals have a ⊕ Chvostek's sign all the time.
  - **Trousseau's sign:** Elicited by inflating a BP cuff to 20 mmHg above systolic pressure for three minutes. A ⊕ response is carpal spasm (⊕ in 1–4% of normals).
- Soft tissue calcium deposition (cataract; calcification of basal ganglia).
- **Cardiac:** Prolonged QT interval.
- **Dermatologic:** Dry, flaky skin with brittle nails.

Differential

- **Hypoparathyroidism:** Most often **postsurgical,** but may also be autoimmune, familial, infiltrative (e.g., hemochromatosis or Wilson's), or idiopathic. Treat with chronic oral calcitriol (1,25-DHD) and calcium.
- **Pseudohypoparathyroidism:** A heritable disorder of **target organ resistance to PTH.** Has two forms: **isolated PTH resistance** or that associated with an abnormal phenotype—**Albright's hereditary osteodystrophy** (short stature, round face, short neck, brachydactyly). Treatment is the same as that for hypoparathyroidism.
- **Vitamin D deficiency:**
  - Risk factors include malabsorptive states (e.g., IBD, celiac sprue, post–gastric bypass surgery, chronic pancreatitis), lack of sun exposure, and dark skin.
  - Long-term deficiency in adults leads to **osteomalacia,** which presents with myopathy (proximal muscle pain and weakness) and poor bone mineralization with pseudofractures.
  - In children it leads to **rickets** (bony deformities, e.g., rachitic rosary, bowing of the lower extremities, frontal bossing).
  - **Dx: Low 25-HD level** (< 20 ng/mL). Hypocalcemia, hypophosphatemia, 2° hyperparathyroidism, and ↑ alkaline phosphatase may also be seen.
  - **Tx:** Oral vitamin D replacement at high doses; calcium.
- **Abnormal calcitriol metabolism:** Resistance or abnormal production—e.g., hereditary rickets.
- **Acute deposition or complex formation of calcium:**
  - **Acute hyperphosphatemia:** Tumor lysis, parenteral phosphate administration, excessive oral phosphate.
  - Acute pancreatitis.
  - Blood transfusion (citrate buffer present in packed RBC precipitates with calcium).
  - Hungry bone syndrome (status post parathyroidectomy).
- **Hypomagnesemia:** Low magnesium impairs the secretion and action of PTH.

Diagnosis

First check calcium and correct for albumin or check ionized calcium; then check phosphorus, magnesium, and PTH (see Table 6.24). If PTH is elevated or normal, check 25-HD and renal function.

Treatment

- **Acute:** In the setting of tetany, initiate a continuous IV calcium drip while starting oral calcium; give calcitriol if needed.
- **Chronic:** Oral calcium and calcitriol if needed.

Male and 2° Osteoporosis

2° osteoporosis should also be considered in women, especially those with Z-scores < –2.

2° osteoporosis is defined as osteoporosis due to an identifiable underlying disease. See the Women's Health chapter for information regarding postmenopausal osteoporosis.

Symptoms/Exam

Asymptomatic until a fracture occurs. Typical osteoporotic fractures are hip, vertebral compression, and Colles' fractures (a type of distal radius fracture).

Diagnosis

- BMD measurement by DEXA at the lumbar spine, total hip, and femoral neck.
  - The **T-score** is defined as the number of standard deviations below the average bone density for a young sex-matched cohort.
  - The **Z-score** is defined as the number of standard deviations below the average bone density for an age- and sex-matched cohort.
- The definition of osteoporosis is based on World Health Organization (WHO) criteria:
  - **Osteopenia:** T-score < –1 and > –2.5.
  - **Osteoporosis:** T-score < –2.5.
- Further evaluation should include a search for 2° causes of osteoporosis based on clinical suspicion of any existing disorder that can cause or present as osteoporosis. These include the following (see Table 6.25 for a full list):
  - 25-HD level.
  - Serum calcium, phosphorus, and PTH.
  - 24-hour urinary calcium and creatinine.
  - SPEP/UPEP.

TABLE 6.24. Laboratory Findings Associated with Hypocalcemia

	Calcium	Phosphorus	PTH	Other
Hypoparathyroidism	↓	↑	↓	
PTH resistance	↓	↑	↑	
Vitamin D deficiency	↓	↓	↑	↓ 25-HD
1,25-DHD resistance	↓	↓	↑	↑ 1,25-DHD

TABLE 6.25. 2° Causes of Osteoporosis

Endocrine Causes	GI Disorders	Marrow/Hematologic Disorders	Other
Cushing's syndrome	Liver disease	Multiple myeloma	Immobilization
Hypogonadism (male or female)	Malabsorptive conditions (mediated primarily via vitamin D deficiency):	Leukemias/lymphomas	Alcohol abuse
Hyperprolactinemia (by inducing hypogonadism)	■ Gastrectomy	Systemic mastocytosis	Tobacco use
Hyperthyroidism	■ Inflammatory bowel disorders	Hemophilia	Osteogenesis imperfecta
Hyperparathyroidism	■ Gastric bypass	Thalassemia	Rheumatoid arthritis
Vitamin D deficiency	■ Pancreatic insufficiency		Ankylosing spondylitis
			Eating disorders

- Testosterone level (in men); ask about menstrual history in women.
- TSH, especially in those with a history of hyperthyroidism or on levothyroxine replacement.

Treatment

- **Calcium 1500 mg/day with 800–1000 IU vitamin D per day** should be used in all patients with osteopenia or osteoporosis who do not have contraindications.
- **Bisphosphonates** (alendronate, risedronate, ibandronate) improve BMD and markedly ↓ the risk of fracture.
- **Teriparatide** (recombinant PTH) is the only anabolic agent approved for severe osteoporosis.
- **Calcitonin** is associated with minimal fracture prevention. Effective as an analgesic for acute vertebral fracture pain.
- **Raloxifene,** a selective estrogen receptor modulator, can be used only in women and also prevents breast cancer.

Complications

Fractures. Hip fractures are associated with 30% mortality in men. This mortality rate is higher than that for hip fractures in women. Vertebral fractures are associated with chronic pain and disability.

Paget's Disease

Accelerated bone turnover. Affects 4% of people > 40 years of age. **Most prevalent in northern Europe.**

Immobilizing a patient with active Paget's can lead to hypercalcemia.

Symptoms

Include pain, fractures, and deformity, most commonly in the **sacrum, spine, femur, skull, and pelvis.** Two-thirds of patients are asymptomatic.

Exam

Depends on which bones are involved. Exam may reveal skull enlargement, frontal bossing, bowed legs, and cutaneous erythema, warmth, and tenderness over the affected site.

Differential

Includes any localized bony tumor or cancer.

Diagnosis

- **Laboratory tests: ↑ alkaline phosphatase** and bone turnover markers are seen (e.g., osteocalcin, urinary hydroxyproline, N-telopeptide). Ca^{++} and phosphorus are normal.
- **Imaging studies:**
  - **Plain radiography:** Involved bones are expanded and denser than normal. Erosions are seen in the skull (osteoporosis circumscripta). Affected weight-bearing bones may be bowed.
  - **Bone scan:** ↑ uptake is seen in affected areas.

The most common fractures in Paget's disease are vertebral crush fractures.

Treatment

Bisphosphonates are the treatment of choice and lead to remission in most patients. Choices include IV pamidronate or zoledronic acid, oral alendronate, risedronate, and IV/PO ibandronate.

Complications

The complications of Paget's disease are outlined in Table 6.26.

Paget's is one of the rare causes of high-output CHF due to hypervascularity of the bony lesions.

MALE HYPOGONADISM

The testes are composed of seminiferous tubules, where sperm are produced (80–90% of testicular mass), and Leydig cells, which produce androgens.

Symptoms/Exam

- **Prepubertal androgen deficiency:** Poor 2° sexual development (small phallus and testes; sparse pubic, axillary, facial, chest, and back hair; high-pitched voice; low muscle mass); eunuchoid skeletal proportions.
- **Postpubertal androgen deficiency:** ↓ libido, erectile dysfunction, low energy. If prolonged, a ↓ in facial and body hair may be seen.

TABLE 6.26. Complications of Paget's Disease

Rheumatologic	Neurologic	Cardiac	Neoplastic[a]	Metabolic
Osteoarthritis Gout	Deafness (from involvement of cranial nerves, with bony entrapment) Spinal cord compression Peripheral nerve entrapment (carpal and tarsal tunnel syndromes)	High-output CHF	Osteosarcoma or chondrosarcoma Giant cell tumor	Immobilization-induced hypercalcemia/ hypercalciuria Nephrolithiasis

[a] Occur in 1% of Paget's cases.

Differential

- **Hypothalamic/pituitary disorders:** Low testosterone with normal or low LH and FSH.
  - **Panhypopituitarism.**
  - **LH and FSH deficiency:** If associated with anosmia, **Kallmann's** syndrome.
- **Gonadal disorders:** Usually characterized by low testosterone and elevated LH and FSH.
  - **Klinefelter's syndrome:** The most common genetic cause of male hypogonadism (1/500). XXY karyotype. Can be associated with intellectual impairment.
  - **Adult seminiferous tubule failure:** Etiologies include orchitis, leprosy, irradiation, alcoholism, uremia, cryptorchidism, lead poisoning, and chemotherapeutic agents (e.g., cyclophosphamide, methotrexate); may be idiopathic. Characterized by infertility, normal virilization, and normal testosterone levels (because the Leydig cells are unaffected).
  - **Adult Leydig cell failure (andropause):** A gradual ↓ in testicular function after age 50, with declining testosterone levels.
  - **Bilateral anorchia (absence of testes):** At birth, normal male phenotype with cryptorchidism. Failed 2° sexual development.
- **Defects in androgen biosynthesis.**
- **Defects in androgen action:**
  - **Complete androgen insensitivity:** Also known as **testicular feminization**—XY, with female phenotype, absence of uterus, absence of sexual hair, and infertility. Patients are usually raised as girls.
  - **Incomplete androgen insensitivity:** Phenotype varies with degree of insensitivity.

If LH is low in the setting of a low testosterone level, an MRI is indicated to evaluate the pituitary gland.

Androgen therapy in hypogonadal men can lead to gynecomastia.

Diagnosis

Check testosterone first. If low, repeat testosterone with LH and FSH (see Table 6.27). Diagnosis requires low testosterone measured with a reliable assay in the morning (due to normal diurnal variation) on several occasions.

Treatment

- **Androgen replacement:** Can be done with IM testosterone injections, patches, or gel.
- If an underlying disorder is diagnosed (e.g., pituitary tumor), treat appropriately.

TABLE 6.27. Diagnosis of Hypogonadism Based on Lab Tests

Disorder	Testosterone	LH	FSH
1° gonadal failure (Leydig cell failure)	↓	↑	↑
Seminiferous tubule failure	Normal	Normal	↑
Hypothalamic or pituitary dysfunction	↓	Normal or ↓	Normal or ↓
Partial androgen insensitivity	↑	↑	↑

- Treatment with testosterone requires monitoring for adverse effects such as prostatic enlargement or unmasking of clinically silent prostate cancer (PSA), erythrocytosis (CBC), low HDL (lipid panel), and obstructive sleep apnea.

Complications

Infertility; osteoporosis can develop in the absence of androgens but can usually be prevented with appropriate testosterone replacement.

*MEN 1 can be remembered as the **"3 P's"—P**arathyroid, **P**ancreas, and **P**ituitary.*

ENDOCRINE TUMORS

Multiple Endocrine Neoplasia (MEN)

A group of autosomal-dominant syndromes characterized by multiple endocrine tumors due to defective tumor suppressor genes (see Table 6.28).

- **MEN 1:** Screen if there is a ⊕ family history with serum calcium/PTH, serum gastrin, and serum prolactin.
- **MEN 2:** Screen for the *RET* proto-oncogene mutation if there is a ⊕ family history of MEN 2 or in any patient with medullary thyroid cancer or bi-

Any sporadic medullary thyroid cancer patient needs to be considered for genetic screening with RET proto-oncogene, seen in 7% of these patients.

TABLE 6.28. Characteristics of the MEN Syndromes

	MEN 1 Wermer's	MEN 2A Sipple's	MEN 2B
Hyperparathyroidism	95%	25%	Rare
Pancreatic tumors[a]	30–80%	—	—
Pituitary tumors	20–25%	—	—
Medullary thyroid cancer	—	80–90%	100%
Pheochromocytoma	—	40%	50%
Mucosal neuromas	—	—	100%
Ganglioneuromas of bowel	—	—	> 40%
Marfanoid habitus	—	—	75%
Carcinoid	20%	—	—
Adrenal adenomas	40%	—	—
Subcutaneous lipomas	30%	—	—
Genetics	*MENIN* gene	*RET* proto-oncogene	*RET* proto-oncogene

[a] Pancreatic tumors can be gastrinomas, associated with Zollinger-Ellison syndrome, insulinomas, glucagonomas, VIPomas, or nonfunctioning tumors.

lateral pheochromocytomas. If a *RET* proto-oncogene mutation is found:
  - Obtain calcitonin, plasma or urine metanephrines, serum calcium/PTH.
  - Prophylactic thyroidectomy is recommended in children with this mutation at 4–6 years of age.
- When hyperparathyroidism is part of either MEN syndrome, it is more likely to be multiglandular hyperplasia.

Carcinoids cause the syndrome only when they are gut carcinoids, metastatic to the liver, or 1° lesions draining into the systemic circulation.

Carcinoid Tumors and Syndrome

Carcinoid tumors are GI neuroendocrine tumors that are most commonly located in the small bowel. Most are hormonally inert, but some can secrete excessive **serotonin,** prostaglandins, and kinins.

Carcinoids of the bronchus can present as Cushing's syndrome because they can secrete ACTH in addition to serotonin precursors.

Symptoms/Exam

- Classic carcinoid syndrome consists of episodic **flushing,** watery **diarrhea,** and **hypotension** with or without asthma.
- **Valvular heart disease** is a common complication.
- Emotional stress, certain foods (e.g., tryptophan-containing foods), and straining with defecation can provoke symptoms.

Diagnosis

- **24-hour urine for 5-HIAA** (5-hydroxyindoleacetic acid, a serotonin metabolite).
- An indium-labeled octreotide scan can detect occult lesions.
- Stage with CXR and a chest/abdominal CT scan.

Carcinoid tumors can be associated with carcinoid crisis, in which multiple proteins, including serotonin, histamine, and tryptophans, are released acutely, causing extreme BP changes, bronchoconstriction, and arrhythmias. It can occur spontaneously or after tumor palpation, chemotherapy, or hepatic arterial embolization. It can be fatal and should be treated with an octreotide drip and supportive care.

Treatment

- Surgical resection is first-line treatment.
- Symptomatic relief may be obtained with octreotide.

Zollinger-Ellison Syndrome (Gastrinoma)

Caused by hypersecretion of **gastrin** by tumors of the pancreas or duodenum.

Symptoms/Exam

Usually presents as refractory PUD despite *H. pylori* treatment or multiple ulcers in the duodenum and jejunum.

Differential

Other causes of elevated gastrin should be considered, including **therapy with PPIs or H_2 blockers,** pernicious anemia, chronic atrophic gastritis, and gastric carcinoma.

Diagnosis

- **Elevated fasting serum gastrin levels** in the presence of gastric acid (pH < 5) and **refractory PUD.**
- If the patient is taking an H_2 blocker or a PPI, it must be stopped for at least one week before diagnostic testing.
- Localize by abdominal imaging or octreotide scan.

TREATMENT

Surgical resection is recommended.

If a type 1 DM patient who has previously been well controlled on insulin regimen presents with new-onset hypoglycemia, consider Addison's disease, as type 1 DM patients are at ↑ risk for other autoimmune diseases.

AUTOIMMUNE POLYGLANDULAR SYNDROMES (APS)

Autoimmune, genetic syndromes leading to multiple glandular hypofunction (see Table 6.29).

TABLE 6.29. Autoimmune Polyglandular Syndromes Types I and II

	APS I	APS II
Alternative name	APCED (autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy syndrome).	Schmidt's syndrome.
Genetics	Autosomal recessive—mutation in *AIRE* (autoimmune regulator gene).	Linked to HLA-DR3 or HLA-DR4. Female-to-male ratio = 3:1.
Endocrine manifestations	Hypoparathyroidism[a]—90%. Hypoadrenalism[a]—60%. Hypogonadism—45%. Hypothyroidism—12%.	Hypoadrenalism[b]—70%. Autoimmune thyroid disease[b] (hypo- or hyperthyroidism)—70%. Type 1 DM[b]—50%. Hypogonadism—5–50%.
Nonendocrine manifestations	Mucocutaneous candidiasis[a]—75%. Malabsorption—25%. Alopecia—20%. Pernicious anemia—15%. Autoimmune hepatitis—10%. Vitiligo—4%.	Pernicious anemia—15%. Vitiligo—4%. Celiac disease—3%. Autoimmune hepatitis.

[a] Diagnosis requires two of these three diseases.

[b] Diagnosis requires at least two of these three diseases.

NOTES

CHAPTER 7

Gastroenterology and Hepatology

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Infectious Esophagitis

Most common in immunosuppressed patients (e.g., those with AIDS or malignancies, post-transplant, and patients undergoing chemotherapy) and in the setting of chronic steroid use or recent antibiotic use. Common pathogens include *Candida albicans,* HSV, and CMV.

Symptoms/Exam

- Presents with odynophagia, dysphagia, and chest pain.
- Oral lesions are not reliable diagnostic indicators.
- *C. albicans* is the etiologic agent in < 75% of cases and CMV or HSV in < 50%.
- Exam reveals shoddy cervical lymphadenopathy.

Differential

- **Noninfectious esophagitis:** Reflux, pill, caustic ingestion, radiation, eosinophilic, autoimmune (e.g., Crohn's, Behçet's),
- Functional dyspepsia, esophageal stricture, mass lesion, motility disorders, graft-versus-host disease.

Diagnosis

- In immunocompromised patients, attempt a trial of empiric antifungal therapy (e.g., fluconazole). In immunocompetent hosts, proceed with endoscopy.
- Upper endoscopy with biopsy is the treatment of choice if the empiric trial yields no response. Findings are as follows:
  - ***C. albicans*:** Linear, adherent plaques that may be yellow or white.
  - **CMV:** Few large, superficial ulcerations.
  - **HSV:** Numerous small, deep ulcerations.
  - **Idiopathic AIDS ulcers:** Low CD4 count; large ulcerations.

Treatment

- Treat or adjust underlying immunosuppression.
- ***C. albicans*:** Treatment depends on host immune status.
  - **Immunocompetent patients:** Topical therapy; nystatin swish and swallow five times a day × 7–14 days. Test for HIV.
  - **Immunocompromised patients:** Oral therapy, initially with fluconazole 100–200 mg/day. If the patient is unresponsive, consider increasing fluconazole or giving itraconazole, other azoles, caspofungin, or amphotericin.
- **CMV:** Ganciclovir 5 mg/kg IV BID × 3–6 weeks.
- **HSV:** Acyclovir 200 mg PO five times a day or valacyclovir 1000 g PO BID.
- **Idiopathic ulcers:** Trial of prednisone.

Complications

Stricture, malnutrition, hemorrhage.

Pill Esophagitis

Variables include contact time, drug type, and pill characteristics. Most cases arise without preexisting swallowing problems. Pills can remain in a normal esophagus > 5 minutes or for much longer in the presence of stricture or dysmotility. Risk is higher if pills are large, round, lightweight, or extended-release formulations.

Symptoms/Exam

Presents with odynophagia, dysphagia, and chest pain.

Differential

Infectious and other noninfectious esophagitis, GERD, functional dyspepsia, esophageal stricture or mass lesion, esophageal motility disorders.

Diagnosis

- **Review medications.** Common causative agents include the following:
  - **NSAIDs:** Aspirin, naproxen, ibuprofen, indomethacin.
  - **Antibiotics:** Tetracyclines (especially doxycycline), clindamycin (look for a young patient with acne presenting with odynophagia).
  - **Antivirals:** Foscarnet, AZT, ddC.
  - **Supplements:** Iron and potassium.
  - **Cardiac:** Quinidine, nifedipine, captopril, verapamil.
  - **Bisphosphonates:** Alendronate, pamidronate.
  - **Antiepileptics:** Phenytoin.
  - **Asthma/COPD medications:** Theophylline.
- **Upper endoscopy:** Evaluate for stricture or mass lesion.

Treatment

- Discontinue the suspected drug. Expect symptom relief within 1–6 weeks.
- Patients should drink eight ounces of water with each pill and remain upright at least 30 minutes afterward.
- Proton pump inhibitors (PPIs) may facilitate healing in the setting of concurrent GERD.

Patients with achalasia often lift their arms over their heads or extend their necks to aid in swallowing.

Achalasia

An idiopathic esophageal motility disorder with loss of peristalsis, high lower esophageal sphincter (LES) resting pressure, and failure of LES relaxation. Age at onset is 25–60; incidence ↑ with age. Indistinguishable from esophageal dysmotility caused by **Chagas' disease.**

Symptoms/Exam

- Presents with progressive dysphagia to solids and then to liquids as well as with slow eating (**"last person at the table to finish meal").**
- Regurgitation of undigested food, weight loss, and chest pain are also characteristic. Heartburn may result from the fermentation of retained food.

Differential

Chagas' disease (*Trypanosoma cruzi*), esophageal tumors, pseudoachalasia (a process mimicking achalasia that is typically 2° to tumor invasion into the esophageal neural plexus), webs, strictures, Zenker's diverticulum, oropharyngeal dysphagia (muscular dystrophies, myasthenia gravis, Parkinson's disease),

spastic dysmotility disorders (diffuse esophageal spasm, nutcracker esophagus; see Table 7.1), esophageal hypomotility (scleroderma).

Diagnosis

- **CXR:** Demonstrates an air-fluid level in a dilated esophagus.
- **Barium esophagography:** May reveal a dilated esophagus with loss of peristalsis and poor emptying or a smooth, symmetrically tapered distal esophagus with a "**bird's beak**" appearance.
- **Endoscopy:** Required to exclude esophageal strictures and tumor.
- **Esophageal manometry:** Used to confirm the diagnosis. Shows complete **absence of peristalsis, high LES resting pressure,** and **incomplete LES relaxation.**
- **Endoscopic ultrasound:** Occasionally used to exclude pseudoachalasia.

Treatment

- **Nitrates and calcium channel antagonists:** Relax LES tone, but have only modest efficacy.
- **Botulinum toxin injection:** Injected into the LES. Performed endoscopically and associated with an 85% initial response, but > 50% of patients require repeated injection within six months. Ideal if the patient is a poor candidate for more invasive treatment.
- **Pneumatic dilation:** Of those treated, > 75% have a durable response. The perforation rate is 3–5%. Does not compromise surgical therapy.
- **Surgery:** Laparoscopic Heller myotomy with partial fundoplication (preventing severe reflux that can occur with myotomy). Of all cases, > 85% have a durable response.

Diffuse Esophageal Spasm and Nutcracker Esophagus

Diffuse esophageal spasm is marked by uncoordinated contractions, whereas nutcracker esophagus is characterized by excessively **high-amplitude** contractions. Both show a female predominance; onset is usually after age 40.

TABLE 7.1. Differential Diagnosis of Dysphagia

	Achalasia	Nutcracker Esophagus	Diffuse Esophageal Spasm	Scleroderma
Peristalsis	Absent	Normal	Simultaneous contractions	Absent
LES tone	Normal to ↑ with incomplete relaxation	Normal to ↑	Normal to ↑	↓
Esophageal body tone (amplitude)	Low	Focally ↑ (distal)	Normal to high	Low
Predominant symptom	Progressive dysphagia	Chest pain	Chest pain	Heartburn and dysphagia

Unlike achalasia, diffuse esophageal spasm and nutcracker esophagus often present with chest pain rather than with dysphagia.

Symptoms/Exam

- Substernal chest pain is seen in 80% of patients; pain is nonexertional and worsens with meals.
- A globus ("lump in the throat") sensation is also characteristic.
- Associated with dysphagia to both solids and liquids.
- Regurgitation is less common than in achalasia. Weight loss is rare.

Differential

Cardiac chest pain, GERD, achalasia, Chagas' disease, esophageal tumors, esophageal dysmotility, peptic stricture, esophagitis, diverticula.

Diagnosis

Diagnose as follows (see also Table 7.1):

- **Barium esophagography:** Peristalsis is present but with delayed transit; esophageal spasms are focal (in nutcracker esophagus) or at multiple sites with a "**corkscrew**" appearance (in diffuse esophageal spasm).
- **Endoscopy:** Not useful in diagnosis, but excludes other differential diagnoses, such as stricture, tumor, and esophagitis.
- **Esophageal manometry:** Reveals elevated LES pressure associated with nutcracker esophagus and simultaneous contractions with diffuse esophageal spasm.
- **Ambulatory esophageal pH:** Used to evaluate for gastroesophageal reflux.

Plummer-Vinson syndrome includes esophageal webs, dysphagia, and iron deficiency anemia.

Treatment

- **Nitrates and calcium channel antagonists:** Relax LES tone, but have only modest efficacy.
- PPIs.
- No clear benefit is derived from botulinum toxin injection, esophageal dilation, or surgical myotomy.

Esophageal Rings, Webs, and Strictures

Schatzki rings cause intermittent large-bolus solid-food dysphagia ("steakhouse syndrome").

Esophageal rings, webs, and strictures are distinguished as follows (see also Tables 7.2 and 7.3):

- **Lower esophageal (Schatzki) rings:** Common (found in 6–14% of upper GI exams); located in the distal esophagus. Often associated with hiatal hernia, congenital defects, or GERD.
- **Webs:** Less common; located in the proximal esophagus. Congenital.
- **Strictures:** Result from injury (e.g., reflux, caustic, anastomosis).

Symptoms/Exam

Dysphagia with solids is more severe than that with liquids.

Differential

Cardiac chest pain, GERD, achalasia, Chagas' disease, esophageal tumors, esophageal hypomotility (scleroderma), peptic stricture.

Diagnosis

- **Barium esophagography:** May be diagnostic. Normal peristalsis; luminal abnormality is seen.
- **Endoscopy:** Required to exclude esophageal stricture or tumor.

TABLE 7.2. Differential of Esophageal Rings, Webs, and Strictures

	RING	WEB	STRICTURE
Etiology	Congenital or peptic injury.	Congenital.	Peptic injury, caustic injury.
Esophageal location	Distal.	Proximal.	Mid-distal.
Treatment	Dilation.	Dilation.	Dilation.

TREATMENT

Esophageal dilation; PPIs to ↓ the recurrence of peptic stricture.

Barrett's Esophagus

Intestinal metaplasia of the distal esophagus 2° to chronic GERD. Normal esophageal squamous epithelium is replaced by columnar epithelium and goblet cells ("specialized epithelium"). Found in some 5–10% of patients with chronic GERD, and incidence ↑ with GERD duration. Most common in Caucasian men > 55 years of age; overall incidence is greater in males than in females. The risk of adenocarcinoma is 0.5% per year. Risk factors include male gender, Caucasian ethnicity, and smoking.

Screen for Barrett's esophagus in patients with chronic GERD symptoms, especially in Caucasian men. If Barrett's is not present, there is no need for further screening.

DIAGNOSIS

- **Upper endoscopy:** Suggestive but not diagnostic, as it is a histologic diagnosis. **Salmon-colored islands or "tongues"** are seen extending upward from the distal esophagus.
- **Biopsy:** Diagnostic.
  - Shows metaplastic **columnar epithelium** and **goblet cells.**
  - Specialized intestinal metaplasia on biopsy is associated with an ↑ risk of **adenocarcinoma** (not squamous).

TABLE 7.3. Causes of Esophageal Dysphagia

CAUSE	CLUES TO DIAGNOSIS
Mechanical obstruction:	**Solids more than liquids:**
Schatzki ring	Intermittent dysphagia; not progressive
Peptic stricture	Chronic heartburn; progressive dysphagia
Esophageal cancer	Progressive dysphagia; age over 50
Motility disorders:	**Solid and liquids:**
Achalasia	Progressive dysphagia
Diffuse esophageal spasm	Intermittent, not progressive; may be accompanied by chest pain
Scleroderma	Chronic heartburn; Raynaud's phenomenon

Adapted, with permission, from Tierney LM et al. *Current Medical Diagnosis & Treatment,* 44th ed. New York: McGraw-Hill, 2005: 547.)

Treatment

- Indefinite PPI therapy (GERD should be treated prior to surveillance, as inflammation may confound the interpretation of dysplasia).
- Adenocarcinoma surveillance is necessary only if patients are candidates for esophagectomy.
- Upper endoscopy with four-quadrant biopsies every 2 cm of endoscopic lesions.
- Screening (based on criteria from the American Society of Gastrointestinal Endoscopy) is as follows:
  - After initial diagnosis, repeat EGD in one year for surveillance with biopsies.
  - Proceed according to EGD findings:
    - **No dysplasia:** Repeat EGD every three years.
    - **Low-grade dysplasia:** Repeat EGD within six months. If findings are unchanged, extend surveillance to yearly intervals.
    - **High-grade dysplasia:** Management is controversial but includes early esophagectomy or intensive endoscopic surveillance every three months until cancer is diagnosed, followed by esophagectomy. Verify with an expert pathologist. Ablative therapies may be attempted (e.g., photodynamic therapy, argon plasma coagulation, endoscopic mucosal resection).

Dyspepsia

Typically defined as one or more of the following: postprandial fullness, early satiation, and epigastric burning or pain. Distinct from but can present with GERD (i.e., retrosternal burning). In the United States, the prevalence of dyspepsia is 25%, but only 25% of those affected seek care. Of these, **> 60% have nonulcerative dyspepsia and < 1% have gastric cancer.**

Symptoms/Exam

May present with upper abdominal pain or discomfort, fullness, bloating, early satiety, belching, nausea, and retching or vomiting.

Differential

Nonulcerative dyspepsia (> 60%), food intolerance (overeating, high-fat foods, alcohol, lactose intolerance), drug intolerance (NSAIDs, iron, narcotics, alendronate, theophylline, antibiotics), PUD (10–25%), GERD (15–20%), gastric cancer (< 1%), chronic pancreatitis, pancreatic cancer, biliary colic, IBS.

In patients < 50 years of age with no alarm features, gastric cancer is a rare etiology of dyspepsia, and direct endoscopy is not a cost-effective measure.

Diagnosis/Treatment

- **Look for alarm features:** May include new-onset dyspepsia in patients **> 50 years** of age, unintended **weight loss, melena, iron deficiency anemia, persistent vomiting, hematemesis, dysphagia, odynophagia,** abdominal mass, a history of PUD, previous gastric **surgery,** and a family history of **gastric cancer.**
  - **If alarm features are present:** Perform prompt endoscopy.
  - **If no alarm features are present:** Assess diet and provide education; discontinue suspect medications. Consider a trial of empiric acid suppression; consider testing for and treating *H. pylori* (see below).
- **Determine the local prevalence of *H. pylori*.**

- **If > 10%:** Test for *H. pylori* by serology, stool antigen, or breath test. If ⊕, institute *H. pylori* eradication therapy. If ⊖, initiate a trial of acid suppression for 4–8 weeks.
- **If < 10%:** Institute a trial of acid suppression for 4–8 weeks.

- **For persistent symptoms:**
  - If the patient received *H. pylori* therapy, test for eradication with a stool antigen or breath test, **not with serology.** If disease is not eradicated, attempt a different regimen. If eradicated, refer to endoscopy.
  - If the patient received a trial of PPIs, refer to endoscopy.
- **Endoscopy:**
  - **If unrevealing:** Diagnose with nonulcerative dyspepsia and provide reassurance; consider a trial of low-dose TCAs (desipramine 10–25 mg QHS) and possible cognitive-behavioral therapy.
  - **If revealing:** Manage as indicated.
- Table 7.4 summarizes treatment options for PUD.

Endoscopic biopsy, H. pylori *stool antigen, and urea breath test can assess active* H. pylori *infection and gauge treatment success.* H. pylori *serology measures only past exposure and cannot be used to confirm eradication.*

Gastroesophageal Reflux Disease (GERD)

Caused by transient relaxation of the LES. In the United States, 40% of adults report having GERD symptoms at least once per month, and 7% report having daily symptoms. Although most patients have mild GERD, 40–50% develop esophagitis, 5% ulcerative esophagitis, 4–20% esophageal strictures, and 5–10% Barrett's esophagus. Risk factors include pregnancy and hiatal hernia.

Symptoms

- **Typical presentation:**
  - A retrosternal burning sensation (heartburn) accompanied by regurgitation that begins in the epigastrium and radiates upward (typically occurring within one hour of a meal, during exercise, or when lying recumbent) and is at least partially relieved by antacids.
  - **Water brash** (excess salivation), **bitter taste,** globus sensation (throat fullness), odynophagia, dysphagia, halitosis, and otalgia are also commonly seen.
- **"Atypical" symptoms (up to 50%):** Nocturnal cough, asthma, hoarseness, noncardiac chest pain.

Exam

Exam is often normal, or patients may present with **poor dentition** and wheezing.

Differential

Infectious esophagitis (CMV, HSV, *Candida*), pill esophagitis (alendronate [Fosamax], tetracycline), PUD, dyspepsia, biliary colic, angina, esophageal dysmotility.

Diagnosis

- For **typical symptoms,** treat with an empiric trial of PPIs for 4–6 weeks. Response to PPIs is diagnostic.
- If the patient is **unresponsive** to therapy or has **alarm symptoms** (dysphagia, odynophagia, weight loss, anemia, long-standing symptoms, blood in stool, age > 50), proceed as follows:
  - **Barium esophagography:** Has a limited role, but can identify strictures.

TABLE 7.4. Treatment Options for Peptic Ulcer Disease

Findings	Treatment Options[a]
Active *H. pylori*–associated ulcer	1. Treat with an anti–*H. pylori* regimen for 10–14 days. Possible treatment options include: ▪ PPI BID, clarithromycin 500 mg BID, amoxicillin 1 g BID (or metronidazole 500 mg BID if penicillin allergic). ▪ PPI BID, bismuth subsalicylate two tablets QID, tetracycline 500 mg QID, metronidazole 250 mg QID. 2. After completion of a 10- to 14-day course of *H. pylori* eradication therapy, continue treatment with PPIs once daily or H_2 receptor antagonists (as below) for 4–8 weeks to promote healing.
Active ulcer not attributable to *H. pylori*	**Consider other causes**—e.g., NSAIDs, Zollinger-Ellison syndrome, gastric malignancy. Treatment options are as follows: 1. **PPIs:** ▪ **Uncomplicated duodenal ulcers:** Treat for four weeks. ▪ **Uncomplicated gastric ulcers:** Treat for eight weeks. 2. **H_2 receptor antagonists:** ▪ **Uncomplicated duodenal ulcers:** Cimetidine 800 mg, ranitidine or nizatidine 300 mg, famotidine 40 mg QD at bedtime for six weeks. ▪ **Uncomplicated gastric ulcers:** Cimetidine 400 mg, ranitidine or nizatidine 150 mg, famotidine 20 mg BID for eight weeks. ▪ **Complicated ulcers:** PPIs are the preferred drugs.
Prevention of ulcer relapse	1. **NSAID-induced ulcers:** Prophylactic therapy for high-risk patients (patients with prior ulcer disease or ulcer complications; those on corticosteroids or anticoagulants; those > 70 with serious comorbid illnesses). Treatment options include the following: ▪ PPI QD. ▪ COX-2-selective NSAID (celecoxib, valdecoxib). ▪ In special circumstances, misoprostol 200 μg TID-QID. 2. **Chronic "maintenance" therapy:** Indicated in patients with recurrent ulcers who either are *H. pylori* ⊖ or have failed attempts at eradication therapy. Give once-daily PPIs or H_2 receptor antagonists at bedtime (cimetidine 400–800 mg, nizatidine or ranitidine 150–300 mg, famotidine 20–40 mg).

[a] PPIs are administered before meals. Avoid metronidazole regimens in areas of known high resistance or in patients who have failed a course of treatment that included metronidazole.

Adapted, with permission, from Tierney LM et al. *Current Medical Diagnosis & Treatment,* 44th ed. New York, McGraw-Hill, 2005: 572.

- **Upper endoscopy with biopsy**: The standard exam in the presence of **alarm symptoms** (dysphagia, odynophagia, weight loss, bleeding, anemia). Normal in > 50% of patients with GERD (most have nonerosive reflux disease), or may reveal endoscopic esophagitis grades 1 (mild) to 4 (severe erosions, strictures, Barrett's esophagus). Strictures can be dilated.
- **Ambulatory esophageal pH monitoring**: The gold standard, but often unnecessary. Indicated for correlating symptoms with pH parameters when endoscopy is normal and (1) symptoms are unresponsive to medical therapy, (2) antireflux surgery is being considered, or (3) there are atypical symptoms (e.g., chest pain, cough, wheezing).

Treatment

- **Behavioral modification:** Elevate the head of the bed six inches; stop tobacco and alcohol use. Advise patients to eat smaller meals, reduce fat intake, lose weight, avoid recumbency after eating, and avoid certain foods (e.g., mint, chocolate, coffee, tea, carbonated drinks, citrus and tomato juice). Effective in 25% of cases.
- **Antacids (calcium carbonate, aluminum hydroxide):** For mild GERD. Fast, but afford only short-term relief.
- **H_2 receptor antagonists (cimetidine, ranitidine, famotidine, nizatidine):** For mild GERD or as an adjunct for nocturnal GERD while the patient is on PPIs. Effective in 50–60% of cases.
- **PPIs (omeprazole, lansoprazole, rabeprazole, pantoprazole, esomeprazole):** The mainstay of therapy for mild to severe GERD. Generally safe and effective, but now associated with pneumonia, atrophic gastritis (hypergastrinemia), enteric infections (*C. difficile*), and hip fractures. Daily dosage is effective in 80–90% of patients. **Fewer than 5%** of patients are **refractory** to twice-daily dosage.
- **Surgical fundoplication (Nissen or Belsey wrap):**
  - Often performed laparoscopically. Indicated for patients who cannot tolerate medical therapy or who have persistent regurgitation. **Contraindicated** in patients with an esophageal motility disorder.
  - **Outcome:** More than 50% of patients require continued acid suppressive medication, and > 20% develop new symptoms (dysphagia, bloating, dyspepsia).
- **Endoscopic antireflux procedures:** Remain investigational.

For true GERD, PPIs are highly effective, with < 5% of patients unresponsive to twice-daily doses.

Atypical symptoms (cough, wheezing, chest pain) often occur without typical heartburn symptoms.

After surgical fundoplication for GERD, > 50% of patients still require continued acid-suppressive medication, and > 20% develop new symptoms (dysphagia, bloating, dyspepsia).

Complications

- **Peptic strictures:** Affect 8–20% of GERD patients; present with dysphagia. Malignancies must be excluded via endoscopy and biopsy; can then be treated with endoscopic dilation followed by indefinite PPI therapy.
- **Upper GI bleeding:** Hematemesis, melena, anemia 2° to ulcerative esophagitis.
- **Posterior laryngitis:** Chronic hoarseness from vocal cord ulceration and granulomas.
- **Asthma:** Typically has an adult onset; nonatopic and unresponsive to traditional asthma interventions.
- **Cough:** Affects 10–40% of GERD patients, most without typical GERD symptoms.
- **Noncardiac chest pain:** After a full cardiac evaluation, consider an empiric trial of PPIs or ambulatory esophageal pH monitoring.
- **Other:** Barrett's esophagus, adenocarcinoma.

Gastroparesis

Delayed gastric emptying in the absence of obstruction. Most commonly related to diabetes, viral infection, neuropsychiatric disease, or postsurgical complications.

Symptoms/Exam

- Presents with postprandial fullness, bloating, abdominal distention, early satiety, nausea, and vomiting of digested food.
- Exam is normal. Mild to moderate upper abdominal tenderness may be seen during episodes. Occasionally, a **succussion splash** is heard.

Gastroparesis can be a sign of undiagnosed diabetes.

Differential

- Poor glycemic control, postsurgical **(postvagotomy or Roux-en-Y),** nonulcer dyspepsia, medications (anticholinergics, opiates).
- Hypothyroidism, scleroderma, muscular dystrophies, paraneoplastic syndrome (small cell lung cancer), amyloidosis.

Diagnosis

"Idiopathic" gastroparesis can result from viral infections in young, healthy patients and is often self-limited, remitting within a few months.

- **Solid-phase nuclear medicine gastric emptying scan:** Following the administration of a radiolabeled meal, normal gastric retention is < 90%, < 60%, and < 10% at 60, 120, and 240 minutes, respectively.
- **Labs:** Electrolytes, hemoglobin A_{1c} (HbA_{1c}), ANA, TSH.
- **Endoscopy:** To rule out structural lesions and ulcers causing obstruction.
- **Gastroduodenal manometry:** Not widely available, but can often distinguish myopathic from neuropathic patterns.

Treatment

- **Dietary:** Small, frequent meals; low-fat, low-fiber diet.
- Tight glycemic control in diabetics.
- ↓ or discontinue opiates and anticholinergics.
- **Medications:**
  - **Cisapride:** Most effective, but its use is restricted owing to **QT-interval prolongation.**
  - **Metoclopramide:** A dopamine antagonist used as an antiemetic. ↓ effectiveness and adverse effects (extrapyramidal symptoms) are seen with long-term use.
  - **Domperidone:** A dopamine antagonist that is not approved for use in the United States.
  - **Erythromycin:** IV use has short-term efficacy; PO use is less effective chronically.
- **Jejunostomy tube:** For intractable, severe gastroparesis without small bowel dysmotility.
- **Total parenteral nutrition (TPN):** For intractable, severe gastroparesis with small bowel dysmotility.
- **Gastric pacing:** Investigational.

LOWER GI TRACT

Acute Diarrhea

Defined as diarrhea of **< 14 days'** duration. Usually toxin mediated or infectious, mild, and self-limited; cases are managed on an outpatient basis. Diarrhea accounts for 1.5% of all hospitalizations in the United States. ↑ morbidity is seen in children, the elderly, and the immunosuppressed. Etiologies include the following:

- **Bacterial:** *E. coli*, *Campylobacter* (associated with Guillain-Barré syndrome), *Salmonella*, *Shigella*, *C. difficile*, *Yersinia*, *Aeromonas.*
- **Viral:** Adenovirus, rotavirus, Norwalk agent.
- **Parasites:** *Entamoeba histolytica* (associated with liver abscesses); *Giardia lamblia*; *Cryptosporidium*, *Microsporidium*, and MAC in those with AIDS.
- **Drugs:** Antibiotics, NSAIDs, quinidine, β-blockers, magnesium-base antacids, PPIs, colchicine, theophylline, acarbose.
- **Other:** Food allergies; initial presentation of chronic diarrhea.

Symptoms/Exam

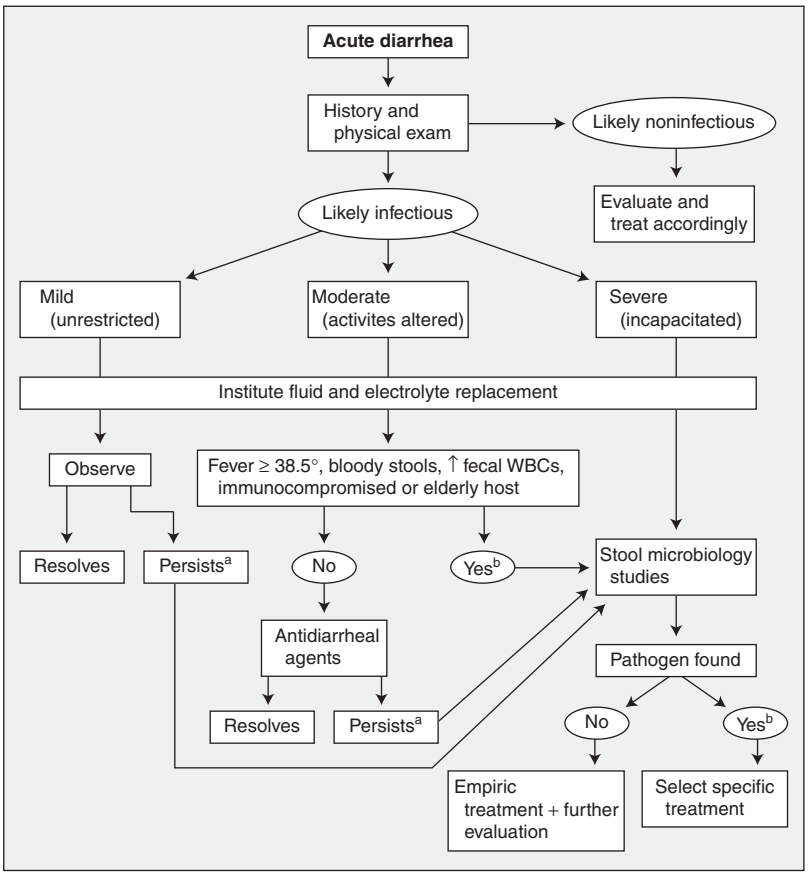
- Diarrhea accompanied by urgency, tenesmus, abdominal bloating, and pain.
- Exam may reveal tachycardia, orthostasis, ↓ skin turgor with dehydration, abdominal pain, and distention.

Differential

Causes of chronic diarrhea (food intolerance, pancreatic insufficiency, medications, IBD, laxatives, malignancy).

Diagnosis

- **Alarm features:** Evaluation is indicated in the presence of alarm features—e.g., fever > 38.5°C, severe abdominal pain, bloody diarrhea, immune compromise, age > 70 years, or severe dehydration (see Figure 7.1 and Table 7.5).
- **No alarm features** (short duration, nonbloody diarrhea, nontoxic exam): Treat with oral rehydration and symptomatic therapy. If no improvement is seen, evaluation is indicated.



[a]Consider empiric treatment with metronidazole before evaluation.
[b]Consider empiric treatment with quinolone before evaluation.

FIGURE 7.1. Algorithm for the management of acute diarrhea.

(Reproduced, with permission, from Kasper DL et al. *Harrison's Principles of Internal Medicine*, 16th ed. New York: McGraw-Hill, 2005: 227.)

TABLE 7.5. Causes of Acute Infectious Diarrhea

	VIRAL	PROTOZOAL	BACTERIAL
Noninflammatory diarrhea	Norwalk virus, Norwalk-like virus, rotavirus.	*Giardia lamblia, Cryptosporidium.*	**Preformed endotoxin production:** *S. aureus, Bacillus cereus, Clostridium perfringens.* **Enterotoxin production:** Enterotoxigenic *E. coli* (ETEC), *Vibrio cholerae.*
Inflammatory diarrhea	CMV.	*Entamoeba histolytica.*	**Cytotoxin production:** Enterohemorrhagic *E. coli* (EHEC), *Vibrio parahaemolyticus, C. difficile.* **Mucosal invasion:** *Shigella, Campylobacter jejuni, Salmonella,* enteroinvasive *E. coli* (EIEC), *Aeromonas, Plesiomonas, Yersinia enterocolitica, Chlamydia, Neisseria gonorrhoeae, Listeria monocytogenes.*

Reproduced, with permission, from Tierney LM et al. *Current Medical Diagnosis & Treatment,* 44th ed. New York: McGraw-Hill, 2005: 527.

Acute diarrhea (< 4 weeks' duration) is usually infectious and self-limited.

- Evaluation includes the following:
  - **Blood tests:** CBC, electrolytes, BUN, creatinine, ESR, ameba serology.
  - **Stool tests:** Stool culture and sensitivity, O&P, *Giardia* antigen, *C. difficile* toxin, leukocytes.
  - **Endoscopy:** Flexible sigmoidoscopy or colonoscopy with biopsy.

TREATMENT

- **Mild diarrhea:**
  - Oral rehydration (Pedialyte, Gatorade).
  - BRAT diet (bananas, rice, applesauce, toast).
  - **Antidiarrheals:** Loperamide 4 mg initially and then 2 mg after each stool (maximum 8 mg/day).
- **Severe diarrhea:** Oral or IV rehydration.
- **Empiric antibiotics:**
  - Indicated only in the presence of fever > 38.5°C, tenesmus, bloody stools, and fecal leukocytes (awaiting culture).
  - Ciprofloxacin 500 mg PO or 400 mg IV BID × 3–5 days.
  - Antibiotics are **not** recommended for nontyphoidal *Salmonella*, *Campylobacter*, *Aeromonas*, *Yersinia*, or *E. coli* O157:H7.
  - Antibiotics are recommended for shigellosis, cholera, extraintestinal salmonellosis, traveler's diarrhea, and amebiasis.
  - Giardiasis and *C. difficile* are treated with metronidazole.

Chronic Diarrhea

Diarrhea of > **4 weeks'** duration. Table 7.6 lists the etiologies of chronic diarrhea.

TABLE 7.6. Causes of Chronic Diarrhea

TYPE	CLUES	CAUSES
Osmotic diarrhea	↓ stool volume with fasting; ↑ stool osmotic gap.	**Medications:** Antacids, lactulose, sorbitol. **Disaccharidase deficiency:** Lactose intolerance. **Factitious diarrhea:** Magnesium (antacids, laxatives).
Secretory diarrhea	Large volume (> 1 L/day): Little change with fasting; normal stool osmotic gap.	**Hormonally mediated:** VIPoma, carcinoid, medullary carcinoma of the thyroid (calcitonin), Zollinger-Ellison syndrome (gastrin). Factitious diarrhea (laxative abuse); phenolphthalein, cascara, senna. Villous adenoma. Bile salt malabsorption (ileal resection, Crohn's ileitis, postcholecystectomy). Medications.
Inflammatory conditions	Fever, hematochezia, abdominal pain.	**IBD:** Ulcerative colitis, Crohn's. **Malignancy:** Lymphoma, adenocarcinoma (with obstruction and pseudodiarrhea). **Other:** Microscopic colitis, radiation enteritis.
Malabsorption syndromes	Weight loss, abnormal lab values, fecal fat > 10 g/24 hours.	**Small bowel mucosal disorders:** Celiac sprue, tropical sprue, Whipple's disease, eosinophilic gastroenteritis, small bowel resection (short bowel syndrome), Crohn's disease. **Lymphatic obstruction:** Lymphoma, carcinoid, infectious (TB, *Mycobacterium avium–intracellulare*), Kaposi's sarcoma, sarcoidosis, retroperitoneal fibrosis. **Pancreatic disease:** Chronic pancreatitis, pancreatic carcinoma. **Bacterial overgrowth:** Motility disorders (diabetes, vagotomy), scleroderma, fistulas, small intestinal diverticula.
Motility disorders	Systemic disease or prior abdominal surgery.	**Postsurgical:** Vagotomy, partial gastrectomy, blind loop with bacterial overgrowth. **Systemic disorders**: Scleroderma, DM, hyperthyroidism. **IBS.**
Chronic infections		**Parasites:** *Giardia lamblia, Entamoeba histolytica.* **AIDS related:** ■ **Viral:** CMV. ■ **Bacterial:** *C. difficile, Mycobacterium avium* complex. ■ **Protozoal:** Microsporidia (*Enterocytozoon bieneusi, Cryptosporidium, Isospora belli*)

Adapted, with permission, from Tierney LM et al. *Current Medical Diagnosis & Treatment,* 44th ed. New York: McGraw-Hill, 2005: 530.

SYMPTOMS/EXAM

- Presents with diarrhea accompanied by abdominal bloating and pain.
- Exam reveals tachycardia, orthostasis, ↓ skin turgor with dehydration, abdominal pain, and distention.

Diagnosis

Diagnose as follows (see also Table 7.7):

- Rule out acute diarrhea, lactose intolerance, parasitic infection, ileal resection, medications, and systemic disease.
- **Characterize the diarrhea:** Watery, inflammatory, fatty/malabsorption.
- **Conduct a focused initial evaluation:**
  - **Blood tests:** CBC, electrolytes, ESR, albumin, HbA_{1c}. Clues are as follows:
    - **ESR:** Elevated if diarrhea is inflammatory.
    - **Iron deficiency anemia:** Divalent cations such as iron absorbed through the duodenum. The presence of iron deficiency anemia may point to celiac sprue.
    - **Antigliadin or antiendomysial antibodies:** Associated with celiac sprue.
  - **Neuroendocrine tumors:** VIP (VIPoma), calcitonin (medullary thyroid carcinoma), gastrin (Zollinger-Ellison syndrome), glucagon.
  - **Stool tests:** Electrolytes (calculate osmotic gap), 24-hour collection for weight and quantitative fat, standard cultures plus tests for *Aeromonas* and *Plesiomonas*, O&P, and AIDS-related infection (*M. avium* complex, *Cryptosporidium*, *Microsporidium*, CMV).
- **Stool test clues:**
  - **Weight:** If the 24-hour stool weight is > 1000 g, suspect secretory diarrhea; if < 250 g, suspect factitious diarrhea or IBS.
  - **Osmotic gap:** Calculated as 290 − 2 × (stool Na + stool K). A gap of < 50 mOsm/kg suggests secretory diarrhea; > 125 mOsm/kg suggests osmotic diarrhea.
  - **pH:** A pH < 5.6 implies carbohydrate malabsorption.
  - **Fecal occult blood test (FOBT):** Suggests inflammatory diarrhea, but often ⊕ with other types.

TABLE 7.7. Differential Diagnosis of Chronic Diarrhea

	Osmotic	Secretory	Inflammatory	Fatty/Malabsorption
History	Stool volume ↓ with fasting.	Large stool volume (> 1 L/day); no change with fasting.	Fever, abdominal pain, hematochezia.	Weight loss, greasy stools.
Exam	—	Severe dehydration.	Abdominal tenderness.	Glossitis.
Blood tests	—	Neuroendocrrine peptides.	Leukocytosis, elevated ESR.	Anemia, hypoalbuminemia.
Stool tests	Osm gap > 125, Mg > 45, pH < 5.6.	24-hour stool weight > 1000 g, osm < 50.	Leukocytes, fecal blood.	7–10 g fat/24 hours.
Differential	Laxative use, carbohydrate malabsorption.	Bacterial, viral, bile acid malabsorption, collagenous colitis, vasculitis, neuroendocrine, nonosmotic laxatives.	IBD, *C. difficile* colitis, invasive bacterial, viral, parasitic, ischemic, radiation, lymphoma, colon cancer.	Pancreatic exocrine insufficiency, celiac sprue, Whipple's disease, small bowel bacterial overgrowth, mesenteric ischemia.

- **Leukocytes:** Presence suggests inflammatory diarrhea.
- **Fat:** Spot testing is not specific; a 24-hour fat > 7–10 g implies malabsorption.
- **Laxative screen:** Elevated magnesium (> 45 mmol/L), phosphate, sulfate levels.

- **Urine test clues:** Neuroendocrine tumors—5-HIAA (carcinoid), VMA, metanephrines, histamine.
- **Endoscopy:** Flexible sigmoidoscopy or colonoscopy with biopsy; consider upper endoscopy.
- **Other:** A $\oplus$ H_2 breath test after a glucose/lactulose load suggests bacterial overgrowth or lactose intolerance.

TREATMENT

The treatment of chronic diarrhea is as follows (see also Figure 7.2):

- **Mild diarrhea:** See the previous section.
- **Osmotic diarrhea:**

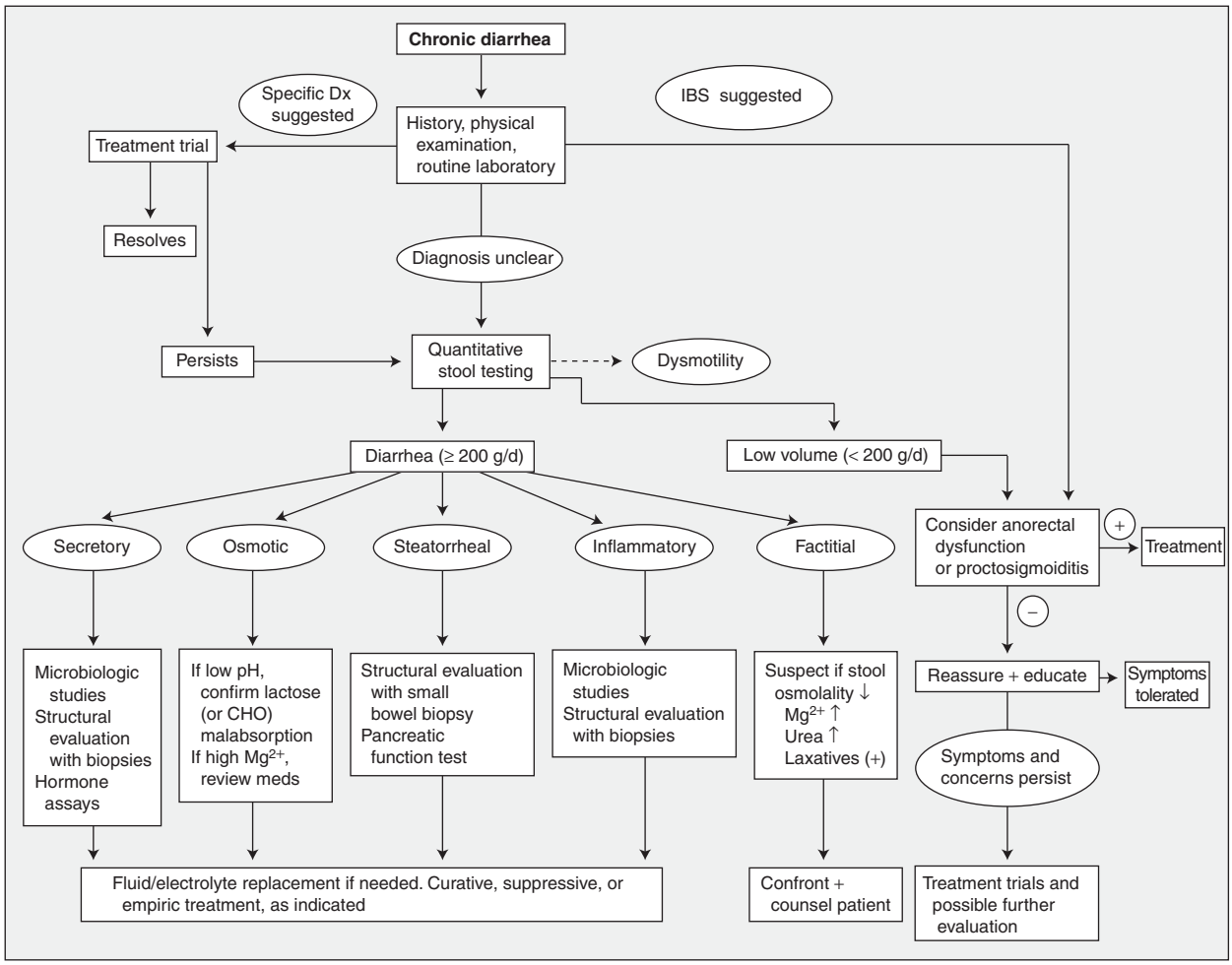


FIGURE 7.2. Algorithm for the management of chronic diarrhea.

(Reproduced, with permission, from Kasper DL et al. *Harrison's Principles of Internal Medicine*, 16th ed. New York: McGraw-Hill, 2005: 230.)

In the United States, surreptitious laxative use accounts for 15% of referrals for chronic diarrhea and 25% of documented cases of secretory diarrhea.

- **Carbohydrate malabsorption (lactose, fructose, sorbitol):** Dietary modification, lactase supplements.
- **Celiac sprue:** Gluten restriction.
- **Whipple's disease/tropical sprue:** Antibiotics.
- **Bacterial overgrowth:** Antibiotics; ↑ glycemic control in diabetics.

- **Secretory diarrhea:**
  - Clonidine 0.1–0.3 mg PO TID.
  - Octreotide 50–250 μg SQ TID.
  - Cholestyramine 4 g PO QD to QID.
- **Inflammatory diarrhea: IBD**—sulfasalazine, 5-ASA (mesalamine), corticosteroids, azathioprine, 6-mercaptopurine (6-MP).
- **Fatty diarrhea: Pancreatic exocrine insufficiency**—pancreatic enzyme supplements.
- **AIDS diarrhea:** Rule out CMV. Eighty-seven percent of cases resolve following immune reconstitution inflammatory syndrome with HAART when CD4 levels are > 50/μL.

Celiac Sprue

A **gluten-sensitive enteropathy** interfering with digestion and absorption of food nutrients. Often presents with diarrhea and failure to thrive, although it may be asymptomatic. Its prevalence is estimated at 1 in 300 to 1 in 500 and is highest among those of western **European** descent. Shows a bimodal presentation in the first 8–12 months of life and between 20 and 40 years of age. It also has a strong hereditary component (10% prevalence among first-degree relatives). The mechanism is thought to be antigen presentation of gluten-derived peptides by HLA-DQ2/DQ8 to T cells, leading to duodenal **villous atrophy, intraepithelial lymphocytes,** and **crypt hyperplasia.** The disease course may be complicated by intestinal **lymphomas and adenocarcinomas.**

Symptoms/Exam

Iron deficiency anemia may be present in celiac sprue as a result of iron malabsorption.

- Presents with **chronic diarrhea,** steatorrhea, bloating, abdominal pain, flatulence, and weight loss.
- Fatigue, anemia, bleeding diathesis, osteopenia, and stunted growth are also seen.
- **Dermatitis herpetiformis** (pruritic papulovesicles over the extensor surfaces) is a common feature, as are cheilosis and glossitis.
- Associated conditions include diabetes, Down syndrome, abnormal AST/ALT, hypothyroidism, and hyposplenism

Differential

Bacterial overgrowth, collagenous colitis, IBD, IBS, pancreatic insufficiency, lactose intolerance, infectious gastroenteritis.

Diagnosis

- **Serology: Anti–tissue transglutaminase (anti-TTG)** and **antiendomysial antibody** have high sensitivity and specificity. Levels may fluctuate with disease activity and may be absent in IgA deficiency. Antigliadin antibody is less sensitive and specific.
- **Labs:** Reveal anemia (iron deficiency from iron malabsorption, folate), hypocalcemia, hypokalemia, and hypomagnesemia.
- **Endoscopy:** Shows **blunted duodenal villi.**
- Definitive diagnosis is made with the triad of a ⊕ serology, histology, and clinical/serologic response to the withdrawal of gluten from the diet.

Treatment

- Treatment is dietary but may include steroids for refractory disease.
  - **Diet:** Removal of gluten is essential but may be difficult given the ubiquity of wheat flour.
  - **Steroids:** Consider in the small percentage of patients who are refractory to a gluten-free diet. Consider malignancy in patients who are unresponsive to corticosteroids.
- **Calcium and vitamin D** for osteopenia; **pneumococcal vaccine** for hyposplenism.

Celiac sprue improves with the removal of gluten from the diet. Consider steroid therapy or rule out malignancy in those failing to respond to dietary changes.

Complications

- The risk of **malignancy** (enteropathy-associated T-cell and non-Hodgkin **lymphoma** and **adenocarcinoma**) is ↑.
- Compliance in pregnant women is important because of the ↑ risk of miscarriage and congenital malformation.
- Noncompliance during childhood leads to failure to thrive or stunted growth.

Irritable Bowel Syndrome (IBS)

Abdominal **discomfort or pain** during the **prior three months** that is relieved by defecation and associated with a change in stool frequency or form. Forty percent of patients have impaired ability to work, avoid social functions, cancel appointments, or stop travel because of the severity of their symptoms. Onset is typically in the late teens to 20s and/or **after infectious gastroenteritis.** In the developed world, women are more commonly affected than men, but in India the opposite is the case. Some 30–40% of patients have a **history of physical or sexual abuse.**

Symptoms/Exam

- Intermittent or chronic abdominal discomfort or pain; bloating, belching, excess flatus, early satiety, nausea, vomiting, diarrhea, constipation.
- Exam is often normal, or patients present with mild to moderate abdominal tenderness.

Differential

IBD, colon cancer, chronic constipation (low-fiber/low-fluid intake, drugs, hypothyroidism), chronic diarrhea (**celiac sprue,** parasitic infections, bacterial overgrowth, lactase deficiency), chronic pancreatitis, endometriosis.

Diagnosis

- Exclude organic disease.
- **Labs:** CBC, TFTs, serum albumin, ESR, FOBT.
- **If diarrhea:**
  - Stool for O&P and C. *difficile* toxin.
  - Celiac sprue serology (antiendomysial and antigliadin antibodies; anti-TTG antibodies).
  - **24-hour stool collection:** A value > 300 g is atypical for IBS.
  - **Severe upper abdominal pain/dyspepsia:** Consider endoscopy (flexible sigmoidoscopy for those < 40 years of age; colonoscopy for those > 40 years).

New-onset IBS often follows a diagnosis of infectious gastroenteritis.

Treatment

- Provide reassurance.
- Tactfully explain visceral hypersensitivity and validate symptoms.
- **Dietary trials:** Lactose-free, high-fiber diet.
- **Antispasmodics:** Dicyclomine, hyoscyamine, peppermint oil.
- **Antidepressants:** Desipramine, amitriptyline, fluoxetine, paroxetine.
- **Constipation-predominant type:**
  - ↑ fluid intake.
  - Provide bowel habit training.
  - Tegaserod 6 mg BID.
  - Osmotic laxatives.
- **Diarrhea-predominant type:** Loperamide, cholestyramine.

The first step in the evaluation of constipation is to understand the patient's true complaint.

Constipation

Normal bowel movement frequency is 3–12 per week. Constipation is defined as < 3 bowel movements per week or excessive difficulty and straining at defecation. Prevalence is high in the Western world and is **highest among children and the elderly.** Etiologies are as follows:

Normal bowel movement frequency ranges from 3 to 12 times per week.

- **Dietary:** Low fiber, inadequate fluids.
- **Behavioral:** Short-term stress, travel, disrupted routine.
- **Structural:** Colonic mass or stricture, rectal prolapse, Hirschsprung's disease, solitary rectal ulcer syndrome.
- **Systemic:** Diabetes, **hypothyroidism, hypokalemia, hypercalcemia,** autonomic dysfunction.
- **Medications:** Narcotics, diuretics, calcium channel blockers, anticholinergics, psychotropic drugs, clonidine.
- **Dysmotility:** Pelvic floor dysfunction, slow transit (pseudo-obstruction, psychogenic), IBS.

Symptoms/Exam

- Presents with abdominal bloating or pain as well as with nausea and anorexia.
- Exam is often normal but may present with abdominal distention, tenderness, and/or mass; external hemorrhoids, anal fissures, and fecal impaction; or rectal prolapse with straining.

Diagnosis/Treatment

- Look for a history of the following:
  - Fewer than three bowel movements per week.
  - Excessive difficulty and straining at defecation.
  - Fecal incontinence, rectal prolapse, anal pain.
- **Initial evaluation:**
  - **Labs:** CBC, serum electrolytes **(especially potassium and calcium),** TSH, FOBT.
  - **Age < 50 years and normal labs:** Initiate a trial of ↑ fiber (20–30 g/day); fluid intake.
  - **Age ≥ 50 or < 50 years with a failed fiber/fluid trial or fecal occult blood or anemia:** Barium enema; flexible sigmoidoscopy or colonoscopy.

- **Patients with no obstructive or medical disease:**
  - ↓ or discontinue suspect drugs, followed by stepwise addition of (1) stool softeners (docusate), (2) osmotic laxatives (magnesium hydroxide, lactulose, sorbitol, polyethylene glycol), (3) enemas (tap water, mineral oil, soap suds, phosphate), and (4) colonic stimulants (bisacodyl, senna).
- **Refractory constipation:**
  - **Pelvic floor dysfunction:** Anorectal manometry and balloon expulsion studies and defecography. Treat with biofeedback.
  - **Slow-transit constipation:** Radiopaque marker studies and scintigraphy with serial examination of marker transit using radiographs.

Diverticulosis

Results from weakening of the colonic wall. In industrialized nations, has a 30–50% prevalence in patients > 50 years of age. Rates ↑ with low dietary fiber and advancing age. In the United States, the predominant location is the left colon.

Symptoms

Approximately 70% of patients with diverticula remain asymptomatic; 20% will develop diverticulitis, and 10% will develop diverticular bleeding. In asymptomatic patients, the disorder is associated with excessive flatulence and pellet-like stools.

Exam

Exam may be normal, or patients may present with mild abdominal distention and pellet-like stools.

Differential

Colorectal cancer, IBS.

Diagnosis

- No diagnosis is needed in patients who are asymptomatic.
- **Barium enema:** Accurate for diverticulosis, but insufficient to rule out colorectal cancer.
- **Colonoscopy:** Recommended for routine colorectal cancer screening in patients > 50 years of age.

Treatment

Dietary fiber 20–30 g/day; coarse bran or supplements (psyllium) to ↑ stool bulk and ↓ colonic pressure. May also prevent the formation of new diverticula.

Complications

- **Diverticular bleeding** affects 10–20% of patients with diverticulosis.
- Presents with painless rectal bleeding, usually from a single diverticulum (more frequently in the right colon).

- Spontaneous cessation is common (80%), but approximately one-third of patients have recurrent bleeding.
- Treat with colonoscopy and angiography with embolization; consider elective colonic resection after the second recurrence.

Diverticulitis is the most common cause of colovesical fistula.

Diverticulitis

Microperforation of the diverticula with associated inflammation. Occurs in 10–25% of those with diverticulosis and commonly affects the sigmoid colon; frequency ↑ with advancing age.

Symptoms

LLQ pain (93–100%); fever, nausea, vomiting, constipation, diarrhea, urinary frequency ("sympathetic cystitis").

Exam

Exam may reveal LLQ tenderness, localized involuntary guarding, percussion tenderness, and tender LLQ fullness or mass.

Differential

Appendicitis, IBD, perforated colon cancer, UTI, ischemic colitis, infectious colitis, sigmoid volvulus.

Diagnosis

Mild diverticulitis may be treated on an outpatient basis if there are no significant comorbidities, minimal symptoms, and no peritoneal signs.

- **Labs:** Reveal leukocytosis with PMN predominance.
- **UA:** Evaluate for UTI; consider colovesical fistula with pyuria and bacteriuria.
- **Flat and upright AXR:** A thickened colonic (sigmoid) wall is suggestive; free air suggests bowel perforation.
- **CT with IV and PO contrast:** The test of choice; has high accuracy. Look for a thickened bowel wall and pericolic fat stranding. Evaluate for complications (bowel perforation, abscess, fistula).
- **Colonoscopy:** Exclude malignancy eight weeks after resolution.

Treatment

Consider elective "prophylactic" resection after the second attack of diverticulitis or diverticular bleeding.

- Outpatient treatment is sufficient if there are no significant comorbidities, minimal symptoms, and no peritoneal signs. Often requires hospitalization.
- Treat with IV fluids, bowel rest, and NG suction for ileus or obstruction.
- **Broad-spectrum antibiotics:** Cover anaerobes, gram-⊖ bacilli, and gram-⊕ coliforms. Administer a 7- to 10-day course. IV ampicillin/sulbactam (Unasyn) or piperacillin/tazobactam (Zosyn); PO quinolones; amoxicillin/clavulanate (Augmentin).
- **Surgery:** For perforation, abscess, fistula, obstruction, or recurrent diverticulitis (> 2 episodes).

Complications

- **Peritonitis:** Not excluded by the absence of free air. Associated with high mortality (6–35%); **necessitates urgent surgical intervention.**

- **Abscess:** Pelvic abscess is most common. Percutaneous CT-guided drainage is often possible.
- **Fistula:** Colovesical fistulas (to the bladder) are found in men more often than in women. Other fistulas are to the vagina, small bowel, and uterus. Surgical intervention is often postponed until the infection is treated.

GI BLEEDING

Lower Gastrointestinal Bleeding (LGIB)

Defined as bleeding from a source distal to the ligament of Treitz, which divides the third and fourth portions of the duodenum. Of all cases, > 95% are from a colonic source and > 85% are self-limited. The hospitalization rate is 20 in 100,000 adults per year; risk ↑ 200-fold from the third to the ninth decade. Mortality is 3–5%. Etiologies include the following:

- Diverticulosis (40%).
- Vascular ectasia.
- Neoplasm, IBD, ischemic colitis, hemorrhoids, infectious, postpolypectomy.
- NSAID ulcers, radiation colitis, rectal varices, solitary rectal ulcer syndrome. Consider an upper GI source.

Symptoms

Usually asymptomatic, but may present with abdominal cramps and, to a lesser extent, pain. Orthostasis is seen in severe cases.

Exam

Hematochezia (bright red blood, maroon stools) or melena; pallor; abdominal distention with mild tenderness; hypotension; tachycardia.

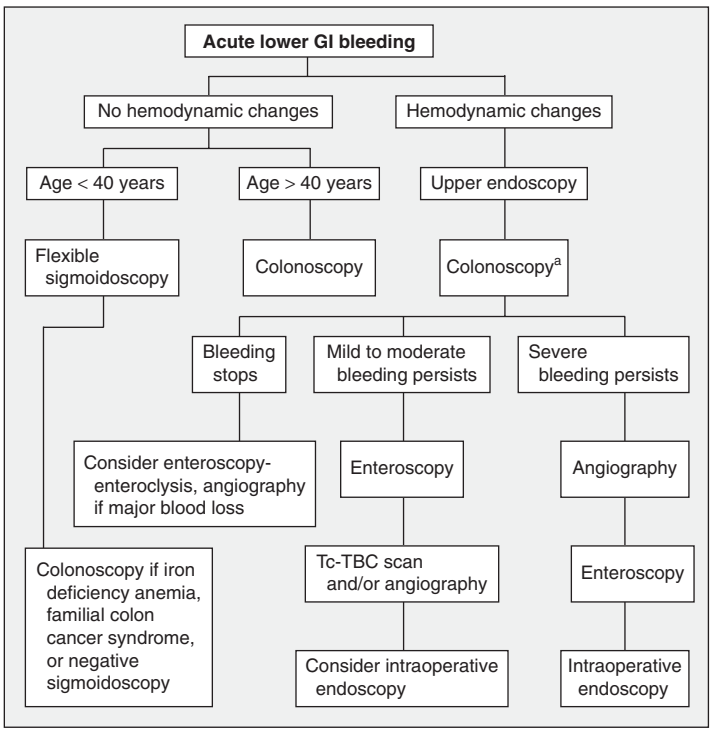
Diagnosis

- **Demographics and history:**
  - **Age group:** Distinguish elderly, asymptomatic patients (diverticular/vascular ectasias) from young patients who present with pain (infectious, inflammatory).
  - **Description of first blood seen by patient:** Bright red blood indicates a distal or rapid proximal source; black or maroon blood points to a more proximal source.
- Anoscopy to exclude an anal source; stool cultures if infection is suspected.
- **Mild to moderate LGIB:** Consider nasogastric lavage. Urgent colonic purge (over 4–6 hours); then colonoscopy.
- **Massive LGIB:**
  - **EGD:** Upper GI bleeding (UGIB) must be excluded with EGD. **Ten percent of UGIB cases present with hematochezia.**
  - **Technetium-labeled RBC scan and/or mesenteric angiography:** If > 6 units of blood are transfused, consider surgical intervention.
  - **Minimum bleeding rates:** Tagged RBC scan, 0.1–0.5 mL/min; mesenteric angiogram, 1.0 mL/min.
- **Diagnostic colonoscopy:** Typically performed 12–48 hours after presentation and stabilization.

Treatment

Treatment is as follows (see also Figure 7.3):

- **Stabilization:**
  - NPO; consider an NG tube and place two large-bore IVs.
  - If the patient is in shock, treat with aggressive IV fluids and cross-matched blood with a **hematocrit goal of 25–30%.**
  - In the presence of active LGIB and platelets < 50,000/μL or if there is known impaired function (uremia, aspirin), transfuse platelets or desmopressin. With active LGIB and INR > 1.5, transfuse FFP.
- **Medical therapy:** H_2 receptor antagonists and PPIs have no role in the treatment of LGIB. Discontinue ASA and NSAIDs.
- **Urgent therapeutic colonoscopy:** Large-volume purge > 6 L; cautery or injection of epinephrine or clipping. Colonoscopy is technically challenging with brisk LGIB (urgent colonic purge requires sedation; visualization is often poor).
- **Mesenteric angiography/embolization:** The intervention of choice for brisk LGIB. Associated with 80–90% cessation rates for those with a diverticular or vascular ectasia etiology, although 50% experience rebleeding.
- **Surgery: Indicated with active LGIB** involving > 4–6 units of blood in 24 hours or > 10 units total. If the site is well localized, consider hemicolectomy; otherwise perform total abdominal colectomy.



[a]If massive bleeding does not allow time for colonic lavage, proceed to angiography.

FIGURE 7.3. Suggested algorithm for patients with acute LGIB.

(Reproduced, with permission, from Kasper DL et al. *Harrison's Principles of Internal Medicine*, 16th ed. New York: McGraw-Hill, 2005: 237.)

Acute Upper Gastrointestinal Bleeding (UGIB)

Ten percent of UGIB patients present with hematochezia.

Incidence is 100 in 100,000 adults per year and ↑ with advancing age. Mortality is 10% and usually results from complications of underlying disease rather than from exsanguination. The risk of rebleeding is low if bleeding occurred > 48 hours before presentation (see Table 7.8). Etiologies include the following:

- PUD (55%).
- Gastroesophageal varices, vascular ectasia, Mallory-Weiss tear, erosive gastritis/esophagitis, Cameron's ulcer.
- **Other:** Dieulafoy's lesion, aortoenteric fistula, hemobilia.

Symptoms/Exam

Hematocrit is a poor early indicator of the amount of blood loss in UGIB.

- Patients present with nausea, retching, hematemesis (bright red blood or "coffee ground" emesis), dyspepsia, abdominal pain, melena or hematochezia, and orthostasis.
- Exam may reveal melena or hematochezia, pallor, hypotension, and tachycardia. Stigmata of chronic liver disease (spider angioma, ascites, jaundice) or a history of alcohol use are usually found among those with variceal hemorrhage.

Diagnosis

As little as 50 mL of blood in the GI tract can cause melena.

- **History:** Assess NSAID use (peptic ulcer), retching prior to hematemesis (Mallory-Weiss tear), alcohol abuse (esophagitis, Mallory-Weiss tear, varices), prior abdominal aortic graft (aortoenteric fistula), chronic GERD (esophagitis), and weight loss/iron deficiency (malignancy) (see Table 7.9).
- **NG tube lavage:** Useful if ⊕ (red blood, coffee grounds); if ⊖ (clear or bilious), does not exclude UGIB. **Ten percent** of UGIB cases have a ⊖ lavage.
- **EGD:** Perform after stabilization and resuscitation; often done < 12 hours from admission. Diagnostic, **prognostic,** and therapeutic.
- ***H. pylori* testing:** Perform on all patients with peptic ulcers.

TABLE 7.8. Risk Assessment in Patients with UGIB

	Low	Moderate	High
History	Age < 60.	Age < 60.	Age > 60, comorbidities, onset while in hospital.
Exam	SBP > 100, HR < 100.	SBP > 100, HR > 100.	SBP < 100, HR > 100.
EGD	Small, clean-based ulcer; erosions; no lesion found.	Ulcer with pigmented spot or adherent clot.	Active bleeding, varices, ulcer > 2 cm, visible vessel.
Rebleed risk	< 5%.	10–30%.	40–50%.
Triage	Ward/home.	Ward.	ICU.

TABLE 7.9. Sources of Bleeding in Patients Hospitalized for Acute UGIB

Source of Bleeding	Proportion of Patients (%)
Ulcers	35–62
Varices	4–31
Mallory-Weiss tears	4–13
Gastroduodenal erosions	3–11
Erosive esophagitis	2–8
Malignancy	1–4
No source identified	7–25

Reproduced, with permission, from Kasper DL et al. *Harrison's Principles of Internal Medicine,* 16th ed. New York: McGraw-Hill, 2005: 235.

Treatment

Ten percent of documented UGIB cases have a ⊖ NG tube lavage.

- **Stabilization:** As with LGIB (see above).
- **Medical therapy:** H_2 receptor antagonists do not alter the outcome. Give high-dose oral PPIs twice daily upon presentation. Initiate an IV PPI drip if EGD suggests a high risk of rebleeding (i.e., active bleeding, visible vessel, adherent clot). Reduces the relative risk of bleeding by 50%. IV octreotide for suspected variceal hemorrhage; continue for three days if verified by EGD.
- **Endoscopy:** Of all patients with active UGIB at EGD, > 90% can be effectively treated with banding, sclerosant, epinephrine, and/or electrocautery. Predictors of rebleeding include significant comorbidities, size of lesion, and high-risk stigmata (visible vessel, adherent clot).
- **Refractory or recurrent UGIB:**
  - Esophageal balloon tamponade (Minnesota or Sengstaken-Blakemore tubes) for varices as a bridge to **TIPS.**
  - Angiogram with intra-arterial **embolization or surgery** for refractory nonvariceal bleeding.
- ***H. pylori* eradication:** For all peptic ulcers causing UGIB with (*H. pylori* testing.

INFLAMMATORY BOWEL DISEASE (IBD)

Crohn's disease and ulcerative colitis are the primary chronic autoimmune inflammatory diseases of the bowel. Table 7.10 summarizes the distinguishing features of both.

Crohn's Disease

A chronic, recurrent disease with patchy or "**skipped**" **transmural** inflammation of **any segment** of the GI tract from the mouth to the anus. Demonstrates a propensity for the **ileum** and proximal colon, with 33% involving only the

TABLE 7.10. Distinguishing Features of IBD

Feature	Crohn's Disease	Ulcerative Colitis
Genetic predisposition	*NOD2, CARD15.*	Presumed genetic component.
Worse with smoking	Yes.	Possible improvement.
Age at onset	Bimodal: 15–25, 55–65 years.	Bimodal: 20–40, 60–70 years.
Abdominal pain	Sharp, focal.	Crampy; associated with bowel movement.
Bowel obstruction	Common.	Rare.
Gross hematochezia	Occasionally.	Common.
GI involvement	Mouth to anus; typically terminal ileum/proximal colon.	Colon only; rectum with continuous progression proximally.
Pattern	Segmental, transmural, eccentric.	Continuous, mucosal, circumferential.
Ulceration	Superficial to deep, linear, serpiginous.	Superficial.
Histology	Noncaseating granulomas.	Crypt abscesses.
p-ANCA ⊕	20%.	70%.
ASCA ⊕	65%.	15%.
Fistula/stricture	Common.	Uncommon.
Extraintestinal manifestations	Uncommon.	Common.
Infliximab response	Often.	Occasionally.
Surgery curative	Never.	Often.

terminal ileum, 50% involving both the small bowel and colon, and 20% only the colon. Incidence is 4–8 in 100,000. More common among **Ashkenazi Jews,** those with a ⊕ family history, and smokers; **smoking** may exacerbate disease. Shows a **bimodal** age of onset at 15–25 and 55–65 years of age. The clinical course is characterized by the development of fistulas and strictures. ***NOD2*** mutations confer susceptibility.

Symptoms

RLQ or periumbilical pain, **nonbloody diarrhea,** low-grade fever, malaise, weight loss, anal pain, oral aphthous ulcers, postprandial bloating, kidney stones (↑ oxalate absorption 2° to fat malabsorption).

Of all IBD cases, > 10% cannot clearly be classified as ulcerative colitis or Crohn's disease.

Exam

Fever, tachycardia, abdominal tenderness and/or mass, perianal fissures/fistulas/skin tags, extraintestinal manifestations (pyoderma gangrenosum, erythema nodosum, ankylosing spondylitis, sacroiliitis, uveitis).

Differential

Ulcerative colitis, IBS, infectious enterocolitis (*Yersinia, Entamoeba histolytica*, TB), mesenteric ischemia, intestinal lymphoma, celiac sprue.

Diagnosis

Smoking is associated with worsening Crohn's disease, while ulcerative colitis may ***improve*** *with smoking.*

- **Labs:**
  - Look for anemia (chronic disease, iron deficiency, vitamin B_{12} deficiency), leukocytosis, low serum albumin, elevated CRP, and elevated ESR.
  - There is a **poor correlation between lab results and disease severity.**
- **Stool studies:** Rule out infection with culture, O&P, and *C. difficile* toxin.
- **Colonoscopy:**
  - Assess the extent and severity of disease. Key words are skipped lesions, cobblestone, stricture, fistula, and ulcerations.
  - Biopsies demonstrate acute and chronic inflammation; **noncaseating granulomas** are seen < 25% of the time but are highly suggestive of Crohn's disease.
- **Small bowel follow-through:** Evaluate for small bowel involvement.
- **CT scan:** Consider if there is concern for abdominal abscess/fistula.
- **Immunologic markers:** Useful in indeterminate disease (Crohn's vs. ulcerative colitis, particularly if surgery is indicated). Markers used (see Table 7.11) include p-ANCA and ASCA.

Crohn's colitis carries a risk of colon cancer similar to that of ulcerative colitis.

Treatment

- **5-ASA agents:**
  - **Sulfasalazine:** Give 1.5–2.0 g BID. Released in the colon; **not active in the small bowel.** Used for induction and maintenance.
  - **Mesalamine (Pentasa, Asacol):** Up to 4.8 g daily in divided doses. Asacol is released in the colon; Pentasa is **released in the small bowel.** Associated with > 40% remission in mild to moderate ileocecal Crohn's disease.
- **Antibiotics:**
  - **Useful even with no obvious infection.**
  - Metronidazole 10 mg/kg/day or ciprofloxacin 500 mg BID. Rifaximin (a nonabsorbable antibiotic) is also used.
- **Corticosteroids:**
  - Suppress acute flares; useful in small and large bowel disease.
  - Give prednisone 40–60 mg/day during acute flares with taper after response.
  - Significant long-term side effects include diabetes, hypertension, cataracts, metabolic bone disease, and psychosis.

TABLE 7.11. Interpretation of p-ANCA and ASCA Values

Test	Result	Interpretation	Characteristics
p-ANCA	–	Suggests Crohn's.	95% PPV,
ASCA	+		92% specificity.
p-ANCA	+	Suggests ulcerative colitis.	88% PPV,
ASCA	–		98% specificity.

- Budesonide is an oral steroid with less systemic absorption; it is used for maintenance only.
- **Immunomodulatory drugs:**
  - Used for maintenance only, not for induction, as onset of action may take six weeks.
  - Used to minimize steroid exposure.
  - **Azathioprine (Imuran):** Give 2.0–2.5 mg/kg. Therapeutic effects are delayed 6–8 weeks; significant bone marrow suppression requires frequent initial monitoring.
  - **6-MP:** Give 1.0–1.5 mg/kg; similar to azathioprine. Thiopurine methyltransferase activity measurement may help with the titration of 6-MP.
  - **Methotrexate:** Second- or third-line maintenance therapy.
- **Infliximab (Remicade):** Recombinant anti-TNF. Give a 5 mg/kg IV infusion. For moderate to severe fistulizing disease; **contraindicated for disease with strictures.** Repeat IV infusions every 2–4 weeks for three doses; then consider maintenance doses every eight weeks. **TB must be ruled out** prior to use (PPD, CXR). Long-term treatment is associated with waning efficacy and ↑ allergic reactions.
- **Surgery:** Some 50% of patients will require surgery for obstruction or abscess if refractory to medical therapy.

TB exposure and active stricturing disease must be ruled out before infliximab is administered.

Complications

Strictures/obstruction, fistulas, abscess, colorectal cancer, malabsorption, nephrolithiasis, cholelithiasis.

Ulcerative Colitis

A chronic, recurrent disease with diffuse **continuous** mucosal inflammation of the colon extending proximally from the rectum. Of all cases, > 50% are isolated to the rectum and sigmoid colon and < 20% involve the entire colon. Incidence is 3–15 in 100,000; age at onset is typically 20–40 years, but the disease also occurs in patients < 10 years of age and in the elderly. More common among Ashkenazi Jews, nonsmokers, and those with a family history; **smoking may attenuate disease.** Course is marked by repeated flares and remissions.

Symptoms/Exam

- Bloody diarrhea, crampy abdominal pain, fecal urgency, tenesmus, and weight loss are characteristic.
- Fever, tachycardia, and abdominal tenderness; red blood on DRE.

- Extraintestinal findings may include ankylosing spondylitis, sacroiliitis, erythema nodosum, pyoderma gangrenosum, and uveitis.

Differential

Infectious colitis, ischemic colitis, Crohn's colitis.

Diagnosis

- **Labs:**
  - Anemia (chronic disease, iron deficiency, hematochezia), leukocytosis, low serum albumin, elevated CRP, elevated ESR.
  - There is a **good correlation between labs (hematocrit, albumin, ESR) and disease severity.**
  - Elevated **alkaline phosphatase** is seen in the presence of coexisting 1° sclerosing cholangitis.
  - **Stool studies:** Rule out infection with culture, O&P, and *C. difficile* toxin.
- **Imaging:** For moderate and severe activity. AXR reveals loss of haustrations, leading to a "**lead pipe**" appearance and colonic dilation.
- **Colonoscopy:** Avoid if there is a severe flare. Evaluate the colon and terminal ileum. Look for rectal involvement (95–100%), **continuous circumferential ulcerations,** and **pseudopolyps.** The terminal ileum is occasionally inflamed from "**backwash ileitis.**" Biopsies demonstrate acute and chronic inflammation, **crypt abscesses,** and absence of granulomas.

Treatment

Treatment depends on **severity** and on the **location** of active disease.

NSAID use can induce a flare of ulcerative colitis or Crohn's disease.

- **Distal disease:** Mesalamine or hydrocortisone suppository (rectal involvement) or enema (up to the splenic flexure).
- **Distal and proximal disease:** Oral or IV agents.
- **Mild to moderate activity:**
  - Sulfasalazine 1.5–3.0 g PO BID.
  - Mesalamine 2.4–4.8 g PO QD in divided doses.
  - Prednisone 40–60 mg PO QD if no response after 2–4 weeks.
- **Severe activity:**
  - Methylprednisolone 48–60 mg IV QD or hydrocortisone 300 mg IV QD.
  - Roughly 50–75% of patients achieve remission in 7–10 days.
  - If no response is seen within 7–10 days, **colectomy** is usually indicated.
  - Consider a trial of cyclosporine or an anti-TNF agent prior to colectomy.
- **Maintenance therapy:**
  - Sulfasalazine 1.0–1.5 g PO BID.
  - Mesalamine 800–1200 mg PO TID.
- **Surgery:**
  - Can be curative and can eliminate the risk of colon cancer.
  - Proctocolectomy with ileostomy is curative.
  - Proctocolectomy with ileoanal anastomosis is often curative, but 25% have "pouchitis," or inflammation of the neorectum.

The risk of colon cancer in those with ulcerative colitis for > 10 years is 0.5–1.0% per year; colonoscopy is recommended every 1–2 years beginning eight years after diagnosis.

Complications

Toxic megacolon (dilated colon, leukocytosis, fever, rebound tenderness), 1° sclerosing cholangitis, colorectal cancer, extraintestinal manifestations (see Table 7.12).

TABLE 7.12. Extraintestinal Manifestations of Ulcerative Colitis and Their Relationship to Disease Activity

Related	Often Related	Unrelated
Arthritis	Pyoderma gangrenosum	Ankylosing spondylitis
Erythema nodosum	Uveitis	1° sclerosing cholangitis
Oral aphthous ulcers		
Episcleritis		

ISCHEMIC BOWEL DISEASE

Acute Mesenteric Ischemia

Most common in the elderly and in those with valvular heart disease, atrial fibrillation, or atherosclerotic disease. In young patients, occurs with **atrial fibrillation, vasculitis, hypercoagulable** states (OCP use in young female smokers), and vasoconstrictor abuse. After infarction, mortality is 70–90%.

Symptoms

Presents with acute-onset, severe abdominal pain ("**out of proportion to exam**") as well as with sudden forceful bowel movements, often with maroon or bright red blood and nausea.

Exam

- **Early:** Agitation, writhing, a soft abdomen with hyper- or hypoactive bowel sounds, ⊕ fecal blood.
- **Later:** Distention, progressive tenderness, peritoneal signs, hypotension, fever.

Differential

Pancreatitis, diverticulitis, appendicitis, aortic dissection, perforated peptic ulcer, nephrolithiasis.

Diagnosis

- Maintain a **high index of suspicion** for patients > 50 years of age with CHF, cardiac arrhythmias, recent MI, recent catheterization, or hypotension.
- **Labs:** Leukocytosis, metabolic acidemia (late finding only), elevated serum **amylase** (with normal lipase) and lactate.
- **AXR:** Demonstrates air-fluid levels and "**thumbprinting**" in the small bowel wall.
- **CT:** Shows bowel wall thickening, luminal dilation, pneumatosis intestinalis and portal venous gas, necrotic bowel, and vascular thrombosis.
- **Visceral angiogram:** Important diagnostically; may also be therapeutic.

Early visceral angiography is critical in the diagnosis and management of acute mesenteric ischemia.

Treatment

- Correct hypotension, hypovolemia, and cardiac arrhythmias.
- Bowel rest; broad-spectrum IV antibiotics.
- Angiography followed by thrombolysis or immediate surgery.
- Anticoagulation should be postponed until > 48 hours after laparotomy.

Ischemic Colitis

Most common in the elderly and in patients with atherosclerotic or cardiovascular disease. Ranges from self-limited to life-threatening disease. **Watershed areas** (the splenic flexure and rectosigmoid junction of the colon) are the most common sites affected. Exsanguination and infarction are uncommon.

Symptoms/Exam

- Crampy left lower abdominal pain, hematochezia, nausea.
- Abdominal exam is benign or reveals mild LLQ tenderness.

Differential

IBD, infectious colitis, diverticulitis.

Ischemic colitis typically affects the colonic "watershed" areas of the splenic flexure and rectosigmoid junction but spares the rectum.

Diagnosis

- **Labs:** Leukocytosis, anemia.
- **AXR: "Thumbprinting"** is seen on the colon wall.
- **CT:** Shows bowel wall thickening, luminal dilation, and pericolonic fat stranding. Vascular occlusion (e.g., mesenteric venous thrombosis) is uncommon.
- **Flexible sigmoidoscopy:** Contraindicated if peritoneal signs are present. Performed with minimal insufflation. Look for **segmental changes sparing the rectum** (due to preserved collateral circulation from hemorrhoidal plexus) and hemorrhagic nodules. Pale, dusky, ulcerative mucosa.

Treatment

- Correct hypotension, hypovolemia, and cardiac arrhythmias.
- Minimize vasopressors; give broad-spectrum IV antibiotics.
- Monitor for progression with serial exams and radiographs.
- If there are signs of infarction (guarding, rebound tenderness, fever), laparotomy, revascularization, or bowel resection may be needed.

PANCREATIC DISORDERS

Acute Pancreatitis

Ascaris lumbricoides *causes up to 20% of cases of acute pancreatitis in Asia.*

In the United States, > 80% of acute pancreatitis cases result from binge drinking or biliary stones; only 5% of heavy drinkers develop pancreatitis. Twenty percent of cases are complicated by necrotizing pancreatitis. Etiologies are as follows:

Gallstones and alcohol are the main causes of pancreatitis in the United States.

- **EtOH** and **gallstones** and, to a lesser extent, trauma.
- **Drugs:** Azathioprine, pentamidine, sulfonamides, thiazide diuretics, 6-MP, valproic acid, didanosine.
- **Metabolic:** Hyperlipidemia or hypercalcemia.
- **Mechanical:** Pancreas divisum, sphincter of Oddi dysfunction, mass.
- **Infectious:** Viruses (e.g., mumps) and, to a lesser extent, bacteria and parasites (e.g., *Ascaris lumbricoides*).
- **Other:** Scorpion bites, hereditary pancreatitis (an autosomal-dominant mutation of the trypsinogen gene), CF, pregnancy.

Symptoms

- Presents with sudden-onset, persistent, deep epigastric pain, often with radiation to the back, that **worsens when patients are supine and improves when they sit or lean forward.**
- Severe nausea, vomiting, and fever are also seen.

Exam

- Exam reveals upper abdominal tenderness with guarding and rebound.
- Other findings include the following:
  - **Severe cases:** Distention, ileus, hypotension, tachycardia.
  - **Rare:** Umbilical (**Cullen's sign**) or flank (**Grey Turner's sign**) ecchymosis.
  - **Other:** Mild jaundice with stones or xanthomata with hyperlipidemia.

Differential

Biliary colic, cholecystitis, mesenteric ischemia, intestinal obstruction/ileus, perforated hollow viscus, inferior MI, dissecting aortic aneurysm, ectopic pregnancy.

Diagnosis

- **Labs** (see also Table 7.13):
  - Leukocytosis (10,000–30,000/μL); elevated amylase (more sensitive) and lipase (more specific).
  - There is no clinical use for serial amylase or lipase.
  - High serum glucose.
  - An **ALT > 3 times normal suggests biliary stones over EtOH; an AST:ALT ratio > 2 favors EtOH.** CRP declines with improvement.
- **Differential for elevated amylase:** Pancreatitis, pancreatic tumors, cholecystitis, perforation (esophagus, bowel), intestinal ischemia or infarction, appendicitis, ruptured ectopic pregnancy, mumps, ovarian cysts, lung cancer, macroamylasemia, renal insufficiency, HIV, DKA, head trauma. **Lipase is usually normal in nonpancreatic amylase elevations.**
- **AXR:** May show gallstones, "**sentinel loop**" (an air-filled small bowel in the LUQ), and "**colon cutoff sign**" (abrupt ending of the transverse colon).
- **RUQ ultrasound:** Reveals cholelithiasis without cholecystitis. Choledocholithiasis (common duct stones) are often missed or have passed.

CT is prognostic in severe pancreatitis and is used to evaluate for necrotizing pancreatitis. Necrotizing pancreatitis warrants empiric antibiotics (imipenem).

TABLE 7.13. Assessment of Pancreatitis Severity by Ranson's Criteria[a]

24 HOURS: "GA LAW"	48 HOURS: "C HOBBS"
Glucose > 200 mg/dL	**C**a < 8 mg/dL
Age > 55	**H**ematocrit drop < 10%
LDH > 350 U/L	$\mathbf{O}_2$, arterial Po_2 < 60 mmHg
AST > 250 U/L	**B**ase deficit > 4 mEq/L
WBC > 16,000 /μL	**B**UN rise > 5 mg/dL
	Sequestered fluid > 6 L

[a] Mortality risk: 1% with 0–2 criteria; 16% with 3–4 criteria; 40% with 5–6 criteria; 100% with 7–8 criteria.

- **CT:** Performed initially to exclude abdominal catastrophes. At 48–72 hours, exclude necrotizing pancreatitis. There is an ↑ risk of **renal failure** from contrast dye.

For persistent pancreatitis, no improvement on antibiotics (> 1 week), or suspicion of infected necrosis, consider CT with FNA to rule out infected necrosis, which requires surgical debridement.

TREATMENT

- NPO with nasojejunal tube feeds or total parenteral nutrition with severe disease and anticipated NPO status for > 3–5 days.
- Aggressive IV hydration.
- Pain control with narcotics. Avoid morphine, as it ↑ sphincter of Oddi tone.
- Broad-spectrum IV antibiotics (imipenem) for severe necrotizing pancreatitis.
- For **gallstone pancreatitis** (elevated serum bilirubin, signs of biliary sepsis), perform ERCP for stone removal and cholecystectomy following recovery **but prior to discharge.**

COMPLICATIONS

- **Necrotizing pancreatitis:**
  - Suspected in the setting of a persistently elevated WBC count (7–10 days), high fever, and shock (organ failure).
  - Has a poor prognosis (up to 30% mortality and 70% risk of complications).
  - If infected necrosis is suspected, perform percutaneous aspiration. If organisms are present on smear, surgical debridement is indicated.
- **Pancreatic pseudocyst:** A collection of pancreatic fluid walled off by granulation tissue. Occurs in approximately 30% of cases but resolves spontaneously in about 50%. Drainage is not required unless the pseudocyst is present > 6–8 weeks and is enlarging and symptomatic.
- **Other:** Pseudoaneurysm, renal failure, ARDS, splenic vein thrombosis (which can lead to isolated gastric varices).

Chronic Pancreatitis

Persistent inflammation of the pancreas with irreversible histologic changes, recurrent abdominal pain, and loss of exocrine/endocrine function. Marked by atrophic gland, dilated ducts, and calcifications, although all are late findings. Characterized by the size of pancreatic ducts injured; "big duct" injury is from EtOH. Risk factors include EtOH (amount and duration) and smoking. Associated with an ↑ risk of pancreatic cancer; 10- and 20-year survival rates are 70% and 45%, with death usually resulting from nonpancreatic causes. Etiologies are as follows:

- **EtOH (80%)** and, to a lesser extent, hereditary pancreatitis (CF, trypsinogen mutation).
- **Autoimmune:** Rare and associated with diffuse enlargement of the pancreas, ↑ IgG4, and autoantibodies; associated with other autoimmune disorders (e.g., Sjögren's, SLE, 1° sclerosing cholangitis).
- **Obstructive:** Pancreas divisum, sphincter of Oddi dysfunction, mass.
- **Metabolic:** Malnutrition, hyperlipidemia, hyperparathyroid-associated hypercalcemia.

Symptoms

- Presents with recurrent, deep epigastric pain, often radiating to the back, that worsens with food intake and when patients lie supine and **improves when they sit or lean forward.** Episodes may last anywhere from hours to 2–3 weeks.
- Also presents with anorexia, fear of eating (**sitophobia**), nausea/vomiting, and, later, weight loss and steatorrhea.

Chronic pancreatitis of the "small duct" type may exhibit very subtle structural changes and is often associated with normal functional tests but marked symptoms.

Exam

- Exam is normal. Mild to moderate upper abdominal tenderness may be found during episodes.
- Rarely, there may be a palpable epigastric mass (pseudocyst) or spleen (from splenic vein thrombosis).

Differential

Biliary colic, mesenteric ischemia, PUD, nonulcer dyspepsia, inferior MI, perforation, IBS, drug-seeking behavior.

Diagnosis

Diagnosis is as follows (see also Table 7.14):

- No single test is adequate; routine labs are normal. Amylase and lipase are not always elevated during episodes.
- **Functional tests:**
  - Often normal in "small duct" chronic pancreatitis; not ⊕ until 30–50% of the gland is destroyed.
  - **Seventy-two-hour fecal fat test on 100-g/day fat diet:** ⊕ in the presence of > 7 g of fat in stool.
  - **Stool chymotrypsin and elastase:** Absent or low levels.
  - **Secretin test:** Most sensitive, but impractical. Give IV secretin and then measure pancreatic secretion via a nasobiliary tube.
- **Structural tests:** Except for endoscopic ultrasound (**EUS**), imaging studies are insensitive, as architectural changes do not occur until late in the disease course; diagnosis is improved with EUS +/– FNA. Pancreatic calcifications are visualized on plain AXRs (30%); "big duct" injury is seen on CT.

TABLE 7.14. Diagnosis of Chronic Pancreatitis

	"Big Duct"	"Small Duct"
Seen on ultrasound or CT	Yes	No
Seen on ERCP	Yes	Maybe
Etiology	EtOH	Non-EtOH >> EtOH
Loss of function (exocrine/endocrine)	Common	Less common
Responsive to decompression (stenting, surgery)	Often	Rarely

- **Histology:** The gold standard, but impractical; obtained by EUS FNA. Reveals fibrosis, mixed lymphocyte and monocyte infiltrate, and architectural changes.

Treatment

- Alcohol abstinence.
- Fat-soluble vitamins (vitamins A, D, E, and K); pancreatic enzymes.
- Pain control with narcotics (avoid morphine) and celiac plexus injection.
- ERCP with short-term pancreatic duct stenting and stone removal.
- **Surgical therapy** is appropriate for intractable pain and failure of medical therapy; modalities include pancreatectomy, pancreaticojejunostomy (Puestow), and pseudocyst drainage.

Complications

- **Malabsorption:** Fat-soluble vitamins (A, D, E, and K); pancreatic enzymes.
- **Metabolic bone disease:** Osteopenia (33%) and osteoporosis (10%). Manage with calcium, vitamin D, and bisphosphonates.
- **Other:** Brittle DM, pancreatic pseudocyst, pseudoaneurysm, hemosuccus pancreaticus (bleeding from the pancreatic duct into the GI tract), splenic vein thrombosis, pancreatic cancer.

BILIARY DISEASE

Tables 7.15 and 7.16 classify diseases with jaundice and biliary tract disease.

Cholelithiasis (Gallstones) and Acute Cholecystitis

More common in women; incidence ↑ with age. In the United States, 10% of men and 20% of women > 65 years of age are affected; > 70% are cholesterol stones (see Table 7.17). Among patients with incidental asymptomatic gallstones, only 15% have biliary colic at 10 years, and 2–3% have cholecystitis/cholangitis.

- **Cholecystitis:** The most common complication of cholelithiasis. More than 90% of cases are due to cholelithiasis with stone impacted in the cystic duct. Spontaneous resolution occurs in > 50% of cases within 7–10 days.
- **Acalculous cholecystitis (without gallstones):** Usually seen in critically ill patients with no oral intake or following major surgical procedures; occurs after ischemia-related chronic gallbladder distention.

Acalculous cholecystitis is generally seen in the critically ill with no oral intake or after major surgical procedures.

Symptoms

- **Cholelithiasis:** Often asymptomatic or may present as follows:
  - **Common:** Biliary colic (crampy, wavelike RUQ pain), abdominal bloating, dyspepsia.
  - **Uncommon:** Nausea/vomiting (except in small bowel obstruction from **gallstone ileus**).
- **Cholecystitis:** Sudden-onset, severe RUQ or epigastric pain that may radiate to the right shoulder, accompanied by nausea/vomiting and fever. Jaundice suggests common bile duct stones (choledocholithiasis) or compression of the common bile duct by an inflamed, impacted cystic duct **(Mirizzi's syndrome).**

TABLE 7.15. Classification of Jaundice

Type of Hyperbilirubinemia	Location and Cause
Unconjugated hyperbilirubinemia (predominant indirect-acting bilirubin)	↑ bilirubin production (e.g., hemolytic anemias, hemolytic reactions, hematoma, pulmonary infarction). Impaired bilirubin uptake and storage (e.g., posthepatitis hyperbilirubinemia, Gilbert's syndrome, Crigler-Najjar syndrome, drug reactions). **Hereditary cholestatic syndromes:** Faulty excretion of bilirubin conjugates (e.g., Dubin-Johnson syndrome, Rotor's syndrome).
Conjugated hyperbilirubinemia (predominant direct-acting bilirubin)	**Hepatocellular dysfunction:** ■ Biliary epithelial damage (e.g., hepatitis, hepatic cirrhosis). ■ Intrahepatic cholestasis (e.g., certain drugs, biliary cirrhosis, sepsis, postoperative jaundice). ■ Hepatocellular damage or intrahepatic cholestasis resulting from miscellaneous causes (e.g., spirochetal infections, infectious mononucleosis, cholangitis, sarcoidosis, lymphomas, industrial toxins). **Biliary obstruction:** Choledocholithiasis, biliary atresia, carcinoma of the biliary duct, sclerosing cholangitis, choledochal cyst, external pressure on the common duct, pancreatitis, pancreatic neoplasms.

Adapted, with permission, from Tierney LM et al. *Current Medical Diagnosis & Treatment,* 44th ed. New York: McGraw-Hill, 2005: 630.

Exam

- **Cholelithiasis:** RUQ tenderness is commonly seen, but exam may be normal.
- **Cholecystitis:** RUQ tenderness and voluntary guarding; ⊕ **Murphy's sign** (inspiratory arrest with palpation of the RUQ); fever; jaundice in < 25% of cases.

Differential

- Choledocholithiasis, cholangitis, perforated peptic ulcer, acute pancreatitis.
- Diverticulitis (hepatic flexure, transverse colon), right-sided pneumonia.

Diagnosis

- **Cholelithiasis:** Often an incidental finding on abdominal ultrasound or CT.
- **Cholecystitis:**
  - **Labs:** Leukocytosis with neutrophil predominance; elevated total bilirubin (1–4 mg/dL) and transaminases (2–4 times normal) even without choledocholithiasis. Elevated alkaline phosphatase and amylase.
  - **RUQ ultrasound:** Less sensitive than HIDA scan but more readily available. Shows gallbladder wall **thickening, pericholecystic fluid,** and localization of stones. A radiographic **Murphy's sign** (focal gall-

TABLE 7.16. Diseases of the Biliary Tract

	Clinical Features	Laboratory Features	Diagnosis	Treatment
Asymptomatic gallstones	None.	Normal.	Ultrasound.	None.
Symptomatic gallstones	Biliary colic.	Normal.	Ultrasound.	Laparoscopic cholecystectomy.
Cholesterolosis of gallbladder	Usually asymptomatic.	Normal.	Oral cholecystography.	None.
Adenomyomatosis	May cause biliary colic.	Normal.	Oral cholecystography.	Laparoscopic cholecystectomy if symptomatic.
Porcelain gallbladder	Usually asymptomatic; high risk of gallbladder cancer.	Normal.	X-ray or CT.	Laparoscopic cholecystecomy.
Acute cholecystitis	Epigastric or RUQ pain, nausea, vomiting, fever, Murphy's sign.	Leukocytosis.	Ultrasound, HIDA scan.	Antibiotics, laparoscopic cholecystectomy.
Chronic cholecystitis	Biliary colic, constant epigastric or RUQ pain, nausea.	Normal.	Oral cholecystography, ultrasound (stones), cholecystectomy (nonfunctioning gallbladder).	Laparoscopic cholecystectomy.
Choledocholithiasis	Asymptomatic or biliary colic, jaundice, fever; gallstone pancreatitis.	Cholestatic LFTs; leukocytosis and blood cultures in cholangitis; elevated amylase and lipase in pancreatitis.	Ultrasound (dilated ducts), ERCP.	Endoscopic sphincterotomy and stone extraction; antibiotics for cholangitis.

Adapted, with permission, from Tierney LM et al. *Current Medical Diagnosis & Treatment,* 44th ed. New York: McGraw-Hill, 2005: 663.

bladder tenderness under a transducer) has a 90% positive predictive value. Low sensitivity (50%) for choledocholithiasis.

- **HIDA scan:** High sensitivity (95%) and specificity (90%). Assesses cystic duct patency; ⊕ in the setting of a ⊖ gallbladder uptake with preserved excretion into the small bowel. **CCK** stimulation assesses gallbladder contractility and aids in the diagnosis of acalculous cholecystitis.

TABLE 7.17. Types of Gallstones

	Cholesterol	Black Pigmented	Brown Pigmented
Regional/ethnic predictors	Western countries, Pima Indians, Caucasians >> blacks.	Africa, Asia.	Africa, Asia.
Risk factors	Age, female gender, pregnancy, estrogens, DM, obesity, rapid weight loss, elevated triglycerides, prolonged fasting, ileal disease **(Crohn's),** ileal resection, CF.	Chronic hemolysis **(sickle cell),** cirrhosis, high-protein diet.	Biliary infections, foreign bodies (stents, sutures), low-protein diet.

Treatment

- **Asymptomatic cholelithiasis:** No specific treatment is indicated (even in DM).
- **Symptomatic cholelithiasis:**
  - Consider prophylactic cholecystectomy.
  - Cholecystectomy can be postponed until recurrent symptoms are seen.
  - The risk of **recurrent symptoms is 30–50% per year;** the risk of **complications is 1–2% per year.**
- **Cholecystitis:**
  - **Antibiotics can be withheld** in the setting of **mild and uncomplicated disease.**
  - **IV antibiotics:** Provide coverage of gram-⊖ enteric bacteria and enterococcus with antibiotics such as ampicillin and gentamicin (or ampicillin/sulbactam if the patient is ill).
  - Bowel rest.
  - Cholecystectomy should be performed after symptom resolution but prior to discharge.

Complications

- **Gangrenous cholecystitis:** The most common complication of cholecystitis (affects up to 20%), particularly in diabetics and the elderly. Patients appear septic.
- **Emphysematous cholecystitis:** 2° infection of the gallbladder with gas-forming organisms. More common in diabetics and the elderly; associated with high mortality. Gangrene and perforation may follow.
- **Cholecystenteric fistula:** Uncommon. Stone erodes through the gallbladder into the duodenum. Large stones (> 2.5 cm) can cause small bowel obstruction **(gallstone ileus).**
- **Mirizzi's syndrome:** Common bile duct obstruction by an inflamed impacted cystic duct. Uncommon.
- **Gallbladder hydrops.**
- **Porcelain gallbladder:** Intramural calcification. Associated with an ↑ risk of gallbladder cancer; cholecystectomy is indicated.

Choledocholithiasis and Cholangitis

Choledocholithiasis is defined as stones in the common bile duct. Cholangitis can be defined as biliary tree obstruction and subsequent suppurative infection.

Symptoms

- **Choledocholithiasis:** Similar to cholelithiasis, except **jaundice is more common in choledocholithiasis.** Other symptoms include biliary colic (crampy, wavelike RUQ pain), abdominal bloating, and dyspepsia. May be asymptomatic.
- **Cholangitis:** Similar to cholecystitis but frequently more severe, presenting with fever, jaundice, and RUQ pain (Charcot's triad). May also include mental status changes and hypotension (Reynolds' pentad).

Exam

- **Choledocholithiasis:** Exam is normal or reveals mild RUQ tenderness along with jaundice.
- **Cholangitis:**
  - Fever and RUQ tenderness with peritoneal signs (90%), jaundice (> 80%), hypotension, and altered mental status (15%).
  - **Charcot's triad (RUQ pain, jaundice, fever):** Present in only 70% of patients.
  - **Reynolds' pentad (Charcot's triad plus hypotension and altered mental status):** Points to impending septic shock.

Charcot's triad = RUQ pain, jaundice, and fever/chills. Reynolds' pentad = Charcot's triad plus hypotension and altered mental status.

Differential

- **Choledocholithiasis:** Mass lesions (e.g., pancreatic and ampullary carcinoma, cholangiocarcinoma, bulky lymphadenopathy), parasitic infection (e.g., ascariasis), AIDS cholangiopathy, 1° sclerosing cholangitis, recurrent pyogenic cholangitis.
- **Cholangitis:** Perforated peptic ulcer, hepatitis, acute pancreatitis, appendicitis, hepatic abscess, diverticulitis, right-sided pneumonia.

Diagnosis

- **Choledocholithiasis:**
  - **Labs:** No leukocytosis; elevated total bilirubin (> 2 mg/dL), transaminases (2–4 times normal), and alkaline phosphatase.
  - **RUQ ultrasound:** Has low sensitivity (< 50%).
  - **CT:** Has higher sensitivity than RUQ ultrasound.
- **Cholangitis:**
  - **Labs:** Leukocytosis with neutrophil predominance; elevated total bilirubin (> 2 mg/dL), transaminases (> 2–4 times normal), alkaline phosphatase, and amylase; bacteremia.
  - **RUQ ultrasound:** Shows dilation of the common bile duct and cholelithiasis. Less likely to visualize choledocholithiasis.
  - **ERCP:** Perform < 48 hours after presentation, ideally after IV antibiotics and fluids. Requires sedation. Both diagnostic and therapeutic.
  - **MRCP:** Noninvasive and sensitive for diagnosis.
  - **EUS:** The most sensitive diagnostic study, but not readily available.
  - **Percutaneous transhepatic cholangiography (PTHC):** An alternative if ERCP is unavailable, unsafe, or unsuccessful. Does not require sedation.

Treatment

- **Choledocholithiasis:**
  - **High suspicion** (total bilirubin > 2, alkaline phosphatase > 150, elevated AST/ALT): ERCP with sphincterotomy/stone removal prior to surgery followed by laparoscopic cholecystectomy.
  - **Intermediate suspicion:** Intraoperative cholangiography, MRCP, or EUS. If MRCP or EUS is ⊕ for choledocholithiasis, proceed to ERCP.
- **Cholangitis:**
  - **Broad-spectrum IV antibiotics:** IV ampicillin/sulbactam (Unasyn) or ticarcillin/clavulanate (Timentin). If the patient is responsive to antibiotics, biliary decompression can be elective; otherwise, it is indicated emergently.
  - **ERCP:** Biliary decompression and drainage (sphincterotomy, stone removal, biliary stenting).
  - **PTHC:** A temporary alternative to ERCP that allows for biliary decompression (stenting and drainage).
  - Cholecystectomy after recovery for cholangitis due to gallstones.
  - **Recurrent pyogenic cholangitis:** Affects Southeast Asians between 20 and 40 years of age; characterized by pigmented intrahepatic bile duct stones, biliary strictures, and repeated cholangitis. Treatment includes stenting and drainage. Often isolated to the left lobe of the liver; resection may be considered.

Complications

Gallstone pancreatitis, gram-⊖ sepsis, intrahepatic abscesses.

AIDS Cholangiopathy

An opportunistic biliary infection caused by CMV, *Cryptosporidium*, or *Microsporidium*. CD4 is usually < 200/mL.

Symptoms/Exam

Presents with RUQ pain/tenderness, fever, hepatomegaly, and diarrhea. Jaundice is uncommon.

Differential

Biliary stones, cholecystitis, 1° sclerosing cholangitis.

Diagnosis

- **Labs:** Markedly elevated alkaline phosphatase.
- **ERCP:** Intra- and/or extrahepatic biliary stricturing; papillary stenosis.
- **Aspiration and culture of bile are key to diagnosis.**

Treatment

- ERCP with sphincterotomy and biliary stenting.
- IV antibiotics based on bile cultures.
- Treat underlying immunosuppression/HIV.

1° Sclerosing Cholangitis

A chronic cholestatic disease characterized by fibrosing inflammation of the intrahepatic and extrahepatic biliary system **without an identifiable cause.**

Seventy-five percent of patients with 1° sclerosing cholangitis have IBD, but the reverse is the case for only a small subset of IBD patients.

Most common among middle-aged males; median survival from the time of diagnosis is 12 years. Commonly associated with **IBD** (more frequently ulcerative colitis than Crohn's) and, to a lesser extent, with other autoimmune disorders (celiac sprue, sarcoidosis, Sjögren's syndrome, SLE, autoimmune hepatitis). Also associated with an ↑ risk of **cholangiocarcinoma.**

Symptoms/Exam

- Presents with gradual onset of fatigue and severe pruritus followed by jaundice and weight loss. Fever occurs with recurrent cholangitis.
- Exam reveals jaundice, hepatosplenomegaly, hyperpigmentation, xanthomas, excoriations, and stigmata of fat-soluble vitamin deficiency.

Differential

2° sclerosing cholangitis—biliary stones, congenital anomalies, infections, AIDS cholangiopathy, recurrent pyogenic cholangitis.

Diagnosis

1° sclerosing cholangitis is diagnosed by ERCP and shows a "beads on a string" appearance involving both intra- and extrahepatic bile ducts.

- Maintain a high clinical suspicion in patients with IBD, as the **diagnosis of IBD typically precedes that of 1° sclerosing cholangitis.** Diagnosis can be confirmed only by ERCP. Magnetic resonance cholangiography (MRC) is less sensitive and less specific.
- **Labs:** Look for a **cholestatic pattern** consisting of alkaline phosphatase > 1.5 times normal for six months plus a modest ↑ in bilirubin and transaminases.
- **Autoantibodies:** The sensitivity of **p-ANCA** is 70%; that of ANA is 25%.
- **Liver biopsy:** Look for pericholangitis and the classic "**onion skin**" periductal fibrosis, focal proliferation and obliteration of bile ducts, cholestasis, and copper deposition.
- **ERCP:** Shows irregularity of the intra- and extrahepatic biliary tree, classically with a "**beads on a string**" appearance. 2° causes of sclerosing cholangitis usually have **only** extrahepatic bile duct involvement except with recurrent pyogenic cholangitis (intrahepatic biliary dilation and stones).

Treatment

- Focus on symptom control and on the prevention and management of complications. Medical therapy to prevent or delay disease progression is largely ineffective.
- **Symptom control:** Treat pruritus (cholestyramine, ursodiol, phenobarbital, rifampin).
- **Medical therapy:** Immunosuppression (corticosteroids, cyclosporine, azathioprine, methotrexate), antifibrogenics (colchicine), others (penicillamine, ursodeoxycholic acid). **The natural history of 1° sclerosing cholangitis is not significantly changed by current medical therapy.**
- **Liver transplantation:** The treatment of choice for end-stage liver failure; five-year survival is 75%.

Complications

- **Steatorrhea/fat-soluble vitamin deficiency:** Treat with bile acids, digestive enzymes, and vitamins A, D, E, and K.
- **Metabolic bone disease:** Treat with Ca^{++} and bisphosphonates.
- **Recurrent bacterial cholangitis and dominant strictures:** Treat with antibiotics and biliary stent and drainage.
- **Other:** Biliary stones, **cholangiocarcinoma,** portal hypertension, end-stage liver disease.

1° Biliary Cirrhosis

A chronic cholestatic disease that primarily affects **middle-aged women of all races.** Prevalence is 19–240 cases in one million; 90–95% are women. Age at onset is 30–70; often associated with **autoimmune** disorders such as Sjögren's, RA, thyroid disease, celiac sprue, and CREST syndrome.

Symptoms

May be asymptomatic (50–60% at the time of diagnosis) or present with fatigue, **severe and intractable pruritus prior to jaundice,** and malabsorptive diarrhea. Commonly associated with Sjögren's syndrome, arthritis, and Raynaud's phenomenon.

Exam

- Exam reveals hepatomegaly, splenomegaly, skin pigmentation, excoriations (from pruritus), xanthelasma, and xanthomas. Kayser-Fleischer rings are rare (result from copper retention, as in Wilson's disease).
- Late findings include jaundice and the stigmata of cirrhosis.

Differential

Biliary obstruction (stones, benign or malignant mass), autoimmune hepatitis, 1° and 2° sclerosing cholangitis, drug-induced cholestasis (phenothiazines, steroids, TMP-SMX, tolbutamide), infiltrative diseases (sarcoidosis, lymphoma, TB).

Diagnosis

- Suspect in the setting of unexplained cholestasis or elevated serum alkaline phosphatase.
- **Labs:**
  - **Cholestatic pattern:** Look for an alkaline phosphatase level > 3–4 times normal, an elevated GGT, and a slight ↑ in transaminases. Serum bilirubin is normal early in disease but is elevated later in the disease course.
  - **Serum autoantibodies: Antimitochondrial antibodies (AMA) are detected in 95% of cases.** ANA (70%), SMA (66%), RF (70%), and antithyroid antibodies (40%) are also seen.
  - **Other: ↑ serum IgM,** total cholesterol, HDL, ceruloplasmin, and urinary copper.
- **Imaging:** Ultrasound is initially useful for excluding biliary tract obstruction; MRI/CT can show nonprogressive periportal adenopathy. Signs of portal hypertension are usually absent at the time of diagnosis.
- **Liver biopsy:** Important for diagnosis, staging, and prognosis. The pathognomonic finding is the **"florid" duct lesion** (duct degeneration with periductular granulomatous inflammation), which is uncommon.
- **ERCP:** Needed only to exclude 1° and 2° sclerosing cholangitis.

Antimitochondrial antibody (present in 95% of patients) and elevated serum IgM are the best laboratory diagnostic tools for 1° biliary cirrhosis.

Treatment

- Disease-modifying therapy has limited efficacy. Symptom control and the prevention and treatment of complications are most important in management.
- **Ursodeoxycholic acid:** The only FDA-approved disease-modifying agent; promotes endogenous bile acid secretion and may also have immunologic

effects. Give 13–15 mg/kg/day. Colchicine and methotrexate are less commonly used.
- **Liver transplantation:** The most effective treatment for decompensated 1° biliary cirrhosis. Five-year survival is 85%; rates of recurrent 1° biliary cirrhosis at 3 and 10 years are 15% and 30%, respectively. The need for liver transplantation can be predicted by the Mayo Clinic model (based on patient age, total bilirubin, PT, and serum albumin).

Complications

- **Malabsorption:** Treat with fat-soluble vitamins (A, D, E, and K) and pancreatic enzymes.
- **Metabolic bone disease:** Osteopenia (affects 33%) and osteoporosis (affects 10%). Manage with calcium, vitamin D, and bisphosphonates.
- **Cirrhosis:** Late ascites, encephalopathy, portal hypertension.

HEPATITIS

Hepatitis A (HAV) and Hepatitis E (HEV)

Spread by fecal-oral transmission; cause acute **(not chronic)** hepatitis. More common in developing countries. The annual incidence of HAV in the United States is 70,000, whereas **HEV is rare and limited to travelers of endemic regions** (Southeast and Central Asia, the Middle East, Northern Africa, and, to a lesser extent, Mexico). HAV is typically asymptomatic, benign, and self-limited in children but can range from mild to severe acute hepatitis in adults. The rate of fatal acute liver failure from HAV is < 4% in patients < 49 years of age but can be as high as 17% in those > 49 years of age. **HEV is more severe** than HAV, **particularly in pregnancy,** a setting in which **mortality is approximately 20%.**

Symptoms

- Presents with flulike illness, malaise, anorexia, weakness, fever, RUQ pain, jaundice, and pruritus. Children are typically asymptomatic.
- Atypical presentations include acute liver failure, cholestasis (prolonged, deep jaundice), and relapsing disease (2–18 weeks after initial presentation).
- Figure 7.4 illustrates the typical course of HAV.

Exam

Jaundice, RUQ tenderness.

Differential

Acute HBV or, less frequently, HCV; mononucleosis, CMV, HSV, drug-induced hepatitis, acute alcoholic hepatitis, autoimmune hepatitis.

HAV and HEV cause variably severe acute hepatitis but do not cause chronic hepatitis.

Diagnosis

- **History:** Inquire about ill contacts, substandard water supply, travel (HEV), and contaminated food **(shellfish and green onions).**
- **Labs:**
  - **HAV:** Anti-HAV IgM (acute infection); anti-HAV IgG (prior exposure, vaccination); anti-HAV total measures IgM and IgG (acute infection, prior exposure, vaccination).
  - **HEV:** Anti-HEV IgM (acute infection); anti-HEV (prior exposure).

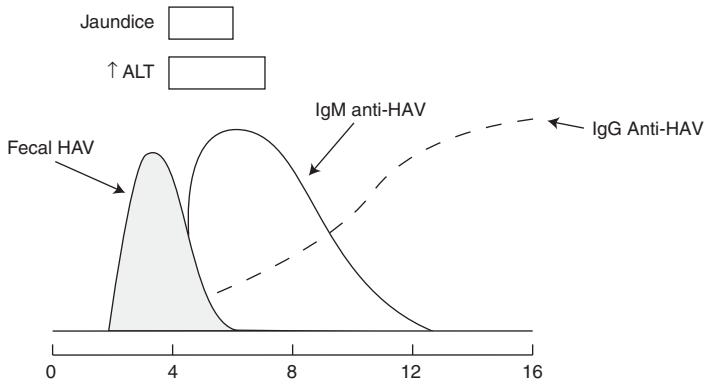


FIGURE 7.4. Typical course of acute HAV.

(Reproduced, with permission, from Kasper DL et al. *Harrison's Principles of Internal Medicine*, 16th ed. New York: McGraw-Hill, 2005: 1822.)

TREATMENT

- No specific drug treatment is available for HAV or HEV.
- Supportive care.
- Consider early delivery for pregnant women with HEV (no proven benefit).

PREVENTION

- **Vaccination:** The HAV vaccine is safe and effective, but no vaccine for HEV is currently available.
- **Indications for HAV vaccine:** Travelers to endemic regions, men who have sex with men, IV drug users, Native Americans, those with chronic liver disease (**all HCV** ⊕), food handlers, day care center workers.
- **HAV immunoglobulin:** Effective for postexposure prophylaxis. For those traveling immediately to endemic areas, supplement with the first HAV vaccine shot.

Hepatocellular carcinoma can occur before cirrhosis from HBV, but this is not true of HCV.

Hepatitis B (HBV) and Hepatitis D (HDV)

Some 400 million people worldwide have chronic HBV, including > 1 million in the United States. Transmission can be perinatal (the most common cause worldwide), sexual, or percutaneous. Age at infection is **inversely related** to the risk of chronic infection. Of all patients with chronic HBV, 15–20% develop cirrhosis and 10–15% develop hepatocellular carcinoma. **HDV infection requires HBV coinfection.** In the United States, HDV is found primarily among IV drug users and hemophiliacs.

SYMPTOMS

- **Acute HBV:** Presents with flulike illness, malaise, weakness, low-grade fever, serum sickness–like symptoms (arthritis, urticaria, angioedema), and RUQ pain followed by jaundice (see Figure 7.5).
- **Chronic HBV:** Can be asymptomatic.
- **Extrahepatic manifestations:** Serum sickness, polyarteritis nodosa, glomerulonephritis.

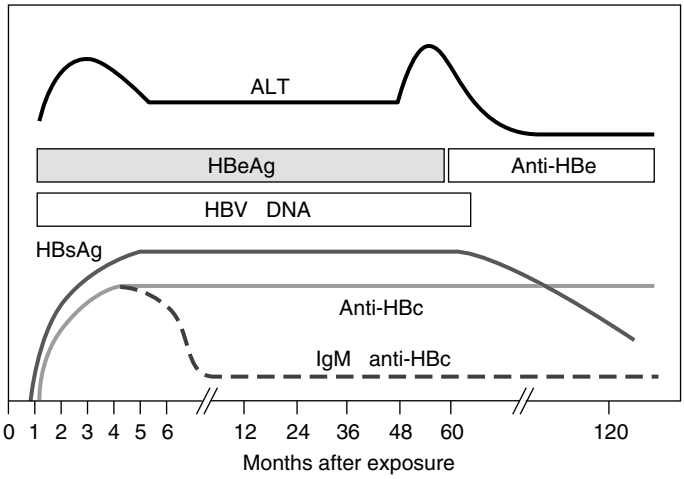


FIGURE 7.5. Typical course of acute HBV.

(Reproduced, with permission, from Kasper DL et al. *Harrison's Principles of Internal Medicine*, 16th ed. New York: McGraw-Hill, 2005: 1825.)

EXAM

- **Acute:** Icteric sclera, arthritis, RUQ tenderness.
- **Chronic:** Stigmata of cirrhosis (spider angiomata, palmar erythema, gynecomastia).

DIFFERENTIAL

- **Other acute viral diseases:** HAV, HCV, mononucleosis, CMV, HSV.
- Spirochetal (**leptospirosis,** syphilis) and rickettsial disease **(Q fever).**
- **Other chronic liver diseases:** Autoimmune disease, hemochromatosis, α_1-antitrypsin deficiency, Wilson's disease, alcoholic/nonalcoholic steatohepatitis.

DIAGNOSIS

- **HBsAg:** Surface antigen indicates **active** infection (see Table 7.18).
- **Anti-HBs:** Antibody to HBsAg indicates past viral infection or immunization.
- **Anti-HBc:** IgM is an early marker of infection; IgG is the best marker for prior HBV exposure. IgM may also become detectable in reactivation of HBV.
- **HBeAg:** Proportional to the quantity of intact virus and therefore infectivity. Some HBV variants (called **precore mutants**) cannot make HBeAg. Precore mutants have lower spontaneous remission, are less responsive to treatment, and are associated with a higher risk of cirrhosis and hepatocellular carcinoma. Precore mutants are diagnosed by their high HBV DNA and ⊖ HBeAg.
- **Anti-HDV:** Indicates past or present HDV infection. **Does not indicate immunity.**
- **HBV DNA:** Indicates active replication. A level of $> 10^5$ copies/mL is considered active; $> 10^2$ copies/mL are detectable by new assays.
- **Liver biopsy:** Not routinely needed prior to treatment. Indicated if the diagnosis is in question or to determine the degree of inflammation or fibrosis/cirrhosis.

TABLE 7.18. Serologic Patterns in HBV Infection and Their Interpretation

HBsAg	Anti-HBs	Anti-HBc	HBeAg	Anti-HBe	Interpretation
+	–	IgM	+	–	Acute hepatitis B.
+	–	IgG[a]	+	–	Chronic hepatitis B with active viral replication.
+	–	IgG	–	+	Chronic hepatitis B with low viral replication.
+	+	IgG	+ or –	+ or –	Chronic hepatitis B with heterotypic anti-HBs (about 10% of cases).
–	–	IgM	+ or –	–	Acute hepatitis B.
–	+	–	–	–	Vaccination (immunity).
–	–	IgG	–	–	False ⊕; less commonly, infection in remote past.

[a] Low levels of IgM anti-HBc may also be detected.

Reproduced, with permission, from Tierney LM et al. *Current Medical Diagnosis & Treatment,* 44th ed. New York: McGraw-Hill, 2005: 634.

Treatment

- **Acute exposure/needlestick prophylaxis:** The CDC recommends that hepatitis B immune globulin (HBIG) be given **within 24 hours along with vaccine** if the patient was not previously immunized.
- **Pegylated interferon-α_{2a}:** Given SQ; associated with many side effects (e.g., constitutional, psychiatric, bone marrow toxicity, flare of autoimmune disease, hepatic decompensation). Contraindicated in cirrhosis. The best responses to treatment are obtained with active hepatic inflammation (high ALT) and low HBV DNA levels.
- **Lamivudine:** Given PO. Well tolerated, but resistance may develop.
- **Adefovir:** Given PO. Well tolerated and may be used to treat lamivudine-resistant virus; has lower rates of resistance than lamivudine. Associated with renal insufficiency.
- **Newer antivirals:** Entecavir, telbivudine, emtricitabine/tenofovir (used for HIV coinfection).
- Treat HDV by treating HBV.
- **HBV cirrhosis:** Indefinite treatment with an antiviral agent.
- **Liver transplantation:** The treatment of choice for decompensated cirrhosis.

Needlestick transmission rates follow the rule of 3's: HBV 30%, HCV 3%, HIV 0.3%.

Hepatitis C (HCV)

Transmitted by percutaneous or mucosal blood exposure. Risk factors include blood transfusions before 1992, IV drug use, and occupational exposure (needlesticks). Spontaneous resolution occurs in 15–45% of patients, with the

Both HCV and HBV can cause cryoglobulinemia and glomerulonephritis.

highest rates of resolution in children and young women. Chronic infection occurs in the remainder of patients. Cirrhosis occurs in 20% within 20–30 years. The risk of carcinoma is 1–4% per year after cirrhosis.

Symptoms

- **Acute HCV:** Presents with flulike illness, malaise, weakness, low-grade fever, myalgias, and RUQ pain followed by jaundice. Only 30% of patients are symptomatic in acute disease.
- **Chronic HCV:** Often asymptomatic, or may present with cryoglobulinemia associated with a vasculitic skin rash **(leukocytoclastic vasculitis), arthralgias,** sicca syndrome, and **glomerulonephritis.** In the setting of cirrhosis, presents with fatigue, muscle wasting, dependent edema, and easy bruising.

Exam

- **Acute:** Icterus; RUQ tenderness.
- **Chronic:** Stigmata of cirrhosis (spider angiomata, palmar erythema, gynecomastia, ascites).

Differential

- **Other acute viral diseases:** HAV, HBV, mononucleosis, CMV, HSV.
- Spirochetal (**leptospirosis,** syphilis) and rickettsial disease **(Q fever).**
- **Other chronic liver diseases:** HBV, hemochromatosis, α_1-antitrypsin deficiency, Wilson's disease, nonalcoholic steatohepatitis, autoimmune hepatitis.

Diagnosis

- **Screening:** HCV antibody ($\oplus$ 4–6 weeks after infection), qualitative PCR (in acute infection; can be $\oplus$ 1–2 weeks after infection). Screen patients with risk factors or persistently elevated transaminases.
- **Confirmatory:** Qualitative PCR or recombinant immunoblot assay (RIBA).
- **Prognostic:** Liver biopsy.

Treatment

- **Regimen:** Treat with SQ interferon (pegylated or standard) and PO ribavirin × 24 weeks (non–genotype 1) or × 48 weeks (genotype 1). Check quantitative RNA at 12 weeks; if there is less than a 2-log drop, consider stopping treatment.
  - **Predictive:** Quantitative PCR (a low viral load indicates a better treatment response). Genotypes 2 and 3 are associated with a better treatment response than genotype 1.
  - **Indications for treatment:** Age 18–60, HCV viremia, elevated aminotransferase levels.
  - **Contraindications:** Psychosis, severe depression, symptomatic coronary or cerebrovascular disease, **decompensated cirrhosis,** uncontrolled seizures, severe bone marrow insufficiency, pregnancy or inability to use birth control, retinopathy, autoimmune disease.
- **Acute infection/needlestick prophylaxis:** Currently not recommended.
- **Chronic HCV:** Treatment is curative in up to 80% of genotype 2/3 cases but is < 50% for genotype 1.

- **Cryoglobulinemia:** Treatment of acute flares includes plasmapheresis +/– steroids. Long-term effectiveness is seen with interferon plus ribavirin, and data on rituximab appear promising.

Autoimmune Hepatitis

Characterized by hypergammaglobulinemia, periportal hepatitis, and autoimmune markers. Typically chronic, but 25% of cases are characterized by acute onset and rare fulminant hepatic failure. Prevalence depends on gender and ethnicity; women are affected three times more often than men. Incidence among Northern American and European Caucasians is 1 in 100,000. Less common in non-Caucasians; in Japan, incidence is 0.01 in 100,000. The risk of cirrhosis is 17–82% at five years. The main prognostic factors are severity of inflammation/fibrosis on liver biopsy and HLA type. Associated with other autoimmune diseases.

Advanced liver disease is a poor prognostic sign for treatment response but not a contraindication to the treatment of autoimmune hepatitis.

Symptoms

Fatigue (85%), jaundice, RUQ pain. **Pruritus suggests an alternate diagnosis.**

Exam

- Hepatomegaly, jaundice, splenomegaly (with or without cirrhosis).
- **Acute:** Icteric sclera, arthritis, RUQ tenderness.
- **Chronic:** Stigmata of cirrhosis (spider angiomata, palmar erythema, gynecomastia, ascites).

Differential

Wilson's disease, viral hepatitis (HBV, HCV), α_1-antitrypsin deficiency, hemochromatosis, drug-induced hepatitis, alcoholic and nonalcoholic steatohepatitis.

The decision to treat autoimmune hepatitis is dependent on the severity of hepatic inflammation, not hepatic dysfunction.

Diagnosis

- **International Autoimmune Hepatitis Group (IAHG) criteria:** A definite or probable diagnosis of autoimmune hepatitis is made according to the following criteria: (1) magnitude of hypergammaglobulinemia, (2) autoantibody expression, and (3) certainty of exclusion of other diagnoses. (see Table 7.19).
- **Extrahepatic associations:** Present in 10–50% of cases.
  - **Frequent:** Autoimmune thyroid disease, ulcerative colitis, synovitis.
  - **Uncommon:** RA, DM, CREST syndrome, vitiligo, alopecia.

Autoimmune hepatitis is associated with a high rate of anti-HCV false positives, so the diagnosis must be confirmed by checking a PCR assay for HCV viremia.

Treatment

- **Treatment indications:** Active symptoms, biochemical markers (elevated ALT, AST, or gamma globulin), histologic markers (periportal hepatitis, bridging necrosis). The best treatment responses are obtained in the setting of active hepatic inflammation (high ALT).
- **Relative contraindications:** Asymptomatic patients with mild biochemical inflammation (AST < 3 times normal); cirrhosis without histologic necroinflammation.
- **Prednisone monotherapy:** Give 60 mg QD; tapering schedule varies and is controversial.

TABLE 7.19. Differential Diagnosis of Immunologic Disease of the Liver[a]

Disease	Gender	LFTs	Other Labs	Diagnosis	Association	Treatment
1° sclerosing cholangitis	M > F	AP > 1.5 times ULN.	p-ANCA.	ERCP reveals "beads on a string."	Ulcerative colitis in 70%.	Liver transplant.
1° biliary cirrhosis	F >> M	AP > 3-4 times ULN; total bilirubin elevated.	AMA (95%), IgM.	Biopsy reveals paucity of bile ducts and granulomatous cholangitis.	Autoimmune (thyroiditis, CREST, sicca in 50%).	Ursodeoxycholic acid → liver transplant.
Autoimmune hepatitis	F > M	Elevated AST/ ALT.	ANA, ASMA, anti-LKM antibody, elevated IgG.	Biopsy reveals interface hepatitis and plasma cell infiltrate.		Prednisone, azathioprine.

[a] ULN = upper limit of normal; AP = alkaline phosphatase; ASMA = anti–smooth muscle antibody; anti-LKM antibody = anti–liver/kidney microsome antibody.

- **Steroid-sparing therapy:** Lower-dose prednisone (30 mg QD); then taper over 4–6 weeks in combination with azathioprine 50–75 mg QD.
- **Treatment end points:** Defined at the end of steroid taper.
  - **Remission:** No symptoms; AST < 2 times normal; normalization of bilirubin and gamma globulin; biopsy with minimal inflammation.
  - **Treatment failure:** Progressive symptoms; AST or bilirubin > 67% of pretreatment values.
- **Liver transplantation:** Should be considered in the presence of decompensated liver disease, severe inflammation, and necrosis on liver biopsy with treatment failure or no biochemical improvement during the first two weeks of therapy.

Drug-Induced Hepatitis

Elevated serum LDH suggests drug-induced hepatitis over viral hepatitis.

Ranges from subclinical disease with abnormal LFTs to fulminant hepatic failure. Accounts for 40% of acute hepatitis cases in U.S. adults > 50 years of age; for 25% of cases of fulminant hepatic failure; and for 5% of jaundice cases in hospitalized patients. Drug-induced hepatitis can be characterized as intrinsic (direct toxic effect) or idiosyncratic (immunologically mediated injury) and as necroinflammatory (hepatocellular), cholestatic, or mixed. Risk factors include advanced age, female gender, use of an increasing number of prescription drugs, underlying liver disease, renal insufficiency, and poor nutrition.

Symptoms/Exam

May present with constitutional symptoms, jaundice, RUQ pain, and pruritus. Often asymptomatic.

Differential

Viral hepatitis, ischemic hepatitis, Wilson's disease, α_1-antitrypsin deficiency, hemochromatosis, nonalcoholic steatohepatitis.

When ALT > 1000, consider drug/toxic, ischemic, congestive, and viral hepatitis.

Diagnosis

Diagnose as follows (see also Table 7.20):

- **Exclude other causes:** Obtain a liver ultrasound with duplex and hepatitis serologies.
- **History:** Take a detailed drug history that includes dosage, duration, and use of concurrent OTC, alternative, and recreational drugs.
- **Labs: Elevated serum LDH;** transaminases typically range from 2–4 times normal (subclinical) to 10–100 times normal.
- **Drug withdrawal:** Most drug-induced hepatitis will improve with discontinuation of the toxic agent.
- **Liver biopsy:** Most useful for **excluding** other etiologies. Eosinophilic inflammatory infiltrate suggests drug-induced hepatitis; histologic patterns can implicate drug classes.

Treatment

- Discontinue the implicated drug.
- Supportive care.
- **Liver transplantation:** Drug-induced fulminant hepatic failure has a low likelihood of spontaneous recovery.

