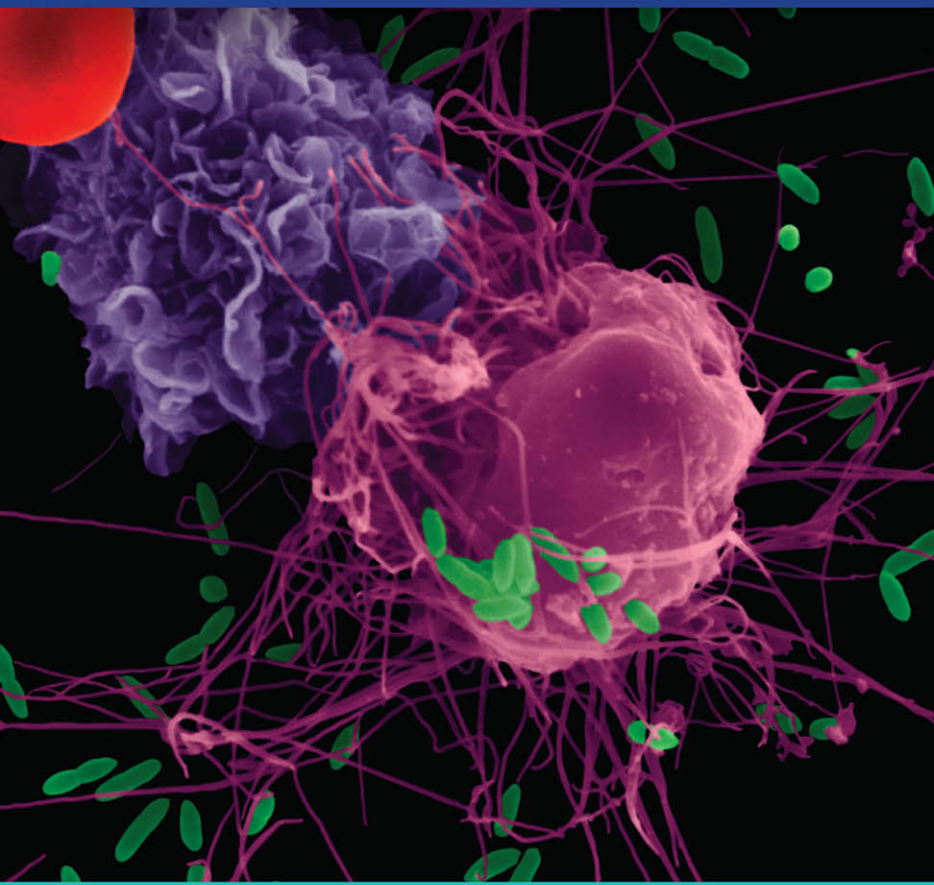
PHARMACOTHERAPY HANDBOOK

NINTH EDITION



Barbara G. Wells ▪ Joseph T. DiPiro
Terry L. Schwinghammer ▪ Cecily V. DiPiro

Mc Graw Hill Education

Pharmacotherapy Handbook

Ninth Edition

NOTICE

Medicine is an ever-changing science. As new research and clinical experience broaden our knowledge, changes in treatment and drug therapy are required. The authors of this work have checked with sources believed to be reliable in their efforts to provide information that is complete and generally in accord with the standards accepted at the time of publication. However, in view of the possibility of human error or changes in medical sciences, neither the authors nor the publisher nor any other party who has been involved in the preparation or publication of this work warrants that the information contained herein is in every respect accurate or complete, and they disclaim all responsibility for any errors or omissions or the results obtained from use of the information contained in this work. Readers are encouraged to confirm the information contained herein with other sources. For example and in particular, readers are advised to check the product information sheet included in the package of each drug they plan to administer to be certain that the information contained in this work is accurate and that changes have not been made in the recommended dose or in the contraindications for administration. This recommendation is of particular importance in connection with new or infrequently used drugs.

Pharmacotherapy Handbook

Ninth Edition

Barbara G. Wells, PharmD, FASHP, FCCP
Dean Emeritus and Professor Emeritus
Executive Director Emeritus, Research Institute of Pharmaceutical Sciences
School of Pharmacy, The University of Mississippi
Oxford, Mississippi

Joseph T. DiPiro, PharmD, FCCP
Professor and Dean
Archie O. McCalley Chair
School of Pharmacy
Virginia Commonwealth University
Richmond, Virginia

Terry L. Schwinghammer, PharmD, FCCP, FASHP, FAPhA, BCPS
Professor and Chair, Department of Clinical Pharmacy
School of Pharmacy, West Virginia University
Morgantown, West Virginia

Cecily V. DiPiro, PharmD
Consultant Pharmacist
Richmond, Virginia



New York Chicago San Francisco Athens Lisbon London Madrid
Mexico City Milan New Delhi Singapore Sydney Toronto

Copyright © 2015 by McGraw-Hill Education. All rights reserved. Except as permitted under the United States Copyright Act of 1976, no part of this publication may be reproduced or distributed in any form or by any means, or stored in a database or retrieval system, without the prior written permission of the publisher.

ISBN: 978-0-07-182129-2

MHID: 0-07-182129-5

The material in this eBook also appears in the print version of this title: ISBN: 978-0-07-182128-5, MHID: 0-07-182128-7.

eBook conversion by codeMantra
Version 1.0

All trademarks are trademarks of their respective owners. Rather than put a trademark symbol after every occurrence of a trademarked name, we use names in an editorial fashion only, and to the benefit of the trademark owner, with no intention of infringement of the trademark. Where such designations appear in this book, they have been printed with initial caps.

McGraw-Hill Education eBooks are available at special quantity discounts to use as premiums and sales promotions or for use in corporate training programs. To contact a representative, please visit the Contact Us page at www.mhprofessional.com.

Previous edition copyright © 2012, 2006, 2003, 2000, by The McGraw-Hill Companies, Inc.; copyright © 1998 by Appleton & Lange.

TERMS OF USE

This is a copyrighted work and McGraw-Hill Education and its licensors reserve all rights in and to the work. Use of this work is subject to these terms. Except as permitted under the Copyright Act of 1976 and the right to store and retrieve one copy of the work, you may not decompile, disassemble, reverse engineer, reproduce, modify, create derivative works based upon, transmit, distribute, disseminate, sell, publish or sublicense the work or any part of it without McGraw-Hill Education's prior consent. You may use the work for your own noncommercial and personal use; any other use of the work is strictly prohibited. Your right to use the work may be terminated if you fail to comply with these terms.

THE WORK IS PROVIDED "AS IS." McGRAW-HILL EDUCATION AND ITS LICENSORS MAKE NO GUARANTEES OR WARRANTIES AS TO THE ACCURACY, ADEQUACY OR COMPLETENESS OF OR RESULTS TO BE OBTAINED FROM USING THE WORK, INCLUDING ANY INFORMATION THAT CAN BE ACCESSED THROUGH THE WORK VIA HYPERLINK OR OTHERWISE, AND EXPRESSLY DISCLAIM ANY WARRANTY, EXPRESS OR IMPLIED, INCLUDING BUT NOT LIMITED TO IMPLIED WARRANTIES OF MERCHANTABILITY OR FITNESS FOR A PARTICULAR PURPOSE. McGraw-Hill Education and its licensors do not warrant or guarantee that the functions contained in the work will meet your requirements or that its operation will be uninterrupted or error free. Neither McGraw-Hill Education nor its licensors shall be liable to you or anyone else for any inaccuracy, error or omission, regardless of cause, in the work or for any damages resulting therefrom. McGraw-Hill Education has no responsibility for the content of any information accessed through the work. Under no circumstances shall McGraw-Hill Education and/or its licensors be liable for any indirect, incidental, special, punitive, consequential or similar damages that result from the use of or inability to use the work, even if any of them has been advised of the possibility of such damages. This limitation of liability shall apply to any claim or cause whatsoever whether such claim or cause arises in contract, tort or otherwise.

Contents

Preface ix
Acknowledgments x

SECTION 1: BONE AND JOINT DISORDERS

Edited by Terry L. Schwinghammer

1. Gout and Hyperuricemia 1
2. Osteoarthritis 9
3. Osteoporosis 16
4. Rheumatoid Arthritis 26

SECTION 2: CARDIOVASCULAR DISORDERS

Edited by Terry L. Schwinghammer

5. Acute Coronary Syndromes 37
6. Arrhythmias 48
7. Cardiac Arrest 59
8. Dyslipidemia 65
9. Heart Failure 75
10. Hypertension 87
11. Ischemic Heart Disease 102
12. Shock 111
13. Stroke 120
14. Venous Thromboembolism 125

SECTION 3: DERMATOLOGIC DISORDERS

Edited by Terry L. Schwinghammer

15. Acne Vulgaris 135
16. Dermatologic Drug Reactions and Common Skin Conditions 141
17. Psoriasis 147

SECTION 4: ENDOCRINOLOGIC DISORDERS

Edited by Terry L. Schwinghammer

18. Adrenal Gland Disorders 155
19. Diabetes Mellitus 161
20. Thyroid Disorders 176

SECTION 5: GASTROINTESTINAL DISORDERS

Edited by Joseph T. DiPiro and Terry L. Schwinghammer

21. Cirrhosis and Portal Hypertension 185
22. Constipation 194
23. Diarrhea 200
24. Gastroesophageal Reflux Disease 206
25. Hepatitis, Viral 213

26. Inflammatory Bowel Disease 221
27. Nausea and Vomiting 231
28. Pancreatitis 244
29. Peptic Ulcer Disease 251

SECTION 6: GYNECOLOGIC AND OBSTETRIC DISORDERS

Edited by Barbara G. Wells

30. Contraception 257
31. Menopausal, Perimenopausal, and Postmenopausal Hormone Therapy 276
32. Pregnancy and Lactation 291

SECTION 7: HEMATOLOGIC DISORDERS

Edited by Cecily V. DiPiro

33. Anemias 301
34. Sickle Cell Disease 308

SECTION 8: INFECTIOUS DISEASES

Edited by Joseph T. DiPiro

35. Antimicrobial Regimen Selection 313
36. Central Nervous System Infections 323
37. Endocarditis 333
38. Fungal Infections, Invasive 347
39. Gastrointestinal Infections 361
40. Human Immunodeficiency Virus Infection 368
41. Influenza 387
42. Intraabdominal Infections 394
43. Respiratory Tract Infections, Lower 405
44. Respiratory Tract Infections, Upper 418
45. Sepsis and Septic Shock 427
46. Sexually Transmitted Diseases 433
47. Skin and Soft-Tissue Infections 448
48. Surgical Prophylaxis 466
49. Tuberculosis 476
50. Urinary Tract Infections 490
51. Vaccines, Toxoids, and Other Immunobiologics 500

SECTION 9: NEUROLOGIC DISORDERS

Edited by Barbara G. Wells

52. Alzheimer's Disease 511
53. Epilepsy 518
54. Headache: Migraine and Tension-Type 543
55. Pain Management 557
56. Parkinson's Disease 578
57. Status Epilepticus 587

SECTION 10: NUTRITION SUPPORT

Edited by Cecily V. DiPiro

58. Obesity 599
59. Nutrition Evaluation and Support 605

SECTION 11: ONCOLOGIC DISORDERS

Edited by Cecily V. DiPiro

60. Breast Cancer 619
61. Colorectal Cancer 631
62. Lung Cancer 642
63. Lymphomas 647
64. Prostate Cancer 654

SECTION 12: OPHTHALMIC DISORDERS

Edited by Cecily V. DiPiro

65. Glaucoma 665

SECTION 13: PSYCHIATRIC DISORDERS

Edited by Barbara G. Wells

66. Anxiety Disorders 673
67. Bipolar Disorder 694
68. Major Depressive Disorder 712
69. Schizophrenia 731
70. Sleep-Wake Disorders 747
71. Substance-Related Disorders 755

SECTION 14: RENAL DISORDERS

Edited by Cecily V. DiPiro

72. Acid–Base Disorders 771
73. Acute Kidney Injury 779
74. Chronic Kidney Disease 787
75. Electrolyte Homeostasis 798

SECTION 15: RESPIRATORY DISORDERS

Edited by Terry L. Schwinghammer

76. Allergic Rhinitis 813
77. Asthma 821
78. Chronic Obstructive Pulmonary Disease 835

SECTION 16: UROLOGIC DISORDERS

Edited by Cecily V. DiPiro

79. Benign Prostatic Hyperplasia 845
80. Erectile Dysfunction 850
81. Urinary Incontinence 865

APPENDICES

Edited by Barbara G. Wells

Appendix 1. Allergic and Pseudoallergic Drug Reactions 873
Appendix 2. Geriatrics 877
Appendix 3. Drug-Induced Hematologic Disorders 882
Appendix 4. Drug-Induced Liver Disease 887
Appendix 5. Drug-Induced Pulmonary Disease 889
Appendix 6. Drug-Induced Kidney Disease 898

Index 903

Preface

The pocket companion to *Pharmacotherapy: A Pathophysiologic Approach*, 9th edition, is designed to provide practitioners and students with critical information that can be easily used to guide drug therapy decision making in the clinical setting. To ensure brevity and portability, the bulleted format provides the user with essential textual information, key tables and figures, and treatment algorithms. In order to reduce the number of pages and thus allow it to fit more easily in a pocket, the publisher undertook a slight redesign to save space, and the authors made every effort to write as clearly and succinctly as possible.

Corresponding to the major sections in the main text, disorders are alphabetized within the following sections: Bone and Joint Disorders, Cardiovascular Disorders, Dermatologic Disorders, Endocrinologic Disorders, Gastrointestinal Disorders, Gynecologic and Obstetric Disorders, Hematologic Disorders, Infectious Diseases, Neurologic Disorders, Nutritional Disorders, Oncologic Disorders, Ophthalmic Disorders, Psychiatric Disorders, Renal Disorders, Respiratory Disorders, and Urologic Disorders. Drug-induced conditions associated with allergic and pseudoallergic reactions, hematologic disorders, liver diseases, pulmonary disorders, and kidney disease appear in five tabular appendices. Information on the management of pharmacotherapy in the elderly is also included as an appendix.

Each chapter is organized in a consistent format:

- Disease state definition
- Pathophysiology
- Clinical presentation
- Diagnosis
- Treatment
- Evaluation of therapeutic outcomes

The treatment section may include goals of treatment, general approach to treatment, nonpharmacologic therapy, drug selection guidelines, dosing recommendations, adverse effects, pharmacokinetic considerations, and important drug-drug interactions. When more in-depth information is required, the reader is encouraged to refer to the primary text, *Pharmacotherapy: A Pathophysiologic Approach*, 9th edition.

It is our sincere hope that students and practitioners find this book helpful as they continuously strive to deliver highest-quality patient-centered care. We invite your comments on how we may improve subsequent editions of this work.

Barbara G. Wells
Joseph T. DiPiro
Terry L. Schwinghammer
Cecily V. DiPiro

Please provide your comments about this book—Wells et al, *Pharmacotherapy Handbook*, 9th edition—to its authors and publisher by writing to pharmacotherapy@mcgraw-hill.com. Please indicate the author and title of this handbook in the subject line of your e-mail.

Acknowledgments

The editors wish to express their sincere appreciation to the authors whose chapters in the 9th edition of *Pharmacotherapy: A Pathophysiologic Approach* served as the basis for this book. The dedication and professionalism of these outstanding practitioners, teachers, and clinical scientists are evident on every page of this work. The authors of the chapters from the 9th edition are acknowledged at the end of each respective handbook chapter.

Edited by Terry L. Schwinghammer

CHAPTER 1

Gout and Hyperuricemia

- *Gout* involves hyperuricemia, recurrent attacks of acute arthritis with monosodium urate (MSU) crystals in synovial fluid leukocytes, deposits of MSU crystals in tissues in and around joints (tophi), interstitial renal disease, and uric acid nephrolithiasis.

PATHOPHYSIOLOGY

- Uric acid is the end product of purine degradation. An increased urate pool in individuals with gout may result from overproduction or underexcretion.
- Purines originate from dietary purine, conversion of tissue nucleic acid to purine nucleotides, and de novo synthesis of purine bases.
- Overproduction of uric acid may result from abnormalities in enzyme systems that regulate purine metabolism (eg, increased activity of phosphoribosyl pyrophosphate [PRPP] synthetase or deficiency of hypoxanthine-guanine phosphoribosyl transferase [HGPRT]).
- Uric acid may be overproduced because of increased breakdown of tissue nucleic acids, as with myeloproliferative and lymphoproliferative disorders. Cytotoxic drugs can result in overproduction of uric acid due to lysis and the breakdown of cellular matter.
- Dietary purines are insignificant in generation of hyperuricemia without some derangement in purine metabolism or elimination.
- Two thirds of uric acid produced daily is excreted in urine. The remainder is eliminated through gastrointestinal (GI) tract after degradation by colonic bacteria. Decline in urinary excretion to a level below rate of production leads to hyperuricemia and increased pool of sodium urate.
- Drugs that decrease renal uric acid clearance include diuretics, nicotinic acid, salicylates (<2 g/day), ethanol, pyrazinamide, levodopa, ethambutol, cyclosporine, and cytotoxic drugs.
- Deposition of urate crystals in synovial fluid results in inflammation, vasodilation, increased vascular permeability, complement activation, and chemotactic activity for polymorphonuclear leukocytes. Phagocytosis of urate crystals by leukocytes results in rapid lysis of cells and discharge of proteolytic enzymes into cytoplasm. The ensuing inflammatory reaction causes intense joint pain, erythema, warmth, and swelling.
- Uric acid nephrolithiasis occurs in 10% to 25% of patients with gout. Predisposing factors include excessive urinary excretion of uric acid, acidic urine, and highly concentrated urine.
- In acute uric acid nephropathy, acute renal failure occurs because of blockage of urine flow from massive precipitation of uric acid crystals in collecting ducts and ureters. Chronic urate nephropathy is caused by long-term deposition of urate crystals in the renal parenchyma.
- Tophi (urate deposits) are uncommon and are a late complication of hyperuricemia. Most common sites are the base of the fingers, olecranon bursae, ulnar aspect of forearm, Achilles tendon, knees, wrists, and hands.

CLINICAL PRESENTATION

- Acute gout attacks are characterized by rapid onset of excruciating pain, swelling, and inflammation. The attack is typically monoarticular, most often affecting the first metatarsophalangeal joint (podagra), and then, in order of frequency, the insteps, ankles, heels, knees, wrists, fingers, and elbows. Attacks commonly begin at night, with the patient awakening with excruciating pain. Affected joints are erythematous, warm, and swollen. Fever and leukocytosis are common. Untreated attacks last from 3 to 14 days before spontaneous recovery.
- Acute attacks may occur without provocation or be precipitated by stress, trauma, alcohol ingestion, infection, surgery, rapid lowering of serum uric acid by uric acid–lowering agents, and ingestion of drugs known to elevate serum uric acid concentrations.

DIAGNOSIS

- Definitive diagnosis requires aspiration of synovial fluid from the affected joint and identification of intracellular crystals of MSU monohydrate in synovial fluid leukocytes.
- When joint aspiration is not feasible, a presumptive diagnosis is based on presence of characteristic signs and symptoms, as well as the response to treatment.

TREATMENT

- Goals of Treatment: Terminate the acute attack, prevent recurrent attacks, and prevent complications associated with chronic deposition of urate crystals in tissues.

ACUTE GOUTY ARTHRITIS (FIG. 1–1)

Nonpharmacologic Therapy

- Local ice application is the most effective adjunctive treatment. Dietary supplements (eg, flaxseed, celery root) are not recommended.

Pharmacologic Therapy

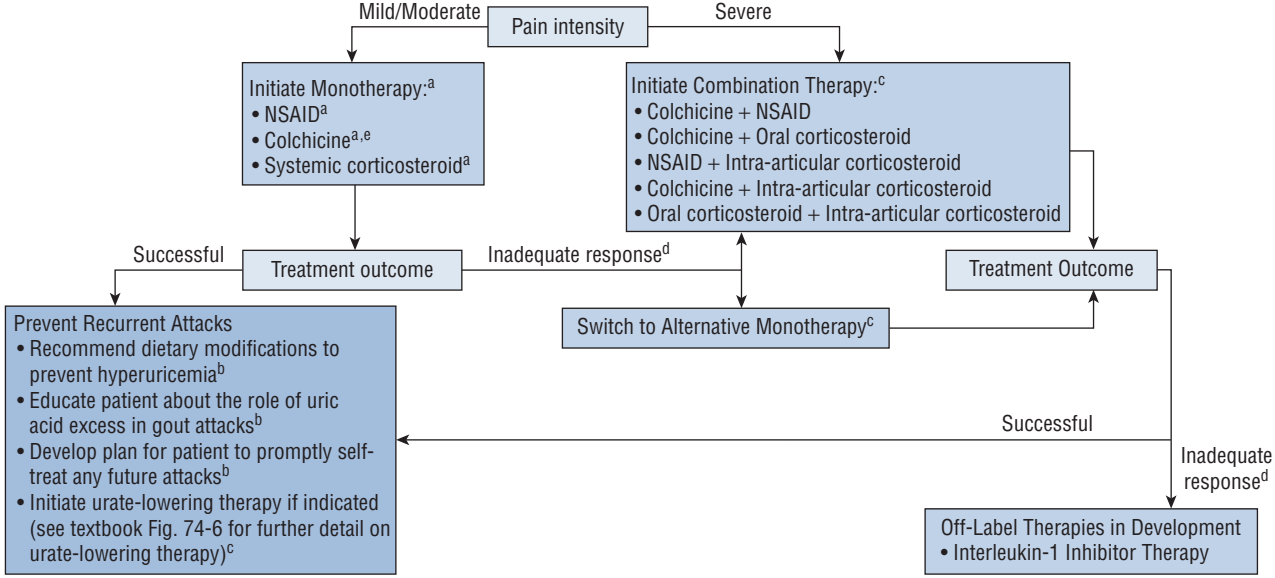
- Most patients may be treated successfully with nonsteroidal anti-inflammatory drugs (NSAIDs), corticosteroids, or colchicine.

NSAIDS

- NSAIDs have excellent efficacy and minimal toxicity with short-term use. Indomethacin, naproxen, and sulindac have Food and Drug Administration (FDA) approval for gout, but others are likely to be effective (**Table 1–1**).
- Start therapy within 24 hours of attack onset and continue until complete resolution (usually 5–8 days). Tapering may be considered after resolution, especially if comorbidities such as hepatic or renal insufficiency make prolonged therapy undesirable.
- The most common adverse effects involve the GI tract (gastritis, bleeding, perforation), kidneys (renal papillary necrosis, reduced creatinine clearance [CL_{cr}]), cardiovascular system (increased blood pressure, sodium and fluid retention), and central nervous system (CNS) (impaired cognitive function, headache, dizziness).
- Selective cyclooxygenase-2 (COX-2) inhibitors (eg, celecoxib) may be an option for patients unable to take nonselective NSAIDs, but the risk-to-benefit ratio in acute gout is unclear, and cardiovascular risk must be considered.

CORTICOSTEROIDS

- Corticosteroid efficacy is equivalent to NSAIDs; they can be used systemically or by intra-articular (IA) injection. Systemic therapy is necessary if an attack is polyarticular.



[a] Evidence Grade Level A: Supported by multiple randomized clinical trials or meta-analyses
[b] Evidence Grade Level B: Derived from a single randomized trial, or nonrandomized studies
[c] Evidence Grade Level C: Consensus opinion of experts, case studies, or standard-of-care
[d] 'Inadequate Response' is defined as <20% improvement in pain score within 24 hours or <50% at ≥24 hours
[e] Colchicine is recommended only if started within 36 hours of symptom onset

FIGURE 1–1. Algorithm for management of an acute gout attack.

TABLE 1–1 Dosage Regimens of Oral Nonsteroidal Anti-inflammatory Drugs for Treatment of Acute Gout

Generic Name	Initial Dose	Usual Range
Etodolac	300 mg twice daily	300–500 mg twice daily
Fenoprofen	400 mg three times daily	400–600 mg three to four times daily
Ibuprofen	400 mg three times daily	400–800 mg three to four times daily
Indomethacin	50 mg three times daily	50 mg three times daily initially until pain is tolerable then rapidly reduce to complete cessation
Ketoprofen	75 mg three times daily or 50 mg four times daily	50–75 mg three to four times daily
Naproxen	750 mg followed by 250 mg every 8 h until the attack has subsided	—
Piroxicam	20 mg once daily or 10 mg twice daily	—
Sulindac	150 mg twice daily	150–200 mg twice daily for 7–10 days
Celecoxib	800 mg followed by 400 mg on day 1, then 400 mg twice daily for 1 week	—

- **Prednisone** or **prednisolone** oral dosing strategies: (1) 0.5 mg/kg daily for 5 to 10 days followed by abrupt discontinuation; or (2) 0.5 mg/kg daily for 2 to 5 days followed by tapering for 7 to 10 days. Tapering is often used to reduce the hypothetical risk of a rebound attack upon steroid withdrawal.
- **Methylprednisolone dose pack** is a 6-day regimen starting with 24 mg on day 1 and decreasing by 4 mg each day.
- **Triamcinolone acetonide** 20–40 mg given by IA injection may be used if gout is limited to one or two joints. IA corticosteroids should generally be used with oral NSAID, colchicine, or corticosteroid therapy.
- **Methylprednisolone** (a long-acting corticosteroid) given by a single intramuscular (IM) injection followed by oral corticosteroid therapy is another reasonable approach. Alternatively, IM corticosteroid monotherapy may be considered in patients with multiple affected joints who cannot take oral therapy.
- Short-term corticosteroid use is generally well tolerated. Use with caution in patients with diabetes, GI problems, bleeding disorders, cardiovascular disease, and psychiatric disorders. Avoid long-term use because of risk for osteoporosis, hypothalamic–pituitary–adrenal axis suppression, cataracts, and muscle deconditioning.
- **Adrenocorticotropic hormone (ACTH)** gel 40 to 80 USP units may be given IM every 6 to 8 hours for 2 or 3 days and then discontinued. Limit use for patients with contraindications to first-line therapies (eg, heart failure, chronic renal failure, history of GI bleeding) or patients unable to take oral medications.

COLCHICINE

- **Colchicine** is highly effective in relieving acute gout attacks; when it is started within the first 24 hours of onset, about two thirds of patients respond within hours. Use only within 36 hours of attack onset because the likelihood of success decreases substantially if treatment is delayed.

- Colchicine causes dose-dependent GI adverse effects (nausea, vomiting, and diarrhea). Non-GI effects include neutropenia and axonal neuromyopathy, which may be worsened in patients taking other myopathic drugs (eg, statins) or in renal insufficiency. Do not use concurrently with P-glycoprotein or strong CYP450 3A4 inhibitors (eg, clarithromycin) because reduced biliary excretion may lead to increased plasma colchicine levels and toxicity. Use with caution in renal or hepatic insufficiency.
- **Colcrys** is an FDA-approved colchicine product available in 0.6 mg oral tablets. The recommended dose is 1.2 mg (two tablets) initially, followed by 0.6 mg (one tablet) 1 hour later. Although not an FDA-approved regimen, the American College of Rheumatology (ACR) gout treatment guidelines suggest that colchicine 0.6 mg once or twice daily can be started 12 hours after the initial 1.2 mg dose and continued until the attack resolves.

HYPERURICEMIA IN GOUT

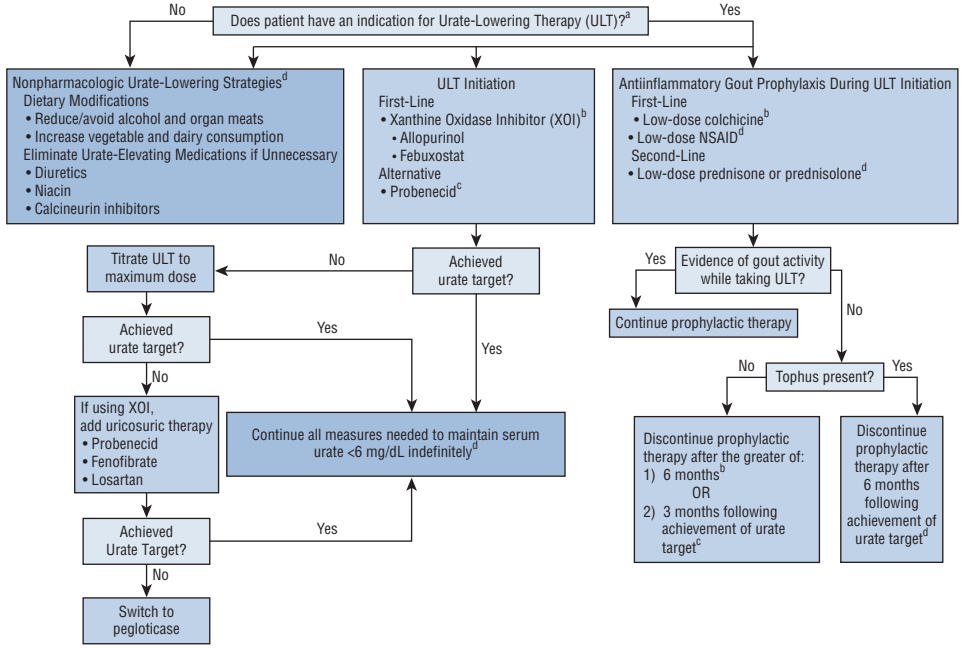
- Recurrent gout attacks can be prevented by maintaining low uric acid levels, but adherence with nonpharmacologic and pharmacologic therapies is poor.

Nonpharmacologic Therapy

- Patient education should address the recurrent nature of gout and the objective of each lifestyle/dietary modification and medication.
- Promote weight loss through caloric restriction and exercise in all patients to enhance renal urate excretion.
- Alcohol restriction is important because consumption correlates with gout attacks. ACR guidelines recommend limiting alcohol use in all gout patients and avoidance of any alcohol during periods of frequent gout attacks and in patients with advanced gout under poor control.
- Dietary recommendations include limiting consumption of high-fructose corn syrup and purine-rich foods (organ meats and some seafood) and encouraging consumption of vegetables and low-fat dairy products.
- Evaluate the medication list for potentially unnecessary drugs that may elevate uric acid levels. Gout is not necessarily a contraindication to use of thiazide diuretics in hypertensive patients. Low-dose aspirin for cardiovascular prevention should be continued in patients with gout because aspirin has a negligible effect on elevating serum uric acid.

Pharmacologic Therapy (Fig. 1–2)

- After the first attack of acute gout, prophylactic pharmacotherapy is recommended if patients have two or more attacks per year, even if serum uric acid is normal or only minimally elevated. Other indications include presence of tophi, chronic kidney disease, or history of urolithiasis.
- Urate-lowering therapy can be started during an acute attack if anti-inflammatory prophylaxis has been initiated.
- The goal of urate-lowering therapy is to achieve and maintain serum uric acid less than 6 mg/dL (357 μmol/L), and preferably less than 5 mg/dL (297 μmol/L) if signs and symptoms of gout persist.
- Urate lowering should be prescribed for long-term use. Serum urate can be reduced by decreasing synthesis of uric acid (xanthine oxidase inhibitors) or by increasing renal excretion of uric acid (uricosurics).
- Apply a step-wise approach to hyperuricemia (see Fig. 1–2). Xanthine oxidase inhibitors are recommended first-line therapy; the uricosuric agent probenecid is recommended as alternative therapy in patients with a contraindication or intolerance to xanthine oxidase inhibitors. In refractory cases, combination therapy with a xanthine oxidase inhibitor plus a drug with uricosuric properties (probenecid, losartan, or fenofibrate) is suggested. Pegloticase may be used in severe cases in which the patient cannot tolerate or is not responding to other therapies.



[a]Indications for ULT include: (1) presence of tophus, (2) ≥2 gout attacks per year, (3) CKD stage 2 or worse, or (4) past urolithiasis
[b]Evidence Grade Level A: Supported by multiple randomized clinical trials or meta-analyses
[c]Evidence Grade Level B: Derived from a single randomized trial, or nonrandomized studies
[d]Evidence Grade Level C: Consensus opinion of experts, case studies, or standard-of-care

FIGURE 1–2. Algorithm for management of hyperuricemia in gout.

XANTHINE OXIDASE INHIBITORS

- Xanthine oxidase inhibitors reduce uric acid by impairing conversion of hypoxanthine to xanthine and xanthine to uric acid. Because they are effective in both overproducers and underexcretors of uric acid, they are the most widely prescribed agents for long-term prevention of recurrent gout attacks.
- **Allopurinol** lowers uric acid levels in a dose-dependent manner. ACR guidelines recommend a starting dose no greater than 100 mg daily and then gradually titrating every 2 to 5 weeks up to a maximum dose of 800 mg/day until the serum urate target is achieved. Patients with chronic kidney disease (stage 4 or worse) should start at a dose no greater than 50 mg per day. Conservative dosing is intended to avoid allopurinol hypersensitivity syndrome and prevent acute gout attacks common during initiation of urate-lowering therapy.
- Mild adverse effects of allopurinol include skin rash, leukopenia, GI problems, headache, and urticaria. More severe adverse reactions include severe rash (toxic epidermal necrolysis, erythema multiforme, or exfoliative dermatitis) and allopurinol hypersensitivity syndrome characterized by fever, eosinophilia, dermatitis, vasculitis, and renal and hepatic dysfunction that occurs rarely but is associated with a 20% mortality rate.
- **Febuxostat** (Uloric) also lowers serum uric acid in a dose-dependent manner. The recommended starting dose is 40 mg once daily. Increase the dose to 80 mg once daily for patients who do not achieve target serum uric acid concentrations after 2 weeks of therapy. Febuxostat is well tolerated, with adverse events of nausea, arthralgias, and minor hepatic transaminase elevations. Febuxostat does not require dose adjustment in mild to moderate hepatic or renal dysfunction. Due to rapid mobilization of urate deposits during initiation, give concomitant therapy with colchicine or an NSAID for at least the first 8 weeks of therapy to prevent acute gout flares.

URICOSURICS

- **Probenecid** increases renal clearance of uric acid by inhibiting the postsecretory renal proximal tubular reabsorption of uric acid. Patients with a history of urolithiasis should not receive uricosurics. Start therapy with uricosurics at a low dose to avoid marked uricosuria and possible stone formation. Maintaining adequate urine flow and alkalinization of the urine during the first several days of therapy may also decrease likelihood of uric acid stone formation.
- Initial probenecid dose is 250 mg twice daily for 1 to 2 weeks, then 500 mg twice daily for 2 weeks. Increase the daily dose thereafter by 500-mg increments every 1 to 2 weeks until satisfactory control is achieved or a maximum dose of 2 g/day is reached.
- Major side effects of probenecid include GI irritation, rash and hypersensitivity, precipitation of acute gouty arthritis, and stone formation. Contraindications include impaired renal function (CL_{cr} <50 mL/min or <0.84 mL/s) and overproduction of uric acid.

PEGLOTICASE

- **Pegloticase** (Krystexxa) is a pegylated recombinant uricase that reduces serum uric acid by converting uric acid to allantoin, which is water soluble. Pegloticase is indicated for antihyperuricemic therapy in adults refractory to conventional therapy.
- The dose is 8 mg by IV infusion over at least 2 hours every 2 weeks. Because of potential infusion-related allergic reactions, patients must be pretreated with antihistamines and corticosteroids. Pegloticase is substantially more expensive than first-line urate-lowering therapies.
- The ideal duration of pegloticase therapy is unknown. Development of pegloticase antibodies resulting in loss of efficacy may limit the duration of effective therapy.
- Because of its limitations, reserve pegloticase for patients with refractory gout who are unable to take or have failed all other urate-lowering therapies.

ANTIIFLAMMATORY PROPHYLAXIS DURING INITIATION OF URATE-LOWERING THERAPY

- Initiation of urate-lowering therapy can precipitate an acute gout attack due to remodeling of urate crystal deposits in joints after rapid lowering of urate concentrations. Prophylactic antiinflammatory therapy should be used to prevent such gout attacks.
- The ACR guidelines recommend low-dose oral colchicine (0.6 mg twice daily) and low-dose NSAIDs (eg, naproxen 250 mg twice daily) as first-line prophylactic therapies, with stronger evidence supporting use of colchicine. For patients on long-term NSAID prophylaxis, a proton pump inhibitor or other acid-suppressing therapy is indicated to protect from NSAID-induced gastric problems.
- Low-dose corticosteroid therapy (eg, prednisone ≤10 mg/day) is an alternative for patients with intolerance, contraindication, or lack of response to first-line therapy. The potential severe adverse effects of prolonged corticosteroid therapy preclude their use as first-line therapy.
- Continue prophylaxis for at least 6 months or 3 months after achieving target serum uric acid, whichever is longer. For patients with one or more tophi, continue prophylactic therapy for 6 months after achieving the serum urate target (see Fig. 1–2).

EVALUATION OF THERAPEUTIC OUTCOMES

- Check the serum uric acid level in patients suspected of having an acute gout attack, particularly if it is not the first attack, and a decision is to be made about starting prophylaxis. However, acute gout can occur with normal serum uric acid concentrations.
- Monitor patients with acute gout for symptomatic relief of joint pain, as well as potential adverse effects and drug interactions related to drug therapy. Acute pain of an initial gout attack should begin to ease within about 8 hours of treatment initiation. Complete resolution of pain, erythema, and inflammation usually occurs within 48 to 72 hours.
- For patients receiving urate-lowering therapy, obtain baseline assessment of renal function, hepatic enzymes, complete blood count, and electrolytes. Recheck the tests every 6 to 12 months in patients receiving long-term treatment.
- During titration of urate-lowering therapy, monitor serum uric acid every 2 to 5 weeks; after the urate target is achieved, monitor uric acid every 6 months.
- Because of the high rates of comorbidities associated with gout (diabetes, chronic kidney disease, hypertension, obesity, myocardial infarction, heart failure, stroke), elevated serum uric acid levels or gout should prompt evaluation for cardiovascular disease and the need for appropriate risk reduction measures. Clinicians should also look for possible correctable causes of hyperuricemia (eg, medications, obesity, malignancy, alcohol abuse).

See Chapter 74, Gout and Hyperuricemia, authored by Michelle A. Fravel, Michael E. Ernst, and Elizabeth C. Clark, for a more detailed discussion of this topic.

CHAPTER 2

Osteoarthritis

- *Osteoarthritis* (OA) is a common, progressive disorder affecting primarily weight-bearing diarthrodial joints, characterized by progressive deterioration and loss of articular cartilage, osteophyte formation, pain, limitation of motion, deformity, and disability.

PATHOPHYSIOLOGY

- *Primary* (*idiopathic*) *OA,* the most common type, has no known cause.
- *Secondary OA* is associated with a known cause, such as trauma, metabolic or endocrine disorders, and congenital factors.
- OA usually begins with damage to articular cartilage through injury, excessive joint loading from obesity or other reasons, or joint instability or injury. Damage to cartilage increases activity of chondrocytes in attempt to repair damage, leading to increased synthesis of matrix constituents with cartilage swelling. Normal balance between cartilage breakdown and resynthesis is lost, with increasing destruction and cartilage loss.
- Subchondral bone adjacent to articular cartilage undergoes pathologic changes and releases vasoactive peptides and matrix metalloproteinases (MMPs). Neovascularization and increased permeability of adjacent cartilage occur, which contribute to cartilage loss and chondrocyte apoptosis.
- Cartilage loss causes joint space narrowing and painful, deformed joints. Remaining cartilage softens and develops fibrillations, followed by further cartilage loss and exposure of underlying bone. New bone formations (osteophytes) at joint margins distant from cartilage destruction are thought to help stabilize affected joints.
- Inflammatory changes can occur in the joint capsule and synovium. Crystals or cartilage shards in synovial fluid may contribute to inflammation. Interleukin-1, prostaglandin E_2, tumor necrosis factor-α (TNF-α), and nitric oxide in synovial fluid may also play a role. Inflammatory changes result in synovial effusions and thickening.
- Pain may result from distention of the synovial capsule by increased joint fluid; microfracture; periosteal irritation; or damage to ligaments, synovium, or the meniscus.

CLINICAL PRESENTATION

- Risk factors include increasing age, obesity, repetitive use through work or leisure activities, joint trauma, and genetic predisposition.
- Predominant symptom is deep, aching pain in affected joints. Pain accompanies joint activity and decreases with rest.
- Joints most commonly affected are the distal interphalangeal (DIP) and proximal interphalangeal (PIP) joints of the hand, first carpometacarpal joint, knees, hips, cervical and lumbar spine, and first metatarsophalangeal (MTP) joint of the toe.
- Limitation of motion, stiffness, crepitus, and deformities may occur. Patients with lower extremity involvement may report weakness or instability.
- Upon arising, joint stiffness typically lasts less than 30 minutes and resolves with motion.
- Presence of warm, red, and tender joints suggests inflammatory synovitis.
- Physical examination of affected joints reveals tenderness, crepitus, and possibly enlargement. Heberden and Bouchard nodes are bony enlargements (osteophytes) of the DIP and PIP joints, respectively.

DIAGNOSIS

- Diagnosis is made through patient history, physician examination, radiologic findings, and laboratory testing.
- American College of Rheumatology (ACR) criteria for classification of OA of the hips, knees, and hands include presence of pain, bony changes on examination,

normal erythrocyte sedimentation rate (ESR), and radiographs showing osteophytes or joint space narrowing.
- For hip OA, patient must have hip pain and two of the following: (1) ESR less than 20 mm/h, (2) radiographic femoral or acetabular osteophytes, and/or (3) radiographic joint space narrowing.
- For knee OA, patient must have knee pain and radiographic osteophytes in addition to one or more of the following: (1) age more than 50 years, (2) morning stiffness lasting 30 minutes or less, (3) crepitus on motion, (4) bony enlargement, (6) bony tenderness, and/or (7) palpable joint warmth.
- ESR may be slightly elevated if inflammation is present. Rheumatoid factor is negative. Analysis of synovial fluid reveals high viscosity and mild leukocytosis (<2000 white blood cells/mm^3 [$<2 \times 10^9$/L]) with predominantly mononuclear cells.