Acetaminophen Toxicity

- The most common cause of drug-induced hepatitis and drug-induced fulminant hepatic failure. The toxic dose is > 4 g in nonalcoholics and > 2 g in alcoholics, but much higher doses are frequently associated with fulminant hepatic failure.

TABLE 7.20. Characterization of Drug-Induced Hepatitis

	Intrinsic	Idiosyncratic
Relation to dosage	Dose dependent.	Dose independent.
Frequency	More common.	Less common.
Onset	Hours to days after starting drug.	Weeks to months after starting drug.
Toxicity	Direct toxic effect.	Immune-mediated toxicity.
Prognosis	Good.	Poor.
Implicated drugs	Acetaminophen, carbon tetrachloride, alcohol, *Amanita phalloides,* aflatoxins.	NSAIDs, INH, sulfonamides, valproic acid, phenytoin, ketoconazole.

Acetaminophen in modest doses (e.g., < 2 g/day) is much safer than NSAIDs for patients with cirrhosis.

- **Dx:**
  - Maintain a high clinical suspicion with marked elevation of transaminases.
  - **Acetaminophen level:** Predict toxicity with the Rumack-Matthew nomogram (assesses acetaminophen concentration, time after ingestion, and risk for toxicity). Elevated levels precede transaminitis.
  - **Prognostic factors predicting death or need for liver transplant:** Arterial blood pH < 7.3 **or** hepatic encephalopathy grade 3 **or** 4 with INR > 6.5 and serum creatinine > 3.4 mg/dL.
- **Tx:**
  - N-acetylcysteine 140 mg/kg PO; then 70 mg/kg q 4 h × 17 doses.
  - Liver transplantation.

Alcoholic Liver Disease

Alcoholic hepatitis is not a prerequisite to alcoholic cirrhosis.

Alcohol accounts for 100,000 deaths per year in the United States, and 20% of these deaths are related to alcoholic liver disease, which carries a risk of progressive liver disease. Patients at risk include those exceeding the critical intake threshold (80 g/day in men and 20 g/day in women), females, blacks, those with poor nutritional status, and those with HBV or HCV infection. The spectrum of disease includes fatty liver (steatosis), acute alcoholic hepatitis, and alcoholic **(Laënnec's)** cirrhosis.

Symptoms

- **Steatosis:** Asymptomatic or mild RUQ pain.
- **Acute alcoholic hepatitis:** Fever, anorexia, RUQ pain, jaundice, nausea, vomiting.
- **Alcoholic cirrhosis:** Patients may be asymptomatic or may present with anorexia, fatigue, and ↓ libido. Associated with an ↑ risk of variceal hemorrhage.

Exam

- Exam may reveal hepatomegaly, splenomegaly, cachexia, jaundice, spider telangiectasias, **Dupuytren's contractures,** parotid gland enlargement, gynecomastia, and testicular atrophy.
- There are no symptoms specific to alcoholic liver disease.

Differential

Nonalcoholic steatohepatitis, nonalcoholic fatty liver disease, autoimmune hepatitis, hemochromatosis, α_1-antitrypsin deficiency, Wilson's disease, viral hepatitis, toxic or drug-induced hepatitis.

Diagnosis

- **History of habitual alcohol consumption:** The **CAGE questionnaire** is sensitive for alcohol abuse.
- **Alcoholic steatosis:** Modest elevation of **AST > ALT in a 2:1 ratio;** liver biopsy shows small (microvesicular) and large (macrovesicular) fat droplets in the cytoplasm of hepatocytes.
- **Alcoholic hepatitis:** Marked leukocytosis, modest elevation of AST > ALT in a 2:1 ratio, and markedly elevated serum bilirubin. Liver biopsy shows steatosis, hepatocellular necrosis, **Mallory bodies** (eosinophilic hyaline deposits), ballooned hepatocytes, and **lobular PMN inflammatory infiltrate.**

- **Alcoholic cirrhosis:** Liver biopsy shows micro- or macronodular cirrhosis and perivenular fibrosis that is not usually seen in other types of cirrhosis.

Discriminant function (DF) measures the severity of alcoholic hepatitis. A DF > 32 predicts one-month mortality as high as 50%. DF = [4.6 × (patient's PT – control PT)] + serum bilirubin.

Treatment

- The mainstays of treatment are alcohol abstinence and improved nutrition. Social support (e.g., AA) and medical therapy (e.g., disulfiram, naltrexone) can assist with abstinence.
- **Alcoholic steatosis:** Can resolve with abstinence and improved nutrition.
- **Alcoholic hepatitis:**
  - **Corticosteroids: Improve survival** when discriminant function (DF) is > 32 **and** there are no contraindications (active GI bleeding, active infection, serum creatinine > 2.3). DF is a function of PT/INR and total bilirubin.
  - **Other therapies under study: Medium-chain triglycerides** and **pentoxifylline.** Pentoxifylline has anti-TNF effects but is less effective than corticosteroids when DF is > 32.
  - **Long-term therapy:** Antioxidants, S-adenosylmethionine (SAMe), silymarin, vitamins A and E.
- **Alcoholic cirrhosis:** Hepatic function can significantly improve with abstinence and improved nutrition.
- **Liver transplantation:** Often precluded by active or recent alcohol abuse or use. Recidivism rates are high. Most transplant centers require at least six months of documented abstinence prior to listing for liver transplant.

Alcoholic hepatitis can be treated with corticosteroids when DF > 32 ***and*** *there are no contraindications (active GI bleeding, active infection, serum creatinine > 2.3).*

Nonalcoholic Fatty Liver Disease

The spectrum of disease ranges from benign steatosis (fatty liver) to steatohepatitis (hepatic inflammation). Prevalence in the United States is 15–25%. Steatohepatitis is found in 8–20% of morbidly obese individuals independent of age. Disease is generally benign and indolent but can progress to cirrhosis in 15–20% of cases. Risk factors for severe disease include female gender, age > 45 years, body mass index (BMI) > 30, AST/ALT > 1, and type 2 DM.

Nonalcoholic fatty liver disease is the third most common cause of abnormal LFTs in adult outpatients after medication and alcohol.

Symptoms

Presents with fatigue, malaise, and, to a lesser extent, RUQ fullness or pain. Asymptomatic in > 50% of patients.

Exam

- Hepatomegaly is common, but examination may be limited in the obese.
- Stigmata of chronic liver disease.

Differential

- Alcoholic liver disease.
- **Nutrition:** TPN, kwashiorkor, rapid weight loss.
- **Drugs:** Estrogens, corticosteroids, chloroquine.
- **Metabolic:** Wilson's disease, abetalipoproteinemia.
- **Iatrogenic:** Weight reduction surgery with jejunoileal bypass, gastroplasty, or small bowel resection.

Diagnosis

Diagnose as follows:

- Exclude causes of liver disease, specifically alcoholic liver disease.

Normal LFTs do not exclude nonalcoholic fatty liver disease.

- **Aminotransaminases:**
  - Typically **ALT > AST** (× 2–4) **(vs. alcoholic liver disease, in which AST > ALT);** poor correlation with the presence and extent of inflammation. **A normal AST and ALT cannot exclude nonalcoholic fatty liver disease.**
  - **The AST/ALT ratio ↑ with severity of liver disease,** which is typical of cirrhosis of all etiologies.
- BMI is an independent predictor of the degree of hepatocellular fatty infiltration.
- Ultrasound or CT scan.
- Liver biopsy is the gold standard. The grade of inflammation and stage of fibrosis predict disease course and response to therapeutic intervention.

Treatment

- Gradual weight loss. Rapid weight loss may ↑ inflammation and fibrosis.
- Treat hyperlipidemia and diabetes.
- No FDA-approved therapy is available.
- Therapeutic agents under study include metformin, rosiglitazone, ursodeoxycholic acid,, and vitamin E.

Screen for hemochromatosis with fasting serum transferrin saturation (TS) and ferritin; TS > 45% with an elevated ferritin suggests but does not confirm the diagnosis.

METABOLIC LIVER DISEASE

Hereditary Hemochromatosis

An **autosomal-recessive** disease. Homozygote prevalence is 1 in 300 persons. The most common genetic disease in Northern Europeans; the Caucasian carrier rate is 1 in 10. Associated with a major mutation in chromosome 6, the ***HFE* gene.** Patients have a normal life expectancy if there is no cirrhosis and the patient is adherent to treatment; survival is lower if the patient has **cirrhosis at the time of diagnosis.** Cirrhosis with hereditary hemochromatosis carries a high risk of hepatocellular carcinoma (200 times that of the control population).

Symptoms

Arthritis (pseudogout), skin color change, RUQ pain, symptoms of chronic liver disease (fatigue, anorexia, muscle wasting), loss of libido, impotence and dysmenorrhea, heart failure, DM. Often asymptomatic (10–25%).

Suspect hemochromatosis with type 2 DM, degenerative arthritis, or unexplained hypogonadism, heart failure, or liver disease.

Exam

Hepatomegaly, skin hyperpigmentation (bronze skin), stigmata of chronic liver disease, hypogonadism.

Differential

- **Chronic liver diseases:** HBV, HCV, alcoholic liver disease, nonalcoholic fatty liver disease, Wilson's disease, α_1-antitrypsin deficiency, autoimmune hepatitis.
- **2° iron overload diseases:** Homozygous α-thalassemia; multiple previous blood transfusions.

Diagnosis

- Suspect hereditary hemochromatosis with an unexplained **high serum ferritin** or **iron saturation even with normal LFTs.**

- **Fasting serum transferrin saturation (TS) and ferritin:** If TS > 45% and ferritin is elevated, hereditary hemochromatosis is suggested; check *HFE* genotype. A TS < 45% and normal ferritin exclude hereditary hemochromatosis.
- ***HFE* genotyping:** Homozygote is diagnostic **only if** (1) age < 40 years, (2) ferritin < 1000, and (3) transaminases are normal. Otherwise, confirmation with liver biopsy is necessary.
- **Liver biopsy:** The best means of making a definitive diagnosis; a hepatic Prussian blue stain with **iron index > 1.9** is diagnostic. Also used for disease staging (influences prognosis; hepatocellular carcinoma screening is needed if the patient is cirrhotic).

Treatment

- Alcohol abstinence.
- Avoid high-dose vitamin C.
- **Phlebotomy:** Weekly or biweekly until serum ferritin < 50 ng/mL; then 3–4 times per year indefinitely.
- Screen first-degree family members.
- In the setting of cirrhosis, screen for hepatocellular carcinoma.
- Liver transplantation is appropriate for decompensated liver disease.

Complications

DM, restrictive cardiomyopathy, joint disease (chondrocalcinosis, degenerative arthritis, pseudogout), hepatocellular carcinoma, ↑ incidence of bacterial infections (especially *Vibrio*, *Yersinia*, and *Listeria* spp).

α_1-Antitrypsin Deficiency

α_1-antitrypsin protects tissues from protease-related degradation. The deficiency is encoded on chromosome 14 and has an **autosomal-codominant** transmission. The Z allele is the most common deficiency, particularly in those of Northern European descent. α_1-antitrypsin deficiency is severe when homozygous (e.g., PiZZ) and is intermediate when heterozygous (e.g., PiMZ). Liver disease can be seen in the neonatal period. The incidence of liver disease at ages 20, 50, and > 50 are 2%, 5%, and 15%, respectively, with males affected more often than females. There is a high incidence of hepatocellular carcinoma in those with cirrhosis. A high prevalence of HBV and HCV markers suggests synergistic liver injury.

Consider α_1-antitrypsin deficiency in any adult who presents with chronic hepatitis or cirrhosis of unclear etiology.

Symptoms/Exam

- Neonatal cholestasis, occult cirrhosis, shortness of breath/dyspnea on exertion, panniculitis.
- Exam reveals signs of cirrhosis (spider angiomata, palmar erythema, gynecomastia) and emphysema (clubbing, barrel chest).

α_1-antitrypsin deficiency is associated with bilateral basilar pulmonary emphysema.

Differential

- **Other metabolic liver diseases with childhood presentation:** Hereditary tyrosinemia, Gaucher's disease, glycogen storage disease, CF.
- **Chronic liver diseases:** HBV, HCV, hemochromatosis, Wilson's disease, autoimmune hepatitis, nonalcoholic fatty liver disease, alcohol.

Diagnosis

- **Extrahepatic manifestations:** Basilar and panacinar emphysema, pancreatic fibrosis, panniculitis.
- **Serum α_1-antitrypsin concentration:** For screening; α_1-antitrypsin is an acute-phase reactant. False-⊕ tests may be obtained with inflammation (even if PiZZ).
- **Serum α_1-antitrypsin phenotyping:** The screening and diagnostic test of choice.
- **Liver biopsy:** Characteristic eosinophilic α_1-antitrypsin globules are seen in the endoplasmic reticulum of periportal hepatocytes.

Treatment

- **Avoid cigarette smoking and alcohol; weight loss if the patient is obese.**
- Liver transplantation.

Wilson's Disease

The classic biochemical pattern of Wilson's disease consists of low alkaline phosphatase, marked hyperbilirubinemia, and modest aminotransaminase elevation (AST > ALT).

An uncommon **autosomal-recessive** disease. Usually presents between ages 3 and 40; associated with mutations in the *WD* gene on chromosome 13. ↓ biliary copper excretion results in toxic copper deposition in tissues.

Symptoms

- Presents with abnormal behavior, personality change, psychosis, tremor, dyskinesia, arthropathy (pseudogout), and jaundice.
- **Clinical presentation:** Can be acute, subacute, or chronic.
- **Organ involvement** (in descending order of frequency): Hepatic, neurologic, psychiatric, hematologic, renal (Fanconi's syndrome), other (ophthalmologic, cardiac, skeletal, endocrinologic, dermatologic).
- The mean age at onset of hepatic symptoms is 8–12 years.

Exam

- Exam reveals Kayser-Fleischer rings, icterus, slowed mentation, hypophonia, and tremor.
- Clinical stigmata of cirrhosis are associated with **chronic** disease.

Characteristics of Wilson's disease—

ABCD

Asterixis
Basal ganglia deterioration
Ceruloplasmin ↓
Cirrhosis
Copper ↑
Carcinoma (hepatocellular)
Choreiform movements
Dementia

Differential

- **Infiltrative diseases:** Hemochromatosis.
- **Chronic liver diseases:** HBV, HCV, hemochromatosis, α_1-antitrypsin deficiency, autoimmune hepatitis.
- **Copper overload diseases:** Hereditary aceruloplasminemia, idiopathic copper toxicosis, Indian childhood cirrhosis.

Diagnosis

- Suspect Wilson's disease in patients **3–40 years of age** with unexplained LFTs or liver disease associated with **neurologic or psychiatric changes, Kayser-Fleischer rings, hemolytic anemia,** and a ⊕ family history.
- **Liver biochemistry tests:** Show characteristically low alkaline phosphatase, marked hyperbilirubinemia, and modest aminotransaminase elevations (AST > ALT).
- **Ceruloplasmin (CP):** Typically **low in Wilson's disease,** but a low CP is both insensitive (15% of cases have normal CP, since CP is an acute-phase

reactant) and nonspecific (CP is also low in nephrotic syndrome, protein-losing enteropathy, and malabsorption).
- **Urinary copper excretion: High** if symptomatic (100–1000 μg/24 hours; level may indicate disease severity). Normal excretion is < 40 μg/24 hours.
- **Liver biopsy:** Shows high hepatic copper concentration (> 250 μg/g); may also be seen in 1° biliary cirrhosis, 1° sclerosing cholangitis, fibrosis, or cirrhosis.
- **Other: Serum copper concentration, slit-lamp exam.**

Treatment

- **D-penicillamine:** Improvement lags 6–12 months following treatment; maintenance is typically required.
- **Other:** Trientine, zinc, ammonium.
- **Liver transplantation:** For acute hepatic or medically refractory Wilson's disease; reverses metabolic defect and induces copper excretion.

ADVANCED LIVER DISEASE

Cirrhosis

The final common pathway of many liver diseases that cause hepatocellular injury and lead to fibrosis and nodular regeneration. Reversal may occur with treatment of some chronic liver diseases (e.g., HBV, HCV).

Symptoms

- Fatigue, anorexia, muscle wasting, loss of libido, impotence, dysmenorrhea.
- Decompensation associated with GI bleeding, encephalopathy (sleep-wake reversal, ↓ concentration), ascites.
- **Platypnea** (dyspnea induced by sitting upright and relieved by recumbency) and **orthodeoxia** (low Pa_{O_2} when sitting upright that is relieved by recumbency).

Exam

- **Stigmata of chronic liver disease:** Palmar erythema, spider telangiectasia.
- **Dupuytren's contractures,** gynecomastia, testicular atrophy, bilateral parotid enlargement, **Terry's nails** (white, obscure nails).
- **Portal hypertension: Caput medusae,** splenomegaly, ascites.
- **Hepatic encephalopathy: Fetor hepaticus,** asterixis, confusion.

Differential

- HCV, HBV, alcohol.
- Hemochromatosis.
- 1° sclerosing cholangitis, 1° biliary cirrhosis, Wilson's disease, α_1-antitrypsin deficiency, cryptogenic liver disease, nonalcoholic steatohepatitis, autoimmune hepatitis, vascular disease (Budd-Chiari, veno-occlusive, right heart failure).
- Drug toxicity (methotrexate, amiodarone, nitrofurantoin), other (sarcoidosis, schistosomiasis, hypervitaminosis A, CF, glycogen storage disease).

Diagnosis

Diagnose as follows (see also Tables 7.21 and 7.22):

TABLE 7.21. Child-Turcotte-Pugh Scoring

	1 Point	2 Points	3 Points
Ascites	Absent	Nontense	Tense
Encephalopathy	Absent	Grades 1–2	Grades 3–4
Bilirubin (mg/dL)	< 2.0	2–3	> 3.0
Albumin (mg/dL)	> 3.5	2.8–3.5	< 2.8
PT (seconds over normal)	1–3	4–6	> 6

- **Liver biopsy:** The gold standard; also useful in assessing etiology.
- Physical exam.
- **Labs:** Thrombocytopenia (splenic sequestration); elevated INR and low albumin (↓ hepatic synthetic function); elevated alkaline phosphatase, serum bilirubin, and GGT (cholestasis); normal or elevated transaminases.
- **Imaging:** Ultrasound with duplex (ascites, biliary dilation, hepatic masses, vascular patency), CT (more specific than ultrasound for cirrhosis and masses, portal hypertension), MRI (excellent specificity for hepatic masses).

Vaccination for HAV is indicated in al patients with chronic liver disease, including cirrhotics.

Treatment

- Avoid alcohol, iron supplements (except in iron deficiency), NSAIDs, and benzodiazepines; minimize narcotics; limit acetaminophen to < 2 g/day.
- Fluid restriction is unimportant (unless serum Na < 125), and protein restriction should not be recommended.
- Administer pneumococcal and influenza vaccines.
- Prophylactic measures are as follows:
  - **1° prophylaxis:** HAV and HBV vaccination; nonselective β-blockers for documented esophageal varices.
  - **2° prophylaxis:** Antibiotics for spontaneous bacterial peritonitis (SBP); esophageal variceal banding or nonselective β-blockers +/– long-acting nitrates. Patients typically show low adherence/tolerance to β-blockers/nitrates.
- Treat underlying disease.
- Consider screening for hepatocellular carcinoma with ultrasound and serum AFP every six months.

TABLE 7.22. Child-Turcotte-Pugh Classification

CTP Score	Child-Pugh Class	Three-Year Survival (%)
5–6	A	> 90
7–9	B	50–60
10–15	C	30

- Treat complications (see below).
- **Liver transplantation:** Refer to a transplant center if minimal listing criteria are met or if uncertainty exists about eligibility for transplant.

Refer to a liver transplant center when minimal listing criteria are present.

Complications

Hepatic encephalopathy, varices, ascites/SBP, hepatorenal syndrome, hepatopulmonary syndrome, hepatocellular carcinoma; portopulmonary syndrome.

Varices

Endoscopic variceal band ligation is the endoscopic treatment of choice for 2° prophylaxis of EVH.

- Esophageal variceal hemorrhage (EVH) accounts for one-third of all deaths in cirrhotics. **Mortality with each EVH episode is 30–50%.** Alcoholic cirrhotics have the highest risk.
- **Tx:**
  - **Acute variceal hemorrhage:** Large-bore IVs, resuscitation (goal hematocrit of 28%, platelets > 50, INR < 1.6), octreotide drip, empiric antibiotics, PPI, and early endoscopy. A hematocrit greater than 30% is associated with elevated portal pressures.
  - **Esophageal variceal bleeding prophylaxis:**
    - **1°:** Nonselective β-blockers (nadolol, propranolol).
    - **2°:** Endoscopic ablation (banding or sclerotherapy); nonselective β-blockers +/– long-acting nitrates; portocaval shunt (TIPS or surgical).
  - Gastric and rectal varices are not treatable endoscopically.
  - **Portal hypertensive gastropathy:** A common source of bleeding. Treat with portocaval shunt (TIPS or surgical) or liver transplant.

Ascites and Spontaneous Bacterial Peritonitis (SBP)

SAAG ≥ 1.1 g/dL is 96% accurate in detecting portal hypertension.

In the United States, > 80% of ascites cases are due to chronic liver disease (cirrhosis or alcoholic hepatitis). Some **10–30% of cirrhotics with ascites develop SBP every year.** Infection-related mortality is 10%, but the **overall in-hospital mortality rate is 30%.**

Symptoms/Exam

Characterized by shifting dullness, fluid wave, and bulging flanks (low sensitivity, moderate specificity). Imaging (ultrasound, CT) is superior to examination. **SBP is often asymptomatic,** but patients may have fever, abdominal pain, and sepsis.

For SBP treatment, the addition of IV albumin to IV antibiotics significantly ↓ renal impairment and mortality.

Differential

The serum-ascites albumin gradient (SAAG) is helpful (see Table 7.23).

Diagnosis

- **Diagnostic paracentesis:** Indicated in the presence of new-onset ascites, ascites present at hospital admission, and ascites with symptoms or signs of infection.
- **Analysis:**
  - **Routine: Cell count, culture, albumin, total protein.**
  - **Optional:** Glucose, LDH, amylase, Gram stain, cytology.
  - **Not useful:** pH, lactate.

TABLE 7.23. Significance of SAAG Values

High SAAG (≥ 1.1)	Low SAAG (< 1.1)
Cirrhosis, hepatocellular carcinoma	Peritoneal carcinomatosis
Alcoholic hepatitis	Peritoneal TB, SBP
Heart failure	Pancreatic
Vascular (Budd-Chiari, PVT)	Nephrotic syndrome
Myxedema	Bowel infarction
Fulminant hepatitis	Serositis

Ninety percent of cirrhotics presenting with ascites will respond to sodium restriction of < 2 g/day along with furosemide with spironolactone (at maximum doses of 160 mg and 400 mg, respectively).

- **SBP diagnosis: Ascites PMN > 250 cells/mL** or a single organism on culture. **The presence of multiple organisms on ascites culture suggests 2° peritonitis.**

Treatment

- **Ascites:**
  - Dietary sodium restriction (< 2 g/day); furosemide and spironolactone (give doses in a 4:10 ratio—e.g., 40 mg to 100 mg, 80 mg to 200 mg). Initiate fluid restriction only if serum Na < 125 mEq/dL.
  - Large-volume paracentesis, portocaval shunt (TIPS), liver transplantation.
- **SBP prophylaxis:** Fluoroquinolone or TMP-SMX. Indicated for cirrhotics hospitalized with GI bleed (three days), ascites with total protein < 1.5 g/dL (while hospitalized), or prior SBP (if the patient has ascites).
- **SBP treatment: Do not wait for culture results to begin treatment.** Give cefotaxime or ceftriaxone IV × 5 days and **IV albumin.**

Hepatic Encephalopathy

Hepatic encephalopathy is a clinical diagnosis. Diagnosis and treatment should not be based on blood ammonia levels.

Neuropsychiatric changes in the setting of liver disease constitute hepatic encephalopathy until proven otherwise. Look for precipitating factors, including infection, GI bleeding, dehydration, hypokalemia, constipation/ileus, hepatocellular carcinoma, dietary protein overload, CNS active drugs (narcotics, benzodiazepines, anticholinergics), uremia, hypoxia, hypoglycemia, and noncompliance with hepatic encephalopathy treatment.

Symptoms/Exam

Insomnia, sleep-wake reversal, personality change, confusion.

Diagnosis

Diagnosis is clinical. **Blood ammonia levels are rarely helpful.**

Treatment

- Correct precipitating factors and anticipate treatment-related adverse effects.
- Oral/NG tube or rectally administered lactulose (adverse effects include dehydration and hypokalemia); oral neomycin (adverse effects include ototoxicity and renal toxicity) or rifaximin; oral metronidazole (adverse effects include neuropathy).
- Zinc, short-term protein restriction, branched-chain amino acid–enriched diet.

Hepatorenal Syndrome

The prognosis is grave; **median survival is 10–14 days.** Two-month mortality is 90%.

Differential

Prerenal azotemia, acute tubular necrosis, drug-induced disorders (NSAIDs, antibiotics, radiographic contrast, diuretics), glomerulonephritis, vasculitis.

Diagnosis

Exclude other cause of renal failure. Discontinue diuretics and then perform a plasma volume expansion trial with 1.5 L IV normal saline or 5% IV albumin. If serum creatinine ↓, suspect another diagnosis.

Treatment

Identify and treat precipitants. Restrict sodium to < 2 g/day if serum Na < 125 mEq/L; then restrict fluids to < 1.5 L/day. Treat infection; liver transplant is often required. **Renal failure from hepatorenal syndrome reverses with liver transplant.**

Liver Transplantation

Liver transplantation is a standard operation with excellent survival rates (80–90% at one year and 60–80% at seven years). The scarcity of available cadaveric donor livers is reflected in the high mortality rates (up to 20% per year) in those awaiting liver transplantation. In 2006, > 6500 liver transplants were performed in the United States; > 14,000 patients were on the waiting list, with **typical waiting times of eight months to three years.** Living-donor liver transplants constitute a promising alternative but comprise < 3% of all liver transplants.

The Process

Liver graft allocation in the United States is a "sickest-first" system that is based on the MELD score (serum creatinine, total bilirubin, INR).

- Determine the presence of other viruses (HAV, HCV, mononucleosis/EBV, CMV, HSV).
- Refer to a transplant center (often the rate-limiting step).
- There are no minimal listing criteria, yet an indication for transplant should be identified.
- Assess indications and contraindications (see below).
- Perform a psychosocial and financial evaluation.
- Present to a selection committee, where a decision is made on whether to place patient on wait list.
- Priority is determined by the Model for End-stage Liver Disease (MELD) score, a function of INR, total bilirubin, and serum creatinine; the higher the score, the higher the priority. For hepatocarcinoma, a MELD score is assigned independent of the calculated MELD score.

Indications

- **Acute hepatic failure:** Acetaminophen overdose, idiosyncratic drug injury, toxins (*Amanita phalloides* ingestion), HAV, HBV flare, acute Budd-Chiari syndrome, Wilson's disease, acute fatty liver of pregnancy, others. As high as 17% have an indeterminate (nonidentifiable) cause.

- **Cirrhosis with decompensation** (in descending order): HCV, EtOH, cryptogenic, 1° biliary cirrhosis, 1° sclerosing cholangitis, HBV, autoimmune hepatitis.
- **Hepatocellular carcinoma:** Not exceeding stage 2 (≤ 3 lesions ≤ 3 cm in size or one lesion ≤ 5 cm with no extrahepatic metastasis). Liver biopsy is not required if two radiographic studies are supportive of the diagnosis.
- **Metabolic liver disease:** Hemochromatosis, α_1-antitrypsin deficiency, Wilson's disease, tyrosinemia, glycogen storage diseases.
- **Extrahepatic metabolic disease:** Urea cycle enzyme deficiency, hyperoxaluria.

CONTRAINDICATIONS

- Compensated cirrhosis without complications (too early).
- Extrahepatic malignancy (excluding skin cancers).
- Hepatocellular carcinoma exceeding stage 2 (see above).
- Active substance abuse and alcohol abuse (generally defined as occurring within the last six months); some centers include active smoking.
- Active untreated sepsis.
- Advanced untreatable cardiopulmonary disease.
- Uncontrolled psychiatric disease.

COMPLICATIONS

*As high as 17% of patients with acute liver failure will have **no identifiable** cause.*

- **Operative:** Biliary complications (25%), wound infections, death.
- **Immunosuppression:** Opportunistic infections (CMV, HSV, fungal, PCP, others), drug-related effects (hypertension, renal insufficiency, DM, cytopenias, tremor, headaches, nausea/vomiting, seizures, others), malignancies (lymphoma, others).
- **Recurrent disease** (in descending order): HCV (> 99% if viremic at transplantation), **alcoholism,** HBV, 1° sclerosing cholangitis, 1° biliary cirrhosis, autoimmune hepatitis.
- **Acute rejection:** Occurs in up to 30% within the first three months after transplant; usually is treatable, and rarely results in graft loss.

CHAPTER 8

Geriatrics

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NUTRITIONAL RECOMMENDATIONS

Nutritional guidelines for the elderly, as outlined by the United States Preventive Services Task Force (USPSTF), are no different from those for the general population. They include the following:

- Reduction of dietary fats.
- ↑ consumption of fruits, vegetables, and whole grains/fiber.

Patients > 75 years of age who are on restricted diets are at risk of protein-calorie malnutrition and inadequate intake of folate, vitamin B_{12}, calcium, and vitamin D.

Vitamin D

- Older individuals are at higher risk for vitamin D deficiency as a result of the following factors:
  - ↓ ability of the skin to produce vitamin D.
  - ↓ sun exposure.
  - ↓ synthesis of 1,25-vitamin D due to a higher prevalence of renal dysfunction.
- Adequate vitamin D intake is particularly important in the elderly because this vitamin improves bone mineral density (BMD) and may reduce the risk of fracture by improving muscle function, thereby decreasing the risk of falls.
- The recommended daily allowance in individuals with a normal BMD is 400–600 IU but ↑ to 800 IU in the setting of osteoporosis.

Vitamin E

There is conflicting evidence that vitamin E may slow (but not prevent) disease progression in those with established Alzheimer's disease. Some studies also suggest a benefit in CAD. However, some data suggest that **high-dose vitamin E (> 400 IU/day) may ↑ all-cause mortality.**

WEIGHT LOSS

Unintended weight loss exceeding 5% in one month or 10% in six months is common in those > 85 years of age as well as among nursing home residents (up to 45%), hospitalized patients (10–30%), and depressed patients, and is **not a normal part of aging.** Although the cause of unintended weight loss cannot be identified in 25% of cases, the following are known etiologic factors (see also the mnemonic **DETERMINE**):

- **Medical:** Chronic heart disease, chronic lung disease, dementia, poor dentition, changes in taste or smell, dysphagia, mesenteric ischemia, cancer, diabetes, hyper- or hypothyroidism.
- **Psychosocial:** Alcoholism, depression, social isolation, limited funds, difficulty shopping for or preparing food, need for assistance with feeding.
- **Pharmacologic:** NSAIDs, antiepileptics, digoxin, SSRIs.

DIAGNOSIS/TREATMENT

- Identify treatable medical, psychological, and social causes.
- Consider age-appropriate (and life expectancy–appropriate) cancer screening (e.g., prostate, colon, breast).

Causes of unintentional weight loss—

DETERMINE

Disease
Eating poorly
Tooth loss/mouth pain
Economic hardship
Reduced social contact
Multiple medicines
Involuntary weight loss/gain
Need for assistance in self-care
Elder years (> 85 years of age)

Loss of lean body mass and ↑ % body fat are normal age-related changes; unintentional weight loss is not.

- Discontinue any offending drugs.
- Appetite stimulants and dietary supplements may ↑ weight but do not improve mortality.
- Tube feeding has complications and seldom improves mortality.

Complications

Associated with high morbidity within two years of onset, including falls, isolation, skin breakdown, and nursing home placement.

IMMUNIZATIONS/PROPHYLAXIS

Influenza vaccine should be administered annually to adults ≥ 65 years of age.

Influenza Vaccine

- More than 90% of influenza-related deaths occur in those > 60 years of age.
- The CDC targets all adults ≥ 65 years of age, nursing home residents, and those with chronic medical conditions for annual vaccination.
- Among community dwellers ≥ 65 years of age, influenza vaccine is > 50% effective in reducing influenza-related illness.
- Among adults living in long-term care settings, immunization can ↓ the incidence of influenza by 30–40%, pneumonia and hospitalizations by 50–60%, and death by 80%.
- The efficacy of vaccination declines in those > 70 years of age owing to diminished immune response, but vaccination remains important in this high-risk group.

Adults ≥ 65 years of age should be vaccinated against pneumococcus and should have a repeat vaccination in ***five years.***

Pneumococcal Vaccine

- Pneumococcal infection is a common cause of bacteremia, pneumonia, and meningitis.
- Of the > 90 serotypes of pneumococcus, most serious infections are caused by the 23 serotypes contained in the 23-valent polysaccharide vaccine.
- Vaccination is 50–80% effective in preventing pneumococcal bacteremia but has no significant effect on outpatient pneumonia or hospitalizations for pneumonia.

If a patient has never received a 1° tetanus series, three doses are required. Otherwise, give a booster dose of the tetanus-diphtheria toxoid every 10 years.

Tetanus Vaccine

- Clinical tetanus is rare in the United States and occurs primarily among older adults who are unvaccinated or underimmunized.
- Patients > 60 years of age account for 60% of all cases of tetanus.

Aspirin

- Because most elderly patients have a five-year heart disease risk exceeding 3%, aspirin prophylaxis is recommended to all those with a life expectancy of > 5 years.
- However, this must be balanced against the patient's individual risk of GI and intracranial bleeding. The optimal dose is unclear.

CANCER SCREENING

When to discontinue cancer screening remains a controversial issue. Although some guidelines do exist, the patient's risk factors, comorbidities, overall functional status, and life expectancy must always be taken into account. General guidelines formulated by the USPSTF are outlined in the subsections that follow.

Cervical Cancer

- Most cervical cancer in the elderly results from inadequate screening at younger ages.
- The USPSTF recommends stopping routine screening at age 65 in women who have had adequate recent screening with Pap smears and are not otherwise at high risk for cervical cancer.
- There is no evidence to support continued screening following total hysterectomy for benign disease.

Breast Cancer

- Few breast cancer screening trials have included women older than age 70. However, the risk of breast cancer ↑ with age and is high in elderly patients.
- Women ≥ 70 years of age with five or more years of life expectancy may be reasonable candidates for continued screening, but the risks and benefits should be discussed with the patient.

Colon Cancer

- The incidence of colorectal cancer approximately doubles each decade from age 40 to 80.
- Unless there is a personal history of colorectal carcinoma or the patient has a particularly long life expectancy, it is reasonable to discontinue screening between ages 75 and 80.

Prostate Cancer

- There is insufficient evidence that prostate cancer screening at any age ↓ morbidity or mortality from prostate cancer.
- If a physician and a patient have decided to proceed with screening, it is reasonable to stop once that patient has less than a 10-year life expectancy.

SENSORY IMPAIRMENT

Vision Loss in the Elderly

- Vision screening should be conducted by Snellen chart even on asymptomatic elderly patients.
- Arcus senilis (see Figure 8.1), defined as loss of pigment in the periphery of the iris, is a common nonpathologic finding in the elderly and does not interfere with vision.
- Common causes of vision loss in the elderly include age-related macular degeneration, glaucoma, cataracts, and diabetic retinopathy (see the section on chronic vision loss in the Ambulatory Medicine chapter).

Age-related macular degeneration, the most common cause of permanent vision loss in the elderly, is characterized by central vision loss and retinal drusen (yellow spots on the macula).

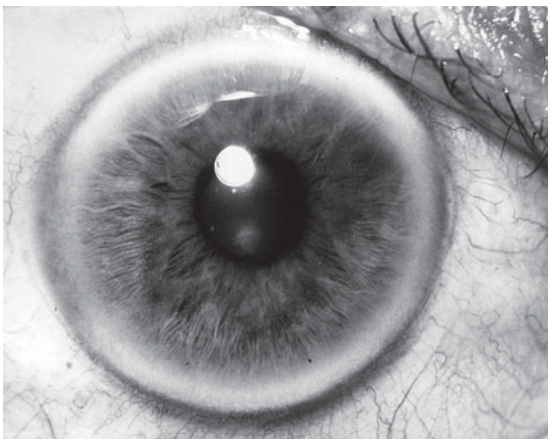


FIGURE 8.1. Arcus senilis.

(Photo by Diane Beeston. Reproduced, with permission, from Riordan-Eva P, Whitcher JP. *Vaughan & Asbury's General Ophthalmology*, 17th ed. New York: McGraw-Hill, 2008: Fig. 6-15.)

Consider sensory impairment in the differential diagnosis of elderly patients with falls, depression, or increasing social isolation.

Hearing Loss in the Elderly

- The prevalence of uncorrected hearing loss in the elderly is roughly 25%. Screening for hearing impairment should be conducted with otoscopic and audiometric testing for those who exhibit deficits.
- **Presbycusis,** a form of sensorineural hearing loss that is most often associated with aging, is felt to be due to loss of hair cells in the cochlea and neurons in CN VIII, leading to a **high-frequency, bilateral, symmetric** hearing loss.

See also the section on hearing loss in the Ambulatory Medicine chapter.

CARDIOVASCULAR MEDICINE

In patients > 85 years of age with multiple comorbidities, hypertension should be treated with caution to prevent orthostatic hypotension, which can contribute to falls.

Hypertension

- Patients between the ages of 60 and 80 should be screened and treated for both systolic and diastolic hypertension.
- The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7) recommends an upper limit of 140 for SBP in the elderly.

Hyperlipidemia

- Evidence exists to support the treatment of hyperlipidemia in elderly patients for the **2° prevention** of cardiovascular outcomes. The goal for patients with CAD is an LDL < 100 mg/dL (per the National Cholesterol Education Program).
- More controversial is the treatment of elders—especially women and the very old—for the 1° prevention of cardiovascular disease.
- Dietary counseling must be based on the patient's overall nutritional status as well as on the risk of malnutrition.
- Statins are normally well tolerated. Rhabdomyolysis, the most serious side effect associated with statin use, is more common in the elderly, most likely as a result of drug-drug interactions.

- Continued screening is recommended by the USPSTF, with consideration given to both life expectancy and overall risk factors.

Atrial Fibrillation (AF)

- The incidence of AF ↑ with age and doubles with each decade over age 55.
- Age alone is not a risk factor for ↑ bleeding events on warfarin. However, older people tend to have more variability in their INR as a result of metabolic changes and the effects of polypharmacy.
- A meta-analysis showed cost-effectiveness and improved quality of life when anticoagulating older patients with AF plus stroke risk factors (e.g., a history of CVA, hypertension, DM).

URINARY INCONTINENCE

Defined as a complaint of involuntary leakage of urine, often resulting in physical, functional, and psychological morbidity as well as diminished quality of life.

- May be partially or wholly attributable to remediable factors **outside the lower urinary tract,** including medical conditions, medications, and functional factors.
- **Lower urinary tract** causes of urinary incontinence include detrusor overactivity, impairment of urethral sphincter mechanisms, an underactive detrusor, and bladder outlet obstruction.
- Although a history, physical exam, and UA are often sufficient to provide a working diagnosis, a minority of patients require referral or specialized testing.

There are four 1° classes of urinary incontinence—**urge, stress, overflow,** and **functional.** See Table 8.1 for a review of the pathophysiology, clinical characteristics, and treatment of each.

Reversible/2° causes of incontinence—

DIAPPERS

Delirium
Infection, urinary (*E. coli* endotoxins have α-blocking properties; UTI can cause detrusor instability)
Atrophic vaginitis/urethritis
Pharmaceuticals (sedative-hypnotics, EtOH, anticholinergics, opiates, α-agonists/antagonists, diuretics, CCBs)
Psychological
Excess urine output (hypercalcemia, hyperglycemia, diuretics, caffeine, nocturnal mobilization of peripheral edema)
Restricted mobility
Stool impaction

Urge Incontinence

A complaint of involuntary leakage accompanied or immediately preceded by urgency. The presumed cause is uninhibited bladder contractions/**detrusor overactivity (DHIC).** The following may lead to detrusor overactivity:

- Age-related changes.
- Interruption of CNS inhibitory pathways (e.g., stroke or cervical stenosis).
- Bladder irritation caused by infection, stones, inflammation, or neoplasm.
- Idiopathic.

Symptoms and treatment are reviewed in Table 8.1.

Detrusor hyperactivity with impaired contractility is the most common cause of lower tract incontinence in elderly patients of either sex.

Stress Incontinence

A complaint of involuntary leakage on effort or exertion such as sneezing or coughing. **Stress incontinence is the most common cause of urinary incontinence in younger women and the second most common cause of incontinence among older women.** It may also occur in older men following transurethral or radical prostatectomy. See Table 8.1 for further details.

TABLE 8.1. Overview of Urinary Incontinence

Type of Incontinence	Mechanism	Characteristics	Treatment Options
Urge	Uninhibited bladder contraction/ detrusor overactivity.	Most common in the elderly. Abrupt urgency with moderate to large leakage. Elevated postvoid residuals without outlet obstruction.	The mainstay is behavioral therapy (frequent voiding, biofeedback). Principles are frequent voluntary voiding to keep the bladder volume low, and training of CNS and pelvic mechanisms to inhibit detrusor contractions. If unsuccessful, add a bladder suppressant (e.g., oxybutynin, tolterodine, trospium). Beware of anticholinergic side effects.
Stress	Intra-abdominal pressure overcomes sphincter closure mechanisms.	Primarily affects younger women. Involves involuntary leakage on exertion such as sneezing or coughing.	Kegel exercises, pessaries, bladder suspension surgery. Estrogen and α-adrenergic agonists (e.g., pseudoephedrine) have yielded mixed results.
Overflow	Incomplete bladder emptying due to impaired detrusor activity and/or outlet obstruction.	Usually affects men with prostatic enlargement or patients with spinal cord injury. Leakage small in volume but continuous. Elevated postvoid residuals; weak stream. Intermittency, hesitancy, and nocturia may also be seen.	**α-adrenergic antagonists (e.g., doxazosin, terazosin):** Beware of orthostatic hypotension. **5α-reductase inhibitors (e.g., finasteride):** The effect is more modest than with α-adrenergic antagonists, and the benefit is delayed. Transurethral resection of the prostate (TURP) improves symptoms in > 75% of cases, but open prostatectomy may be required if the prostate is too large for TURP. Incontinence and erectile dysfunction are possible but rare (< 1%) side effects of TURP.
Functional	Inability to void in a commode due to factors such as poor mobility, vision, or cognition.	May be exacerbated by medical conditions (CHF, DM, low albumin) or medications (especially diuretics).	Fluid management; pads/ protective garments. Urinal/bedside commode. Catheters should be used only as a last resort.

Overflow Incontinence

Many of the medications used for urge incontinence/detrusor hyperactivity will actually worsen overflow incontinence as a result of their anticholinergic side effects. Make sure the cause of incontinence is correctly identified!

A complaint of involuntary dribbling and/or continuous leakage associated with incomplete bladder emptying due to **impaired detrusor contractility and/or obstruction.**

- Outlet obstruction is the second most common cause of urinary incontinence in older men (after detrusor overactivity) resulting from BPH, prostate cancer, or urethral stricture, yet most obstructed men do not have urinary incontinence.
- Obstruction is uncommon in women but may result from corrective surgery for urinary incontinence or from a large, prolapsed cystocele that kinks the urethra during voiding.
- Anticholinergic medications can also cause urinary retention, eventually leading to overflow incontinence.
- Patients with spinal cord injury may be obstructed by detrusor-sphincter dysregulation.
- Table 8.1 reviews common findings and treatments.

Functional Incontinence

Use catheters only as a last resort in functional incontinence.

A complaint of inability to void in a commode as a result of poor mobility, dexterity, vision, or cognition. May be exacerbated by other medical conditions (e.g., CHF, low albumin, poorly controlled diabetes) as well as by medications, especially diuretics. Characteristics and treatment vary depending on the underlying cause. A brief overview is provided in Table 8.1.

Mixed Incontinence

A complaint of involuntary leakage associated with urgency as well as with exertion, effort, sneezing, or coughing. It is likely due to a combination of detrusor overactivity and sphincter impairments associated with stress incontinence. **The most common type of urinary incontinence in older women.** Other, rare etiologies of mixed incontinence include extraurethral causes (from fistulas) and impaired detrusor compliance (an excessive pressure response to filling, usually due to spinal cord injury).

FECAL INCONTINENCE

Fecal incontinence affects 3–10% of community-dwelling elderly.

Defined as continuous or recurrent uncontrolled passage of fecal material (> 10 mL) for at least one month in an individual > 3–4 years of age. Fecal incontinence is a devastating disability that adversely affects self-confidence and can lead to social isolation. It is a common **cause of nursing home placement.**

- Loss of continence can result from dysfunction of the anal sphincter, abnormal rectal compliance, ↓ rectal sensation, or a combination of any of these abnormalities.
- Dysfunction of the levator ani muscle appears to have a strong association with the severity of incontinence.
- Fecal incontinence is usually multifactorial, since these derangements often coexist (see Table 8.2).

TABLE 8.2. Etiologies of Fecal Incontinence

ETIOLOGY	CHARACTERISTICS
Vaginal delivery	Incontinence occurs either immediately or after years. The most common injuries are anal sphincter tears or trauma to the pudendal nerve.
Surgical trauma	Surgery on the anal sphincter or surrounding structures.
Diabetes mellitus (DM)	↓ internal anal sphincter resting pressure. Diarrhea is 2° to autonomic neuropathy.
↓ rectal compliance	Rectal filling fails to produce a sensation of rectal fullness and the urge to defecate.
Impaired rectal sensation	A number of conditions are associated, including DM, MS, dementia, meningomyelocele, and spinal cord injuries.
Fecal impaction	A common cause in the elderly. Produces constant inhibition of internal anal sphincter tone, permitting leakage of liquid stool around the impaction.

Constipation is a common cause of fecal incontinence in the elderly.

DIAGNOSIS

- The history and physical exam can provide insight into the etiology, allowing for focused diagnostic testing.
- The rectal exam should assess for fecal impaction, anal tone, pelvic floor tone, and any masses.
- Inspection of the distal colon and anus with flexible sigmoidoscopy and anoscopy can exclude mucosal inflammation or masses.
- Complaints of diarrhea may be assessed with stool studies and a full colonoscopy.

Stool consistency can be improved by supplementing the diet with a bulking agent, but this may exacerbate incontinence in patients with ↓ rectal compliance (e.g., those with radiation proctitis or a rectal stricture).

TREATMENT

- **Medical therapy:** Antidiarrheal drugs, along with the elimination of medications that are known to cause diarrhea, may be of benefit.
  - The goal is to ↓ stool frequency and improve stool consistency.
  - Formed stool is easier to control than liquid stool.
  - Loperamide is more effective than diphenoxylate for reducing urgency.
  - Anticholinergic agents taken before meals may be helpful in patients who tend to have leakage of stools after eating.
- **Biofeedback therapy:** A painless, noninvasive means of cognitively retraining the pelvic floor and the abdominal wall musculature. However, insufficient evidence exists supporting its efficacy.
- **Surgery:**
  - A number of surgical approaches have been used for the treatment of fecal incontinence, including direct sphincter repair, plication of the posterior part of the sphincter, anal encirclement, implantation of an artificial sphincter, and muscle transfer procedures with or without electrical stimulation.

- Colostomy should be reserved for those with intractable symptoms who are not candidates for other therapies.
- **Nerve stimulation:** Electrical stimulation of the sacral nerve roots can restore continence in patients with structurally intact muscles.
- **Supportive measures:** Can be instituted in most patients. May include avoiding foods or activities known to worsen symptoms, ritualizing bowel habits, and improving perianal skin hygiene. Stool impaction should be corrected and a bowel regimen instituted to prevent recurrence.

SEXUAL DYSFUNCTION

Older men and women frequently remain interested in sex despite a ↓ in overall sexual activity. In men, ↓ activity may result from a variety of factors, including atherosclerosis, neurologic disorders, medications, psychological factors, endocrine problems, social issues, limited availability of partners, ↓ libido, and erectile dysfunction. In women, additional factors include vaginal dryness or burning and vaginal atrophy.

Erectile dysfunction and loss of libido are not normal signs of aging.

Symptoms

- **Men:** Symptoms in men include inadequate erections, ↓ libido, and orgasmic failure.
- **Women:** Symptoms in women include vaginal dryness or burning (atrophy), dyspareunia, slower time to orgasm, a need for prolonged clitoral stimulation, and ↓ libido.

Differential

Medication effects, psychosocial factors, anatomical problems, Peyronie's disease in men.

Diagnosis

- **Men and women:** Diagnosis should include the following:
  - Review problems and the patient's medication list.
  - Ask about substance use—e.g., alcohol, cigarettes, heroin, cocaine.
  - Screen for depression.
  - Assess time spent in foreplay or in stimulation.
- **Labs:**
  - For men, serum testosterone should be considered, although the yield will be low if the man is lacking other signs of hypogonadism.
  - If serum testosterone levels are low or low normal, consider a bioavailable testosterone level. LH and prolactin are not routinely necessary, as the hypothalamic-pituitary axis tends to become less responsive with aging.
  - Other lab tests should be dictated by the history and physical (e.g., glycosylated hemoglobin, lipid panel).

Look for possible depression in older persons with sexual dysfunction.

Treatment

All patients should receive counseling on lifestyle modifications (e.g., ↓ alcohol intake, smoking cessation) and have any psychosocial issues addressed. Any offending medications should be discontinued if possible, and underlying medical problems should be addressed. Specific treatment for sexual dysfunction includes the following:

- **Men:**
  - **Pharmacologic:**
    - **Phosphodiesterase-5 (PDE-5) inhibitors (sildenafil, tadalafil, vardenafil):** Often effective, and the most acceptable option for patients. Caution should be exercised in patients with CAD; these drugs are contraindicated with nitrates, as they may cause hypotension when used in combination.
    - **Testosterone:** Should be used only for true hypogonadism. Associated with multiple side effects and an ↑ risk of prostate disease.
  - **Mechanical: Penile injections or vacuum devices** may be effective but are rarely acceptable to patients. Poor response to vasoactive intracavernous injection suggests a vascular cause of erectile dysfunction.
  - **Other options:** Constriction rings, counseling, surgery for Peyronie's disease, penile prostheses.
- **Women:** Treatment options include topical estrogen creams or rings (if there is no hepatic or cardiac disease), ↑ stimulation time before intercourse, and possibly counseling.

OSTEOPOROSIS

Osteoporosis is most common in elderly women. Risk factors include the following:

- Advanced age
- Female gender
- Postmenopausal status
- Caucasian ethnicity
- Northern European ancestry
- A ⊕ family history
- Prolonged inactivity
- Low calcium or vitamin D intake
- Thin bone structure or build (BMI < 22)
- Medications: steroids, antiepileptics
- Tobacco use
- Excessive alcohol use

Screening DEXA is recommended for all women over age 65, or those over age 60 with osteoporosis risk factors. For a complete discussion on osteoporosis, see the section in the Women's Health chapter.

FALLS

Roughly 30% of all falls occur in individuals ≥ 65 years of age, and approximately 50% occur in those ≥ 80 years of age. Falls also occur more frequently in hospitals and immediate posthospital settings. Additional risk factors include the following:

- Less agile gait
- ↓ positional sense and reflexes
- ↓ sensorium/vision
- Orthostatic hypotension
- Incontinence
- A prior history of a cerebrovascular event
- Parkinson's disease
- A history of syncope

- Alcohol use
- Medications (benzodiazepines, sedatives, neuroleptics, antihistamines, narcotics)

Physical restraints do not prevent falls and lead to ↑ mortality, hospital lengths of stay, pressure sores, nosocomial infection, and emotional distress.

Prevention

Preventive measures include the following:

- Improved lighting and correction of visual deficits.
- Decreasing psychotropic or other known offending medications.
- Vitamin D replacement for those who are deficient (shown to ↓ falls and improve body sway).
- Exercise (particularly strength/flexibility/balance exercises such as tai chi).
- Environmental modifications such as installation of handrails, removal of rugs, use of shower rails and seats, use of ramps, and first-floor setup (placement of the bed, commode, and bath on the same floor—preferably the main level of the residence).
- Use of assistive devices.

Falls result in considerable morbidity, mortality, functional decline, and nursing home admissions.

Complications

- Roughly 50% of falls result in injury, and 10% require hospitalization.
- A prolonged amount of time spent on the floor (as occurs in roughly 3% of all falls) can lead to rhabdomyolysis, dehydration, and hypothermia.
- Associated with nursing home placement and functional decline.

HIP FRACTURES

More than 300,000 people ≥ 65 years of age are hospitalized each year with hip fractures, and roughly 25% of these patients die within one year as a result of the fracture or related complications.

Symptoms

Presents with hip or groin pain after a fall. Patients are often unable to bear weight.

Assess goals of care with the hip fracture patient and, if necessary, with the surrogate decision maker. Operative management may not always be consistent with a frail patient with preexisting immobility and shortened life expectancy.

Exam

With the patient in bed, the leg is shortened and externally rotated. Pain is likely to be observed on palpation or internal/external rotation. Look for other fall-related trauma such as head injury.

Differential

Soft tissue injury, dislocation, avascular necrosis (AVN).

Diagnosis

X-ray studies generally establish the diagnosis, usually on AP pelvis or hip series. Rarely, an MRI is needed to diagnose a subtle fracture or to confirm AVN. Generally, a hip fracture is also diagnostic of osteoporosis, necessitating treatment.

Treatment

The major components of therapy are as follows (see also the mnemonic **O-ROT**):

Treatment of hip fracture—

O-ROT

Orthopedic management (to include prophylactic anticoagulation until ↑ mobility)
Rehab
Osteoporosis treatment
Tertiary fall prevention

- **Orthopedic management:** Usually required, with the exact procedure depending on the type of fracture. Most surgeons now recognize the importance of expediting operative repair (should occur within 24 hours of the fracture).
- **Postoperative rehabilitation:** Should begin immediately or as soon as allowed by surgical recommendations. Includes mobilization, pain management, prevention of complications, and functional adaptation.
- **Osteoporosis treatment:** May include medical therapy as well as hip protectors. Hip protectors may slightly ↓ fracture risk but do not prevent falls.
- **3° prevention of falls** (see above).

Complications

Immobility, venous thromboembolism, functional decline and death.

PRESSURE ULCERS

A higher incidence of pressure ulcers is found in hospitals and nursing homes than in homes with family caregivers. Causes may be divided into extrinsic vs. intrinsic to the patient:

- **Extrinsic:**
  - Sustained pressure, primarily over bony prominences (e.g., sacrum, ischium, heels, trochanters).
  - Shearing forces.
  - Infection, friction, or moisture.
- **Intrinsic:**
  - Immobility.
  - Cognitive dysfunction.
  - Impaired wound healing (may be 2° to diabetes, peripheral vascular disease, venous stasis, or poor nutritional status).
  - Changes in skin structure and integrity associated with aging.

Diagnosis

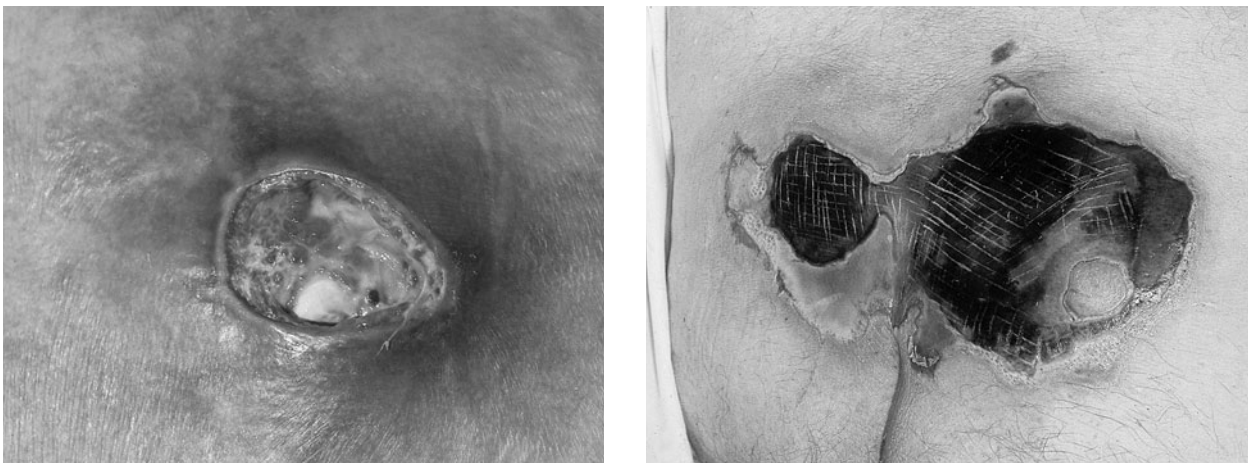
Staging is as follows:

- **Stage I:** Nonblanching erythema over intact skin.
- **Stage II:** Partial-thickness skin loss (epidermis +/– dermis).
- **Stage III:** Full skin loss down to but not through the fascia (see Figure 8.2A).
- **Stage IV:** Tissue loss down to the level of muscle, tendon, or bone. Any undermining/sinus tracts are also considered (see Figure 8.2B).

Treatment

Treatment is based on four main principles:

- **Pressure relief:** Pressure-relieving mattresses and seat cushions; physical therapy; frequent repositioning (every two hours).
- **Debridement of dead or infected tissue:** Sharp, mechanical, or enzymatic debridement may be used.
- **Selection of topical dressing:** The goal is maintenance of a moist wound bed to promote healing.
- **Management of bacterial load: Not all wounds are infected!** There is no need for systemic antibiotics unless there are signs of cellulitis (erythema, pain, warmth, or increasing drainage/odor).



A B

FIGURE 8.2. Stage III (A) and stage IV (B) pressures ulcers.

Note that the criss-cross marks in the necrotic area are from attempts to mechanically debride necrotic tissue. Surgical debridement of necrotic tissue under anesthesia revealed involvement of fascia and bone. (Reproduced, with permission, from Wolff K et al. *Fitzpatrick's Color Atlas & Synopsis of Clinical Dermatology*, 5th ed. New York: McGraw-Hill, 2005: 487.)

Prevention

Preventive measures include competent nursing care, good hygiene and hydration, and adequate nutrition.

SLEEP DISORDERS

Two sleep states have been identified: non–rapid eye movement (NREM) and rapid eye movement (REM). A typical night of sleep begins with NREM, with REM occurring after 80 minutes. Both sleep states then alternate, with REM periods increasing as the night progresses. NREM includes four stages:

- **Stages 1 and 2:** Classified as light sleep. Stage 1 is a transition from wakefulness to sleep.
- **Stages 3 and 4:** Classified as deep, restorative sleep.

Symptoms/Exam

Changes in sleep occur as a normal part of aging. Such changes may affect sleep pattern (the amount and timing of sleep), sleep structure (stages), or both. Specifically, stages 1 and 2 may ↑, while stages 3 and 4 may ↓ . Typical complaints from patients > 65 years of age may thus include the following:

- Difficulty falling asleep.
- Midsleep awakening and ↑ arousal during the night.
- Nonrestorative sleep (may be perceived as ↓ sleep time).
- Earlier bedtime and earlier morning awakening.
- Daytime napping or reversal of sleep-wake cycle.

Differential

- **1° sleep disorders:** Circadian rhythm disorders, sleep apnea, restless leg syndrome, REM behavior disorder.
- **Psychiatric:** Stress, depression, bereavement, anxiety.

- **Pain related:** Neuropathic pain, rheumatologic conditions, malignancy syndromes.
- **Physiologic:** Dyspnea resulting from cardiac and pulmonary conditions (COPD, CHF); nocturia due to DM, BPH, or medications; GERD.
- **Medication related (10–15%):**
  - **Respiratory medications:** Theophylline, β-agonists.
  - **Cardiovascular medications:** Furosemide, quinidine.
  - **Antidepressants:** Desipramine, nortriptyline, imipramine.
  - **Other:** Corticosteroids, caffeine, nicotine.

Diagnosis/Treatment

There is limited evidence supporting the benefit of specialized testing with polysomnography by a primary care physician. However, the following issues should be addressed by the primary physician:

- **Sleep apnea** should be diagnosed and treated.
- **Stressors and psychiatric conditions** should be identified and treated as well.
- The following **sleep hygiene measures** should be recommended:
  - Adherence to a regular morning rise time.
  - Limiting of daytime napping.
  - Exercise during the day but not at night.
  - Avoidance of caffeine, alcohol, and nicotine in the evening.
  - Limiting of nighttime fluid intake to diminish the urge to urinate during sleeping hours.
  - Adjusting the environment to patient preferences (e.g., controlling noise, light, and temperature).
  - Discouraging reading or watching television in bed.
- **Medications:** If all other measures fail and medications must be used, they should always be administered in the lowest effective dose and should be given as intermittent or short-term dosing only. Whereas no medications are recommended in the treatment of insomnia for the older patient, the use of the following medications should be actively discouraged:
  - **Benzodiazepines:** ↑ the likelihood of falls, leading to hip fracture and motor vehicle accidents. Tolerance has also been widely noted.
  - **Antihistamines (e.g., diphenhydramine):** Have anticholinergic effects; tolerance has been noted.
  - **Melatonin:** Deficiency is difficult to measure, and effects on sleep disorders have not been proven. In addition, there is wide variability in dosage in different OTC formulations.

Complications

Untreated sleep disorders result in poor memory, impaired concentration, impaired function, ↑ numbers of accidents and falls, and chronic fatigue.

DEPRESSION

Depression is greatly underdiagnosed in older patients. This may be because elderly patients are more likely to present with somatic complaints or experience delusions, and are less likely than younger patients to report a depressed mood. Epidemiologic data indicate that depression affects 1% of elderly individuals in the general community, 10% of those seeking primary care or in the hospital, and 40% of those who are permanently institutionalized. Risk factors are as follows:

- A prior episode of depression
- A ⊕ family history
- Lack of social support
- Use of alcohol or other substances
- Parkinson's disease
- Recent MI
- A history of CVAs
- Cognitive impairment
- Loss of autonomy/functional impairment
- Multiple comorbid medical conditions
- Uncontrolled pain or insomnia

Differential

Depression has a high prevalence in patients with Parkinson's disease.

The differential diagnosis of depression includes the following:

- **Mild cognitive impairment:** A precedent to dementia (patients are likely to have predominantly depressive symptoms).
- **Parkinson's disease:** The early presentation of Parkinson's may mimic depression. Note, however, that a high percentage of Parkinson's patients develop depression.
- Fatigue and weight loss resulting from diabetes, thyroid disease, malignancy, vitamin B_{12} deficiency, or anemia.
- Sleep disturbance with daytime fatigue and depressed mood as a result of pain, nocturia, and sleep apnea.
- Bereavement, delirium, substance abuse.

Treatment

The mainstay of treatment for major depression is medications +/– psychotherapy.

- **Pharmacotherapy:** General principles for pharmacotherapy in older patients are as follows:
  - Medications are chosen largely on the basis of their side effect profiles (e.g., anxiety, insomnia, pain, weight loss).
  - Consider renal and hepatic function when choosing a medication.
  - Side effects typically last < 4 weeks, but weight gain and sexual dysfunction may last longer.
  - Individual medications and their uses and side effects can be found in Table 8.3.
- **Psychotherapy:** Cognitive-behavioral therapy, problem-solving therapy, and interpersonal psychotherapy are effective either alone or in combination with pharmacotherapy.
- **Electroconvulsive therapy (ECT):**
  - Associated with response rates of 60–70% in patients with refractory depression.
  - Side effects of confusion and anterograde memory impairment may persist for up to six months.
  - First-line therapy for patients who are severely depressed, for those who are at high risk for suicide, and in other situations when a rapid response is urgent (e.g., when a medical condition is severely compromised by depression). Also an option for patients who are not eligible for pharmacotherapy as a result of hepatic, renal, or cardiac disease.

TABLE 8.3. Pharmacotherapy for Depression in the Elderly

Class/Medication	Uses	Side Effects
SSRIs (sertraline, paroxetine, fluoxetine, citalopram)	First-line medications. Equally efficacious in elderly patients. **Usually initiated at half the listed starting dose in elderly patients.** A newer SSRI, duloxetine, is also FDA approved for diabetic neuropathy.	Nausea and sexual dysfunction are most common. Paroxetine and fluvoxamine also have anticholinergic side effects. Fluoxetine is rarely used because of its long half-life and inhibition of cytochrome P-450. If it is discontinued abruptly, patients can experience withdrawal (flulike symptoms, dizziness, headache). One must also be alert to the possibility of serotonin syndrome in patients taking SSRIs and/or MAOIs.
2° amine TCAs (nortriptyline, desipramine)	As effective in older patients as in younger patients. May offer added benefit in patients with neuropathic pain, detrusor instability, or insomnia.	**Anticholinergic side effects** (dry mouth, orthostasis, urinary retention) are common. Also associated with conduction abnormalities. Lethal in overdose and should be avoided in patients with suicidal ideation.
MAOIs and 3° amine TCAs (phenelzine, amitriptyline, imipramine)	Rarely used owing to their side effect profiles and likelihood of drug interactions.	Eating tyramine-containing foods while on MAOIs can cause serotonin syndrome. Both classes are lethal in overdose.
Mirtazapine	Beneficial for depression with sleep abnormalities and in patients with **unintentional weight loss** owing to the side effect profile.	Somnolence, ↑ appetite, modest weight gain, dizziness.
Trazodone	Not as efficacious as other antidepressants. Used to treat insomnia.	Associated with **priapism.** Also causes somnolence.
Venlafaxine	In addition to antidepressant effects, also used to treat anxiety and neuropathic pain.	May ↑ DBP.
Bupropion	Also reduces cravings in smoking cessation. Carries the lowest risk of sexual side effects.	Seizure risk that is dose and titration related.
Psychostimulants (dextroamphetamine, methylphenidate)	Sometimes used in patients with predominantly vegetative symptoms.	Commonly associated with tachycardia, insomnia, and agitation.

DEMENTIA

Defined as an acquired syndrome that involves a decline in memory along with at least one other cognitive domain, such as language, visuospatial capacity, or executive function. This ↓ capacity interferes with social or occupational functioning. Risk factors are as follows:

- **Strong risk factors:**
  - Age (particularly Alzheimer's type)
  - A family history in first-degree relatives
  - Apolipoprotein E ε4 genotype
  - DM
  - Hypercholesterolemia
  - Low and high blood pressure
- **Other risk factors:**
  - Head trauma with loss of consciousness
  - A history of depression
  - Low educational achievement
  - Female gender (for Alzheimer's dementia)
  - Gait impairment (for those with non-Alzheimer's dementia)

Symptoms/Exam

Dementia is characterized by an insidious, progressive course without waxing and waning.

Dementia is more often a complaint of the family than of the patient. Early dementia involves cognitive impairment—e.g., a ↓ in recent memory and difficulty with daily functions. Other clinical characteristics include the following:

- Insidious onset
- Progressive course
- No altered consciousness; no waxing and waning after history and observation
- Reduced coping skills
- Getting lost in familiar places
- Personality changes such as poor impulse control or behavioral disturbance
- Diminishment in simple problem-solving ability
- Trouble with complex tasks (balancing checkbook, making meals)
- Difficulty learning new things
- Language problems (e.g., word finding)

Differential

Alzheimer's disease represents 60–70% of all dementia and is characterized by early loss of short-term memory.

The presentation of dementia can be further broken down by type.

- **Alzheimer's:**
  - Involves early, prominent loss of short-term memory; progressive memory loss; personality changes; and functional impairment.
  - Late in the disease, patients become totally dependent on others for basic care.
- **Vascular (multi-infarct) dementia:**
  - May be due to multiple small strokes or cognitive impairment associated with a single stroke.
  - Often has sudden onset and a stepwise decline.
  - Neurologic deficits on exam are correlated with previous stroke, with presentation varying according to the location of the brain injury.
  - Vascular disease is detected on radiologic exam.

Patients with Lewy body dementia classically have a dramatic worsening of extrapyramidal symptoms when given neuroleptics.

Frontal lobe dementia is characterized by early changes in personality and behavior with relative sparing of memory.

Depression can present as pseudodementia.

- Vascular risk factors and other cardiovascular disease are often present.
- Commonly coexists with Alzheimer's dementia.

- **Dementia with Lewy bodies:**
  - Patients have parkinsonian symptoms without frank Parkinson's disease, with sensitivity to neuroleptic medications.
  - Lewy bodies are found in the brain stem and cortex.
  - Produces disabling cognitive impairment progressing to dementia.
  - Characterized by fluctuation in cognition and persistent visual hallucinations.
- **Parkinson's:** Dementia associated with Parkinson's is most commonly associated with later stages of illness (as opposed to dementia with Lewy bodies).
- **Frontal lobe dementia:**
  - Involves impaired executive function (initiating activity, planning), poor self-awareness of one's deficits, and disinhibited behavior.
  - Pick's disease is one type (Pick bodies are found in the neocortex and the hippocampus).
  - Language disturbances include the following:
    - **Palilalia:** Compulsive repetition of one's speech.
    - **Logorrhea:** Profuse, unfocused speech.
    - **Echolalia:** Spontaneous repetition of words or phrases.
- **Reversible dementia:** It is important to note that these dementias are **potentially reversible**—i.e., not all will improve once the disorder is recognized and addressed.
  - **Medication induced:** Substances can include analgesics, anticholinergics, antipsychotics, and sedatives.
  - **Alcohol withdrawal or intoxication.**
  - **Metabolic disorders:** Includes thyroid disease, vitamin B_{12} deficiency, hyponatremia, hypercalcemia, and hepatic and renal insufficiency.
- **Depression:**
  - Commonly noted as pseudodementia.
  - Depression must be ruled out or aggressively treated prior to the diagnosis of new dementia.
  - Depression presenting as dementia is more likely to progress to dementia.
- **CNS disease:** Includes chronic subdural hematomas, chronic meningitis, and normal pressure hydrocephalus (NPH).
  - The presentation of NPH is described in the mnemonic **W**et, **W**obbly, and **W**acky:
    - **W**et: Urinary incontinence.
    - **W**obbly: Gait disturbance.
    - **W**acky: Cognitive dysfunction.
  - The Miller-Fisher test compares before-and-after gait following the removal of 30 cc of spinal fluid to predict the benefit of ventriculoperitoneal shunt.
  - Caution: Note that radiographic diagnosis of NPH based on head CT scan can be misleading, as age-related diffuse atrophy of brain tissue parenchyma may give the appearance of enlarged ventricles (clinical correlation is warranted).
- **Creutzfeldt-Jakob disease:**
  - A rare, infectious, rapidly progressive dementia that is usually fatal within one year of onset.
  - Diagnosis is based on clinical suspicion upon noticing rapid cognitive impairment accompanied by motor deficits and seizures.
  - EEG may show slow and periodic complexes.

- Brain biopsy on autopsy is the only reliable means of diagnosis.
- The disease is not treatable but is potentially transmissible.

Diagnosis

An MMSE score of > 26 is considered normal; 24–26 points to mild cognitive impairment; and < 24 is consistent with (but not diagnostic of) dementia.

Screening guidelines as set forth by the USPSTF are as follows:

- Some screening test have good sensitivity but only fair specificity in detecting cognitive impairment and dementia.
- The Mini-Mental Status Exam (MMSE) is the best-studied instrument for screening dementia.
  - Accuracy depends on age and highest educational level completed.
  - Sensitivity and specificity vary with cutoff points that are selected.
- It is important to make the diagnosis early in the clinical course to assist in anticipating and adhering to recommendations.
- Remember to check labs for potentially reversible causes of dementia, including HIV and latent syphilis if clinically indicated.
- Neuroimaging is not routinely recommended but should be considered for young patients, those with rapid onset of symptoms, and those with focal neurologic signs.

Treatment

Pharmacologic treatment for dementia includes the following:

- **Cholinesterase inhibitors (donepezil, rivastigmine, galantamine, tacrine):** Have been studied in patients with mild to moderate Alzheimer's dementia. Benefits include improvement or stabilization on neuropsychiatric scales, but benefits appear to be modest at two years. These medications may also have some benefit in treating the behavioral symptoms of dementia.
- **NMDA antagonists (memantine):** May be beneficial in moderate to severe Alzheimer's dementia with or without concomitant acetylcholinesterase use.
- **Gingko biloba:** Studies have shown mixed results.
- **Selegiline:** Has shown no significant difference when compared to a placebo.
- **Vitamin E:** Has shown mixed results with delayed institutionalization in one trial, but results were not robust.
- **Estrogen:** Has shown no clinical benefit.

Complications

Complications of end-stage dementia include malnutrition, pressure ulcers, recurrent infections, nursing home placement, and caregiver burden.

DELIRIUM

Delirium is common in the elderly, particularly in hospitalized patients, occurring in up to 70–90% of older patients in ICUs. Although covered in detail in the Hospital Medicine chapter, it is mentioned here as a common mimicker of dementia. In older patients it is usually multifactorial, with common risk factors as follows:

- Preexisting cognitive impairment (especially dementia)
- Advanced age
- Severe underlying illness

- Number and severity of comorbid conditions
- Functional impairment
- Visual or hearing impairment
- Malnutrition and dehydration

In the elderly, always consider drug-drug interactions due to polypharmacy and adverse drug reactions due to changes in medication distribution, metabolism, and clearance as a cause of delirium.

IATROGENESIS

- Elderly patients are at high risk for iatrogenic complications for many reasons:
  - More frequent admission to hospitals and nursing homes
  - Diminished reserves (cognitive, renal, hepatic)
  - Underdiagnosis or delayed diagnosis of medical conditions due to atypical presentation
  - Difficulty with adherence to complicated medical regimens
- Common iatrogenic complications to be aware of include the following:
  - Nosocomial infections
  - Falls
  - Pressure ulcers
  - Delirium
  - Surgical/perioperative complications
  - Adverse drug reactions/drug-drug interactions
- Risk factors for the development of iatrogenesis are as follows:
  - Self-treatment
  - Lack of coordinated care
  - Recent hospital admission/discharge
  - Impaired cognition
  - Complicated medication regimens

Comorbidities and functional status are more important than age alone when considering who is at risk for iatrogenic complications.

POLYPHARMACY

Polypharmacy, commonly defined as the use of ≥ 5 medications, is a significant cause of hospital admissions and **should be on the differential of any presentation in an older adult.** Annually, at least 35% of community-dwelling older adults experience an adverse drug event. Changes in physiologic function and pharmacokinetics in the older patient promote ↑ sensitivity to medications and hence ↑ the possibility of iatrogenic illness. Specific changes include the following:

- **Medication distribution is altered by the following:**
  - ↓ cardiac output, tissue perfusion, and tissue volume.
  - Reduced protein binding of some drugs (e.g., warfarin, phenytoin) owing to low serum albumin.
  - Water-soluble drugs become more concentrated, and fat-soluble drugs have longer half-lives (volume of distribution).
- **Metabolism:**
  - **Phase I:** Oxidization and reduction by cytochrome P-450. Hepatic enzyme activity is ↑, affecting the metabolism of drugs with high first-pass metabolism (e.g., propranolol).
  - **Phase II:** Conjugation by acetylation, glucuronidation, or sulfation (not affected by aging).
- **Excretion:** Renal function ↓ by as much as 50% by age 85.

Symptoms/Exam

- **Delirium** can result from many drugs, including cold remedies, anticholinergics, and analgesics (common but often overlooked in the elderly).
- Other common symptoms include nausea, anorexia, weight loss, parkinsonism, hypotension, and acute renal failure.

To prevent polypharmacy, "start low and go slow" (but conduct an adequate trial).

Treatment

- Try **nonpharmacologic means** before drugs.
- Improve adherence by keeping the dosing schedule simple (once daily is best), the number of pills low, and medication changes infrequent.
- Continually review the drug list for potential discontinuations.

Complications

The consequences of overprescribing include adverse drug events, drug-drug interactions, duplication of drugs, ↓ quality of life, and unnecessary costs.

PALLIATIVE AND END-OF-LIFE CARE

In the United States, approximately 80% of people die in hospitals or in long-term care facilities. Generally accepted goals of end-of-life care include the following:

- To continue to treat potentially **reversible** disease.
- To help **alleviate suffering,** including physical, psychological, social, and spiritual distress.
- To help the patient **prepare for death.**

The following are required of training programs in the care of the terminally ill:

- Assume an obligation to provide appropriate and humane care to the terminally ill.
- Negotiate goals of care with the patient and family, taking into consideration both the individual's values and preferences and the physician's professional judgment.
- In evaluating an older patient, seek out and consider the observations and opinions of family members and other concerned individuals, and bear in mind that the primary obligation is always to the patient.
- Understand the function and importance of a multidisciplinary approach toward caring for older persons, including appropriate respect for other health professionals and paraprofessionals and their roles in the provision of services.
- Understand that maintenance of function and quality of life are more often goals of care than are cures of disease.

*The ethical principle of double effect allows for treatments that may hasten death if the **primary intention** is to relieve suffering.*

Ethical and Legal Issues

Unique ethical considerations include the following:

- The concept of futile medical interventions, which may lead to conflicts between provider, patient, or family. Can often be resolved through discussions.

- The individual has the right to refuse or withdraw medical treatments. Ethically, there is no difference between *withdrawal* of life-sustaining treatment (e.g., a mechanical ventilator) and *refusing to initiate* such an intervention.
- The potential to hasten death is permissible if the 1° intention is to provide comfort and dignity and to relieve suffering (i.e., it is appropriate to prescribe as much morphine as needed to relieve suffering if congruent with patient goals of care). This is often termed the "ethical principle of **double effect.**"
- **Euthanasia** is defined as hastening a patient's death in response to their request, sometimes called "mercy killing." It is not legal in any state.
- **Physician-assisted suicide** involves a physician giving a patient the information or means to end his or her own life. This is currently legal, with multiple restrictions, only in the state of Oregon.

Medical Decision Making

There are several ways patients can indicate their end-of-life wishes:

- **Advance directives:**
  - Defined as oral or written statements made by patients when they are competent with the purpose of guiding their care should they become incompetent.
  - Valid only for futile care or terminal illness.
  - Not legally binding in all states, but helps guide medical providers and family members in medical decision making based on the patient's previously recorded wishes.
- **Durable power of attorney for health care (DPOA-HC):**
  - The patient designates a surrogate decision maker.
  - The role of the surrogate is to offer "substituted judgment" such as that which would be offered if the **patient** could speak for him/herself.
  - If a patient has not designated a health care agent, decisions default to the next of kin.
- **"Do not resuscitate" (DNR) orders:**
  - Only 15% of all patients who undergo CPR in the hospital survive to hospital discharge.
  - Patients should be informed about likely mortality outcomes as well as the potential adverse consequences of CPR and resuscitation attempts (e.g., fractured ribs, neurologic disability, invasive procedures).

Hospice and Palliative Care

- Focuses on the patient and family rather than the disease; stresses the provision of comfort and pain relief rather than treating illness or prolonging life.
- ↑ patient satisfaction; ↓ family anxiety.
- Patients may be treated at home, in the hospital, or in an inpatient hospice care facility.
- Per Medicare guidelines, requires a physician's estimate of < 6 months of life remaining in order to be reimbursed. However, some patients remain in hospice care much longer, as life expectancy is notoriously difficult to estimate.

Symptom Management

- **Pain:**
  - Very common, yet often undertreated.
  - Use a numeric or analog scale to assess.
  - Help the patient set pain management goals (strike a balance between sedation or "double effect" and total pain relief).
  - Treat chronic pain around the clock with long-acting drugs.
  - ↑ drugs as needed (there is no ceiling for pure opiates).
  - Use caution when combining analgesics (e.g., acetaminophen and NSAIDs).
  - Sedation typically precedes significant respiratory depression.
  - Always add a bowel regimen to prevent constipation in patients receiving continuous opiates.
- **Dyspnea:**
  - Present in up to 50% of dying patients.
  - Identify and treat the underlying cause where possible.
  - Nonspecific treatment with opioids is highly effective.
  - Nonpharmacologic measures include O_2, fresh air, and the use of fans to keep air moving.
  - Benzodiazepines treat the associated anxiety but not the dyspnea itself.
  - In patients with excessive secretions, a scopolamine patch may alleviate dyspnea and "choking" sensations.
- **Nausea and vomiting:**
  - If opiate related, consider a sustained-release formulation, a different agent at an equianalgesic dose, or the addition of a dopamine antagonist antiemetic.
  - If due to an intra-abdominal process such as constipation, gastroparesis, or gastric outlet obstruction, try small food portions, NG tube aspiration, laxative/bowel regimens, prokinetic agents, high-dose corticosteroids, or 5-HT_3 antagonists (e.g., ondansetron).
  - If related to ↑ ICP, use corticosteroids or palliative cranial irradiation as indicated.
  - If due to vestibular disturbance, treat with anticholinergic or antihistaminic agents.
  - Consider around-the-clock dosing of antiemetics.
  - Benzodiazepines and dronabinol may also be quite effective.
- **Constipation:**
  - Often opiate related.
  - Behavioral treatments include increasing activity and fluid/fiber intake.
  - Bowel regimen is required for patients on opiates. Start stool softeners and bowel stimulants prophylactically, and add enemas and other treatments as needed.
- **Delirium and agitation:**
  - Many patients experience confusion before death.
  - Consider the usual reversible causes of delirium (see the previous section in this chapter), and treat if indicated.
  - Consider the psychoactive effects of current medications.
  - Haloperidol or risperidone may be used if reversible causes are not identified and behavioral management is unsuccessful. It may be acceptable to do nothing if the delirium does not bother the patient and family.

*The use of opiates for end-of-life care is **not** associated with the development of addiction or abuse.*

For patients with irreversible conditions, tube feeding has not been shown to improve mortality and comfort but has been shown to lead to complications.

Nutrition and Hydration

- Dying patients who have stopped eating or drinking rarely experience hunger or thirst.
- Dry mouth can be managed with swabs and good oral care.

Withdrawal of Support

- Requests for withdrawal of care must be respected when received from appropriately informed and competent patients or their surrogates.
- Clinicians may recommend discontinuation of inappropriate interventions.

Psychological, Social, and Spiritual Issues

- Patients and families rank emotional support as one of the most important aspects of good end-of-life care.
- Clinicians can provide listening, assurance, and support as well as coordination with psychotherapy and group support.
- Depression must be treated and distinguished from normal anticipatory grief.

ELDER ABUSE

Many forms of elder abuse exist, and while such abuse is **widespread,** it often goes unreported. Victims tend to be women > 80 years of age who may be physically frail and/or confused. Characteristics of abusers include the following:

- Are often relatives or spouses of the victims.
- Often abuse alcohol.
- Are often dependent on the victim for money and housing.
- Adult children are the largest category of abusers across all forms of abuse.

Types of Abuse

Table 8.4 outlines types of elder abuse and their presentation.

Interview Techniques

- Initially, the patient should be interviewed alone.
- Inquire about perceived safety.
- Inquire about the patient's dependency on caregivers, friends, and family.
- Ask specific questions about abuse in reference to the items in the Table 8.4.

Physical Exam

- Be alert to pressure marks, burns, bruises, abrasions, or broken bones.
- May also be manifest by emotional withdrawal, a sudden change in alertness, or the development of depression.
- Bedsores, unattended medical needs, dehydration, and poor hygiene may be signs of neglect.

TABLE 8.4. Types and Characteristics of Elder Abuse

Type	Description
Domestic	Maltreatment of an older adult living at home or in a caregiver's home.
Institutional	Maltreatment of an older adult living in a residential facility.
Self-neglect	Behavior of an older adult who lives alone that threatens his or her own health or safety.
Physical abuse	Intentional infliction of physical pain or injury.
Financial abuse	Improper or illegal use of the resources of an older person without his/her consent, benefiting a person other than the older adult.
Psychological abuse	Infliction of mental anguish (e.g., humiliating, intimidating, threatening).
Neglect	Failure to fulfill a caretaking obligation to provide goods or services (e.g., abandonment; denial of food or health-related services).
Abandonment	Desertion of an elderly person by someone who has assumed responsibility for providing care to that person.
Sexual abuse	Nonconsensual sexual contact of any kind.

Management

- Whenever abuse is confirmed, the highest priority should be placed on protecting the safety of the elderly person while simultaneously respecting that person's autonomy.
- Two key management issues should be addressed:
  - First, does the patient accept or refuse intervention?
  - Second, does the patient have the capacity to accept or refuse intervention?
- If the patient **accepts intervention,** management options are as follows:
  - Implementing a safety plan for patients who are in immediate danger.
  - Providing assistance that addresses the causes of mistreatment (e.g., referral to drug or alcohol rehabilitation for addicted abusers; homemaker services for overwhelmed caregivers).
  - Referring the patient or family members to appropriate services.
- If the patient **has the capacity to accept intervention but refuses,** the physician's options include the following:
  - Educating the patient about the incidence of mistreatment of the elderly and the tendency for mistreatment to ↑ in frequency and severity over time.
  - Providing written information about emergency-assistance numbers and appropriate referrals.

- Developing and reviewing a safety plan.
- Developing a follow-up plan.

- If the patient **does not have the capacity to accept intervention,** the physician should discuss with Adult Protective Services issues such as assistance with financial management, guardianship, and court proceedings.

Reporting Requirements

- All states have laws about domestic or institutional abuse of the elderly, but these laws vary in the following ways:
  - The age at which a victim is covered.
  - The definition of elder abuse:
    - Classification of the abuse as criminal or civil
    - Types of abuse covered
    - Reporting requirements
    - Investigation procedures
    - Remedies
- In many states, the suspicion of abuse constitutes grounds for reporting, and physicians making reports in good faith are immune from legal liability. Often, the reporter remains anonymous.

CHAPTER 9

Hematology

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Approach to Anemia

Defined as a hemoglobin level < 14 g/dL in males and < 12 g/dL in females or a hematocrit < 40% in males and < 37% in females. Many cases have > 1 cause. The best first steps in evaluation are measurement of the absolute reticulocyte count (see Figure 9.1) and review of the **peripheral smear.** The reticulocyte count can be used to categorize anemias as follows:

Checking a reticulocyte count is a good way to begin to evaluate anemia, as it allows you to determine whether the anemia is hypoproliferative or hyperproliferative.

- **Hypoproliferative anemias:** Underproduction of RBCs with a low reticulocyte count. Classically subdivided by the MCV into **micro-, macro-,** and **normocytic** causes (see Table 9.1).
- **Hyperproliferative anemias:** ↑ destruction or loss of RBCs. **Reticulocyte count is elevated.**
  - The two most common causes are **bleeding** and **hemolysis** (covered in a subsequent section).
  - **MCV is not helpful in the evaluation of hyperproliferative anemias.**

Iron Deficiency Anemia

Daily iron loss from exfoliation of the skin and mucosa averages 1 mg/day under normal conditions. In menstruating, pregnant, or lactating females, however, the loss can approach 3–4 mg/day. Each milliliter of whole blood contains approximately 0.5 mg of iron. Thus, even a trivial GI bleed of 10 mL/day (below the threshold of detection for stool guaiac testing) will overwhelm the body's ability to absorb iron, resulting in iron deficiency.

Symptoms/Exam

Pica and pagophagia (ice chip craving) are classic symptoms of iron deficiency.

- General findings of anemia are skin and conjunctival pallor.
- **Features associated with iron deficiency** are as follows:
  - **Pica: Craving for nonfood substances, especially clay.**
  - **Pagophagia:** Craving for ice chips.
  - **Cheilosis:** Fissures at the corners of the mouth.
  - **Glossitis:** Smooth tongue.
  - **Koilonychia:** Spooning of the fingernails.
  - **Dysphagia:** Due to esophageal webs (**Plummer-Vinson syndrome**).

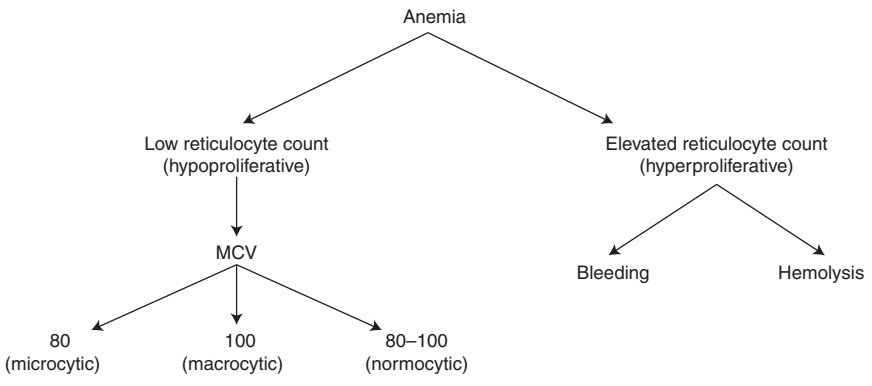

FIGURE 9.1. Algorithm for categorizing anemias.

TABLE 9.1. Classification of Hypoproliferative Anemias

Microcytic (MCV < 80)	Macrocytic (MCV > 100)	Normocytic (MCV 80–100)
"TAIL":	**Megaloblastic:**	ACD
Thalassemia trait	■ B_{12}, folate deficiency	Aplastic anemia
Anemia of chronic disease (ACD)	■ Myelodysplasia	Myelodysplasia
Iron deficiency	■ Myeloma	Renal insufficiency
Lead toxicity	■ Aplastic anemia	Mixed disorder
	■ Pure red cell aplasia	Early disease process
	■ Drug-induced bone marrow suppression	
	■ Alcohol	
	Nonmegaloblastic:	
	■ Liver disease	
	■ Hypothyroidism	

Differential

- Causes of iron deficiency include blood loss from menstruation, GI bleed, and frequent phlebotomy. Inadequate iron ingestion or poor iron absorption is rare; the latter is sometimes associated with celiac disease.
- **Anemia of chronic disease (ACD):** Table 9.2 distinguishes ACD from iron deficiency.
- **Lead poisoning:** Presents with **elevated RBC protoporphyrin, basophilic stippling,** and **lead lines** on the gums (the classic risk factor is occupation as a painter because of the lead in paint).

Diagnosis

- Classic findings are **microcytic, hypochromic** RBCs on peripheral smear with marked **anisocytosis** (see Figure 9.2). However, these findings are present in only a minority of patients.
- **Serum ferritin** is the most useful screen for iron deficiency. Values < 12 μg/L are diagnostic of iron deficiency. Although normal values do not rule it out, values > 100 μg/L make iron deficiency unlikely. Other iron indices are listed in Table 9.2.
- **Bone marrow biopsy** is rarely indicated.

TABLE 9.2. ACD vs. Iron Deficiency Anemia

	ACD	Iron Deficiency
MCV	Normal/low	Low
RDW	Normal	Normal or ↑
Ferritin	Normal/high	Low
TIBC	↓	↑
Soluble transferrin receptor	Normal	↑

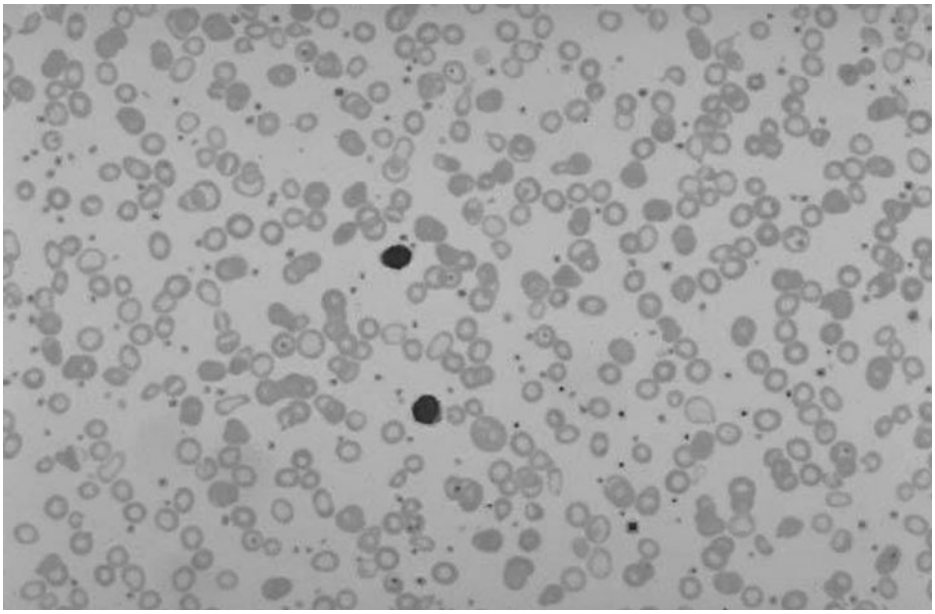

FIGURE 9.2. Iron deficiency anemia.

Note hypochromic cells (prominent central pallor) and microcytosis (RBCs smaller than the nucleus of the lymphocyte). There is also prominent thrombocytosis, a common finding associated with iron deficiency. (Reproduced, with permission, from Tierney LM et al. *Current Medical Diagnosis & Treatment*, 44th ed. New York: McGraw-Hill, 2005.)

- A **therapeutic trial of iron may be diagnostic:**
  - Reticulocytosis from iron typically begins 3–5 days after iron therapy.
  - Rise in hemoglobin lags behind by several days.

Treatment

- **Oral iron replacement:** The goal is approximately 300 mg of elemental iron per day. The most common reason for treatment failure is noncompliance with or intolerance of iron (can cause constipation).
- **Parenteral iron:** Carries a risk of anaphylaxis; use only if the patient has a total inability to tolerate oral iron.
- Treat the underlying cause.

Anemia of Chronic Disease (ACD)

Caused by sequestration of iron in the reticuloendothelial system as a result of an underlying inflammatory disorder. ACD is the **most common cause of anemia in the elderly population;** it often coexists with other causes.

Symptoms/Exam

Presents with symptoms of anemia and underlying disorders (e.g., infectious diseases, rheumatologic disorders, cancer).

Differential

Often needs to be differentiated from iron deficiency anemia (see Table 9.2).

Diagnosis

A diagnosis of exclusion; peripheral smear is nonspecific.

Treatment

- Treat the underlying cause.
- High doses of erythropoietin (30,000–60,000 U/week) may be tried in patients with serum erythropoietin levels < 100–500 IU/L.

Anemia Associated with Chronic Renal Failure

Erythropoietin is produced by the kidneys, and patients with chronic kidney disease often produce inadequate amounts. The anemia is usually normocytic and normochromic.

Symptoms/Exam

Presents with symptoms of anemia and underlying disorder (renal failure).

Differential

Must be distinguished from hemolytic anemia, iron deficiency anemia, blood loss, and other causes of anemia.

Diagnosis

- Evaluate hemoglobin, hematocrit, RBC indices, reticulocyte count, iron, TIBC, percent transferrin saturation, ferritin, and stool occult blood.
- If no other cause is identified and creatinine is ≥ 2, the anemia can be treated as anemia associated with chronic renal failure.
- Measurement of serum erythropoietin levels is generally not indicated.

Treatment

- Subcutaneous erythropoietin administration is recommended to target the hemoglobin to 10–12 g/dL.
- Iron supplementation is usually required to maintain adequate iron stores.

In developed countries, the most common cause of B_{12} deficiency is pernicious anemia.

Vitamin B_{12}/Folate Deficiency

The absorption of vitamin B_{12} requires many factors, including the secretion of intrinsic factor from the stomach and an intact terminal ileum. Vegans are at high risk for B_{12} deficiency, as B_{12} comes solely from animal products, whereas folate is derived from green, leafy vegetables. In developed countries, the 1° cause of B_{12} deficiency is **pernicious anemia (PA)** due to autoimmune destruction of parietal cells. PA is associated with other autoimmune disorders, including thyroiditis, vitiligo, and Addison's disease.

Symptoms/Exam

- Glossitis and atrophic gastritis (in PA).
- Mild icterus due to ineffective erythropoiesis, causing intramedullary hemolysis.
- Neurologic findings are present only in B_{12} deficiency and include the following:
  - **Peripheral sensory neuropathy:** Paresthesias in the distal extremities.

- **Posterior column findings:** Loss of vibratory sensation and proprioception; gait instability.
- Dementia or more subtle personality changes may occur at any time ("megaloblastic madness").
- Neurologic changes are not always reversible with B_{12} replacement.

The neurologic changes associated with B_{12} deficiency are not always reversible with B_{12} replacement.

Differential

The causes of B_{12} and folate deficiency are further outlined in Table 9.3.

Diagnosis

- **Labs:**
  - Low serum B_{12} level or RBC folate level (RBC folate level is more reflective of long-term folate levels than serum folate level).
  - Anemia with **MCV > 100** (may see one without the other).
  - Significant elevations in LDH and elevations in indirect bilirubin.
  - Pancytopenia is seen in severe cases.
  - Elevated levels of homocysteine or methylmalonic acid may be seen. **Methylmalonic acid** is a more sensitive test than B_{12} level and should be checked when B_{12} is in the lower part of the normal range.
- **Smear:** Macro-ovalocytes and **hypersegmented neutrophils** (any neutrophil with ≥ 6 lobes or the majority with ≥ 4 lobes; see Figure 9.3).
- **Bone marrow:** Megaloblastic (hypercellular, ↓ myeloid/erythroid ratio, enlarged RBC precursors with relatively immature nuclei); **may mimic the blastic appearance of acute leukemia.**
- The **Schilling test** establishes the **cause** of B_{12} deficiency. Stages I and II may be combined by using different radioactive labels for each step (see Figure 9.4). This test is rarely done now.
- **Anti–parietal cell antibodies** can be measured to confirm PA as the cause of B_{12} deficiency.

Methylmalonic acid is a more sensitive test than B_{12} level to evaluate for serum B_{12} deficiency.

Treatment

- **Parenteral B_{12}:** Recommended for the initial treatment of B_{12} deficiency in light of the possibility of generalized malabsorption.
  - **Initial replacement:** Give 100 μg IM daily × 1 week, then every week × 1 month.
  - **Maintenance:** Give 100 μg IM every month.

TABLE 9.3. Causes of B_{12}/Folate Deficiency

B_{12} Deficiency	Folate Deficiency
Dietary deficiencies—very rare; typically found in strict vegans	**Inadequate intake:**
↓ intrinsic factor—the most common cause; typically from pernicious anemia (autoimmune destruction of parietal cells)	▪ Malnutrition ▪ Alcoholism ▪ Malabsorption (e.g., tropical sprue)
Gastrectomy	↑ **demand:**
Ileal resection	▪ Pregnancy
Crohn's disease	▪ Hemodialysis (folate lost in dialysate)
Tapeworm infestation (*D. latum*)	▪ Chronic hemolytic anemia
Bacterial overgrowth of terminal ileum	▪ Psoriasis

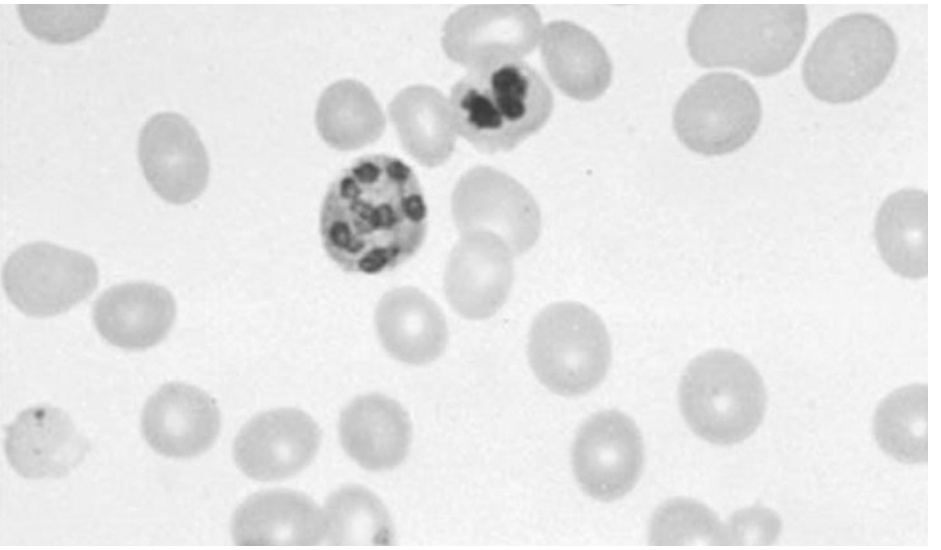

FIGURE 9.3. Megaloblastic anemia.

Note the macro-ovalocytes and prominent hypersegmented neutrophil. (Reproduced, with permission, from Kasper DL et al. *Harrison's Principles of Internal Medicine*, 16th ed. New York: McGraw-Hill, 2005: 605.)

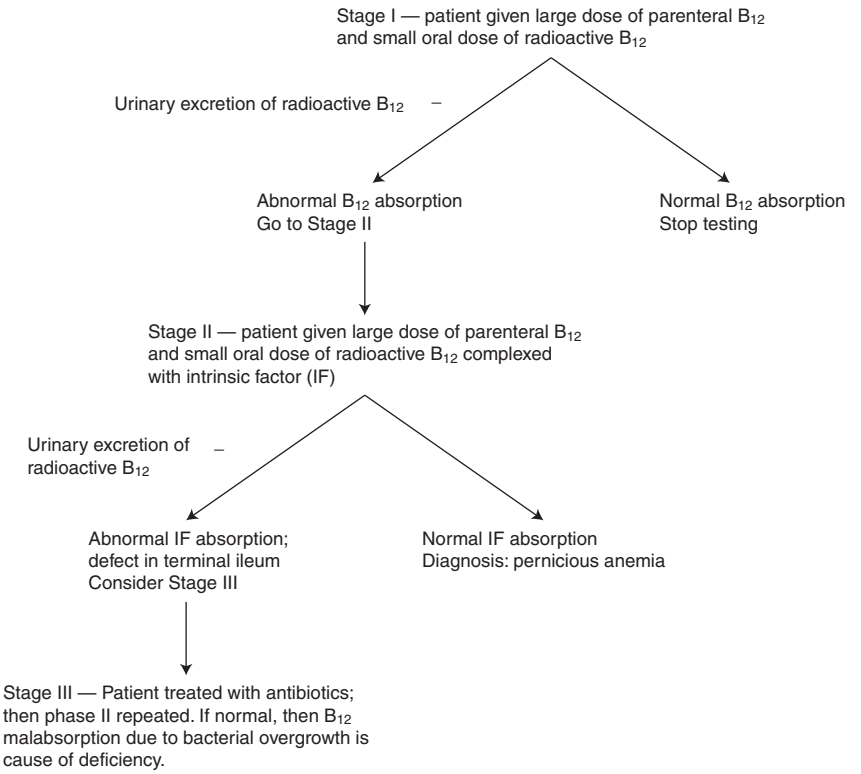

FIGURE 9.4. Algorithm for the diagnosis of B_{12} deficiency.

- **Oral B_{12}:** Equally effective for routine replacement, assuming that the patient is capable of absorbing. The recommended dose is 1–2 mg PO daily.
- **Oral folate:** A dose of 1 mg PO daily is adequate for folate deficiency.

Hemolytic Anemia

Hemolysis is classically categorized as either extravascular or intravascular on the basis of the putative location of RBC destruction and several associated features (see Table 9.4). **Other laboratory findings** include the following:

- **LDH** is often mildly elevated; striking elevations are characteristic of intravascular hemolysis.
- Indirect hyperbilirubinemia may occur up to 4 mg/dL; higher values usually indicate concomitant liver dysfunction.
- Chronic intravascular hemolysis may result in chronic hemoglobinuria, leading to iron deficiency.

Differential

- **Immune hemolysis (extravascular):** Divided into **warm** or **cold** antibodies, referring to the temperature at which the responsible autoantibody will bind erythrocytes and thus predict several other characteristics (see Table 9.5).
- **Microangiopathic hemolytic anemias (intravascular):** Characterized by **schistocytes** and a ⊖ **Coombs'** test. Usually caused by fibrin strands in damaged microvasculature, resulting in sheared RBCs. Almost all are associated with thrombocytopenia.
- **Oxidative hemolytic anemia:** A classic example is **G6PD deficiency,** in which erythrocytes have a ↓ ability to withstand oxidative stress.

TABLE 9.4. Extravascular vs. Intravascular Hemolytic Anemia

Feature	Extravascular	Intravascular
Site of RBC destruction	Spleen	Bloodstream, liver
Peripheral smear findings	Spherocytes (see Figure 9.5)	Schistocytes (see Figure 9.6)
Serum haptoglobin	Normal or mildly ↓	Markedly ↓
Urine hemosiderin	Unchanged	↑
Examples	Warm antibody immune hemolysis Hypersplenism Delayed transfusion reaction	Cold antibody immune hemolysis Acute transfusion reaction Microangiopathic hemolysis Oxidative hemolytic anemia (e.g., G6PD deficiency) PNH Hemoglobinopathies (sickle cell anemia) Infection related (malaria, *Clostridium, Babesia*)

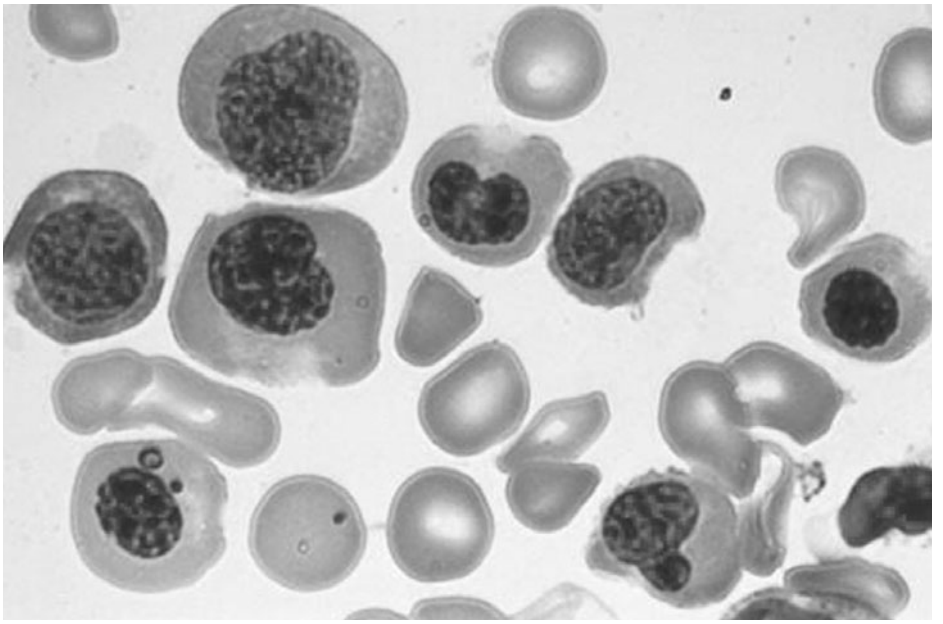

FIGURE 9.5. Spherocytes.

Characteristic spherocytes (small, round RBCs without central pallor) are present in addition to signs of markedly ↑ RBC synthesis (polychromasia, nucleated RBCs) in a patient with extravascular immune hemolysis. (Reproduced, with permission, from R.S. Hillman, MD, and K.A. Ault, MD, the American Society of Hematology Slide Bank. Copyright © American Society of Hematology. All rights reserved.)

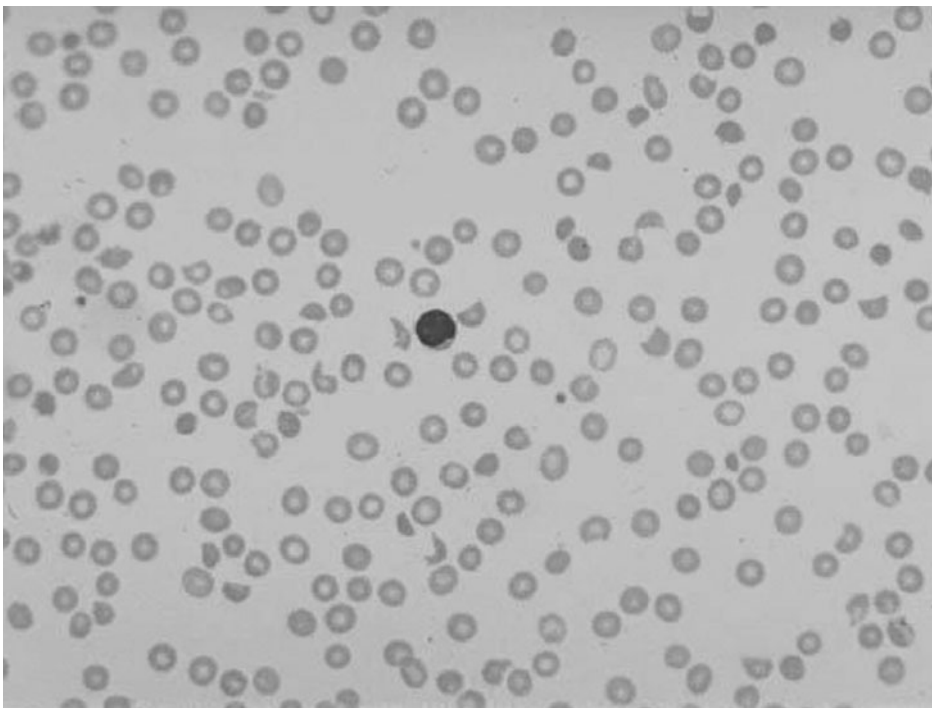

FIGURE 9.6. Schistocytes.

A large number of fragmented RBCs is characteristic of microangiopathic or intravascular hemolysis. In this case, the patient had HUS. (Courtesy of Lloyd Damon, MD.)

TABLE 9.5. Immune Hemolysis Categories

	Warm Antibody	Cold Antibody
Autoantibody	IgG	IgM
Direct antiglobulin test	⊕ for IgG	⊕ for IgM, complement
Peripheral smear	Spherocytes	Schistocytes
Site of RBC destruction	Spleen	Spleen
Associated conditions	Autoimmune diseases; CLL, lymphoma; α-methyldopa	*Mycoplasma* infection, EBV, CLL, lymphoma
Treatment	Steroids, splenectomy, immunosuppression	Warming extremities, plasmapheresis, alkylator medications

- **Any oxidative stress may precipitate hemolysis,** including viral infections, drugs (e.g., dapsone, sulfonamides, antimalarials, and nitrofurantoin), and dietary factors (e.g., fava beans).
- **Peripheral smear** shows **bite cells** (see Figure 9.7), **spherocytes,** and **Heinz bodies** (requires a special stain to see).
- **Lab tests:** Elevated LDH, elevated indirect bilirubin during acute hemolysis; G6PD activity (remember that measuring this during an acute hemolytic episode will result in a false-⊖ test).

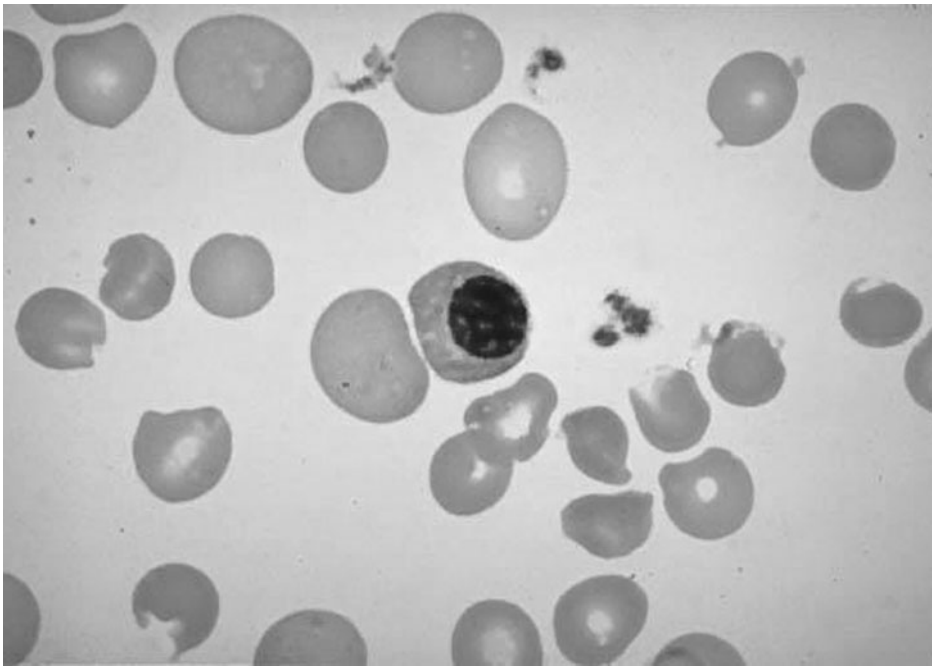

FIGURE 9.7. Bite cells.

Several characteristic bite cells are present in this patient with G6PD deficiency with acute oxidative hemolysis. (Courtesy of Lloyd Damon, MD.)

The classic triad for PNH is hemolysis, pancytopenia, and thrombosis. Flow cytometry for CD55 and CD59 is the diagnostic test of choice.

- **Paroxysmal nocturnal hemoglobinuria (PNH):** A rare clonal stem cell disorder caused by defective expression of RBC membrane proteins (CD55 and CD59).
  - Characterized by episodic complement-mediated intravascular hemolysis.
  - Previously diagnosed by Ham's test (acidified serum hemolysis) or by sucrose hemolysis test. Currently the **best test is to perform flow cytometry for CD55 and CD59.**
  - Associated with several hematologic complications, including **pancytopenia, venous thromboses** (especially Budd-Chiari), and progression to myelodysplasia, aplastic anemia, or AML. Can also cause massive hemoglobinuria, resulting in acute renal failure, as well as iron deposition, resulting in chronic renal failure and proximal tubule dysfunction.
- **Sickle cell anemia:** This subtype is covered in the hemoglobinopathy section below.

MICROANGIOPATHIES

Table 9.6 outlines the distinguishing features and treatment of microangiopathies.

TABLE 9.6. Differential and Treatment of Microangiopathies

Causes of Microangiopathy	Distinguishing Features	Treatment
DIC	Associated with severe infection, sepsis, and intravascular thrombus. Consumptive coagulopathy. **Elevated PT and PTT;** low fibrinogen.	Treat the underlying condition; cryoprecipitate (FFP if indicated).
TTP	Elevated LDH, neurologic symptoms, normal coagulation tests (unless concomitant DIC).	**Plasmapheresis with FFP,** steroids; **no platelet transfusions.**
HUS	Elevated LDH, renal insufficiency, normal coagulation tests (unless concomitant DIC).	Hemodialysis if necessary; may be self-limited.
Preeclampsia	Peripartum period; hypertension.	Early delivery; diuretics, antihypertensives.
HELLP syndrome	Peripartum period; elevated liver enzymes; probably a variant of eclampsia.	Early delivery.
Malignant hypertension	Hypertension.	Antihypertensives.
Vasculitis	Features of specific vasculitis.	Treat the underlying condition.
Miscellaneous (metastatic cancer, mechanical heart valve, severe burns)		Treat the underlying condition.

Thrombotic Thrombocytopenic Purpura (TTP)

The classic pentad for TTP is fever, microangiopathic hemolytic anemia, thrombocytopenia, neurologic changes, and renal failure.

A rare disorder of unknown etiology that is characterized by microangiopathy, **elevated LDH,** and neurologic changes tempered by appropriate clinical suspicion. The **classic pentad—fever, microangiopathic hemolytic anemia, thrombocytopenia, neurologic changes, and renal failure**—is seen in **< 10% of cases.**

Symptoms/Exam

- Patients usually present with anemia, bleeding, or neurologic abnormalities.
- Neurologic changes can be subtle and may include personality changes, headache, confusion, lethargy, or coma.

Differential

Associated conditions include the following:

- **Medications:** Cyclosporine, tacrolimus, quinine, ticlopidine, clopidogrel, mitomycin C, estrogens.
- **Pregnancy:** Overlaps with eclampsia and HELLP.
- **Autoimmune disorders:** SLE, antiphospholipid antibody syndrome, scleroderma, vasculitis.
- HIV.
- **Bone marrow transplantation:** Autologous or allogeneic.

Diagnosis

There is no one diagnostic test that is specific for TTP, but LDH is almost always elevated.

- Peripheral smear shows evidence of thrombocytopenia with microangiopathy (i.e., **schistocytes**), **PT/PTT should be normal unless DIC is also present.**
- ADAMTS13, the von Willebrand factor–cleaving protease that is deficient in TTP, can be measured, but the test is not entirely reliable and is generally too slow to be clinically useful. No standardized lab test exists for TTP, but **LDH is almost always elevated.**
- **It is unusual for platelets to be < 50,000/μL** unless another disorder is also present.

Treatment

- **Plasmapheresis:** Plasma exchange using FFP has a high response rate. Must be continued daily until neurologic symptoms resolve and LDH remains stable.
- If the patient is in a facility that lacks the capability for plasmapheresis, treatment can be temporized with FFP infusion.
- Splenectomy is also used for relapsing cases.
- Platelet transfusion is contraindicated unless serious bleeding is present.

Hemolytic-Uremic Syndrome (HUS)

- Similar to TTP, but **without neurologic changes and with more prominent renal failure.**
- **Sx/Exam:**
  - Characterized by microangiopathy, elevated LDH, and **renal failure.**
  - Primarily a self-limited disease in children that is **associated with diarrheal illnesses** (e.g., ***E. coli* O157:H7,** *Shigella*, *Campylobacter*), but may be associated with the same medications and conditions as TTP.

- **Tx:** Treat with supportive care and renal replacement therapy as needed for uremic symptoms. Plasma exchange is generally part of the treatment in adults unless the HUS is associated with diarrheal illness, in which case it has not been shown to be of benefit.

HEMOGLOBINOPATHIES

Thalassemias

- In normal patients, adult hemoglobin (HbA) is **primarily (97–99%) composed of two α chains plus two β chains** ($\alpha_2\beta_2$). In **thalassemia,** there is a ↓ amount of either α or β chain. As a result, HbA is reduced, while there is an ↑ in variant forms of hemoglobin such as HbA_2 and HbF. There are **two general types of thalassemias: α and β**.
  - **α-thalassemias:** Seen in patients from **Southeast Asia and China;** rarely seen in blacks.
  - **β-thalassemias:** Seen in patients from the **Mediterranean;** rarely seen in Asians or blacks.
- The severity of α-thalassemia depends on the number of α-globin genes functioning (see Table 9.7).
- β-thalassemia can be further subdivided into three types: β-thalassemia major, intermedia, and minor (see Table 9.8).
- **Dx:** Peripheral smear typically shows microcytosis, hypochromia, and basophilic stippling (β-thalassemia only). With increasing severity, ↑ nucleated RBCs and target cells are seen (see Figure 9.8).

Sickle Cell Anemia

Characterized by a homozygous defect in the β-globin gene that produces HbS. Heterozygotes have the sickle cell trait and are clinically normal except under extreme stress. Sickling is ↑ by **dehydration, acidosis, or hypoxia. Peripheral smear** shows **target cells, Howell-Jolly bodies,** and classic **sickle cells** (see Figure 9.9).

Symptoms/Exam

The clinical manifestations of sickle cell anemia are due to unstable sickle cells that hemolyze and aggregate to cause vaso-occlusion.

TABLE 9.7. Differential Diagnosis of α-Thalassemias

	α-Thalassemia Trait	Hemoglobin H Disease	Hydrops Fetalis
α-globin chains	2–3	1	0
Hematocrit	28–40%	22–32%	N/A
Hemoglobin electrophoresis	**Normal**	10–40% HbH	N/A
Clinical course	Normal life span	Chronic hemolytic anemia, exacerbated by stress	Universally lethal as neonate

TABLE 9.8. Differential Diagnosis of β-Thalassemias

	β-Thalassemia Major (Cooley's Anemia)	β-Thalassemia Intermedia	β-Thalassemia Minor
β-globin synthesis	Almost complete absence	Moderately ↓	Near normal (heterozygous)
Hematocrit	< 10% without transfusions	Variably low	28–40%
HbA	0%	0–30%	80–95%
HbA_2	4–10%	0–10%	4–8%
HbF	90–96%	90–100%	1–5%
Life span	20–30 years	Adult	Normal
Transfusion dependent	Yes	Variable	No
Clinical notes	Bony anomalies, hepatosplenomegaly, jaundice, transfusional iron overload	Mild bony anomalies; mild hepatosplenomegaly	Asymptomatic; mild microcytic anemia

- **Acute vaso-occlusion** manifests as pain crises, acute chest syndrome, priapism, stroke, and splenic sequestration.
- **Chronic vaso-occlusion** presents as renal papillary necrosis, avascular necrosis, autosplenectomy, and retinal hemorrhage.
- **Chronic hemolytic anemia** presents as jaundice, pigment gallstones, and aplastic crisis.

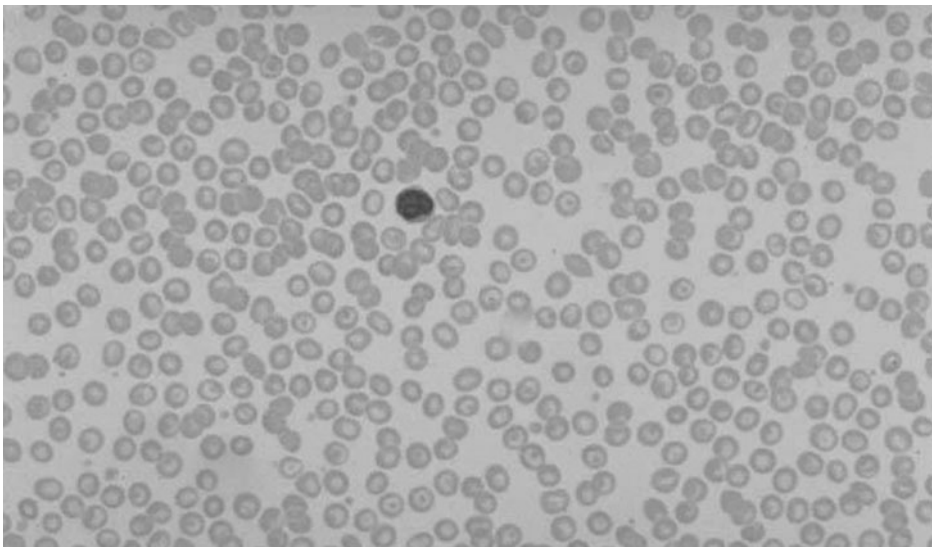

FIGURE 9.8. β-thalassemia major.

Note the microcytic, hypochromic cells, target cells, and nucleated RBCs. (Courtesy of Lloyd Damon, MD.)

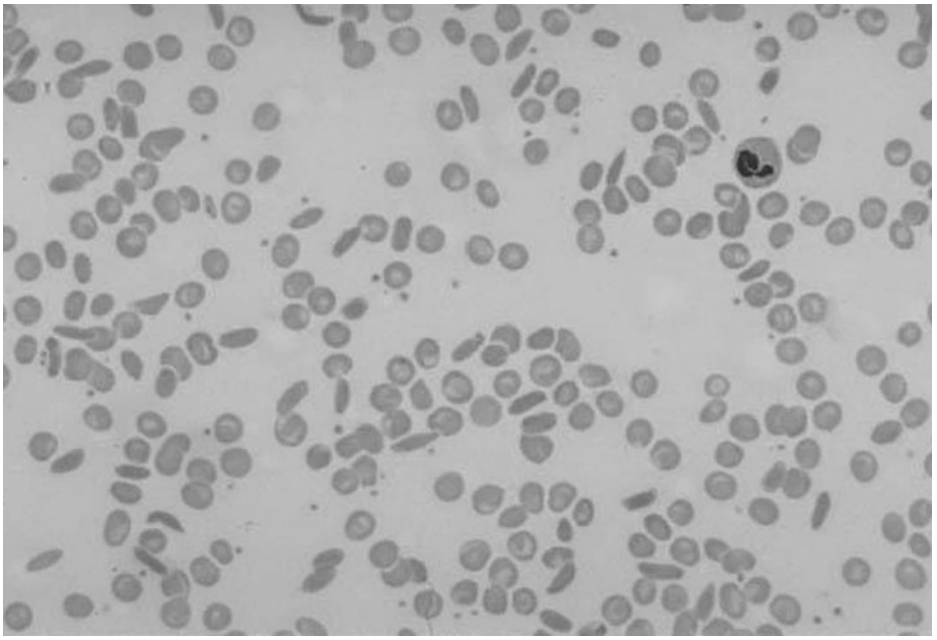

FIGURE 9.9. Sickle cell anemia.

Multiple sickle forms are characteristic. (Courtesy of Lloyd Damon, MD.)

- **Pain crises** can result from vaso-occlusion in any organ or tissue, typically in bones.
  - Triggered by factors that promote sickling: hypoxia, dehydration, and infection.
  - Commonly manifest as pain in the back and long bones lasting for hours to days.
- **Acute chest syndrome** results from vaso-occlusion in the pulmonary microvasculature and ↑ **mortality.**
  - Characterized by **chest pain, hypoxia, fever, pulmonary infarcts, or infiltrates on CXR.**
  - May be impossible to differentiate from pulmonary embolism (PE) and pneumonia.
  - Repeated episodes can lead to pulmonary hypertension and cor pulmonale.

TREATMENT

- **Maintenance:**
  - Although not universally accepted, folate supplementation may be required.
  - Pneumococcal vaccination.
  - Screen yearly for retinal disease and renal dysfunction.
  - Consider hydroxyurea in patients with > 3 pain crises per year requiring hospitalization or in those with repeated episodes of acute chest syndrome.
- **Acute episodes:**
  - Treat pain crises with aggressive hydration, analgesics, supplemental O_2 , and incentive spirometry.
  - Transfusions should be avoided given the risk of alloimmunization and iron overload. However, transfusions are indicated for severe vaso-

occlusive emergencies (acute chest syndrome, priapism, stroke). Transfuse until HbS is < 30%; **exchange transfusion if necessary to keep hemoglobin ≤ 10 g/dL.**

- **Acute chest syndrome:** In addition to hydration, analgesics, O_2, and transfusion, acute chest syndrome should be treated with **antibiotics covering for *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Mycoplasma pneumoniae*, and *Chlamydia pneumoniae*.** May require ICU admission.

Acute chest syndrome should be treated with careful hydration, adequate analgesics, O_2, and either transfusion to a hemoglobin of 10 g/dL or exchange transfusion if the hemoglobin is already over or near 10 g/dL. In addition, antibiotics to cover for S. pneumoniae, H. influenzae, M. pneumoniae, *and* C. pneumoniae *should be administered.*

OTHER CBC ABNORMALITIES

Erythrocytosis

Defined as a hematocrit > 54% in males and > 51% in females. Categorized mainly as 1° (polycythemia rubra vera) or 2° (reactive). The causes of **2° erythrocytosis** are listed in Table 9.9.

Diagnosis

Repeat CBC or obtain records to ensure accuracy.

- If hematocrit is > 60% in males or > 56% in females, it is by definition an elevated RBC mass, and measurement of RBC mass is not necessary.
- Exclude obvious causes of 2° erythrocytosis (see Table 9.9).
- Take a careful history, review the peripheral smear, and order appropriate labs and imaging studies (see Table 9.10).
- In smokers, pulse oximetry is sufficient to measure arterial O_2 saturation. An O_2 saturation < 92% is low enough to cause erythrocytosis.
- In nonsmokers, an ABG with carboxyhemoglobin level is necessary.
- Low erythropoietin levels are suggestive of polycythemia vera but are not perfectly sensitive or specific.
- Low ferritin and high B_{12}/folate levels are associated with polycythemia vera and not with 2° erythrocytosis.

TABLE 9.9. Causes of 2° Erythrocytosis

Type	Etiology
Congenital	High-affinity hemoglobin, congenitally low 2,3-DPG, autonomous high erythropoietin.
Arterial hypoxemia	High altitude, cyanotic heart disease, COPD, sleep apnea.
Renal lesions	Renal tumors, renal cysts, hydronephrosis, renal artery stenosis.
Liver lesions	Hepatoma, hepatitis.
Tumors	Adrenal adenoma, carcinoid, uterine fibroids, cerebellar hemangioblastoma.
Medications	Androgens.

TABLE 9.10. Evaluation of Erythrocytosis

Labs	Imaging
Arterial O_2 saturation	RBC mass
Ferritin, B_{12}, folate, creatinine, LFTs, uric acid	Abdominal ultrasound or CT scan
Serum erythropoietin	
JAK2 mutation	

Treatment

No specific management of 2° erythrocytosis is necessary. The treatment of polycythemia vera is covered in a separate section.

Thrombocytopenia

Defined as a platelet count < 150×10^9/L. Its causes are outlined in Table 9.11.

Diagnosis

- Examine a peripheral smear.

TABLE 9.11. Causes of Thrombocytopenia

Cause	Examples
↑ destruction	**Immune thrombocytopenia:** ■ **1°:** Autoimmune (ITP). ■ **2°:** Lymphoid malignancies, HIV, SLE, alloimmunization from prior platelet transfusions. ■ **Drug induced:** Gold, abciximab, ticlopidine, quinine, heparin. ■ **Post-transfusion purpura.** **Microangiopathies:** ■ TTP, HUS, eclampsia. ■ DIC, sepsis. ■ Severe hypertension. **Mechanical:** ■ Artificial heart valves. ■ Hemangiomas. ■ Central venous catheters. **Hypersplenism**
↓ production	Essentially any cause of marrow suppression can produce thrombocytopenia in isolation. See the pancytopenia discussion below. Probably the most important is drug-induced thrombocytopenia.
Other	**Dilutional:** From massive blood transfusions and fluid resuscitation. **Pseudothrombocytopenia:** From platelet clumping.

  - Rule out platelet clumping. Ask for a count/smear done in citrate, as EDTA (the anticoagulant most often employed in tubes used to collect a CBC) can cause clumping of platelets not seen on smear.
  - Look for evidence of microangiopathy (i.e., schistocytes), marrow suppression (megaloblastic changes, dysplastic changes), and immature platelets (giant platelets) suggesting ↑ platelet turnover.
- Take a careful drug history.
  - Acetaminophen, H_2 blockers, sulfa drugs, furosemide, captopril, digoxin, and β-lactam antibiotics are all associated with thrombocytopenia.
  - Never forget **heparin-induced thrombocytopenia** (see the discussion of clotting disorders below).
- Consider bone marrow biopsy if other findings suggest marrow dysfunction.
- Platelet-associated antibody tests are **not** useful.
- ITP is a diagnosis of exclusion.

Treatment

- Treat the underlying cause.
- Platelet transfusions in the absence of bleeding are usually unnecessary. Specific guidelines are given in the discussion of transfusion medicine below. Platelet transfusions are **contraindicated** in TTP/HUS and heparin-induced thrombocytopenia.

Thrombocytosis

Defined as a platelet count > 450×10^9/L. The main distinction is **reactive thrombocytosis** vs. **myeloproliferative disorder.** The steps involved in the evaluation of thrombocytosis are outlined in Table 9.12.

TABLE 9.12. Evaluation of Thrombocytosis

Steps in Evaluation	Comments
Repeat CBC and examine peripheral smear	Elevated platelet count may be spurious or transient. Clues to reactive thrombocytosis may be present.
Stratify by degree of thrombocytosis	A platelet count < 600k is unlikely to be essential thrombocythemia. A platelet count > 1000k is less likely to be reactive thrombocytosis, but many "platelet millionaires" still have reactive thrombocytosis.
Identify causes of reactive thrombocytosis	Iron deficiency anemia, RA, IBD, infection or inflammatory states, postsplenectomy, active malignancy, myelodysplasia with 5q-, sideroblastic anemia.
Rule out other myeloproliferative syndromes	Consider testing for the *JAK2* mutation for essential thrombocythemia. *BCR-ABL* by PCR in CML. Elevated RBC mass in polycythemia. Characteristic peripheral smear and splenomegaly in myelofibrosis.
Consider a bone marrow biopsy	Megakaryocyte morphology can suggest essential thrombocythemia. Examination for myelodysplasia, sideroblasts.

Neutrophilia

- Defined as an absolute neutrophil count > 10 × 109/L. The main distinction is between myeloproliferative disorder **(typically CML)** and reactive neutrophilia.
- Reactive neutrophilia is readily apparent from the history (inflammation, infection, severe burns, glucocorticoid, epinephrine) and from examination of a peripheral smear (Döhle bodies, toxic granulations).

Causes of 2° eosinophilia—

NAACP

Neoplastic
Asthma/**A**llergic
Addison's
Collagen-vascular disease
Parasites

Eosinophilia

- Defined as an absolute eosinophil count > 0.5 × 10^9/L. May be 1° (idiopathic) or 2°.
- **Idiopathic hypereosinophilia syndrome:**
  - Extremely rare and heterogeneous.
  - A prolonged eosinophilia of unknown cause with the potential to affect multiple organs by eosinophil infiltration.
  - Almost all cases have bone marrow infiltration, but heart, lung, and CNS involvement predicts a worse outcome.
  - Some cases are treatable with imatinib mesylate (Gleevec).
- **2° eosinophilia:** Remember the mnemonic **NAACP.**
- Note that several drugs (nitrofurantoin, penicillin, phenytoin, ranitidine, sulfonamides) and toxins (Spanish toxic oil, tryptophan) have been reported to cause eosinophilia.

Neutropenia

- Defined as an absolute neutrophil count (ANC) < 1.5 × 10^9/L (< 1.2 in blacks). Causes are outlined in Table 9.13.
- **Gram-⊕ organisms** account for **60–70% of cases of neutropenic fever.**
- See the discussion of neutropenic fever in the Oncology chapter.

Pancytopenia

- Almost always represents ↓ or ineffective bone marrow activity. Differentiated as follows:
  - **Intrinsic bone marrow failure:** Aplastic anemia, myelodysplasia, acute leukemia, myeloma, drugs (chemotherapy, chloramphenicol, sulfonamides, antibiotics).
  - **Infectious:** HIV, post-hepatitis, parvovirus B19.
  - **Marrow infiltration:** TB, disseminated fungal infection (especially coccidioidomycosis and histoplasmosis), metastatic malignancy.

TABLE 9.13. Causes of Neutropenia

Impaired Production	↑ Destruction
Cytotoxic chemotherapy and other drugs	Autoimmune neutropenia
Aplastic anemia and other causes of marrow failure	Felty's syndrome
	Sepsis
Congenital	HIV
Cyclic neutropenia	Acute viral illness

- Peripheral smear morphology is often helpful in diagnosis (see Tables 9.14 and 9.15).

BONE MARROW FAILURE SYNDROMES

Aplastic Anemia

Marrow failure with hypocellular bone marrow and no dysplasia. Typically seen in young adults or the elderly. Subtypes are as follows:

- **Autoimmune (1°) aplastic anemia:** The **most common type.** Assumed when 2° causes have been ruled out.
- **2° aplastic anemia:** Can be caused by multiple factors.
  - **Toxins:** Benzene, toluene, insecticides.
  - **Drugs:** Gold, chloramphenicol, clozapine, sulfonamides, tolbutamide, phenytoin, carbamazepine, and many others.
  - Post-chemotherapy or radiation.
  - **Viral:** Post-hepatitis, parvovirus B19, HIV, CMV, EBV.
  - **Other:** PNH, pregnancy.

Symptoms/Exam

- Presents with symptoms of pancytopenia (fatigue, bleeding, infections).
- **Adenopathy and splenomegaly are not generally seen.**

Diagnosis

- **Labs: Pancytopenia** and **markedly ↓ reticulocytes** are classically seen.
- **Peripheral smear:** Pancytopenia without dysplastic changes.
- **Bone marrow:** Hypocellular without dysplasia.

Treatment

- Supportive care as necessary (transfusions, antibiotics).
- **1° aplastic anemia:**
  - Definitive treatment is allogeneic bone marrow transplant.

TABLE 9.14. Summary of Peripheral Smear Morphology—RBCs

RBC Form	Associated Conditions
Schistocytes	Microangiopathy, intravascular hemolysis.
Spherocytes	Extravascular hemolysis, hereditary spherocytosis.
Target cell	Liver disease, hemoglobinopathy.
Teardrop cell	Myelofibrosis, thalassemia.
Burr cell (echinocyte)	Uremia.
Spur cell (acanthocyte)	Liver disease.
Howell-Jolly body	Postsplenectomy, functional asplenia.

TABLE 9.15. Summary of Peripheral Smear Morphology—WBCs

WBC Form	Associated Conditions
Atypical lymphocyte	Mononucleosis, toxoplasmosis, CMV, HIV.
Döhle body, toxic granulations	Infections, sepsis.
Hypersegmented neutrophil	B_{12} deficiency.
Auer rods	AML.
Pelger-Huët anomaly	Myelodysplasia, congenital.

  - Remissions can sometimes be induced with antithymocyte globulin and cyclosporine.
- **2° aplastic anemia:** Treat by correcting the underlying disorder.

Pure Red Cell Aplasia (PRCA)

Marrow failure in erythroid lineage only.

Symptoms/Exam

Symptoms are related to anemia.

Differential

After other causes of isolated anemia have been excluded, distinguish autoimmune PRCA from that stemming from abnormal erythropoiesis.

- **Autoimmune: Thymoma,** lymphoma/CLL, HIV, SLE, **parvovirus B19.**
- **Abnormal erythropoiesis:** Hereditary spherocytosis, sickle cell anemia, drugs (phenytoin, chloramphenicol).

Diagnosis

- **CBC:** Presents with anemia that is often profound, but WBC and platelet counts are normal. Markedly ↓ reticulocytes.
- **Peripheral smear:** No dysplastic changes.
- **Bone marrow biopsy:** Abnormal erythroid maturation and characteristic giant pronormoblasts are seen in parvovirus B19 infection.
- Obtain parvovirus B19 serology or PCR.

Treatment

- IVIG may be helpful in cases due to parvovirus.
- Remove thymoma if present.
- Immunosuppression with antithymocyte globulin and cyclosporine.

Myelodysplastic Syndrome (MDS)

A clonal stem cell disorder that is characterized by dysplasia resulting in ineffective hematopoiesis, and that exists on a continuum with acute leukemia. **Eighty percent of patients are > 60 years of age.** MDS is associated with

myelotoxic drugs and ionizing radiation and carries the risk of transforming to AML (but seldom to ALL). Its prognosis is related to the percentage of blasts, cytogenetics, and the number of cytopenias (see Table 9.16).

Symptoms/Exam

Symptoms are related to those of cytopenias.

Differential

Dysplasia can occur with vitamin B_{12} deficiency, viral infections (including HIV), and exposure to marrow toxins, so these factors must be ruled out before a diagnosis of MDS can be made.

5q– syndrome is a subset of MDS associated with a deletion of the long arm of chromosome 5. The disorder is associated with a better outcome as well as with a better response to treatment with lenalidomide.

Diagnosis

Peripheral smear shows dysplasia (see Figure 9.10).

- **RBCs:** Macrocytosis, macro-ovalocytes.
- **WBCs:** Hypogranularity; hypolobulation (pseudo–Pelger-Huët).
- **Platelets:** Giant or hypogranular.
- **Bone marrow:** Dysplasia; typically hypercellular. Cytogenetics can be normal or abnormal.

Treatment

- Supportive care with transfusions and growth factors (generally associated with a poor response).
- Chemotherapy and anticytokine agents (e.g., thalidomide and lenalidomide).
- Bone marrow transplantation is occasionally performed in younger patients.

TABLE 9.16. Classification of Myelodysplastic Syndromes

Subtype	Cytopenia	Blasts	Other
Refractory anemia (RA)	At least one lineage.	< 1% in peripheral blood, < 5% in bone marrow.	
Refractory anemia with ringed sideroblasts (RARS)	At least one lineage.	< 1% in peripheral blood, < 5% in bone marrow.	> 15% ringed sideroblasts in marrow.
Refractory anemia with excess blasts (RAEB)	Two or more lineages.	< 5% in peripheral blood, 5–20% in bone marrow.	
Chronic myelomonocytic leukemia (CMML)		< 5% in peripheral blood, < 20% in bone marrow.	Peripheral blood monocytosis ($> 1 \times 10^9$/L).
Refractory anemia with excess blasts in transformation (RAEB-T)			No longer used.

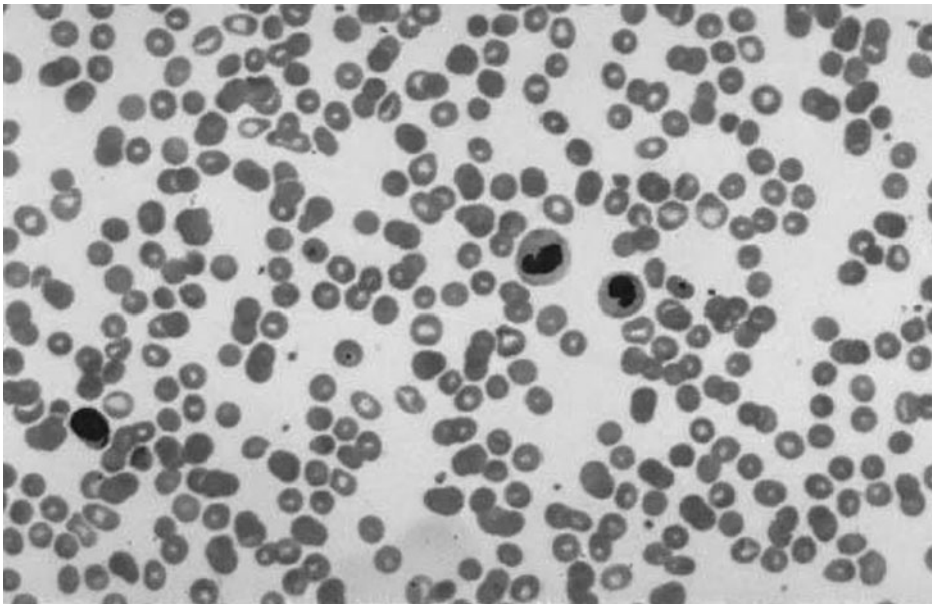

FIGURE 9.10. Myelodysplasia.

Both neutrophils in this slide demonstrate hypogranulation and hypolobation (pseudo–Pelger-Huët anomaly), suggesting myelodysplasia. (Courtesy of Lloyd Damon, MD.)

MYELOPROLIFERATIVE SYNDROMES

A group of syndromes characterized by **clonal ↑ of bone marrow RBCs, WBCs, platelets, or fibroblasts.** Each is defined by the cell lineages predominantly affected. Syndromes have **considerable clinical overlap,** and it is often difficult to distinguish them (see Table 9.17).

Polycythemia Vera

Defined as an abnormal ↑ in all blood cells, predominantly RBCs. The most common of the myeloproliferative disorders, it shows no clear age predominance.

Erythromelalgia = erythema, warmth, and pain in the distal extremities. It is often associated with polycythemia vera.