TREATMENT

- Goals of Treatment: (1) educate patient, family members, and caregivers; (2) relieve pain and stiffness; (3) maintain or improve joint mobility; (4) limit functional impairment; and (5) maintain or improve quality of life.

NONPHARMACOLOGIC THERAPY

- Educate patient about disease process and extent, prognosis, and treatment. Promote dietary counseling, exercise, and weight loss program for overweight patients.
- Physical therapy—with heat or cold treatments and an exercise program—helps maintain range of motion and reduce pain and need for analgesics.
- Assistive and orthotic devices (canes, walkers, braces, heel cups, insoles) can be used during exercise or daily activities.
- Surgical procedures (eg, osteotomy, arthroplasty, joint fusion) are indicated for functional disability and/or severe pain unresponsive to conservative therapy.

PHARMACOLOGIC THERAPY (TABLE 2–1)

General Approach

- Drug therapy is targeted at relief of pain. A conservative approach is warranted because OA often occurs in older individuals with other medical conditions.
- Apply an individualized approach (**Figs. 2–1** and **2–2**). Continue appropriate nondrug therapies when initiating drug therapy.

Knee and Hip OA

- **Acetaminophen** is a preferred first-line treatment; it may be less effective than oral nonsteroidal anti-inflammatory drugs (NSAIDs) but has less risk of serious gastrointestinal (GI) and cardiovascular events.
- If a patient fails acetaminophen, **nonselective NSAIDs or cyclooxygenase-2 (COX-2) selective inhibitors** (eg, **celecoxib**) are recommended. COX-2 inhibitors pose less risk for adverse GI events than nonselective NSAIDs, but this advantage may not be sustained beyond 6 months and is substantially reduced for patients taking aspirin. Proton pump inhibitors (PPIs) and misoprostol reduce adverse GI events in patients taking NSAIDs.
- For knee OA, **topical NSAIDs** are recommended if acetaminophen fails and are preferred over oral NSAIDs in patients older than 75 years. Topical NSAIDs provide similar pain relief with fewer adverse GI events than oral NSAIDs but may be associated with adverse events at the application site.
- **Intra-articular (IA) corticosteroid injections** are recommended for both hip and knee OA when analgesia with acetaminophen or NSAIDs is suboptimal. Injections can be given with concomitant oral analgesics for additional pain control. Do not administer injections more frequently than once every 3 months to minimize systemic adverse effects.

TABLE 2–1 Medications for the Treatment of Osteoarthritis

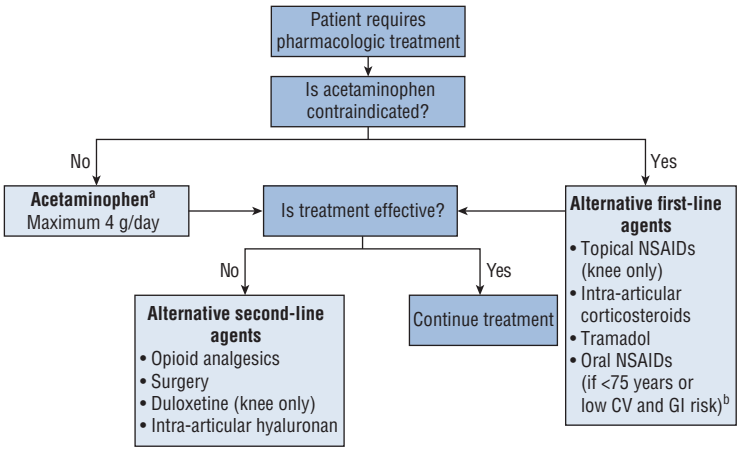
Drug	Starting Dose	Usual Range
Oral analgesics		
Acetaminophen	325–500 mg 3 times a day	325–650 mg every 4–6 h or 1 g 3–4 times/day
Tramadol	25 mg in the morning	Titrate dose in 25-mg increments to reach a maintenance dose of 50–100 mg 3 times a day.
Tramadol ER	100 mg daily	Titrate to 200–300 mg daily
Hydrocodone/acetaminophen	5 mg/325 mg 3 times daily	2.5–10 mg/325–650 mg 3–5 times daily
Oxycodone/acetaminophen	5 mg/325 mg 3 times daily	2.5–10 mg/325–650 mg 3–5 times daily
Topical analgesics		
Capsaicin 0.025% or 0.075%		Apply to affected joint 3–4 times per day.
Diclofenac 1% gel		Apply 2 or 4 g per site as prescribed, 4 times daily.
Diclofenac 1.3% patch		Apply one patch twice daily to the site to be treated, as directed.
Diclofenac 1.5% solution		Apply 40 drops to the affected knee, applying and rubbing in 10 drops at a time. Repeat for a total of 4 times daily.
Intra-articular corticosteroids		
Triamcinolone	5–15 mg per joint	10–40 mg per large joint (knee, hip, shoulder)
Methylprednisolone acetate	10–20 mg per joint	20–80 mg per large joint (knee, hip, shoulder)
NSAIDs		
Aspirin (plain, buffered, or enteric-coated)	325 mg 3 times a day	325–650 mg 4 times a day
Celecoxib	100 mg daily	100 mg twice daily or 200 mg daily
Diclofenac IR	50 mg twice a day	50–75 mg twice a day
Diclofenac XR	100 mg daily	100–200 mg daily
Diflunisal	250 mg twice a day	500–750 mg twice a day
Etodolac	300 mg twice a day	400 to 500 mg twice a day
Fenoprofen	400 mg 3 times a day	400–600 mg 3–4 times a day
Flurbiprofen	100 mg twice a day	200–300 mg/day in 2–4 divided doses
Ibuprofen	200 mg 3 times a day	1200–3200 mg/day in 3–4 divided doses
Indomethacin	25 mg twice a day	Titrate dose by 25–50 mg/day until pain controlled or maximum dose of 50 mg 3 times a day

(continued)

TABLE 2–1 Medications for the Treatment of Osteoarthritis *(Continued)*

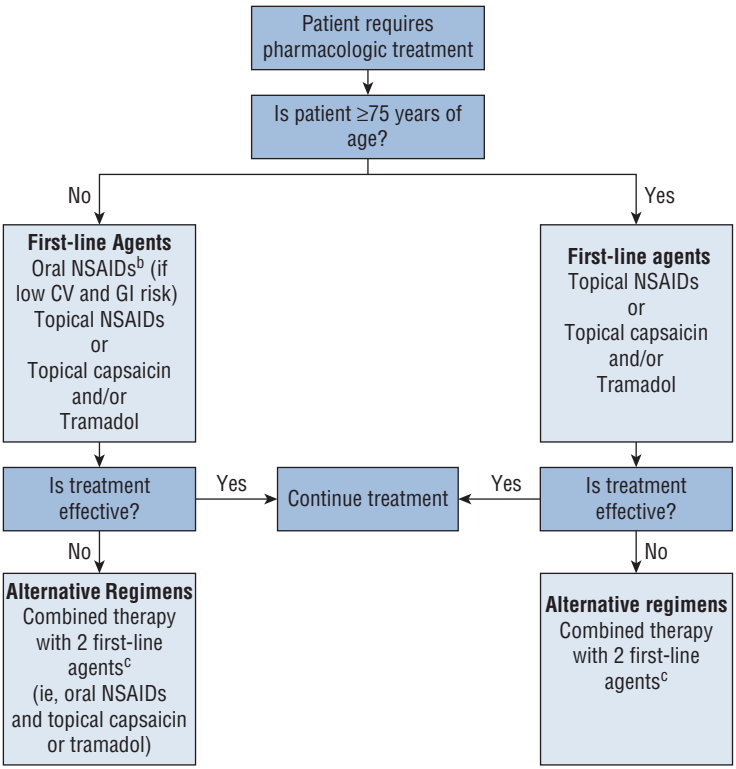
Drug	Starting Dose	Usual Range
Indomethacin SR	75 mg SR once daily	Can titrate to 75 mg SR twice daily if needed
Ketoprofen	50 mg 3 times a day	50–75 mg 3–4 times a day
Meclofenamate	50 mg 3 times a day	50–100 mg 3–4 times a day
Mefenamic acid	250 mg 3 times a day	250 mg 4 times a day
Meloxicam	7.5 mg daily	15 mg daily
Nabumetone	500 mg daily	500–1000 mg 1–2 times a day
Naproxen	250 mg twice a day	500 mg twice a day
Naproxen sodium	220 mg twice a day	220–550 mg twice a day
Naproxen sodium CR	750–1000 mg once daily	500–1500 mg once daily
Oxaprozin	600 mg daily	600–1200 mg daily
Piroxicam	10 mg daily	20 mg daily
Salsalate	500 mg twice a day	500–1000 mg 2–3 times a day

CR, controlled-release; ER, extended-release; IR, immediate-release; SR, sustained-release; XR, extended-release.



Note: Selection of a medication should consider patient-specific characteristics.
[a]The patient must be counseled regarding all acetaminophen-containing products.
[b]When used for chronic management of OA, consider addition of a proton pump inhibitor.

FIGURE 2–1. Treatment recommendations for hip and knee osteoarthritis (OA). (CV, cardiovascular; GI, gastrointestinal; NSAID, nonsteroidal anti-inflammatory drug.)



[a]Selection of a medication should consider patient-specific characteristics
[b]When used for chronic management of OA, consider addition of a proton pump inhibitor
[c]Should not combine topical NSAIDs and oral NSAIDs

FIGURE 2–2. Treatment recommendations for hand osteoarthritis (OA). (CV, cardiovascular; GI, gastrointestinal; NSAID, nonsteroidal anti-inflammatory drug.)

- **Tramadol** is recommended for hip and knee OA in patients who have failed scheduled full-dose acetaminophen and topical NSAIDs, who are not appropriate candidates for oral NSAIDs, and who are not able to receive IA corticosteroids. Tramadol can be added to partially effective acetaminophen or oral NSAID therapy.
- **Opioids** should be considered in patients not responding adequately to nonpharmacologic and first-line pharmacologic therapies. Patients who are at high surgical risk and cannot undergo joint arthroplasty are also candidates for opioid therapy. Adverse events limit routine use of opioids for treatment of OA pain.
- **Duloxetine** can be used as adjunctive treatment in patients with partial response to first-line analgesics (acetaminophen, oral NSAIDs). It may be a preferred second-line medication in patients with both neuropathic and musculoskeletal OA pain.
- **IA hyaluronic acid** is not routinely recommended for knee OA pain. Injections do not provide clinically meaningful improvement and may be associated with serious adverse events (eg, increased pain, joint swelling, and stiffness).
- **Glucosamine and/or chondroitin and topical rubefacients** (eg, **methyl salicylate, trolamine salicylate)** lack uniform efficacy for hip and knee pain and are not preferred treatment options.

Hand OA

- **Topical NSAIDs** are a first-line option for hand OA. Diclofenac has efficacy similar to oral ibuprofen and oral diclofenac with fewer adverse GI events, albeit with some local application site events.
- **Oral NSAIDs** are an alternative first-line treatment for patients who cannot tolerate the local skin reactions or who received inadequate relief from topical NSAIDs.
- **Capsaicin cream** is an alternative first-line treatment and demonstrates modest improvement in pain scores. It is a reasonable option for patients unable to take oral NSAIDs. Adverse effects are primarily skin irritation and burning.
- **Tramadol** is an alternative first-line treatment and is a reasonable choice for patients who do not respond to topical therapy and are not candidates for oral NSAIDs because of high GI, cardiovascular, or renal risks. Tramadol may also be used in combination with partially effective acetaminophen, topical therapy, or oral NSAIDs.

Drug Class Information

- Acetaminophen is usually well tolerated, but potentially fatal hepatotoxicity with overdose is well documented. Avoid in chronic alcohol users or patients with liver disease. Renal toxicity is possible with long-term use; use of nonprescription combination products containing acetaminophen and NSAIDs is discouraged because of increased risk of renal failure.
- NSAIDs cause minor GI complaints such as nausea, dyspepsia, anorexia, abdominal pain, flatulence, and diarrhea in 10% to 60% of patients. They may cause gastric and duodenal ulcers and bleeding through direct (topical) or indirect (systemic) mechanisms. Risk factors for NSAID-associated ulcers and ulcer complications (perforation, gastric outlet obstruction, and GI bleeding) include history of complicated ulcer, concomitant use of multiple NSAIDs (including aspirin) or anticoagulants, use of high-dose NSAIDs, and age more than 70 years. Options for reducing the GI risk of nonselective NSAIDs include using (1) the lowest dose possible and only when needed, (2) misoprostol four times daily with the NSAID, (3) a PPI or full-dose H_2-receptor antagonist daily with the NSAID. COX-2 selective inhibitors (eg, celecoxib) may reduce risk of GI events but increase risk of cardiovascular events. NSAIDs may also cause kidney diseases, hepatitis, hypersensitivity reactions, rash, and CNS complaints of drowsiness, dizziness, headaches, depression, confusion, and tinnitus. All nonselective NSAIDs inhibit COX-1–dependent thromboxane production in platelets, thereby increasing bleeding risk. Avoid NSAIDs in late pregnancy because of risk of premature closure of ductus arteriosus. The most potentially serious drug interactions include use of NSAIDs with lithium, warfarin, oral hypoglycemics, methotrexate, antihypertensives, angiotensin-converting enzyme inhibitors, β-blockers, and diuretics.
- Topical NSAIDs are associated with fewer GI and other adverse events than oral NSAIDs except for local application site reactions (eg, dry skin, pruritus, rash). Patients using topical products should avoid oral NSAIDs to minimize the potential for additive side effects.
- IA corticosteroids can provide excellent pain relief, particularly when joint effusion is present. After aseptic aspiration of the effusion and corticosteroid injection, initial pain relief may occur within 24 to 72 hours, with peak relief occurring after 7 to 10 days and lasting for 4 to 8 weeks. Local adverse effects can include infection, osteonecrosis, tendon rupture, and skin atrophy at the injection site. Systemic corticosteroid therapy is not recommended in OA, given lack of proven benefit and well-known adverse effects with long-term use.
- Capsaicin must be used regularly to be effective, and it may require up to 2 weeks to take effect. Adverse effects are primarily local with one third of patients experiencing burning, stinging, and/or erythema that usually subsides with repeated application. Warn patients not to get cream in their eyes or mouth and to wash hands after application. Application of the cream, gel, or lotion is recommended four times daily, but twice-daily application may enhance long-term adherence with adequate pain relief.

- Tramadol is associated with opioid-like adverse effects such as nausea, vomiting, dizziness, constipation, headache, and somnolence. However, tramadol is not associated with life-threatening GI bleeding, cardiovascular events, or renal failure. The most serious adverse event is seizures. Although not classified as a controlled substance, drug-seeking behaviors have been reported with tramadol use. There is increased risk of serotonin syndrome when tramadol is used with other serotonergic medications, including duloxetine.
- Start opioid analgesics in low doses, allowing a sufficient duration between dose increases to assess efficacy and safety. Sustained-release compounds usually offer better pain control throughout the day. Common adverse effects include nausea, somnolence, constipation, dry mouth, and dizziness. Opioid dependence, addiction, tolerance, hyperalgesia, and issues surrounding drug diversion may be associated with long-term treatment.
- Duloxetine may cause nausea, dry mouth, constipation, anorexia, fatigue, somnolence, and dizziness. Serious rare events include Stevens-Johnson syndrome and liver failure. Concomitant use with other medications that increase serotonin concentration (including tramadol) increases risk of serotonin syndrome.
- Hyaluronic acid (sodium hyaluronate) injections have limited benefit for patients with knee OA and have not been shown to benefit patients with hip OA. Injections are well tolerated, but acute joint swelling, effusion, and stiffness, as well as local skin reactions (eg, rash, ecchymoses, or pruritus) have been reported. Six intra-articular preparations and regimens are available for OA knee pain:

  ✓ **Sodium hyaluronate 20 mg/2 mL** (Hyalgan) once weekly for five injections
  ✓ **Sodium hyaluronate 20 mg/2 mL** (Euflexxa) once weekly for three injections
  ✓ **Sodium hyaluronate 25 mg/2.5 mL** (Supartz) once weekly for five injections
  ✓ **Hylan polymers 16 mg/2 mL** (Synvisc) once weekly for three injections
  ✓ **Hylan polymers 48 mg/6 mL** (Synvisc-One) single injection (with efficacy for up to 26 weeks)
  ✓ **Hyaluronan 30 mg/2 mL** (Orthovisc) once weekly for three injections

- Glucosamine adverse effects are mild and include flatulence, bloating, and abdominal cramps; do not use in patients with shellfish allergies. The most common adverse effect of chondroitin is nausea.

EVALUATION OF THERAPEUTIC OUTCOMES

- To monitor efficacy, assess baseline pain with a visual analog scale, and assess range of motion for affected joints with flexion, extension, abduction, or adduction.
- Depending on the joint(s) affected, measurement of grip strength and 50-ft walking time can help assess hand and hip/knee OA, respectively.
- Baseline radiographs can document extent of joint involvement and follow disease progression with therapy.
- Other measures include the clinician's global assessment based on patient's history of activities and limitations caused by OA, the Western Ontario and McMaster Universities Arthrosis Index, Stanford Health Assessment Questionnaire, and documentation of analgesic or NSAID use.
- Ask patients about adverse effects from medications. Monitor for signs of drug-related effects, such as skin rash, headaches, drowsiness, weight gain, or hypertension from NSAIDs.
- Obtain baseline serum creatinine, hematology profile, and serum transaminases with repeat levels at 6- to 12-month intervals to identify specific toxicities to the kidney, liver, GI tract, or bone marrow.

See Chapter 71, Osteoarthritis, authored by Lucinda M. Buys and Mary Elizabeth Elliott, for a more detailed discussion of this topic.

Osteoporosis

CHAPTER 3

- *Osteoporosis* is a bone disorder characterized by low bone density, impaired bone architecture, and compromised bone strength predisposing to fracture.

PATHOPHYSIOLOGY

- Bone loss occurs when resorption exceeds formation, usually from high bone turnover when number and/or depth of bone resorption sites greatly exceed ability of osteoblasts to form new bone.
- Bone mineral density (BMD) is reduced and bone structural integrity is impaired due to increased immature bone that is not yet adequately mineralized.
- Men and women begin to lose bone mass starting in the third or fourth decade because of reduced bone formation. Estrogen deficiency during menopause increases osteoclast activity, increasing bone resorption more than formation. Men do not undergo a period of accelerated bone resorption similar to menopause. Secondary causes and aging are the most common contributing factors to male osteoporosis.
- Age-related osteoporosis results from hormone, calcium, and vitamin D deficiencies leading to accelerated bone turnover and reduced osteoblast formation.
- Drug-induced osteoporosis may result from systemic corticosteroids, thyroid hormone replacement, antiepileptic drugs (eg, phenytoin and phenobarbital), depot medroxyprogesterone acetate, and other agents.

CLINICAL PRESENTATION

- Many patients are unaware that they have osteoporosis and only present after fracture. Fractures can occur after bending, lifting, or falling or independent of any activity.
- The most common fractures involve vertebrae, proximal femur, and distal radius (wrist or Colles fracture). Vertebral fractures may be asymptomatic or present with moderate to severe back pain that radiates down a leg. Pain usually subsides after 2 to 4 weeks, but residual low-back pain may persist. Multiple vertebral fractures decrease height and sometimes curve the spine (kyphosis or lordosis) with or without significant back pain.
- Patients with a nonvertebral fracture frequently present with severe pain, swelling, and reduced function and mobility at the fracture site.

DIAGNOSIS

- The World Health Organization (WHO) fracture prediction model for treatment risk stratification uses these risk factors to predict the percent probability of fracture in the next 10 years: age, race/ethnicity, sex, previous fragility fracture, parent history of hip fracture, body mass index, glucocorticoid use, current smoking, alcohol (three or more drinks per day), rheumatoid arthritis, and select secondary causes with femoral neck BMD data optional.
- Physical examination findings: bone pain, postural changes (ie, kyphosis), and loss of height (>1.5 in [3.8 cm]).
- Laboratory testing: complete blood count, creatinine, blood urea nitrogen, calcium, phosphorus, alkaline phosphatase, albumin, thyroid-stimulating hormone, free testosterone, 25-hydroxyvitamin D, and 24-hour urine concentrations of calcium and phosphorus.
- Measurement of central (hip and spine) BMD with dual-energy x-ray absorptiometry (DXA) is the diagnostic standard. Measurement at peripheral sites (forearm, heel, and phalanges) with ultrasound or DXA is used only for screening and for determining need for further testing.

- A T-score compares the patient's measured BMD to the mean BMD of a healthy, young (20- to 29-year-old), gender-matched, white reference population. The T-score is the number of standard deviations from the mean of the reference population.
- Diagnosis of osteoporosis is based on low-trauma fracture or central hip and/or spine DXA using WHO T-score thresholds. Normal bone mass is T-score above −1, low bone mass (osteopenia) is T-score between −1 and −2.4, and osteoporosis is T-score at or below −2.5.

TREATMENT

- Goals of Treatment: The primary goal of osteoporosis care is prevention. Optimizing peak bone mass when young reduces the future incidence of osteoporosis. After low bone mass or osteoporosis develops, the objective is to stabilize or improve bone mass and strength and prevent fractures. Goals in patients with osteoporotic fractures include reducing pain and deformity, improving function, reducing falls and fractures, and improving quality of life.
- **Figure 3–1** provides an osteoporosis management algorithm for postmenopausal women and men ages 50 and older.

NONPHARMACOLOGIC THERAPY

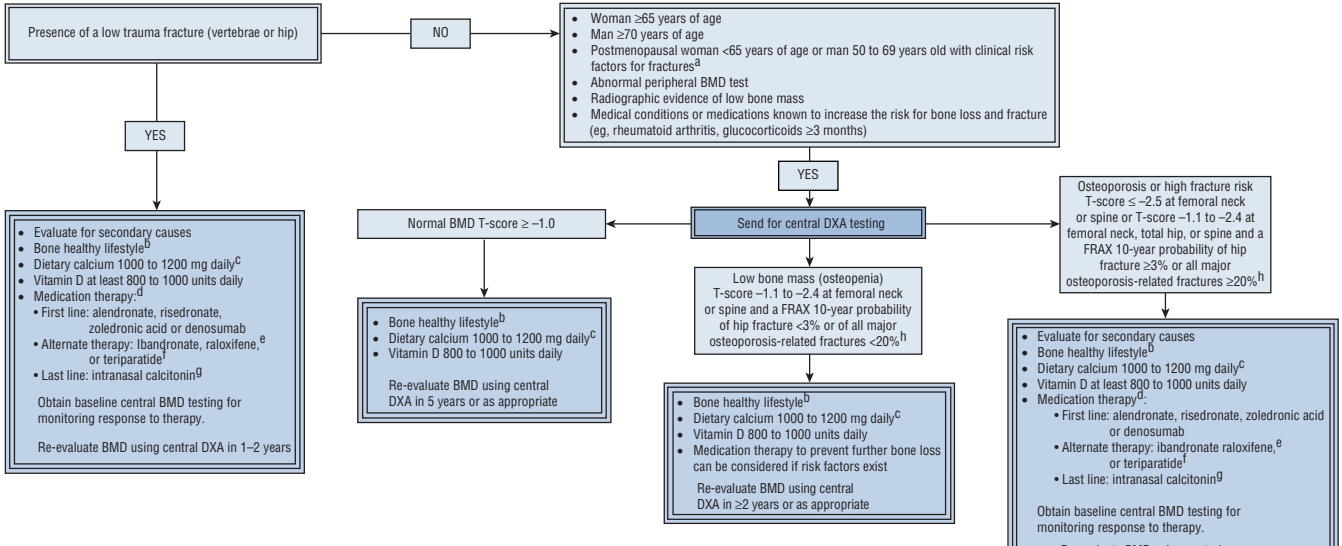
- All individuals should have a balanced diet with adequate intake of **calcium** and **vitamin D** (**Table 3–1**). Achieving daily calcium requirements from calcium-containing foods is preferred.
  - ✓ Consumers can calculate the amount of calcium in a food serving by adding a zero to the percentage of the daily value on food labels. One serving of milk (8 oz or 240 mL) has 30% of the daily value of calcium; this converts to 300 mg of calcium per serving.
  - ✓ To calculate the amount of vitamin D in a food serving, multiply the percent daily value of vitamin D listed on the food label by 4. For example, 20% vitamin D = 80 units.
- Alcohol consumption should not exceed one drink per day for women and two drinks per day for men.
- Ideally, caffeine intake should be limited to two or fewer servings per day.
- Smoking cessation helps optimize peak bone mass, minimize bone loss, and ultimately reduce fracture risk.
- Weight-bearing aerobic and strengthening exercises can decrease risk of falls and fractures by improving muscle strength, coordination, balance, and mobility.

PHARMACOLOGIC THERAPY

ANTIRESORPTIVE THERAPY

Calcium Supplementation

- **Calcium** increases BMD, but its effects are less than those of other therapies. Fracture prevention is only documented with concomitant vitamin D therapy; calcium should be combined with vitamin D and osteoporosis medications when needed. Because the fraction of calcium absorbed decreases with increasing dose, maximum single doses of 600 mg or less of elemental calcium are recommended.
- **Calcium carbonate** is the salt of choice because it contains the highest concentration of elemental calcium (40%) and is least expensive. It should be ingested with meals to enhance absorption in an acidic environment.
- **Calcium citrate** absorption is acid independent and need not be taken with meals. It may have fewer GI side effects (eg, flatulence) than calcium carbonate.
- **Tricalcium phosphate** contains 38% calcium, but calcium-phosphate complexes could limit overall calcium absorption. It might be helpful in patients with hypophosphatemia that cannot be resolved with increased dietary intake.



[a]Major clinical risk factors for fracture: current smoker, low body weight or body mass index, history of osteoporosis/low trauma fracture in a first-degree relative, personal history of fracture as an adult (after age 50 years), excessive alcohol intake
[b]Bone-healthy lifestyle includes smoking cessation, limit alcohol intake, well-balanced diet with adequate calcium and vitamin D intakes, weight-bearing/resistance exercises, and fall prevention
[c]Dietary calcium preferred. If diet is inadequate, supplement as necessary
[d]Sometimes men with hypogonadism also receive testosterone replacement; sometimes women with menopausal symptoms receive low dose hormone therapy for a short time
[e]Raloxifene can be a good option in women at high risk for breast cancer
[f]Teriparatide can be considered a first-line option in patients with a very high risk of fracture (eg, T-score <–3.5 or multiple low trauma fractures) or intolerant to other medications
[g]Calitonin is last-line due to limited fracture data and a recent concern over possible slight increased cancer risk.
[h]WHO absolute fracture risk assessment tool (FRAX) for osteoporotic fracture risk estimations

FIGURE 3–1. Algorithm for management of osteoporosis in postmenopausal women and men ages 50 and older. BMD, bone mineral density; DXA, dual-energy x-ray absorptiometry.

TABLE 3–1 Calcium and Vitamin D: Recommended Dietary Allowances and Upper Limits

Group and Ages	Elemental Calcium (mg)	Vitamin D (units)[a]
Infants		
Birth to 6 months	200–1000	400–1000
6–12 months	260–1500	400–1500
Children		
1–3 years	700–2500	600–2500
4–8 years	1000–2500	600–3000
9–18 years	1300–3000	600–4000
Adults		
19–50 years	1000–2500	600–4000[b]
51–70 years (men)	1000–2000	600–4000[b]
51–70 years (women)	1200–2000	600–4000[b]
>70 years	1200–200	800–4000[b]

[a]Other guidelines recommend intake to achieve a 25(OH) vitamin D concentration of ≥30 ng/mL [75 nmol/L], which is higher than the Institute of Medicine goal of ≥20 ng/mL [50 nmol/L].
[b]2010 National Osteoporosis Foundation Guidelines recommend 400–800 units for adults younger than 50 years and 800–1000 units for adults 50 years and older.

- Constipation is the most common adverse reaction; treat with increased water intake, dietary fiber (given separately from calcium), and exercise. Calcium carbonate can sometimes cause flatulence or upset stomach. Calcium causes kidney stones rarely.

Vitamin D Supplementation

- **Vitamin D** supplementation maximizes intestinal calcium absorption and BMD; it may also reduce fractures and falls.
- Supplementation is usually provided with daily nonprescription cholecalciferol (vitamin D_3) products. Higher-dose prescription ergocalciferol (vitamin D_2) regimens given weekly, monthly, or quarterly may be used for replacement and maintenance therapy.
- The recommended dietary allowances in **Table 3–1** should be achieved through food and supplementation with a goal to maintain the 25 (OH) vitamin D concentration at 30 ng/mL (75 nmol/L) or higher.
- Because the half-life of vitamin D is about 1 month, recheck the vitamin D concentration after about 3 months of therapy.

Bisphosphonates

- Bisphosphonates (Table 3–2) inhibit bone resorption and become incorporated into the bones, giving them long biologic half-lives of up to 10 years.
- Of the antiresorptive agents available, bisphosphonates provide some of the higher BMD increases and fracture risk reductions. Fracture reductions are demonstrated as early as 6 months.
- BMD increases are dose dependent and greatest in the first 6 to 12 months of therapy. After discontinuation, the increased BMD is sustained for a prolonged period that varies depending on the bisphosphonate used.
- **Alendronate**, **risedronate**, and **IV zoledronic acid** are Food and Drug Administration (FDA)–indicated for postmenopausal, male, and glucocorticoid-induced osteoporosis. **IV and oral ibandronate** are indicated only for postmenopausal osteoporosis.
- Bisphosphonates must be administered carefully to optimize clinical benefit and minimize adverse GI effects. Each oral tablet should be taken in the morning with at least 6 oz of plain tap water (not coffee, juice, mineral water, or milk) at least 30 minutes (60 minutes for oral ibandronate) before consuming any food, supplement, or medication. An exception is delayed-release risedronate, which is administered immediately after breakfast with at least 4 oz of plain water. The patient should

TABLE 3–2 Medications Used to Prevent and Treat Osteoporosis

Drug	Adult Dosages	Pharmacokinetics	Adverse Effects	Drug Interactions
Calcium	Supplement dose is the difference between adequate daily intake, which varies by age (see Table 3–1), and dietary intake. Divided doses may be needed.	Absorption—predominantly active transport with some passive diffusion, fractional absorption 10%–60%, fecal elimination of unabsorbed and renal elimination of absorbed calcium	Constipation, gas, upset stomach, rare kidney stones	Carbonate products—decreased absorption with proton pump inhibitors Decreased absorption of iron, tetracycline, quinolones, bisphosphonates, phenytoin, and fluoride when given concomitantly Antagonist of verapamil May induce hypercalcemia with thiazide diuretics Fiber laxatives, oxalates, phytates, and sulfates can decrease calcium absorption if given concomitantly
Vitamin D_3 (cholecalciferol)	Adequate intake (see Table 3–1); higher doses may be required if malabsorption or multiple anticonvulsants.	Hepatic metabolism to 25(OH) vitamin D and then renal metabolism to active compound $1,25(OH)_2$ vitamin D, other active and inactive metabolites	Hypercalcemia, (weakness, headache, somnolence, nausea, and/or cardiac rhythm disturbance), hypercalciuria	Phenytoin, barbiturates, carbamazepine, and rifampin increase vitamin D metabolism
Vitamin D_2 (ergocalciferol)	For vitamin D deficiency, 50,000 units orally once or twice weekly for 8–12 weeks; repeat as needed until therapeutic concentrations; occasionally, 50,000 units monthly for maintenance			Cholestyramine, colestipol, orlistat, and mineral oil decrease vitamin D absorption
$1,25(OH)_2$ vitamin D (calcitriol, Rocaltrol PO, Calcijex IV)	0.25–0.5 mcg orally or 1–2 mcg/mL IV daily for renal osteodystrophy, hypoparathyroidism, or refractory rickets			Might induce hypercalcemia with thiazide diuretics in hypoparathyroid patients

Bisphosphonates				
Alendronate (Fosamax, Binosto effervescent tablets)	*Prevention*: 5 mg orally daily or 35 mg orally weekly *Treatment*: 10 mg orally daily or 70 mg orally weekly; 70-mg dose available as oral tablet, effervescent tablet, or combination tablet with vitamin D_3 2800 or 5600 units	Poorly absorbed—<1% decreasing to zero with food or beverage intake—long $T_{1/2}$ (<10 years); renal elimination (of absorbed) and fecal elimination (unabsorbed)	Transient musculoskeletal pain, nausea, dyspepsia (oral); transient flu-like illness (injectable) Rare: GI perforation, ulceration, and/or bleeding (oral); ONJ, atypical femoral shaft fracture, severe musculoskeletal pain	Do not coadminister with any other medication or supplements (including calcium and vitamin D)
Ibandronate (Boniva)	*Prevention*: 150 mg orally monthly *Treatment*: 150 mg orally monthly; 3 mg IV every 3 months			
Risedronate (Actonel, Atelvia delayed release)	*Prevention and Treatment*: 5 mg orally daily, 35 mg orally weekly, 150 mg orally monthly		Rare: GI perforation, ulceration, and/or bleeding (oral); musculoskeletal pain, ONJ, atypical fractures	
Zoledronic acid (Reclast)	*Prevention*: 5 mg IV infusion every 2 years *Treatment*: 5 mg IV infusion yearly			

(*continued*)

TABLE 3–2 Medications Used to Prevent and Treat Osteoporosis *(Continued)*

Drug	Adult Dosages	Pharmacokinetics	Adverse Effects	Drug Interactions
RANK ligand inhibitor				
Denosumab (Prolia)	*Treatment*: 60 mcg subcutaneously every 6 months	T_{max} 10 days, $T_{1/2}$ 25.4 days	Flatulence, dermatitis, eczema, rash Rare: serious infections, ONJ, atypical fractures, hypocalcemia	
Estrogen agonist/antagonists				
Raloxifene (Evista)	60 mg orally daily	Hepatic metabolism	Hot flushes, leg cramps, venous thromboembolism, peripheral edema Rare: cataracts and gallbladder disease; black-box warning for fatal stroke	None
Calcitonin				
Calcitonin salmon (Miacalcin, Fortical)	200 units (1 spray) intranasally daily, alternating nares every other day; 100 units subcutaneously daily	Renal elimination; 3% nasal availability	Nasal: rhinitis, epistaxis Injection: nausea, flushing, local inflammation	None
Recombinant human parathyroid hormone (PTH 1–34 units)				
Teriparatide, (Forteo)	20 mcg subcutaneously daily for up to 2 years	95% bioavailability T_{max} ~30 min $T_{1/2}$ ~60 min Hepatic metabolism	Pain at injection site, nausea, headache, dizziness, leg cramps Rare: increase in uric acid, slightly increased calcium	None

GI, gastrointestinal; IV, intravenous; ONJ, osteonecrosis of the jaw; PO, by mouth; T_{max}, time to maximum concentration; $T_{1/2}$, half-life.

remain upright (sitting or standing) for at least 30 minutes after alendronate and risedronate and 1 hour after ibandronate administration to prevent esophageal irritation and ulceration.
- Weekly alendronate, weekly and monthly risedronate, and monthly oral and quarterly IV ibandronate therapy produce equivalent BMD changes to their respective daily regimens. If a patient misses a weekly dose, it can be taken the next day. If more than 1 day has elapsed, that dose is skipped until the next scheduled ingestion. If a patient misses a monthly dose, it can be taken up to 7 days before the next scheduled dose.
- The most common bisphosphonate adverse effects include nausea, abdominal pain, and dyspepsia. Esophageal, gastric, or duodenal irritation, perforation, ulceration, or bleeding may occur. The most common adverse effects of IV bisphosphonates include fever, flu-like symptoms, and local injection-site reactions.
- Rare adverse effects include osteonecrosis of the jaw (ONJ) and subtrochanteric femoral (atypical) fractures. ONJ occurs more commonly in patients with cancer, chemotherapy, radiation, and glucocorticoid therapy receiving higher-dose IV bisphosphonate therapy.

Denosumab

- **Denosumab** (Prolia) is a RANK ligand inhibitor that inhibits osteoclast formation and increases osteoclast apoptosis. It is indicated for treatment of osteoporosis in women and men at high risk for fracture. It is also approved to increase bone mass in men receiving androgen-deprivation therapy for nonmetastatic prostate cancer and in women receiving adjuvant aromatase inhibitor therapy for breast cancer who are at high risk for fracture.
- Denosumab is administered as a 60-mg subcutaneous injection in the upper arm, upper thigh, or abdomen once every 6 months.
- Adverse reactions are included in **Table 3–2**. Denosumab is contraindicated in patients with hypocalcemia until the condition is corrected.

Mixed Estrogen Agonists/Antagonists

- **Raloxifene** is an estrogen agonist in bone but an antagonist in breast and uterine tissue. It is approved for prevention and treatment of postmenopausal osteoporosis.
- Raloxifene decreases vertebral fractures and increases spine and hip BMD, but to a lesser extent than bisphosphonates. After discontinuation, the beneficial effect is lost, and bone loss returns to age- or disease-related rates.
- Raloxifene is well tolerated overall. Hot flushes, leg cramps, and muscle spasms are common. Endometrial bleeding occurs rarely. Thromboembolic events are uncommon but can be fatal. Raloxifene is contraindicated in women with an active or past history of venous thromboembolic disease. Discontinue therapy if patient anticipates extended immobility. Prescribing information contains a black-box warning urging caution in women at risk for stroke.

Calcitonin

- **Calcitonin** is an endogenous hormone released from the thyroid gland when serum calcium is elevated. Salmon calcitonin is used clinically because it is more potent and longer lasting than the mammalian form.
- Calcitonin is indicated for osteoporosis treatment for women at least 5 years past menopause. It is reserved as a last-line treatment because efficacy is less robust than with other antiresorptive therapies.
- Only vertebral fractures have been documented to decrease with intranasal calcitonin therapy. Calcitonin does not consistently affect hip BMD and does not decrease hip fracture risk.
- Calcitonin may provide some pain relief in patients with acute vertebral fractures. If the nasal product is used for this purpose, it should be prescribed for short-term treatment (4 weeks) and should not be used in place of other more effective and less

expensive analgesics, nor should it preclude use of more appropriate osteoporosis therapy.
- Intranasal dose is 200 units daily, alternating nares every other day. Subcutaneous administration of 100 units daily is available but rarely used because of adverse effects and cost.

Estrogen Therapy

- Estrogens are FDA-indicated for prevention of osteoporosis in women at significant risk and for whom other osteoporosis medications cannot be used.
- Hormone therapy (estrogen with or without a progestogen) significantly decreases fracture risk. Increases in BMD are less than with bisphosphonates, denosumab, or teriparatide but greater than with raloxifene or calcitonin. Oral and transdermal estrogens at equivalent doses and continuous or cyclic regimens have similar BMD effects. Effect on BMD is dose dependent, with some benefit seen with lower estrogen doses. When therapy is discontinued, bone loss accelerates and fracture protection is lost.
- Use the lowest effective dose that prevents and controls menopausal symptoms, and discontinue therapy as soon as possible.

Testosterone

- Testosterone is not FDA-indicated for osteoporosis, but the male osteoporosis guideline recommends testosterone alone for men with testosterone concentrations of less than 200 ng/dL [6.9 nmol/L] if low fracture risk and in combination with an osteoporosis medication if high fracture risk. Do not use testosterone replacement solely for prevention or treatment of osteoporosis.
- Testosterone may increase BMD in men with low testosterone concentrations but has no effect if testosterone concentrations are normal. No fracture data are available.

ANABOLIC THERAPIES

Teriparatide

- **Teriparatide** (Forteo) is a recombinant product representing the first 34 amino acids in human parathyroid hormone (PTH). Teriparatide increases bone formation, bone remodeling rate, and osteoblast number and activity.
- Teriparatide is FDA-indicated for treatment of postmenopausal women at high risk for fracture, for increase in BMD in men with idiopathic or hypogonadal osteoporosis at high fracture risk, for men or women intolerant to other osteoporosis medications, and for patients with glucocorticoid-induced osteoporosis.
- The drug reduces fracture risk in postmenopausal women, but no fracture data are available in men or for patients taking corticosteroids. Lumbar spine BMD increases are higher than with other osteoporosis medications. Although wrist BMD is decreased, wrist fractures are not increased.
- Discontinuation of therapy results in decreased BMD, which can be alleviated with subsequent antiresorptive therapy. Due to concern over osteosarcoma, teriparatide is approved for use for only up to 2 years.
- The teriparatide dose is 20 mcg subcutaneously once daily in the thigh or abdomen for up to 2 years (see **Table 3–2**). Give the initial dose with the patient either lying or sitting, in case orthostatic hypotension occurs. Each prefilled 3-mL pen device delivers a 20-mcg dose each day for up to 28 days; keep the pen device refrigerated.
- Transient hypercalcemia rarely occurs. Teriparatide is contraindicated in patients at increased risk for osteosarcoma.

GLUCOCORTICOID-INDUCED OSTEOPOROSIS

- Glucocorticoids decrease bone formation through decreased proliferation and differentiation, as well as enhanced apoptosis of osteoblasts. They also increase bone resorption, decrease calcium absorption, and increase renal calcium excretion.

- Bone losses are rapid, with the greatest decrease occurring during the first 6 to 12 months of therapy. Oral doses as low as 2.5 mg prednisone or equivalent daily have been associated with fractures. Glucocorticoid-induced osteoporosis has also been associated with inhaled glucocorticoids, although most data suggest no major bone effects.
- Measure baseline BMD, using central DXA for all patients starting on prednisone 5 mg or more daily (or equivalent) for at least 6 months. Consider BMD testing at baseline in patients being started on shorter durations of systemic glucocorticoids if they are at high risk for low bone mass and fractures. Because bone loss can occur rapidly, repeat central DXA every 6 to 12 months if needed.
- All patients starting or receiving systemic glucocorticoid therapy (any dose or duration) should practice a bone-healthy lifestyle and ingest 1200 to 1500 mg elemental calcium and 800 to 1200 units of vitamin D daily to achieve therapeutic 25(OH) vitamin D concentrations. Use the lowest possible corticosteroid dose and duration.
- Treatment guidelines divide recommendations for prescription medication use by fracture risk, age, menopause and childbearing status, glucocorticoid dose and duration, and fragility fracture. Oral alendronate and risedronate and IV zoledronic acid are FDA approved for glucocorticoid-induced osteoporosis. The American College of Rheumatology guidelines recommend that all patients newly starting on systemic glucocorticoids (≥5 mg/day of prednisone equivalent) for an anticipated duration of at least 3 months should receive preventive bisphosphonate therapy. Teriparatide can be used if bisphosphonates are not tolerated or contraindicated.

EVALUATION OF THERAPEUTIC OUTCOMES

- Examine patients receiving pharmacotherapy for low bone mass at least annually. Assess medication adherence and tolerance at each visit.
- Ask patients about possible fracture symptoms (eg, bone pain or disability) at each visit. Assessment of fracture, back pain, and height loss can help identify worsening osteoporosis.
- Obtain central DXA BMD measurements every 1 to 2 years after initiating a medication to monitor response. More frequent monitoring may be warranted in patients with conditions associated with higher rates of bone loss (eg, glucocorticoid use).

See Chapter 73, Osteoporosis and Other Metabolic Bone Diseases, authored by Mary Beth O'Connell and Jill S. Borchert, for a more detailed discussion of this topic.

Rheumatoid Arthritis

CHAPTER 4

- *Rheumatoid arthritis* (RA) is a chronic, progressive inflammatory disorder of unknown etiology characterized by polyarticular symmetric joint involvement and systemic manifestations.

PATHOPHYSIOLOGY

- RA results from dysregulation of humoral and cell-mediated immunity. Most patients produce antibodies called *rheumatoid factors*; these seropositive patients tend to have a more aggressive course than seronegative patients.
- Immunoglobulins (Ig) activate the complement system, which amplifies the immune response by enhancing chemotaxis, phagocytosis, and release of lymphokines by mononuclear cells that are then presented to T lymphocytes. Processed antigen is recognized by the major histocompatibility complex proteins on the lymphocyte surface, resulting in activation of T and B cells.
- Tumor necrosis factor-α (TNF-α), interleukin-1 (IL-1), and IL-6 are proinflammatory cytokines important in initiation and continuance of inflammation.
- Activated T cells produce cytotoxins and cytokines, which stimulate further activation of inflammatory processes and attract cells to areas of inflammation. Macrophages are stimulated to release prostaglandins and cytotoxins. T-cell activation requires both stimulation by proinflammatory cytokines as well as interaction between cell surface receptors, called *costimulation*. One such costimulation interaction is between CD28 and CD80/86.
- Activated B cells produce plasma cells, which form antibodies that, in combination with the complement system, result in accumulation of polymorphonuclear leukocytes. These leukocytes release cytotoxins, oxygen-free radicals, and hydroxyl radicals that promote damage to synovium and bone.
- Signaling molecules are important for activating and maintaining inflammation. Janus kinase (JAK) is a tyrosine kinase responsible for regulating leukocyte maturation and activation. JAK also has effects on production of cytokines and immunoglobulins.
- Vasoactive substances (histamine, kinins, prostaglandins) are released at sites of inflammation, increasing blood flow and vascular permeability. This causes edema, warmth, erythema, and pain, and facilitates granulocyte passage from blood vessels to sites of inflammation.
- Chronic inflammation of synovial tissue lining the joint capsule results in tissue proliferation (pannus formation). Pannus invades cartilage and eventually the bone surface, producing erosions of bone and cartilage and leading to joint destruction. End results may be loss of joint space and joint motion, bony fusion (ankylosis), joint subluxation, tendon contractures, and chronic deformity.

CLINICAL PRESENTATION

- Nonspecific prodromal symptoms developing over weeks to months include fatigue, weakness, low-grade fever, anorexia, and joint pain. Stiffness and myalgias may precede development of synovitis.
- Joint involvement tends to be symmetric and affect small joints of the hands, wrists, and feet; elbows, shoulders, hips, knees, and ankles may also be affected.
- Joint stiffness typically is worse in the morning, usually exceeds 30 minutes, and may persist all day.
- On examination, joint swelling may be visible or apparent only by palpation. Tissue is soft, spongy, warm, and may be erythematous. Joint deformities may involve subluxations of wrists, metacarpophalangeal joints, and proximal interphalangeal joints (swan neck deformity, boutonnière deformity, and ulnar deviation).

- Extra-articular involvement may include rheumatoid nodules, vasculitis, pleural effusions, pulmonary fibrosis, ocular manifestations, pericarditis, cardiac conduction abnormalities, bone marrow suppression, and lymphadenopathy.

DIAGNOSIS

- The American College of Rheumatology (ACR) and the European League Against Rheumatism (EULAR) revised criteria for diagnosis of RA in 2010. These criteria are intended for patients early in their disease and emphasize early manifestations. Late manifestations (bone erosions, subcutaneous nodules) are no longer in the diagnostic criteria. Patients with synovitis of at least one joint and no other explanation for the finding are candidates for assessment. The criteria use a scoring system with a combined score of 6 or more out of 10 indicating that the patient has definite RA.
- Laboratory abnormalities include normocytic, normochromic anemia; thrombocytosis or thrombocytopenia; leukopenia; elevated erythrocyte sedimentation rate and C-reactive protein; positive rheumatoid factor (60%–70% of patients); positive anticitrullinated protein antibody (ACPA) (50%–85% of patients); and positive antinuclear antibodies (25% of patients).
- Aspirated synovial fluid may reveal turbidity, leukocytosis, reduced viscosity, and normal or low glucose relative to serum concentrations.
- Early radiologic findings include soft tissue swelling and osteoporosis near the joint (periarticular osteoporosis). Erosions later in the disease course are usually seen first in the metacarpophalangeal and proximal interphalangeal joints of the hands and metatarsophalangeal joints of the feet.

TREATMENT

- Goals of Treatment: The ultimate goal is to induce complete remission or low disease activity. Additional goals are to control disease activity and joint pain, maintain ability to function in daily activities, slow destructive joint changes, and delay disability.

NONPHARMACOLOGIC THERAPY

- Adequate rest, weight reduction if obese, occupational therapy, physical therapy, and use of assistive devices may improve symptoms and help maintain joint function.
- Patients with severe disease may benefit from surgical procedures such as tenosynovectomy, tendon repair, and joint replacements.
- Patient education about the disease and the benefits and limitations of drug therapy is important.

PHARMACOLOGIC THERAPY

General Approach

- Start disease-modifying antirheumatic drugs (DMARDs) as soon as possible after disease onset because early treatment results in more favorable outcomes.
- DMARDs slow RA disease progression. Common nonbiologic DMARDs include **methotrexate (MTX)**, **hydroxychloroquine**, **sulfasalazine**, and **leflunomide** (**Fig. 4–1**). The order of selection is not clearly defined, but MTX is often chosen initially because long-term data suggest superior outcomes compared with other DMARDs and lower cost than biologic agents.
- Combination therapy with two or more nonbiologic DMARDs may be effective when single-DMARD treatment is unsuccessful. Recommended combinations include (1) MTX plus hydroxychloroquine, (2) MTX plus leflunomide, (3) MTX plus sulfasalazine, and (4) MTX plus hydroxychloroquine plus sulfasalazine.
- Biologic DMARDs include the anti-TNF agents **etanercept**, **infliximab**, **adalimumab**, **certolizumab**, and **golimumab**; the costimulation modulator **abatacept**; the IL-6 receptor antagonist **tocilizumab**; and **rituximab**, which depletes peripheral B cells. Biologic DMARDs have proven effective for patients failing treatment with nonbiologic DMARDs (**Fig. 4–2**).

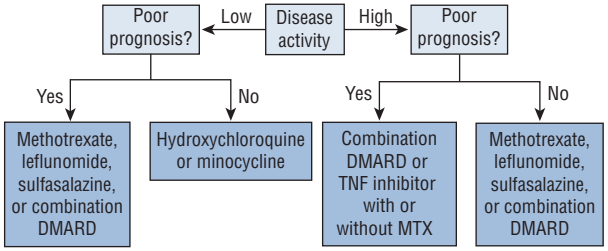


FIGURE 4–1. Algorithm for treatment of rheumatoid arthritis in early disease. Poor prognosis is defined as limitation in function, extra-articular findings (rheumatoid nodules, vasculitis, Felty syndrome, Sjögren syndrome, rheumatoid lung findings, erosions on radiograph), bone erosions, and positive rheumatoid factor or anticitrullinated protein antibody. (DMARD, disease-modifying antirheumatic drug; MTX, methotrexate; NSAID, nonsteroidal anti-inflammatory drug; TNF, tumor necrosis factor.)

- Anti-TNF biologics may also be used in patients with early disease of high activity and poor prognostic factors, regardless of previous DMARD use. Features of poor prognosis include functional limitation, extra-articular disease (eg, rheumatoid nodules, vasculitis) positive rheumatoid factor or ACPA, or bone erosions. Anti-TNF biologics can be used as either monotherapy or in combination with other DMARDs. Use of biologics in combination with MTX is more effective than biologic monotherapy.
- DMARDs less frequently used include **anakinra** (IL-1 receptor antagonist), **azathioprine**, **penicillamine**, **gold salts** (including **auranofin**), **minocycline**, **cyclosporine**, and **cyclophosphamide**. These agents have either less efficacy or higher toxicity, or both.
- Nonsteroidal anti-inflammatory drugs (NSAIDs) and/or corticosteroids may be used for symptomatic relief if needed. They provide relatively rapid improvement compared with DMARDs, which may take weeks to months before benefit is seen. However, NSAIDs have no impact on disease progression, and corticosteroids have potential for long-term complications.
- See **Tables 4–1** and **4–2** for usual dosages and monitoring parameters for DMARDs and NSAIDs used in RA.

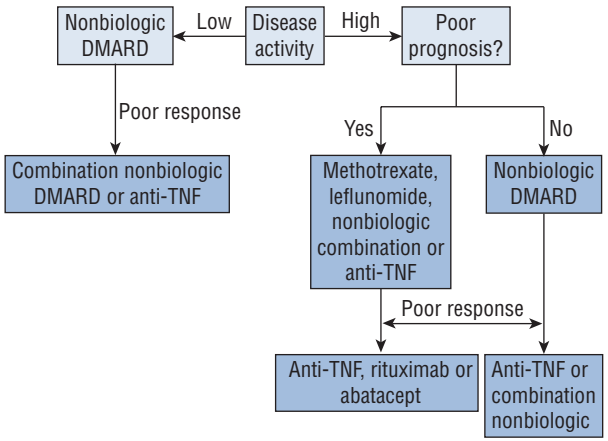


FIGURE 4–2. Algorithm for treatment of rheumatoid arthritis in established disease (>6 months). (DMARD, disease-modifying antirheumatic drug; anti-TNF, anti-tumor necrosis factor.)

TABLE 4–1 Usual Doses and Monitoring Parameters for Antirheumatic Drugs

Drug	Usual Dose	Initial Monitoring Tests	Maintenance Monitoring Tests
NSAIDs	See Table 4–3	S_{cr} or BUN, CBC every 2–4 weeks after starting therapy for 1–2 months; salicylates: serum salicylate levels if therapeutic dose and no response	Same as initial plus stool guaiac every 6–12 months
Corticosteroids	Oral, IV, IM, IA, and soft-tissue injections: variable	Glucose; blood pressure every 3–6 months	Same as initial
Methotrexate	Oral or IM: 7.5–15 mg/week	Baseline: AST, ALT, ALK-P, albumin, total bilirubin, hepatitis B and C studies, CBC with platelets, S_{cr}	CBC with platelets, AST, albumin every 1–2 months
Leflunomide	Oral: 100 mg daily for 3 days, then 10–20 mg daily, *or* 10–20 mg daily without loading dose	Baseline: ALT, CBC with platelets	CBC with platelets and ALT monthly initially, then every 6–8 weeks
Hydroxychloroquine	Oral: 200–300 mg twice daily; after 1–2 months may decrease to 200 mg once or twice daily	Baseline: color fundus photography and automated central perimetric analysis	Ophthalmoscopy every 9–12 months and Amsler grid at home every 2 weeks
Sulfasalazine	Oral: 500 mg twice daily, then increase to 1 g twice daily	Baseline: CBC with platelets, then every week for 1 month	Same as initial every 1–2 months
Minocycline	Oral: 100–200 mg daily	None	None
Etanercept	50 mg SC once weekly or 25 mg twice weekly	Tuberculin skin test	None
Infliximab	3 mg/kg IV at 0, 2, 6 weeks, then every 8 weeks	Tuberculin skin test	None
Adalimumab	40 mg SC every 2 weeks	Tuberculin skin test	None
Certolizumab	400 mg (2 doses of 200 mg) SC at weeks 0, 2, 4, then 200 mg every 2 weeks	Tuberculin skin test	None
Golimumab	50 mg SC once monthly	Tuberculin skin test	None
Rituximab	1000-mg IV infusion given twice, 2 weeks apart	Tuberculin skin test	None

(*continued*)

TABLE 4–1 Usual Doses and Monitoring Parameters for Antirheumatic Drugs (*Continued*)

Drug	Usual Dose	Initial Monitoring Tests	Maintenance Monitoring Tests
Abatacept	IV infusion: 30-min weight-based infusion: <60 kg = 500 mg; 60–100 kg = 750 mg; >100 kg = 1000 mg SC injection: 125 mg SC within 24 h after a single IV infusion loading dose of ~10 mg/kg; then 125 mg SC every 7 days	Tuberculin skin test	None
Tocilizumab	4–8 mg/kg IV every 4 weeks	Tuberculin skin test, AST/ALT, CBC with platelets, lipids	AST/ALT, CBC with platelets, lipids every 4–8 weeks
Anakinra	100 mg SC daily	Tuberculin skin test, neutrophil count	Neutrophil count monthly for 3 months, then quarterly for up to 1 year
Tofacitinib	Oral: 5 mg twice daily	Tuberculin skin test, CBC with differential; hepatic enzymes, lipids	CBC with differential after 4–8 weeks and every 3 months thereafter
Auranofin	Oral: 3 mg once or twice daily	Baseline: UA, CBC with platelets	Same as initial every 1–2 months
Gold thiomalate	IM: 10 mg test dose, then weekly dosing 25–50 mg; after response may increase dosing interval	Baseline and until stable: UA, CBC with platelets preinjection	Same as initial every other dose
Azathioprine	Oral: 50–150 mg daily	CBC with platelets, AST every 2 weeks for 1–2 months	Same as initial every 1–2 months
Penicillamine	Oral: 125–250 mg daily, may increase by 125–250 mg every 1–2 months; max 750 mg/day	Baseline: UA, CBC with platelets, then every week for 1 month	Same as initial every 1–2 months, but every 2 weeks if dose changes
Cyclophosphamide	Oral: 1–2 mg/kg/day	UA, CBC with platelets every week for 1 month	Same tests as initial but every 2–4 weeks
Cyclosporine	Oral: 2.5 mg/kg/day divided twice daily	S_{cr}, blood pressure every month	Same as initial

ALK-P, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BUN, blood urea nitrogen; CBC, complete blood cell count; IA, intra-articular; IM, intramuscular; IV, intravenous; NSAIDs, nonsteroidal anti-inflammatory drugs; SC, subcutaneous; S_{cr}, serum creatinine; UA, urinalysis.

TABLE 4–2 Clinical Monitoring of Drug Therapy in Rheumatoid Arthritis

Drug	Toxicities Requiring Monitoring	Symptoms to Inquire About[a]
NSAIDs and salicylates	GI ulceration and bleeding, renal damage	Blood in stool, black stool, dyspepsia, nausea/vomiting, weakness, dizziness, abdominal pain, edema, weight gain, shortness of breath
Corticosteroids	Hypertension, hyperglycemia, osteoporosis[b]	Blood pressure, polyuria, polydipsia, edema, shortness of breath, visual changes, weight gain, headaches, broken bones or bone pain
Methotrexate	GI (stomatitis, nausea/vomiting, diarrhea), myelosuppression (thrombocytopenia, leukopenia), hepatic (elevated enzymes, rarely cirrhosis), pulmonary (fibrosis, pneumonitis), rash	Symptoms of myelosuppression, shortness of breath, nausea/vomiting, lymph node swelling, coughing, mouth sores, diarrhea, jaundice
Leflunomide	Hepatotoxicity, myelosuppression, GI distress, alopecia	Nausea/vomiting, gastritis, diarrhea, hair loss, jaundice
Hydroxychloroquine	GI (nausea/vomiting, diarrhea), ocular (benign corneal deposits, blurred vision, scotomas, night blindness, preretinopathy), dermatologic (rash, alopecia, pigmentation), neurologic (headache, vertigo, insomnia)	Visual changes, including a decrease in night or peripheral vision, rash, diarrhea
Sulfasalazine	GI (anorexia, nausea/vomiting, diarrhea), dermatologic (rash, urticaria), myelosuppression (leukopenia, rarely agranulocytosis), elevated hepatic enzymes	Symptoms of myelosuppression, photosensitivity, rash, nausea/vomiting
Etanercept, adalimumab, certolizumab, golimumab, tocilizumab, anakinra	Local injection site reactions, infection	Symptoms of infection
Infliximab, rituximab, abatacept	Immune reactions, infection	Postinfusion reactions, symptoms of infection
Tofacitinib	Infection, malignancy, GI perforation, upper respiratory tract infection, headache, diarrhea, nasopharyngitis, elevated hepatic enzymes and lipids	Symptoms of infection or myelosuppression, shortness of breath, blood in stool, black stool, dyspepsia
Gold (intramuscular or oral)	Myelosuppression, proteinuria, rash, stomatitis	Symptoms of myelosuppression, edema, rash, oral ulcers, diarrhea
Azathioprine	Myelosuppression, hepatotoxicity, lymphoproliferative disorders	Symptoms of myelosuppression (extreme fatigue, easy bleeding or bruising, infection), jaundice

(*continued*)

TABLE 4–2 Clinical Monitoring of Drug Therapy in Rheumatoid Arthritis (*Continued*)

Drug	Toxicities Requiring Monitoring	Symptoms to Inquire About[a]
Penicillamine	Myelosuppression, proteinuria, stomatitis, rash, dysgeusia	Symptoms of myelosuppression, edema, rash, diarrhea, altered taste perception, oral ulcers
Cyclophosphamide	Alopecia, infertility, GI distress, hemorrhagic cystitis, myelosuppression, nephrotoxicity, cardiotoxicity	Nausea/vomiting, gastritis, diarrhea, hair loss, urination difficulties, chest pain, rash, respiratory difficulties
Cyclosporine	Hepatotoxicity, nephrotoxicity, hypertension, headache, malignancy, infections, GI distress	Nausea/vomiting, diarrhea, symptoms of infection, symptoms of elevated blood pressure

GI, gastrointestinal; NSAIDs, nonsteroidal anti-inflammatory drugs.
[a]Altered immune function increases infection, which should be considered particularly in patients taking azathioprine, methotrexate, corticosteroids, or other drugs that may produce myelosuppression.
[b]Osteoporosis is not likely to manifest early in treatment, but all patients should be taking appropriate steps to prevent bone loss.

Nonsteroidal Anti-inflammatory Drugs

- NSAIDs inhibit prostaglandin synthesis, which is only a small portion of the inflammatory cascade. They possess both analgesic and anti-inflammatory properties and reduce stiffness, but they do not slow disease progression or prevent bony erosions or joint deformity. Common NSAID dosage regimens are shown in **Table 4–3**.

Nonbiologic DMARDs

METHOTREXATE

- **Methotrexate (MTX)** inhibits cytokine production and purine biosynthesis, and may stimulate adenosine release, all of which may lead to anti-inflammatory properties. Onset is as early as 2 to 3 weeks, and 45% to 67% of patients remained on it in studies ranging from 5 to 7 years.
- Concomitant folic acid may reduce some adverse effects without loss of efficacy. Monitor liver injury tests periodically, but a liver biopsy is recommended during therapy only in patients with persistently elevated hepatic enzymes. MTX is teratogenic, and patients should use contraception and discontinue the drug if conception is planned.
- MTX is contraindicated in pregnant and nursing women, chronic liver disease, immunodeficiency, pleural or peritoneal effusions, leukopenia, thrombocytopenia, preexisting blood disorders, and creatinine clearance of less than 40 mL/min (0.67 mL/s).

LEFLUNOMIDE

- **Leflunomide** (Arava) inhibits pyrimidine synthesis, which reduces lymphocyte proliferation and modulation of inflammation. Efficacy for RA is similar to that of MTX.
- A loading dose of 100 mg/day for 3 days may result in therapeutic response within the first month. The usual maintenance dose of 20 mg/day may be lowered to 10 mg/day in cases of GI intolerance, alopecia, or other dose-related toxicity.
- Leflunomide is contraindicated in patients with preexisting liver disease. It is teratogenic and must be avoided during pregnancy.

TABLE 4–3 Dosage Regimens for Nonsteroidal Anti-inflammatory Drugs

	Recommended Total Daily Anti-inflammatory Dosage		
Drug	***Adult***	***Children***	**Dosing Schedule**
Aspirin	2.6–5.2 g	60–100 mg/kg	4 times daily
Celecoxib	200–400 mg	–	Once or twice daily
Diclofenac	150–200 mg	–	3 or 4 times daily; extended release: twice daily
Diflunisal	0.5–1.5 g	–	Twice daily
Etodolac	0.2–1.2 g (max 20 mg/kg)	–	2–4 times daily
Fenoprofen	0.9–3 g	–	4 times daily
Flurbiprofen	200–300 mg	–	2–4 times daily
Ibuprofen	1.2–3.2 g	20–40 mg/kg	3 or 4 times daily
Indomethacin	50–200 mg	2–4 mg/kg (max 200 mg)	2–4 times daily; extended release: once daily
Meclofenamate	200–400 mg	–	3–4 times daily
Meloxicam	7.5–15 mg	–	Once daily
Nabumetone	1–2 g	–	Once or twice daily
Naproxen	0.5–1 g	10 mg/kg	Twice daily; extended release: once daily
Naproxen sodium	0.55–1.1 g	–	Twice daily
Nonacetylated salicylates	1.2–4.8 g	–	2–6 times daily
Oxaprozin	0.6–1.8 g (max 26 mg/kg)	–	1–3 times daily
Piroxicam	10–20 mg	–	Once daily
Sulindac	300–400 mg	–	Twice daily
Tolmetin	0.6–1.8 g	15–30 mg/kg	2–4 times daily

HYDROXYCHLOROQUINE

- **Hydroxychloroquine** is often used in mild RA or as an adjuvant in combination DMARD therapy. It lacks the myelosuppressive, hepatic, and renal toxicities seen with some other DMARDs, which simplifies monitoring. Onset may be delayed for up to 6 weeks, but the drug should not be considered a therapeutic failure until after 6 months of therapy with no response.
- Periodic ophthalmologic examinations are necessary for early detection of reversible retinal toxicity.

SULFASALAZINE

- **Sulfasalazine** use is often limited by adverse effects. Antirheumatic effects should be seen within 2 months.
- GI symptoms may be minimized by starting with low doses, dividing the dose evenly throughout the day, and taking it with food.

MINOCYCLINE

- Minocycline may inhibit metalloproteinases active in damaging articular cartilage. It may be an alternative for patients with mild disease and without features of poor prognosis.

TOFACITINIB

- **Tofacitinib** (Xeljanz) is a nonbiologic JAK inhibitor indicated for patients with moderate to severe RA who have failed or have intolerance to MTX.
- The Food and Drug Administration (FDA)–approved dose is 5 mg twice daily as monotherapy or in combination with other nonbiologic DMARDs.
- Labeling includes black-box warnings about serious infections, lymphomas, and other malignancies. Live vaccinations should not be given during treatment.
- Long-term safety data and impact on radiographic joint damage are needed before tofacitinib's place in the therapy will be clear.

Biologic DMARDs

- Biologic DMARDs may be effective when nonbiologic DMARDs fail to achieve adequate responses but are considerably more expensive.
- Other than anakinra and tocilizumab, these agents have no toxicities requiring laboratory monitoring, but they do carry a small increased risk for infection, including tuberculosis. Tuberculin skin testing should be performed before treatment to detect latent tuberculosis.
- Biologic agents should be at least temporarily discontinued in patients who develop infections while on therapy until the infection is cured. Live vaccines should not be given to patients taking biologic agents.

TNF-α INHIBITORS

- Inhibitors of TNF-α are generally the first biologic DMARDs used. About 30% of patients eventually discontinue use owing to inadequate efficacy or adverse effects. In such situations, addition of a nonbiologic DMARD may be beneficial if the patient is not already taking one. Choosing an alternative TNF inhibitor may benefit some patients; treatment with rituximab or abatacept may also be effective in patients failing TNF inhibitors. Combination biologic DMARD therapy is not recommended because of increased infection risk.
- Congestive heart failure (HF) is a relative contraindication for anti-TNF agents due to reports of increased cardiac mortality and HF exacerbations. Patients with New York Heart Association class III or IV and an ejection fraction of 50% or less should not use anti-TNF therapy. Discontinue the drugs if HF worsens during treatment.
- Anti-TNF therapy has been reported to induce a multiple sclerosis (MS)–like illness or exacerbate MS in patients with the disease. Discontinue therapy if patients develop neurologic symptoms suggestive of MS.
- TNF inhibitors are associated with increased risk of cancer, especially lymphoproliferative cancers. The drugs contain a black-box warning about increased risk of lymphoproliferative and other cancers in children and adolescents treated with these drugs.
- See Tables 4–1 and 4–2 for dosing and monitoring information.
  - ✓ **Etanercept** (Enbrel) is a fusion protein consisting of two p75-soluble TNF receptors linked to an Fc fragment of human IgG_1. It binds to and inactivates TNF, preventing it from interacting with the cell-surface TNF receptors and thereby activating cells. Clinical trials using etanercept in patients who failed DMARDs demonstrated responses in 60% to 75% of patients. It slows erosive disease progression more than oral MTX in patients with inadequate response to MTX monotherapy.
  - ✓ **Infliximab** (Remicade) is a chimeric anti-TNF antibody fused to a human constant-region IgG_1. It binds to TNF and prevents its interaction with TNF receptors on inflammatory cells. To prevent formation of an antibody response to this foreign protein, MTX must be given orally in doses used to treat RA for as long as the patient continues infliximab. In clinical trials, the combination of infliximab and MTX halted progression of joint damage and was superior to MTX monotherapy. An acute infusion reaction with fever, chills, pruritus, and rash may occur within

1 to 2 hours after administration. Autoantibodies and lupus-like syndrome have also been reported.

✓ **Adalimumab** (Humira) is a human IgG_1 antibody to TNF-α that is less antigenic than infliximab. It has response rates similar to other TNF inhibitors.

✓ **Golimumab** (Simponi) is a human antibody to TNF-α with activity and precautions similar to other TNF-α inhibitors.

✓ **Certolizumab** (Cimzia) is a humanized antibody specific for TNF-α with precautions and side effects similar to other TNF-α inhibitors.

ABATACEPT

- **Abatacept** (Orencia) is a costimulation modulator approved for patients with moderate to severe disease who fail to achieve an adequate response from one or more DMARDs. By binding to CD80/CD86 receptors on antigen-presenting cells, abatacept inhibits interactions between the antigen-presenting cells and T cells, preventing T cells from activating to promote the inflammatory process.

RITUXIMAB

- **Rituximab** (Rituxan) is a monoclonal chimeric antibody consisting of human protein with the antigen-binding region derived from a mouse antibody to CD20 protein found on the cell surface of mature B lymphocytes. Binding of rituximab to B cells results in nearly complete depletion of peripheral B cells, with a gradual recovery over several months.
- Rituximab is useful in patients failing MTX or TNF inhibitors. Give methylprednisolone 100 mg 30 minutes prior to rituximab to reduce incidence and severity of infusion reactions. Acetaminophen and antihistamines may also benefit patients who have a history of reactions. MTX should be given concurrently in the usual doses for RA to achieve optimal therapeutic outcomes.

TOCILIZUMAB

- **Tocilizumab** (Actemra) is a humanized monoclonal antibody that attaches to IL-6 receptors, preventing the cytokine from interacting with IL-6 receptors. It is approved for adults with moderately to severely active RA who have failed to respond to one or more anti-TNF biologic agents. It is used as either monotherapy or in combination with MTX or another DMARD.

ANAKINRA

- **Anakinra** (Kineret) is an IL-1 receptor antagonist; it is less effective than other biologic DMARDs and is not included in the current ACR treatment recommendations. However, select patients with refractory disease may benefit. It can be used alone or in combination with any of the other DMARDs except TNF-α inhibitors.

Corticosteroids

- **Corticosteroids** have anti-inflammatory and immunosuppressive properties. They interfere with antigen presentation to T lymphocytes, inhibit prostaglandin and leukotriene synthesis, and inhibit neutrophil and monocyte superoxide radical generation.
- Oral corticosteroids (eg, **prednisone** and **methylprednisolone**) can be used to control pain and synovitis while DMARDs are taking effect ("bridging therapy").
- Low-dose, long-term corticosteroid therapy may be used to control symptoms in patients with difficult-to-control disease. Prednisone doses below 7.5 mg/day (or equivalent) are well tolerated but are not devoid of long-term adverse effects. Use the lowest dose that controls symptoms. Alternate-day dosing of low-dose oral corticosteroids is usually ineffective in RA.
- High-dose oral or IV bursts may be used for several days to suppress disease flares. After symptoms are controlled, taper the drug to the lowest effective dose.

- The intramuscular route is preferable in nonadherent patients. Depot forms (**triamcinolone acetonide**, **triamcinolone hexacetonide**, and **methylprednisolone acetate**) provide 2 to 6 weeks of symptomatic control. Onset of effect may be delayed for several days. The depot effect provides a physiologic taper, avoiding hypothalamic-pituitary axis suppression.
- Intra-articular injections of depot forms may be useful when only a few joints are involved. If effective, injections may be repeated every 3 months. Do not inject any one joint more than two or three times per year.
- Adverse effects of systemic glucocorticoids limit long-term use. Consider dosage tapering and eventual discontinuation at some point during chronic therapy.

EVALUATION OF THERAPEUTIC OUTCOMES

- Clinical signs of improvement include reduction in joint swelling, decreased warmth over actively involved joints, and decreased tenderness to joint palpation.
- Symptom improvement includes reduction in joint pain and morning stiffness, longer time to onset of afternoon fatigue, and improvement in ability to perform daily activities.
- Periodic joint radiographs may be useful in assessing disease progression.
- Laboratory monitoring is of little value in assessing response to therapy but is essential for detecting and preventing adverse drug effects (see **Table 4–2**).
- Ask patients about the presence of symptoms that may be related to adverse drug effects (see **Table 4–3**).

See Chapter 72, Rheumatoid Arthritis, authored by Kimberly Wahl and Arthur A. Schuna, for a detailed discussion of this topic.

CHAPTER 5

Acute Coronary Syndromes

- *Acute coronary syndromes* (ACSs) include all syndromes compatible with acute myocardial ischemia resulting from imbalance between myocardial oxygen demand and supply.
- ACSs are classified according to electrocardiographic (ECG) changes into (1) ST-segment-elevation (STE) myocardial infarction (MI) or (2) non–ST-segment-elevation (NSTE) ACS, which includes NSTE MI and unstable angina (UA).

PATHOPHYSIOLOGY

- Endothelial dysfunction, inflammation, and formation of fatty streaks contribute to development of atherosclerotic coronary artery plaques.
- The cause of ACS in more than 90% of patients is rupture, fissuring, or erosion of an unstable atheromatous plaque. A clot forms on top of the ruptured plaque. Exposure of collagen and tissue factor induces platelet adhesion and activation, which promote release of adenosine diphosphate (ADP) and thromboxane A_2 from platelets producing vasoconstriction and platelet activation. A change in the conformation of the glycoprotein (GP) IIb/IIIa surface receptors of platelets occurs that cross-links platelets to each other through fibrinogen bridges.
- Simultaneously, activation of the extrinsic coagulation cascade occurs as a result of exposure of blood to the thrombogenic lipid core and endothelium, which are rich in tissue factor. This leads to formation of a fibrin clot composed of fibrin strands, cross-linked platelets, and trapped red blood cells.
- Ventricular remodeling occurs after MI and is characterized by left ventricular dilation and reduced pumping function, leading to cardiac failure.
- Complications of MI include cardiogenic shock, heart failure (HF), valvular dysfunction, arrhythmias, pericarditis, stroke secondary to left ventricular (LV) thrombus embolization, venous thromboembolism, and LV free-wall rupture.

CLINICAL PRESENTATION

- Predominant symptom is midline anterior chest discomfort (usually at rest), severe new-onset angina, or increasing angina that lasts at least 20 minutes. Discomfort may radiate to the shoulder, down the left arm, to the back, or to the jaw. Accompanying symptoms may include nausea, vomiting, diaphoresis, and shortness of breath.
- No specific features indicate ACS on physical examination. However, patients with ACS may present with signs of acute HF or arrhythmias.

DIAGNOSIS

- Obtain 12-lead ECG within 10 minutes of presentation. Key findings indicating myocardial ischemia or MI are STE, ST-segment depression, and T-wave inversion. Appearance of a new left bundle-branch block with chest discomfort is highly specific for acute MI. Some patients with myocardial ischemia have no ECG changes, so biochemical markers and other risk factors for coronary artery disease (CAD) should be assessed.
- Biochemical markers of myocardial cell death are important for confirming diagnosis of acute MI. Diagnosis is confirmed with detection of rise and/or fall of cardiac

biomarkers (cardiac troponin preferred) with at least one value above the 99th percentile of the upper reference limit and at least one of the following: (1) symptoms of ischemia; (2) new significant ST-segment–T-wave changes or new left bundle-branch block; (3) pathological Q waves; or (4) imaging evidence of new loss of viable myocardium or new regional wall motion abnormality. Typically, a blood sample is obtained once in the emergency department, then 6 to 9 hours later.

- Patient symptoms, past medical history, ECG, and biomarkers are used to stratify patients into low, medium, or high risk of death, MI, or likelihood of failing pharmacotherapy and needing urgent coronary angiography and percutaneous coronary intervention (PCI).

TREATMENT

- Goals of Treatment: Short-term goals include: (1) early restoration of blood flow to the infarct-related artery to prevent infarct expansion (in the case of MI) or prevent complete occlusion and MI (in UA), (2) prevention of death and other complications, (3) prevention of coronary artery reocclusion, (4) relief of ischemic chest discomfort, and (5) resolution of ST-segment and T-wave changes on ECG. Long-term goals include control of cardiovascular (CV) risk factors, prevention of additional CV events, and improvement in quality of life.

GENERAL APPROACH

- General measures include hospital admission, oxygen if saturation is low, continuous multilead ST-segment monitoring for arrhythmias and ischemia, frequent measurement of vital signs, bedrest for 12 hours in hemodynamically stable patients, use of stool softeners to avoid Valsalva maneuver, and pain relief.
- Obtain serum potassium, magnesium, glucose, and creatinine; baseline complete blood cell count (CBC) and coagulation tests; and fasting lipid panel. Draw lipid panel within the first 24 hours of hospitalization because values for cholesterol (an acute phase reactant) may be falsely low after that period.
- It is important to triage and treat patients according to their risk category (**Fig. 5–1**).
- Patients with STE MI are at high risk of death, so initiate immediate efforts to reestablish coronary perfusion and adjunctive pharmacotherapy.

NONPHARMACOLOGIC THERAPY

- For patients with STE MI presenting within 12 hours of symptom onset, the reperfusion treatment of choice is early reperfusion with primary PCI of the infarct artery within 90 minutes of first medical contact.
- For patients with NSTE ACS, practice guidelines recommend coronary angiography with either PCI or coronary artery bypass graft (CABG) surgery revascularization as early treatment for high-risk patients; such an approach may also be considered for patients not at high risk.

EARLY PHARMACOTHERAPY FOR STE MI (FIG. 5–2)

- In addition to reperfusion therapy, American College of Cardiology Foundation/American Heart Association (ACCF/AHA) guidelines recommend that all patients with STE MI and without contraindications should receive within the first day of hospitalization and preferably in the emergency department: (1) intranasal oxygen (if oxygen saturation is low), (2) sublingual (SL) nitroglycerin (NTG), (3) aspirin, (4) a $P2Y_{12}$ platelet inhibitor, (5) and anticoagulation with bivalirudin, unfractionated heparin (UFH), or enoxaparin.
- Administer a GP IIb/IIIa inhibitor with UFH to patients undergoing primary PCI. Give IV β-blockers and IV NTG to select patients. Initiate oral β-blockers the first day in patients without cardiogenic shock. Administer morphine to patients with refractory angina as an analgesic and venodilator that lowers preload. Start an angiotensin-converting enzyme (ACE) inhibitor within 24 hours in patients who have either anterior wall MI or LVEF of 40% or less and no contraindications.

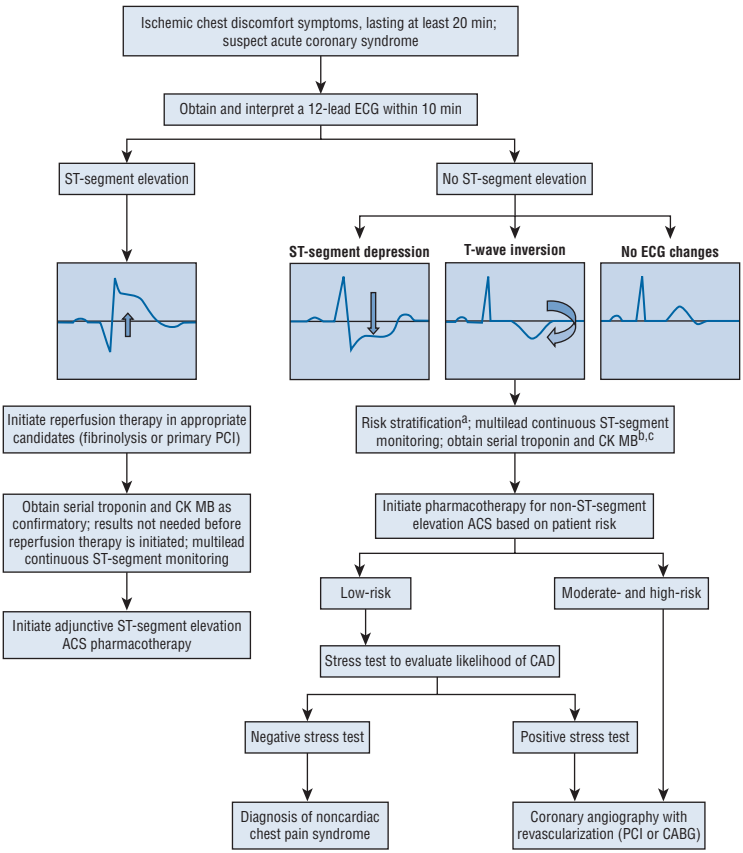


FIGURE 5–1. Evaluation of the acute coronary syndrome patient. [a]As described in textbook Table 7-1. [b]"Positive": Above the myocardial infarction decision limit. [c]"Negative": Below the myocardial infarction decision limit. (ACS, acute coronary syndrome; CABG, coronary artery bypass graft; CAD, coronary artery disease; CK MB, creatine kinase myocardial band; ECG, electrocardiogram; PCI, percutaneous coronary intervention. (Modified with permission from Spinler SA. Evolution of antithrombotic therapy used in acute coronary syndromes. In: Richardson MM, Chant C, Cheng JWM, et al, eds. *Pharmacotherapy Self-Assessment Program. Book 1: Cardiology, 7th ed.* Lenexa, KS: American College of Clinical Pharmacy; 2010.)