Symptoms/Exam

- **Splenomegaly** is common.
- Symptoms are related to higher blood viscosity and expanded blood volume and include dizziness, headache, tinnitus, blurred vision, and plethora.
- **Erythromelalgia** is frequently associated with polycythemia vera and is characterized by erythema, warmth, and pain in the distal extremities. May progress to digital ischemia.
- Other findings include generalized **pruritus,** epistaxis, hyperuricemia, and iron deficiency from chronic GI bleeding.

Diagnosis

- Exclude 2° erythrocytosis.
- Bone marrow aspirate and biopsy with cytogenetics.
- A mutation of ***JAK2,*** a tyrosine kinase, is found in 65–95% of patients. Although not yet part of the diagnostic criteria, it can be used to help distin-

TABLE 9.17. Differentiation of Myeloproliferative Disorders

	WBC	Hematocrit	Platelets	RBC Morphology	Comments
Polycythemia vera	Normal or ↑	↑	Normal or ↑	Normal	*JAK2* ⊕ in about 90% of cases.
CML	↑	Normal or ↓	Normal	Normal	Philadelphia chromosome or *BCR-ABL* ⊕ in > 95% of cases.
Myelofibrosis	Variable	**Usually** ↓	Variable	**Abnormal**	*JAK2* ⊕ in 40–60% of cases.
Essential thrombocythemia	Normal or ↑	Normal	↑	Normal	*JAK2* ⊕ in 50–60% of cases.

guish polycythemia vera from 2° erythrocytosis in unclear cases (but note that *JAK2* is mutated in other myeloproliferative disorders and is not diagnostic for polycythemia vera).
- **Diagnostic criteria from the Polycythemia Vera Study Group** are outlined in Table 9.18.

Treatment

- **No treatment clearly affects the natural history of the disease,** so treatment should be aimed at controlling symptoms.
- **Phlebotomy** to keep hematocrit < 45% treats viscosity symptoms.
- Helpful medications include the following:
  - Hydroxyurea or anagrelide to keep platelet count < 400,000; both medications have been shown to prevent thromboses.
  - Allopurinol if uric acid is elevated.
  - The current standard is to recommend **low-dose aspirin** in patients with erythromelalgia or other microvascular manifestations. **Avoid aspirin in patients with a history of GI bleeding or platelets greater than $1 \times 10^9/\mu L$** (except in the setting of erythromelalgia or microvascular symptoms).

Complications

Predisposes to both clotting and bleeding; may progress to myelofibrosis or acute leukemia.

TABLE 9.18. Polycythemia Vera Study Group Criteria[a]

"A" Criteria	"B" Criteria
A1: Raised RBC mass or hematocrit ≥ 60% in males, 56% in females.	**B1:** Platelet count > 400,000.
A2: Absence of cause of 2° erythrocytosis.	**B2:** Neutrophil count > 10,000 (> 12,500 in smokers).
A3: Palpable splenomegaly.	**B3:** Splenomegaly by imaging.
A4: Abnormal marrow karyotype.	**B4:** Characteristic bone marrow colony growth (almost never used) or low serum erythropoietin.

[a] A1 + A2 + A3 or A4 = polycythemia vera; A1 + A2 + any two B = polycythemia vera.

CML is associated with the Philadelphia chromosome, t(9;22), in 90–95% of cases. First-line treatment is generally a tyrosine kinase inhibitor called imatinib that targets the unique gene product of the Philadelphia chromosome, BCR-ABL.

Chronic Myelogenous Leukemia (CML)

An excessive accumulation of neutrophils that can transform to an acute process. It is defined by chromosomal translocation **t(9;22),** the **Philadelphia chromosome.**

Symptoms/Exam

- Hepatosplenomegaly is variable.
- Pruritus, flushing, diarrhea, fatigue, and night sweats are commonly seen.
- **Leukostasis symptoms** (visual disturbances, headache, dyspnea, MI, TIA/CVA, priapism) typically occur when the **WBC count is > 300,000.**

Diagnosis

- Labs reveal a markedly elevated neutrophil count.
- Basophilia, eosinophilia, and thrombocytosis may also be seen (see Figure 9.11).
- Leukocyte alkaline phosphatase (LAP) is low but rarely needed.
- The **Philadelphia chromosome is present in 90–95% of cases.** Detectable by **cytogenetics** or by **PCR** for the ***BCR-ABL*** fusion gene, performed on peripheral WBCs.
- Bone marrow biopsy is not necessary for diagnosis but is often done to determine the prognosis.
- The disease has three phases based on the percentage of blasts in peripheral blood:
  - **Chronic phase:** Bone marrow and circulating blasts < 10%.
  - **Accelerated phase:** Bone marrow or circulating blasts 10–20%.
  - **Blast crisis:** Bone marrow or circulating blasts ≥ 20%.

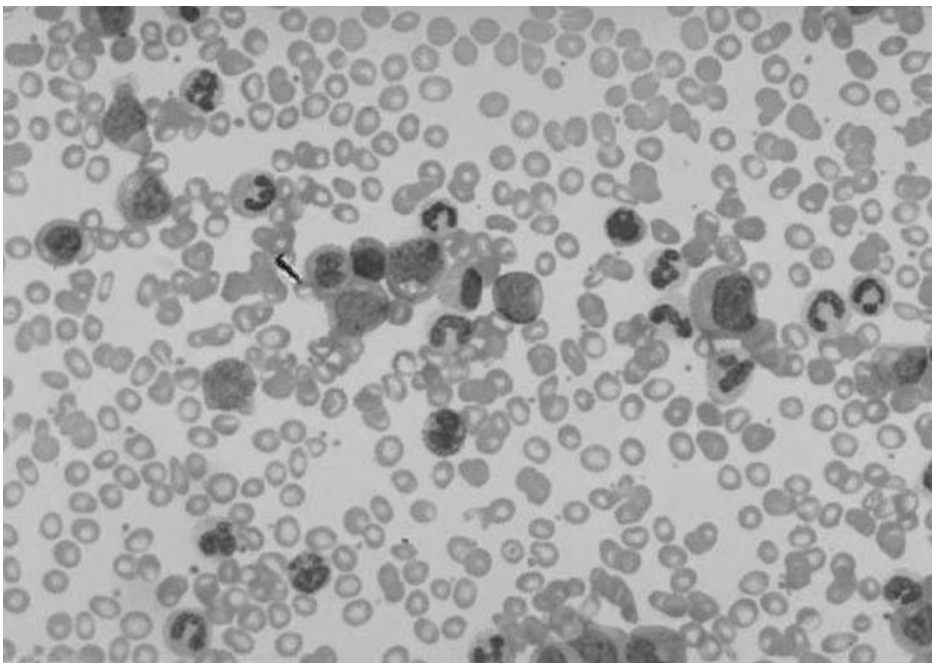

FIGURE 9.11. Chronic myelogenous leukemia.

Note the large number of immature myeloid forms in the peripheral blood, including metamyelocytes, myelocytes, and promyelocytes, as well as a large number of eosinophils and basophils. (Courtesy of Lloyd Damon, MD.)

Treatment

- The only curative therapy remains allogeneic bone marrow transplantation.
- Major remissions can virtually always be achieved with **imatinib mesylate (Gleevec).** The durability of these responses remains uncertain, but after five years > 80% of patients remain in cytogenetic remission.
- Temporizing therapies to ↓ WBC counts include hydroxyurea, α-interferon, and low-dose cytarabine.

Complications

The natural history is progression from the chronic phase to the accelerated phase (median 3–4 years) and then to blast crisis.

Myelofibrosis (Agnogenic Myeloid Metaplasia)

Fibrosis of bone marrow leading to **extramedullary hematopoiesis** (marked splenomegaly, bizarre peripheral blood smear). Affects adults > 50 years of age and can be 2° to marrow insults, including other myeloproliferative disorders, radiation, toxins, and metastatic malignancies.

Symptoms/Exam

- Characterized by symptoms of cytopenias. Fatigue and bleeding are especially common.
- Abdominal fullness due to massive **splenomegaly and hepatomegaly.**

Diagnosis

- **CBC:** Individual cytopenias or **pancytopenia.**
- **Abnormal peripheral smear: Teardrops,** immature WBCs, nucleated RBCs, giant degranulated platelets (see Figure 9.12).
- The presence of the *JAK2* mutation is not part of the diagnostic criteria and not specific but strongly suggests the diagnosis.

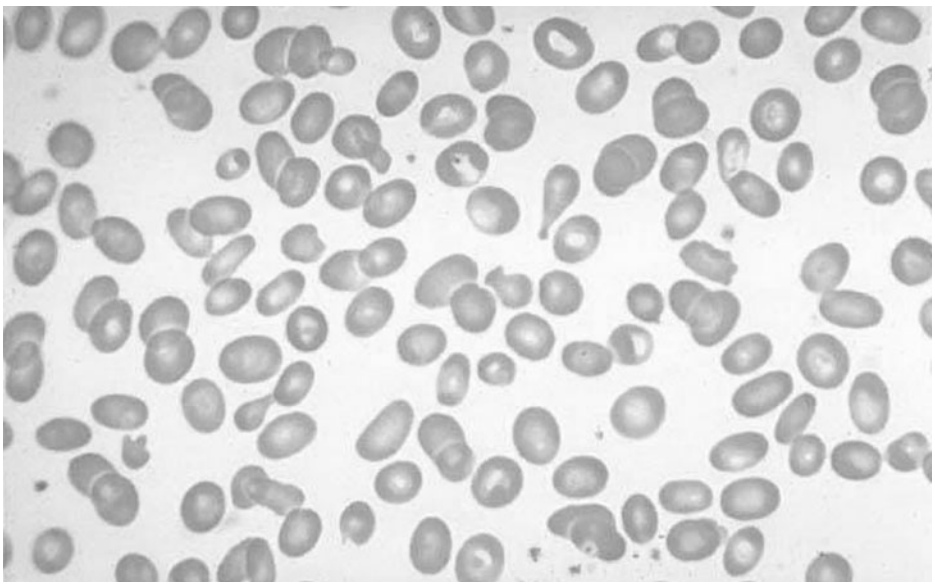

FIGURE 9.12. Myelofibrosis.

Note the large number of teardrop cells suggestive of bone marrow infiltrative disease. (Courtesy of Lloyd Damon, MD.)

- Bone marrow aspirate is frequently a **dry tap (no aspirate can be obtained)**; biopsy shows marked fibrosis.

Treatment

- Treatment is mostly supportive.
- Give transfusions as necessary, but may be difficult with hypersplenism.
- Splenectomy or splenic irradiation is appropriate if the spleen is painful or if transfusion requirements are unacceptably high.
- α-interferon or thalidomide is occasionally helpful.
- Allogeneic bone marrow transplantation for selected patients.

Complications

May evolve into AML with an extremely poor prognosis.

Essential Thrombocythemia

A clonal disorder with elevated platelet counts and a tendency toward thrombosis and bleeding. Has an indolent course with a **median survival > 15 years** from diagnosis.

Symptoms/Exam

- Patients are usually asymptomatic at presentation.
- Occasionally presents with erythromelalgia, pruritus, and thrombosis (at risk for both arterial and venous clots).

Diagnosis

- Primarily a **diagnosis of exclusion.** The first step is to rule out 2° causes of thrombocytosis (see separate section).
- Diagnosed by a persistent platelet count > 600,000 with no other cause of thrombocytosis.
- Like polycythemia vera, can be associated with mutation of the tyrosine kinase *JAK2* (in 50% of patients). Not part of diagnostic criteria, but can be useful in distinguishing essential thrombocythemia from other causes of thrombocytosis.

Treatment

- No treatment is needed if there is no evidence of thrombotic phenomena and the platelet count is < 500,000.
- Control platelet count with hydroxyurea, α-interferon, or anagrelide.
- Consider platelet pheresis for elevated platelets with severe bleeding or clotting.

Complications

The risk of converting to acute leukemia is approximately 5% over a patient's lifetime.

PLASMA CELL DYSCRASIAS

A group of disorders characterized by abnormal production of a paraprotein and often due to a monoclonal proliferation of plasma cells.

Multiple Myeloma

Symptoms are due to two aspects of myeloma:

- **Plasma cell infiltration: Lytic bone lesions, hypercalcemia, anemia,** plasmacytomas.
- **Paraprotein:** Depression of normal immunoglobulins leads to **infections;** excess protein may cause **renal tubular disease, amyloidosis,** or **narrowed anion gap** (due to positively charged paraproteins).

Diagnosis

The diagnostic criteria for multiple myeloma are delineated below and summarized in Table 9.19.

- CBC, creatinine, calcium, β_2-microglobulin, LDH.
- **SPEP with immunofixation electrophoresis (IFE), UPEP with IFE:** To identify the M spike. Not all serum paraproteins are detectable in urine and vice versa.
- Bone marrow aspirate and biopsy.
- **Skeletal bone plain film survey: Lytic lesions** are seen in 60–90% of patients.
- Myeloma is characterized by purely osteolytic lesions, so **bone scan is ⊖ and alkaline phosphatase is normal.**
- If other findings are consistent, the presence of the *JAK2* mutation is highly suggestive of the diagnosis.

Treatment

- **Myeloma is incurable** except in rare patients who can receive allogeneic stem cell transplantation. Autologous stem cell transplantation is sometimes done and appears to prolong survival.
- Methods for reducing symptoms and preventing complications are listed in Table 9.20.

Complications

Infection, renal failure, pathologic bony fractures, hypercalcemia, anemia.

Amyloidosis

A rare disorder characterized by the deposition of amyloid material throughout the body. Amyloid is composed of amyloid P protein and a fibrillar component. **The most common are AA and AL amyloid** (see Table 9.21).

TABLE 9.19. Diagnostic Criteria for Multiple Myeloma[a]

Major Criteria	Minor Criteria
Bone marrow with > 30% plasma cells.	Bone marrow plasmacytosis 10–30%.
Monoclonal spike on SPEP > 3.5 g/dL for IgG or > 2 g/dL for IgA, or ≥ 1 g/24 hours of light chain on UPEP in the presence of amyloidosis.	Monoclonal globulin spike less than levels in column 1.
	Lytic bone lesions.
Plasmacytoma on tissue biopsy.	Residual normal IgM < 50 mg/dL, IgA < 100 mg/dL, or IgG < 600 mg/dL.

[a] Diagnosis is established with one major and one minor criterion or with three minor criteria.

TABLE 9.20. Treatment of Multiple Myeloma

Goal	Treatment
Reduce paraprotein	High-dose chemotherapy with autologous stem cell rescue (standard of care, but limited to patients with good functional status). Allogeneic bone marrow transplantation (experimental). Steroid and alkylator combination chemotherapy. Biological molecules (thalidomide, bortezomib).
Prevent skeletal complications	IV bisphosphonate if any evidence of skeletal compromise (bony lesions, osteopenia, hypercalcemia). No data for oral bisphosphonates. Radiation therapy and/or orthopedic surgery for impending pathologic fractures in weight-bearing bones.
Prevent infections	Pneumococcal and *Haemophilus* vaccines if not already immune. Reduce paraprotein. All fevers should be presumed infectious until proven otherwise.
Alleviate anemia	Reduce paraprotein. Consider erythropoietin or transfusion if severely symptomatic.
Prevent renal failure	Reduce paraprotein. Prevent hypercalcemia, dehydration.

Symptoms/Exam

The characteristics of amyloidosis are somewhat dependent on the type of amyloid and organs involved:

- **Renal:** Proteinuria, nephrotic syndrome, renal failure.
- **Cardiac:** Infiltrative cardiomyopathy, conduction block, arrhythmia, low-voltage ECG, hypertrophy, and a **"speckled" pattern on echocardiography.**
- **GI tract:** Dysmotility, obstruction, malabsorption.
- **Soft tissues: Macroglossia, carpal tunnel syndrome,** "shoulder pad sign," "raccoon eyes."

TABLE 9.21. Amyloid Types and Fibrillar Components

Type	Fibrillar Component	Association
AA	Acute-phase apolipoproteins	Chronic inflammation (TB, osteomyelitis, leprosy, familial Mediterranean fever)
AL	Immunoglobulin light chain	Plasma cell dyscrasia (e.g., multiple myeloma)
ATTR	Transthyretin	Familial
AM	β_2-microglobulin	Hemodialysis

- **Nervous system:** Peripheral neuropathy.
- **Hematopoietic:** Anemia, dysfibrinogenemia, factor X deficiency, bleeding.
- **Respiratory:** Hypoxia, nodules.

Diagnosis

- **Tissue biopsy:** Amyloid yields the characteristic **apple-green birefringence** with Congo red stain.
- The choice of biopsy site depends on the clinical situation:
  - Biopsy of involved tissue has the highest yield.
  - Fat pad aspirate or rectal biopsies are generally low yield but minimally invasive.
- Once amyloid has been identified, investigate whether major organs are involved.
  - Check ECG and 24-hour urinary protein.
  - SPEP to screen for plasma cell dysplasia.
  - Consider malabsorption studies and echocardiography.

Other Diseases Associated with a Paraprotein

- **Monoclonal gammopathy of undetermined significance (MGUS):**
  - Presence of M spike without other criteria for myeloma.
  - One percent per year convert to myeloma, so monitor regularly for the development of myeloma.
- **Waldenström's macroglobulinemia** (see Table 9.22):
  - A low-grade B-cell neoplasm characterized by **IgM** paraprotein.
  - Exam findings include lymphadenopathy, splenomegaly, hepatomegaly, and dilated, tortuous veins on retinal exam ("**sausage link**" veins).
  - **Hyperviscosity syndrome:**
    - Elevated serum viscosity from IgM can occur, causing blurry vision, headaches, bleeding, and strokes. Emergent plasmapheresis can be used to lower serum viscosity by removing the IgM paraprotein. Serum viscosity can be measured and followed.

TABLE 9.22. Distinguishing Features of Various Monoclonal Paraproteinemias

	Myeloma	MGUS	Waldenström's Macroglobulinemia	Amyloidosis
Abnormal cell	Plasma cell	Plasma cell	Lymphoplasmacytes	Plasma cell
Lytic bone lesions	Present	Absent	Absent	Absent
Paraprotein	> 3.5 g IgG or > 2 g IgA	Less than myeloma	Any IgM	Any
Bone marrow	> 10% plasma cells	< 10% plasma cells	Lymphoplasmacytes	Amyloid deposition
Tissue involvement	Plasmacytomas	None	None	Amyloid deposition
Splenomegaly or adenopathy	Absent	Absent	Present	Absent

- Characterized by an indolent clinical course; treatment is the same as that for low-grade non-Hodgkin's lymphoma.

BLEEDING DISORDERS

Approach to Abnormal Bleeding

Excessive bleeding due to a defect in one of three variables: **blood vessels, coagulation factors,** or **platelets.**

Blood Vessel Disorders

- A rare cause of abnormal bleeding.
- Weakness of the vessel wall may be **hereditary** (e.g., Ehlers-Danlos, Marfan's) or **acquired** (e.g., vitamin C deficiency or "scurvy," trauma, vasculitis).
- Bleeding is typically **petechial or purpuric,** occurring around areas of trauma or pressure (e.g., BP cuffs, collars, belt lines).

Coagulation Factor Disorders

- Pose a significant bleeding risk only when clotting factor activity falls below 10%.
- **Hemarthroses** or deep tissue bleeds are most likely.
- Clotting factor disorders are either inherited or acquired (see also Tables 9.23 and 9.24).
- **Inherited disorders** include the following (see separate sections):
  - **Hemophilia A:** Deficiency in factor **VIII.**
  - **Hemophilia B:** Deficiency in factor **IX.**
  - **von Willebrand's disease (vWD).**
- **Acquired disorders** are as follows:

TABLE 9.23. Diagnosis of Clotting Factor Disorders

Condition	PT	PTT	Mixing Study
Factor VII deficiency, warfarin use, vitamin K deficiency	Elevated	Normal	Corrects
Hemophilia	Normal	Elevated	Corrects
Heparin	Normal	Elevated	No correction unless heparin-adsorbed
Factor VIII inhibitor	Normal	Elevated	No correction
Lupus anticoagulant	Normal	Elevated	No correction (test with Russell viper venom)
DIC	Elevated	Elevated	Minimal correction
Liver disease	Elevated	Elevated	Corrects
Dysfibrinogenemia	Elevated	Elevated	Variable correction (test with reptilase time)

TABLE 9.24. Comparison of Special Coagulation Tests

Test	Objective
Mixing study	To distinguish factor deficiency from inhibitor.
Reptilase time	To test for dysfibrinogenemia.
Russell viper venom test	To test for lupus anticoagulant.
Ristocetin cofactor assay	To test for vWF activity.

- **Factor inhibitors:** Elderly patients or patients with autoimmune diseases may acquire inhibitor, usually against factor VII or factor VIII.
- **Anticoagulants:** Warfarin or heparin.
- **Amyloid:** Associated with absorption of factor X in amyloid protein.
- **Dysfibrinogenemia:** Seen in liver disease, HIV, lymphoma, and DIC.

Platelet Disorders

- Cause **petechiae,** mucosal bleeding, and menorrhagia; **exacerbated by aspirin** and other medications.
- Bleeding time is usually not necessary to determine.
- Defects may be **quantitative** (see the thrombocytopenia section) **or qualitative.**
- **Qualitative platelet disorders:**
  - The **most common inherited defect is von Willebrand's factor (vWF) deficiency** (see separate section).
  - **Others:** Medications (aspirin, NSAIDs, IIB/IIIA inhibitors), uremia, and rare inherited defects (Glanzmann's, Bernard-Soulier).

Hemophilia

Hemophilias are **X-linked** deficiencies in clotting factors, so almost all patients are **male.**

- **Hemophilia A** = factor VIII deficiency (**"A eight").**
- **Hemophilia B** = factor IX deficiency (**"B nine").**

Symptoms/Exam

- Characterized by spontaneous bleeding in deep tissues, GI tract, and joints (hemarthroses).
- Variable in severity due to baseline percent factor activity.

Diagnosis

- Labs reveal a normal PT and a prolonged PTT; **mixing study corrects the defect (unless inhibitor is present).**
- Factor VIII or factor IX activity is low (0–10%).

Treatment

- There are two options for factor replacement:

  - **Recombinant factor:** Associated with less danger of HIV and HCV transmission than purified factor, but expensive.
  - **Purified factor concentrates:** Currently much safer than previous concentrates.
- Patients should be taught to self-administer factor in the event of spontaneous bleeding.
- Prophylaxis before procedures is as follows:
  - **Minor procedures:** For hemophilia A, DDAVP can be used if baseline factor VIII is 5–10%. Otherwise, replace with factor concentrates to 50–100% activity.
  - **Major procedures:** Replace with factor concentrate to 100% activity for the duration of the procedure with levels of at least 50% for 10–14 days (until the wound is healed).
- Acute bleeding:
  - **Minor bleeding:** Replace with factor concentrate to 25–50% activity.
  - **Major bleeding** (hemarthroses, deep tissue bleeding): Replace to 50% activity for 2–3 days.

Consider vWD in a patient with a normal platelet count in one of the following common clinical scenarios:

- *Heavy menses.*
- *Bleeding after a minor dental procedure or arthroscopic surgery.*
- *A history of frequent epistaxis or epistaxis after starting aspirin.*
- *A bleeding history that improves during pregnancy or on OCPs (estrogen ↑ vWF levels, so vWD often improves with the presence of additional hormones).*

von Willebrand's Disease (vWD)

The **most common inherited bleeding disorder.** vWF complexes with factor VIII to induce platelet aggregation, and if there is dysfunction or deficiency of vWF, adequate platelet aggregation does not occur.

Symptoms/Exam

- Exhibits a bleeding pattern similar to that of a platelet disorder **(petechiae, mucosal bleeding/epistaxis, heavy menses, exacerbated by aspirin).**
- Bleeding is generally provoked (e.g., by aspirin, trauma, surgery, circumcision, or dental work).

Diagnosis

- There are three basic types; type I (↓ vWF) is the most common (see Table 9.25).
- Labs reveal a normal PT and a normal or prolonged PTT.
- **Workup:** If vWD is suspected, check ristocetin cofactor assay, von Willebrand antigen, and factor VIII activity level

TABLE 9.25. Diagnosis of von Willebrand's Disease

Type	Factor VIII Antigen	vWF Activity (Ristocetin Cofactor)	Notes
I	Low/normal	Low	The most common form.
IIA	Low/normal	Absent	Abnormal vWF multimers.
IIB	Low/normal	Low/normal	Abnormal vWF multimers; **cannot use DDAVP.**
III	Low	Absent	

Treatment

- Avoid NSAIDs.
- Prophylaxis before procedures includes the following:
  - DDAVP is acceptable for minor procedures **except** in type IIB.
  - Purified factor VIII for major procedures.

Disseminated Intravascular Coagulation (DIC)

Consumptive coagulopathy is characterized by **thrombocytopenia, elevated PT and PTT,** and **schistocytes** on peripheral smear in association with serious illness. Acute DIC is often a catastrophic event. In contrast, chronic DIC shows milder features and is associated with chronic illness (disseminated malignancy, intravascular thrombus).

Symptoms/Exam

- **Bleeding:** Oozing from venipuncture sites or wounds, spontaneous tissue bleeding, mucosal bleeding.
- **Clotting:** Digital gangrene, renal cortical necrosis, **underlying serious illness** (typically sepsis, trauma, or malignancy).

Diagnosis

- Low fibrinogen (can be within the normal range but 50% ↓ from baseline), platelets.
- Prolonged PT; variably prolonged PTT.
- The presence of microangiopathy (e.g., **schistocytes**) and **elevated D-dimer** is characteristic, although schistocytes are seen in only 50% of cases.

Treatment

- Treat the underlying cause.
- If there is no serious bleeding or clotting, no specific therapy is needed.
- Adjuncts include the following:
  - Cryoprecipitate to achieve a fibrinogen level > 100–150 mg/dL.
  - Platelet transfusions in the setting of severe bleeding and a platelet count < 50.
  - Heparin at 4–6 U/kg/hr can treat thrombotic complications, but titrate to a high normal PTT to prevent excessive bleeding. A hematologist should be involved if a heparin drip is being used in light of the risk of bleeding.

Idiopathic Thrombocytopenic Purpura (ITP)

A disorder of reduced platelet survival, typically by immune destruction in the spleen. ITP commonly occurs in childhood with viral illnesses but may also affect young adults. Subtypes are as follows:

- **1°:** No identifiable cause.
- **2°:** Medications (gold, quinine, β-lactam antibiotics), CLL, SLE.

Symptoms/Exam

- Typically presents with **petechiae, purpura, mucosal bleeding,** and **menorrhagia.**
- **Spleen size is normal.**

If a patient has ITP with platelets > 30,000–50,000 and no bleeding, consideration should be given to surveillance with no active treatment.

Diagnosis

- Diagnosis is made by excluding other causes of thrombocytopenia.
- Antiplatelet antibodies, platelet survival times, degree of ↑ in platelet count after platelet transfusion, and bone marrow biopsy are **not** needed for diagnosis. However, if the patient is over the age of 60, a bone marrow biopsy is recommended to evaluate for myelodysplasia as the cause of thrombocytopenia.

Treatment

Consensus guidelines are that treatment is not necessary if platelet counts are > 30,000–50,000 and there is no bleeding. In the presence of acute bleeding, platelets can be transfused. Further treatment guidelines are given in Table 9.26.

CLOTTING DISORDERS

Approach to Thrombophilia

Venous thromboembolism (VTE) is **common,** affecting 1–3 per 1000 persons per year. Risk factors include pregnancy, surgery, smoking, prolonged immobilization, hospitalization for any cause, and active malignancy. In patients with a prior clot, recurrence rates are approximately 0.5% per year even when fully anticoagulated, with the highest risk occurring in the first year. An inherited thrombophilic state may be suspected in the following conditions:

- An unprovoked clot occurring in a young person (< 50 years of age).
- A clot in an unusual location (e.g., mesenteric vein, sagittal sinus).
- An unusually extensive clot.
- Arterial and venous clots.
- A strong family history.

TABLE 9.26. Treatment of ITP

Treatment	Dose	Efficacy	Notes
Prednisone	1 mg/kg/day × 4–6 weeks	60% response rate	Time to remission is 1–3 weeks. **First-line treatment, but 90% of adults will relapse.**
IVIG	1 g/kg × 1 or 0.4 g/kg/day × 2	80–90% response rate	Rapid remission, but short-lived. Used for acute bleeding risk.
Splenectomy	N/A	70% remission rate	May require looking for accessory spleen.
Danazol	600 mg/day	10–80% response rate	Usually second line.
Anti-RhD	50 μg/kg × 1	80–90% response rate	Induces hemolytic anemia; works only with Rh-⊕ patients.
Rituximab	375 mg/m² q wk × 4 doses	30% response rate in chronic refractory ITP	Can cause allergic reactions.

Differential

Look for a pattern of clots (see Table 9.27).

Diagnosis

Diagnostic testing during an **acute** thrombotic episode includes the following and is outlined in Table 9.27:

- Obtain a **targeted history and physical:**
  - **CBC and peripheral smear** to screen for myeloproliferative syndrome.
  - **Baseline PTT** to screen for antiphospholipid antibody syndrome. If PTT is prolonged before anticoagulation, evaluate with a Russell viper venom test (if ⊕, suggests the presence of a lupus anticoagulant).
- Diagnostic testing in a **nonacute setting** proceeds as follows:
  - Best done when considering whether to stop or prolong anticoagulation.
  - Stop warfarin until PT returns to baseline (warfarin interferes with many of the tests).
  - Anticoagulation may be continued if needed with low-molecular-weight heparin (LMWH).
  - A typical "hypercoagulable panel" for venous thrombophilia includes the following:
    - Factor V Leiden.
    - Prothrombin 20210 mutation.
    - Resistance to activated protein C.
    - Tests for antiphospholipid antibody (Russell viper venom time, anticardiolipin antibody, and VDRL; see the section on antiphospholipid antibody syndrome for additional details).
    - Homocysteine level.
  - If there is a high probability of inherited thrombophilia, add proteins C and S and antithrombin III activity.

Looking for very rare genetic conditions to explain a common problem is not cost-effective. Evaluation for rare causes of thrombophilia should be done only after common causes have been eliminated and in consultation with a hematologist.

TABLE 9.27. Differential Diagnosis of Clotting Disorders

Clot Location	Differential Diagnosis
Arterial and venous	Malignancy
	Heparin-induced thrombocytopenia (HIT) syndrome
	Hyperhomocysteinemia
	PNH
	Myeloproliferative diseases
	Antiphospholipid antibody syndrome
Venous only	Factor V Leiden
	Prothrombin 20210 mutation
	Protein C or S deficiency
	Antithrombin III deficiency
	Oral estrogens
	Postsurgical, pregnancy, immobilization
Arterial only	Atherosclerosis
	Vasculitis

Treatment

Tables 9.28 and 9.29 provide an overview of anticoagulation.

Specific Thrombophilic Disorders

Factor V Leiden

Characterized by a gene frequency of 5% in unselected Caucasian populations and 0.05% in Asians and Africans. In unselected patients with DVT or PE, the incidence is 20%, and in patients with a high likelihood of inherited thrombophilia, (young age, family history) it is 50%. Heterozygotes have a three- to eightfold ↑ in the risk of venous thrombosis; homozygotes have a 50- to 80-fold ↑ risk. In those with a history of **venous clots only,** there is no ↑ in the risk of arterial clots.

TABLE 9.28. Guide to Anticoagulant Medications

Medications	Pros	Cons	Tests Used to Monitor
Unfractionated heparin (UFH)	Short half-life; can turn off quickly if the patient bleeds. Although falling out of favor, still appropriate for acute coronary syndromes, cardiopulmonary bypass, acute thrombotic events, mechanical heart valves, and anticoagulation in renal failure.	Requires continuous IV infusion. Long-term use is associated with osteoporosis. Carries a risk of HIT.	Need to monitor PTT and platelet count at least daily (for HIT). Reversible with protamine.
LMWH	No need to monitor PTT, as dosing is weight based.	Excretion is impaired in renal failure. Not reversible with protamine. Requires injection.	Will not prolong PTT; if monitoring is required, measure anti–factor Xa activity.
Warfarin	Oral.	Slow to reach therapeutic effect; requires the addition of UFH or LMWH when starting for an acute clot. Teratogenic; many drug interactions. Warfarin skin necrosis (rare).	Monitor with INR; appropriate INR and duration vary by clinical situation (see Table 9.29). Reversible with FFP or vitamin K.
Direct thrombin inhibitors (lepirudin or argatroban)	Used for anticoagulation in patients with HIT.	Irreversible thrombin inhibitors; require continuous IV infusion.	Monitor with PTT.

TABLE 9.29. Guidelines for INR: Range and Duration of Anticoagulation

Condition	INR	Duration
Provoked DVT/PE	2–3	6–18 weeks after offending condition is resolved
Non-life-threatening DVT/PE	2–3	3–6 months
Life-threatening or severe DVT/PE	2–3	6–12 months vs. indefinite
Hereditary thrombophilia	2–3	6–12 months vs. indefinite
Atrial fibrillation	2–3	Indefinite
Mitral stenosis with evidence of thrombosis or atrial fibrillation	2–3	Indefinite
Antiphospholipid antibody syndrome	2.5–3.0	Indefinite
Mechanical heart valve	3–4	Indefinite

Diagnosis

The issue of whom to test for factor V Leiden is controversial. Table 9.30 outlines guidelines for making such a determination.

Treatment

The duration of anticoagulation after the first event should be as follows:

- **Heterozygous:** Same as for patients without the mutation.
- **Homozygous:** Extended anticoagulation is generally recommended.

Prevention

Guidelines for prophylaxis include the following:

- Routine prophylaxis is generally not recommended if there is no history of clotting.
- Standard prophylaxis for surgical procedures.
- Recommend against smoking and OCPs.
- Prophylaxis during air travel is controversial.

TABLE 9.30. Testing for Factor V Leiden

Probably Test	Unclear Whether to Test	Testing Not Recommended
Unprovoked clot at young age (< 50 years)	All patients with unprovoked clots	General population
Clot in an unusual location or of unusual severity	Clot after surgery or pregnancy despite prophylaxis	All pregnant women
⊕ family history		Women considering OCPs
Recurrent thrombosis		Presurgical screening
Thrombosis provoked by pregnancy or OCPs		

Prothrombin 20210 Mutation

Characterized by a gene frequency of 2–3% in the general population, with a Caucasian predominance. The mutation causes a higher level of prothrombin, leading to a hypercoagulable state. In unselected patients with DVT or PE, 7% have the mutation. Heterozygotes have a threefold ↑ risk of thrombosis. Homozygous patients probably have a higher risk, but it is not well quantified. The disorder is not as well studied as factor V Leiden, but the approach and recommendations are similar.

Protein C and S Deficiency/Antithrombin III Deficiency

Rarer but higher risk than factor V Leiden or prothrombin mutations. Given the rarity of these deficiencies, **testing is extremely low yield** in the absence of strong evidence of familial thrombophilia.

Hyperhomocysteinemia

Can be **genetic** (caused by a mutation in genes for cystathionine β-synthase or methylene tetrahydrofolate reductase) or **acquired** (due to a deficiency in B_6, B_{12}, or folate or to smoking, older age, or renal insufficiency). Associated with a twofold ↑ risk of venous thrombosis. Screen with a fasting serum homocysteine level and treat with folate supplementation. Most authorities also recommend vitamins B_6 and B_{12}.

Antiphospholipid Antibody Syndrome (APLA)

A syndrome of **vascular thrombi** or **recurrent spontaneous abortions** associated with laboratory evidence of autoantibody against phospholipids. Antiphospholipid antibodies are present in up to 5% of the general population, but the vast majority are transient and clinically insignificant.

Diagnosis

Diagnosis requires a clinical event **and** antiphospholipid antibody. Clinical characteristics are as follows:

- Venous and/or arterial thrombi.
- Thrombocytopenia.
- Livedo reticularis.
- Recurrent spontaneous abortions.
- **Antiphospholipid antibody:** Can include a variety of autoantibodies, but only one need be present.
  - **Lupus anticoagulant:** A clue to this may be prolonged PTT; confirm with a mixing study and a Russell viper venom test.
  - **Anticardiolipin antibody.**
  - **Others:** Antiphosphatidylserine, anti-β_2 glycoprotein I, **false-⊕** VDRL.

Heparin-Induced Thrombocytopenia (HIT)

There are two types of HIT, as outlined in Table 9.31. Type I is characterized by a mild fall in platelet count that occurs in the first two days after heparin is initiated and usually returns to normal with continued heparin use. It has no clinical consequences. Type II is the more serious type and is an immune-mediated disorder, in which antibodies form against the heparin-platelet factor 4 (PF4) complex.

TABLE 9.31. Types of Heparin-Induced Thrombocytopenia

Type	Dose-Dependent	Severity of Thrombocytopenia	Timing of Thrombocytopenia	Clinically Significant	Etiology
I	Yes	Mild	Immediate	No	Heparin-induced platelet clumping
II	No	Moderate/severe	4–7 days after exposure	**Yes**	Antibody against heparin-platelet complex

Symptoms/Exam

Type II HIT presents as follows:

- A ↓ in platelet count after 4–7 days of exposure to heparin.
- May cause **arterial or venous clots.**
- Less common with LMWH than with UFH.
- Exposure to any dose of heparin (heparin flushes, heparin-coated catheters, minidose SQ heparin) can cause this syndrome.

Diagnosis

- Type II HIT requires a high degree of clinical suspicion.
- Lab testing includes the following:
  - **Antibody against PF4.**
  - **Functional assay:** Detects abnormal platelet activation in response to heparin (heparin-induced platelet activation [HIPA], serotonin release).

Treatment

- If any suspicion exists, immediately stop all heparin; do not wait for lab tests, as catastrophic thrombosis and/or bleeding can occur.
- If the degree of suspicion is high, **treat with direct thrombin inhibitors** (lepirudin, argatroban) until platelet counts recover given the high risk of thrombosis.
- **Warfarin monotherapy is contraindicated in acute HIT** in view of the risk of skin necrosis.

Prevention

- Preferential use of LMWH given the lower incidence of HIT.
- If the patient has a history of HIT, do not use any heparin unless the procedure cannot be done with another anticoagulant and until 3–6 months have elapsed and lab tests are ⊖ for HIT. Do not reuse heparin unless clinically necesssary.

TRANSFUSION MEDICINE

Pretransfusion Testing

Pretransfusion tests include the following:

- **Type and cross:** Use when transfusion is **probable** (e.g., in an acutely bleeding patient). Test recipient plasma for reactivity against RBC from the donor—i.e., indirect Coombs' test on **donor** RBCs.

- **Type and screen** (aka "type and hold"): Use when transfusion is **possible** (e.g., in preoperative evaluation). Screen recipient plasma for antibody against a standardized RBC panel—i.e., perform an indirect Coombs' test on **reference** RBCs.
- Consider the risks of transfusions (see Table 9.32).

TABLE 9.32. Risks of Transfusion Therapy

	Risk	Clinical Features	Treatment	Cause	Comments
Febrile nonhemolytic reactions	1–4 in 1000	Chills, rigors within 12 hours of transfusion.	Acetaminophen, diphenhydramine.	WBC or bacterial contaminant, cytokines.	Most common reaction.
Allergic reaction	1–4 in 1000	Urticaria or bronchospasm.	As usual for urticaria or bronchospasm.	Allergic reaction to plasma contaminant.	Seen in IgA deficiency; prevented through use of washed RBCs.
Delayed hemolysis	1 in 1000	Extravascular hemolysis 5–10 days after transfusion: jaundice, drop in hematocrit, ⊕ Coombs' test, microspherocytes in peripheral smear.	Supportive care; send sample to blood bank to work up new alloantibody.	Low-titer antibodies against minor blood antigens.	Multiparous women or multiply transfused patients may be at ↑ risk.
Transfusion-related acute lung injury (TRALI)	1 in 5000	Noncardiogenic pulmonary edema, usually within six hours of transfusion.	Supportive care.	Donor antibodies binding to recipient leukocytes in pulmonary capillaries.	Most cases resolve after 96 hours.
Acute hemolytic transfusion reaction	1 in 12,000	Chills, fever, backache, headache, hypotension, tachypnea, tachycardia. DIC may occur in severe cases.	Vigorous hydration to prevent acute tubular necrosis. If hemolysis is severe, consider forced diuresis with mannitol and urinary alkalinization.	Severe intravascular hemolysis due to preexisting antibody against donor RBCs (typically ABO).	Usually due to a clerical error.
HBV	1 in 66,000				
HCV	1 in 103,000				
HIV	1 in 676,000				

Management of Transfusion Reactions

- Stop the transfusion immediately.
- Contact the blood bank immediately to start double-checking paperwork.
- Draw CBC, direct antiglobulin test, LDH, haptoglobin, indirect bilirubin, free hemoglobin, PT/PTT, UA, and urine hemoglobin.
- Repeat type and screen and draw blood culture. Send all untransfused blood with attached tubing back to the blood bank.

Transfusion Products

Table 9.33 lists common types of transfusion products and their applications.

Platelet Transfusion Threshold

The criteria for determining the platelet transfusion threshold are controversial but are as follows:

- A bleeding patient with a platelet count < 50,000.
- CNS bleeding with a platelet count < 100,000.
- Major surgery with a platelet count < 50,000.
- Asymptomatic with a platelet count < 10,000.
- Asymptomatic but febrile with a platelet count < 20,000.

TABLE 9.33. Types of Transfusion Products

Product	Distinguishing Features	Use
Whole blood	Contains RBC and plasma.	Provides oxygen-carrying capacity and plasma volume expansion. For patients with massive blood loss (e.g., trauma).
Packed RBCs	RBC concentrated from donor unit.	Standard RBC product. Each unit raises hemoglobin 1 g/dL.
Washed RBCs	RBCs with plasma removed.	Prevent allergic reactions.
Irradiated RBCs	Irradiation.	Prevent graft-versus-host disease.
Leukocyte-depleted RBCs	Deplete donor leukocytes with WBC filter.	Prevent alloimmunization, febrile reactions, and CMV transmission.
Random donor platelets	Pooled platelets from six donors.	Each "six pack" should raise platelet count by 30,000–50,000.
Single-donor platelets	Platelets extracted from a single donor by apheresis.	Use if the patient is alloimmunized; each unit should bump platelets by 30,000–50,000.
FFP	All clotting factors, but high fluid volume.	To correct coagulopathy of liver disease or excess warfarin.
Cryoprecipitate	Factor VIII, fibrinogen, and vWF.	Use in DIC if fibrinogen is < 100. Associated with a high risk for transmitting infection because it is not heat inactivated.

TABLE 9.34. Malignant vs. Reactive Adenopathy

	FAVORS MALIGNANT	FAVORS REACTIVE
Patient characteristics	Smoker; older age.	Age < 40.
Size	Larger.	Lesions < 1 cm are almost always benign.
Consistency	Hard, matted, nontender, fixed.	Rubbery, mobile, tender.
Location	Supraclavicular (Virchow's node); periumbilical (Sister Mary Joseph's nodule).	Inguinal nodes up to 2 cm are normal.

MISCELLANEOUS HEMATOLOGY

Lymphadenopathy

The 1° goal is to distinguish **malignant** from **reactive** adenopathy (see Table 9.34).

DIFFERENTIAL

See Table 9.35 for a list of common causes.

TABLE 9.35. Causes of Lymphadenopathy

	GENERALIZED	REGIONAL
Infectious	Mononucleosis Hepatitis Acute HIV *Brucella* Syphilis Fungal diseases Scrub typhus Toxoplasmosis	Keratoconjunctivitis Cat-scratch disease Tularemia *Yersinia pestis* Chancroid Lymphogranuloma venereum Trachoma Scrofula
Neoplastic	Lymphoma CLL Post-transplant lymphoproliferation	Metastatic malignancy Histologic transformation
Other	Collagen vascular disease Angioimmunoblastic lymphadenopathy Phenytoin Serum sickness	Castleman's disease Kawasaki's disease Kikuchi's disease Sarcoidosis

Porphyrias

A variety of disorders that have in common genetic **defects in heme synthesis.** Two types may present in adults: acute intermittent porphyria and porphyria cutanea tarda.

Acute Intermittent Porphyria

Caused by a defect in **porphobilinogen deaminase. Autosomal dominant;** most common in women in their 20s.

Symptoms/Exam

- Presents with attacks of severe **abdominal pain.**
- Peripheral **neuropathy,** seizures, **psychosis,** and basal ganglia syndromes are also seen.
- SIADH.
- Many factors and medications can **trigger attacks,** including menses, alcohol, barbiturates, phenytoin, sulfonamides, caffeine, estrogens, food additives, and starvation.

Diagnosis

Look for excess aminolevulinic acid or porphobilinogen in the urine.

Complications

Cirrhosis and hepatocellular carcinoma, heart block, hypopituitarism, hypogonadism, hypoadrenalism, **diabetes,** arthropathy.

Vitamin Deficiencies

Table 9.36 outlines common vitamin deficiencies and their associated disorders.

TABLE 9.36. Common Vitamin Deficiencies

Vitamin	Deficiency	Clinical Symptoms
A (retinol)		Night blindness, conjunctival xerosis, Bitot's spots (white spots on conjunctiva), keratomalacia.
B_1 (thiamine)	Dry beriberi, wet beriberi	Peripheral neuropathy, Wernicke-Korsakoff syndrome; high-output CHF, vascular leak.
B_2 (riboflavin)		Cheilosis, angular stomatitis, glossitis, weakness, corneal vascularization, anemia.
Niacin	Pellagra	**D**ermatitis, **D**iarrhea, **D**ementia (then **D**eath)—the **3 (or 4) D's.**
B_6 (pyridoxine)		Peripheral neuropathy, seizures, anemia (may be precipitated by INH).
C (ascorbic acid)	Scurvy	Perifollicular hemorrhage, petechiae, bleeding gums, hemarthrosis, poor wound healing.
D		Osteomalacia in adults; rickets in children.
E (α-tocopherol)		Areflexia, ophthalmoplegia, ↓ proprioception.

NOTES

CHAPTER 10

Hospital Medicine

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Pulmonary Embolism (PE)

Almost all PE patients have dyspnea, pleurisy, or tachypnea, and the absence of all three argues against the diagnosis.

Responsible for 50,000 deaths and up to 250,000 hospitalizations per year. The mortality rate for untreated venous thromboembolic disease exceeds 15%. Risk factors include **prior thromboembolic disease, malignancy, recent surgery, immobility, inherited thrombophilia,** and **certain medications** (OCPs, HRT). Tobacco use and obesity are also associated with venous thromboembolism.

Symptoms/Exam

- There are no specific signs or symptoms for PE.
- **Dyspnea and pleurisy** are each seen in > 50% of cases.
- Less common are hemoptysis, fever, and cough.
- **Tachypnea, rales,** and/or **tachycardia** may be seen.

Diagnosis

The results of the V/Q scan must be interpreted in conjunction with the pretest clinical probability.

- **Clinical gestalt** is a powerful predictor of the likelihood of PE (see Table 10.1).
- **Modified Wells criteria** (see Table 10.2) more precisely refine the clinical gestalt.
  - **Wells score ≤ 4:** PE is unlikely. A low Wells score and a normal D-dimer rule out PE.
  - **Wells score > 4:** Further testing for PE is indicated.
- **D-dimer:**
  - Most useful for excluding PE in low-risk patients (those with a modified Wells score ≤ 4) when levels are low or normal.
  - **The specificity of an elevated D-dimer is poor,** as there are many reasons D-dimers may be elevated, particularly in older, hospitalized patients.
- **ABGs:** Respiratory alkalosis with an ↑ alveolar-arterial (A-a) oxygen gradient is classically seen, although ABGs may be normal.
- **ECG:**
  - Nonspecific anterior T-wave inversions and sinus tachycardia are the most common ECG findings.
  - Evidence of new right heart strain—e.g., new RBBB, right axis deviation, and the combination of an S wave in lead I and a Q wave with an inverted T wave in lead III (**S1Q3T3**)—is less common but more suggestive of PE.
- **CXR:** Often shows nonspecific pleural effusion or atelectasis. Two rare findings suggest PE:

*A D-dimer test is more useful in **ruling out** PE when normal; an elevated D-dimer is not specific for PE.*

TABLE 10.1. Accuracy of Clinical Gestalt in Determining the Likelihood of PE[a]

Clinical Likelihood	Actual Incidence
Low (< 20%)	9%
Moderate (20–80%)	30%
High (> 80%)	68%

[a] According to the Prospective Investigation of Pulmonary Embolism Diagnosis (PIOPED) study.

TABLE 10.2. Modified Wells Criteria for Pulmonary Embolism[a]

Clinical Findings That Increase Risk	Points
Clinical symptoms of DVT (leg swelling, pain with palpation)	3.0
Other diagnosis less likely than PE	3.0
Heart rate > 100	1.5
Immobilization (≥ 3 days) or surgery in the previous four weeks	1.5
Previous DVT/PE	1.5
Hemoptysis	1.0
Malignancy	1.0

[a] Scores > 4: PE is likely; scores ≤ 4: PE is unlikely.

  - **Hampton's hump:** A pleural-based density representing intraparenchymal hemorrhage.
  - **Westermark's sign:** The stump of a central pulmonary artery with focal oligemia (radiolucency).
- **Lower extremity venous Doppler ultrasound:** A thrombus is present in approximately 30% of PE cases.
- **CT angiogram:** See Figure 10.1 and Table 10.3.
- **Ventilation-perfusion (V/Q) scanning:** See Figure 10.2 and Table 10.3 and 10.4.
- **Pulmonary angiogram:** See Table 10.3.

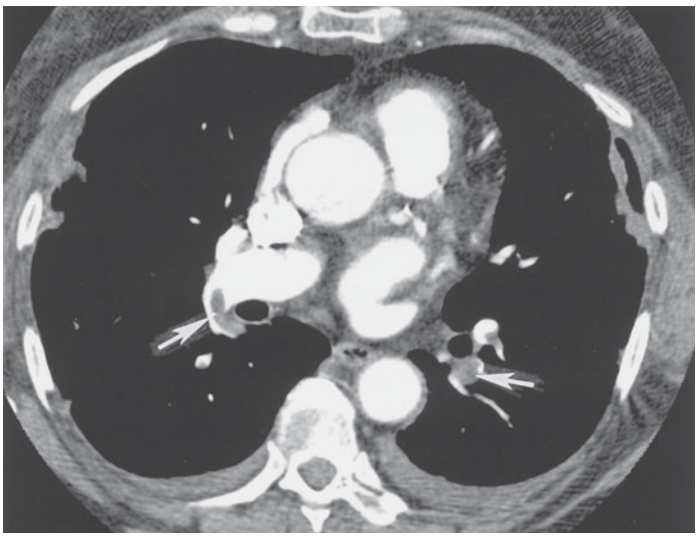


FIGURE 10.1. CT angiogram demonstrating bilateral filling defects due to pulmonary emboli (arrows).

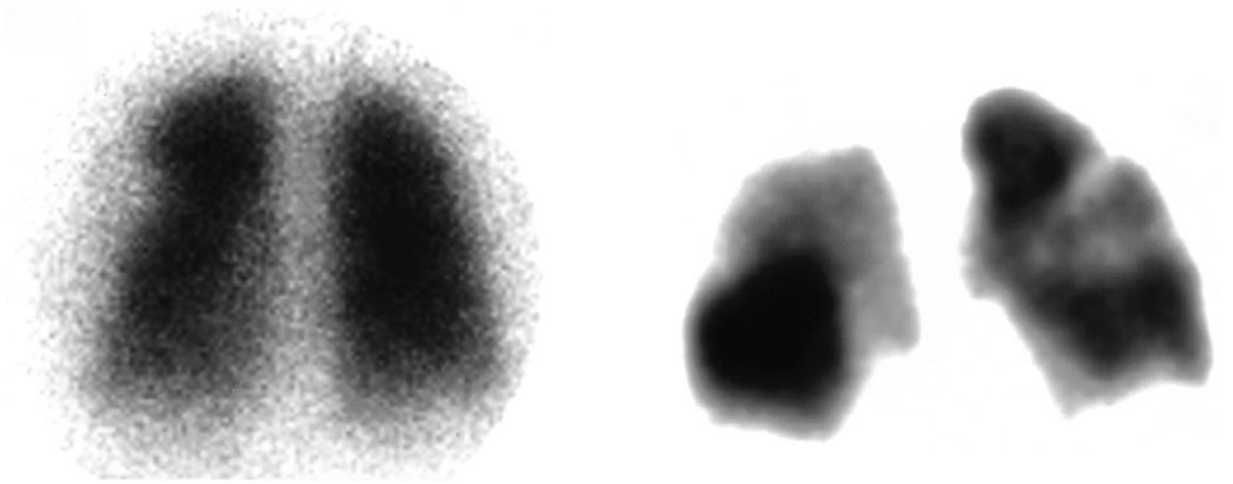
(Reproduced, with permission, from Chen MY et al. *Basic Radiology,* 1st ed. New York: McGraw-Hill, 2004.)

TABLE 10.3. Pros and Cons of Diagnostic Tests in Pulmonary Embolism

Modality	Pros	Cons	Comments
V/Q scan	Noninvasive; results are well characterized.	Often not available after normal business hours; frequently nondiagnostic.	Performs best when baseline CXR is normal.
CT angiography	Specific; may reveal alternative diagnosis; better availability than V/Q in most hospitals.	Risk of contrast dye nephropathy; uncertain sensitivity, especially for smaller thrombi.	Sensitivity < 90%; a ⊖ CT angiogram does not rule out PE.
Pulmonary angiography	The gold standard.	Most invasive; requires local expertise.	Perform only if other tests fail to establish the diagnosis.

Treatment

- **Anticoagulation:**
  - Start with **IV unfractionated heparin** (using weight-based dosing adjusted to maintain PTT 1.5–2.0 times normal range) or **low-molecular-weight heparin (LMWH)** (e.g., enoxaparin 1 mg/kg SQ q 12 h).
  - Once the patient is adequately anticoagulated with heparin, **warfarin** should be started.
  - The **duration of therapy** is somewhat controversial, but at least six months of therapy with an INR of 2–3 for a first episode is typical. Longer therapy is reserved for patients with recurrent events or with risk factors for thrombophilia.
- **Direct thrombin inhibitors.**



A B

FIGURE 10.2. Lung scan for a 63-year-old woman who presented with idiopathic pulmonary embolism.

The lung scan showed normal ventilation (A) and multiple segmental perfusion defects (B), indicating a V/Q mismatch and a high probability of pulmonary embolism. (Reproduced, with permission, from Crawford MH. *Current Diagnosis & Treatment in Cardiology*, 2nd ed. New York: McGraw-Hill, 2003: 369.)

TABLE 10.4. Probability of PE Based on V/Q Results and Clinical Probability

V/Q Scan Result	High Clinical Probability	Intermediate Clinical Probability	Low Clinical Probability
High	95[a]	86	56
Intermediate	66	28	15
Low	40	15	4
Normal perfusion	0	6	2

[a] That is, 95% of patients with a high-probability V/Q scan and a high clinical probability were found to have a PE on angiography.

- **IVC filters** are reserved for patients with contraindications to anticoagulation (see Table 10.5) or for those with recurrent events despite adequate anticoagulation. IVC filters ↓ the risk of PE in the short term (up to two weeks) but are associated with more recurrent lower extremity DVTs at two years.
- **Thrombolysis** is controversial:
  - Supported in massive PE (i.e., for those with refractory hypotension due to PE).
  - Controversy exists regarding its role in patients with PE and right heart strain who have normal hemodynamics.
- **Surgical or catheter thrombectomy:** Last-ditch options for patients with hemodynamic compromise who fail or are not candidates for thrombolysis.

Deep Venous Thrombosis (DVT)

Risk factors for DVT are the same as those for PE.

Symptoms/Exam

- **Pain, swelling,** or **erythema** of the affected extremity is most common.
- A **palpable cord** and low-grade **fever** are less commonly seen.
- Most thrombi occur in the **lower extremities,** although upper extremity thrombosis is increasing in frequency coincident with the use of long-term central venous catheters.

TABLE 10.5. Contraindications to Anticoagulation

Absolute	Relative
Hemorrhagic stroke	Recent internal bleeding (within six months)
Active internal bleeding	Prior hemorrhagic stroke
Suspected aortic dissection	Thrombocytopenia
	CNS mass lesion (especially renal cell carcinoma, melanoma)

- Rarely, **phlegmasia cerulea dolens** (complete venous obstruction resulting in a painful, swollen, and bluish extremity) may be seen (see Figure 10.3)

Differential

- Musculoskeletal injury, including trauma.
- Cellulitis.
- **Ruptured Baker's cyst:** A bursal sac located behind the knee that, when ruptured, can cause pain, swelling, and erythema down into the calf region.
- **Reflex sympathetic dystrophy:** A neurally mediated syndrome of pain and swelling in an extremity, often occurring after minor trauma.

Orthopedic patients or surgery patients with other major risk factors should be treated with LMWH or fondaparinux (or SCDs if anticoagulants are contraindicated).

Diagnosis

Compression/duplex ultrasonography, impedance plethysmography, contrast venography (see Table 10.6).

Treatment

- As with PE, **IV unfractionated heparin** or LMWH may be used in all patients without contraindications. Outpatient therapy is appropriate in select patients. Criteria for outpatient treatment are as follows:
  - Clinical stability with normal vital signs.
  - Low risk of bleeding.
  - Normal or near-normal renal function.

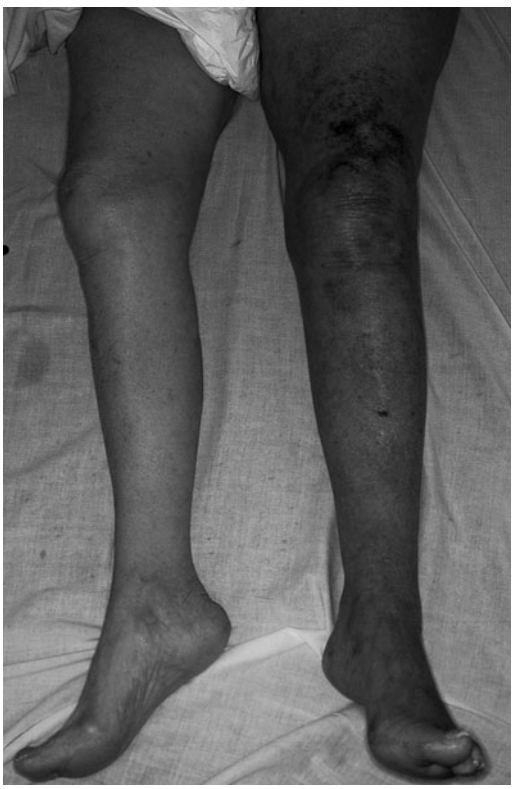


FIGURE 10.3. Phlegmasia cerulea dolens of the left lower extremity.

Note the bluish discoloration and swelling. (Courtesy of Daniel L. Savitt, MD.)

TABLE 10.6. Tests for DVT

Modality	Pros	Cons	Comments
Compression/duplex ultrasonography	Noninvasive; sensitivity and specificity > 95%.	Poor for thrombosis in calf veins or above the inguinal ligament.	The first-line test of choice. Consider repeat testing (in 3–5 days) if ⊖ but there is a high clinical suspicion.
Impedance plethysmography	Sensitive and specific.	Not widely available; cumbersome.	Rarely done.
Contrast venography	The gold standard.	Most invasive; requires radiocontrast dye.	Perform only if other tests fail to establish the diagnosis.
D-dimer	Useful for ruling out the diagnosis when combined with low clinical suspicion.	Poor specificity; widespread assay variability.	Assay variability has limited widespread use.

- Adequate outpatient follow-up to ensure compliance and to monitor for complications.
- **Warfarin** can be started as soon as adequate anticoagulation with heparin has been achieved.
- The **duration of therapy** and indications for an **IVC filter** are the same as those for PE.
- **Thrombolytic therapy** may result in fewer long-term complications (postphlebitic syndrome) at the expense of an ↑ risk of bleeding. Consider in patients (especially younger patients) with massive DVT, including phlegmasia cerulea dolens. IV therapy is equivalent to catheter-directed therapy.

Average-risk surgical patients (those without additional major risk factors) and medical inpatients should receive DVT prophylaxis with unfractionated heparin, a LMWH (e.g., enoxaparin, dalteparin, or fondaparinux) or nonpharmacologic therapy (e.g., TED hose or SCDs) if anticoagulation is contraindicated.

Prevention

- Hospitalized medical and surgical patients are at risk for venous thromboembolic disease. Prophylaxis should thus be considered in all hospitalized patients.
- Although many regimens are effective, appropriate medications and doses vary according to the specific clinical scenario (see also Table 10.7):
  - **SQ "minidose" heparin:** Usually 5000 U SQ BID-TID.
  - **SQ LMWH:** Given at lower doses than those used for full anticoagulation—e.g., enoxaparin 40 mg SQ, QD; dalteparin 5000 U SQ, QD; fondaparinux 2.5 mg SQ, QD.
  - **Elastic stockings** (thromboembolic disease stockings, or TEDS) and **sequential compression devices (SCDs).**
- Prophylaxis can be stopped in high-risk orthopedic patients who are discharged on anticoagulation once they are able to fully weight bear and ambulate (approximately 2–3 weeks postoperatively).

The lack of an adequate loading dose may result in frustrating efforts to "catch up" with the pain.

ACUTE PAIN MANAGEMENT

Several basic principles guide the management of acute pain in the hospitalized patient:

- The patient's description of symptoms is the most reliable indicator of pain. **Pain scales,** including the 10-point analog scale, should be used.

TABLE 10.7. Selected Methods for the Prevention of Venous Thromboembolism

Risk Group	Recommendations for Prophylaxis
General surgery[a]	
Low risk	Early ambulation.
Moderate risk	Elastic stockings (ES), low-dose unfractionated heparin (LDUH),[c] or LMWH, or intermittent pneumatic compression (IPC) plus early ambulation if possible.
Higher risk	LDUH, LMWH, or IPC.
Higher risk plus ↑ risk of bleeding	ES or IPC.
Very high risk	LDUH or higher-dose LMWH plus ES or IPC.
Selected very high risk	Consider adjusted-dose perioperative warfarin (ADPW), INR 2.0–3.0, or postdischarge LMWH.
Orthopedic surgery	
Elective total hip replacement surgery	SQ LMWH, ADPW, or adjusted-dose heparin started preoperatively plus IPC or ES.
Elective total knee replacement surgery	LMWH, ADPW, or IPC.
Hip fracture surgery	LMWH or ADPW.
Neurosurgery	
Intracranial neurosurgery	IPC with or without ES; LDUH and postoperative LMWH are acceptable alternatives. IPC or ES plus LDUH or LMWH may be more effective than either modality alone in high-risk patients.
Acute spinal cord injury	LMWH; IPC and ES may have additional benefit when used with LMWH. In the rehabilitation phase, conversion to full-dose warfarin may provide ongoing protection.
Trauma patients with an identifiable risk factor for thromboembolism	LMWH; IPC or ES if there is a contraindication to LMWH. Consider duplex ultrasound screening in very high risk patients; IVC filter insertion is appropriate if proximal DVT has been identified and anticoagulation is contraindicated.
Medical patients	
Most medical patients with expected length of stay > 3 days[b]	SQ LDUH or a LMWH. Nonpharmacologic therapy with ES or IPC if anticoagulation is contraindicated.

[a] **Low risk** = minor procedures, age < 40, and no clinical risk factors. **Moderate risk** = minor procedures with additional thrombosis risk factors; age 40–60 and no other clinical risk factors; major operations with age < 40 and no additional clinical risk factors. **Higher risk** = major operation; age > 40 or with additional risk factors. **Very high risk** = multiple risk factors.

[b] Especially patients with cancer, CHF, or severe pulmonary disease.

[c] LDUH 5000 U SQ q 8–12 h starting 1–2 hours before surgery.

Adapted, with permission, from Tierney LM et al. *Current Medical Diagnosis & Treatment,* 44th ed. New York: McGraw-Hill, 2005: 283.

- Minor pain will respond to **nonopioid analgesics,** including acetaminophen and NSAIDs, or to low-potency opioids such as codeine.
- For moderate or severe pain, the **potent opioids (morphine, hydromorphone, fentanyl)** should be used. An **appropriate loading dose** is necessary with repeat doses every 10–15 minutes until pain relief has been achieved (see Tables 10.8 and 10.9).
- Maintain pain relief with **patient-controlled anesthesia (PCA)** or **regularly scheduled** nurse-administered medication.

TABLE 10.8. Initial Dosing of Opioids

	Parenteral Starting Dose	Oral Starting Dose
Hydromorphone	0.5–1.5 mg q 3–4 h	6 mg q 3–4 h
Hydrocodone	—	10 mg q 3–4 h
Oxycodone	—	10 mg q 3–4 h
Methadone	—	5 mg q 6–8 h
Morphine	5–10 mg q 3–4 h	30 mg q 3–4 h
Meperidine	50–100 mg q 3 h	—
Codeine	—	60 mg q 3–4 h

  - In chronically opioid-dependent patients, start continuous opioid infusions immediately.
  - In opioid-naïve patients, start continuous infusion only after the opioid requirement has been determined (12–18 hours).
- Pain control should be reassessed often and medications/doses adjusted frequently. Patients with active pain should not be treated with PRN medications alone.
- Attempt a rapid transition to **long-acting preparations** once the amount of opioid required to relieve pain has been determined.
- **Adjunctive measures** should be considered in all patients. The use of **nonsteroidal agents** in conjunction with opioids may be especially effective for postoperative pain. TCAs and gabapentin may also be effective for neuropathic pain.

IV-equivalent doses can be remembered as differing (roughly) by a factor of 10 (i.e., fentanyl is 10 times as strong as hydromorphone, which is 10 times as strong as morphine, which is 10 times as strong as meperidine).

TABLE 10.9. Opioid Equivalency

Medication	Common Trade Names	Equivalent Parenteral Dose (mg)	Equivalent PO Dose (mg)	$T_{1/2}$ (hours)
Fentanyl	—	0.1	—	1–2
Hydromorphone	Dilaudid	1.5	7.5	2–3
Hydrocodone	Lortab, Vicodin	—	20	3–5
Oxycodone	Percocet, Percodan	—	20	3–5
Methadone	—	—	20	15–30
Morphine	Many	10	30	2–4
Meperidine	Demerol	75–100	—	2–4
Codeine	Many	—	200	2–3

DELIRIUM

Occurs in up to 30% of hospitalized elderly patients. Patients often have multiple risk factors, including the following:

- **Underlying medical conditions:** Infection, fever, depression, alcohol abuse, metabolic derangement.
- **Multiple medications:** Opioids, anticholinergics, benzodiazepines.
- **Other:** Advanced age, male gender, preexisting dementia, alterations in the sleep-wake cycle.

Symptoms/Exam

Avoidance of unnecessary medications and medical devices is key to preventing and treating delirium.

- **Altered sensorium** is the most common clinical feature.
- The severity of impairment **waxes and wanes** over time.
- **Cognitive functioning** is usually significantly affected. Patients are easily distracted and are often difficult to engage in conversation.
- **Paranoia** and **persecutory delusions** are common.

Diagnosis

- Conduct a detailed evaluation, including a physical exam, review of the medication list, and appropriate lab studies (e.g., electrolytes, serum calcium, UA, and CXR in the setting of new pulmonary findings).
- **CT** of the head is rarely useful, but consider in patients who are anticoagulated or have a history of trauma.
- **LP** should be performed only in the rare patient in whom there is clinical suspicion for meningitis.

Treatment/Prevention

- **Recognition of risk** and **prevention** are key. Up to one-third of delirium cases are preventable through the management of following risk factors:
  - **Cognitive impairment:** Limiting of unnecessary medications; frequent reorientation.
  - **Sleep deprivation:** Maintain the sleep-wake cycle.
  - **Visual impairment:** Encourage the use of visual aids.
  - **Hearing impairment:** Encourage the use of hearing aids.
  - **Immobility:** Remove unnecessary medical devices.
  - **Dehydration:** Ensure adequate fluid intake.
- **Treatment** should focus on the following:
  - Using the above measures in prevention.
  - Treating the underlying cause.
  - Removal of exacerbating factors (especially medications and medical devices).
  - When given in low doses, **haloperidol** can be effective as a second-line therapy.
  - The use of the second-generation antipsychotic agents (**risperidone, olanzapine, and quetiapine**) may be associated with ↑ mortality and should be prescribed with great caution.

GI PROPHYLAXIS IN THE HOSPITALIZED PATIENT

GI bleeding 2° to stress-induced gastric mucosal disease **occurs in up to 5–6% of critically ill patients.** Hemodynamically significant bleeding is rare (1–2%), but mortality is significantly ↑. Risk factors include a history of head

TABLE 10.10. Prophylaxis for GI Bleeding

Treatment	Pros	Cons
Sucralfate	Effective.	Interferes with the absorption of multiple medications; frequent dosing. Must be administered PO or through a feeding tube.
H_2 receptor blockers	Effective; can be given IV or PO.	May be associated with an ↑ risk of nosocomial pneumonia.

trauma, burns, sepsis, and hepatic or renal dysfunction. **Coagulopathy** and **respiratory failure necessitating mechanical ventilation for at least 48 hours** are the most powerful risk factors for stress-related hemorrhage. Prophylactic measures include the following:

- **Sucralfate** and **H_2 receptor blockers:** Both result in at least a 50% reduction in the likelihood of bleeding (see Table 10.10).
- **Antacids:** May be effective but are rarely used.
- **Enteral feeding:** May ↓ bleeding risk.
- PPIs are not as well studied for this indication but may be reasonable for those who can tolerate oral therapy.

Patients who have cardiac disease or symptoms that require urgent or emergent evaluation and treatment, regardless of their pending surgery, should have their surgery delayed until their cardiac issues have been addressed.

PERIOPERATIVE MANAGEMENT

Preoperative Cardiac Evaluation

- Cardiac disease is a frequent cause of perioperative morbidity and mortality, with 50,000 patients developing perioperative MIs per year.
- **Preoperative cardiac risk assessment** is mandatory in all patients undergoing noncardiac surgery.
  - Risk assessment can be completed using a validated **risk prediction score** (see Table 10.11)
  - Assessment of cardiac risk involves evaluation of three elements: **patient-specific variables, exercise capacity, and surgery-specific risk** (see Figure 10.4)
  - Patients with severe symptoms, or those with a high-intermediate-risk score (see Figure 10.4) with unknown functional status, may be at ↑ risk for perioperative cardiac death or MI.

"Prophylactic" CABG and/or angioplasty/stenting should not be done unless it is likely to ↑ long-term survival.

TABLE 10.11. Revised (Simplified) Cardiac Risk Index

Risk Factor	Scoring
■ Higher-risk surgery (thoracic, abdominal, or major vascular operation) ■ Ischemic heart disease ■ CHF ■ Diabetes requiring insulin ■ Cerebrovascular disease (a history of stroke or TIA) ■ Renal insufficiency (Cr > 2)	Add one point for each risk factor. Risk of major complications is 0.4%, 0.9%, 7%, and 11% for 0, 1, 2, and 3 or more points, respectively.

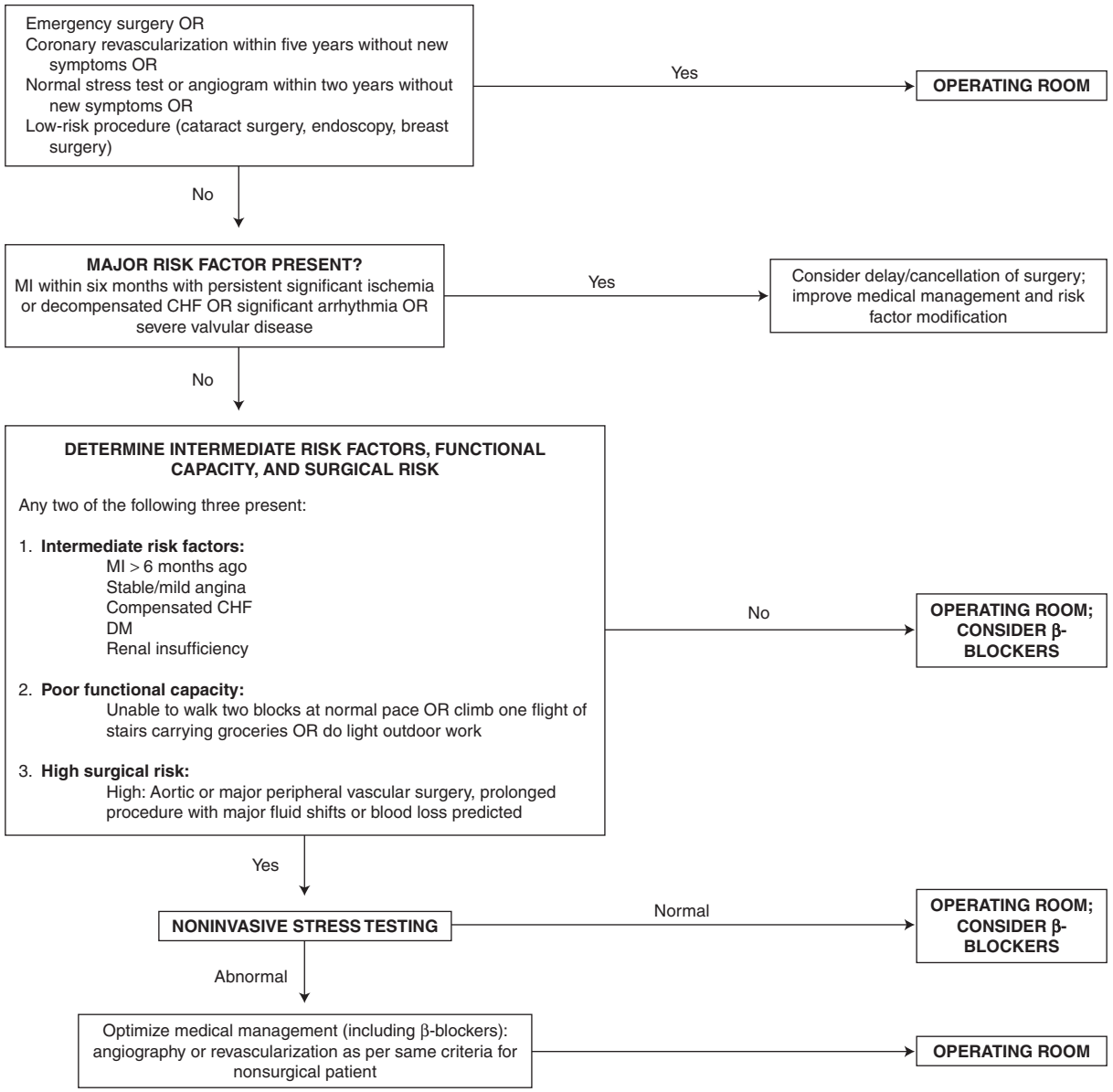


FIGURE 10.4. Algorithm for further cardiac evaluation and intervention.

- The role of ischemia evaluation prior to noncardiac surgery is evolving. A recent study of patients undergoing vascular surgery at ↑ risk for perioperative cardiac events did just as well with a strategy of optimal medical management without further testing (i.e., β-blockers) as they did with a strategy involving noninvasive testing.
- Patients considered for noninvasive ischemia testing independent of the planned noncardiac surgery should generally undergo such testing only if the test result might lead to coronary revascularization.
- Exercise treadmill testing, dipyridamole-thallium scintigraphy, and dobutamine stress echocardiography, when normal, predict a low risk of perioperative cardiac complications (comparable to patients with a low-risk clinical assessment).
- In patients with known CAD who cannot exercise but have a high risk of cardiac complications by clinical assessment, dobutamine stress echocardiography is the preferred test.

- **Perioperative β-blockade:**
  - β-blockers benefit patients undergoing major noncardiac surgery who are at ↑ risk (i.e., those with a revised cardiac risk index ≥ 2; see Table 10.11).
  - Patients with no risk factors are at low risk, and β-blockers may have limited benefit or may be harmful.
  - When a β-blocker is given, β_1-cardioselective agents (e.g., metoprolol or atenolol) should be used.

Perioperative β-blockers greatly ↓ the risk of perioperative MI and mortality in patients who have or are at risk for CAD.

Preoperative Pulmonary Evaluation

- The risk factors for perioperative pulmonary complications include the following:
  - Chest or abdominal surgery
  - Chronic lung disease
  - Current tobacco use
  - Morbid obesity
  - Age > 60
  - Prior stroke
  - Altered mental status
  - Neck or intracranial surgery
- Preventive measures are as follows:
  - **Smoking cessation:** Can significantly ↓ the risk of complications if completed at least two months preoperatively.
  - **Incentive spirometry, including deep breathing exercises:** May ↓ the risk of complications and should be taught to the patient preoperatively.
  - **Optimization of chronic lung disease:** A critical measure.
  - **Pulmonary function testing:** Not routinely useful in guiding treatment, but can yield an indication of the severity of underlying disease, and may help evaluate unexplained pulmonary symptoms.
  - **ABG analysis** is not routinely necessary.
  - **Antibiotics** should not be given routinely.

PFTs, CXR, and ABGs are not part of a routine preoperative pulmonary risk assessment. Obtain these only if you would do so even if the patient were not undergoing surgery.

Poor perioperative glycemic control is associated with a higher incidence of infection as well as with delayed wound healing.

Perioperative Management of Chronic Medical Conditions

Table 10.12 lists guidelines for the perioperative management of chronic conditions.

TABLE 10.12. Pre- and Postoperative Management of Chronic Disorders

Condition	Potential Complications	Preoperative Management	Postoperative Management
DM, on insulin as outpatient	Hypo- and hyperglycemia, DKA, infection.	Give 50% of usual long-acting insulin the morning of surgery (the exception being glargine, which should be given at the usual dose the evening before surgery) with glucose drip.	Strongly consider insulin drip titrating to normoglycemia; otherwise restart long-acting insulin with supplemental short-acting insulin (rapid titration of long-acting insulin).
DM, not on insulin	Hypo- and hyperglycemia; nonketotic hyperosmolar state.	Omit oral hypoglycemic the day prior to surgery.	Consider insulin drip; use regularly scheduled short-acting insulin if needed and restart oral agent once able.
Chronic steroid use (especially greater than the equivalent of 20 mg prednisone for three weeks)	Adrenal crisis (rare).	Continue usual dose.	Can usually just give chronic dose; consider "stress-dose" steroids for longer/major surgeries (hydrocortisone 100 mg q 8 h × 2–3 days).
Liver disease	Mortality, hemorrhage, infection.	Optimize treatment of underlying complications; high morbidity and mortality for Child-Pugh Class C patients.	Optimize treatment of underlying complications.

NUTRITION IN THE HOSPITALIZED PATIENT

Nutritional guidelines for hospitalized patients are as follows (see also Table 10.13):

- **Oral supplements** are appropriate if the patient can tolerate oral intake.
- **Enteral tube feedings** are the mode of choice for patients with functional GI tracts who cannot be fed orally.
  - **NG or nasoduodenal tubes** (especially in patients at high risk for aspiration): Appropriate for patients requiring temporary support.
  - **Tube enterostomies:** Used when long-term nutritional support is anticipated. **Jejunostomy** may ↓ the risk of aspiration but requires a surgical procedure, in contrast to the endoscopically placed **gastrostomy** tube.
- **Total parenteral nutrition (TPN):** When delivered through dedicated central venous access, TPN is another long-term option, but it is difficult to manage and is associated with multiple adverse events (see Table 10.14). Appropriate for patients with significant GI tract disease or dysfunction.
- **Peripheral parenteral nutrition (PPN):** Another, albeit short-term, option.

TABLE 10.13. Indications for Enteral Feeding, TPN, and PPN

	Indications	Pros	Cons
Enteral feeding	Nutritional needs cannot be met through oral feeding and supplements.	Less invasive; lower incidence of infectious complications. Preserved mucosal immunity and bowel integrity. More rapid transition to regular oral feeding.	Requires a functional GI tract; necessitates tube placement. Associated with an ↑ incidence of aspiration, although the risk may be lower with jejunal tubes vs. gastric tubes.
TPN	Long-term need (> 1–2 weeks) for supplement or replacement nutrition; inability to use the GI tract.	Long-term therapy is possible.	The need for maintenance of central venous access can lead to catheter-related complications (2–3%). Catheter-related thromboses; metabolic complications (see Table 10.14).
PPN	Short-term need (< 1–2 weeks) for supplemental or replacement nutrition; inability to use the GI tract.	Does not require central venous access.	Effective only as a short-term option (1–2 weeks). Large-volume infusion.

OVERDOSE/TOXIC INGESTION

*Agents **not** bound by activated charcoal include lithium, ethanol/methanol/ethylene glycol, hydrocarbons, and heavy metals.*

General guidelines for overdose and toxic ingestion are as follows (see also Table 10.15):

- **Supportive care** is the mainstay of treatment.
- **Airway protection,** including endotracheal intubation, if necessary.
- **Volume/electrolyte repletion.**
- **Activated charcoal** binds most medications and is given to most patients.
- **Gastric lavage** is associated with a high complication rate and should be considered only with recent (< 1–4 hours prior to presentation), serious ingestions or when delayed gastric emptying is suspected (e.g., anticholinergic agents). If mental status is an issue, intubate prior to lavage.
- **Emetic agents** (e.g., ipecac) are generally not used in adults because they ↑ the risk of aspiration and because their efficacy is questionable when given > 1 hour after an ingestion.
- Screen all patients for **coingestions** for which there is a specific antidote or treatment (e.g., acetaminophen, aspirin).

ACUTE COMPLICATIONS OF SUBSTANCE ABUSE

Table 10.16 delineates guidelines for treating acute complications associated with the ingestion of controlled substances.

TABLE 10.14. Metabolic Complications of TPN

Complication	Treatment
Abnormal LFTs	↓ carbohydrate load; reconfigure the balance between fats, carbohydrates, and amino acids.
Acalculous cholecystitis (4% with long-term TPN)	Surgery.
Elevated BUN	Assess volume status; if adequate, ↓ the infusion rate and/or amino acid load.
Hyperglycemia	Frequent glucose checks; addition of insulin to TPN.
Micronutrient deficiencies (zinc, selenium, vitamin B_{12}, copper)	Regular supplementation.
Refeeding syndrome (hypophosphatemia, hypokalemia, hypomagnesemia)	Consider decreasing the infusion rate; electrolyte supplementation.

Manifestations of tricyclic (anticholinergic) overdose: ***"mad as a hatter, red as a beet, dry as a bone, blind as a bat, hot as a hare"*** *– i.e., confused, flushed, dry mouth, visual changes.*

The combination of an elevated anion gap and an elevated osmolar gap suggests ingestion of ethanol, methanol, or ethylene glycol.

WITHDRAWAL SYNDROMES

Ethanol Withdrawal

Most chronic alcoholics experience some withdrawal symptoms upon cessation of drinking, although only a small minority will develop delirium tremens (DTs). Mortality is approximately 5%; risk factors include advanced age, temperature > 40°C, and preexisting hepatic or pulmonary disease. Patients with a history of alcohol withdrawal syndrome may be prone to developing it again.

Symptoms/Exam

- Symptoms usually begin 2–3 days (but occasionally up to seven days) after the last drink. Withdrawal seizures almost always occur within 36 hours of stopping drinking.
- **Tremulousness with anxiety** is most common and may progress to agitation and delirium with hallucinations.
- **DTs** usually occur several days after the last drink.
- **Hypertension, tachycardia,** and **hyperthermia** are common.
- Some patients experience **alcoholic hallucinosis**—auditory or tactile hallucinations that occur with an otherwise clear sensorium.

Treatment

- **Benzodiazepines** (e.g., lorazepam or diazepam): The cornerstone of treatment.
  - **Symptom-triggered schedules:** Administer benzodiazepines as directed by the Clinical Institute Withdrawal Assessment for Alcohol Scale (CIWA) score. May result in the use of lower doses of medications than other schedules, but requires frequent reassessment.
  - **Fixed schedules:** Provide regular benzodiazepines regardless of symptoms. May result in oversedation.

TABLE 10.15. Characteristics and Treatment of Common Ingestions

Substance	Manifestations	Lab Tests	Treatment	Comments
Acetaminophen	Initially presents with nausea and vomiting. An asymptomatic interval is followed by recurrent nausea, abdominal pain, and jaundice.	Elevated acetaminophen level as a function of time of ingestion; > 150 μg/dL at four hours indicates the need for treatment. LFTs begin to rise within 12 hours, peaking at 4–6 days. AST and ALT may be markedly elevated (> 10,000 IU). PT is most indicative of prognosis (a PT < 90 predicts an 80% survival rate). Renal failure is seen in up to 50% of cases with hepatic failure.	Activated charcoal if within four hours of ingestion or when delayed absorption is suspected. *N*-acetylcysteine (140 mg/kg load followed by 70 mg/kg q 4 h × 17 doses). An IV preparation is available if the patient is unable to tolerate PO. Immediate transfer to a liver transplant center for progressive coagulopathy, acidosis, or liver failure.	*N*-acetylcysteine is most effective within 10 hours but may be effective significantly later. Chronic alcoholics may be subject to hepatotoxicity at lower doses of acetaminophen.
Aspirin	Nausea and vomiting; tinnitus, GI bleeding and volume depletion, mental status changes.	Anion-gap metabolic acidosis with concomitant respiratory alkalosis. Elevated PT. Elevated serum salicylate.	Activated charcoal and gastric lavage. Sodium bicarbonate with alkalinization of serum and urine (goal pH 7.4–7.5) to ↓ toxicity and promote renal elimination. Hemodialysis in the setting of severe acidosis, altered mental status, or levels > 80–100 mg/dL.	The threshold for hemodialysis should be lowered to 60 mg/dL for chronic ingestion.
Lithium	Altered mental status progressing to coma. Tremor, hyperreflexia, clonus. Vomiting and diarrhea.	Elevated serum lithium level. Toxicity may occur at low levels with chronic administration.	Volume repletion; consider alkalinization of urine. Dialysis for a lithium level > 4 mEq/L (> 2.5 mEq/L if the patient is significantly symptomatic) or in the setting of concomitant renal failure.	Levels may "rebound" after dialysis and require repeat dialysis. Not bound by activated charcoal.

TABLE 10.15. Characteristics and Treatment of Common Ingestions *(continued)*

Substance	Manifestations	Lab Tests	Treatment	Comments
SSRIs	Somnolence, agitation; nausea, vomiting, tachycardia.	None.	Supportive care.	Rarely fatal.
TCAs	Dilated pupils, dry mouth, tachycardia (almost always present), flushed skin, seizures, ↓ mental status, ileus, urinary retention, hypotension, pulmonary edema.	Widened QRS (> 0.12). Pronounced R wave in aVR (> 3 mm). AV block and ventricular dysrhythmias.	Activated charcoal; consider gastric lavage (since anticholinergic effects may delay gastric emptying, consider up to 12 hours following ingestion). Alkalinization (with intermittent boluses of bicarbonate) may ameliorate cardiotoxicity. Lidocaine but not procainamide for ventricular dysrhythmia; norepinephrine or epinephrine (not dopamine) for hypotension.	Maintain a low threshold for admission (especially for patients with anticholinergic symptoms and signs). Pronounced R waves in aVR may be most predictive of cardiac complications.
Methanol	Altered mental status, seizures, nausea, vomiting, visual disturbances, blindness.	Anion-gap metabolic acidosis. Elevated osmolar gap ($osm_{measured} - osm_{calculated}$). Elevated serum methanol level.	If the patient presents within 1–2 hours of ingestion, use gastric lavage. Charcoal is ineffective. Immediate hemodialysis for severe poisoning (i.e., a level of > 50 mg/dL or an osmolar gap > 10; severe acidosis; mental status changes/ seizures). IV fomepizole (or ethanol titrated to a level of 100–200 mg/dL when fomepizole is not available) for less severe poisoning or as a temporizing measure. Sodium bicarbonate for acidosis.	Mortality is > 80% with seizures or coma. The lethal dose is 75–100 mL.

TABLE 10.15. Characteristics and Treatment of Common Ingestions *(continued)*

Substance	Manifestations	Lab Tests	Treatment	Comments
Ethylene glycol	Same as methanol. Oxalate crystals in the urine. Fluorescence of urine with Wood's lamp. Acute renal failure.	Anion-gap metabolic acidosis. Elevated osmolar gap ($osm_{measured} - osm_{calculated}$). Elevated serum ethylene glycol.	Treatment is the same as that for methanol, except hemodialysis with ethylene glycol level > 20 mg/dL.	The lethal dose is 100 mL.
Isopropyl alcohol	Altered mental status progressing to coma; ataxia; hypotension 2° to myocardial depression.	Elevated osmolar gap ($osm_{measured} - osm_{calculated}$). Lack of metabolic acidosis. Ketonuria.	If the patient presents within 1–2 hours of ingestion, treat with gastric lavage. Hemodialysis for coma or for a plasma isopropanol level > 400 mg/dL; also consider for hypotension as well as with concomitant hepatic or renal dysfunction.	The lethal dose is 150 mL.
Carbon monoxide	Headache, altered mental status, seizures, coma. Also nausea and abdominal pain.	Elevated carboxy-hemoglobin saturation (values may normally be up to 15% in smokers). Pulse oximetry and Po_2 may be normal.	High-flow O_2 via an endotracheal tube for severe cases. Hyperbaric oxygen if immediately available for severe poisoning as well as for pregnant patients (controversial).	Cherry-red lips are infrequently seen. Po_2 and pulse oximetry may be falsely reassuring.

- **β-blockers, clonidine, and carbamazepine:** May be useful adjuncts, but their use should not supplant the role of benzodiazepines.
- Screen for nutritional deficiencies; all patients should receive **thiamine** supplementation.
- **Withdrawal seizures** are also treated with benzodiazepines (other anti-seizure medications are generally not necessary). Consider prophylactic treatment with benzodiazepines at the time of admission in patients with a history of withdrawal seizures.

Opioid Withdrawal

Less likely than ethanol withdrawal to cause serious morbidity and mortality.

TABLE 10.16. Manifestations and Treatment of Acute Complications of Substance Abuse

Substance	Manifestations	Lab Tests	Treatment	Comments
Gamma-hydroxybutyrate (GHB)	Somnolence and respiratory depression; bradycardia; muscle twitching and seizures.	None.	Consider activated charcoal if ingestion was very recent. Supportive care.	Most patients recover spontaneously within six hours.
Opioids	Somnolence followed by respiratory depression and coma. Constricted pupils, hypotension, bradycardia, apnea, hypothermia. Pulmonary edema and aspiration are possible. Meperidine and tramadol may cause seizures.	⊕ urine tox screen (except methadone and tramadol).	Supportive care. Naloxone 0.4–1.0 mg PRN (the effect of naloxone lasts only two hours, and repeated doses may be necessary).	Fentanyl may require very high doses of naloxone. Patients should be observed for at least 24 hours, or longer for methadone coingestion. Screen for coingestion (many opioids, such as Tylox and Percocet, are compounded with acetaminophen).
Cocaine	Agitation, palpitations, chest pain. Tachycardia, hypertension. Myocardial ischemia/infarction. Stroke.	Tox screen. Always obtain an ECG to assess for ischemic changes.	Benzodiazepines.	Avoid β-blockers with myocardial ischemia. If a β-blocker is used for hypertension, a vasodilating agent should be added.
Amphetamines (including MDMA)	Agitation, tachycardia, hypertension, hyperthermia, seizures, rhabdomyolysis.	Elevated CK with rhabdomyolysis.	Benzodiazepines. Specific treatment of complications (cooling for hyperthermia; hydration and alkalinization for rhabdomyolysis).	
Ethanol	Disinhibition, agitation, slurred speech. Somnolence progressing to stupor with respiratory depression and coma.	Elevated blood alcohol level.	Supportive care. Attention to nutritional deficiencies in chronic alcoholics. Screen for coingestions.	

Symptoms/Exam

- Symptoms include **anxiety, nausea,** and **diarrhea** accompanied by **rhinorrhea, lacrimation,** and **diaphoresis.** More significant symptoms include **severe myalgias** and **tremulousness.**
- **Hypertension, tachycardia, tachypnea,** and **fever** may develop; pupils are enlarged.

Treatment

- **Methadone** is useful for moderate to severe symptoms.
  - Titrate to symptom relief at four- to six-hour intervals.
  - A symptom scale may be used to determine dosage.
- **Clonidine** may also be useful as either adjunctive or 1° therapy.

HYPERTENSIVE URGENCY AND EMERGENCY

- A **hypertensive emergency** occurs when an elevated BP leads to active end-organ damage that is likely to result in death or serious morbidity in the absence of immediate treatment.
- **Hypertensive urgency** occurs with severe hypertension (> 220/120) without end-organ complications.
- BP reduction should be performed quickly but with caution.

Hypertensive emergencies may occur at BPs that are not considered "critically" high.

Symptoms/Exam

- SBP is usually > 220 mmHg; DBP is usually > 120 mmHg. The BP level tolerated may be dependent on the chronic baseline BP.
- **Funduscopic exam** may reveal papilledema and flame hemorrhages.
- **Hypertensive encephalopathy** is marked by nausea/vomiting, headache, confusion, lethargy, and/or irritability.
- Focal neurologic deficits suggest **intracranial hemorrhage.**
- Severe chest pain radiating to the back and differential pulses in the upper extremities may occur with **aortic dissection.**
- **Ischemic chest pain** may be present as an individual process or as a complication of dissection.

Poorly controlled essential hypertension is by far the most common cause of hypertensive urgency/emergency.

Differential

- Poorly controlled essential hypertension.
- Rebound hypertension after antihypertensive medications (e.g., oral clonidine, β-blockers) are abruptly stopped.
- Pheochromocytoma.
- Hyperthyroidism.
- Volume overload (often with renal failure).

Diagnosis

Evaluation is directed by the presence of suspected complications:

- **CT of the head** in patients with mental status changes or focal neurologic deficits to exclude intracranial hemorrhage.
- **MRI** in hypertensive encephalopathy may demonstrate **posterior leukoencephalopathy** (white matter edema in the parietal and occipital areas).
- **Emergent transesophageal echocardiography or thoracic CT** in suspected aortic dissection.
- **Electrocardiography** in patients with suspected myocardial ischemia.

Mean arterial pressure should be lowered by no more than 20–25% within the first hour. BP should subsequently be lowered to a level of approximately 160/100 over the ensuing 4–6 hours.

TABLE 10.17. Medications for Hypertensive Emergency

Medication	Pros	Cons
Nitroprusside	Very effective; easily titrated; predictable BP response. Short-acting.	May cause nausea and vomiting. Thiocyanate toxicity is possible, especially in patients with renal or hepatic insufficiency.
Fenoldopam	Useful in renal failure; predictable BP response.	May cause nausea, headache, and reflex tachycardia. ↑ intraocular pressure (avoid with glaucoma).
Labetalol	Excellent for hyperadrenergic states.	May precipitate bronchospasm and heart block.
Enalapril	Easily transitioned to oral therapy.	Response may be extreme in high renin states. Use with care in renal insufficiency. Can cause hyperkalemia.
Nicardipine	Potent antihypertensive.	Avoid with dissection and myocardial ischemia.
Hydralazine	Useful in pregnancy.	May cause reflex tachycardia. Avoid with dissection and myocardial ischemia.

Rapid-acting oral or sublingual nifedipine should be avoided, as it may lower BP too drastically and precipitate stroke.

Treatment

- **Pharmacologic** treatment is dictated by the specific end-organ complications (see Tables 10.17 and 10.18).
- **Nitroprusside** and **labetalol** are the most commonly used medications.
- In hypertensive emergency, **BP should be lowered within one hour,** and parenteral agents are almost always necessary.
- **The immediate goal is not normotension,** as a dramatic reduction in BP can overwhelm the cerebral autoregulatory mechanism, causing ischemic stroke. A reduction in mean arterial pressure up to 20% over the first several hours is an accepted guideline.

TABLE 10.18. Medications for Specific Complications of Hypertensive Emergency

Indication	Drugs of Choice	Contraindicated
Aortic dissection	Nitroprusside and labetalol	Nicardipine, hydralazine
Pulmonary edema	Nitroprusside, nitroglycerin	
Myocardial ischemia/infarction	Nitroglycerin, labetalol	Nicardipine, hydralazine
Hypertensive encephalopathy	Nitroprusside	
Eclampsia	Labetalol, hydralazine	Enalapril
Acute renal failure	Fenoldopam, labetalol	
Scleroderma hypertensive crisis	ACEIs	

- In hypertensive urgency, **oral medications are most useful,** and BP may be controlled at a more leisurely rate. Outpatient treatment is appropriate in most instances.
- **Captopril** and **clonidine** are particularly effective in hypertensive urgency.

SYNCOPE

Defined as a transient loss of consciousness and postural tone; accounts for 3% of all ER visits and up to 6% of all hospital admissions.

Symptoms/Exam

The history and physical exam establish a diagnosis in almost 50% of patients with syncope. However, specific findings are dependent on the underlying etiology, and knowledge of the differential diagnosis is critical (see Table 10.19).

The history and physical establish a diagnosis of syncope in nearly 50% of cases.

Patients < 45 years of age with a normal ECG and no history of structural heart disease are at low risk for an adverse outcome in syncope. Older patients—especially those with risk factors for or a history suggestive of cardiac disease or arrhythmia—should undergo more detailed testing, including echocardiography and noninvasive testing for CAD.

Diagnosis

Testing in addition to the history and physical and **ECG** should be individualized. Extensive testing is often fruitless but should be considered in those with risk factors for an adverse outcome (e.g., patients over 45, those a history of CHF or a ventricular arrhythmia, and those with an abnormal ECG).

- **ECG:** Identifies a definitive cause in only 5% of patients, but may provide evidence of unsuspected cardiac disease and should thus be obtained in most patients.
- **Ambulatory ECG (Holter) monitoring:** Detects arrhythmia as the cause of syncope in < 5% of patients, but may detect a normal rhythm during symptoms in 15% of patients, thereby effectively excluding an arrhythmic cause. The yield is somewhat higher with **loop recorders and event monitors,** especially in patients with infrequent symptoms.
- **Electrophysiologic testing:** May be performed in those at high risk for arrhythmia.
- **Upright tilt-table testing:** Reserve for patients with recurrent events in whom an arrhythmic cause has been excluded and a neurally mediated cause is suspected.
- **Carotid sinus massage with cardiac monitoring:** Should be completed in older patients without a readily identifiable cause of syncope or in those with symptoms suggestive of carotid sinus hypersensitivity. A three-second pause is diagnostic and may indicate the need for pacemaker insertion.
- **Echocardiography:** Obtain if historical or physical findings suggest left ventricular dysfunction or valvular disease.
- Testing for CAD, including **stress electrocardiography and stress imaging studies,** is necessary when the history or ECG is suggestive of myocardial ischemia.
- **CT and MRI** of the head are rarely indicated unless there was concomitant head trauma. **EEG** is useful only when seizures are suspected.

Testing for neurologic disease with CT and MRI is very low yield in syncope in the absence of specific neurologic signs and symptoms.

Treatment

- Treatment is directed at the underlying condition.
- Hospitalize if risk factors for cardiac syncope are present or if syncope is suspected to be 2° to arrhythmic or obstructive/low cardiac output, as patients with cardiogenic syncope are at ↑ risk for sudden death.

TABLE 10.19. Differential Diagnosis of Syncope

Mechanism	Suggestive Features
Orthostatic hypotension	History of presyncope upon standing; advanced age; a drop in BP (SBP by 20 mmHg or DBP by 10 mmHg) upon standing.
Medication-related	Diuretics, antihypertensives, polypharmacy.
Autonomic insufficiency	Shy-Drager syndrome or multiple system atrophy.
Neurally mediated (**vasovagal,** vasomotor, neurocardiogenic, situational)	Preceded by nausea, flushing, diaphoresis, and tachycardia. Autonomic symptoms often persist upon awakening. Occurrence during emotional stress or pain, or in specific situations (e.g., while coughing, micturating, or defecating).
Carotid sinus hypersensitivity	A specific type of neurally mediated syncope seen in older patients, classically provoked by neck stretching (e.g., while shaving or while looking over the shoulder when driving a car in reverse).
Cardiac arrhythmia (tachyarrhythmia, bradyarrhythmia)	No premonitory symptoms or residual symptoms upon awakening; history of cardiovascular disease.
Valvular heart disease (aortic stenosis, pulmonic stenosis)	Characteristic murmur on exam.
Myocardial ischemia/infarction	Associated chest pain.
Hypertrophic obstructive cardiomyopathy (HOCM)	Characteristic murmur on exam.
Aortic dissection	Chest pain radiating to the back; differential pulses in upper extremities.
PE	Pleurisy; dyspnea; history of venous thromboembolism.
Atrial myxoma	Tumor plop on auscultation.
Migraine	Subsequent headache.
Vertebrobasilar insufficiency (VBI)	Tinnitus, dysarthria, diplopia; focal neurologic findings. It is very unusual to have VBI as a cause of syncope without other brain stem findings.
Seizures	Postictal state.
Psychiatric	Signs and symptoms of psychiatric disease.

COMMUNITY-ACQUIRED PNEUMONIA

With > 3.5 million cases annually prompting > 1 million hospitalizations, community-acquired pneumonia is the sixth leading cause of death in the United States.

Certain historical features may suggest a specific microbiologic etiology for community-acquired pneumonia, but none is adequately specific to establish a diagnosis.

SYMPTOMS/EXAM

- **Fever, dyspnea,** or **cough** productive of **purulent sputum** are most commonly seen.
- **Pleuritic chest pain** and **chills/rigors** are also possible.
- Patients who are immunocompromised, reside in an institution, have recently been hospitalized, or are at risk for aspiration should be considered separately.

DIAGNOSIS

- **CXR:** Shows an infiltrate, but radiographic findings cannot predict the microbiologic cause. False-⊖ results have been reported in patients who are dehydrated on admission.
- **Sputum Gram stain and culture:** Although controversial and only marginally predictive of microbiology, they are recommended for inpatients and can be considered in outpatients as well.
- **Blood cultures:** Provide reliable data and may allow for the tailoring of antimicrobial therapy. They are ⊕ in approximately 10% of cases.
- Tests for specific etiologies, including serologies for Q fever and psittacosis as well as culture and antigen testing for *Legionella*, should be obtained only when there is a high clinical suspicion (see Table 10.20).

Blood cultures are the most definitive way to establish a diagnosis in community-acquired pneumonia.

TABLE 10.20. Causative Organisms and Historical Features of Community-Acquired Pneumonia

ORGANISM	CAUSE (%)	SUGGESTIVE HISTORICAL FEATURES
Streptococcus pneumoniae	20–60	Acute onset; often follows URI; underlying COPD.
Haemophilus influenzae	3–10	Often follows URI; COPD.
S. aureus	3–5	May follow influenza infection; cavitary disease.
Legionella spp.	2–8	Exposure to humidifiers, hot tubs, or air-conditioning cooling towers; pleuritic chest pain and pleural effusion are common; diarrhea; hyponatremia.
Klebsiella, other gram-⊖ rods	3–10	Ethanol abuse; DM; residence in a nursing home.
Mycoplasma pneumoniae	1–6	Commonly affects young adults in summer and fall; associated rash and bullous myringitis.
Chlamydia pneumoniae	4–10	Commonly affects young adults; often follows prolonged sore throat.
Q fever (*Coxiella burnetii*)	Rare	Exposure to livestock (cattle, goats, sheep); elevated LFTs.
Chlamydia psittaci	Rare	Exposure to birds, including parrots, pigeons, and chickens; headache; temperature-pulse dissociation.

TABLE 10.21. System for Risk Class Assignment of Community-Acquired Pneumonia[a]

Patient Characteristic	Points Assigned[b]
Demographic factor:	
Age: men	Number of years
Age: women	Number of years minus 10
Nursing home resident	10
Comorbid illnesses:	
Cancer (except basal or squamous cell of skin)	30
Liver disease	20
CHF (systolic or diastolic dysfunction)	10
History of TIA or CVA	10
Renal disease (acute or chronic)	10
Physical examination finding:	
Altered mental status	20
Respiratory rate ≥ 30 breaths/min	20
SBP < 90 mmHg	20
Temperature ≤ 35°C or ≥ 40°C	15
Pulse ≥ 125 bpm	10
Laboratory or radiographic finding:	
Arterial pH < 7.35	30
BUN ≥ 30 mg/dL	20
Sodium < 130 mEq/L	20
Glucose > 250 mg/dL	10
Hematocrit < 30%	10
Arterial Po_2 < 60 mmHg	10
Pleural effusion	10

[a] As determined by the Pneumonia Patient Outcomes Research Team (PORT) prediction rule.

[b] A total point score for a given patient is obtained by summing the patient's age in years (age minus 10 for women) and the points for each applicable characteristic.

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Treatment

- **Outpatient therapy** is appropriate in many patients. The **Fine index (also known as the pneumonia severity index, or PSI)** can help guide decisions regarding the need for hospitalization (see Tables 10.21 and 10.22).
- **Antibiotic treatment** is largely empirical, covering typical and atypical agents. Appropriate choices include the following:
  - Extended-spectrum fluoroquinolones (e.g., moxifloxacin, levofloxacin).
  - A third-generation cephalosporin plus a macrolide.
  - A β-lactam/β-lactamase inhibitor combination plus a macrolide.
- In **severe community-acquired pneumonia,** consider "double coverage" for *Pseudomonas* (i.e., two antibiotics with antipseudomonal activity).
- **Prompt initiation of antimicrobial therapy** (within eight hours of presentation) has a significant beneficial effect on mortality.

TABLE 10.22. Recommendations for Site of Care for Community-Acquired Pneumonia by PORT Risk Class

Number of Points	Risk Class	Mortality at 30 Days (%)	Recommended Site of Care
Absence of predictors	I	0.1–0.4	Outpatient
≤ 70	II	0.6–0.7	Outpatient
71–90	III	0.9–2.8	Outpatient or brief inpatient
91–130	IV	8.2–9.3	Inpatient
≥ 130	V	27.0–31.1	Inpatient

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- **Early conversion from parenteral to oral therapy** should be considered in patients with decreasing leukocytosis, improvement in cough/dyspnea, and no fever for at least eight hours.
- Patients may be **discharged** without delay at the time of conversion to oral therapy as long as they meet discharge criteria (see Table 10.23).
- **Duration of treatment** is variable. Most clinicians prescribe 7–10 days of therapy, reserving longer courses (at least two weeks) for infections thought to be caused by *S. aureus*, *Legionella*, *Mycoplasma*, and *Chlamydia* spp.
- **Repeat CXR** is not indicated during hospitalization except when complications (e.g., pleural effusion) are suspected. A follow-up film to ensure clearing and to assess for underlying processes in 4–6 weeks is appropriate, especially in smokers and older patients.

There is no benefit to observing patients in the hospital after conversion to oral therapy once they have met the criteria for clinical stability.

ENVIRONMENTAL (ACCIDENTAL) HYPOTHERMIA

Risk factors for environmental hypothermia include **advanced age, alcohol or drug use, cognitive impairment,** and **psychiatric disease.**

TABLE 10.23. Criteria for Discharge in Community-Acquired Pneumonia

Criterion	Components
Clinical stability	■ Improvement in cough/dyspnea ■ Adequate O_2 saturation (> 90%) ■ Afebrile (temperature < 37.8°C) ■ Resolution of tachycardia (HR < 100 bpm) ■ Resolution of tachypnea (RR < 24) ■ Resolution of hypotension (SBP > 90 mmHg)
No evidence of complicated infection	For example, extrapulmonary or pleural involvement.
Ability to tolerate oral medications	

Residence in a cold climate is not mandatory for hypothermia to develop.

Symptoms/Exam

- **Cold water exposure is common.**
- **Temperature** is < 35°C.
  - **Mild hypothermia** occurs with temperatures 33–35°C.
  - **Moderate** and **severe hypothermia** occurs with temperatures < 33°C.
- **Lethargy, irritability,** and **confusion** are common.
- **Tachycardia, tachypnea, and shivering** occur with mild exposure.
- **Loss of shivering, bradycardia, hypotension, respiratory depression,** and **coma** are seen with more severe hypothermia.

Differential

Environmental (accidental) exposure, occult sepsis, myxedema, adrenal insufficiency, hypopituitarism, DKA, hepatic failure.

Diagnosis

- **Laboratory abnormalities** include metabolic acidosis, hypo- and hyperglycemia, DIC, hyperkalemia, and hyperamylasemia.
- ECG may show **Osborne or J waves** (notching of the terminal aspect of the QRS complex, best seen in lead V_4), **slow atrial fibrillation, and prolonged cardiac intervals** (see Figure 10.5).

Ventricular dysrhythmias occur during rewarming; ventricular fibrillation is treated with bretylium if available. Otherwise, the standard ACLS protocol is appropriate.

Treatment

The treatment of accidental hypothermia is as follows (see also Table 10.24):

- **Limit movement and manipulation of the patient;** unnecessary stimulation (including central line and NG tube placement) can result in ventricular dysrhythmias.
- **Empiric antibiotics** are unnecessary except in the immunocompromised and elderly.
- **Bradycardia** should generally not be treated, especially given the risk of ventricular fibrillation with placement of a pacing wire.
- If **cardiac arrest** occurs, resuscitation should not cease until the core tem-

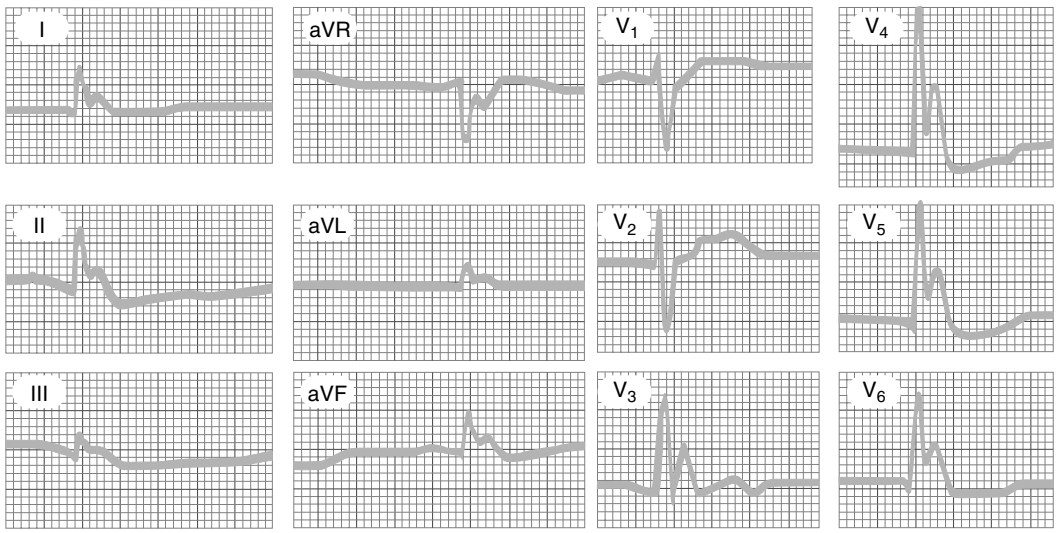

FIGURE 10.5. Osborne wave in hypothermia.

(Courtesy of Ralph Brindis.)

TABLE 10.24. Rewarming Techniques in Accidental Hypothermia

Method	Description	Indications	Comments
Passive external rewarming	Removal of wet clothes; coverage with blankets.	Mild hypothermia.	Limited efficacy.
Active external rewarming	Warmed blankets (including hot air blankets over the torso only); warmed baths.	Mild hypothermia.	Limited efficacy; rewarming of the extremities can cause paradoxical worsening because of the return of chilled blood from the extremities.
Active internal or core rewarming[a]	Warmed IV fluids; warmed humidified air.	Moderate and severe hypothermia.	Widely available; limited efficacy.
	Extracorporeal blood rewarming via cardiopulmonary, arteriovenous, or venovenous bypass.	Moderate and severe hypothermia; cardiac arrest.	The most effective technique, but invasive, and requires the use of specialized knowledge and equipment.
	Peritoneal/pleural lavage with warmed fluids.	Moderate and severe hypothermia.	Useful when extracorporeal techniques are not available.

[a] The decision to proceed with invasive active internal rewarming is individualized to the patient and dependent on both temperature and clinical manifestations. Noninvasive measures may suffice for most patients with moderate hypothermia.

perature reaches at least 32°C—"**a patient with hypothermia is not dead until he/she is warm and dead.**"

ACUTE EXACERBATIONS OF ASTHMA

Reactive airway disease is present in > 15 million Americans and results in almost 500,000 hospital admissions and 5000 deaths annually. **Intercurrent infection,** especially viral, is the most common cause. Bacterial infections, environmental exposure to smoke or allergens, GERD, medical noncompliance, and use of certain medications (NSAIDs, β-blockers) are also potential factors.

Symptoms/Exam

- Presents with **dyspnea, wheezing, coughing,** and **chest tightness.**
- Fever and purulent sputum usually represent a complicating process such as pneumonia.
- Indicators of a severe asthma exacerbation include the following (each presents individually in < 50% of cases):
  - Absence of wheezing with poor air movement
  - Tachypnea (> 30 breaths/min)
  - Tachycardia (> 130 bpm)
  - Pulsus paradoxus (> 15 mmHg)
  - Accessory respiratory muscle use
  - Altered mental status

Differential

Remember that "**all that wheezes is not asthma.**" Consider CHF, PE, upper airway obstruction, vocal cord dysfunction, Churg-Strauss syndrome, ABPA, and foreign body aspiration.

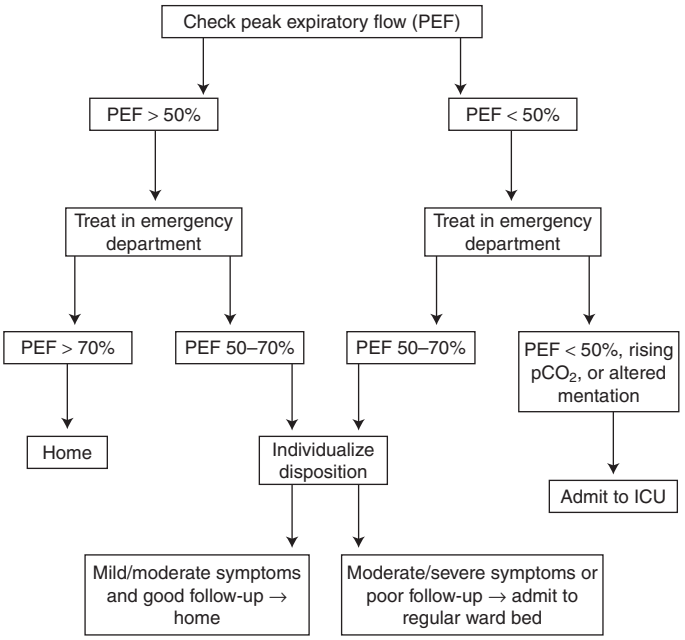

FIGURE 10.6. Disposition of patients with asthma exacerbations on the basis of PEF.

A PEF < 50% predicted indicates severe airflow obstruction.

A normal or ↑ Pco_2 indicates severe airway obstruction.

DIAGNOSIS

- **Peak expiratory flow rate (PEF)** is most predictive of the severity of the exacerbation and should guide therapy as well as all decisions regarding disposition (see Figure 10.6).
- **ABG analysis** is reserved for those with a severe ↓ in PEF or suspected hypoventilation; usually shows a ↓ P_{CO_2} unless the patient is developing ventilatory failure.
- **CXR** is usually normal and is necessary only when a 2° process is suspected.

TREATMENT

Treatment should proceed as outlined below (see also Table 10.25):

- **Systemic corticosteroids:** The mainstay of treatment.
  - ↓ the need for hospitalization and subsequent relapse rate when begun immediately; may require 6–8 hours to provide a significant effect.
  - Oral and IV preparations are equally effective.

TABLE 10.25. Treatment of Acute Asthma Exacerbations

ALL PATIENTS	SELECTED PATIENTS	NOT USEFUL/HARMFUL
Corticosteroids	Antibiotics	Theophylline
Inhaled bronchodilators	O_2	Injected bronchodilators
	Mechanical ventilation	Chest physiotherapy
	? Noninvasive mechanical ventilation	Mucolytic agents
		Magnesium

- **Inhaled bronchodilator therapy:**
  - **Combination therapy** (β_2-agonists and ipratropium bromide) should be given to all patients with moderate to severe exacerbations.
  - **Drug delivery** is equivalent to handheld metered-dose inhalers (MDIs) and nebulizer therapy, although the latter may be more effective in patients who have difficulty using inhalers or are in respiratory distress.
  - Methylxanthines are no longer recommended, as they add no benefit to the above therapy.
- **Antibiotics:** Generally unnecessary; reserve for patients with evidence of an underlying bacterial infection. If administering antibiotics, consider a macrolide, as *M. pneumoniae* and *C. pneumoniae* are identified in roughly 5% of asthma exacerbations.
- **O_2 therapy:** Should be provided to keep O_2 saturations above 90%.
- **Endotracheal intubation and mechanical ventilation:** Reserve for patients who do not respond to the above therapies and continue to experience severe airflow obstruction. Indications for mechanical ventilation include the following:
  - Persistent hypercapnia
  - Altered mental status
  - Progressive and persistent acidemia (pH < 7.30)
  - Respiratory fatigue
- The efficacy of **noninvasive mechanical ventilation** is not well established.

Complications

Risk factors for death in asthma exacerbations are as follows:

- Previous severe exacerbations/ICU admissions/intubation.
- More than two hospitalizations or three ER visits in the past year.
- Use of corticosteroids or > 2 canisters of β_2-agonist MDIs per month.
- Difficulty in perceiving the presence or severity of airflow obstruction.
- Low socioeconomic status.
- Illicit drug use.
- Serious comorbidities.

ACUTE EXACERBATIONS OF CHRONIC OBSTRUCTIVE PULMONARY DISEASE

The fourth leading cause of death in the United States, COPD accounts for > 500,000 hospital admissions and > 100,000 deaths annually.

Symptoms/Exam

- Three features are commonly present: worsening **dyspnea,** ↑ **cough,** and **change in sputum volume or purulence.**
- A **mild** exacerbation includes one of these symptoms; **moderate,** two; and **severe,** all three.
- ↓ **air movement; prolonged expiratory time.** Wheezes and extrapulmonary sounds are not always present.
- **Use of accessory muscles of respiration, pursed-lip breathing, cyanosis.**
- Other symptoms are usually referable to a concomitant process (e.g., fever with pneumonia; pleurisy with PE).

Diagnosis

- The diagnosis is made clinically. A diligent search for exacerbating or concomitant processes should be completed in all patients. Exacerbating factors the following:

- Superimposed infection, most commonly viral
- PE
- Pneumothorax
- Myocardial ischemia/infarction
- CHF
- Environmental exposures (including cigarette smoke)

- **Spirometry** is of low utility in guiding acute management and is poorly predictive of disease severity when obtained in an acute setting.
- **PEF measurements** are far less reliable in COPD exacerbations than in asthma.
- A **CXR** should be obtained in all patients to assess the possibility of pneumonia and other exacerbating factors.
- **ABG analysis** is not mandatory but should be considered in those at risk for hypercarbia and those with altered mental status.

Treatment

COPD treatment—

ABC-ON

Antibiotics
Bronchodilators
Corticosteroids
Oxygen
Noninvasive mechanical ventilation

Treatment for COPD exacerbations differs from that for asthma exacerbations (see Table 10.26).

- **Antibiotics:** Should be started in patients with exacerbations severe enough to warrant hospitalization. Antibiotics should cover *S. pneumoniae* and *H. influenzae*.
- **Factors favoring hospitalization** include the following:
  - Severe underlying disease
  - Hypercarbia
  - Hypoxemia
  - Lack of response to ER treatment
  - Lack of in-home support
  - Poor baseline functional status
- **Bronchodilator therapy:** Should be initiated in all patients. Includes a β_2-agonist (most commonly albuterol) and/or the anticholinergic agent ipratropium bromide.
  - Limited data exist to suggest the superiority of combination therapy over monotherapy in an acute setting.

TABLE 10.26. Treatment of Acute Exacerbations of Asthma vs. COPD

Treatment	Asthma	COPD
PEF useful	Yes	No
Systemic corticosteroids	Yes	Yes
Antibiotics	No	Yes
O_2	Yes	Yes
Combination bronchodilator therapy[a]	Yes	Unclear
Noninvasive mechanical ventilation	Unclear	Yes

[a] β_2-agonist and ipratropium bromide.

TABLE 10.27. Medicare criteria for LTOT

- $Pao_2 \leq 55$ mmHg or O_2 saturation $\leq 88\%$

OR

- Pao_2 56–59 mmHg or O_2 saturation $\leq 89\%$ with
  - P pulmonale on ECG or
  - Lower extremity edema or
  - Hematocrit $\geq 55\%$

OR

- $Pao_2 \leq 55$ mmHg or O_2 saturation $\leq 88\%$ with exercise or sleep (for use with sleep or exercise)

  - Drug delivery with handheld MDIs is equivalent to that with nebulizer therapy, although the latter may be more effective in patients who have difficulty using inhalers or are in respiratory distress.
- **Corticosteroids (oral and parenteral):** Result in an ↑ FEV_1.
  - A two-week course of therapy is as effective as an extended eight-week course.
  - Inhaled corticosteroids have no role in the treatment of hospitalized patients (with the possible exception of the continuation of chronic therapy).
- **O_2 therapy:** Should be considered in all patients, and should not be withheld because of concerns about suppressing respiratory drive. O_2 should be titrated to provide an O_2 saturation of at least 88%.
- **Noninvasive mechanical ventilation:** Reduces the need for invasive mechanical ventilation and shortens the length of stay in the intensive care setting; may also improve survival.
- **Smoking cessation counseling, nicotine replacement therapy:** For all patients who are actively smoking.
- **Long-term O_2 therapy (LTOT):** Improves mortality in severe COPD; all patients should be screened for eligibility (see Table 10.27).
- **Pulmonary rehabilitation:** Includes breathing exercises, support networks, and exercise education; can additionally improve quality of life.
- **Theophylline** and methylxanthines should not be initiated as therapy for an acute exacerbation but may be continued if taken as part of chronic maintenance therapy. Chest physiotherapy and mucolytic therapy are ineffective as acute interventions.

Oxygen should not be withheld when indicated because of fears of suppressing respiratory drive.

NOTES

CHAPTER 11

Infectious Diseases

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José M. Eguía, MD

ACTINOMYCES VS. *NOCARDIA*

Actinomycosis can spread without regard to tissue planes.

Table 11.1 contrasts the clinical presentation, diagnosis, and treatment of *Actinomyces* infections with that of *Nocardia* infections.

ASPLENIA-RELATED INFECTIONS

Postsplenectomy sepsis has a short viral-like prodrome followed by abrupt deterioration and shock. Encapsulated organisms involved include *Streptococcus pneumoniae* (> 50%), *Neisseria meningitidis*, and *Haemophilus influenzae*. Other organisms include *Capnocytophaga* (dog or cat contact), *Salmonella* (sickle cell anemia), *Babesia*, and malaria (more fulminant).

PREVENTION

- **Vaccinate** against *S. pneumoniae*, *H. influenzae* type b (unvaccinated older individuals), and *N. meningitidis*. Vaccinate ≥ 2 weeks before elective splenectomy or > 2 weeks after surgery.
- Give a supply of antibiotics to be taken as **self-administered therapy** for fever (e.g., amoxicillin to be taken at the onset of fever, followed by immediate evaluation in urgent care). **Daily prophylaxis** for a defined period (e.g., penicillin for 3–5 years following splenectomy) is recommended for children but not adults.

BABESIOSIS

An *Ixodes* tick–borne illness caused by *Babesia microti*, an intracellular protozoan that infects RBCs. Found in coastal New England and Long Island and, to a lesser extent, in the upper Midwest and the West Coast. Infections peak in summer and early fall.

SYMPTOMS

- Fever, chills, headache, myalgia, and fatigue.
- Severe hemolytic disease can manifest with abdominal pain, jaundice, splenomegaly, and dark urine.

TABLE 11.1. Diagnosis and Treatment of *Actinomyces* and *Nocardia* Infections

	ACTINOMYCES	*NOCARDIA*
Gram stain	Gram-⊕, branching rod.	Gram-⊕, branching rod.
Acid-fast stain	⊖.	Weakly AFB ⊕.
Pathology	Sulfur granules and draining sinuses.	Abscess.
Infected host	Immunocompetent; poor dentition or IUD user.	Immunocompromised.
Sites of infection	Mandible, lung, abdomen/pelvis.	Lung, CNS, skin.
Treatment	Penicillin for 6–12 months.	TMP-SMX for 3–6 months.

- Healthy individuals may be asymptomatic or have mild illness with intermittent symptoms for weeks to months. Older, asplenic, or immunocompromised patients (including HIV-⊕ patients) present with more severe symptoms.

Exam

Presents with fever, hepatosplenomegaly, jaundice, and occasionally petechiae or ecchymoses.

Diagnosis

- **Peripheral blood smears** show intracellular parasites in 1–10% of RBCs (or up to 85% if severe). The classic "**Maltese cross**" tetrads may be seen, but more commonly ***Babesia* parasites look like *Plasmodium falciparum* signet-ring forms with no other parasitic stages seen** (see Figure 11.1).
- Labs show **hemolytic anemia,** mild leukopenia, **thrombocytopenia,** elevated LFTs, and hemoglobinuria.
- Antibody tests are available.
- PCR may be more sensitive for detecting low levels of parasitemia.

Treatment

- Most infections are **self-limited.**
- For sicker, asplenic, or immunocompromised patients, use clindamycin plus quinine or atovaquone plus azithromycin. Doxycycline and most antimalarial drugs are ineffective.
- **Exchange transfusion** has been used as adjunctive therapy in patients with a high degree of hemolysis or parasitemia (> 10%) or with the more severe European forms of the disease.

Complications

- Patients may develop shock or ARDS. Deaths in the United States have occurred in patients both with and without spleens.
- Coinfection with ***Borrelia burgdorferi* (Lyme disease) and/or *Anaplasma phagocytophilum* (human granulocytotropic anaplasmosis)** should be suspected in any patient with babesiosis.

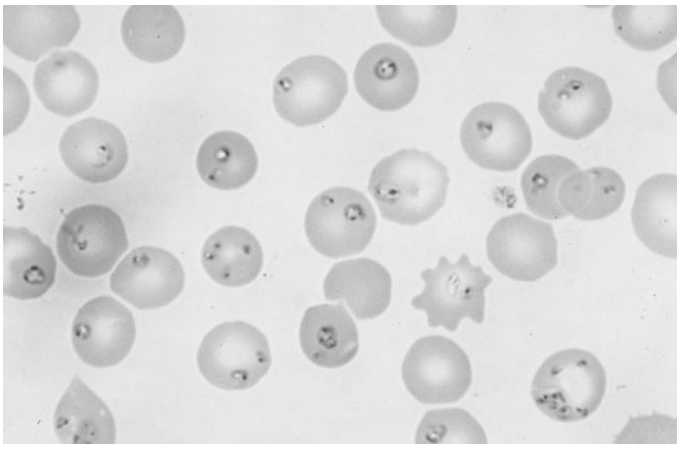

FIGURE 11.1. Babesiosis on a blood smear.

Note the parasites within RBCs resembling malaria. (Reproduced, with permission, from Lichtman MA et al. *Williams Hematology*, 7th ed. New York: McGraw-Hill, 2005: Plate I-10.)

BARTONELLA

A pleomorphic gram-⊖ rod. *Bartonella henselae* is transmitted by kittens or feral cats, *Bartonella quintana* by body lice. Clinical manifestations vary depending on (1) the transmitted species and (2) the immune status of the host. *B. henselae* can cause **cat-scratch disease,** bacillary angiomatosis, and peliosis hepatis (multiple blood-filled cysts within the liver). *B. quintana* infection may result in **trench fever, bacteremia, endocarditis,** bacillary angiomatosis, and peliosis hepatis.

SYMPTOMS/EXAM

- **Cat-scratch disease (*B. henselae*; immunocompetent patients):** Presents with fever, malaise, a papule or pustule at the site of the cat scratch or bite, and regional adenopathy (usually in the head, neck, or axillae).
- **Bacillary angiomatosis and peliosis hepatis (*B. henselae* and *B. quintana*; AIDS patients):** The skin nodules of bacillary angiomatosis are friable, red-to-purplish lesions that may ulcerate. Peliosis hepatis produces fever, weight loss, abdominal pain, and hepatosplenomegaly; imaging shows hypodense, cystic, blood-filled structures in the liver, spleen, or lymph nodes. May be a cause of fever of unknown origin (FUO) in AIDS patients.
- **Trench fever (*B. quintana*; immunocompetent patients):** Relapsing febrile paroxysms last up to five days each and are sometimes accompanied by headache, myalgias, hepatosplenomegaly, and leukocytosis. Seen in the homeless and in those from war-torn regions.

DIFFERENTIAL

- **Cat-scratch disease:** TB, atypical mycobacterial infection, toxoplasmosis, brucellosis, sporotrichosis, tularemia, plague, leishmaniasis, histoplasmosis, infectious mononucleosis.
- **Bacillary angiomatosis:** Kaposi's sarcoma, pyogenic granuloma.
- **Trench fever:** Endocarditis, TB, typhoid fever.

DIAGNOSIS

- Blood cultures (not sensitive), serologic tests.
- Lymph node aspirate in cat-scratch disease may show sterile pus.
- Lymph node biopsy shows granulomas that may coalesce to form stellate necrosis. Warthin-Starry silver stain demonstrates bacilli.

TREATMENT

- Erythromycin, azithromycin, doxycycline.
- Cat-scratch disease usually resolves in several months and may not require treatment other than needle aspiration for symptom relief.

BIOTERRORISM AGENTS

Table 11.2 outlines infectious agents that could potentially be used in acts of bioterrorism.

Consider bioterrorism-related disease when observing the sudden onset of multiple cases of severe illness (often with flulike prodromes) with a fulminant course and high mortality.

TABLE 11.2. Potential Bioterrorism Agents

Agent/ Disease	Clinical Findings	Syndrome	Differential	Initial Diagnostic Testing	Immediate Infection Control	Treatment
Inhalational anthrax	Nonspecific flulike illness followed by abrupt onset of fever, chest pain, and dyspnea without CXR findings of pneumonia; progression to shock and death in 24–36 hours.	Acute respiratory distress with fever.	Pulmonary embolism, dissecting aortic aneurysm.	CXR with widened mediastinum; gram-⊕ rods in blood.	Standard precautions.	Ciprofloxacin, doxycycline, penicillin.
Pneumonic plague	Apparent severe community-acquired pneumonia, but with hemoptysis, cyanosis, GI symptoms, and progression to shock and death in 2–4 days.	Acute respiratory distress with fever.	Community-acquired pneumonia, hantavirus pulmonary syndrome, meningococcemia, rickettsial disease.	Gram-⊖ rods or coccobacilli with a "safety pin" appearance in sputum, blood, or lymph nodes.	Standard and droplet precautions.	Ciprofloxacin, doxycycline, gentamicin, streptomycin.
Smallpox	Severe flulike prodrome followed by a generalized papular rash that begins on the face and extremities and uniformly progresses to vesicles and pustules, headache, vomiting, back pain, and delirium.	Acute rash with fever.	Varicella (chickenpox), disseminated herpes zoster, monkeypox.	Clinical diagnosis.	Standard, droplet, airborne, and contact precautions.	Supportive care.
Viral hemorrhagic fever (e.g., Ebola)	Fever with mucosal bleeding, petechiae, thrombocytopenia, and hypotension.	Acute rash with fever.	Meningococcemia, malaria, typhus, leptospirosis, TTP, HUS.	Clinical diagnosis.	Standard and contact precautions.	Supportive care.
Tularemia	Fever, rigors, headache, myalgia, coryza, and sore throat followed by substernal discomfort, dry cough, pleuritis, or pneumonitis.	Influenza-like illness.	Influenza, atypical pneumonia, SARS, anthrax, smallpox, plague, Q fever.	CXR with infiltrate, hilar adenopathy, or effusion; small gram-⊖ coccobacilli in sputum or blood.	Standard precautions.	Ciprofloxacin, doxycycline, gentamicin, streptomycin.

TABLE 11.2. Potential Bioterrorism Agents *(continued)*

Agent/ Disease	Clinical Findings	Syndrome	Differential	Initial Diagnostic Testing	Immediate Infection Control	Treatment
Cutaneous anthrax	Pruritic maculopapule that ulcerates by day 2, progressing to vesicles and a painless black eschar with extensive nonpitting edema.	Localized ulcer and extensive edema.	Staphylococcal lymphadenitis, ecthyma gangrenosum.	Gram-⊕ rods in vesicle fluid.	Standard precautions.	Ciprofloxacin, doxycycline, penicillin.

Adapted from the California State Department of Health and the Centers for Disease Control and Prevention.

CATHETER-RELATED INFECTIONS

Include catheter-related bloodstream infections (CRBSIs) as well as exit-site, tunnel, and pocket infections. The most commonly isolated etiologic agents are coagulase-⊖ staphylococci, *S. aureus*, enterococci, and *Candida albicans.*

Candidemia in the setting of a tunneled or nontunneled catheter necessitates catheter removal in all circumstances.

Symptoms/Exam

- **Clinical findings are unreliable.** Fever and chills are sensitive but not specific findings. Inflammation and purulence around the catheter and bloodstream infection are specific but not sensitive.
- Risk factors for complicated *S. aureus* bacteremia include community acquisition, skin findings suggesting acute systemic infection, persistent fever at 72 hours, and ⊕ follow-up blood culture results at 48–96 hours.
- **Blood cultures:** Obtain two sets of cultures, at least one of which is drawn percutaneously. Compare **time to positivity;** if the blood culture drawn through a catheter becomes ⊕ > 2 hours before the peripheral blood culture, CRBSI is suggested.
- **Catheter cultures:** Should be performed only if CRBSI is suspected. The **semiquantitative (roll plate) method,** in which the catheter tip is rolled across an agar plate, is most commonly used. A **colony count > 15** following overnight incubation suggests catheter-related infection.

Transesophageal echocardiography is a cost-effective means of ruling out endocarditis in S. aureus *CRBSI. Transthoracic echocardiography is less sensitive.*

Treatment

- **Catheter removal** is indicated in most cases of **nontunneled** CRBSI. For **tunneled catheters and implantable devices,** consider removal in the setting of severe illness or documented infection (**especially *S. aureus*, gram-⊖ rods,** or ***Candida***) or if complications occur.
- **Initial antibiotic therapy:** Treatment is usually **empiric** with vancomycin (to cover MRSA).
- **Duration of treatment:** Patients with **uncomplicated bacteremia** should be treated for **10–14 days;** those with **complicated infections** (e.g., persistently ⊕ blood cultures after catheter removal, endocarditis, septic thrombophlebitis, osteomyelitis) should be treated for **4–6 weeks.**

Complications

Septic thrombophlebitis, infective endocarditis, septic pulmonary emboli, osteomyelitis, or other complications due to septic emboli.

C. difficile *is a common cause of otherwise unexplained leukocytosis in hospitalized patients.*

CLOSTRIDIUM DIFFICILE COLITIS

Risk factors for *C. difficile* colitis include antibiotic use (particularly clindamycin, cephalosporins, and ampicillin), cancer chemotherapy, bowel surgery, and multiple-organ failure. Diarrhea usually occurs after **one week** of antibiotic therapy but may arise up to **ten weeks** later.

SYMPTOMS/EXAM

Presents with diarrhea (**watery** much more often than **bloody**), abdominal pain and distention, fever, and **leukocytosis.**

DIFFERENTIAL

Antibiotic side effects without *C. difficile*, neutropenic enterocolitis/**typhlitis,** IBD, ischemic bowel, laxatives/stool softeners.

Diarrhea that arises during antibiotic treatment may also be caused by adverse drug effects (amoxicillin, amoxicillin/clavulanic acid, erythromycin).

DIAGNOSIS

- **Fecal WBCs and stool cultures are not useful.**
- **Detection of *C. difficile* toxins: Toxin assays are necessary** because 5% of healthy patients and 25% of hospitalized patients have *C. difficile* in their stools, but only one-third have toxin-mediated disease.
  - **Cytotoxin assay:** Stool supernatant is directly applied to cell culture. Cell lysis suggests the presence of toxin.
  - **Enzyme immunoassay (EIA) for *C. difficile* toxin:** The most frequently used test. Has lower sensitivity than cytotoxin assay, but sensitivity ↑ with repeat testing.
- **Radiographs are often normal** but may show colonic distention and thickening ("thumbprinting" may be seen on plain abdominal films).
- **Endoscopy** shows friable, edematous colonic mucosa with raised yellow plaques (pseudomembranes); specific but not sensitive.

TREATMENT

- **Stop antibiotics** if possible.
- Avoid antidiarrheal agents and opiates.
- Contact isolation.
- Give **PO** or IV **metronidazole** (PO is preferred) or PO vancomycin (oral vancomycin is as effective as metronidazole but is more costly and carries the risk of vancomycin-resistant enterococcus; **IV vancomycin is not effective**).
- The **relapse** rate is 15%, with relapses usually occurring **within two weeks** of treatment cessation.
  - For first-time recurrences, treat again with the same regimen.
  - For refractory cases, consider tapering or pulse-dosing PO treatment, cholestyramine (binds toxin) or bacitracin, vancomycin plus rifampin, or fecal implants (instillation of normal feces in the patient's colon to repopulate with normal flora).

COMPLICATIONS

Ileus, toxic megacolon, perforation (all may be accompanied by a ↓ in diarrhea); hemorrhage, sepsis.

EHRLICHIOSIS/ANAPLASMOSIS

Tick-borne illnesses transmitted by rickettsia-like bacteria. There are two main types:

- **Human monocytic ehrlichiosis (HME):** Caused by *Ehrlichia chaffeensis*; found in southern states such as Arkansas and Missouri (where Rocky Mountain spotted fever is also present).
- **Human granulocytic anaplasmosis (HGA): Formerly known as human granulocytic ehrlichiosis.** Caused primarily by *Anaplasma phagocytophilum*; found in the Northeast and upper Midwest (where Lyme disease and babesiosis are also present).

Symptoms/Exam

Most cases are asymptomatic, but some may present with fever, malaise, myalgias, and headache (flulike symptoms occurring in the spring and summer months) as well as with nausea, arthralgias, anorexia, and chills. HME and HGA are clinically indistinguishable.

Ehrlichiosis has been called "spotless" Rocky Mountain spotted fever in that there is clinical and epidemiologic overlap.

Differential

Rocky Mountain spotted fever, leptospirosis, influenza, infectious mononucleosis, aseptic meningitis, dengue fever, typhoid fever.

Diagnosis

- **Leukopenia** and **thrombocytopenia;** often **elevated LFTs.**
- **Peripheral blood buffy-coat smear** may show **morulae** (meaning "mulberries" in Latin), a cluster of organisms in the cytoplasm of WBCs. The test is insensitive, especially for HME.
- Acute and convalescent antibody titers are most sensitive (> 95% of patients develop antibodies within four weeks of symptom onset).
- PCR.

Treatment

Doxycycline (chloramphenicol or rifampin in pregnancy).

Complications

Pneumonitis, septic shock, hepatitis, renal failure, DIC. May be fatal, especially in older and asplenic patients.

ENCEPHALITIS

HSV and arboviruses (e.g., **West Nile virus,** eastern and western equine virus, St. Louis virus) are the most common causes of encephalitis in the United States. Patients may report travel (e.g., Japanese B virus), tick bite (e.g., Rocky Mountain spotted fever, Lyme disease, ehrlichiosis), or animal bite (e.g., rabies). Postinfectious cases are seen 1–3 weeks after URI, measles infection, or smallpox vaccination.

Encephalitis that develops in the summer or fall is often due to arboviruses. In late spring or early summer, think of tick-borne infections. In the winter or spring, think of measles, mumps, and HSV.

Symptoms

Presents with **fever,** headache, neck stiffness, altered mental status (from mild lethargy to confusion, stupor, and coma), and alterations in speech and behavior.

In contrast with meningitis, encephalitis is an infection of the brain parenchyma and is characterized by cognitive deficits.

Exam

- Exam reveals focal neurologic signs, including motor weakness, accentuated DTRs, hemiparesis, cranial nerve palsies (especially CN III and CN VI), and seizures.
- A rash may be seen with Lyme disease, Rocky Mountain spotted fever, and VZV; weakness and flaccid paralysis may be seen with West Nile virus.

Differential

Brain abscess, 1° or 2° brain tumor, subdural hematoma, SLE, drugs/toxic encephalopathy.

Diagnosis

The 1° goal is to **distinguish HSV from other causes.**

- CSF findings are usually abnormal but nonspecific. **RBCs** may be seen in HSV encephalitis.
- EEG shows diffuse slowing of brain waves. **HSV encephalitis may localize to the temporal lobes** with highly characteristic slow-wave (2- to 3-Hz) complexes.
- MRI with gadolinium shows multifocal lesions (white matter demyelination may be seen in postinfectious cases). Temporal lobe involvement is seen with HSV.
- Acute and convalescent serologies.
- Special CSF testing for specific arboviral IgM antibodies. **PCR for HSV is sensitive and specific in most studies.**

Treatment

- Supportive care (antipyretics, antiseizure medications, lower ICP, mechanical ventilation); IV acyclovir for HSV and VZV.
- The effect of steroids or IVIG on postinfectious encephalitis is unclear.

Complications

Patients with HSV encephalitis have high mortality (70%) and serious sequelae, especially if treatment is delayed. Arboviral infections are largely subclinical except for eastern equine virus, which has > 50% mortality in infants and older adults but is the least common.

ENDOCARDITIS

Infection of the heart valves. Classified as **native valve endocarditis (NVE)** or **prosthetic valve endocarditis (PVE).** IV drug users are a special population at risk, particularly for tricuspid valve endocarditis (see Table 11.3).

Symptoms

- **Acute bacterial endocarditis:** High fever (80%), chills, and embolic phenomena; often no murmur.
- **Subacute endocarditis: Indolent course;** presents with **nonspecific symptoms** such as low-grade fever, chills, night sweats, malaise, weight loss, anorexia, and more immunologic manifestations.

Exam

- Presents with fever, heart murmur, **Osler's nodes** ("**OUCH**ler's" nodes—painful nodules on the finger and toe pads), **splinter hemorrhages** (reddish-

TABLE 11.3. Etiologies of Endocarditis

Type	Etiology
NVE	Viridans streptococci, other streptococci, *S. aureus,* enterococci.
PVE	*S. epidermidis, S. aureus.*
IV drug use	*S. aureus.*
"Culture-⊖" endocarditis	Recent antibiotic use. **HACEK organisms:** *Haemophilus, Actinobacillus, Cardiobacterium, Eikenella, Kingella.* ***Candida* and *Aspergillus:*** IV drug users, long-term indwelling catheters, immunosuppressed. **Rare causes:** *Chlamydia psittaci,* the "ellas" (*Bartonella, Legionella, Brucella, Coxiella*), Whipple's disease.

brown streaks in the proximal nail beds), **petechiae** (especially conjunctival and mucosal), **Janeway lesions** (nontender hemorrhagic macules on the palms and soles), and **Roth's spots**.

- Patients with right-sided disease may develop right-sided heart failure or pulmonary findings, including pleuritic chest pain, cough, and radiographic abnormalities (multiple peripheral infiltrates with cavitation or effusions).

Differential

Atrial myxoma, marantic endocarditis (nonbacterial thrombotic endocarditis, seen in cancer and chronic wasting diseases), **L**ibman-**S**acks **E**ndocarditis (seen in **SLE;** autoantibodies to heart valve), acute rheumatic fever, suppurative thrombophlebitis, catheter-related sepsis, renal cell carcinoma, carcinoid syndrome.

Diagnosis

- **Labs:** Leukocytosis with left shift, mild anemia, elevated ESR. UA may show proteinuria, **microscopic hematuria,** and RBC casts.
- **Blood cultures** are critical in establishing a diagnosis and are ⊕ in 85–95% of cases. It is recommended that **three sets** of blood cultures be taken at least **one hour apart** (before antibiotics).
- **Echocardiography:** Transthoracic echocardiography (TTE) has 60–75% sensitivity; transesophageal echocardiography (TEE) has 95% sensitivity. Both are 95% specific.
- **Duke criteria:** Diagnosis is as follows:
  - **Definitive diagnosis:**
    - **Pathologic criteria:** A ⊕ valve culture or histology.
    - **Clinical criteria: Two major, one major plus three minor, or five minor criteria.**
      - **Major criteria: ⊕ blood cultures** (two or more sets drawn at separate sites and times) and either a **new murmur** or an **oscillating vegetation on echocardiogram.**
      - **Minor criteria: Predisposing conditions (valvular heart disease or IV drug use), fever, embolic disease** (pulmonary or intracra-

Streptococcus bovis *and* Clostridium septicum *endocarditis/bacteremia are seen in patients with bowel pathology and should prompt upper and lower GI endoscopies.*

PR prolongation in a patient with endocarditis may suggest conduction abnormalities due to an aortic valve ring abscess.

nial infarcts, mycotic aneurysm, conjunctival hemorrhages, Janeway lesions), **immunologic phenomena** (glomerulonephritis, Osler's nodes, Roth's spots, RF), and a ⊕ **blood culture** not meeting the major criteria.

- **Possible diagnosis: Clinical criteria of one major plus one minor or three minor criteria.**

Treatment

- **NVE (empiric):** Typically started with vancomycin plus gentamicin. Adjust antibiotics on the basis of culture results and treat for 4–6 weeks.
- **PVE (empiric):** Vancomycin plus rifampin plus gentamicin. Adjust antibiotics on the basis of culture results and treat for six weeks.
- **Persistent fever after one week of appropriate antibiotic therapy** raises concern for a perivalvular or myocardial abscess or a septic embolic focus.
- **Reappearance of fever** after initial defervescence suggests septic emboli, drug fever, interstitial nephritis, or, less commonly, the emergence of resistant organisms.
- **Indications for surgery during active infection** include refractory CHF (50% mortality if surgery is delayed), valvular obstruction, myocardial abscess, perivalvular extension (new conduction abnormalities), persistent bacteremia, fungal endocarditis, and most cases of PVE.

Prevention

- **Antibiotic prophylaxis** is recommended for prosthetic heart valves, patients with a history of infective endocarditis, those with cyanotic heart disease (unrepaired or within six months after repair), or heart transplant recipients with valvulopathy. (AHA 2007 guidelines no longer recommend it for hypertrophic cardiomyopathy, valvular disease, and mitral valve prolapse with a murmur or thickened leaflet.)
- **Procedures for which prophylaxis is recommended** include dental extractions and periodontal procedures; incision or biopsy of respiratory mucosa (e.g., tonsillectomy, transbronchial biopsy); and procedures on infected skin or musculoskeletal structures (e.g., abscess drainage). Prophylaxis may also be reasonable for patients with enterococcal UTIs who will have invasive urinary procedures. (AHA 2007 guidelines no longer recommend prophylaxis for GI or GU procedures.)
  - **For dental procedures:** PO amoxicillin, IV ampicillin, or IV/PO clindamycin 30–60 minutes before the procedure.
  - **For procedures on infected skin or musculoskeletal structures:** PO cephalexin, IV nafcillin or cefazolin 30–60 minutes before the procedure. For severe penicillin allergy or suspected MRSA, use clindamycin or vancomycin.

Complications

- **CHF:** Caused by valvular destruction or myocarditis. **The most common cause of death due to endocarditis.**
- **Embolic phenomena:** Mycotic aneurysms, infarcts, or abscesses in the CNS, kidney, coronary arteries, or spleen. Right-sided disease usually causes pulmonary emboli but may also cause systemic emboli with a **patent foramen ovale** (⊕ bubble study on echocardiogram).
- Arrhythmias and heart block.
- Myocardial or perivalvular abscess (especially with *S. aureus*); may extend to cause pericarditis and tamponade.

FEBRILE NEUTROPENIA

Defined as a single oral temperature of ≥ 38.3°C (101°F) or ≥ 38°C (100.4°F) for ≥ 1 hour in a neutropenic patient (< 500 cells/mm^3 or < 1000 and expected to ↓ to ≤ 500 cells/mm^3). Patients have usually received cancer chemotherapy in the **preceding 7–10 days.** Causes include infection and, to a lesser extent, mucositis, drugs, and the malignancy itself.

Symptoms/Exam

- Patients may be asymptomatic with little or no inflammatory response.
- Subtle signs include pain at commonly infected sites—e.g., the periodontium, pharynx, lower esophagus, abdomen, lung, perineum/anus, eye (fundus), or skin (vascular catheter access sites, bone marrow aspiration sites, nails).

Diagnosis

- Physical examination (excluding rectal examination), CBC with differential, BUN, creatinine, transaminases, and blood cultures (peripheral and/or catheter). Culture other inflamed or purulent sites for bacteria/fungi.
- CXR if there are respiratory signs/symptoms.

Treatment

- **High-risk patients: Hospitalize and give empiric IV antibiotics** after a prompt and thorough initial evaluation (cefepime, ceftazidime, imipenem, or meropenem +/– aminoglycoside +/– vancomycin).
- **Low-risk patients:** Those who may be treated on an **outpatient basis with empiric PO antibiotics** include patients < 60 years of age; those with mild or no symptoms, no hypotension, no COPD, and no prior fungal infection; those with solid tumors; and those who are outpatients at the time of fever onset. If prompt access to medical care is available, patients can be treated with a PO outpatient regimen. **Other patients are high risk** and should be hospitalized for IV antibiotics and further evaluation.
- **Indications for empiric vancomycin:** Hypotension, suspected serious catheter-related infections (e.g., cellulitis, bacteremia), known colonization with drug-resistant pneumococci or MRSA, preliminary blood cultures with gram-⊕ bacteria.
- Remove vascular access devices (e.g., Hickman-Broviac catheters, subcutaneous ports) in the presence of subcutaneous tunnel/periport infection, septic emboli, hypotension, or nonfunctioning catheters.
- Granulocyte transfusions are not recommended for routine use.
- **Hematopoietic growth factors (G-CSF)** are recommended only if a long delay is expected in bone marrow recovery or if there is concern for severe illness.
- Patients who remain febrile should be reassessed after **3–5 days.** Options are as follows:
  - Continue the **same regimen** if clinically stable.
  - **Change** or **add antibiotics** (e.g., vancomycin) if there is progressive disease.
  - Add an **antifungal agent** if the patient is expected to remain neutropenic for 5–7 more days.

Classically defined as a **temperature > 38.3°C** that lasts at least **three weeks** and remains undiagnosed despite evaluation for **more than two outpatient visits** or **three hospital days.** Etiologies vary depending on the patient's age, immune status, and geographic location. In the United States, infection (33%), cancer (25%), and, to a lesser extent, autoimmune diseases (13%) are responsible for most identified cases. Infection is likely if the patient is older or from a developing country, as well as in the setting of nosocomial, neutropenic, or HIV-associated FUO. Etiologies are as follows:

FUO is most commonly due to unusual presentations of common diseases rather than to rare diseases.

- **Infectious: TB, endocarditis,** and **occult abscesses** are the most common infectious causes of FUO in immunocompetent patients. Consider 1° HIV infection or opportunistic infections due to unrecognized HIV.
- **Neoplastic: Lymphoma** and **leukemia** are the most common cancers causing FUO. Other causes include hepatoma, renal cell carcinoma, and atrial myxoma.
- **Autoimmune:** Adult Still's disease, SLE, cryoglobulinemia, polyarteritis nodosa, giant cell (temporal) arteritis/polymyalgia rheumatica (more common in the elderly).
- **Miscellaneous:** Other causes of FUO include drug fever, hyperthyroidism or thyroiditis, Crohn's disease, Whipple's disease, familial Mediterranean fever, recurrent pulmonary embolism, retroperitoneal hematoma, and factitious fever.
- In roughly 10–15% of cases, the cause is not diagnosed. **Most of these cases resolve spontaneously.**

Exam

Repeated physical exams may yield subtle findings in the fundi, conjunctivae, sinuses, temporal arteries, and lymph nodes. Heart murmurs, splenomegaly, and perirectal or prostatic fluctuance/tenderness should be assessed.

Diagnosis

- **History:** Ask about immune status, cardiac valve disorders, drug use, travel, TB exposure history, exposure to animals and insects, occupational history, all medications (prescription, over-the-counter, and herbals), sick contacts, and family history of fever.
- **Labs/imaging:**
  - Obtain routine labs, blood cultures (off antibiotics; hold culture bottles for two weeks), CXR, and PPD. If indicated, obtain cultures of other body fluids (sputum, urine, stool, CSF) as well as a blood smear (malaria, babesiosis) and an HIV test.
  - Echocardiography for vegetations; CT/MRI if neoplasms or abscesses are suspected.
  - Use more specific tests selectively (ANA, RF, viral cultures, antibody/antigen tests for viral and fungal infections).
- Invasive procedures are generally low yield except for temporal artery biopsy in the elderly, liver biopsy in patients with LFT abnormalities, and bone marrow biopsy for HIV.

Treatment

- If there are no other symptoms, treatment may be deferred until a definitive diagnosis is made.
- Broad-spectrum antibiotics if the patient is severely ill or neutropenic.

FOOD-BORNE ILLNESS

Table 11.4 outlines the causes and treatment of food-borne illness, grouped according to incubation period.

Patients are usually afebrile in toxin-mediated food-borne illness.

FUNGAL INFECTIONS

See Figure 11.2 for typical forms of fungi that might be seen in tissues examined by histopathology. Common fungal infections are discussed below.

Candidiasis

The opportunistic yeast *Candida* is a commensal found on the skin, GI tract, and female genital tract. **Superficial infection** is especially common among diabetics. Risk factors for **deep or disseminated infection** include **immune compromise** (HIV, malignancy, neutropenia, or steroids), multiple or prolonged **antibiotic** treatment, and **invasive procedures.** *C. albicans* is the most common cause.

Symptoms/Exam/Diagnosis

- **Candiduria:** Yeast in urine **usually represents colonization** and not infection. Seen in patients with Foley catheters or antibiotic use. Diagnose infection by detecting pyuria or yeast in urine casts; treat if the patient is symptomatic or neutropenic, has undergone renal transplant, or is awaiting urinary tract procedures.
- **Intertrigo ("diaper rash"):** Pruritic vesiculopustules rupture to form macerated or fissured beefy-red areas at skin folds. Satellite lesions may be present. Seen in both immunocompetent and immunosuppressed patients.
- **Oral thrush:** Presents with burning sensations of the tongue or mucosa with white, **curdlike patches that can be scraped away to reveal a raw surface.** Seen in patients with AIDS or malignancy or in those who use inhaled steroids for asthma. Diagnosis can be confirmed with KOH prep or Gram stain.
- **Candidal esophagitis:** Presents with dysphagia, odynophagia, and substernal chest pain. Seen in patients with AIDS, leukemia, and lymphoma. Diagnosed by the endoscopic appearance of white patches or from biopsy showing mucosal invasion. May occur concurrently with HSV or CMV esophagitis.
- **Candidemia and disseminated candidiasis:** Diagnose through cultures of blood, body fluids, or aspirates. Mortality is 40%. Candidemia may lead to endophthalmitis (eye pain, blurred vision), osteomyelitis, arthritis, or endocarditis.
- **Hepatosplenic candidiasis:** Presents with fever and abdominal pain that emerge as neutropenia resolves following bone marrow transplant. Associated with a high mortality rate. Diagnosed by ultrasound or CT imaging showing abscesses. Blood cultures are frequently ⊖.

All patients with candidemia should have an ophthalmologic exam to rule out candidal endophthalmitis.

Treatment

- **Candiduria:** Most cases do not need treatment.
- **Intertrigo and oral thrush:** May be treated with **topical antifungals** (nystatin, clotrimazole or miconazole creams, or nystatin suspension swish and swallow).

TABLE 11.4. Causes of Food-Borne Illness

Disease/Associations	Agent	Symptoms	Treatment
Incubation period < 2 hours: likely toxin or chemical agent			
Ciguatera (grouper, snapper)	Neurotoxin from algae that grow in tropical reefs.	Perioral paresthesias and shooting pains in the legs (may persist for months); bradycardia/hypotension if severe.	Emetics/lavage within three hours; IV fluids; atropine/pressors, mannitol.
Scombroid (tuna, mahi-mahi, mackerel)	Histamine-like substance in spoiled fish.	Burning mouth/metallic taste; flushing, dizziness, headache, GI symptoms; urticaria/bronchospasm if severe.	Antihistamines.
MSG poisoning ("Chinese restaurant syndrome")	Acetylcholine.	Burning sensation in the neck/chest/abdomen/extremities; sweating, bronchospasm, tachycardia.	No treatment.
Incubation period 2–14 hours: likely toxin			
S. aureus (dairy, eggs, mayonnaise, meat products)	Preformed heat-stable enterotoxin.	Vomiting, epigastric pain.	No treatment.
Bacillus cereus	Preformed toxin (like *S. aureus*) or sporulation and toxin production in vivo (like *C. perfringens*).	Vomiting, epigastric pain, diarrhea.	No treatment.
Clostridium perfringens (frequently from reheated meats, stews, gravies)	Toxin is released after heat-resistant clostridial spores germinate in the intestines.	Lower GI symptoms.	No treatment.
Incubation period > 14 hours: bacteria, viruses			
Campylobacter (most common)		Fever, diarrhea.	Ciprofloxacin or azithromycin.
Salmonella		Same as above.	Same as above.
Shigella	Shiga toxin.	Same as above.	Same as above.
Enteroinvasive *E. coli*		Same as above.	Same as above.
Yersinia		Same as above.	TMP-SMX or ciprofloxacin.
Vibrio parahaemolyticus (undercooked seafood)		Same as above.	No treatment.

TABLE 11.4. Causes of Food-Borne Illness *(continued)*

Disease/Associations	Agent	Symptoms	Treatment
Enterohemorrhagic *E. coli* O157:H7 (undercooked ground beef, contaminated produce)	Shiga toxin.	Usually afebrile; bloody diarrhea; HUS in 5% of cases.	No antibiotics (may ↑ risk of HUS).
Enterotoxigenic *E. coli* ("traveler's diarrhea")	Enterotoxins.	Usually afebrile; diarrhea.	Ciprofloxacin.
Norwalk-like virus (cruise ship outbreaks)		Usually afebrile; vomiting, headaches, diarrhea.	No treatment.

- **Esophagitis and other deep or disseminated infections:** Systemic therapy with fluconazole, amphotericin, voriconazole, or caspofungin.
- Replace vascular catheters at a new site (do not exchange over a wire!).
- *C. albicans* is usually susceptible to fluconazole and can be distinguished from other etiologic agents within several hours by a ⊕ germ tube test (i.e., the yeast grows a germ tube or pseudohyphae). Patients who have been on fluconazole prophylaxis may have resistant *C. albicans* or non-albicans species (e.g., *C. glabrata*, *C. krusei*).

Complications

Patients with persistent candidemia after catheter removal may have peripheral septic thrombophlebitis or septic thrombosis of the central veins.

Aspergillosis

Aspergillus fumigatus and other species are widespread in soil, water, compost, potted plants, ventilation ducts, and marijuana.

Symptoms/Exam

- **Allergic bronchopulmonary aspergillosis (ABPA):** Presents with episodic bronchospasm, fever, and brown-flecked sputum. Seen in patients with underlying asthma or CF. CXR shows patchy, fleeting infiltrates and lobar consolidation or atelectasis. Labs show eosinophilia, elevated serum IgE, and ⊕ serum IgG precipitins.
- **Aspergilloma of the lungs or sinus:** May be asymptomatic or present with hemoptysis, chronic cough, weight loss, and fatigue. Seen in patients with previous TB, sarcoidosis, emphysema, or PCP. CXR and CT may show an **air-crescent sign** or a rim of air around a fungus ball in a preexisting upper lobe cavity. Labs show ⊕ serum IgG precipitins.
- **Invasive aspergillosis:**
  - Presents with dry cough, pleuritic chest pain, and persistent fever with a new infiltrate or nodule despite broad-spectrum antibiotics. Seen in patients with prolonged neutropenia, advanced AIDS, diabetes, and chronic granulomatous disease as well as in those on high-dose steroids or immunosuppressants.

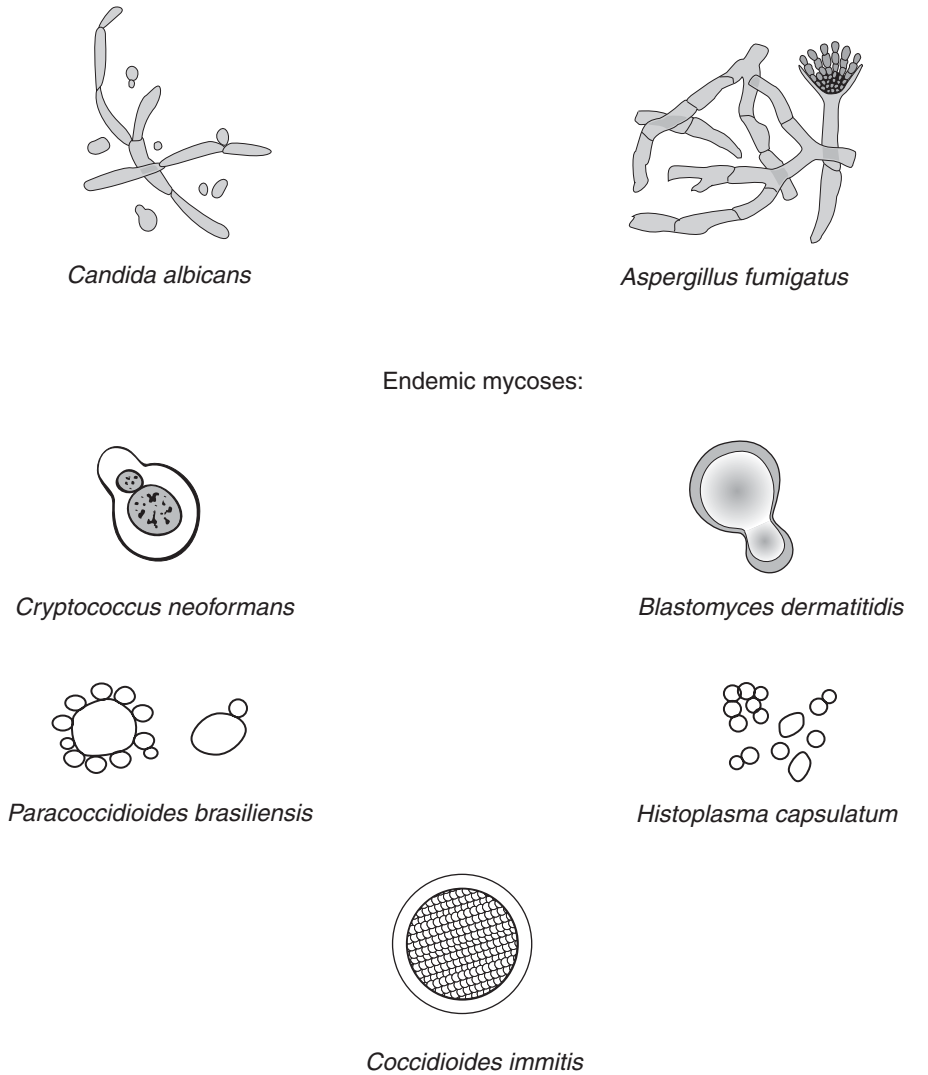

FIGURE 11.2. Characteristic forms of fungi in human tissue (37°C).

(Reproduced, with permission, from Bhushan V, Le T. *First Aid for the USMLE Step 1: 2005.* New York: McGraw-Hill, 2005: 191.)

- **Imaging:** CXR and CT may show wedge-shaped lesions from tissue infarction, an **air-crescent sign** from cavitation of a necrotic nodule, or a **halo sign** of a necrotic nodule with surrounding hemorrhage.
- **Labs:** The *Aspergillus* galactomannan assay is approved for diagnosis in patients with hematologic malignancies and following bone marrow transplant. IgG precipitins and blood cultures are rarely ⊕. In high-risk patients, ⊕ sputum or bronchial washing cultures are strongly suggestive, but definitive diagnosis requires a biopsy demonstrating tissue invasion.
- **Patients are often severely ill, and empiric antifungal therapy may be reasonable in high-risk patients.**

DIFFERENTIAL

- **ABPA:** TB, CF, lung cancer, eosinophilic pneumonia, bronchiectasis.
- **Aspergilloma:** Invasive aspergillosis.

- **Invasive aspergillosis:** Aspergilloma, cavitating lung tumor, nosocomial *Legionella* infection.

Treatment

- **ABPA:** Systemic corticosteroids plus itraconazole × 8 months improves lung function and ↓ steroid requirements.
- **Aspergilloma:** Surgical excision for massive hemoptysis. Antifungals play a limited role.
- **Invasive aspergillosis:** Voriconazole, amphotericin, or caspofungin.

Complications

- **ABPA:** Bronchiectasis, pulmonary fibrosis.
- **Aspergilloma:** Massive hemoptysis; contiguous spread to the pleura or vertebrae.
- **Invasive aspergillosis:** High mortality, especially in bone marrow and liver transplant patients.

Cryptococcosis

Cryptococcus neoformans is an encapsulated budding yeast found worldwide in soil, bird (pigeon) droppings, and eucalyptus trees. Risk factors for the disease are HIV-related immunosuppression, Hodgkin's disease, leukemia, and steroid use. *C. neoformans* is the most common fungal infection in AIDS patients (usually associated with a CD4 count < 100) and is the most common cause of fungal meningitis in all patients.

Symptoms/Exam

- **Meningitis:** Mental status changes, headache, nausea, cranial nerve palsies. **HIV patients usually lack obvious meningeal signs.**
- May also cause atypical pneumonia (pulmonary infection is usually asymptomatic) or skin lesions (umbilicated papules resembling molluscum contagiosum), or may involve the bone, eye, or GU tract.

Cryptococcemia (a ⊕ serum CrAg or blood culture) indicates disseminated disease even with a normal LP.

Differential

Meningitis due to TB, neurosyphilis, toxoplasmosis, coccidioidomycosis, histoplasmosis, HSV encephalitis, meningeal metastases.

Diagnosis

- **LP:** Patients often have high opening pressure, low glucose, high protein, and lymphocytic pleocytosis. **Patients with more advanced immunosuppression may have a bland CSF profile even with meningitis.** India ink or Gram stain of CSF may show budding yeast with a thick capsule (both are < 50% sensitive).
- **Polysaccharide cryptococcal antigen (CrAg) in serum or CSF:** Serum CrAg is > 99% sensitive in AIDS patients with meningitis but is less sensitive in non-AIDS patients. CSF CrAg is only 90% sensitive. A serum CrAg titer of > 1:8 indicates active disease.
- **Fungal culture** of blood, CSF, urine, sputum, or bronchoalveolar lavage.
- CT or MRI may show hydrocephalus or occasionally nodules (cryptococcomas).

Unlike what is typically seen in bacterial meningitis, HIV patients with cryptococcal meningitis often have minimal symptoms and a bland CSF.

Serum CrAg titers are not useful for monitoring treatment response of meningitis in immunosuppressed patients. CSF CrAg titers should ↓ during successful treatment.

Treatment

- **HIV-⊖ patients**: For mild to moderate lung disease, treat with oral fluconazole × 6–12 months. For meningitis, cryptococcemia, or severe lung disease, treat with amphotericin plus 5-flucytosine × 2 weeks followed by oral fluconazole 400 mg/day for at least 10 weeks.
- **HIV-⊕ patients:**
  - For mild to moderate lung disease, treat with fluconazole 200–400 mg/day.
  - For severe lung disease, treat with amphotericin until symptoms are controlled followed by fluconazole.
  - For meningitis, give **induction/consolidation therapy** with amphotericin plus 5-flucytosine × 2 weeks followed by oral fluconazole 400 mg/day × 10 weeks.
- Patients with HIV need **long-term maintenance therapy** with oral fluconazole 200 mg/day. It may be reasonable to stop prophylaxis if the CD4 count ↑ to > 100–200 for > 6 months in response to antiretrovirals.
- **Repeat LP** until symptoms resolve in patients with coma or other signs of elevated ICP.

Complications

A poorer prognosis for meningitis is seen in patients with abnormal mental status, those > 60 years of age, and those with evidence of high organism load or lack of immune response (as indicated by cryptococcemia, high initial CrAg titer in CSF or serum, high CSF opening pressure, < 20 WBCs in CSF, low glucose, and ⊕ India ink).

Coccidioidomycosis

Coccidioides immitis is found in the arid **southwestern United States,** central California, northern Mexico, and Central and South America. It is found in soil, and outbreaks occur after earthquakes or dust storms. Risk factors include exposure to soil and the outdoors (construction workers, archaeologists, farmers).

Symptoms/Exam

- **1° infection ("valley fever," "desert rheumatism"):** Usually presents with self-limited flulike symptoms, fever, dry cough, pleuritic chest pain, and headache, often accompanied by **arthralgias, erythema nodosum, or erythema multiforme.** CXR may be normal or may show unilateral infiltrates, nodules, or thin-walled cavities. Some patients (5%) may develop chronic pneumonia, ARDS, or persistent lung nodules.
- **Disseminated disease (1%):** Chronic meningitis, skin lesions (papules, pustules, warty plaques), osteomyelitis, or arthritis.

Differential

Atypical pneumonia, TB, sarcoidosis, histoplasmosis, blastomycosis.

Diagnosis

- **Serologic tests** (complement fixation assays); titers ≥ 1:32 indicate more severe disease and a higher risk of dissemination.
- **Histology** may show giant **spherules** in infected tissues.

- **Cultures** of respiratory secretions or aspirates of bone and skin lesions may grow the organism (alert the laboratory if the diagnosis is suspected; *Coccidioides* is highly infectious to lab workers).

Treatment

- Treatment may not be necessary for acute disease but may be reasonable in patients at risk for dissemination.
- Fluconazole, itraconazole, or amphotericin for disseminated disease.

Complications

Disseminated disease is more common in nonwhites, pregnant women, and patients with HIV, diabetes, or immunosuppression.

Histoplasmosis

Histoplasma capsulatum is found in the **Mississippi** and **Ohio River valleys.** The organism is found in moist soil and in bat and bird droppings. Risk factors include exploring caves and cleaning chicken coops or attics.

Symptoms/Exam

- **1° infection: Most patients are asymptomatic.** However, patients may present with fever, dry cough, and substernal chest discomfort. CXR may show patchy infiltrates that become nodular or exhibit multiple small nodules and hilar or mediastinal adenopathy. Some patients may develop chronic upper lobe cavitary pneumonia or mediastinal fibrosis (dysphagia, SVC syndrome, or airway obstruction).
- **Disseminated disease:** Presents with **hepatosplenomegaly,** adenopathy, **painless palatal ulcers,** meningitis, and pancytopenia from bone marrow infiltration. Patients with HIV may develop colonic disease (diarrhea, perforation or obstruction from mass lesions).

Differential

Atypical pneumonia, influenza, coccidioidomycosis, blastomycosis, TB, sarcoidosis, lymphoma.

Diagnosis

- **Urinary antigen test** is most useful in HIV/AIDS patents with disseminated disease.
- **Histology with silver stain** of bone marrow, lymph node, or liver.
- Cultures of blood or bone marrow are ⊕ in immunosuppressed patients with disseminated disease.
- Serologic tests (complement fixation and immunodiffusion assays) are often ⊕ in immunocompetent patients.

Treatment

- Treatment is not needed for acute pulmonary disease.
- Itraconazole or amphotericin for chronic cavitary pneumonia, mediastinal fibrosis, or disseminated histoplasmosis.

Complications

Severe or disseminated disease is more common in patients infected with a large inoculum and in elderly, immunosuppressed, and HIV patients.

Blastomycosis

Blastomyces dermatitidis is found in the **central United States** (as is *Histoplasma*) as well as in the upper Midwest and Great Lakes regions. Risk factors include exposure to woods and streams.

Symptoms/Exam

Acute pneumonia. May lead to warty, crusted, or ulcerated **skin lesions** or to osteomyelitis, epididymitis, or prostatitis.

Diagnosis

Microscopy and culture of respiratory secretions; biopsy or aspirate material shows large yeast with **broad-based budding.**

Treatment

Itraconazole or amphotericin for all infected patients.

GUILLAIN-BARRÉ SYNDROME

Acute symmetric ascending weakness or paralysis with areflexia; paresthesias may also be present distally. Usually occurs within 30 days of a respiratory or GI infection, especially *Campylobacter* enteritis, CMV, EBV, or mycoplasmal infection. Differential diagnosis includes the following:

- **Focal cord lesion:** Usually asymmetric; shows early sphincter involvement.
- **Rabies:** Follows wild animal exposure.
- **West Nile virus.**
- **Botulism:** Also presents with diplopia and ocular palsies.
- **Tick paralysis:** Look for an attached tick, frequently on the scalp.
- **Polio:** Usually asymmetric; fever is present.
- **Toxins:** Heavy metals, organophosphates.

HANTAVIRUS PULMONARY SYNDROME

First identified in the southwestern United States in 1993; cases have since been reported across the country. Infection follows inhalation of **aerosols of dried rodent urine, saliva, or feces.** The disease begins as a nonspecific **febrile syndrome** (sudden fever, myalgias) with **rapid progression** to respiratory failure/ARDS and shock. Patients have leukocytosis, hemoconcentration, and thrombocytopenia. Diagnose by serology or by immunohistochemical staining of sputum or lung tissue. **Ribavirin** has been used experimentally, but mortality remains 50%.

HUMAN IMMUNODEFICIENCY VIRUS (HIV)

HIV targets and destroys CD4+ T lymphocytes, leading to AIDS. Risk factors include unprotected sexual intercourse, IV drug use, maternal infection, needlesticks, and mucosal exposure to body fluids; also at risk are patients who received blood products before 1985. Prognostic factors are CD4 count and HIV RNA viral load. CD4 count measures the degree of immune compromise and predicts the risk of opportunistic infections; viral load measures HIV replication rate, gauges the efficacy of antiretrovirals, and predicts CD4 count decline.

Symptoms/Exam

- **1° HIV infection:** May be asymptomatic. Acute retroviral syndrome presents 2–6 weeks after initial infection with fever, sore throat, lymphadenopathy, and a truncal maculopapular rash or mucocutaneous ulcerations. Other signs and symptoms include myalgias, arthralgias, diarrhea, headache, nausea, vomiting, weight loss, aseptic meningitis, and thrush.
- **Chronic HIV infection:** Fatigue, fevers, night sweats, diarrhea, persistent lymphadenopathy, and weight loss. Suspect in patients with thrush, oral hairy leukoplakia, herpes zoster, seborrheic dermatitis, oral aphthous ulcers, or recurrent vaginal candidiasis.

Differential

Acute retroviral syndrome resembles infectious mononucleosis, acute CMV infection, aseptic meningitis, and syphilis.

Diagnosis

- **ELISA/EIA and rapid HIV antibody tests:** Detect antiviral antibodies; used to diagnose HIV. Usually ⊕ by **three months** after initial infection. Because false-⊕ results may occur (especially in low-risk populations being screened), confirm by **Western blot.**
- **HIV RNA viral load:** Not approved by the FDA for **diagnosing** HIV. Has high sensitivity even in patients who have not yet developed antibodies. False-⊕ results may occur, usually in the form of a low copy number (e.g., < 10,000 copies/mL); true-⊕ results in antibody-⊖ patients with acute infection are usually > 100,000 copies/mL.
- **p24 core antigen:** Highly specific but less sensitive (85–90%) and less readily available than HIV viral load. Approved by the FDA for diagnosing acute HIV.
- **Detuned ELISA:** Licensed for research only. ELISA antibody-⊕ serum samples are diluted and retested; if the ELISA test is ⊖ after dilution, it indicates a lower concentration, less specific antibodies, and seroconversion within the last 4–6 months.

Treatment

- Current recommendations (International AIDS Society-USA, 2006) are to **start HIV treatment in all patients who are symptomatic. Treatment of asymptomatic patients should be started when the CD4 count is 200–350 cells/mm³.**
- Consider initiating antiretrovirals in patients with acute retroviral syndrome.
- Use three drugs—usually two nucleoside analogs (AZT, 3TC, d4T, ddI, abacavir, tenofovir, emtricitabine) plus a non-nucleoside analog (nevirapine or efavirenz) **or** a protease inhibitor (fosamprenavir, indinavir, nelfinavir, saquinavir, atazanavir, or lopinavir/ritonavir) that may be ritonavir "boosted." Protease inhibitors can have significant drug interactions.
- **During pregnancy, women should be offered standard therapy** in the form of two nucleoside reverse transcriptase inhibitors (including AZT) plus nevirapine or a protease inhibitor. Consider starting after 10–14 weeks of gestation to minimize the risk of teratogenicity. **Efavirenz is contraindicated during pregnancy.**

Do not use HIV viral load as a factor in deciding when to initiate antiretroviral therapy.

Complications

Progressive immunosuppression from HIV leads to opportunistic infections and malignancies (see Figure 11.3). Prophylactic measures against some of these conditions are outlined in Table 11.5.

HIV-RELATED OPPORTUNISTIC INFECTIONS

Table 11.6 outlines common HIV-related opportunistic infections with treatment guidelines.

INFECTION CONTROL PRECAUTIONS

Isolation and barriers are used to prevent the transmission of microorganisms from patients to other patients, visitors, or health care workers (see Table 11.7).

INFECTIOUS MONONUCLEOSIS

Caused by the Epstein-Barr virus (EBV). Commonly seen in late adolescence and early adulthood (college or military populations). Clinical course is generally benign, with patients recovering in 2–3 weeks.

Symptoms

Presents with the triad of **fever, sore throat** (may be severe), and **generalized lymphadenopathy,** often with an abrupt onset. Patients may have a viral-like prodrome as well as retro-orbital headache or abdominal fullness (from hepatosplenomegaly).

Exam

- Lymphadenopathy (especially of the posterior cervical nodes), pharyngitis, and splenomegaly.

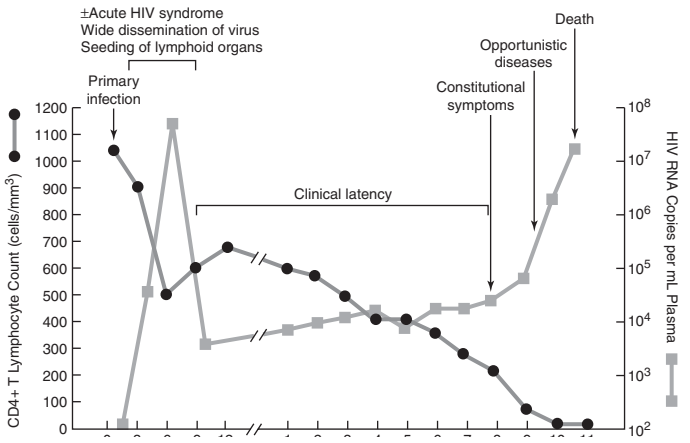

FIGURE 11.3. Clinical decision points in HIV infection/disease in adults.

(Adapted, with permission, from Fauci AS et al. Immunopathologic mechanisms of HIV infection. *Ann Intern Med* 1996; 124:654.)

TABLE 11.5. Prophylaxis Against AIDS-Related Opportunistic Infections

Pathogen	Indications for Prophylaxis	Medication	Comments
Pneumocystis jiroveci pneumonia (PCP)	CD4 count < 200/mm³ or a history of oral thrush. Prophylaxis may be stopped if CD4 > 200 for ≥ 3 months on highly active antiretroviral therapy (HAART).	TMP-SMX or dapsone +/– pyrimethamine or pentamidine nebulizers or atovaquone.	Single-strength tablets of TMP-SMX are effective and may be less toxic than double-strength tablets.
Mycobacterium avium complex (MAC)	CD4 count < 50/mm³. Prophylaxis may be stopped if CD4 > 100 for ≥ 3 months on HAART.	Azithromycin, clarithromycin, rifabutin.	Azithromycin can be given once weekly. Rifabutin can ↑ hepatic metabolism of other drugs.
Toxoplasma	CD4 count < 100/mm³ and *Toxoplasma* IgG ⊕. Prophylaxis may be stopped if CD4 > 100–200 for ≥ 3 months on HAART.	TMP-SMX or dapsone +/– pyrimethamine or atovaquone.	Covered by all PCP regimens except pentamidine.
Mycobacterium tuberculosis	PPD > 5 mm; history of a ⊕ PPD that was inadequately treated; close contact with a person with active TB.	INH sensitive: INH × 9 months (include pyridoxine).	For INH-resistant strains, use rifampin or rifabutin +/– pyrazinamide.
Candida	Frequent or severe recurrences.	Fluconazole or itraconazole.	
HSV	Frequent or severe recurrences.	Acyclovir, famciclovir, valacyclovir.	
Pneumococcus	All patients.	Pneumococcal vaccine.	Some disease may be prevented with TMP-SMX, clarithromycin, and azithromycin. Repeat when CD4 > 200.
Influenza	All patients.	Influenza vaccine.	
HBV	All susceptible patients (i.e., hepatitis B core antibody ⊖)	Hepatitis B vaccine (three doses).	
HAV	All susceptible patients at ↑ risk for HAV infection or with chronic liver disease (e.g., chronic HBV or HCV).	Hepatitis A vaccine (two doses).	IV drug users, men who have sex with men, and hemophiliacs are at ↑ risk.

- A maculopapular rash occurs in 10% of patients (especially in those given ampicillin), and palatal petechiae may be seen. RUQ tenderness is more common than hepatomegaly.

TABLE 11.6. Diagnosis and Treatment of Selected Opportunistic Infections in HIV/AIDS Patients

	Clinical Presentation	Diagnosis	1° Therapy	Alternative Therapy	Other
Pneumocystis jiroveci pneumonia (PCP)	Nonproductive cough, fever, and dyspnea. Symptoms often progress over weeks. CD4 is often < 200.	CXR frequently shows bilateral interstitial infiltrates but may be normal. Hypoxia with ambulation; elevated LDH. Confirm with organism seen on silver-stained sputum sample or bronchoscopy.	TMP-SMX. If Po_2 < 70 mmHg at room air, add prednisone.	Pentamidine or dapsone plus TMP or primaquine plus clindamycin or atovaquone.	Maintenance therapy should be continued following initial therapy.
Mycobacterium avium complex (MAC)	Fever, night sweats, weight loss, fatigue, diarrhea, abdominal pain. Diffuse lymphadenopathy and hepatosplenomegaly may be seen. CD4 is often < 50.	Pancytopenia, elevated alkaline phosphatase, low albumin. CT of the abdomen may reveal diffuse lymphadenopathy and hepatosplenomegaly. Diagnosed by culture of the organism from a sterile site (blood or lymph node).	Clarithromycin plus ethambutol +/– rifabutin.	Azithromycin plus ethambutol +/– rifabutin.	Maintenance therapy should be continued following initial therapy.
Toxoplasma gondii encephalitis	Fever, headache, altered mental status, seizure, and/or focal neurologic changes. Presentation may be very subtle. CD4 is often < 100.	Head CT with contrast or MRI with ring-enhancing lesions (often multiple). *Toxoplasma* IgG is ⊕ in 95% of patients. LP may be normal or may show ↑ protein and mononuclear pleocytosis.	Pyrimethamine plus sulfadiazine.	Pyrimethamine plus clindamycin or TMP-SMX or pyrimethamine plus atovaquone.	Leucovorin should be given with pyrimethamine. Steroids should be given only if there is mass effect from intracranial lesions.

TABLE 11.6. Diagnosis and Treatment of Selected Opportunistic Infections in HIV/AIDS Patients *(continued)*

	Clinical Presentation	Diagnosis	1° Therapy	Alternative Therapy	Other
Cryptococcus neoformans	**Meningitis:** Headache, malaise, nausea, fever, visual changes, CN deficits, meningismus. Often subacute. **Pneumonia:** May be asymptomatic or present with pulmonary symptoms. CD4 is often < 100.	**CSF:** High opening pressure, elevated protein, low glucose, and lymphocytosis. Twenty-five percent of patients may have normal studies. ⊕ CrAg; CSF culture ⊕. **Blood:** ⊕ CrAg; blood cultures ⊕.	**Induction:** Amphotericin B plus flucytosine × 14 days. **Consolidation:** Fluconazole 400 mg QD × 10 weeks. **Maintenance:** Fluconazole 200 mg QD indefinitely.	Liposomal amphotericin B plus flucytosine or fluconazole plus flucytosine.	May require multiple LPs to relieve high ICP. Chronic maintenance therapy may be discontinued after the completion of treatment with a CD4 > 150 for six months on HAART.
CMV	**Retinitis:** Painless loss of vision, floaters. **Esophagitis:** Odynophagia. **Colitis:** Diarrhea (watery or bloody), abdominal pain. CD4 is often < 50.	**Ophthalmologic exam:** Large plaques with perivascular exudates and hemorrhages. **Endoscopy:** Hemorrhages, ulcerations; 10% are normal. Confirm with biopsy.	Ganciclovir.	Valganciclovir, foscarnet, or cidofovir. Consider intraocular ganciclovir implants for severe retinitis.	Ganciclovir may cause bone marrow suppression. CMV may also cause pneumonitis, myelitis, or encephalitis.
Cryptosporidiosis	Persistent watery diarrhea; occasional nausea, vomiting, and/or fever. Can cause HIV cholangiopathy. CD4 < 100.	Must request stool exam for *Cryptosporidia* (modified AFB, trichrome, or DFA); not seen on standard O&P exam.	Initiation of HAART is the only treatment shown to have benefit.	Possible benefit from paromomycin.	Symptomatic relief with antimotility agents and electrolyte repletion. Cholangiopathy requires ERCP and HAART.

Differential

- **CMV:** Consider if there was a recent blood transfusion. Symptoms are usually systemic; sore throat and lymphadenopathy are uncommon. Diagnose with a ⊕ CMV IgM.
- **Heterophil-⊖ EBV:** Usually affects children; has milder symptoms.
- **Acute toxoplasmosis:** Presents with nontender head and neck lym-

TABLE 11.7. Infection Control Measures

Precaution	Prevents Transmission of	Barriers to Be Used	Should Be Used for (Examples)
Standard	Transient flora from patients or surfaces.	Hand washing; gloves for contact with all body fluids and mucosa. Face shields and gowns if splashes of body fluids are possible.	Everybody!
Airborne	Droplet nuclei (≤ 5 μm) or dust particles that remain suspended for long distances.	Negative-pressure rooms and use of surgical masks when transporting patients. Health care workers should use fitted N-95 masks. Consider face shields.	TB, measles, SARS, vesicular rashes (chickenpox, zoster, smallpox).
Droplet	Large droplets that travel < 3 feet and are generated by coughing, sneezing, talking, suctioning, or bronchoscopy.	Private rooms and use of surgical masks when patients are transported. Health care workers should use surgical masks.	Meningococcal or *H. influenzae* meningitis, influenza, pertussis.
Contact	Direct and indirect contact.	Private rooms (patients may be grouped together); limit patient transport. Dedicated equipment (e.g., stethoscopes). Health care workers should use gowns and gloves for all patients.	Some fecally transmitted infections (HAV, *C. difficile*), vesicular rashes (chickenpox, zoster, smallpox), SARS.

phadenopathy and mild lymphocytosis. Diagnose with *Toxoplasma* IgM and IgG seroconversion.

- **1° HIV infection:** Fever, lymphadenopathy, pharyngitis, maculopapular rash, and, less commonly, aseptic meningitis.
- **HAV or HBV:** Characterized by markedly elevated AST and ALT.
- **Syphilis.**
- **Rubella:** A prominent rash begins on the face and progresses to the trunk and extremities. Has a shorter course (only several days).
- **Streptococcal pharyngitis:** Presents with fever, tender submandibular or anterior cervical lymphadenopathy, and pharyngotonsillar exudates with no cough. Splenomegaly is not seen. Diagnose with rapid streptococcal test and throat culture if antigen test is ⊖.

Diagnosis

- Neutropenia (mild left shift); **atypical lymphocytes** (see Figure 11.4) in 70% of cases (WBC 12,000–18,000 and occasionally 30,000–50,000); thrombocytopenia; mildly elevated LFTs.
- **Heterophil antibodies** (Monospot) are found in 90% of cases (may initially be ⊖ and then turn ⊕ in 2–3 weeks). Other EBV serologies are rarely needed.
- Anti-VCA IgM is ⊕ at presentation; anti-EBNA and anti-S antibodies are ⊕ in 3–4 weeks. Anti-VCA IgG antibodies are ⊕ if patients were previously exposed. Cold agglutinins are found in 80% of cases after 2–3 weeks.

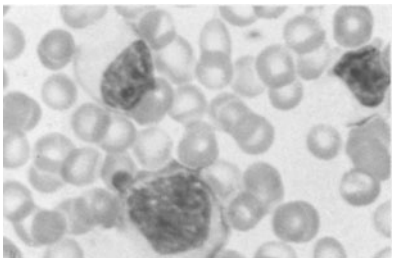

FIGURE 11.4. Atypical lymphocytosis seen in infectious mononucleosis and other infections.

These reactive T lymphocytes are large with eccentric nuclei and bluish-staining RNA in the cytoplasm. (Reproduced, with permission, from Braunwald E et al. *Harrison's Principles of Internal Medicine,* 15th ed. New York: McGraw-Hill, 2001.)

TREATMENT

No treatment is necessary in the majority of cases. Steroids are used on rare occasions for tonsillar obstruction, severe thrombocytopenia, autoimmune hemolytic anemia, and CNS complications.

COMPLICATIONS

Autoimmune hemolytic anemia (< 3%). Splenic rupture is rare but may occur in weeks 2–3 (patients should avoid contact sports and heavy lifting). Meningoencephalitis is rare, and patients usually recover completely.

LYME DISEASE

A tick-borne illness caused by *Borrelia burgdorferi* (found in the Northeast, mid-Atlantic, and upper Midwest more than the West) and other *Borrelia* species (found in Europe and Asia). Prevalence is based on the distributions of the tick vectors *Ixodes scapularis* (found in the Northeast and upper Midwest) and *I. pacificus* (found in the West). Transmitted primarily by nymphal stages that are active in late spring and summer. Requires tick attachment for > 24 hours.

The rash of early Lyme disease, erythema migrans, is often missed and resolves in 3–4 weeks without treatment.

SYMPTOMS/EXAM

- **Early localized infection:** Occurs one week (3–30 days) after tick bite. Presents with **erythema migrans** (60–80%), which appears as an expanding red lesion with "bull's eye" central clearing on the thigh, groin, or axilla (see Figure 11.5). Often accompanied by fever, myalgias, and lymphadenopathy.
- **Early disseminated infection:**
  - Occurs days to weeks after onset of the initial erythema migrans lesion. Skin lesions are like erythema migrans but are smaller and often multiple.
  - Neurologic involvement may include cranial neuritis (CN VII palsy is most common and may be bilateral), peripheral neuropathy, and/or aseptic meningitis. Cardiac abnormalities include AV block (rarely requiring a permanent pacemaker), myopericarditis, and mild left ventricular dysfunction.
  - Migratory **myalgias, arthralgias, fatigue,** and malaise are common during this phase.

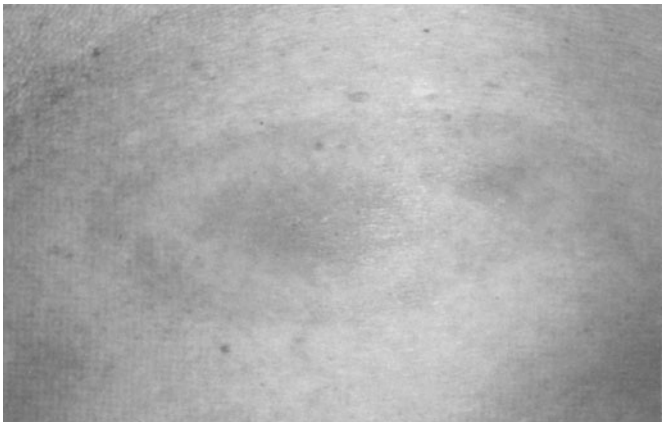

FIGURE 11.5. Erythema chronicum migrans seen in Lyme disease.

The classic "bull's eye" lesion consists of an outer ring where the spirochetes are found, an inner ring of clearing, and central erythema due to an allergic response at the site of the tick bite. Note that some lesions may consist only of the outer annular erythema with central clearing. (Reproduced, with permission, from Braunwald E et al. *Harrison's Principles of Internal Medicine*, 15th ed. New York: McGraw-Hill, 2001.)

Lyme disease may present as asymmetric oligoarticular arthritis, frequently of the knee or other large joints.

- **Late Lyme disease:** Occurs months to years later in untreated patients. Arthritis may develop in large joints (commonly the knee; shows PMN predominance) or small joints. Attacks last weeks to months **with complete remission between recurrences** and become less frequent over time. Chronic neurologic findings include subacute encephalopathy (memory, sleep, or mood disturbances) and peripheral sensory polyneuropathy (pain or paresthesias; abnormal EMG).
- **Congenital Lyme disease:** Cases of congenital transmission resulting in fetal death have been reported.

Diagnosis

Ixodes scapularis *bites can lead to coinfection with Lyme disease, human granulocytic anaplasmosis, and/or babesiosis.*

The testing strategy depends on the pretest probability of disease (per the American College of Physicians 1997 guidelines):

- **High likelihood (> 80%, e.g., erythema migrans in an endemic area):** Clinical diagnosis is sufficient. Serology is often ⊖ in early disease and is not needed to confirm the diagnosis.
- **Low likelihood (< 20%, e.g., nonspecific complaints with no objective findings):** Serologic testing is not indicated, and patients should not be treated (⊕ results will likely be false ⊕s).
- **Intermediate likelihood (20–80%, e.g., some typical findings and residence in an endemic area):** Combine ELISA with a confirmatory Western blot (as with HIV). In the first month of symptoms, test IgM and IgG antibodies in acute and convalescent sera; later, test only IgG antibodies.
- Patients with neuroborreliosis usually have a ⊕ serum serology. CSF antibody testing is not necessary.
- PCR of plasma and tissue (but not CSF) is sensitive, but no guidelines exist.

Treatment

- **Early Lyme disease:** Doxycycline or amoxicillin × 14–21 days (an alternative is cefuroxime). In the presence of meningitis, radiculopathy, or third-

degree AV block, treat with ceftriaxone or cefotaxime × 14–28 days (or, alternatively, IV penicillin or doxycycline). Treatment response for early Lyme disease is excellent. Jarisch-Herxheimer reactions occur in 5–10% of patients during the first days of treatment.

- **Late infection (arthritis):** Doxycycline or amoxicillin × 28 days. For the first arthritis recurrence, repeat doxycycline or ceftriaxone × 14 days. For further recurrences, treat symptomatically and consider synovectomy. For late neurologic disease, treat with ceftriaxone × 14–28 days; response may be slow and incomplete.

Patients with a tick attached for < 24 hours do not need treatment for Lyme disease.

PREVENTION

Patients in endemic areas with a tick that is partially engorged or attached for **> 24 hours** may benefit from doxycycline 200 mg PO × 1 dose. Testing of ticks for infectious organisms is not recommended. Lyme disease vaccine is no longer available.

COMPLICATIONS

- Some patients may have treatment-resistant (autoimmune) arthritis for months to years despite appropriate antibiotics. *B. burgdorferi* DNA is not found in the joint, and patients do not respond to antibiotics.
- Following appropriately treated Lyme disease, some patients may develop poorly defined, subjective complaints (myalgia, arthralgia, fatigue, memory impairment). **These patients do not benefit from repeated or prolonged antibiotic treatment.** The most common reason for apparent antibiotic failure in Lyme disease is misdiagnosis.

MENINGITIS

SYMPTOMS/EXAM

As for encephalitis. Atypical presentations are more likely in neonates, young children, and the elderly. Etiologies are as follows:

- **Acute meningitis:**
  - **Acute neutrophilic meningitis:** Caused by bacteria (see Table 11.8).
  - **Acute eosinophilic meningitis:** Caused by *Angiostrongylus cantonensis*, or rat lung worm; results from ingestion of undercooked mollusks or contaminated vegetables. Endemic in Southeast Asia and the Pacific Islands; associated with peripheral eosinophilia.
- **Chronic meningitis:**
  - Characterized by symptoms lasting from weeks to months with persistent CSF pleocytosis (usually lymphocytic):
  - Etiologic agents include TB (40%), atypical mycobacteria, *Cryptococcus* (7%), *Coccidioides*, *Histoplasma*, *Blastomyces*, 2° syphilis, Lyme disease, and Whipple's disease. The etiology is frequently unknown (34%). Noninfectious causes include CNS or metastatic neoplasms (8%), leukemia, lymphoma, vasculitis, sarcoid, and subarachnoid or subdural bleeds.
  - **Chronic neutrophilic meningitis:** May be caused by *Nocardia*, *Actinomyces*, *Aspergillus*, *Candida*, SLE, or CMV in advanced AIDS.
  - **Chronic eosinophilic meningitis:** Associated with *Coccidioides*, parasites, lymphoma, and chemical agents.
  - **Chronic meningitis and cranial nerve palsies:** Caused by Lyme disease, syphilis, sarcoid (CN VII—Bell's palsy), and TB (CN VI—lateral rectus palsy).

TABLE 11.8. Initial Antimicrobial Therapy for Purulent Meningitis of Unknown Cause

Age Group	Common Microorganisms	Empiric Antibiotics—First Choice[a,b]	Severe Penicillin Allergy
Adults 18–50 years of age	*S. pneumoniae, N. meningitidis.*	Ceftriaxone/cefotaxime +/– vancomycin.[c]	Chloramphenicol + vancomycin.[c]
Adults > 50 years of age	*S. pneumoniae, Listeria monocytogenes,* gram-⊖ bacilli.	Ceftriaxone/cefotaxime + ampicillin +/– vancomycin.[c]	Chloramphenicol (*N. meningitidis*) + TMP-SMX (*Listeria*) + vancomycin.[c]
Impaired cellular immunity (or alcohol abuse)	*S. pneumoniae, L. monocytogenes,* gram-⊖ bacilli (*Pseudomonas*).	Ceftazidime + ampicillin +/– vancomycin.[c]	TMP-SMX + vancomycin.[c]
Post-neurosurgery or post–head trauma	*S. pneumoniae, S. aureus,* gram-⊖ bacilli (including *Pseudomonas*).	Ceftazidime + vancomycin (for possible MRSA).	Aztreonam or ciprofloxacin + vancomycin.

[a] May add steroids (dexamethasone 10 mg q 6 h × 2–4 days) for patients who present with acute community-acquired meningitis that is likely to have been caused by *S. pneumoniae.*

[b] Doses for meningitis are higher than those for other indications: ceftriaxone 2 g IV q 12 h, cefotaxime 2 g IV q 4 h, vancomycin 1 g IV q 12 h or 500–750 mg IV q 6 h, ampicillin 2 g IV q 4 h, or ceftazidime 2 g IV q 8 h.

[c] In areas where penicillin-resistant pneumococcus is prevalent, vancomycin should be included in the regimen.

Adapted, with permission, from Tierney LM et al. *Current Medical Diagnosis & Treatment,* 44th ed. New York: McGraw-Hill, 2005: 1251.

- **Aseptic meningitis:**
  - Usually viral with a benign course. Treat with nonspecific supportive care.
  - Associated with enteroviruses and arboviruses in the late summer and early fall and with mumps in the spring.
  - Also associated with HSV-2 (recurrent—Mollaret's meningitis) as well as with HIV and drug reactions (TMP-SMX, IVIG, NSAIDs, carbamazepine). Unlike HSV-1 encephalitis, HSV-2 meningitis has a benign course, but treatment and/or suppression can be considered.
  - Less common but treatable causes include 2° syphilis (penicillin), Lyme disease (ceftriaxone), and leptospirosis (doxycycline).

Diagnosis/Treatment

- **Fulminant presentation (< 24 hours) or ill-appearing patients:** Give antibiotics **within 30 minutes;** give dexamethasone along with or prior to antibiotics. Then perform a history and physical and obtain a CT/MRI (if indicated) and LP.
- **Subacute course and stable patients:** Obtain a history and physical and obtain a CT/MRI (if indicated), blood cultures, and LP; then give empiric treatment.
- Obtain a head CT/MRI before LP if a mass lesion is suspected (e.g., with papilledema, coma, seizures, focal neurologic findings, or immunocompromised patients).
- CSF Gram stain sensitivity is 75% (60–90%); CSF culture sensitivity is

75% (70–85%) for bacterial meningitis (see Table 11.9). Sensitivity is unchanged if antibiotics are administered < 4 hours before culture.

Prevention

- **N. *meningitidis* chemoprophylaxis:** Given to household contacts, roommates, or cellmates; those with direct contact with the patient's oral secretions (kissing, sharing utensils, endotracheal intubation, suctioning, day care contacts if < 7 days); and special cases (immunocompromised, outbreaks).
- Also given to index patients if not treated with cephalosporin (penicillins and chloramphenicol do not reliably penetrate the nasal mucosa). Possible regimens include rifampin 600 mg PO BID × 4 doses, ciprofloxacin 500 mg PO × 1 dose, or ceftriaxone 250 mg IM × 1 dose.
- **N. *meningitidis* vaccine (serotypes A, C, Y, and W-135, not B):** Given for epidemics as well as to military recruits, pilgrims to Mecca, and travelers to the African Sahel (meningitis belt), Nepal, and northern India. May also be given to college freshman living in dormitories, asplenic patients, and those with terminal complement (C5–C9) and properdin deficiencies.

TABLE 11.9. CSF Profiles in Various CNS Diseases

Diagnosis	RBCs (per μL)	WBCs (per μL)	Glucose (mg/dL)	Protein (mg/dL)	Opening Pressure (cm H_2O)	Appearance
Normal[a]	< 10	< 5	~2/3 of serum	15–45	10–20	Clear
Bacterial meningitis	Normal	↑ (PMNs)	↓	↑	↑	Cloudy
Aseptic/viral meningitis, encephalitis	Normal	↑ (lymphs)[b]	Normal	Normal or ↑	Normal or ↑	Usually clear
Chronic meningitis (TB, fungal)	Normal	↑ (lymphs)[b]	↓	↑	↑	Clear or cloudy
Spirochetal meningitis (syphilis, Lyme disease)	Normal	↑ (lymphs)[b]	Normal	↑	Normal or ↑	Clear or cloudy
Neighborhood reaction[c]	Normal	Variable	Normal	Normal or ↑	Normal or ↑	Usually clear
SAH, cerebral contusion	↑↑	↑	Normal	↑↑	Normal or ↑	Yellow or red

[a] Traumatic tap usually yields 1 WBC/800 RBCs and 1 mg protein/1000 RBCs.

[b] May have PMN predominance in early stages.

[c] May be seen with brain abscess, epidural abscess, vertebral osteomyelitis, sinusitis/mastoiditis, septic thrombus, and brain tumor.

- ***H. influenzae* type b chemoprophylaxis:** Give rifampin to household contacts of unvaccinated children < 4 years of age; consider for day care contacts.
- ***H. influenzae* type b vaccine:** Routine childhood immunization; consider in adult patients with asplenia.

To remember gram-positive cocci—

The Grapes of Staph (like *The Grapes of Wrath*): Staphylococci are frequently seen in grapelike clusters.

***Strep* = strip:** Streptococci are often seen in long strips or chains.

MICROBIOLOGY PRINCIPLES

Gram-⊕ Cocci

- **In clusters (sometimes chains or pairs):** *Staphylococcus.*
  - **Coagulase ⊕:** *S. aureus.*
  - **Coagulase ⊖:** Examples include *S. epidermidis* and *S. saprophyticus.*
- **In chains or pairs:** *Streptococcus.*
  - **Lancet-shaped pairs:** *S. pneumoniae* (see Figure 11.6).
- **In pairs:** *Enterococcus.*

To remember gram-positive rods—

Bad ChORal ACTs Need CLOSe and PROPer LISTening

Bacillus
CORynebacterium
ACTinomyces
Nocardia
CLOStridium
PROPionibacterium
LISTeria

Gram-⊕ Rods

- **Large with spores:** *Bacillus, Clostridium.*
- **Small, pleomorphic (diphtheroids):** *Corynebacterium, Propionibacterium.*
- **Filamentous, branching, beaded:**
  - **Aerobic:** *Nocardia.*
  - **Anaerobic:** *Actinomyces.*
- **Other:** *Listeria, Lactobacillus, Erysipelothrix.*

Gram-⊖ Cocci

- **In pairs (diplococci):** *Neisseria gonorrhoeae, N. meningitidis, Moraxella (Branhamella) catarrhalis.*
- **Other:** *Acinetobacter.*

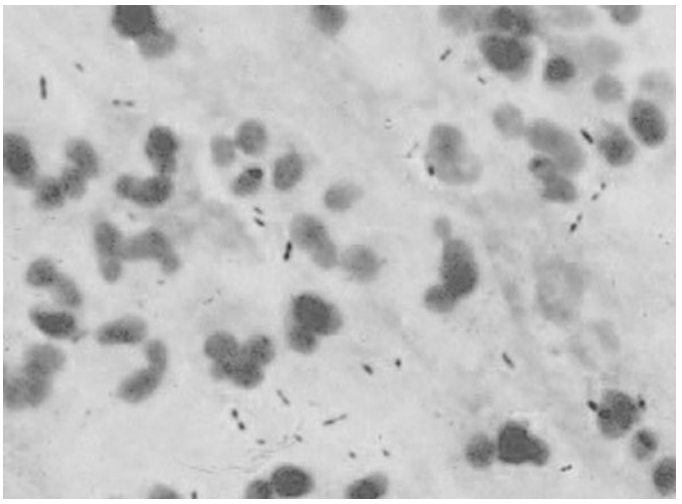

FIGURE 11.6. Pneumococcal pneumonia.

This Gram-stained sputum sample shows many neutrophils and lancet-shaped gram-⊕ cocci in pairs and chains, indicating infection with *S. pneumoniae.* (Reproduced, with permission, from Kasper DL et al. *Harrison's Principles of Internal Medicine,* 16th ed. New York: McGraw-Hill, 2005: 810.)

Gram-⊖ Rods

- **Enterobacteriaceae (lactose fermenters):** *E. coli*, *Serratia*, *Klebsiella*, *Enterobacter*, *Citrobacter*.
- **Nonfermenters:** *Proteus*, *Serratia*, *Edwardsiella*, *Salmonella*, *Shigella*, *Morganella*, *Yersinia*, *Acinetobacter*, *Stenotrophomonas*, *Pseudomonas*.
- **Anaerobes:** *Bacteroides*, *Fusobacterium*.
- **Fusiform (long, pointed):** *Fusobacterium*, *Capnocytophaga*.
- **Other:** *Haemophilus*.

To remember lactose-fermenting gram-negative rods—

SEEK Carbs

Serratia
E. coli
Enterobacter
Klebsiella
Citrobacter

Acid-Fast Bacteria

- Mycobacteria.
- *Nocardia* (weakly or partially acid-fast).

NONTUBERCULOUS (ATYPICAL) MYCOBACTERIA

Nontuberculous (atypical) mycobacteria are natural inhabitants of water and soil. They can cause clinical disease in both immunocompetent and immunocompromised patients and are often difficult to diagnose and treat.

Symptoms/Exam

- ***Mycobacterium avium:*** Most frequently presents as **cavitary upper lobe lesions** in patient with underlying pulmonary disease (COPD). However, otherwise normal hosts can develop **midlung nodular bronchiectasis.** In HIV/AIDS patients, a systemic disease with fever, abdominal pain, lymphadenopathy, and hepatosplenomegaly is most frequently seen.
- ***Mycobacterium kansasii:*** Primarily a pulmonary pathogen presenting in a manner **similar to *M. tuberculosis*.** Patients may or may not be immunocompromised and often have an underlying lung disease.
- ***Mycobacterium marinum:*** The 1° presentation consists of **skin ulcers** and **nodular lymphangitis** in patients with exposure to freshwater and saltwater, including marine organisms, swimming pools, and fish tanks.
- **Rapidly growing mycobacteria (*M. abscessus*, *M. fortuitum*, *M. chelonae*):** *M. abscessus* is the most virulent of these pathogens, causing **nodular or cavitary pulmonary disease** and often causing **skin or soft tissue infections.** Disseminated or localized skin and soft tissue infections are the most common clinical manifestation of *M. fortuitum* (associated with nail salons) and *M. chelonae*.

Think of pulmonary Mycobacterium avium–intracellulare *in an elderly, nonsmoking woman with cough, malaise, and midlung nodular bronchiectasis on CXR.*

Differential

- **Cavitary or nodular lung disease:** *M. tuberculosis*, endemic mycoses (coccidioidomycosis, histoplasmosis, blastomycosis, paracoccidioidomycosis), *Nocardia*, aspergillosis, neoplasms.
- **Skin ulcers or nodular lymphangitis:** *Sporothrix schenckii*, *Nocardia brasiliensis*, *M. marinum*, *Leishmania braziliensis*, *Francisella tularensis*.

Diagnosis

- **Pulmonary disease: All three of the following criteria** must be satisfied.
  - **Clinical criteria:** Compatible signs and symptoms (cough, fatigue, fever, weight loss) with reasonable exclusion of other diseases.
  - **Radiographic criteria:** CXR with persistent or progressive infiltrates with cavitation and/or nodules or CT with multiple small nodules or multifocal bronchiectasis.

The diagnosis of nontuberculous Mycobacterium *infection usually includes at least three sputum smear and culture (preferably morning) specimens.*

- **Bacteriologic criteria:** Three ⊕ cultures with ⊖ AFB smears **or** two ⊕ cultures with one ⊕ AFB smear **or** a single bronchoscopy or tissue biopsy with growth from a sterile site.
- **Nodular lymphangitis:** A ⊕ culture from biopsy.

TREATMENT

Treatment for these infections requires multiple drug regimens for prolonged courses of therapy. Many of these organisms (particularly the rapidly growing mycobacteria) are resistant to multiple antimicrobial agents. Consultation with a specialist is recommended.

COMPLICATIONS

Pulmonary disease can result in progressive lung cavitation and destruction with dissemination. Skin and soft tissue disease can be locally destructive or lead to disseminated infection.

OSTEOMYELITIS

Spread may be contiguous (80%) or hematogenous (20%).

- **Local spread:** Occurs in diabetics and in patients with vascular insufficiency, prosthetic joints, decubitus ulcers, trauma, and recent neurosurgery.
- **Hematogenous spread:** Affects IV drug users, those with sickle cell disease, and the elderly.

Common causes are as follows:

- Etiologic agents include *S. aureus* and, to a lesser extent, coagulase-⊖ staphylococci (prosthetic joints or postoperative infections), streptococci, anaerobes (bites, diabetic foot infections, decubitus ulcers), *Pasteurella* (animal bites), *Eikenella* (human bites), and *Pseudomonas* (nail punctures through sneakers).
- **Other causes:** *Salmonella* (sickle cell), *M. tuberculosis* (foreign immigrants, HIV), *Bartonella* (HIV), *Brucella* (unpasteurized dairy products).
- **By location:** *Pseudomonas* affects the sternoclavicular joint and symphysis pubis (in IV drug users); *Brucella* affects the sacroiliac joint, knee, and hip. TB affects the lower thoracic vertebrae (Pott's disease).

SYMPTOMS/EXAM

- **Contiguous spread:** Local redness, warmth, and tenderness; patients are afebrile and are not systemically ill.
- **Hematogenous spread:** Sudden fever; pain, and tenderness over the affected bone. May present with pain only (no fever).
- **Vertebral osteomyelitis with epidural abscess:** Spinal pain followed by radicular pain and weakness.
- **Prosthetic hip and knee infections:** May present only as pain on weight bearing.

DIAGNOSIS

- **Probing to bone (diabetic patients):** Approximately 66% sensitive and 85% specific (PPV 89%).

- **Plain x-rays:** Reveal bony erosions or periosteal elevation ≥ 2 weeks after infection. Less helpful in trauma or diabetic/vascular patients with neuropathy (frequent stress fractures).
- **CT scans.**
- **MRI:** Approximately 90% sensitive and specific (abnormal marrow edema; surrounding soft tissue infection). Especially useful for diagnosing vertebral osteomyelitis.
- **Nuclear scans:** Three- or four-phase studies with technetium-99 are preferred. Most useful for distinguishing bone from soft tissue inflammation when the diagnosis is ambiguous.
- **Microbiology:** Obtain bone culture at debridement or by needle aspiration; sinus tract cultures are not reliable. With hematogenous osteomyelitis, ⊕ blood cultures may obviate the need for bone biopsy.

TREATMENT

- After debridement of necrotic bone (with cultures taken), empiric antibiotics should be chosen to cover the likely pathogens (see above).
- IV antibiotics should be given for 4–6 weeks, although oral quinolones may be equally effective in some circumstances.
- The choice of agent is guided by microbiology. In patients who are not candidates for definitive therapy, long-term suppressive antibiotics may be used.
- Surgery is indicated for spinal cord decompression, bony stabilization, removal of necrotic bone in chronic osteomyelitis, and reestablishment of vascular supply.

PREVENTION

Diabetics with neuropathy (detected by the 10-g monofilament test) should be taught to examine their feet on a daily basis and should be examined by a clinician at least once every three months.

COMPLICATIONS

Vertebral osteomyelitis with epidural abscess; chronic osteomyelitis.

PYELONEPHRITIS

Caused by the same bacteria as those responsible for uncomplicated UTI. With the exception of *S. aureus*, most cases are caused by organisms ascending from the lower urinary tract; *S. aureus* is most frequently hematogenous and produces intrarenal or perinephric abscesses. Renal struvite stones (staghorn calculi) are frequently associated with recurrent UTI due to urease-producing bacteria (*Proteus*, *Pseudomonas*, and enterococci).

SYMPTOMS

Presents with flank pain and fever. Patients often have lower urinary tract symptoms (dysuria, urgency, and frequency) that sometimes occur 1–2 days before the upper tract symptoms. They may also have nausea, vomiting, or diarrhea.

EXAM

Exam reveals fever, CVA tenderness, and mild abdominal tenderness.

Fever and WBC casts on UA are seen in pyelonephritis but not in cystitis.

Differential

Renal stones, renal infarcts, cholecystitis, appendicitis, diverticulitis, acute prostatitis/epididymitis.

Diagnosis

UA shows pyuria and bacteriuria and may also exhibit hematuria or WBC casts. CBC reveals leukocytosis with left shift. Urine culture is usually ⊕, and blood culture may be ⊕ as well.

Treatment

- Fluoroquinolone × 7 days or ampicillin plus gentamicin or ceftriaxone × 14 days.
- Radiologic evaluation for complications may be useful in patients who are severely ill or immunocompromised; those who are not responding to treatment; or those in whom complications are likely (e.g., pregnant patients, diabetics, and those with nephrolithiasis, reflux, transplant surgery, or other GU surgery).
  - X-rays can detect stones, calcification, masses, and abnormal gas collections.
  - Ultrasound is rapid and safe.
  - Contrast-enhanced CT is most sensitive but may affect renal function.

Complications

- Perinephric abscess should be considered in patients who remain febrile 2–3 days after appropriate antibiotics; UA may be normal and cultures ⊖. Patients are treated by percutaneous or surgical drainage plus antibiotics.
- Intrarenal abscesses (e.g., infection of a renal cyst) < 5 cm in size usually respond to antibiotics alone.
- Diabetics may develop emphysematous pyelonephritis, which usually requires nephrectomy and is associated with a high mortality rate.

ROCKY MOUNTAIN SPOTTED FEVER

A tick-borne illness caused by *Rickettsia rickettsii*. The vector is the *Dermacentor* tick, which needs to feed for only 6–10 hours before injecting the organism (a much shorter attachment time than for Lyme disease). Most commonly found in the mid-Atlantic and South Central states (**not** the Rocky Mountain states). The highest rates are seen in late spring and summer and in children and men with occupational tick exposures.

Think of Rocky Mountain spotted fever and start treatment early in patients with a recent tick bite (especially in the mid-Atlantic or South Central states) along with fever, headache, and myalgias followed by a centripetal rash.

Symptoms/Exam

- **Initial symptoms (seven days after a tick bite)** are fever, myalgias, and headaches.
- A maculopapular rash (in 90%) starts four days later and progresses to petechiae or purpura. The rash first appears on the wrists and ankles and then spreads centrally and to the palms and soles.
- Patients may develop severe headache, irritability, and even delirium or coma.

Differential

Meningococcemia, measles, typhoid fever, ehrlichiosis (HME or HGA), viral hemorrhagic fevers (e.g., dengue), leptospirosis, vasculitis.

Diagnosis

- Diagnosis is made clinically (symptoms and signs plus recent tick bite); treatment should be started as soon as Rocky Mountain spotted fever is suspected.
- Diagnosis can be made by biopsy of early skin lesions or confirmed retrospectively by serologic testing.
- Labs may show thrombocytopenia, elevated LFTs, and hyponatremia. The Weil-Felix test (for antibodies cross-reacting to *Proteus*) is no longer considered reliable.

Treatment

Doxycycline, chloramphenicol (for pregnant or doxycycline-allergic patients).

Complications

Pneumonitis, pulmonary edema, renal failure, and death after 8–15 days.

SEXUALLY TRANSMITTED DISEASES (STDS)

Table 11.10 outlines STDs that result in genital ulcers as well as urethral or cervical discharge. Refer to the Women's Health chapter for further discussion of STDs, cervical cancer screening, and chlamydia screening.

STRONGYLOIDIASIS

Infection with the helminth *Strongyloides stercoralis* is endemic in warm climates such as the southeastern United States, Appalachia, Africa, Asia, the Caribbean, and Central America. Unlike most other parasitic worms, *Strongyloides* can reproduce in the small intestine, leading to a high worm burden. Autoinfection and dissemination are seen in hosts with deficient cell-mediated immunity (e.g., AIDS, chronic steroids, organ transplants, leukemia, lymphoma).

Consider hyperinfection with Strongyloides stercoralis *in patients with vague abdominal complaints or fleeting pulmonary infiltrates plus eosinophilia, or in immunosuppressed patients who develop systemic gram-⊖ or enterococcal infection.*

Symptoms/Exam

- **Normal hosts:** May be asymptomatic or present with vague epigastric pain, nausea, bloating, diarrhea, or weight loss due to malabsorption. Serpiginous papules or urticaria ("larva currens") may be seen around the buttocks, thighs, and lower abdomen as larvae migrate from the rectum and externally autoinfect the host.
- **Immunocompromised hosts:** Hyperinfection or disseminated strongyloidiasis can develop. Worms leave the GI tract and travel to the lungs and elsewhere. Patients present with fever, severe abdominal pain, dyspnea, productive cough, hemoptysis, and local symptoms (e.g., CNS, pancreas, eyes).

Differential

Local enteric disease mimics PUD, sprue, or ulcerative colitis. Hyperinfection resembles overwhelming bacterial or fungal sepsis.

Diagnosis

- Stool or duodenal aspirates can be tested for ova and parasites. In hyperinfection, larvae may be seen in sputum, bronchoalveolar lavage, CSF, and urine. Paradoxically, **eosinophilia is prominent in normal hosts with dis-**

TABLE 11.10. Diagnosis and Treatment of Selected STDs

Disease	Pathogen	Clinical Presentation	Diagnosis	Treatment Options
Causes of genital ulcers:				
Chancroid	*Haemophilus ducreyi*	**Painful** erythematous papule evolving into a pustule that erodes into an **ulcer with purulence. Marked lymphadenitis (buboes).**	Gram stain shows small gram-⊖ rods in parallel alignment ("school of fish"); culture, PCR.	**Drain buboes.** **Azithromycin 1 g PO × 1,** ceftriaxone 250 mg IM × 1, ciprofloxacin 500 mg PO BID × 3 days, or erythromycin 500 mg PO TID × 7 days.
HSV	Human herpes simplex virus 1 or 2	**Painful** multiple vesicular or ulcerative lesions. Reactive lymphadenopathy is common.	Tzanck smear shows multinucleated giant cells (50% sensitivity); culture, DFA, PCR, IgG ELISA.	**Acyclovir 400 mg PO TID or 200 mg PO 5ID × 7–10 days,** famciclovir 250 mg PO TID × 7–10 days, or valacyclovir 1 g PO BID × 7–10 days. Consider suppressive or episodic treatment for recurrent infection.
Granuloma inguinale	*Klebsiella granulomatis* (formerly known as *Calymmatobacterium granulomatis*)	**Painless, progressive ulcerative lesions without regional lymphadenopathy. Beefy-red ulcers** bleed on contact. Rare in the United States; endemic in tropical regions.	Culture is low yield. Biopsy shows dark-staining Donovan bodies. PCR is available.	**Doxycycline 100 mg PO BID × ≥ 3 weeks and until all lesions have completely healed.** Alternative regimens include azithromycin, ciprofloxacin, erythromycin, or TMP-SMX for ≥ 3 weeks until all lesions have completely healed.
Lympho-granuloma venereum	*Chlamydia trachomatis* (serovars L1, L2, or L3)	**Painless,** small ulcer at the site of inoculation. **Large, tender, fluctuant, inguinal lymphadeno-pathy ("buboes").** Rectal disease may result in hemorrhagic proctocolitis. Strictures and fistulae may form.	Culture is low yield; serology is most commonly used. PCR is available.	**Drain buboes.** **Doxycycline 100 mg PO BID** or erythromycin 500 mg PO QID × **21 days.**

TABLE 11.10. Diagnosis and Treatment of Selected STDs *(continued)*

Disease	Pathogen	Clinical Presentation	Diagnosis	Treatment Options
Syphilis	*Treponema pallidum*	**Painless** solitary ulcer (rarely multiple). May have painless, rubbery lymphadenopathy.	Darkfield microscopy, DFA of tissue. RPR/VDRL confirmed by FTA-ABS (RPR/VDRL may take 12 weeks to turn ⊕).	**For 1° syphilis: Benzathine penicillin G 2.4 million U IM × 1.** For penicillin-allergic patients, give doxycycline 100 mg PO BID × 14 days or tetracycline 500 mg PO QID × 14 days.
Causes of urethritis and cervicitis:				
Gonococcal (GC)	*Neisseria gonorrhoeae*	Purulent discharge. May have **pharyngitis, proctitis, and PID.** Disseminated GC infection is associated with two syndromes: (1) fever, tenosynovitis, and painful vesiculopustular skin lesions or (2) purulent arthritis without skin lesions.	Gram stain of urethral or cervical swab shows intracellular gram-⊖ diplococci (see Figure 11.7). Culture on Thayer-Martin media, nucleic acid amplification test (NAAT), DNA probe.	Ceftriaxone 125 mg IM × 1, cefpodoxime 400 mg PO × 1, ciprofloxacin 500 mg PO × 1, ofloxacin 400 mg PO × 1, or levofloxacin 250 mg PO × 1 **plus treatment for chlamydia if chlamydial infection is not ruled out.**[a]
Nongonococcal (NG)	***Chlamydia trachomatis.*** Less common pathogens include *Mycoplasma genitalium,* HSV, *Trichomonas vaginalis,* and *Ureaplasma urealyticum.*	**Mucoid or watery discharge, dysuria.** Other syndromes include proctitis, epididymitis, and PID. Has a known association with postinfectious reactive arthritis.	**Urethritis:** Mucopurulent or purulent discharge; Gram stain of urethral secretions shows > 5 WBCs/hpf plus leukocyte esterase on first-void urine. ***Chlamydia trachomatis:*** NAAT on the urethra, vagina, or urine; culture.	Azithromycin 1 g PO × 1, doxycycline 100 mg PO BID × 7 days. Alternative regimens include erythromycin, ofloxacin, or levofloxacin × 7 days.

[a] Quinolones are no longer recommended by the CDC for treatment of GC infections in the United States due to high rates of resistance.

ease but is uncommon in patients with hyperinfection. Serology is available.

- CXR shows transient (normal host) or diffuse, persistent pulmonary infiltrates (hyperinfection).

Treatment

Thiabendazole, albendazole, or ivermectin. Discontinue steroids and other immunosuppressive agents.

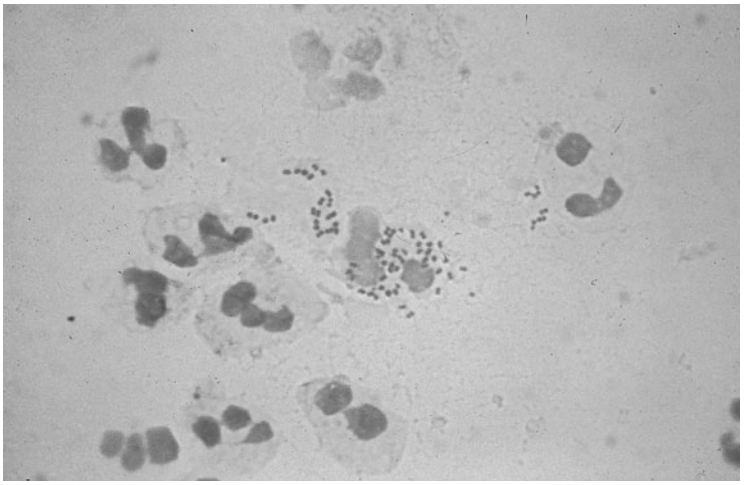

FIGURE 11.7. Gonococcal urethritis: Gram stain of *Neisseria gonorrhoeae.*

Multiple gram-⊖ diplococci are seen within PMNs as well as in the extracellular areas of a smear from a urethral discharge. (Reproduced, with permission, from Wolff K et al. *Fitzpatrick's Color Atlas & Synopsis of Clinical Dermatology*, 5th ed. New York: McGraw-Hill, 2005: 906.)

COMPLICATIONS

Ileus or small bowel obstruction can result from enteric worms. Hyperinfection and tracking of enteric bacteria (gram-⊖ rods, enterococci) can lead to bacteremia, meningitis, UTI, or pneumonia.

SOFT TISSUE INFECTIONS

Table 11.11 outlines the etiology, clinical presentation, and treatment of common soft tissue infections (see also Figure 11.8).

SYPHILIS

Caused by the spirochete *Treponema pallidum*.

SYMPTOMS/EXAM

- **1° syphilis:** Usually presents with a chancre, a single painless papule that erodes to form a clean-based ulcer with raised/indurated edges (may be multiple or atypical for HIV-⊕ patients or minimal for those with previous syphilis). Also presents with **regional nontender lymphadenopathy.** The incubation period is three weeks (ranging from three days to three months). The chancre resolves in 3–6 weeks, but lymphadenopathy persists.
- **2° syphilis:**
  - Presents with a **maculopapular rash** that may include the palms and soles; **condylomata lata** in intertriginous areas (painless, broad, grayish-white to erythematous plaques that are highly infectious; see Figure 11.9); **alopecia** (see Figure 11.10); or a **mucous patch** (condylomata lata on the mucosa).

TABLE 11.11. Common Soft Tissue Infections

Organism	Patient Characteristics	Source of Organism	Clinical Features	Treatment (Examples)
Group A streptococcus and occasionally groups B, C, and G	Normal.	Skin flora.	Cellulitis, erysipelas.	Dicloxacillin, cephalexin, clindamycin (penicillin if documented strep only).
S. aureus	Same as above.	Same as above.	Furunculosis, abscess, cellulitis.	Same as above.
Vibrio vulnificus, other *Vibrio* spp.	Cirrhosis.	Shellfish or seawater exposure.	Hemorrhagic bullae, septic shock.	Ceftazidime, doxycycline.
Mycobacterium marinum	*Normal.*	Fish tanks.	Nonhealing ulcer, nodular lymphangitis.	Rifampin plus ethambutol, TMP-SMX.
Mycobacterium fortuitum	Normal.	Nail salon foot baths.	Furuncles.	Excision.
Pseudomonas, Aeromonas	Normal.	Hot tubs, freshwater exposure.	***Pseudomonas:*** Folliculitis. ***Aeromonas:*** Spreading cellulitis.	Quinolones.
Pseudomonas	Neutropenia.	—	Ecthyma gangrenosum (hemorrhagic bullae that ulcerate; see Figure 11.8).	Quinolones.
Noninfectious agents	IBD, rheumatoid arthritis.	—	Pyoderma gangrenosum (a pustule/nodule that ulcerates).	Steroids.
Erysipelothrix	Fishermen, crab handlers.	—	Hands, fingers.	Penicillin, ampicillin, quinolone.
Bacillus anthracis	Hide tanners and wool workers (postal workers).	Soil (bioterrorism agent).	Nonpainful ulcer/eschar, extensive edema.	Doxycycline, quinolones.
Francisella tularensis (tularemia)	Trappers and skinners of wild rodents.	Ticks, rabbits.	Regional lymphadenopathy, pneumonia.	Doxycycline, streptomycin.
Pasteurella, Capnocytophaga	Normal.	Animal bites or scratches.	***Pasteurella:*** Rapidly progressing cellulitis. ***Capnocytophaga:*** DIC, sepsis in asplenic and cirrhotic patients.	Amoxicillin/clavulanate.

TABLE 11.11. Common Soft Tissue Infections *(continued)*

Organism	Patient Characteristics	Source of Organism	Clinical Features	Treatment (Examples)
Sporothrix schenckii	Gardeners, rose handlers.	Thorned plants.	Nodular lymphangitis.	Itraconazole.
Pityriasis rosea	After a viral URI, patients develop a herald patch followed by a generalized eruption.	—	Round, pink scaling patches; "Christmas tree" distribution on the back.	UV light; topical steroids and antihistamines for itching.

- **Systemic symptoms** include low-grade fever, malaise, pharyngitis, laryngitis, lymphadenopathy (especially epitrochlear), anorexia, weight loss, arthralgias, headache, and meningismus (aseptic meningitis).
- Occurs 2–8 weeks after the 1° chancre, but may overlap.

- **Latent syphilis:** ⊕ serology but no current symptoms.
  - **Early latent** (< 1 year): Characterized by a fourfold ↑ in antibody titer; associated with a known history of 1° or 2° syphilis and an infected partner.
  - **Late latent** (> 1 year or unknown duration): One-third of patients progress to 3° syphilis.
- **3° syphilis:**
  - May include **aortitis** (aneurysm rupture is the leading cause of death from syphilis) or destructive **gummas** (bone, skin, mucocutaneous areas).
  - **Neurosyphilis** is usually asymptomatic (in CSF, WBC > 5, elevated protein, low glucose, ⊕ CSF-VDRL). CNS symptoms include **tabes dorsalis** (demyelination of the posterior columns leading to a wide-

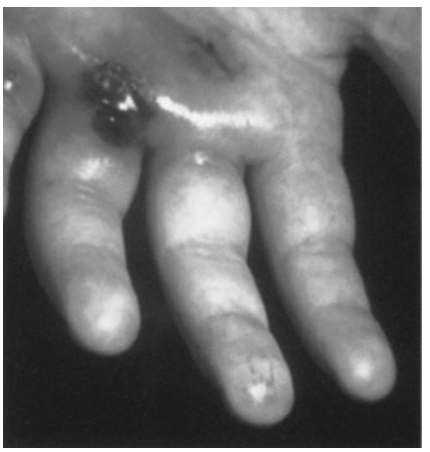

FIGURE 11.8. Ecthyma gangrenosum with *Pseudomonas* in a neutropenic patient.

Note the red papule with a necrotic center. (Reproduced, with permission, from Kasper DL et al. *Harrison's Principles of Internal Medicine*, 16th ed. New York: McGraw-Hill, 2005: 890.)

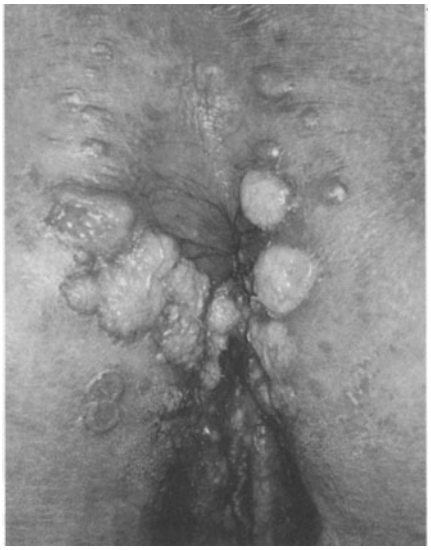

FIGURE 11.9. Condylomata lata in 2° syphilis.

(Reproduced, with permission, from Kasper DL et al. *Harrison's Principles of Internal Medicine*, 16th ed. New York: McGraw-Hill, 2005: 979.)

based gait and foot slap), **Argyll Robertson pupil** (an irregular, small pupil that accommodates but does not respond to light), and meningovascular syphilis (subacute encephalopathy with multifocal ischemic infarcts).

- Occurs 1–20 years after initial infection.

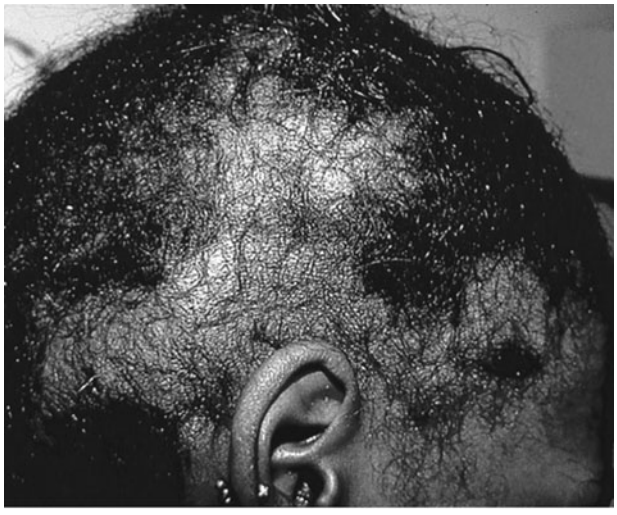

FIGURE 11.10. Alopecia of 2° syphilis.

Hair loss may be one of the only cutaneous manifestations of 2° syphilis that may present either as patchy, "moth-eaten" alopecia or as generalized thinning. (Reproduced, with permission, from Wolff K et al. *Fitzpatrick's Dermatology in General Medicine*, 7th ed. New York: McGraw-Hill, 2008.)

Differential

Table 11.12 outlines the differential diagnosis of lesions on the palms and soles. The differential of genital ulcer disease is as follows:

- 1° syphilis.
- HSV.
- Chancroid (*Haemophilus ducreyi*).
- **Lymphogranuloma venereum (*Chlamydia trachomatis* serovars L1–L3).**
- **Granuloma inguinale, donovanosis (*Klebsiella granulomatis*).**
- **Trauma, excoriation** (e.g., zippers, scabies).
- **Other:** Psoriasis, Behçet's, Reiter's, lichen planus.

TABLE 11.12. Differential Diagnosis of Lesions on the Palms and Soles

	Cause	Lesion Features	Distribution
Rocky Mountain spotted fever	*Rickettsia rickettsii.*	Macules, then petechiae (see Figure 11.11).	Wrists/ankles, then centrally, then palms and soles late in the disease course.
2° syphilis	*Treponema pallidum.*	Reddish-brown, copper-colored papules; never vesicular (see Figure 11.12).	Condylomata lata or mucous patches on mucosa.
Erythema multiforme	Drug reaction, HSV, or *Mycoplasma* infection.	Target lesions (see Figure 11.13).	Symmetric over the elbows, knees, palms, and soles. May become diffuse and involve the mucosa.
Acute meningococcemia	*N. meningitidis.*	Blanching macules, then gun-metal-gray petechiae and purpura (see Figure 11.14).	Distal extremities; then spreads to the trunk and "pressure spots" over hours.
Smallpox	Orthopoxvirus.	Deep, round, tense vesicles and pustules.	Start on the face and extremities; then move to the trunk (centrifugal).
Endocarditis	*Staphylococcus, Streptococcus,* others.	Janeway lesions are painless, hemorrhagic macules (see Figure 11.15). Osler's nodes are subcutaneous, tender, pink or purplish nodules.	Janeway lesions appear on the palms and soles, Osler's nodes on the pads of digits.
Hand-foot-and-mouth disease	Coxsackie A16 virus.	Tender vesicles.	Peripheral and in the mouth. Outbreaks occur within families.
Rat-bite fever	*Streptobacillus moniliformis.*	Maculopapules or purpura.	May be more severe at the joints of the arms and legs.
Atypical measles	Paramyxovirus (in patients who received killed virus vaccine from 1963 to 1967).	Maculopapules; may be hemorrhagic.	Most marked on the extremities. Typical measles has a central distribution (face/chest).

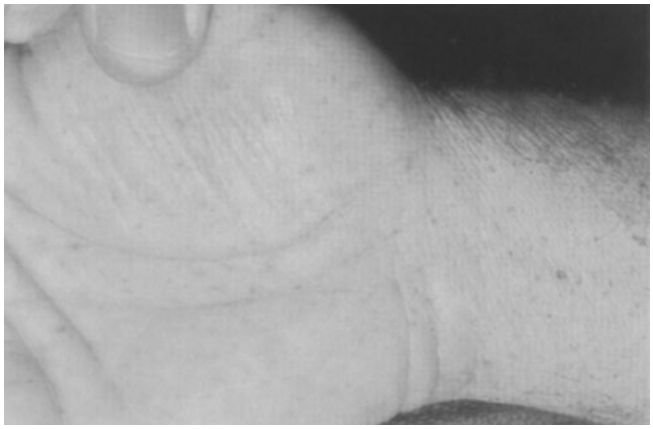

FIGURE 11.11. Rocky Mountain spotted fever.

(Reproduced, with permission, from Braunwald E et al. *Harrison's Principles of Internal Medicine*, 15th ed. New York: McGraw-Hill, 2001: Plate IID-45.)

DIAGNOSIS

- Direct visualization of motile spirochetes by darkfield microscopy from condylomata lata or mucous patches.
- **VDRL and RPR:** Nontreponemal, nonspecific antibody tests are useful for screening (detect antibodies that cross-react with beef cardiolipin). The **prozone effect** may be seen in 2° syphilis or pregnancy (high antibody titers produce ⊖ tests that become ⊕ as the sample is diluted). The sensitivity of VDRL/RPR is 70% in 1° syphilis and 99% in 2° syphilis. False ⊕s have a titer of ≤ 1:8.
- **FTA-ABS and MHA-TP:** Specific treponemal antibody tests that are used to confirm VDRL and RPR. Remain ⊕ for life (patients are "serofast").

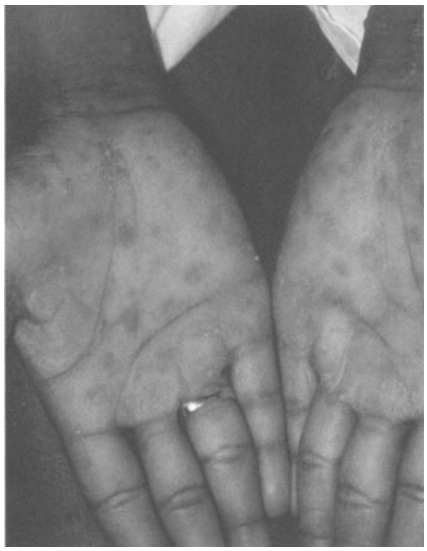

FIGURE 11.12. 2° syphilis.

(Reproduced, with permission, from Kasper DL et al. *Harrison's Principles of Internal Medicine*, 16th ed. New York: McGraw-Hill, 2005: 979.)

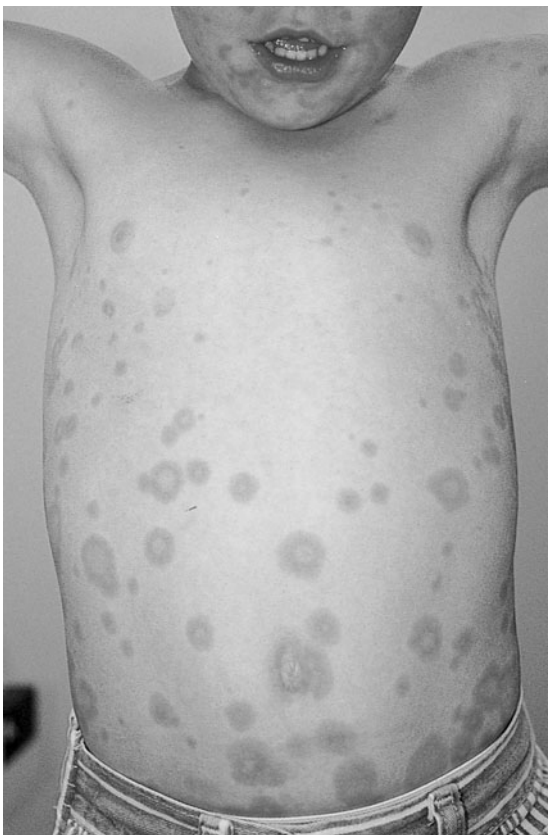

FIGURE 11.13. Erythema multiforme.

(Courtesy of Michael Redman, PA-C.)

- Patients at high risk of developing neurosyphilis should undergo LP and have a **CSF-VDRL** test. CSF-VDRL is specific but not sensitive for neurosyphilis (sensitivity 30–70%).
- **Indications for LP:** Indicated for patients with neurologic symptoms,

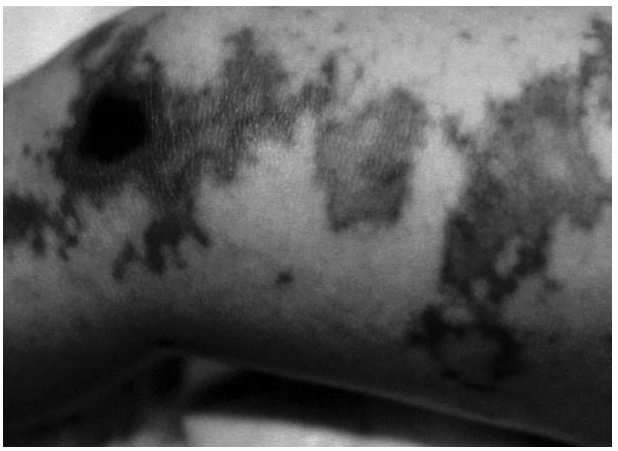

FIGURE 11.14. Acute meningococcemia.

(Reproduced, with permission, from Wolff K et al. *Fitzpatrick's Color Atlas & Synopsis of Clinical Dermatology*, 5th ed. New York: McGraw-Hill, 2005: 643.)

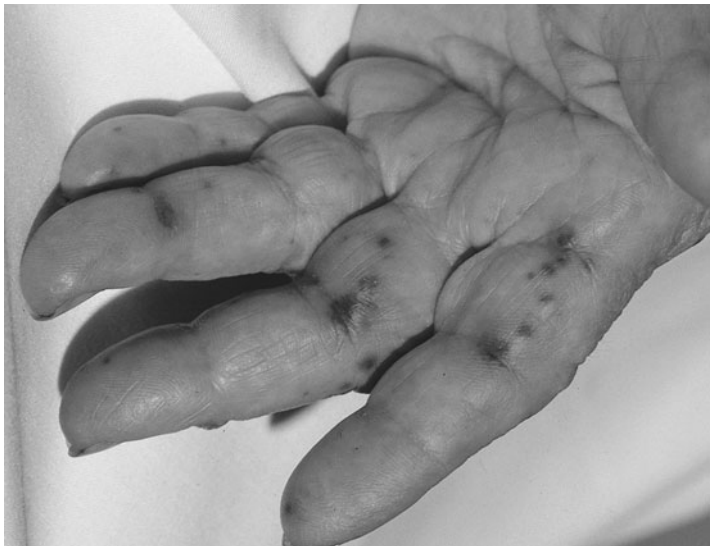

FIGURE 11.15. Janeway lesions in endocarditis.

(Reproduced, with permission, from Wolff K et al. *Fitzpatrick's Color Atlas & Synopsis of Clinical Dermatology*, 5th ed. New York: McGraw-Hill, 2005: 636.)

serum RPR ≥ 1:32, current aortitis or gummas, and previous treatment failure. LP for all HIV-⊕ patients has been recommended by some but is controversial.

Treatment

- Think of syphilis as **early** (1°, 2°, early latent), **late** (late latent or 3°), or **neurosyphilis.**
- Patients with **early syphilis** should receive benzathine penicillin G 2.4 MU IM × 1 or doxycycline or ceftriaxone. Failures occur with azithromycin (especially if the patient is infected with HIV).
- Those with **late syphilis** should receive benzathine penicillin G 2.4 MU IM q week × 3 or doxycycline.
- Patients with **neurosyphilis** require penicillin G 3 MU IV q 4 h × 10–14 days.
- **Pregnant women who are allergic to penicillin should be desensitized and treated with penicillin to prevent congenital syphilis.**
- Repeat RPR or VDRL at 3, 6, 12, and 24 months; titer should ↓ **at least fourfold** 6–9 months after the treatment of 1° or 2° syphilis. If the test remains ⊕ after that time period, it suggests treatment failure, reinfection, or HIV.
- Treat again if clinical signs persist or recur or if VDRL/RPR titer does not ↓ **fourfold.**
- **Jarisch-Herxheimer reactions** are commonly seen in the first 24 hours of treatment and are characterized by low-grade fever, headache, myalgias, malaise, and new skin lesions. Thought to be due to cytokine release, and may be seen after treatment of other spirochetal illnesses (e.g., Lyme disease, relapsing fever). Treat with antipyretics.

Usually affects healthy individuals; associated with **exotoxins** released by certain strains of *S. aureus* or group A streptococci (rarely groups B, C, or G). May cause a concurrent infection (osteomyelitis, occult abscesses, erysipelas, necrotizing fasciitis or myositis, 2° infection of chickenpox wounds) or simply colonize a mucosal, postoperative, or burn-wound surface.

- **Streptococcal TSS:** Commonly associated with concurrent invasive infections. Invasive group A streptococcal strains usually have type 1 M protein, a cell-surface protein that is antiphagocytic and may serve as a superantigen. Strains may also produce streptococcal pyrogenic exotoxins A, B, or C.
- **Staphylococcal TSS:** Associated with menses and with the use of hyperabsorbable tampons that have now been withdrawn from the market ("menstrual TSS"). Most cases are now nonmenstrual TSS due to vaginal or surgical wound colonization. Strains may produce superantigens TSST-1 (75%) or staphylococcal enterotoxins B and C.

Symptoms/Exam

- Staphylococcal or streptococcal isolation, evidence of end-organ damage (renal insufficiency, coagulopathy, abnormal LFTs), rash, ARDS, generalized edema or effusions, soft tissue necrosis.
- Staphylococcal TSS also requires fever and a diffuse macular rash that may subsequently desquamate (especially on the palms and soles). Other features include vomiting, diarrhea, severe myalgias, and confusion.
- Streptococcal TSS may be preceded by an influenza-like prodrome or by increasing pain at a deep site of infection.
- TSS is rarely preceded by streptococcal pharyngitis.

Differential

Gram-⊖ septic shock, Rocky Mountain spotted fever, leptospirosis, measles, DVT.

Diagnosis

- Routine labs, including CK.
- Vaginal examination.
- Cultures of blood, wounds, and vaginal mucosa.
- Evaluate for invasive streptococcal infection or occult staphylococcal infection.

Treatment

- Aggressive hydration and surgical debridement of deep-seated streptococcal infection and necrotic tissue are critical. Administer empiric broad-spectrum antibiotics.
- If the appropriate organism is isolated, narrow therapy to penicillin plus clindamycin (for streptococci) or nafcillin/oxacillin (vancomycin for MRSA) and perhaps clindamycin (for staphylococci).
- Clindamycin is added because it may ↓ toxin production and is active against organisms in the stationary phase; the cell wall–acting penicillins are most effective against rapidly growing bacteria. Consider adding IVIG.

Complications

Death (in 30% of streptococcal or 3% of staphylococcal TSS), gangrene of the extremities, ARDS, chronic renal failure.

TRAVEL MEDICINE

General Guidelines

Most cases of fever in returned travelers are due to common illnesses such as influenza, viral URI, pneumonia, and UTI. The most common travel-related infections are malaria (see below), typhoid fever, hepatitis, dengue, and amebic liver abscess. Life-threatening infections that are treatable if diagnosed early include falciparum malaria, typhoid fever, and meningococcemia (consider these in all returned travelers with fever).

Symptoms/Exam

- **Careful travel history:** Determine the countries visited, urban vs. rural locales, accommodation type, immunizations, chemoprophylaxis, and sexual history.
- **Specific exposures:** Determine if there was freshwater contact (leptospirosis, schistosomiasis) or exposure to unpasteurized dairy (brucellosis), mosquitoes (malaria, dengue), ticks (rickettsial diseases, tularemia), or sick contacts (meningococcus, TB, viral hemorrhagic fevers).
- Examine for lymphadenopathy, maculopapular rash (dengue, leptospirosis, acute HIV, acute HBV), eschars at the site of a tick bite (rickettsial disease), and splenomegaly (malaria, typhoid, brucellosis).

For fever after recent travel (< 21 days), consider malaria, typhoid fever, dengue, leptospirosis, rickettsial illnesses, and meningococcemia. For longer incubation periods (> 21 days), consider non-falciparum malaria, TB, hepatitis, amebic liver abscess, acute HIV, and brucellosis.

Differential

- **Malaria** (see below).
- **Typhoid fever:** Presents with fever, malaise, and abdominal discomfort, often without GI symptoms. Exam reveals splenomegaly, pulse-temperature dissociation, and evanescent rose spots. Diagnose by blood cultures growing *Salmonella*; treat with ciprofloxacin or levofloxacin. Vaccine is 70% effective.
- **Hepatitis:** HAV and HEV are transmitted by the fecal-oral route and may have nonspecific prodromes. HBV and HCV are transmitted by sexual contact, shared needles, or blood transfusions.
- **Dengue:** Endemic in equatorial and subtropical areas. Patients have abrupt onset of fever, retro-orbital headache, and myalgias. Exam shows a blanching rash. Treatment is supportive.
- **Leptospirosis:** Recent outbreaks have affected eco-travelers in Hawaii and Indonesia. May be biphasic, with fever, chills, and headache that resolve but are followed 1–3 days later by conjunctivitis, a maculopapular rash, hepatosplenomegaly, and aseptic meningitis. Severe cases (Weil's syndrome) have jaundice, renal failure, pulmonary hemorrhage, and hypotension. Treat with penicillin or doxycycline (patients may get **Jarisch-Herxheimer reactions**).
- **Rickettsial illnesses:** Include Mediterranean spotted fever and African tick typhus. Fever, headaches, myalgias, eschars, and maculopapular rashes spread from the trunk outward to the palms and soles (unlike rashes in Rocky Mountain spotted fever, which spread inward). Treat with doxycycline.

- **Amebiasis (*Entamoeba histolytica*):** May cause bloody dysentery or liver abscesses. Diagnose by stool microscopy showing cysts or trophozoites with ingested RBCs. Colonoscopy shows typical "flask-shaped" ulcers. Serologic tests are 95% sensitive for diagnosing liver abscess. Treat with metronidazole followed by paromomycin to eradicate stool cysts. **Amebic liver abscesses do not require drainage.**
- **Acute schistosomiasis: Swimmer's itch** refers to multiple pruritic, papular lesions at the entry site of a fluke that often appear 24–48 hours following exposure. It may result from infection with human or nonhuman species. **Katayama fever** is an immunologic reaction to the organism that may occur 4–8 weeks following infection, resulting in acute onset of fever, myalgias, arthralgias, dry cough, and diarrhea with associated diffuse lymphadenopathy and hepatosplenomegaly.
- **Acute HIV and other STDs.**
- **Traveler's diarrhea:** Caused by enterotoxigenic *E. coli* (> 50%), *Campylobacter*, and, to a lesser extent, *Shigella*, *Salmonella* (< 15% each), and parasites (*Giardia*, *Entamoeba*, *Cryptosporidium*). Onset is usually within one week of arrival, with watery diarrhea lasting 2–4 days; patients are **usually afebrile.** Dysentery with bloody diarrhea and fever may be seen with *Shigella* or *Entamoeba*. Treat with hydration, antimotility agents (avoid in dysenteric cases), and antibiotics to shorten disease duration (ciprofloxacin × 1–3 days, azithromycin).

Diagnosis

- Routine tests include CBC, liver and renal chemistries, UA, and CXR.
- Evaluate the differential for eosinophilia; obtain thick and thin blood smears for malaria (may need to repeat every 8–12 hours for two days). Blood cultures for typhoid fever and meningococcus; stool for culture and ova/parasites.

Prevention

- Avoid untreated water, ice cubes, undercooked foods ("boil it, cook it, peel it, or forget it"), stray or wild animals, swimming in freshwater, and insect bites (use insect repellents containing 30–35% DEET or permethrin to coat mosquito netting or clothes).
- Malaria prophylaxis (see below).
- **Safe-sex counseling.**
- **Regular adult immunizations:** Tetanus, diphtheria, measles/mumps/rubella (MMR), and polio vaccinations should be up to date. Influenza and pneumococcal vaccine for some adults; hepatitis B vaccine for sexually active adults and health care workers.
- **Vaccines for most travelers to developing countries:** Hepatitis A and typhoid (for rural areas). Consider immune globulin (for hepatitis A in travelers leaving < 2–3 weeks after vaccination), meningococcus (for Nepal, sub-Saharan Africa, and pilgrims to Mecca), Japanese encephalitis (for rural China and southern Asia), yellow fever (required by certain countries), and rabies.
  - **Live attenuated vaccines (avoid during pregnancy or if immunosuppressed):** MMR, **oral** polio, **oral** typhoid, yellow fever, and oral cholera (not recommended for use).
  - **Egg-based vaccines:** Influenza, yellow fever.

Malaria

A common cause of fever in the tropics and in returned travelers or immigrants. *Plasmodium falciparum* is the most dangerous species and has a high prevalence in sub-Saharan Africa. Other species include *P. vivax*, *P. malariae*, and *P. ovale*. Malaria is transmitted by *Anopheles* mosquitoes or is acquired congenitally, through blood transfusions, or from stowaway mosquitoes ("airport malaria"). Nonimmune individuals (e.g., young children, visitors, migrants returning to the tropics after living in nonendemic areas) and pregnant women are at risk for severe disease.

Symptoms/Exam

- Fever, chills, malaise, headache, myalgias, and GI symptoms occur primarily when parasitized RBCs burst open, eventually leading to cyclic symptoms every 48 or 72 hours.
- Signs include hemolytic anemia, splenomegaly, hypoglycemia, thrombocytopenia, transaminitis, indirect hyperbilirubinemia, and hemoglobinuria ("blackwater fever").
- Illness usually occurs 1–2 weeks after infection with *P. falciparum*, but incubation may be longer for other species.
- Nephrotic syndrome due to immune complexes is most common with *P. malariae*. Relapsing illness may be seen after months or years with *P. vivax* and *P. ovale* because these have dormant liver stages or hypnozoites.
- Mature *P. falciparum* parasites (schizonts) bind to vascular endothelium, leading to capillary obstruction and ischemia. If left untreated, this can lead to hypoglycemia, cerebral malaria (seizures, coma), nephritis, renal failure, and pulmonary edema. Falciparum malaria also leads to high rates of parasitized RBCs, causing severe anemia.

Diagnosis

- **Order blood smears in all febrile travelers or returned immigrants from endemic areas.** Giemsa- or Wright-stained **thick and thin smears** are the best diagnostic tests.
- ***P. falciparum* must be distinguished from other species** (see Figure 11.16) because it requires hospital admission and is the only species with significant drug resistance. *P. falciparum* is usually characterized by > 1%

A blood smear showing a banana-shaped gametocyte or RBCs infected with multiple signet-ring forms is diagnostic for Plasmodium falciparum *infection, the most severe form of malaria.*

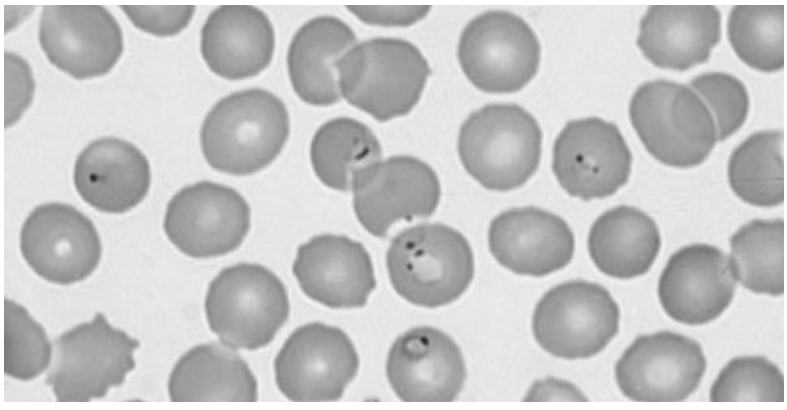

FIGURE 11.16. Falciparum malaria on a thin blood smear.

Young signet-ring-shaped parasites are seen for all species of *Plasmodium*, but only *P. falciparum* shows multiple parasites within a single RBC. (Reproduced, with permission, from Lichtman MA et al. *Williams Hematology*, 7th ed. New York: McGraw-Hill, 2005.)

parasitized RBCs, > 1 parasite/RBC, banana-shaped gametocytes, and lack of mature schizonts. It is also associated with travel to Africa, severe disease, and symptoms that occur within two months of travel.

- ***P. vivax*** is as widespread as but generally less virulent than *P. falciparum* (see Figure 11.17). ***P. malariae*** and ***P. ovale*** are much less common causes of malaria.

Treatment

*P. **V**ivax and P. **O**vale may lead to **V**ery **O**ld infections, presenting months or years after individuals leave an endemic area. Be sure to include primaquine at the end of treatment regimens to eradicate the chronic liver stages.*

- Treat *P. vivax*, *P. ovale*, and *P. malariae* with chloroquine. Treat *P. vivax* and *P. ovale* with primaquine as well to eradicate chronic liver stages (if patients have normal G6PD levels).
- **For *P. falciparum*, assume chloroquine resistance** (unless acquired in Central America, Haiti, or the Middle East) and treat with quinine plus doxycycline, quinine plus sulfadoxine/pyrimethamine (Fansidar), Fansidar alone, mefloquine, or atovaquone/proguanil (Malarone). Artesunate and artemisinin compounds are the fastest-acting malaricidal agents, but they are unavailable in the United States. **Repeat blood smears at 48 hours** to document a > 75% ↓ in parasitized RBCs. Exchange transfusion may be used for severe malaria or in the presence of > 15% parasitemia.
- In the United States, IV quinidine is often used because IV quinine may be unavailable. Primaquine may lead to severe hemolytic anemia, so screen for G6PD deficiency before using it. Adverse effects of mefloquine include irritability, bad dreams, GI upset, and, to a lesser extent, seizures and psychosis. Sulfadoxine/pyrimethamine is a sulfa drug and may lead to Stevens-Johnson syndrome. Atovaquone/proguanil has GI toxicities. Halofantrine (rarely used in the United States) may lead to QT prolongation. Doxycycline leads to photosensitivity and GI upset. During pregnancy, chloroquine is safe, and quinine, sulfadoxine/pyrimethamine, and doxycycline may be used despite potential fetal risks because morbidity and mortality are so high.

Prevention

Avoid mosquito bites (use bed netting, window screens, insecticides, and insect repellents with 30–35% DEET). **Chloroquine is effective in Central America, Haiti, and parts of the Middle East.** For most other areas, the

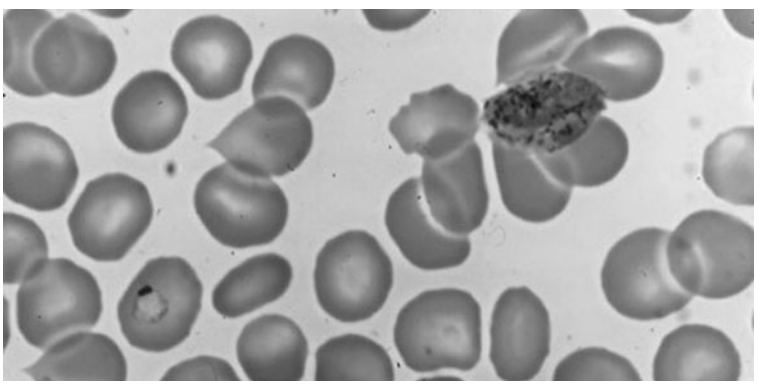

FIGURE 11.17. Vivax malaria on a thin blood smear.

Blood smear of *Plasmodium vivax* showing both a ring form and a female gametocyte. (Reproduced, with permission, from Lichtman MA et al. *Lichtman's Atlas of Hematology*. New York: McGraw-Hill, 2007: Figure III.A.20.)

CDC recommends mefloquine or atovaquone/proguanil. For Southeast Asia (the Thai-Burmese and Thai-Cambodian border areas), use doxycycline or atovaquone/proguanil, as resistance to all other antimalarials is common.

TUBERCULOSIS (TB)

In the United States, *Mycobacterium tuberculosis* is most commonly found among the disadvantaged (homeless, malnourished, crowded living conditions) and in immigrants from developing countries.

Symptoms/Exam

- **1° TB:** Usually asymptomatic with no radiographic signs, but 5% of patients (usually infants, elderly, and the immunosuppressed) develop **progressive 1° infection.**
- **Latent tuberculosis infection (LTBI):** Patients are infected (usually skin test ⊕) but do not have symptoms of active disease. Bacilli are contained by granuloma-forming T cells and macrophages.
- **Active TB/reactivation disease:** Approximately 10% of LTBI patients develop active disease, **5% within the first two years of infection** and 5% over the rest of their lives. **Risk factors for reactivation** include recent infection (within two years), HIV, hematologic malignancy, immunosuppressive medications (e.g., steroids, especially > 15 mg prednisone daily), diabetes, illicit drug use, silicosis, and gastrectomy.
  - **Pulmonary TB:** Presents with subacute cough (initially dry and then productive, sometimes with blood-streaked sputum) as well as with malaise, fever, sweats, and weight loss. Exam is normal or reveals apical rales, rhonchi, or wheezing.
  - **Extrapulmonary TB:** Lymphatic (painless cervical lymph node swelling) and pleural disease are most common. Other sites of infection may be seen, especially in patients with advanced HIV. Fever may be seen with more extensive disease.

Differential

Pneumonia or lung abscess (bacterial, fungal, PCP), malignancy (of the lung or elsewhere), Crohn's disease (for GI TB), UTI (renal TB may yield a "sterile pyuria"), HIV infection, colonization by atypical mycobacteria (in patients with underlying emphysema or bronchiectasis).

Diagnosis

- **Radiographic findings in active pulmonary TB** show infiltrates, nodules (including hilar), cavities (especially the apical or posterior segments of the upper lobes or the superior segments of the lower lobes), and calcifications. **Advanced HIV patients and the elderly may have normal or atypical radiographs.**
- **Sputum smears** are most sensitive in patients with cavitary disease. Bacilli are visualized by acid-fast (Ziehl-Neelsen, Kinyoun) or fluorochrome (rhodamine-auramine) stain.
- **Cultures** of sputum, blood, or tissue are the **gold standard** but may take weeks to months to grow. Sensitivities help guide treatment.
- **Nucleic acid amplification and/or hybridization tests** are adjuncts to smear and culture that are approved by the FDA for rapid identification of TB in respiratory smears (not extrapulmonary sites). Not available in all laboratories.

Previous BCG vaccination status should not be a consideration when interpreting a reactive PPD.

- For extrapulmonary disease, **histopathology** shows granulomas with caseating necrosis; AFB stains may show bacilli. For pleural TB, biopsy of the pleura showing granulomas is more sensitive than pleural fluid culture.
- **Tuberculin skin testing** identifies patients with latent or active infection but is not 100% sensitive or specific; false ⊖s are seen in elderly, malnourished, and immunosuppressed patients as well as in those with overwhelming TB infection. A blood test that measures the release of α-interferon from lymphocytes in response to PPD is also available for the diagnosis of LTBI.
- The **Quantiferon-TB Gold assay** measures the release of γ-interferon in whole blood in response to stimulation by synthetic peptide mixtures simulating two proteins secreted by *M. tuberculosis*. This test is approved for the diagnosis of LTBI and TB disease. It has a sensitivity similar to that of PPD but ↑ specificity, and it does not require a follow-up visit for reading (as is required by PPD skin testing).

Treatment

*Because of potential drug interactions, HIV patients on protease inhibitors should receive **rifabutin** instead of rifampin for the treatment of TB.*

- Patients with suspected active TB should be placed in **respiratory isolation** if hospitalized. Cases should be reported to public health authorities.
- For most cases of TB, the CDC recommends starting **treatment with four drugs;** INH, rifampin, pyrazinamide, and ethambutol are most commonly used. Modify once susceptibility results are available. Ethambutol may be omitted if the transmitted organism is known to be fully susceptible.
- In patients on protease inhibitors, non-nucleoside reverse transcriptase inhibitors, itraconazole, methadone, or other medications metabolized by the liver, **rifabutin** may be used instead of rifampin because it is associated with less cytochrome P-450 induction.
- Steroids may be helpful for meningitis and pericarditis.
- **Strongly consider using directly observed therapy** to maximize compliance. Treat most adults for six months. Patients with HIV/AIDS or miliary/meningeal disease are sometimes treated longer.

Prevention

- **Screening and treatment of LTBI:** Patients who are at risk for reactivation disease should be screened regardless of age ("a decision to screen is a decision to treat"). The Mantoux tuberculin skin test measures **induration** (not erythema) transversely on the forearm 2–3 days after intradermal injection of tuberculin; a visible wheal must be seen at the time of injection. ⊕ skin tests should be followed by a CXR to rule out active pulmonary disease. Table 11.13 outlines CDC guidelines governing tuberculin skin test positivity.
- The CDC recommends treatment of LTBI (formerly called "prophylaxis") in HIV-⊖ persons with INH QD or BIW × 9 months or with rifampin QD × 4 months. The use of combination rifampin/pyrazinamide for two months has been associated with severe and fatal hepatitis and should be avoided.
- New health care workers and others who will be tested repeatedly should have **two-step testing,** with a repeat skin test after 1–3 weeks if they are initially ⊖ (≤ 10 mm). If the second test is ⊕, it is likely due to a boosting response, and the person is considered a "reactor" but not a "recent converter." A **skin-test conversion** indicating recent infection is defined as an ↑ of ≥ 10 mm of induration within a two-year period. **Anergy testing** is not recommended. **Previous BCG vaccination** should be disregarded, as persistent reactivity is unlikely after > 10 years.

TABLE 11.13. CDC Guidelines for Tuberculin Skin Test Positivity

≥ 5 mm of Induration (for Patients at Highest Risk of Reactivation)	≥ 10 mm of Induration	≥ 15 mm of Induration (for Patients at Lowest Risk of Reactivation)
HIV. Immunosuppression due to organ transplants or other medications (prednisone ≥ 15 mg/day for one month or more). Close contacts of TB cases. CXR with fibrotic changes consistent with prior TB.	Recent immigrants (≤ 5 years) from developing countries. Residents or established employees of jails, long-term care facilities, or homeless shelters. IV drug users. Chronic illnesses such as silicosis, diabetes, chronic renal failure, leukemia, or lymphoma; head and neck or lung cancers; 10% weight loss; gastrectomy.	Patients with no risk factors for TB. New employees of high-risk institutions (at work entry).

Complications

- Treatment failure is usually due to medication nonadherence (> 95%).
- While patients are on treatment, **monitor monthly for clinical symptoms.** Consider **monthly LFTs** for those with baseline liver disease. In the presence of severe hepatitis (e.g., AST and ALT five times greater than the upper limit of normal), discontinue all hepatotoxic drugs and reintroduce one at a time every 3–4 days while monitoring symptoms and LFTs.
- **Other baseline monitoring:** Visual acuity and color vision (patients on ethambutol), uric acid (pyrazinamide), and audiometry (streptomycin). Give **pyridoxine** (vitamin B_6) to HIV patients to ↓ the risk of INH-related peripheral neuritis.

VARICELLA-ZOSTER VIRUS (VZV)

1° infection causes chickenpox. Reactivation of latent infection leads to herpes zoster, or "shingles." Immunosuppressed individuals can have more severe disease.

Symptoms/Exam

- **Chickenpox:** Incubation period is **10–20 days.** Presents with prominent fever, malaise, and a pruritic rash starting on the face, scalp, and trunk and spreading to the extremities. The rash is initially maculopapular and turns into vesicles ("dewdrops on a rose petal") and then into pustules that rupture, leading to crusts. **Multiple stages are present simultaneously.**
- **Herpes zoster:** Dermatomal tingling or pain followed by rash.

Differential

- **Smallpox:** Lesions are deeper and painful; **all lesions occur at the same stage.**

- **Disseminated HSV:** Especially in the setting of a skin disorder; diagnose by culture.
- **Meningococcemia:** Petechiae, purpura, sepsis.

Diagnosis

- Usually a clinical diagnosis.
- Confirm by scraping of lesions (culture or direct fluorescent antibody staining for virus).
- Tzanck smear of vesicle base for multinucleate giant cells.
- PCR of CSF for CNS complications.

Treatment

- **Acyclovir, valacyclovir,** and **famciclovir** reduce duration and severity and may prevent complications in adult chickenpox (if treated within **24 hours**) and shingles (if treated within **72 hours**).
- The addition of prednisone to acyclovir in immunocompetent patients with shingles may ↓ the risk of postherpetic neuralgia.
- **VariZIG** may prevent complications in immunocompromised or pregnant patients.

Smallpox rash starts on the face and extremities and moves to the trunk, where it is sparse. Generally, chickenpox rash also begins on the face and scalp and moves rapidly to the trunk, where it is denser, with relative sparing of the extremities.

Prevention

- **Chickenpox:** Vaccine can be given up to three days after exposure to patients with active lesions. **This live attenuated vaccine should not be given to immunosuppressed patients.**
- **Herpes zoster:** None. The effect of vaccine on risk of shingles is unknown.

Complications

- **Chickenpox:**
  - **Interstitial pneumonia** may occur, especially in pregnant women.
  - **Bacterial infections** (group A strep).
  - **Encephalitis.**
  - **Transverse myelitis.**
  - Varicella may **disseminate** or be multidermatomal in immunosuppressed patients (HIV, steroids, malignancy).
  - **Reye's syndrome** (fatty liver, encephalopathy) may develop in children with chickenpox (or influenza) after taking **aspirin.**
- **Herpes zoster:**
  - **Postherpetic neuralgia** is most common in the elderly and may be prevented by starting antivirals **within 72 hours** of rash onset. The effect of steroids is less clear.
  - **Ophthalmic zoster** may lead to blindness; patients with lesions on the tip of the nose should have an ophthalmologic consult.
- **Ramsay Hunt syndrome:** Presents with vesicles on the ear, facial palsy, loss of taste on the anterior two-thirds of the tongue, and vertigo. Tinnitus/deafness may occur.

CHAPTER 12

Nephrology

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Alan Pao, MD

Hyponatremia

Symptoms/Exam

- Symptoms and signs relate to the rate and severity of the decline in Na^+.
- May be asymptomatic or range from nausea and vomiting to confusion and lethargy or seizures and coma.

The vast majority of clinically significant hyponatremias will have a P_{osm} < 280 mOsm/kg. The main reason to check plasma osmolality is to exclude the unusual isotonic and hypertonic causes.

Differential

An algorithm for the evaluation and differential diagnosis of hyponatremia is given in Figure 12.1.

Diagnosis

- Determine tonicity:

$$\text{Plasma osmolality } (P_{osm}) = (2 \times Na^+) + (\text{BUN}/2.8) + (\text{glucose}/18)$$

- For hypotonic hyponatremias, determine volume status:

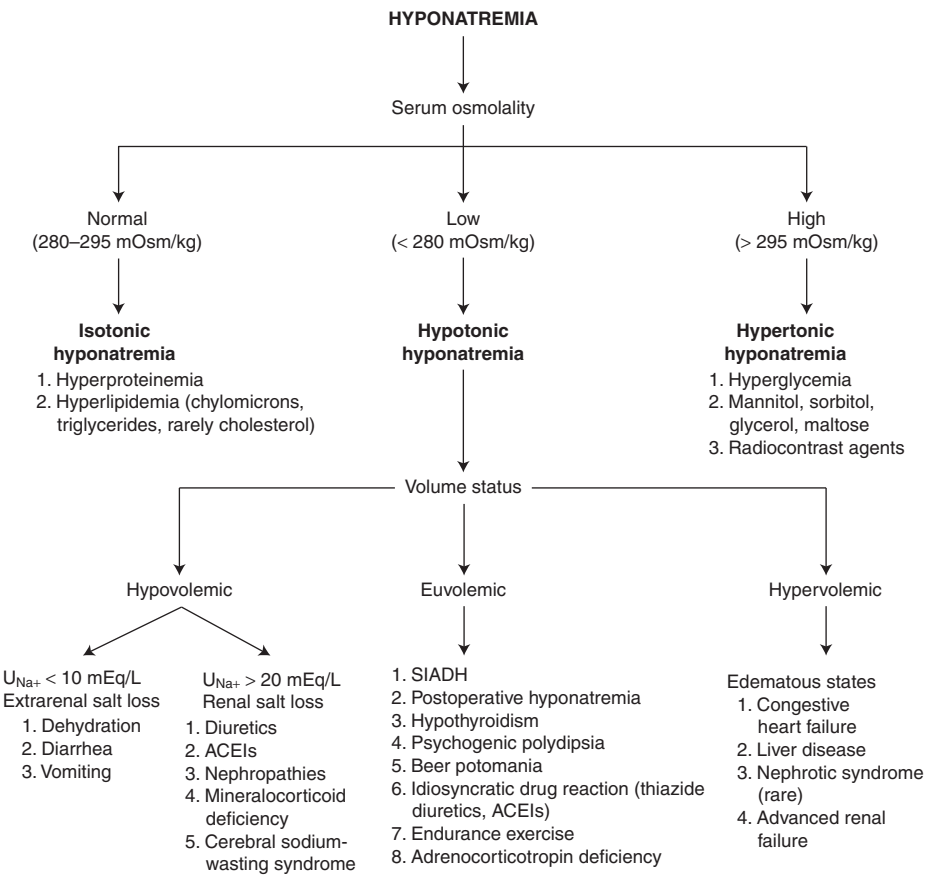


FIGURE 12.1. Algorithm for the evaluation of hyponatremia.

(Adapted from *American Journal of Medicine*, 72(3):496, Narins RG et al, Diagnostic strategies in disorders of fluid, electrolyte, and acid-base homeostasis, Copyright © 1982 with permission from Elsevier.)

- **Clinical exam:** Look for volume overload (elevated JVP, S3 gallop, ascites, edema) or volume depletion (dry mucous membranes, flat JVP).
- A **urine Na^+ < 10** suggests hypovolemia.
- A **fractional excretion of Na^+ (Fe_{Na+}) < 1%** is a more accurate predictor of low volume status than urine Na^+ (U_{Na+}):

$$Fe_{Na+} = \text{excreted } Na^+/\text{filtered } Na^+ = (U_{Na+} \times P_{Cr}) / (P_{Na+} \times U_{Cr})$$

  where P_{Cr} = plasma creatinine, P_{Na+} = plasma sodium, and U_{Cr} = urine creatinine.
- **$U_{osm} > P_{osm}$ or $U_{osm} > 100$ mOsm/kg** suggests a high-ADH state due to hypovolemia or SIADH.

Treatment

To prevent central pontine myelinolysis, do not ↑ sodium more than 12 mEq/L over a 24-hour period.

- Fluid management depends on the **volume status** of the patient.
  - **Hypervolemia:** Fluid restriction or diuretics.
  - **Euvolemia:** Fluid restriction.
  - **Hypovolemia:** Isotonic or hypertonic saline.
- The rate of correction of Na^+ depends on how quickly it dropped and how symptomatic the patient is.
  - **Acute symptomatic hyponatremia:** Na^+ should be raised until symptoms resolve (1–2 mEq/L per hour). Hypertonic (3%) saline is often required, usually with a loop diuretic.
  - **Symptomatic chronic hyponatremia:** Na^+ should be raised more slowly (0.5–1 mEq/L per hour). Hypertonic saline may be required.
  - **Asymptomatic chronic hyponatremia:** No immediate correction is required; fluid management as outlined above often suffices.
- Treat the underlying cause.

SIADH

Remember the "**big three**" causes of SIADH: any CNS disorder, any pulmonary disorder, and medications (especially psychiatric meds).

The "big three" causes of SIADH: any CNS disorder, any pulmonary disorder, and medications (especially psych meds).

Symptoms/Exam

Symptoms are those due to hyponatremia and to the underlying cause of SIADH.

Differential

- **CNS disorders:**
  - **Head trauma:** SAH, subdural hematoma.
  - **Infection:** Meningitis, encephalitis, brain abscess.
  - **Other:** Tumors, CVA, MS.
- **Pulmonary disorders:** Small cell lung cancer, pneumonia, lung abscess, TB, pneumothorax.
- **Drugs:** Chlorpropamide, TCAs, haloperidol.
- **Malignant neoplasia.**

Diagnosis

- Low P_{osm}.
- Hyponatremia with normal volume status.
- $U_{osm} > P_{osm}$.
- **SIADH is a diagnosis of exclusion.**

Treatment

- **Water restriction.**
- **Second-line agents:** Hypertonic saline and loop diuretic.
- **Chronic SIADH:** Demeclocycline

Hypernatremia

Hypernatremia is almost always due to free water deficits (and only rarely to an ↑ in body sodium).

Symptoms/Exam

- Hypernatremia leads to hyperosmolality, which pulls water from cells, leading to cellular dehydration and to **CNS symptoms** (lethargy, weakness, irritability, altered mentation, seizures, coma).
- **Volume depletion** presents as dry mucous membranes, hypotension, and low urine output.

If U_{osm} is low in a hypernatremic patient, consider DI.

Differential

- **↑ water loss (U_{osm} > 600 mOsm/kg):**
  - **Insensible loss:** ↑ sweating, burns.
  - **GI loss:** Diarrhea.
- **Renal loss (polyuria):**
  - Postobstructive or post-ATN diuresis.
  - Diabetes mellitus.
  - **Diabetes insipidus (U_{osm} < 600 mOsm/kg):** Suspect in a hypernatremic patient with copious amounts of dilute urine (see the Endocrinology chapter for a full discussion).
- **Excess Na^+ retention:** Rare; due to hypertonic saline infusion.

Diagnosis

- Diagnosis is usually apparent from the clinical presentation.
- Measure U_{osm}; it should be high in the hypovolemic patient (the kidney is trying to hold on to water, so the urine becomes concentrated).

Treatment

- **Calculate free-water deficit:**

$$\text{Deficit} = \text{normal body water (NBW)} - \text{current body water (CBW)} = 0.5 \times \text{body weight in kg} \left[(\text{plasma } Na^+ - 140)/140\right]$$

- Replace the calculated free-water deficit. Na^+ should be lowered 1 mEq/L per hour, not to exceed 12 mEq/L in a 24-hour period.
- If the patient is hypotensive and volume depleted, isotonic saline should be used initially; hypotonic saline can be used once tissue perfusion is adequate.
- Check plasma sodium levels frequently to avoid overcorrection.

POTASSIUM DISORDERS

Hyperkalemia

Symptoms/Exam

May be asymptomatic or may present with symptoms ranging from muscle weakness to ventricular fibrillation (VF).

Differential

- **High K^+ dietary intake.**
- **Extracellular K^+ shift:** Metabolic acidosis, insulin deficiency, α-adrenergic blockade, rhabdomyolysis, tumor lysis syndrome, digitalis overdose, succinylcholine, periodic paralysis—hyperkalemic form.
- **Low urine K^+ excretion:** Renal failure, ↓ effective circulating volume, hypoaldosteronism.
  - **↓ renin-angiotensin system activity:** Hyporeninemic hypoaldosteronism, ACEIs, NSAIDs, cyclosporine.
  - **↓ adrenal synthesis:** Addison's disease.
  - **Aldosterone resistance:** High-dose TMP, pentamidine, K^+-sparing diuretics.

Diagnosis

- The cause is often apparent after a careful history, a review of meds, and basic labs (chemistry panel with BUN, creatinine, and CK).
- Check ECG as an indicator of severity:
  - **Mild:** Normal or peaked T waves.
  - **Moderate:** QRS prolongation or flattened P waves.
  - **Severe:** VF.
- Additional labs for special situations include the following:
  - **Tumor lysis syndrome:** High LDH, uric acid, and phosphorus; low calcium.
  - **Hypoaldosteronemic states:** Check **transtubular K^+ gradient (TTKG)** (a value < 5 is suggestive of hypoaldosterone state):

$$TTKG = (U_{K+}/P_{K+}) / (U_{osm}/P_{osm})$$

    where U_{K+} = urine potassium and P_{K+} = plasma potassium.

Treatment

- **Reduce cardiac excitability:** IV calcium.
- **Shift K^+ entry into cells:** Glucose and insulin, β_2-adrenergic agonists (e.g., inhaled albuterol), $NaHCO_3$.
- **Remove excess K^+:** Diuretics, cation-exchange resin (Kayexalate), dialysis.

Hypokalemia

Symptoms/Exam

- **Symptoms usually occur when $P_{K+} < 2.5–3.0$ mEq/L.**
- Presents with weakness, rhabdomyolysis, and cardiac arrhythmias.

Differential

- **Low K^+ dietary intake.**
- **Intracellular K^+ shift:** Alkalemia, ↑ insulin availability, ↑ α-adrenergic activity, periodic paralysis (classically associated with thyrotoxicosis).
- **GI K^+ loss:** Diarrhea.
- **Renal K^+ loss:**
  - Diuretics.
  - Vomiting.
  - **Mineralocorticoid excess:** 1° hyperaldosteronism, Cushing's disease, European licorice ingestion and syndrome of apparent mineralocorticoid excess, hyperreninemia.
  - Liddle's syndrome.

- Hypomagnesemia.
- Bartter's and Gitelman's syndromes.

Diagnosis

- 24-hour urine collection for K^+:
  - **< 25 mEq/day:** Extrarenal loss.
  - **> 25 mEq/day:** Renal K^+ wasting.
- Spot urine collection for K^+ (less accurate but easier to obtain):
  - **< 15 mEq/L:** Extrarenal loss.
  - **> 15 mEq/L:** Urine K^+ wasting. Check plasma renin activity and serum/urine aldosterone levels (see the Endocrinology chapter).
- **Additional labs for special situations:** Periodic paralysis may be associated with thyroid disease; check TSH.

Differential diagnosis of anion-gap metabolic acidosis—

MUDPILES

Methanol ingestion—can cause blindness and optic disk hyperemia
Uremia
Diabetic ketoacidosis
Paraldehyde ingestion
Isoniazid overdose
Lactic acidosis—commonly due to tissue hypoxia from circulatory shock
Ethylene glycol ingestion—look for calcium oxalate crystals in urine
Salicylate ingestion—classically presents with concomitant respiratory alkalosis

Treatment

- **Replete KCl.** The average total body K^+ deficit is 200–400 mEq when $P_{K+} = 3.0$ mEq/L.
- The IV K^+ correction rate should not exceed 10 mEq/L per hour for a peripheral line or 20 mEq/L per hour for a central line.

ACID-BASE DISORDERS

Figure 12.2 illustrates an overall approach toward the diagnosis and management of acid-base disorders.

Metabolic Acidosis

There are **two main categories** of metabolic acidosis: **anion gap and non–anion gap.** Refer to Figure 12.2 for further details.

Treatment

See Table 12.1.

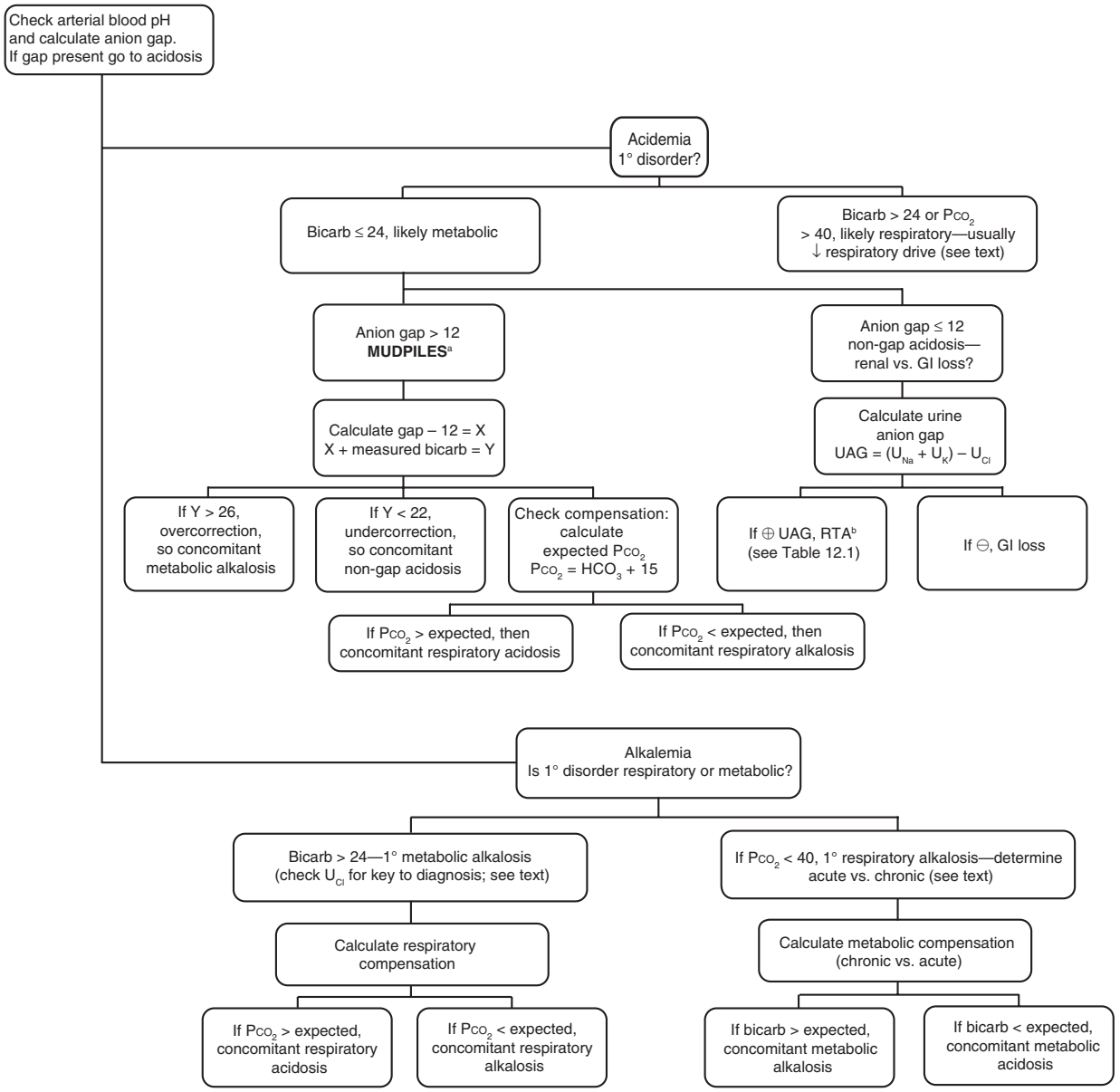
Metabolic Alkalosis

Due to one of four main causes: volume depletion, chloride depletion, potassium depletion, or hyperaldosteronism. **Urine chloride** concentration is the key test used to distinguish various causes.