Fibrinolytic Therapy

- A fibrinolytic agent is indicated in patients with STE MI presenting within 12 hours of the onset of chest discomfort who have at least 1 mm of STE in two or more contiguous ECG leads and are unable to undergo primary PCI within 120 minutes of medical contact. Limit use of fibrinolytics between 12 and 24 hours after symptom onset to patients with ongoing ischemia.
- It is not necessary to obtain the results of biochemical markers before initiating fibrinolytic therapy.
- Absolute contraindications to fibrinolytic therapy include: (1) history of hemorrhagic stroke (at any time), (2) ischemic stroke within 3 months, (3) active internal bleeding, (4) known intracranial neoplasm, (5) known structural cerebrovascular lesion, (6)

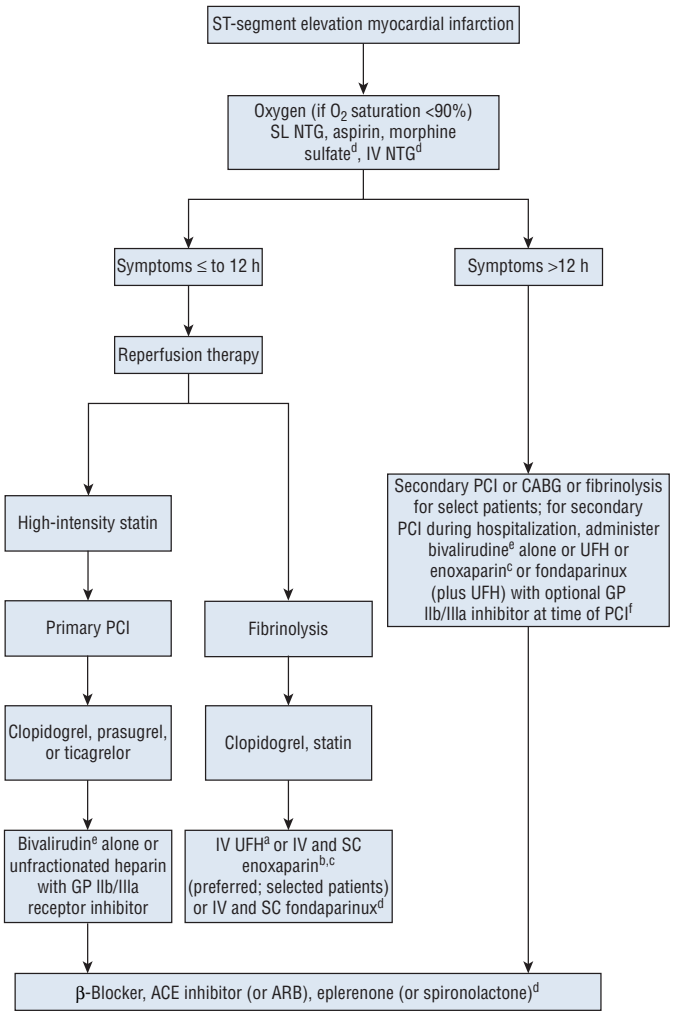


FIGURE 5–2. Initial pharmacotherapy for ST-segment elevation myocardial infarction. [a]For at least 48 hours. [b]See textbook Table 24–2 for dosing and specific types of patients who should not receive enoxaparin. [c]For the duration of hospitalization, up to 8 days. [d]For select patients, see textbook Table 24–2. [e]If pretreated with UFH, stop UFH infusion for 30 minutes prior to administration of bivalirudin (bolus plus infusion). [f] Increased risk of major bleeding and ICH if a GP IIb/IIIa inhibitor is added to an anticoagulant for PCI following fibrinolysis, especially in the elderly; weigh risk versus benefit (ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; CABG, coronary artery bypass graft surgery; GP, glycoprotein; NTG, nitroglycerin; PCI, percutaneous coronary intervention; SC, subcutaneous; SL, sublingual; UFH, unfractionated heparin.) (Modified with permission from Spinler SA. Evolution of antithrombotic therapy used in acute coronary syndromes. In: Richardson MM, Chant C. Cheng JWM, et al, eds. *Pharmacotherapy Self-Assessment Program*. 7th ed. Book 1: *Cardiology*. Lenexa, KS: American College of Clinical Pharmacy; 2010.)

suspected aortic dissection, and (7) significant closed head or facial trauma within 3 months. Primary PCI is preferred in these situations.

- A fibrin-specific agent (alteplase, reteplase, or tenecteplase) is preferred over the non–fibrin-specific agent streptokinase.
- Treat eligible patients as soon as possible, but preferably within 30 minutes from the time they present to the emergency department, with one of the following regimens:
  - ✓ **Alteplase:** 15 mg IV bolus followed by 0.75 mg/kg infusion (maximum 50 mg) over 30 minutes, followed by 0.5 mg/kg infusion (maximum 35 mg) over 60 minutes (maximum dose 100 mg)
  - ✓ **Reteplase:** 10 units IV over 2 minutes, followed 30 minutes later with another 10 units IV over 2 minutes
  - ✓ **Tenecteplase:** A single IV bolus dose given over 5 seconds based on patient weight: 30 mg if less than 60 kg; 35 mg if 60 to 69.9 kg; 40 mg if 70 to 79.9 kg; 45 mg if 80 to 89.9 kg; and 50 mg if 90 kg or greater
  - ✓ **Streptokinase:** 1.5 million units in 50 mL of normal saline or 5% dextrose in water IV over 60 minutes
- Intracranial hemorrhage (ICH) and major bleeding are the most serious side effects. The risk of ICH is higher with fibrin-specific agents than with streptokinase. However, the risk of systemic bleeding other than ICH is higher with streptokinase than with fibrin-specific agents.

Aspirin

- Administer **aspirin** to all patients without contraindications within 24 hours before or after hospital arrival. It provides additional mortality benefit in patients with STE ACS when given with fibrinolytic therapy.
- In patients experiencing an ACS, non–enteric-coated aspirin, 160 to 325 mg, should be chewed and swallowed as soon as possible after the onset of symptoms or immediately after presentation to the emergency department regardless of the reperfusion strategy being considered. Patients undergoing PCI not previously taking aspirin should receive 325 mg non–enteric-coated aspirin.
- A daily maintenance dose of 75 to 162 mg is recommended thereafter and should be continued indefinitely. Because of increased bleeding risk in patients receiving aspirin plus a $P2Y_{12}$ inhibitor, low-dose aspirin (81 mg daily) is preferred following PCI.
- Discontinue other nonsteroidal anti-inflammatory drugs (NSAIDs) and cyclooxygenase-2 (COX-2) selective inhibitors at the time of STE MI due to increased risk of death, reinfarction, HF, and myocardial rupture.
- The most frequent side effects of aspirin include dyspepsia and nausea. Inform patients about the risk of GI bleeding.

Platelet $P2Y_{12}$ Inhibitors

- **Clopidogrel**, **prasugrel**, and **ticagrelor** block a subtype of ADP receptor (the $P2Y_{12}$ receptor) on platelets, preventing binding of ADP to the receptor and subsequent expression of platelet GP IIb/IIIa receptors, reducing platelet aggregation.
- A $P2Y_{12}$ receptor inhibitor in addition to aspirin is recommended for all patients with STE MI. For patients undergoing primary PCI, give clopidogrel, prasugrel, or ticagrelor, in addition to aspirin, to prevent subacute stent thrombosis and longer-term CV events.
- The recommended duration of $P2Y_{12}$ inhibitors for a patient undergoing PCI (either STE MI or NSTE ACS) is at least 12 months for patients receiving either a bare metal or drug-eluting stent.
- If CABG surgery is planned, withhold clopidogrel and ticagrelor for 5 days, and prasugrel at least 7 days, to reduce risk of postoperative bleeding, unless the need for revascularization outweighs the bleeding risk.
- **Clopidogrel:** 300 mg oral loading dose followed by 75 mg orally daily in patients receiving a fibrinolytic or who do not receive reperfusion therapy. Avoid loading dose in patients aged 75 years or more. A 600-mg oral loading dose is recommended before primary PCI, except that 300 mg should be given if within 24 hours of fibrinolytic therapy.

- **Prasugrel:** 60 mg oral loading dose followed by 10 mg orally once daily for patients weighing 60 kg (132 lb) or more.
- **Ticagrelor:** 180 mg oral loading dose in patients undergoing PCI, followed by 90 mg orally twice daily.
- The most frequent side effects of clopidogrel and prasugrel include nausea, vomiting, and diarrhea, (2%–5% of patients). Thrombotic thrombocytopenic purpura (TTP) has been reported rarely with clopidogrel. Ticagrelor is associated with nausea (4%), diarrhea (3%), dyspnea (14%), and, rarely, ventricular pauses and bradyarrhythmias.
- In patients with STE MI receiving fibrinolysis, early therapy with clopidogrel 75 mg once daily during hospitalization and up to 28 days reduces mortality and reinfarction without increasing risk of major bleeding. In adults younger than 75 years receiving fibrinolytics, the first dose of clopidogrel can be a 300-mg loading dose.
- For patients with STE MI who do not undergo reperfusion therapy with either primary PCI or fibrinolysis, clopidogrel is the preferred $P2Y_{12}$ inhibitor added to aspirin and should be continued for at least 14 days (and up to 1 year). Ticagrelor may also be an option in medically managed patients with ACS.

Glycoprotein IIb/IIIa Receptor Inhibitors

- GP IIb/IIIa receptor inhibitors block the final common pathway of platelet aggregation, namely cross-linking of platelets by fibrinogen bridges between the GP IIb and IIIa receptors on the platelet surface.
- Abciximab (IV or intracoronary administration), eptifibatide, or tirofiban may be administered in patients with STE MI undergoing primary PCI who are treated with UFH. Do not administer GP IIb/IIIa inhibitors to patients with STE MI who will not be undergoing PCI.
- **Abciximab:** 0.25 mg/kg IV bolus given 10 to 60 minutes before the start of PCI, followed by 0.125 mcg/kg/min (maximum 10 mcg/min) for 12 hours.
- **Eptifibatide:** 180 mcg/kg IV bolus, repeated in 10 minutes, followed by infusion of 2 mcg/kg/min for 18 to 24 hours after PCI.
- **Tirofiban:** 25 mcg/kg IV bolus, then 0.15 mcg/kg/min up to 18 to 24 hours after PCI.
- Routine use of a GP IIb/IIIa receptor inhibitor is not recommended in patients who have received fibrinolytics or in those receiving bivalirudin because of increased bleeding risk.
- Bleeding is the most significant adverse effect. Do not use GP IIb/IIIa inhibitors in patients with a history of hemorrhagic stroke or recent ischemic stroke. Risk of bleeding is increased in patients with chronic kidney disease; reduce the dose of eptifibatide and tirofiban in renal impairment. An immune-mediated thrombocytopenia occurs in approximately 5% of patients with abciximab and fewer than 1% of patients receiving eptifibatide or tirofiban.

Anticoagulants

- Either **UFH** or **bivalirudin** is preferred for patients undergoing primary PCI, whereas for fibrinolysis, either UFH, **enoxaparin**, or **fondaparinux** may be used.
- UFH initial dose for primary PCI is 50 to 70 units/kg IV bolus if a GP IIb/IIIa inhibitor is planned and 70 to 100 U/kg IV bolus if no GP IIb/IIIa inhibitor is planned; give supplemental IV bolus doses to maintain the target activated clotting time (ACT).
- UFH initial dose with fibrinolytics is 60 U/kg IV bolus (maximum 4000 units), followed by constant IV infusion of 12 U/kg/h (maximum 1000 U/h). Adjust the UFH infusion dose frequently to maintain a target activated partial thromboplastin time (aPTT) of 1.5 to 2 times control (50–70 seconds). Measure the first aPTT at 3 hours in patients with STE ACS who are treated with fibrinolytics and at 4 to 6 hours in patients not receiving thrombolytics or undergoing primary PCI.
- Enoxaparin dose is 1 mg/kg subcutaneous (SC) every 12 hours (creatinine clearance [Cl_{cr}] ≥30 mL/min) or 24 hours if impaired renal function (Cl_{cr} 15–29 mL/min). For patients with STE MI receiving fibrinolytics, enoxaparin 30 mg IV bolus is followed immediately by 1 mg/kg SC every 12 hours if younger than 75 years. In patients

75 years and older, give enoxaparin 0.75 mg/kg SC every 12 hours. Continue enoxaparin throughout hospitalization or up to 8 days.
- Bivalirudin dose for PCI in STE MI is 0.75 mg/kg IV bolus, followed by 1.75 mg/kg/h infusion. Discontinue at the end of PCI or continue at 0.25 mg/kg/h if prolonged anticoagulation is necessary.
- Fondaparinux dose is 2.5 mg IV bolus followed by 2.5 mg SC once daily starting on hospital day 2.
- For patients undergoing PCI, discontinue anticoagulation immediately after the procedure. In patients receiving an anticoagulant plus a fibrinolytic, continue UFH for a minimum of 48 hours and enoxaparin and fondaparinux for the duration of hospitalization, up to 8 days. In patients who do not undergo reperfusion therapy, anticoagulant therapy may be administered for up to 48 hours for UFH or for the duration of hospitalization for enoxaparin or fondaparinux.

β-Adrenergic Blockers

- If no contraindications, administer a β-blocker early (within the first 24 hours) and continue indefinitely.
- Benefits result from blockade of β_1 receptors in the myocardium, which reduces heart rate, myocardial contractility, and BP, thereby decreasing myocardial oxygen demand. Reduced heart rate increases diastolic time, thus improving ventricular filling and coronary artery perfusion.
- β-Blockers reduce risk for recurrent ischemia, infarct size, reinfarction, and ventricular arrhythmias.
- Usual doses of β-blockers, with target resting heart rate of 50 to 60 beats/min:
  - ✓ **Metoprolol:** 5 mg by slow (over 1–2 minutes) IV bolus, repeated every 5 minutes for total initial dose of 15 mg. If a conservative regimen is desired, reduce initial doses to 1 to 2 mg. Follow in 1 to 2 hours by 25 to 50 mg orally every 6 hours. If appropriate, initial IV therapy may be omitted.
  - ✓ **Propranolol:** 0.5 to 1 mg slow IV push, followed in 1 to 2 hours by 40 to 80 mg orally every 6 to 8 hours. If appropriate, the initial IV therapy may be omitted.
  - ✓ **Atenolol:** 5 mg IV dose, followed 5 minutes later by a second 5 mg IV dose, then 50 to 100 mg orally once daily beginning 1 to 2 hours after the IV dose. The initial IV therapy may be omitted.
- The most serious side effects early in ACS include hypotension, acute HF, bradycardia, and heart block. Initial acute administration of β-blockers is not appropriate for patients presenting with acute HF but may be attempted in most patients before discharge after treatment of acute HF.
- Continue β-blockers for at least 3 years in patients with normal LV function and indefinitely in patients with LV systolic dysfunction and LVEF of 40% or less.

Statins

- Administer a high-intensity statin, either **atorvastatin** 80 mg or **rosuvastatin** 40 mg, to all patients prior to PCI (regardless of prior lipid-lowering therapy) to reduce the frequency of periprocedural MI following PCI.

Nitrates

- NTG causes venodilation, which lowers preload and myocardial oxygen demand. In addition, arterial vasodilation may lower BP, thereby reducing myocardial oxygen demand. Arterial dilation also relieves coronary artery vasospasm and improves myocardial blood flow and oxygenation.
- Immediately upon presentation, administer one **SL NTG** tablet (0.4 mg) every 5 minutes for up to three doses to relieve chest pain and myocardial ischemia.
- **Intravenous NTG** is indicated for patients with an ACS who do not have a contraindication and who have persistent ischemia, HF, or uncontrolled high BP. The usual dose is 5 to 10 mcg/min by continuous infusion, titrated up to 100 mcg/min until relief of symptoms or limiting side effects (eg, headache or hypotension). Continue treatment for approximately 24 hours after ischemia is relieved.

- Oral nitrates play a limited role in ACS because clinical trials have failed to show a mortality benefit for IV followed by oral nitrate therapy in acute MI.
- The most significant adverse effects of nitrates include tachycardia, flushing, headache, and hypotension. Nitrates are contraindicated in patients who have taken the oral phosphodiesterase-5 inhibitors sildenafil or vardenafil within the prior 24 hours or tadalafil within the prior 48 hours.

Calcium Channel Blockers

- After STE MI, calcium channel blockers (CCBs) are used for relief of ischemic symptoms in patients who have contraindications to β-blockers. There is little clinical benefit beyond symptom relief, so avoid CCBs in acute management of all ACSs unless there is a clear symptomatic need or contraindication to β-blockers.
- A CCB that lowers heart rate (diltiazem or verapamil) is preferred unless the patient has LV systolic dysfunction, bradycardia, or heart block. In those cases, either amlodipine or felodipine is preferred. Avoid nifedipine because it causes reflex sympathetic activation, tachycardia, and worsened myocardial ischemia.
  - ✓ **Diltiazem:** 120 to 360 mg sustained release orally once daily
  - ✓ **Verapamil:** 180 to 480 mg sustained release orally once daily
  - ✓ **Amlodipine:** 5 to 10 mg orally once daily

EARLY PHARMACOTHERAPY FOR NSTE ACS (FIG. 5–3)

- Early pharmacotherapy for NSTE ACS is similar to that for STE ACS.
- In absence of contraindications, treat all patients in the emergency department with **intranasal oxygen** (if oxygen saturation is low), **SL NTG**, **aspirin**, and an **anticoagulant** (**UFH**, **enoxaparin**, **fondaparinux**, or **bivalirudin**).
- High-risk patients should proceed to early angiography and may receive a GP IIb/IIIa inhibitor (optional with either UFH or enoxaparin but should be avoided with bivalirudin).
- Administer a **$P2Y_{12}$ inhibitor** to all patients.
- Give **IV β-blockers** and **IV NTG** to select patients.
- Initiate **oral β-blockers** within the first 24 hours in patients without cardiogenic shock.
- Give **morphine** to patients with refractory angina, as described previously.
- Fibrinolytic therapy is never administered in NSTE ACS.

Aspirin

- **Aspirin** reduces risk of death or MI by approximately 50% compared with no antiplatelet therapy in patients with NSTE ACS. Dosing of aspirin is the same as for STE ACS, and aspirin is continued indefinitely.

Anticoagulants

- For patients treated by an early invasive approach with early coronary angiography and PCI, administer **UFH**, **enoxaparin**, or **bivalirudin**.
- If an initial conservative strategy is planned (no coronary angiography or revascularization), enoxaparin, UFH, or low-dose **fondaparinux** is recommended.
- Continue therapy for at least 48 hours for UFH, until the patient is discharged from the hospital (or 8 days, whichever is shorter) for either enoxaparin or fondaparinux, and until the end of the PCI or angiography procedure (or up to 72 hours after PCI) for bivalirudin.
- For NSTE ACS, the dose of UFH is 60 U/kg IV bolus (maximum 4000 units), followed by a continuous IV infusion of 12 U/kg/h (maximum 1000 U/h). Titrate the dose to maintain aPTT between 1.5 and 2 times control.

$P2Y_{12}$ Inhibitors

- When an initial invasive strategy is selected, there are two initial options for dual antiplatelet therapy depending on choice of $P2Y_{12}$ inhibitor:
  1. Aspirin plus early use of clopidogrel or ticagrelor (in the emergency department)
  2. Aspirin plus double-bolus dose eptifibatide plus an eptifibatide infusion or high-dose tirofiban bolus plus infusion administered at the time of PCI.

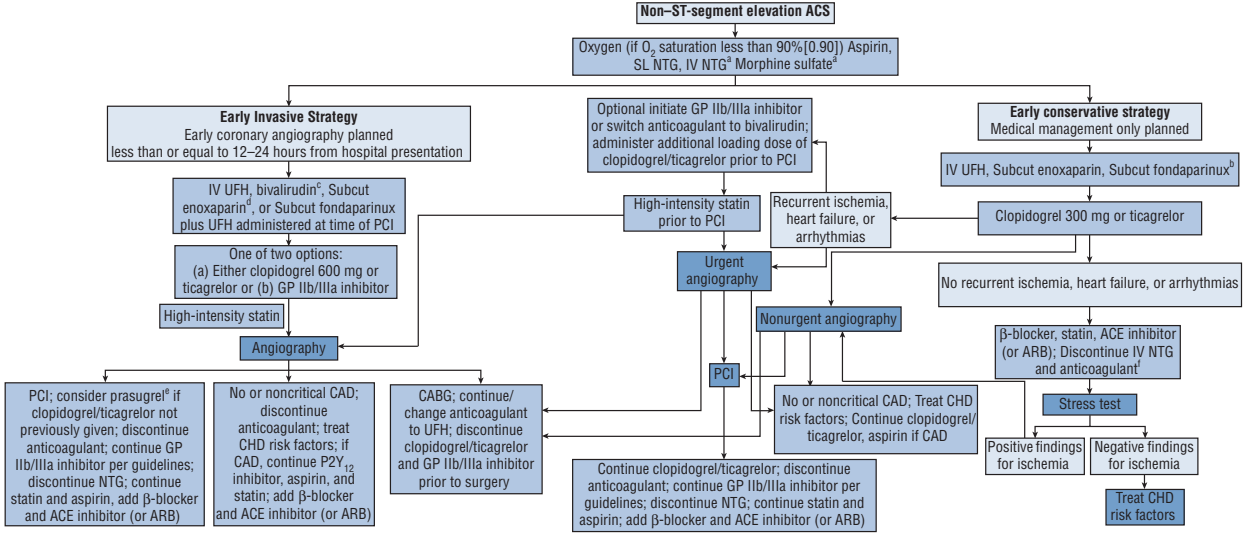


FIGURE 5–3. Initial pharmacotherapy for non–ST-segment elevation ACS. [a]For selected patients. [b]Preferred in patients at high risk for bleeding. [c]If pretreated with UFH, stop UFH infusion for 30 minutes prior to administration of bivalirudin bolus plus infusion. [d]May require IV supplemental dose of enoxaparin. [e]Do not use if prior history of stroke/TIA, age older than 75 years, or body weight 60 kg or less. [f]SC enoxaparin or UFH can be continued at a lower dose for venous thromboembolism prophylaxis. (ACS, acute coronary syndrome; ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; CABG, coronary artery bypass graft; CAD, coronary artery disease; CHD, coronary heart disease; GP, glycoprotein; IV, intravenous; NSTE, non–ST-segment elevation; NTG, nitroglycerin; PCI, percutaneous coronary intervention; SC, subcutaneous; SL, sublingual; STE MI, ST-segment-elevation myocardial infarction; TIA, transient ischemic attack; UFH, unfractionated heparin.) (Modified with permission from Spinler SA, de Denus S. Acute coronary syndromes. In: Chisholm-Burns M, Wells BG, Schwinghammer TL, Malone PM, Kolesar JM, DiPiro JT, eds. *Pharmacotherapy Principles and Practice*. 3rd ed. New York, NY: McGraw-Hill; 2013:133–167.)

- For subsequent antiplatelet therapy in patients undergoing PCI initially treated with regimen 1 above, a GP IIb/IIIa inhibitor (abciximab, eptifibatide, or high-dose tirofiban) can be added, and then clopidogrel continued with low-dose ASA.
- For patients undergoing PCI initially treated with option 2, clopidogrel, prasugrel, or ticagrelor can be started within 1 hour after PCI and the $P2Y_{12}$ inhibitor continued with low-dose aspirin. Following PCI, continue dual oral antiplatelet therapy for at least 12 months.
- For patients receiving an initial conservative strategy, either clopidogrel or ticagrelor can be administered in addition to aspirin. Continue dual antiplatelet therapy for at least 12 months.

Glycoprotein IIb/IIIa Receptor Inhibitors

- The role of GP IIb/IIIa inhibitors in NSTE ACS is diminishing as $P2Y_{12}$ inhibitors are used earlier, and bivalirudin is often selected as the anticoagulant.
- Routine administration of eptifibatide (added to aspirin and clopidogrel) prior to angiography and PCI in NSTE ACS does not reduce ischemic events and increases bleeding risk. Therefore, the two antiplatelet initial therapy options described in the previous section are preferred.
- For low-risk patients and a conservative management strategy, there is no role for routine GP IIb/IIIa inhibitors because bleeding risk exceeds the benefit.

Nitrates

- Administer SL NTG followed by IV NTG to patients with NSTE ACS and ongoing ischemia, HF, or uncontrolled high BP. Continue IV NTG for approximately 24 hours after ischemia relief.

β-Blockers

- In the absence of contraindications, administer oral β-blockers to all patients with NSTE ACS within 24 hours of hospital admission. Benefits are assumed to be similar to those seen in patients with STE MI.
- Continue β-blockers indefinitely in patients with LVEF of 40% or less and for at least 3 years in patients with normal LV function.

Calcium Channel Blockers

- As described previously for STE ACS, CCBs should not be administered to most patients with ACS.

SECONDARY PREVENTION FOLLOWING MI

- Goals of Treatment: The long-term goals after MI are to: (1) control modifiable coronary heart disease (CHD) risk factors; (2) prevent development of systolic HF; (3) prevent recurrent MI and stroke; (4) prevent death, including sudden cardiac death; and (5) prevent stent thrombosis after PCI.

PHARMACOTHERAPY

- Start pharmacotherapy that has been proven to decrease mortality, HF, reinfarction or stroke, and stent thrombosis prior to hospital discharge for secondary prevention.
- After MI from either STE MI or NSTE ACS, all patients (in the absence of contraindications) should receive indefinite treatment with aspirin (or clopidogrel if aspirin contraindications), an ACE inhibitor, and a "high-intensity" statin for secondary prevention of death, stroke, or recurrent infarction.
- Start ACE inhibitors and continue indefinitely in all patients after MI to reduce mortality, decrease reinfarction, and prevent HF. Most patients with CAD (not just those

with ACS or HF) benefit from an ACE inhibitor. The dose should be low initially and titrated to the dose used in clinical trials if tolerated, for example:
✓ **Captopril:** 6.25 to 12.5 mg initially; target dose 50 mg two or three times daily
✓ **Enalapril:** 2.5 to 5 mg initially; target dose 10 mg twice daily
✓ **Lisinopril:** 2.5 to 5 mg initially; target dose 10 to 20 mg once daily
✓ **Ramipril:** 1.25 to 2.5 mg initially; target dose 5 mg twice daily or 10 mg once daily
✓ **Trandolapril:** 1 mg initially; target dose 4 mg once daily

- An angiotensin receptor blocker may be prescribed for patients with ACE inhibitor cough and a low LVEF and HF after MI:
  ✓ **Candesartan:** 4 to 8 mg initially; target dose 32 mg once daily
  ✓ **Valsartan:** 40 mg initially; target dose 160 mg twice daily
- Continue a β-blocker for at least 3 years in patients without HF or an ejection fraction of 40% or less and indefinitely in patients with LV systolic dysfunction or HF symptoms. A CCB can be used to prevent anginal symptoms in patients who cannot tolerate or have contraindications to β-blockers but should not be used routinely in the absence of such findings.
- Continue a $P2Y_{12}$ inhibitor for at least 12 months for patients undergoing PCI and for patients with NSTE ACS receiving a medical management strategy. Continue clopidogrel for at least 14 days in patients with STE MI not undergoing PCI.
- To reduce mortality, consider a mineralocorticoid receptor antagonist (eplerenone or spironolactone) within the first 7 days after MI in all patients already receiving an ACE inhibitor (or ARB) and a β-blocker and have an LVEF of 40% or less and either HF symptoms or diabetes mellitus. The drugs are continued indefinitely.
  ✓ **Eplerenone:** 25 mg initially; target dose 50 mg once daily
  ✓ **Spironolactone:** 12.5 mg initially; target dose 25 to 50 mg once daily
- All patients with CAD should receive dietary counseling and a statin to reach appropriate targets based on current practice guidelines.
- Prescribe a short-acting SL NTG or lingual NTG spray for all patients to relieve anginal symptoms when necessary. Chronic long-acting nitrates have not been shown to reduce CHD events after MI and are not used in ACS patients who have undergone revascularization unless the patient has chronic stable angina or significant coronary stenosis that was not revascularized.
- For all ACS patients, treat and control modifiable risk factors such as hypertension (HTN), dyslipidemia, obesity, smoking, and DM.

EVALUATION OF THERAPEUTIC OUTCOMES

- Monitoring parameters for efficacy for both STE and NSTE ACS include: (1) relief of ischemic discomfort, (2) return of ECG changes to baseline, and (3) absence or resolution of HF signs and symptoms.
- Monitoring parameters for adverse effects are dependent on the individual drugs used. In general, the most common adverse reactions from ACS therapies include hypotension and bleeding.

See Chapter 7, Acute Coronary Syndromes, authored by Sarah A. Spinler and Simon De Denus, for a more detailed discussion of this topic.

Arrhythmias

CHAPTER 6

- *Arrhythmia* is loss of cardiac rhythm, especially irregularity of heartbeat.

PATHOPHYSIOLOGY

SUPRAVENTRICULAR ARRHYTHMIAS

- Common supraventricular tachycardias requiring drug treatment are atrial fibrillation (AF), atrial flutter, and paroxysmal supraventricular tachycardia (PSVT). Other arrhythmias that usually do not require drug therapy are not discussed here (eg, premature atrial complexes, sinus arrhythmia, sinus tachycardia).

Atrial Fibrillation and Atrial Flutter

- AF has extremely rapid (400–600 atrial beats/min) and disorganized atrial activation. There is loss of atrial contraction (atrial kick), and supraventricular impulses penetrate the atrioventricular (AV) conduction system to variable degrees, resulting in irregular ventricular activation and irregularly irregular pulse (120–180 beats/min).
- Atrial flutter has rapid (270–330 atrial beats/min) but regular atrial activation. Ventricular response usually has a regular pattern and a pulse of 300 beats/min. This arrhythmia occurs less frequently than AF but has similar precipitating factors, consequences, and drug therapy.
- The predominant mechanism of AF and atrial flutter is reentry, which is usually associated with organic heart disease that causes atrial distention (eg, ischemia or infarction, hypertensive heart disease, and valvular disorders). Additional associated disorders include acute pulmonary embolus and chronic lung disease, resulting in pulmonary hypertension and cor pulmonale, and states of high adrenergic tone such as thyrotoxicosis, alcohol withdrawal, sepsis, and excessive physical exertion.

Paroxysmal Supraventricular Tachycardia Caused by Reentry

- PSVT arising by reentrant mechanisms includes arrhythmias caused by AV nodal reentry, AV reentry incorporating an anomalous AV pathway, sinoatrial (SA) nodal reentry, and intraatrial reentry.

VENTRICULAR ARRHYTHMIAS

Premature Ventricular Complexes

- Premature ventricular complexes (PVCs) can occur in patients with or without heart disease.

Ventricular Tachycardia

- Ventricular tachycardia (VT) is defined by three or more repetitive PVCs occurring at a rate greater than 100 beats/min. It is a wide QRS tachycardia that may result acutely from severe electrolyte abnormalities (hypokalemia or hypomagnesemia), hypoxia, drug toxicity (eg, digoxin), or (most commonly) during an acute myocardial infarction (MI) or ischemia complicated by heart failure (HF). The chronic recurrent form is almost always associated with organic heart disease (eg, idiopathic dilated cardiomyopathy or remote MI with left ventricular [LV] aneurysm).
- Sustained VT is that which requires intervention to restore a stable rhythm or persists a relatively long time (usually >30 s). Nonsustained VT self-terminates after a brief duration (usually <30 s). *Incessant VT* refers to VT occurring more frequently than sinus rhythm, so that VT becomes the dominant rhythm. Monomorphic VT has a consistent QRS configuration, whereas polymorphic VT has varying QRS complexes. Torsade de pointes (TdP) is a polymorphic VT in which the QRS complexes appear to undulate around a central axis.

Ventricular Proarrhythmia

- *Proarrhythmia* refers to the development of a significant new arrhythmia, such as VT, ventricular fibrillation (VF), or TdP, or worsening of an existing arrhythmia. Proarrhythmia results from the same mechanisms that cause other arrhythmias or from an alteration in the underlying substrate due to the antiarrhythmic agent. TdP is a rapid form of polymorphic VT associated with evidence of delayed ventricular repolarization due to blockade of potassium conductance. TdP may be hereditary or acquired. Acquired forms are associated with many clinical conditions and drugs, especially class Ia and class III I_{Kr} blockers.

Ventricular Fibrillation

- VF is electrical anarchy of the ventricle resulting in no cardiac output and cardiovascular collapse. Sudden cardiac death occurs most commonly in patients with coronary artery disease and those with LV dysfunction. VF associated with acute MI may be classified as either (1) primary (an uncomplicated MI not associated with HF) or (2) secondary or complicated (an MI complicated by HF).

BRADYARRHYTHMIAS

- Sinus bradyarrhythmias (heart rate <60 beats/min) are common, especially in young, athletically active individuals, and are usually asymptomatic and do not require intervention. However, some patients have sinus node dysfunction (sick sinus syndrome) because of underlying organic heart disease and the normal aging process, which attenuates SA nodal function. Sinus node dysfunction is usually representative of diffuse conduction disease, which may be accompanied by AV block and by paroxysmal tachycardias such as AF. Alternating bradyarrhythmias and tachyarrhythmias are referred to as the tachy–brady syndrome.
- AV block or conduction delay may occur in any area of the AV conduction system. AV block may be found in patients without underlying heart disease (eg, trained athletes) or during sleep when vagal tone is high. It may be transient when the underlying etiology is reversible (eg, myocarditis, myocardial ischemia, after cardiovascular surgery, or during drug therapy). β-Blockers, digoxin, or nondihydropyridine calcium antagonists may cause AV block, primarily in the AV nodal area. Class I antiarrhythmics may exacerbate conduction delays below the level of the AV node. AV block may be irreversible if the cause is acute MI, rare degenerative diseases, primary myocardial disease, or congenital heart disease.

CLINICAL PRESENTATION

- Supraventricular tachycardias may cause clinical manifestations ranging from no symptoms to minor palpitations or irregular pulse to severe and even life-threatening symptoms. Patients may experience dizziness or acute syncopal episodes, symptoms of HF, anginal chest pain, or, more often, a choking or pressure sensation during the tachycardia episode.
- AF or atrial flutter may be manifested by the entire range of symptoms associated with other supraventricular tachycardias, but syncope is uncommon. Arterial embolization from atrial stasis and poorly adherent mural thrombi may result in embolic stroke.
- PVCs often cause no symptoms or only mild palpitations. The presentation of VT may vary from totally asymptomatic to pulseless hemodynamic collapse. Consequences of proarrhythmia range from no symptoms to worsening of symptoms to sudden death. VF results in hemodynamic collapse, syncope, and cardiac arrest.
- Patients with bradyarrhythmias experience symptoms associated with hypotension, such as dizziness, syncope, fatigue, and confusion. If LV dysfunction exists, patients may experience worsening HF symptoms.

DIAGNOSIS

- Electrocardiogram (ECG) is the cornerstone of diagnosis for cardiac rhythm disturbances.
- Cardiac auscultation can reveal the irregularly irregular pulse characteristic of AF.
- Proarrhythmia can be difficult to diagnose because of the variable nature of underlying arrhythmias.
- TdP is characterized by long QT intervals or prominent U waves on the surface ECG.
- Specific maneuvers may be required to delineate the etiology of syncope associated with bradyarrhythmias. Diagnosis of carotid sinus hypersensitivity can be confirmed by performing carotid sinus massage with ECG and blood pressure monitoring. Vasovagal syncope can be diagnosed using the upright body-tilt test.
- Based on ECG findings, AV block is usually categorized as first-, second-, or third-degree AV block.

TREATMENT

- Goals of Treatment: The desired outcome depends on the underlying arrhythmia. For example, the goals of treating AF or atrial flutter are restoring sinus rhythm, preventing thromboembolic complications, and preventing further recurrences.

GENERAL APPROACH

- Use of antiarrhythmic drugs has declined because major trials showed increased mortality with use in several situations, the realization of proarrhythmia as a significant side effect, and the advancing technology of nondrug therapies, such as ablation and the implantable cardioverter-defibrillator (ICD).

CLASSIFICATION OF ANTIARRHYTHMIC DRUGS

- Drugs may depress the automatic properties of abnormal pacemaker cells by decreasing the slope of phase 4 depolarization and/or by elevating threshold potential. Drugs may alter conduction characteristics of the pathways of a reentrant loop.
- The Vaughan Williams classification is most frequently used (**Table 6–1**). Class Ia drugs slow conduction velocity, prolong refractoriness, and decrease the automatic properties of sodium-dependent (normal and diseased) conduction tissue. Class Ia drugs are effective for both supraventricular and ventricular arrhythmias.
- Although categorized separately, class Ib drugs probably act similarly to class Ia drugs, except that class Ib agents are considerably more effective in ventricular than supraventricular arrhythmias.
- Class Ic drugs slow conduction velocity while leaving refractoriness relatively unaltered. Although effective for both ventricular and supraventricular arrhythmias, their use for ventricular arrhythmias has been limited by the risk of proarrhythmia.
- Class I drugs are sodium channel blockers. Antiarrhythmic sodium channel receptor principles account for drug combinations that are additive (eg, **quinidine** and **mexiletine**) and antagonistic (eg, **flecainide** and **lidocaine**), as well as potential antidotes to excess sodium channel blockade (sodium bicarbonate).
- Class II drugs include **β-adrenergic antagonists**; effects result from antiadrenergic actions. β-Blockers are most useful in tachycardias in which nodal tissues are abnormally automatic or are a portion of a reentrant loop. These agents are also helpful in slowing ventricular response in atrial tachycardias (eg, AF) by effects on the AV node.
- Class III drugs prolong refractoriness in atrial and ventricular tissue and include very different drugs that share the common effect of delaying repolarization by blocking potassium channels.

  ✓ **Amiodarone** and **sotalol** are effective in most supraventricular and ventricular tachycardias. Amiodarone displays electrophysiologic characteristics consistent with each type of antiarrhythmic drug. It is a sodium channel blocker with relatively fast on-off kinetics, has nonselective β-blocking actions, blocks potassium channels, and has slight calcium-blocking activity. Sotalol inhibits outward potassium movement during repolarization and also possesses nonselective β-blocking actions.

TABLE 6–1 Classification of Antiarrhythmic Drugs

Class	Drug	Conduction Velocity[a]	Refractory Period	Automaticity	Ion Block
Ia	Quinidine Procainamide Disopyramide	↓	↑	↓	Sodium (intermediate) Potassium
Ib	Lidocaine Mexiletine	0/↓	↓	↓	Sodium (fast on/off)
Ic	Flecainide Propafenone[b]	↓↓	0	↓	Sodium (slow on/off)
II[c]	β-Blockers	↓	↑	↓	Calcium (indirect)
III	Amiodarone[d] Dofetilide Dronedarone[d] Sotalol[b] Ibutilide	0	↑↑	0	Potassium
IV[c]	Verapamil Diltiazem	↓	↑	↓	Calcium

0, no change; ↑, increased; ↓, decreased.
[a] Variables for normal tissue models in ventricular tissue.
[b] Also has β-blocking actions.
[c] Variables for sinoatrial and atrioventricular nodal tissue only.
[d] Also has sodium, calcium, and β-blocking actions.

✓ **Dronedarone**, **ibutilide**, and **dofetilide** are indicated only for treatment of supraventricular arrhythmias.

- Class IV drugs inhibit calcium entry into cells, which slows conduction, prolongs refractoriness, and decreases SA and AV nodal automaticity. **Calcium channel antagonists** are effective for automatic or reentrant tachycardias that arise from or use the SA or AV nodes.
- See **Table 6–2** for recommended doses of oral antiarrhythmic drugs, **Table 6–3** for usual IV antiarrhythmic doses, and **Table 6–4** for common side effects.

ATRIAL FIBRILLATION OR ATRIAL FLUTTER

- Treatment of AF involves several sequential goals. First, evaluate need for acute treatment (usually with drugs that slow ventricular rate). Next, consider methods to restore sinus rhythm, considering risks involved (eg, thromboembolism). Lastly, consider ways to prevent long-term complications, such as recurrent arrhythmia and thromboembolism (**Fig. 6–1**).
- In patients with new-onset AF or atrial flutter with signs and/or symptoms of hemodynamic instability (eg, severe hypotension, angina, and/or pulmonary edema), direct-current cardioversion (DCC) is indicated to restore sinus rhythm immediately (without regard to the risk of thromboembolism).
- If patients are hemodynamically stable, the focus should be directed toward controlling ventricular rate. Use drugs that slow conduction and increase refractoriness in the AV node as initial therapy. In patients with normal LV function (left ventricular ejection fraction [LVEF] >40%), IV β-blockers (**propranolol**, **metoprolol**, and **esmolol**), **diltiazem**, or **verapamil** are recommended as first-line therapy. If a high adrenergic state is the precipitating factor, IV β-blockers can be highly effective and should be considered first. In patients with LVEF less than or equal to 40%, avoid IV diltiazem and verapamil, and use IV β-blockers with caution. In patients having an exacerbation of HF symptoms, use IV **digoxin** or **amiodarone** as first-line therapy for ventricular rate control. IV amiodarone can also be used in patients who

TABLE 6–2 Typical Maintenance Doses of Oral Antiarrhythmic Drugs

Drug	Dose	Dose Adjusted
Disopyramide	100–150 mg every 6 h 200–300 mg every 12 h (SR form)	HEP, REN
Quinidine	200–300 mg sulfate salt every 6 h 324–648 mg gluconate salt every 8–12 h	HEP
Mexiletine	200–300 mg every 8 h	HEP
Flecainide	50–200 mg every 12 h	HEP, REN
Propafenone	150–300 mg every 8 h 225–425 mg every 12 h (SR form)	HEP
Amiodarone	400 mg 2 or 3 times daily until 10 g total, then 200–400 mg daily[a]	
Dofetilide	500 mcg every 12 h	REN[b]
Dronedarone	400 mg every 12 h (with meals)[c]	
Sotalol	80–160 mg every 12 h	REN[d]

HEP, hepatic disease; REN, renal dysfunction; SR, sustained-release.
[a]Usual maintenance dose for atrial fibrillation is 200 mg/day (may further decrease dose to 100 mg/day with long-term use if patient is clinically stable in order to decrease risk of toxicity); usual maintenance dose for ventricular arrhythmias is 300 to 400 mg/day.
[b]Dose should be based on creatinine clearance; should not be used when creatinine clearance <20 mL/min (<0.33 mL/s).
[c]Avoid in severe hepatic impairment.
[d]Avoid in atrial fibrillation when creatinine clearance less than 40 mL/min (<0.67 mL/s).

are refractory or have contraindications to β-blockers, nondihydropyridine calcium channel blockers, and digoxin.