In patients with non-anion-gap metabolic acidosis, a history of diarrhea points to GI bicarbonate loss; in the absence of diarrhea, consider RTA. The urine anion gap can confirm clinical suspicion.

Diagnosis/Treatment

- **Urine Cl^- < 10 mEq/L implies hypovolemia** (the kidney is trying to retain Na^+ and Cl^-, so urine Cl^- is low).
  - **GI loss:** Vomiting, NG suction, or chloride-losing diarrhea.
  - Diuretics.
  - **Gain of HCO_3:** Administration of $NaHCO_3$ or antacids.
  - **Treatment:** NaCl infusion.
- **Urine Cl^- > 10 mEq/L** = chloride-resistant metabolic alkalosis. **Broken down according to BP:**
  - **Hypertension:** Implies excess mineralocorticoid action (retain Na; lose H^+ and K^+):
    - 1° hyperaldosteronism or hyperreninemia.



a. Measure BUN and creatinine, lactate, serum or urine ketones, and salicylate level.
- Calculate the **osmolal gap** to rule out ingestion of an alcohol:

  Osm gap = measured osm – calculated osm

  Calculated osm = $(2 \times Na^+) + (BUN/2.8) + (glucose/18)$
- **An osm gap > 20 indicates the ingestion of an alcohol:** Ethanol, methanol, ethylene glycol.

b. Diagnosis of specific RTA:
- **If high serum K:** Type 4 RTA.
- **If normal or low:** Look at the **urine pH.**
- If > **5.5,** distal RTA.
- If < **5.0,** proximal RTA (usually associated with glycosuria, low-grade proteinuria, or hypophosphatemia).

FIGURE 12.2. Approach to acid-base disorders.

- Liddle's syndrome.
- European black licorice ingestion or syndrome of apparent mineralocorticoid excess.
- 11- or 17-hydroxylase deficiency.

TABLE 12.1. Characteristics of Different Types of Renal Tubular Acidosis[a]

	Type 1 (Distal)	Type 2 (Proximal)	Type 4
Basic defect	↓ distal acidification.	Diminished proximal HCO_3^- reabsorption.	Aldosterone deficiency or resistance.
Urine pH during acidemia	> 5.3.	Variable: > 5.3 if above reabsorptive threshold; < 5.3 if below.	Usually < 5.3.
Plasma HCO_3^-, untreated	May be < 10 mEq/L.	Usually 14–20 mEq/L.	Usually > 15 mEq/L.
Fractional excretion of HCO_3^- at normal plasma HCO_3^-	< 3% in adults; may reach 5–10% in young children.	> 15–20%.	< 3%.
Diagnosis	Response to $NaHCO_3$ or NH_4Cl.	Response to $NaHCO_3$.	Measure plasma aldosterone concentration.
Plasma K^+	Usually ↓ or normal; elevated with voltage defect.	Normal or ↓.	Elevated.
Dose of HCO_3^- to normalize plasma HCO_3^- (in mEq/kg/day)	1–2 in adults; 4–14 in children.	10–15.	1–3; may require no alkali if hyperkalemia is corrected.
Nonelectrolytic complications	Nephrocalcinosis and renal stones.	Rickets or osteomalacia.	None.

[a] What had been called type 3 RTA is actually a variant of type 1 RTA.

Adapted, with permission, from Rose BD, Post TW. *Clinical Physiology of Acid-Base and Electrolyte Disorders,* 5th ed. New York: McGraw-Hill, 2001: 613.

- **Normotension:** Profound hypokalemia (leads to ↑ ammonium production), Bartter's syndrome, refeeding alkalosis.
- Treat the underlying cause.

Respiratory acidosis and respiratory alkalosis can ***never*** *be present simultaneously—you can't hypoventilate and hyperventilate at the same time!*

Respiratory Acidosis

Differential

- **Depressed medullary respiratory center:**
  - **Drugs:** Opiates, anesthetics, sedatives.
  - Central sleep apnea.
- **Obstructed upper airway:** Obstructive sleep apnea, aspiration.
- **Impaired respiratory muscle or chest wall function:** Guillain-Barré syndrome, myasthenia gravis, severe hypokalemia, severe hypophosphatemia, spinal cord injury, poliomyelitis, MS, myxedema, kyphoscoliosis.
- **Impaired alveolar gas exchange:** Exacerbation of underlying chronic lung disease, cardiogenic pulmonary edema, ARDS, pneumothorax, COPD.

Diagnosis

- An arterial pH < 7.40 and an arterial pCO_2 > 40 mmHg confirm respiratory acidosis.
- Calculate the alveolar-arterial (A-a) oxygen gradient to differentiate intrinsic pulmonary from extrapulmonary disease where:
  - Alveolar pO_2 (pAO_2) = FiO_2 (atmospheric pressure − water vapor pressure) − (pCO_2/0.8).
  - For patients at sea level breathing room air, pAO_2 can be estimated by $pAO_2 = 150 - (pCO_2/0.8)$.
  - Arterial pO_2 (paO_2) as measured by ABG.
  - The normal ($pAO_2 - paO_2$) gradient is 10–20 mmHg. An A-a gradient > 20 implies intrinsic pulmonary disease causing impaired gas exchange.
- Compensation for acute vs. chronic respiratory acidosis is as follows:
  - **Acute:** For every 10-mmHg ↑ in pCO_2, plasma HCO_3 ↑ 1 mEq/L.
  - **Chronic** (after 3–5 days): For every 10-mmHg ↑ in pCO_2, plasma HCO_3 ↑ 3 mEq/L.

Treatment

- Correct the underlying disorder.
- Mechanical ventilation if necessary.

Respiratory Alkalosis

Symptoms/Exam

- **Tachypnea.**
- **CNS symptoms:** Lightheadedness, altered mental status.
- **Hypocalcemia symptoms:** Paresthesias, circumoral numbness, carpopedal spasms.

Differential

The differential diagnosis of respiratory alkalosis is outlined in Table 12.2.

Diagnosis

- pH > 7.40 and pCO_2 < 40 constitute respiratory alkalosis.
- Compensation for acute vs. chronic respiratory alkalosis is as follows:
  - **Acute:** For every 10-mmHg ↓ in pCO_2, plasma HCO_3 ↓ 2 mEq/L.
  - **Chronic** (after 3–5 days): For every 10-mmHg ↓ in pCO_2, plasma HCO_3 ↓ 4 mEq/L.

Treatment

Correct the underlying disorder.

Mixed Acid-Base Disorders

See Figure 12.2.

Triple Acid-Base Disorders—The "Triple Ripple"

- Defined as metabolic acidosis + metabolic alkalosis + respiratory acidosis or alkalosis.

TABLE 12.2. Differential Diagnosis of Respiratory Alkalosis

HYPOXIA	CNS-MEDIATED DISORDERS	PULMONARY DISEASE	OTHER
↓ inspired oxygen tension	Voluntary hyperventilation (e.g., anxiety-hyperventilation syndrome)	Interstitial lung disease	Mechanical overventilation
High altitude	Neurologic disease	Pneumonia	
V/Q inequality	CVA (infarction, hemorrhage)	Pulmonary embolism	
Hypotension	Infection	Pulmonary edema	
Severe anemia	Trauma		
	Tumor		
	Pharmacologic and hormonal stimulation—e.g., salicylates, nicotine, xanthines, pregnancy (progesterone)		
	Hepatic failure		
	Gram-⊖ septicemia		
	Recovery from metabolic acidosis		
	Heat exposure		

- Classic causes include the following:
  - **Diabetic or alcoholic ketoacidosis:** Non-anion-gap and anion-gap metabolic acidosis (ketoacidosis), metabolic alkalosis (vomiting and hypovolemia), and compensatory respiratory alkalosis.
  - **Salicylate toxicity:** Anion-gap metabolic acidosis (from salicylic acid), metabolic alkalosis (vomiting), and 1° respiratory alkalosis (salicylates directly stimulate the respiratory center).

Nephrolithiasis

Calcium oxalate stones account for the vast majority of cases. The condition is four times more common in men; peak incidence is between the ages of 20 and 40.

A 24-hour urine collection (volume, pH, sodium, calcium oxalate, phosphorus, citrate, uric acid, cystine, creatinine) is warranted for recurrent nephrolithiasis.

SYMPTOMS/EXAM

- Flank pain +/– radiation to the groin.
- Urinary frequency, urgency, and dysuria.
- Microscopic or gross hematuria.

DIAGNOSIS

- Collect and analyze the stone!
- **Labs:**
  - UA (look for blood, assess urine pH, rule out UTI).
  - Plasma Ca^{+}, phosphorus, uric acid, electrolytes (assess renal function, acidosis, hypokalemia).
  - PTH level.

- The radiologic modality of choice is noncontrast spiral CT (but this may miss indinavir stones). A plain AXR will see only radiopaque (calcium-containing) stones.

Treatment

- **General treatment for all stones consists of a high volume of daily fluid intake.**
- It is important to note that **a low-calcium diet may actually ↑ the risk of calcium stone formation** (thought to be a result of ↑ intestinal oxalate absorption).
- Specific treatment guidelines are outlined in Table 12.3. Clues from the history are as follows:
  - **Recurrent UTIs:** Struvite stones.
  - **Prior malignancies:** Uric acid stones (tumor lysis).
  - **IBD:** Oxalate stones.
  - Medications, family history.

ACUTE RENAL FAILURE (ARF)

Approach to ARF

Checking urine Na or calculating Fe_{Na} is reliable only when the patient is oliguric and not taking diuretics.

- Some accepted definitions of ARF include serum creatinine > 0.5 mg/dL, doubling of serum creatinine, and a 25–50% ↑ in serum creatinine. ATN and volume depletion account for the majority of hospital cases. Guidelines for the diagnosis of ARF are as follows (see also Tables 12.4 and 12.5):

TABLE 12.3. Types, Mechanisms, and Treatment of Kidney Stones

Type	Mechanisms and Disease Associations	Treatment[a]	Notes
Calcium oxalate	**Hypercalciuria:** Hyperparathyroidism, malignancy, granulomatous diseases. **Hyperoxaluria:** Short gut syndrome, IBD. **Hypocitraturia:** Metabolic acidosis from RTA, chronic kidney disease, chronic diarrhea.	**Ca^{++} restriction is not helpful** (may lead to hyperoxaluria). Thiazides, potassium citrate, moderate protein intake.	Citrate is the 1° stone formation inhibitor.
Uric acid	**Acidic urine (pH < 5.5):** Diet high in animal protein. **Hyperuricosuria:** Gout, tumor lysis syndrome.	Allopurinol, potassium citrate, moderate protein intake.	
Cystine	**Hypercystinuria:** Cystinuria.	Tiopronin (Thiola).	
Struvite ($Mg-NH_4$ + phosphate)	**Alkaline urine (pH > 6.5):** UTI with urease-splitting organisms (*Proteus mirabilis*).	Treat the underlying infection.	Recurrent UTIs may be due to a residual nidus of infection from the stone.
Medication-related	Triamterene, acyclovir, indinavir.		

[a] In addition to large-volume water intake.

The differential diagnosis of ARF with a low Fe_{Na} (< 1%) includes the following:

- *Prerenal azotemia*
- *Glomerulonephritis*
- *Contrast nephropathy*
- *Rhabdomyolysis*
- *Early obstructive nephropathy*

- Review medications for nephrotoxic drugs.
- Assess volume status.
- Obtain urine electrolytes to calculate Fe_{Na} (if oliguric).
- Assess urine sediment (see the discussion of urine sediment as a guide to kidney injury).
- Renal ultrasound to rule out obstruction and assess kidney size

- In the setting of oliguric renal failure, the clinician must distinguish prerenal azotemia from ATN. Table 12.6 outlines the differences between these two states.

Treatment

- Treat the underlying cause or remove the offending agent.
- Support renal function through dialysis if necessary (see the mnemonic **AEIOU**).
- There is **no role for "renal dose" dopamine!**

Indications for dialysis—

AEIOU

Acidosis
Electrolytes: hyperkalemia
Ingestions: severe acidemia
Overload: pulmonary edema
Uremia

Specific Causes of ARF

Acute Tubular Necrosis (ATN)

Symptoms/Exam

Urine sediment shows a muddy brown cast (see Figure 12.3).

Differential

- **Ischemic:** Prolonged prerenal azotemia; **sepsis;** massive hemorrhage; NSAIDs, ACEIs, ARBs; contrast dye.
- **Toxic:**
  - **Endogenous toxins:**
    - Myoglobin → rhabdomyolysis (see Table 12.7).

TABLE 12.4. Etiologies of Acute Renal Failure

Prerenal	Intrinsic Renal[a]	Postrenal
Volume depletion Circulatory shock Severe CHF Severe cirrhosis (hepatorenal syndrome)	**Tubular injury—acute tubular necrosis (ATN):** ■ Ischemia ■ Contrast dye ■ Myeloma ■ Heme pigment (rhabdomyolysis, hemolysis) ■ Aminoglycosides **Interstitium—acute interstitial nephritis (AIN):** ■ Allergic and drug reactions (especially NSAIDs) **Glomerular—glomerulonephritis (GN):** See separate section. **Cholesterol emboli syndrome.**	Urinary tract obstruction

[a] See section on ARF on how to use urine sediment to guide differential.

TABLE 12.5. Clinical Features, Urinary Findings, and Confirmatory Tests in the Differential Diagnosis of ARF

Cause of ARF	Suggestive Clinical Features	Typical UA	Confirmatory Tests
I. PRERENAL ARF	Evidence of true volume depletion (thirst, postural or absolute hypotension and tachycardia, low JVP, dry mucous membranes/axillae, weight loss, fluid output > input) or ↓ "effective" circulatory volume (e.g., heart failure, liver failure); treatment with NSAIDs or ACEIs.	Hyaline casts; Fe_{Na} < 1%, U_{Na} < 10 mmol/L, specific gravity (SG) > 1.018.	Occasionally requires invasive hemodynamic monitoring. Rapid resolution of ARF occurs upon restoration of renal perfusion.
II. INTRINSIC RENAL ARF			
A. Diseases involving large renal vessels			
1. Renal artery thrombosis	History of atrial fibrillation or recent MI; flank or abdominal pain.	Mild proteinuria; occasional red cells.	Elevated LDH with normal transaminases; renal arteriogram.
2. Atheroembolism	Age usually > 50 years, recent manipulation of the aorta, retinal plaques, subcutaneous nodules, palpable purpura, livedo reticularis, vasculopathy, hypertension, anticoagulation.	Often normal; eosinophiluria; rarely casts.	Eosinophilia, hypocomplementemia, skin biopsy, renal biopsy.
3. Renal vein thrombosis	Evidence of nephrotic syndrome or pulmonary embolism; flank pain.	Proteinuria, hematuria.	Inferior vena cavogram and selective renal venogram.
B. Diseases of small vessels and glomeruli			
1. Glomerulonephritis/vasculitis	Compatible clinical history (e.g., recent infection), sinusitis, lung hemorrhage, skin rash or ulcers, arthralgias, new cardiac murmur, history of HBV or HCV infection.	Red cell or granular casts, red cells, white cells, mild proteinuria.	Low C3, C4, ANCA, anti-GBM antibody, ANA, ASO, anti-DNase, cryoglobulins, blood cultures, renal biopsy.
2. HUS/TTP	Compatible clinical history (e.g., recent GI infection, cyclosporine, anovulants), fever, pallor, ecchymoses, neurologic abnormalities.	May be normal, red cells, mild proteinuria, rarely red cell/granular casts.	Anemia, thrombocytopenia, schistocytes on blood smear, ↑ LDH, renal biopsy.
3. Malignant hypertension	Severe hypertension with headaches, cardiac failure, retinopathy, neurologic dysfunction, papilledema.	Red cells, red cell casts, proteinuria.	LVH by echo/ECG; resolution of ARF with BP control.

TABLE 12.5. Clinical Features, Urinary Findings, and Confirmatory Tests in the Differential Diagnosis of ARF *(continued)*

Cause of ARF	Suggestive Clinical Features	Typical UA	Confirmatory Tests
C. ARF mediated by ischemia or toxins (ATN)			
1. Ischemia	Recent hemorrhage, hypotension (e.g., cardiac arrest), surgery.	Muddy brown granular or tubular epithelial cell casts; Fe_{Na} > 1%, U_{Na} > 20 mmol/L, SG < 1.015.	Clinical assessment and UA are usually sufficient for diagnosis.
2. Exogenous toxins	Recent radiocontrast study, nephrotoxic antibiotics or anticancer agents often coexistent with volume depletion, sepsis, or chronic renal insufficiency.	Muddy brown granular or tubular epithelial cell casts; Fe_{Na} > 1%; U_{Na} > 20 mmol/L; SG < 1.015.	Clinical assessment and UA are usually sufficient for diagnosis.
3. Endogenous toxins	History suggestive of rhabdomyolysis (seizures, coma, ethanol abuse, trauma).	Urine supernatant ⊕ for heme.	Hyperkalemia, hyperphosphatemia, hypocalcemia, ↑ circulating myoglobin, CPK (MM), and uric acid.
	History suggestive of massive hemolysis (blood transfusion).	Urine supernatant pink and ⊕ for heme.	Hyperkalemia, hyperphosphatemia, hypocalcemia, hyperuricemia, pink plasma ⊕ for hemoglobin.
	History suggestive of tumor lysis (recent chemotherapy), myeloma (bone pain), or ethylene glycol ingestion.	Urate crystals, dipstick-⊖ proteinuria, oxalate crystals, respectively.	Hyperuricemia, hyperkalemia, hyperphosphatemia (for tumor lysis); circulating or urinary monoclonal spike (for myeloma); tox screen, acidosis, osmolal gap (for ethylene glycol).
D. Acute diseases of the tubulointerstitium			
1. Allergic interstitial nephritis	Recent ingestion of drug and fever, rash, or arthralgias.	White cell casts, white cells (frequently eosinophiluria), red cells, rarely red cell casts, proteinuria (occasionally nephrotic).	Systemic eosinophilia, skin biopsy of rash (leukocytoclastic vasculitis) renal biopsy.

TABLE 12.5. Clinical Features, Urinary Findings, and Confirmatory Tests in the Differential Diagnosis of ARF *(continued)*

Cause of ARF	Suggestive Clinical Features	Typical UA	Confirmatory Tests
2. Acute bilateral pyelonephritis	Flank pain and tenderness, toxic, febrile.	Leukocytes, proteinuria, red cells, bacteria.	Urine and blood cultures.
III. POSTRENAL ARF	Abdominal or flank pain; palpable bladder.	Frequently normal; hematuria if stones, hemorrhage, malignancy, or prostatic hypertrophy.	Plain film, renal ultrasound, IVP, retrograde or anterograde pyelography, CT scan.

Adapted, with permission, from Kasper DL et al. *Harrison's Principles of Internal Medicine,* 16th ed. New York: McGraw-Hill, 2005: 1648.

- Hemoglobin.
- **Light chain deposition.**
- Urate.

- **Exogenous toxins:**
  - **Radiocontrast** (see Table 12.7).
  - Oxalate (ethylene glycol ingestion).
  - **Medications:** Antimicrobials (**aminoglycosides,** pentamidine, **amphotericin B**), antivirals (ritonavir), chemotherapy (cisplatin, ifosfamide, 5-FU), lithium.

Acute Interstitial Nephritis (AIN)

Symptoms/Exam

- Fever, rash, eosinophilia, arthralgias.
- Sudden-onset renal failure.

Differential

- **Drugs** (bolded items are most common):
  - **Antimicrobials:** β-lactams (penicillin, ampicillin, methicillin), fluoroquinolones, rifampin, sulfonamides.

TABLE 12.6. Prerenal Azotemia vs. Acute Tubular Necrosis

	Prerenal Azotemia	Acute Tubular Necrosis
Fe_{Na}	< 1%	> 1%
BUN/Cr	> 20:1	10–15:1
U_{osm}	High.	Similar to serum osm.
Urine sediment	Bland.	Muddy brown casts.
Response to fluids	Rapidly improves.	Poor; may take 2–3 weeks for recovery. Often requires dialysis in the interim.

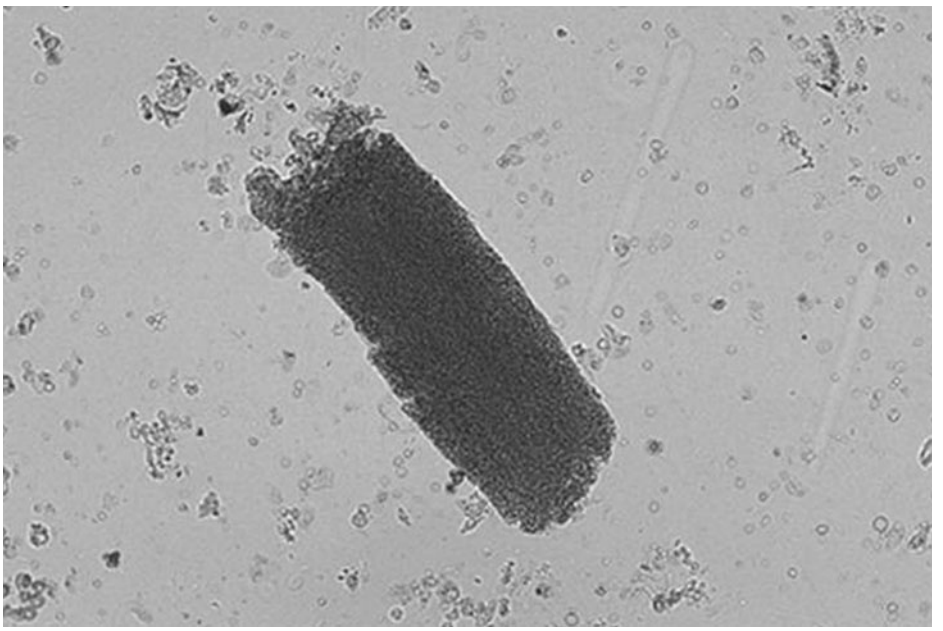


FIGURE 12.3. Muddy brown cast.

(Courtesy of R. Rodriguez.)

NSAID-induced nephropathy may include the following:

- *ARF from afferent arteriolar vasoconstriction in the setting of prerenal azotemia.*
- *AIN and minimal change disease.*
- *Analgesic nephropathy (papillary necrosis–chronic interstitial nephritis).*

  - **NSAIDs** and **COX-2 inhibitors.**
  - **Other:** Phenytoin, allopurinol, cimetidine, furosemide, indinavir.
- **Infections:** Many bacteria, viruses, and parasites.
- **Systemic disease:** Sarcoidosis, Sjögren's syndrome, SLE.
- **Idiopathic.**

Diagnosis

- Urine microscopy reveals **WBC casts.**
- Hansel stain on urine WBCs yields > 1% eosinophils (low sensitivity).
- Peripheral blood eosinophilia (low sensitivity).
- Renal biopsy typically shows interstitial inflammation with mononuclear cells, with normal glomeruli.

Treatment

- Withdraw or eradicate the offending agent.
- Corticosteroids.

Complications

Chronic interstitial nephritis is a potential complication of AIN. It presents as progressive renal failure with mild proteinuria and inactive sediment. Chronic interstitial nephritis may also be caused by the following:

- **Analgesic nephropathy** (papillary necrosis and chronic interstitial nephritis).
- **Chronic reflux.**
- **Heavy metals** (**lead,** arsenic).
- **Systemic diseases:** Sickle cell, SLE, Sjögren's.

TABLE 12.7. Features of Contrast Dye Nephropathy and Rhabdomyolysis

	Contrast Nephropathy	Rhabdomyolysis
Risk factors	Underlying kidney disease. Diabetes. Concomitant use of ACEIs, ARBs, or NSAIDs. Volume depletion or sepsis.	Muscle trauma, ischemia, or inflammation. **Toxins:** Alcohol, cocaine, statins, reverse transcriptase inhibitors. **Metabolic:** Hypokalemia, hypophosphatemia. **Genetic:** McArdle's disease.
Other clinical features	Creatinine peaks 24–72 hours after dye load and then typically improves.	Elevated serum CK. Urine dipstick ⊕ for blood, but no RBCs on microscopy. Other lab changes include hyperkalemia, hyperphosphatemia, hyperuricemia, and hypocalcemia.
Treatment	Fluids: Isotonic $NaHCO_3$ 3 mL/kg bolus over one hour followed by 1 mL/kg/hr for six hours. *N*-acetylcysteine (600 mg BID the day before and the day of contrast). Dialysis is rarely needed.	Early, aggressive volume repletion. Urine alkalization with $NaHCO_3$ may help. Dialysis may be needed.
Notes	Unlike other ATNs, Fe_{Na+} is low (due to intrarenal vasoconstriction).	⊕ urine dipstick for blood due to myoglobin pigments in urine.

Urinary Tract Obstruction

In order for obstruction to cause ARF, there must be bilateral obstruction or obstruction of a single functioning kidney. Obstruction of > 2 weeks' duration is likely to cause permanent damage.

Differential

Anything that blocks urine flow to the outside may cause urinary tract obstruction, including the following:

- **Neurogenic bladder.**
- **Malignancies:** Prostatic hypertrophy or malignancy, cervical cancer, bladder cancer, lymphoma, pelvic lymphadenopathy.
- **Kidney stones.**
- **Retroperitoneal fibrosis.**

Diagnosis

- Oliguria or anuria.
- **Labs:** Type 4 RTA, elevated creatinine.
- **Fe_{Na}:** Low (< 1%) early after obstruction; higher later in the course of disease.
- Foley catheter placement reveals a large postvoid residual.
- **Ultrasonography** reveals **hydronephrosis.**

Treatment

- Relieve the obstruction.
- Volume repletion during postobstructive diuresis.

Hepatorenal Syndrome (HRS)

Seen in severe liver disease with portal hypertension. Pathophysiology is characterized by intense renal salt and water retention leading to oliguric renal failure.

Diagnosis

- **Major criteria:**
  - Low GFR.
  - No preexisting renal disease.
  - Absence of shock, sepsis, fluid loss, or nephrotoxic drugs.
  - No improvement of renal function with 1.5 L of plasma expander.
- **Supporting criteria:**
  - Urine volume < 500 cc/day.
  - $U_{Na+} < 10$ mEq/L.
  - $U_{osm} > P_{osm}$.
  - Serum $Na^+ < 130$ mEq/L.
  - Low Fe_{Na+} (< 1%).

Renal failure in severe liver disease is not always HRS! HRS is a diagnosis of exclusion.

Treatment

- Albumin infusion.
- **Splanchnic vasoconstrictors:** Vasopressin analogs (terlipressin, ornipressin), midodrine, octreotide.
- Transjugular intrahepatic portosystemic shunt (TIPS).
- Renal replacement therapy as a bridge to liver transplantation.
- **Liver transplantation** is definitive therapy.

HRS is a marker of severe liver disease that can be reversed only by liver transplantation.

Cholesterol Emboli Syndrome

See the section in the Rheumatology chapter.

GLOMERULAR DISEASES

Glomerulonephritis (Nephritic)

Symptoms/Exam

Presents with hypertension, edema, and oliguria +/– hematuria.

Differential

The differential diagnosis of glomerulonephritis can be broken down on the basis of serum complement levels (see Figure 12.4).

Diagnosis

- Urine microscopy reveals **RBC casts** (see Figure 12.5).
- **Renal biopsy** is definitive.

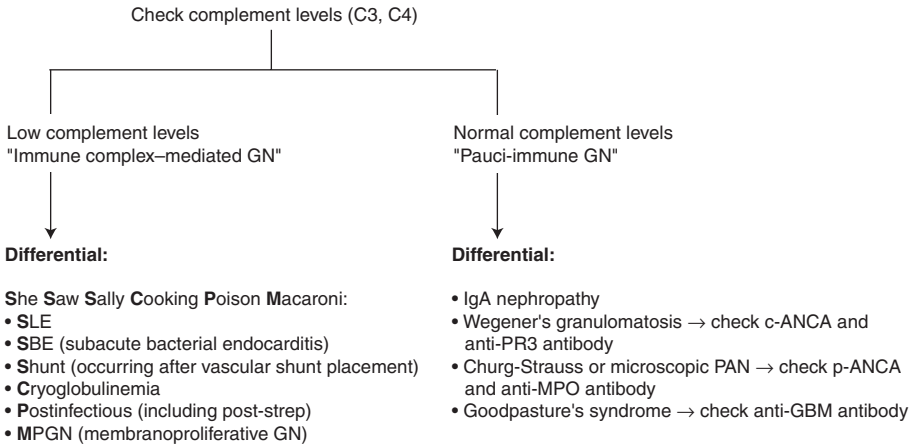


FIGURE 12.4. Differential diagnosis of glomerulonephritis.

TREATMENT

See Tables 12.8 and 12.9.

Nephrotic Syndrome

Diabetes mellitus is the most common systemic disease that results in nephrotic syndrome in U.S. adults. The most common pathologic subtypes of "idiopathic" nephrotic syndrome in adults are **membranous nephropathy (and focal segmental glomerulosclerosis among African-Americans).**

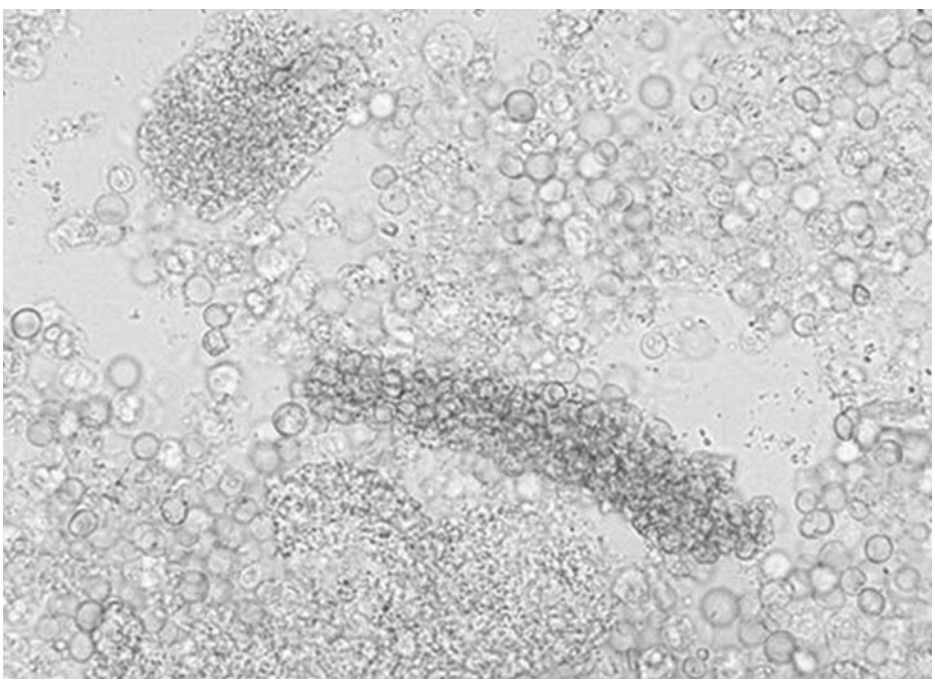


FIGURE 12.5. Red blood cell cast.

(Courtesy of R. Rodriguez.)

TABLE 12.8. Low-Complement Glomerulonephritis

Disease	Presentation	Diagnosis	Pathology	Treatment
SLE	Any of the 11 criteria for SLE (see the Rheumatology chapter). Lupus nephritis can be the presenting feature.	Anti-dsDNA, anti-Smith antibodies.	Can be proliferative or membranous alone.	Can use ACEIs/ARBs plus steroids and cyclophosphamide depending on severity. End-stage renal disease (ESRD) occurs in 8–15% of SLE patients.
Postinfectious	Occurs 2–3 weeks after pharyngitis or skin infection. Classically seen with streptococcal infections, but other infections may trigger GN as well.	Elevated ASO and anti-DNase B antibodies (for poststreptococcal GN).	Diffuse proliferative GN. Electron microscopy (EM) shows subepithelial "humps."	Renal failure typically resolves in six weeks. Only 5% of cases require dialysis acutely.
Membranoproliferative glomerulonephritis (MPGN)	**Cryoglobulin-related MPGN:** Arthralgias, palpable purpura, history of HCV infection. Microscopic hematuria with mild to heavy proteinuria. May be chronic or rapidly progressive.	⊕ cryoglobulins, RF. Check HBV, HCV, and HIV serologies.	Hypercellular glomerulus. EM reveals subendothelial deposits.	Treat HCV-related disease and cryoglobulinemia with α-interferon and ribavirin.
Endocarditis	Fevers, new heart murmur in a patient with a predisposition (e.g., abnormal heart valves, recent dental procedure, IV drug abuse).	Blood cultures, echocardiography.	May have renal impairment due to crescentic GN, cryoglobulinemia, ATN, or AIN.	Antibiotics. General rule: If endocarditis is cured, renal impairment will be cured.

Patients with nephrotic syndrome are hypercoagulable (and thus have an ↑ incidence of venous and arterial thrombi)

Symptoms/Exam

- **Four features comprise nephrotic syndrome:**
  - Anasarca/peripheral edema
  - Hypoalbuminemia (serum albumin < 3 g/dL)
  - Hyperlipidemia
  - Proteinuria > 3.5 g/day
- Additional features include hypercoagulability.

Differential

- **Idiopathic or 1° nephrotic syndrome:** Has four main pathologic subtypes (see Table 12.10).
- **2° to systemic disease:** Includes malignancy (classically lymphoma or myeloma), infections (HIV, HBV or HCV, syphilis, leprosy, malaria),

TABLE 12.9. Normal-Complement Glomerulonephritis

Disease	Presentation	Diagnosis	Pathology	Treatment	Clinical Course
IgA nephropathy	More common in Asians and Hispanics. Episodic hematuria with or without proteinuria (usually within 24 hours of URI).	Renal biopsy.	Normal or mesangial expansion. Immunofixation shows diffuse mesangial IgA immune deposits.	**All patients:** ACEIs. **If proteinuria < 3 g/day:** Fish oil. **If proteinuria > 3 g/day:** Steroids.	Twenty percent have progressive renal failure in 20 years. Ten to twenty percent progress to ESRD in 10 years. Worse prognosis with hypertension, elevated creatinine, or proteinuria.
Wegener's granulomatosis	Upper respiratory tract disease and nodular cutaneous lesions are more common. Rapidly progressive glomerulonephritis (RPGN).	c-ANCA and anti-proteinase 3 (PR3) antibody ⊕. Renal biopsy.	Segmental fibrinoid necrosis. Crescentic formation. Immunofluorescence (IF) ⊖.	Steroids with PO cyclophosphamide. Plasmapheresis.	Variable course depending on localized indolent vs. systemic fulminant presentation.
Microscopic polyarteritis nodosa (PAN)	Upper respiratory tract disease is less common. RPGN.	p-ANCA and antimyeloperoxidase (MPO) antibody ⊕. Renal biopsy.	As above.	Steroids with PO cyclophosphamide.	As above.
Churg-Strauss syndrome	Asthma and eosinophilia. Peripheral neuropathy is more common.	p-ANCA and anti-MPO antibody ⊕. Renal biopsy.	As above.	Steroids with PO cyclophosphamide.	Renal involvement is usually mild.
Goodpasture's syndrome	Pulmonary hemorrhage. RPGN.	Anti-GBM antibody ⊕. Renal biopsy.	Diffuse proliferative GN. Variable necrosis and crescent formation. IF linear deposition, IgG along GBM.	Steroids with PO cyclophosphamide. Plasmapheresis.	RPGN is associated with poor renal survival.

TABLE 12.10. 1° Causes of Nephrotic Syndrome

Disease	Presentation	Pathology	Treatment	Clinical Course
Minimal change disease	Sudden onset with heavy proteinuria. More common in children.	Normal light microscopy. EM shows epithelial foot process fusion.	Steroids.	Responds to steroids but often relapses. Renal failure is uncommon.
Focal segmental glomerulosclerosis	↑ frequency in African-Americans.	Focal segmental glomerulosclerosis.	Steroids, cyclosporin A; cyclophosphamide.	Higher frequency of ESRD compared to minimal change disease.
Membranous nephropathy	↑ frequency in Caucasians. Proteinuria with microhematuria. Predilection to clotting: renal vein thrombosis.	Thickened capillary loops with subepithelial "spikes." EM shows subepithelial deposits.	Observation if slow progression. Steroids alternating with either cyclophosphamide or chlorambucil.	Twenty-five percent spontaneously remit. Slow progression to renal failure.
MPGN	Can present with either nephritic or nephrotic features.	Hypercellular glomerulus with lobular architecture. EM shows subendothelial deposits.	**Non-nephrotic:** Observe. **Nephrotic or worsening renal function:** Steroids.	Fifty percent die or progress to ESRD within five years of renal biopsy.

Multiple myeloma may affect the kidney in many ways:

- *Cast nephropathy (most common): Due to light chains*
- *Amyloidosis → nephrotic syndrome*
- *Proximal tubule involvement → Fanconi's syndrome*
- *Hypercalcemia*
- *Hyperuricemia*
- *Hypovolemia*

amyloidosis, and a variety of others. See Table 12.11 for the most common causes.

- **Most common systemic diseases:** Diabetes, systemic amyloidosis.

Diagnosis

As above, plus the following:

- **UA:** In addition to proteinuria, oval fat bodies or "**Maltese crosses**" may be visualized under polarized light.
- A 24-hour urine protein is the best way to quantify the extent of proteinuria. Calculate the spot urine protein-creatinine ratio (divide spot protein over creatinine to approximate 24-hour protein excretion in grams).
- Renal biopsy is definitive.
- Additional labs to search for 2° causes include hemoglobin A_{1c}, SPEP/UPEP, and serologies for HBV, HCV, HIV, and syphilis.

Treatment

- **General measures:**
  - Control peripheral edema with loop diuretics.
  - Maintain good nutrition.

TABLE 12.11. 2° Causes of Nephrotic Syndrome

Disease	Presentation	Pathology	Treatment	Clinical Course	Notes
HIV-associated nephropathy	High viral load. Low CD4 count. Nephrotic-range proteinuria. No peripheral edema.	Focal segmental glomerulosclerosis. Large dilated microcysts. Interstitial inflammatory infiltrate.	Initiation of HAART. Steroids if there is evidence of interstitial nephritis.	If untreated, may progress to ESRD within a few months. ESRD patients have been known to come off dialysis with the initiation of HAART.	Most common in African-Americans and Hispanics. Kidneys are large and echogenic on renal ultrasound.
Diabetic nephropathy	Onset 5–10 years after diagnosis in type 1 DM; more variable in type 2.	Mesangial expansion. Kimmelstiel-Wilson nodule. Tubulointerstitial fibrosis.	Glycemic control. Target LDL < 100. Target BP < 130/80.	Progresses from hyperfiltration to microalbuminuria to nephrotic to ESRD.	The leading cause of ESRD in the United States. ACEIs are first-line agents for type 1 DM. ACEIs or ARBs are first-line agents for type 2 DM.
Multiple myeloma (light chain deposition disease)	More severe renal failure with cast nephropathy.	$\kappa > \lambda$ light chain involvement. Glomerular or tubulointerstitial Congo-red stain (–) deposits.	Melphalan and prednisone. Plasma exchange if light chains in serum.	Mean survival is 44 months if no cast nephropathy.	Monoclonal gammopathy on SPEP/UPEP. Light chains will not be detected by urine dipstick for protein.
AL amyloidosis	Twenty-five percent with overt multiple myeloma. More severe proteinuria. Less ARF.	$\lambda > \kappa$ light chain involvement. Glomerular or tubulointerstitial deposition. Congo-red stain (+) deposits.	Melphalan and prednisone.	Mean survival 4–13 months.	

- Give ACEIs to slow proteinuria.
- Lipid lowering—generally target an LDL < 100.

- **Treat the underlying disease.**

ESSENTIAL HYPERTENSION

See the section in the Ambulatory Medicine chapter.

2° HYPERTENSION

Comprises 5% of cases of hypertension.

Symptoms/Exam

Suspect 2° hypertension if:

- Age at onset of hypertension is < 30.
- Age at onset of hypertension is > 50.
- Rapid onset of severe hypertension in < 3–5 years.
- Hypertension is refractory to multiple medications.
- Hypokalemia is present.

Differential

- **Renal:** Renovascular disease, renal parenchymal disease, polycystic kidney disease, Liddle's syndrome, syndrome of apparent mineralocorticoid excess, hypercalcemia.
- **Endocrine:** Hyper- or hypothyroidism, 1° hyperaldosteronism, Cushing's syndrome, pheochromocytoma, congenital adrenal hyperplasia (see also the Endocrinology chapter).
- **Drugs:**
  - **Prescription:** Estrogen, cyclosporin A, steroids.
  - **OTC:** Pseudoephedrine, NSAIDs.
  - **Illicit:** Smoking, ethanol, cocaine.
- **Neurogenic:** ↑ ICP, spinal cord section.
- **Miscellaneous:** Aortic coarctation, obstructive sleep apnea, polycythemia vera.

Diagnosis

- History, including medications and illicit substance use; physical exam.
- See Table 12.12.

TABLE 12.12. Tests for the Evaluation of 2° Hypertension

Basic Tests	Special Screening Studies
TSH	**Renovascular disease:** ACEI radionuclide scan, renal duplex Doppler flow studies, or MRI angiography.
Hematocrit to screen for polycythemia vera	**Pheochromocytoma:** 24-hour urine assay for creatinine, metanephrines, and catecholamines, or plasma-free metanephrines and normetanephrines.
Serum potassium (low potassium suggests 1° aldosteronism)	**Cushing's syndrome:** Overnight dexamethasone suppression test or 24-hour urine cortisol and creatinine.
Serum creatinine and/or BUN for renal failure	**1° aldosteronism:** Plasma aldosterone-renin activity ratio.
CXR to look for coarctation	

Treatment

- Treat the underlying cause.
- See the Ambulatory Medicine chapter for a summary of antihypertensive medications.
- **Hypertensive emergency:** See the Hospital Medicine chapter.

Renovascular Hypertension

Diminished renal blood flow causes elevated renin and aldosterone levels, which eventually results in hypertension (see Table 12.13).

Symptoms/Exam

- Age at onset of hypertension is < 30 or > 50 years.
- Rapid onset of hypertension in < 3–5 years.
- Severe hypertension despite an appropriate three-drug regimen.
- Flash pulmonary edema.
- Hypokalemia.
- **Serum creatinine ↑ after initiation of ACEI treatment.**

Diagnosis

Imaging (duplex ultrasonography, MRA, CT angiography, angiography) reveals > 75% stenosis. Sensitivity and specificity are operator dependent.

Treatment

- **Medical therapy:** If BP control is adequate, it is **not** necessary to proceed with a revascularization procedure.
- **Percutaneous transluminal angioplasty (PTA):** Effective for fibromuscular dysplasia.
- **PTA/stent:** May be effective for atherosclerotic patients.
- **Surgical intervention:** The benefit is unclear.

CHRONIC KIDNEY DISEASE (CKD)

CKD is defined as permanent loss of renal function or evidence of renal injury (albuminuria) of > 3 months' duration. **End-stage renal disease (ESRD)**

TABLE 12.13. Causes of Renovascular Hypertension

	Atherosclerosis (More Common)	Fibromuscular Dysplasia
Affected gender	Men and women	Women
Age	> 50	15–40
Total occlusion	Common	Rare
Ischemic atrophy	Common	Rare
Angioplasty	Less amenable	Highly amenable
Cure rate	Poor	Good

is defined as permanent loss of renal function that requires renal replacement therapy; GFR < 15 cc/min.

Treatment

The treatment of risk factors associated with the progression of renal disease is as follows:

- **Proteinuria:**
  - The most important predictor of progression of renal disease.
  - **ACEIs/ARBs are beneficial for diabetic and nondiabetic nephropathies.**
- **Hypertension:**
  - Target BP < 130/80.
  - **First-line agents: ACEIs.**
  - **Second-line agents: Diuretics** are effective in BP control owing to ↑ Na^+ retention in CKD patients.
- **Lipids:** Target LDL < 100.
- **Smoking cessation.**
- **Nutrition:** Protein restriction is controversial.

Complications

Complications from CKD/ESRD should be managed as follows:

- **Anemia:**
  - Erythropoietin (EPO) injections (level of Hg controversial).
  - Replete iron stores if ferritin < 100 ng/mL or transferrin saturation (T_{sat}) < 20% (IV iron can be used in hemodialysis patients).
- **Renal osteodystrophy** (see Figure 12.6): Typically initiate phosphate control with calcium-based phosphate binder ($CaCO_3$ or calcium acetate). 1,25-OH vitamin D (calcitriol) may be used to control PTH.
- **Hyperkalemia:** Dietary restriction, diuretics.
- **Acidosis:**
  - $NaHCO_3$ supplementation to prevent ⊖ bone balance.
  - Titrate therapy by measuring 24-hour urine for citrate.
- **Pericarditis (can present as a rub, chest pain, or ECG abnormalities):** Initiate dialysis or ↑ dialysis dose.
- **Dialysis-related problems** include the following:
  - **Vascular catheter–related infections:**
    - *S. aureus* is the most likely cause, followed by coagulase-⊖ staphylococcus.
    - Empiric treatment with first-generation cephalosporin (IV); add vancomycin if there is a high local prevalence of methicillin-resistant *S. aureus* (MRSA).
    - Remove the catheter in the presence of a fungal infection, sepsis, endocarditis, or persistent bacteremia.
  - **Peritoneal catheter–associated peritonitis:**
    - *S. aureus*, *S. epidermidis*, and enteric gram-⊖ rods are the dominant organisms.
    - The first clues are a cloudy appearance to peritoneal fluid, fever, or abdominal pain.
    - Diagnose with Gram stain (> 100 WBCs in peritoneal fluid) and culture of peritoneal fluid.

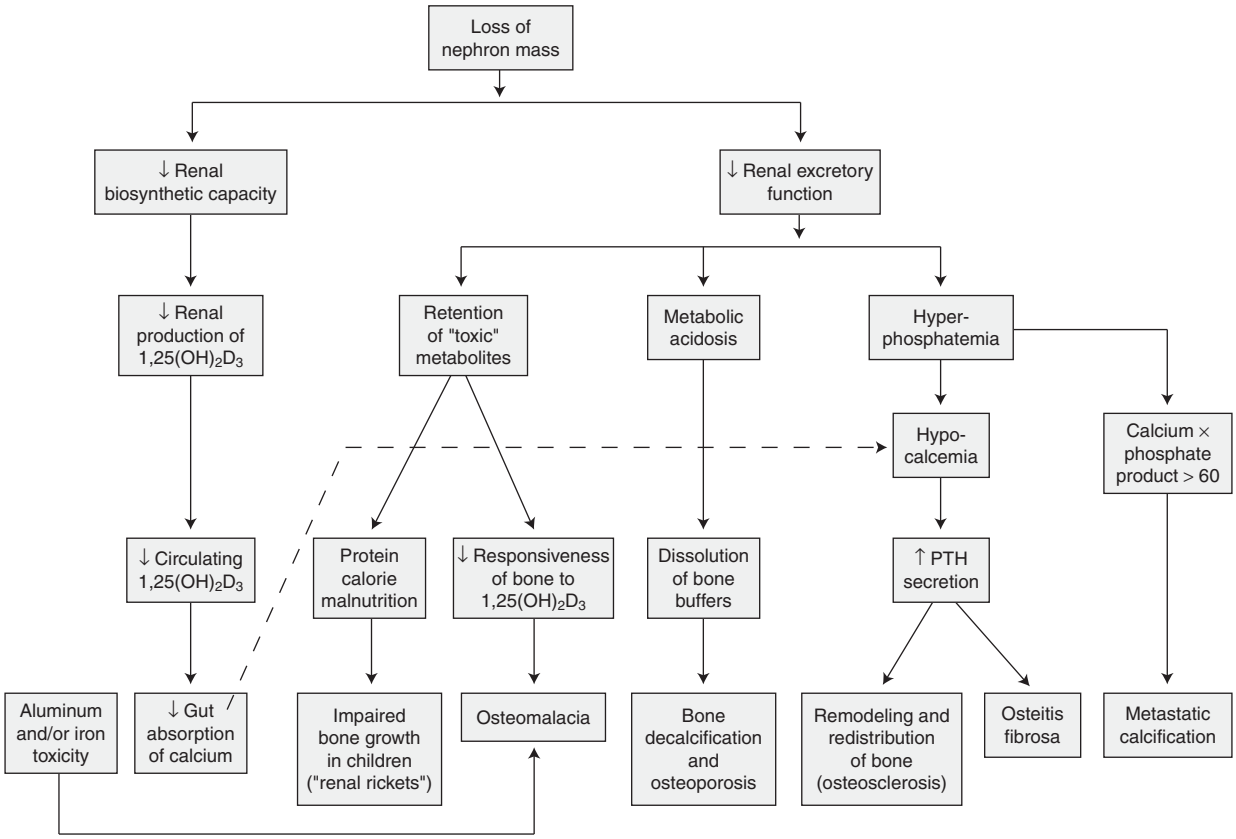


FIGURE 12.6. Pathogenesis of bone disease in chronic kidney disease.

(Reproduced, with permission, from Brenner BM, Lazarus JM. Chronic renal failure. In Wilson JD et al. *Harrison's Principles of Internal Medicine*, 12th ed. New York: McGraw-Hill, 1991.)

- Can often be treated with infusion of antibiotics into the peritoneum. For severe cases, add IV antibiotics and possibly catheter removal.
- If peritoneal culture grows fungus, anaerobes, or multiple organisms, suspect 2° peritonitis due to a perforated abdominal viscus.

GENETIC DISORDERS AND CONGENITAL DISEASES OF THE KIDNEY

Table 12.14 outlines genetic defects related to electrolyte balance. Table 12.15 presents the relationship of various genetic disorders to congenital diseases.

TABLE 12.14. Genetic Defects in Electrolyte Balance

Syndrome	Classic Defect	Presentation	Treatment
Bartter's syndrome	$Na^+/K^+/2Cl^-$ cotransporter, ROMK K^+ channel, CLCNKB Cl^- channel, or barttin (hypofunction).	Renal salt wasting. Hypokalemia, metabolic alkalosis, and normal serum magnesium. Normal/↓ BP. Childhood onset.	High-salt diet, K^+ repletion, NSAIDs.
Gitelman's syndrome	Na^+/Cl^- cotransporter (hypofunction).	Renal salt wasting. Hypokalemia, metabolic alkalosis, and severe hypomagnesemia. Normal/↓ BP.	K^+ and Mg^{2+} repletion, amiloride.
Pseudohypoaldosteronism, type 1, autosomal recessive	Epithelial Na^+ channel, β or γ subunits (hypofunction).	Renal salt wasting. Hyperkalemia, normal/↓ BP. ↑ serum aldosterone levels. Childhood onset.	High-salt diet.
Liddle's syndrome	Epithelial Na^+ channel, β or γ subunits (hyperfunction).	Renal salt retention. Hypokalemia, metabolic alkalosis, hypertension. ↓ serum aldosterone levels.	Amiloride.
Syndrome of apparent mineralocorticoid excess	11β-hydroxysteroid dehydrogenase 2 (failure to inactive cortisol).	Renal salt retention. Hypokalemia, metabolic alkalosis, hypertension. ↓ serum aldosterone levels.	Spironolactone, K^+-sparing diuretics, dexamethasone.

TABLE 12.15. Genetic Disorders and Congenital Diseases of the Kidney

Disease	Defect	Presentation	Diagnosis	Notes
Alport's syndrome	Type IV collagen of the GBM, cochlea, and lens.	**Hematuria:** Affects males and female carriers of X-linked Alport's syndrome; can worsen after URI. **ESRD:** Affects all males with X-linked Alport's syndrome; female carriers of X-linked Alport's syndrome do not have significant renal disease. Sensorineural deafness; ocular defects.	Renal biopsy showing a thickened GBM with splitting and splintering of the lamina densa on EM.	Renal transplantation. Reports of de novo Goodpasture's syndrome after renal transplantation due to exposure of type IV collagen from the allograft to the Alport's syndrome recipient.
Autosomal-dominant polycystic kidney disease (ADPKD)	PKD1 or polycystin-1; PKD2 or polycystin-2.	Kidney enlargement due to multiple cyst formation. Hypertension; mitral valve prolapse; polycystic liver disease. Intracranial aneurysms (familial clustering).	Family history of ADPKD. Renal ultrasound showing: ■ Two cysts with age < 30 years. ■ Two cysts in each kidney with age > 30–59 years. ■ Four cysts in each kidney with age > 60 years.	ACEIs or ARBs for hypertension. Renal transplantation for ESRD.
Medullary sponge kidney	A developmental abnormality characterized by dilated medullary and papillary collecting ducts, leading to a "spongy-looking" medulla.	Patients can be asymptomatic. Hematuria. Calcium oxalate or phosphate nephrolithiasis.	IVP. Retention of contrast media in the collecting ducts of the medulla, leading to a "bouquet of flowers" appearance.	Benign clinical course.
Thin basement membrane disease	Unclear.	Microhematuria. Proteinuria is rare.	Thin GBM on renal biopsy.	Benign clinical course, but there is a small risk for progression to kidney disease.

TABLE 12.15. Genetic Disorders and Congenital Diseases of the Kidney *(continued)*

Disease	Defect	Presentation	Diagnosis	Notes
Cystinuria (the classic aminoaciduria)	rBAT/b0,+AT transporter, leading to incomplete reabsorption of dibasic amino acids (**C**ystine, **O**rnithine, **L**ysine, and **A**rginine-**"COLA"**) in the proximal tubule of the nephron.	Cystine nephrolithiasis (cystine calculi are radiopaque on plain films).	24-hour urine collection for cystine and dibasic amino acids.	↓ urine cystine concentration < 300 mg/L. ↑ fluid intake. Tiopronin (forms a more soluble form of cystine through a mixed disulfide thiol-cystine complex).
Fabry's disease	α-galactosidase A (αGalA gene) leads to intracellular accumulation of neutral glycosphingolipids with terminal-linked galactosyl moieties.	Abnormal glycosphingolipid accumulation. ■ **Renal:** Moderate proteinuria by age 30, occasional microhematuria, gradual progression to ESRD. ■ **Cardiovascular:** CAD, CHF, arrhythmias. ■ **Autonomic dysfunction:** Hypohidrosis, acral paresthesias, altered intestinal mobility. ■ **Dermatologic:** Angiokeratomas.	Reduced αGalA levels in serum or urine. Renal biopsy shows glomeruli packed with clear vacuoles filled with glycosphingolipid deposits (myelin figures and zebra bodies).	Agalsidase β (Fabrazyme), renal transplantation.

CHAPTER 13

Neurology

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Basic Exam

The most important part of the workup of any neurologic disorder—and a critical part of any attempt to localize a lesion—is the history and physical exam. The history should focus on the following factors:

- **Symptom onset:**
  - **Acute onset (seconds to minutes):** Most likely caused by a **vascular event** (e.g., stroke), a **seizure,** or a complicated **migraine.**
  - **Subacute onset (hours to days):** More likely caused by **infectious processes, inflammatory diseases,** or **autoimmune disorders** (e.g., MS).
  - **Insidious onset (months to years):** More likely caused by slowly growing **structural lesions** (e.g., tumors) or **neurodegenerative disorders.**
- **Age/gender:** In young patients, especially women, consider **autoimmune processes** high on the differential. Neurodegenerative illnesses are more common in older patients.
- **Location of symptoms:** Classic symptoms of common neurologic disease processes by location are as follows:
  - **Myopathies (muscle): Symmetric proximal weakness** of all extremities.
  - **Neuromuscular junction: Fluctuating weakness** (eyes, proximal extremities) throughout the course of the day.
  - **Polyneuropathy: Symmetric distal sensory loss and weakness of all extremities,** often with ↓ or absent reflexes in affected areas.
  - **Myelopathy (spinal cord): Symmetric weakness of both legs or both arms and both legs, sparing the face, along with bowel and bladder** involvement.
  - **Brain stem: Cranial nerve deficits, double vision, dysarthria, dysphagia, nystagmus.**
  - **Visual pathway:** Distinguishing **monocular from binocular defects** is key to localization within the cerebral hemisphere and eyes (see Figure 13.1).

Coma Exam

The term *coma* refers to a condition in which patients are unresponsive, show no purposeful movement, and do not open their eyes to painful stimuli. It requires the impairment of either **both cerebral hemispheres** or the reticular activating system of the **brain stem.** Generally caused by one of three processes:

- A **structural** problem affecting the **brain stem** (e.g., mass effect with herniation, stroke).
- An **electrical** problem (ongoing seizure activity even if not clinically apparent—e.g., nonconvulsive status epilepticus).
- A **metabolic** process (e.g., anoxic brain injury, hepatic encephalopathy, severe electrolyte disturbances, infection).

Examination of brain stem reflexes differentiates the anatomic location of coma. If brain stem reflexes are abnormal, the lesion is in the brain stem.

Symptoms/Exam

- Evaluate brain stem function by checking cranial nerves—i.e., pupillary response to light; extraocular movements of the eyes to either turning the head side to side or placing cold water in one ear (should not be done if

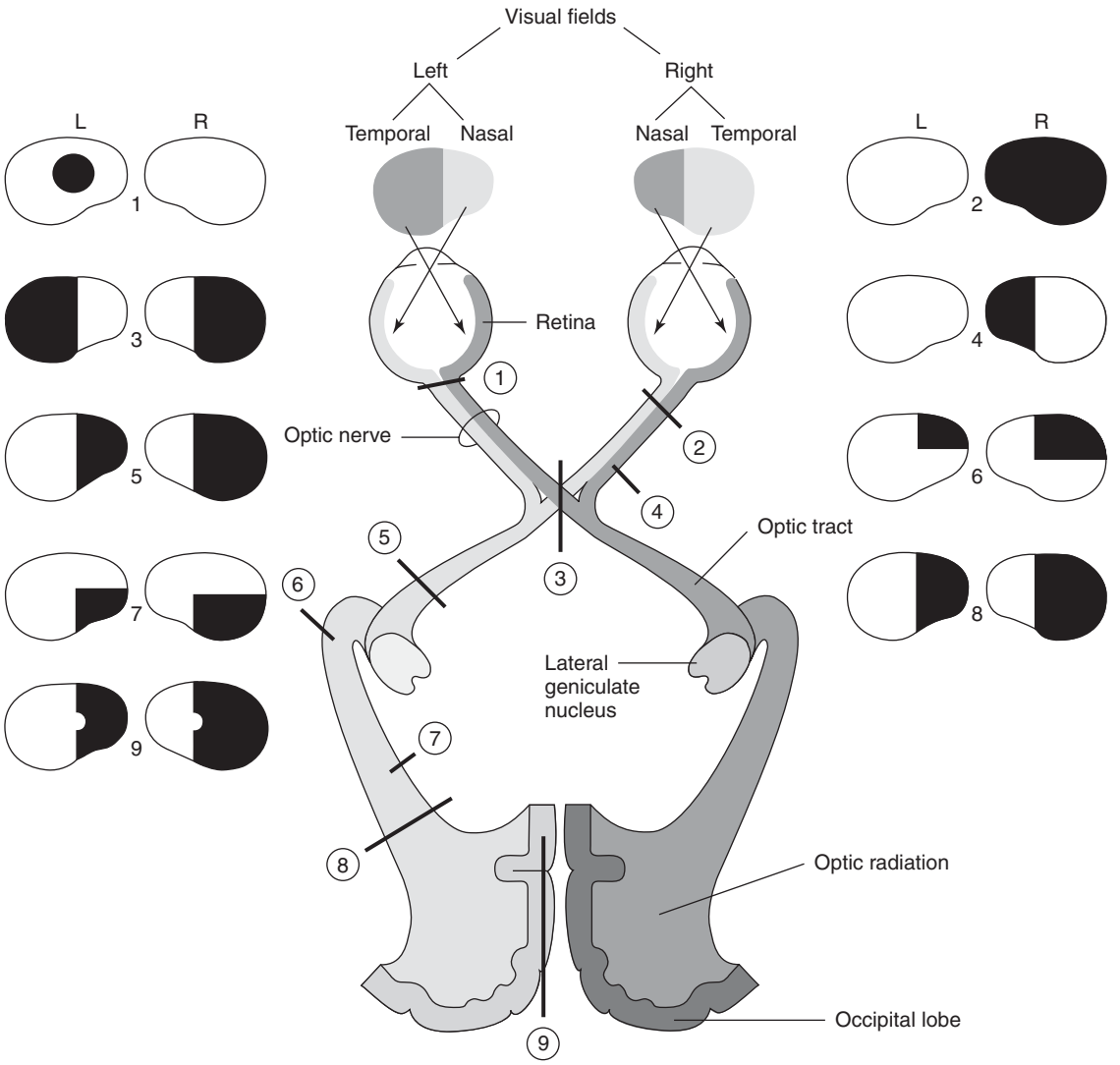


FIGURE 13.1. Common visual field defects and their anatomic bases.

1. **Central scotoma** caused by inflammation of the optic disk (optic neuritis) or optic nerve (retrobulbar neuritis). 2. **Total blindness of the right eye** from a complete lesion of the right optic nerve. 3. **Bitemporal hemianopia** caused by pressure exerted on the optic chiasm by a pituitary tumor. 4. **Right nasal hemianopia** caused by a perichiasmal lesion (e.g., calcified internal carotid artery). 5. **Right homonymous hemianopia** from a lesion of the left optic tract. 6. **Right homonymous superior quadrantanopia** caused by partial involvement of the optic radiation by a lesion in the left temporal lobe (Meyer's loop). 7. **Right homonymous inferior quadrantanopia** caused by partial involvement of the optic radiation by a lesion in the left parietal lobe. 8 and 9. **Right homonymous hemianopia** from a complete lesion of the left optic radiation with or without macular sparing resulting from a lesion such as a posterior cerebral artery occlusion. (Reproduced, with permission, from Aminoff MJ et al. *Clinical Neurology*, 6th ed. New York: McGraw-Hill, 2005, Figure 4-7.)

the status of cervical spine stability is unknown); corneal reflexes; gag reflex; cough reflex; and spontaneous respirations.

- Motor response to central and peripheral pain is also critical, as asymmetric responses suggest a focal intracranial lesion.
- Patients with coma caused by a structural problem generally have **abnormal brain stem reflexes,** as their coma is caused by direct compression of the brain stem.

- Patients with metabolic or electrical coma typically have intact brain stem reflexes.

Diagnosis/Treatment

- Focus on correctable problems, including easily detectable metabolic disorders (e.g., hypoglycemia, drug overdose, electrolyte abnormalities, uremia, liver failure) and structural problems (e.g., subdural hematoma). Patients need urgent imaging of the brain as well as basic laboratory workup.
- Patients with unexplained coma should also have an EEG to rule out nonconvulsive status epilepticus as well as CSF studies to rule out infectious causes of encephalopathy.

NEURODIAGNOSTIC TESTING

Lumbar Puncture (LP)

A tool used for the measurement of CSF pressure, for CSF analysis, and occasionally for therapeutic removal of CSF.

- Most often performed in the L3 or L4 interspaces (at the level of the superior iliac crests). The needle is advanced to the subarachnoid space.
- Opening pressure should be measured but is valid only when obtained with the patient in the lateral decubitus position (i.e., with the spinal needle located at the same level as the heart).
- Patients with papilledema, focal neurologic signs, or immunosuppression should have imaging prior to LP to evaluate for mass effect and herniation risk. Imaging of the spine should precede LP in patients with spinal cord signs or symptoms.

Electroencephalography (EEG)

A tool for the investigation of seizure disorders, unexplained coma, metabolic encephalopathies, viral encephalitis, prion diseases, anoxic brain injury, and sleep disorders. Conditions with notable EEG findings include the following:

- **Metabolic encephalopathy:** Hepatic encephalopathy is the classic metabolic coma. EEG typically shows generalized periodic triphasic waves.
- **Viral encephalitis:**
  - **HSV encephalitis:** The classic EEG finding consists of periodic lateralizing epileptiform discharges (PLEDs) originating over one or both temporal lobes.
  - **Subacute sclerosing panencephalitis (SSPE):** EEG typically shows a flat background punctuated by periodic generalized large-amplitude slow-wave discharges.
- **Prion disease:** EEGs in patients with Creutzfeldt-Jakob disease show periodic generalized sharp waves.

Computed Tomography (CT)

CT imaging of the brain is inferior to MRI for most studies but is the imaging study of choice for investigating **acute hemorrhage** (e.g., SAH, epidural hematoma) and **bone pathology** (e.g., skull or vertebral fractures).

CT is often used in patients with contraindications to MRI such as pacemakers and implanted defibrillators.

Magnetic Resonance Imaging (MRI)

The best imaging modality for most diseases of the brain and spinal cord, including neoplastic, vascular, demyelinating, infectious, and structural diseases (e.g., spondylosis of the spine).

Cerebral Angiography

The gold standard for investigating vascular abnormalities of the CNS, including stenosis, aneurysms, AVMs, and cerebral vasculitis. Also useful for preoperative evaluation of vascular supply to intracranial tumors (e.g., meningiomas). Cerebral **venography** is the gold standard for diagnosing venous sinus thrombosis.

Electromyography/Nerve Conduction Studies (EMG/NCS)

- EMGs examine spontaneous and voluntary muscle activity by using a needle electrode placed directly into the muscle. They are useful for studying and differentiating radiculopathies (spinal root injuries), motor neuron disease, neuropathies, neuromuscular junction diseases, and myopathies.
- NCSs are obtained by stimulating peripheral nerves and recording either sensory or motor responses along the course of the nerve.

Evoked Potentials (EPs)

Obtained by measuring the time course of a specific CNS response to a given stimulus.

- **Visual EPs** are generated by recording cortical response (using EEG electrodes) elicited by a visual stimulus. A delay in response suggests that the conduction velocity along the visual pathway is slow, often a sign of demyelination (e.g., in **MS**).
- **Brain stem and sensory EPs** are useful for evaluating potential demyelinating lesions of the brain stem and dorsal columns of the spinal cord. Often used to obtain supportive evidence of CNS demyelination.
- **Sensory and motor EPs** are used for intraoperative monitoring during neurosurgical procedures involving the spinal cord or brain stem and can be helpful prognostically in hypoxic-ischemic encephalopathy.

HEADACHE

- All patients presenting with headache merit a detailed history and neurologic evaluation, including a funduscopic exam for papilledema.
- **Sx/Exam:** The following findings in patients with headache should prompt further investigation (e.g., imaging, basic labs, LP):
  - Abrupt-onset, severe headache; progressive, persistent headache; visual complaints; fever; jaw claudication; exacerbation by maneuvers that ↑ ICP (e.g., Valsalva, cough); onset after age 40–50; a history of malignancy; awakening from sleep.
  - Focal neurologic deficits, papilledema, meningeal signs, scalp tenderness.
- **Dx:** Disorders to remember when evaluating a patient with headache include SAH, temporal arteritis, venous sinus thrombosis, pseudotumor cerebri (intracranial hypertension), intracranial hypotension, meningitis/encephalitis, and brain tumor.

Migraine Headache

Roughly 10–20% of the U.S. population have experienced migraine headaches, with 80% beginning before age 30. Most patients are **young women** (the female-to-male ratio is 3:1). Ninety percent of patients have a strong family history.

Symptoms

- **Benign, recurrent headaches** that classically produce **unilateral pulsating pain** associated with symptoms such as **photophobia,** phonophobia, anorexia, **nausea,** and vomiting.
- Episodes typically last 4–72 hours, and patients often report improvement with resting in a **dark, quiet room.**
- Subtypes are as follows:
  - **Classic migraine (migraine with aura):** Occurs in 20% of patients. The most common auras are **visual,** including "fortification spectra" and scotomas (blind spots).
  - **Common migraine:** Most migraine patients do not have preceding auras.
  - **Migraine variants:** Named for associated focal neurologic deficits and/or vascular territories; include hemiplegic migraine, basilar migraine (brain stem symptoms such as ataxia, vertigo, and slurred speech), and ophthalmoplegic migraine (unilateral CN III palsy and pupillary abnormality).

Exam

- Patients with classic and common migraines have **normal neurologic exams.**
- In patients with headache and focal neurologic deficits, a migraine variant remains a diagnosis of exclusion. These patients require workup for other causes of headache and focal deficits (e.g., vascular event, infection, intracranial mass).

Tension headache is usually a nonthrobbing, bilateral head pain that is not usually associated with nausea, vomiting, or prodromal visual disturbances.

Differential

Other headache syndromes, including tension and cluster headache.

Diagnosis

Based on the history, with a focus on the exact character of the headaches as well as the presence of a strong family history.

Treatment

- Management is divided into two categories: **abortive therapy** for the migraine itself (taken only at the time of the migraine) and **prophylactic therapy** for preventing future attacks (taken daily).
- Prophylactic therapy is given only to patients with frequent severe migraines and includes **TCAs** (e.g., amitriptyline), β-blockers (e.g., propranolol), calcium channel blockers (e.g., verapamil), and **antiseizure medications** (e.g., valproic acid, topiramate). **Abortive therapy** includes the following:
  - **Vasoconstrictors:**
    - **Triptans:** 5-HT_1 serotonin receptor agonists (e.g., sumatriptan, frovatriptan, eletriptan, naratriptan, almotriptan, rizatriptan, zolmitriptan) produce vasoconstriction. **Do not use** in patients with

vascular disease (e.g., CAD, peripheral vascular disease) or in pregnant women.
    - **Ergotamines:** Also to be avoided in patients with vascular disease and in pregnant women.
- **Others:**
    - **Acetaminophen/butalbital/caffeine** (Fioricet): Butalbital is a barbiturate and has addictive properties.
    - **Isometheptene/dichloralphenazone/acetaminophen** (Midrin): Avoid in patients taking MAOIs.
    - **Antiemetics:** Prochlorperazine, promethazine.

Cluster Headache

Classically occurs in **young men** 20–40 years of age (the male-to-female ratio is 5:1). A family history of similar headaches is uncommon.

Symptoms

- The cardinal feature is **periodicity.** Headaches occur **many times daily** at **distinct times** over several weeks; onset with sleep is especially characteristic.
- Clusters spontaneously remit for months to years before recurring, typically at the same time of year as previous attacks. **Alcohol** is a classic trigger.
- Cluster headaches do not have auras (vs. migraines). A typical attack is characterized by abrupt-onset, severe **unilateral periorbital pain** with associated **ipsilateral autonomic symptoms** (tearing of the eye and nares; rarely Horner's). Headaches typically last 30–120 minutes.

Exam

- Patients are restless and agitated, often pacing the room (vs. migraine patients).
- Look for tearing, nasal discharge, and/or ptosis (e.g., **Horner's**) ipsilateral to the location of eye pain.

Differential

Other headache syndromes, including migraine (see Table 13.1) and **chronic paroxysmal hemicrania,** which has similar symptoms, but with multiple (20–40) daily attacks lasting 5–10 minutes each and no periodicity (exquisitely sensitive to **indomethacin**).

Treatment

- As with migraines, treatment includes abortive and prophylactic therapies.
- **Prophylactic** medications are started once cluster headaches begin but are not used during remissions given that months to years may elapse between clusters. Such medications include **verapamil** (first-line prophylactic treatment for cluster headache), **prednisone** (a taper of oral steroids is often used at the beginning of a cluster), lithium, valproate, and methysergide.
- **Abortive therapy** includes the following:
    - **O_2 inhalation:** Give 5–10 L/min for 10–15 minutes.
    - **Intranasal lidocaine ointment:** Produces a block of the sphenopalatine ganglion and aborts the headache.
    - **Triptans:** Also useful for acute attacks.

TABLE 13.1. Cluster Headache vs. Migraine

	MIGRAINE	CLUSTER HEADACHE
Typical patient	Young woman	Young man
Triggered by alcohol	No	Yes
Periodicity	No	Yes
Aura	Yes (with classic form)	No
Autonomic symptoms	No	Yes
Response to O_2	No	Yes

Trigeminal Neuralgia (Tic Douloureux)

A **unilateral** facial pain syndrome affecting middle-aged and elderly patients. Most commonly occurs in the sixth decade. Onset in young patients should raise suspicion for an underlying disorder (e.g., MS, brain stem neoplasm).

Symptoms

Characterized by abrupt-onset, short-duration (seconds) episodes of severe **unilateral lancinating electrical pain,** typically **radiating along the jaw** in the distribution of the second and third divisions of CN V (the trigeminal nerve). Attacks are often **triggered by sensory stimuli** to the face (e.g., touch, wind, shaving, chewing).

Exam

Neurologic exam is **normal.** Any abnormalities on exam, including sensory loss of the face in the distribution of the pain, suggests an alternative diagnosis and mandates further evaluation (e.g., imaging, LP).

Differential

Cluster headache, chronic paroxysmal hemicrania, dental abscess, internal jugular thrombophlebitis. Distinguishable by history and physical.

Treatment

Carbamazepine is first-line therapy. Alternatives include oxcarbazepine, valproate, phenytoin, baclofen, gabapentin, and benzodiazepines.

Idiopathic Intracranial Hypertension (Pseudotumor Cerebri)

A headache syndrome related to chronically elevated ICP. Classically seen in **young, obese women.** Associations have been noted with medications such as tetracycline derivatives, steroids, and vitamin A as well as with disorders such as SLE, Behçet's syndrome, and uremia.

Symptoms

- Patients usually note a progressive **global headache** that worsens when they lie flat, often worsening at night and **upon awakening.**

The term papilledema *signifies optic disk edema resulting from raised intracranial pressure.*

- Exacerbated by maneuvers that elevate ICP (e.g., Valsalva, cough, sneeze).
- Elevated ICP can produce **transient visual obscurations** (blurring or blackout of vision in either or both eyes for seconds), double vision from CN VI palsies, and/or progressive loss of peripheral vision. Total blindness can result.

Exam

Papilledema is the key finding (see Figure 13.2). Patients may also have ↓ visual acuity and/or **loss of peripheral vision.** CN VI palsies may result from elevated ICP.

Differential

Intracranial mass, venous sinus thrombosis, migraine variant (see Table 13.2).

Diagnosis

- Patients with headache and papilledema should first undergo **brain imaging,** preferably with MRI. In patients with pseudotumor, MRI is normal, including ventricular size.
- **MR venography** to exclude venous sinus thrombosis.
- **LP** should be performed with the patient in the lateral decubitus position, with pressure measured after the patient's legs are extended and relaxed. LP reveals an **opening pressure > 200 mm H_2O,** normal protein and glucose, and no cells.

Treatment

- Based on lowering ICP. **Acetazolamide,** a carbonic anhydrase inhibitor that reduces CSF production and ICP, is first-line therapy. Lasix can also be used.
- Serial LPs, optic nerve fenestration, and permanent shunting of CSF are used for refractory cases.
- **Weight loss** is an important component of management in most patients.
- Serial **ophthalmologic evaluation** is mandatory for these patients, as visual loss can be severe and permanent.

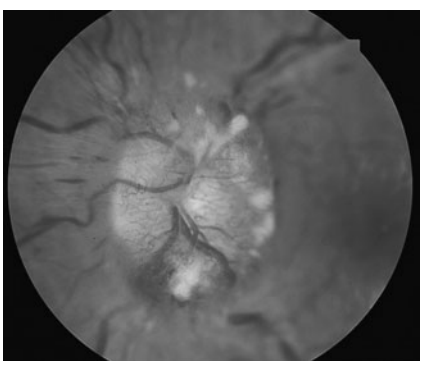


FIGURE 13.2. Papilledema.

This obese young women with pseudotumor cerebri was misdiagnosed as a migraineur until fundus examination was performed showing optic disk elevation, hemorrhages, and cotton-wool spots. (Reproduced, with permission, from Kasper DL et al. *Harrison's Principles of Internal Medicine,* 16th ed. New York: McGraw-Hill, 2005: 169.)

TABLE 13.2. Classic Case Presentations of the Various Headache Syndromes

Migraine	Cluster Headache	Trigeminal Neuralgia	Pseudotumor Cerebri
■ A 25-year-old woman resting uncomfortably in a dark, quiet room complains of unilateral head pain associated with nausea and photophobia. ■ The headache was preceded by an aura of flashing colored lights.	■ A 32-year-old man pacing the ER has severe unilateral periorbital pain associated with tearing of the ipsilateral eye and nose. ■ He has had three attacks per day over the past week, each occurring at the exact same time every day and lasting 20–40 minutes each. ■ The headache began after the patient drank alcohol at a party.	■ A 58-year-old woman presents with attacks of brief, unilateral, severe electrical sensations radiating along the jaw.	■ A 22-year-old obese woman presents with a two-month history of progressive headaches. ■ The headaches were initially associated with intermittent blurry vision but are now accompanied by a progressive ↓ in visual acuity.

Medication Rebound Headache

Overuse of analgesic medications for headache syndromes (e.g., narcotics, triptans, ergotamines, barbiturates) can paradoxically produce refractory chronic daily headaches. Prophylactic medications are ineffective until patients have been weaned off the offending analgesic medications. Often requires a slow taper of the analgesic to prevent withdrawal symptoms.

CEREBROVASCULAR DISEASE

Approximately 85% of strokes are ischemic (due to occlusion of arterial flow), with the remaining 15% caused by hemorrhage either in or around the brain (due to rupture of cerebral arteries or veins).

- A **stroke** is characterized by acute-onset focal neurologic deficits due to disruption of blood flow (by either occlusion or rupture) to a given area of the brain. By traditional definition, the neurologic deficits last > 24 hours. The residual deficit is related to underlying infarction of the brain.
- A **transient ischemic attack (TIA)** is fundamentally similar to stroke, but by traditional definition the deficits resolve within 24 hours. (In the overwhelming majority of TIAs, the deficits actually resolve in < 1 hour.) In TIAs, a region of the brain is briefly ischemic, but flow is restored before permanent infarction occurs.

The differential of an acute-onset focal neurologic deficit includes stroke, seizure, and complicated migraine.

The nature of the focal neurologic deficits caused by strokes depends on the vascular territory involved and the region of the brain supplied. Such deficits can first be divided into anterior or posterior circulation symptoms.

- **Anterior circulation** (see Table 13.3): Arise from the **internal carotid artery (ICA)** and include the **ophthalmic artery,** the **anterior cerebral artery (ACA),** and the **middle cerebral artery (MCA).**
- **Posterior circulation** (see Table 13.4):

TABLE 13.3. Strokes Affecting the Anterior Circulation

Affected Area	Signs/Symptoms
Ophthalmic artery	Ipsilateral monocular vision loss (amaurosis fugax).
ACA	Contralateral leg weakness and sensory loss.
MCA	**Dominant hemisphere:** Aphasia, contralateral face/arm weakness and sensory loss. **Nondominant hemisphere:** Contralateral face/arm weakness and sensory loss, homonymous hemianopia.

Amaurosis fugax = a TIA of the eye.

- Arise from **both vertebral arteries** as they travel up along the upper cervical spinal cord and fuse to form the **basilar artery.** The basilar artery travels along the brain stem, ultimately dividing into the **two posterior cerebral arteries (PCAs)** that supply the occipital lobes.
- Three large pairs of arteries come off the vertebrobasilar system to supply the cerebellum: the **anterior inferior cerebellar arteries (AICA), posterior inferior cerebellar arteries (PICA),** and **superior cerebellar arteries (SCA).** Small perforating arterioles coming directly off the basilar artery provide vital supply to the brain stem.

Ischemic Stroke

Caused by occlusion of arterial blood flow to the brain, which in turn is caused by either **extracranial embolism** of clot to the large intracranial vessels or **progressive thrombosis** of small intracranial arterioles.

Embolic Stroke

Occurs when an extracranial thrombus dislodges and embolizes to and occludes one of the large intracranial vessels (ophthalmic, ACA, MCA, PCA, vertebral, basilar, AICA, PICA, or SCA). Emboli most commonly arise from atherosclerotic plaques of the extracranial **ICA** (artery-to-artery emboli) or from the **heart.** Common sources include the following:

- **Atrial fibrillation (AF),** with clot arising in the left atrial appendage.
- **Valvular disease** (e.g., endocarditis, prosthetic valves) is also associated with cardiogenic emboli.
- Patients with severe left ventricular dysfunction and regional wall motion abnormalities following MI can form **ventricular thrombi** that embolize.

TABLE 13.4. Strokes Affecting the Posterior Circulation

Affected Area	Signs/Symptoms
PCA	Contralateral visual field deficits (homonymous hemianopia).
Cerebellum	Vertigo, nystagmus, nausea, vomiting, ipsilateral incoordination.
Brain stem	Double vision, vertigo, nausea, vomiting, and cranial nerve deficits.

- Severe atheromatous disease of the proximal **aortic arch** can also generate cerebrovascular emboli.
- **Paradoxical emboli** can arise from right-to-left shunting of venous thrombi and emboli across an atrial septal defect.

Exam

Patients with embolic stroke need aggressive investigation of the potential embolic source to determine if specific intervention is warranted. Key points to direct workup are as follows:

- An embolic stroke involving the posterior circulation (cerebellum, brain stem, occipital lobes) is not caused by ICA emboli.
- **Amaurosis fugax** (acute transient monocular vision loss) is most commonly caused by cholesterol emboli from an atherosclerotic plaque of the **ipsilateral ICA.**
- Embolic strokes involving the anterior circulation (ACA or MCA) can be 2° to either internal carotid emboli or cardiogenic emboli.

Diagnosis

- **Imaging studies** are as follows:
  - **Brain:** A head CT is the initial study of choice for acute stroke, primarily to evaluate for intracranial hemorrhage. MRI is best for characterizing the location and size of ischemic strokes.
  - **Internal carotid:** Use Doppler ultrasound, CTA, or MRA of the extracranial carotid arteries to evaluate for significant stenosis (> 70%).
  - **Heart:** Transesophageal echocardiography (TEE) is superior to transthoracic echocardiography (TTE) for evaluating potential cardiac sources of emboli.
- Other important studies include the following:
  - **ECG:** The initial screening test for cardiac arrhythmias, especially AF or flutter.
  - **Cardiac telemetry:** Monitoring patients on continuous cardiac telemetry for 24–48 hours can help detect paroxysmal AF.
  - Patients < 50 years of age with unexplained embolic stroke should be evaluated for underlying hypercoagulable states (e.g., antiphospholipid syndrome, antithrombin III, protein S and C deficiency, factor V Leiden mutation).

Think brain stem lesion if there are crossed symptoms such as a cranial nerve deficit with contralateral weakness.

Treatment

Specific treatments to ↓ the risk of recurrent embolic strokes are as follows:

- **Symptomatic internal carotid stenosis:** Patients with embolic stroke involving the anterior circulation who are found to have **> 70% stenosis** of the ipsilateral ICA benefit from **carotid endarterectomy. Carotid stenting** is another less proven alternative.
- **Atrial fibrillation:** Warfarin therapy with a goal INR of 2–3 is the optimal treatment for patients with paroxysmal or chronic AF.
- **Cardiogenic emboli:** In practice, specific identifiable cardiac sources (e.g., left ventricular thrombus) are typically treated with warfarin for 4–6 months.
- **Cryptogenic embolic stroke:** In embolic stroke patients for whom no clear source is identified, antiplatelet medications are the treatment of choice to prevent recurrent strokes.

Thrombotic Stroke

Occurs when a small cerebral artery gradually occludes 2° to progressive local thrombosis. The classic vessels involved are the small penetrating terminal arterioles that supply the **brain stem** and the **deep structures of the cerebral hemispheres,** including the basal ganglia, thalami, and internal capsule.

- The internal capsule is of particular importance in that it contains the **descending motor fibers** from the motor cortex as they travel toward the brain stem and spinal cord. Occlusion of these small arterioles produces a discrete "**lacunar**" **infarct** of the small area of brain supplied by the terminal arteriole.
- Lacunar infarcts typically occur in vital structures (e.g., brain stem, internal capsule) and, despite their small size, can have devastating effects. The four classic "lacunar" strokes are as follows:
  - **Pure motor hemiparesis:** Presents with isolated weakness of the face, arm, and leg on one side of the body. Sensation is normal, and no "cortical signs" (e.g., aphasia, visual field deficits) are present.
  - **Dysarthria–clumsy hand syndrome:** Essentially a variant of pure motor hemiparesis, with isolated slurred speech and unilateral hand weakness and incoordination.
  - **Ataxia hemiparesis:** Patients have mild weakness of the face, arm, and leg on one side associated with marked ataxia of the same side of the body.
  - **Pure sensory loss:** Patients have complete loss of sensation on one side of the body.
  - **Other lacunar strokes:** The "named" brain stem strokes (e.g., Wallenberg's; see Table 13.5) are typically caused by a small vessel lacunar stroke from thrombosis.

Diagnosis

Imaging studies, particularly with MRI, are key in demonstrating strokes caused by small vessel thrombosis. This can limit the necessary workup (e.g., there is no need to pursue aggressive diagnostic tests for an embolic source) and focus treatment (e.g., warfarin therapy is not appropriate treatment for small vessel thrombotic strokes).

Treatment

- The 1° **risk factors** for small vessel thrombotic strokes are **hypertension, diabetes, hyperlipidemia,** and **smoking.** Prevention of small vessel throm-

TABLE 13.5. Specific Brain Stem Strokes

Name	Location	Symptoms
Wallenberg's syndrome	Lateral medulla	Ipsilateral loss of pain and temperature on the face. Contralateral loss of pain and temperature on the body. Ipsilateral Horner's, vertigo, slurred speech.
"Locked-in" syndrome	Pons	Intact mental status; quadriparesis; patients are able to do no more than move eyes up and blink.
Weber syndrome	Midbrain	Ipsilateral CN III palsy; contralateral hemiparesis.

botic ischemic strokes rests primarily on aggressive control of these risk factors.
- Antiplatelet therapy reduces the risk of recurrent strokes in this patient population; choices include aspirin, clopidogrel, and ASA/dipyridamole.
- **Acute management of ischemic stroke** is as follows:
  - Only patients with acute ischemic stroke symptoms of < 3 hours' duration can receive IV thrombolysis with tPA. Other exclusions for tPA include coagulopathy (INR > 1.7), thrombocytopenia (platelets < 100,000), uncontrolled hypertension (SBP > 185), and prior intracranial hemorrhage. The 1° risk of tPA treatment is intracranial hemorrhage.
  - Use of IV heparin in patients with ischemic stroke who do not qualify for tPA remains controversial. Available data suggest that antiplatelet therapy is the most appropriate treatment for this patient population. Heparin is more commonly used in arterial dissection.

Hemorrhagic Stroke

Caused by rupture of blood vessels within the brain parenchyma. As with ischemic stroke, focal symptoms depend on the location of the hemorrhage. In contrast to ischemic stroke, intraparenchymal hemorrhages are usually associated with **headache** and rapid **deterioration in level of consciousness.**

- The leading cause of hemorrhagic strokes is **hypertension. Hypertensive hemorrhages classically occur in four subcortical structures: the basal ganglia, thalamus, cerebellum, and pons (part of the brain stem).**
- Intraparenchymal hemorrhages occurring within the cortical white matter (so-called **lobar hemorrhages**) can be caused by hypertension but raise suspicion for other etiologies, such as metastatic lesions, vascular abnormalities (e.g., AVMs), hemorrhagic conversion of an ischemic stroke, infections (especially septic emboli), and cerebral amyloid angiopathy.

Treatment

Largely supportive. **Cerebellar hemorrhages** should be considered a neurosurgical emergency, as swelling and herniation onto the brain stem can be lethal. In the case of most other locations of intracerebral hemorrhage, evidence does not support urgent evacuation.

Extraparenchymal Bleeds

The three types of extraparenchymal intracranial hemorrhages are **epidural, subdural,** and **subarachnoid.** The most common cause of all extraparenchymal intracranial hemorrhages is **head trauma.**

Epidural Hematomas

- Typically caused by trauma to the side of the head, usually near the ear, resulting in injury to the **middle meningeal artery** (MMA). The MMA runs between the skull and the dura, and injury thus produces bleeding into the epidural space. Such hematomas can expand rapidly, as they are produced by **arterial bleeding.**
- **Sx/Exam:** Although seen in < 25% of patients, the classic presentation is that of head trauma with brief (seconds to minutes) loss of consciousness

followed by a "lucid period" in which mental status and level of alertness are normal for minutes to hours. Followed by a rapid decline in mental status.
- **Dx:** Since the dura is tacked down to the skull at the suture lines, epidural bleeds will tamponade in a confined space and will not cross the sutures, leading to the characteristic "lens-shaped" hematoma on CT scan.
- **Tx:** Symptomatic epidural hematomas must be treated with urgent neurosurgical decompression.

Subdural Hematomas

- Typically caused by head trauma that leads to a rapid deceleration of the skull (e.g., car accident) and subsequent shearing of the cerebral bridging veins as they travel through the subdural space into the draining venous sinuses. Most often seen in **elderly** who have **falls.** Spontaneous subdural hematomas may also occur, particularly in patients with underlying coagulopathy or thrombocytopenia.
- **Sx/Exam:** Can produce mass effect, which typically manifests as a progressive decline in mental status.
- **Dx:** Head CT reveals hematoma layering along the outer surface of the cerebral cortex. Must be in the differential of any elderly patient with dementia.
- **Tx:** As with epidural hematomas, symptomatic subdural hematomas require neurosurgical decompression.

Subarachnoid Hemorrhage (SAH)

Within the first 72 hours, up to 10% of SAHs are not seen on CT, underscoring the importance of lumbar puncture following imaging if the diagnosis is suspected. After 72 hours, the rate of ⊖ CT scans ↑ substantially.

- The most common cause of nontraumatic SAH is a **ruptured intracranial aneurysm.**
- **Sx/Exam:** Patients experience abrupt-onset severe headache (**"the worst headache of my life"** or "thunderclap" headache) often associated with nausea and vomiting. There may also be a ↓ level of consciousness and focal neurologic deficits.
- **Dx:**
  - **Head CT** is the initial imaging study of choice. If CT is ⊖, perform an **LP** to look for **xanthochromia.**
  - Patients with a confirmed SAH should then have conventional **cerebral angiography** to determine the presence, location, and anatomy of the aneurysm.
- **Tx:** The first priority is to secure the aneurysm as soon as possible, as the risk of rebleeding is significant in the first 48 hours. Currently, aneurysms are treated with either **neurosurgical clipping** or **endovascular coiling.**
- **Cx:**
  - The major complications following SAH are related to **vasospasm** of the cerebral vessels. **Nimodipine** reduces complications from vasospasm and is given to all patients with SAH. Vasospasm is also treated with **"triple-H therapy"** (hypertension, hypervolemia, and hemodilution) in an effort to augment blood flow in areas of vasospasm.
  - Other complications include obstructive hydrocephalus and hyponatremia from **cerebral salt wasting.**

SEIZURES

A **seizure** is a paroxysmal neurologic event caused by abnormal, synchronous discharges from populations of cortical neurons. Symptoms can vary widely and can include overt convulsions, subtle alterations of consciousness (e.g., staring spells), or simple sensations (e.g., odd smells or sounds). **Epilepsy** is a condition in which patients have **unprovoked recurrent seizures.** The key step in diagnosis and treatment is to determine whether the initial seizure activity is **generalized** or **focal** in onset.

1° Generalized Seizures

Originate with abrupt-onset, simultaneous synchronized discharges of neurons throughout both cerebral hemispheres. Selected subtypes are as follows:

- **Tonic-clonic (grand mal):**
  - The most common generalized seizure type; typically seen in genetic epilepsy syndromes and in seizures arising from metabolic abnormalities (e.g., hyponatremia, alcohol withdrawal, medications, CNS infections).
  - Begin with stiffening of the extremities (**tonic** phase), often associated with a guttural cry from contraction of the expiratory muscles, followed by rhythmic **clonic** jerking of the extremities.
  - Associated urinary incontinence, tongue biting, and postictal confusion is typically found.
- **Myoclonic:**
  - A **myoclonic jerk** is an abrupt, brief, single contraction of a muscle group that produces a quick contraction and movement. **Myoclonic seizures** are characterized by frequent but asynchronous, nonrhythmic multifocal myoclonic jerks. Myoclonic jerks are most commonly seen with metabolic derangements (especially **uremia**) and are usually not epileptic.
  - An important genetic cause of myoclonic seizures is **juvenile myoclonic epilepsy;** patients often have "staring spells" during childhood (brief alterations in consciousness often associated with eye blinking or chewing movements) and subsequently develop both myoclonic and tonic-clonic seizures in adolescence. They also experience myoclonic jerks when entering into or emerging from sleep.
- **Atonic:** The epilepsy type that can most resemble syncope clinically. Characterized by the abrupt loss of all muscle tone associated with a brief loss of consciousness. Primarily seen with inherited forms of childhood epilepsy.

Symptoms/Exam

Although symptoms can vary, most generalized seizures are associated with a period of postictal confusion and lethargy.

Diagnosis

- **Labs:** Routine evaluation of patients with new seizures includes metabolic labs, including electrolytes such as sodium and calcium, as well as screening for renal or liver dysfunction. LP should be considered when infection or inflammatory disease is a concern.
- **Imaging:** A brain MRI should be done to investigate for structural abnormalities, with particular attention paid to the temporal lobes.

- **EEG:** EEG obtained prior to and during a seizure may show symmetric and synchronous generalized epileptiform discharges at the onset.

Treatment

- "Broad-spectrum" anticonvulsants such as **valproic acid,** topiramate, and lamotrigine are considered first-line treatment for 1° generalized seizures.
- Although phenytoin and carbamazepine may be helpful in patients with secondarily generalized tonic-clonic seizures, these medications can actually exacerbate seizures in 1° generalized epilepsy and should thus be avoided.
- Two unique types of generalized epilepsy are **juvenile myoclonic epilepsy,** which is best treated with **valproic acid,** and **absence epilepsy,** which is classically treated with **ethosuximide.**

Complications

Table 13.6 outlines the side effects associated with common anticonvulsants used for seizure treatment. Other medication-related complications are as follows:

Many anticonvulsants are associated with early osteoporosis, and early screening and prevention is key.

- **Anticonvulsants and OCPs:** Drugs that induce the liver cytochrome P-450 system (e.g., phenytoin and carbamazepine) can lead to ↓ effective levels of other medications, including OCPs. All female patients taking such anticonvulsants should be counseled to consider other means of birth control or use OCPs with high levels of estrogen.
- **Anticonvulsants and birth defects:** Use of anticonvulsants during pregnancy is associated with an ↑ risk of birth defects, particularly **neural tube defects.** All women of childbearing age who use anticonvulsants should be advised to take at least 0.4 mg/day of folate. Pregnant women with epilepsy should be treated with a single anticonvulsant at the lowest therapeutic dose; valproic acid is particularly teratogenic.

Prolonged simple partial seizures are called epilepsia partialis continua and are difficult to control.

Focal (Partial) Seizures

Much more common than 1° generalized seizures, focal seizures originate from a small, discrete focal lesion within the brain that gives rise to abnormal synchronized neuronal discharges. This activity may then spread to involve other areas of the brain. Subtypes are as follows:

- **Simple partial seizures:**
  - Focal seizures in which **no alteration of consciousness** is noted.

TABLE 13.6. Classic Anticonvulsant Side Effects

Drug	Side Effects
Phenytoin	Gum hyperplasia, ataxia, peripheral neuropathy, lymphoproliferative disorder, Stevens-Johnson syndrome.
Carbamazepine	Hyponatremia, lymphopenia, Stevens-Johnson syndrome. Induces its own metabolism; the initial dose can then become ineffective.
Valproate	Tremor, drowsiness, weight gain, hirsutism, thrombocytopenia, liver failure.

- Initial symptoms depend on the location of the seizure focus and commonly include twitching/jerking of one side of the body (focal motor seizures) or sensations of strange smells or sounds.

- **Complex partial seizures:**
  - Evolve from simple partial seizures as the initial focal seizure activity spreads to involve some but not all of both cerebral hemispheres. In fact, the **stereotypical warning or aura** that many patients report is simply the manifestation of the initial simple partial seizure.
  - As seizure activity spreads, patients develop an **impairment of consciousness** and **behavioral arrest** during which they display stereotypical behaviors known as **automatisms** (e.g., lip smacking, chewing, pulling at clothes).
  - In contrast to simple partial seizures, complex partial seizures are associated with postictal confusion and lethargy.
- **Complex partial seizures with 2° generalization:**
  - In many patients with prolonged complex partial seizures, seizure activity can ultimately spread to involve the entire cerebral cortex. The manifestation of the "2° generalization" of the initial focal seizure activity is usually generalized tonic-clonic activity.
  - Generalized seizures can thus be either **1°** (generalized seizure activity at onset) or **2°** (initial focal activity that spreads to involve the entire cortex).
- **Todd's paralysis:**
  - Patients with focal-onset seizures often have transient (minutes to hours) focal weakness or paralysis following seizure termination. This weakness usually involves the area of the body first affected by the seizure, providing an important clue to the focus of seizure onset.
  - A patient with a generalized tonic-clonic seizure who is subsequently noted to have a postictal left hemiparesis likely had a focal-onset seizure that began in the right hemisphere and secondarily generalized.
- **Temporal lobe epilepsy:** The most common cause of simple and complex partial seizures is **temporal lobe pathology,** most commonly 2° to abnormalities of the **hippocampus.** Hippocampal sclerosis/calcification is seen on imaging. The classic auras of odd smells, sounds, or tastes are associated with temporal lobe epilepsy.

Diagnosis

Given that focal (partial) seizures arise from focal lesions, brain imaging studies are typically abnormal; EEG often shows localized (i.e., asymmetric) epileptiform activity. HSV encephalitis must be ruled out via CSF studies in patients with new-onset temporal lobe seizures.

Treatment

- **Medications:** Focal-onset seizures are best treated with anticonvulsants such as **phenytoin, carbamazepine,** phenobarbital, and valproic acid. Newer medications such as gabapentin, levetiracetam, lamotrigine, and topiramate are also useful.
- **Vagal nerve stimulators:** Although their mechanism of action remains unclear, vagal nerve stimulators can ↓ the frequency of focal-onset seizures by 25% in patients with medically refractory seizures. A pacemaker-like device is implanted in the chest with leads attached to one of the vagal nerves.

- **Surgery:** Patients with focal-onset seizures often have an identifiable brain lesion on imaging studies. This is particularly true of temporal lobe epilepsy 2° to hippocampal lesions. In such patients with medically refractory seizures, **surgical resection** of the causative lesion (e.g., temporal lobectomy) can produce striking results, with up to 50–75% of patients becoming seizure free.

Complications

See Table 13.6 and the accompanying discussion.

Status Epilepticus

Traditionally defined as (1) continuous seizure activity lasting > 30 minutes, or (2) recurrent seizures without return of normal consciousness between seizures. Practically speaking, seizure activity lasting > 5 minutes is unlikely to remit spontaneously and carries the risk of permanent neuronal injury. Generally, ongoing or recurrent seizure activity lasting > 5 minutes is thus considered a medical emergency and treated as status epilepticus.

Treatment

Treatment guidelines are as follows:

- **ABCs.**
- **Labs:** Draw labs for metabolic abnormalities (e.g., glucose, sodium, calcium).
- **Pharmacologic:**
  - Administer thiamine and glucose.
  - Benzodiazepines are first-line anticonvulsants for status epilepticus. Give lorazepam 0.1 mg/kg IV at 1–2 mg/min.
  - Fosphenytoin (20 mg/kg "phenytoin equivalents" IV at 150 mg/min) should then be started immediately even if seizures terminate with lorazepam.
  - If seizures persist, the next step is to give a second load of phenytoin or fosphenytoin using an additional 5–10 mg/kg IV load or move directly to the next step.
  - If seizures continue, the next step is to administer pentobarbital, midazolam, or propofol. Use of any of these medications typically requires continuous EEG recordings, mechanical ventilation, and cardiac pressors.

MOVEMENT DISORDERS

Hypokinetic Disorders

Parkinson's Disease

An idiopathic progressive neurodegenerative disorder affecting the dopaminergic neurons of the substantia nigra (see Figure 13.3). Incidence is 10–20 in 100,000, and prevalence is 100–150 in 100,000. Average age of onset is 60, and the male-to-female ratio is 1.5:1.

Symptoms/Exam

The **cardinal features** are **resting tremor** ("**pill rolling**"), **bradykinesia**, "**cogwheel**" **rigidity,** and **postural instability.** Symptoms typically begin **asymmet-**

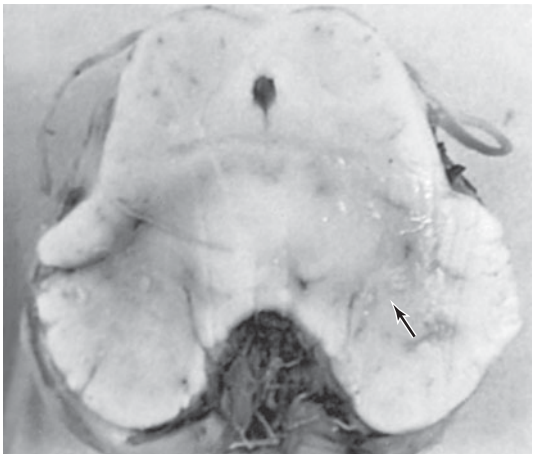


FIGURE 13.3. Parkinson's disease.

Midbrain of a 45-year-old woman with Parkinson's disease, showing depigmentation of the substantia nigra (arrow). (Reproduced, with permission, from Waxman S. *Clinical Neuroanatomy*, 25th ed. New York: McGraw-Hill, 2003: Figure 13-9.)

rically, usually in one extremity. Cognition is preserved in idiopathic Parkinson's disease until late in the course.

Parkinson's features—

TRAP

Tremor
Rigidity
Akinesia
Postural instability

Differential

Parkinson-plus syndromes present with parkinsonian features as well as with additional symptoms (see below). Other causes of parkinsonism include cerebrovascular disease; recurrent head trauma (e.g., boxing); toxin exposure (including illicit drugs such as MPTP and heavy metals such as manganese); and antidopaminergic medications (e.g., traditional antipsychotics).

Diagnosis

The diagnosis of idiopathic Parkinson's disease relies on the history and physical combined with response to levodopa. Young patients as well as those with atypical features should undergo further workup (e.g., imaging studies, toxin screens).

Treatment

- **Medical:** Medical treatment includes the following:
  - **Levodopa/carbidopa:** The gold standard for symptomatic treatment. Levodopa, a precursor of dopamine, is administered with carbidopa, a decarboxylase inhibitor that inhibits peripheral conversion of levodopa to dopamine. Should be taken on an empty stomach to maximize absorption.
  - **Dopamine agonists:** Direct agonists of D_2 dopamine receptors.
  - **Catechol-*O*-methyltransferase (COMT) inhibitors:** One pathway of dopamine degradation is via COMT; inhibition of this enzyme raises endogenous dopamine levels.
  - **MAO-B inhibitors:** Another pathway of dopamine degradation is via MAO; inhibition of this enzyme likewise raises endogenous dopamine levels.
- **Surgical:** Surgical treatment options primarily include deep brain stimulation of the globus pallidus interna or subthalamic nucleus.

*Think of **progressive supranuclear palsy** in a patient presenting with parkinsonian-like symptoms with dementia, deficits in vertical gaze (e.g., inability to look down), and postural instability that is often unresponsive to levodopa.*

Parkinson-Plus Syndromes

A number of neurodegenerative diseases produce parkinsonian features along with a variety of other symptoms, including cognitive decline and cerebellar abnormalities (see Table 13.7). In general, Parkinson-plus syndromes respond poorly if at all to levodopa. A Parkinson-plus syndrome should thus be considered in **any patient who presents with parkinsonism associated with cerebellar or cognitive symptoms,** especially when the parkinsonian features do not respond to levodopa therapy.

Hyperkinetic Disorders

Huntington's Disease

An **autosomal-dominant** disorder characterized by progressive **chorea, dementia,** and **psychiatric** symptoms. Huntington's is a neurodegenerative disorder particularly affecting the caudate nucleus of the basal ganglia and is caused by a **polyglutamine (CAG) trinucleotide repeat expansion** in the Huntington gene on **chromosome 4.** This repeat can expand with successive generations, leading to the phenomenon of **anticipation**—earlier age of onset and more severe symptoms in successive generations.

Diagnosis

- The clinical presentation combined with a strong family history suggests the disease.
- CT/MRI show marked **atrophy of the caudate nucleus** and exclude other structural abnormalities.
- Genetic testing now provides definitive evidence of the trinucleotide repeat expansion.

Treatment

- No treatment is currently available for the underlying disease process.
- Chorea can be treated symptomatically with neuroleptics (e.g., haloperidol), dopamine-depleting agents (e.g., reserpine, tetrabenazine), and GABAergic agents (e.g., clonazepam).
- Genetic counseling is indicated for patients' children.

TABLE 13.7. Clinical Features of Parkinson-Plus Syndromes

Syndrome	Key Features
Dementia with Lewy bodies	Cognitive decline, visual hallucinations, marked daily fluctuations in mental status.
Progressive supranuclear palsy	Cognitive decline. Extraocular abnormalities, especially vertical gaze. Prominent rigidity of the entire body, leading to frequent falls.
Corticobasal degeneration	Cognitive decline; "alien limb" phenomenon; limb apraxia (inability to perform learned motor tasks such as brushing teeth or saluting).
Multiple-system atrophy	Encompasses a group of Parkinson-plus syndromes. Autonomic dysfunction, especially orthostatic hypotension, may occur early. Ataxia is common in the cerebellar form.

Wilson's Disease

An **autosomal-recessive** disorder characterized by progressive neuropsychiatric symptoms and liver dysfunction. Caused by mutations of a copper ATPase transporter gene on chromosome 13. Copper deposition most prominently occurs in the liver and basal ganglia (specifically the lentiform nuclei) of the brain; asymptomatic deposition is also seen in Descemet's membrane of the cornea. Liver dysfunction is typically seen prior to neuropsychiatric illness (onset of liver disease occurs at 10–15 years of age); most patients present as adolescents and young adults.

Symptoms

Patients have prominent extrapyramidal symptoms (tremor, dystonia, rigidity, bradykinesia) and cerebellar symptoms (ataxia, incoordination, slurred speech); common psychiatric symptoms include depression, psychosis, and personality changes.

Exam

- As a rule, all Wilson's disease patients with neuropsychiatric symptoms will have **Kayser-Fleischer rings** (greenish-brown rings along the limbus of the cornea from copper deposition); a **slit-lamp** evaluation is often necessary to detect them.
- The classic tremor of Wilson's disease is a coarse proximal upper extremity tremor classically described as a "**wing-beating" tremor.**

Diagnosis

Consider Wilson's disease in young patients presenting with psychiatric disorders and liver abnormalities.

- Consider in any young patient presenting with progressive neurologic (especially extrapyramidal) or psychiatric symptoms, even in the absence of liver disease.
- Diagnosis is supported by laboratory evidence of low serum copper and ceruloplasmin (a protein into which copper is normally incorporated in the hepatocyte) and high urinary copper.
- Liver biopsy reveals copper deposition.

Treatment

- **Penicillamine,** a copper chelating agent, has classically been used to treat Wilson's disease, although side effects are common. In particular, a **myasthenia gravis syndrome** with ⊕ titers of anti-ACh receptor antibodies can be induced by penicillamine therapy.
- Other treatment options include trientine and oral zinc.

Essential Tremor

An idiopathic **postural tremor** that typically affects the **hands** and **head.** It is seen equally in men and women, although hand tremor is most prominent in men and head tremor most prominent in women. Tremor onset may occur early between 35 and 45 years of age. Family history is often strongly ⊕.

Symptoms

- In contrast to Parkinson's, essential tremor is not seen at rest but rather comes out with activity. The tremor is slightly faster than that of Parkinson's disease (8–10 Hz vs. 4–5 Hz).

- Most patients report a temporary but **striking improvement** in tremor with **alcohol** ingestion; conversely, physical and emotional stress exacerbate the tremor, as do medications such as caffeine and steroids.

Exam

- Postural tremor of the hands is tested by having patients maintain their arms fully extended from their bodies.
- Hand tremor can also come out with activity, although this should not be confused with a cerebellar tremor, in which tremor worsens as the hands approach a target. Tremor of the jaw is frequently seen.
- In patients with essential tremor, strength is normal. In contrast to Parkinson's disease, no abnormalities in muscle tone are present.

Differential

In a young patient, Wilson's disease should be considered. Other causes of tremor include endocrine disorders (especially thyroid dysfunction), electrolyte abnormalities (including calcium and sodium), medications (especially lithium, antidepressants, stimulants, and neuroleptics), and **Parkinson's disease.**

Treatment

The classic treatments are **β-blockers** (e.g., **propranolol**) and **primidone.** Benzodiazepines and gabapentin have also been used when first-line treatments fail.

Tourette's Syndrome

A disorder characterized by **brief involuntary actions (motor and vocal tics)** and **psychiatric disturbances.** Onset typically occurs in adolescents < 18 years of age, with a male-to-female ratio of 5:1. Two-thirds of patients have some amelioration of symptoms in adulthood, but complete remission is rare.

Symptoms/Exam

- **Motor tics** can be simple (e.g., eye twitching, blinking, shoulder shrugging) or complex (e.g., mimicking another's actions, or **echopraxia**). **Vocal tics** can be simple sounds (e.g., barking) or single words; classic vocal tics include **speaking obscenities (coprolalia)** and **mimicking another's speech (echolalia),** although neither is common. Tics are often exacerbated by physical or emotional stress.
- Associated neuropsychiatric disorders include **OCD** and ADHD.

Differential

The differential for motor tics includes dystonia (see below) and ballismus. Patients may have one or more simple motor or vocal tics without meeting the criteria for Tourette's syndrome. 1° psychiatric illness must also be considered in patients with vocal tics.

Treatment

Neuroleptics (e.g., haloperidol, risperidone), **clonidine,** and **benzodiazepines** (e.g., clonazepam, diazepam) often help reduce the frequency of tics.

Dystonia

Neuroleptics such as haloperidol can cause an acute dystonic reaction. Treat with anticholinergics.

- A syndrome characterized by repetitive, sustained contractions of agonist/antagonist muscles groups that typically produce painful **twisting/writhing movements** and/or **abnormal tonic postures** of the head or extremities.
- Can be focal or generalized. Focal dystonias most commonly include those that involve the musculature of the neck **(torticollis),** eyes **(blepharospasm),** and hands **(writer's cramp).**
- Etiologies include inherited/genetic, neurodegenerative (e.g., Huntington's, Wilson's, Parkinson's), rheumatologic (e.g., SLE, antiphospholipid syndrome), metabolic (e.g., thyroid disease), and toxin/medication related (e.g., **neuroleptics,** OCPs).
- **Tx:** Treat **focal** dystonia with **selective injection of botulinum toxin.** For **generalized** dystonia, stop the offending medication and treat with **anticholinergics** such as benztropine or diphenhydramine. Deep brain stimulation is effective for refractory cases.

Restless Leg Syndrome (RLS)

Characterized by intense, uncomfortable paresthesias of the legs (often described as a "crawling" or "creeping" sensation) that are relieved by leg movement and are worse at night upon going to bed. Generally idiopathic, but also seen in patients with a wide variety of chronic illnesses (e.g., Parkinson's, anemia, diabetes, COPD, thyroid disease, connective tissue diseases, neuropathies) and as a side effect of drugs (e.g., caffeine, lithium, calcium channel blockers).

Symptoms/Exam

- Paresthesias are most severe when the legs are **at rest** (e.g., while sitting or lying), especially at night as patients try to sleep, and are **relieved by continued movement** of the legs.
- Patients may also have periodic limb movements of sleep (PLMS)—frequent stereotypical movements of the leg.
- Neurologic exam is normal unless RLS is related to an underlying neurologic disorder.

Treatment

Dopaminergic medications administered before bedtime (e.g., levodopa/carbidopa, pramipexole) are the **standard treatment** for RLS. Other useful agents include **benzodiazepines, narcotics,** and **gabapentin.**

MULTIPLE SCLEROSIS (MS)

An autoimmune inflammatory disease affecting the myelin of the CNS. Characterized by focal demyelinating plaques that occur at different times and locations within the CNS. Typically affects the optic nerves, corpus callosum, periventricular white matter, brain stem, and spinal cord. Generally seen in **younger women.** Incidence ↑ with latitude of birth and is twice as high in patients of Northern European descent as in patients of African descent.

Symptoms

- In addition to focal abnormalities, patients often suffer from chronic **fatigue.**

- Symptoms are **exacerbated by heat and exercise** (the Uhthoff phenomenon); old deficits may also be worsened by underlying illness, especially infections such as UTIs or URIs.

EXAM

*MS is a **clinical** diagnosis. The diagnosis is likely if patients report **two or more** clinically distinct episodes of typical neurologic symptoms.*

Classic lesions and exam findings include the following:

- **Optic nerve: Optic neuritis** presents as unilateral subacute vision loss associated with pain with eye movement. Exam shows pallor of the optic nerve (may be normal in the acute setting), ↓ visual acuity, difficulty with color discrimination, and a **relative afferent pupillary defect** (RAPD, or Marcus Gunn pupil; see Figure 13.4).
- **Brain stem:** A demyelinating lesion of the medial longitudinal fasciculus yields an **internuclear ophthalmoplegia.** Patients complain of double vision when looking to one side; exam reveals inability to adduct the eye ipsilateral to the lesion during voluntary horizontal gaze. Adduction of the eye can be brought out by testing convergence, which remains normal (see Figure 13.5).

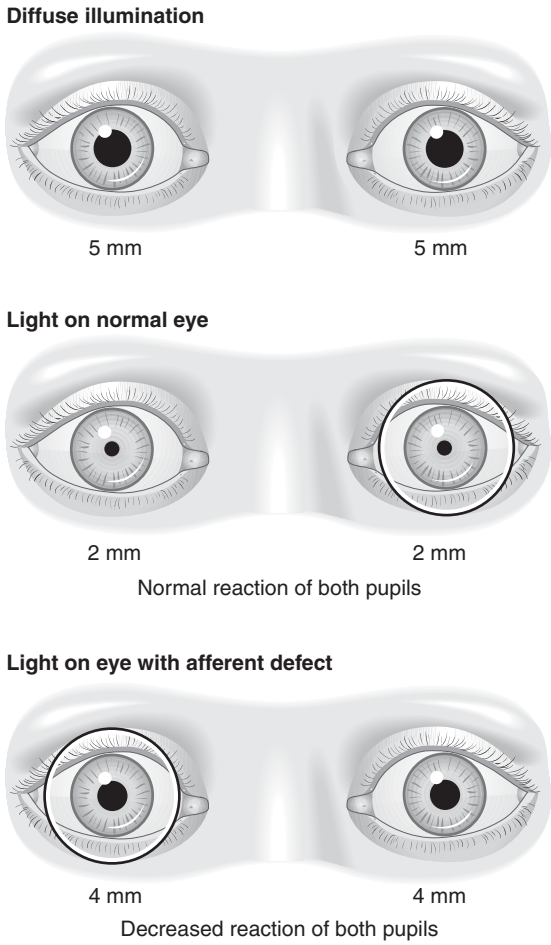


FIGURE 13.4. Afferent pupillary defect (Marcus Gunn pupil).

(Reproduced, with permission, from Riordan-Eva P, Whitcher JP. *Vaughan & Asbury's General Ophthalmology*, 16th ed. New York: McGraw-Hill, 2004: Figure 14-32.)

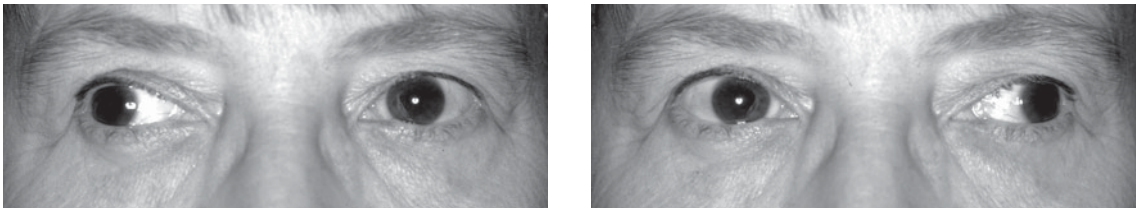


FIGURE 13.5. Bilateral internuclear ophthalmoplegia due to multiple sclerosis.

(Reproduced, with permission, from Riordan-Eva P, Whitcher JP. *Vaughan & Asbury's General Ophthalmology*, 16th ed. New York: McGraw-Hill, 2004: Figure 14-12.)

- **Spinal cord:** Transverse myelitis symptoms (**paresthesias,** sensory level, bowel/bladder dysfunction, **UMN signs**) are common.
- **Lhermitte's sign** (electrical radiation down the spine elicited by neck flexion) is a classic finding and is likely related to dorsal column involvement.

Consider MS in a young patient presenting with any of the following: subacute loss of vision; double vision when looking to one side; an electrical sensation running down the spine when the neck is flexed; subacute spinal cord symptoms (e.g., paresthesias and bowel/bladder dysfunction); and worsening of neurologic symptoms with heat or exercise.

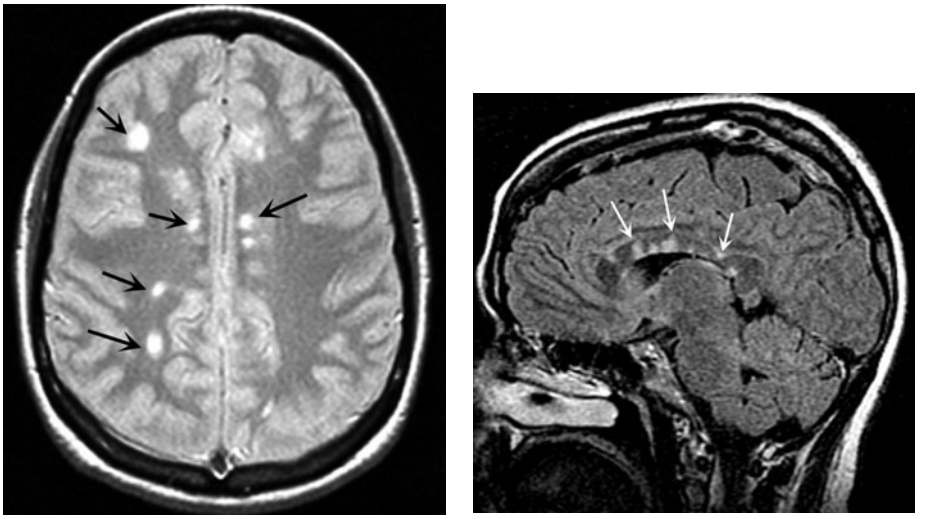
Diagnosis

- **Clinical criteria:** No laboratory or imaging test is diagnostic for MS, and thus the diagnosis must be based on clinical criteria. Definitive diagnosis requires evidence from the history and exam of at least two distinct attacks involving two separate CNS regions. Imaging and laboratory data support the diagnosis.
- **MRI:** MRI abnormalities are seen in > 90% of patients. Most have multiple punctate/ovoid lesions involving the periventricular white matter ("Dawson's finger" lesions extending from the ventricles at right angles), **corpus callosum,** brain stem, and spinal cord. These are best seen on T2-weighted images. Acute "active" lesions enhance with gadolinium contrast (see Figure 13.6).
- **CSF:** Typical findings include normal opening pressure, mild lymphocytic pleocytosis (5–40 WBCs/mm^3), normal glucose, and normal to mildly ↑ protein. Eighty percent of patients have > 2 **oligoclonal bands and an elevated CSF** IgG index, but neither is specific for MS.
- **EPs:** Occasionally used to obtain supportive evidence of demyelination if MRI and CSF results are inconclusive. For evaluation of MS, visual EPs are often used.

MRI is the imaging modality of choice for MS, but it is used only to support the clinical diagnosis.

Treatment

- **Disease-modifying therapies** include the following:
  - **β-interferon and glatiramer acetate—"ABC drugs" (Avonex, Betaseron, Copaxone):** These drugs have been shown to ↓ the frequency and severity of relapses in patients with relapsing-remitting MS. Table 13.8 outlines the administration of these drugs and delineates their potential side effects.
  - **Glucocorticoids:** High-dose IV glucocorticoids (Solu-Medrol 1 g IV QD × 3–5 days), which are typically used to treat acute attacks and the presence of new enhancing lesions on MRI, appear to be superior to oral steroids (especially for treating optic neuritis) in leading to faster recovery. However, the administration of glucocorticoids has no impact on overall disease progression or long-term disability.
- **Specific symptoms** are targeted with appropriate medications:
  - **Hyperreflexic bladder:** Oxybutynin.
  - **Fatigue:** Amantadine, modafinil.



A B

FIGURE 13.6. MRI findings in multiple sclerosis.

(A) Axial image from T2-weighted sequence demonstrates multiple bright signal abnormalities in white matter, typical for MS. (B) Sagittal T2-weighted FLAIR (fluid-attenuated inversion recovery) image in which the high signal of CSF has been suppressed. CSF appears dark, while areas of brain edema or demyelination appear high in signal, as shown here in the corpus callosum (arrows). Lesions in the anterior corpus callosum are frequent in MS and rare in vascular disease. (Reproduced, with permission, from Kasper DL et al. *Harrison's Principles of Internal Medicine*, 16th ed. New York: McGraw-Hill, 2005: 2465.)

- **Paroxysmal symptoms** (e.g., tonic spasms): Carbamazepine.
- **Spasticity:** Baclofen, diazepam.

NEUROMUSCULAR JUNCTION DISORDERS

Myasthenia Gravis (MG)

An **autoimmune** disorder that is usually caused by autoantibodies to the nicotinic ACh receptor (nAChR), resulting in impaired transmission at the neuromuscular junction. Occurs in **young women** (ages 20–30) and **older men** (ages 50–70). Associated with other autoimmune diseases, particularly **thyroid** disorders.

TABLE 13.8. Administration and Side Effects of "ABC Drugs"

Drug	Administration	Side Effects
Interferon-β1a (Avonex)	Weekly IM	Flulike symptoms, depression
Interferon-β1b (Betaseron)	QOD SQ	Flulike symptoms
Glatiramer acetate (Copaxone)	Daily SQ	Flushing, chest tightness

Symptoms

The hallmark is **fluctuating, fatigable weakness** classically affecting the **eye muscles.** There are two forms: (1) **ocular,** which is isolated to the extraocular and eyelid muscles, giving double vision and ptosis; and (2) **generalized,** which typically involves ocular, facial, and proximal limb muscles, giving rise to ocular symptoms as well as to facial weakness, trouble swallowing and speaking, respiratory dysfunction, and limb weakness. Patients with ocular MG may progress to generalized MG.

Exam

- **Ptosis,** often asymmetric, can be brought out by testing prolonged upgaze; an ice pack briefly placed on the eye will improve ptosis.
- **Extraocular muscle palsies** are typically seen on lateral gaze.
- **Easy fatigability** of proximal muscles with repeated strength testing.
- **Preserved DTRs** and sensation.

The side effects of pyridostigmine include ↑ secretions and diarrhea; at high doses, weakness can occur that may mimic a myasthenic crisis.

Differential

- Lambert-Eaton myasthenic syndrome (see Table 13.9).
- **Drug-induced MG: Penicillamine** can cause a reversible antibody-⊕ MG syndrome.
- **Botulism:** Typically presents with cranial nerve palsies, including the extraocular muscles. Patients have CSF pleocytosis and often absent reflexes.

Diagnosis

- **Anti-nAChR antibodies:** Present in > 80% of generalized MG and 50% of ocular MG cases.
- **Anti-MuSK antibodies:** Present in 20% of "seronegative" MG patients.
- **Tensilon test:** Tensilon (edrophonium), a short-acting AChE inhibitor, can give instantaneous improvement to an objectively weak muscle. Caution must be used, as it may precipitate cardiac arrhythmias.

The 5 W's of myasthenia gravis:

Waxing and
Waning (fluctuating)
Weakness with
Work (fatigability), mostly in
Women

TABLE 13.9. Myasthenia Gravis vs. Lambert-Eaton Myasthenic Syndrome

Characteristic	Myasthenia Gravis	Lambert-Eaton Myasthenic Syndrome
Antibody target channel	nAChR	Voltage-gated calcium channel
Associated cancer	Thymoma	Small cell lung cancer
Eye muscle involvement	Yes	No
Autonomic symptoms	No	Yes
Reflexes	Normal	Hypoactive
Repetitive strength testing	Rapid fatigue	Initial improvement
Repetitive nerve stimulation	Decremental response	Initial enhancement

- **EMG/NCS:** Direct testing of the muscle with EMG/NCS remains the **best test for MG.** Repetitive nerve stimulation reveals a **decremental** motor response, the correlate of clinical fatigability.

Treatment

- **AChE inhibitors:** Include pyridostigmine.
- **Immunomodulators:** Include glucocorticoids, cytotoxic drugs, plasma exchange, and IVIG.
- **Thymectomy:** Patients require **chest imaging** to evaluate for thymic abnormalities, as 70% have hyperplasia and 10% have thymomas. Thymectomy is recommended for most patients < 60 years of age with generalized MG.
- **Myasthenic crisis:** Elective intubation if **FVC** falls < 15 mL/kg.

Complications

Often exacerbated by stress, fever, infections, and certain medications, including antibiotics (especially **aminoglycosides**), as well as by antiarrhythmics such as procainamide and β-blockers.

Lambert-Eaton Myasthenic Syndrome (LEMS)

An **autoimmune** (sometimes **paraneoplastic**) syndrome caused by autoantibodies to presynaptic voltage-gated calcium channels, leading to impaired transmission at the neuromuscular junction. Typically seen in men and women > 40 years of age. More than half have an underlying malignancy, with the majority being **small cell lung cancer.**

Symptoms

- Presents with proximal muscle weakness, especially in the legs, that **briefly improves with exertion** before eventually fatiguing.
- Muscle aches are also seen, as are **autonomic symptoms** (dry mouth, impotence, constipation, postural hypotension).
- In contrast to MG, LEMS patients do **not** experience double vision or ptosis (see Table 13.9).

Exam

Normal cranial nerve exam; proximal weakness of the legs and arms that **initially improves** with repeated testing; **hyporeflexia.**

Differential

MG, myopathy (e.g., polymyositis/dermatomyositis).

Diagnosis

- **EMG/NCS:** Direct testing of the muscle with EMG remains the **best test for LEMS.** In contrast to MG, high-frequency repetitive nerve stimulation in LEMS reveals an **initial enhancement** of motor responses, the correlate of clinical improvement upon initial exertion.
- **Neoplastic workup:** Diagnosis of LEMS often precedes the diagnosis of cancer by a year or more. Initial evaluation should be directed at possible small cell lung cancer.

Treatment

- 1° treatment is directed at treating the underlying malignancy.
- 3,4-diaminopyridine (DAP) may facilitate neuromuscular transmission but is difficult to obtain in the United States.
- IVIG and plasma exchange may improve symptoms.

AMYOTROPHIC LATERAL SCLEROSIS (ALS)

A progressive degenerative disease of the UMNs (arising in the motor cortex) and LMNs (arising in the brain stem and anterior horn of the spinal cord). Affects males and females equally, with onset between 50 and 70 years of age. Life expectancy is 3–5 years, with death usually occurring 2° to aspiration pneumonia or respiratory failure. Five to ten percent of cases are familial. One genetic cause is autosomal-dominant transmission of a mutation in the copper-zinc superoxide dismutase *(SOD 1)* gene on chromosome 21.

The hallmark of ALS is the combination of both upper and lower motor neuron signs and symptoms.

Symptoms

- Presents with difficulty swallowing, nasal speech, "head drop" from neck weakness, shortness of breath, "muscle twitches," muscle cramps, and progressive generalized weakness. The **eye muscles are typically spared;** bowel and bladder function is typically preserved.
- Cognitive dysfunction in the form of **frontotemporal dementia** has been shown to be fairly common late in the disorder.

Exam

Exam findings include both UMN and LMN signs.

- **Signs of UMN injury:** Spasticity (↑ muscle tone), hyperreflexia, Babinski sign.
- **Signs of LMN injury:** Atrophy (especially of the tongue and muscles of the hands); fasciculations (muscle twitches).

Differential

Cervical spondylosis resulting in cervical cord injury, hexosaminidase A deficiency (Tay-Sachs), West Nile viral LMN syndrome, syringomyelia, thyrotoxicosis, hyperparathyroidism, paraneoplastic syndromes.

Diagnosis

- **EMG/NCS** reveal evidence of widespread LMN injury (e.g., fibrillations, **fasciculations**) and UMN injury that does not fall in a nerve root distribution. Sensory nerve studies are normal.
- **Spinal fluid** analysis is normal.
- **Cervical spine imaging** to evaluate for the possibility of cervical spondylosis with cord compression, a surgically treatable disease.

Treatment

- **Riluzole,** a presumed glutamate antagonist, is the only FDA-approved medication for ALS. Improves survival by approximately six months.
- **Noninvasive positive-pressure ventilation** improves survival and should be offered if **FVC** falls to < 50% predicted.
- **Percutaneous endoscopic gastrostomy tube placement** allows for ↑ nutrition in the face of dysphagia and leads to ↑ muscle mass and longer survival.

General Characteristics

A large group of heterogeneous diseases of the peripheral nerves. Overall prevalence is approximately 3% but ↑ to 8% in older patient populations. The character, distribution, pathology, and progressive course of symptoms are vital for directing workup and treatment.

Character

Peripheral nerves carry distinct fiber types: sensory, motor, and autonomic. Many disorders selectively attack specific fiber types, while others indiscriminately affect all types. The nature of symptoms depends on which fiber types are injured.

- **Sensory nerves:** Paresthesias (burning, numbness, tingling) are common initial symptoms, with overt sensory loss occurring with progression of disease.
- **Motor nerves:** Weakness, atrophy, twitching (fasciculations).
- **Autonomic nerves:** Postural hypotension, impotence, nausea, diarrhea, dry mouth.

Distribution

- **Polyneuropathies:** Result from diseases that affect multiple peripheral nerves in a diffuse and synchronous fashion. Many polyneuropathies are "length dependent," affecting the longest nerves first. Produces the classic "stocking-glove" distribution of symmetric involvement of all four distal extremities.
- **Mononeuropathies:** Diseases of an individual peripheral nerve (e.g., radial nerve palsy), with symptoms restricted to its specific distribution.
- **Mononeuritis multiplex:** A unique syndrome in which multiple individual peripheral nerves are progressively injured in an asymmetric and asynchronous fashion.

Pathology

The location of injury in peripheral neuropathies involves either the **axon** or its insulating **myelin** covering. Identifying its location helps focus the differential and direct treatment.

- **Axonal** neuropathies are more likely **metabolic** in nature. As they involve direct injury to the nerve, recovery is often more limited and slow. NCS shows **low amplitude.**
- **Demyelinating** neuropathies are often **inflammatory** and thus treatable; as the neuron itself is not directly injured, recovery is often the rule as remyelination occurs. NCS shows **slow conduction velocity.**

Acute Polyneuropathies

Acute-onset, rapidly progressive polyneuropathies, particularly those with motor or autonomic involvement, can produce life-threatening complications

over days to weeks. These require aggressive workup and treatment. Many are inflammatory or toxic in nature.

Guillain-Barré Syndrome (GBS)

A postinfectious autoimmune **acute demyelinating polyneuropathy.** Given the decline of polio, it is now the most common cause of acute flaccid paralysis. GBS classically follows an acute GI illness caused by ***Campylobacter jejuni*,** as antibodies directed toward its bacterial lipopolysaccharide cross-react with peripheral nerve myelin; other infections (e.g., HIV, *Mycoplasma*) have also been associated with GBS.

Symptoms

- Symptoms such as back pain or lower extremity paresthesias typically begin 1–2 weeks after the infection, followed by **symmetric weakness that begins in the feet** and gradually ascends over hours to days. Weakness severity can range from mild to complete quadriplegia with respiratory failure. Autonomic symptoms are prominent, and cardiac instability can be life-threatening. Despite sensory symptoms (paresthesias), the sensory examination is often normal.
- A unique variant, Miller-Fisher syndrome, produces symptoms of ophthalmoplegia, ataxia, and areflexia, with little weakness of the extremities.
- Overall, GBS is a **monophasic** disease, with maximal symptoms seen by four weeks.

Only 30% of patients with GBS report an antecedent illness.

Exam

Cardinal features on exam are **areflexia** and **symmetric progressive weakness.**

Diagnosis

- CSF shows "albuminocytologic dissociation"—**isolated elevated protein** with normal WBC counts.
- Miller-Fisher syndrome is associated with anti-GQ1b antibodies.
- NCS reveals demyelinating changes of the proximal peripheral nerves.
- Serial PFTs with **maximum inspiratory force** and **FVC** are important for following diaphragmatic function, which often portends ventilatory failure.

Treatment

Standard treatment is either **IVIG** or **plasmapheresis;** steroids are not beneficial. Mechanical ventilation should be considered when FVC falls to 15 mL/kg. Do not wait for P_{CO_2} to rise. Keep patients with autonomic symptoms on **cardiac telemetry.**

Vasculitic Neuropathies

- **Acute axonal neuropathies** are seen in a wide variety of systemic vasculitides (infectious and inflammatory) and connective tissue diseases. Vasculitic infarction of individual peripheral nerves occurs in an asynchronous and asymmetric fashion, producing a multifocal neuropathy involving both sensory and motor fibers; this random involvement of multiple individual peripheral nerves is called **mononeuritis multiplex.**

- **Sx/Exam:** Include severe **pain, paresthesias,** and **weakness.** Progression occurs over days to weeks.
- **Dx:** NCS reveals axonal injury to multiple unrelated peripheral nerves; nerve biopsy typically shows axonal injury and inflammatory cell involvement of the nerve's vascular supply.
- **Tx:** Requires aggressive treatment with both steroids and an immunomodulator such as cyclophosphamide or methotrexate.

Other Etiologies

Additional etiologies of acute-onset, rapidly progressive polyneuropathies include brachial neuritis, acute intermittent porphyria, toxin exposure (arsenic, lead), and infections (diphtheria, Lyme disease, HCV).

Chronic Polyneuropathies

Most polyneuropathies are indolent in onset and progression, with symptoms noted gradually and advancing over months to years.

Charcot-Marie-Tooth Disease

- The classic inherited polyneuropathy. Its prevalence is 1 in 2500, making it the most common inherited neurologic disorder. The family history is strongly ⊕, with most forms being autosomal dominant.
- **Sx/Exam:** Symptoms begin in the first and second decades, usually with distal weakness in the legs. Patients have high-arched feet (pes cavus) and hammer toes; progressive atrophy and weakness of the hands and feet; distal sensory loss; and reduced or absent reflexes. Life expectancy is typically normal, but significant morbidity results from progressive weakness.
- **Tx:** No treatment is currently available.

Chronic Inflammatory Demyelinating Polyneuropathy (CIDP)

A symmetric, insidious-onset demyelinating disease of the peripheral nerves. Often considered to be related to but distinct from **GBS,** as both share similar clinical and pathologic findings (including areflexia, weakness, elevated CSF protein, demyelination, and response to IVIG or plasmapheresis). CIDP, however, has **no associated antecedent illness** and evolves over **weeks to months,** often with a **relapsing and remitting** course.

Diabetic Neuropathy

- **Diabetes** is the most common cause of peripheral neuropathy in the United States, typically presenting as a slow-onset, distal, symmetric axonal polyneuropathy. Approximately 8–10% of all patients with diabetes develop neuropathy, usually associated with onset of diabetic retinopathy and nephropathy.
- **Sx/Exam:** This "length-dependent" neuropathy affects the longest nerves first, initially producing paresthesias and pain in the feet; progression leads to a stocking-glove distribution of sensory and motor deficits. Sensory, motor, and autonomic nerves can be affected, with sensory symptoms predominating.

- **Tx:** Prevention of onset or progression depends on tight glycemic control. Neuropathic pain symptoms (burning, pain) can be treated with TCAs such as amitriptyline, SSRIs such as duloxetine, and anticonvulsants such as gabapentin or carbamazepine.

Metabolic/Infectious Neuropathies

Many insidious and chronic polyneuropathies are **metabolic** in nature, with common causes being nutritional deficiencies (e.g., vitamin B_{12}), toxin exposure (e.g., alcohol), and drug exposure (e.g., vincristine, INH, dapsone). In addition, many **infections** cause indolent polyneuropathies, including HIV and HSV; leprosy (Hansen's disease, caused by *Mycobacterium leprae*) remains one of the most common causes of polyneuropathy worldwide.

Mononeuropathies

Carpal Tunnel Syndrome

- The most common mononeuropathy; caused by compression of the **median nerve** at the flexor retinaculum of the wrist. Risk factors include repetitive hand-finger activities such as typing.
- **Sx:** Classic symptoms include progressive wrist pain; awakening at night with hand numbness; and paresthesias and weakness of the thumb and index finger.
- **Exam:**
  - Findings include **atrophy of the thenar eminence** (the palmar muscle bulk at the base of the thumb), weakness of thumb opposition, and sensory abnormalities of the thumb and index finger.
  - Two classic bedside tests for carpal tunnel are **Phalen's sign** (hyperflexion of the wrists leading to ↑ paresthesias) and **Tinel's sign** (tapping over the median nerve at the level of the wrist eliciting electrical radiating sensations along the thumb and index finger).
- **Dx:** NCS provides the best objective test for median nerve abnormalities at the wrist.
- **Tx:** Options include immobilization with wrist splints, NSAIDs, local steroid injections, and surgical release at the wrist.

Patients with carpal tunnel syndrome often have ↑ symptoms at night that are relieved by shaking or wringing their hands.

Radial Nerve Palsy

- Typically results from acute injury to the nerve in the spiral groove of the humerus, most commonly by **fracture of the humerus** or direct compression of the nerve (**"Saturday night palsy"**).
- **Sx/Exam:** The most prominent symptom is **"wrist drop"** due to paralysis of the wrist extensor muscles; weakness of elbow extension (triceps) is also common.
- **Dx:** NCS helps identify the exact location and extent of the injury.
- **Tx: Treatment is mainly supportive. Wrist splints may help restore function temporarily.**

Ulnar Neuropathy

- An overuse injury commonly caused by repetitive elbow flexion leading to trauma or compression at the elbow, particularly near the medial epicondyle. Common in thin women.

- **Sx/Exam:** Presents with paresthesias involving the fourth and fifth fingers, with weakness of the muscles that spread the fingers apart (the interossei), leading to the appearance, in its most chronic form, of a "**claw hand.**"
- **Tx: Splinting the elbows** at night is first-line treatment and is most helpful in conjunction with NSAIDs if there is pain. Surgical release or transposition of the nerve near the elbow is often tried but is not always beneficial.

Peroneal Nerve Compression

- **Sx/Exam:** Compression of the **peroneal nerve** near the fibular head produces a "**foot drop**" 2° to weakness of foot dorsiflexors, as well as paresthesias along the lateral aspect of the lower leg. Compression can be 2° to frequent leg crossing, trauma, or local masses (e.g., cysts).
- **Tx:** Involves identifying the risk factors for compression, initiating physical therapy, and using an ankle-foot orthosis; surgery is occasionally needed when a local mass is identified as the etiology of compression.

Bell's Palsy

- An acute-onset, unilateral paralysis of CN VII (the **facial nerve**).
- **Sx/Exam:**
  - The upper and lower halves of one-half of the face are affected, resulting in inability to fully close the eye or move the mouth on that side. Facial weakness from a central cause (e.g., a stroke) typically spares the upper half of the face, producing unilateral lower facial weakness.
  - In most cases, the etiology remains unclear, although an infectious or postinfectious cause is considered likely. Ramsay Hunt syndrome, in which unilateral facial paralysis is associated with herpetic blisters in the external auditory canal, supports this hypothesis.
- **Tx:** Treatment of idiopathic Bell's palsy with steroids is indicated if initiated early in the course. Eye protection (artificial tears; use of an eye patch at night) is crucial for preventing corneal abrasions.

MYOPATHIES

Diseases of skeletal muscle associated with **progressive, symmetric weakness,** fatigue, and/or pain, classically involving the **proximal extremities.** Patients typically complain of difficulty reaching above their heads, combing their hair, rising from a chair, or walking up and down stairs. Other than pain, **no sensory symptoms** are noted. Major types include inherited, mitochondrial, inflammatory, metabolic, and toxic. Key diagnostic tests are serum CPK, EMG/NCS, and muscle biopsy.

- Patients with **elevated CPK levels** and symptoms suggestive of a myopathy should undergo **EMG/NCS testing.**
- **Muscle biopsy** is generally reserved for patients in whom EMG identifies a myopathy but not its cause. The target should be a symptomatic muscle (e.g., a proximal muscle such as the deltoid or quadriceps). Like EMG/NCS, muscle biopsy helps determine the location of injury and its underlying cause.

Inflammatory Myopathies

Presumed autoimmune diseases of skeletal muscles. Major types are **polymyositis, dermatomyositis,** and **inclusion body myositis,** each of which has distinctive patterns of muscle weakness, associated symptoms, and muscle pathology. Both polymyositis and dermatomyositis are most commonly seen in patients 40–60 years of age, occurring twice as frequently in women; inclusion body myositis is most commonly seen in patients > 50 years of age and occurs three times more frequently in men than in women.

Polymyositis

- Most commonly seen in patients 40–60 years of age, occurring twice as frequently in women than in men.
- **Sx/Exam:** Typically presents as slowly progressive, symmetric weakness in the **proximal extremities** and the **neck flexors.** Many patients develop slurred speech as well as muscle pain and tenderness.
- **Dx:**
  - Serum CPK and ESR are usually elevated.
  - EMG shows nonspecific myopathic changes.
  - Muscle biopsy reveals a characteristic pattern and distribution of inflammation that can help distinguish polymyositis from dermatomyositis and inclusion body myositis.
- **Tx: Initial** treatment is with high-dose prednisone. Patients who fail to respond require more aggressive treatment with immunomodulators such as azathioprine or methotrexate. Overall response to treatment is good, but long-term management may be required.

Dermatomyositis

- Like polymyositis, most commonly seen in patients 40–60 years of age, occurring twice as frequently in women.
- **Sx/Exam:** An inflammatory myopathy characterized by progressive proximal weakness associated with multiple distinct skin changes. These include the following:
  - Periorbital edema and a purplish discoloration (**heliotrope rash**) of the upper eyelids, nose, and cheeks.
  - **Gottron's papules,** the classic purplish papules that develop on the dorsal surface of the MCP and interphalangeal joints.
- **Dx:**
  - As with polymyositis, CPK and ESR are elevated and EMG shows nonspecific myopathic changes. Muscle biopsy shows a distinct pattern of inflammation characteristic of dermatomyositis, helping distinguish it from polymyositis and inclusion body myositis.
  - In children, it is often associated with systemic vasculitis; in adults, it is occasionally the result of a paraneoplastic process from an underlying malignancy. Thus, adults usually have a screening evaluation for underlying malignancy.
- **Tx:** The treatment of idiopathic dermatomyositis is the same as that of polymyositis.

Consider an age-appropriate screen for malignancy (e.g., CXR and/or colonoscopy) in patients with dermatomyositis.

Inclusion Body Myositis

- A unique inflammatory myopathy that primarily affects older men.
- **Sx:**
  - Preferentially affects the finger and forearm flexors of the upper extremities and the quadriceps of the lower extremities.
  - Onset is insidious, with most patients complaining of difficulty with finger dexterity and grip strength as well as buckling of the knees while walking.
- **Exam:** Presents with prominent wasting of the finger and forearm flexors and quadriceps.
- **Dx:**
  - CPK is often normal; EMG shows nonspecific myopathic changes.
  - Muscle biopsy reveals inflammatory changes as well as the presence of rimmed vacuoles (inclusion bodies) within abnormal muscle fibers.
- **Tx:** Despite its apparent inflammatory nature, inclusion body myositis does not respond well to either steroids or immunomodulators, and most patients lose the ability to ambulate within 10 years of diagnosis.

Metabolic Myopathies

- Multiple endocrine abnormalities are associated with myopathies; CPK is often normal, and EMG shows nonspecific myopathic changes.
- Hyperthyroidism can lead to severe proximal muscle weakness and atrophy; hypothyroidism usually produces more muscle cramps with delayed relaxation of DTRs, although weakness is actually uncommon.
- These abnormalities are usually reversible with correction of the thyroid abnormality. Glucocorticoid excess, whether endogenous (e.g., Cushing's) or exogenous (e.g., steroid treatment), produces a myopathy with a typical proximal muscle pattern.

Toxic Myopathies

Many medications are associated with toxic myopathies, and the condition is usually reversible upon withdrawal of the offending toxin. As with other myopathies, the usual pattern is one of progressive, symmetric proximal muscle weakness. Common offending medications include statins, cimetidine, penicillamine, chloroquine, niacin, and zidovudine (AZT). Other toxins associated with myopathy include alcohol and heroin.

PARANEOPLASTIC SYNDROMES

PET scans (looking for small malignancies) are indicated if a definitive paraneoplastic syndrome is identified.

Most paraneoplastic syndromes result either from substances produced by tumor cells or from autoimmune complications of the response of the innate immune system to the cancer. Neurologic paraneoplastic syndromes appear to be caused by antibodies that cross-react with specific neuronal populations (see Table 13.10). Symptom onset is gradual, occurring over weeks to months; constitutional symptoms of the underlying tumor often lag by many months. Neurologic symptoms often become prominent even when the underlying tumor is difficult to detect. Thus, early identification of a neurologic paraneoplastic syndrome provides an opportunity to search for and aggressively treat the underlying tumor.

TABLE 13.10. Etiologies and Associated Antibodies of Paraneoplastic Syndromes

Syndrome	Underlying Cancer	Associated Antibody
Lambert-Eaton myasthenic syndrome	Small cell lung cancer	Anti-voltage-gated calcium channel
Subacute cerebellar degeneration	Ovarian or breast cancer	Anti-Yo (Purkinje cells)
Limbic encephalitis	Small cell lung cancer	Anti-Hu
Sensory neuronopathy	Small cell lung cancer	Anti-Hu
Opsoclonus-myoclonus	Breast cancer or neuroblastoma (children)	Anti-Ri

Lambert-Eaton Myasthenic Syndrome

The classic neurologic paraneoplastic syndrome is described above.

Subacute Cerebellar Degeneration

Associated with **ovarian or breast cancer** and **anti-Yo antibodies** (which cross-react specifically with cerebellar Purkinje cells). Most patients are middle-aged women who experience subacute-onset, progressive slurred speech as well as ataxia and limb incoordination.

Limbic Encephalitis

Associated with **small cell lung cancer** and **anti-Hu antibodies** as well as other autoantibodies. Patients present with subacute behavioral problems, memory difficulties, and focal-onset seizures. The clinical picture is similar to that of HSV encephalitis (both primarily affect the limbic system), but the latter is acute in onset and often fulminant, whereas paraneoplastic limbic encephalitis is more subacute and slowly progressive.

Sensory Neuronopathy

Also associated with **small cell lung cancer** and **anti-Hu antibodies.** Patients present with slowly progressive sensory loss that first affects the lower extremities. Neurologic exam reveals preserved motor strength, sensory loss, incoordination related to loss of proprioception, and areflexia.

Opsoclonus-Myoclonus

In adults, associated with **breast cancer** and occasionally small cell lung cancer; in **children,** classically associated with a **neuroblastoma.** The associated antibody is anti-Ri. Patients experience opsoclonus (involuntary, erratic, rapid jerking of the eyes in either the horizontal or vertical direction) and myoclonus (brief, quick, jerklike contractions).

NOTES

CHAPTER 14

Oncology

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Chemotherapeutic Agents

Principles of Chemotherapy

Chemotherapeutic agents act by interfering with the mechanisms of cell division. Targets include DNA synthesis, microtubules, and direct DNA damage.

Patterns of Toxicity

Table 14.1 outlines common and serious toxicities of various chemotherapeutic agents. All chemotherapies can cause bone marrow suppression and nausea/vomiting.

Targeted Therapies

Novel agents or standard treatments that have a specific molecular target and often have fewer and less severe side effects than conventional chemotherapy. Such modalities include hormonal therapy, cytokines, monoclonal antibodies, and small molecules that target enzymes. Monoclonal antibodies are often combined with standard chemotherapeutic regimens. Table 14.2 outlines common targeted therapies and their indications.

Principles of Oncology

Combination Regimens

- The **rationale for the use of combination regimens** is as follows:
  - Allows for maximum cell kill with less toxicity.
  - Prevents cross-resistance (different drugs lead to different mechanisms of resistance).
  - Synergistic effects between drugs with nonoverlapping toxicities.
- **Dose-dense therapy:** An active area of research.
  - Does not let tumor cells recover before the next dose of chemotherapy.
  - Minimize chance for resistance.
  - Used in breast cancer, but otherwise remains largely experimental.
  - Requires red and white blood cell growth factors.

Response to Therapy

Defined as follows:

- **Complete response:** Disappearance of all evidence of disease for at least four weeks.
- **Partial response: Reduction by at least 30%** of the sum of the largest diameter of all measurable lesions with no new disease appearing, maintained for at least four weeks.
- **Progressive disease:** Any growth of existing disease or new lesions during treatment.

TABLE 14.1. Common and Serious Toxicities of Common Chemotherapeutic Agents

Drug	Side Effects	Monitoring Required
Alkylators (cyclophosphamide, ifosfamide)	**Hemorrhagic cystitis,** neurotoxicity (ifosfamide), severe nausea/vomiting.	UA to monitor for hematuria; **mesna** to bind to toxic metabolite (acrolein).
Anthracyclines (doxorubicin, epirubicin, idarubicin, mitoxantrone)	Dose-dependent cardiac toxicity (CHF), nausea/vomiting, bone marrow suppression.	Baseline echocardiogram and echocardiogram after a specified amount of chemotherapy (e.g., 300 mg/m^2 for doxorubicin).
Bleomycin	**Pulmonary fibrosis.**	Baseline PFTs.
Capecitabine	**Hand-foot syndrome** (painful erythema and desquamation of skin on the palms and soles).	
Cytarabine	Neurotoxicity, rash.	Cerebellar exam prior to each dose; steroids if rash is severe.
5-fluorouracil (5-FU)	**Hand-foot syndrome.**	
Gemcitabine	**Rare interstitial fibrosis.**	No special monitoring.
Irinotecan	Diarrhea.	Administer with Lomotil.
Methotrexate	Renal failure; hepatic enzyme elevation.	Check for effusions before administration (clearance is slowed if they are present, increasing the risk of renal failure). LFT monitoring is required.
Platinums (carboplatin, cisplatin)	**Neuropathy,** otoxicity, renal failure, potassium and magnesium wasting, severe nausea/vomiting (cisplatin).	Monitor renal function; conduct a neurologic exam prior to each dose. Conduct an audiologic exam at baseline (cisplatin only) if the patient has any hearing complaints.
Taxanes (docetaxel, paclitaxel)	Allergic reactions, fluid retention, **neuropathy.**	**Premedicate with steroids.**
Vinca alkaloids (vinblastine, vincristine)	**Neuropathy** (including motor neuropathy) with **severe constipation.**	Determine if the patient has had a bowel movement within 48 hours of a dose.

Chemotherapy Resistance

- ***MDR1:*** The multidrug resistance gene; encodes a pump that removes toxins from cancer cells.
- **Drug-specific resistance mechanisms:** Involve upregulation of downstream enzymes, antiapoptotic proteins, and the like.

TABLE 14.2. Common Targeted Agents and Their Uses

Drug	Major Indications	Side Effects
Hormonal agents	**GnRH agonists** (goserelin, leuprolide): Androgen deprivation for prostate cancer.	**Osteoporosis, hot flashes, anemia, weight gain.**
	Tamoxifen: Adjuvant therapy for breast cancer.	As above, but **without osteoporosis.**
	Aromatase inhibitors (anastrozole, letrozole, exemestane): Adjuvant therapy for breast cancer.	As above, **with osteoporosis.**
Targeted enzymes	**Erlotinib** (EGFR inhibitor): Non–small cell lung cancer (NSCLC).	**Acneiform rash;** rare pulmonary fibrosis.
	Imatinib (*BCR-ABL* tyrosine kinase inhibitor): CML, gastrointestinal stromal tumor (GIST).	Edema, transaminitis.
	Sorafenib (VEGF inhibitor): Renal cell carcinoma.	**Diarrhea, rash, hand-foot syndrome, hypertension.**
	Sunitinib (VEGF inhibitor): Renal cell carcinoma, GIST.	**Diarrhea, rash, hypothyroidism.**
Cytokines	**Interferon:** CML, melanoma, renal cell carcinoma.	**Depression** with suicidal ideation; **bone marrow suppression.**
	Interleukin-2: Renal cell carcinoma, melanoma.	**Hypotension, renal failure, edema.**
Monoclonal antibodies	**Alemtuzumab** (anti-CD52 antibody): CLL.	Bone marrow suppression.
	Bevacizumab (VEGF inhibitor): Metastatic colorectal cancer, NSCLC.	**Bleeding, hypertension, proteinuria.**
	Cetuximab (EGFR inhibitor): Head and neck cancer, metastatic colorectal cancer.	**Acneiform rash.**
	Gemtuzumab (anti-CD33 antibody): Relapsed AML.	Bone marrow suppression.
	Rituximab (anti-CD20 antibody): B-cell lymphomas.	**Allergic reactions.**
	Trastuzumab (*HER2/neu* antibody): Breast cancer with *HER2/neu* overexpression.	**Cardiac toxicity (CHF).**

Adjuvant and Neoadjuvant Chemotherapy

- **Adjuvant chemotherapy:** Chemotherapy given **after surgery** to reduce the risk of recurrence.
- **Neoadjuvant chemotherapy:** Chemotherapy given **before surgery** to make resection easier and reduce recurrence by targeting micrometastases.

Radiation Therapy

Mechanism of Action

- Radiation induces ionization in biological tissues that damages DNA (cancer cells are less capable of repair than normal cells).
- Side effects include the following:
  - **CNS:** Memory loss, confusion, personality changes, anorexia, lethargy.

- **GI tract:** Nausea, mucositis, dry mouth.
- **Hematologic:** Bone marrow suppression, leukemia.
- **Musculoskeletal:** Osteonecrosis (classically of the jaw; risk ↑ with dental work).
- **Pulmonary:** Fibrosis.
- **Skin:** Desquamation, hair loss, scarring.
- **Spinal cord:** Paralysis (rare).

Methods of Administration

- **External beam radiation therapy:** The most commonly used modality. Toxicities can be minimized through use of the following:
  - **Conformal radiation therapy (CRT):** Shaping the radiation beam to precisely fit the tumor outline.
  - **Intensity-modulated radiation therapy (IMRT):** Shaping the intensity of the radiation beam.
- **Brachytherapy (implants):** The radiation source (in the form of **seeds**) is implanted within the tumor. Most often used in the treatment of **prostate cancer.**
- **Stereotactic radiosurgery:** A three-dimensional technique that delivers the radiation dose in one session, with a high dose of radiation delivered to a very small volume. Used primarily for treating brain tumors to avoid the toxicity of whole brain radiation.

Surgical Oncology

- Surgery may be employed to diagnose (via biopsy of lymph node or soft tissue mass) or to treat. Surgical treatment may be curative or palliative.
- Resection is predicated on the ability to achieve ⊖ margins, usually with at least 1 cm of normal tissue if possible, or more in special circumstances.
- **Debulking,** or removal of tumor without obtaining ⊖ margins, plays a role in a few diseases, such as **ovarian cancer.**
- Direct manipulation of tumor is avoided where possible in order to prevent local recurrence.

ONCOLOGIC EMERGENCIES

Superior Vena Cava (SVC) Syndrome

Compression of the SVC by tumor or thrombosis of the SVC.

Symptoms/Exam

- Presents with facial edema or erythema, shortness of breath, orthopnea, hoarseness, and arm or neck swelling.
- Exam reveals edema of the face, tongue, neck, and arms; dilation of upper body veins; and plethora of the face (see Figure 14.1).

Diagnosis

CT of the chest and neck, Doppler ultrasound, CXR. **Lack of lower extremity edema distinguishes SVC syndrome from right-sided heart failure.**

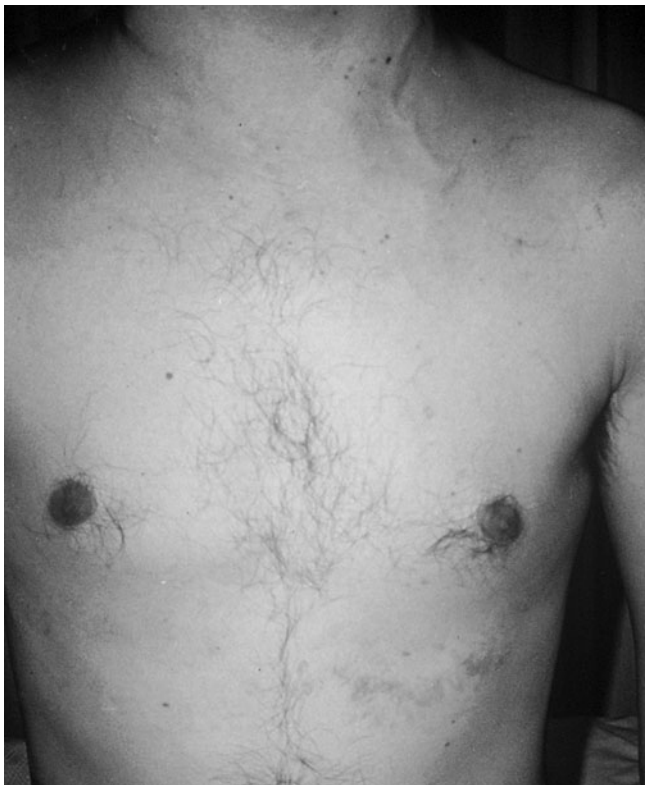

FIGURE 14.1. Superior vena cava syndrome.

A 27-year-old man with SVC syndrome. Note the prominent collateral veins of the chest and neck. (Courtesy of William K. Mallon, MD.)

TREATMENT

- **Corticosteroids and diuretics** provide symptomatic relief of edema and dyspnea.
- Initiate **radiotherapy or chemotherapy** depending on the malignancy.
- Institute thrombolytic therapy, stent, or anticoagulation if due to thrombosis.

COMPLICATIONS

Laryngeal and cerebral edema are life-threatening complications.

Spinal Cord Compression

Affects 1–5% of patients with metastatic cancer. Diagnostic and treatment delays are associated with paralysis and loss of bladder and bowel control.

SYMPTOMS

- **Early:** Presents with pain localized to the spine or radicular pain due to nerve root compression. Pain is exacerbated with movement, coughing, lying down, sneezing, or Valsalva/straining. **Pain generally precedes functional loss by weeks to months.**
- **Late:** Muscle weakness, sensory loss/sensory level, urinary retention, constipation, sphincter dysfunction, paralysis, autonomic dysfunction.

Once patients with spinal cord compression lose their ability to ambulate, they usually do not recover it.

In addition to a standard neurologic exam, the physical examination for spinal cord compression should include evaluation of rectal tone and examination for saddle anesthesia.

EXAM

- Tenderness to palpation or percussion over the affected area of the spine.
- Focal neurologic findings, UMN signs, abnormal plantar responses, sensory loss, rectal tone.
- **Cauda equina syndrome** refers to compression of the cauda equina (below L1), but the physiology and treatment are the same as those for cord compression.

DIAGNOSIS

- Obtain a thorough history and neurologic examination.
- **Plain films are not helpful in ruling out cord compression.**
- **MRI is the gold standard for diagnosis.** Gadolinium enhances the ability to visualize epidural metastases without bony involvement.
- If MRI is unavailable, CT scan or CT myelography can confirm the diagnosis.

TREATMENT

- The outcome depends on rapid assessment and diagnosis.
- If patients can walk at diagnosis, they will likely preserve their function with appropriate treatment.
- Early steroid administration reduces swelling and pressure on the cord. Administer high-dose bolus dexamethasone 10 mg IV followed by 4–10 mg PO/IV q6h.
- Definitive treatment options include immediate surgical decompression, radiation therapy (for radiation-sensitive malignancies), or, rarely, chemotherapy. **Consult neurosurgery, radiation oncology, and oncology early.**

Tumors that commonly metastasize to bone—

BLT with Mayo, Mustard, and Kosher Pickle

Breast
Lung
Thyroid
Multiple **M**yeloma
Kidney (renal cell)
Prostate

Tumor Lysis Syndrome

Rapid release of intracellular contents due to rapid lysis of cancer cells with life-threatening metabolic consequences. **Most commonly found in acute leukemias and lymphomas** (particularly Burkitt's lymphoma), especially after the initial doses of chemotherapy, but can also occur spontaneously. Also seen in bulky metastatic testicular cancer and small cell lung cancer. Rarely seen in other solid tumors.

*Calcium is **low** in tumor lysis syndrome because excess phosphate binds calcium. Potassium, uric acid, phosphorus, and LDH are elevated.*

SYMPTOMS/EXAM

- **Hyperuricemia, hyperkalemia, hyperphosphatemia, HYPOcalcemia** (the excess phosphate binds calcium).
- A markedly elevated LDH points to a risk of tumor lysis.
- May lead to oliguric renal failure.

DIAGNOSIS

Closely monitor serum laboratory values, including potassium, uric acid, calcium, phosphorus, and creatinine (q4h initially; then as clinically indicated).

TREATMENT

- Identify patients at risk before starting chemotherapy.
- Urine can be alkalinized with sodium bicarbonate infusion to achieve a urinary pH > 7.5 (although minimal evidence exists to support this).

- Allopurinol should be started before chemotherapy to reduce the level of hyperuricemia (monitor for changes in creatinine clearance and adjust the dose if necessary).
- Treatment is directed at managing electrolyte abnormalities, maintaining adequate hydration, and instituting dialysis if necessary.
- Consider the use of uricase, an expensive enzyme that metabolizes uric acid, in cases of severe tumor lysis (generally considered when uric acid is > 10).

Neutropenic Fever

Fever generally defined as > 38.3°C with an absolute neutrophil count (ANC) of 500/μL or less. An ANC < 100/μL carries the highest risk of rapidly fatal infection. Etiologies are as follows:

- **Bacteria** (gram-⊖ bacilli, gram-⊕ cocci): The most commonly implicated pathogens; increasing in incidence as a result of the ↑ use of indwelling catheters. **Coagulase-⊖ staphylococci are now the most common cause of bacteremia.**
- **Fungal infections:** More common in patients on broad-spectrum antibacterial therapy, those on corticosteroids, or those with prolonged neutropenia such as that following allogeneic bone marrow transplant. The most common fungal pathogens are *Candida* and *Aspergillus*.
- **Viruses:** Viral infections occurring during neutropenia include the herpesviruses (CMV, HSV, VZV, EBV) and respiratory viruses (RSV, influenza A and B, parainfluenza, rhinovirus, adenovirus).

Exam

Physical examination is directed at uncovering potential sources of infection and should focus on venous access sites and examination of the oropharynx, lungs, abdomen, and skin.

Diagnosis

- Obtain two sets of blood cultures, a urine culture, a culture of any catheter or catheter drainage, and a CXR.
- Additional evaluation is dictated by signs and symptoms.

Treatment

- **Initial empiric antibiotic therapy:** Administer broad-spectrum antibiotics covering gram-⊖ bacilli (including *Pseudomonas*), taking into account local drug resistance patterns.
- **Monotherapy:** Ceftazidime, cefepime, imipenem-cilastatin, meropenem, piperacillin-tazobactam.
- **Combination therapy:** An aminoglycoside plus antipseudomonal penicillin +/– β-lactamase inhibitors.
- **Vancomycin:** Generally not used as part of first-line empiric therapy except under the following conditions:
  - In the presence of a central line that appears infected.
  - If the patient was receiving fluoroquinolones or TMP-SMX as prophylaxis prior to the onset of neutropenic fever.
  - If blood culture shows gram-⊕ cocci.

- In the setting of known colonization with MRSA.
- In the presence of hypotension or sepsis with no identified pathogen.

- **G-CSF/GM-CSF:** May be considered in the setting of pneumonia, invasive fungal infection, or progressive infection.
- **Duration of treatment:**
  - Generally, broad-spectrum therapy must continue until the ANC recovers to 500/μL or greater and the patient is afebrile for 48 hours.
  - If fever resolves and no organism is identified but the patient remains neutropenic, IV broad-spectrum antibiotics should continue for at least seven days; then consider switching to oral medications.
  - If fever is unresponsive after 3–5 days, consider adding vancomycin and/or antifungals.

BREAST CANCER

Genetic syndromes markedly ↑ the risk for breast cancer, although they account for a minority of cases of breast cancer.

The risk of breast cancer ↑ with age. The lifetime risk for women is roughly 1 in 10. Risk factors are as follows:

- **Genetic syndromes:** For most patients, no identified genetic predisposition exists. Those with a genetic predisposition should be screened beginning at least 10 years before the earliest-onset cancer in the family history.
  - ***BRCA1:*** Associated with a dramatic risk of breast cancer (56–85% lifetime risk), ovarian cancer (15–45% lifetime risk), and prostate cancer (less frequent). Has an autosomal-dominant inheritance; Ashkenazi Jews are at highest risk.
  - ***BRCA2:*** Associated with breast and ovarian cancer as well as with pancreatic cancer and melanoma. *BRCA1* and *BRCA2* account for 50% of all inherited breast cancers.
  - **Cowden's syndrome:** A rare *PTEN* gene mutation. The lifetime risk of breast cancer is 25–50%.
  - ***ATM* mutation.**
  - **Li-Fraumeni syndrome:** Breast cancer along with sarcomas, brain tumors, leukemia, lymphoma, and adrenal cancer.
- Other risk factors include a family history of early-age breast cancer diagnosis in family members, early menarche, late menopause, obesity, nulliparity or late age at first pregnancy, use of estrogen replacement therapy, and OCP use (controversial).

Inflammatory breast cancer is an aggressive form of breast cancer that is characterized by thickened skin (peau d'orange, or skin of the orange) and is usually accompanied by dermal lymphatic invasion. Breast conservation (lumpectomy) is generally considered inappropriate for local control.

Differential

Fibrocystic disease, fibroadenoma, atypical hyperplasia, abscess, adenosis, scars, mastitis. **Note:** No changes in screening intervals are recommended for these findings.

Diagnosis

- Breast cysts can be evaluated with ultrasound and can then be aspirated.
- Breast masses require either fine-needle aspiration (FNA) or core needle biopsy, possibly followed by excisional biopsy.
- **Any mass that is felt on exam must be further evaluated with biopsy even if no abnormality is seen on mammogram.**
- **Algorithm: Palpated mass → mammogram and/or breast ultrasound → biopsy (or aspiration if the lesion is thought to be a cyst).**

Treatment

Treatment of **early-stage breast cancer** is as follows:

- **Ductal carcinoma in situ (DCIS):** A premalignant condition that is at high risk of turning into a cancer. Treatment involves excision with ⊖ margins **(lumpectomy) and radiation therapy** to the breast.
- **Lobular carcinoma in situ (LCIS):** A condition associated with an ↑ risk of breast cancer arising **elsewhere** in **both** breasts. Treatment with tamoxifen may be considered, but close follow-up and observation are indicated.
- **Invasive ductal or lobular carcinoma:**
  - Lumpectomy followed by radiation therapy is equivalent to mastectomy in terms of overall survival, but the risk of local recurrence is lower with mastectomy.
  - **Sentinel lymph node biopsy** involves injecting dye or tracer in the tumor and identifying which lymph node takes it up. The node or nodes are then excised and assessed for metastasis. Complete axillary node dissection is warranted only in sentinel-node or clinically node-⊕ tumors.
  - Mastectomy for large or multifocal tumors, or for patient preference.
- **Adjuvant therapy:** Guidelines for the use of adjuvant therapy are as follows:
  - In general, any patient with an **infiltrating** ductal or lobular cancer **> 1 cm** or with ⊕ **lymph nodes** should receive adjuvant therapy.
  - Hormone therapy with **tamoxifen** (for **five years**) or an **aromatase inhibitor** is effective **only in patients with estrogen- or progesterone-receptor-⊕** (ER- or PR-⊕) breast cancers. Aromatase inhibitors should be used only in postmenopausal patients. Chemotherapy may be needed even in patients with ER- or PR-⊕ tumors. For ER/PR-⊖ tumors, chemotherapy is the recommended adjuvant treatment. Tamoxifen reduces the risk of recurrence by approximately 40%; chemotherapy reduces the risk by approximately 25%.

Treatment of **advanced (metastatic) breast cancer** is as follows:

- **First-line treatment:** For ER/PR-⊕ postmenopausal women, first-line treatment consists of an aromatase inhibitor. Aromatase inhibitors prevent the conversion of adrenal androgens into estrogens by targeting aromatase enzymes in muscle and fat.
- **Second-line hormonal therapy:** For ER/PR-⊕ women, second-line therapy includes tamoxifen, a selective estrogen receptor modulator.
- If patients progress or are **hormone receptor** ⊖, treat with **chemotherapy.** Active drugs include paclitaxel, docetaxel, doxorubicin, methotrexate, vinorelbine, capecitabine, and 5-FU.
- **Patients with overexpression of *HER2*:**
  - Comprise 10% of patients with breast cancer.
  - Associated with a poorer prognosis.
  - May respond to trastuzumab (Herceptin), a humanized monoclonal antibody against the *HER2* receptor.

Hormonal therapies such as tamoxifen and aromatase inhibitors are effective only in patients with ER- and/or PR-⊕ tumors.

Prevention

See the discussion of cancer screening in the Ambulatory Medicine chapter.

Squamous cell cancers cause hypercalcemia due to the secretion of parathyroid hormone–related protein (PTHrP). Such cancers can also cavitate.

Smoking cessation is the best means of preventing lung cancer (and recurrent lung cancer). Eighty-seven percent of all cases of lung cancer are related to smoking, with the risk significantly higher in patients who have been exposed to asbestos and who also smoke. Lung cancer presents with weight loss, cough, hemoptysis, fatigue, recurrent bronchitis, and chest pain. It is divided into two categories on the basis of pathology: non–small cell lung cancer (NSCLC) and small cell lung cancer (SCLC).

Non–Small Cell Lung Cancer (NSCLC)

The most common type of lung cancer. Has multiple histologies (bronchoalveolar, adeno-, and squamous), all with the same treatment and natural history. **Accurate staging is key to determining the appropriate therapy.**

Diagnosis

CXR, CT of the chest and abdomen, blood work (including a liver panel); possibly a PET scan.

NSCLC with a pleural effusion is stage IIIB and is unresectable.

Treatment

- Treat according to stage:
  - **Stage I or II:** Consider surgical resection.
  - **Stage IIIA (spread to ipsilateral mediastinal lymph nodes):** May warrant resection. Adjuvant chemotherapy may be administered after surgery.
  - **Stage IIIB (spread to contralateral mediastinal lymph nodes or with a pleural effusion):** Consider chemotherapy and radiation.
  - **Stage IV (metastatic disease):** Chemotherapy has been shown to improve quality of life and modestly prolong survival compared with the best supportive care.
- Commonly used drugs for NSCLC include cisplatin, carboplatin, paclitaxel, docetaxel, gemcitabine, pemetrexed, vinorelbine, erlotinib, and, recently, bevacizumab.

Small Cell Lung Cancer (SCLC)

The majority of paraneoplastic syndromes are seen with SCLC. The exception is hypercalcemia due to PTHrP secretion, which is due to squamous cell cancer.

Characterized by early metastasis; **surgical resection is not part of therapy.** Often associated with neuroendocrine and paraneoplastic features.

Diagnosis

Has two stages (not staged via the TNM system used for most other solid tumors):

- **Limited:** All the visible cancer can be encompassed by a single radiation port in the chest.
- **Extensive:** Anything that is not limited.

Treatment

- Chemotherapy and radiation given together improve outcomes in limited-stage disease, but the prognosis remains poor.

- Chemotherapy alone is the treatment of choice for patients with extensive-stage disease, yielding high response rates. However, virtually all patients relapse.
- Since **SCLC has high rates of brain metastasis (up to 3–5%),** prophylactic cranial irradiation should be considered in all patients with a complete response to chemotherapy or chemoradiotherapy. Drugs of choice include etoposide and cisplatin.

MESOTHELIOMA

A neoplasm arising from the mesothelial surfaces of the peritoneum and pleural cavities, pericardium, and tunica vaginalis. Asbestos exposure ↑ the risk. Smoking and asbestos exposure are synergistic.

Symptoms/Exam

Presents with dyspnea and nonpleuritic chest pain.

Diagnosis

- Thoracentesis or pleural biopsy. Occasionally video-assisted thoracoscopic (VATS) biopsy is needed.
- Approximately 60% of patients have right-sided disease on x-ray; 5% have bilateral disease. Most commonly presents with a large unilateral pleural effusion.

Treatment

- Surgical resection if possible.
- Debulking of tumor, thoracentesis, pleurodesis; supportive measures to ↓ the impact of pleural-based disease.
- Chemotherapy is only modestly effective, and the prognosis is poor.

THYMOMA

An anterior mediastinal tumor that is often detected during the workup of **myasthenia gravis.** Most are benign, but some progress to thymic carcinoma. Other paraneoplastic syndromes associated with thymoma include **pure red cell aplasia.**

Ten percent of patients with myasthenia gravis have thymomas. Thirty percent of patient with thymomas have myasthenia gravis.

Differential

Germ cell tumor, lymphoma, thyroid mass.

Treatment

Resection is the most effective treatment. If spread occurs outside the mediastinum, chemotherapy and radiation may be used as well but have limited efficacy.

SQUAMOUS CELL CARCINOMA (SCC) OF THE HEAD AND NECK

Many SCCs are curable. Major risk factors include tobacco (cigarettes, chewing tobacco, cigars), alcohol use, and HPV. Lesions progress as follows: leukoplakia → erythroplakia → dysplasia → carcinoma in situ → invasive carcinoma. The highest risk of morbidity and mortality associated with head and neck cancer results from local extension rather than from metastasis.

Symptoms

May present with a hoarse voice, a globus sensation, otalgia, a sore in the mouth or throat, a lump in the throat, numbness in the face or throat, odynophagia, dysphagia, lymphadenopathy, tinnitus, or hearing loss.

Exam

Evaluate the scalp, cranial nerves, lymph nodes, and oral cavity.

Diagnosis

- Pan–upper endoscopy should be performed under anesthesia to evaluate the entire aerodigestive tract.
- FNA is standard to establish involvement of cervical lymph nodes.
- Core needle biopsy is not done on newly diagnosed lesions owing to concerns over tumor recurrence in the needle tract.
- MRI or CT of the head and neck; CXR.

Treatment

Treatment depends on the anatomical site (e.g., the oral cavity, base of tongue, oropharynx, pharynx, hypopharynx, or larynx) and on the presence of lymph node involvement:

- **Early-stage tumors in the oral cavity, base of tongue, or lips:** May be treated with radiation or surgery alone.
- **Early-stage tumors of the oropharynx:** Radiation is the preferred modality.
- **Cervical lymph node involvement:** Treat with surgery, radiation, or chemoradiation. Patients often require a PEG tube to get through radiation, which has significant oral toxicity. Commonly used chemotherapeutic agents include cisplatin, carboplatin, 5-FU, paclitaxel, docetaxel, methotrexate, and, recently, cetuximab.
- For some patients with laryngeal cancer, voice-sparing treatments (partial laryngectomy, chemoradiotherapy) should be considered; as many as 25% can avoid laryngectomy.

NASOPHARYNGEAL CARCINOMA

Associated with EBV infection, not tobacco or alcohol. **Endemic to China and parts of Africa.**

Symptoms/Exam

Presents with a change in hearing, a sensation of ear stuffiness, tinnitus, nasal obstruction, and/or a mass in the neck.

Diagnosis

The same as that for SCC of the head and neck.

Treatment

Not a surgical disease; requires chemotherapy (cisplatin) with concurrent radiation. Two-thirds of patients are cured.

THYROID CANCER

Thyroid nodules are more common in women but are more likely to be malignant in men. Radiation exposure (e.g., Chernobyl; treatment of childhood acne) is a major risk factor. The "**90%**" mnemonic applies for thyroid nodules:

- **90% of nodules are benign.**
- **90% of nodules are cold** on RAI uptake scan; 15–20% of these are malignant and 1% of hot nodules are malignant.
- **90% of thyroid malignancies present as a thyroid nodule or lump.**
- > 90% of cancers are either papillary or follicular, which carry the best prognoses.

Refer to the Endocrinology chapter for a more detailed discussion of thyroid cancer.

ESOPHAGEAL CANCER

Risk factors include cigarette smoking, alcohol use, obesity, and **Barrett's esophagus.**

Symptoms/Exam

Presents with dysphagia, odynophagia, weight loss, cough, and hoarseness.

Diagnosis

- **Staging evaluation:** Evaluate with endoscopy and biopsy, chest CT, endoscopic ultrasound, and bronchoscopy (to rule out tracheal invasion).
- **Pathology:** The 1° histologies are squamous cell and adenocarcinoma (increasing in incidence; associated with obesity and GERD).

Treatment

- **Localized esophageal cancer:** Treat with chemoradiation (5-FU plus cisplatin and external beam radiotherapy) or surgery. Postoperative chemoradiation should be considered for locally advanced cancers.
- **Metastatic disease: Few good options are available;** drugs include cisplatin, paclitaxel, 5-FU, and gemcitabine.
- PEG tubes are often required to get patients through chemoradiation (as in head and neck cancer).

GASTRIC CANCER

The most common cancer in Asia; associated with a diet of smoked and pickled foods that is **high in nitrates** and low in vegetables. Working in coal mining and in nickel, rubber, and timber processing are additional risk factors.

Symptoms/Exam

Pain, anorexia, weight loss, vomiting, GI bleeding.

Diagnosis

- Endoscopy and biopsy.
- Staging evaluation includes CT of the chest, abdomen, and pelvis, as well as endoscopic ultrasound.
- Adenocarcinoma is the predominant histology.

Treatment

- Surgery is the preferred therapy for resectable gastric cancer.
- Adjuvant chemoradiotherapy is indicated after surgery for patients with locally advanced gastric cancer.
- Treat metastatic gastric cancer with chemotherapeutic agents such as ECF (epirubicin, cisplatin, 5-FU).

Gastrointestinal Stromal Tumors (GISTs)

Sarcoma of the stomach wall. Associated with an activating mutation in the **c-*kit*** oncogene.

Treatment

- Standard treatment is surgery; conventional chemotherapy is ineffective.
- For patients with metastatic GIST, targeted therapy with **imatinib** (the same agent used for CML), which inhibits c-*kit*, can lead to dramatic and prolonged responses in patients with previously untreatable and incurable disease.

PANCREATIC CANCER

A highly lethal cancer with a median survival of 9–12 months and a **five-year survival of 3%.** At diagnosis, > 50% are metastatic or unresectable. Risk factors include tobacco exposure and diabetes mellitus.

Symptoms/Exam

- Presents with jaundice, pain, glucose intolerance, and a palpable gallbladder **(Courvoisier's sign).**
- **Painless jaundice** is a sign of intrapancreatic bile duct obstruction and may allow for early detection of resectable disease.
- The serum marker **CA 19-9** can be useful in monitoring treatment but is not specific enough to be used for diagnosis

Diagnosis

CT of the abdomen with fine cuts through the pancreas (pancreatic protocol CT); endoscopic ultrasound; ERCP.

Treatment

- **Resectable disease:**
  - Defined as that which does not involve the major vessels or celiac axis, with no distant metastases.
  - The only curative therapy is pancreaticoduodenectomy (the Whipple procedure).
  - **Adjuvant therapy** after the Whipple procedure consists of chemoradiation with 5-FU.
- **Unresectable disease:** Treatment for unresectable cases includes the following:
  - Palliation of symptoms with gemcitabine-based chemotherapy, radiation, a biliary stent, or choledochojejunostomy to ↓ jaundice.
  - A nerve block to the celiac plexus may relieve pain.
- **Advanced pancreatic cancer:** Gemcitabine-based chemotherapy is associated with symptomatic relief and prolonged survival but has a low response rate.

CARCINOID TUMORS

Carcinoid tumors are neuroendocrine tumors that are most commonly located in the small bowel. Most are hormonally inert, but some can secrete excessive **serotonin,** prostaglandins, and kinins.

For further detail, refer to the section on carcinoid tumors and syndrome in the Endocrinology chapter.

HEPATOCELLULAR CARCINOMA

Risk factors include HBV (especially vertical transmission), HCV, alcohol abuse (especially in combination with HCV), hemochromatosis, α_1-antitrypsin deficiency, and androgen and estrogen therapy.

DIAGNOSIS

- High-risk patients should be screened with α-fetoprotein (AFP) and hepatic ultrasound, although the appropriate interval has not been established.
- Markedly elevated AFP in concert with consistent imaging and high-risk liver disease may obviate the need for a biopsy.
- In a patient with a history of colon cancer, it is important to rule out the possibility of an isolated liver metastasis, which should be resected if possible.
- The fibrolamellar variant is associated with the best prognosis.

TREATMENT

- Resection is the treatment of choice if liver function is adequate and anatomy permits.
- Patients with cirrhosis may be offered transplant for single tumors < 5 cm or three tumors < 3 cm each.
- Chemoembolization, intratumoral ethanol injection, cryotherapy, and radiofrequency ablation are all options for unresectable patients.
- There is no standard chemotherapy with proven efficacy. The multikinase inhibitor sorafenib has been shown to prolong survival in patients with good hepatic function.

COLORECTAL CANCER

Genetic syndromes include the following:

- **Hereditary nonpolyposis colorectal cancer (HNPCC):** Characterized by few polyps (nonpolyposis); associated with endometrial, gastric, renal, ovarian, and skin cancer and with the mismatch repair genes *MLH1/2* and *MSH1/2*.
- **Familial adenomatous polyposis (FAP):** Characterized by thousands of polyps; the treatment of choice is colectomy. Associated with a mutation in the *APC* gene.
- **Li-Fraumeni syndrome:** Associated with the p53 mutation.

HNPCC has few polyps, but FAP has thousands of polyps, and thus treatment for FAP is colectomy.

SYMPTOMS/EXAM

Presentation is highly variable. May be asymptomatic or present with symptoms ranging from abdominal pain to colonic obstruction, lower GI bleeding, or weight loss.

Lymph node involvement by colon cancer implies at least stage III disease and merits adjuvant chemotherapy.

Treatment

- **Treat according to stage.**
  - **Stage I:** Partial colectomy; no further therapy.
  - **Stage II:** Partial colectomy. Adjuvant therapy is controversial. Consider adjuvant chemotherapy for certain high-risk features (e.g., high-grade disease, obstruction, perforation, very large tumors).
  - **Stage III:** Partial colectomy. These cancers with lymph node involvement all merit adjuvant chemotherapy. The standard is 5-FU or 5-FU/leucovorin/oxaliplatin (abbreviated as FOLFOX) .
  - **Stage IV:** Palliative colectomy or colon diversion to prevent obstruction. Chemotherapy for metastatic disease is generally palliative. **The exception is stage IV disease due to one or more resectable hepatic metastases, which can still be curable with resection** (the liver is generally the first site of metastasis). In this case, surgery should be aggressively pursued.
- **Chemotherapeutic agents:** Two medications are the mainstay of chemotherapy for colon cancer:
  - **5-FU:** Converted to F-dUMP; inhibits thymidine production and interferes with DNA synthesis.
  - **Leucovorin (folinic acid):** Stabilizes the bond between F-dUMP and thymidylate synthetase, enhancing the efficacy of 5-FU.
  - Other drugs include irinotecan, oxaliplatin, cetuximab, and bevacizumab.
- **Rectal cancer:** Owing to the anatomy of the rectum, surgical approaches have less room for adequate margins (and the desire to preserve the rectal sphincter if possible). Therefore, **radiation therapy is often given either before or after surgery** in addition to or in combination with chemotherapy.

Colon cancer with one or more resectable liver metastases can still be curable with surgery. This is one of the few metastatic cancers that can be cured.

Prevention

See the discussion of cancer screening in the Ambulatory Medicine chapter.

PROSTATE CANCER

The most common cancer diagnosed in men. A ⊕ family history and African-American ethnicity are both risk factors.

Symptoms/Exam

- Often associated with urinary obstruction and concurrent prostatitis.
- **Screening measures** are as follows:
  - All patients with nodules warrant biopsy.
  - Those with a PSA > 4 merit biopsy.
  - A PSA that is < 4 but rapidly rising should be considered for biopsy.
  - A lower **percent free PSA** is associated with a higher risk of prostate cancer being present. In patients with a PSA < 4, this may aid in determining whether to biopsy.

Most men die with their prostate cancer, not from it.

Diagnosis

- DRE; transrectal ultrasound biopsy.
- The **Gleason score** involves the evaluation of grade under the microscope; tumors are graded from 2 to 10, with 2 being almost benign and 10 being highly aggressive. Has a prognostic impact on outcomes in almost every stage of prostate cancer.

Treatment

- **Localized disease:** Three major options are available for the treatment of **localized prostate cancer:**
  - **Watchful waiting:** For patients with significant comorbidities, elderly patients, or those with low-risk disease.
  - **External beam radiation therapy:** For patients with a risk of extraprostatic spread or contraindications to surgery.
  - **Brachytherapy:** Implantation of radioactive seeds in the prostate gland.
  - **Radical prostatectomy:** For patients with a long life expectancy and a high likelihood that cancer is confined to the prostate.
- **Advanced disease: Advanced prostate cancer** (i.e., recurrence after local therapies or metastatic disease) is treated in the following manner:
  - **Androgen deprivation:** The most effective medical therapy. Methods are as follows:
    - Bilateral orchiectomy.
    - LHRH agonists (suppress testosterone secretion by inhibiting FSH/LH release from the pituitary).
    - Oral antiandrogens are least proven but have fewer side effects. They are generally used only in combination with LHRH agonists (LHRH agonists + oral antiandrogens = combined androgen blockade). Medical complications include hot flashes, anemia, weight gain, erectile dysfunction, osteopenia, osteoporosis, and diabetes mellitus.
  - **Hormone-refractory metastatic prostate cancer** warrants the following approach:
    - Treat with chemotherapy; docetaxel with prednisone is currently first-line therapy.
    - Adjunctive therapy with zoledronic acid (bisphosphonate) to strengthen bones and prevent skeletal complications.

The decision to screen for prostate cancer should include a thorough discussion with the patient about risks (false positives, uncertain efficacy in reducing death from prostate cancer) and benefits (earlier diagnosis and treatment may improve survival).

Prevention

See the discussion of cancer screening in the Ambulatory Medicine chapter.

KIDNEY CANCER

Risk factors include obesity, smoking, and von Hippel–Lindau syndrome (associated with retinal angiomas, CNS hemangioblastomas, and kidney cancer).

Exam/Diagnosis

- Must be ruled out in patients with hematuria. Pursue IVP or CT with contrast.
- Rarely, patients may present with polycythemia due to excess erythropoietin production.
- Diagnosis is based on radiologic appearance. Biopsy of a renal mass is generally not done given the risk of seeding the tumor.

Treatment

- For localized disease, treatment is nephrectomy.
- Cytokine-based therapy (**IL-2, interferon**) can cause regression of tumors in metastatic disease (10–20%).
- Targeted therapy with multikinase inhibitors such as sunitinib and sorafenib has become standard therapy for metastatic disease.

- **Temsirolimus,** an mTOR inhibitor, also prolongs survival in patients with kidney cancer.
- Roughly 3–5% of patients who receive **high-dose IL-2** may have durable remissions.
- Nephrectomy may be indicated in the setting of metastatic disease if the kidney tumor itself represents the bulk of the cancer.

TESTICULAR CANCER

The most common cancer in younger men aged 15–35; a 2° peak occurs in men > 60 years of age. An undescended testicle is a major risk factor. Other risk factors include prior testicular cancer, Klinefelter's syndrome, and a ⊕ family history. The five-year survival rate for all patients with germ cell tumors is roughly 95%.

Symptoms/Exam

- Presents with a scrotal mass and low back pain (from retroperitoneal lymphadenopathy).
- Testicular pain does **not** indicate a benign etiology.
- Approximately 10% present as extragonadal germ cell tumors with no testis primary.

Diagnosis

- Evaluate with testicular ultrasound to identify a mass.
- **Never biopsy the testis;** an inguinal orchiectomy is needed to make the diagnosis.
- Serum markers elevated in 80% of germ cell patients are AFP and β-hCG.
- There are two major pathologic classifications:
  - **Seminoma: Never has an elevated AFP;** may have elevated β-hCG.
  - **Nonseminoma:** Includes embryonal carcinoma, yolk sac carcinoma, choriocarcinoma, teratoma, and seminoma (when histology is mixed seminoma and nonseminoma, treat as nonseminoma). Patients may have an elevated AFP and β-hCG.

Treatment

In patients who have metastatic testicular cancer at the time of diagnosis, the affected testicle must be removed despite treatment with chemotherapy because chemotherapy does not penetrate well into the testicles.

The treatment of germ cell cancers is determined by prognostic features and stage.

- **Early-stage seminoma:**
  - If disease is limited to the testis, treat with inguinal orchiectomy alone.
  - Observation, chemotherapy, and radiation therapy are all appropriate if the patient is felt to be at high risk for retroperitoneal lymph node metastasis.
  - If there is evidence of retroperitoneal metastasis on imaging, treat with radiotherapy.
- **Advanced seminoma:** Chemotherapy is standard and results in high cure rates (> 85%).
- **Early-stage nonseminoma:** Inguinal orchiectomy +/– retroperitoneal lymph node dissection +/– adjuvant chemotherapy.
- **Advanced nonseminoma:** Treat with chemotherapy. Results are almost as good as those achieved with seminoma.

- **Prognostic features:** Adverse prognostic factors include high tumor markers, the presence of visceral metastasis outside the lungs (e.g., liver, soft tissue, brain), and a mediastinal primary site.
- **Chemotherapeutic regimens for germ cell tumors** include bleomycin, etoposide, and cisplatin (BEP) or etoposide and cisplatin (EP).
- Intensive follow-up is essential, as even relapsed patients have high rates of cure. Follow-up measures to monitor for recurrence include CT scans, markers, and physical examination at frequent intervals.

COMPLICATIONS

- Fertility problems persist in 50% of germ cell tumor patients and are thought to be related to underlying pathology as much as to treatment. Sperm banking should be considered prior to the initiation of chemotherapy.
- Other long-term complications include an ↑ incidence of cardiovascular disease, hypertension, and 2° malignancies (a new testicular primary and 2° acute leukemia are the most likely).

BLADDER CANCER

Risk factors for bladder cancer include cigarette smoking, analgesic abuse (phenacetin), chronic urinary tract inflammation, infection with *Schistosoma haematobium*, Balkan nephropathy (a rare inherited disorder), and aniline dyes.

SYMPTOMS/EXAM

Presents with hematuria, difficulty voiding, renal failure, and bladder irritation/pain.

DIAGNOSIS

- Cystoscopy and biopsy, cytology, CT of the abdomen and pelvis, CXR, and bone scan if alkaline phosphatase is elevated.
- The most common pathology in the United States is transitional cell carcinoma, although SCC is also found, most frequently in parts of the world in which schistosomiasis is common.

TREATMENT

- **Superficial bladder cancer** (not penetrating into the detrusor muscle): Treat with local therapies such as excision, intravesicular BCG, or intravesicular chemotherapy.
- **Muscle-invasive bladder cancer:** Radical cystectomy.
- Neoadjuvant combination chemotherapy (chemotherapy before radical cystectomy) may ↓ the risk of recurrence and improve survival.
- Adjuvant chemotherapy (chemotherapy after radical cystectomy) is not yet proven to prolong survival, but it is often administered in high-risk patients.
- For metastatic disease, the standard of care is gemcitabine and cisplatin as first-line chemotherapy.

CERVICAL CANCER

Almost half of women with cervical cancer are diagnosed before age 35. Risk factors include sexual activity at an early age, HPV infection (subtypes 16, 18,

31, 33, and 35), multiple partners, cigarette smoking, and concurrent HIV infection.

Symptoms/Exam

The most common presenting symptom is vaginal bleeding between menses.

Diagnosis

- Colposcopy and biopsy.
- The majority of cancers are squamous cell, although adenocarcinoma accounts for 20% of all cervical cancers.

Treatment

- Options for early-stage disease include radiation therapy, cone excisional biopsy, and simple hysterectomy.
- For more advanced disease, combined chemotherapy and radiation therapy is standard; radical hysterectomy/pelvic exenteration is also used.

Prevention

See the discussion of cancer screening in the Ambulatory Medicine chapter.

ENDOMETRIAL CANCER

The most common genital tract malignancy in women, occurring primarily in postmenopausal women. Risks include unopposed estrogen (either endogenous or exogenous), obesity (due to ↑ aromatization of androgens to estrogens), and high levels of animal fat in diet. Childbearing ↓ the risk; tamoxifen is associated with an ↑ risk.

Symptoms/Exam

Postmenopausal uterine bleeding always requires evaluation.

Diagnosis

- Transvaginal ultrasound, endometrial sampling, or D&C.
- Adenocarcinoma (endometrioid) is the most common histology.

Treatment

- Radical hysterectomy, bilateral salpingo-oophorectomy, and lymph node sampling are the treatment of choice, with adjuvant radiation therapy for selected patients.
- Progestins and paclitaxel/doxorubicin/cisplatin play a role in treating metastatic disease.

OVARIAN CANCER

Epithelial ovarian cancer arises from cells that coat the ovary, which are similar to peritoneal epithelial cells. Risk is reduced by multiparity, OCP use, breast-feeding, and tubal ligation. *BRCA1*, *BRCA2*, and HNPCC are genetic risk factors; a ⊕ family history is a risk factor even in the absence of a genetic syndrome.

Symptoms/Exam

- There are very few symptoms in early-stage disease.
- ↑ abdominal girth, early satiety, rectal pressure, and urinary frequency are found in advanced disease.

Diagnosis

- Close surveillance is warranted for patients with a genetic predisposition. Although an optimal surveillance regimen has not been identified, annual examination, transvaginal ultrasound, and CA-125 are often performed, and prophylactic oophorectomy is considered.
- Different pathologies are associated with different prognoses:
  - Mucinous and clear cell cancers have a poorer prognosis.
  - Borderline tumors have a good prognosis.

Treatment

- TAH-BSO.
- Early-stage tumors can be treated with adjuvant chemotherapy (often paclitaxel/carboplatin) for high-risk features.
- Advanced tumors require surgical debulking of peritoneal metastasis followed by chemotherapy.
- A survival benefit has been shown for intraperitoneal chemotherapy in advanced (stage III) disease, although there is added toxicity.
- The treatment of ovarian germ cell tumors is similar to that of testicular cancer.

SARCOMA

Sarcomas are a heterogeneous group of cancers of mesenchymal tissue. Genetic risk factors include familial retinoblastoma, which is associated with osteosarcoma. Other risk factors include prior radiation therapy and chronic lymphedema. Subtypes are as follows:

- **Bone sarcomas:**
  - **Osteosarcoma:** Affects long bones in children and adolescents; associated with Paget's disease in the elderly.
  - **Chondrosarcomas:** Affect older adults.
  - **Malignant fibrous histiocytoma:** Affects older adults.
  - **Ewing's sarcoma:** Affects children and adolescents, classically arising in the diaphysis.
- **Soft tissue sarcomas:** Sites involved include the extremities, trunk, retroperitoneum, and visceral organs (e.g., leiomyosarcomas, GISTs).

Symptoms/Exam

Symptoms depend on the site but often include swelling and pain of an extremity.

Diagnosis

- FNA or open biopsy.
- The needle tract from the biopsy must be excised at surgery to prevent seeding of tumor.
- MRI is often more effective at imaging sarcomas.
- Sarcomas rarely metastasize to the lymph nodes; the most common metastatic site is the lung.

Treatment

- Most patients with bone sarcomas receive neoadjuvant chemotherapy followed by wide excision and then adjuvant chemotherapy.
- Pre- and postoperative chemotherapy for other sarcomas is controversial but is often administered.
- Radiotherapy is often given after surgery to achieve local tumor control.
- Limb-salvaging procedures should be attempted when possible.
- Patients with surgically resectable metastases should undergo surgery, which may cure selected patients.
- Ewing's sarcoma is highly sensitive to combination chemotherapy; five-year survival rates are high.
- Combination chemotherapy is recommended for metastatic disease; MAI (mesna, Adriamycin, and ifosfamide) is the current regimen of choice.

ANAL CANCER

HIV and genital warts due to HPV are independent and additive risk factors for anal cancer.

The most common histologies are squamous cell and cloacogenic (transitional cell), which behave similarly. The major risk factor is anal intercourse leading to HPV infection; genital warts are a risk factor and are potentiated by HIV infection.

Symptoms/Exam

- Patients often present with anal bleeding, pain, or the sensation of a mass in the anal canal.
- Lymph node drainage depends on the anatomic location. If the tumor is located below the dentate line, drainage is to the inguinal lymph nodes, which are the first site of metastasis. If the tumor is located above the dentate line, drainage is to the paravertebral and perirectal nodes.
- Spreads stepwise from the anus to the regional lymph nodes and then hematogenously to the liver.

Treatment

- Very small tumors can be surgically removed.
- Larger tumors or those with spread to the lymph nodes require chemoradiotherapy.

Prevention

Screen with anal Pap smear in high-risk patients.

Tumors that commonly metastasize to brain—

"Lots of Bad Stuff Kills Glia"

Lung
Breast
Skin (melanoma)
Kidney (renal cell CA)
Gastrointestinal

1° BRAIN TUMORS

Characterized by a bimodal age distribution; affect pediatric patients and those > 20 years of age (the peak is between 75 and 85 years). Subtypes are as follows:

- **Gliomas:** Most common; range from low grade to high grade (glioblastoma multiforme). Genetic syndromes that may predispose include tuberous sclerosis, NF1, Turcot's syndrome, and Li-Fraumeni syndrome, but these are rare causes.
- **Meningiomas:** Benign tumors that cause morbidity by mass effect.

Symptoms/Exam

- Present with symptoms referable to elevated ICP (headache, nausea, vomiting).
- Neurologic deficits, seizures, and strokelike phenomena are also seen.

Diagnosis

Diagnosis is best made on MRI followed by biopsy or surgical resection.

Treatment

- Surgery is the definitive therapy for brain tumors.
- Radiation may be considered for recurrent disease.
- Stereotactic or gamma-knife radiotherapy may be used for small tumors.
- Chemotherapy has limited utility in malignant gliomas, although oligodendrogliomas are highly chemosensitive (associated with chromosome 1p and 19q loss).
- Chemotherapeutic agents for 1° brain tumors include temozolomide and combination PCV (procarbazine, CCNU, vincristine).

Consider metastases to the leptomeninges (carcinomatous meningitis) as a cause of neurologic deficits or altered mental status in patients with advanced cancer. Leptomeningeal metastases are most common in breast cancer, signify a poor prognosis, and respond poorly to intrathecal chemotherapy.

Brain Metastases

Occur in 15% of patients with solid tumors, most commonly lung and breast cancer. In general, metastases portend a poor prognosis.

Treatment

- Patients with a solitary brain metastasis and no evidence of residual cancer elsewhere may be candidates for surgical resection followed by whole brain radiotherapy to prevent new metastases.
- For patients with multiple brain metastases, whole brain radiotherapy is the treatment of choice.
- Stereotactic radiosurgery or gamma-knife radiotherapy may be considered for those with solitary or few metastases.
- Brain metastases usually respond poorly to systemic chemotherapy due to poor penetration of chemotherapy through the blood-brain barrier.
- **Prophylactic** antiepileptic medication is not indicated.

Metastases reaches the brain via hematogenous spread, often passing through the lungs first, so check a CXR in any patient with brain metastases.

CARCINOMA OF AN UNKNOWN PRIMARY SITE

Comprise 2% of all cancer diagnoses.

Diagnosis

- Pathologic evaluation is the key component of workup.
- Immunohistochemical stains or electron microscopy may reveal the likely tissue of origin.
- Evaluation focuses on age- and gender-specific risk factors:
  - Check HCG and AFP in all patients (for germ cell tumor). Other tumor markers (e.g., CEA, CA-125, CA 19-9, CA 15-3) are useful for monitoring response to treatment but are too nonspecific to aid in diagnosis.
  - CT of the chest, abdomen, and pelvis.
  - PET scan is controversial but may be useful in locating a primary site.
  - Mammography and breast examination in women; testicular examination, DRE, and PSA testing in men.
  - Colonoscopy in all patients over 50.

Treatment

Some special scenarios are as follows:

- **Women with axillary lymph nodes containing adenocarcinoma:** Should be treated like breast cancer—i.e., with mastectomy and axillary lymph node dissection. Consider adjuvant therapy.
- **Patients with cervical lymph nodes and SCC:** Should be treated like SCC of the head and neck following thorough ENT evaluation.
- **Patients with inguinal lymph nodes and SCC:** Careful evaluation of the anal canal, the penis in men, and the vagina, uterus, cervix, and vulva in women.
- **Young men with poorly differentiated carcinoma and mediastinal or retroperitoneal mass:** Treat as germ cell tumor patients; evaluate for occult testicular cancer.
- **Men with bone metastasis:** Evaluate with PSA testing for prostate cancer.
- **Women with peritoneal carcinomatosis:** Treat for ovarian cancer.
- **Chemotherapy regimen for patients not falling into the above categories:** Etoposide and a platinum (cisplatin or carboplatin). The addition of paclitaxel may improve response and survival.

ACUTE LEUKEMIAS

Patients with acute leukemias can present with ***leukostasis****, which occurs with very high blast counts (WBC > 100,000 in AML and > 150,000 in ALL). Rigid blasts clog the microcirculation, leading to local hypoxemia, which most often causes CNS and pulmonary symptoms. It is considered an* ***oncologic emergency*** *and is treated with leukapheresis.*

Genetic disorders associated with acute leukemia include Down syndrome, Bloom's syndrome, Fanconi's anemia, and ataxia-telangiectasia. Risk factors include chemical exposure (e.g., benzene, petroleum products), hair dyes, smoking, and prior chemotherapy or radiation.

Symptoms/Exam

Present with bone pain and symptoms of pancytopenia (fatigue due to anemia, infection due to leukopenia, and bleeding due to thrombocytopenia).

Diagnosis

- Evaluate CBC and peripheral blood smear for blasts.
- **Bone marrow aspirate and biopsy** to assess for blasts, to include immunohistochemistry, cytogenetic evaluation, and flow cytometry.
- Check PT, PTT, D-dimer, and fibrinogen to evaluate for DIC.
- Check uric acid, LDH, potassium, creatinine, phosphorus, and calcium to evaluate for tumor lysis.

Acute Lymphoblastic Leukemia (ALL)

May have either B- (75%) or T-cell lineage. The Philadelphia chromosome t(9;22) is common and portends a poor prognosis. Adult ALL is more aggressive and less curable than childhood ALL. Patients with T-cell ALL should be tested for HTLV-1 (endemic to southern Japan, the Caribbean, the South Pacific, and sub-Saharan Africa).

Differential

ALL is distinguished from lymphoblastic lymphoma by more extensive bone marrow involvement (> 25%).

Treatment

- **Combination chemotherapy:** Vincristine, prednisone, methotrexate, doxorubicin, and asparaginase.
- **Treatment regimen:**
  - Induction chemotherapy.
  - Several cycles of high-dose consolidation chemotherapy.
  - Prolonged maintenance low-dose chemotherapy.
- CNS prophylaxis with intrathecal chemotherapy is mandatory for **all** patients regardless of CNS involvement (systemic chemotherapy does not sufficiently penetrate the blood-brain barrier).

Acute Myeloid Leukemia (AML)

More common than ALL in adults.

Diagnosis

Bone marrow biopsy with > 20% marrow blasts. **FAB classification** is as follows:

- **M0:** Undifferentiated.
- **M1:** Myeloid.
- **M2:** Myeloid with differentiation.
- **M3:** Promyelocytic leukemia (APL).
- **M4:** Myelomonocytic leukemia.
- **M5:** Monocytic.
- **M6:** Erythroid
- **M7:** Megakaryocytic

Treatment

- Induction chemotherapy with cytarabine (Ara-C) and an anthracycline.
- Consolidation therapy using high-dose Ara-C may lead to durable remission or cure.
- Bone marrow transplant (allogeneic or autologous) is considered in patients who relapse or who have cytogenetic changes that put them at high risk for recurrence.

Acute Promyelocytic Leukemia (AML-M3, APL)

Characterized by heavily granulated promyelocytic blasts; associated with t(15;17) involving the retinoic acid receptor. DIC is present in the majority of patients at diagnosis.

AML-M3 is unique among AMLs for its propensity to cause DIC and for its high curability when treated with ATRA.

Treatment

- Treatment involves the differentiating agent *all*-trans retinoic acid (ATRA), given during induction chemotherapy and as maintenance therapy.
- **Retinoic acid syndrome:** Characterized by pulmonary infiltrates, respiratory failure, fever, capillary leak syndrome, and cardiovascular collapse. Treated early with high-dose corticosteroids and temporary cessation of ATRA.

Chronic Myelogenous Leukemia (CML)

A myeloproliferative disorder resulting from malignant transformation of hematopoietic stem cells. Characterized by translocation of the *BCR* gene adjacent to ABL kinase, leading to a fusion protein *(BCR-ABL)*, the **Philadelphia chromosome t(9;22).**

Symptoms/Exam

- **Chronic phase:** Generally asymptomatic, but some patients present with fatigue, early satiety, LUQ pain, and/or weight loss. Hepatosplenomegaly is common. The WBC count is elevated but stable (predominantly myeloid series).
- **Accelerated phase:** Signaled by the presence of ↑ blasts and early forms in the peripheral blood; represents a transition to more aggressive disease.
- **Blast crisis:** Presentation is similar to that of acute leukemia. Highly refractory to conventional therapy; most often symptomatic (night sweats, weight loss, bone pain, fevers, cytopenias).

Diagnosis

Physical exam; review of peripheral blood smear; bone marrow biopsy with cytogenetics.

Treatment

- The old standard of care was allogeneic bone marrow transplant within two years of diagnosis or α-interferon and cytarabine for patients who could not undergo allogeneic transplant. Treatment has changed dramatically since the introduction of imatinib (see below).
- Busulfan and hydroxyurea play a role in reducing blood counts but are palliative and not curative.
- **Imatinib:**
  - A specific tyrosine kinase inhibitor targeting fusion protein *BCR-ABL*.
  - More than 90% of patients in the chronic phase will have complete normalization of blood counts (morphologic or hematologic remission) and 65% will have normal cytogenetics after one year of imatinib therapy (cytogenetic remission).
  - Only 10% of patients in blast phase have complete hematologic remission; 15% have major cytogenetic response.
  - Side effects are mild (nausea, rash, edema, transaminitis).
  - The optimal way to use imatinib in CML has yet to be determined, and long-term outcomes are not yet clear.

Chronic Lymphocytic Leukemia (CLL)

The most common leukemia in adults. Median survival is 10–15 years. Autoimmune phenomena are common.

Exam/Diagnosis

- More patients are identified in the early stage by virtue of their elevated lymphocyte count.
- Most patients are asymptomatic.

- Evaluation includes a detailed physical exam for lymphadenopathy, organomegaly, flow cytometry of peripheral blood, and bone marrow biopsy (not always done).
- **Evans' syndrome:** Common in CLL; involves autoimmune hemolytic anemia and thrombocytopenia.
- **Rai staging** is as follows:
  - **0:** Lymphocytosis alone.
  - **1:** Lymphocytosis and lymphadenopathy.
  - **2:** Lymphocytosis and enlarged spleen or liver.
  - **3:** Lymphocytosis and anemia.
  - **4:** Lymphocytosis and thrombocytopenia.

Treatment

- Treatment should be directed toward relieving disease-related symptoms, rapidly progressive disease, autoimmune hemolytic anemia or thrombocytopenia, and infection.
- Many different treatment approaches are available, including alkylating agents (chlorambucil, cyclophosphamide), nucleoside analogs (fludarabine, cladribine, pentostatin), and monoclonal antibodies (alemtuzumab).
- Treatment is highly effective in palliation but is not curative. Patients who are not symptomatic are generally not treated.
- For young patients, allogeneic bone marrow transplant should be considered.

Complications

Richter's transformation: CLL may transform into a large cell lymphoma in 3–10% of patients; associated with a very poor prognosis.

HODGKIN'S LYMPHOMA

The malignant cell is the Reed-Sternberg cell ("owl-eye" cell). Has a bimodal age distribution.

Symptoms/Exam

- Some 40% of patients present with systemic symptoms (B symptoms), which consist of weight loss, fever, and night sweats.
- Symptoms are also related to the site of involvement.

Diagnosis

- **Excisional** biopsy for architecture (FNA is not sufficient).
- Staging includes physical examination of lymph nodes, examination of Waldeyer's ring, detection of hepatosplenomegaly, CT of the chest/abdomen/pelvis, CXR, and measurement of laboratory values, including CBC, LDH, ESR, and alkaline phosphatase.
- Routine staging laparotomy (splenectomy) has fallen out of favor.

Treatment

- **Early-stage disease (localized lymphadenopathy):**
  - Subtotal nodal irradiation or mantle irradiation,
  - Chemotherapy with ABVD (Adriamycin, bleomycin, vincristine, and dacarbazine) or the Stanford V protocol followed by radiation of the involved field.

- **Advanced disease:** Combination chemotherapy with ABVD is standard.
- **Refractory disease:** Patients with refractory disease should be considered for high-dose chemotherapy followed by autologous stem cell transplant.

Complications

Long-term complications include myelodysplasia and acute leukemia, 2° cancers (breast cancer in women treated with nodal irradiation), cardiomyopathy (2° to doxorubicin), pulmonary toxicity (2° to bleomycin), infertility, hypothyroidism, and neuropathy.

NON-HODGKIN'S LYMPHOMA (NHL)

A heterogeneous group of cancers of B and T cells. The incidence of NHL is increasing for unknown reasons.

Symptoms/Exam

Include B symptoms (weight loss, fever, night sweats) and symptoms referable to lymph node masses or extranodal masses.

Diagnosis/Treatment

- Diagnosis is based on histology, immunohistochemistry, and flow cytometry.
- Both FNA and excisional biopsy are acceptable.
- Classification schemes include the Rappaport classification, the Working Formulation, the Revised European-American Lymphoma (REAL) classification, and the WHO classification.
- NHL can be roughly divided into three subtypes based on the natural history:
  - **Low grade:** Indolent; demonstrates high response rates to chemotherapy, but **generally not curable**. Treatment is based on reducing symptoms. Median survival is 6–10 years.
  - **Intermediate grade:** Curable. The standard chemotherapy, CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone), cures approximately half of all patients and is given in 6–8 cycles of therapy. Evidence indicates that adding **rituximab, an anti-CD20 antibody** that targets B-cell lymphoma cells, **improves survival.**
  - **High grade:** Highly aggressive and rapidly growing cancers, but potentially **curable with chemotherapy.** Lymphoblastic lymphomas are treated like ALL. Burkitt's lymphoma is associated with EBV in Africa. There is a risk of tumor lysis syndrome with high-grade lymphomas.
- **Important subtypes** are as follows:
  - **Mucosa-associated lymphoid tissue (MALT) lymphoma:** Gastric mucosa–associated lymphoma is linked to *H. pylori* infection; > 80% of cases regress with antimicrobial therapy.
  - **Mantle cell lymphoma:** Acts like an intermediate-grade lymphoma in aggressiveness but is not curable with conventional chemotherapy (as with low-grade lymphoma). Median survival is three years.
- The International Prognostic Index predicts outcomes on the basis of pretreatment patient characteristics.

Poor prognostic features in NHL include age > 60, LDH > 1× normal, poor performance status, stage of disease, and extranodal disease.

IMPORTANT TRANSLOCATIONS

- **Burkitt's lymphoma:** t(8;14).
- **Follicular lymphoma:** t(14;18).
- **Philadelphia chromosome:** t(9;22) (CML and a subset of ALL).
- **Good-prognosis AML (M4-Eo):** inv16.
- **Acute promyelocytic leukemia:** t(15;17) retinoic acid receptor and promyelocytic leukemia gene.

HIV AND CANCER

- HIV is associated with an ↑ incidence of NHL, anal cancer, cervical cancer, Kaposi's sarcoma, and Hodgkin's disease.
- **Kaposi's sarcoma** is associated with **HHV-8** and is treated with HAART, α-interferon, topical retinoids, localized radiation, or liposomal doxorubicin.
- The optimal treatment of NHL in HIV is not clear, but NHL accounts for 15% of AIDS-related deaths.
- CNS NHL risk is also ↑ in HIV.
- The risk for cervical cancer and anal cancer is ↑ by HPV and impaired cellular immunity.

SUPPORTIVE CARE/GROWTH FACTORS

Nausea and Vomiting

- **Types** include the following:
  - **Acute emesis:** Occurs within 24 hours of receiving chemotherapy.
  - **Delayed emesis:** Begins after 24 hours (associated with cisplatin, carboplatin, or cyclophosphamide).
  - **Anticipatory emesis:** A conditioned response in patients who have had poor nausea control with previous treatments.
- **Treatment options** are as follows:
  - **Selective 5-HT3 receptor serotonin antagonists:** Ondansetron, granisetron, dolasetron.
  - **Metoclopramide:** Must be given in high IV doses, but causes extrapyramidal side effects at those doses.
  - **Droperidol:** Dopaminergic blockade.
  - **Other:** Prochlorperazine, dexamethasone, lorazepam, dronabinol and cannabinoids, NK1 receptor antagonists.
  - Combinations of agents are usually necessary to achieve emetic control.

Myeloid Growth Factors (G-CSF, GM-CSF)

- Used for the prophylaxis of febrile neutropenia; indicated only in chemotherapy regimens with more than a 20% risk of neutropenic fever.
- **Indications:** Patients with neutropenia and sepsis, pneumonia, or fungal infection should get myeloid CSF in addition to antibiotics.
  - There is no indication for giving myeloid growth factors with uncomplicated neutropenic fever.
  - Safe to give in acute leukemia; reduces infectious complications.

The predominant side effect of G-CSF is bone pain, most often in the sternum and long bones.

- Other uses for myeloid CSFs include mobilization of stem cells for transplant.
- **Side effects:** The most common G-CSF side effect is bone pain.
- **Administration:** Dosing begins at least 24–48 hours after chemotherapy administration and should always stop at least 24 hours before subsequent chemotherapy.
- **Pegfilgrastim** is a long-acting, pegylated version of G-CSF.

Erythropoietin

- Anemia in cancer and/or chemotherapy impairs quality of life. Erythroid growth factors are approved for use in chemotherapy-associated anemia.
- **Administration:**
  - The FDA-approved dose is 150 U/kg SQ TIW.
  - The most commonly used dose is 40,000 U SQ weekly.
  - Patients often need supplemental iron to respond to erythropoietin.
- Darbepoetin alfa is a new agent with a long half-life; may use less frequent dosing (q 2–3 weeks).

Anorexia

- Caused by cancer and/or chemotherapy.
- Interventions include the following:
  - Nutritional counseling.
  - **Appetite stimulants:** Dronabinol, cyproheptadine, corticosteroids, megestrol acetate.

Fatigue

- Usually multifactorial and includes anorexia, anemia, depression, infection, hypoxia, deconditioning, and hypogonadism. Both causes and symptoms must be treated.
- **Management:**
  - Anemia is often a contributing factor; treat with transfusions or erythropoietic growth factors in chemotherapy treated patients.
  - Corticosteroids, megestrol acetate, counseling, physical therapy, and exercise may all help in selected patients.
  - Stimulants may be used in selected terminally ill patients.

CHAPTER 15

Psychiatry

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PSYCHIATRY PEARLS

- All psychiatric illnesses can be divided into four major categories (see Figure 15.1). As with other illness, symptoms suggest categories that can then be further clarified. In general, there are no objective laboratory tests for psychiatric diagnostic clarification, so a careful history is essential.
- Some psychiatric syndromes are diagnoses of exclusion; therefore, likely medical etiologies must be ruled out before such diagnoses can be made.
- Pharmacologic treatment follows from diagnosis or 1° symptoms (see Figure 15.1). Psychotic disorders are treated with antipsychotics; anxiety disorders are treated with anxiolytic agents. Mood disorders are treated with antidepressants or mood stabilizers, depending on unipolarity or bipolarity.
- Some psychiatric syndromes have symptoms from two major disease categories (e.g., schizoaffective disorder, which has both psychotic and mood disorder symptoms). For these syndromes, treatment generally involves medication with > 1 category, targeting each symptom separately.
- The choice of medication in each class should be based on several factors:
  - Proven efficacy for the illness being treated.
  - Patient demographics.
  - The likely side effect profile and tolerability to the patient.
  - Patient preference (to maximize patient compliance).
  - Drug-drug interactions with other medications.
  - The choice of benzodiazepine to use should be based on the nature of the anxiety symptom being treated (see Figure 15.2).

See Table 15.1 for case presentations of the common psychiatric disorders.

ANXIETY DISORDERS

Panic Disorder

Consists of at least **two** untriggered panic attacks, with impaired function due to **fear of having another.** Age of onset is in the 20s; the male-to-female ratio is 1:1. Prevalence is up to 4%.

SYMPTOMS

Panic attacks must develop abruptly and peak within 10 minutes. They must also include at least four of the following: tachycardia, diaphoresis, shortness

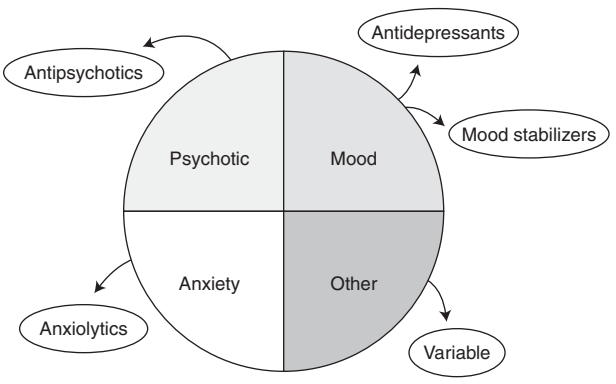

FIGURE 15.1. Pharmacologic management of psychiatric illness.

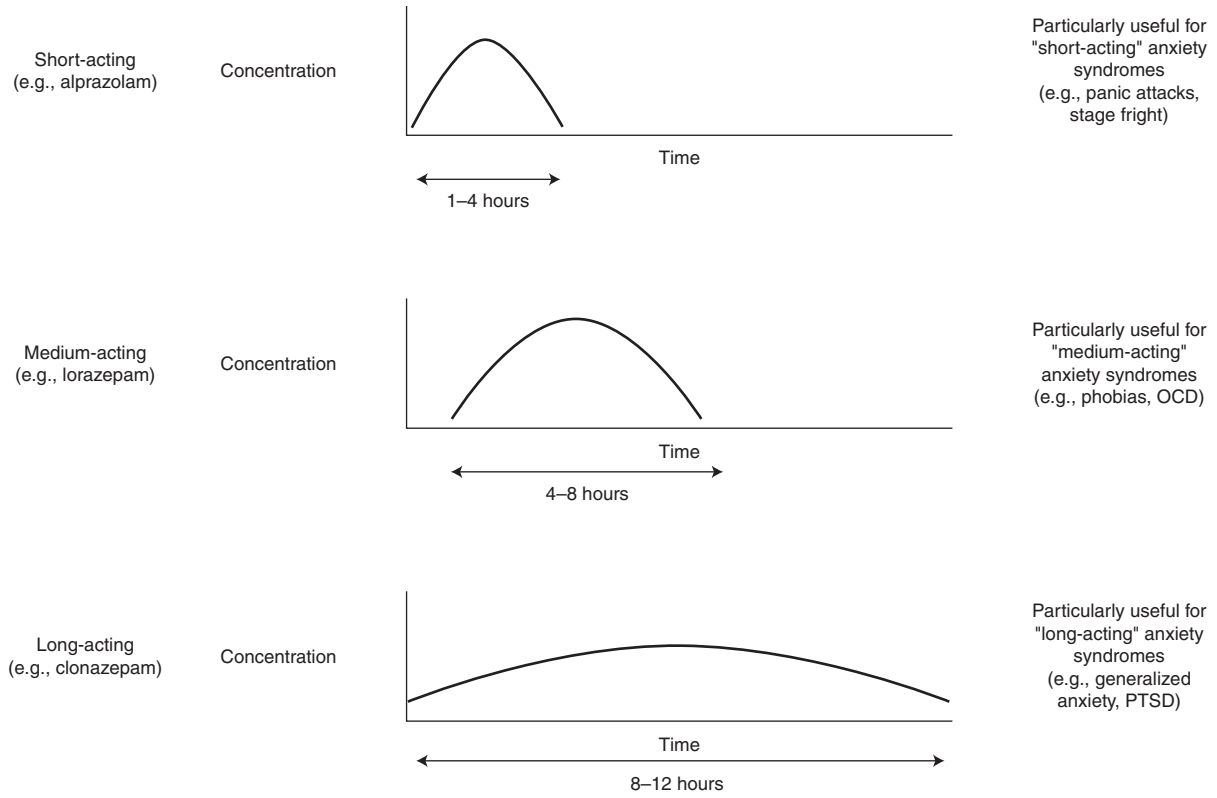

FIGURE 15.2. Length of action of benzodiazepines.

of breath, chest pain, nausea, dizziness, paresthesias, chills, derealization/depersonalization, and fear of losing control/going crazy/dying. A panic attack may be triggered or may occur spontaneously.

Panic disorder can occur with or without agoraphobia (fear of open spaces or of being alone in a crowd or leaving the home).

Differential

- **Endocrine:** Hypoglycemia, hypothyroidism, hyperthyroidism, hyperparathyroidism, pheochromocytoma.
- **Neurologic:** Seizure disorders, vestibular dysfunction, neoplasms.
- **Pharmacologic:** Acute intoxication, medication-induced symptoms.
- **Cardiovascular:** Arrhythmias, MI.
- **Pulmonary:** COPD, asthma exacerbation, pulmonary embolus.
- **Psychiatric:**
  - **Generalized anxiety disorder:** Patients typically have more chronic baseline anxiety.
  - **Obsessive-compulsive disorder (OCD):** Patients generally have recurrent repetitive thoughts (obsessions) and mannerisms (compulsions).
  - **Post-traumatic stress disorder (PTSD):** Patients have a history of a traumatic event and no history of panic attacks.

Diagnosis

Rule out all likely medical etiologies (e.g., ECG, electrolyte panel, CXR).

Treatment

- **Behavioral:** Various forms of behavioral psychotherapies.
- **Medication:** Benzodiazepine anxiolytic agents; β-blockers; antidepressants.

TABLE 15.1. Classic Case Presentations of Common Psychiatric Disorders

Major Depressive Episode	Generalized Anxiety Disorder	Bipolar Disorder	Schizophrenia
■ A 36-year-old woman with mild psychomotor retardation and dark circles under her eyes complains of excessive fatigue, as well as waking up in the middle of the night and being unable to fall back asleep. ■ She also has difficulty concentrating on child care, guilt about being a "bad mother," and lack of pleasure in activities she once enjoyed. ■ Her symptoms began three months ago and have gradually worsened to the point at which she can no longer perform her normal work and child care duties.	■ A 42-year-old man with mild psychomotor agitation complains that for the past six months, "my nerves have been shot." ■ He mentions that he worries "all the time and over everything" and can't fall asleep, adding that he often "snaps at his wife." ■ The patient also has chronic neck and shoulder tension as well as mild daily headaches that are relieved by acetaminophen.	■ A 25-year-old woman you have been treating for depression comes to your office in heavy makeup and a revealing red dress "because my husband told me I have to; he says my personality has changed. I think he just can't handle my womanhood." ■ The woman, previously demure and shy, frequently stands up to admire the artwork in your office, which she describes as "unusually sensual; I might have to test your kissing ability some day." She speaks very quickly and becomes angry whenever interrupted ("aren't doctors supposed to listen?"), but her anger dissipates within seconds and is replaced by feelings of exhilaration and joy. ■ She leaves after only a few questions but gives you a $100 "tip," stating that "I'll be rich soon anyway now that I've finally started my consulting business." She sings on her way out of the office.	■ A 19-year-old disheveled male is brought to your office by his parents, who state that their son "just got kicked out of college for harassing the dean." They add that they had to fly across the country to come get him because he "couldn't figure out how to get to the airport." ■ On interview, the man seldom speaks unless asked a question and rarely makes eye contact except to ask you if his eyes look okay, "because I see colors too brightly now." Occasionally he seems to talk to himself, stating, "Yeah, yeah, I know, but I like the doctor." ■ When asked why he left college, the man states that "no one there can handle the truth—the truth of the elders of the dean and his spies."

Generalized Anxiety Disorder

Defined as uncontrollable worry about a **broad range of topics** (e.g., work/school, relationships, health) over time (i.e., more days than not for at least **six months**). Age of onset is variable; the male-to-female ratio is 1:2. Prevalence is up to 8%.

Symptoms

Patients have poor control over the worry and at least **three** of the following: restlessness, poor concentration, irritability, easy fatigue, muscle tension, and sleep disturbances. Symptoms **must cause functional impairment** (i.e., they interfere with social or occupational functioning).

Generalized anxiety disorder is characterized by anxiety in many different situations (e.g., at work, during mealtimes, in social situations, while falling asleep).

Differential

- **PTSD:** Patients must have a history of a traumatic event.
- **Major depressive disorder:** Patients usually have depressed mood and other physical symptoms.
- **OCD:** Patients typically have recurrent repetitive thoughts (obsessions) and mannerisms (compulsions), and anxiety is only around the obsessions.

Diagnosis

Rule out all likely medical etiologies.

Treatment

- **Behavioral:** Various forms of individual and group psychotherapies.
- **Medication: Long-acting** benzodiazepine anxiolytic agents (e.g., clonazepam); antidepressants.

Complications

Often leads to **depression** if left untreated.

Specific Phobias

Fear of specific items. Age of onset is in **late childhood;** the male-to-female ratio is 1:2. Prevalence is up to 5%.

Symptoms

Excessive or unreasonable fear of a particular trigger; **patients realize that their response is excessive.** Must also cause **functional impairment** (i.e., must interfere with social or occupational functioning).

Differential

- **Panic disorder:** Panic attacks can be untriggered.
- **PTSD:** Patients avoid things only after having a traumatic event.
- **Generalized anxiety disorder:** Patients have chronic baseline anxiety about many things, not just when they are exposed to a trigger.

Treatment

- **Behavioral:** Exposure-response prevention therapy (exposes the patient to the stressor and prevents their usual fleeing response; desensitizes the patient to the stressor).
- **Medication:** β-blockers; short-acting benzodiazepine (e.g., alprazolam).

Specific phobias are the most common anxiety disorder.

Obsessive-Compulsive Disorder (OCD)

Obsessions and compulsions that cause significant impairment that is recognized as excessive or unreasonable. Age of onset is in childhood or early adulthood; the male-to-female ratio is 1:1. Prevalence is up to 3%.

Symptoms

- **Obsessions:** Recurrent or persistent thoughts that **cause** anxiety.
- **Compulsions:** Behaviors or rituals that temporarily relieve anxiety.
- **Patients must recognize that their symptoms are unreasonable** and that their obsessions are their own thoughts.

Differential

- **Delusional disorder:** Patients **do not** find the thoughts unreasonable.
- **Schizophrenia:** Patients have psychotic symptoms along with affective flattening, asociality, and avolition.
- **Generalized anxiety disorder:** Patients have anxiety in several different areas of their lives that are generally not relieved by compulsive acts.

Obsessions cause ↑ anxiety that is temporarily relieved by compulsions.

Treatment

- **Behavioral:** Exposure-response prevention therapy; cognitive-behavioral therapy (teaches patients how to diminish their cognitive distortions of the stressor and how to change their behavioral response).
- **Medication:** Clomipramine, SSRIs (e.g., paroxetine, sertraline, fluvoxamine). **Higher doses than those used for depression are usually required.**

Complications

Often leads to depression if left untreated.

Post-traumatic Stress Disorder (PTSD)

Reaction to a traumatic event characterized by reexperiencing, avoidance, and ↑ arousal. Age of onset is variable; the **male-to-female ratio is 1:2.** Prevalence is up to 3%, but 30% of Vietnam veterans are affected.

Symptoms

Patients must have a perceived life-threatening trauma and all **three** of the following:

1. Reexperiencing (flashbacks, nightmares, etc.).
2. Avoidance (places, thoughts, feelings, people related to the trauma).
3. ↑ arousal (insomnia, hyperstartle, poor concentration, anger outbursts).

Patients must have all symptoms for a minimum of one month.

Differential

- **Depression:** Patients do not have flashbacks to a traumatic event.
- **Generalized anxiety disorder:** Patients do not have a history of a traumatic event or flashbacks.
- **Adjustment disorder:** Patients have stress, anxiety, depression, or behavioral changes that are related to a specific trigger but do not have all three 1° symptoms: reexperiencing, avoidance, and ↑ arousal.

Treatment

- **Behavioral:** Various forms of individual and group psychotherapy.
- **Medication:** SSRIs, sleep agents (e.g., trazodone), long-acting benzodiazepines (e.g., clonazepam). Prazosin is sometimes given for nightmares.

Prevention

Some research suggests that reducing autonomic activation (with β-blockers) shortly after the trauma may ↓ the likelihood of developing PTSD.

In acute stress disorder, symptoms last < 1 month. In PTSD, symptoms last > 1 month.

Complications

- Long-term use of benzodiazepines can lead to psychological dependence. Prescribe with caution/selectivity.
- Avoidance of stimuli associated with the trauma can generalize to avoidance of wide-ranging things (which become secondarily associated with the trauma in the patient's mind). This leads to a far greater negative impact on the patient's life.

MOOD DISORDERS

Major Depressive Disorder

Age of onset is variable; the male-to-female ratio is 1:2. Lifetime prevalence in men is 10% and in women 20%. Risk is higher if there is a family history. **Untreated episodes usually last four or more months.**

Depression is the fourth largest cause of morbidity worldwide.

Symptoms

- Patients must have **depressed mood** *or* **loss of interest/pleasure (anhedonia)** *and* **five** of the **SIG E CAPS** symptoms (see mnemonic).
- Symptoms must represent a **change from baseline;** cause **functional impairment** (e.g., work, school, or social activities); and **last at least two weeks continuously.**

Differential

- **Adjustment disorder:** Patients have a known stressor that causes a reaction similar to a depressive episode, but the reaction is less severe and is triggered specifically by that stressor.
- **Dysthymic disorder:** Patients have "low-level depression" (i.e., depression involving fewer than five **SIG E CAPS** symptoms) that **lasts at least two years.**
- **Anxiety disorders:** Generalized anxiety disorder, PTSD, OCD.
- **Medical "masqueraders":** Hypothyroidism, anemia, pancreatic cancer, Parkinson's disease.
- **Substance-induced mood disorder:** Illicit drugs, thiazide diuretics, digoxin, glucocorticoids, benzodiazepines, cimetidine, ranitidine, cyclosporine, sulfonamides, metoclopramide.

Symptoms of major depressive disorder—

SIG E CAPS

Sleep (hypersomnia or insomnia)
Interest (loss of interest or pleasure in activities)
Guilt (feelings of worthlessness or inappropriate guilt)
Energy (↓)
Concentration (↓)
Appetite (↑ or ↓)
Psychomotor agitation or retardation
Suicidal ideation

Diagnosis

Eliminate potential medical etiologies (e.g., check TSH and CBC).

Treatment

- **Behavioral:** Various forms of individual and group psychotherapies.
- **Medication:** SSRIs; other classes of antidepressants. Choose medication on the basis of the symptom profile and anticipated side effect tolerability.
- **Electroconvulsive therapy (ECT):** Often reserved for medication-resistant depression; **especially useful in the elderly.**

Psychotherapy and antidepressants together are more effective for depression than either treatment alone.

COMPLICATIONS

- Severely depressed patients can develop psychotic symptoms (e.g., auditory hallucinations, paranoid ideations, ideas of reference). These symptoms can be treated with a low dose of an antipsychotic agent.
- **Suicidality:** One of the major comorbidities of untreated depression is suicidality.
  - Women generally have more attempts, but those of men are usually more lethal.
  - Clinicians must assess the degree of risk (e.g., consider the number of prior attempts, degree of premeditation, lethality of method, and access to the proposed method) and hospitalize if necessary to ensure patient safety.

Bipolar Affective Disorder

Extreme mood swings between mania and depression. Age of onset is most commonly in the 20s and the 30s; the male-to-female ratio is 1:1. Prevalence is 1%. Risk is higher if there is a family history. There are two types: **type I,** which alternates between mania and depression, and **type II,** which alternates between depression and hypomania (i.e., fewer symptoms for a shorter duration).

Symptoms of manic episodes—

DIG FAST

Distractibility
Insomnia (↓ need for sleep)
Grandiosity (↑ self-esteem)
Flight of ideas (or racing thoughts)
↑ **A**ctivities/psychomotor **A**gitation
Pressured **S**peech
Thoughtlessness (poor judgment—e.g., spending sprees, unsafe sex)

SYMPTOMS

- The symptoms of bipolar affective disorder are described by the mnemonic **DIG FAST.**
- Manic episodes **must last at least four days or lead to hospitalization** in order to be called mania. Anything less is considered hypomania.
- See the entry on depression for symptoms of the depressive episodes of bipolar disorder; remember the mnemonic **SIG E CAPS.**

DIFFERENTIAL

- **Major depressive disorder:** Patients have no history of a manic episode.
- **Schizoaffective disorder:** Patients have both **psychotic symptoms** and mood symptoms. Psychotic symptoms occur in the **absence** of mood symptoms.
- **Schizophrenia:** Patients do not have mood symptoms.

Treating a bipolar patient with antidepressant monotherapy can lead to a manic episode.

TREATMENT

- **Acute manic episode:** Hospitalize; consider antipsychotic agents (e.g., haloperidol, olanzapine, risperidone). ↑ doses of mood stabilizers (lithium carbonate, valproic acid, carbamazepine).
- **Maintenance treatment:** Give mood stabilizers such as those listed above. Titrate to the lowest effective dose to maintain mood stability.
- **Depressive episodes:** Antidepressants alone may trigger mania, so use carefully; consider individual and group psychotherapies.

PREVENTION

- ↑ the mood stabilizer dose in the presence of imminent symptoms of mania.
- Educate patients to recognize the earliest signs of mania/depression (sleep changes are often the first sign), and encourage them to seek additional help early.

Complications

- In severe phases of mania or depression, patients can have psychotic symptoms.
- **Left untreated, many patients have progressively more rapid cycling** (more frequent and shorter-duration episodes).

PSYCHOTIC DISORDERS

Schizophrenia

A history of **severe** and **persistent** psychotic symptoms (≥ 1 month) in the context of chronic impairment in function (> 6 months). There are several subtypes. **Age of onset is mostly in the late teens or 20s** for men and in the 20s–30s for women; the male-to-female ratio is 1:1. Prevalence is 0.5–1.0%; risk is higher if there is a family history.

Psychotic = "break with reality."

Symptoms

Patients must have **two** or more of the following:

- **Delusions:** Fixed false beliefs.
- **Hallucinations:** Most often auditory, but can be visual, olfactory, gustatory, or tactile.
- **Disorganized speech or thoughts.**
- **Grossly disorganized or catatonic behavior.**
- **Negative symptoms:** Affective flattening, avolition, alogia (poverty of speech), asociality.

The 4 A's of schizophrenia:

Affective flattening
Asociality
Alogia (paucity of speech)
Auditory hallucinations

Differential

- **Bipolar affective disorder:** Patients have psychotic symptoms only during extreme manic or depressive episodes.
- **Schizoaffective disorder:** Patients have psychotic symptoms **but also have prominent mood symptoms** (either depression or mania).
- **Delusional disorder:** Patients have **one** fixed false belief that is nonbizarre and that does not necessarily have a broad impact on functioning.
- **Developmental delay (mental retardation):** Patients do not have overtly psychotic symptoms and **have not deteriorated from a higher-functioning baseline.**
- **OCD: Patients are aware** that their obsessions (recurring repetitive thoughts) are their own thoughts.
- **Depression with psychotic features:** Patients have psychotic symptoms that occur **only** during depressive episodes, and the **depressive symptoms can occur without psychotic symptoms.**
- **Generalized anxiety disorder:** Patients have severe and chronic anxiety but no psychotic symptoms.
- **Substance-induced psychosis:** Especially associated with amphetamine or cocaine, both of which can cause paranoia and hallucinations. Patients have other signs/symptoms of substance use.
- **Medical "masqueraders":** Examples include neurosyphilis, herpes encephalitis, dementia, and delirium.
- **Neurologic "masqueraders":** Include complex partial seizures and Huntington's disease.

Olanzapine and several other atypical antipsychotics can cause significant weight gain and the risk of type 2 DM.

There is often a prodromal phase of schizophrenia involving negative symptoms without the positive symptoms (delusions or hallucinations).

Patients newly diagnosed with schizophrenia ("first break") are at high risk for suicide attempts.

DIAGNOSIS

Diagnose by history. **Neuropsychological testing** can be helpful in clarifying the diagnosis but often is not indicated.

TREATMENT

- Choose an antipsychotic agent that minimizes both symptoms and side effect profile.
- **First-line agents are now the atypical antipsychotics** (e.g., olanzapine, risperidone, quetiapine, ziprasidone, aripiprazole) because they have fewer motor side effects than do typical antipsychotics (e.g., haloperidol). However, atypicals are much more expensive and can cause significant weight gain.
- **Acute psychotic episodes:** Hospitalize; ↑ the dose of antipsychotic agent and consider the use of anxiolytic agents (e.g., alprazolam, clonazepam). Group therapy can provide a forum for reality checks if patients can tolerate them.
- **Maintenance treatment: Titrate to the lowest effective dose of antipsychotic agent to maintain stability.** Group therapy and structured day programs provide safety, socialization skills, and reality checks.

COMPLICATIONS

- Left untreated, will lead to a "**downward drift**" in socioeconomic class.
- Long-term use of typical antipsychotics (e.g., haloperidol) can lead to **tardive dyskinesias**—i.e., involuntary choreoathetoid movements of the face, lips, tongue, and trunk.
  - Tardive dyskinesias should be treated by minimizing doses of neuroleptics or by switching to an atypical neuroleptic (e.g., olanzapine, risperidone, quetiapine).
  - Can also be treated with a benzodiazepine (e.g., alprazolam, clonazepam) or a β-blocker (e.g., propranolol).

Delusional Disorder

Patients have a fixed false belief (delusion) that is nonbizarre. Prevalence is 0.025%. Age of onset is from the mid-20s to the 90s; the male-to-female ratio is roughly 1:1.

SYMPTOMS

- The delusion is often highly specific and organized into a system (i.e., patients can describe wide and varying evidence to support the delusion). This leads to hypervigilance and hypersensitivity.
- There is usually a relative lack of other symptoms, and patients often remain high functioning otherwise.

DIFFERENTIAL

- **Schizophrenia:** Patients often have a history of auditory hallucinations or other psychotic symptoms, such as prominent negative symptoms (affective flattening, avolition, alogia, asociality). Frequently, there is greater functional impairment.
- **Substance-induced delusions:** Particularly associated with amphetamine and cannabis.

- **Medical conditions:** Hyper-/hypothyroidism, Parkinson's, Huntington's, Alzheimer's, CVAs, metabolic causes (hypercalcemia, uremia, hepatic encephalopathy), other causes of delirium.

Delusional disorder is far less common than schizophrenia and is less responsive to medications.

Treatment

- Patients are often likely to refuse treatment and/or medications. Low-dose atypical antipsychotics may be helpful,
- Do not pretend that the delusion is true, but do not argue with patients to prove it false. Instead, gently remind them of your goal of maximizing functionality.

Complications

Many patients do not seek treatment, leading to progressive isolation and a ↓ in productivity and/or functional status.

SUBSTANCE ABUSE DISORDERS

Chronic Abuse/Dependence

Substance abuse is a maladaptive pattern of use that occurs despite adverse consequences. Dependence is abuse and physiologic tolerance.

Treatment

All the dependencies are characterized by **relapsing and remitting** patterns. Optimal treatment varies from patient to patient but usually involves **combinations** of the following:

- **Pharmacologic substitutes:** Replace the substance of abuse with a longer-acting and less addictive pharmacologic equivalent. Examples include methadone for heroin, chlordiazepoxide (Librium) for alcohol, and clonazepam for short-acting benzodiazepines. Can be used either in a detoxification program (e.g., 21 days) or as maintenance therapy (e.g., methadone maintenance).
- **Pharmacologic antagonists:** ↓ the pleasurable response associated with the substance of abuse. Examples include the following:
  - **Antabuse (disulfiram) for alcohol:** Blocks the efficacy of alcohol dehydrogenase, causing buildup of acetaldehyde.
  - **Naltrexone:** Thought to ↓ alcohol craving.
- **Therapeutic communities:** Provide a safe, structured environment in which to boost attempts at maintaining early sobriety. Can be inpatient (residential) or outpatient, brief or long-term.
- **Self-help organizations:** Provide a regular and ongoing community of peers to maintain ongoing sobriety. Examples include Alcoholics Anonymous (AA) and Narcotics Anonymous (NA).
- **Family support/education:** Provide support to family members; offer an environment in which to learn from and commiserate with others. An example is Al-Anon.
- **Individual counseling/therapy:** Various techniques focus on the following:
  - Understanding and eliminating triggers for relapse.
  - **Harm reduction approach:** Minimizing use of the substance, which minimizes its functional impact on patients' lives.
  - **Abstinence model:** Getting patients to accept that they cannot minimize use but must abstain in order to improve their functional quality of life.

- **Psychoeducation:** Educating patients regarding issues such as the cycle of relapses and remissions; the chronic nature of the illness; and available resources.

For information on the treatment of acute intoxication or withdrawal syndromes, see the Hospital Medicine chapter.

Complications

Chronic substance dependence leads to significant loss of productivity, functionality, and quality of life.

OTHER DISORDERS

Somatoform Disorders

A group of disorders in which patients complain of physical symptoms that have no clear medical etiologies. Affect 15% of all psychiatric patients and 20% of medical inpatients. Certain subtypes are more common in women (e.g., conversion disorder, pain disorder); others are more common in men (e.g., factitious disorder, malingering). All generally occur more often in those with lower socioeconomic status and education.

Symptoms

- Vary across the specific disorders, but all are insufficiently explained by medical causes alone.
- Demonstrate inconsistent findings and often lead to many unnecessary hospitalizations, procedures, and workups. Specific subtypes include the following:
  - **Somatization disorder:** Complaints are in at least **two** organ systems.
  - **Conversion disorder:** Complaints are in the **neurologic** system.
  - **Pain disorder:** Complaints are of pain (predominantly).
- **Hypochondriasis:** Complaints and fear are of serious diseases.
- **Body dysmorphic disorder:** Complaints are about a perceived defective body or body part.
- **Factitious disorder:** Complaints are **consciously simulated by the patient** (vs. somatization disorder).
- **Malingering:** Complaints are **consciously simulated by the patient with specific 2° goals** as a 1° motivator (vs. factitious disorder).

Diagnosis

- Eliminate likely medical etiologies through standard medical workups. A balance must be struck between sufficient workup to rule out realistic causes and exhaustive workup to rule out extremely rare causes.
- Psychiatric consultation can help clarify specific diagnoses and therefore potential treatment options that could be most helpful.

Treatment

- **Minimize** the number of different providers involved in the care of the patient.
- Establish and maintain a **long-term, trusting doctor-patient relationship;** schedule regular outpatient visits and routinely inquire about psychosocial stressors.

- On each visit, perform at least a partial physical exam directed at the organ system of complaint, and gradually change the agenda to inquire about psychosocial issues in an empathic manner.
- **Refer patients to a mental health professional** to help them express their feelings, thereby minimizing physical symptoms as a proxy for those feelings.
- **Treat any 2° depression** (i.e., depression 2° to the sense of hopelessness associated with having the somatoform disorder).
- Some patients may benefit from the use of an anxiolytic agent (e.g., alprazolam).
- Be aware that some patients will develop psychological dependence on medications, so prescribe selectively.

Informal "curbside" consults of colleagues can be quite helpful and are preferable to the formal introduction of yet another medical provider.

Attention-Deficit Hyperactivity Disorder (ADHD)

Persistent (> 6 months) problems with **inattention** and/or **hyperactivity and impulsivity.** Prevalence is 3–5%; the male-to-female ratio is 3–5:1.

Diagnosis

- Inattention, including at least **six** of the following:
  1. Poor attention to tasks, play activities, or schoolwork.
  2. Poor listening skills.
  3. Poor follow-through on instructions.
  4. Poor organizational skills.
  5. Avoidance of tasks requiring sustained mental effort.
  6. Frequent loss of things.
  7. Easy distractibility and forgetfulness.
  8. Frequent careless mistakes.
- Hyperactivity-impulsivity, including at least six of the following:
  1. Fidgetiness.
  2. Leaves rooms where sitting is expected.
  3. Excessive running/climbing.
  4. Subjective thoughts of restlessness.
  5. Difficulties with leisure activities.
  6. Acts as if "driven by a motor."
  7. Talks excessively.
  8. Interrupts others often.

In order for an adult to be diagnosed with ADHD, symptoms must have been present in childhood and must cause functional impairment.

Adults tend to have less hyperactivity than do children.

Differential

- **Med-seeking behavior:** Patients often present with a history of substance abuse (especially amphetamine abuse).
- **Bipolar affective disorder:** Inattention/racing thoughts occur only during manic episodes; are accompanied by a lack of need for sleep and by grandiosity/euphoria; and are cyclical in nature.
- **Substance-induced symptoms:** Especially amphetamine intoxication. Look for associated signs/symptoms of substance abuse.

Patients with ADHD describe stimulants as slowing them down rather than making them "high."

Treatment

- **Stimulants** (methylphenidate, others): ↑ the dose as needed.
- **Antidepressants:** If there is a risk of abuse/dependence, bupropion (Wellbutrin) is a nonaddictive and reasonable first-line agent.
- **Behavioral therapy:** Focus on changing maladaptive behaviors and on learning more effective ones.

2° amenorrhea may be a sign of an eating disorder in a young woman.

Eating Disorders

Marked disturbances in eating behavior. There are **two** major types:

- **Anorexia nervosa:** Patients have misperceptions of body weight, generally weigh < 85% of their ideal body weight, and self-impose severe dietary limitations. Affects 0.5–1.0% of adolescent girls; the male-to-female ratio is 1:10–20. More common in developed/Western societies and in more affluent socioeconomic strata.
- **Bulimia nervosa:** Episodic uncontrolled binges of food consumption followed by compensatory weight loss strategies (e.g., self-imposed vomiting, laxative and diuretic abuse, excessive exercise). Affects 1–3% of young women; the male-to-female ratio is 1:10.

Symptoms

- Both anorexia and bulimia involve a marked misperception of body image and poor self-esteem.
- **Anorexia only:** Actual body weight must be < 85% of ideal body weight (for height and age). Also presents with **lanugo,** dry skin, lethargy, bradycardia, hypotension, cold intolerance, hypothermia, and hypocarotenemia.
- **Bulimia only:** Patients must have at least **three** months of binge-purging activity that occur at least **twice a week.** They must also have a sense of **loss of control** during food consumption binges. Patients often have signs of frequent vomiting (e.g., low chloride levels, pharyngeal lesions, **tooth enamel decay,** scratches on the dorsal surfaces of the fingers) and **enlarged parotid glands.**

Differential

Medical causes of weight loss and amenorrhea; failure to thrive.

Diagnosis

Diagnose by history. A collateral history obtained from other family members is often helpful.

Treatment

- Correct electrolyte abnormalities.
- Psychotherapy.
- **Antidepressants:** SSRIs.

Personality Disorders

Persistent maladaptive characteristic patterns of behavior **that have been present since childhood** and cause **significant impairment in patients' functioning in society.** All are coded on Axis II.

Symptoms

There are several types, most often subdivided into clusters:

- **Cluster A** (aka the "**weird**" personality disorders):
  - Schizoid
  - Schizotypal
  - Paranoid
- **Cluster B** (aka the "**wild**" personality disorders):
  - Borderline

- Histrionic
- Narcissistic
- Antisocial

- **Cluster C** (aka the "**wimpy**" personality disorders):
  - Dependent
  - Obsessive-compulsive personality
  - Avoidant

People with Cluster B personality disorders will sometimes "split" medical personnel—i.e., they will give ***incompatible*** *impressions to different providers about their emotional state and motivation for treatment.*

Differential

Mental retardation (will have below-normal intelligence).

Diagnosis

Without a significant amount of collateral information, it is difficult to diagnose patients with personality disorders on a single visit. Because there must be a persistent pattern of behavior, patients should ideally be observed over time to ensure accurate diagnosis and referral.

Treatment

- Personality disorders are both longstanding and pervasive and are thus **resistant to treatment.**
- **Dialectical behavioral therapy** has been shown to be an effective treatment of **borderline personality disorder.** Brief **cognitive-behavioral therapy** groups may also maximize effective coping strategies and minimize functional impact on patients' lives.
- **Mood stabilizers** (e.g., valproic acid, lithium, carbamazepine) may be of use in **antisocial** and **borderline personality disorders. SSRIs** (e.g., fluoxetine, sertraline, paroxetine) may be useful in treating **borderline, dependent,** and **avoidant personality disorders.**

PATIENT COMPETENCE AND DECISION-MAKING CAPACITY

Patient **competence** refers to a patient's ability to regularly make medical decisions on his/her own behalf. It involves a **legal assessment** and is generally a long-term decision made outside the hospital or clinic setting. Patient **capacity** refers to the ability of a person to make an **informed decision** about a particular clinical decision (e.g., to operate or not) and always occurs in the context of a specific treatment encounter. Therefore, the fundamental question with regard to **patient decision-making capacity** is "Does the patient have the ability to make the decision in question on his/her own behalf, or should you (or someone else; see the discussion of medical ethics in the Ambulatory Medicine chapter) make decisions for him/her?" The answer depends on the **context** of care:

- **Patients with acute/emergent medical issues** (e.g., massive hemorrhage, delirium): In most states, doctors have the right to perform emergent medical care. Although not explicitly defined, "emergent" is generally thought of as "when there is an imminent loss of life or limb." Technically, without explicit patient or representative consent, you must confine your care to the treatment of emergent conditions.
- **Patients with acute psychiatric issues** (e.g., actively psychotic, floridly manic, dangerously suicidal): Again, laws vary from state to state, but most states allow for emergent psychiatric treatment. This may include medications (IM or IV if necessary), locked hospitalization, locked seclusion, or physical restraints.

- **Patients with subacute medical conditions** (e.g., nonemergent medical or surgical procedures): Patients have the right to refuse recommended treatment as long as they:
  - **Know and can repeat** the nature of the medical condition.
  - **Know and can repeat** the benefits/risks of and alternatives to the recommended treatment.
  - **Consistently** express their rationale for their decision.
- **Patients with subacute psychiatric conditions** (e.g., schizophrenia but not actively psychotic; depression but not currently actively suicidal; bipolar but not floridly manic): Recommended medical treatment should be offered just as if there were no psychiatric condition (see above).
  - Laws regarding recommended psychiatric care vary significantly across states. Some states allow doctors significant power in forcing unwanted treatment, while others give patients significant rights to refuse, which can be overturned only in a court of law.
  - Remember that if/when the condition becomes acute/emergent, most states allow psychiatric treatment.
- **Patients with advance directives:** By definition, patients may sign advance directives only when they have the mental capacity to do so.
  - As long as the advance directive explicitly addresses the recommended/anticipated treatment, doctors must adhere to the patient's prestated wishes even if those wishes will lead to a worse outcome (including death).
  - When the directive does not explicitly address an emergent or subacute medical condition (and the patient cannot respond), staff and/or the patient's family/friends must attempt to infer what the patient's wishes would be and treat accordingly.

CONFIDENTIALITY IN PSYCHIATRY

The following are some exceptions to confidentiality in psychiatric practice:

- If the patient is suicidal or homicidal, protective steps may have to be taken that breach confidentiality.
- Child abuse must be reported to protective services.
- If the plaintiff in a lawsuit has made his or her medical or psychiatric condition an issue, the defendant has the right to know about and to obtain the records of the plantiff's evaluation and treatment.
- A court may order a physician to disclose confidential information.
- The results of a court-ordered pretrial evaluation may be available to the defense attorney, the prosecuting attorney, and the judge.
- The results of a disability evaluation will be available to the attorney or agency that requested the evaluation.

SPECIAL POPULATIONS IN PSYCHIATRY

Geriatric Patients

Early dementia can often present as depression.

Psychotic and anxiety disorders (with the exception of relationship or trauma-related disorders) tend not to present initially late in life, but late-life onset of depression is common.

- **Medication side effects:** Geriatric patients are more sensitive to medications that cause orthostasis or cognitive impairment.
- **Depression:** In general, depression that first presents in late life is more difficult to treat than depression that first presents in early or midlife.

- **Dementia:** In many cases, depression can be the first clinical sign of mild cognitive impairment or early dementia, especially Alzheimer's disease.

Adolescents on psychiatric medicines should be monitored very closely for agitation or anxiety side effects.

Adolescent Patients

Mid- to late adolescence is the most common time for early signs of schizophrenia or bipolar disorder to begin, with significant impairments in functioning tending to occur in the late teens to early 20s.

- **Depression:** In adolescents (and children), irritability can often be more prominent than sadness or anhedonia when diagnosing depression.
- **Suicidality:** Adolescents are more prone to impulsive acts, so close monitoring when beginning antidepressant medications (which can sometimes cause anxiety or agitation as side effects) is crucial.

Patients with HIV/AIDS

Psychomotor slowing and personality change can sometimes be seen in HIV-associated cognitive impairment. Some antiretroviral medications (e.g., efavirenz) can have significant psychiatric side effects.

THERAPEUTIC DRUGS IN PSYCHIATRY

Adverse Effects

Table 15.2 outlines both common and potentially serious adverse effects associated with psychiatric drugs.

Important Drug-Drug Interactions

- **Carbamazepine:**
  - An autoinducer of cytochrome P-450 isoenzyme, so the level needs to be rechecked and the dose often ↑ after several weeks of use.
  - ↓ serum level of OCPs.
  - Erythromycin, INH, and H_2 blockers all ↑ carbamazepine levels.
- **Valproic acid:** Levels are ↑ by aspirin and anticoagulants.
- **Benzodiazepines:**
  - Levels are ↑ by disulfiram, ketoconazole, valproic acid, erythromycin, and cimetidine.
  - Diazepam (Valium) and alprazolam (Xanax) ↑ levels of digoxin and phenytoin.

Nonpsychiatric Medication Classes with Psychiatric Side Effects

- **Antiretrovirals** (e.g., efavirenz): Delirium, mania, irritability, cognitive impairment.
- **Dopamine agonists** (e.g., pergolide, carbidopa-levodopa): Hallucinations, paranoia.
- **Antihistamines** (e.g., diphenhydramine, hydroxyzine): Delirium, cognitive impairment.
- **Anticholinergics** (e.g., benztropine, oxybutynin): Delirium, cognitive impairment.
- **Steroids** (e.g., prednisone): Mania, psychosis, elation, depression.

TABLE 15.2. Adverse Effects of Commonly Administered Psychiatric Drugs

Class	Examples	Common Side Effects	Medically Serious Side Effects
SSRIs	Paroxetine (Paxil), fluoxetine (Prozac), sertraline (Zoloft), citalopram (Celexa), fluvoxamine (Luvox)	Sedation, weight gain, GI discomfort, sexual dysfunction.	Serotonin syndrome (tachycardia, hypertension, fever, hyperthermia, myoclonus, convulsions, coma).
Antidepressants	Bupropion (Wellbutrin) Venlafaxine (Effexor)	Insomnia, "jitteriness." Constipation, dizziness.	Lowered seizure threshold. Lowered seizure threshold, hypertension.
Mood stabilizers	Lithium	Cognitive dulling, tremor, sedation, nausea, diarrhea, T-wave flattening.	Lithium toxicity, hypothyroidism (in long-term use), nephrogenic diabetes insipidus.
Mood stabilizers/ anticonvulsants	Valproic acid (Depakote)	Weight gain, sedation, cognitive dulling.	Thrombocytopenia.
	Carbamazepine (Tegretol)	Same as above.	SIADH, agranulocytosis, Stevens-Johnson rash.
Typical high-potency antipsychotics	Haloperidol (Haldol), fluphenazine (Prolixin)	Sedation.	Acute dystonic reactions, neuroleptic malignant syndrome, tardive dyskinesia (in long-term use).
Typical midpotency antipsychotics	Thioridazine (Mellaril), chlorpromazine (Thorazine)	Sedation, anticholinergic side effects (dry mouth, constipation, urinary retention, tachycardia).	Acute dystonic reactions, neuroleptic malignant syndrome, tardive dyskinesia (in long-term use).
Typical low-potency antipsychotics	Perphenazine (Trilafon), trifluoperazine (Stelazine)	Orthostatic hypotension.	Acute dystonic reactions, neuroleptic malignant syndrome, tardive dyskinesia (in long-term use).
Atypical antipsychotics	Olanzapine (Zyprexa)	Weight gain, sedation.	Hypercholesterolemia, possible diabetes mellitus.
	Risperidone (Risperdal)	Weight gain.	Hyperprolactinemia; side effects of typical antipsychotics (when used in high doses).
	Clozapine (Clozaril)	Drooling, weight gain.	Agranulocytosis.
	Quetiapine (Seroquel)	Sedation, orthostasis.	Hypotension.
	Ziprasidone (Geodon)	Sedation.	QTc prolongation.
	Aripiprazole (Abilify)	Restlessness.	

CHAPTER 16

Pulmonary Medicine

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Lung Physical Findings

Table 16.1 outlines physical findings typically associated with common lung conditions.

Lung Volumes

Common definitions pertaining to lung volumes are as follows (see also Figure 16.1):

- **Residual volume (RV):** Air in the lung at maximal expiration.
- **Expiratory reserve volume (ERV):** Air that can be exhaled after normal expiration.
- **Tidal volume (TV):** Air that enters and exits the lungs during normal respirations; generally 500 cc.
- **Inspiratory reserve volume (IRV):** Air in excess of TV that enters the lungs at full inspiration.
- **Functional reserve capacity (FRC):** RV + ERV.
- **Inspiratory capacity (IC):** TV + IRV.
- **Total lung capacity (TLC):** RV + ERV + TV + IRV.

Capacities are the sum of two or more volumes.

Alterations in Lung Function

Table 16.2 outlines changes in lung function associated with obstructive and restrictive lung disease. Table 16.3 lists common pulmonary disorders by category.

ABG Interpretation

ABGs can distinguish respiratory acidosis from respiratory alkalosis.

- **Acute respiratory acidosis:** pH ↓ by 0.08 for each 10-mmHg rise in P_{CO_2}.
- **Acute respiratory alkalosis:** pH ↑ by 0.08 for each 10-mmHg fall in Pa_{CO_2}.

TABLE 16.1. Physical Findings Associated with Common Lung Conditions

	Tracheal Shift	Thoracic Expansion	Fremitus	Resonance	Breath Sounds	Egophony	Other
Consolidation (open bronchus)	–	↓	↑	↓	Tubular	Ipsilateral	Whispered pectoriloquy
Consolidation (atelectasis)	Ipsilateral	↓	↓	↓	↓	–	–
Pleural effusion	Contralateral	↓	↓	↓	↓	+ or –	–
Pneumothorax	Contralateral	–	↓	↑	↓	–	Coin test

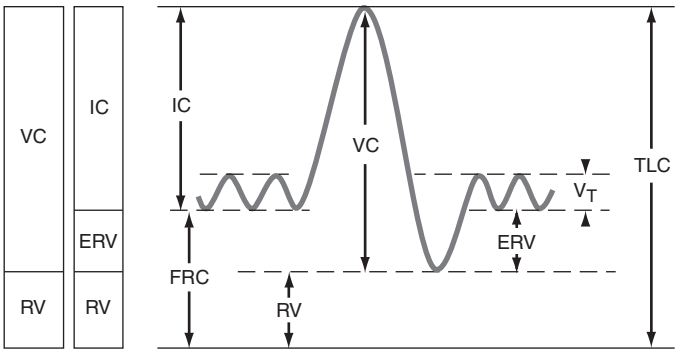

FIGURE 16.1. Lung volumes.

Lung volumes, shown by block diagram (left) and by spirogram tracing (right). VC, vital capacity; V_T, tidal volume. (Reproduced, with permission, from Weinberger SE. *Principles of Pulmonary Medicine*, 3rd ed. Philadelphia: W.B. Saunders, 1998, Copyright © 1998 Elsevier.)

CXR

- Often the first diagnostic test performed to evaluate pulmonary symptoms.
- Can reveal infiltrates, nodules, masses, effusion, and mediastinal and hilar abnormalities (see Tables 16.4 and 16.5).

CT Scan

- Offers several advantages over routine CXRs:
  - Cross-sectional images allow for the comparison of different lesions that might be superimposed on CXR.
  - Better at characterizing lesions both by density and by size.
  - Particularly valuable in evaluating mediastinal and hilar disease.
- CT angiography (in which contrast is injected and images are rapidly acquired by helical scanning) can be used to detect pulmonary embolism (PE) in segmental or larger vessels.
- High-resolution CT provides individual cross-sectional images of 1–2 mm and allows for better recognition of bronchiectasis, emphysema, and interstitial lung disease (ILD).

TABLE 16.2. Obstructive vs. Restrictive Lung Disease[a]

	FEV_1/FVC	TLC	RV	VC	MIP	MEP
Obstructive	↓	N to ↑	↑	↓	N	N
Restrictive						
Pulmonary parenchymal	N to ↑	↓	↓	↓	N	N
Extraparenchymal neuromuscular	N	↓	↑	↓	↓	↓
Extraparenchymal chest wall	N	↓	↑	↓	N	N

[a] FEV_1 = forced expiratory volume in one second; FVC = forced vital capacity; MIP = maximum inspiratory pressure; MEP = maximum expiratory pressure.

TABLE 16.3. Diagnostic Categories of Common Pulmonary Disorders

Obstructive	Restrictive—Parenchymal	Restrictive—Extraparenchymal
Asthma	Idiopathic pulmonary fibrosis	**Neuromuscular:**
COPD	Sarcoidosis	Diaphragmatic weakness/paralysis
Bronchiectasis	Drug- or radiation-related ILD	Myasthenia gravis
CF	Collagen vascular disease–related ILD	Guillain-Barré syndrome
		ALS
		Cervical spine injury
		Chest wall:
		Kyphoscoliosis
		Obesity
		Post-thoracoplasty

PET Scan

- A useful technique for the evaluation of solitary pulmonary nodules at least 1 cm in size.
- Radiolabeled fluorodeoxyglucose is injected and rapidly transported into neoplastic cells, which then "light up" with PET imaging.

V/Q Scan

- Often used in the evaluation of PEs.
- Technetium-labeled albumin injected into the vein becomes trapped in the pulmonary capillaries, thereby following the distribution of blood flow.
- Radiolabeled xenon gas is inhaled to demonstrate the distribution of ventilation.
- Defects in perfusion that follow the distribution of a vessel and are not accompanied by defects in ventilation are called **mismatched defects** and may represent PEs.

Pulmonary Angiography

- Used to visualize the pulmonary arterial system.

TABLE 16.4. Infiltrates Found on CXR

Upper Lobe—ASTECS	Lower Lobe—BADASSER
Ankylosing spondylitis	**B**ronchiectasis
Sarcoidosis	**A**spiration
Tuberculosis	**D**ermatomyositis/polymyositis
Eosinophilic granulomatosis	**A**sbestosis
Cystic fibrosis (CF)	**S**cleroderma
Silicosis	**S**LE, **S**jögren's syndrome
	Early Hamman-Rich syndrome
	Rheumatoid arthritis (RA)

TABLE 16.5. Masses Found on CXR

Anterior Mediastinal "7 T's"	Posterior Mediastinal
Teratoma	Bronchial cysts
Thymoma	Enterogenic cysts
Thymolipoma	Abscess
Thymic carcinoma/carcinoid	Non-Hodgkin's lymphoma
Thymic cyst	Neurogenic tumors
Thoracic thyroid	Pericardial cysts/plasmacytoma
Terrible lymphoma	Hodgkin's lymphoma

- Contrast medium is injected through a catheter placed in the pulmonary artery.
- A **filling defect** or **cutoff** is often seen in cases of PE.
- Can also be used to investigate suspected pulmonary AVMs.

Bronchoscopy

- Allows for the direct visualization of the endobronchial tree.
- **Bronchoalveolar lavage** is a technique used to sample cells and organisms from the alveolar space using aliquots of sterile saline. It is most helpful for diagnosing infectious and neoplastic disease.
- **Transbronchial biopsy** is performed by passing a small forceps through the bronchoscope into the small airways to obtain parenchymal tissue. Transbronchial biopsy may be helpful in differentiating infection, neoplasm, ILD, granulomatous disease, and bronchiolitis obliterans with organizing pneumonia.
- **Transbronchial needle aspiration** involves the passing of a hollow-bore needle through the airway into a mass lesion or an enlarged lymph node. This is particularly useful in cases of mediastinal or hilar adenopathy, allowing for the differentiation of neoplasm, sarcoidosis, fungal disease, and mycobacterial disease.

COUGH

Cough is one of the most common conditions for which patients seek medical attention. A systematic approach makes it possible to diagnose the cause in the majority of cases.

Symptoms

- Inquire about postnasal drip syndromes, asthma, GERD, treatment with ACEIs, and smoking.
- A productive cough usually represents an infectious or chronic process such as bronchiectasis. Cough productive of blood may represent malignancy, infection, or the first sign of connective tissue disease (e.g., Goodpasture's syndrome, Wegener's granulomatosis).

Exam

The physical exam should focus on the nasal mucosa, lungs, heart, and extremities (for clubbing). Boggy nasal mucosa may be a sign of postnasal drip.

Expiratory wheezing or crackles point to the need for further testing of the lower respiratory tract.

Diagnosis

Estimating the duration of cough is often the first step toward establishing the diagnosis.

- **Acute cough:** Of < 3 weeks' duration.
  - Viral infections are the most common cause.
  - Other causes include allergic rhinitis, acute bacterial sinusitis, COPD exacerbation, and infection with *Bordetella pertussis.*
  - May also be the presenting symptom of left heart failure, asthma, or conditions that predispose patients to aspiration.
- **Subacute cough:** Of 3–8 weeks' duration.
  - Postinfectious cough is the most common etiology.
  - Subacute bacterial sinusitis, asthma, and infection with *B. pertussis* may all cause cough lasting 3–8 weeks.
- **Chronic cough:** Of > 8 weeks' duration.
  - Roughly 95% of cases are caused by postnasal drip, GERD, asthma, chronic bronchitis, bronchiectasis, or ACEI use.
  - It is important to remember that cough may have multiple etiologies.

Treatment

Treatment depends on symptoms and response to treatment.

DYSPNEA

Dyspnea is the uncomfortable awareness of difficult, labored, or unpleasant breathing. Normal resting patients are unaware of the act of breathing. Dyspnea can be caused by a variety of conditions, but roughly 95% of cases are due to one of five major causes: cardiac (e.g., CHF), pulmonary (e.g., COPD, asthma, ILD), psychogenic factors, GERD, and deconditioning.

Symptoms/Exam

In determining the cause of dyspnea, it is critical to ascertain (1) the time course over which the symptoms occurred (see Table 16.6) and (2) the extent of physical exertion that is required to produce the sensation. Further distinctions are as follows:

- **Orthopnea:** Dyspnea upon lying in the supine position. Characteristic of CHF and, in rare cases, of bilateral diaphragmatic paralysis.
- **Trepopnea:** Dyspnea upon lying in the lateral decubitus position. Most often occurs in patients with CHF.
- **Platypnea:** Dyspnea upon assuming the upright position.
  - Usually associated with lower lobe pulmonary AVMs or microvascular shunts due to hepatopulmonary syndrome.
  - Also associated with **orthodeoxia,** or arterial desaturation in the upright position that improves when lying supine.
  - **Platypnea-orthodeoxia syndrome** is seen in lower lobe pulmonary AVMs or microvascular shunts due to **hepatopulmonary syndrome.**

Diagnosis/Treatment

- Conduct a systematic diagnostic and therapeutic evaluation for the cause of dyspnea.

TABLE 16.6. Differential Diagnosis of Dyspnea

	Acute Dyspnea (minutes to hours)	Chronic Dyspnea (days to years)
Pulmonary disorders	Pneumonia/bronchitis Pulmonary embolism Pneumothorax Bronchospasm (asthma, COPD) Obstruction (anaphylaxis, aspiration)	COPD Asthma ILD Deconditioning Pulmonary hypertension
Cardiovascular disorders	Ischemia CHF Cardiac tamponade	Cardiomyopathy

- Review the history and physical exam with particular attention to the most common causes (see above).
- Obtain a CXR.
- Depending on the findings above, obtain the following:
  - PFTs with spirometry and responsiveness to methacholine or bronchodilator; lung volumes; diffusion capacity; O_2 saturation at rest and with exercise; and flow volume loops (see Figure 16.2).
  - Noninvasive cardiac studies, including ECG and echocardiography +/– stress testing.
  - Chest CT; 24-hour esophageal pH monitoring.
- Final determination of the cause of dyspnea is made by observing which therapy relieves the symptoms.

WHEEZING

A wheeze is a continuous musical sound lasting > 100 msec. Wheezes can be high or low pitched, can consist of single or multiple tones, and can occur during inspiration or expiration.

Symptoms/Exam

- Expiratory wheezes obtained by history or examination do **not** always point to a diagnosis of asthma, and inspiratory wheezes do **not** always suggest upper airway obstruction. When upper airway obstruction is present, however, patients typically develop dyspnea when the obstruction is < 8 mm in diameter and stridor when the diameter is < 5 mm.
- Polyphonic wheezes consisting of multiple notes suggest dynamic compression of the large, more central airways. Monophonic wheezes classically suggest disease of the smaller lower airways (see Figure 16.2 for examples of flow volume loops in patients with upper airway obstruction). **Variable extrathoracic obstruction** is most commonly encountered in clinical practice.

Differential

Table 16.7 outlines the differential diagnosis of wheezing. Remember, "All that wheezes is not asthma." The differential is broad, but when asthma is di-

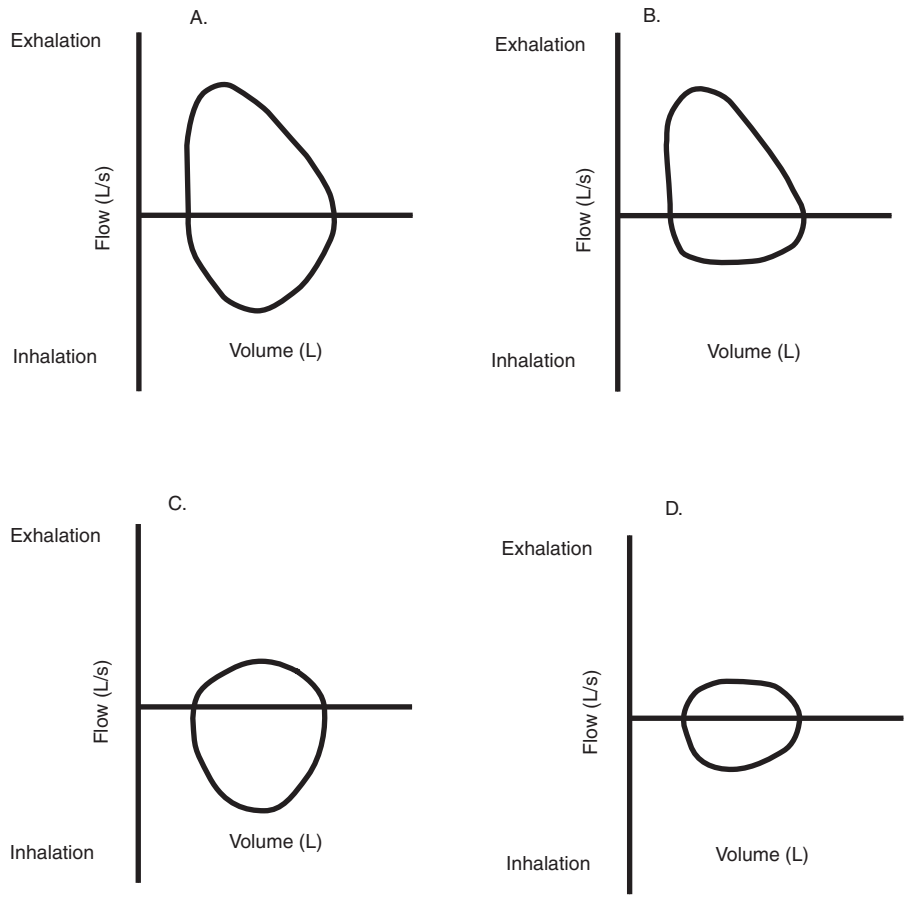

FIGURE 16.2. Flow volume loops.

(A) Normal pattern. (B) Variable extrathoracic obstruction (e.g., vocal cord paralysis or dysfunction). (C) Variable intrathoracic obstruction (e.g., bronchogenic cysts). (D) Fixed obstruction (e.g., prolonged intubation and resultant tracheal stenosis).

TABLE 16.7. Differential Diagnosis of Wheezing

Upper Airway Obstruction		Lower Airway Obstruction
Extrathoracic	**Intrathoracic**	
Vocal cord dysfunction	Tracheal stenosis	ABPA
Postnasal drip	Foreign body	Asthma
Laryngeal edema	Benign tumors	Aspiration
Malignancy	Tracheomalacia	Bronchiolitis
Relapsing polychondritis	Malignancy	Bronchiectasis
Wegener's granulomatosis		CF
		COPD
		CHF
		Parasitic infections
		PE

agnosed, also consider vocal cord dysfunction, allergic bronchopulmonary aspergillosis (ABPA), and postnasal drip.

Diagnosis/Treatment

- Flow volume loops can help differentiate intrathoracic from extrathoracic obstruction. ABPA is suggested by peripheral eosinophilia, ↑ serum IgE levels, immediate wheal-and-flare skin reactivity to *Aspergillus* antigens, and/or serum precipitants.
- Treatment for other etiologies of wheezing depends on the specific cause. Lack of improvement after treatment is initiated should alert the physician either to alter therapy or to investigate other potential etiologies.

HEMOPTYSIS

Defined as the coughing up of blood from the trachea, bronchial tubes, and lungs. Can range from blood-streaked sputum to life-threatening bleeding. **Massive hemoptysis** is defined as the coughing up of > 100–600 mL of blood in a 24-hour period. Bronchitis, bronchogenic carcinoma, and bronchiectasis are the most common causes of hemoptysis (see Table 16.8), but up to 30% of patients have no identifiable cause even after extensive evaluation.

Symptoms/Exam

The history should focus on common causes:

- A history of TB or sarcoidosis may indicate the presence of an aspergilloma.
- Frequent, multiple episodes of pneumonia as a child could point to bronchiectasis.
- A diastolic heart murmur might suggest mitral stenosis as a possible and frequently overlooked cause.
- A history of epistaxis, telangiectasias, and a bruit in the posterior aspect of the lungs may represent hereditary hemorrhagic telangiectasia with a ruptured pulmonary AVM.
- Renal insufficiency and hemoptysis may point to Wegener's granulomatosis or Goodpasture's syndrome.
- Weight loss, tobacco abuse, and cachexia may suggest malignancy.

TABLE 16.8. Differential Diagnosis of Hemoptysis

Most Common Causes	Other Causes
Bronchitis	Aspergilloma
Bronchogenic carcinoma	CHF
Bronchiectasis	CF
	Goodpasture's syndrome
	Lung abscess
	Mitral stenosis
	Pulmonary AVM
	PE/infarction
	Sarcoidosis
	TB
	Wegener's granulomatosis

Differential

Blood expectorated from the upper respiratory tract and the upper GI tract can mimic blood coming from the trachea and below.

Diagnosis

- Routine evaluation for all patients with hemoptysis should include a history and physical exam, a CBC with differential, UA, coagulation studies, an ECG, and a CXR. Bronchoscopy should also be strongly considered.
- Additional special studies (based on the history and physical) include expectorated sputum for acid-fast bacilli and cytology; a thoracic CT scan; blood testing for BUN, creatinine, ANA, ANCA, and anti-GBM antibody; ABG analysis on room air; 100% O_2 to evaluate for shunt; and pulmonary arteriography.

Treatment

Treatment for hemoptysis is divided into two categories: supportive and definitive.

- **Supportive care:** Typically includes bed rest with supplemental O_2 and blood products if needed. In general, medications with antitussive effects should be avoided, as an effective cough is necessary to clear blood from the airways. If gas exchange becomes compromised, endotracheal intubation may become necessary. Generally, worsening of gas exchange precedes the need for transfusion.
- **Definitive treatment:**
  - **Nonmassive hemoptysis:** Treatment is directed at the specific cause (e.g., antibiotics for superinfected aspergilloma).
  - **Massive hemoptysis:** Treatment is directed toward bringing about abrupt cessation of bleeding.
    - Urgent bronchoscopy may help localize the site of bleeding; angiography of the bronchial arteries (a more common site of bleeding than the pulmonary arteries) has been shown to identify the bleeding site in > 90% of patients.
    - When angiography is combined with embolization, bleeding can successfully be stopped in > 90% of cases. Emergency surgery for massive hemoptysis is controversial and is usually reserved for those who have failed embolization.

HYPOXEMIA

Defined as a ↓ in blood O_2 (in general, a Pa_{O_2} of < 80 mmHg). An age adjustment given by the formula 80 – [(age – 20)/4] is used to define the lower limit of normal Pa_{O_2}.

Symptoms/Exam

Hypoxemia can lead to tissue hypoxia and cause impaired judgment and motor dysfunction. When hypoxia is long-standing, it leads to fatigue, drowsiness, and delayed reaction time. With severe hypoxia, the respiratory centers in the brain stem are affected, and death usually results from respiratory failure.

Diagnosis

- Calculation of the alveolar-arterial (A-a) oxygen gradient aids in narrowing the differential diagnosis (see Table 16.9). The A-a gradient is defined as

TABLE 16.9. Diagnosis of Hypoxemia by A-a Gradient and Response to Supplemental O_2

Etiology	A-a Gradient	Response to Supplemental O_2	Common Causes
Right-to-left shunt	Wide	Minimal	Pneumonia, pulmonary AVM
Hypoventilation	Normal	Hypoxemia corrects	Drug overdose, ALS, Guillan-Barré syndrome
V/Q mismatch	Wide	Hypoxemia corrects	PE, obstructive lung disease

$PiO_2 - (PaO_2 - PaCO_2/8)$. Assuming sea level, an FiO_2 of 0.21, and 37°C, PiO_2 becomes 150 mmHg. A conservative estimate of a normal A-a gradient is 4 + age (years) / 4.

- There are five general mechanisms of hypoxemia:
  - **Shunt:** Occurs with perfusion of a nonventilated lung (pneumonia) or when there is a communication between the arterial and venous systems bypassing the lungs (intracardiac shunt or AVM).
  - **Hypoventilation:** Defined as ↓ minute ventilation, resulting in an ↑ in $PaCO_2$ (as CO_2 ↑, PaO_2 ↓ according to the alveolar gas equation). Results in a **normal** A-a gradient, which is logical in that there is no 1° pulmonary process.
  - **Ventilation-perfusion (V/Q) mismatch:** Results when there is no perfusion to areas of ventilated lung. The classic example is PE.
  - **Reduced inspired O_2** either from ↓ total atmospheric pressure (P_{atm}) or from ↓ FiO_2: Transient exposure to low inspired O_2 is common on airline flights in which the cabin is pressurized to 5000–10,000 feet (PiO_2 = 100 mmHg). FiO_2 is preserved (~21%), but total P_{atm} is ↓. In patients with severe lung disease, PaO_2 may drop as low as 40 mmHg. May also result from closed-space rescues (FiO_2 < 21%) or structure fires.
  - **Diffusion abnormality:** A reduction in diffusion capacity **rarely** leads to abnormal pulmonary gas exchange at rest. It is estimated that DL_{CO} must fall to 10% of the individually predicted value to lead to hypoxemia.

Hypoxemia due to shunt does not correct with 100% O_2 therapy.

Treatment

All patients with hypoxemia should be treated with supplemental O_2. Patients with a $PaO_2 \leq 55$ mmHg or with an O_2 saturation of ≤ 88% should be treated with long-term O_2 therapy. Patients with a $PaO_2 \leq 59$ mmHg or an O_2 saturation of ≤ 89% and evidence of cor pulmonale also qualify for long-term O_2 (to help reduce right heart failure).

CHRONIC OBSTRUCTIVE PULMONARY DISEASE (COPD)

A disease state characterized by chronic airflow limitation that is no longer fully reversible, is usually progressive, and results from chronic bronchitis and emphysema.

- **Chronic bronchitis** is defined clinically as chronic productive cough for three consecutive months in two consecutive years.
- **Emphysema** is defined pathologically as abnormal enlargement of the airspaces distal to the terminal bronchioles with wall destruction.

- The most important risk factor for developing COPD is cigarette smoking. α_1-antitrypsin (AAT) deficiency is also a well-characterized genetic abnormality that predisposes individuals to the development of early-onset COPD.

Symptoms/Exam

- Symptoms are usually not present until the individual has smoked > 1 pack of cigarettes per day for 20 years.
- Typically presents with chronic cough in the fourth or fifth decade of life. Dyspnea usually occurs only with moderate exercise, and not until the sixth or seventh decade of life.
- Chest wall hyperinflation, prolonged expiration, wheezing, and distant breath and heart sounds may be present.
- The patient may use accessory muscles and pursed-lip breathing ("**pink puffer**"), and cyanosis may be present as well ("**blue bloater**"). Neck vein distention, a tender liver, and lower extremity edema suggest cor pulmonale.

Differential

Acute bronchitis, asthma, bronchiectasis, CF, CHF.

Diagnosis

Along with a history and physical exam, testing modalities that are useful for diagnosing COPD and for evaluating the progression of disease include CXR, PFTs, ABG analysis, and AAT screening.

- **CXR:** Typically demonstrates ↓ lung markings, ↑ retrosternal airspace, and flattened diaphragms.
- **PFTs:** Essential for diagnosis as well as for the evaluation of treatment and disease progression.
- **ABG analysis:** Acute exacerbations show hypoxemia and hypercarbia with acute respiratory acidosis.
- **AAT screening:** AAT deficiency accounts for < 1% of COPD cases. Low levels of AAT lead to basilar emphysema. CXR may show ↓ **lung markings, predominantly in the bases** (usually in the apices with COPD from tobacco use).
- **BODE index:** More effective than FEV_1 at predicting the risk of death from any cause in patients with COPD. The **BODE** index consists of: **B**MI, **O**bstruction of airflow (FEV_1), **D**yspnea (as measured by the modified Medical Research Council dyspnea scale), and **E**xercise capacity (six-minute walk).

Treatment

- **Acute exacerbations:** Where possible, the cause of the exacerbation should be treated.
  - **β_2-adrenergic** and **anticholinergic agents** are first-line therapy.
  - **O_2 therapy** is often necessary to treat hypoxemia. Hypercarbia can result either from a ↓ respiratory drive with ↑ Pa_{O_2} or from ↑ V/Q mismatch with hyperoxia, but O_2 therapy must not be withheld owing to fears of hypercarbia.
  - **Systemic corticosteroids** in oral or IV form help ↓ the length of exacerbations and improve FEV_1 in hospitalized patients.

- **Antibiotics** are recommended by the American Thoracic Society for patients with an acute exacerbation who have a **change in sputum amount, consistency, or color.**
- **Noninvasive positive pressure ventilation** is of benefit for patients with **severe** acute exacerbations of COPD, as it reduces in-hospital mortality, ↓ the need for intubation, and diminishes hospital length of stay.