- After treatment with AV nodal blocking agents and a subsequent decrease in ventricular response, assess the patient for the possibility of restoring sinus rhythm if AF persists.
- If sinus rhythm is to be restored, initiate anticoagulation prior to cardioversion because return of atrial contraction increases risk of thromboembolism. Patients become at increased risk of thrombus formation and a subsequent embolic event if the duration of AF exceeds 48 hours.
  - ✓ Patients with AF for longer than 48 hours or an unknown duration should receive warfarin (target international normalized ratio [INR] 2.0–3.0), a low-molecular-weight heparin (subcutaneously at treatment doses), or dabigatran for at least 3 weeks prior to cardioversion. If cardioversion is successful, continue anticoagulation with either warfarin or dabigatran for at least 4 weeks.
  - ✓ Patients with AF less than 48 hours in duration do not require anticoagulation prior to cardioversion, but they should receive either IV unfractionated heparin or a low-molecular-weight heparin (subcutaneously at treatment doses) at presentation prior to and proceeding to cardioversion. If cardioversion is successful, continue anticoagulation with either warfarin or dabigatran for at least 4 weeks.
- After prior anticoagulation (or after transesophageal echocardiography demonstrated absence of a thrombus, obviating need for warfarin), methods for restoring sinus rhythm are pharmacologic cardioversion and DCC. DCC is quick and more often successful, but it requires prior sedation or anesthesia and has a small risk of serious complications, such as sinus arrest or ventricular arrhythmias. Advantages of initial drug therapy are that an effective agent may be determined in case long-term therapy is required. Disadvantages are significant side effects, such as drug-induced TdP, drug-drug interactions, and lower cardioversion rate for drugs compared

TABLE 6–3 Intravenous Antiarrhythmic Dosing

Drug	Clinical Situation	Dose
Amiodarone	Pulseless VT/VF	300 mg IV/IO push (can give additional 150 mg IV/IO push if persistent VT/VF), followed by infusion of 1 mg/min for 6 h, then 0.5 mg/min
	Stable VT (with a pulse)	150 mg IV over 10 min, followed by infusion of 1 mg/min for 6 h, then 0.5 mg/min
	AF (termination)	5 mg/kg IV over 30 min, followed by infusion of 1 mg/min for 6 h, then 0.5 mg/min
Diltiazem	PSVT; AF (rate control)	0.25 mg/kg IV over 2 min (may repeat with 0.35 mg/kg IV over 2 min), followed by infusion of 5 to 15 mg/h
Ibutilide	AF (termination)	1 mg IV over 10 min (may repeat if needed)
Lidocaine	Pulseless VT/VF	1–1.5 mg/kg IV/IO push (can give additional 0.5–0.75 mg/ kg IV/IO push every 5–10 min if persistent VT/VF [maximum cumulative dose = 3 mg/kg]), followed by infusion of 1 to 4 mg/min (1–2 mg/min if liver disease or HF)
	Stable VT (with a pulse)	1–1.5 mg/kg IV push (can give additional 0.5–0.75 mg/kg IV push every 5–10 min if persistent VT [maximum cumulative dose = 3 mg/kg]), followed by infusion of 1–4 mg/min (1–2 mg/min if liver disease or HF)
Procainamide	AF (termination); stable VT (with a pulse)	15–18 mg/kg IV over 60 min, followed by infusion of 1–4 mg/min
Sotalol[a]	AF/AFl (SR maintenance) Ventricular arrhythmias	75–150 mg IV once or twice daily (infused over 5 h)[b]
Verapamil	PSVT; AF (rate control)	2.5–5 mg IV over 2 min (may repeat up to maximum cumulative dose of 20 mg); can follow with infusion of 2.5–10 mg/h

AF, atrial fibrillation; AFl, atrial flutter; HF, heart failure; IO, intraosseous; PSVT, paroxysmal supraventricular tachycardia; VF, ventricular fibrillation; VT, ventricular tachycardia.

[a]Use only when patients are unable to take sotalol orally.

[b]Administer IV sotalol at the same frequency as oral sotalol (based on creatinine clearance). Oral sotalol may be converted to IV sotalol as follows: 80 mg oral = 75 mg IV; 120 mg oral = 112.5 mg IV; 160 mg oral = 150 mg IV.

with DCC. There is good evidence for efficacy of class III pure Ik blockers (**ibutilide** and **dofetilide**), class Ic drugs (eg, **flecainide** and **propafenone**), and **amiodarone** (oral or IV). With the "pill in the pocket" approach, outpatient, patient-controlled self-administration of a single, oral loading dose of either flecainide or propafenone can be relatively safe and effective for termination of recent-onset AF in select patients without sinus or AV node dysfunction, bundle-branch block, QT interval prolongation, Brugada's syndrome, or structural heart disease. It should only be considered for patients who have been successfully cardioverted with these drugs on an inpatient basis.

- Long-term antithrombotic therapy is recommended to prevent stroke. Patients with a CHADS2 (acronym derived from stroke risk factors: congestive heart failure, hypertension, age >75 years, diabetes, and prior stroke or transient ischemic attack) score of 2 or greater, 1, or 0 are considered to be at high risk, intermediate risk, and low risk for stroke, respectively. For patients at high or intermediate risk for stroke, oral anticoagulation is preferred over aspirin or aspirin plus clopidogrel; dabigatran

TABLE 6–4	Side Effects of Antiarrhythmic Drugs
Disopyramide	Anticholinergic symptoms (dry mouth, urinary retention, constipation, and blurred vision), nausea, anorexia, TdP, HF, conduction disturbances, ventricular arrhythmias
Procainamide[a]	Hypotension, TdP, worsening HF, conduction disturbances, ventricular arrhythmias
Quinidine	Cinchonism, diarrhea, abdominal cramps, nausea, vomiting, hypotension, TdP, worsening HF, conduction disturbances, ventricular arrhythmias, fever, hepatitis, thrombocytopenia, hemolytic anemia
Lidocaine	Dizziness, sedation, slurred speech, blurred vision, paresthesia, muscle twitching, confusion, nausea, vomiting, seizures, psychosis, sinus arrest, conduction disturbances
Mexiletine	Dizziness, sedation, anxiety, confusion, paresthesia, tremor, ataxia, blurred vision, nausea, vomiting, anorexia, conduction disturbances, ventricular arrhythmias
Flecainide	Blurred vision, dizziness, dyspnea, headache, tremor, nausea, worsening HF, conduction disturbances, ventricular arrhythmias
Propafenone	Dizziness, fatigue, bronchospasm, headache, taste disturbances, nausea, vomiting, bradycardia or AV block, worsening HF, ventricular arrhythmias
Amiodarone	Tremor, ataxia, paresthesia, insomnia, corneal microdeposits, optic neuropathy/neuritis, nausea, vomiting, anorexia, constipation, TdP (<1%), bradycardia or AV block (IV and oral use), pulmonary fibrosis, liver function test abnormalities, hepatitis, hypothyroidism, hyperthyroidism, photosensitivity, blue-gray skin discoloration, hypotension (IV use), phlebitis (IV use)
Dofetilide	Headache, dizziness, TdP
Dronedarone	Nausea, vomiting, diarrhea, serum creatinine elevations, bradycardia, worsening HF, liver toxicity, pulmonary fibrosis, TdP (<1%)
Ibutilide	Headache, TdP, hypotension
Sotalol	Dizziness, weakness, fatigue, nausea, vomiting, diarrhea, bradycardia, TdP, bronchospasm, worsening HF

AV, atrioventricular; HF, heart failure; IV, intravenous; TdP, torsade de pointes.
[a]Side effects are listed for IV formulation only; oral formulations are no longer available.

should be used rather than warfarin. For patients at low risk for stroke, either no antithrombotic therapy or aspirin is recommended; however, no therapy is preferred. If the decision is made to initiate antithrombotic therapy in low-risk patients, aspirin 75–325 mg/day can be used.

- In patients with nonvalvular AF, warfarin, dabigatran, rivaroxaban, and apixaban are all indicated for prevention of initial and recurrent strokes.
  - ✓ **Dabigatran** 150 mg twice daily is an effective alternative to warfarin for initial or recurrent stroke prevention in patients with at least one additional risk factor for stroke and a CrCl greater than 30 mL/min (>0.50 mL/s).
  - ✓ **Rivaroxaban** 20 mg daily is an alternative to warfarin in patients at moderate-to-high risk of stroke (eg, prior history of TIA, stroke or systemic embolism, or at least 2 additional risk factors for stroke).
  - ✓ **Apixaban** 5 mg twice daily is an effective alternative to warfarin in patients with at least one risk factor for stroke. Apixaban is also an alternative to aspirin in patients with at least 1 risk factor for stroke and who are considered unsuitable candidates for warfarin.

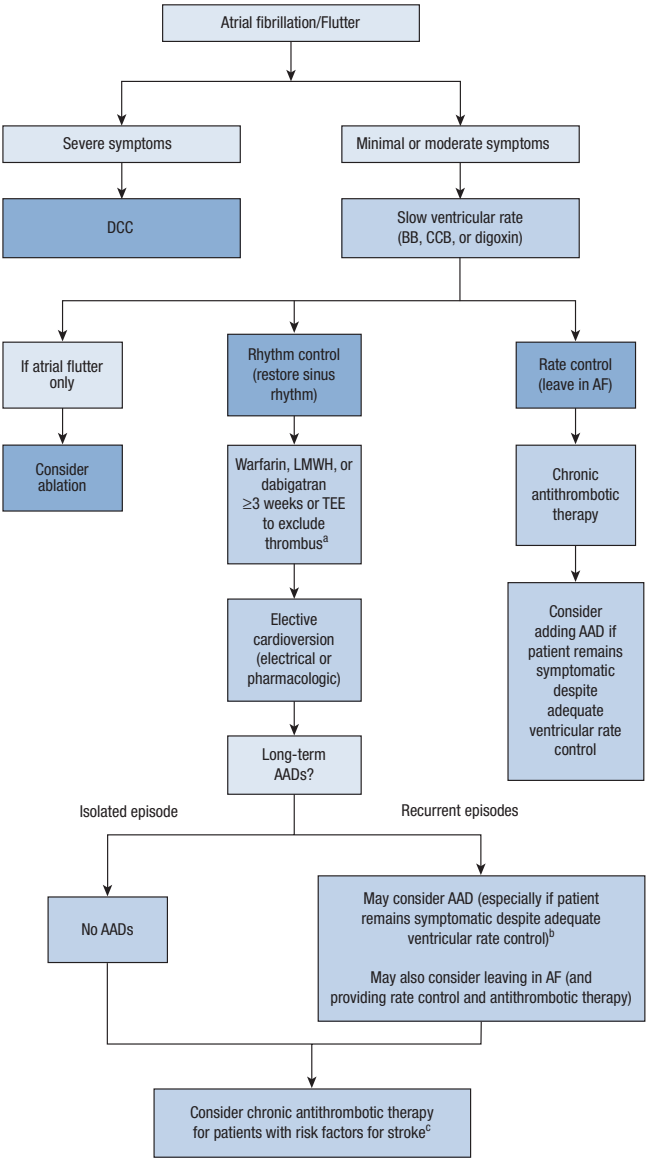


FIGURE 6–1. Algorithm for the treatment of atrial fibrillation (AF) and atrial flutter. (BB, β-blocker; CCB, calcium channel blocker [ie, verapamil or diltiazem]; DCC, direct-current cardioversion.) [a]If AF less than 48 hours, anticoagulation prior to cardioversion is unnecessary; may consider transesophageal echocardiogram (TEE) if patient has risk factors for stroke. [b]Consider ablation for patients who fail or do not tolerate one or more antiarrhythmic drugs (AADs). [c]Consider chronic antithrombotic therapy in all patients with AF and risk factors for stroke regardless of whether or not they remain in sinus rhythm.

- Dual antiplatelet therapy with aspirin plus clopidogrel is recommended over aspirin monotherapy for patients at high or intermediate risk for stroke who are not candidates for oral anticoagulation for reasons other than bleeding (ie, patient preference, unable to adhere to monitoring requirements).
- Consider chronic antithrombotic therapy for all patients with AF and risk factors for stroke regardless of whether or not they remain in sinus rhythm.
- AF often recurs after initial cardioversion because most patients have irreversible underlying heart or lung disease. A meta-analysis confirmed that **quinidine** maintained sinus rhythm better than placebo; however, 50% of patients had recurrent AF within 1 year, and quinidine increased mortality, presumably due in part to proarrhythmia. Class Ic or III antiarrhythmic agents are reasonable alternatives to consider for maintaining sinus rhythm. Because the class Ic drugs flecainide and propafenone increase the risk of proarrhythmia, they should be avoided in patients with structural heart disease. Amiodarone is the most effective and most frequently used class III agent for preventing AF recurrences despite its potential for significant organ toxicity.

PAROXYSMAL SUPRAVENTRICULAR TACHYCARDIA

- The choice between pharmacologic and nonpharmacologic methods for treating PSVT depends on symptom severity (Fig. 6–2). Treatment measures are directed first at terminating the acute episode and then at preventing recurrences. For patients with severe symptoms (eg, syncope, near syncope, anginal chest pain, or severe HF), synchronized DCC is the treatment of choice. If symptoms are mild to moderate, nondrug measures that increase vagal tone to the AV node (eg, unilateral carotid sinus massage and Valsalva maneuver) can be used initially. If these methods fail, drug therapy is the next option.

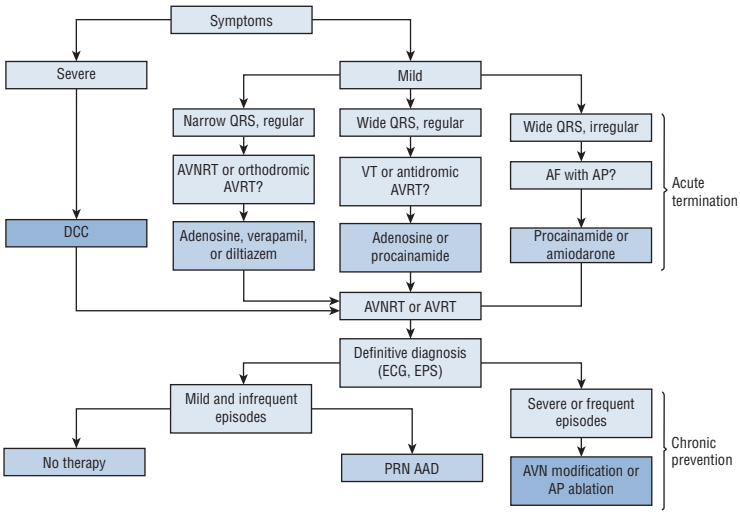


FIGURE 6–2. Algorithm for the treatment of acute (*top portion*) paroxysmal supraventricular tachycardia and chronic prevention of recurrences (*bottom portion*). *Note:* For empiric bridge therapy prior to radiofrequency ablation procedures, do not use calcium channel blockers (or other atrioventricular [AV] nodal blockers) if the patient has AV reentry with an accessory pathway. (AAD, antiarrhythmic drugs; AF, atrial fibrillation; AP, accessory pathway; AVN, atrioventricular nodal; AVNRT, atrioventricular nodal reentrant tachycardia; AVRT, atrioventricular reentrant tachycardia; DCC, direct-current cardioversion; ECG, electrocardiographic monitoring; EPS, electrophysiologic studies; PRN, as needed; VT, ventricular tachycardia.)

- The choice among drugs is based on the QRS complex (see **Fig. 6–2**). Drugs can be divided into three broad categories: (1) those that directly or indirectly increase vagal tone to the AV node (eg, **digoxin**); (2) those that depress conduction through slow, calcium-dependent tissue (eg, **adenosine**, **β-blockers**, and **nondihydropyridine calcium channel blockers**); and (3) those that depress conduction through fast, sodium-dependent tissue (eg, **quinidine**, **procainamide**, **disopyramide**, and **flecainide**).
- **Adenosine** has been recommended as the drug of first choice for patients with PSVT because its short duration of action will not cause prolonged hemodynamic compromise in patients with wide QRS complexes who actually have VT rather than PSVT.
- After acute PSVT is terminated, long-term prophylaxis is indicated if frequent episodes necessitate therapeutic intervention or if episodes are infrequent but severely symptomatic. Serial testing of antiarrhythmic agents can be performed via ambulatory ECG recordings (Holter monitors) or telephonic transmissions of cardiac rhythm (event monitors) or by invasive electrophysiologic techniques in the laboratory.
- Consider transcutaneous catheter ablation using radiofrequency current on the PSVT substrate in any patient who would have previously been considered for chronic antiarrhythmic drug treatment. It is highly effective and curative, rarely results in complications, obviates need for chronic antiarrhythmic drug therapy, and is cost effective.

PREMATURE VENTRICULAR COMPLEXES

- In apparently healthy individuals, drug therapy is unnecessary because PVCs without associated heart disease carry little or no risk. In patients with risk factors for arrhythmic death (recent MI, LV dysfunction, or complex PVCs), limit chronic therapy to **β-blockers** because only they have been proven to prevent mortality in these patients.

VENTRICULAR TACHYCARDIA

Acute Ventricular Tachycardia

- If severe symptoms are present, institute synchronized DCC immediately to restore sinus rhythm and correct precipitating factors if possible. If VT is an isolated electrical event associated with a transient initiating factor (eg, acute myocardial ischemia or digitalis toxicity), there is no need for long-term antiarrhythmic therapy after precipitating factors are corrected.
- Patients with mild or no symptoms can be treated initially with antiarrhythmic drugs. IV **procainamide**, **amiodarone**, or **sotalol** may be considered in this situation; **lidocaine** is an alternative agent. Deliver synchronized DCC if the patient's status deteriorates, VT degenerates to VF, or drug therapy fails.

Sustained Ventricular Tachycardia

- Patients with chronic recurrent sustained VT are at high risk for death; trial-and-error attempts to find effective therapy are unwarranted. Neither electrophysiologic studies nor serial Holter monitoring with drug testing is ideal. These findings and the side effect profiles of antiarrhythmic agents have led to nondrug approaches.
- The automatic ICD is a highly effective method for preventing sudden death due to recurrent VT or VF.

Ventricular Proarrhythmia

- The typical form of proarrhythmia caused by the class Ic antiarrhythmic drugs is a rapid, sustained, monomorphic VT with a characteristic sinusoidal QRS pattern that is often resistant to resuscitation with cardioversion or overdrive pacing. IV **lidocaine** (competes for the sodium channel receptor) or **sodium bicarbonate** (reverses the excessive sodium channel blockade) have been used successfully by some clinicians.

Torsade de Pointes

- For an acute episode of torsade de pointes (TdP), most patients require and respond to DCC. However, TdP tends to be paroxysmal and often recurs rapidly after DCC.

- IV **magnesium sulfate** is the drug of choice for preventing recurrences of TdP. If ineffective, institute strategies to increase heart rate and shorten ventricular repolarization (ie, temporary transvenous pacing at 105–120 beats/min or pharmacologic pacing with **isoproterenol** or **epinephrine** infusion). Discontinue agents that prolong the QT interval and correct exacerbating factors (eg, hypokalemia and hypomagnesemia). Drugs that further prolong repolarization (eg, IV procainamide) are contraindicated. Lidocaine is usually ineffective.

Ventricular Fibrillation

- Manage patients with pulseless VT or VF (with or without associated myocardial ischemia) according to American Heart Association guidelines for cardiopulmonary resuscitation and emergency cardiovascular care (see Chap. 7).

BRADYARRHYTHMIAS

- Treatment of sinus node dysfunction involves elimination of symptomatic bradycardia and possibly managing alternating tachycardias such as AF. Asymptomatic sinus bradyarrhythmias usually do not require therapeutic intervention.
- In general, a permanent ventricular pacemaker is the long-term therapy of choice for patients with significant symptoms.
- Drugs commonly employed to treat supraventricular tachycardias should be used with caution, if at all, in the absence of a functioning pacemaker.
- Symptomatic carotid sinus hypersensitivity also should be treated with permanent pacemaker therapy. Patients who remain symptomatic may benefit from adding an α-adrenergic stimulant such as **midodrine**.
- Vasovagal syncope has traditionally been treated successfully with oral β-blockers (eg, **metoprolol**) to inhibit the sympathetic surge that causes forceful ventricular contraction and precedes the onset of hypotension and bradycardia. Other drugs that have been used successfully (with or without β-blockers) include fludrocortisone, anticholinergics (**scopolamine patches** and **disopyramide**), α-adrenergic agonists (**midodrine**), adenosine analogues (**theophylline** and **dipyridamole**), and selective serotonin reuptake inhibitors (**sertraline** and **paroxetine**).

Atrioventricular Block

- If patients with Mobitz II or third-degree AV block develop signs or symptoms of poor perfusion (eg, altered mental status, chest pain, hypotension, and/or shock) administer **atropine** (0.5 mg IV given every 3–5 minutes, up to 3 mg total dose). Transcutaneous pacing can be initiated in patients unresponsive to atropine. Infusions of **epinephrine** (2–10 mcg/min) or **dopamine** (2–10 mcg/kg/min) can also be used in the event of atropine failure. These agents usually do not help if the site of the AV block is below the AV node (Mobitz II or trifascicular AV block).
- Chronic symptomatic AV block warrants insertion of a permanent pacemaker. Patients without symptoms can sometimes be followed closely without the need for a pacemaker.

EVALUATION OF THERAPEUTIC OUTCOMES

- The most important monitoring parameters include: (1) mortality (total and due to arrhythmic death), (2) arrhythmia recurrence (duration, frequency, and symptoms), (3) hemodynamic consequences (rate, blood pressure, and symptoms), and (4) treatment complications (side effects or need for alternative or additional drugs, devices, or surgery).

See Chapter 8, The Arrhythmias, authored by Cynthia A. Sanoski and Jerry L. Bauman, for a more detailed discussion of this topic.

CHAPTER 7

Cardiac Arrest

- *Cardiac arrest* involves cessation of cardiac mechanical activity as confirmed by absence of signs of circulation (eg, detectable pulse, unresponsiveness, and apnea).

PATHOPHYSIOLOGY

- Coronary artery disease is the most common finding in adults with cardiac arrest and causes ~80% of sudden cardiac deaths. In pediatric patients, cardiac arrest typically results from respiratory failure or progressive shock.
- Two different pathophysiologic conditions are associated with cardiac arrest:
  - ✓ Primary: arterial blood is typically fully oxygenated at the time of arrest.
  - ✓ Secondary: results from respiratory failure in which lack of ventilation leads to severe hypoxemia, hypotension, and cardiac arrest.
- Cardiac arrest in adults usually results from arrhythmias. Historically, ventricular fibrillation (VF) and pulseless ventricular tachycardia (PVT) were most common. The incidence of VF in out-of-hospital arrests is declining, which is of concern because survival rates are higher after VF/PVT than with cardiac arrest resulting from nonshockable rhythms like asystole or pulseless electrical activity (PEA).
- Because in-hospital cardiac arrest is typically preceded by hypoxia or hypotension, asystole or PEA occurs more commonly than VF or PVT.
- Only 14% of pediatric patients with in-hospital arrest present with VF or PFT as the initial rhythm.

CLINICAL PRESENTATION

- Cardiac arrest may be preceded by anxiety, shortness of breath, chest pain, nausea, vomiting, and diaphoresis.
- After an arrest, individuals are unresponsive, apneic, and hypotensive without a detectable pulse. Extremities are cold and clammy, and cyanosis is common.

DIAGNOSIS

- Rapid diagnosis is vital to success of cardiopulmonary resuscitation (CPR). Patients must receive early intervention to prevent cardiac rhythms from degenerating into less treatable arrhythmias.
- Diagnosis is made by observation of clinical manifestations consistent with cardiac arrest. Diagnosis is confirmed by vital signs, especially heart rate and respirations.
- Electrocardiography (ECG) identifies the cardiac rhythm, which in turn determines drug therapy.
  - ✓ VF is electrical anarchy of the ventricle resulting in no cardiac output and cardiovascular collapse.
  - ✓ PEA is absence of a detectable pulse and presence of some type of electrical activity other than VF or PVT.
  - ✓ Asystole is presence of a flat line on the ECG.

TREATMENT

- Goals of Treatment: Resuscitation goals are to preserve life, restore health, relieve suffering, limit disability, and respect the individual's decisions, rights, and privacy. This can be accomplished via CPR by return of spontaneous circulation (ROSC) with effective ventilation and perfusion as quickly as possible to minimize hypoxic damage to vital organs. After successful resuscitation, primary goals include optimizing

tissue oxygenation, identifying precipitating cause(s) of arrest, and preventing subsequent episodes.

GENERAL APPROACH

- The 2010 American Heart Association (AHA) guidelines for CPR and emergency cardiovascular care (ECC) state that the likelihood of successful outcome is enhanced if five critical elements in the "chain of survival" are implemented promptly: (1) immediate recognition of cardiac arrest and activation of the emergency response system, (2) early CPR with an emphasis on chest compressions, (3) rapid defibrillation, (4) effective advanced cardiac life support (ACLS), and (5) integrated post-cardiac arrest care.
- Basic life support given by healthcare providers trained in CPR includes the following actions performed in this order:
  - ✓ First, determine patient responsiveness. If unresponsive with no breathing or no normal breathing (ie, only gasping), activate the emergency medical response team and obtain an automated external defibrillator (AED) if available.
  - ✓ Check for pulse, but if not definitely felt within 10 seconds, begin CPR and use the AED when available.
  - ✓ Begin CPR with 30 chest compressions at a rate of at least 100/min and a compression depth of at least 2 in (5 cm) in adults and at least one third of the anteroposterior chest diameter in infants and children (~1.5 in [4 cm] in infants and 2 in [5 cm] in children).
  - ✓ Open the airway and deliver two rescue breaths, then repeat chest compressions. Follow each cycle of 30 chest compressions by two rescue breaths.
  - ✓ Continue cycles of 30 compressions/2 breaths until an AED arrives and is ready for use or emergency medical service (EMS) providers take over care.
  - ✓ If AED is available, check rhythm to determine if defibrillation is advised. If so, deliver one shock with immediate resumption of chest compressions/rescue breaths. After five cycles, reevaluate the rhythm to determine need for further defibrillation. Repeat this sequence until help arrives or the rhythm is no longer shockable.
  - ✓ If rhythm is not shockable, continue chest compressions/rescue breath cycles until help arrives or spontaneous circulation returns. If rhythm is not shockable, it is likely to be either asystole or PEA.
- Once ACLS providers arrive, further definitive therapy is given following the ACLS algorithm shown in **Fig. 7–1**.
- Central venous catheter access results in faster and higher peak drug concentrations than peripheral venous administration, but central line access is not needed in most resuscitation attempts. However, if a central line is already present, it is the access site of choice. If IV access (either central or peripheral) has not been established, insert a large peripheral venous catheter. If this is not successful, insert an intraosseous (IO) device.
- If neither IV nor IO access can be established, lidocaine, epinephrine, naloxone, and vasopressin may be administered endotracheally. The endotracheal dose should generally be 2 to 2.5 times larger than the IV/IO dose.

TREATMENT OF VENTRICULAR FIBRILLATION AND PULSELESS VENTRICULAR TACHYCARDIA

Nonpharmacologic Therapy

- Administer electrical defibrillation with one shock using 360 J (monophasic defibrillator) or 120 to 200 J (biphasic defibrillator). After defibrillation is attempted, restart CPR immediately and continue for about five cycles (~2 min) before analyzing the rhythm or checking a pulse. If there is still evidence of VF/PVT after 2 minutes, then give pharmacologic therapy with repeat attempts at single-discharge defibrillation.
- Obtain endotracheal intubation and IV access when feasible, but not at the expense of stopping chest compressions. Once an airway is achieved, ventilate patients with 100% oxygen.

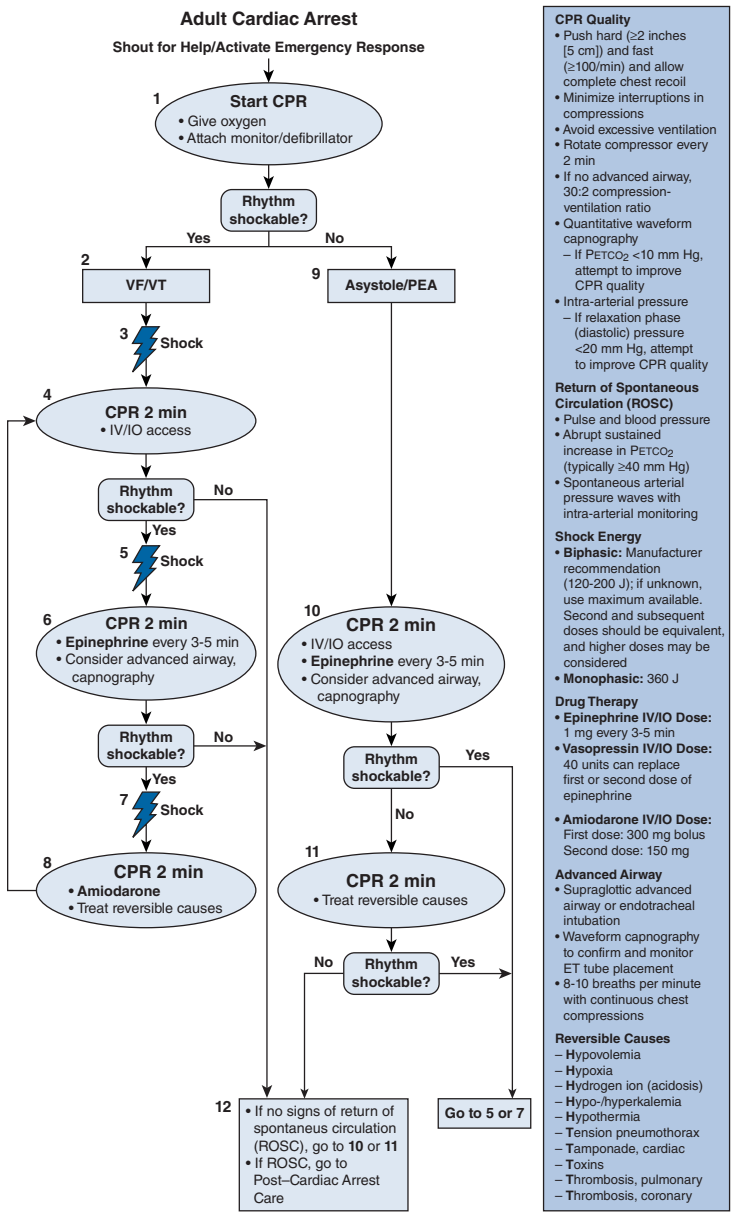


FIGURE 7–1. Advanced cardiac life support (ACLS) cardiac arrest algorithm. (CPR, cardiopulmonary resuscitation; PEA, pulseless electrical activity; VF, ventricular fibrillation; VT, ventricular tachycardia.) (*Reprinted with permission: 2010 American Heart Association Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care, Part 8: Adult Advanced Cardiovascular Life Support. Circulation 2010;122(Suppl 3):S729–S767. © 2010 American Heart Association, Inc.*)

Pharmacologic Therapy

EPINEPHRINE

- **Epinephrine** is a drug of first choice for treating VF, PVT, asystole, and PEA. It is an agonist of both α and β receptors, but effectiveness is primarily due to α effects. It increases systemic arteriolar vasoconstriction, thereby improving coronary and cerebral perfusion pressure during the low-flow state associated with CPR.
- The recommended adult dose of epinephrine is 1 mg administered by IV or IO injection every 3 to 5 minutes. Higher doses may be administered to treat specific disorders such as β-blocker and calcium channel blocker overdose.

VASOPRESSIN

- **Vasopressin** is a potent nonadrenergic vasoconstrictor that increases blood pressure (BP) and systemic vascular resistance. Its vasoconstrictive properties are due primarily to effects on V_1 receptors. The 2010 AHA guidelines indicate that vasopressin 40 units IV/IO can replace the first or second dose of epinephrine.

ANTIARRHYTHMICS

- The purpose of antiarrhythmic drug therapy after unsuccessful defibrillation and vasopressor administration is to prevent development or recurrence of VF and PVT by raising the fibrillation threshold. However, clinical evidence demonstrating improved survival to hospital discharge is lacking.
- **Amiodarone** is the recommended antiarrhythmic in patients with VF/VT unresponsive to CPR, defibrillation, and vasopressors. The dose is 300 mg IV/IO followed by a second dose of 150 mg.
- **Lidocaine** may be used if amiodarone is unavailable, but it has not been shown to improve rates of ROSC, admission to the hospital, or survival to discharge compared with amiodarone. The initial dose is 1 to 1.5 mg/kg IV. Additional doses of 0.5 to 0.75 mg/kg can be administered at 5- to 10-minute intervals to a maximum dose of 3 mg/kg if VF/PVT persists.

MAGNESIUM

- Severe hypomagnesemia has been associated with VF/PVT, but routine administration of magnesium during cardiac has not improved clinical outcomes. Two trials showed improved ROSC in cardiac arrests associated with torsades de pointes. Therefore, limit magnesium administration to these patients. The dose is 1 to 2 g diluted in 10 mL of 5% dextrose in water administered IV/IO push over 15 minutes.

THROMBOLYTICS

- Thrombolytic use during CPR has been investigated because most cardiac arrests are related to either myocardial infarction (MI) or pulmonary embolism (PE). Although several studies demonstrated successful use, few have shown improvements to hospital discharge, and an increase in intracranial hemorrhage was noted. Therefore, fibrinolytic therapy should not be used routinely in cardiac arrest but can be considered when PE is the presumed or known cause of the arrest.

TREATMENT OF PULSELESS ELECTRICAL ACTIVITY AND ASYSTOLE

Nonpharmacologic Therapy

- Successful treatment of PEA and asystole depends on diagnosis of the underlying cause. Potentially reversible causes include: (1) hypovolemia, (2) hypoxia, (3) acidosis, (4) hyper- or hypokalemia, (5) hypothermia, (6) hypoglycemia, (7) drug overdose, (8) cardiac tamponade, (9) tension pneumothorax, (10) coronary thrombosis, (11) pulmonary thrombosis, and (12) trauma.
- PEA and asystole are treated the same way. Both conditions require CPR, airway control, and IV access. Avoid defibrillation in asystole because the resulting parasympathetic discharge can reduce the chance of ROSC and decrease the likelihood of survival. If available, transcutaneous pacing can be attempted.

Pharmacologic Therapy

- **Epinephrine** 1 mg administered by IV or IO injection every 3 to 5 minutes.
- **Vasopressin** 40 units IV/IO can replace the first or second dose of epinephrine.
- Atropine should not be routinely administered for treatment of asystole or PEA because there are no prospective controlled trials showing benefit and there is conflicting evidence from retrospective and observational reports. The 2010 AHA guidelines removed atropine from the ACLS cardiac arrest algorithm.

ACID–BASE MANAGEMENT

- Acidosis occurs during cardiac arrest because of decreased blood flow or inadequate ventilation. Chest compressions generate only ~20% to 30% of normal cardiac output, leading to inadequate organ perfusion, tissue hypoxia, and metabolic acidosis. Lack of ventilation causes CO_2 retention, leading to respiratory acidosis. The combined acidosis reduces myocardial contractility and may cause arrhythmias.
- Routine use of sodium bicarbonate in cardiac arrest is not recommended because there are few clinical data supporting its use, and it may have detrimental effects. It can be used in special circumstances (eg, preexisting metabolic acidosis, hyperkalemia, and tricyclic antidepressant overdose). The dosage should be guided by laboratory analysis if possible.

POSTRESUSCITATIVE CARE

- ROSC from a cardiac arrest may be followed by a post-cardiac arrest syndrome characterized by brain injury, myocardial dysfunction, systemic ischemia/reperfusion response, and persistent precipitating pathology.
- It is imperative to ensure adequate airway and oxygenation. Raise the head of the bed to 30 degrees to reduce risk for aspiration, ventilator-associated pneumonia, and cerebral edema. After use of 100% oxygen during the resuscitation effort, titrate the oxygen fraction down as tolerated to avoid oxygen toxicity. Overventilation can be avoided by using end-tidal (ET) CO_2 measurements targeting an $ETCO_2$ of 40–45 mm Hg [5.3–6.0 kPa]).
- Evaluate for ECG changes consistent with acute myocardial infarction as soon as possible and perform revascularization as appropriate.
- Hypothermia can protect from cerebral injury by suppressing chemical reactions that occur after restoration of blood flow. The 2010 AHA guidelines recommend that unconscious adult patients with ROSC after out-of-hospital VF cardiac arrest be cooled to 32–34°C (89.6–93.2°F) for 12 to 24 hours. Cooling may also be considered for comatose adults patients with ROSC after out-of-hospital arrests with an initial rhythm of asystole or PEA or after in-hospital cardiac arrest of any initial rhythm. There is insufficient evidence to recommend therapeutic hypothermia in children. Potential complications of hypothermia include coagulopathy, dysrhythmias, hyperglycemia, increased incidence of pneumonia and sepsis, and profound effects on drug distribution and elimination.

EVALUATION OF THERAPEUTIC OUTCOMES

- Monitoring should occur both during the resuscitation attempt and in the postresuscitation phase. The optimal outcome following CPR is an awake, responsive, spontaneously breathing patient. Ideally, patients must remain neurologically intact with minimal morbidity after the resuscitation.
- Assess and document heart rate, cardiac rhythm, and BP throughout the resuscitation attempt and after each intervention. Determination of the presence or absence of a pulse is paramount to deciding which interventions are appropriate.
- Coronary perfusion pressure (CPP) and central venous oxygen saturation ($ScvO_2$) can provide useful information on the patient's response to therapy.
- $ETCO_2$ monitoring is a safe and effective method to assess cardiac output during CPR and has been associated with ROSC.

- Consider the precipitating cause of the cardiac arrest (eg, MI, electrolyte imbalance, primary arrhythmia). Review prearrest status carefully, particularly if the patient was receiving drug therapy.
- Address any altered cardiac, hepatic, and renal function resulting from ischemic damage during the arrest.
- Assess neurologic function by the Cerebral Performance Category and the Glasgow Coma Scale.

See Chapter 2, Cardiac Arrest, authored by Jeffrey F. Barletta and Jeffrey L. Wilt, for a more detailed discussion of this topic.

CHAPTER 8

Dyslipidemia

- *Dyslipidemia* is elevated total cholesterol, low-density lipoprotein (LDL) cholesterol, or triglycerides; low high-density lipoprotein (HDL) cholesterol; or a combination of these abnormalities.

PATHOPHYSIOLOGY

- Cholesterol, triglycerides, and phospholipids are transported in blood as complexes of lipids and proteins (lipoproteins). Elevated total and LDL cholesterol and reduced HDL cholesterol are associated with development of coronary heart disease (CHD).
- Risk factors such as oxidized LDL, mechanical injury to endothelium, and excessive homocysteine can lead to endothelial dysfunction and cellular interactions culminating in atherosclerosis. Eventual clinical outcomes may include angina, myocardial infarction (MI), arrhythmias, stroke, peripheral arterial disease, abdominal aortic aneurysm, and sudden death.
- Atherosclerotic lesions arise from transport and retention of plasma LDL through the endothelial cell layer into the extracellular matrix of the subendothelial space. Once in the artery wall, LDL is chemically modified through oxidation and nonenzymatic glycation. Mildly oxidized LDL recruits monocytes into the artery wall, which transform into macrophages that accelerate LDL oxidation. Oxidized LDL provokes an inflammatory response mediated by chemoattractants and cytokines.
- Repeated injury and repair within an atherosclerotic plaque eventually lead to a fibrous cap protecting the underlying core of lipids, collagen, calcium, and inflammatory cells. Maintenance of the fibrous plaque is critical to prevent plaque rupture and coronary thrombosis.
- Primary or genetic lipoprotein disorders are classified into six categories: I (chylomicrons), IIa (LDL), IIb (LDL + very-low-density lipoprotein [VLDL]), III (intermediate-density lipoprotein), IV (VLDL), and V (VLDL + chylomicrons). Secondary forms of dyslipidemia also exist, and several drug classes may affect lipid levels (eg, progestins, thiazide diuretics, glucocorticoids, β-blockers, isotretinoin, protease inhibitors, cyclosporine, mirtazapine, and sirolimus).
- The primary defect in familial hypercholesterolemia is inability to bind LDL to the LDL receptor (LDL-R). This leads to a lack of LDL degradation by cells and unregulated biosynthesis of cholesterol.

CLINICAL PRESENTATION

- Most patients are asymptomatic for many years. Symptomatic patients may complain of chest pain, palpitations, sweating, anxiety, shortness of breath, abdominal pain, or loss of consciousness or difficulty with speech or movement.
- Depending on the lipoprotein abnormality, signs on physical examination may include cutaneous xanthomas, peripheral polyneuropathy, high blood pressure, and increased body mass index or waist size.

DIAGNOSIS

- Measure fasting lipoprotein profile (total cholesterol, LDL, HDL, triglycerides) in all adults 20 years of age or older at least once every 5 years.
- Measure plasma cholesterol, triglyceride, and HDL levels after a 12-hour fast because triglycerides may be elevated in nonfasting individuals; total cholesterol is only modestly affected by fasting.
- Two determinations, 1 to 8 weeks apart are recommended to minimize variability and obtain a reliable baseline. If the total cholesterol is greater than 200 mg/dL (>5.17 mmol/L), a second determination is recommended, and if the values are greater than 30 mg/dL (>0.78 mmol/L) apart, use the average of three values.

- History and physical examination should assess: (1) presence or absence of cardiovascular risk factors or definite cardiovascular disease; (2) family history of premature cardiovascular disease or lipid disorders; (3) presence or absence of secondary causes of dyslipidemia, including concurrent medications; and (4) presence or absence of xanthomas, abdominal pain, or history of pancreatitis, renal or liver disease, peripheral vascular disease, abdominal aortic aneurysm, or cerebral vascular disease (carotid bruits, stroke, or transient ischemic attack).
- Diabetes mellitus and the metabolic syndrome are considered CHD risk equivalents; their presence in patients without known CHD is associated with the same level of risk as patients without them but having confirmed CHD.
- Lipoprotein electrophoresis is sometimes performed to determine which class of lipoproteins is involved. If the triglycerides are less than 400 mg/dL (4.52 mmol/L), and neither type III dyslipidemia nor chylomicrons are detected by electrophoresis, then one can calculate VLDL and LDL concentrations: VLDL = triglycerides ÷ 5; LDL = total cholesterol – (VLDL + HDL). Initial testing uses total cholesterol for case finding, but subsequent management decisions should be based on LDL.

TREATMENT

- Goals of Treatment: Lower total and LDL cholesterol to reduce the risk of first or recurrent events such as MI, angina, heart failure, ischemic stroke, or peripheral arterial disease.

GENERAL APPROACH

- The National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III) recommends that fasting lipoprotein profile and risk factor assessment be used in initial classification of adults.
- If the total cholesterol is less than 200 mg/dL (>5.17 mmol/L), then the patient has a desirable blood cholesterol level (**Table 8–1**). If the HDL is also greater than 40 mg/dL (>1.03 mmol/L), no further follow-up is recommended for patients without known CHD and who have fewer than two risk factors (**Table 8–2**). In patients with borderline-high blood cholesterol (200–239 mg/dL; 5.17–6.18 mmol/L), assessment of risk factors is needed to more clearly define disease risk.

TABLE 8–1 Classification of Total, LDL, and HDL Cholesterol and Triglycerides

Total cholesterol	
<200 mg/dL (<5.17 mmol/L)	Desirable
200–239 mg/dL (5.17–6.20 mmol/L)	Borderline high
≥240 mg/dL (≥6.21 mmol/L)	High
LDL cholesterol	
<100 mg/dL (<2.59 mmol/L)	Optimal
100–129 mg/dL (2.59–3.35 mmol/L)	Near or above optimal
130–159 mg/dL (3.36–4.13 mmol/L)	Borderline high
160–189 mg/dL (4.14–4.90 mmol/L)	High
≥190 mg/dL (≥4.91 mmol/L)	Very high
HDL cholesterol	
<40 mg/dL (<1.03 mmol/L)	Low
≥60 mg/dL (≥1.55 mmol/L)	High
Triglycerides	
<150 mg/dL (<1.70 mmol/L)	Normal
150–199 mg/dL (1.70–2.25 mmol/L)	Borderline high
200–499 mg/dL (2.26–5.64 mmol/L)	High
≥500 mg/dL (≥5.65 mmol/L)	Very high

HDL, high-density lipoprotein; LDL, low-density lipoprotein.

TABLE 8–2 Major Risk Factors (Exclusive of LDL Cholesterol) That Modify LDL Goals[a]
Age Men: ≥45 years Women: ≥55 years or premature menopause without estrogen replacement therapy
Family history of premature CHD (definite myocardial infarction or sudden death before 55 years of age in father or other male first-degree relative or before 65 years of age in mother or other female first-degree relative)
Cigarette smoking
Hypertension (≥140/90 mm Hg or on antihypertensive medication)
Low HDL cholesterol (<40 mg/dL [<1.03 mmol/L])[b]

CHD, coronary heart disease; HDL, high-density lipoprotein; LDL, low-density lipoprotein.
[a] Diabetes is regarded as a CHD risk equivalent.
[b] HDL cholesterol (≥60 mg/dL [≥1.55 mmol/L]) counts as a "negative" risk factor; its presence removes one risk factor from the total count.

- Decisions regarding classification and management are based on the LDL cholesterol levels listed in **Table 8–3**.
- Four risk categories modify the goals and modalities of LDL-lowering therapy:
  1. Highest risk = Known CHD or CHD risk equivalents; risk for coronary events is at least as high as for established CHD (ie, >20% per 10 years, or 2% per year).
  2. Moderately high risk = 2 or more risk factors in which 10-year risk for CHD is 10% to 20%.

TABLE 8–3 LDL Cholesterol Goals and Cutpoints for Therapeutic Lifestyle Changes (TLCs) and Drug Therapy in Different Risk Categories

Risk Category	LDL Goal, mg/dL (mmol/L)	LDL Level at Which to Initiate TLC, mg/dL (mmol/L)	LDL Level at Which to Consider Drug Therapy, mg/dL (mmol/L)
High risk: CHD or CHD risk equivalents (10-year risk >20%)	<100 (<2.59) (optional goal: <70 [<1.81])	≥100 (≥2.59)	≥100 (≥2.59) (<100 [<2.59]: consider drug options)[a]
Moderately high risk: 2+ risk factors (10-year risk 10–20%)	<130 (<3.36)	≥130 (≥3.36)	≥130 (≥3.36) (100-129 [2.59–3.35]: consider drug options)
Moderate risk: 2+ risk factors (10-year risk <10%)	<130 (<3.36)	≥130 (≥3.36)	≥160 (≥4.14)
Lower risk: 0 or 1 risk factor[b]	<160 (<4.14)	≥160 (≥4.14)	≥190 (≥4.91) (160-189 [4.14–4.90]: LDL-lowering drug optional)

CHD, coronary heart disease; LDL, low-density lipoprotein.
[a] Some authorities recommend use of LDL-lowering drugs in this category if LDL cholesterol <100 mg/dL (<2.59 mmol/L) cannot be achieved by TLC. Others prefer to use drugs that primarily modify triglycerides and HDL (eg, nicotinic acid or fibrates). Clinical judgment also may call for deferring drug therapy in this subcategory.
[b] Almost all people with zero or one risk factor have a 10-year risk less than 10%; thus, 10-year risk assessment in people with zero or 1 risk factor is not necessary.

3. Moderate risk = 2 or more risk factors and a 10-year risk of 10% or less.
4. Lowest risk = 0 to 1 risk factor, which is usually associated with a 10-year CHD risk of less than 10%.

- *Note*: New cholesterol treatment guidelines issued in late 2013 are not considered here.

NONPHARMACOLOGIC THERAPY

- Begin therapeutic lifestyle changes (TLCs) on the first visit, including dietary therapy, weight reduction, and increased physical activity. Advise overweight patients to lose 10% of body weight. Encourage physical activity of moderate intensity 30 minutes a day for most days of the week. Assist patients with smoking cessation and control of hypertension.
- The objectives of dietary therapy are to progressively decrease intake of total fat, saturated fat, and cholesterol and to achieve a desirable body weight (**Table 8–4**).
- Increased intake of soluble fiber (oat bran, pectins, psyllium) can reduce total and LDL cholesterol by 5% to 20%. However, they have little effect on HDL-C or triglycerides. Fiber products may also be useful in managing constipation associated with bile acid resins (BARs).
- Fish oil supplementation reduces triglycerides and VLDL-C, but it either has no effect on total and LDL-C or may elevate these fractions. Other actions of fish oil may account for any cardioprotective effects.
- Ingestion of 2 to 3 g daily of plant sterols reduces LDL by 6% to 15%. They are usually available in commercial margarines.
- If all recommended dietary changes were instituted, the estimated average reduction in LDL would range from 20% to 30%.

PHARMACOLOGIC THERAPY

- The effect of drug therapy on lipids and lipoproteins is shown in **Table 8–5**.
- Recommended drugs of choice for each lipoprotein phenotype are given in **Table 8–6**.
- Available products and their doses are provided in **Table 8–7**.

Bile Acid Resins

- BARs (**cholestyramine**, **colestipol**, **colesevelam**) bind bile acids in the intestinal lumen, with a concurrent interruption of enterohepatic circulation of bile acids, which decreases the bile acid pool size and stimulates hepatic synthesis of bile acids from cholesterol. Depletion of the hepatic cholesterol pool increases cholesterol biosynthesis and the number of LDL-Rs on hepatocyte membranes, which enhances the

TABLE 8–4 Macronutrient Recommendations for the Therapeutic Lifestyle Change (TLC) Diet

Component[a]	Recommended Intake
Total fat	25–35% of total calories
Saturated fat	<7% of total calories
Polyunsaturated fat	Up to 10% of total calories
Monounsaturated fat	Up to 20% of total calories
Carbohydrates[b]	50–60% of total calories
Cholesterol	<200 mg/day
Dietary fiber	20–30 g/day
Plant sterols	2 g/day
Protein	~15% of total calories
Total calories	To achieve and maintain desirable body weight

[a]Calories from alcohol not included.
[b]Carbohydrates should derive from foods rich in complex carbohydrates, such as whole grains, fruits, and vegetables.

TABLE 8–5 Effects of Drug Therapy on Lipids and Lipoproteins

Drug	Mechanism of Action	Effects on Lipids	Effects on Lipoproteins
Cholestyramine, colestipol, and colesevelam	↑ LDL catabolism ↓ Cholesterol absorption	↓ Cholesterol	↓ LDL ↑ VLDL
Niacin	↓ LDL and VLDL synthesis	↓ Triglyceride ↓ Cholesterol	↓ VLDL ↓ LDL ↑ HDL
Gemfibrozil, fenofibrate, and clofibrate	↑ VLDL clearance ↓ VLDL synthesis	↓ Triglyceride ↓ Cholesterol	↓ VLDL ↓ LDL ↑ HDL
Lovastatin, pravastatin, simvastatin, fluvastatin, atorvastatin, and rosuvastatin	↑ LDL catabolism ↓ LDL synthesis	↓ Cholesterol	↓ LDL
Mipomersen	Inhibits apolipoprotein B-100 synthesis	↓ Cholesterol	↓ LDL, non-HDL
Lomitapide	Inhibits microsomal triglyceride transfer protein	↓ Cholesterol	↓ LDL, non-HDL
Ezetimibe	Blocks cholesterol absorption across the intestinal border	↓ Cholesterol	↓ LDL

↑, increased; ↓, decreased.

TABLE 8–6 Lipoprotein Phenotype and Recommended Drug Treatment

Lipoprotein Type	Drug of Choice	Combination Therapy
I	Not indicated	–
IIa	Statins Cholestyramine or colestipol Niacin Ezetimibe	Niacin or BARs Statins or niacin Statins or BARs
IIb	Statins Fibrates Niacin Ezetimibe	BARs, fibrates, or niacin Statins, niacin, or BARs[a] Statins or fibrates
III	Fibrates Niacin Ezetimibe	Statins or niacin Statins or fibrates
IV	Fibrates Niacin	Niacin Fibrates
V	Fibrates Niacin	Niacin Fish oils

BARs, bile acid resins; fibrates include gemfibrozil or fenofibrate.
[a] BARs are not used as first-line therapy if triglycerides are elevated at baseline because hypertriglyceridemia may worsen with BARs alone.

TABLE 8–7 Comparison of Drugs Used in the Treatment of Dyslipidemia[a]

Drug	Dosage Forms	Usual Daily Dose	Maximum Daily Dose
Cholestyramine (Questran)	Bulk powder/4 g packets	8 g three times daily	32 g
Cholestyramine (Cholybar)	4 g resin per bar	8 g three times daily	32 g
Colestipol hydrochloride (Colestid)	Bulk powder/5 g packets	10 g twice daily	30 g
Colesevelam (Welchol)	625 mg tablets	1,875 mg twice daily	4,375 mg
Niacin	50, 100, 250, and 500 mg tablets; 125, 250, and 500 mg capsules	0.5–1 g three times daily	6 g
Extended-release niacin (Niaspan)	500, 750, and 1,000 mg tablets	1,000–2,000 mg once daily	2,000 mg
Extended-release niacin + lovastatin (Advicor)	Niacin/lovastatin 500 mg/20 mg tablets Niacin/lovastatin 750 mg/20 mg tablets Niacin/lovastatin 1,000 mg/20 mg tablets	500 mg/20 mg – –	1,000 mg/20 mg – –
Fenofibrate (Tricor)	67, 134, and 200 mg capsules (micronized); 54 and 160 mg tablets; 40 and 120 mg tablets; 50 and 160 mg tablets	54 mg or 67 mg	201 mg
Gemfibrozil (Lopid)	300 mg capsules	600 mg twice daily	1.5 g
Lovastatin (Mevacor)	20 and 40 mg tablets	20–40 mg	80 mg
Pravastatin (Pravachol)	10, 20, 40, and 80 mg tablets	10–20 mg	40 mg
Simvastatin (Zocor)	5, 10, 20, 40, and 80 mg tablets	10–20 mg	80 mg
Atorvastatin (Lipitor)	10, 20, 40, and 80 mg tablets	10 mg	80 mg
Rosuvastatin (Crestor)	5, 10, 20, and 40 mg tablets	5 mg	40 mg
Pitavastatin (Livalo)	1, 2, and 4 mg tablets	2 mg	4 mg
Ezetimibe (Zetia)	10 mg tablet	10 mg	10 mg
Simvastatin/ezetimibe (Vytorin)	Simvastatin/ezetimibe 10 mg/10 mg, 20 mg/10 mg, 40 mg/10 mg, and 80 mg/10 mg	Simvastatin/ezetimibe 20 mg/10 mg	Simvastatin/ezetimibe 80 mg/10 mg
Lomitapide (Juxtapid)	5, 10, 20 mg capsules	5 mg initially, increasing at 2 week intervals to response or max dose	60 mg
Mipomersen (Kynamro)	200 mg/mL for subcutaneous injection	200 mg subcutaneously once weekly	200 mg subcutaneously once weekly

[a] This table does not include all drugs used for treating dyslipidemia.

rate of catabolism from plasma and lowers LDL levels. Increased hepatic cholesterol biosynthesis may be paralleled by increased hepatic VLDL production; consequently, BARs may aggravate hypertriglyceridemia in patients with combined dyslipidemia.

- BARs are useful in treating primary hypercholesterolemia (familial hypercholesterolemia, familial combined dyslipidemia, and type IIa hyperlipoproteinemia).
- Common GI complaints include constipation, bloating, epigastric fullness, nausea, and flatulence. They can be managed by increasing fluid intake, increasing dietary bulk, and using stool softeners.
- The gritty texture and bulk may be minimized by mixing the powder with orange drink or juice. Colestipol may have better palatability than cholestyramine because it is odorless and tasteless. Tablet forms may help improve adherence.
- Other potential adverse effects include impaired absorption of fat-soluble vitamins A, D, E, and K; hypernatremia and hyperchloremia; GI obstruction; and reduced bioavailability of acidic drugs such as warfarin, nicotinic acid, thyroxine, acetaminophen, hydrocortisone, hydrochlorothiazide, loperamide, and possibly iron. Drug interactions may be avoided by alternating administration times with an interval of 6 hours or more between the BARs and other drugs.

Niacin

- **Niacin** (nicotinic acid) reduces hepatic synthesis of VLDL, which in turn reduces synthesis of LDL. Niacin also increases HDL by reducing its catabolism.
- The principal use of niacin is for mixed dyslipidemia or as a second-line agent in combination therapy for hypercholesterolemia. It is a first-line agent or alternative for treatment of hypertriglyceridemia and diabetic dyslipidemia.
- Cutaneous flushing and itching appear to be prostaglandin mediated and can be reduced by taking aspirin 325 mg shortly before niacin ingestion. Taking the niacin dose with meals and slowly titrating the dose upward may minimize these effects. Concomitant alcohol and hot drinks may magnify the flushing and pruritus from niacin, and they should be avoided at the time of ingestion. GI intolerance is also a common problem.
- Laboratory abnormalities may include elevated liver function tests, hyperuricemia, and hyperglycemia. Niacin-associated hepatitis is more common with sustained-release preparations, and their use should be restricted to patients intolerant of regular-release products. Niacin is contraindicated in patients with active liver disease, and it may exacerbate preexisting gout and diabetes.
- **Niaspan** is a prescription-only, extended-release niacin formulation with pharmacokinetics intermediate between prompt- and sustained-release products. It has fewer dermatologic reactions and a low risk of hepatotoxicity. Combination with statins can produce large reductions in LDL and increases in HDL.
- Nicotinamide should not be used in the treatment of dyslipidemia because it does not effectively lower cholesterol or triglyceride levels.

HMG-CoA Reductase Inhibitors

- Statins (**atorvastatin**, **fluvastatin**, **lovastatin**, **pitavastatin**, **pravastatin**, **rosuvastatin**, and **simvastatin**) inhibit 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase, interrupting conversion of HMG-CoA to mevalonate, the rate-limiting step in cholesterol biosynthesis. Reduced LD synthesis and enhanced LDL catabolism mediated through LDL-Rs appear to be the principal mechanisms for lipid-lowering effects.
- When used as monotherapy, statins are the most potent total and LDL cholesterol–lowering agents and among the best tolerated. Total and LDL cholesterol are reduced in a dose-related fashion by 30% or more when added to dietary therapy.
- Combination therapy with a statin and a BAR is rational because the numbers of LDL-Rs are increased, leading to greater degradation of LDL cholesterol; intracellular synthesis of cholesterol is inhibited; and enterohepatic recycling of bile acids is interrupted.
- Combination therapy with a statin and ezetimibe is also rational because ezetimibe inhibits cholesterol absorption across the gut border and adds 12% to 20% further reduction when combined with a statin or other drug.

- Constipation occurs in less than 10% of patients taking statins. Other adverse effects include elevated alanine aminotransferase, elevated creatine kinase levels, myopathy, and, rarely, rhabdomyolysis.

Fibric Acids

- Fibrate monotherapy (**gemfibrozil**, **fenofibrate**, **clofibrate**) is effective in reducing VLDL, but a reciprocal rise in LDL may occur, and total cholesterol values may remain relatively unchanged. Plasma HDL concentrations may rise 10% to 15% or more with fibrates.
- Gemfibrozil reduces synthesis of VLDL and, to a lesser extent, apolipoprotein B with a concurrent increase in the rate of removal of triglyceride-rich lipoproteins from plasma. Clofibrate is less effective than gemfibrozil or niacin in reducing VLDL production.
- GI complaints occur in 3% to 5% of patients. Rash, dizziness, and transient elevations in transaminase levels and alkaline phosphatase may also occur. Gemfibrozil and probably fenofibrate enhance gallstone formation rarely.
- A myositis syndrome of myalgia, weakness, stiffness, malaise, and elevations in creatine kinase and aspartate aminotransferase may occur and seems to be more common in patients with renal insufficiency.
- Fibrates may potentiate the effects of oral anticoagulants, and the international normalized ratio (INR) should be monitored very closely with this combination.

Ezetimibe

- **Ezetimibe** interferes with absorption of cholesterol from the brush border of the intestine, making it a good choice for adjunctive therapy. It is approved as monotherapy and for use with a statin. The dose is 10 mg once daily, given with or without food. When used alone, it results in ~18% reduction in LDL cholesterol. When added to a statin, ezetimibe lowers LDL by an additional 12% to 20%. A combination product (Vytorin) containing ezetimibe 10 mg and simvastatin 10, 20, 40, or 80 mg is available. Ezetimibe is well tolerated; ~4% of patients experience GI upset. Because cardiovascular outcomes with ezetimibe have not been evaluated, it should be reserved for patients unable to tolerate statin therapy or those who do not achieve satisfactory lipid lowering with a statin alone.

Fish Oil Supplementation

- Diets high in omega-3 polyunsaturated fatty acids (from fish oil), most commonly eicosapentaenoic acid (EPA), reduce cholesterol, triglycerides, LDL, and VLDL and may elevate HDL cholesterol.
- Fish oil supplementation may be most useful in patients with hypertriglyceridemia, but its role in treatment is not well defined.
- **LOVAZA** (**omega-3-acid ethyl esters**) is a prescription form of concentrated fish oil EPA 465 mg and docosahexaenoic acid 375 mg. The daily dose is 4 g, which can be taken as four 1-g capsules once daily or two 1-g capsules twice daily. This product lowers triglycerides by 14% to 30% and raises HDL by ~10%.
- Complications of fish oil supplementation such as thrombocytopenia and bleeding disorders have been noted, especially with high doses (EPA 15–30 g/day).

TREATMENT RECOMMENDATIONS

- Treatment of type I hyperlipoproteinemia is directed toward reduction of chylomicrons derived from dietary fat with the subsequent reduction in plasma triglycerides. Total daily fat intake should be no more than 10 to 25 g, or ~15% of total calories. Secondary causes of hypertriglyceridemia should be excluded, and, if present, the underlying disorder should be treated appropriately.
- Primary hypercholesterolemia (familial hypercholesterolemia, familial combined dyslipidemia, and type IIa hyperlipoproteinemia) is treated with **BARs**, **statins**, **niacin**, or **ezetimibe**.

- Combined hyperlipoproteinemia (type IIb) may be treated with **statins**, **niacin**, or **gemfibrozil** to lower LDL-C without elevating VLDL and triglycerides. Niacin is the most effective agent and may be combined with a BAR. A BAR alone in this disorder may elevate VLDL and triglycerides, and their use as single agents for treating combined hyperlipoproteinemia should be avoided.
- Type III hyperlipoproteinemia may be treated with **fibrates** or **niacin**. Although fibrates have been suggested as the drugs of choice, niacin is a reasonable alternative because of the lack of data supporting a cardiovascular mortality benefit from fibrates and because of potentially serious adverse effects. Fish oil supplementation may be an alternative therapy.
- Type V hyperlipoproteinemia requires stringent restriction of dietary fat intake. Drug therapy with **fibrates** or **niacin** is indicated if the response to diet alone is inadequate. **Medium-chain triglycerides**, which are absorbed without chylomicron formation may be used as a dietary supplement for caloric intake if needed for both types I and V.

Combination Drug Therapy

- Combination therapy may be considered after adequate trials of monotherapy and for patients documented to be adherent to the prescribed regimen. Two or three lipoprotein profiles at 6-week intervals should confirm the lack of response prior to initiation of combination therapy.
- Screen carefully for contraindications and drug interactions with combined therapy, and consider the extra cost of drug product and monitoring.
- In general, a **statin** plus a **BAR** or **niacin** plus a **BAR** provides the greatest reduction in total and LDL cholesterol.
- Regimens intended to increase HDL levels should include either **gemfibrozil** or **niacin**, bearing in mind that **statins** combined with either of these drugs may result in a greater incidence of hepatotoxicity or myositis.
- Familial combined dyslipidemia may respond better to a fibrate and a statin than to a fibrate and a BAR.

TREATMENT OF HYPERTRIGLYCERIDEMIA

- Lipoprotein pattern types I, III, IV, and V are associated with hypertriglyceridemia, and these primary lipoprotein disorders should be excluded prior to implementing therapy.
- A family history positive for CHD is important in identifying patients at risk for premature atherosclerosis. If a patient with CHD has elevated triglycerides, the associated abnormality is probably a contributing factor to CHD and should be treated.
- High serum triglycerides (see **Table 8–1**) should be treated by achieving desirable body weight, consumption of a low saturated fat and cholesterol diet, regular exercise, smoking cessation, and restriction of alcohol (in select patients).
- The sum of LDL and VLDL (termed *non-HDL* [total cholesterol – HDL]) is a secondary therapeutic target in persons with high triglycerides (≥200 mg/dL [≥2.26 mmol/L). The goal for non-HDL with high serum triglycerides is set at 30 mg/dL (0.78 mmol/L) higher than that for LDL on the premise that a VLDL level less than or equal to 30 mg/dL (0.78 mmol/L) is normal.
- Drug therapy with **niacin** should be considered in patients with borderline-high triglycerides but with risk factors of established CHD, family history of premature CHD, concomitant LDL elevation or low HDL, and genetic forms of hypertriglyceridemia associated with CHD. Alternative therapies include **gemfibrozil** or **fenofibrate**, **statins**, and **fish oil**. The goal of therapy is to lower triglycerides and VLDL particles that may be atherogenic, increase HDL, and reduce LDL.
- Very high triglycerides are associated with pancreatitis and other adverse consequences. Management includes dietary fat restriction (10–20% of calories as fat), weight loss, alcohol restriction, and treatment of coexisting disorders (eg, diabetes). Drug therapy includes **gemfibrozil** or **fenofibrate**, **niacin**, and higher-potency statins (**atorvastatin**, **pitavastatin**, **rosuvastatin**, and **simvastatin**). Successful treatment is defined as reduction in triglycerides to less than 500 mg/dL (5.65 mmol/L).

TREATMENT OF LOW HDL CHOLESTEROL

- Low HDL cholesterol is a strong independent risk predictor of CHD. ATP III redefined low HDL cholesterol as less than 40 mg/dL (<1.03 mmol/L) but specified no goal for HDL raising. In low HDL, the primary target remains LDL, but treatment emphasis shifts to weight reduction, increased physical activity, and smoking cessation, and to **fibrates** and **niacin** if drug therapy is required.

TREATMENT OF DIABETIC DYSLIPIDEMIA

- Diabetic dyslipidemia is characterized by hypertriglyceridemia, low HDL, and minimally elevated LDL. Small, dense LDL (pattern B) in diabetes is more atherogenic than larger, more buoyant forms of LDL (pattern A).
- ATP III considers diabetes to be a CHD risk equivalent, and the primary target is to lower the LDL to less than 100 mg/dL (<2.59 mmol/L). When LDL is greater than 130 mg/dL (>3.36 mmol/L), most patients require simultaneous TLCs and drug therapy. When LDL is between 100 and 129 mg/dL (2.59 and 3.34 mmol/L), intensifying glycemic control, adding drugs for atherogenic dyslipidemia (**fibrates** and **niacin**) and intensifying LDL-lowering therapy are options. **Statins** are considered by many to be the drugs of choice because the primary target is LDL.

EVALUATION OF THERAPEUTIC OUTCOMES

- Short-term evaluation of therapy for dyslipidemia is based on response to diet and drug treatment as measured by total cholesterol, LDL-C, HDL-C, and triglycerides.
- Many patients treated for primary dyslipidemia have no symptoms or clinical manifestations of a genetic lipid disorder (eg, xanthomas), and monitoring may be solely laboratory based.
- In patients treated for secondary intervention, symptoms of atherosclerotic cardiovascular disease, such as angina and intermittent claudication, may improve over months to years. Xanthomas or other external manifestations of dyslipidemia should regress with therapy.
- Obtain lipid measurements in the fasting state to minimize interference from chylomicrons. Monitoring is needed every few months during dosage titration. Once the patient is stable, monitoring at intervals of 6 months to 1 year is sufficient.
- Patients on BAR therapy should have a fasting panel checked every 4 to 8 weeks until a stable dose is reached; check triglycerides at a stable dose to ensure they have not increased.
- Niacin requires baseline tests of liver function (alanine aminotransferase), uric acid, and glucose. Repeat tests are appropriate at doses of 1,000 to 1,500 mg/day. Symptoms of myopathy or diabetes should be investigated and may require creatine kinase or glucose determinations. Patients with diabetes may require more frequent monitoring.
- Patients receiving statins should have a fasting lipid panel 4 to 8 weeks after the initial dose or dose changes. Obtain liver function tests at baseline and periodically thereafter. Some experts believe that monitoring for hepatotoxicity and myopathy should be triggered by symptoms.
- For patients with multiple risk factors and established CHD, evaluate for progress in managing other risk factors such as BP control, smoking cessation, exercise and weight control, and glycemic control (if diabetic).
- Evaluation of dietary therapy with diet diaries and recall survey instruments allows information about diet to be collected in a systematic fashion and may improve patient adherence to dietary recommendations.

See Chapter 11, Dyslipidemia, authored by Robert L. Talbert, for a more detailed discussion of this topic.

CHAPTER 9

Heart Failure

- *Heart failure* (HF) is a progressive clinical syndrome caused by inability of the heart to pump sufficient blood to meet the body's metabolic needs. HF can result from any disorder that reduces ventricular filling (diastolic dysfunction) and/or myocardial contractility (systolic dysfunction).

PATHOPHYSIOLOGY

- Causes of systolic dysfunction (decreased contractility) are reduced muscle mass (eg, myocardial infarction [MI]), dilated cardiomyopathies, and ventricular hypertrophy. Ventricular hypertrophy can be caused by pressure overload (eg, systemic or pulmonary hypertension and aortic or pulmonic valve stenosis) or volume overload (eg, valvular regurgitation, shunts, high-output states).
- Causes of diastolic dysfunction (restriction in ventricular filling) are increased ventricular stiffness, ventricular hypertrophy, infiltrative myocardial diseases, myocardial ischemia and MI, mitral or tricuspid valve stenosis, and pericardial disease (eg, pericarditis and pericardial tamponade).
- The leading causes of HF are coronary artery disease and hypertension.
- As cardiac function decreases after myocardial injury, the heart relies on compensatory mechanisms: (1) tachycardia and increased contractility through sympathetic nervous system activation; (2) the Frank–Starling mechanism, whereby increased preload increases stroke volume; (3) vasoconstriction; and (4) ventricular hypertrophy and remodeling. Although these compensatory mechanisms initially maintain cardiac function, they are responsible for the symptoms of HF and contribute to disease progression.
- In the *neurohormonal model* of HF, an initiating event (eg, acute MI) leads to decreased cardiac output; the HF state then becomes a systemic disease whose progression is mediated largely by neurohormones and autocrine/paracrine factors. These substances include angiotensin II, norepinephrine, aldosterone, natriuretic peptides, arginine vasopressin, endothelin peptides, and other circulating biomarkers (eg, C-reactive protein).
- Common precipitating factors that may cause a previously compensated HF patient to decompensate include myocardial ischemia and MI, atrial fibrillation, pulmonary infections, nonadherence with diet or drug therapy, and inappropriate medication use. Drugs may precipitate or exacerbate HF because of their negative inotropic, cardiotoxic, or sodium- and water-retaining properties.

CLINICAL PRESENTATION

- Patient presentation may range from asymptomatic to cardiogenic shock.
- Primary symptoms are dyspnea (particularly on exertion) and fatigue, which lead to exercise intolerance. Other pulmonary symptoms include orthopnea, paroxysmal nocturnal dyspnea, tachypnea, and cough.
- Fluid overload can result in pulmonary congestion and peripheral edema.
- Nonspecific symptoms may include fatigue, nocturia, hemoptysis, abdominal pain, anorexia, nausea, bloating, ascites, poor appetite, mental status changes, and weight gain.
- Physical examination findings may include pulmonary crackles, S_3 gallop, cool extremities, Cheyne–Stokes respiration, tachycardia, narrow pulse pressure, cardiomegaly, symptoms of pulmonary edema (extreme breathlessness and anxiety, sometimes with coughing and pink, frothy sputum), peripheral edema, jugular venous distention, hepatojugular reflux, and hepatomegaly.

DIAGNOSIS

- Consider diagnosis of HF in patients with characteristic signs and symptoms. A complete history and physical examination with appropriate laboratory testing are essential in evaluating patients with suspected HF.
- Laboratory tests for identifying disorders that may cause or worsen HF include complete blood cell count; serum electrolytes (including calcium and magnesium); renal, hepatic, and thyroid function tests; urinalysis; lipid profile; and A1C. B-type natriuretic peptide (BNP) will generally be greater than 100 pg/mL.
- Ventricular hypertrophy can be demonstrated on chest radiograph or electrocardiogram (ECG). Chest radiograph may also show pleural effusions or pulmonary edema.
- Echocardiogram can identify abnormalities of the pericardium, myocardium, or heart valves and quantify left ventricular ejection fraction (LVEF) to determine if systolic or diastolic dysfunction is present.
- The New York Heart Association Functional Classification System is intended primarily to classify *symptomatic* HF patients according to the physician's subjective evaluation. Functional class (FC)-I patients have no limitation of physical activity, FC-II patients have slight limitation, FC-III patients have marked limitation, and FC-IV patients are unable to carry on physical activity without discomfort.
- The American College of Cardiology/American Heart Association (ACC/AHA) staging system provides a more comprehensive framework for evaluating, preventing, and treating HF (see further discussion below).

TREATMENT OF CHRONIC HEART FAILURE

- Goals of Treatment: Improve quality of life, relieve or reduce symptoms, prevent or minimize hospitalizations, slow disease progression, and prolong survival.

GENERAL APPROACH

- The first step is to determine the etiology or precipitating factors. Treatment of underlying disorders (eg, hyperthyroidism) may obviate the need for treating HF.
- Nonpharmacologic interventions include cardiac rehabilitation and restriction of fluid intake (maximum 2 L/day from all sources) and dietary sodium (<2–3 g of sodium/day).
- **ACC/AHA stage A:** These are patients at high risk for developing heart failure. The emphasis is on identifying and modifying risk factors to prevent development of structural heart disease and subsequent HF. Strategies include smoking cessation and control of hypertension, diabetes mellitus, and dyslipidemia. Although treatment must be individualized, **angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs)** are recommended for HF prevention in patients with multiple vascular risk factors.
- **ACC/AHA stage B:** In these patients with structural heart disease but no HF signs or symptoms, treatment is targeted at minimizing additional injury and preventing or slowing the remodeling process. In addition to treatment measures outlined for stage A, patients with a previous MI should receive both **ACE inhibitors** (or **ARBs** in patients intolerant of ACE inhibitors) and **β-blockers** regardless of the ejection fraction. Patients with reduced ejection fractions should also receive both agents, regardless of whether they have had an MI.
- **ACC/AHA stage C:** These patients have structural heart disease and previous or current HF symptoms. Most should receive the treatments for stages A and B, as well as initiation and titration of a **diuretic** (if clinical evidence of fluid retention), **ACE inhibitor**, and **β-blocker** (if not already receiving a β-blocker for previous MI, left ventricular [LV] dysfunction, or other indication). If diuresis is initiated, and symptoms improve once the patient is euvolemic, long-term monitoring can begin. If symptoms do not improve, an **aldosterone receptor antagonist**, **ARB** (in ACE inhibitor–intolerant patients), **digoxin**, and/or **hydralazine/isosorbide dinitrate** (ISDN) may be useful with carefully screened patients. Other general measures

include moderate sodium restriction, daily weight measurement, immunization against influenza and pneumococcus, modest physical activity, and avoidance of medications that can exacerbate HF.

- **ACC/AHA stage D:** These are patients with refractory HF (ie, symptoms at rest despite maximal medical therapy). They should be considered for specialized therapies, including mechanical circulatory support, continuous IV positive inotropic therapy, cardiac transplantation, or hospice care (when no additional treatments are appropriate).

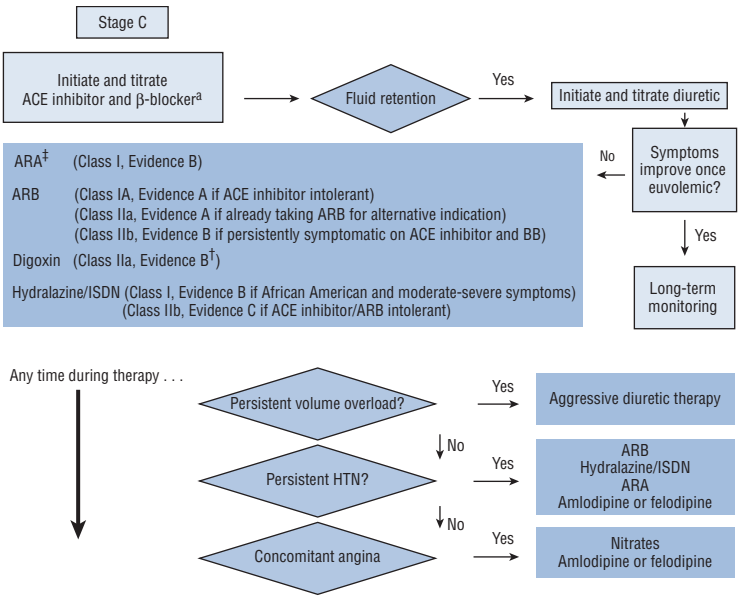
PHARMACOLOGIC THERAPY

Drug Therapies for Routine Use in Stage C Systolic Heart Failure

(Fig. 9–1)

DIURETICS

- Compensatory mechanisms in HF stimulate excessive sodium and water retention, often leading to systemic and pulmonary congestion. Consequently, diuretic therapy (in addition to sodium restriction) is recommended for all patients with clinical evidence of fluid retention. However, because they do not alter disease progression or prolong survival, they are not mandatory for patients without fluid retention.
- Thiazide diuretics (eg, **hydrochlorothiazide**) are relatively weak and are used alone infrequently in HF. However, thiazides or the thiazide-like diuretic **metolazone** can be used in combination with a loop diuretic to promote very effective diuresis. Thiazides may be preferred over loop diuretics in patients with only mild fluid



[a] If not already receiving this therapy for previous MI, LV dysfunction, or other indication.
‡ If moderately severe to severe symptoms.
† Indication is to reduce hospitalization.

FIGURE 9–1. Treatment algorithm for patients with ACC/AHA stage C heart failure. (ACE, angiotensin-converting enzyme; ARA, aldosterone receptor antagonist; ARB, angiotensin receptor blocker; BB, β-blocker; HTN, hypertension; ISDN, isosorbide dinitrate; LV, left ventricular; MI, myocardial infarction.)

TABLE 9–1 Loop Diuretic Use in Heart Failure

	Furosemide	Bumetanide	Torsemide
Usual daily dose (oral)	20–160 mg/day	0.5–4 mg/day	10–80 mg/day
Ceiling dose[a]			
Normal renal function	80–160 mg	1–2 mg	20–40 mg
CL_{cr} 20–50 mL/min	160 mg	2 mg	40 mg
CL_{cr} <20 mL/min	400 mg	8–10 mg	100 mg
Bioavailability	10%–100% Average: 50%	80%–90%	80%–100%
Affected by food	Yes	Yes	No
Half-life	0.3–3.4 h	0.3–1.5 h	3–4 h

CL_{cr}, creatinine clearance.
[a]Ceiling dose: single dose above which additional response is unlikely to be observed

retention and elevated blood pressure (BP) because of their more persistent antihypertensive effects.

- Loop diuretics (**furosemide**, **bumetanide**, and **torsemide**) are usually necessary to restore and maintain euvolemia in HF. In addition to acting in the thick ascending limb of the loop of Henle, they induce a prostaglandin-mediated increase in renal blood flow that contributes to their natriuretic effect. Unlike thiazides, loop diuretics maintain their effectiveness in the presence of impaired renal function, although higher doses may be necessary.
- Ranges of doses and ceiling doses for loop diuretics in patients with varying degrees of renal function are listed in **Table 9–1**.

ANGIOTENSIN-CONVERTING ENZYME INHIBITORS

- ACE inhibitors (**Table 9–2**) decrease angiotensin II and aldosterone, attenuating many of their deleterious effects, including reducing ventricular remodeling,

TABLE 9–2 ACE Inhibitors Routinely Used for Treatment of Heart Failure

Generic Name	Brand Name	Initial Dose	Target Dosing–Survival Benefit[a]	Prodrug	Elimination[b]
Captopril	Capoten	6.25 mg three times daily	50 mg three times daily	No	Renal
Enalapril	Vasotec	2.5–5 mg twice daily	10 mg twice daily	Yes	Renal
Lisinopril	Zestril, Prinivil	2.5–5 mg daily	20–40 mg daily[c]	No	Renal
Quinapril	Accupril	5 mg twice daily	20–40 mg twice daily[d]	Yes	Renal
Ramipril	Altace	1.25–2.5 mg twice daily	5 mg twice daily	Yes	Renal
Fosinopril	Monopril	5–10 mg daily	40 mg daily[d]	Yes	Renal/hepatic
Trandolapril	Mavik	0.5–1 mg daily	4 mg daily	Yes	Renal/hepatic
Perindopril	Aceon	2 mg daily	8–16 mg daily	Yes	Renal/hepatic

[a]Target doses associated with survival benefits in clinical trials.
[b]Primary route of elimination.
[c]Note that in the ATLAS trial (Circulation 1999;100:2312–2318), no significant difference in mortality was found between low-dose (~5 mg/day) and high-dose (~35 mg/day) lisinopril therapy.
[d]Effects on mortality have not been evaluated.

myocardial fibrosis, myocyte apoptosis, cardiac hypertrophy, norepinephrine release, vasoconstriction, and sodium and water retention.
- Clinical trials have produced unequivocal evidence that ACE inhibitors improve symptoms, slow disease progression, and decrease mortality in patients with HF and reduced LVEF (stage C). These patients should receive ACE inhibitors unless contraindications are present. ACE inhibitors should also be used to prevent the development of HF in at-risk patients (ie, stages A and B).

β-BLOCKERS

- There is overwhelming clinical trial evidence that certain β-blockers slow disease progression, decrease hospitalizations, and reduce mortality in patients with systolic HF.
- The ACC/AHA guidelines recommend use of β-blockers in all stable patients with HF and a reduced LVEF in the absence of contraindications or a clear history of β-blocker intolerance. Patients should receive a β-blocker even if symptoms are mild or well controlled with ACE inhibitor and diuretic therapy. It is not essential that ACE inhibitor doses be optimized before a β-blocker is started because the addition of a β-blocker is likely to be of greater benefit than an increase in ACE inhibitor dose.
- β-Blockers are also recommended for asymptomatic patients with a reduced LVEF (stage B) to decrease the risk of progression to HF.
- Initiate β-blockers in stable patients who have no or minimal evidence of fluid overload. Because of their negative inotropic effects, start β-blockers in very low doses with slow upward dose titration to avoid symptomatic worsening or acute decompensation. Titrate to target doses when possible to provide maximal survival benefits.
- Carvedilol, metoprolol succinate (CR/XL), and bisoprolol are the only β-blockers shown to reduce mortality in large HF trials. Because bisoprolol is not available in the necessary starting dose of 1.25 mg, the choice is typically limited to either carvedilol or metoprolol succinate. On the basis of regimens proven in large clinical trials to reduce mortality, initial and target oral doses are as follows:
  - ✓ **Carvedilol**, 3.125 mg twice daily initially; target dose 25 mg twice daily (the target dose for patients weighing >85 kg [187 lb] is 50 mg twice daily).
  - ✓ **Carvedilol CR**, 10 mg once daily initially; target dose 80 mg once daily. This product should be considered in patients with difficulty maintaining adherence to the immediate-release carvedilol formulation.
  - ✓ **Metoprolol succinate CR/XL**, 12.5 to 25 mg once daily initially; target dose 200 mg once daily.
  - ✓ **Bisoprolol**, 1.25 mg once daily initially; target dose 10 mg once daily.
- Doses should be doubled no more often than every 2 weeks, as tolerated, until the target dose or the maximally tolerated dose is reached. Patients should understand that dose up-titration is a long, gradual process and that achieving the target dose is important to maximize benefits. Further, the response to therapy may be delayed, and HF symptoms may actually worsen during the initiation period.