- **Stable chronic COPD:**
  - Smoking cessation.
  - **Immunizations** for influenza and pneumococcus are recommended.
  - **β_2-adrenergic** and **anticholinergic agents** help improve pulmonary function and reduce dyspnea. A meta-analysis showed that the long-acting β_2-adrenergic agent salmeterol is more effective than ipratropium at improving pulmonary function.
  - **O_2** if indicated.
  - Long-term use of corticosteroids is controversial.
  - **Pulmonary rehabilitation** is associated with improved exercise tolerance and reduced pulmonary symptoms.
  - **Lung volume reduction surgery** provides the most benefit for the subgroup of patients who do not respond to pulmonary rehabilitation, have severe emphysema in the upper lobes, and have a low risk of surgery. Other subgroups derive less benefit from this treatment and may even be harmed by it.
  - **Single- or double-lung transplantation** is often indicated for willing patients with a low FEV_1, hypercarbia, and cor pulmonale. Five-year survival following transplantation for COPD is approximately 40%.

Oxygen therapy is the only intervention known to ↑ life expectancy in hypoxemic COPD patients.

BRONCHIECTASIS

Defined as the irreversible dilatation and destruction of bronchi with inadequate clearance of mucus in the airways. Characterized by dilated airways and focal constrictive areas and, in some cases, by large, cystic, grapelike clusters resulting from progressive dilatation of the airways. Cycles of infection and inflammation lead to permanent remodeling and dilatation with viscous sputum production.

Symptoms

- Patients often have cough productive of yellow or green sputum together with dyspnea and hemoptysis.
- May follow an episode or episodes of childhood pneumonia.
- Associated with postinfectious conditions (*Pseudomonas*, *Haemophilus*, TB, pertussis, measles, influenza, RSV, HIV), immunodeficiency (CVID, IgA deficiency), congenital conditions (CF, Young's syndrome, 1° ciliary dyskinesia, Kartagener's syndrome), autoimmune disease (SLE, RA, Sjögren's syndrome, relapsing polychondritis, IBD), or hypersensitivity (ABPA).

Exam

Physical exam reveals crackles and wheezes. Acute exacerbations typically include changes in sputum production, ↑ dyspnea, ↑ cough and wheezing, fatigue, low-grade fever, ↓ pulmonary function, changes in chest sounds, and radiographic changes.

Differential

COPD, interstitial fibrosis, pneumonia, asthma.

Diagnosis

Tests useful in making the diagnosis or in determining the underlying cause of bronchiectasis include the following:

- **CBC, including differential.**
- **Serum immunoglobulins:** Aid in screening for CVID, IgA/IgG deficiency, and ABPA (elevated serum total IgE).
- **High-resolution CT:** Currently the best tool for diagnosing bronchiectasis; aids in mapping airway abnormalities. Distribution may help with diagnosis:
  - **Central predominance:** ABPA.
  - **Upper lobe predominance:** CF.
  - **Lower lobe predominance:** Idiopathic.
- **Spirometry:** Helps quantify the degree of airway obstruction.
- **Sputum sample** for bacterial, fungal, and mycobacterial culture.
- **Sweat chloride test for CF.**
- **ANA, RF,** and **anti-Ro/La.**

Treatment

- **Antibiotics:** The standard of care for acute exacerbations. A reasonable first-line choice would include a fluoroquinolone.
- **Bronchodilators:** Helpful when used routinely, as many patients have hyperresponsiveness that likely results from airway inflammation.
- **Inhaled corticosteroids:** Can reduce inflammation and improve dyspnea, cough, and pulmonary function in severe cases.
- **Airway clearance techniques:** Include chest physiotherapy, flutter devices, and percussive vests; aid in the clearance of secretions.
- **Mucolytic agents:** Agents such as **DNase** have been shown to be helpful in stable CF but are ineffective and potentially harmful in patients with stable idiopathic bronchiectasis.
- **Surgical resection** remains an option for patients with localized focal bronchiectasis.
- **Double-lung transplantation** has been performed in patients with severe bronchiectasis.

CYSTIC FIBROSIS (CF)

The most common lethal autosomal-recessive disorder in Caucasians, affecting 1 in every 3500 births. The disease is caused by mutations in the CF transmembrane conductance regulator (CFTR), leading to chloride channel dysfunction. Classically characterized by multisystem involvement of the sinuses, lungs, pancreas, liver, gallbladder, intestines, and bones and, in males, the vas deferens.

Even though most CF patients are diagnosed in childhood, 7% will be diagnosed as adults and tend to have upper lobe bronchiectasis.

Symptoms/Exam

- Most CF patients are diagnosed during childhood. A history of failure to thrive as a child, persistent respiratory infections (*Pseudomonas*), nasal polyposis, sinusitis, intestinal obstruction, malabsorption, recurrent pancreatitis, hepatobiliary disease, and male infertility are suggestive of CF.
- Seven percent of CF patients are diagnosed as adults, and these patients tend to present with upper lobe bronchiectasis.

- Exam may reveal ↑ chest AP diameter, upper lung field crackles, nasal polyps, hepatomegaly, and clubbing.
- Acute exacerbations are typically characterized by ↑ sputum production, dyspnea, fatigue, weight loss, and a decline in FEV_1.

Differential

Immunodeficiency, asthma, ABPA.

Diagnosis

Diagnosis requires both clinical and laboratory evidence of CFTR dysfunction.

- **Sweat chloride concentration:** The best screening test for CF for a patient with a suggestive clinical picture. Normal sweat chloride is < 40 mmol/L.
- **Genotyping:** Screening for the presence of two CFTR mutations known to cause CF. Newer tests screen for > 1000 different known mutations.
- **Nasal potential difference:** Directly evaluates CFTR function by measuring ion transport in the epithelial cells lining the interior of the nose.
- **CXR:** Shows hyperinflation, bronchiectasis, and upper lobe infiltrates. Nodules often represent mucoid impaction in the airways.

Treatment

- **Acute pulmonary exacerbations:** Treat with chest physical therapy, bronchodilators, DNase, and usually two antipseudomonal antibiotics.
- **Chronic stable CF:**
  - **Inhaled tobramycin:** Slows the decline in FEV_1 and is used for long-term therapy.
  - **Nebulized DNase:** Improves FEV_1 and should be offered to patients with daily cough, sputum production, and airflow obstruction.
  - **Azithromycin:** Improves FEV_1 and reduces pulmonary exacerbations in those infected with *Pseudomonas*.
  - **Aerobic exercise, flutter devices, external percussive vests:** Help with regular airway clearance.
  - **Pancreatic enzymes** and the **fat-soluble vitamins A, D, E, and K:** Given for malabsorption.
  - **Nutritional counseling:** Essential for proper health maintenance and to help prevent diabetic complications, osteoporosis, and weight loss.
  - **Double-lung transplantation:** Remains an option for severe progressive pulmonary disease.

INTERSTITIAL LUNG DISEASE (ILD)

Represents a wide spectrum of disorders affecting the parenchyma of the lung. More than 200 known disorders are characterized by diffuse lung involvement. It is useful to separate such disorders into those of unknown and known etiology and then to further distinguish them by the presence or absence of inflammation, fibrosis, or granulomas (see Tables 16.10 and 16.11). Sarcoidosis, idiopathic pulmonary fibrosis (IPF), and fibrosis associated with connective tissue disease are the most common forms of ILD. IPF, which is also called usual interstitial pneumonia (UIP), is the most specific form of the idiopathic interstitial pneumonias and has a distinct appearance on histopathology.

TABLE 16.10. Interstitial Lung Disease Characterized by Inflammation or Fibrosis

Known Etiology	Unknown Etiology
Asbestosis	Idiopathic interstitial pneumonias:
Drug reaction:	■ IPF[a]
■ Amiodarone	■ Acute interstitial pneumonia (Hamman-Rich syndrome)
■ Chemotherapeutic agents	■ Desquamative interstitial pneumonia
Radiation exposure	■ Respiratory bronchiolitis–associated pneumonia
	■ Nonspecific interstitial pneumonia
	■ Bronchiolitis obliterans with organizing pneumonia
	Connective tissue disease[a]
	■ SLE
	■ RA
	■ Scleroderma
	■ Dermatomyositis/polymyositis
	■ Sjögren's syndrome
	Crohn's disease/ulcerative colitis
	Amyloidosis
	Alveolar proteinosis
	Lymphangiomyomatosis
	Heritiable disease:
	■ Neurofibromatosis
	■ Tuberous sclerosis
	■ Hermansky-Pudlak syndrome

[a] The most common ILDs.

Symptoms/Exam

- A detailed history should focus on the onset of symptoms, family history, smoking history, and occupational and environmental exposures. Dyspnea is the most common presenting symptom.
- Gradual onset is consistent with IPF, whereas acute onset of dyspnea is more typical of Hamman-Rich syndrome or hypersensitivity pneumonitis (HP).
- A family history may help with cases of tuberous sclerosis and neurofibromatosis. Occupational and environmental exposures are also critical, as they may help diagnose asbestosis or HP.

Nonspecific interstitial pneumonia (NSIP) has a clinical presentation similar to that of usual interstitial pneumonia; however, NSIP responds to corticosteroids and has a better prognosis.

TABLE 16.11. Interstitial Lung Disease Characterized by Granulomas

Known Etiology	Unknown Etiology
Hypersensitivity pneumonitis	Sarcoidosis[a]
Berylliosis	Eosinophilic granulomatosis
	Wegener's granulomatosis
	Churg-Strauss syndrome

[a] Among the most common ILDs.

- Physical exam usually demonstrates **dry bibasilar crackles.** Inspiratory **squeaks** suggest a diagnosis of bronchiolitis obliterans with organizing pneumonia.

Diagnosis

- **Lab studies:** To confirm the presence of a connective tissue disorder.
- **CXR:** Usually demonstrates a bibasilar interstitial pattern. May have upper lobe nodular pattern or honeycombing as well.
- **High-resolution CT:**
  - Helps **characterize** the disease, which may obviate the need for biopsy.
  - Helps **quantify** the extent of disease.
  - Helps **identify** the area to sample if biopsy is necessary.
- **PFTs:** Useful for evaluating the extent of lung involvement. Commonly have a restrictive defect (low TLC), a normal or ↑ FEV_1/FVC ratio, and a ↓ DL_{CO}.
- **Lung biopsy:** For disease confirmation and activity. Fiberoptic bronchoscopy with transbronchial biopsy is helpful in diagnosing sarcoidosis, eosinophilic granulomatosis, and HP. Open lung biopsy is preferred for making the diagnosis of IPF.

The classic CT findings for IPF are bibasilar and peripheral interstitial infiltrates.

Treatment

Treatment is disease specific and usually supportive:

- **O_2** for hypoxemia (Pa_{O_2} < 55 mmHg) at rest or with exercise.
- **Glucocorticoids** are usually recommended, but no placebo-controlled trials have yet been conducted, and there is no direct survival benefit.
- **Immunosuppressive therapy** with cyclophosphamide or azathioprine +/– steroids has been used with varying success.
- Lung transplantation is reserved for patients < 65 years of age with severe, refractory disease.

PLEURAL EFFUSION

Defined as the abnormal accumulation of fluid in the pleural space. In the United States, the most common causes are CHF, pneumonia, and cancer. Classified as **transudative** or **exudative.**

- **Transudative effusion:** Occurs because of an imbalance between hydrostatic and oncotic pressures. The main causes of transudative pleural effusion are CHF, cirrhosis, nephrotic syndrome, and PE.
- **Exudative effusion:** Occurs when inflammation leads to altered vascular permeability and protein-rich pleural fluid. Common causes of exudative pleural effusions are malignancy, bacterial and viral pneumonia, TB, PE, pancreatitis, esophageal rupture, collagen vascular disease, chylothorax, and hemothorax.

Symptoms/Exam

- Patients often present with dyspnea and pleuritic chest pain.
- Examination of the chest typically demonstrates dullness to percussion, ↓ or absent fremitus, and ↓ breath sounds on the affected side.
- Elevated neck veins, an S3 gallop, and edema suggest CHF, whereas productive cough, fever, and signs of consolidation suggest pneumonia. Lymphadenopathy may suggest malignancy, whereas ascites points to a hepatic cause.

Diagnosis

- **CXR:** May demonstrate blunting of the costophrenic angle. Decubitus films help determine if fluid is free flowing or loculated. The presence of > 1 cm of fluid on decubitus CXR suggests the presence of a significant amount of fluid.
- **Diagnostic thoracentesis:** Performed on clinically significant effusions; fluid is analyzed to distinguish transudate from exudate using Light's criteria (see Table 16.12) as well as to obtain pH, color, turbidity, cell count, glucose, Gram stain, bacterial/fungal/mycobacterial cultures, and cytology (see Table 16.13). Pleural fluid amylase, triglycerides, cholesterol, and hematocrit may also be analyzed given the appropriate clinical scenario (see Table 16.13).
- **Pleural biopsy:** May aid in the diagnosis of cancer or TB effusion.
- **Evaluation for PE.**

Treatment

- **Transudative pleural effusion:** Treatment is aimed at the underlying cause with therapeutic thoracentesis if the patient is symptomatic.
- **Exudative pleural effusion:**
  - **Malignant:** Consider pleurodesis in symptomatic patients who are unresponsive to chemotherapy or radiation.
  - **Parapneumonic:** Drainage of the pleural space is indicated if there is evidence of empyema (pH < 7.2, pus, glucose < 40 mg/dL, Gram stain ⊕).
  - **Hemothorax:** Requires drainage or fibrothorax will likely develop.
  - **Tuberculous:** Usually resolves with treatment of TB.

Drain a pleural effusion if pH is < 7.2, glucose is < 40 mg/dL, or Gram stain is ⊕.

PNEUMOTHORAX

Defined as the presence of air in the pleural space. Traditionally classified as spontaneous, iatrogenic, or traumatic.

- **Spontaneous pneumothorax:** Not caused by any obvious precipitating factor. Classified as either 1° (usually occurring in tall, thin males without clinically apparent lung disease) or 2° (occurring in patients with underlying lung disease or in women with a history of endometriosis around the time of menses).
- **Iatrogenic pneumothorax:** The result of diagnostic (thoracentesis) or therapeutic intervention (central venous catheter placement).
- **Traumatic pneumothorax:** Occurs with penetrating or blunt trauma that causes air to enter the pleural space as well as with acute compression of the chest that causes alveolar rupture.

TABLE 16.12. Light's Criteria for Distinguishing Transudate from Exudate

	Pleural/Serum Protein	Pleural/Serum LDH	Pleural Fluid LDH > 2/3 Normal
Transudate	< 0.5	< 0.6	No
Exudate	> 0.5	> 0.6	Yes

TABLE 16.13. Pleural Fluid Analysis and Interpretation

Pleural Fluid Test	Interpretation
pH	Pleural pH < 7.2 with parapneumonic effusion indicates the need for drainage.
Hematocrit	> 50% of peripheral hematocrit suggests hemothorax.
Glucose	< 60 mg/dL usually suggests a complicated parapneumonic effusion or malignancy. Can be seen with rheumatoid and lupus pleuritis, TB, and Churg-Strauss syndrome.
Triglycerides	> 110 mg/dL suggests chylothorax.
Cholesterol	> 250 mg/dL suggests pseudochlylothorax.
Lymphocytes	> 50% lymphocytes likely to be either tuberculous or malignant.
Eosinophils	> 10% most commonly due to pneumothorax. Less common causes include drug reaction, asbestos exposure, paragonimiasis, and Churg-Strauss syndrome.

Symptoms/Exam

- Most patients present with unilateral chest pain (either sharp or steady pressure) and acute shortness of breath.
- The physical exam may be normal if the pneumothorax is small.
- If the pneumothorax is large, exam may reveal ↓ chest movement, hyperresonance, ↓ fremitus, and ↓ breath sounds. Tachycardia, hypotension, and tracheal deviation should raise suspicion of tension pneumothorax.

Differential

Acute PE, MI, pleural effusion, pneumonia, pericardial tamponade.

Diagnosis

Confirmed through the identification of a thin visceral pleural line away from the chest wall on upright PA CXR. A CT scan of the thorax may help when the CXR is difficult to interpret because of severe underlying lung disease (e.g., CF).

Treatment

- Treatment involves both evacuating air from the pleural space and preventing recurrence.
  - **Small 1° pneumothoraces:** Usually resolve with simple observation and O_2 therapy. Supplemental O_2 accelerates the reabsorption of gas from the pleural space to about 8–9% per day.
  - **Larger, more symptomatic 1° spontaneous pneumothoraces:** May be drained either with simple aspiration or with placement of a small-bore chest tube.
- **2° spontaneous pneumothorax:** Treat with a larger-bore chest tube attached to a water-seal device.
  - Persistent air leaks and recurrences are more common with 2° than with 1° spontaneous pneumothorax.

- For those with 2° spontaneous pneumothorax, recurrence is often prevented with instillation of sclerosing agents (e.g., talc) through the chest tube, video-assisted thoracoscopic surgery, or limited thoracotomy.
- Interventions to prevent recurrence in patients with 1° spontaneous pneumothorax are usually recommended only after the second ipsilateral pneumothorax. Pilots and divers with 1° spontaneous pneumothorax should be cautioned against such activity in the future because of the risk of contralateral pneumothorax.

Tension pneumothorax is a medical emergency requiring immediate decompression of the pleural space with a 14-gauge needle in the second intercostal space at the midclavicular line.

PULMONARY COMPLICATIONS OF HIV

Pulmonary disease is a leading cause of morbidity and mortality among individuals with HIV. Although opportunistic infections continue to account for the preponderance of disease in such patients, noninfectious manifestations of HIV are becoming increasingly prevalent with the widespread use of highly active antiretroviral therapy (HAART). Table 16.14 outlines both infectious and noninfectious pulmonary disorders associated with HIV.

Symptoms

Look for the following:

- A history of IV drug abuse (TB and pneumonia are more common in this setting).
- Risk factors for TB.
- Adherence with TMP-SMX prophylaxis.
- Timing of the initiation of HAART to evaluate for immune reconstitution.

Initiation of HAART therapy may result in recrudescence of infections that had previously remained dormant, such as TB.

Exam

Focus on extrapulmonary manifestations of a systemic disease. Skin, lymph node, and funduscopic exams can narrow the differential to fungal, mycobacterial, or neoplastic etiologies. The CD4 count and viral load are also helpful in narrowing the differential.

Diagnosis

- Obtain a CXR and an expectorated sputum. The pattern of infiltrate on the CXR can suggest a diagnosis (see Figure 16.3). Induce sputum if the patient is not producing sputum.
- A chest CT is helpful if the CXR is normal. ABGs and DL_{CO} may also be useful adjuncts in some situations.

TABLE 16.14. Infectious and Noninfectious Pulmonary Manifestations of HIV

Infectious	Noninfectious
Bacterial pneumonia	Emphysema
PCP	Lung carcinoma
TB	Non-Hodgkin's lymphoma
Fungal pneumonia	Lymphocytic interstitial pneumonia
Viral: CMV, VZV	Kaposi's sarcoma
Nocardia	

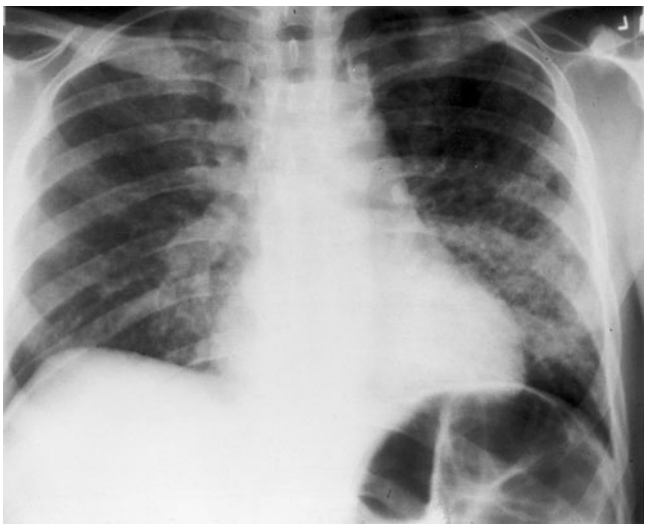

FIGURE 16.3. CXR of an HIV-infected patient with PCP.

Note the bilateral diffuse interstitial infiltrates in "bat-wing" perihilar prominence. It should be noted, however, that up to 25% of HIV patients with PCP may have a normal chest roentgenogram. (Reproduced, with permission, from Kasper DL et al. *Harrison's Principles of Internal Medicine*, 16th ed. New York: McGraw-Hill, 2005: 1195.)

- In patients who are critically ill and those not responding to empiric therapy, fiberoptic bronchoscopy should be performed.

TREATMENT

Unless a patient is critically ill, establishing a diagnosis before empiric treatment is preferred.

PULMONARY EMBOLISM (PE)

Defined as obstruction of the pulmonary vasculature that is usually caused by venous thromboembolism (DVT). May also be the result of air, bone marrow, arthroplasty cement, tumor, infection, amniotic fluid, or talc. Ranges from clinically insignificant to massive embolus with sudden death. Risk factors are included in **Virchow's triad:**

- **Hypercoagulable state:** Associated with recent surgery, trauma, obesity, OCPs, pregnancy, cancer, immobilization, central venous catheters, and disorders of coagulation (antiphospholipid antibody, protein C/S deficiency, antithrombin III deficiency, factor V Leiden, and the prothrombin gene mutation).
- **Endothelial damage:** Associated with recent surgery or trauma or with previous DVT.
- **Stasis:** Associated with obesity, immobilization, CHF, and recent surgery.

SYMPTOMS/EXAM

Patients often present with acute-onset shortness of breath and pleuritic chest pain. Cough and hemoptysis may also be present. Physical examination may demonstrate low-grade fever, tachypnea, tachycardia, a loud P2, and JVD. Homans' sign and palpable cords on the calf may be present.

Differential

MI, aortic dissection, pneumonia, pneumothorax, pericarditis, anxiety.

Diagnosis

Accurate diagnosis remains difficult. PE should be **suspected** when a patient presents with sudden-onset chest pain, dyspnea, tachycardia, and a normal CXR. Diagnostic modalities include the following:

- **ABG:** May demonstrate **respiratory alkalosis,** hypoxemia, and an ↑ A-a gradient.
- **CXR:** Often normal, but may show **Hampton's hump** (a wedge-shaped infarct) or **Westermark's sign** (relative oligemia in the region of the embolus), pleural effusion, or atelectasis.
- **ECG:** Sinus tachycardia is the most common finding. Less commonly seen is an S1Q3T3 pattern (S in lead I, Q in lead III, and an inverted T in lead III) suggesting right heart strain.
- **D-dimer:** Some studies suggest a high negative predictive value with low pretest probability. However, the negative predictive value is much less in populations with a high prevalence of PE. Test characteristics vary by assay type, and assays also appear to be affected by embolus size and location. Currently not recommended as a single diagnostic test.
- **V/Q scan:** May demonstrate segmental regions of ventilation without perfusion (V/Q mismatch). Results are given as normal or low, indeterminate, or high probability for PE.
- **Lower extremity ultrasound:** May be used in conjunction with low or indeterminate V/Q scans to aid in the diagnosis of venous thromboembolism.
- **Spiral CT with IV contrast:** Sensitive for detecting proximal clots, but less sensitive with more distal emboli.
- **Pulmonary arteriogram:** The gold standard, but requires an invasive procedure with a skilled operator.

Treatment

- **Unfractionated heparin:** Bolus intravenously and continue using weight-based nomogram.
- **Low-molecular-weight heparin:** Can be given to low-risk patients with PE in place of IV unfractionated heparin.
- **Warfarin:** Long-term anticoagulation (six months) is usually recommended for those with no risk factors for future PEs.
- **Thrombolytics:** Generally recommended for patients with shock and no contraindications. Controversy exists for additional indications (e.g., right ventricular strain).

PULMONARY HYPERTENSION

Defined as a mean pulmonary artery pressure > 25 mmHg at rest or > 30 mmHg with exercise. 1° or idiopathic pulmonary hypertension (PPH) is a rare disease with an incidence of 1–2 per million and roughly a 3:1 female-to-male ratio. PPH may be familial or may occur sporadically. 2° pulmonary hypertension is more common and is associated with the following:

- **Disorders of the respiratory system:** COPD, CF, pulmonary fibrosis.
- **Cardiac disease:** Congenital heart disease, left ventricular dysfunction, mitral valve disease.

- **Vascular disorders:** Chronic thromboembolic disease; pulmonary arterial hypertension 2° to HIV, collagen vascular disease (scleroderma, SLE, RA), or drugs (fenfluramine, phentermine, cocaine, methamphetamines); pulmonary veno-occlusive disease; pulmonary capillary hemangiomatosis; portopulmonary hypertension.
- **Other:** Sarcoidosis.

Symptoms/Exam

- Patients with pulmonary hypertension typically complain of progressive dyspnea on exertion. In more advanced stages, patients may have exertional dizziness and even syncope.
- Raynaud's phenomenon is common in patients with PPH but may suggest an underlying collagen vascular disease. Cough and hemoptysis are rare in PPH but may be present in cases of pulmonary capillary hemangiomatosis. Hoarseness may also be present because of impingement of the left recurrent laryngeal nerve by a dilated pulmonary artery.
- Patients may have JVD, a right ventricular heave and right-sided S4, an ↑ P2, a murmur of tricuspid regurgitation, and the Graham Steell murmur of pulmonic insufficiency.
- In advanced disease, patients may present with hepatomegaly, pulsatile liver, and ascites.

Differential

Left ventricular systolic failure, left ventricular diastolic dysfunction, causes of 2° pulmonary hypertension.

Diagnosis

Treatment-based diagnostic evaluation to identify underlying disease is as follows:

- **Echocardiogram:** Provides an estimate of pulmonary artery pressure and helps identify left ventricular dysfunction, mitral valve disease, and congenital heart disease.
- **CXR:** Usually shows enlargement of the central pulmonary arteries with "pruning" of the peripheral vessels; may also show changes suggestive of COPD.
- **PFTs:** Help identify ILD, emphysema, and thoracic cage abnormalities as a cause of pulmonary hypertension.
- **V/Q scan:** All patients with pulmonary hypertension should have V/Q scanning to rule out chronic thromboembolic disease and should also have a subsequent pulmonary angiogram if subsegmental or segmental defects are present.
- **Sleep study:** For patients with loud snoring and daytime hypersomnolence; can identify obstructive sleep apnea as a potentially reversible cause of pulmonary hypertension.
- **Serologic testing:** For SLE, RA, scleroderma, and HIV. LFTs should also be performed as part of the workup.
- **Lung biopsy:** Rarely necessary and, in general, poorly tolerated.
- Patients should undergo **right heart catheterization** for the following purposes:
  - To confirm elevated pulmonary artery pressures and the absence of pulmonary venous hypertension.
  - To aid in determining prognosis, as those with high right atrial pressure and low cardiac index have the shortest survival rates.

- To help determine the most appropriate therapy when used in conjunction with a vasodilator trial. An acute responder has ↓ mean pulmonary arterial pressure with an ↑ or unchanged cardiac index.

Treatment

- In 2° pulmonary hypertension caused by disorders of the respiratory system (O_2, steroids, bronchodilators), chronic thromboembolic disease (anticoagulation, IVC filter, thromboendarterectomy), and pulmonary venous hypertension (afterload reduction, mitral valve repair/replacement), **treatment is aimed at disease.**
- In patients with PPH and other forms of pulmonary arterial hypertension, **treatment is based on response to vasodilators.**
  - **Acute responders** should be treated with anticoagulation and calcium channel blockers.
  - **Nonresponders** with New York Heart Association (NYHA) functional class III or IV should be treated with diuretics, anticoagulation, and bosentan, treprostinil, or epoprostenol. Bilateral lung transplantation remains a viable option for those who decline clinically despite maximal medical therapy.

SOLITARY PULMONARY NODULE

Defined as an isolated round lesion < 3 cm in diameter that is surrounded by pulmonary parenchyma. Abnormalities > 3 cm are termed masses and are usually malignant. Cancer affects 10–70% of those with solitary pulmonary nodules. Most benign lesions are infectious granulomas.

Symptoms/Exam

Patients are often asymptomatic but may present with cough, hemoptysis, and dyspnea. Older age and a history of cigarette smoking raise the suspicion of cancer. Patients should be questioned about prior TB and histoplasmosis. Physical examination of the lungs is frequently normal. However, examination of the lymphatic system may demonstrate lymphadenopathy.

Differential

Granuloma (old TB, histoplasmosis, foreign body reaction), bronchogenic carcinoma, metastatic disease (usually > 1), bronchial adenoma, round pneumonia.

Diagnosis

- Solitary pulmonary nodules are usually discovered incidentally.
- **Comparison of serial CXRs:** The **initial** step in determining the progression and extent of the nodule. Stability of findings on CXR for two years is considered a sign that the lesion is benign.
- **Chest CT:** Offers improved estimation of nodule size, characteristics (e.g., pattern of calcification), and interval growth (see Table 16.15). Contrast enhancement allows for the simultaneous evaluation of the mediastinum for lymphadenopathy.
- **PET scan:** May help provide staging information in the case of lung cancer. The diagnostic accuracy of detecting mediastinal involvement among patients with lung cancer is 65% by CT, 90% by PET, and > 95% using a combination of CT and PET.

Lesions that ↑ in size or change in character are likely malignant and should be resected, assuming low surgical risk and no evidence of metastatic disease.

TABLE 16.15. Chest CT Patterns and Associated Disease

Pattern	Disease
Calcification	
Laminated	Granulomatous disease
Popcorn	Hamartoma
Eggshell	Silicosis
Stippled	Malignancy
Eccentric	Malignancy
Margin contour	
Smooth	Likely benign
Scalloped	Intermediate risk of malignancy
Spiculated	Likely malignant
Corona radiata	Malignancy
Air-bronchus sign	Pneumonia; bronchoalveolar carcinoma

Treatment

- Currently, there are no evidence-based guidelines to address the approach to the solitary pulmonary nodule.
- When the probability of cancer is low (age < 35, nonsmokers, smooth nodules with a diameter < 1.5 cm), the lesion should be monitored with serial HRCT at three-month intervals.
- When the probability of cancer is high (age > 35, smokers, spiculated nodules with a diameter > 2 cm), the lesion should be resected if preoperative risk is acceptable and there are no other contraindications to surgery.
- When the probability of cancer is intermediate, additional testing (PET, transthoracic needle biopsy) may be warranted.

SARCOIDOSIS

A systemic disease of unknown etiology that primarily affects the lungs and lymphatics and is characterized by noncaseating granulomas. Commonly affects young and middle-age adults, often presenting with bilateral hilar adenopathy, pulmonary infiltrates, and skin lesions. The liver, lymphatics, salivary glands, heart, CNS, and bones may be involved as well.

Symptoms/Exam

Patients may present with nonspecific constitutional symptoms such as fever, fatigue, anorexia, weight loss, and arthralgias. Physical examination may reveal dry crackles, lymphadenopathy, parotid enlargement, splenomegaly, uveitis, or skin changes (erythema nodosum).

Differential

Mycobacterial, fungal, bacterial (tularemia and brucellosis), and parasitic (toxoplasmosis) infection. Also includes berylliosis, lymphoma, hypersensitivity pneumonitis, Wegener's granulomatosis, and Churg-Strauss syndrome.

Diagnosis

Diagnosis is made by a combination of clinical, radiographic, and histologic findings along with exclusion of other diseases that have a similar clinical picture. Workup should attempt to provide histologic evidence, evaluate the extent of disease, assess for disease progression, and determine whether therapy will benefit the patient.

The combination of bilateral hilar adenopathy, erythema nodosum, and joint symptoms (Löfgren's syndrome) usually resolves with corticosteroid treatment.

- **Baseline studies:**
  - **History:** Emphasis on occupational and environmental exposure.
  - **Physical exam:** Emphasis on the lung, skin, eye, liver, spleen, and heart.
  - Biopsy to obtain histologic confirmation of noncaseating granulomas.
  - CXR, PFTs, ECG.
  - Ophthalmologic evaluation.
  - LFTs, calcium, BUN/creatinine.
  - ACE level (not sensitive; value for monitoring disease is unclear).
- **Follow-up studies:**
  - Monitoring for resolution or progression of disease and for new-organ involvement.
  - Referral to subspecialists if there is evidence of disease progression or new-organ involvement.

Treatment

Systemic corticosteroids.

SLEEP-DISORDERED BREATHING

Sleep apnea is defined as intermittent cessation in airflow at the nose and mouth during sleep. It may be obstructive or central. Patients with **obstructive sleep apnea** (OSA) have episodic closure of the upper airway during sleep with continued respiratory efforts. Patients with **central sleep apnea** (CSA) have cessation of both airflow and respiratory efforts. CSA is often associated with CNS disorders, respiratory muscle weakness, cardiovascular disease, or pulmonary congestion, but it may also be idiopathic.

Symptoms/Exam

- Daytime hypersomnolence, impaired cognition, snoring, witnessed gasping or choking at night, and witnessed apneic episodes while sleeping are common.
- Patients may have obesity, a large neck circumference, and hypertension but may otherwise be normal.
- Patients with severe disease may have associated left ventricular failure, pulmonary hypertension, and right heart failure.

The key observation in making the diagnosis of central sleep apnea is that apneas are not accompanied by respiratory effort.

Diagnosis

The overnight sleep study (polysomnogram) is used to identify onset of sleep and its various stages as well as to document apnea, hypopnea, and arousal. The polysomnogram can also help distinguish CSA from OSA. An overnight oximetry study may aid in the following:

- To **confirm** the diagnosis of sleep apnea when the pretest probability is high and the patient has recurrent episodes of O_2 desaturation.
- To **exclude** the diagnosis when the pretest probability is low and the patient has no O_2 desaturation.

Treatment

Options include weight loss, nasal continuous positive airway pressure (CPAP), and avoidance of alcohol and sedatives. Uvulopalatopharyngoplasty and mandibular advancement have had success in only a select group of patients. Tracheostomy provides instant relief but is often not first-line treatment.

LUNG TRANSPLANTATION

For patients with severe impairment due to lung disease and limited expected survival, lung transplantation offers the potential to improve quality of life as well as to prolong life. However, complications are frequent and may ultimately lead to graft dysfunction, which limits long-term survival. The limited number of acceptable donor lungs and the increasing number of candidates have led to long waiting times (e.g., 6–24 months) for lung transplantation. Currently, severe emphysema is the most common indication for lung transplantation in the United States. Other disorders for which it is indicated include CF, IPF, sarcoidosis, PPH, and pulmonary fibrosis related to collagen vascular disease.

Candidate Selection

- Transplantation should be offered only to those with severe, advanced obstructive, fibrotic, or pulmonary vascular disease who have failed medical therapy and have a high likelihood of dying within the next 2–3 years. The following are recommended age limits for candidates:
  - **Heart-lung transplantation:** ≤ 55 years of age.
  - **Double-lung transplantation:** ≤ 60 years of age.
  - **Single-lung transplantation:** ≤ 65 years of age.
- Contraindications include severe extrapulmonary organ dysfunction, active or recent cigarette smoking, active cancer, drug dependence, severe malnutrition or obesity, and poor rehabilitation potential.

Organ Distribution

The allocation of lungs prior to 2005 was based solely on time accrued on the waiting list, regardless of severity of illness or medical emergency. In 2005, a lung allocation score was adapted to prioritize candidates based on wait list urgency and post-transplant survival.

Surgical Procedures

Single-lung transplantation is the most common procedure and is frequently performed for patients with emphysema or IPF. Double-lung transplantation is usually performed for patients with CF or bronchiectasis. Heart-lung transplantation is usually reserved for patients with Eisenmenger's syndrome and for those with severe lung disease and left ventricular dysfunction or advanced CAD.

Treatment Course and Outcomes

Immunosuppressive therapy is started in the perioperative period and is continued for life. Common long-term regimens include cyclosporine or tacrolimus in combination with azathioprine or mycophenolate mofetil and prednisone.

- **Quality of life:** Global improvement within the first three months after transplantation, but limited long-term data.
- **Complications:** Ischemia-reperfusion injury, bronchial anastomosis dehiscence or stenosis, infections (bacterial, CMV, aspergillosis), and acute and chronic rejection are not infrequent and may limit survival.
- **Survival:** One-, three-, and five-year survival rates after lung transplantation are approximately 70%, 60%, and 50%, respectively.

NOTES

CHAPTER 17

Rheumatology

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APPROACH TO ARTHRITIS

Tables 17.1 through 17.3 outline general approaches toward the differential diagnosis of arthritis and other rheumatic diseases. **Contraindications to arthrocentesis** include the following:

- Overlying soft tissue infection or cellulitis.
- Severe coagulopathy or bleeding disorder (INR > 3.0).

TABLE 17.1. Differential Diagnosis of Arthritis

Disease	Inflammation	Joint Pattern	Peripheral Joint Involvement	Spinal Disease	Key Distinguishing Features
Rheumatoid arthritis (RA)	+	Symmetric/ polyarticular	Wrist/MCPs, PIPs/ MTPs, ankles, knees	No (except C-spine)	Polyarticular, symmetric, small joints.
SLE	+	Symmetric/ polyarticular	Wrist/MCPs/PIPs	No	Extra-articular manifestations of SLE.
Ankylosing spondylitis	+	Usually oligoarticular	Hips, shoulders, knees	Yes	Low back pain.
Psoriatic arthritis	+	Asymmetric/ oligoarticular	Dactylitis, DIPs	Yes	History of cutaneous psoriasis.
Reactive arthritis	+	Asymmetric/ oligoarticular	Larger, weight-bearing joints; knees/ ankles	Yes	History of URI, diarrheal illness, or STD.
IBD-associated arthritis	+	Asymmetric/ oligoarticular	Larger joints	Yes	GI manifestations (e.g., diarrhea, bloody stools).
Gout	+	Monoarticular, polyarticular	First MTP, ankle, knee, MCPs/PIPs	No	Acute, exquisitely painful to touch.
Osteoarthritis	–	Monoarticular/ oligoarticular, polyarticular	DIPs, first carpal-metacarpal, knees, hips	Yes	Noninflammatory, i.e., worse at end of the day and with activity; improves with rest.

TABLE 17.2. Characteristics of Synovial Fluid

Sign	Normal	Group 1: Noninflammatory (osteoarthritis, hypothyroidism)	Group 2: Inflammatory (RA, gout, spondyloarthropathy)	Group 3: Septic
Clarity	Transparent	Transparent	Slightly opaque	Opaque
Color	Clear	Yellow	Yellow-opalescent	Yellow-green
Viscosity	High	High	Low	Usually low
Culture	⊖	⊖	⊖	Often ⊕
WBCs/mm^3	< 200	200–2000	2000–50,000	> 50,000
PMNs (%)	< 25	< 25	> 50	> 75

RHEUMATOID ARTHRITIS (RA)

Affects 1–2% of the U.S. population; exhibits a female-to-male predominance of 3:1. Its prevalence ↑ with age, with a typical age at onset of 20–40. Symptoms and signs indicative of **inflammatory** joint disease include the following:

- Morning pain and/or stiffness > 30 minutes.
- Gelling phenomenon, or worsening of symptoms with prolonged joint inactivity.
- Improvement in symptoms with use of the joint.
- The presence of erythema, warmth, and/or swelling in the joint.

Symptoms/Exam

- Frequently associated with a prodrome of low-grade fever and malaise.
- The most common joints affected are the hands, wrists, toes, ankles, and knees, although all joints with movable articulations can be involved.
- **Diagnostic criteria (requires four out of seven lasting > 6 weeks)** are as follows:
  - Morning stiffness
  - Arthritis involving three or more joint areas
  - Arthritis involving the hands
  - Symmetric arthritis
  - Serum rheumatoid factor (RF)
  - Radiographic changes consistent with disease
  - Rheumatoid nodules

Most extra-articular manifestations of RA are observed in patients who are RF ⊕ and have long-standing erosive articular disease.

Diagnosis

- **Classic radiographic findings:** Periarticular osteopenia, joint space narrowing, juxta-articular erosions, erosions of the ulnar styloids.
- **Common laboratory findings:**
  - **RF:**
    - Usually an IgM antibody directed against an Fc fragment of IgG.
    - Present in 70–80% of patients with established disease.

TABLE 17.3. Laboratory Serologies in SLE and Other Rheumatic Diseases

	% Disease Association[a]							
	RA	**SLE**	**SS**	**DS**	**LS**	**P/DM**	**Wegener's**	**Comments**
ANA tests:								
ANA	30–60	95–100	95	80–95	80–95	80–95	0–15	Often used as a screening test; a ⊖ test virtually excludes SLE.
Anti-dsDNA	0–5	60						Titer generally correlates with disease activity.
Anti-Smith		10–25						Specific for SLE.
Anti-RNP	0–10	30		20–30	20–30			Antibody must be present to make the diagnosis of mixed connective tissue disease.
Anti-SSA (Ro)	0–5	15–20	60–70					Associated with neonatal lupus and subacute cutaneous lupus erythematosus.
Anti-SSB (La)	0–2	5–20	60–70					Associated with neonatal lupus.
Anticentromere					50			
Anti-SCL-70				33	20			
Non-ANA tests:								
RF	70–80	20	75	25	25	33	50	
CCP	47–76							
ANCA		1–5					93–96	
Anti-Jo-1						20–30		

[a] SS = Sjögren's syndrome; DS = diffuse scleroderma; LS = limited scleroderma; P/DM = polymyositis/dermatomyositis.

- Usually present in patients with extra-articular disease.
- Extremely high titers correlate with severe RA and nodular disease
- Not specific for RA; can be seen in other collagen vascular diseases and chronic infections (e.g., HCV).

- **Anti–cyclic citrullinated peptide (anti-CCP):**
  - Present in 47–76% of patients with RA.

Anti-CCP is more specific but less sensitive than RF for diagnosing RA.

- **More specific (95%) than RF antibody.**
- Testing for both RF and anti-CCP is better for diagnosing RA than testing for either antibody alone.
- Anti-CCP-⊕ patients are at ↑ risk for rapid joint disease and radiographic progression of RA.

- **Other findings:**
  - ESR and C-reactive protein are frequently elevated but are neither sensitive nor specific.
  - Anemia of chronic disease.
  - A normal or elevated platelet count (vs. a low platelet count in SLE).
  - Neutropenia can be seen with Felty's syndrome.

TNF inhibitors can lead to activation of latent tuberculosis.

- **Extra-articular manifestations:**
  - Rheumatoid nodules, vasculitis, interstitial lung disease.
  - Serositis (pleuritis, pericarditis).
  - Ocular disease (episcleritis, uveitis, scleritis, keratitis).
  - Sjögren's syndrome.
  - Caplan's syndrome (large nodulosis of the lungs associated with anthracite coal exposure).
  - Amyloidosis.
  - Felty's syndrome (What is Felty's? The **ANS**wer = **A**rthritis, **N**eutropenia, and **S**plenomegaly).
  - Accelerated atherosclerosis; CAD.

Approximately 1 in 60 patients taking TNF inhibitors will get an opportunistic infection, and 1 in 150 will get a malignancy.

Treatment

Early use of disease-modifying antirheumatic drugs (DMARDs) is key. NSAIDs are important for symptom flares, but the American College of Rheumatology recommends starting DMARD therapy within three months of diagnosis, either with single agents or with combination therapy. Table 17.4 outlines the indications for the various antirheumatic drugs as well as their appropriate dosages, contraindications, and potential side effects.

SYSTEMIC LUPUS ERYTHEMATOSUS (SLE) AND DRUG-INDUCED LUPUS

Systemic Lupus Erythematosus

Shows a female-to-male predominance of 9:1. Three times more common among African-Americans than among whites. Both genetic and environmental factors are involved. Nearly 90% of patients have joint symptoms.

Differential

The differential diagnosis of SLE is outlined in Table 17.5.

Diagnosis

An elevated PTT in a patient with SLE suggests the presence of antiphospholipid antibodies.

- Four of the 11 clinical and laboratory criteria listed in Table 17.6 are needed for diagnosis.
- ANA testing is nearly 100% sensitive but is not specific for SLE (see Table 17.3).
- Antibodies to dsDNA and Smith are specific (> 90% and > 95%, respectively) but not sensitive (50–60% and 30%, respectively).
- Antibody titers to dsDNA can correlate with disease activity, particularly renal disease.

TABLE 17.4. Comparison of Antirheumatic Drugs

Drug	Indication	Dosage	Initial Monitoring	Routine Monitoring	Contra-indications	Side Effects
Methotrexate	First-line DMARD.	Weekly.	CXR, hepatitis serologies, CBC, LFTs, creatinine.	CBC, LFTs.	Hepatic disease.	Myelosuppression, hypersensitivity pneumonitis, pulmonary fibrosis, hepatotoxicity, cirrhosis.
Sulfasalazine	First- or second-line DMARD.	Daily.	CBC, G6PD (if suspected).	CBC.	G6PD deficiency (can cause hemolysis).	GI intolerance, neutropenia, thrombocytopenia.
Leflunomide	First- or second-line DMARD.	Daily, but $t_{1/2}$ is > 2 weeks.	Hepatitis serologies, CBC, LFTs, creatinine.	CBC, LFTs, creatinine.		Myelosuppression, hepatotoxicity, rash, diarrhea.
TNF-α inhibitors	Second-line DMARDs; usually added after 3–6 months if there is no/little response to other DMARDs.	**Infliximab:** Infusion q 6–8 weeks. **Adalimumab:** SQ injection q 2 weeks. **Etanercept:** SQ injection 1–2 times per week.	PPD, CXR.		Malignancy, active or untreated latent TB.	Immunosuppression with an ↑ incidence of opportunistic infections and malignancy.
Antimalarials (hydroxychloroquine)	Weak DMARD used in mild RA.	Daily.		Yearly eye exam.		
Corticosteroids	First-line DMARD, but use lowest dose possible and wean off to prevent long-term complications.	Daily.	BP, glucose, metabolic panel, lipids.	Bone densitometry (DEXA), glucose, lipids.		Glucose intolerance, hypertension, cataracts, osteoporosis, avascular necrosis.

TABLE 17.4. Comparison of Antirheumatic Drugs *(continued)*

Drug	Indication	Dosage	Initial Monitoring	Routine Monitoring	Contra-indications	Side Effects
Azathioprine	Used for severe/ refractory RA.	Daily.	CBC, LFTs, creatinine.	CBC with change in dose.	Not to be used concomitantly with allopurinol.	Myelosuppression, immunosuppression, hepatotoxicity, lymphoproliferative disorders.
Minocycline	Weak DMARD.	Daily.				Dizziness, hyperpigmentation, deposition into bone.

- Antibodies to Smith and ANA titers do not correlate with disease activity.
- Depressed serum complement levels (CH50, C3, C4) are frequently seen in SLE but can normalize in remission.

Treatment

Nonpharmacologic treatment includes sun avoidance, sun protection, rest, and avoidance of stress. Pharmacologic treatment can be broken down according to disease severity:

- **Mild disease** (skin/joint involvement, oral ulcers, serositis) (see Figure 17.1):
  - NSAIDs.
  - Topical corticosteroids for skin disease.
  - Low-dose systemic corticosteroids (< 10 mg/day).
  - Antimalarial medications (i.e., hydroxychloroquine; good for mild symptoms and skin disease).

TABLE 17.5. Differential Diagnosis of SLE

Differential	Distinguishing Factors
Drug-induced lupus (must be excluded)	See text.
RA	Erosive arthritis.
Mixed connective tissue disease	Less severe renal disease; features of systemic sclerosis and/or inflammatory myopathy.
Vasculitis	Different serologies (see Table 17.3).
Acute drug reaction	Identification of offending agent.
Systemic sclerosis	Predominance of skin changes.

TABLE 17.6. Diagnostic Criteria for SLE[a]

	CRITERIA
Skin/**S**unlight	1. Malar rash 2. Discoid rash 3. Photosensitivity
Serosa/mucous membranes	4. Oral ulcers 5. Serositis (pleuritis/pericarditis)
Synovitis	6. Arthritis
Seizures, **"S"**ychosis	7. Neurologic disease
"S"ellular casts, proteinuria	8. Renal disease (any one of the following): a. > 0.5 g/day proteinuria b. ≥ 3+ dipstick protein c. Cellular casts
"S"ytopenias	9. Hematologic disorders (any one of the following): a. Hemolytic anemia b. Leukopenia (< 4000/mL) c. Lymphopenia (< 1500/mL) d. Thrombocytopenia (< 100,000/mL)
Serologies	10. ⊕ ANA 11. Immunologic abnormalities (any one of the following): a. Antibodies to native DNA b. Anti-Smith antibodies c. Antiphospholipid antibodies: (1) False-⊕ serologic test for syphilis (2) Evidence of anticardiolipin antibodies (3) Evidence of lupus anticoagulant

[a] Four out of 11 are needed for diagnosis.

- **Moderate disease** (cytopenias/hemolytic anemia, serositis, mild pneumonitis, mild myocarditis):
  - Moderately dosed systemic corticosteroids (approximately 0.5 mg/kg/day).
  - Steroid-sparing agents such as azathioprine, methotrexate (good for skin and arthritis), and mycophenolate mofetil.
- **Severe disease** (nephritis, severe CNS disease, vasculitis, pulmonary hemorrhage):
  - High-dose corticosteroids (≥ 1 mg/kg/day).
  - IV cyclophosphamide (proven efficacy for nephritis; less established for other indications).
  - Azathioprine.
  - Mycophenolate mofetil.
  - IVIG (for antibody-mediated cytopenias).
  - Plasmapheresis (in extreme circumstances).

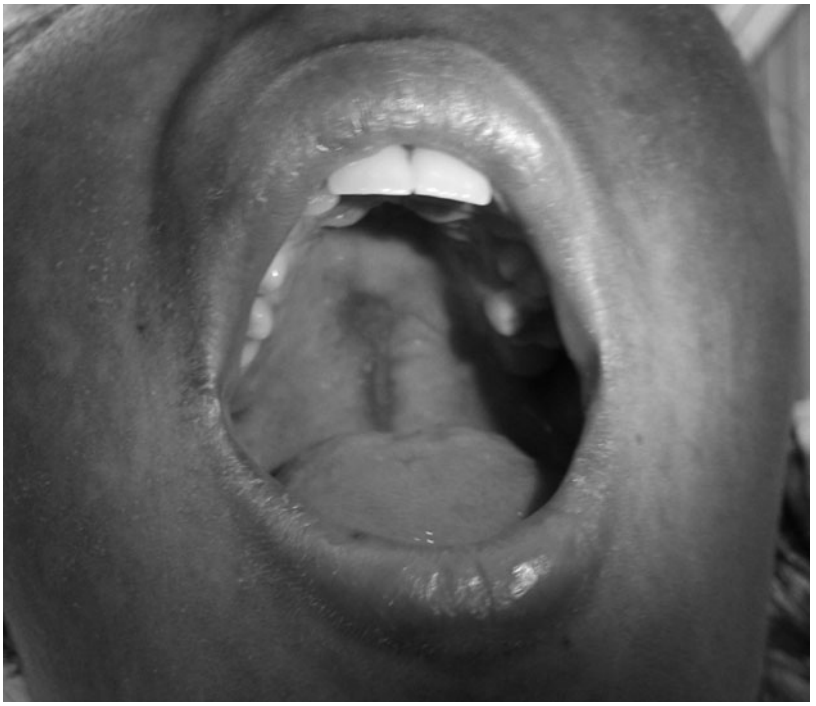

FIGURE 17.1. Oral ulcer on hard palate of patient with SLE.

Complications

In addition to disease-related organ-specific damage, complications are as follows:

- Accelerated atherosclerosis, CAD.
- Transitional cell carcinoma and hematologic malignancies if the patient received cyclophosphamide.
- Opportunistic infections.

Drug-Induced Lupus

The most commonly associated drugs are hydralazine, procainamide, INH, quinidine, methyldopa, and chlorpromazine.

Differential

Hallmarks that distinguish drug-induced lupus from SLE include the following:

- Equal prevalence among both sexes.
- Lack of severe renal and neurologic involvement.
- Lack of antibodies to DNA.
- Frequently normal levels of serum complement.
- Abatement of clinical and laboratory features upon discontinuation of the inciting agent.
- The presence of **antihistone antibodies** (sensitive but not specific for drug-induced lupus).

Neonatal Lupus

Neonatal lupus is classically associated with anti-SSa (anti-Ro) and anti-SSb (anti-La) antibodies.

Clinical features of neonatal lupus are as follows:

- A photosensitive rash, complete heart block, hepatitis, thrombocytopenia, hemolytic anemia.
- Passive transfer of maternal anti-Ro/SSA and anti-La/SSB antibodies in utero associated with disease.
- Most features remit when titers of antibodies wane in the neonate.
- Complete heart block is permanent.

SJÖGREN'S SYNDROME

Characterized by lymphocytic and plasma cell infiltration of affected exocrine glands throughout the body. Can be 1° in etiology or 2° to another autoimmune disorder. Sjögren's exhibits a significant female-to-male predominance (9:1) and most commonly affects middle-aged individuals.

Symptoms/Exam

The clinical characteristics of Sjögren's syndrome are as follows (common ABIM-tested associations are in boldface):

- **Dry mouth (xerostomia), dental caries,** impaired taste and/or smell, dysphagia.
- **Keratoconjunctivitis sicca: Burning, itching eyes;** diminished lacrimation; thickened/sticky tears; photophobia.
- Parotid enlargement.
- Dryness of the skin and vaginal mucosa.
- **Pancreatitis.**
- Interstitial lung disease, **lymphocytic interstitial pneumonitis,** tracheobronchitis sicca.
- **Type 1 RTA;** interstitial nephritis.
- Neuropsychiatric diseases of various etiologies.
- Vasculitis.

Differential

Drugs (e.g., anticholinergic medications), HCV, HIV, and sarcoidosis may present with dry eyes and dry mouth. HIV and sarcoidosis may also present with glandular infiltration.

Diagnosis

- **Biopsy** of minor lip/salivary gland reveals lymphocytic foci in glands.
- **Labs:** Frequently ⊕ ANA, RF, and anti-SSA/anti-SSB (see Table 17.3); hypergammaglobulinemia.
- **Other:** Ancillary testing can demonstrate ↓ tear production, low salivary flow, and sicca.

Treatment

Seek symptom relief with the following:

- Artificial tears and saliva.
- Sugarless candies and frequent sipping of water.
- Aggressive oral hygiene.
- Avoidance of anticholinergic and decongestant medications.
- Cholinergic agonist medications to stimulate saliva production.

COMPLICATIONS

Lymphoproliferative disorders, including lymphomas; Waldenström's macroglobulinemia.

SERONEGATIVE SPONDYLOARTHROPATHIES

The four seronegative spondyloarthropathies are grouped because:

- *"Seronegative" = serologies ⊖ for ANA and RF.*
- *"Spondylo-" = spinal arthritis.*

Include four disorders: ankylosing spondylitis, psoriatic arthritis, IBD-associated arthritis, and reactive arthritis, or Reiter's syndrome (see Table 17.7).

Ankylosing Spondylitis

Shows a predominance of **males over females;** characterized by an early age of onset (generally < 35 years). Prevalence is 0.2–0.5% among whites in the United States (higher prevalence among Scandinavians).

SYMPTOMS

- Inflammatory low back pain that worsens in the morning and with inactivity but improves with exercise.
- Progressive pain and stiffening of the spine.
- Transient acute arthritis (pain and swelling) of the larger peripheral joints.

EXAM

- Tenderness of the sacroiliac joints to palpation.
- Reduced lumbar lordosis; reduced chest expansion diameter.
- Limited range of motion of the neck.
- Enthesitis—i.e., pain of the Achilles tendon pain on palpation.

TABLE 17.7. Features of Seronegative Spondyloarthropathies

DISEASE	SACROILIITIS	% WITH ⊕ HLA-B27	OTHER MANIFESTATIONS
Ankylosing spondylitis	Symmetric	90	Uveitis, aortitis.
Psoriatic arthritis	Asymmetric	75	Skin disease in 80% of cases; DIP arthritis is common.
Reactive arthritis	Asymmetric	50 (when sacroiliitis is present)	The classic triad is conjunctivitis, urethritis, and arthritis (more commonly of larger peripheral joints than of the spine); keratoderma blennorrhagicum (pustular rash on soles of feet).
IBD-associated arthritis	Symmetric	50 (when sacroiliitis is present)	GI disease is usually present; more commonly Crohn's than ulcerative colitis.

Differential

- RA (affects numerous symmetric, small peripheral joints).
- Noninflammatory, mechanical low back pain.
- Diffuse idiopathic skeletal hyperostosis.
- Osteitis condensans ilii (sclerosis of the iliac bone in childbearing women).
- Infectious sacroiliitis (e.g., TB, brucellosis).

Diagnosis

- Diagnosed in the setting of a consistent history.
- **Imaging:** Look for radiographic evidence of sacroiliitis and/or spinal involvement (see Figure 17.2):
  - Bilateral sclerosis of the sacroiliac joints.
  - Squared-off vertebral bodies.
  - "Shiny" corners of vertebral bodies.
  - Symmetric, bamboo-like syndesmophytes between vertebral bodies.
- **Labs:**
  - HLA-B27 is ⊕ in the majority of cases but is **not diagnostic** (seen in 8% of the normal Caucasian population).
  - Elevated ESR and ⊖ RF.

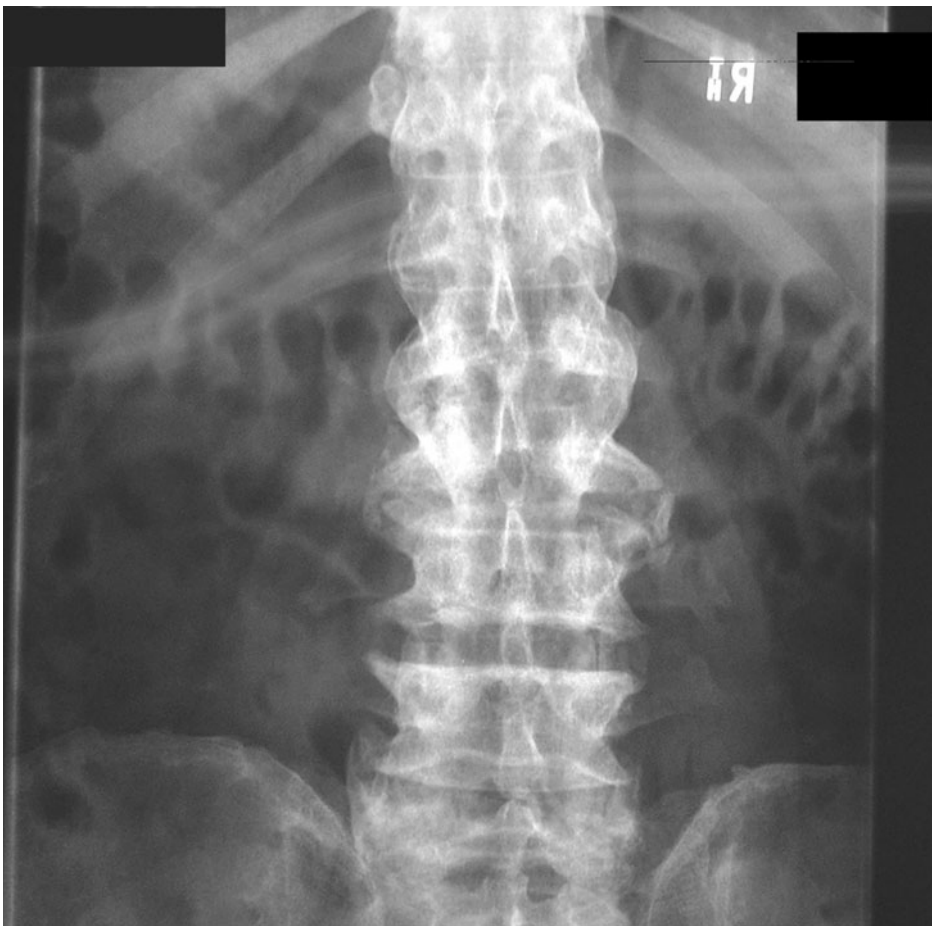

FIGURE 17.2. Spinal x-ray showing changes associated with a spondyloarthropathy.

Before initiating TNF inhibitor medication, always place a PPD to screen for active or latent TB.

Apical pulmonary fibrosis in ankylosing spondylitis can look like TB.

Treatment

- NSAIDs.
- Sulfasalazine or methotrexate for peripheral arthritis.
- TNF-α antagonists.
- Aggressive **physical therapy** to enable spinal fusion in an advantageous position.

Complications

All of the following are classic associations:

- Anterior uveitis.
- Aortitis and aortic regurgitation (more rarely, cardiac conduction system involvement).
- Apical pulmonary fibrosis (mimics TB—be careful!).
- Pseudoarthroses can occur when a fused spine is severed in a traumatic accident, which can cause spinal cord compromise.

Psoriatic Arthritis

Peripheral arthritis, dactylitis, and enthesitis (inflammation of the tendinous insertions of the joints; seen with other HLA-B27-related diseases as well). Found in 15–20% of patients with psoriatic skin disease. Skin disease precedes arthritis in 80% of cases (see Figure 17.3).

Symptoms/Exam

The clinical presentation of psoriatic arthritis is further outlined in Table 17.8.

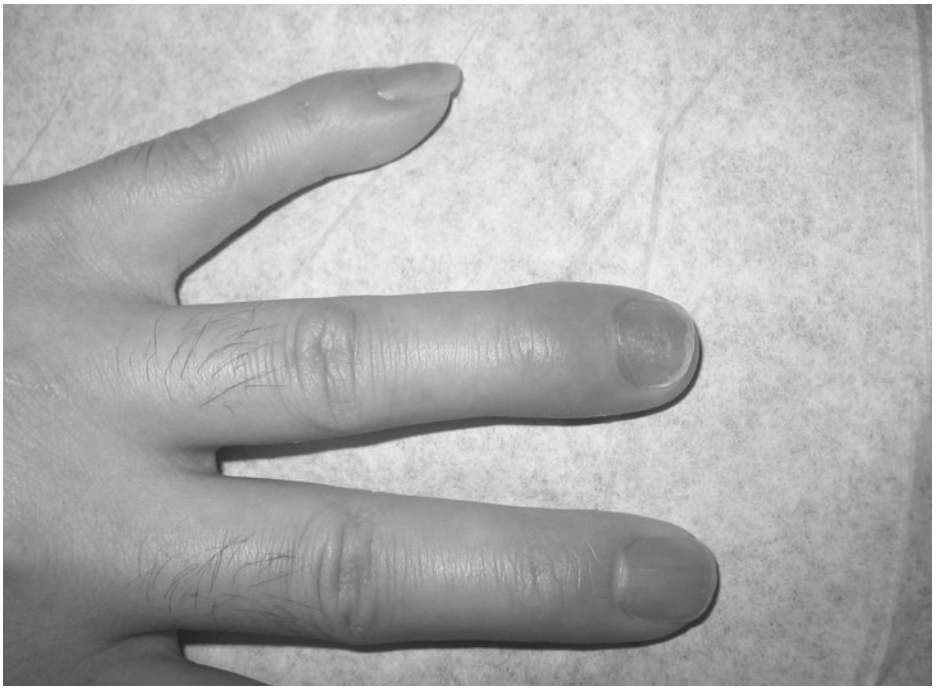

FIGURE 17.3. Onycholysis in a psoriatic arthritis patient.

TABLE 17.8. Five Major Patterns in Psoriatic Arthritis

Pattern	Joint Involvement
DIP involvement	Can be monoarticular or asymmetric; nail pitting and onycholysis (see Figure 17.3).
Pseudorheumatoid	Symmetric, smaller-joint polyarthritis.
Oligoarticular	Erosive arthritis, dactylitis ("sausage digit").
Arthritis mutilans	Severe, osteolytic, deforming (telescoping digits).
Spondylitis	Sacroiliitis and/or ankylosing spondylitis.

Diagnosis

- Characteristic presentation.
- Radiographic findings include the following:
  - Marginal erosions of bone.
  - Characteristic "pencil-in-cup" deformities of distal digits.
  - Periosteal bone formations and calcifications of entheses.
  - Sacroiliitis and spondylitic changes of the spine (frequently asymmetric).

Psoriasis precedes most cases of psoriatic arthritis.

Treatment

- NSAIDs; methotrexate, sulfasalazine, and other DMARDs for peripheral arthritis; TNF-α inhibitors.
- **Avoid corticosteroids if possible** (tapering can cause skin disease to flare).

Reactive Arthritis

Males (particularly young men) are affected more often than females. Eighty percent of white and 50–60% of African-American patients are HLA-B27 ⊕. May be idiopathic or may develop within days to weeks of antecedent infection:

- **GI disease:** *Salmonella*, *Shigella*, *Campylobacter*, *Yersinia*.
- **GU disease (urethritis):** *Chlamydia*.

Symptoms/Exam

- Presents with frequently asymmetric involvement of larger, weight-bearing joints.
- Spinal involvement is seen in 20% of patients.
- Conjunctivitis, urethritis, and mucocutaneous ulcerations are seen, as is keratoderma blennorrhagicum (pustular eruptions on the soles of the feet).
- Systemic signs (fever, weight loss) are not unusual.

Differential

Septic and gonococcal arthritis, crystal-induced arthritis, seronegative RA, other seronegative spondyloarthropathies.

Diagnosis

- Inflammatory pattern on arthrocentesis.
- Culture of affected joints is sterile.
- Test for chlamydia if the history or exam is suggestive.

Treatment

- NSAIDs; antibiotics for chlamydia-related reactive arthritis.
- Sulfasalazine, methotrexate, and other DMARDs can be given for recalcitrant peripheral arthritis.

Complications

Aortitis and aortic regurgitation (rare).

Inflammatory Bowel Disease (IBD)–Associated Arthritis

Twenty percent of patients with IBD have associated arthritis. Associated more often with Crohn's disease than with ulcerative colitis. Arthritis usually appears after the onset of GI disease.

Symptoms/Exam

- **Peripheral arthritis, enthesitis, and dactylitis:**
  - Asymmetric, oligoarticular.
  - Large joint involvement.
  - Frequently nonerosive.
  - Flares in concert with intestinal disease.
- **Spinal arthritis:**
  - Symmetric inflammatory sacroiliitis and spondylitis.
  - Mimics ankylosing spondylitis.
  - The course of the disease is independent of intestinal disease.

Differential

Ankylosing spondylitis, enteropathic reactive arthritis, Whipple's disease, seronegative RA.

Treatment

NSAIDs; treatment of intestinal disease (controls peripheral arthritis).

CRYSTALLINE-INDUCED ARTHROPATHIES

Include gout, pseudogout, and calcium pyrophosphate dihydrate deposition disease.

Hyperuricemia ↑ the risk of gout, but most patients with hyperuricemia will not get gout.

Hyperuricemia

The causes of hyperuricemia and its relation to gout are delineated in Table 17.9.

Gout

Usually associated with abnormal uric acid metabolism and hyperuricemia; can be associated with uric acid stones and urate nephropathy (renal toxicity).

TABLE 17.9. Causes of Hyperuricemia

Overproduction of Uric Acid	Underexcretion of Uric Acid
Genetic metabolic defects:	Idiopathic
Lesch-Nyhan syndrome	Chronic renal disease
Glycogen storage diseases	Medication induced:
Psoriasis	Thiazide diuretics
Myeloproliferative disorders/large tumor	Loop diuretics
burden malignancies	Cyclosporine
Idiopathic	Metabolic:
	Lactic acidosis
	Alcoholism
	Ketoacidosis
	Lead nephropathy (saturnine gout)

Males are affected more often than females (9:1). Onset is generally after age 30; almost always **postmenopausal** in women.

Symptoms

- Presents with sudden-onset, self-limited, recurrent, acute mono- or oligoarticular arthritis.
- Can progress to chronic deforming polyarthritis after multiple attacks.
- Additional features are as follows:
  - **Tophi:** Deposits of uric acid crystals in joints, bone, tendon, cartilage, and subcutaneous tissues.
  - **Podagra:** Refers to gout of the first MTP, the most commonly affected joint.
  - Other affected joints include the knees, ankles, feet, elbows, and hands.
- Asymptomatic periods (**intercritical periods**) can last months or years.

Exam

- Exam reveals erythema, swelling, warmth, and tenderness to palpation of affected joints.
- Cellulitis-like erythema of overlying skin and soft tissue is also seen.
- Classically exhibits a monoarticular presentation, but can be oligoarticular or polyarticular in long-standing disease.
- Look for the presence of tophi on the external ears, elbows, hands, and feet (see Figure 17.4).
- Fever is common but rarely exceeds 39°C.

Differential

Cellulitis, septic arthritis, pseudogout, reactive arthritis, RA, lead poisoning.

Diagnosis

- Uric acid is abnormally elevated at some point in 95% of cases, but **this is not diagnostic, does not correlate with disease activity, and is not needed to make a diagnosis.**
- Synovial fluid aspiration reveals the following:
  - An inflammatory pattern.

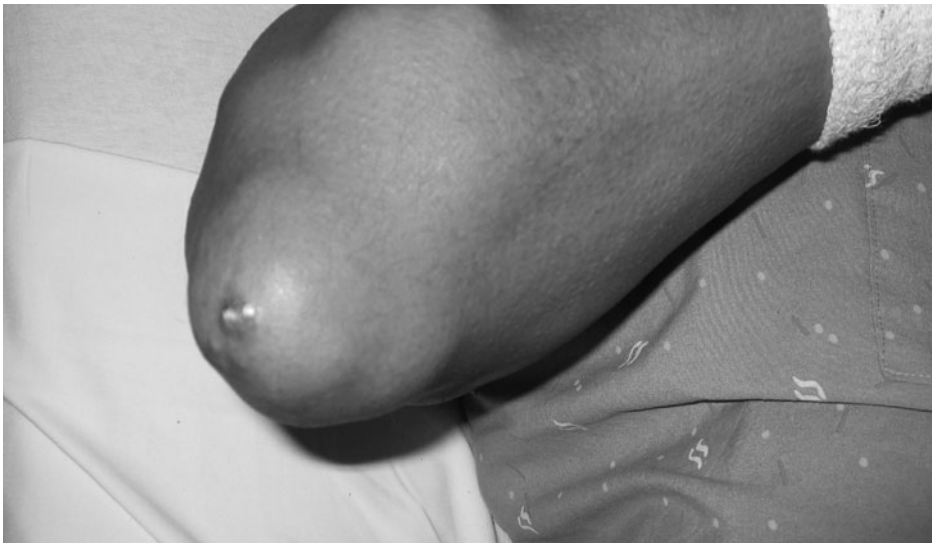

FIGURE 17.4. Tophaceous gout of the elbow.

- Sterile cultures.
- Negatively birefringent, needle-like crystals (the crystals are yellow under polarized light, when the red compensator is pointed in parallel to the crystals (think **yeLLow = paraLLel;** see Figure 17.5). Radiographs of chronic tophi show "rat-bite" erosions adjacent to affected joints (see Figure 17.6).

- Measure urinary uric acid excretion to distinguish underexcreters from overproducers of uric acid (< 600–800 mg/day = underexcretion).

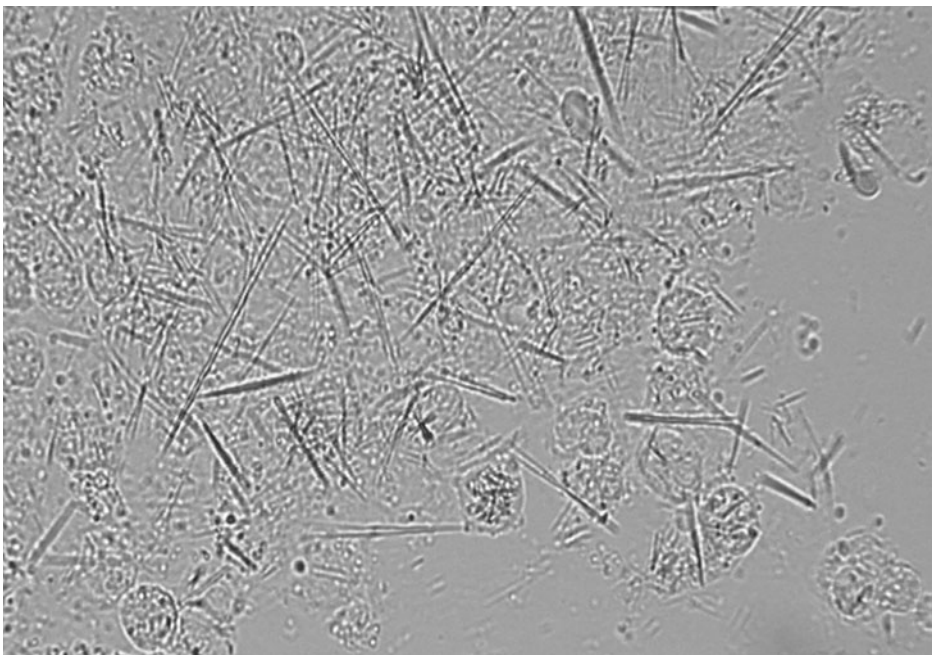

FIGURE 17.5. Gout crystals.

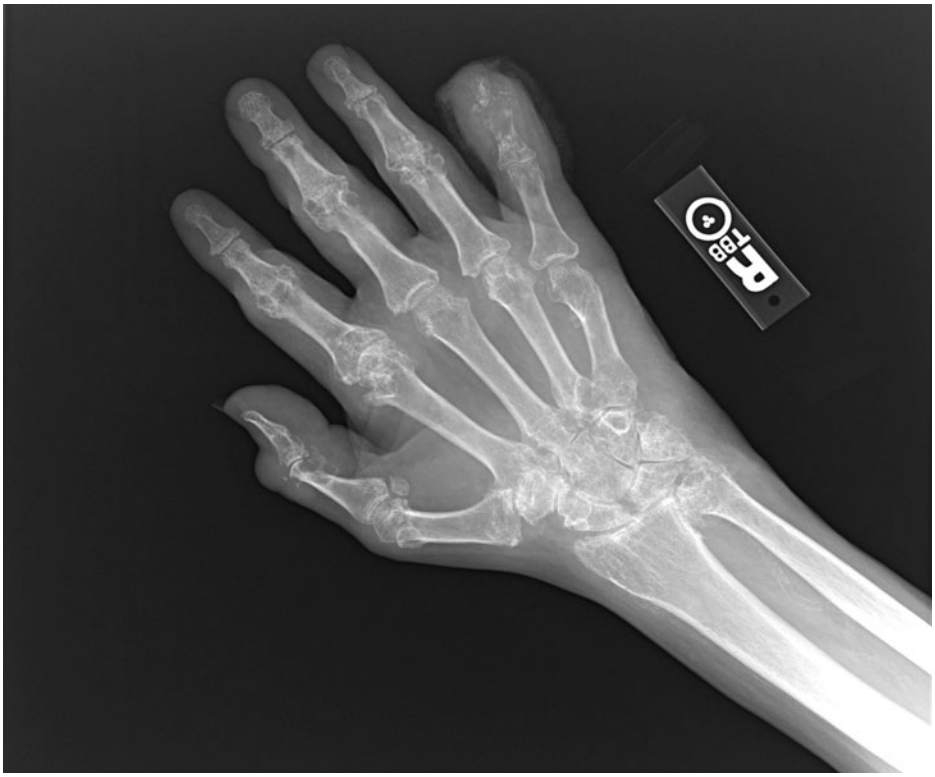

FIGURE 17.6. Radiograph of the hand showing osteolysis of the fifth digit and PIP, MCP, and carpal erosions 2° to tophaceous gout.

TREATMENT

Guidelines for the treatment of gout are outlined in Table 17.10.

COMPLICATIONS

Complications associated with treatment are as follows:

- **Allopurinol:**
  - An acute gouty attack may occur if allopurinol is used without a concomitant NSAID, colchicine, or corticosteroid.
  - Hypersensitivity syndrome may also be seen (↑ in renal disease and elevated serum metabolite levels).
  - Fever, desquamating rash, hepatitis, vasculitis.
  - Allopurinol ↑ the effect and toxicity of azathioprine (blocks its metabolism).
- **Probenecid:**
  - Hypersensitivity.
  - Loss of efficacy in patients with advanced renal disease.
  - Precipitates urate nephropathy and nephrolithiasis if used in tophaceous gout or in patients with a history of urate calculi.

Accelerated or unusual distribution of degenerative joint disease should raise suspicion for CPPD.

Calcium Pyrophosphate Dihydrate Deposition Disease (CPPD)

Arthritis associated with CPPD crystal deposition may be hereditary or associated with metabolic disease, or it may occur 2° to aging. Four percent of the

TABLE 17.10. Treatment of Gout

Drug	Usage
Acute attack	
NSAIDs (indomethacin)	Until symptoms resolve (1–2 weeks, 50–75 mg TID).
Colchicine	Within 48 hours of onset of attack (0.6 mg/hr until resolution of toxicity).
Corticosteroids	Oral in NSAID-intolerant patients; intra-articular injections for monoarticular disease.
After attack	
Nothing	Many patients will experience few if any future attacks and choose no further uric acid therapy.
Diet	Low purine (at best, can lower uric acid 1 mg/dL); alcohol avoidance.
Medication management	Discontinue precipitating medications.
Colchicine	Give 0.6 mg QD BID to prevent future attacks; 0.6/day × 1–2 weeks while initiating uric acid–lowering therapies.
Allopurinol (xanthine oxidase inhibitor)	Best for uric acid overproducers, tophaceous gout, and urate nephropathy. Usual dose is 300 mg/day; lower initial starting dose if patient has ↓ creatinine clearance.
Probenecid	Best for uric acid underexcreters (promotes uricosuria). Give 500 mg/day (starting) to 2 g/day.

adult population are found to have articular CPPD deposits at the time of death, and by the ninth decade nearly half of the population have been found to have chondrocalcinosis.

Symptoms/Exam

There are three patterns of CPPD disease:

- **Pseudo-osteoarthritis (pseudo-OA) pattern:**
  - Accounts for 50% of symptomatic CPPD patients.
  - The knee is most commonly affected, followed by the wrists, MCPs, hips, shoulders, elbows, and ankles.
  - Patients with these chronic symptoms of pseudo-OA may have superimposed episodes of acute joint inflammation.
- **Pseudogout pattern:**
  - Accounts for roughly 25% of CPPD patients.
  - Acute pseudogout is marked by inflammation in one or more joints that lasts for several days to two weeks.
  - Fifty percent of attacks affect the knee, but attacks have been documented in all joints, including the first MTP.
  - May occur spontaneously or be provoked by trauma, surgery, or severe illness such as stroke or MI.
  - Patients are usually asymptomatic between episodes.
  - Differentiation from gout or infection may be difficult and requires arthrocentesis.
- **Pseudo-RA pattern:**
  - Roughly 5% of patients with CPPD deposition manifest a "pseudorheumatoid" pattern, including multiple joint involvement with symmetric distribution and low-grade inflammation.
  - Accompanying morning stiffness, fatigue, synovial thickening, flexion contractures, and elevated ESR often lead to a misdiagnosis of RA.
  - The presence of high-titer RF, CCP antibody, and typical rheumatoid bony erosions favors the diagnosis of "true" RA.

CPPD as part of underlying metabolic disorders:

- *Hemochromatosis*
- *Hypophosphatemia*
- *Hypomagnesemia*
- *Hyperparathyroidism*
- *Hypothyroidism*
- *Diabetes*

Diagnosis

- Serum urate level is normal.
- **Chondrocalcinosis** is visualized on x-rays of the knees and wrists.
- Synovial fluid aspiration reveals the following:
  - An inflammatory fluid profile in acute attacks.
  - Weakly ⊕ birefringent **rhomboid-shaped crystals** (the opposite of urate).

Treatment

NSAIDs; intra-articular injection of corticosteroid; colchicine for chronic chemoprevention.

Chondrocalcinosis

An accelerated degenerative joint disease characterized by osteoarthritis of unusual joints (e.g., the shoulders, ankles, elbows, and MCPs). Characterized by a frequently asymptomatic deposition of CPPD crystals along articular surfaces. Aggressive disease or unusual age at presentation should prompt evaluation and treatment of an underlying metabolic disorder.

INFLAMMATORY MYOPATHIES

Table 17.11 outlines the clinical characteristics of various inflammatory myopathies.

Polymyositis

A systemic inflammatory disorder that specifically targets the proximal musculature. Women are affected more often than men by a ratio of 2:1; the average age of onset is 40–60 years. May have a mild association with malignancy.

Symptoms/Exam

- Presents with progressive muscle weakness of the neck and upper and lower extremities.
- **Weakness** is more common than **pain.**
- **Proximal muscles are affected more than distal muscles.**
- Patients may have difficulty swallowing.

Differential

- Inclusion body myositis **(distal muscles are affected more than proximal muscles).**
- Polymyalgia rheumatica (**pain** is more common than weakness).
- Myositis 2° to other autoimmune diseases.
- Myositis 2° to malignancy.
- Medication-related myopathies (steroid, statin, colchicine).
- Toxin- or endocrine/metabolic-related myopathy.
- Myasthenia gravis.
- Genetic myopathies.

Diagnosis

- Look for elevated markers of muscle enzymes (CK and/or aldolase) for both diagnosis and disease follow-up.

TABLE 17.11. Characteristics of Inflammatory Myopathies

	Pain	Muscle Weakness	Skin Involvement	Response to Steroids
Polymyositis	–	Proximal	–	+
Dermatomyositis	–	Proximal	+	+
Inclusion body myositis	–	Distal	–	–
Polymyalgia rheumatica	++	None	–	++

- EMG is nonspecific and shows abnormal polyphasic potentials, fibrillations, and high-frequency action potentials.
- Biopsy of affected muscle shows endomysial lymphocytic inflammatory infiltrate.

Treatment

- Corticosteroids (0.5–1.0 mg/kg/day).
- DMARDs (methotrexate, azathioprine) for steroid sparing or recalcitrant disease.

Complications

- **Antisynthetase syndrome:** Interstitial lung disease, Raynaud's phenomenon, arthritis (associated with **anti-Jo-1 antibodies**).
- **Other:** Myocarditis, respiratory muscle failure, swallowing difficulties and aspiration.

Dermatomyositis

Often associated with occult malignancy. Amyopathic dermatomyositis is a variant with a characteristic skin disease.

Symptoms/Exam

- Symptoms are similar to those of polymyositis.
- Additional features are as follows:
  - **Gottron's papules:** A scaly rash over the extensor surfaces (see Figure 17.7).
  - **Shawl sign:** Erythema in a sun-exposed V-neck or shoulder distribution.
  - **Heliotrope rash:** A violaceous rash over the eyelids, sometimes with periorbital edema.
  - **Facial erythema:** A diffuse, dusky rash.
  - **Mechanic hands:** Dystrophic cuticles of the hands.
  - **Other:** Periungual erythema and dilated periungual capillaries.

Once dermatomyositis is diagnosed, serious investigation of underlying occult malignancy should be sought, especially age-appropriate cancer screening.

Diagnosis

- Similar to polymyositis.
- Muscle biopsy shows perivascular and perifascicular lymphocytic inflammatory infiltrate with destruction of microvasculature.

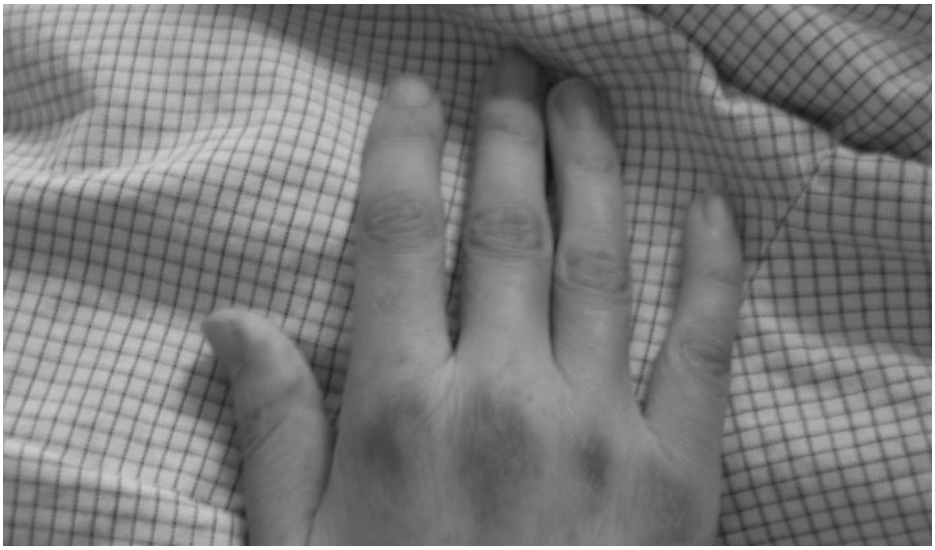

FIGURE 17.7. Gottron's papules in patient with dermatomyositis.

TREATMENT

- Similar to that of polymyositis.
- IVIG for refractory cases.
- Age-appropriate and symptom-directed cancer screening. Consider screening women for ovarian cancer with pelvic ultrasound and/or CA-125 level.
- Treat underlying malignancy (if present).

Inclusion Body Myositis

- Characterized by distal more than proximal muscle weakness; weakness is more often asymmetric than symmetric. Older white males are more frequently affected.
- More insidious in onset than polymyositis or dermatomyositis.
- **Dx:** Characteristic inclusion bodies are seen on muscle biopsy.
- **Tx:** "Treatment resistant" compared to other inflammatory myopathies.

SYSTEMIC SCLEROSIS (SCLERODERMA)

The clinical characteristics of systemic sclerosis are outlined below and in Table 17.12.

Limited Scleroderma

SYMPTOMS/EXAM

- Characterized primarily by the **CREST** syndrome: **C**alcinosis, **R**aynaud's phenomenon, **E**sophageal dysmotility, **S**clerodactyly (sclerodermatous skin changes confined to the upper extremity distal to the wrist), and **T**elangiectasias.
- Lung disease tends to be pulmonary hypertension.
- Also presents with arthralgia and arthritis, fever and malaise, abnormal periungual capillary dropout or dilatation, digital ulcerations, and tapering of the distal digits.

TABLE 17.12. Characteristics of Systemic Sclerosis

Disease Type	Frequency of Cases (%)	Organs Involved	Antibodies
Limited scleroderma	80	CREST, pulmonary hypertension	ANA, anticentromere
Progressive systemic sclerosis	20	Proximal skin, kidney, heart, lung, GI tract	ANA, anti-SCL-70

Treatment

Treatment is outlined in Table 17.13.

Complications

The prognosis is generally more favorable than that of diffuse scleroderma, but later-onset pulmonary hypertension and other vasculopathic processes affect mortality.

Progressive (Diffuse) Systemic Sclerosis

Symptoms/Exam

- Presents with skin involvement **proximal to the wrists,** including the arms, chest, and face.
- Also characterized by the following:
  - Tendon friction rubs.
  - Early **scleredema** (soft tissue swelling of affected joints).
  - Lung disease tends to be interstitial lung disease.
  - Features of CREST.

Differential

Morphea and linear scleroderma (characteristic localized skin disease), limited scleroderma, scleromyxedema, eosinophilic fasciitis, eosinophilia-myalgia syndrome.

Treatment

Treatment is outlined in Table 17.14.

TABLE 17.13. Symptomatic Treatment of Limited Scleroderma

Disorder	Treatment
Raynaud's	Body-warming techniques, calcium channel blockers.
Digital ulcerations	Raynaud's therapies as above; aspirin, topical nitrates, prostacyclin analogs.
Esophageal dysmotility	Elevate the head of the bed and avoid late-night meals; H_2 blockers or PPIs.
Pulmonary hypertension	O_2, calcium channel blockers, prostacyclin analogs, bosentan.

TABLE 17.14. Symptomatic Treatment of Diffuse Scleroderma

Organ	Complications	Treatment
Kidney	Renal crisis (malignant hypertension, renal failure, and microangiopathic hemolytic anemia).	ACEIs.
Lung	Interstitial pneumonitis, interstitial fibrosis.	Corticosteroids,[a] immunosuppressants.
Heart	Myocarditis, myocardial fibrosis, heart failure, pericardial effusions, conduction system disease.	Corticosteroids,[a] immunosuppressants, CHF therapy, pacemakers.
GI	Delayed gastric emptying, intestinal malabsorption, bacterial overgrowth.	Frequent small meals, promotility agents, antibiotics.

[a] Corticosteroids are usually avoided in scleroderma (unless severe organ-related disease leaves little other choice) because they may precipitate renal crisis.

VASCULITIS

Approach to Vasculitis

Vasculitis can be classified as either 1° or 2°. Figure 17.8 categorizes 1° vasculitis according to vessel size. 2° causes of vasculitis are as follows:

- **Infections:** Particularly indolent, chronic infections such as subacute bacterial endocarditis and HCV.
- **Medications:** Hypersensitivity vasculitis, leukocytoclastic vasculitis, ANCA-associated vasculitis.
- Collagen vascular disease.
- Malignancy.

1° Vasculitis Syndromes

Wegener's Granulomatosis

Necrotizing **granulomatous** arteritis of the small arteries, arterioles, and capillaries. Characterized by cavitating **nodules of the upper and lower respira-**

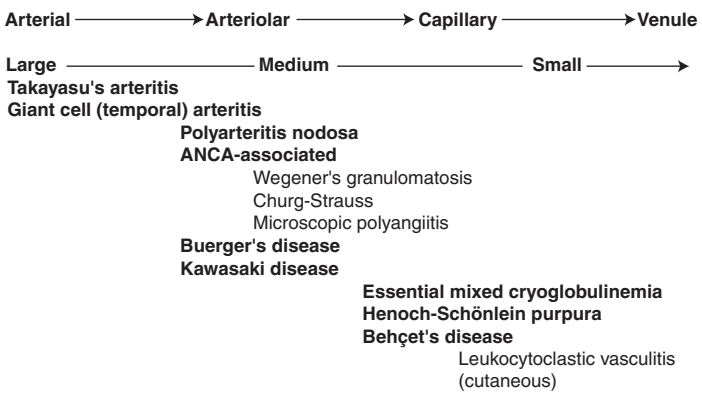

FIGURE 17.8. Classification of 1° vasculitis according to size of vessel involved.

tory tract (lungs and sinuses) and by **glomerulonephritis.** Organs and systems affected include the upper and lower respiratory tract, kidney, eye, ear, nerve, skin, gingiva, and joints.

Symptoms/Exam

- Fever, malaise, weight loss.
- Sinusitis, epistaxis, otitis media, gingivitis, stridor, mastoiditis.
- Cough, hemoptysis, dyspnea.
- Arthritis, scleritis, neuropathy, skin rashes, hematuria.

Diagnosis

- **Labs:**
  - Elevated ESR; normal serum complement levels.
  - **ANCA** ⊕: c-ANCA (anti-proteinase 3) more than **p-ANCA.**
- **Imaging:** CXR and chest CT show fixed pulmonary nodules, cavities, and/or infiltrates.
- UA with active sediment.
- Characteristic biopsy.

Treatment

- **Induction:** Cyclophosphamide and corticosteroids.
- **Remission:** Methotrexate, azathioprine.

Churg-Strauss Angiitis

*The triad of asthma, eosinophilia, **and a** ⊕ **p-ANCA** strongly suggests Churg-Strauss syndrome.*

Males are affected more often than females. Organs and systems affected include the lung, heart, nerve, and kidney.

Symptoms/Exam

- **Asthma,** nasal polyps, allergic rhinitis.
- Mono- and peripheral neuropathy (mononeuritis multiplex).
- Fever, rash, myalgias, arthralgias, weight loss.
- Cough, dyspnea, angina pectoris.
- Glomerulonephritis is less common than in other ANCA-associated diseases.

Diagnosis

- **Labs:**
  - **Peripheral eosinophilia.**
  - Normal serum complement levels (anti-myeloperoxidase).
  - ⊕ **p-ANCA** (anti-myeloperoxidase).
- **Imaging:** CXR shows fleeting pulmonary infiltrates.
- Biopsy of affected tissue demonstrates extravascular eosinophils.

Treatment

- High-dose corticosteroids,
- Immunosuppressants for renal or nerve/CNS involvement or for steroid-unresponsive disease.

Microscopic Polyangiitis (MPA)

Medium- or, more commonly, small-vessel vasculitis and capillaritis. Characterized by pulmonary hemorrhage and by glomerulonephritis and renal failure. Organs and systems affected include the lung, kidney, nerve, and skin. Often confused with polyarteritis nodosa, or PAN (see Table 17.15).

Symptoms/Exam

- Fever, malaise, myalgias, arthralgias, weight loss.
- Hemoptysis, dyspnea.
- Hematuria/active sediment.
- Mono-/polyneuropathy, skin rashes (palpable purpura).

Diagnosis

- **Labs:**
  - Elevated ESR; normal serum complement levels.
  - ⊕ **p-ANCA (anti-myeloperoxidase).**
- Tissue biopsy demonstrates alveolar hemorrhage/necrotizing capillaritis/glomerulonephritis.

Treatment

Corticosteroids; cytotoxic agents.

Polyarteritis Nodosa (PAN)

Necrotizing arteritis of medium-sized vessels. Active infection with **HBV** predisposes to the development of disease. Organs affected include the kidney, nerves, GI/mesentery, brain, skin, heart, testes, and joints. Often confused with microscopic polyangiitis, or MPA (see Table 17.15).

Symptoms/Exam

- Fever, malaise, weight loss, hypertension, testicular pain, **abdominal pain.**
- Arthritis or arthralgias; myalgias.
- **Neuropathies** (mono- or polyneuritis).
- **Skin rash** (livedo reticularis, nodules, ulcerations).

Diagnosis

- **Labs:**
  - Elevated ESR.

TABLE 17.15. Polyarteritis Nodosa vs. Microscopic Polyangiitis

	PAN	MPA
Vessel size	Medium	Medium and small
Skin	Ulcer/nodule/livedo reticularis	Palpable purpura
Lung	Rare	Capillaritis/alveolar hemorrhage
Renal	Renal artery aneurysms/renal infarction	Glomerulonephritis

- The majority of cases are **ANCA** ⊖.
- Normal serum complement levels.
- HBV serologies.

- **Imaging:** Angiography shows aneurysmal dilations of affected arteries (see Figure 17.9).
- Site-directed biopsy.

Treatment

CK is normal in PMR, and there is no weakness. Remember that PMR is an "-algia," not an "-itis."

- High-dose corticosteroids.
- Cytotoxic immunosuppressive agents (e.g., cyclophosphamide).

Polymyalgia Rheumatica (PMR)

Associated with proximal/axial skeletal pain and stiffness; fever, malaise, and weight loss; and elevated ESR. Rare before age 50; usually affects **older females.** Associated with giant cell (temporal) arteritis.

Symptoms/Exam

Up to 20% of PMR patients have giant cell arteritis, whereas up to 60% of giant cell patients have PMR.

- Joints affected include the shoulders, hip girdles, and low back and, less commonly, the peripheral joints.
- **No muscular weakness is seen** (vs. polymyositis).
- Fever, malaise, and weight loss can be profound.

Diagnosis

- Characteristic joint involvement (shoulders, hips).
- Elevated ESR (> 40).
- Constitutional features.
- Prompt response to corticosteroids.

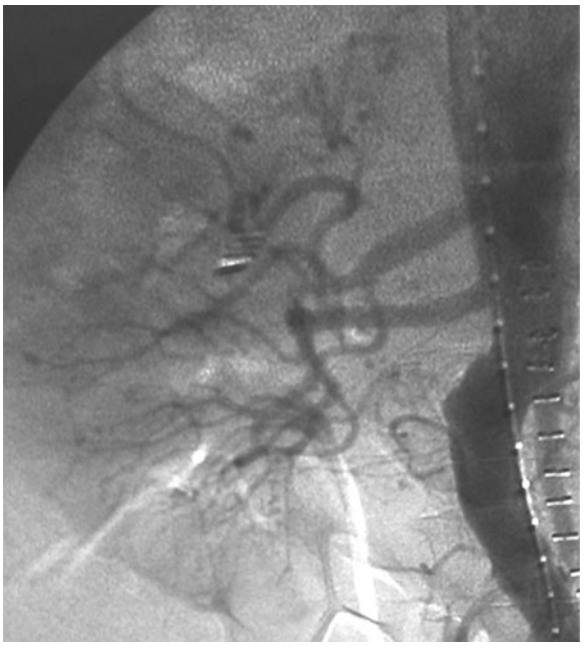

FIGURE 17.9. Polyarteritis nodosa of the right kidney.

Note the aneurysms in the superior pole of the kidney.

Treatment

- Small to moderate doses of corticosteroids (i.e., prednisone 5–20 mg day).
- Daily aspirin.

Failure to consider giant cell arteritis as a cause of new fever, headache, or vision loss in the elderly can result in permanent vision loss if biopsy and high-dose steroids are delayed.

Giant Cell Arteritis

Arteritis of large and medium-sized vessels. The most common vasculitis in North America and Europe; affects patients > 50 years of age. Blindness results from involvement of posterior ciliary arteries/ischemic optic neuritis. Has a strong association with PMR.

Symptoms/Exam

- Severe headache.
- Scalp/temporal artery tenderness.
- Jaw claudication, sore throat, amaurosis fugax.
- Fever, malaise, and weight loss.

Diagnosis

- Age > 50.
- Elevated ESR (> 50).
- New-onset headache.
- Tender, nodular, or pulseless temporal artery.
- Characteristic angiographic findings.
- Characteristic temporal artery biopsy showing granulomatous, lymphocytic infiltrate; multinucleated giant cells; and fragmented internal elastic laminae.

Because giant cell arteritis is a patchy process, biopsies should be taken at several sites and from both temporal arteries.

Treatment

High-dose corticosteroids (i.e., prednisone 40–60 mg/day).

Takayasu's Arteritis

Pulseless aortitis and vasculitis of the large vessels/branches of the aorta. Most prevalent in East Asia; **women < 40 years of age** are most commonly affected.

Symptoms/Exam

- Fever, malaise, myalgia, arthralgia, weight loss, progressive claudication.
- Evidence of limb and/or organ ischemia.
- Hypertension, bruits, and abnormal pulses; **systolic BP discrepancies measured between limbs;** aortic valvular regurgitation murmur.

Diagnosis

- Elevated ESR is common but not universal.
- CXR may suggest aortic abnormalities.
- Angiography of the aorta/branches shows stenoses/aneurysms (see Figure 17.10).
- Biopsy reveals granulomatous arteritis +/– variable numbers of giant cells.

Takayasu's arteritis is also known as "pulseless disease" because the arteries it involves–the aorta and its branches–can narrow, resulting in reduced radial and femoral pulses and BP.

Treatment

- Corticosteroids.
- Aggressive BP control.
- Surgical bypass of ischemic vessels once systemic disease is controlled.

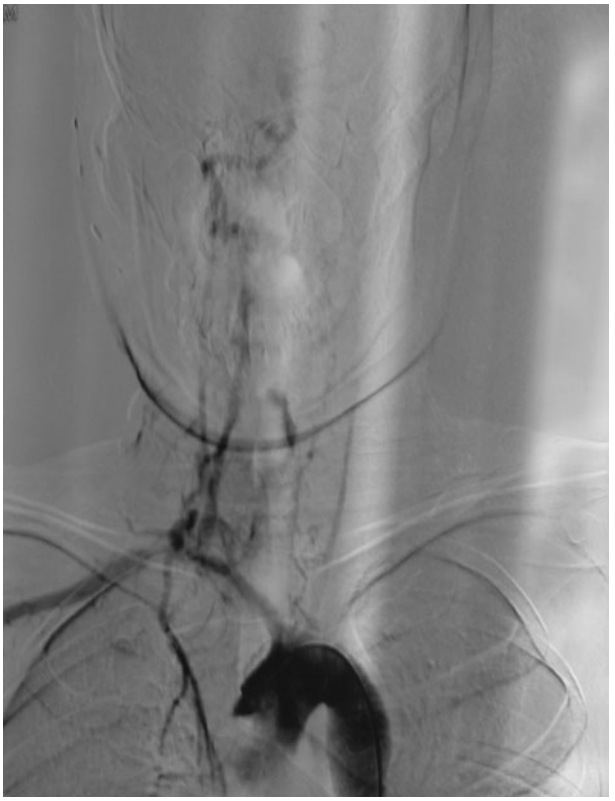

FIGURE 17.10. Angiography showing right subclavian stenosis in patient with Takayasu's arteritis.

Other Vasculitides

Cryoglobulinemia

HCV infection is the most common cause of cryoglobulinemia in the United States.

- All cryoglobulins are immune complexes that precipitate at ≤ 4°C. Cryoglobulinemias are divided into three types:
  - **Type 1:** Monoclonal (seen in multiple myeloma and Waldenström's macroglobulinemia). Acrocyanosis (blue digits) and hyperviscosity complications are more common than vasculitis.
  - **Type 2:** Monoclonal antibodies (RF) against polyclonal immune targets.
  - **Type 3:** Polyclonal antibodies (RF) against polyclonal immune targets.
- Types 2 and 3 can both be **idiopathic** or caused by **HCV** or other chronic infections, malignancies, or collagen vascular diseases (especially Sjögren's syndrome).
- **Sx/Exam:** Clinically, signs of vasculitis are seen—e.g., glomerulonephritis, palpable purpura, and neuropathy.

Buerger's Disease (Thromboangiitis Obliterans)

- Thromboses of medium-sized arteries and veins, usually of the hands or feet. Most commonly affects **males who smoke** heavily.
- **Tx:** Treat by discontinuing smoking.

Behçet's Disease

Three rheumatic diseases associated with oral ulcers are Behçet's, SLE, and reactive arthritis.

- Recurrent **oral and genital ulcerations,** skin ulcerations, **pathergy** (worsening of ulcerations with provocation), and erythema nodosum. Other characteristics are as follows:
  - **Ocular disease:** Keratitis, hypopyon, uveitis, retinal vasculitis, blindness.
  - **CNS abnormalities:** Cerebral vasculitis, meningoencephalitis, myelitis, cranial neuropathies.
  - Seronegative arthritis, pulmonary artery aneurysms, thrombophlebitis.
- **Tx:** Treat with corticosteroids and/or immunosuppressants.

Relapsing Polychondritis

The differential diagnosis for saddle-nose deformity is Wegener's granulomatosis and relapsing polychondritis.

- Episodic inflammatory attacks involving the **cartilage of the ears, nose, larynx, and trachea.**
- May be idiopathic or 2° to another autoimmune, collagen vascular, or malignant disease.
- Noncartilaginous involvement includes fever, polyarthritis, scleritis, uveitis, middle/inner ear inflammation, hearing loss, and vasculitis.
- **Tx:** Treat with corticosteroids, dapsone, colchicine, and immunosuppressants (for refractory disease).
- **Cx:** Complications include chronic deformities of the ear (cauliflower ear), nasal septum collapse **(saddle nose),** laryngotracheal chondritis and stenoses, hearing loss, vertigo, tinnitus, and valvular heart disease.

INFECTIOUS ARTHRITIS

Nongonococcal Arthritis

Prosthetic infections: Think S. epidermidis.

Acute-onset, **monoarticular** joint pain, swelling, warmth, and erythema. The knee is the most commonly involved joint (affecting 50% of cases). Gram-⊕ species (***S. aureus, Streptococcus***) are common causative organisms. Gram-⊖ species (*E. coli*, *Pseudomonas*) are less commonly involved. Risk factors include the following:

- Age > 80
- Diabetes mellitus
- IV drug use
- Endocarditis
- Recent joint surgery
- Skin infection
- RA
- Joint prostheses

Symptoms/Exam

Fevers, chills, inability to bear weight or pain with joint motion, large joint effusions, very hot and tender joint.

A synovial WBC > 100,000 is 99% specific for nongonococcal septic arthritis.

Diagnosis

- Blood cultures are ⊕ in < 50% of cases.
- Arthrocentesis reveals leukocytosis (usually > 50,000, > 90% PMN predominance) and a ⊕ culture; Gram stain is ⊕ in only 75% of cases (*S. aureus*).

- X-rays are nonspecific but may reveal demineralization, joint erosions, narrowing, osteomyelitis, and periostitis.

Treatment

- IV antibiotics are often needed for up to six weeks.
- Serial arthrocentesis if effusion reaccumulates; surgical drainage if the patient fails medical therapy or the disease involves inaccessible sites (e.g., the hip).

Complications

Articular destruction; septicemia. The mortality rate for in-hospital septic arthritis is 7–15% despite antibiotic therapy.

Gonococcal Arthritis (Disseminated Infection)

Most common in patients < 40 years of age; women are more frequently affected than men.

Symptoms/Exam

Recurrent bouts of disseminated gonococcal infection should prompt evaluation for complement deficiency (C5–C9).

- **Migratory** polyarthralgias and tenosynovitis.
- A papulopustular skin rash that may involve the palms and soles.
- Fever.

Diagnosis

- Arthrocentesis reveals leukocytosis (commonly > 50,000); 10% Gram stain ⊕, and < 50% culture ⊕.
- Blood cultures, rectal and throat swab cultures, urethral cultures (70–86% sensitive).

Treatment

- Give IV antibiotics (third-generation cephalosporin) until clinical improvement is seen, followed by the oral equivalent or a quinolone antibiotic for a 7- to 10-day total course.
- Empiric therapy or testing for chlamydia is recommended.

Tuberculous Arthritis

Most common in children, immunosuppressed patients, and the elderly. Can occur shortly after 1° infection or as a reactivation phenomenon. Fewer than 50% of patients with tuberculous arthritis will have an abnormal CXR. Patients with spinal disease (Pott's) rarely have extraspinal involvement.

Symptoms/Exam

- Insidious-onset, subacute or chronic monoarticular joint swelling, pain, and warmth followed by destructive arthritis, contractures, and abscess/sinus drainage.
- **Pott's disease** presents as insidious onset of back pain with involvement of the thoracic and lumbar spine.

Diagnosis

Isolation of acid-fast bacilli from joint fluid or synovial biopsy.

Treatment

As for pulmonary TB, but a longer treatment course may be necessary.

Complications

Joint destruction, invasion of adjacent soft tissues and bone, paraplegia (Pott's disease).

Lyme Arthritis

Early Lyme disease (stages 1 and 2) may have migratory arthralgias and myalgias along with flulike symptoms and an erythema migrans rash. **Advanced Lyme disease** (stage 3) presents as an **acute monoarthritis of the knee;** less common is oligo- or polyarthritis.

Diagnosis

- **Arthrocentesis:** PMN-predominant leukocytosis (average ~25,000); cultures for *Borrelia burgdorferi* are typically ⊖.
- **American College of Physicians recommendations for diagnosis:** Objective arthritis with both ELISA and Western blot confirmatory tests to *B. burgdorferi*.

The joint most commonly involved in Lyme arthritis (stage 3) is the knee.

Treatment

Treat advanced Lyme arthritis (stage 3) with doxycycline (4 weeks) or ceftriaxone (2–4 weeks).

FIBROMYALGIA

Criteria for the diagnosis of fibromyalgia include the following:

- A history of widespread pain involving all four quadrants of the body (and axial spine) for three or more months
- Pain in 11 of 18 tender points (occiput, low cervical trapezius, supraspinatus, second rib, lateral epicondyle, gluteal, greater trochanter, knee) on digital palpation by 4 kg of pressure—the approximate amount of pressure required to blanch the examiner's nail (see Figure 17.11).

Differential

The differential diagnosis of fibromyalgia is outlined in Table 17.16.

Treatment

Nonpharmacologic treatment is as follows:

- Education; cognitive-behavioral therapy.
- **Aerobic exercise:** "Start low and go slow" with a focus on adherence to a lifelong program.
- **Complementary therapies:**
  - Almost all patients with fibromyalgia use complementary and alternative medicine, at least in part because of distrust of physicians and frustration with the limited efficacy of much traditional care. Acupuncture, hypnotherapy, relaxation techniques (yoga, Tai Chi, and meditation), and osteopathic manipulation appear to have some efficacy.

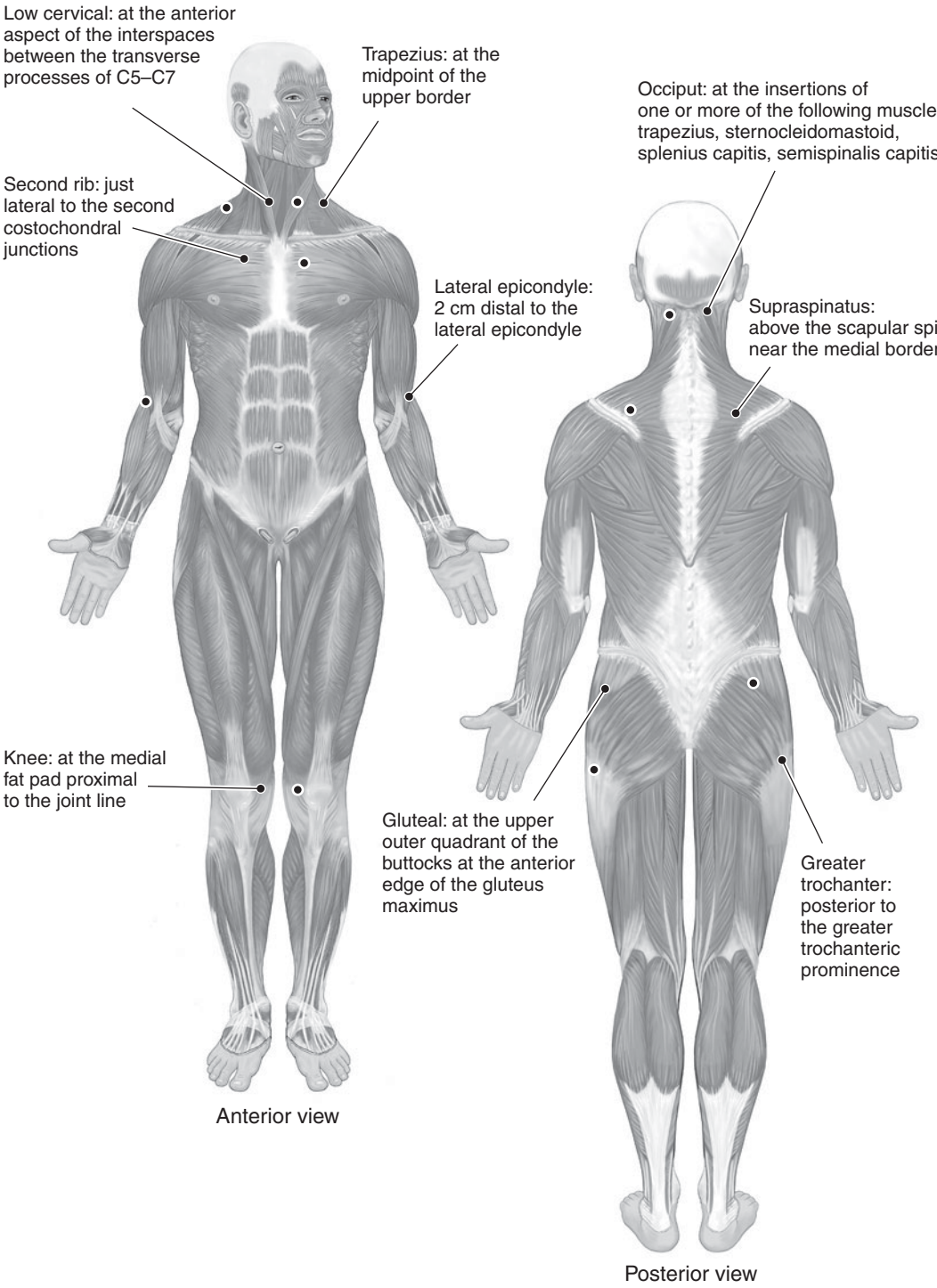

FIGURE 17.11. The 18 tender points used in the diagnosis of fibromyalgia.

Classification criteria are those of the American College of Rheumatology. (Reproduced, with permission, from Imboden JB et al. *Current Diagnosis & Treatment in Rheumatology*, 2nd ed. New York: McGraw-Hill, 2006.)

TABLE 17.16. Differential Diagnosis of Fibromyalgia

Disease Category	Examples
Endocrine disorders	Hypothyroidism,[a] Addison's disease, Cushing's disease, hyperparathyroidism.
Autoimmune disorders	Polymyalgia rheumatica,[a] RA, SLE, polymyositis.
Medications	Lipid-lowering drugs, antiviral agents, tapering of corticosteroids.
Infection	HCV,[a] HIV, parvovirus, Lyme disease, subacute bacterial endocarditis.
Malignancy	Myeloma; breast, lung, or prostate cancer.
Neurologic disorders	Carpal tunnel syndrome,[a] MS,[a] sleep apnea,[a] cervical stenosis.[a]
Psychiatric disorders	
Vitamin D deficiency	

[a] Commonly encountered diagnoses.

- Trigger-point injections and myofascial release are of uncertain benefit. Randomized, controlled clinical trials of dry needling, saline injections, anesthetic injections, botulinum toxin, acupuncture, and sham acupuncture as therapies have not shown significant benefit beyond nonspecific, placebo-related effects. Ultrasound treatment of myofascial "trigger points" is no more effective in reducing pain than sham ultrasound.

Pharmacologic treatment includes the following:

- **First-line agents:** Low-dose TCAs (e.g., **amitriptyline**) at bedtime in combination with a centrally acting muscle relaxant (e.g., **cyclobenzaprine**) divided 2–4 times daily. Studies show conflicting results regarding the efficacy of SSRIs in fibromyalgia.
- **Sleep disturbances:** If good sleep hygiene and sleep medications are ineffective, request a formal sleep study to identify sleep apnea and restless leg syndrome, which are particularly common in fibromyalgia.
- **Depression:** Encourage formal or informal counseling and treat pharmacologically.

Complications

The adverse impact of fibromyalgia on the patient, family, and society is high. More than 25% of patients receive some type of disability or other compensation payment.

MISCELLANEOUS DISEASES

Consider Still's in a young adult with fever of unknown origin and markedly elevated ferritin (usually > 1000) whose workup for infection and malignancy is ⊖.

Adult Still's Disease

- **Sx/Exam:** Presents with high-spiking **fevers,** diaphoresis, chills, sore throat, an evanescent salmon-colored **rash** coincident with fevers, erosive arthritis, serositis, and lymphadenopathy.
- **Dx:** Laboratory findings include **leukocytosis**, anemia, seronegativity, transaminitis, and **hyperferritinemia.**
- **Tx:** Treat with NSAIDs and corticosteroids.

Sarcoidosis

- Arthritis associated with sarcoidosis is either acute or chronic. See the Pulmonary Medicine chapter for nonarticular manifestations of sarcoidosis.
- **Acute sarcoid arthritis = Löfgren's syndrome,** which presents with **periarthritis** (most commonly of the ankle/knee), **erythema nodosum,** and **hilar adenopathy** on CXR. Resolution of acute disease occurs in 2–16 weeks with minimal therapy, NSAIDs, and colchicine.
- **Chronic sarcoid arthritis** usually involves minimally inflamed joints with synovial swelling/granulomata. Treat with NSAIDs, corticosteroids, and immunosuppressants.

Cholesterol Emboli Syndrome

Precipitated by invasive arterial procedures in patients with atherosclerotic disease. Features include fever, livedo reticularis, cyanosis/gangrene of the digits, vasculitic/ischemic ulcerations, **eosinophilia, renal failure,** and other end-organ damage.

Musculoskeletal Complications of Diabetes Mellitus

Include the following:

- **CPPD:** Pseudogout; acute symptomatic chondrocalcinosis.
- **Diabetic cheiroarthropathy:** Diabetic stiff hand syndrome plus prayer sign on exam.
- **Carpal tunnel syndrome:** Median nerve neuropathy.
- **Flexor tenosynovitis:** "Trigger finger."
- **Adhesive capsulitis:** "Frozen shoulder."
- **Neuropathic arthritis:** Charcot joint, diabetic osteoarthropathy.
- **Other:** Diffuse idiopathic skeletal hyperostosis, Dupuytren contractures, diabetic muscle infarction.

CHAPTER 18

Women's Health

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BREAST MASSES

Symptoms/Exam

- May be found on clinical exam or by the patient.
- Ask about associations with menstrual cycle, pain (if present, could indicate fibrocystic change), and risk factors for breast cancer.

A normal mammogram is not sufficiently sensitive to rule out breast cancer in the context of a palpable abnormality. Tissue diagnosis, or ultrasound confirming a simple cyst, is required for that purpose.

Diagnosis/Treatment

- The clinical breast exam (CBE) should include palpation of the axillae and nipples, inspection for skin changes, and examination of the asymptomatic breast.
- If a dominant mass is present, evaluation should proceed as indicated in Figure 18.1 even when clinical findings appear benign, as the CBE is not sufficiently sensitive to render a definitive diagnosis.
- Women with benign findings on imaging and biopsy should be followed closely for any progression of a palpable abnormality. Excision should be considered if the mass grows or if the patient expresses a preference for definitive management.
- The management of breast malignancies is discussed in detail in the Oncology chapter.

CONTRACEPTION

Table 18.1 describes common contraceptive methods and outlines their contraindications and side effects.

Noncontraceptive benefits of the progestin-releasing IUD include improvement in menorrhagia and dysmenorrhea. This method may be particularly suited to perimenopausal women who are having menstrual irregularities and have completed child-bearing.

PRECONCEPTION CARE

Patients contemplating pregnancy should undergo preventive counseling in order to optimize both maternal and fetal health.

Testing

- Obtain rubella and varicella titers; ensure that the Pap smear is up to date.
- Screen for STDs and other infections (HBV, HIV, TB) if the patient is at high risk.
- Evaluate the status of any chronic medical conditions present (e.g., assess HbA_{1c} levels in diabetics).

Preconception counseling optimizes the chances of a healthy pregnancy and delivery for mother and fetus. Ask all women of reproductive age about their pregnancy plans.

Management

- Nutrition (give folate 0.4 mg/day **before** the patient gets pregnant).
- Ensure that immunizations are up to date.
- Provide genetic counseling if indicated by the family history or by the presence of risk factors.
- Review all medications used by the patient, and advise changes where appropriate.

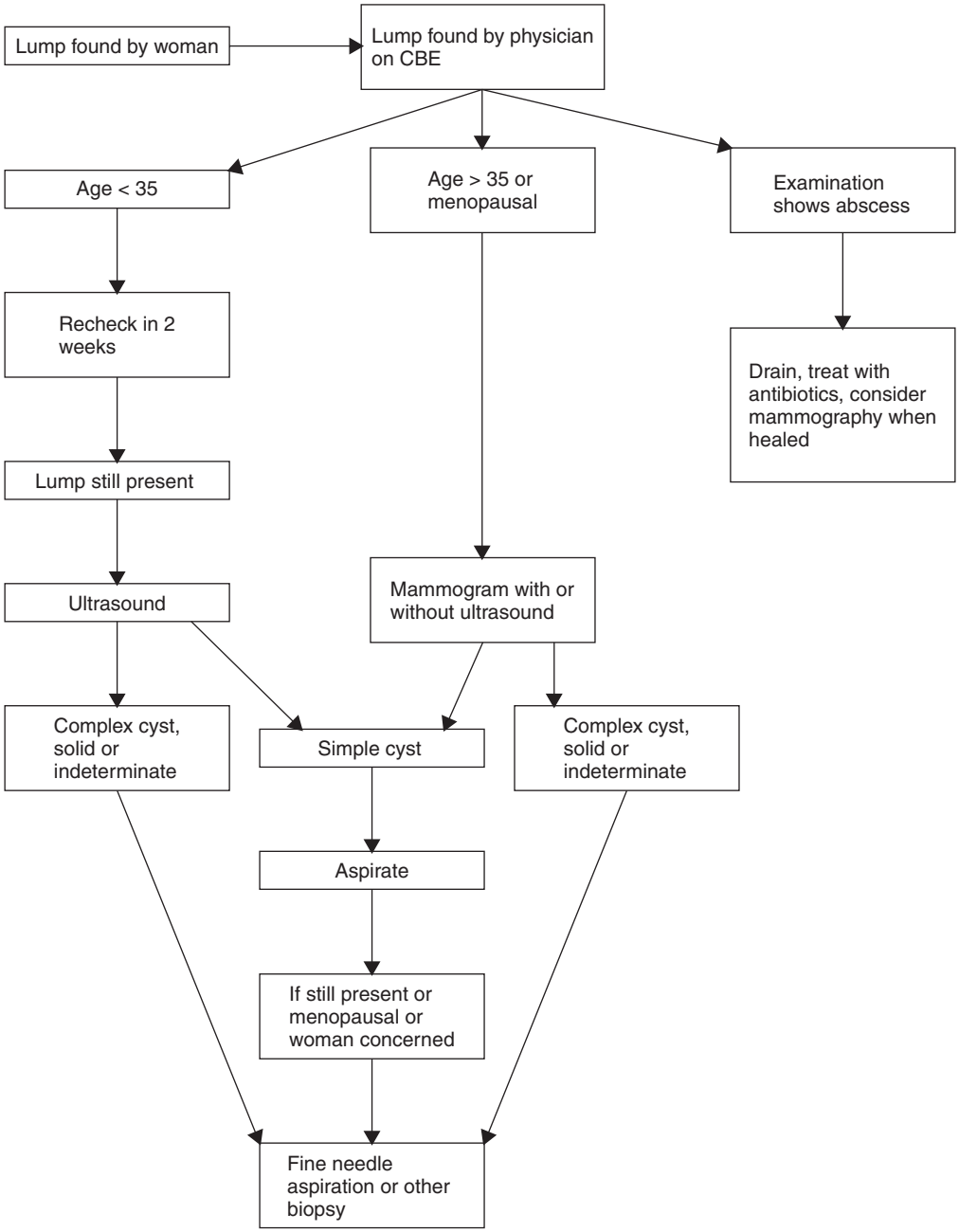


FIGURE 18.1. Evaluation of palpable breast masses.

(Reproducted, with permission, from South-Paul JE et al. *Current Diagnosis & Treatment in Family Medicine,* 2nd ed. New York: McGraw-Hill, 2008: 272.)

MEDICAL CONDITIONS IN PREGNANCY

Teratogenic Drugs

Table 18.2 lists common teratogens. For women with chronic medical conditions, deciding whether to continue a potentially teratogenic medication during pregnancy requires a careful balancing of potential benefits and harms to mother and fetus.

TABLE 18.1. Contraceptive Methods

Method	Description	Side Effects
Behavioral methods		
Coitus interruptus	Withdrawal of the penis before ejaculation.	High failure rate.
Calendar/rhythm method	Determines the fertile period on the basis of the LMP.	High failure rate; cannot be used by women with irregular cycle lengths.
Ovulation method	Uses basal body temperature, cervical mucus consistency, and/or urine LH levels to predict fertile periods.	High failure rate.
Barrier methods		
Diaphragm, cervical cap	A domed sheet of latex filled with spermicide and placed over the cervix. Must be fitted by a physician and remain in the vagina 6–8 hours after intercourse.	Allergy to latex or spermicide; ↑ risk of UTI.
Condom	A latex or polyurethane sheath placed over the penis during intercourse.	Allergy to latex or spermicide.
Intrauterine devices		The risk of infertility does not appear to be ↑ among users at low risk for STDs. Ideal IUD candidates are parous women in monogamous relationships.
Copper IUD (ParaGard)	A copper device placed into the endometrial cavity. Produces a local inflammatory reaction that has a spermicidal effect and also impairs implantation.	↑ vaginal bleeding/cramping. The device may be expelled or may perforate the uterus.
Levonorgestrel IUD (Mirena)	Local effects are the same as those of the copper IUD. Additionally, local progestin release thins the endometrium and thickens cervical mucus.	Menstrual blood loss ↓, and amenorrhea may occur. A small percentage of users have systemic progestin side effects. Progestin effects may be beneficial for women with menorrhagia or dysmenorrhea.
Hormonal methods		
OCPs	Suppress ovulation by inhibiting FSH/LH; thicken cervical mucus (impede sperm passage into the uterus); thin the endometrium (inhibit implantation).	Nausea, breast tenderness, acne, mood changes, hypertension, hepatic adenoma, weight gain, ↑ risk of venous thromboembolism and arterial thrombosis (MI, CVA), particularly among women with other cardiovascular risk factors.
Postcoital/emergency contraception	Progestin (+/– estrogen) taken within five days of intercourse to suppress ovulation or discourage implantation. Levonorgestrel alone (Plan B) is more effective and has fewer side effects than combined estrogen/progestin formulations.	Nausea, vomiting, fatigue, headache, dizziness, breast tenderness.

TABLE 18.1. Contraceptive Methods *(continued)*

Method	Description	Side Effects
Depot medroxyprogesterone acetate (Depo-Provera)	IM injection given every three months. Suppresses ovulation and thickens cervical mucus; thins endometrium.	Irregular vaginal bleeding, depression, weight gain, breast tenderness, delayed restoration of ovulation after discontinuation (6–18 months).
Transdermal contraceptive patch (Ortho Evra)	A combination estrogen/progestin transdermal patch that is changed once a week.	Local dermal reaction; otherwise the same as OCPs. The risk of venous thromboembolism may be higher than with OCPs owing to greater estrogen exposure. Improved compliance compared to OCPs.
Contraceptive vaginal ring (NuvaRing)	An intravaginal ring worn for three weeks of each four-week cycle. The mechanism is the same as that of OCPs.	Same as OCPs, plus small chance of vaginal irritation/discomfort.
Etonogestrel implant (Implanon) (FDA approved 2006)	A single-rod subdermal implant. Suppresses ovulation, thickens cervical mucus, and thins the endometrium. Effective for three years.	Irregular vaginal bleeding; small possibility of device migration and difficult removal.
Surgical sterilization		
Vasectomy	The vas deferens is cut.	Very low risk of local complications. More than 50% of men with reversed vasectomies are fertile.
Tubal ligation	The fallopian tubes are ligated, cauterized, or mechanically occluded.	Tubal ligation may result in bleeding, infection, failure, or ectopic pregnancy; procedure is essentially irreversible.

Hypertension in Pregnancy

Table 18.3 outline the clinical features and management of chronic hypertension, gestational hypertension, and preeclampsia/eclampsia. Additional details on hypertension in pregnancy are provided below.

Preeclampsia

Occurs in 4–5% of pregnancies. Risk factors include the following:

- Primigravidas
- Multiple gestation
- Certain medical conditions (e.g., DM, obesity, autoimmune or renal disease)
- Extremes of age
- Gestational trophoblastic disease
- Factor V Leiden mutations

It is important to reevaluate the antihypertensive regimen prior to conception in any woman who is contemplating pregnancy.

TABLE 18.2. Teratogenic/Fetotoxic Drugs

Drug	Effect
Alcohol	Fetal alcohol syndrome, intrauterine growth retardation (IUGR), cardiac defects.
Cocaine	Bowel atresias, IUGR, microcephaly.
Tobacco	Low birth weight, placental abruption, preterm labor, SIDS.
Streptomycin	CN VIII damage/ototoxicity.
Tetracycline	Tooth discoloration, inhibition of bone growth, small limbs, syndactyly.
Sulfonamides	Kernicterus.
Quinolones	Cartilage damage.
Isotretinoin	Heart and great vessel defects, craniofacial dysmorphism, deafness.
Iodide	Congenital goiter, hypothyroidism, mental retardation.
Methotrexate	CNS malformations, craniofacial dysmorphism, IUGR.
DES	Clear cell adenocarcinoma of the vagina/cervix, genital tract abnormalities (cervical hood, T-shaped uterus, hypoplastic uterus), cervical incompetence.
Thalidomide	Limb reduction (phocomelia), ear and nasal anomalies, cardiac and lung defects, pyloric or duodenal stenosis, GI atresia.
Warfarin	Stippling of bone epiphyses, IUGR, nasal hypoplasia, mental retardation.
NSAIDs	Premature closure of the ductus arteriosus; ↑ risk of spontaneous abortion.
ACEIs	Oligohydramnios; fetal renal damage.
Benzodiazepines	Possible congenital defects, IUGR, "floppy infant" syndrome, neonatal withdrawal syndrome.
Lithium	Ebstein's anomaly; other cardiac disease.
Carbamazepine	Fingernail hypoplasia, IUGR, microcephaly, neural tube defects.
Phenytoin	Nail hypoplasia, IUGR, mental retardation, craniofacial dysmorphism, microcephaly.
Valproic acid	Neural tube defects; craniofacial and skeletal defects.

Treatment

- See Table 18.3 for an outline of preeclampsia management.
- For women with chronic hypertension, the BP regimen should be evaluated prior to conception with the following factors in mind:
  - **Elimination of teratogenic agents** (e.g., **ACEIs and ARBs**).

TABLE 18.3. Hypertensive Disorders of Pregnancy

	Chronic Hypertension	Preeclampsia/Eclampsia	Gestational Hypertension
Timing	Present before pregnancy or persisting > 6 weeks postpartum.	Onset after 20 weeks' gestation (can occur up to six weeks postpartum).	Onset after 20 weeks' gestation. Resolves after delivery.
Clinical features	Known hypertension prior to pregnancy. Normal uric acid level (usually). Often no proteinuria.	**Preeclampsia: Hypertension (> 140/90) and proteinuria with onset after 20 weeks.** Often associated with edema. **Uric acid level is often elevated.** Eclampsia = preeclampsia + seizures.	May resemble preeclampsia, but **proteinuria is absent.**
Complications	↑ risk of preeclampsia. IUGR, placental abruption, fetal demise.	**Fetal:** Intrauterine growth restriction, oligohydramnios, demise. **Maternal:** Edema, **HELLP syndrome** (hemolysis, elevated liver enzymes, low platelets), seizures, death.	May develop into preeclampsia. ↑ risk of subsequent essential hypertension.
Treatment	Treat BP if > 145–150/95–100. Target DBP 80–100. Methyldopa, β-blockers, hydralazine, and calcium channel blockers are often used.	**After 36 weeks' gestation:** Immediate delivery. **Before 36 weeks:** Bed rest, close monitoring of mother and fetus, BP management (goal DBP 90–100). Hospitalization and delivery at any stage of gestation for severe preeclampsia, HELLP, or eclampsia. Magnesium sulfate given after delivery to prevent seizures.	Same as that for chronic hypertension.

- Diuretics are usually avoided despite a lack of clear evidence regarding their potential ill effects.
- β-blockers and calcium channel blockers are generally considered acceptable for use during pregnancy.
- Methyldopa has the longest record of safety during pregnancy but has many side effects.

HELLP Syndrome

- Consists of **H**emolysis, **E**levated **L**iver enzymes, and **L**ow **P**latelets. Considered a variant of preeclampsia.
- May be associated with renal dysfunction (but this is not required for diagnosis).

- **Dx:** Diagnostic criteria are as follows:
  - Microangiopathic hemolytic anemia
  - AST > 70 IU/L
  - Platelets < 100K
- **Tx:** Prompt delivery; supportive measures.
- **Cx:** Although most patients recover fully within weeks, there is a 3–5% maternal mortality rate.

Diabetes in Pregnancy

All women known to be diabetic (type 1 or type 2) should have intensive preconception counseling and receive treatment to a goal HbA_{1c} < 6% prior to conception. Because pregnancy ↑ insulin resistance, preexisting type 2 DM or impaired glucose tolerance may be unmasked when women become pregnant. Guidelines for testing are as follows:

- **High risk:** A glucose tolerance test should be given as soon as possible to women who are at high risk for gestational diabetes mellitus (GDM). These include patients with the following:
  - Marked obesity
  - A personal history of GDM
  - Previous delivery of a large-for-gestational-age (LGA) infant
  - Glycosuria
  - Polycystic ovarian syndrome (PCOS)
  - A strong family history of DM
- **Average risk:** Women who are at average risk for GDM should be tested between 24 and 28 weeks.
- **Low risk:** Women at low risk do not need testing. Criteria are as follows:
  - Age < 25 years
  - Normal weight prior to pregnancy
  - Not members of high-risk ethnic groups (i.e., not African- or Asian-American, Latino, Native American)
  - No first-degree relatives with DM
  - No history of abnormal glucose tolerance
  - No prior poor obstetric outcome

Women who have had GDM have a 50% risk of developing type 2 DM within 10 years after delivery. All such women should have a repeat OGTT at six weeks postpartum as well as periodic surveillance for DM thereafter.

Diagnosis

- Conduct initial screening with a **50-g glucose load.** Then perform a **100-g diagnostic oral glucose tolerance test (OGTT)** in patients with a one-hour glucose ≥ 140 (identifies 80% of women with GDM) or > 130 (↑ the yield to 90%). The OGTT is diagnostic of GDM when two or more of the glucose values are at or above threshold (see Table 18.4).
- Women with preexisting type 1 or type 2 DM should have baseline chemistries, HbA_{1c}, 24-hour urine protein and creatinine clearance, a funduscopic exam, and an ECG.

Treatment

Both maternal and fetal outcomes are improved with tight glycemic control. Tight control should thus be established before conception in women with preexisting DM.

- Obese women should be put on a calorie-restricted diet.
- Insulin is recommended when nutritional therapy fails to maintain self-monitored glucose at target levels.

TABLE 18.4. Diagnostic Criteria for GDM: 100-g Oral Glucose Tolerance Test

Time	Glucose Level (mg/dL)
Baseline (fasting)	≥ 95
One hour	180
Two hours	155
Three hours	140

- Oral agents are not recommended, although there are some early data on the safety of the sulfonylureas.
- Fetal size should be monitored, and patients may be referred for cesarean section if macrosomia is present.

Complications

- **Maternal:** DKA, preeclampsia, preterm labor, polyhydramnios; the need for C-section due to fetal macrosomia.
- **Fetal/neonatal:** Macrosomia; cardiac, renal, and neural tube defects; birth injury (shoulder dystocia); neonatal hypoglycemia; perinatal mortality.

The goal in the mother with preexisting diabetes is good control before conception.

Thyroid Disease in Pregnancy

Normal Changes of Pregnancy

Normal changes in thyroid function during pregnancy include the following:

- ↑ thyroid-binding globulin.
- This will ↑ total serum levels of T_4 and T_3, but free hormone levels should remain normal.
- The normal range for TSH in pregnancy is lower (< 2.5 mIU/L).

Hyperthyroidism

- Affects 0.05–0.20% of pregnant women.
- In general, Graves' disease improves during pregnancy but may **flare in the early postpartum period.**
- **Dx:** As per hyperthyroidism in general, except that **RAI is contraindicated during pregnancy.**
- **Tx:**
  - **Antithyroid medications:** All antithyroid medications cross the placenta and have the potential to cause fetal hypothyroidism in the newborn. **PTU is preferred** over MMI, which can cause aplasia cutis, a rare congenital localized absence of skin that usually affects the scalp.
  - **Other medications: Avoid iodine** therapy, as it can lead to fetal goiter. **Propranolol** may be used transiently to control cardiovascular symptoms.
  - **Surgery:** In the setting of uncontrolled hyperthyroidism, thyroidectomy should be considered and performed during the second trimester if possible.

- **Cx:** If left untreated, complications may include spontaneous abortion (25%), premature delivery (45%), and an ↑ risk of a small-for-gestational-age (SGA) newborn.

Maternal hypothyroidism during pregnancy causes developmental delay in the child. Close monitoring and adequate repletion of thyroid hormone in pregnant women with hypothyroidism is essential starting in the first trimester.

Hypothyroidism

- New-onset hypothyroidism is rare during pregnancy.
- **Tx:**
  - **Thyroid hormone replacement:** In women with preexisting hypothyroidism, a 30–50% ↑ in medication dosage is often needed.
  - Thyroid function should be followed closely. Many experts recommend empirically increasing the LT_4 dose by 25–30% upon diagnosis of pregnancy.
- **Cx:** If left untreated, complications may include the following:
  - **Fetal complications:** Congenital anomalies, perinatal mortality, impaired mental and somatic development.
  - **Maternal complications:** Anemia, preterm labor, preeclampsia, placental abruption, postpartum hemorrhage.

Postpartum Thyroiditis

- An autoimmune disorder.
- Commonly presents as thyrotoxicosis 1–6 months postpartum and evolves into hypothyroidism, often returning to euthyroidism by one year postpartum.
- Twenty-five to thirty percent of women will remain permanently hypothyroid.

INFERTILITY

Inability to conceive after **one year** of unprotected intercourse. Etiologies include the following:

- **Factors related to the male partner:** Includes quantity and quality of sperm.
- **Ovulatory dysfunction:** Ovarian failure, prolactinoma, thyroid disease, PCOS, other causes of anovulation.
- **Luteal-phase defects:** Implantation.
- **Uterine abnormalities:** Congenital, DES exposure, fibroids, polyps, synechiae from prior manipulation.
- **Tubal and peritoneal abnormalities:** Scarring from prior PID, severe endometriosis, adhesions.
- **Cervical abnormalities.**

Exam

The exam is often unremarkable. Look for hirsutism, goiter, galactorrhea, an abnormal pelvic exam in the female partner, and testicular size/masses in the male partner.

Diagnosis

- Take a careful history, including menstrual history, prior pregnancies, sexual history (frequency/timing of coitus), and prior STDs.
- Semen analysis.

- Obtain serum FSH, LH, TSH, and prolactin.
- Have the female partner chart basal body temperature or use a urine LH kit to document ovulation.
- Conduct a postcoital test (examination of cervical mucus after coitus at a fertile time in the cycle).
- Consider hysterosalpingography, pelvic ultrasound, endometrial biopsy, and/or laparoscopy.

It is important to rule out male infertility first, as it is the source of the problem in 40% of cases and is easy to evaluate.

TREATMENT

Treat the underlying cause:

- Urologic treatment for male factor infertility.
- Ovulation induction (clomiphene, gonadotropins, GnRH).
- Laparoscopy (e.g., to remove endometriosis implants).
- Assisted reproductive technologies (IVF).
- Sperm or egg donation.

MENSTRUAL DISORDERS

Abnormal Premenopausal Vaginal Bleeding

Defined as abnormalities in the frequency, duration, volume, and/or timing of menses. Etiologies are listed in Table 18.5. Subtypes include the following:

- **Menorrhagia:** Prolonged and/or excessive uterine bleeding that is cyclic.
- **Metrorrhagia:** Bleeding at irregular and frequent intervals.
- **Menometrorrhagia:** Prolonged and/or excessive bleeding at irregular intervals.
- **Polymenorrhea:** Cycles < 21 days.
- **Oligomenorrhea:** Cycles > 35 days.
- **Amenorrhea:** Absence of menses for ≥ **6 months.**
- **Hypomenorrhea:** Cyclic light flow.

DIAGNOSIS

- A careful history and pelvic examination plus a Pap smear and a urine pregnancy test should all be routinely obtained.
- **Labs:** Laboratory testing depends on the clinical scenario but may include STD testing, TSH, prolactin, and coagulation studies.
- **Additional testing:** Diagnostic tests used to determine the cause of bleeding include ultrasound (fibroids), hysteroscopy (endometrial polyps, some fibroids), and endometrial biopsy (endometrial polyps, hyperplasia, cancer). Women > 35 years of age should routinely undergo endometrial biopsy for irregular bleeding.
- Determination of ovulatory status is important.
  - Clinically, premenstrual symptoms and regular cycles are evidence of ovulation.
  - Irregular cycles and no symptoms preceding the onset of menses suggest anovulation.
  - Basal body temperature measurement and luteal-phase progesterone levels can help confirm ovulatory status.

TABLE 18.5. Causes of Abnormal Premenopausal Bleeding

Cause	Underlying Disorders	Clinical Features
Pregnancy		Amenorrhea; spotting is common in the first trimester.
Anovulation	PCOS, hypothalamic-pituitary-ovarian axis dysfunction, hypothyroidism, prolactinoma, ovarian or adrenal tumor.	Other features of endocrinologic disorders; history of physical or mental stress; eating disorders; high-intensity exercise.
Cervical lesions	Cervical polyps, cervicitis, dysplasia/malignancy.	Spotting, often postcoital; vaginal discharge (infection).
Bleeding disorder	von Willebrand's disease; acquired or other congenital coagulopathies.	Menorrhagia, intermenstrual heavy bleeding; other sites of bleeding.
Fibroids		Dysmenorrhea, pelvic mass, menorrhagia or intermenstrual bleeding.
Endometrial polyps or hyperplasia		Intermenstrual bleeding.
Hormonal medications	OCPs, HRT.	Intermenstrual spotting, amenorrhea, postmenopausal bleeding. Association with use of these medications.
Dysfunctional uterine bleeding	Idiopathic.	Irregular menstrual pattern without an identifiable underlying cause.

Treatment

Treat the underlying cause:

- **Ovulatory, heavy bleeding:** NSAIDs and OCPs both ↓ the amount of bleeding.
- **Anovulatory bleeding:** OCPs and cyclic progestins regularize cycles.
- **Profuse bleeding:** High-dose estrogen, D&C, endometrial ablation, hysterectomy.

Amenorrhea

Defined as 1° or 2° absence of menses. Potential etiologies are listed below. Subtypes are distinguished as follows:

- **1°:** Absence of menses and 2° sexual characteristics by age 14, or absence of menses with or without 2° sexual characteristics by age 16.
- **2°:** Previously normal menses; absence for **three consecutive months.**

Symptoms/Exam

- Ask about pregnancy symptoms, galactorrhea, headaches, visual changes, hirsutism, acne, stress or illness, medications, and menopausal symptoms. There may also be weight loss (e.g., in eating disorders or exercise).

- Look for 2° sexual characteristics, virilization (male-pattern hair loss/growth, acne, clitoromegaly), galactorrhea, and abnormalities on pelvic exam.

Differential

- **Hypothalamic-pituitary disorders:** Physical or emotional stress, eating disorders, hyperprolactinemia.
- **Hyperandrogenism:** PCOS, Cushing's syndrome, androgen-secreting tumor.
- **Uterine structural disorders:** Endometrial scarring after a procedure or infection (Asherman's syndrome).
- **Premature ovarian failure:** Autoimmune, Turner's syndrome, post-chemotherapy.
- **Other:** Pregnancy, menopause.

Diagnosis

2° amenorrhea is diagnosed as follows:

- Rule out pregnancy.
- Check **TSH** and **prolactin.** If both are normal, **administer a progestin challenge.**
- Patients with no withdrawal bleed after a progestin challenge have a hypoestrogenic state and should have their FSH level checked to distinguish between ovarian failure (high FSH), hypothalamic-pituitary axis problems (low FSH), and uterine problems such as Asherman's syndrome (normal FSH).

Treatment

Treat the underlying cause.

MENOPAUSE

Permanent cessation of menstruation (diagnosed after one year without menses). The median age of onset in the United States is 51. Premature menopause/ovarian failure is cessation of menses in patients < 40 years of age.

Symptoms/Exam

Before the complete cessation of menses, irregular cycles with heavier or lighter flow followed by skipped periods are common. Vasomotor instability (hot flashes, night sweats) and symptoms of urogenital atrophy are also common (dryness, dyspareunia, dysuria).

Differential

Consider thyroid disease, prolactinoma, and chronic medical conditions that cause night sweats (e.g., TB, lymphoma) if other symptoms suggestive of those diagnoses are present.