Drug Therapies to Consider for Select Patients

ANGIOTENSIN II RECEPTOR BLOCKERS

- The angiotensin II receptor antagonists block the angiotensin II receptor subtype AT_1, preventing the deleterious effects of angiotensin II, regardless of its origin. They do not appear to affect bradykinin and are not associated with the side effect of cough that sometimes results from ACE inhibitor–induced accumulation of bradykinin. Also, direct blockade of AT_1 receptors allows unopposed stimulation of AT_2 receptors, causing vasodilation and inhibition of ventricular remodeling.
- Although some data suggest that ARBs produce equivalent mortality benefits when compared with ACE inhibitors, the ACC/AHA guidelines recommend use of ARBs only in patients with stage A, B, or C HF who are intolerant of ACE inhibitors. Although there are currently seven ARBs on the market in the United States, only

candesartan and valsartan are FDA-approved for the treatment of HF and are the preferred agents, whether used alone or in combination with ACE inhibitors.

- Therapy should be initiated at low doses and then titrated to target doses:
  - ✓ **Candesartan**, 4 to 8 mg once daily initially; target dose 32 mg once daily.
  - ✓ **Valsartan**, 20 to 40 mg twice daily initially; target dose 160 mg twice daily.
- Assess BP, renal function, and serum potassium within 1 to 2 weeks after therapy initiation and dose increases, with these endpoints used to guide subsequent dose changes. It is not necessary to reach target ARB doses before adding a β-blocker.
- Cough and angioedema are the most common causes of ACE inhibitor intolerance. Caution should be exercised when ARBs are used in patients with angioedema from ACE inhibitors because cross-reactivity has been reported. ARBs are not alternatives in patients with hypotension, hyperkalemia, or renal insufficiency due to ACE inhibitors because they are just as likely to cause these adverse effects.
- Combination therapy with an ARB and ACE inhibitor offers a theoretical advantage over either agent alone through more complete blockade of the deleterious effects of angiotensin II. However, clinical trial results indicate that the addition of an ARB to optimal HF therapy (eg, ACE inhibitors, β-blockers, and diuretics) offers marginal benefits at best with increased risk of adverse effects. The addition of an ARB may be considered with patients who remain symptomatic despite receiving optimal conventional therapy.

ALDOSTERONE ANTAGONISTS

- **Spironolactone** and **eplerenone** block the mineralocorticoid receptor, the target site for aldosterone. In the kidney, aldosterone antagonists inhibit sodium reabsorption and potassium excretion. However, diuretic effects are minimal, suggesting that their therapeutic benefits result from other actions.
- Based on clinical trial results demonstrating reduced mortality, low-dose aldosterone antagonists may be appropriate for: (1) patients with mild to moderately severe systolic HF who are receiving standard therapy, and (2) those with LV dysfunction and either acute HF or diabetes early after MI.
- Aldosterone antagonists must be used cautiously and with careful monitoring of renal function and potassium concentration. They should be avoided in patients with renal impairment, recent worsening of renal function, high-normal potassium levels, or a history of severe hyperkalemia. Spironolactone also interacts with androgen and progesterone receptors, which may lead to gynecomastia, impotence, and menstrual irregularities in some patients.
- Initial doses should be low (spironolactone 12.5 mg/day; eplerenone 25 mg/day), especially in the elderly and those with diabetes or creatinine clearance less than 50 mL/min. A spironolactone dose of 25 mg/day was used in one major clinical trial. The eplerenone dose should be titrated to the target dose of 50 mg once daily, preferably within 4 weeks as tolerated by the patient.

DIGOXIN

- Although digoxin has positive inotropic effects, its benefits in HF are related to its neurohormonal effects. Digoxin does not improve survival in patients with HF but does provide symptomatic benefits.
- In patients with chronic systolic HF and supraventricular tachyarrhythmias such as atrial fibrillation, consider digoxin early in therapy to help control ventricular response rate.
- For patients in normal sinus rhythm, effects on symptom reduction and quality-of-life improvement are evident in patients with mild to severe HF. Therefore, digoxin should be used together with standard HF therapies (ACE inhibitors, β-blockers, and diuretics) in patients with symptomatic HF to reduce hospitalizations.
- Adjust doses to achieve plasma digoxin concentration of 0.5 to 1 ng/mL (0.6–1.3 nmol/L). Most patients with normal renal function can achieve this level with a dose of 0.125 mg/day. Patients with decreased renal function, the elderly, or those receiving interacting drugs (eg, amiodarone) should receive 0.125 mg every other day.

NITRATES AND HYDRALAZINE

- Nitrates (eg, **ISDN**) and **hydralazine** have complementary hemodynamic actions. Nitrates are primarily venodilators, producing reductions in preload. Hydralazine is a direct arterial vasodilator that reduces systemic vascular resistance (SVR) and increases stroke volume and cardiac output.
- The combination of nitrates and hydralazine improves the composite endpoint of mortality, hospitalizations for HF, and quality of life in African Americans who receive standard therapy. A fixed-dose combination product is available that contains ISDN 20 mg and hydralazine 37.5 mg (BiDil). Guidelines recommend addition of hydralazine and nitrates to self-described African Americans with systolic HF and moderate to severe symptoms despite therapy with ACE inhibitors, diuretics, and β-blockers. The combination may also be reasonable for patients of other ethnicities with persistent symptoms despite optimized therapy with an ACE inhibitor (or ARB) and β-blocker. The combination is also appropriate as first-line therapy in patients unable to tolerate ACE inhibitors or ARBs because of renal insufficiency, hyperkalemia, or possibly hypotension.
- Obstacles to successful therapy with this drug combination include the need for frequent dosing (ie, three times daily with the fixed-dose combination product), high frequency of adverse effects (eg, headache, dizziness, GI distress), and increased cost for the fixed-dose combination product.

TREATMENT OF ACUTE DECOMPENSATED HEART FAILURE

GENERAL APPROACH

- *Acute decompensated heart failure (ADHF)* involves patients with new or worsening signs or symptoms (often resulting from volume overload and/or hypoperfusion) requiring additional medical care, such as emergency department visits and hospitalizations.
- Goals of Treatment: Relieve congestive symptoms, optimize volume status, treat symptoms of low cardiac output, and minimize risks of drug therapy so the patient can be discharged in a compensated state on oral drug therapy.
- Hospitalization is *recommended* or *should be considered* depending on patient presentation. Admission to an intensive care unit (ICU) may be required if the patient experiences hemodynamic instability requiring frequent monitoring, invasive hemodynamic monitoring, or rapid titration of IV medications with close monitoring.
- Address and correct reversible or treatable causes of decompensation. Medications that may aggravate HF should be evaluated carefully and discontinued when possible.
- The first step in managing ADHF is to ascertain that optimal treatment with oral medications has been achieved. If fluid retention is evident, aggressive diuresis, often with IV diuretics, should be accomplished. Standard treatment should be optimized with an ACE inhibitor and β-blocker. β-blockers should generally be continued during hospitalization unless recent dose initiation or up-titration was responsible for decompensation. In such cases, β-blocker therapy may be temporarily withheld or dose-reduced. Most patients may continue to receive digoxin at a low dose targeting a trough serum concentration of 0.5–1 ng/mL (0.6–1.3 nmol/L).
- Appropriate management of ADHF is aided by determination of whether the patient has signs and symptoms of fluid overload ("wet" HF) or low cardiac output ("dry" HF) (**Fig. 9–2**).
- Invasive hemodynamic monitoring in select patients may help guide treatment and classify patients into four specific hemodynamic subsets based on cardiac index and pulmonary artery occlusion pressure (PAOP).

PHARMACOTHERAPY OF ACUTE DECOMPENSATED HEART FAILURE

Diuretics

- IV loop diuretics, including **furosemide, bumetanide,** and **torsemide**, are used for ADHF, with furosemide being the most widely studied and used agent.

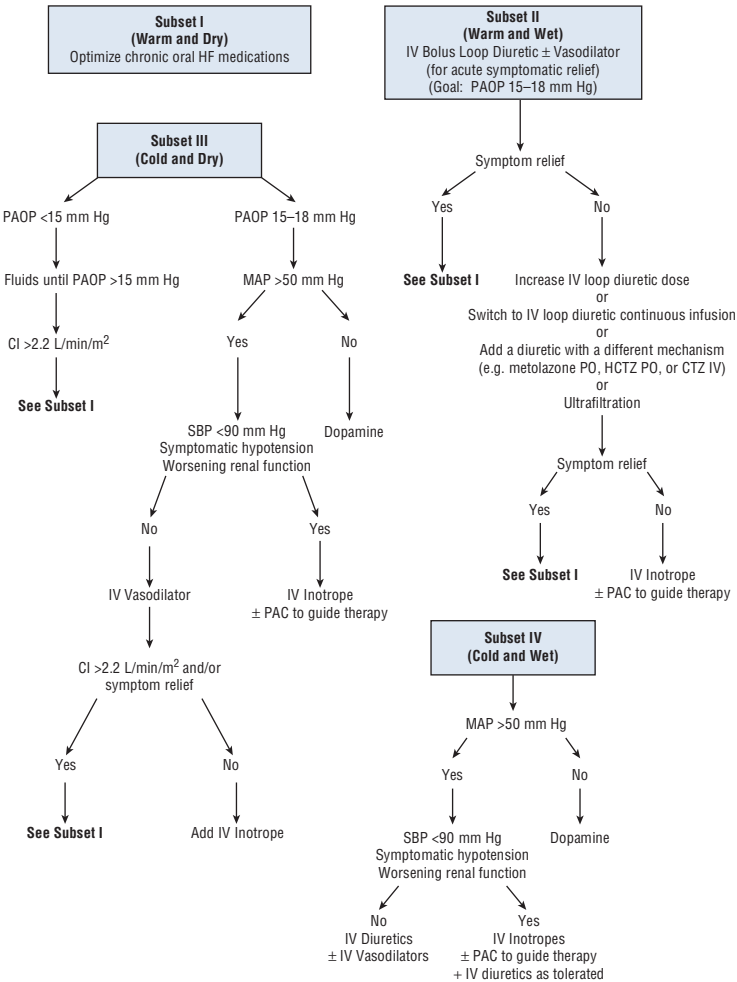


FIGURE 9–2. General treatment algorithm for acute decompensated heart failure (ADHF) based on clinical presentation. IV vasodilators that may be used include nitroglycerin, nesiritide, and nitroprusside. Metolazone or spironolactone may be added if the patient fails to respond to loop diuretics and a second diuretic is required. IV inotropes that may be used include dobutamine and milrinone. (CI, cardiac index; CTZ, chlorothiazide; D/C, discontinue; HCTZ, hydrochlorothiazide; HF, heart failure; MAP, mean arterial pressure; PAC, pulmonary artery catheter; PAOP, pulmonary artery occlusion pressure; SBP, systolic blood pressure.)

- Bolus diuretic administration decreases preload by functional venodilation within 5 to 15 minutes and later (>20 min) via sodium and water excretion, thereby improving pulmonary congestion. However, acute reductions in venous return may severely compromise effective preload in patients with significant diastolic dysfunction or intravascular depletion.

- Because diuretics can cause excessive preload reduction, they must be used judiciously to obtain the desired improvement in congestive symptoms while avoiding a reduction in cardiac output, symptomatic hypotension, or worsening renal function.
- Diuretic resistance may be overcome by administering larger IV bolus doses or continuous IV infusions of loop diuretics. Diuresis may also be improved by adding a second diuretic with a different mechanism of action (eg, combining a loop diuretic with a distal tubule blocker such as **metolazone** or **hydrochlorothiazide**). The loop diuretic–thiazide combination should generally be reserved for inpatients who can be monitored closely for the development of severe sodium, potassium, and volume depletion. Very low doses of the thiazide-type diuretic should be used in the outpatient setting to avoid serious adverse events.

Positive Inotropic Agents

DOBUTAMINE

- **Dobutamine** is a β_1- and β_2-receptor agonist with some α_1-agonist effects. The net vascular effect is usually vasodilation. It has a potent inotropic effect without producing a significant change in heart rate. Initial doses of 2.5 to 5 mcg/kg/min can be increased progressively to 20 mcg/kg/min on the basis of clinical and hemodynamic responses.
- Dobutamine increases cardiac index because of inotropic stimulation, arterial vasodilation, and a variable increase in heart rate. It causes relatively little change in mean arterial pressure compared with the more consistent increases observed with dopamine.
- Although concern over attenuation of dobutamine's hemodynamic effects with prolonged administration has been raised, some effect is likely retained. Consequently, the dobutamine dose should be tapered rather than abruptly discontinued.

MILRINONE

- **Milrinone** inhibits phosphodiesterase III and produces positive inotropic and arterial and venous vasodilating effects (an inodilator). It has supplanted use of amrinone, which has a higher rate of thrombocytopenia.
- During IV administration, milrinone increases stroke volume (and cardiac output) with minimal change in heart rate. It also lowers pulmonary capillary wedge pressure (PCWP) by venodilation and is particularly useful in patients with a low cardiac index and elevated LV filling pressure. However, this decrease in preload can be hazardous for patients without excessive filling pressure, leading to further decline in cardiac index.
- Use milrinone cautiously as a single agent in severely hypotensive HF patients because it will not increase, and may even decrease, arterial BP.
- The usual loading dose of milrinone is 50 mcg/kg over 10 minutes. If rapid hemodynamic changes are unnecessary, eliminate the loading dose because of the risk of hypotension. Most patients are simply started on the maintenance continuous infusion of 0.1 to 0.3 mcg/kg/min (up to 0.75 mcg/kg/min).
- The most notable adverse events are arrhythmia, hypotension, and, rarely, thrombocytopenia. Measure platelet count before and during therapy.
- Routine use of milrinone (and perhaps other inotropes) should be discouraged because recent studies suggest a higher in-hospital mortality rate than with some other drugs. However, inotropes may be needed with certain patients, such as those with low cardiac output states with organ hypoperfusion and cardiogenic shock. Milrinone may be considered for patients receiving chronic β-blocker therapy because its positive inotropic effect does not involve stimulation of β-receptors.

DOPAMINE

- **Dopamine** should generally be avoided in ADHF, but its pharmacologic actions may be preferable to dobutamine or milrinone in patients with marked systemic hypotension or cardiogenic shock in the face of elevated ventricular filling pressures, where

dopamine in doses greater than 5 mcg/kg/min may be necessary to raise central aortic pressure.

- Dopamine produces dose-dependent hemodynamic effects because of its relative affinity for α_1-, β_1-, β_2-, and D_1- (vascular dopaminergic) receptors. Positive inotropic effects mediated primarily by β_1-receptors become more prominent with doses of 2 to 5 mcg/kg/min. At doses between 5 and 10 mcg/kg/min, chronotropic and α_1-mediated vasoconstricting effects become more prominent.

Vasodilators

- Arterial vasodilators reduce afterload and cause a reflex increase in cardiac output. Venodilators reduce preload by increasing venous capacitance, improving symptoms of pulmonary congestion in patients with high cardiac filling pressures. Mixed vasodilators act on both arterial resistance and venous capacitance vessels, reducing congestive symptoms while increasing cardiac output.

NITROPRUSSIDE

- **Sodium nitroprusside** is a mixed arteriovenous vasodilator that acts directly on vascular smooth muscle to increase cardiac index and decrease venous pressure. Despite its lack of direct inotropic activity, nitroprusside exerts hemodynamic effects that are qualitatively similar to those of dobutamine and milrinone. However, nitroprusside generally decreases PCWP, SVR, and BP more than those agents do.
- Hypotension is an important dose-limiting adverse effect of nitroprusside and other vasodilators. Therefore, nitroprusside is primarily used with patients who have a significantly elevated SVR and often requires invasive hemodynamic monitoring.
- Nitroprusside is effective in the short-term management of severe HF in a variety of settings (eg, acute MI, valvular regurgitation, after coronary bypass surgery, decompensated chronic HF). Generally, it will not worsen, and may improve, the balance between myocardial oxygen demand and supply. However, an excessive decrease in systemic arterial pressure can decrease coronary perfusion and worsen ischemia.
- Nitroprusside has a rapid onset and a duration of action less than 10 minutes, which necessitates use of continuous IV infusions. Initiated therapy with a low dose (0.1–0.2 mcg/kg/min) to avoid excessive hypotension, and increase by small increments (0.1–0.2 mcg/kg/min) every 5 to 10 minutes as needed and tolerated. Usual effective doses range from 0.5 to 3 mcg/kg/min. Taper nitroprusside slowly when stopping therapy because of possible rebound after abrupt withdrawal. Nitroprusside-induced cyanide and thiocyanate toxicity are unlikely when doses less than 3 mcg/kg/min are administered for less than 3 days, except in patients with serum creatinine levels greater than 3 mg/dL (>265 µmol/L).

NITROGLYCERIN

- IV **nitroglycerin** decreases preload and PCWP because of functional venodilation and mild arterial vasodilation. It is often the preferred agent for preload reduction in ADHF, especially in patients with pulmonary congestion. In higher doses, nitroglycerin displays potent coronary vasodilating properties and beneficial effects on myocardial oxygen demand and supply, making it the vasodilator of choice for patients with severe HF and ischemic heart disease.
- Initiate nitroglycerin at 5 to 10 mcg/min (0.1 mcg/kg/min) and increase every 5 to 10 minutes as necessary and tolerated. Maintenance doses usually range from 35 to 200 mcg/min (0.5–3 mcg/kg/min). Hypotension and an excessive decrease in PCWP are important dose-limiting side effects. Some tolerance may develop over 12 to 72 hours of continuous administration.

NESIRITIDE

- **Nesiritide** is a recombinant product that is identical to endogenous BNP secreted by the ventricular myocardium in response to volume overload. Nesiritide mimics the vasodilatory and natriuretic actions of the endogenous peptide, resulting in venous and arterial vasodilation; increased cardiac output; natriuresis and diuresis; and

decreased cardiac filling pressures, sympathetic nervous system activity, and renin–angiotensin–aldosterone system activity.

- The role of nesiritide in pharmacotherapy of ADHF remains controversial. Compared with nitroglycerin or nitroprusside, it produces marginal improvement in clinical outcomes and is substantially more expensive. Concerns about potential negative effects on renal function and increased morality are also unsettled.

Vasopressin Receptor Antagonists

- The vasopressin receptor antagonists currently available affect one or two arginine vasopressin (AVP; antidiuretic hormone) receptors, V_{1A} or V_2. Stimulation of V_{1A} receptors (located in vascular smooth muscle cells and myocardium) results in vasoconstriction, myocyte hypertrophy, coronary vasoconstriction, and positive inotropic effects. V_2 receptors are located in renal tubules, where they regulate water reabsorption.
  - ✓ **Tolvaptan** selectively binds to and inhibits the V_2 receptor. It is an oral agent indicated for hypervolemic and euvolemic hyponatremia in patients with syndrome of inappropriate antidiuretic hormone (SIADH), cirrhosis, and HF. Tolvaptan is typically initiated at 15 mg orally daily and then titrated to 30 or 60 mg daily as needed to resolve hyponatremia. It is a substrate of cytochrome P450-3A4 and is contraindicated with potent inhibitors of this enzyme. The most common side effects are dry mouth, thirst, urinary frequency, constipation, and hyperglycemia.
  - ✓ **Conivaptan** nonselectively inhibits both the V_{1A} and V_2 receptors. It is an IV agent indicated for hypervolemic and euvolemic hyponatremia due to a variety of causes; however, it is not indicated for hyponatremia associated with HF.
- Monitor patients closely to avoid excessively rapid rise in serum sodium that could cause hypotension or hypovolemia; discontinue therapy if that occurs. Therapy may be restarted at a lower dose if hyponatremia recurs or persists and/or these side effects resolve.
- The role of vasopressin receptor antagonists in the long-term management of HF is unclear. In clinical trials, tolvaptan improved hyponatremia, diuresis, and signs/symptoms of congestion. However, one study failed to demonstrate improvement in global clinical status at discharge or a reduction in 2-year all-cause mortality, cardiovascular mortality, and HF rehospitalization.

MECHANICAL CIRCULATORY SUPPORT

- The **intraaortic balloon pump (IABP)** is typically employed in patients with advanced HF who do not respond adequately to drug therapy, such as those with intractable myocardial ischemia or patients in cardiogenic shock. IV vasodilators and inotropic agents are generally used in conjunction with the IABP to maximize hemodynamic and clinical benefits.
- **Ventricular assist devices** are surgically implanted and assist, or in some cases replace, the pumping functions of the right and/or left ventricles. They can be used in the short-term (days to several weeks) for temporary stabilization of patients awaiting an intervention to correct underlying cardiac dysfunction. They can also be used long term (several months to years) as a bridge to heart transplantation.

SURGICAL THERAPY

- Orthotopic cardiac transplantation is the best therapeutic option for patients with chronic irreversible New York Heart Association class IV HF, with a 10-year survival of ~50% in well-selected patients.

EVALUATION OF THERAPEUTIC OUTCOMES

CHRONIC HEART FAILURE

- Ask patients about the presence and severity of symptoms and how symptoms affect daily activities.

- Evaluate efficacy of diuretic treatment by disappearance of the signs and symptoms of excess fluid retention. Physical examination should focus on body weight, extent of jugular venous distention, presence of hepatojugular reflux, and presence and severity of pulmonary congestion (rales, dyspnea on exertion, orthopnea, and paroxysmal nocturnal dyspnea) and peripheral edema.
- Other outcomes are improvement in exercise tolerance and fatigue, decreased nocturia, and a decrease in heart rate.
- Monitor BP to ensure that symptomatic hypotension does not develop as a result of drug therapy.
- Body weight is a sensitive marker of fluid loss or retention, and patients should weigh themselves daily and report changes to their healthcare provider so that adjustments can be made in diuretic doses.
- Symptoms may worsen initially on β-blocker therapy, and it may take weeks to months before patients notice symptomatic improvement.
- Routine monitoring of serum electrolytes and renal function is mandatory in patients with HF.

ACUTE DECOMPENSATED HEART FAILURE

- Initial stabilization requires adequate arterial oxygen saturation, cardiac index, and blood pressure. Functional end-organ perfusion may be assessed by mental status, renal function sufficient to prevent metabolic complications, hepatic function adequate to maintain synthetic and excretory functions, stable heart rate and rhythm, absence of ongoing myocardial ischemia or MI, skeletal muscle and skin blood flow sufficient to prevent ischemic injury, and normal arterial pH (7.34–7.47) and serum lactate concentration. These goals are most often achieved with a cardiac index greater than 2.2 L/min/m^2, mean arterial BP greater than 60 mm Hg, and PCWP 15 mm Hg or greater.
- Daily monitoring should include weight, strict fluid intake and output measurements, and HF signs/symptoms to assess the efficacy of drug therapy. Monitoring for electrolyte depletion, symptomatic hypotension, and renal dysfunction should be performed frequently. Vital signs should be assessed frequently throughout the day.
- Discharge from the ICU requires maintenance of the preceding parameters in the absence of ongoing IV infusion therapy, mechanical circulatory support, or positive-pressure ventilation.

See Chapter 4, Chronic Heart Failure, authored by Robert B. Parker, Jean M. Nappi, and Larisa H. Cavallari, and Chap. 5, Acute Decompensated Heart Failure, authored by Jo E. Rodgers and Brent N. Reed, for a more detailed discussion of this topic.

CHAPTER 10

Hypertension

- *Hypertension* is defined as persistently elevated arterial blood pressure (BP). The seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC7) classifies adult BP as shown in **Table 10–1**.
- Isolated systolic hypertension is diastolic blood pressure (DBP) values less than 90 mm Hg and systolic blood pressure (SBP) values of 140 mm Hg or more.
- Hypertensive crisis (BP >180/120 mm Hg) may be categorized as hypertensive emergency (extreme BP elevation with acute or progressing target-organ damage) or hypertensive urgency (high BP elevation without acute or progressing target-organ injury).

PATHOPHYSIOLOGY

- Hypertension may result from a specific cause (secondary hypertension) or from an unknown etiology (primary or essential hypertension). Secondary hypertension (<10% of cases) is usually caused by chronic kidney disease (CKD) or renovascular disease. Other conditions are Cushing syndrome, coarctation of the aorta, obstructive sleep apnea, hyperparathyroidism, pheochromocytoma, primary aldosteronism, and hyperthyroidism. Some drugs that may increase BP include corticosteroids, estrogens, nonsteroidal anti-inflammatory drugs (NSAIDs), amphetamines, sibutramine, cyclosporine, tacrolimus, erythropoietin, and venlafaxine.
- Factors contributing to development of primary hypertension include:
  - ✓ Humoral abnormalities involving the renin–angiotensin–aldosterone system (RAAS), natriuretic hormone, or insulin resistance and hyperinsulinemia;
  - ✓ Disturbance in the CNS, autonomic nerve fibers, adrenergic receptors, or baroreceptors;
  - ✓ Abnormalities in renal or tissue autoregulatory processes for sodium excretion, plasma volume, and arteriolar constriction;
  - ✓ Deficiency in synthesis of vasodilating substances in vascular endothelium (prostacyclin, bradykinin, and nitric oxide) or excess vasoconstricting substances (angiotensin II, endothelin I);
  - ✓ High sodium intake or lack of dietary calcium.
- Main causes of death are cerebrovascular accidents, cardiovascular (CV) events, and renal failure. Probability of premature death correlates with the severity of BP elevation.

CLINICAL PRESENTATION

- Patients with uncomplicated primary hypertension are usually asymptomatic initially.
- Patients with secondary hypertension may have symptoms of the underlying disorder. Patients with pheochromocytoma may have headaches, sweating, tachycardia, palpitations, and orthostatic hypotension. In primary aldosteronism, hypokalemic symptoms of muscle cramps and weakness may be present. Patients with Cushing syndrome may have weight gain, polyuria, edema, menstrual irregularities, recurrent acne, or muscular weakness in addition to classic features (moon face, buffalo hump, and hirsutism).

DIAGNOSIS

- Elevated BP may be the only sign of primary hypertension on physical examination. Diagnosis should be based on the average of two or more readings taken at each of two or more clinical encounters.
- Signs of end-organ damage occur primarily in the eye, brain, heart, kidneys, and peripheral blood vessels.

TABLE 10–1 Classification of Blood Pressure in Adults

Classification	Systolic (mm Hg)		Diastolic (mm Hg)
Normal	<120	and	<80
Prehypertension	120–139	or	80–89
Stage 1 hypertension	140–159	or	90–99
Stage 2 hypertension	≥160	or	≥100

- Funduscopic examination may reveal arteriolar narrowing, focal arteriolar constrictions, arteriovenous nicking, retinal hemorrhages and exudates, and disk edema. Presence of papilledema usually indicates a hypertensive emergency requiring rapid treatment.
- Cardiopulmonary examination may reveal abnormal heart rate or rhythm, left ventricular (LV) hypertrophy, coronary heart disease, or heart failure (HF).
- Peripheral vascular examination may reveal aortic or abdominal bruits, distended veins, diminished or absent peripheral pulses, or lower extremity edema.
- Patients with renal artery stenosis may have an abdominal systolic-diastolic bruit.
- Baseline hypokalemia may suggest mineralocorticoid-induced hypertension. Protein, blood cells, and casts in the urine may indicate renovascular disease.
- *Laboratory tests*: Blood urea nitrogen (BUN)/serum creatinine, fasting lipid panel, fasting blood glucose, serum electrolytes (sodium and potassium), spot urine albumin-to-creatinine ratio, and estimated glomerular filtration rate (GFR, using the Modification of Diet in Renal Disease [MDRD] equation). A 12-lead electrocardiogram (ECG) should also be obtained.
- *Laboratory tests to diagnose secondary hypertension*: Plasma norepinephrine and urinary metanephrine levels for pheochromocytoma, plasma and urinary aldosterone concentrations for primary aldosteronism, plasma renin activity, captopril stimulation test, renal vein renin, and renal artery angiography for renovascular disease.

TREATMENT

- Goals of Treatment: The overall goal is to reduce morbidity and mortality by the least intrusive means possible. JNC7 guidelines recommend goal BP less than 140/90 mm Hg for most patients, less than 140/80 mm Hg for patients with diabetes mellitus, and less than 130/80 mm Hg for patients with CKD who have persistent albuminuria (>30 mg urine albumin excretion per 24 hours).

NONPHARMACOLOGIC THERAPY

- Lifestyle modifications: (1) weight loss if overweight, (2) adoption of the Dietary Approaches to Stop Hypertension (DASH) eating plan, (3) dietary sodium restriction ideally to 1.5 g/day (3.8 g/day sodium chloride), (4) regular aerobic physical activity, (5) moderate alcohol consumption (two or fewer drinks per day), and (6) smoking cessation.
- Lifestyle modification alone is sufficient for most patients with prehypertension but inadequate for patients with hypertension and additional CV risk factors or hypertension-associated target-organ damage.

PHARMACOLOGIC THERAPY

- Initial drug selection depends on the degree of BP elevation and presence of compelling indications for selected drugs.
- **Angiotensin-converting enzyme (ACE) inhibitors**, **angiotensin II receptor blockers (ARBs)**, **calcium channel blockers (CCBs)**, and **thiazide diuretics** are acceptable first-line options.
- **β-Blockers** are used to either treat a specific compelling indication or as combination therapy with a first-line antihypertensive agent for patients without a compelling indication (**Table 10–2**).
- Most patients with stage 1 hypertension should be treated initially with a first-line antihypertensive drug or a two-drug combination (**Fig. 10–1**). Combination therapy

TABLE 10–2 First-Line and Other Common Antihypertensive Agents

Class/Subclass/Drug (brand name)	Usual Dose Range (mg/day)	Daily Frequency
Angiotensin-converting enzyme inhibitors		
Benazepril (Lotensin)	10–40	1 or 2
Captopril (Capoten)	12.5–150	2 or 3
Enalapril (Vasotec)	5–40	1 or 2
Fosinopril (Monopril)	10–40	1
Lisinopril (Prinivil, Zestril)	10–40	1
Moexipril (Univasc)	7.5–30	1 or 2
Perindopril (Aceon)	4–16	1
Quinapril (Accupril)	10–80	1 or 2
Ramipril (Altace)	2.5–10	1 or 2
Trandolapril (Mavik)	1–4	1
Angiotensin II receptor blockers		
Azilsartan (Edarbi)	40–80	1
Candesartan (Atacand)	8–32	1 or 2
Eprosartan (Teveten)	600–800	1 or 2
Irbesartan (Avapro)	150–300	1
Losartan (Cozaar)	50–100	1 or 2
Olmesartan (Benicar)	20–40	1
Telmisartan (Micardis)	20–80	1
Valsartan (Diovan)	80–320	1
Calcium channel blockers		
Dihydropyridines		
Amlodipine (Norvasc)	2.5–10	1
Felodipine (Plendil)	5–20	1
Isradipine (DynaCirc)	5–10	2
Isradipine SR (DynaCirc SR)	5–20	1
Nicardipine sustained-release (Cardene SR)	60–120	2
Nifedipine long-acting (Adalat CC, Procardia XL)	30–90	1
Nisoldipine (Sular)	10–40	1
Nondihydropyridines		
Diltiazem sustained-release (Cardizem SR)	180–360	2
Diltiazem sustained-release (Cardizem CD, Cartia XT, Dilacor XR, Diltia XT, Tiazac, Taztia XT)	120–480	1
Diltiazem extended-release (Cardizem LA)	120–540	1 (morning or evening)
Verapamil sustained-release (Calan SR, Isoptin SR, Verelan)	180–480	1 or 2
Verapamil controlled-onset extended-release (Covera HS)	180–420	1 (in the evening)
Verapamil chronotherapeutic oral drug absorption system (Verelan PM)	100–400	1 (in the evening)
Diuretics		
Thiazides		
Chlorthalidone (Hygroton)	12.5–25	1
Hydrochlorothiazide (Esidrix, HydroDiuril, Microzide, Oretic)	12.5–50	1
Indapamide (Lozol)	1.25–2.5	1
Metolazone (Mykrox)	0.5–1	1
Metolazone (Zaroxolyn)	2.5–10	1

(*continued*)

TABLE 10–2 First-Line and Other Common Antihypertensive Agents (*Continued*)

Class/Subclass/Drug (brand name)	Usual Dose Range (mg/day)	Daily Frequency
Triamterene (Dyrenium)	50–100	1 or 2
Triamterene/hydrochlorothiazide (Dyazide)	37.5–75/25–50	1
Loops		
Bumetanide (Bumex)	0.5–4	2
Furosemide (Lasix)	20–80	2
Torsemide (Demadex)	5–10	1
Potassium sparing		
Amiloride (Midamor)	5–10	1 or 2
Amiloride/hydrochlorothiazide (Moduretic)	5–10/50–100	1
β-Blockers		
Cardioselective		
Atenolol (Tenormin)	25–100	1
Betaxolol (Kerlone)	5–20	1
Bisoprolol (Zebeta)	2.5–10	1
Metoprolol tartrate (Lopressor)	100–400	2
Metoprolol succinate extended-release (Toprol XL)	50–200	1
Nonselective		
Nadolol (Corgard)	40–120	1
Propranolol (Inderal)	160–480	2
Propranolol long-acting (Inderal LA, InnoPran XL)	80–320	1
Timolol (Blocadren)	10–40	1
Intrinsic sympathomimetic activity		
Acebutolol (Sectral)	200–800	2
Carteolol (Cartrol)	2.5–10	1
Penbutolol (Levatol)	10–40	1
Pindolol (Visken)	10–60	2
Mixed α- and β-blockers		
Carvedilol (Coreg)	12.5–50	2
Carvedilol phosphate (Coreg CR)	20–80	1
Labetalol (Normodyne, Trandate)	200–800	2
Cardioselective and vasodilatory		
Nebivolol (Bystolic)	5–20	1

is recommended for patients with stage 2 hypertension, preferably with two first-line agents.

- There are six compelling indications where specific antihypertensive drug classes provide unique benefits (**Fig. 10–2**).
- Other antihypertensive drug classes (α_1-blockers, direct renin inhibitors, central α_2-agonists, peripheral adrenergic antagonists, and direct arterial vasodilators) are alternatives that may be used for select patients after first-line agents (**Table 10–3**).

Angiotensin-Converting Enzyme Inhibitors

- ACE inhibitors are a first-line option, and if they are not the first agent used, they should be the second agent tried in most patients.
- ACE inhibitors block conversion of angiotensin I to angiotensin II, a potent vasoconstrictor and stimulator of aldosterone secretion. ACE inhibitors also block

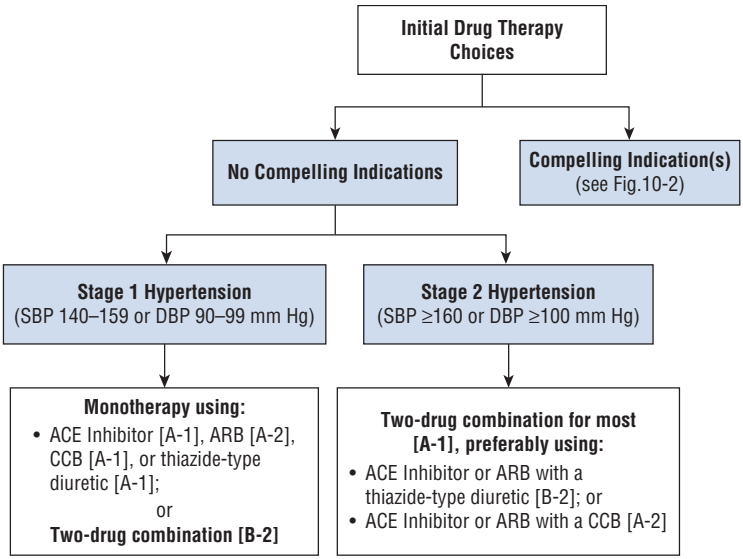


FIGURE 10–1. Algorithm for treatment of hypertension. Drug therapy recommendations are graded with strength of recommendation and quality of evidence in brackets. Strength of recommendations: A, B, C are good, moderate, and poor evidence to support recommendation, respectively. Quality of evidence: (1) evidence from more than one properly randomized, controlled trial; (2) evidence from at least one well-designed clinical trial with randomization, from cohort or case-controlled studies, or dramatic results from uncontrolled experiments or subgroup analyses; (3) evidence from opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert communities. (ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; CCB, calcium channel blocker; DBP, diastolic blood pressure; SBP, systolic blood pressure.)

degradation of bradykinin and stimulate synthesis of other vasodilating substances, including prostaglandin E_2 and prostacyclin.

- Starting doses should be low with slow dose titration. Acute hypotension may occur at the onset of therapy, especially in patients who are sodium- or volume-depleted, in HF exacerbation, very elderly, or on concurrent vasodilators or diuretics. Start administering doses in such patients, using half the normal dose followed by slow dose titration.
- ACE inhibitors decrease aldosterone and can increase serum potassium concentrations. Hyperkalemia occurs primarily in patients with CKD or those also taking potassium supplements, potassium-sparing diuretics, ARBs, or a direct renin inhibitor.
- Acute renal failure is a rare but serious side effect; preexisting kidney disease increases risk. Bilateral renal artery stenosis or unilateral stenosis of a solitary functioning kidney renders patients dependent on the vasoconstrictive effect of angiotensin II on efferent arterioles, making these patients particularly susceptible to acute renal failure.
- GFR declines in patients receiving ACE inhibitors because of inhibition of angiotensin II vasoconstriction on efferent arterioles. Serum creatinine concentrations often increase, but modest elevations (eg, absolute increases <1 mg/dL [88 µmol/L]) do not warrant treatment changes. Discontinue therapy or reduce dose if larger increases occur.

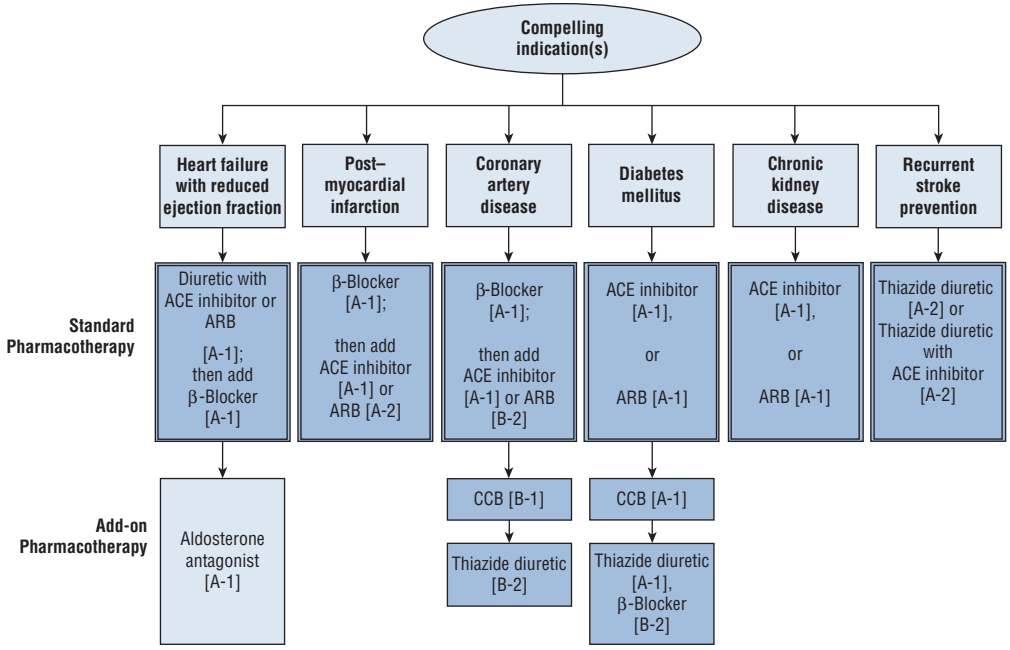


FIGURE 10–2. Compelling indications for individual drug classes. Compelling indications for specific drugs are evidence-based recommendations from outcome studies or existing clinical guidelines. (ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; CCB, calcium channel blocker.)

TABLE 10–3 Alternative Antihypertensive Agents

Class Drug (Brand Name)	Usual Dose Range (mg/day)	Daily Frequency
α_1-Blockers		
Doxazosin (Cardura)	1–8	1
Prazosin (Minipress)	2–20	2 or 3
Terazosin (Hytrin)	1–20	1 or 2
Direct renin inhibitor		
Aliskiren (Tekturna)	150–300	1
Central α_2-agonists		
Clonidine (Catapres)	0.1–0.8	2
Clonidine patch (Catapres-TTS)	0.1–0.3	1 weekly
Methyldopa (Aldomet)	250–1,000	2
Peripheral adrenergic antagonist		
Reserpine (generic only)	0.05–0.25	1
Direct arterial vasodilators		
Minoxidil (Loniten)	10–40	1 or 2
Hydralazine (Apresoline)	20–100	2 to 4

- Angioedema occurs in fewer than 1% of patients. Drug withdrawal is necessary, and some patients may require drug treatment and/or emergent intubation. An ARB can generally be used in patients with a history of ACE inhibitor–induced angioedema, with careful monitoring.
- A persistent dry cough occurs in up to 20% of patients and is thought to be due to inhibition of bradykinin breakdown.
- ACE inhibitors (as well as ARBs and direct renin inhibitors) are contraindicated in pregnancy.

Angiotensin II Receptor Blockers

- Angiotensin II is generated by the renin–angiotensin pathway (which involves ACE) and an alternative pathway that uses other enzymes such as chymases. ACE inhibitors block only the renin–angiotensin pathway, whereas ARBs antagonize angiotensin II generated by either pathway. The ARBs directly block the angiotensin II type 1 receptor that mediates the effects of angiotensin II.
- Unlike ACE inhibitors, ARBs do not block bradykinin breakdown. Although this accounts for the lack of cough as a side effect, there may be negative consequences because some of the antihypertensive effect of ACE inhibitors may be due to increased levels of bradykinin.
- All ARBs have similar antihypertensive efficacy and fairly flat dose-response curves. Addition of a CCB or thiazide diuretic significantly increases antihypertensive efficacy.
- ARBs have a low incidence of side effects. Like ACE inhibitors, they may cause renal insufficiency, hyperkalemia, and orthostatic hypotension. ARBs are contraindicated in pregnancy.