Diagnosis

- Clinical diagnosis is generally adequate.
- FSH > 30 mU/mL is diagnostic of menopause but is usually unnecessary. FSH levels fluctuate widely prior to the cessation of menstruation and generally add very little to the diagnosis or management of symptoms.

Treatment

Estrogen works best for the symptoms of menopause, but the risks associated with its use must be carefully considered.

- **Hormone replacement therapy** (HRT) is currently the most effective treatment for vasomotor and urogenital symptoms. However, the Women's Health Initiative randomized trial showed ↑ risks of venous thromboembolism, breast cancer, CAD, stroke, cognitive decline, and urinary incontinence among HRT users. In light of these risks, current recommendations for HRT use are as follows:
  - Use the lowest dose for the shortest duration needed to treat symptoms (attempt to taper or discontinue every six months).
  - Do not use HRT to prevent a chronic health condition.
  - There are no clear advantages to one mode of administration (oral, transdermal) over another.
  - Women with a uterus need to take estrogen plus a progestin to protect against endometrial cancer. Women who have undergone hysterectomy may take estrogen alone.
- **Non-HRT treatment** of the symptoms of menopause should be considered:
  - **Vaginal symptoms:** Intravaginal estrogen (low dose), moisturizers, lubricants.
  - **Vasomotor instability:** Clonidine, venlafaxine and SSRIs, gabapentin, herbal medications (black cohosh, soy), exercise, management of physical environment (e.g., layered clothing, fans).

POSTMENOPAUSAL BLEEDING

Any vaginal bleeding that occurs after menopause should be considered abnormal. Etiologies include endometrial atrophy (most common), exogenous hormones, nongynecologic sources, endometrial hyperplasia or polyps, endometrial cancer, and cervical cancer.

Symptoms

Patients may complain of "spotting" or of heavier, menses-like bleeding.

Exam

All postmenopausal bleeding, with the exception of that occurring during the first few months of hormone replacement therapy, requires evaluation.

- Conduct a pelvic exam to look for anatomic abnormalities, including vaginal atrophy, vaginal lesions, or cervical polyps, and palpate for uterine masses.
- A Pap smear must be obtained to look for cervical cancer.

Diagnosis

- Endometrial biopsy is the gold standard for diagnosis.
- Ultrasound is an alternative first test; if the endometrial lining is < 5 mm thick, endometrial biopsy may be deferred unless unexplained bleeding continues.

Treatment

Treat the underlying cause.

OSTEOPOROSIS

Bone loss leading to an ↑ risk of fractures, particularly of the vertebrae, hip, and long bones (proximal femur and distal radius). The mortality from com-

plications of hip fractures is equal to that from breast cancer in women > 50 years of age. Risk factors and disease associations include the following:

- White or Asian ethnicity
- Low weight
- Menopause (especially early or surgical menopause)
- Glucocorticoid use or Cushing's syndrome
- Estrogen deficiency states (e.g., anorexia nervosa)
- Tobacco or alcohol use
- A family history of osteoporosis
- Older age
- A history of falls
- Poor eyesight
- Immobilization
- Calcium/vitamin D deficiency or malabsorption (e.g., celiac disease, IBD)
- Thyrotoxicosis or levothyroxine overreplacement
- Hyperparathyroidism
- Medications (antiepileptic drugs, heparin)

See the Endocrinology chapter for further details on the 2° causes of osteoporosis and osteoporosis in men.

Symptoms/Exam

- May be asymptomatic or may present with back pain, loss of height, or nonspinal fractures.
- Exam may be normal. Patients may be thin and have a "dowager's hump" (kyphosis).

Diagnosis

- **DEXA imaging** measures bone mineral density (BMD) at the spine and hip.
  - Osteoporosis is diagnosed if BMD (as measured by the T-score) is ≥ 2.5 standard deviations below that of a young, normal woman (**T-score < -2.5**).
  - Osteopenia is defined as a T-score between −1.0 and −2.5.
- Z-scores compare a patient's BMD with age- and gender-matched norms. A low Z-score (< −2) should raise suspicion for 2° causes of osteoporosis.
- Osteoporosis can be diagnosed clinically in the presence of vertebral or other fragility fractures (e.g., hip fractures, Colles' fracture of the wrist).
- Quantitative CT and ultrasound are other methods sometimes used to diagnose osteoporosis.

Osteopenia is defined as a T-score of −1.0 to −2.5. Osteoporosis is diagnosed when the T-score is < −2.5.

Treatment

- Calcium 1500 mg QD; vitamin D 800 IU QD; weight-bearing exercises for all women unless contraindications exist.
- Smoking cessation.
- Fall prevention measures (handrails, assistive devices for ambulation, balance exercises) for frail patients.
- Bisphosphonates (alendronate, risedronate) are first-line agents. They improve BMD and ↓ the incidence of vertebral and hip fractures by up to > 50%.
- Estrogen slows BMD loss and thus helps prevent osteoporosis, but it is not generally recommended for this indication because of its adverse effects.

Bisphosphonates and teriparatide are the two classes of drug that ↓ the rate of nonvertebral fracture in osteoporotic patients.

- Raloxifene, a selective estrogen receptor modulator (SERM), improves bone density and ↓ the risk of vertebral fractures by 40% but does not appear to prevent nonvertebral (e.g., hip) fracture.
- Calcitonin is helpful for pain after an acute fracture but is not as effective as other treatments in the long term.
- Vertebroplasty may be considered for symptoms related to spinal compression fracture.
- Teriparatide (recombinant PTH), injected daily, is the only therapy that ↑ bone formation (all other drugs are antiresorptive). Although guidelines for its use are evolving, it is generally reserved for patients with severe osteoporosis or for those who have failed other treatments.

HIRSUTISM

↑ male-pattern hair growth. A clinical manifestation of ↑ androgen levels. Potential etiologies are listed below.

Symptoms

- ↑ hair growth, often of facial or chest hair.
- May present with associated amenorrhea and signs of virilization (e.g., deepening voice, male-pattern baldness, clitoromegaly, male body habitus).

Exam

- Note body habitus (obesity).
- Look for male-pattern hair growth and/or androgenic alopecia, acne, signs of Cushing's syndrome, and virilization.
- Abdominal and pelvic exam for mass lesions.

Differential

- Many cases of hirsutism are idiopathic or familial. PCOS is the most common medical condition associated with hirsutism (see below). Other etiologies include the following:
  - Congenital adrenal hyperplasia (late-onset 21-hydroxylase deficiency)
  - Medications (androgenic progestins in OCPs, danazol, minoxidil, cyclosporine)
  - Cushing's syndrome
  - Sertoli-Leydig cell ovarian tumor
  - Luteoma of pregnancy
  - Androgen-secreting adrenal neoplasm (50% of these are malignant)
- Features associated with neoplastic causes of hirsutism include the following:
  - Abrupt onset, short duration (< 1 year), or sudden progressive worsening
  - Onset in the third decade of life or later (not peripubertal)
  - Virilization

Virilization and/or abrupt onset of hirsutism may point to an androgen-secreting tumor.

Diagnosis

- **No labs** are indicated for patients with **long-standing hirsutism,** regular menses, and familial factors.
- Consider checking testosterone, androstenedione, and DHEAS to rule out ovarian or adrenal neoplasm.

- Image the adrenals (CT) and ovaries (ultrasound or MRI) if androgen levels are significantly elevated. Mild elevations of testosterone level are common in PCOS.

Treatment

- Treat the underlying cause.
- **Nonpharmacologic treatment:** Shaving, depilatories, electrolysis, laser treatment, eflornithine hydrochloride cream.
- **Antiandrogen therapy:** OCPs, spironolactone, finasteride.

POLYCYSTIC OVARIAN SYNDROME (PCOS)

A syndrome characterized by menstrual irregularity and hyperandrogenism. Onset is typically **peripubertal** and slowly progressive. The name PCOS can be misleading, as polycystic ovaries are not required for the diagnosis of PCOS (and many women without PCOS have polycystic ovaries by ultrasound).

Symptoms/Exam

- Patients seek treatment for **hirsutism, acne, oligomenorrhea/amenorrhea,** or infertility.
- Obesity, acne, hypertension, and acanthosis nigricans may be present. Enlarged, cystic ovaries may be found on bimanual exam.

Differential

- **Irregular menses:** See the section on menstrual disorders.
- **Androgen excess:** Adrenal or ovarian tumor, congenital adrenal hyperplasia, Cushing's syndrome.

Diagnosis

- **Minimal criteria:** Menstrual irregularity (amenorrhea or oligomenorrhea), hyperandrogenism (clinical or biochemical). Other characteristics may include infertility and insulin resistance.
- **Labs:** A **serum LH-to-FSH ratio > 3:1** is typical of PCOS, and serum testosterone is often mildly elevated. Labs are most helpful for excluding other causes of amenorrhea or hirsutism (see the sections on those topics above); no specific values for any of these tests is diagnostic of PCOS.
- **Imaging:** Ultrasound may reveal enlarged ovaries with numerous large cysts. However, such polycystic ovaries are seen in up to 25% of normal women, so their presence is not specific for PCOS.
- Many patients with PCOS have insulin resistance and are **at risk for type 2 DM and metabolic syndrome.** Fasting lipids and glucose should be measured periodically.

The presence of polycystic ovaries is neither necessary nor sufficient to make the diagnosis of PCOS.

Treatment

- Treatment depends on the target symptom, but **weight loss and OCPs are best overall.**
- Symptom-specific treatment is as follows:
  - **Insulin resistance:** Weight reduction; possibly metformin.
  - **Infertility:** Clomiphene, metformin.
  - **Hirsutism, acne:** Hair removal methods, OCPs, spironolactone, other acne treatment.

- **Endometrial protection:** OCPs or intermittent progestin therapy.
- **Cardiovascular protection:** Control of cardiac risk factors.

CHRONIC PELVIC PAIN

Chronic pelvic pain is defined as pain below the umbilicus lasting at least 3–6 months. It is often multifactorial and challenging to diagnose and treat. The most common underlying conditions leading to a chronic pelvic pain syndrome are as follows:

- **Gynecologic:** Endometriosis, chronic PID, adenomyosis, uterine fibroids, pelvic adhesions.
- **GI:** IBS.
- **GU:** Interstitial cystitis.
- **Musculoskeletal:** Fibromyalgia.
- **Psychiatric:** Depression, somatization, domestic violence, narcotic and other substance abuse.

Diagnosis

- Conduct a careful history and physical exam, focusing on features of the common etiologic conditions above.
- Evaluate the patient's psychosocial status, including mood and abuse history.
- **Labs:** CBC, cultures, ultrasound, laparoscopy, UA, pregnancy test.

Treatment

- Treat the underlying cause when one is apparent.
- Effective treatment of idiopathic chronic pelvic pain requires a multidisciplinary approach involving a psychologist.

DOMESTIC VIOLENCE

The leading cause of injuries in women. Abuse may be physical, mental (including denial of financial or health care access), or sexual. Affects individuals from all socioeconomic groups. May also occur in same-sex relationships. Pregnancy may initiate or exacerbate abuse.

Symptoms

- All patients should be screened. See the mnemonic **SAFE** for screening and follow-up questions.
- Patients may present with no symptoms or with a variety of clinical scenarios, including the following:
  - Multiple somatic complaints
  - Chronic pain syndromes
  - Depression
  - Injuries unexplained by the history (especially multiple injuries in various stages of healing)
  - A possible delay in seeking care

Exam

Conduct a mental status exam, and look for signs of new, old, or chronic trauma. If the partner is present, make sure he/she leaves the room so that the patient can be interviewed alone.

Domestic violence questions—

SAFE

Stress and **S**afety:
Do you feel safe in your relationship?
What happens when you and your partner disagree?

Afraid or **A**bused:
Have you or your children ever been physically threatened or abused?
Have you ever been forced to have sexual intercourse?

Friend or **F**amily awareness:
Are your friends or family aware of what is happening?
Would they support and help you?

Emergency **E**scape plan:
Are you in danger now, and would you like to go to a shelter or talk with someone?
Do you have a place where you and your children could go in an emergency?

Differential

Psychological illness, physical illness, somatization.

Treatment

- Conduct a risk assessment (frequency, weapons, substance abuse, threats of suicide, homicide).
- Determine if the patient has a safety plan.
- Refer to appropriate support services, and report the abuse to law enforcement. Accurate documentation of any injuries is important for potential future legal proceedings.

STD SCREENING

More than 15 million cases of STD are diagnosed in the United States each year. Cervicitis, urethritis, PID, and genital ulcers are common manifestations of STDs. See the Ambulatory Medicine chapter for a detailed discussion of HSV, chancroid, and 1° syphilis. HIV and HBV are discussed in the Infectious Diseases chapter.

Chlamydia

All women ≤ 25 should be screened for chlamydia. Asymptomatic chlamydia infection can lead to PID, ectopic pregnancy, and tubal infertility.

Chlamydia infection is common, and infection may be asymptomatic in up to 70% of affected women. Chlamydia infection is a major cause of PID, ectopic pregnancy, and infertility.

- Risk factors for chlamydia include age < 25, new or multiple sexual partners, inconsistent use of barrier methods, and a prior history of any STD.
- The United States Preventive Services Task Force (USPSTF) recommends periodic chlamydia screening for all sexually active women ≤ 25 years of age. Women > 25 may be screened if STD risk factors are present. Pregnant women ≤ 25 years of age should be screened as well.

Cervicitis

Cervical infection may be confused with ectropion (columnar epithelium extending onto the visible portion of the cervix), which is common in young women.

Symptoms

Presents with vaginal discharge, dysuria, pelvic pain, or spotting. Chlamydia infection in particular is frequently asymptomatic (see above).

Exam/Diagnosis

- Look for evidence of systemic illness; conduct a careful pelvic exam.
- Obtain cervical specimens for gonorrhea and chlamydia culture or DNA amplification assay (PCR or LCR). Consider HSV cultures if cervical vesicles or ulceration is present.
- Most STDs are reportable to the local public health department. Partners should be treated.
- Anyone who presents for testing should be offered the **HBV vaccine.**
- Women with chlamydia should be rescreened at 3–4 months and no later than 12 months to check for reinfection.

When treating gonorrhea, also treat for chlamydia, as coinfection frequently exists and diagnostic tests may be ⊖ in some cases.

TREATMENT

Treat cervicitis or urethritis as follows:

- **Gonorrhea:** Cefixime 400 mg PO × 1, ceftriaxone 125 mg IM × 1, or single-dose fluoroquinolone (note that in some areas, fluoroquinolone resistance rates are high).
- **Chlamydia:** Azithromycin 1 g PO × 1 or doxycycline 100 mg PO BID × 7 days.

Pelvic Inflammatory Disease (PID)

Polymicrobial infection of the ascending genital tract, including the endometrium, oviducts, ovaries, uterine wall, and peritoneum. May be acute, subacute, or chronic. Risk factors include multiple sexual partners, unprotected intercourse, young age at first intercourse, mucopurulent cervicitis, IUD use, and prior PID.

SYMPTOMS/EXAM

- Presents with lower abdominal pain, possibly accompanied by fever, nausea, and vomiting. May occur after recent menses, and may present with abnormal discharge.
- Conduct a pelvic exam to look for cervical motion tenderness, discharge, and adnexal tenderness.

DIFFERENTIAL

Ectopic pregnancy, endometriosis, ovarian tumors or cysts, adnexal torsion, UTI/pyelonephritis, appendicitis, diverticulitis, IBD.

DIAGNOSIS

Diagnostic criteria are as follows:

- Lower abdominal, adnexal, and cervical motion tenderness
- Fever > 38.3°C
- Elevated ESR or CRP
- Presence of gonorrhea or chlamydia infection
- Pelvic abscess on ultrasound

Complications of PID—

I FACE PID

Infertility
Fitz-Hugh–Curtis syndrome (perihepatitis or inflammation of the liver capsule and adjacent peritoneal surfaces)
Abscess
Chronic pelvic pain
Ectopic pregnancy
Peritonitis
Intestinal obstruction
Disseminate (sepsis, endocarditis, arthritis, meningitis)

TREATMENT

- Treat for gonorrhea, chlamydia, and anaerobes.
  - **Outpatient regimens:**
    - Ofloxacin 400 mg BID **or** levofloxacin 500 mg QD plus metronidazole 500 mg BID, all × 14 days.
    - Either cefoxitin 2 g IM plus probenecid 1 g PO **or** ceftriaxone 250 mg IM × 1 plus doxycycline 100 mg BID × 14 days.
  - **Inpatient regimens** (see indications for hospitalization below):
    - Cefoxitin 2 g IV q 6 h or cefotetan 2 g q 12 h plus doxycycline 100 mg IV or PO q 12 h.
    - Clindamycin 900 mg IV q 8 h plus gentamicin 1.5 mg/kg q 8 h.
    - Once patients improve, PO regimens must continue for 14 days.
- Hospitalization is advised for the following:
  - For patients who present with tubo-ovarian abscess, peritonitis, high fever, or a high WBC count.
  - For patients who are noncompliant or unable to tolerate PO medications.

- For pregnant patients.
- For those who show no improvement after 48–72 hours of oral therapy.

URINARY TRACT INFECTION (UTI)

Infection of the bladder and/or kidneys. May be complicated or uncomplicated:

- **Uncomplicated:** UTI in a premenopausal, healthy, nonpregnant woman. Species most commonly involved are *E. coli* and *Staphylococcus saprophyticus.* Less common are *Proteus mirabilis*, *Klebsiella* spp., *Enterococcus*, and *Chlamydia.*
- **Complicated:** UTI in anyone else (male, elderly, hospital acquired, pregnant, indwelling catheter, recent catheterization, anatomic abnormalities, recent antibiotics, symptoms > 1 week at presentation, fever, immunosuppression, diabetes, recurrent UTI, history of resistant UTI).

Symptoms

- Presents with dysuria, frequency, and urgency.
- Gross hematuria, fever, flank pain, or suprapubic pain may also be seen.

Exam

- Temperature, abdominal exam, flank tenderness.
- Conduct a pelvic exam if gynecologic etiologies are suspected.

Differential

STDs (gonorrhea or chlamydia urethritis, HSV, trichomoniasis); infectious, atrophic, or irritant vaginitis; interstitial cystitis (presents with recurrent UTI-like symptoms without objective evidence of infection).

Diagnosis

- UA and urine culture if complicated infection or pyelonephritis is suspected.
- Consider urine testing for gonorrhea and chlamydia if urethritis is suspected.

Treatment

- **Uncomplicated infections:** Give a **three-day** course of oral ciprofloxacin or a **seven-day course of nitrofurantoin.** TMP-SMX should be used only in areas with low resistance to this antibiotic.
- **Complicated infections:** A **longer course** of broad-spectrum antibiotics, typically a fluoroquinolone, should be used.

VAGINITIS

The normal environment of the vagina is acidic (pH 3.5–4.5) and contains mixed bacterial flora (lactobacilli, diphtheroids, and *S. epidermidis*). A change in this environment due to medications, illness, or frequent intercourse can lead to bacterial overgrowth.

Symptoms

Patients complain of abnormal discharge (odor, color, quantity) and symptoms such as itching, burning, soreness, dysuria, and dyspareunia.

TABLE 18.6. Wet Mount Criteria in Diagnosing Vaginitis

Diagnosis	Discharge	Cells	pH	Whiff
Bacterial vaginosis	Grayish-white, thin, fishy odor	Clue cells	> 4.5	⊕ with KOH
Yeast	Thick, white, clumpy, adherent ("cottage cheese")	Pseudohyphae with KOH	3.5–4.5	⊖
Trichomoniasis	Profuse, yellow-green, frothy, malodorous	Motile trichomonads	> 4.5	⊕

Exam

Conduct a pelvic exam, particularly for the following:

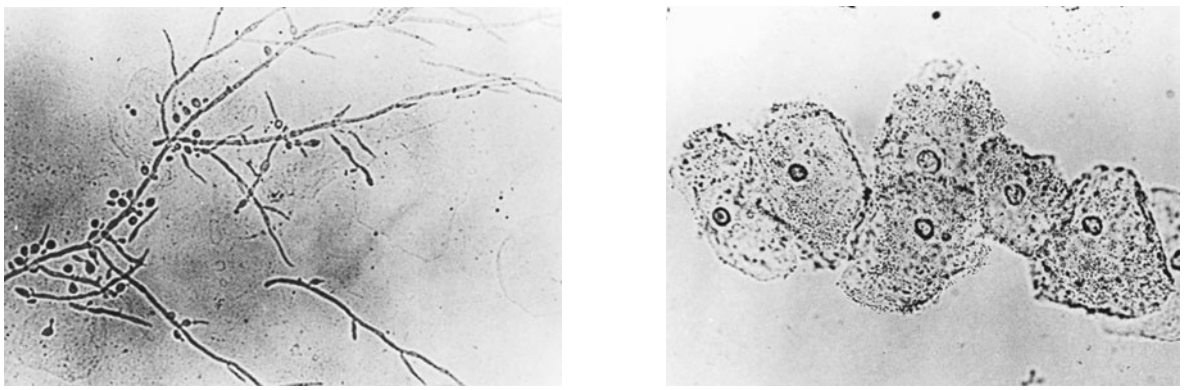
- Vulvar edema/erythema.
- **Discharge:** Quantity, color, adherence, odor.
- **Cervicitis:** Friability, purulent discharge, "**strawberry cervix**" (petechiae in trichomonal infection).

Differential

UTI, normal (physiologic) discharge, cancer, noninfectious/irritants (spermicide, douching), atrophy.

Diagnosis

- Wet mount (pH and microscopy in saline and KOH) (see Table 18.6 and Figure 18.2).
- Consider UA and/or STD testing.



A **B**

FIGURE 18.2. Causes of vaginitis.

(A) Pseudohyphae in candidal vaginitis. (B) Clue cells in bacterial vaginosis. (Reproduced, with permission, from DeCherney AH et al. *Current Obstetric & Gynecologic Diagnosis & Treatment*, 9th ed. New York: McGraw-Hill, 2003: 652, 653.)

Treatment

Treat the underlying cause:

- **Bacterial vaginosis:** Metronidazole (500 mg PO BID × 7 days or 2 g × 1, or topical × 5 days) or clindamycin (PO or topical × 7 days). May resolve spontaneously; recurrence is common.
- **Candidiasis:** Fluconazole 150 mg PO × 1, or various topical azoles (several are available OTC).
- **Trichomoniasis:** Oral metronidazole at the same doses as for bacterial vaginosis.

NOTES

APPENDIX

Abbreviations and Symbols

Abbreviation	Meaning
A-a	alveolar-arterial (oxygen gradient)
AAT	α_1-antitrypsin
ABG	arterial blood gas
ABI	ankle-brachial index
ABPA	allergic bronchopulmonary aspergillosis
ABPA-CB	allergic bronchopulmonary aspergillosis with central bronchiectasis
ABPA-S	allergic bronchopulmonary aspergillosis—seropositive
ABVD	Adriamycin, bleomycin, vincristine, and dacarbazine
ACA	anterior cerebral artery
ACD	anemia of chronic disease
ACEI	angiotensin-converting enzyme inhibitor
ACh	acetylcholine
AChE	acetylcholinesterase
ACL	anterior cruciate ligament
ACLS	advanced cardiac life support
ACTH	adrenocorticotropic hormone
AD	autosomal dominant
ADA	American Diabetes Association
ADH	antidiuretic hormone
ADHD	attention-deficit hyperactivity disorder
ADPKD	autosomal-dominant polycystic kidney disease
ADPW	adjusted-dose perioperative warfarin
AF	atrial fibrillation
AFB	acid-fast bacillus
AFP	α-fetoprotein
AI	adrenal insufficiency
AICA	anterior inferior cerebellar artery
AICD	automatic implantable cardiac defibrillator
AIDS	acquired immunodeficiency syndrome
AIN	acute interstitial nephritis
ALI	acute lung injury
ALL	acute lymphoblastic leukemia
ALS	amyotrophic lateral sclerosis
ALT	alanine aminotransferase
AMA	antimitochondrial antibody
AMD	age-related macular degeneration
AML	acute myeloid leukemia
ANA	antinuclear antibody
ANC	absolute neutrophil count
ANCA	antineutrophil cytoplasmic antibody
AP	alkaline phosphatase, anteroposterior
APL	acute promyelocytic leukemia
APLA	antiphospholipid antibody (syndrome)
APO E2	apolipoprotein E2
APS	autoimmune polyglandular syndrome
AR	autosomal recessive
ARB	angiotensin receptor blocker
ARDS	acute respiratory distress syndrome
ARF	acute respiratory failure
5-ASA	5-aminosalicylic acid
ASA	acetylsalicylic acid
ASCA	anti-*Saccharomyces cerevisiae* antibody
ASD	atrial septal defect
ASMA	anti–smooth muscle antibody
ASO	antistreptolysin O
AST	aspartate aminotransferase
AT	angiotensin, atrial tachycardia
ATN	acute tubular necrosis
ATP III	Adult Treatment Panel (National Cholesterol Education Program)
ATPase	adenosine triphosphatase
ATRA	*all*-trans retinoic acid
AV	arteriovenous, atrioventricular
AVM	arteriovenous malformation
AVN	avascular necrosis
AVNRT	atrioventricular nodal reentrant tachycardia
AVRT	atrioventricular reentrant tachycardia
AXR	abdominal x-ray

Abbreviation	Meaning
AZT	azidothymidine (zidovudine)
BAL	bronchoalveolar lavage
BCC	basal cell carcinoma
BCG	bacille Calmette-Guérin
BEP	bleomycin, etoposide, and Platinol (cisplatin)
BID	twice daily
BIW	twice weekly
BMD	bone mineral density
BMI	body mass index
BMT	bone marrow transplant
BP	blood pressure
BPH	benign prostatic hypertrophy
bpm	beat per minute
BPV	benign positional vertigo
BSE	breast self-examination
BUN	blood urea nitrogen
C1-INH	C1 inhibitor
CABG	coronary artery bypass graft
$CaCO_3$	calcium carbonate
CAD	coronary artery disease
c-ANCA	cytoplasmic antineutrophil cytoplasmic antibody
CBC	complete blood count
CBE	clinical breast examination
CBT	computer-based testing
CBW	current body weight
CCK	cholecystokinin
CCP	cyclic citrullinated peptide
CD	cluster of differentiation
CDC	Centers for Disease Control and Prevention
CEA	carcinoembryonic antigen
CF	cystic fibrosis
CFTR	cystic fibrosis transmembrane regulator
CH50	total complement
CHF	congestive heart failure
CHOP	cyclophosphamide, doxorubicin hydrochloride, Oncovin (vincristine), and prednisone
CI	cardiac index, confidence interval
CIDP	chronic inflammatory demyelinating polyneuropathy
CIWA	Clinical Institute Withdrawal Assessment
CK	creatine kinase
CKD	chronic kidney disease
CK-MB	creatine kinase, MB fraction
CLL	chronic lymphocytic leukemia
CML	chronic myelogenous leukemia
CMML	chronic myelomonocytic leukemia
CMV	cytomegalovirus
CN	cranial nerve
CNS	central nervous system
COMT	catechol-*O*-methyltransferase
COPD	chronic obstructive pulmonary disease
COX	cyclooxygenase
CP	ceruloplasmin
CPAP	continuous positive airway pressure
CPK	creatine phosphokinase
CPPD	calcium pyrophosphate dihydrate
CPR	cardiopulmonary resuscitation
Cr	creatinine
CrAg	cryptococcal antigen
CRBSI	catheter-related bloodstream infection
CREST	calcinosis, Raynaud's phenomenon, esophageal dysmotility, sclerodactyly, and telangiectasia (syndrome)
CRF	corticotropin-releasing factor
CRH	corticotropin-releasing hormone
CRP	C-reactive protein
CRPS	complex regional pain syndrome
CRT	conformal radiation therapy
CSA	central sleep apnea
CSF	cerebrospinal fluid
CT	computed tomography
CTA	computed tomographic angiography
CTCL	cutaneous T-cell lymphoma
CTP	Child-Turcotte-Pugh (scoring)
CVA	cerebrovascular accident, costovertebral angle
CVID	common variable immunodeficiency
CVP	central venous pressure
CXR	chest x-ray
D&C	dilation and curettage
D_2	ergocalciferol
D_3	cholecalciferol
d4T	didehydrodeoxythymidine (stavudine)
DAP	3,4-diaminopyridine
DASH	Dietary Approach to Stop Hypertension (study)
DBP	diastolic blood pressure
DCBE	double-contrast barium enema
DCCT	Diabetes Control and Complication Trial
DCIS	ductal carcinoma in situ
DDAVP	1-deamino (8-D-arginine) vasopressin
ddC	dideoxycytidine
ddI	dideoxyinosine
DEET	diethyltoluamide
DES	diethylstilbestrol
DEXA	dual-energy x-ray absorptiometry
DF	discriminant factor
DFA	direct fluorescent antibody
1,25-DHD	1,25-dihydroxycholecalciferol

Abbreviation	Meaning
DHEA	dehydroepiandrosterone
DHEAS	dehydroepiandrosterone sulfate
DHIC	detrusor hyperactivity with impaired contractility
DI	diabetes insipidus
DIC	disseminated intravascular coagulation
DIP	distal interphalangeal (joint)
DJD	degenerative joint disease
DKA	diabetic ketoacidosis
DL_{CO}	diffusing capacity of carbon monoxide
DM	diabetes mellitus
DMARD	disease-modifying antirheumatic drug
DNA	deoxyribonucleic acid
DNase	deoxyribonuclease
DNR	do not resuscitate
DOC	deoxycorticosterone
2,3-DPG	2,3-diphosphoglycerate
DPOA-HC	durable power of attorney for health care
DPP	dipeptidyl peptidase
DRE	digital rectal examination
dsDNA	double-stranded DNA
DTRs	deep tendon reflexes
DTs	delirium tremens
DVT	deep venous thrombosis
EBNA	Epstein-Barr nuclear antigen
EBV	Epstein-Barr virus
ECF	epirubicin, cisplatin, 5-FU
ECFMG	Educational Commission for Foreign Medical Graduates
ECG	electrocardiography
ECT	electroconvulsive therapy
ED	erectile dysfunction
EDTA	calcium disodium edetate
EECP	enhanced external counterpulsation
EEG	electroencephalography
EF	ejection fraction
EGD	esophagogastroduodenoscopy
EGFR	epidermal growth factor receptor
EHEC	enterohemorrhagic *E. coli*
EIA	enzyme immunoassay
EIEC	enteroinvasive *E. coli*
ELISA	enzyme-linked immunosorbent assay
EM	electron microscopy, erythema multiforme
EMG	electromyography
ENT	ears, nose, and throat
EP	etoposide and Platinol (cisplatin), evoked potential
EPO	erythropoietin
ER	emergency room, estrogen receptor
ERCP	endoscopic retrograde cholangiopancreatography
ERV	expiratory reserve volume
ES	elastic stocking
ESD	end-systolic diameter
ESR	erythrocyte sedimentation rate
ESRD	end-stage renal disease
ETEC	enterotoxigenic *E. coli*
EtOH	ethanol
ETT	exercise treadmill test
EUS	endoscopic ultrasound
EVH	esophageal variceal hemorrhage
FAP	familial adenomatous polyposis
FBHH	familial benign hypocalciuric hypercalcemia
FDA	Food and Drug Administration
F-dUMP	5-fluorodeoxyuridine monophosphate
Fe_{Na}	fractional excretion of sodium
FEV_1	forced expiratory volume in one second
FFP	fresh frozen plasma
FiO_2	fraction of inspired oxygen
FLAIR	fluid-attenuated inversion recovery
FNA	fine needle aspiration
FOBT	fecal occult blood test
FRC	functional reserve capacity
FSH	follicle-stimulating hormone
FSMB	Federation of State Medical Boards
FT_3	free triiodothyronine
FT_4	free thyroxine
FTA-ABS	fluorescent treponemal antibody–absorbed
5-FU	5-fluorouracil
FUO	fever of unknown origin
FVC	forced vital capacity
GABA	γ-aminobutyric acid
GABHS	group A β-hemolytic streptococcus
GAD	glutamic acid decarboxylase
GBM	glomerular basement membrane
GBS	Guillain-Barré syndrome
GC	gonococcal
G-CSF	granulocyte colony-stimulating factor
GDM	gestational diabetes mellitus
GERD	gastroesophageal reflux disease
GFR	glomerular filtration rate
GGT	γ-glutamyltransferase
GH	growth hormone
GHB	γ-hydroxybutyrate
GHRH	growth hormone–releasing hormone
GI	gastrointestinal
GIST	gastrointestinal stromal tumor
GLP	glucose-like peptide
GM-CSF	granulocyte-macrophage colony-stimulating factor
GN	glomerulonephritis
GnRH	gonadotropin-releasing hormone
G6PD	glucose-6-phosphate dehydrogenase

Abbreviation	Meaning
GRTH	generalized resistance to thyroid hormone
GU	genitourinary
H&P	history and physical
HAART	highly active antiretroviral therapy
HACEK	*Haemophilus, Actinobacillus, Cardiobacterium, Eikenella, Kingella*
HAV	hepatitis A virus
HbA_{1c}	hemoglobin A_{1c}
HBeAg	hepatitis B early antigen
HBIG	hepatitis B immune globulin
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
hCG	human chorionic gonadotropin
HCO_3	bicarbonate
HCTZ	hydrochlorothiazide
HCV	hepatitis C virus
25-HD	25-hydroxycholecalciferol
HDL	high-density lipoprotein
HDV	hepatitis D virus
HELLP	hemolysis, elevated LFTs, low platelets (syndrome)
HEV	hepatitis E virus
HF	heart failure
HGA	human granulocytic anaplasmosis
HHV	human herpesvirus
5-HIAA	5-hydroxyindole acetic acid
HIDA	hepato-iminodiacetic acid (scan)
HIPA	heparin-induced platelet activation
HIPAA	Health Insurance Portability and Accountability Act of 1996
HIT	heparin-induced thrombocytopenia
HIV	human immunodeficiency virus
HL	hearing loss
HLA	human leukocyte antigen
HME	human monocytic ehrlichiosis
HMG-CoA	hydroxymethylglutaryl coenzyme A
HNPCC	hereditary nonpolyposis colorectal cancer
HP	hypersensitivity pneumonitis
hpf	high-power field
HPV	human papillomavirus
HR	heart rate
HRCT	high-resolution computed tomography
HRS	hepatorenal syndrome
HRT	hormone replacement therapy
11β-HSD	11β-hydroxysteroid dehydrogenase
HSV	herpes simplex virus
5-HT	5-hydroxytryptamine
HTLV	human T-cell leukemia virus
HUS	hemolytic-uremic syndrome
IABP	intraaortic balloon pump
IAHG	International Autoimmune Hepatitis Group
IBD	inflammatory bowel disease
IBS	irritable bowel syndrome
IC	inspiratory capacity
ICA	internal carotid artery, islet cell antibody
ICD	implantable cardiac defibrillator
ICP	intracranial pressure
ICS	intercostal space
ICU	intensive care unit
IF	intrinsic factor
IFE	immunofixation electrophoresis
Ig	immunoglobulin
IGF	insulin-like growth factor
IL	interleukin
ILD	interstitial lung disease
IM	intramuscular
IMRT	intensity-modulated radiation therapy
INH	isoniazid
INR	International Normalized Ratio
IPC	intermittent pneumatic compression
IPF	idiopathic pulmonary fibrosis
IPSS	inferior petrosal sinus sampling
IRV	inspiratory reserve volume
ITP	idiopathic thrombocytopenic purpura
IUD	intrauterine device
IUGR	intrauterine growth retardation
IV	intravenous
IVC	inferior vena cava
IVF	in vitro fertilization
IVIG	intravenous immunoglobulin
IVP	intravenous pyelography
JNC 7	Joint National Committee on the Prevention, Detection, Evaluation, and Treatment of High Blood Pressure, Seventh Report
JVD	jugular venous distention
JVP	jugular venous pressure
KCl	potassium chloride
KOH	potassium hydroxide
KS	Kaposi's sarcoma
LAD	left anterior descending (artery)
LAP	leukocyte alkaline phosphatase
LBBB	left bundle branch block
LBP	lower back pain
LCIS	lobular carcinoma in situ
LCR	ligase chain reaction
LDCT	low-dose helical CT
LDH	lactate dehydrogenase
LDL	low-density lipoprotein
LDUH	low-dose unfractionated heparin
LEEP	loop electrosurgical excision procedure
LEMS	Lambert-Eaton myasthenic syndrome

Abbreviation	Meaning
LES	lower esophageal sphincter
LFTs	liver function tests
LGA	large for gestational age
LGIB	lower GI bleeding
LH	luteinizing hormone
LHRH	luteinizing hormone–releasing hormone
LKM	liver/kidney microsomal (antibody)
LLQ	left lower quadrant
LMN	lower motor neuron
LMWH	low-molecular-weight heparin
LP	lumbar puncture
LR	likelihood ratio
LT_4	levothyroxine
LTBI	latent tuberculosis infection
LTOT	long-term oxygen therapy
LUQ	left upper quadrant
LV	left ventricular
LVH	left ventricular hypertrophy
MAC	*Mycobacterium avium* complex
MALT	mucosa-associated lymphoid tissue
MAOI	monoamine oxidase inhibitor
MAP	mean arterial pressure
MB	mannose-binding (lectin)
MCA	middle cerebral artery
MCL	medial collateral ligament, midclavicular line
MCP	metacarpophalangeal (joint)
MCV	mean corpuscular volume
MDI	metered-dose inhaler
MDMA	3,4-methylene-dioxymethamphetamine ("Ecstasy")
MDR	multidrug resistance
MDS	myelodysplastic syndrome
MELD	Model for End-Stage Liver Disease
MEN	multiple endocrine neoplasia
MEP	maximum expiratory pressure
MG	myasthenia gravis
MGUS	monoclonal gammopathy of undetermined significance
MHATP	microhemagglutination assay—*Treponema pallidum*
MI	myocardial infarction
MIBG	metaiodobenzylguanidine
MIP	maximum inspiratory pressure
MMA	middle meningeal artery
MMI	methimazole
MMR	measles, mumps, rubella (vaccine)
MMSE	mini-mental status examination
MODY	mature-onset diabetes of the young
6-MP	6-mercaptopurine
MPA	microscopic polyangiitis
MPGN	membranoproliferative glomerulonephritis
MPO	myeloperoxidase
MR	magnetic resonance, mitral regurgitation
MRA	magnetic resonance angiography
MRC	magnetic resonance cholangiography
MRCP	magnetic resonance cholangiopancreatography
MRI	magnetic resonance imaging
MRSA	methicillin-resistant *S. aureus*
MS	multiple sclerosis
MSM	men who have sex with men
MTP	metatarsophalangeal (joint)
MuSK	muscle-specific kinase
NA	Narcotics Anonymous
NAAT	nucleic acid amplification test
nAChR	nicotinic acetylcholine receptor
NAEPP	National Asthma Education and Prevention Program
NBW	normal body weight
NCS	nerve conduction study
NF	neurofibromatosis
NG	nasogastric
NHL	non-Hodgkin's lymphoma
NIH	National Institutes of Health
NMDA	*N*-methyl-D-aspartate
NPO	nil per os (nothing by mouth)
NPV	negative predictive value
NREM	non–rapid eye movement
NS	normal saline
NSAID	nonsteroidal anti-inflammatory drug
NSCLC	non–small cell lung cancer
NSIP	nonspecific interstitial pneumonia
NSTEMI	non-ST-elevation myocardial infarction
NVE	native-valve endocarditis
NYHA	New York Heart Association
O&P	ova and parasites
OA	osteoarthritis
OCD	obsessive-compulsive disorder
OCP	oral contraceptive pill
OGTT	oral glucose tolerance test
OR	operating room
OSA	obstructive sleep apnea
OTC	over the counter
PA	pernicious anemia, posteroanterior
PAC	plasma aldosterone concentration
$Paco_2$	partial pressure of carbon dioxide in arterial blood
PAN	polyarteritis nodosa
p-ANCA	perinuclear antineutrophil cytoplasmic antibody
Pao_2	partial pressure of oxygen in arterial blood
P_{atm}	atmospheric pressure
PCA	patient-controlled anesthesia, posterior cerebral artery

Abbreviation	Meaning
PCI	percutaneous coronary intervention
P_{CO_2}	partial pressure of carbon dioxide
PCOP	pulmonary capillary occlusion pressure
PCOS	polycystic ovarian syndrome
PCP	*Pneumocystis jiroveci* (formerly *carinii*) pneumonia
P_{Cr}	plasma creatinine
PCR	polymerase chain reaction
PCV	procarbazine, CCNU (lomustine), and vincristine
PCW	pulmonary capillary wedge (pressure)
PDA	patent ductus arteriosus
PDE	phosphodiesterase
P/DM	polymyositis/dermatomyositis
PE	pulmonary embolism
PEEP	positive end-expiratory pressure
PEF	peak expiratory flow
PEG	percutaneous endoscopic gastrostomy
PET	positron emission tomography
PFTs	pulmonary function tests
PHN	postherpetic neuralgia
PICA	posterior inferior cerebellar artery
PID	pelvic inflammatory disease
P_{iO_2}	partial pressure of inspired oxygen
PIOPED	Prospective Investigation of Pulmonary Embolism Diagnosis
PIP	proximal interphalangeal (joint)
P_{K+}	plasma potassium
PLED	periodic lateralizing epileptiform discharge
PLMD	periodic limb-movement disorder
PLMS	periodic limb movements in sleep
PMI	point of maximal insertion
PMN	polymorphonuclear (leukocyte)
PMR	polymyalgia rheumatica
P_{Na}	plasma sodium
PNH	paroxysmal nocturnal hemoglobinuria
PO	per os (by mouth)
P_{O_2}	partial pressure of oxygen
P_{osm}	plasma osmolality
PPD	purified protein derivative
PPH	primary pulmonary hypertension
PPI	proton pump inhibitor
PPL	plateau pressure
PPN	peripheral parenteral nutrition
PPV	positive predictive value
PR	progesterone receptor
PRA	plasma renin activity
PRCA	pure red cell aplasia
PRN	as needed
PRTH	pituitary resistance to thyroid hormone
PSA	prostate-specific antigen
PSI	Pneumonia Severity Index
PSVT	paroxysmal supraventricular tachycardia
PT	prothrombin time
PTH	parathyroid hormone
PTHC	percutaneous transhepatic cholangiography
PTHrP	parathyroid hormone–related peptide
PTSD	post-traumatic stress disorder
PTT	partial thromboplastin time
PTU	propylthiouracil
PUD	peptic ulcer disease
PUVA	psoralen and UVA light
PV	polycythemia vera
PVC	premature ventricular contraction
PVE	prosthetic valve endocarditis
PVR	pulmonary vascular resistance
PVX	Pneumovax (vaccine)
QD	once daily
QHS	at bedtime
QID	four times daily
QOD	every other day
RA	rheumatoid arthritis, refractory anemia
RAEB	refractory anemia with excess blasts
RAEB-T	refractory anemia with excess blasts in transformation
RAI	radioactive iodine
RAIU	radioactive iodine uptake
RAPD	relative afferent pupillary defect
RARS	refractory anemia with ringed sideroblasts
RAST	radioallergosorbent test
RBBB	right bundle branch block
RBC	red blood cell
RCT	randomized clinical trial
RDW	red-cell distribution width
REAL	Revised European-American Lymphoma (classification)
REM	rapid eye movement
RF	rheumatoid factor
RICE	rest, ice, compression, and elevation
RLQ	right lower quadrant
RLS	restless leg syndrome
RNA	ribonucleic acid
ROM	range of motion
RPGN	rapidly progressive glomerulonephritis
RPR	rapid plasma reagin
RR	respiratory rate
RSV	respiratory syncytial virus
RTA	renal tubular acidosis
RUQ	right upper quadrant

Abbreviation	Meaning
RV	residual volume, right ventricular
RVG	radionuclide ventriculogram
RVH	right ventricular hypertrophy
SAAG	serum-ascites albumin gradient
SADNI	selective antibody deficiency with normal immunoglobulins
SAH	subarachnoid hemorrhage
SAMe	*S*-adenosyl-L-methionine
SBE	subacute bacterial endocarditis
SBP	spontaneous bacterial peritonitis, systolic blood pressure
SCA	superior cerebellar artery
SCC	squamous cell carcinoma
SCD	sequential compression device
SCLC	small cell lung cancer
SD	standard deviation
SERM	selective estrogen receptor modulator
SES	socioeconomic status
SGA	small for gestational age
SIADH	syndrome of inappropriate secretion of antidiuretic hormone
SIRS	systemic inflammatory response syndrome
SJS	Stevens-Johnson syndrome
SLE	systemic lupus erythematosus
SMA	smooth muscle antibody
SOD	superoxide dismutase
SPEP	serum protein electrophoresis
SQ	subcutaneous
SSKI	saturated solution of potassium iodide
SSPE	subacute sclerosing panencephalitis
SSRI	selective serotonin reuptake inhibitor
STD	sexually transmitted disease
STEMI	ST-elevation myocardial infarction
SVC	superior vena cava
SvO_2	mixed venous arterial saturation
SVR	systemic vascular resistance
SVT	supraventricular tachycardia
$T_{1/2}$	half-life
T_3	triiodothyronine
T_4	thyroxine
TAH-BSO	total abdominal hysterectomy and bilateral salpingo-oophorectomy
TB	tuberculosis
3TC	dideoxythiacytidine (lamivudine)
TCA	tricyclic antidepressant
Td	tetanus and diphtheria (vaccine)
TEDS	thromboembolic disease stockings
TEE	transesophageal echocardiography
TFTs	thyroid function tests
TG	tissue transglutaminase, triglyceride
TIA	transient ischemic attack
TID	three times daily
TIPS	transjugular intrahepatic portosystemic shunt
TIW	three times per week
TLC	therapeutic lifestyle change, total lung capacity
TMP-SMX	trimethoprim-sulfamethoxazole
TNF	tumor necrosis factor
tPA	tissue plasminogen activator
TPN	total parenteral nutrition
TPO	thyroid peroxidase
TRALI	transfusion-related acute lung injury
TRH	thyrotropin-releasing hormone
TS	transferrin saturation
TSH	thyroid-stimulating hormone
TSI	thyroid-stimulating immunoglobulin
TSS	toxic shock syndrome
TSST	toxic shock syndrome toxin
TT_3	total triiodothyronine
TTE	transthoracic echocardiography
TTKG	transtubular K^+ gradient
TTP	thrombotic thrombocytopenic purpura
TUIP	transurethral incision of the prostate
TURP	transurethral resection of the prostate
TV	tidal volume
UA	urinalysis
UAG	urine anion gap
U_{Cr}	urine creatinine
UDCA	ursodeoxycholic acid
UFH	unfractionated heparin
UGIB	upper GI bleeding
UIP	usual interstitial pneumonia
U_{K+}	urine potassium
ULN	upper limit of normal
UMN	upper motor neuron
U_{Na}	urine sodium
U_{osm}	urine osmolality
UPEP	urinary protein electrophoresis
URI	upper respiratory infection
USMLE	United States Medical Licensing Examination
USPSTF	United States Preventive Services Task Force
UTI	urinary tract infection
UV	ultraviolet
VAP	ventilator-assisted pneumonia
VATS	video-associated thoracoscopy
VBI	vertebrobasilar insufficiency
VC	vital capacity
VCA	viral capsid antigen
VDRL	Venereal Disease Research Laboratory
VEGF	vascular endothelial growth factor

Abbreviation	Meaning
VF	ventricular fibrillation
VIP	vasoactive intestinal peptide
VLDL	very low density lipoprotein
VMA	vanillylmandelic acid
V/Q	ventilation-perfusion (ratio)
VSD	ventricular septal defect
V_T	tidal volume
VT	ventricular tachycardia
VTE	venous thromboembolism
vWD	von Willebrand's disease
vWF	von Willebrand's factor
VZIG	varicella-zoster immune globulin
VZV	varicella-zoster virus
WBC	white blood cell
WHO	World Health Organization
WPW	Wolff-Parkinson-White (syndrome)

Index

C

D

E

H

N

O

NOTES

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Peter Chin-Hong, MD

Thomas E. Baudendistel, MD, FACP

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Tao is a well-recognized figure in medical education. As senior editor, he has led the expansion of *First Aid* into a global educational series. In addition, he is the founder of the *USMLERx* online test bank series as well as a cofounder of the *Underground Clinical Vignettes* series. As a medical student, he was editor-in-chief of the University of California, San Francisco *Synapse,* a university newspaper with a weekly circulation of 9000. Tao earned his medical degree from the University of California, San Francisco, in 1996 and completed his residency training in internal medicine at Yale University and fellowship training at Johns Hopkins University. At Yale, he was a regular guest lecturer on the USMLE review courses and an adviser to the Yale University School of Medicine curriculum committee. Dr. Le subsequently went on to cofound Medsn and served as its chief medical officer. He is currently conducting research in asthma education at the University of Louisville.

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Peter is assistant professor in the division of Infectious Diseases at UCSF, director of the Transplant Infectious Diseases program, and site co-leader of the Doris Duke Clinical Research Fellowship Program for medical students. He was born and raised in Trinidad, West Indies, and received his undergraduate and medical degrees at Brown University in Providence, Rhode Island. Seeking a balmier clime, he completed internal medicine residency training and a fellowship in infectious diseases at UCSF, and joined the faculty there in 2002. He is board certified in internal medicine and infectious diseases. He is actively involved in teaching nurses, medical students, residents, and fellows, and is a frequent speaker for UCSF continuing medical education courses, including the annual Internal Medicine Board Certification and Recertification Review. He has authored chapters in various medical texts (including *Current Medical Diagnosis and Treatment, Current Diagnosis and Treatment in Otolaryngology,* and *Current Diagnosis and Treatment in Sexually Transmitted Infections*) and penned several original scientific articles based on an active research program in infectious diseases of immunocompromised hosts. He sees patients at the UCSF Medical Center as well as at the Positive Health Practice, Ward 86, San Francisco General Hospital.

Thomas E. Baudendistel, MD, FACP

Tom is the past chair of the Society of Hospital Medicine's national ethics committee and is the associate program director of the internal medicine residency at California Pacific Medical Center in San Francisco. Prior to joining CPMC in 2002, he was the Dean's Award recipient at the University of Missouri–Columbia School of Medicine, where he received his MD in 1995. He completed his internal medicine residency and chief residency at UCSF and then joined the hospitalist faculty at UCSF in 1999. He is board certified in internal medicine, has lectured nationally on numerous clinical and bioethical topics, and currently is an assistant editor for the *Journal of Hospital Medicine.* He has been a contributor on *Current Consult Medicine, The Patient History: Evidence-Based Approach, Hospital Medicine for the PDA, The Saint-Frances Guide to Inpatient Medicine,* and the *UCSF Housestaff Handbook,* and edited the companion Web page for *Current Medical Diagnosis and Treatment.*

ABOUT THE AUTHORS

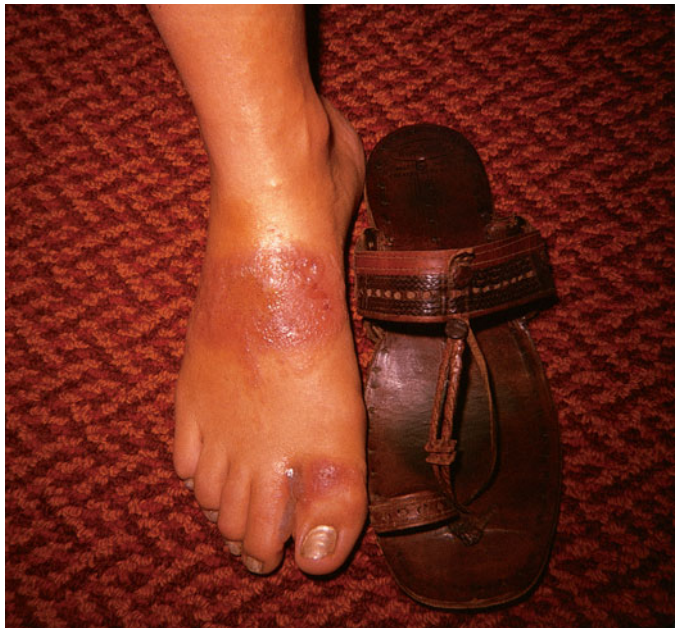

FIGURE 1.2. Contact dermatitis.

Erythematous papules, vesicles, and serous weeping localized to areas of contact with the offending agent are characteristic. (Reproduced, with permission, from Hurwitz RM. *Pathology of the Skin: Atlas of Clinical-Pathological Correlation.* Stamford, CT: Appleton & Lange, 1991: 3.)

FIGURE 2.1. Bacterial conjunctivitis.

Note the conjunctival injection and purulent discharge. (Reproduced, with permission, from Frank Birinyi, MD, as printed in Knoop KJ et al. *Atlas of Emergency Medicine*, 2nd ed. New York: McGraw-Hill, 2002: 30.)

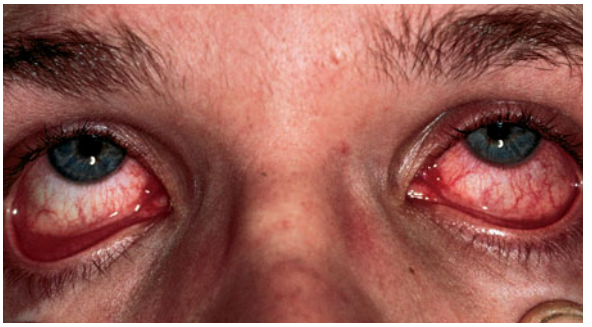

FIGURE 2.2. Viral conjunctivitis.

Note the conjunctival injection and watery discharge. (Reproduced, with permission, from Knoop KJ et al. *Atlas of Emergency Medicine*, 2nd ed. New York: McGraw-Hill, 2002: 31.)

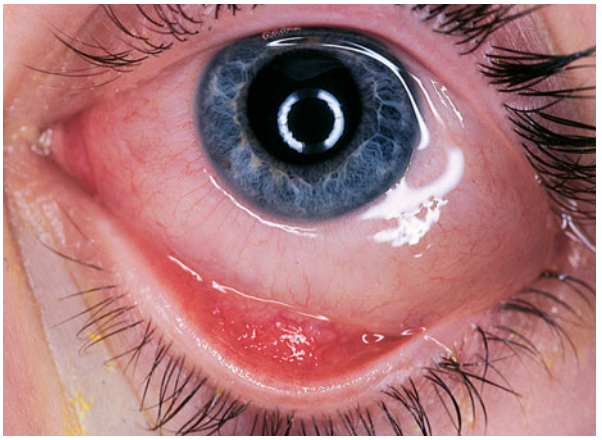

FIGURE 2.3. Allergic conjunctivitis.

Note the edematous, boggy conjunctiva. (Courtesy of Timothy D. McGuirk, DO.)

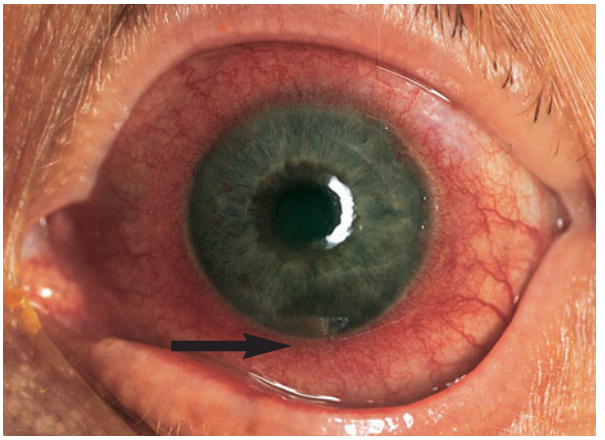

FIGURE 2.4. Anterior uveitis.

Note the conjunctival injection with ciliary flush (circumcorneal erythema) and hypopyon (pus pooling in front of the iris; see arrow). (Reproduced, with permission, from Knoop KJ et al. *Atlas of Emergency Medicine*, 2nd ed. New York: McGraw-Hill, 2002: 52.)

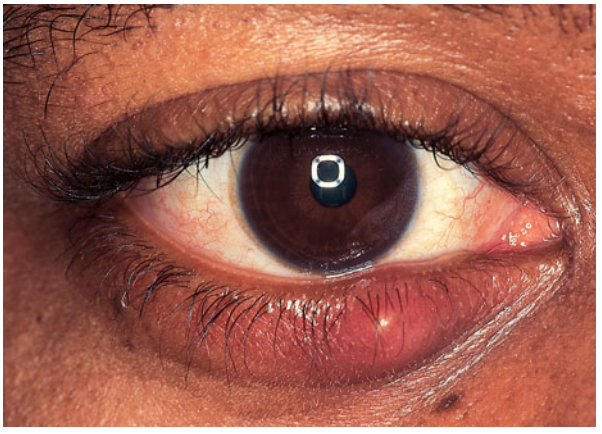

FIGURE 2.8. Hordeolum.

Focal swelling and erythema at the lid margin are seen. (Reproduced, with permission, from Frank Birinyi, MD, as printed in Knoop KJ et al. *Atlas of Emergency Medicine*, 2nd ed. New York: McGraw-Hill, 2002: 38.)

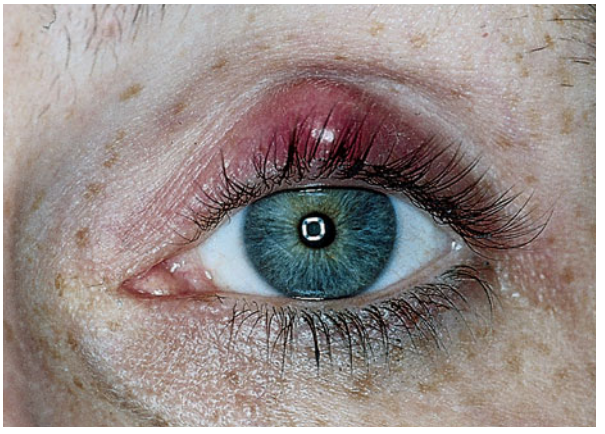

FIGURE 2.9. Chalazion.

Note the nodular focal swelling and erythema. (Reproduced, with permission, from Frank Birinyi, MD, as printed in Knoop KJ et al. *Atlas of Emergency Medicine*, 2nd ed. New York: McGraw-Hill, 2002: 39.)

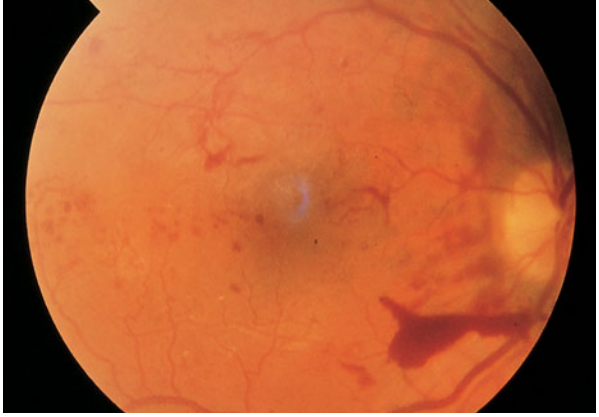

FIGURE 2.12. Vitreous hemorrhage.

The effect of gravity on the vitreous blood creates the appearance of a flat meniscus (keel-shaped blood) in a patient with vitreous hemorrhage associated with proliferative diabetic retinopathy. (Courtesy of Richard E. Wyszynski, MD.)

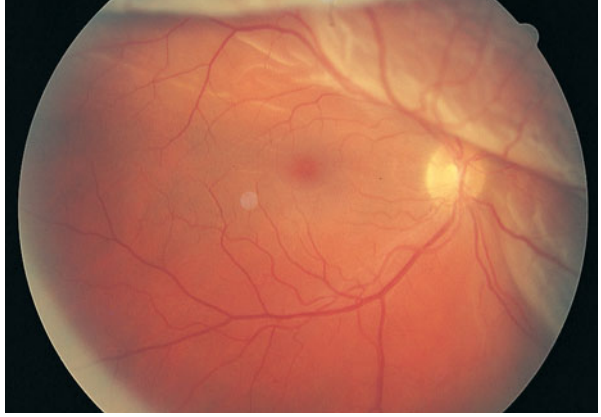

FIGURE 2.13. Retinal detachment.

Note the elevated sheet of retinal tissue with folds. In this patient, the fovea was spared, so acuity was normal but a superior detachment produced an inferior scotoma. (Reproduced, with permission, from Kasper DL et al. *Harrison's Principles of Internal Medicine*, 16th ed. New York: McGraw-Hill, 2004.)

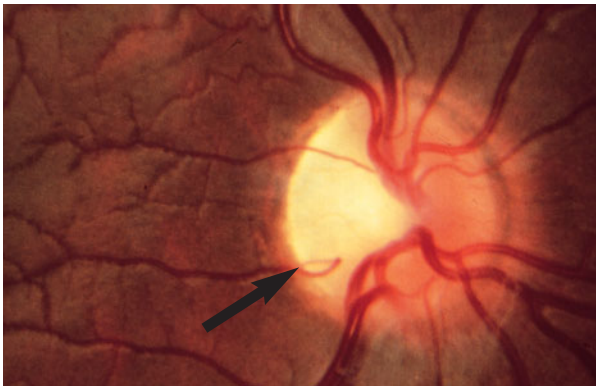

FIGURE 2.14. Optic neuritis.

Optic nerve pallor, either segmental (as in this case; see arrow) or generalized, is a nonspecific change that may be associated with a previous episode of optic neuritis or other insults to the optic nerve. (Courtesy of Richard E. Wyszynski, MD.)

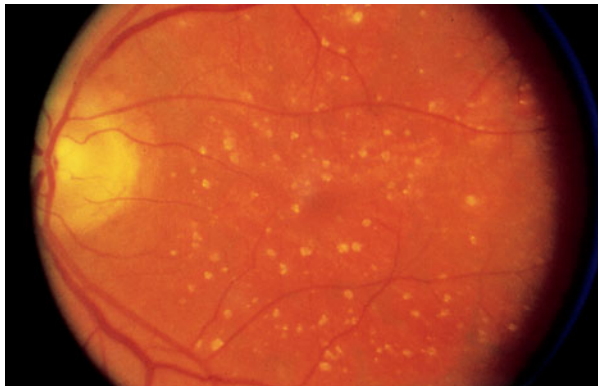

FIGURE 2.15. Age-related macular degeneration.

Note the macular drusen and retinal pigment epithelial atrophy (scalloped pigment loss) that are typical of age-related macular degeneration. (Courtesy of Richard E. Wyszynski, MD.)

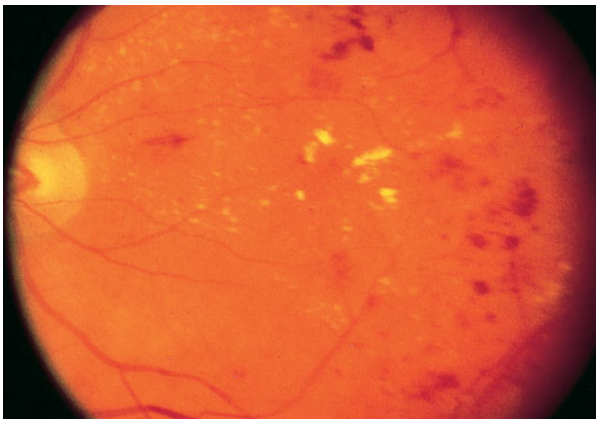

FIGURE 2.16. Nonproliferative diabetic retinopathy.

Hard exudates, dot hemorrhages, blot hemorrhages, flame hemorrhages, and microaneurysms are present. (Courtesy of Richard E. Wyszynski, MD.)

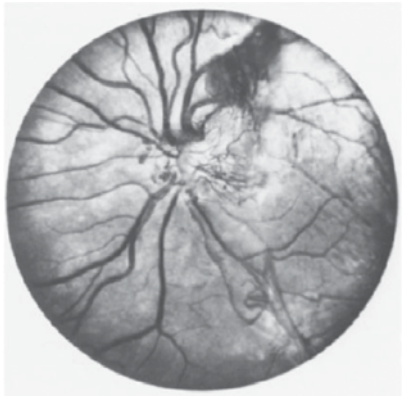

FIGURE 2.17. Proliferative diabetic retinopathy.

There is extensive neovascularization of the disk with an associated small intravitreal hemorrhage that obscures the upper temporal vessels. Along the inferior temporal arcade is another area of neovascularization. (Reproduced, with permission, from Fuster V et al. *Hurst's the Heart*, 11th ed. New York: McGraw-Hill, 2004: Fig. 12-46.)

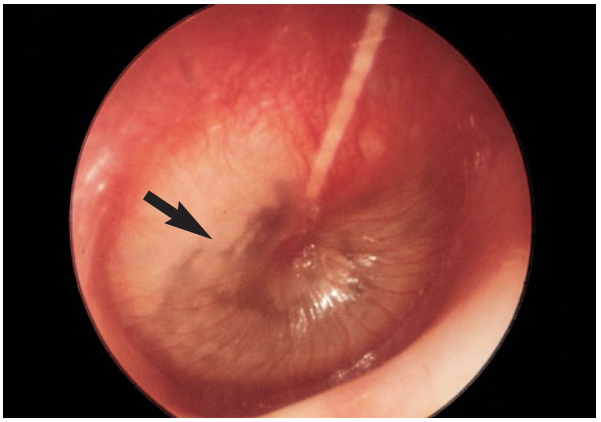

FIGURE 2.19. Acute otitis media.

Note the bulging, dull, erythematous tympanic membrane with pus behind it (see arrow). (Courtesy of Richard A. Chole, MD, PhD.)

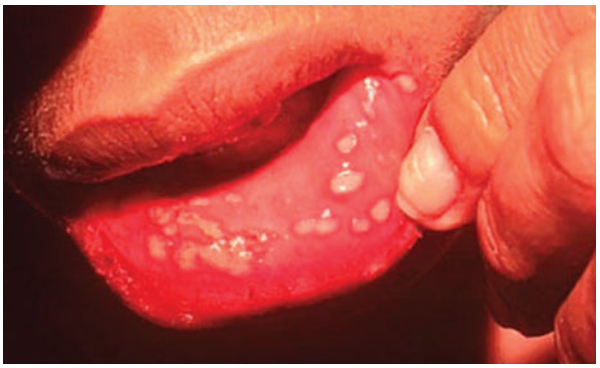

FIGURE 2.22. HSV 1° gingivostomatitis.

Multiple oral ulcerations are seen. (Reproduced, with permission, from Bondi EE et al. *Dermatology: Diagnosis & Treatment.* Stamford, CT: Appleton & Lange, 1991.)

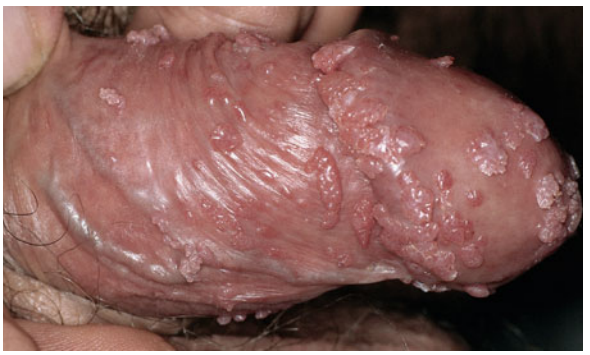

FIGURE 2.24. Penile warts.

Note the multiple soft, filiform papules on the glans penis and prepuce. (Reproduced, with permission, from Wolff K et al. *Fitzpatrick's Color Atlas & Synopsis of Clinical Dermatology,* 5th ed. New York: McGraw-Hill, 2005: 888.)

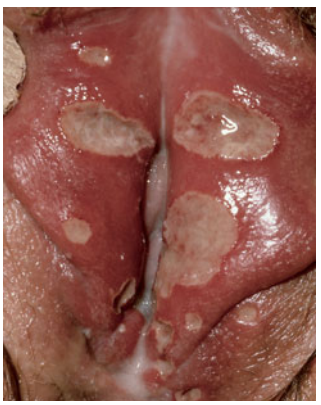

FIGURE 2.26. Chancroid.

Note the multiple painful, punched-out ulcers with undermined borders on the labia. (Reproduced, with permission, from Kasper DL et al. *Harrison's Principles of Internal Medicine,* 16th ed. New York: McGraw-Hill, 2004.)

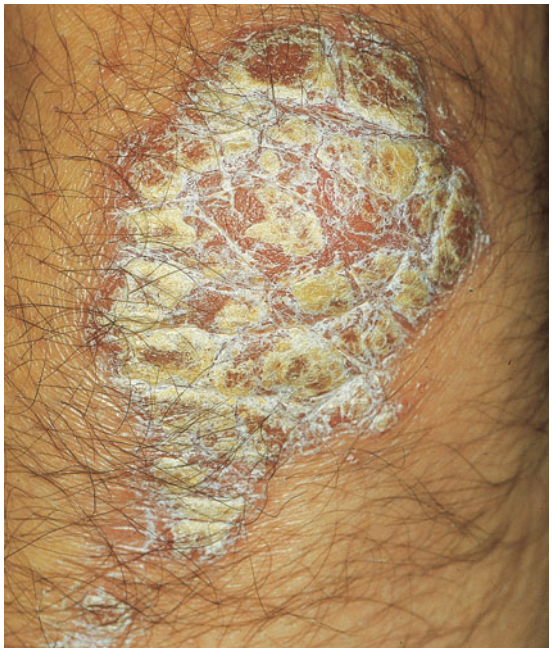

FIGURE 5.3. Psoriasis vulgaris (elbow).

Note the well-demarcated erythematous plaque with thick white scale. (Reproduced, with permission, from Wolff K et al. *Fitzpatrick's Color Atlas & Synopsis of Clinical Dermatology*, 5th ed. New York: McGraw-Hill, 2005: 57.)

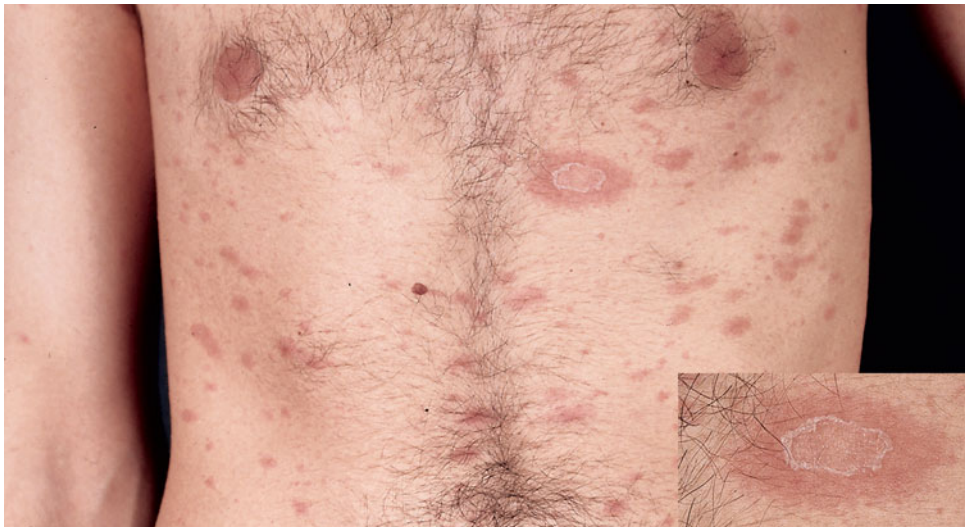

FIGURE 5.4. Pityriasis rosea.

Pink plaques with an oval configuration are seen that follow the lines of cleavage. Inset: Herald patch. The collarette of scale is more obvious on this magnification. (Reproduced, with permission, from Wolff K et al. *Fitzpatrick's Color Atlas & Synopsis of Clinical Dermatology*, 5th ed. New York: McGraw-Hill, 2005: 119.)

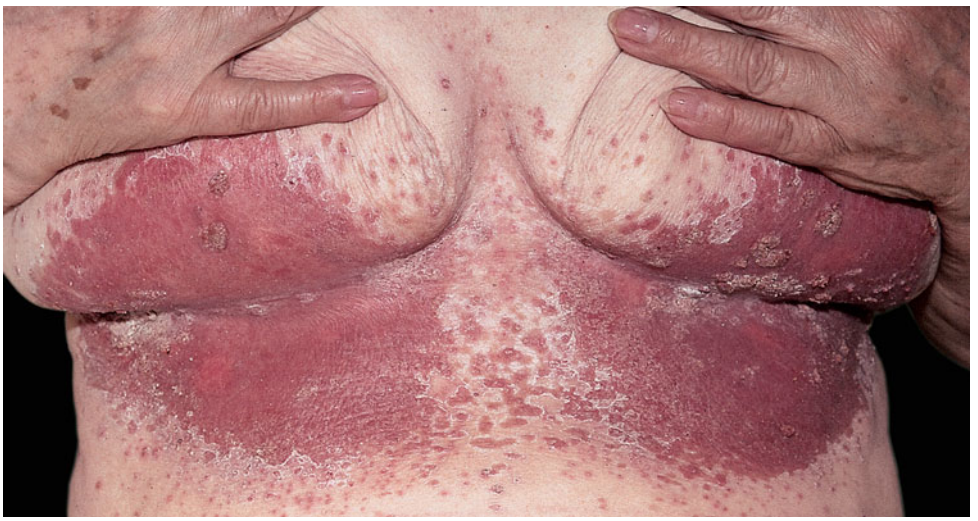

FIGURE 5.7. Cutaneous candidiasis: intertrigo.

Confluent bright red papules with "satellite" pustules are seen. (Reproduced, with permission, from Wolff K et al. *Fitzpatrick's Color Atlas & Synopsis of Clinical Dermatology*, 5th ed. New York: McGraw-Hill, 2005: 719.)

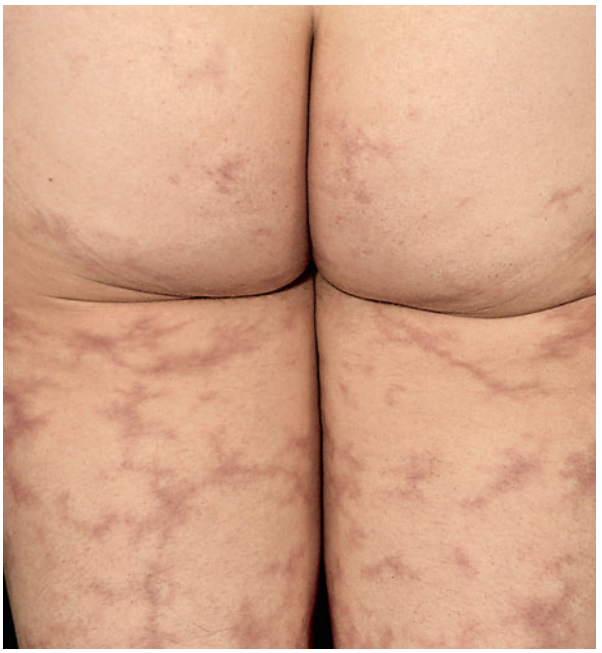

FIGURE 5.11. Symptomatic livedo reticularis.

A bluish, netlike, arborizing pattern is seen on the posterior thighs and buttocks. (Reproduced, with permission, from Wolff K et al. *Fitzpatrick's Color Atlas & Synopsis of Clinical Dermatology*, 5th ed. New York: McGraw-Hill, 2005: 381.)

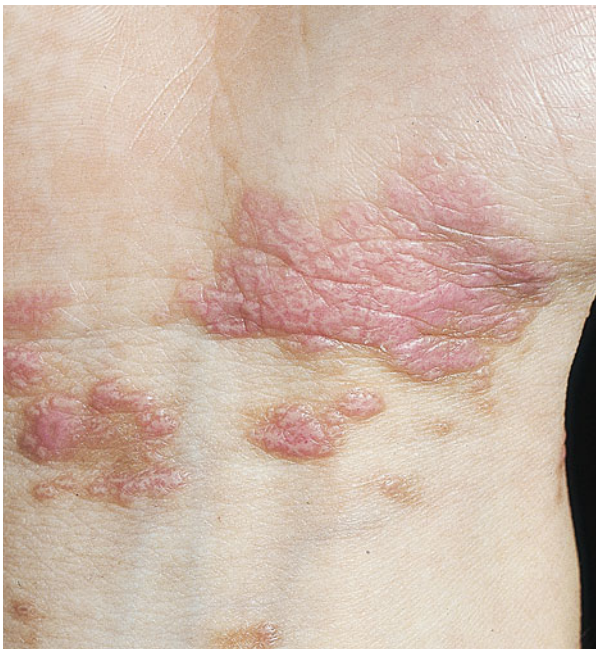

FIGURE 5.12. Lichen planus.

Flat-topped, polygonal, sharply defined, shiny, violaceous papules are seen. (Reproduced, with permission, from Wolff K et al. *Fitzpatrick's Color Atlas & Synopsis of Clinical Dermatology*, 5th ed. New York: McGraw-Hill, 2005: 125.)

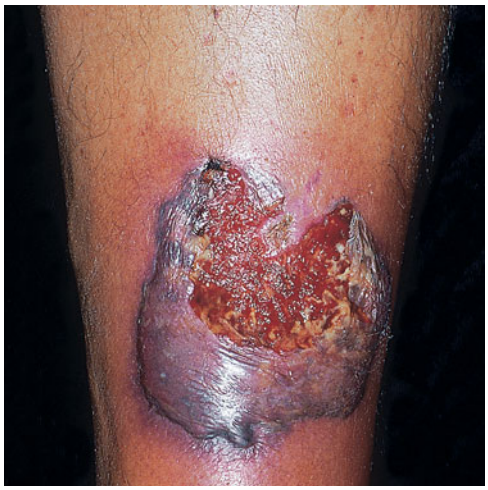

FIGURE 5.13. Pyoderma gangrenosum.

A painful ulcer is seen with a dusky-red peripheral rim and an undermined border. (Reproduced, with permission, from Wolff K et al. *Fitzpatrick's Color Atlas & Synopsis of Clinical Dermatology*, 5th ed. New York: McGraw-Hill, 2005: 153.)

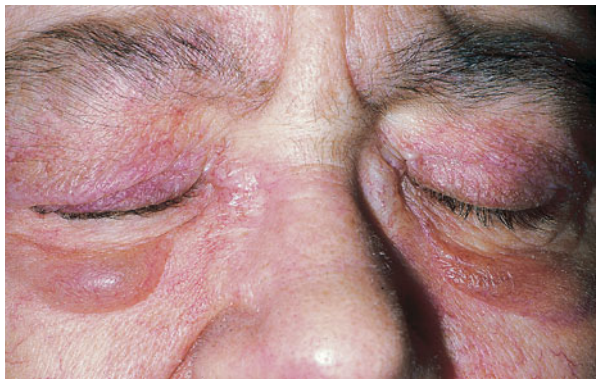

FIGURE 5.14. Dermatomyositis.

Heliotrope (reddish-purple) erythema of the upper eyelids can be seen along with edema of the lower lids. (Reproduced, with permission, from Wolff K et al. *Fitzpatrick's Color Atlas & Synopsis of Clinical Dermatology*, 5th ed. New York: McGraw-Hill, 2005: 373.)

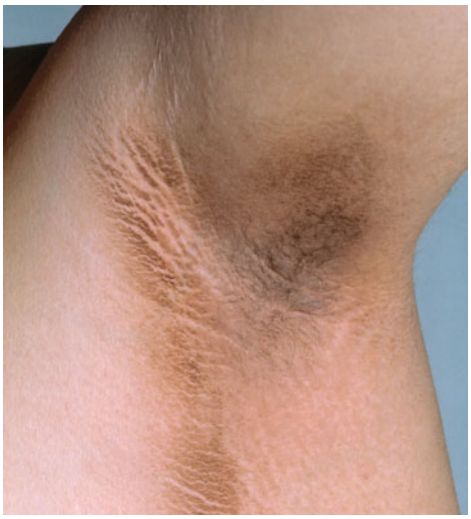

FIGURE 5.15. Acanthosis nigricans.

Note the velvety, dark brown epidermal thickening of the armpit. (Reproduced, with permission, from Wolff K et al. *Fitzpatrick's Color Atlas & Synopsis of Clinical Dermatology*, 5th ed. New York: McGraw-Hill, 2005: 87.)

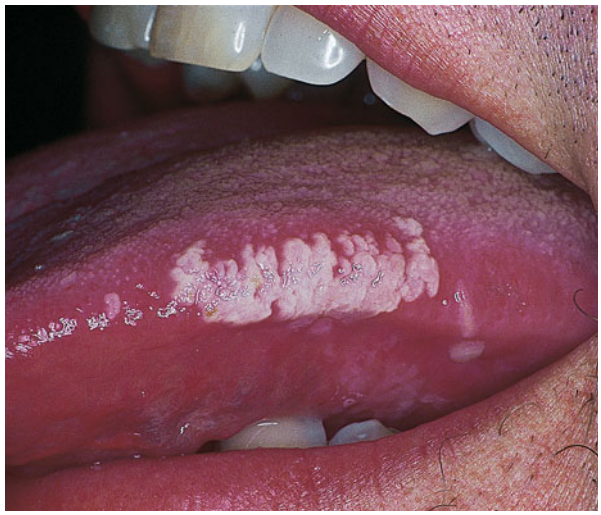

FIGURE 5.16. Oral hairy leukoplakia.

Note the corrugated white plaque on the lateral tongue. Essentially pathognomonic for HIV infection. (Reproduced, with permission, from Wolff K et al. *Fitzpatrick's Color Atlas & Synopsis of Clinical Dermatology*, 5th ed. New York: McGraw-Hill, 2005: 943.)

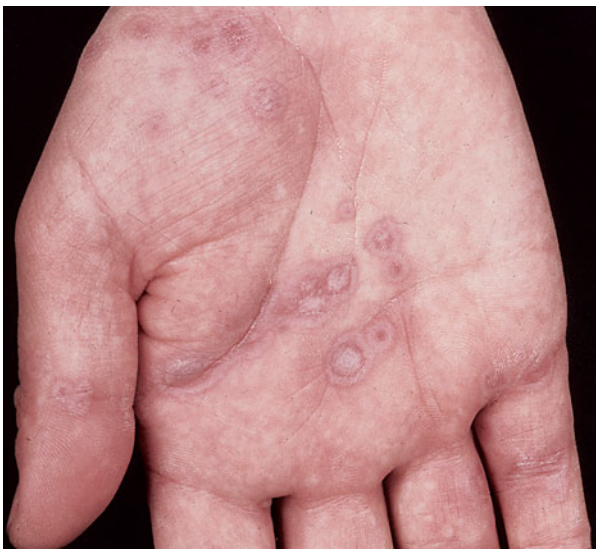

FIGURE 5.21. Erythema multiforme.

Targetoid lesions are seen on the palms. (Reproduced, with permission, from Wolff K et al. *Fitzpatrick's Color Atlas & Synopsis of Clinical Dermatology*, 5th ed. New York: McGraw-Hill, 2005: 141.)

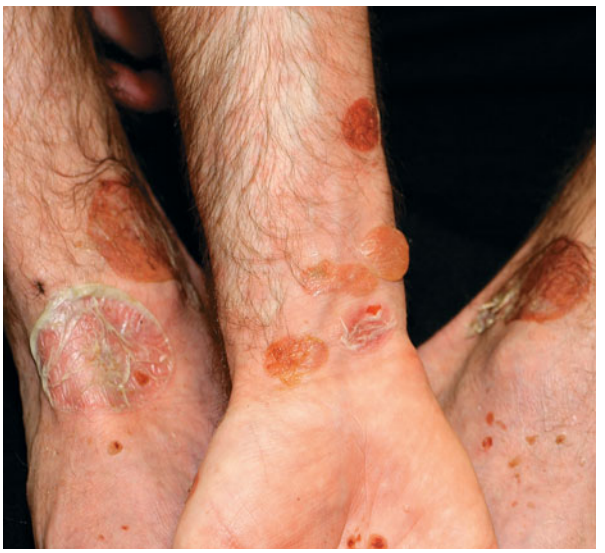

FIGURE 5.22. Bullous pemphigoid.

Tense bullae with serous fluid are seen. (Reproduced, with permission, from Wolff K et al. *Fitzpatrick's Color Atlas & Synopsis of Clinical Dermatology*, 5th ed. New York: McGraw-Hill, 2005: 108.)

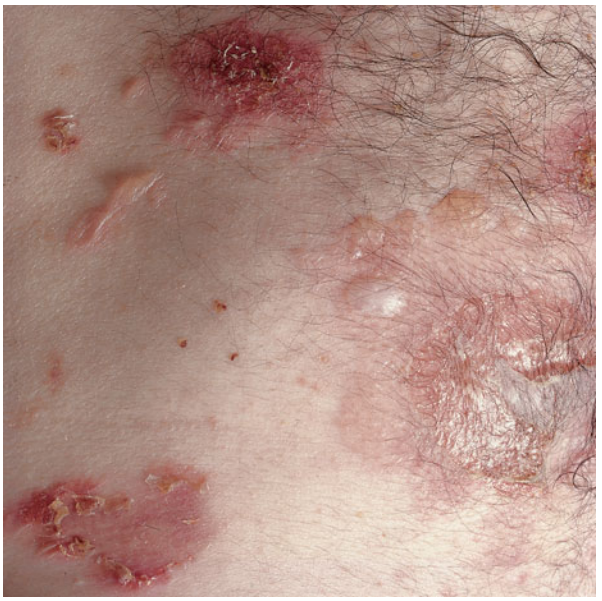

FIGURE 5.23. Pemphigus vulgaris.

Because of the fragility of the blisters, pemphigus vulgaris presents as erosions. (Reproduced, with permission, from Wolff K et al. *Fitzpatrick's Color Atlas & Synopsis of Clinical Dermatology*, 5th ed. New York: McGraw-Hill, 2005: 104.)

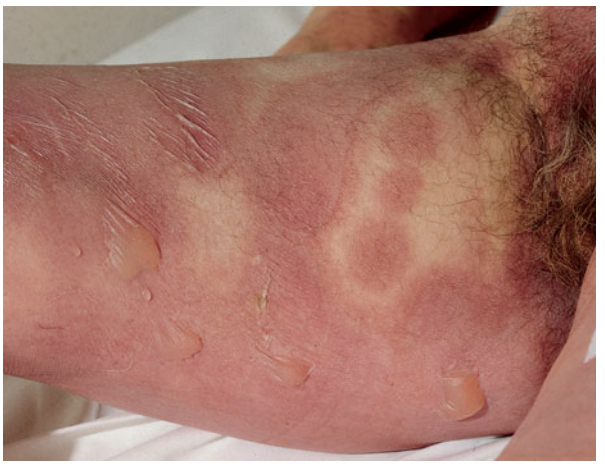

FIGURE 5.24. Stevens-Johnson syndrome.

Generalized eruption of initially targetlike lesions that become confluent, brightly erythematous, and bullous. (Reproduced, with permission, from Wolff K et al. *Fitzpatrick's Color Atlas & Synopsis of Clinical Dermatology*, 5th ed. New York: McGraw-Hill, 2005: 145.)

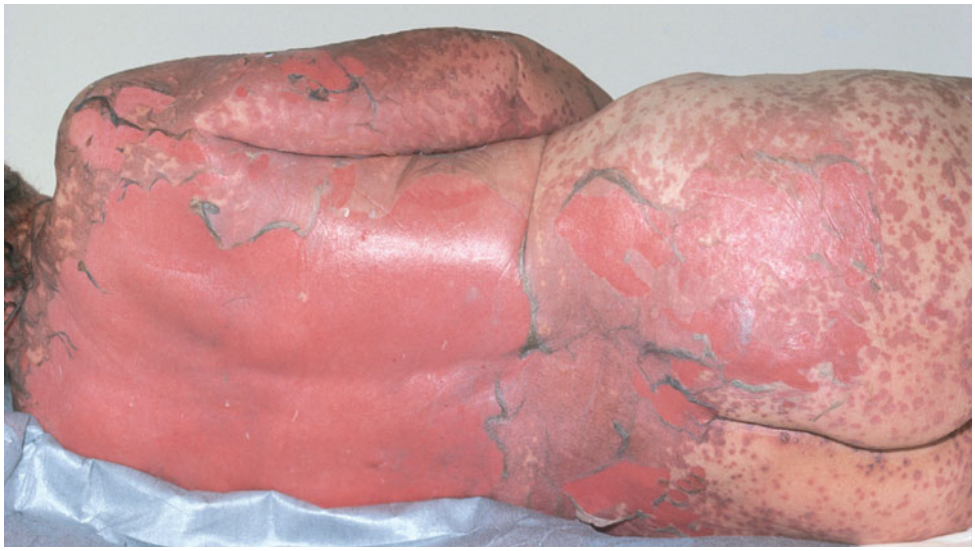

FIGURE 5.25. Toxic epidermal necrolysis.

Bulla formation with rapid desquamation. (Reproduced, with permission, from Wolff K et al. *Fitzpatrick's Color Atlas & Synopsis of Clinical Dermatology*, 5th ed. New York: McGraw-Hill, 2005: 147.)

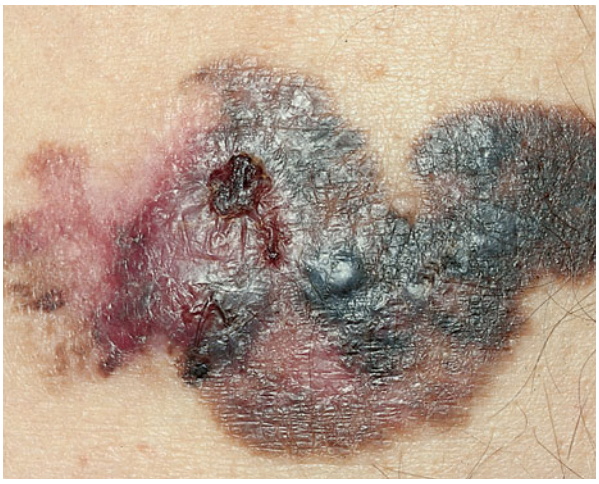

FIGURE 5.26. Superficial spreading melanoma.

A highly characteristic lesion is seen with an irregular pigmentary pattern and scalloped borders. (Reproduced, with permission, from Wolff K et al. *Fitzpatrick's Color Atlas & Synopsis of Clinical Dermatology*, 5th ed. New York: McGraw-Hill, 2005: 318.)

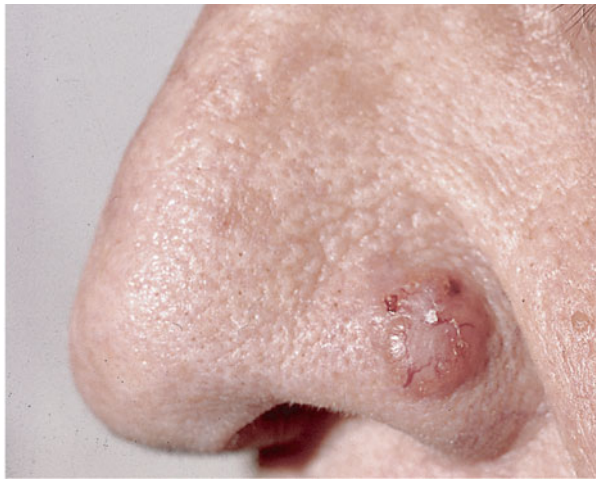

FIGURE 5.27. Nodular basal cell carcinoma.

Note the smooth, pearly nodule with telangiectasias. (Reproduced, with permission, from Wolff K et al. *Fitzpatrick's Color Atlas & Synopsis of Clinical Dermatology*, 5th ed. New York: McGraw-Hill, 2005: 283.)

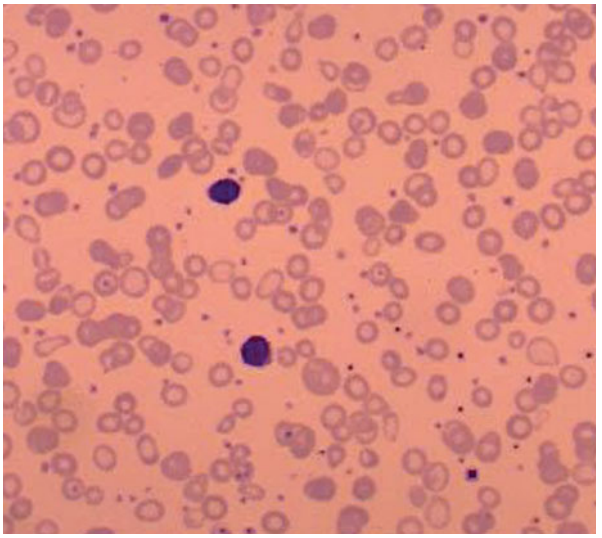

FIGURE 9.2. Iron deficiency anemia.

Note hypochromic cells (prominent central pallor) and microcytosis (RBCs smaller than the nucleus of the lymphocyte). There is also prominent thrombocytosis, a common finding associated with iron deficiency. (Reproduced, with permission, from Tierney LM et al. *Current Medical Diagnosis & Treatment*, 44th ed. New York: McGraw-Hill, 2005.)

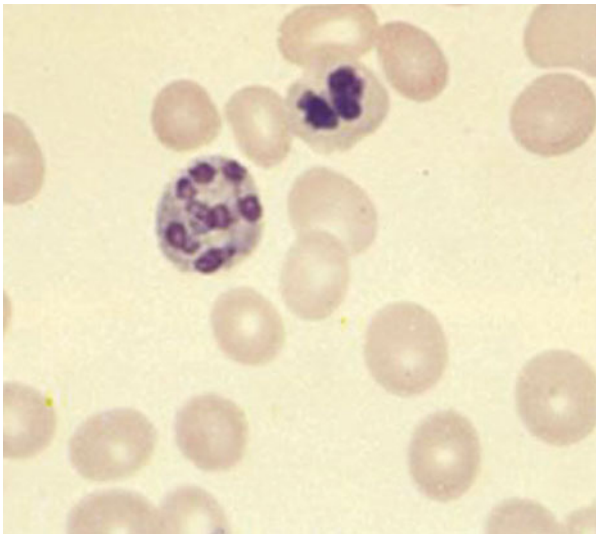

FIGURE 9.3. Megaloblastic anemia.

Note the macro-ovalocytes and prominent hypersegmented neutrophil. (Reproduced, with permission, from Kasper DL et al. *Harrison's Principles of Internal Medicine*, 16th ed. New York: McGraw-Hill, 2005: 605.)

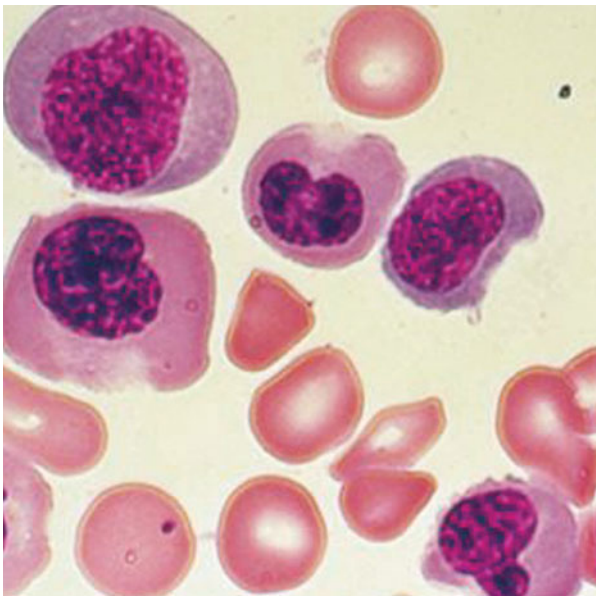

FIGURE 9.5. Spherocytes.

Characteristic spherocytes (small, round RBCs without central pallor) are present in addition to signs of markedly ↑ RBC synthesis (polychromasia, nucleated RBCs) in a patient with extravascular immune hemolysis. (Reproduced, with permission, from R.S. Hillman, MD, and K.A. Ault, MD, the American Society of Hematology Slide Bank. Copyright © American Society of Hematology. All rights reserved.)

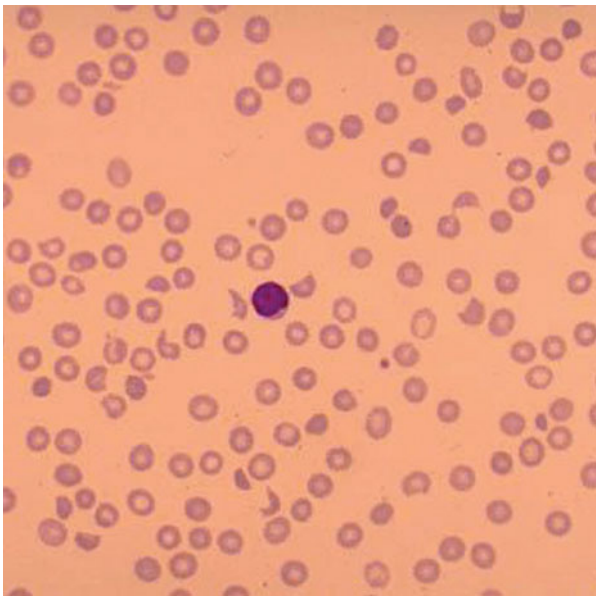

FIGURE 9.6. Schistocytes.

A large number of fragmented RBCs is characteristic of microangiopathic or intravascular hemolysis. In this case, the patient had HUS. (Courtesy of Lloyd Damon, MD.)

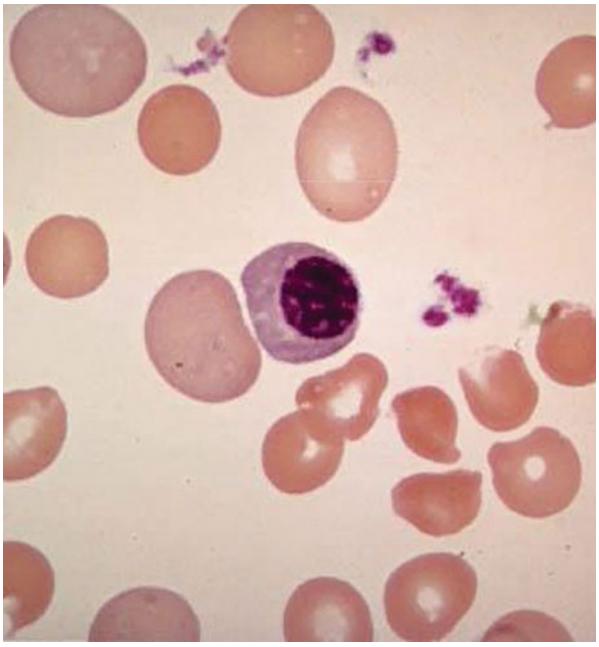

FIGURE 9.7. Bite cells.

Several characteristic bite cells are present in this patient with G6PD deficiency with acute oxidative hemolysis. (Courtesy of Lloyd Damon, MD.)

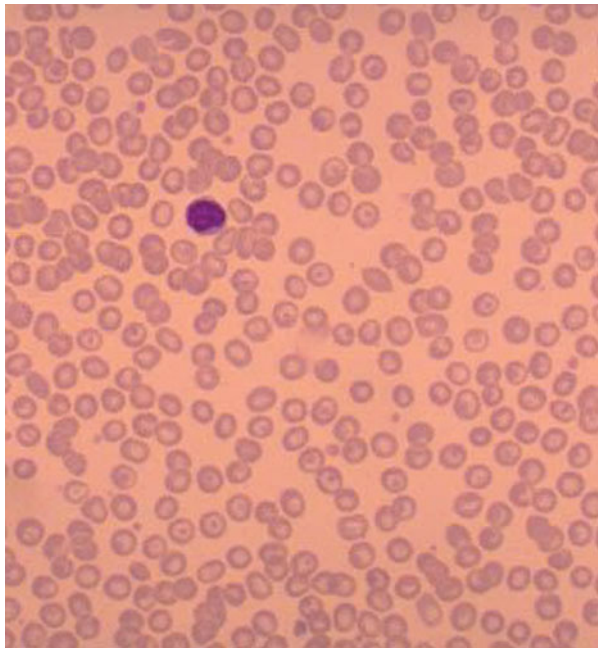

FIGURE 9.8. β-thalassemia major.

Note the microcytic, hypochromic cells, target cells, and nucleated RBCs. (Courtesy of Lloyd Damon, MD.)

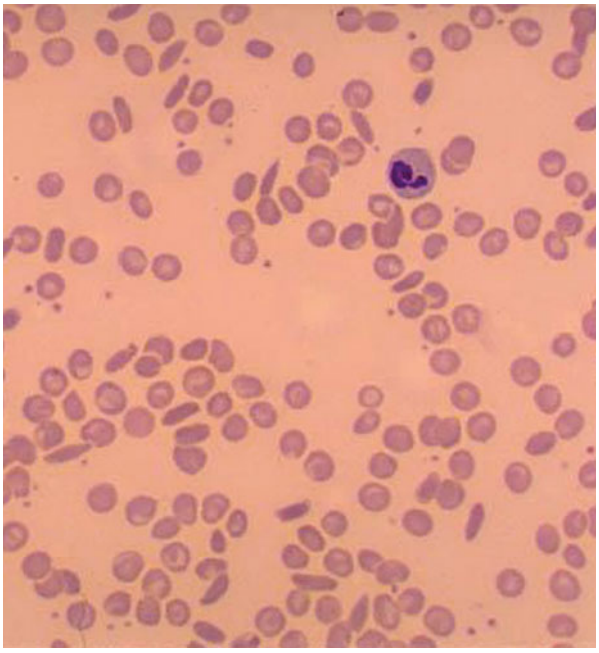

FIGURE 9.9. Sickle cell anemia.

Multiple sickle forms are characteristic. (Courtesy of Lloyd Damon, MD.)

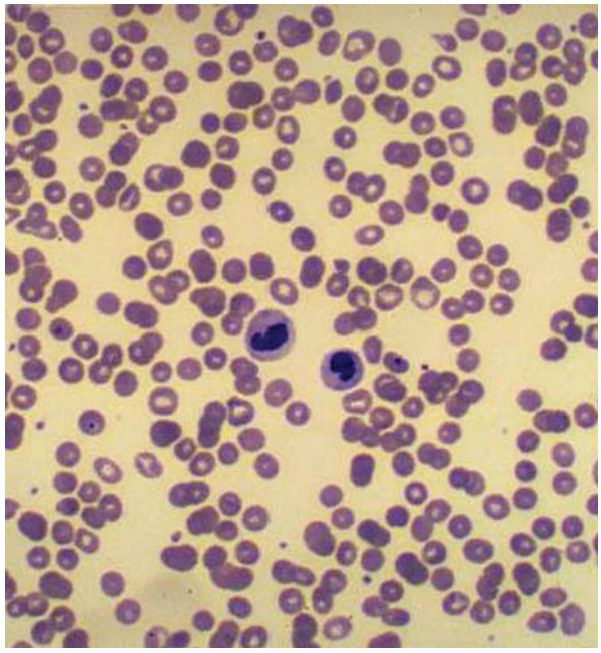

FIGURE 9.10. Myelodysplasia.

Both neutrophils in this slide demonstrate hypogranulation and hypolobation (pseudo–Pelger-Huët anomaly), suggesting myelodysplasia. (Courtesy of Lloyd Damon, MD.)

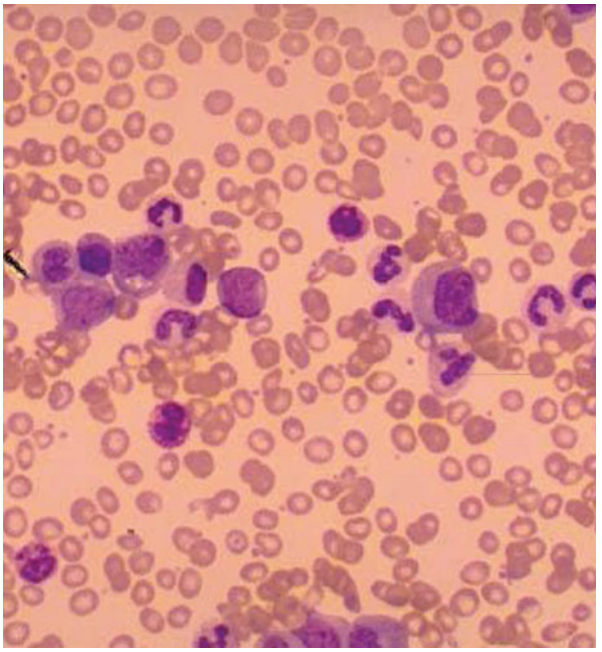

FIGURE 9.11. Chronic myelogenous leukemia.

Note the large number of immature myeloid forms in the peripheral blood, including metamyelocytes, myelocytes, and promyelocytes, as well as a large number of eosinophils and basophils. (Courtesy of Lloyd Damon, MD.)

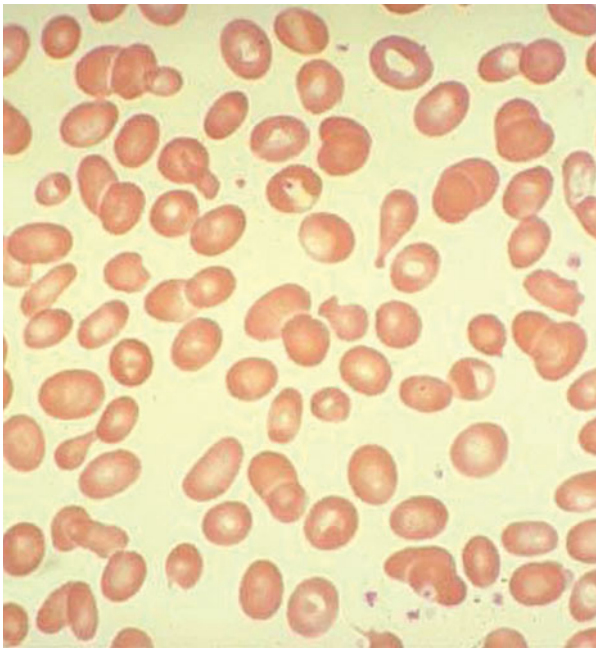

FIGURE 9.12. Myelofibrosis.

Note the large number of teardrop cells suggestive of bone marrow infiltrative disease. (Courtesy of Lloyd Damon, MD.)

HOSPITAL MEDICINE

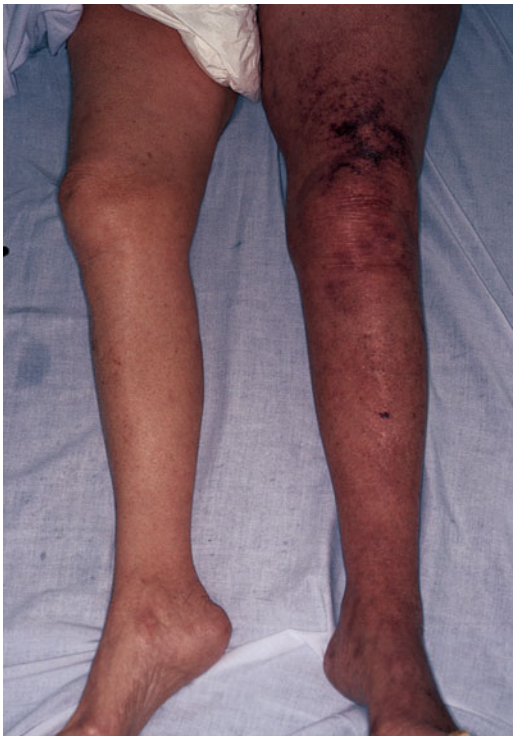

FIGURE 10.3. Phlegmasia cerulea dolens of the left lower extremity.

Note the bluish discoloration and swelling. (Courtesy of Daniel L. Savitt, MD.)

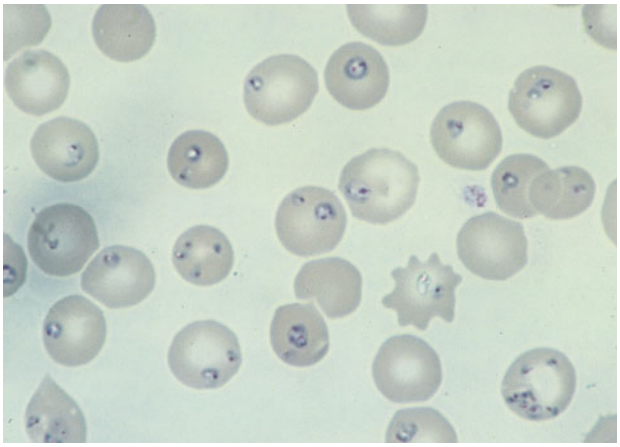

FIGURE 11.1. Babesiosis on a blood smear.

Note the parasites within RBCs resembling malaria. (Reproduced, with permission, from Lichtman MA et al. *Williams Hematology*, 7th ed. New York: McGraw-Hill, 2005: Plate I-10.)

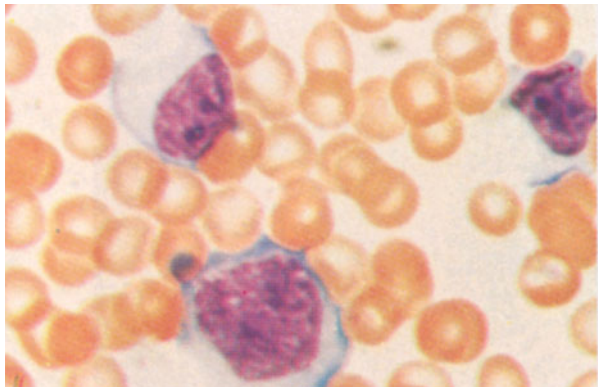

FIGURE 11.4. Atypical lymphocytosis seen in infectious mononucleosis and other infections.

These reactive T lymphocytes are large with eccentric nuclei and bluish-staining RNA in the cytoplasm. (Reproduced, with permission, from Braunwald E et al. *Harrison's Principles of Internal Medicine*, 15th ed. New York: McGraw-Hill, 2001.)

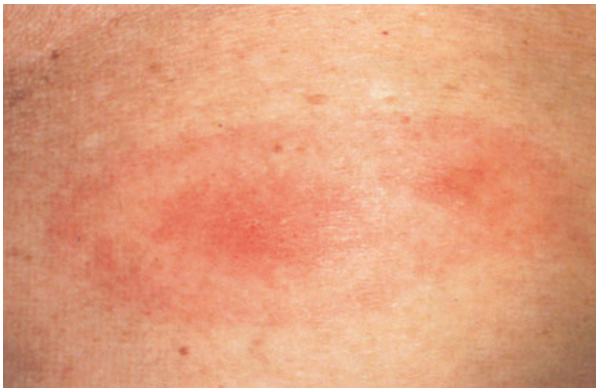

FIGURE 11.5. Erythema chronicum migrans seen in Lyme disease.

The classic "bull's eye" lesion consists of an outer ring where the spirochetes are found, an inner ring of clearing, and central erythema due to an allergic response at the site of the tick bite. Note that some lesions may consist only of the outer annular erythema with central clearing. (Reproduced, with permission, from Braunwald E et al. *Harrison's Principles of Internal Medicine*, 15th ed. New York: McGraw-Hill, 2001.)

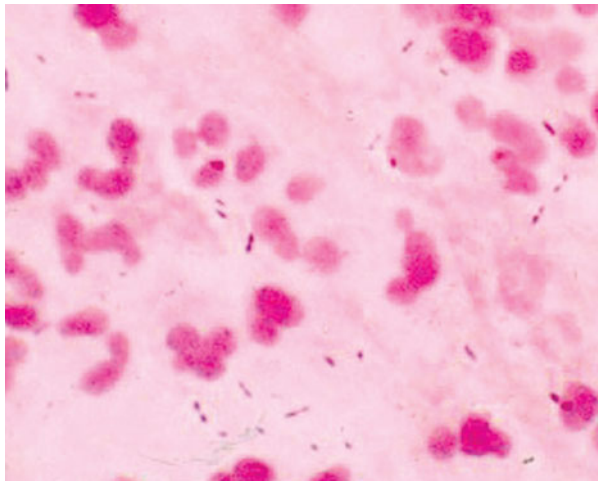

FIGURE 11.6. Pneumococcal pneumonia.

This Gram-stained sputum sample shows many neutrophils and lancet-shaped gram-⊕ cocci in pairs and chains, indicating infection with *S. pneumoniae*. (Reproduced, with permission, from Kasper DL et al. *Harrison's Principles of Internal Medicine*, 16th ed. New York: McGraw-Hill, 2005: 810.)

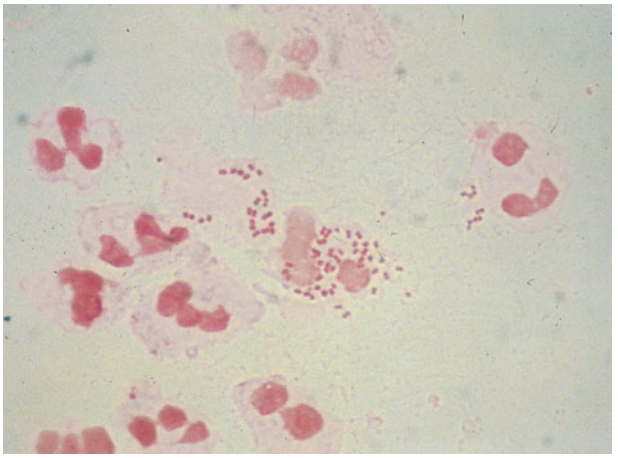

FIGURE 11.7. Gonococcal urethritis: Gram stain of *Neisseria gonorrhoeae.*

Multiple gram-⊖ diplococci are seen within PMNs as well as in the extracellular areas of a smear from a urethral discharge. (Reproduced, with permission, from Wolff K et al. *Fitzpatrick's Color Atlas & Synopsis of Clinical Dermatology*, 5th ed. New York: McGraw-Hill, 2005: 906.)

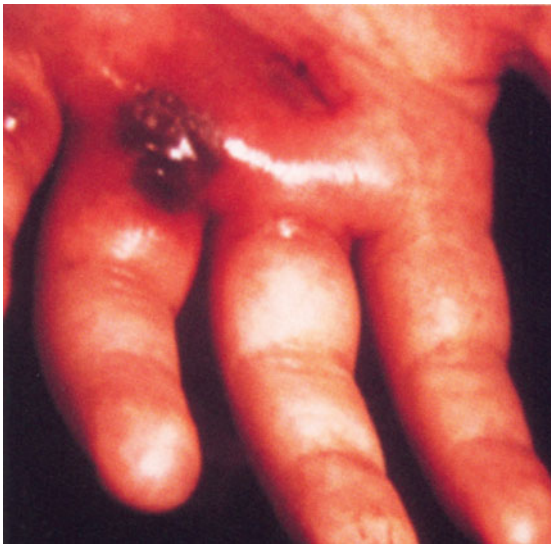

FIGURE 11.8. Ecthyma gangrenosum with *Pseudomonas* in a neutropenic patient.

Note the red papule with a necrotic center. (Reproduced, with permission, from Kasper DL et al. *Harrison's Principles of Internal Medicine*, 16th ed. New York: McGraw-Hill, 2005: 890.)

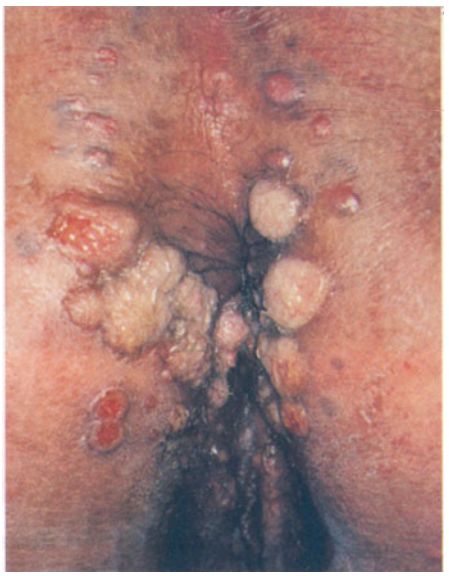

FIGURE 11.9. Condylomata lata in 2° syphilis.

(Reproduced, with permission, from Kasper DL et al. *Harrison's Principles of Internal Medicine*, 16th ed. New York: McGraw-Hill, 2005: 979.)

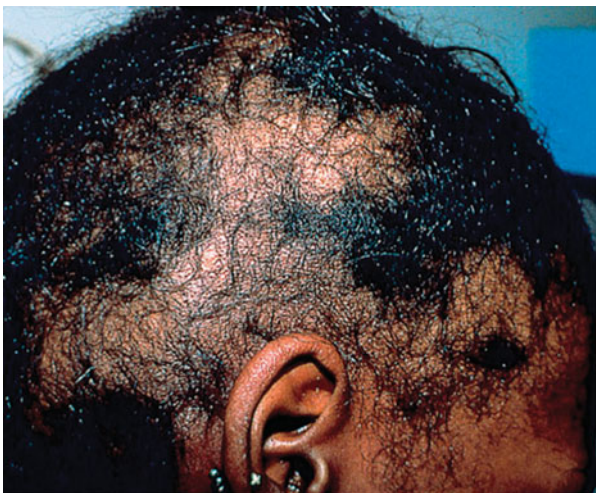

FIGURE 11.10. Alopecia of 2° syphilis.

Hair loss may be one of the only cutaneous manifestations of 2° syphilis that may present either as patchy, "moth-eaten" alopecia or as generalized thinning. (Reproduced, with permission, from Wolff K et al. *Fitzpatrick's Dermatology in General Medicine*, 7th ed. New York: McGraw-Hill, 2008.)

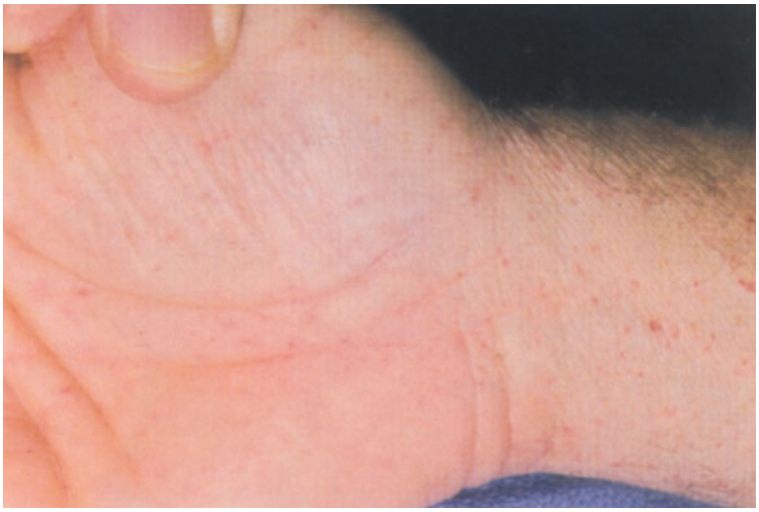

FIGURE 11.11. Rocky Mountain spotted fever.

(Reproduced, with permission, from Braunwald E et al. *Harrison's Principles of Internal Medicine,* 15th ed. New York: McGraw-Hill, 2001: Plate IID-45.)

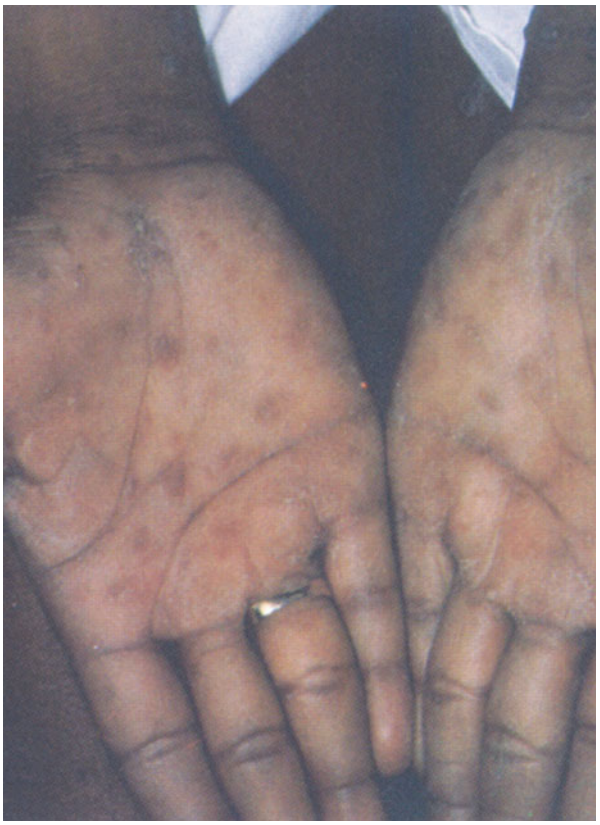

FIGURE 11.12. 2° syphilis.

(Reproduced, with permission, from Kasper DL et al. *Harrison's Principles of Internal Medicine*, 16th ed. New York: McGraw-Hill, 2005: 979.)

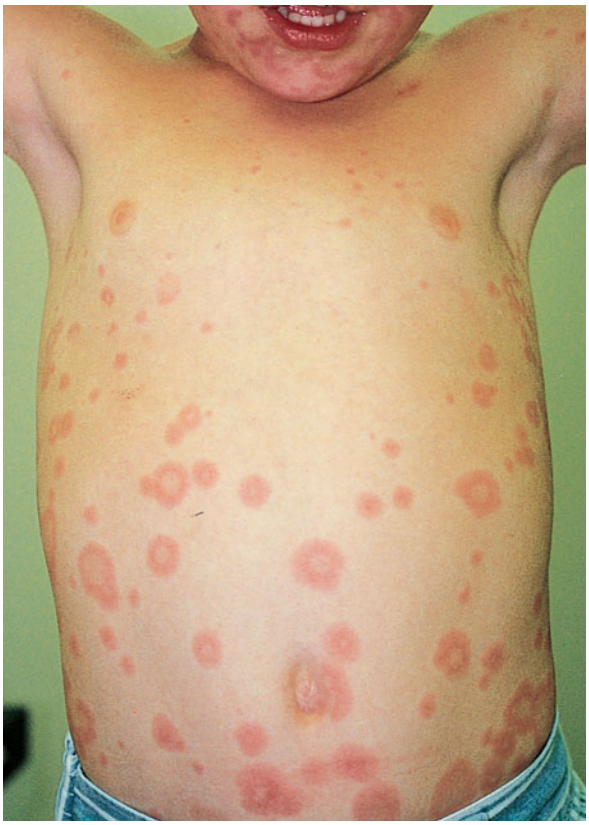

FIGURE 11.13. Erythema multiforme.

(Courtesy of Michael Redman, PA-C.)

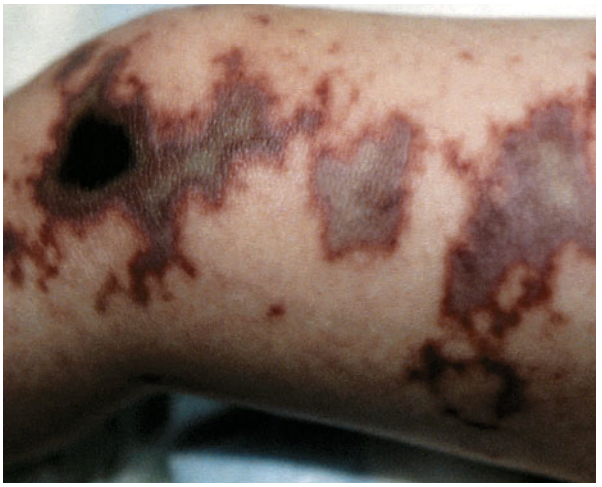

FIGURE 11.14. Acute meningococcemia.

(Reproduced, with permission, from Wolff K et al. *Fitzpatrick's Color Atlas & Synopsis of Clinical Dermatology*, 5th ed. New York: McGraw-Hill, 2005: 643.)

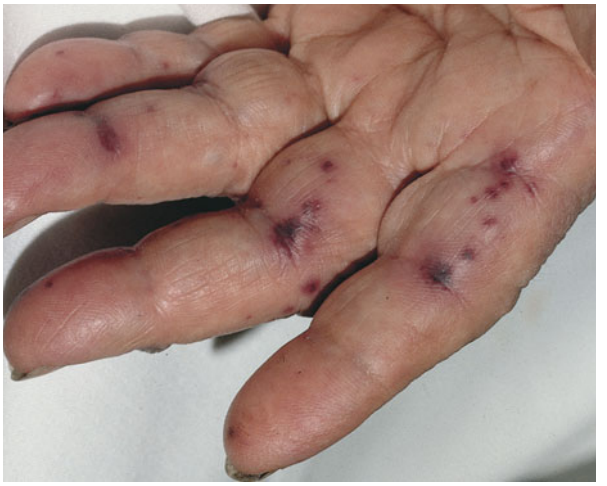

FIGURE 11.15. Janeway lesions in endocarditis.

(Reproduced, with permission, from Wolff K et al. *Fitzpatrick's Color Atlas & Synopsis of Clinical Dermatology*, 5th ed. New York: McGraw-Hill, 2005: 636.)

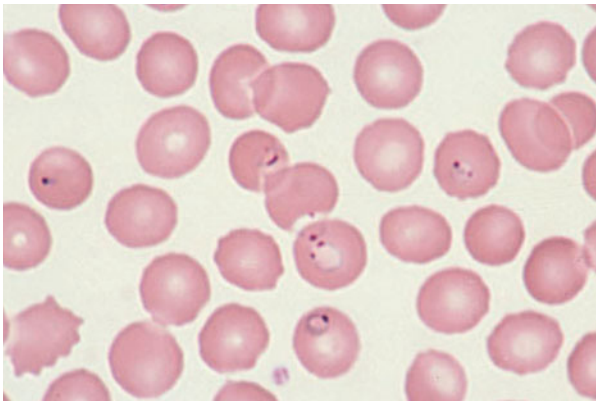

FIGURE 11.16. Falciparum malaria on a thin blood smear.

Young signet-ring-shaped parasites are seen for all species of *Plasmodium*, but only *P. falciparum* shows multiple parasites within a single RBC. (Reproduced, with permission, from Lichtman MA et al. *Williams Hematology*, 7th ed. New York: McGraw-Hill, 2005.)

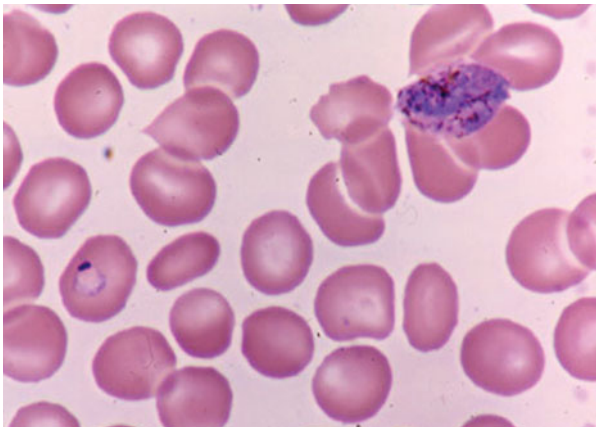

FIGURE 11.17. Vivax malaria on a thin blood smear.

Blood smear of *Plasmodium vivax* showing both a ring form and a female gametocyte. (Reproduced, with permission, from Lichtman MA et al. *Lichtman's Atlas of Hematology*. New York: McGraw-Hill, 2007: Figure III.A.20.)

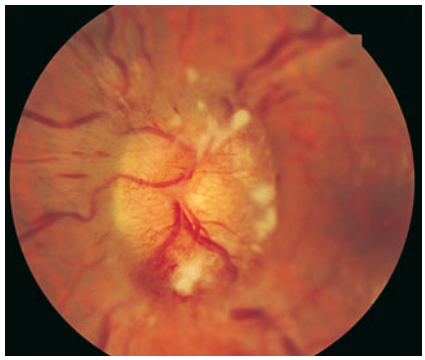

FIGURE 13.2. Papilledema.

This obese young women with pseudotumor cerebri was misdiagnosed as a migraineur until fundus examination was performed showing optic disk elevation, hemorrhages, and cotton-wool spots. (Reproduced, with permission, from Kasper DL et al. *Harrison's Principles of Internal Medicine*, 16th ed. New York: McGraw-Hill, 2005: 169.)

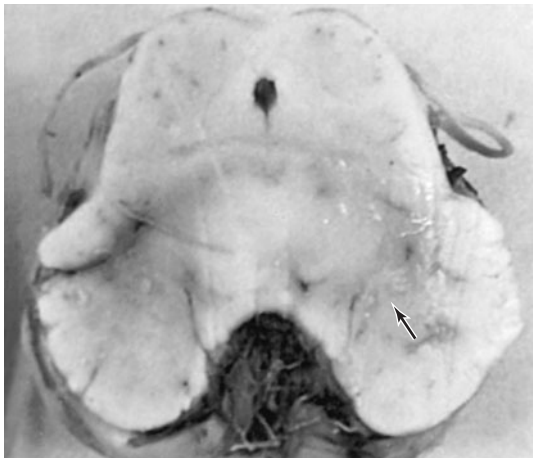

FIGURE 13.3. Parkinson's disease.

Midbrain of a 45-year-old woman with Parkinson's disease, showing depigmentation of the substantia nigra (arrow). (Reproduced, with permission, from Waxman S. *Clinical Neuroanatomy*, 25th ed. New York: McGraw-Hill, 2003: Figure 13-9.)

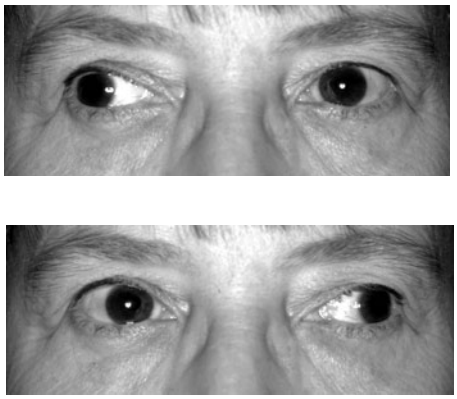

FIGURE 13.5. Bilateral internuclear ophthalmoplegia due to multiple sclerosis.

(Reproduced, with permission, from Riordan-Eva P, Whitcher JP. *Vaughan & Asbury's General Ophthalmology*, 16th ed. New York: McGraw-Hill, 2004: Figure 14-12.)

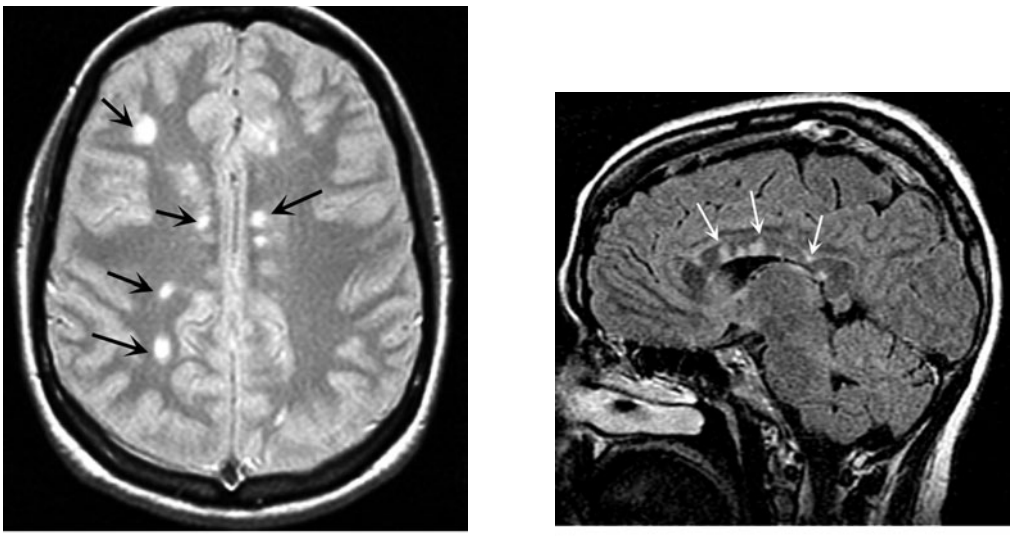

FIGURE 13.6. MRI findings in multiple sclerosis.

(A) Axial image from T2-weighted sequence demonstrates multiple bright signal abnormalities in white matter, typical for MS. (B) Sagittal T2-weighted FLAIR (fluid-attenuated inversion recovery) image in which the high signal of CSF has been suppressed. CSF appears dark, while areas of brain edema or demyelination appear high in signal, as shown here in the corpus callosum (arrows). Lesions in the anterior corpus callosum are frequent in MS and rare in vascular disease. (Reproduced, with permission, from Kasper DL et al. *Harrison's Principles of Internal Medicine*, 16th ed. New York: McGraw-Hill, 2005: 2465.)

RHEUMATOLOGY

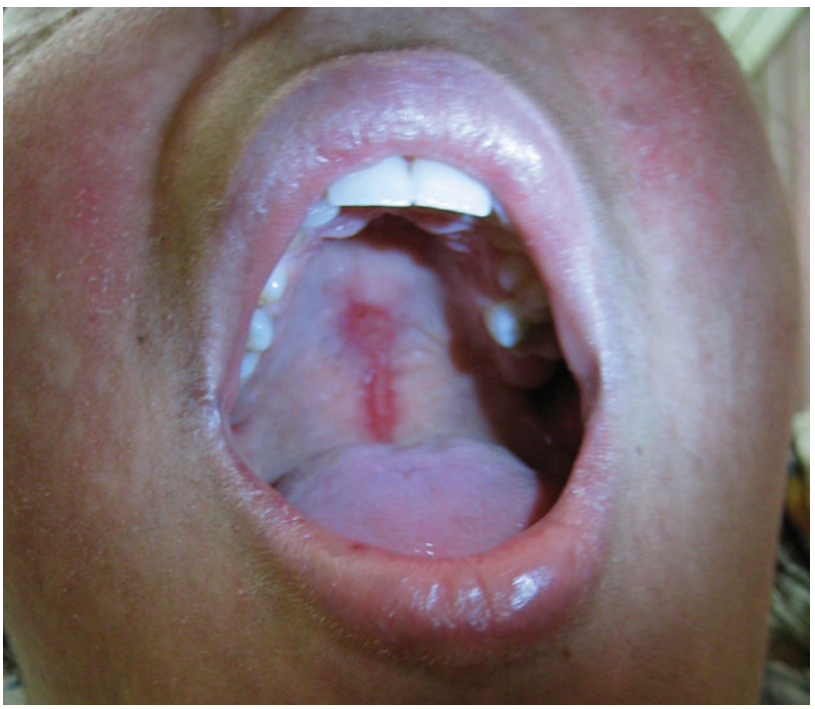

FIGURE 17.1. Oral ulcer on hard palate of patient with SLE.

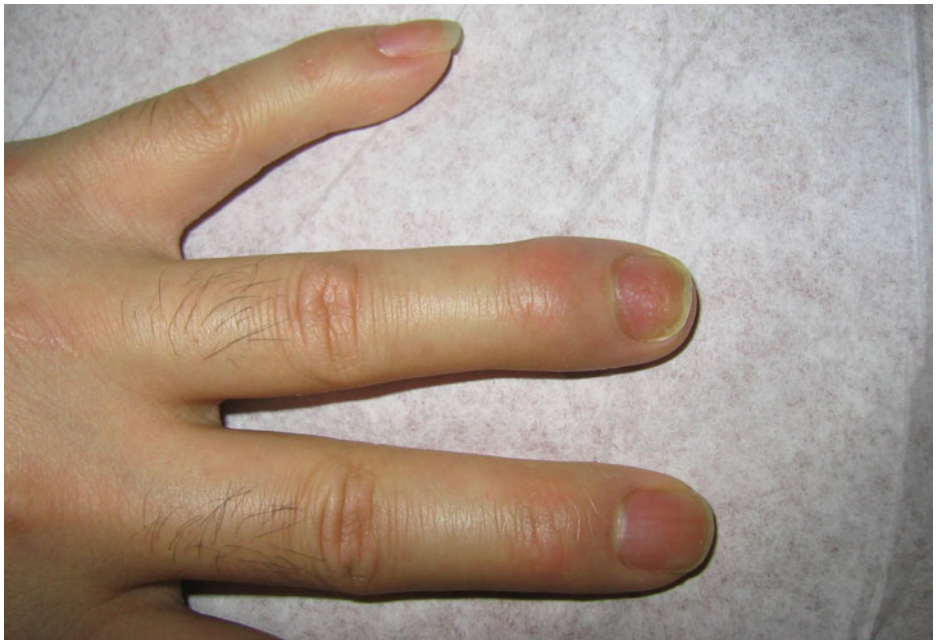

FIGURE 17.3. Onycholysis in a psoriatic arthritis patient.

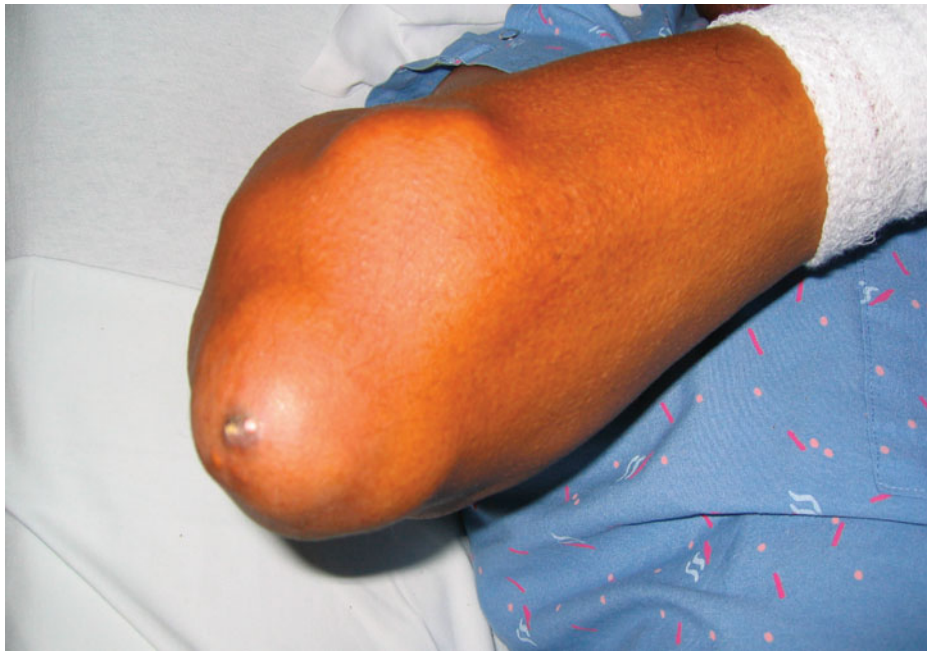

FIGURE 17.4. Tophaceous gout of the elbow.

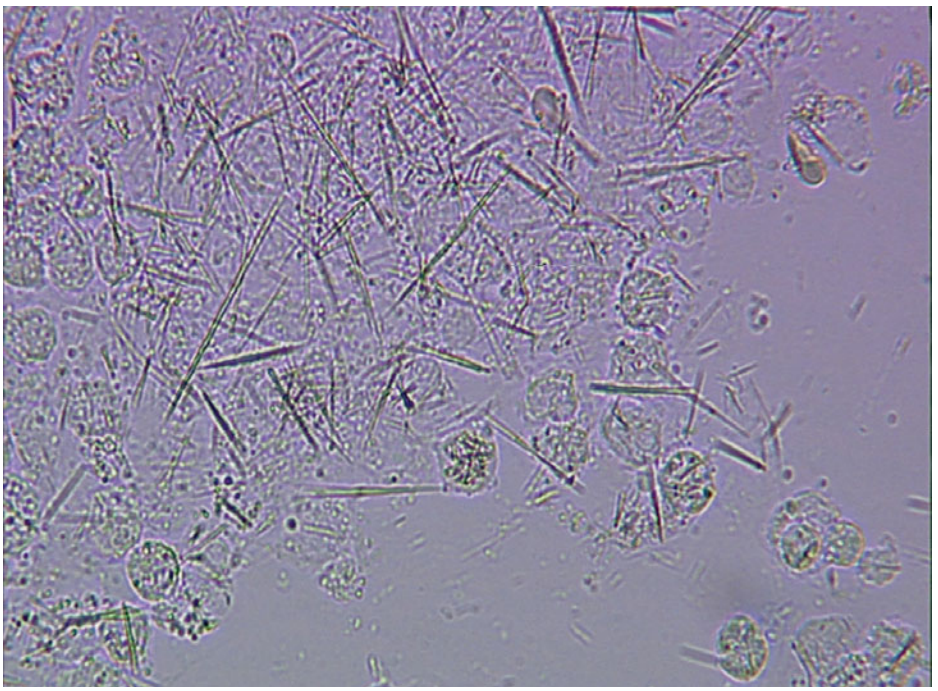

FIGURE 17.5. **Gout crystals.**

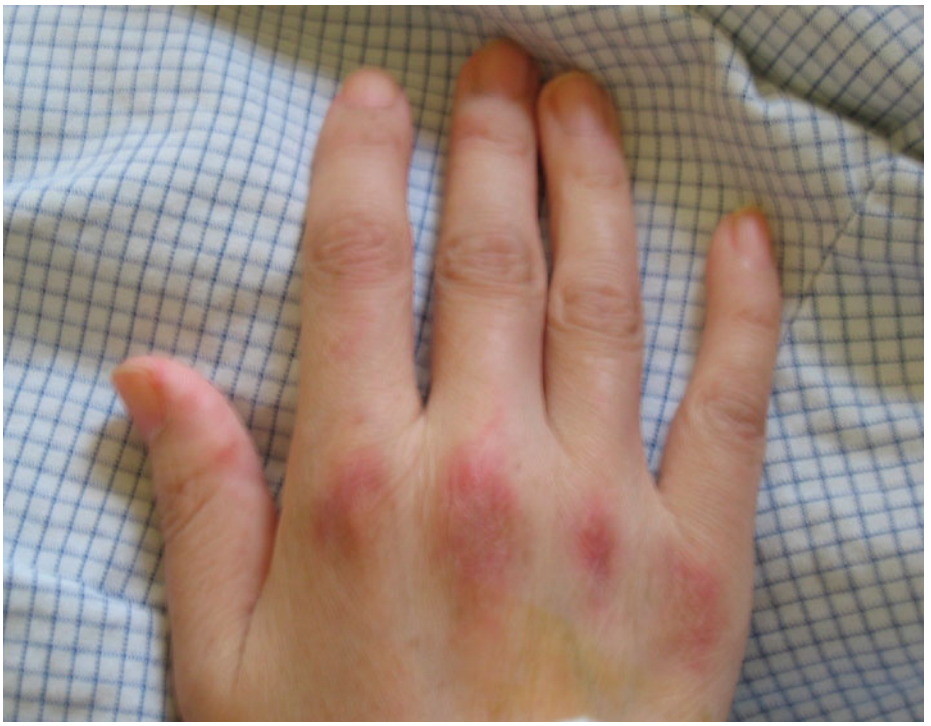

FIGURE 17.7. **Gottron's papules in patient with dermatomyositis.**