Calcium Channel Blockers

- Calcium channel blockers (CCBs) cause relaxation of cardiac and smooth muscle by blocking voltage-sensitive calcium channels, thereby reducing entry of extracellular calcium into cells. This leads to vasodilation and a corresponding reduction in BP. Dihydropyridine calcium channel antagonists may cause reflex sympathetic activation, and all agents (except amlodipine and felodipine) may have negative inotropic effects.
- **Verapamil** decreases heart rate, slows atrioventricular (AV) nodal conduction, and produces a negative inotropic effect that may precipitate HF in patients with

borderline cardiac reserve. **Diltiazem** decreases AV conduction and heart rate to a lesser extent than verapamil.

- Diltiazem and verapamil can cause cardiac conduction abnormalities such as bradycardia, AV block, and HF. Both can cause anorexia, nausea, peripheral edema, and hypotension. Verapamil causes constipation in ~7% of patients.
- Dihydropyridines cause a baroreceptor-mediated reflex increase in heart rate because of potent peripheral vasodilating effects. Dihydropyridines do not decrease AV node conduction and are not effective for treating supraventricular tachyarrhythmias.
- Short-acting nifedipine may rarely increase frequency, intensity, and duration of angina in association with acute hypotension. This effect may be obviated by using sustained-release formulations of nifedipine or other dihydropyridines. Other side effects of dihydropyridines are dizziness, flushing, headache, gingival hyperplasia, and peripheral edema.

Diuretics

- Acutely, diuretics lower BP by causing diuresis. The reduction in plasma volume and stroke volume associated with diuresis decreases cardiac output and BP. The initial drop in cardiac output causes a compensatory increase in peripheral vascular resistance. With chronic therapy, extracellular fluid volume and plasma volume return to near pretreatment levels, and peripheral vascular resistance falls below baseline. Reduced peripheral vascular resistance is responsible for the long-term hypotensive effects.
- **Thiazide diuretics** are the preferred type of diuretic for most hypertensive patients. They mobilize sodium and water from arteriolar walls, which may contribute to decreased peripheral vascular resistance and lowered BP.
- **Loop diuretics** are more potent for inducing diuresis but are not ideal antihypertensives unless relief of edema is also needed. Loops are often preferred over thiazides in patients with CKD when estimated GFR is less than 30 mL/min/1.73 m^2.
- **Potassium-sparing diuretics** are weak antihypertensives when used alone and provide minimal additive effect when combined with a thiazide or loop diuretic. Their primary use is in combination with another diuretic to counteract potassium-wasting properties.
- **Aldosterone antagonists (spironolactone** and **eplerenone)** are also potassium-sparing diuretics but are more potent antihypertensives with a slow onset of action (up to 6 weeks with spironolactone).
- When diuretics are combined with other antihypertensive agents, an additive hypotensive effect is usually observed because of independent mechanisms of action. Furthermore, many nondiuretic antihypertensive agents induce sodium and water retention, which is counteracted by concurrent diuretic use.
- Side effects of thiazides include hypokalemia, hypomagnesemia, hypercalcemia, hyperuricemia, hyperglycemia, dyslipidemia, and sexual dysfunction. Loop diuretics have less effect on serum lipids and glucose, but hypokalemia is more pronounced, and hypocalcemia may occur.
- Hypokalemia and hypomagnesemia may result in cardiac arrhythmias, especially in patients receiving digoxin, patients with LV hypertrophy, and those with ischemic heart disease. Low-dose therapy (eg, 25 mg hydrochlorothiazide or 12.5 mg chlorthalidone daily) causes small electrolyte disturbances.
- Potassium-sparing diuretics may cause hyperkalemia, especially in patients with CKD or diabetes and in patients receiving concurrent treatment with an ACE inhibitor, ARB, direct renin inhibitor, or potassium supplement. Eplerenone has an increased risk for hyperkalemia and is contraindicated in patients with impaired renal function or type 2 diabetes with proteinuria. Spironolactone may cause gynecomastia in up to 10% of patients; this effect occurs rarely with eplerenone.

β-Blockers

- β-Blockers are only considered appropriate first-line agents to treat specific compelling indications (eg, post-MI [myocardial infarction], coronary artery disease). Their hypotensive mechanism may involve decreased cardiac output through negative

chronotropic and inotropic effects on the heart and inhibition of renin release from the kidney.

- **Atenolol**, **betaxolol**, **bisoprolol**, and **metoprolol** are cardioselective at low doses and bind more avidly to β_1-receptors than to β_2-receptors. As a result, they are less likely to provoke bronchospasm and vasoconstriction and may be safer than nonselective β-blockers in patients with asthma, chronic obstructive pulmonary disease (COPD), diabetes, and peripheral arterial disease (PAD). Cardioselectivity is a dose-dependent phenomenon, and the effect is lost at higher doses.
- **Acebutolol**, **carteolol**, **penbutolol**, and **pindolol** possess intrinsic sympathomimetic activity (ISA) or partial β-receptor agonist activity. When sympathetic tone is low, as in resting states, β-receptors are partially stimulated, so resting heart rate, cardiac output, and peripheral blood flow are not reduced when receptors are blocked. Theoretically, these drugs may have advantages in patients with HF or sinus bradycardia. Unfortunately, they do not reduce CV events as well as other β-blockers and may increase risk after MI or in those with high coronary disease risk. Thus, agents with ISA are rarely needed.
- **Atenolol** and **nadolol** have relatively long half-lives and are excreted renally; the dosage may need to be reduced in patients with renal insufficiency. Even though the half-lives of other β-blockers are shorter, once-daily administration still may be effective.
- Myocardial side effects include bradycardia, AV conduction abnormalities, and acute HF. Blocking β_2-receptors in arteriolar smooth muscle may cause cold extremities and aggravate PAD or Raynaud phenomenon because of decreased peripheral blood flow. Increases in serum lipids and glucose appear to be transient and of little clinical importance.
- Abrupt cessation of β-blocker therapy may produce unstable angina, MI, or even death in patients with coronary disease. In patients without heart disease, abrupt discontinuation of β-blockers may be associated with tachycardia, sweating, and generalized malaise in addition to increased BP. For these reasons, the dose should always be tapered gradually over 1 to 2 weeks before discontinuation.

α_1-Receptor Blockers

- **Prazosin**, **terazosin**, and **doxazosin** are selective α_1-receptor blockers that inhibit catecholamine uptake in smooth muscle cells of peripheral vasculature, resulting in vasodilation.
- A first-dose phenomenon characterized by orthostatic hypotension accompanied by transient dizziness or faintness, palpitations, and even syncope may occur within 1 to 3 hours of the first dose or after later dosage increases. The patient should take the first dose (and subsequent first increased doses) at bedtime. Occasionally, orthostatic dizziness persists with chronic administration.
- Sodium and water retention can occur; these agents are most effective when given with a diuretic to maintain antihypertensive efficacy and minimize edema.
- Because doxazosin (and probably other α_1-receptor blockers) may not be as protective against CV events as other therapies, they should be reserved as alternative agents for unique situations, such as men with benign prostatic hyperplasia. If used to lower BP in this situation, they should only be used in combination with first-line antihypertensives.

Direct Renin Inhibitor

- **Aliskiren** blocks the RAAS at its point of activation, resulting in reduced plasma renin activity and BP. BP reductions are comparable to an ACE inhibitor, ARB, or CCB. Aliskiren is approved for monotherapy or in combination with other agents. It should not be used in combination with an ACE inhibitor or an ARB because of a higher risk of adverse effects without additional reduction in CV events.
- Many of the cautions and adverse effects seen with ACE inhibitors and ARBs apply to aliskiren. It is contraindicated in pregnancy.
- Use aliskiren only as an alternative therapy because of lack of long-term studies evaluating CV event reduction and its significant cost compared with generic agents that have outcomes data.

Central α_2-Agonists

- **Clonidine, guanabenz, guanfacine,** and **methyldopa** lower BP primarily by stimulating α_2-adrenergic receptors in the brain, which reduces sympathetic outflow from the vasomotor center and increases vagal tone. Stimulation of presynaptic α_2-receptors peripherally may contribute to reduced sympathetic tone. Consequently, there may be decreases in heart rate, cardiac output, total peripheral resistance, plasma renin activity, and baroreceptor reflexes.
- Chronic use results in sodium and fluid retention. Other side effects include depression, orthostatic hypotension, dizziness, and anticholinergic effects.
- Abrupt cessation may lead to rebound hypertension, perhaps from a compensatory increase in norepinephrine release that follows discontinuation of presynaptic α-receptor stimulation.
- Methyldopa rarely causes hepatitis or hemolytic anemia. A transient elevation in hepatic transaminases occasionally occurs. Discontinue therapy if persistent increases in liver function tests occur, because this may herald onset of fulminant, life-threatening hepatitis. Coombs-positive hemolytic anemia occurs rarely, and 20% of patients exhibit a positive direct Coombs test without anemia. For these reasons, methyldopa has limited usefulness except in pregnancy.

Reserpine

- **Reserpine** depletes norepinephrine from sympathetic nerve endings and blocks transport of norepinephrine into storage granules. When the nerve is stimulated, less than the usual amount of norepinephrine is released into the synapse. This reduces sympathetic tone, decreasing peripheral vascular resistance and BP.
- Reserpine has a long half-life that allows for once-daily dosing, but it may take 2 to 6 weeks before the maximal antihypertensive effect is seen.
- Reserpine can cause significant sodium and fluid retention, and it should be given with a diuretic (preferably a thiazide).
- Reserpine's strong inhibition of sympathetic activity results in parasympathetic activity, which is responsible for side effects of nasal stuffiness, increased gastric acid secretion, diarrhea, and bradycardia.
- Dose-related depression can be minimized by not exceeding 0.25 mg daily.

Direct Arterial Vasodilators

- **Hydralazine** and **minoxidil** cause direct arteriolar smooth muscle relaxation. Compensatory activation of baroreceptor reflexes results in increased sympathetic outflow from the vasomotor center, increasing heart rate, cardiac output, and renin release. Consequently, hypotensive effectiveness of direct vasodilators diminishes over time unless the patient is also taking a sympathetic inhibitor and a diuretic.
- Patients taking these drugs for long-term hypertension therapy should first receive both a diuretic and a β-blocker. The diuretic minimizes the side effect of sodium and water retention. Direct vasodilators can precipitate angina in patients with underlying coronary artery disease unless the baroreceptor reflex mechanism is completely blocked with a β-blocker. Nondihydropyridine CCBs can be used as an alternative to β-blockers in patients with contraindications to β-blockers.
- Hydralazine may cause dose-related, reversible lupus-like syndrome, which is more common in slow acetylators. Lupus-like reactions can usually be avoided by using total daily doses less than 200 mg. Because of side effects, hydralazine has limited usefulness for chronic hypertension management.
- Minoxidil is a more potent vasodilator than hydralazine, and compensatory increases in heart rate, cardiac output, renin release, and sodium retention are more dramatic. Severe sodium and water retention may precipitate congestive HF. Minoxidil also causes reversible hypertrichosis on the face, arms, back, and chest. Reserve minoxidil for very difficult to control hypertension and for patients requiring hydralazine who experience drug-induced lupus.

COMPELLING INDICATIONS

- Six compelling indications represent specific comorbid conditions for which clinical trial data support using specific antihypertensive drug classes to treat both hypertension and the compelling indication (see **Fig. 10–2**).

Left Ventricular Dysfunction (Systolic Heart Failure)

- Standard pharmacotherapy consists of three to four drugs: ACE inhibitor or ARB plus diuretic therapy, followed by addition of an appropriate β-blocker and possibly an aldosterone receptor antagonist.
- Start an ACE inhibitor or ARB in low doses to avoid orthostatic hypotension because of the high renin state in HF.
- Diuretics provide symptomatic relief of edema by inducing diuresis. Loop diuretics are often needed, especially in patients with more advanced disease.
- β-Blocker therapy is appropriate to further modify disease and is a component of standard therapy. Because of the risk of exacerbating HF, β-blockers must be started in very low doses and titrated slowly to high doses based on tolerability. Bisoprolol, carvedilol, and sustained-release metoprolol succinate are the only β-blockers proven to be beneficial in LV dysfunction.
- After implementation of a standard three-drug regimen, an aldosterone antagonist may be considered.

Postmyocardial Infarction

- β-Blockers (without ISA) and ACE inhibitor or ARB therapy are recommended. β-Blockers decrease cardiac adrenergic stimulation and reduce risk of subsequent MI or sudden cardiac death. ACE inhibitors improve cardiac function and reduce CV events after MI. ARBs are alternatives to ACE inhibitors in post-MI patients with LV dysfunction.

Coronary Artery Disease

- β-Blockers (without ISA) are first-line therapy in chronic stable angina and reduce BP, improve myocardial consumption, and decrease demand. Long-acting CCBs are either alternatives (verapamil and diltiazem) or add-on therapy (dihydropyridines) to β-blockers in chronic stable angina. Once ischemic symptoms are controlled with β-blocker and/or CCB therapy, other antihypertensives (eg, ACE inhibitor or ARB) can be added to provide additional CV risk reduction. Thiazide diuretics may be added thereafter to provide additional BP lowering and further reduce CV risk.
- For acute coronary syndromes, first-line therapy includes a β-blocker and ACE inhibitor (or ARB); the combination lowers BP, controls acute ischemia, and reduces CV risk.

Diabetes Mellitus

- Treat all patients with diabetes and hypertension with an ACE inhibitor or ARB. Both classes provide nephroprotection and reduced CV risk.
- CCBs are the most appropriate add-on agents for BP control in patients with diabetes. The combination of an ACE inhibitor with a CCB is more effective in reducing CV events than an ACE inhibitor plus a thiazide diuretic.
- A thiazide diuretic is recommended as an add-on to the previous agents to lower BP and provide additional CV risk reduction.
- β-Blockers, similar to CCBs, are useful add-on agents for BP control in patients with diabetes. They should also be used to treat another compelling indication (eg, post-MI). However, they may mask symptoms of hypoglycemia (tremor, tachycardia, and palpitations but not sweating) in tightly controlled patients, delay recovery from hypoglycemia, and produce elevations in BP due to vasoconstriction caused by unopposed β-receptor stimulation during the hypoglycemic recovery phase. Despite these potential problems, β-blockers can be used safely in patients with diabetes.

Chronic Kidney Disease

- Either an ACE inhibitor or an ARB is first-line therapy to control BP and preserve kidney function in CKD. Treat patients with moderately or severely increased albuminuria to goal BP of 130/80 mm Hg.
- Because these patients usually require multiple-drug therapy, diuretics and a third antihypertensive drug class (eg, β-blocker or CCB) are often needed.

Recurrent Stroke Prevention

- A thiazide diuretic, either as monotherapy or combined with an ACE inhibitor, is recommended for patients with history of stroke or transient ischemic attack. Implement antihypertensive drug therapy only after patients have stabilized after an acute cerebrovascular event.

SPECIAL POPULATIONS

Older People

- Elderly patients may present with either isolated systolic hypertension or elevation in both SBP and DBP. CV morbidity and mortality are more closely related to SBP than to DBP in patients 50 years of age and older.
- Diuretics, ACE inhibitors, and ARBs provide significant benefits and can be used safely in the elderly, but smaller-than-usual initial doses must be used for initial therapy.

Children and Adolescents

- Secondary hypertension is more common in children and adolescents than in adults. Medical or surgical management of the underlying disorder usually normalizes BP.
- Nonpharmacologic treatment (particularly weight loss in obese children) is the cornerstone of therapy of primary hypertension.
- ACE inhibitors, ARBs, β-blockers, CCBs, and thiazide diuretics are all acceptable drug therapy choices.
- ACE inhibitors, ARBs, and direct renin inhibitors are contraindicated in sexually active girls because of potential teratogenic effects.

Pregnancy

- Preeclampsia, defined as BP of 140/90 mm Hg or more that appears after 20 weeks' gestation accompanied by new-onset proteinuria (≥300 mg/24 h), can lead to life-threatening complications for both mother and fetus. **Eclampsia,** the onset of convulsions in preeclampsia, is a medical emergency.
- Definitive treatment of preeclampsia is delivery, and this is indicated if pending or frank eclampsia is present. Otherwise, management consists of restricting activity, bedrest, and close monitoring. Salt restriction or other measures that contract blood volume should be avoided. Antihypertensives are used prior to induction of labor if the DBP is greater than 105 mm Hg, with a target DBP of 95 to 105 mm Hg. IV hydralazine is most commonly used; IV labetalol is also effective.
- Chronic hypertension is defined as elevated BP that was noted before pregnancy began. Methyldopa is considered the drug of choice because of experience with its use. β-Blockers (other than atenolol), labetalol, and CCBs are also reasonable alternatives. ACE inhibitors, ARBs, and the direct renin inhibitor aliskiren are contraindicated in pregnancy.

African Americans

- Hypertension is more common and more severe in African Americans than in those of other races. Differences in electrolyte homeostasis, glomerular filtration rate, sodium excretion and transport mechanisms, plasma renin activity, and BP response to plasma volume expansion have been noted.
- African Americans have an increased need for combination therapy to achieve and maintain BP goals. Start therapy with two drugs in patients with SBP values greater than or equal to 15 mm Hg above goal.

- Thiazides and CCBs are most effective in African Americans. Antihypertensive response is significantly increased when either class is combined with a β-blocker, ACE inhibitor, or ARB.

Pulmonary Disease and Peripheral Arterial Disease

- Although β-blockers (especially nonselective agents) have generally been avoided in hypertensive patients with asthma and COPD because of fear of inducing bronchospasm, data suggest that cardioselective β-blockers can be used safely. Consequently, cardioselective agents should be used to treat a compelling indication (ie, post-MI, coronary disease, or HF) in patients with reactive airway disease.
- PAD is considered a coronary artery disease risk equivalent. β-Blockers can theoretically be problematic because of possible decreased peripheral blood flow secondary to unopposed stimulation of α-receptors that results in vasoconstriction. This can be mitigated by using a β-blocker with α-blocking properties (eg, carvedilol). However, β-blockers are not contraindicated in PAD and have not been shown to adversely affect walking capacity.

HYPERTENSIVE URGENCIES AND EMERGENCIES

- **Hypertensive urgencies** are ideally managed by adjusting maintenance therapy by adding a new antihypertensive and/or increasing the dose of a present medication.
- Acute administration of a short-acting oral drug (**captopril**, **clonidine**, or **labetalol**) followed by careful observation for several hours to ensure a gradual BP reduction is an option.
  - ✓ Oral captopril doses of 25 to 50 mg may be given at 1- to 2-hour intervals. The onset of action is 15 to 30 minutes.
  - ✓ For treatment of hypertensive rebound after withdrawal of clonidine, 0.2 mg is given initially, followed by 0.2 mg hourly until the DBP falls below 110 mm Hg or a total of 0.7 mg has been administered; a single dose may be sufficient.
  - ✓ Labetalol can be given in a dose of 200 to 400 mg, followed by additional doses every 2 to 3 hours.
- **Hypertensive emergencies** require immediate BP reduction to limit new or progressing target-organ damage. The goal is not to lower BP to normal; instead, the initial target is a reduction in mean arterial pressure of up to 25% within minutes to hours. If BP is then stable, it can be reduced toward 160/100 to 110 mm Hg within the next 2 to 6 hours. Precipitous drops in BP may cause end-organ ischemia or infarction. If BP reduction is well tolerated, additional gradual decrease toward the goal BP can be attempted after 24 to 48 hours.
  - ✓ Nitroprusside is the agent of choice for minute-to-minute control in most cases. It is usually given as a continuous IV infusion at a rate of 0.25 to 10 mcg/kg/min. Onset of hypotensive action is immediate and disappears within 1 to 2 minutes of discontinuation. When the infusion must be continued longer than 72 hours, measure serum thiocyanate levels, and discontinue the infusion if the level exceeds 12 mg/dL (~2.0 mmol/L). The risk of thiocyanate toxicity is increased in patients with impaired kidney function. Other adverse effects are nausea, vomiting, muscle twitching, and sweating.
  - ✓ Dosing guidelines and adverse effects of parenteral agents for treating hypertensive emergency are listed in **Table 10–4**.

EVALUATION OF THERAPEUTIC OUTCOMES

- Evaluate BP response 2 to 4 weeks after initiating or making changes in therapy. Once goals BP values are obtained, monitor BP every 3 to 6 months, assuming no signs or symptoms of acute target-organ disease. Evaluate more frequently in patients with a history of poor control, nonadherence, progressive target-organ damage, or symptoms of adverse drug effects.

TABLE 10–4 Parenteral Antihypertensive Agents for Hypertensive Emergency

Drug	Dose	Onset (min)	Duration (min)	Adverse Effects
Clevidipine	1–2 mg/h (32 mg/h max)	2–4	5–15	Headache, nausea, tachycardia, hypertriglyceridemia
Enalaprilat	1.25–5 mg IV every 6 h	15–30	360–720	Precipitous fall in BP in high-renin states; variable response
Esmolol hydrochloride	250–500 mcg/kg/min IV bolus, then 50–100 mcg/kg/min IV infusion; may repeat bolus after 5 min or increase infusion to 300 mcg/min	1–2	10–20	Hypotension, nausea, asthma, first-degree heart block, heart failure
Fenoldopam mesylate	0.1–0.3 mcg/kg/min IV infusion	<5	30	Tachycardia, headache, nausea, flushing
Hydralazine hydrochloride	12–20 mg IV 10–50 mg IM	10–20 20–30	60–240 240–360	Tachycardia, flushing, headache, vomiting, aggravation of angina
Labetalol hydrochloride	20–80 mg IV bolus every 10 min; 0.5–2 mg/min IV infusion	5–10	180–360	Vomiting, scalp tingling, bronchoconstriction, dizziness, nausea, heart block, orthostatic hypotension
Nicardipine hydrochloride	5–15 mg/h IV	5–10	15–30; may exceed 240	Tachycardia, headache, flushing, local phlebitis
Nitroglycerin	5–100 mcg/min IV infusion	2–5	5–10	Headache, vomiting, methemoglobinemia, tolerance with prolonged use
Sodium nitroprusside	0.25–10 mcg/kg/min IV infusion (requires special delivery system)	Immediate	1–2	Nausea, vomiting, muscle twitching, sweating, thiocyanate and cyanide intoxication

BP, blood pressure; IM, intramuscular; IV, intravenous.

- Self-measurements of BP or automatic ambulatory BP monitoring can be useful to establish effective 24-hour control. These techniques are currently recommended only for select situations such as suspected white coat hypertension.
- Monitor patients for signs and symptoms of progressive target-organ disease. Take a careful history for chest pain (or pressure), palpitations, dizziness, dyspnea, orthopnea, headache, sudden change in vision, one-sided weakness, slurred speech, and loss of balance to assess for the presence of complications.
- Monitor funduscopic changes on eye examination, LV hypertrophy on ECG, proteinuria, and changes in kidney function periodically.
- Monitor for adverse drug effects 2 to 4 weeks after starting a new agent or dose increases, then every 6 to 12 months in stable patients. For patients taking aldosterone antagonists, assess potassium concentration and kidney function within 3 days and again at 1 week after initiation to detect potential hyperkalemia.
- Assess patient adherence with the regimen regularly. Ask patients about changes in their general health perception, energy level, physical functioning, and overall satisfaction with treatment.

See Chapter 3, Hypertension, authored by Joseph J. Saseen and Eric J. MacLaughlin, for a more detailed discussion of this topic.

Ischemic Heart Disease

CHAPTER 11

- *Ischemic heart disease* (IHD) is defined as lack of oxygen and decreased or no blood flow to the myocardium resulting from coronary artery narrowing or obstruction. It may present as acute coronary syndrome (ACS), which includes unstable angina and non–ST-segment elevation (NSTE) or ST-segment elevation (STE) myocardial infarction (MI), chronic stable exertional angina, ischemia without symptoms, or ischemia due to coronary artery vasospasm (variant or Prinzmetal angina).

PATHOPHYSIOLOGY

- Major determinants of myocardial oxygen demand (MVo_2) are heart rate (HR), contractility, and intramyocardial wall tension during systole. Because the consequences of IHD usually result from increased demand with a fixed oxygen supply, alterations in MVo_2 are important in producing ischemia and for interventions intended to alleviate it.
- The double product (DP) is the heart rate multiplied by the systolic blood pressure ($DP = HR \times SBP$) and serves as an indirect estimate of MVo_2.
- The caliber of resistance vessels delivering blood to the myocardium and MVo_2 are the primary determinants in the occurrence of ischemia.
- Large epicardial or surface coronary vessels (R_1) offer little resistance to myocardial flow and intramyocardial arteries and arterioles (R_2), which branch into a dense capillary network to supply basal blood flow. Under normal circumstances, resistance in R_2 is much greater than that in R_1. Myocardial blood flow is inversely related to arteriolar resistance and directly related to coronary driving pressure.
- Atherosclerotic lesions occluding R_1 increase arteriolar resistance, and R_2 can vasodilate to maintain coronary blood flow. With greater degrees of obstruction, this response is inadequate, and the coronary flow reserve afforded by R_2 vasodilation is insufficient to meet oxygen demand.
- The diameter and length of obstructing lesions and the influence of pressure drop across an area of stenosis also affect coronary blood flow. Dynamic coronary obstruction can occur in normal vessels and vessels with stenosis in which vasomotion or a spasm may be superimposed on a fixed stenosis. Persisting ischemia may promote growth of collateral blood flow.
- Relatively severe stenosis (>70%) may provoke ischemia and symptoms at rest. Lesions creating obstruction of 50% to 70% may reduce blood flow, but these obstructions are not consistent, and vasospasm and thrombosis superimposed on a "noncritical" lesion may lead to clinical events such as MI.
- Regional loss of ventricular contractility may impose a burden on remaining myocardial tissue, resulting in heart failure (HF), increased MVo_2, and rapid depletion of blood flow reserve. Zones of tissue with marginal blood flow may develop that are at risk for more severe damage if the ischemic episode persists or becomes more severe. Nonischemic areas of myocardium may compensate for severely ischemic and border zones of ischemia by developing more tension than usual in attempt to maintain cardiac output. The left or right ventricular dysfunction that ensues may be associated with an S_3 gallop, dyspnea, orthopnea, tachycardia, fluctuating blood pressure, transient murmurs, and mitral or tricuspid regurgitation. Impaired diastolic and systolic function leads to elevated left ventricular filling pressure.

CLINICAL PRESENTATION

- Many ischemic episodes are asymptomatic (silent ischemia). Patients often have a reproducible pattern of pain or other symptoms that appear after a specific amount of exertion. Increased symptom frequency, severity, or duration, and symptoms at rest suggest an unstable pattern that requires immediate medical evaluation.

- Symptoms may include a sensation of pressure or burning over the sternum or near it, which often radiates to the left jaw, shoulder, and arm. Chest tightness and shortness of breath may also occur. The sensation usually lasts from 30 seconds to 30 minutes.
- Precipitating factors include exercise, cold environment, walking after a meal, emotional upset, fright, anger, and coitus. Relief occurs with rest and within 45 seconds to 5 minutes of taking nitroglycerin.
- Patients with variant (Prinzmetal) angina secondary to coronary spasm are more likely to experience pain at rest and in the early morning hours. Pain is not usually brought on by exertion or emotional stress or relieved by rest; the electrocardiogram (ECG) pattern demonstrates current injury with ST-segment elevation rather than depression.
- Unstable angina is stratified into categories of low, intermediate, or high risk for short-term death or nonfatal MI. Features of high-risk unstable angina include: (1) accelerating tempo of ischemic symptoms in the preceding 48 hours; (2) pain at rest lasting more than 20 minutes; (3) age older than 75 years; (4) ST-segment changes; and (5) clinical findings of pulmonary edema, mitral regurgitation, S_3, rales, hypotension, bradycardia, or tachycardia.
- Episodes of ischemia may also be painless, or "silent," perhaps due to a higher threshold and tolerance for pain than in patients who have pain more frequently.

DIAGNOSIS

- Obtain medical history to identify the nature or quality of chest pain, precipitating factors, duration, pain radiation, and response to nitroglycerin or rest. Ischemic chest pain may resemble pain from noncardiac sources, and diagnosis of anginal pain may be difficult based on history alone.
- Ask the patient about personal risk factors for coronary heart disease (CHD), including smoking, hypertension, and diabetes mellitus.
- Obtain family history that includes information about premature CHD, hypertension, lipid disorders, and diabetes mellitus.
- Findings on cardiac examination may include abnormal precordial systolic bulge, decreased intensity of S_1, paradoxical splitting of S_2, presence of S_3 or S_4, apical systolic murmur, and diastolic murmur.
- **Laboratory tests:** hemoglobin, fasting glucose (to exclude diabetes), and fasting lipid panel. High-sensitivity C-reactive protein (hsCRP); homocysteine level; evidence of *Chlamydia* infection; and elevations in lipoprotein (a), fibrinogen, and plasminogen activator inhibitor may be helpful. Cardiac enzymes are normal in stable angina. Troponin T or I, myoglobin, and creatinine kinase myocardial band (CK-MB) may be elevated in unstable angina.
- Resting ECG is normal in about half of patients with angina who are not experiencing acute ischemia. Typical ST–T-wave changes include depression, T-wave inversion, and ST-segment elevation. Variant angina is associated with ST-segment elevation, whereas silent ischemia may produce elevation or depression. Significant ischemia is associated with ST-segment depression greater than 2 mm, exertional hypotension, and reduced exercise tolerance.
- Exercise tolerance (stress) testing (ETT), thallium myocardial perfusion scintigraphy, radionuclide angiocardiography, ultrarapid computed tomography, and coronary angiography may be performed in certain circumstances. Obtain a chest radiograph if the patient has HF symptoms.

TREATMENT

- Goals of Treatment: Short-term goals are to reduce or prevent anginal symptoms that limit exercise capability and impair quality of life. Long-term goals are to prevent CHD events such as MI, arrhythmias, and HF and to extend the patient's life.

NONPHARMACOLOGIC THERAPY

- Primary prevention through modification of risk factors should reduce prevalence of IHD. Secondary intervention is effective in reducing subsequent morbidity and mortality.
- Risk factors for IHD are additive and can be classified as alterable or unalterable. Unalterable risk factors include gender, age, family history or genetic composition, environmental influences, and, to some extent, diabetes mellitus. Alterable risk factors include smoking, hypertension, hyperlipidemia, obesity, sedentary lifestyle, hyperuricemia, psychosocial factors such as stress, and use of drugs that may be detrimental (eg, progestins, corticosteroids, calcineurin inhibitors).

PHARMACOLOGIC THERAPY

β-Adrenergic Blockers

- Decreased HR, contractility, and blood pressure reduce MVo_2 and oxygen demand in patients with effort-induced angina. β-Blockers do not improve oxygen supply, and, in certain instances, unopposed α-adrenergic stimulation may lead to coronary vasoconstriction.
- β-Blockers improve symptoms in approximately 80% of patients with chronic exertional stable angina, and objective measures of efficacy demonstrate improved exercise duration and delay in the time at which ST-segment changes and initial or limiting symptoms occur. β-Blockade may allow angina patients previously limited by symptoms to perform more exercise and improve cardiovascular performance through a training effect.
- Ideal candidates for β-blockers include patients in whom physical activity is a prominent cause of attacks; those with coexisting hypertension, supraventricular arrhythmias, or post-MI angina; and those with anxiety associated with anginal episodes. β-Blockers may be used safely in angina and HF.
- β-Blockade is effective in chronic exertional angina as monotherapy and in combination with nitrates and/or calcium channel blockers (CCBs). β-Blockers are first line in chronic angina requiring daily maintenance therapy because they are more effective in reducing episodes of silent ischemia and early-morning peak of ischemic activity and improving mortality after Q-wave MI than nitrates or CCBs.
- If β-blockers are ineffective or not tolerated, monotherapy with a CCB or combination therapy may be instituted. Reflex tachycardia from nitrates can be blunted with β-blocker therapy, making this a useful combination.
- Initial doses of β-blockers should be at the lower end of the usual dosing range and titrated to response. Treatment objectives include lowering the resting HR to 50 to 60 beats/min and limiting maximal exercise HR to approximately 100 beats/min or less. HR with modest exercise should be no more than approximately 20 beats/min above resting HR (or a 10% increment over resting HR).
- There is little evidence to suggest superiority of any particular β-blocker. Those with longer half-lives may be administered less frequently, but even **propranolol** may be given twice daily in most patients. Membrane-stabilizing activity is irrelevant in angina treatment. Intrinsic sympathomimetic activity appears to be detrimental in patients with rest or severe angina because the reduction in HR would be minimized, limiting reduction in MVo_2. Cardioselective β-blockers may minimize adverse effects such as bronchospasm, intermittent claudication, and sexual dysfunction. Combined nonselective β- and α-blockade with **labetalol** may be useful in patients with marginal left ventricular (LV) reserve.
- Adverse effects of β-blockade include hypotension, decompensated HF, bradycardia, heart block, bronchospasm, altered glucose metabolism, fatigue, malaise, and depression. Abrupt withdrawal has been associated with increased severity and number of anginal episodes and MI. Tapering of therapy over several days should minimize risk of withdrawal reactions if therapy is to be discontinued.

Nitrates

- Nitrates reduce MVo_2 secondary to venodilation and arterial-arteriolar dilation, leading to a reduction in wall stress from reduced ventricular volume and pressure.

TABLE 11–1 Nitrate Products

Product	Onset (min)	Duration	Initial Dose
Nitroglycerin			
IV	1–2	3–5 min	5 mcg/min
Sublingual/lingual	1–3	30–60 min	0.3 mg
Oral	40	3–6 h	2.5–9 mg 3 times daily
Ointment	20–60	2–8 h	½–1 in
Patch	40–60	>8 h	1 patch
Erythritol tetranitrate	5–30	4–6 h	5–10 mg 3 times daily
Pentaerythritol tetranitrate	30	4–8 h	10–20 mg 3 times daily
Isosorbide dinitrate			
Sublingual/chewable	2–5	1–2 h	2.5–5 mg 3 times daily
Oral	20–40	4–6 h	5–20 mg 3 times daily
Isosorbide mononitrate (ISMN)	30–60	6–8 h	20 mg once or twice daily depending on the product

Direct actions on coronary circulation include dilation of large and small intramural coronary arteries, collateral dilation, coronary artery stenosis dilation, abolition of normal tone in narrowed vessels, and relief of spasm.

- Pharmacokinetic characteristics common to nitrates include large first-pass hepatic metabolism, short half-lives (except for **isosorbide mononitrate** [ISMN]), large volumes of distribution, high clearance rates, and large interindividual variations in plasma concentrations. The half-life of **nitroglycerin** is 1 to 5 minutes regardless of the route, hence the potential advantage of sustained-release and transdermal products. **Isosorbide dinitrate** (ISDN) is metabolized to ISMN. ISMN has a half-life of approximately 5 hours and may be given once or twice daily, depending on the product chosen.
- Nitrate therapy may be used to terminate an acute anginal attack, to prevent effort- or stress-induced attacks, or for long-term prophylaxis, usually in combination with β-blockers or CCBs. Sublingual, buccal, or spray nitroglycerin products are preferred for alleviation of anginal attacks because of rapid absorption (**Table 11–1**). Symptoms may be prevented by prophylactic oral or transdermal products (usually in combination with β-blockers or CCBs), but development of tolerance may be problematic.
- **Sublingual nitroglycerin**, 0.3 to 0.4 mg, relieves pain in approximately 75% of patients within 3 minutes, with another 15% becoming pain free in 5 to 15 minutes. Pain persisting beyond 20 to 30 minutes after use of two or three nitroglycerin tablets suggests ACS, and the patient should be instructed to seek emergency aid.
- Chewable, oral, and transdermal products are acceptable for long-term prophylaxis. Dosing of long-acting preparations should be adjusted to provide a hemodynamic response. This may require oral ISDN doses of 10 to 60 mg as often as every 3 to 4 hours because of tolerance or first-pass metabolism. Intermittent (10–12 hours on, 12–14 hours off) transdermal nitroglycerin therapy may produce modest but significant improvement in exercise time in chronic stable angina.
- Adverse effects include postural hypotension with associated central nervous system (CNS) symptoms, reflex tachycardia, headaches and flushing, and occasional nausea. Excessive hypotension may result in MI or stroke. Noncardiovascular adverse effects include rash (especially with transdermal nitroglycerin), methemoglobinemia with high doses given for extended periods, and measurable ethanol and propylene glycol concentrations with IV nitroglycerin.
- Because both the onset and offset of tolerance to nitrates occur quickly, one strategy to circumvent tolerance is to provide a daily nitrate-free interval of 8 to 12 hours. For example, ISDN should not be used more often than three times daily to avoid tolerance.

- Nitrates may be combined with other drugs with complementary mechanisms of action for chronic prophylaxis. Combination therapy is generally used in patients with more frequent symptoms or symptoms that do not respond to β-blockers alone (nitrates plus β-blockers or CCBs), in patients intolerant of β-blockers or CCBs, and in patients with vasospasm leading to decreased supply (nitrates plus CCBs).

Calcium Channel Blockers

- Direct actions include vasodilation of systemic arterioles and coronary arteries, leading to reduced arterial pressure and coronary vascular resistance, as well as depression of myocardial contractility and conduction velocity of the sinoatrial (SA) and atrioventricular (AV) nodes. Reflex β-adrenergic stimulation overcomes much of the negative inotropic effect, and depression of contractility becomes clinically apparent only in the presence of LV dysfunction and when other negative inotropic drugs are used concurrently.
- **Verapamil** and **diltiazem** cause less peripheral vasodilation than dihydropyridines such as **nifedipine** but greater decreases in AV node conduction. They must be used with caution in patients with preexisting conduction abnormalities and those taking other drugs with negative chronotropic properties.
- MVO_2 is reduced with all CCBs primarily because of reduced wall tension secondary to reduced arterial pressure. Overall, the benefit provided by CCBs is related to reduced MVO_2 rather than improved oxygen supply.
- In contrast to β-blockers, CCBs may improve coronary blood flow through areas of fixed coronary obstruction by inhibiting coronary artery vasomotion and vasospasm.
- Good candidates for CCBs include patients with contraindications or intolerance to β-blockers, coexisting conduction system disease (except for verapamil and diltiazem), Prinzmetal angina, peripheral arterial disease, severe ventricular dysfunction, and concurrent hypertension. **Amlodipine** is probably the CCB of choice in severe ventricular dysfunction, and the others should be used with caution if the EF is less than 40%.

Ranolazine

- Ranolazine reduces calcium overload in ischemic myocytes through inhibition of the late sodium current. It does not affect HR, inotropic or hemodynamic state, or increase coronary blood flow.
- Ranolazine is indicated for treatment of chronic angina. In controlled trials, it modestly improved exercise time by 15 to approximately 45 seconds compared with placebo. In a large ACS trial, ranolazine reduced recurrent ischemia but did not improve the primary efficacy composite end point of cardiovascular death, MI, or recurrent ischemia.
- Because it prolongs the QT interval, reserve ranolazine for patients who have not achieved an adequate response to other antianginal drugs. It should be used in combination with amlodipine, β-blockers, or nitrates.
- Start ranolazine at 500 mg twice daily and increase to 1000 mg twice daily if needed based on symptoms. Obtain baseline and follow-up ECGs to evaluate effects on the QT interval. The most common adverse effects include dizziness, headache, constipation, and nausea.

TREATMENT OF STABLE ISCHEMIC HEART DISEASE

- **Table 11–2** lists select evidence-based drug therapy recommendations of the American College of Cardiology Foundation and American Heart Association. A treatment algorithm is shown in **Fig. 11–1**.
- Guideline-directed medical therapy (GDMT) places a strong emphasis on patient education. Lifestyle modifications include daily physical activity, weight management, dietary therapy, smoking cessation, psychological interventions, limitation of alcohol intake, and management of blood pressure and diabetes.

TABLE 11–2 Selected Evidence-Based Recommendations for Treatment of Stable Exertional Angina Pectoris

Recommendations	Recommendation Grades[a]
Risk Factor Modification	
Moderate- or high-dose statin therapy in the absence of contraindications or adverse effects, in addition to lifestyle changes.	Class I, level A
For patients who do not tolerate statins, a bile acid sequestrant, niacin, or both is reasonable.	Class IIa, level B
If blood pressure is 140/90 mm Hg or higher, drug therapy should be instituted in addition to or after lifestyle modifications.	Class I, level A
For patients with DM, pharmacotherapy to achieve a target A1C might be reasonable.	Class IIb, level A
Medical Therapy to Prevent MI and Death	
Aspirin 75–162 mg/day daily continued indefinitely in the absence of contraindication.	Class I, level A
Clopidogrel is a reasonable alternative when aspirin is contraindicated.	Class I, level B
β-Blocker therapy started and continued for 3 years in patients with normal LV function after MI or ACS.	Class I, level B
β-Blocker (carvedilol, metoprolol succinate, or bisoprolol) in patients with LV systolic dysfunction (LVEF ≤40%) with HF or MI, unless contraindicated.	Class I, level A
ACE inhibitor in patients with HTN, DM, LVEF ≤40%, or CKD, unless contraindicated. ARBs are recommended if intolerant of ACE inhibitors.	Class I, level A
Medical Therapy for Relief of Symptoms	
Sublingual nitroglycerin or nitroglycerin spray for immediate relief of angina.	Class I, level B
β-Blockers as initial therapy for relief of symptoms.	Class I, level B
CCBs or long-acting nitrates for relief of symptoms when β-blockers are contraindicated or cause unacceptable side effects.	Class I, level B
CCBs or long-acting nitrates, in combination with β-blockers, when initial treatment with β-blockers is unsuccessful.	Class I, level B
Long-acting nondihydropyridine calcium antagonists (verapamil, diltiazem) instead of a β-blocker as initial therapy.	Class IIa, level B
Ranolazine can be useful as a substitute for β-blockers if initial treatment with β-blockers causes unacceptable adverse effects or is ineffective or contraindicated.	Class IIa, level B
Ranolazine combined with a β-blocker can be useful when initial β-blocker treatment is unsuccessful.	Class IIa, level B

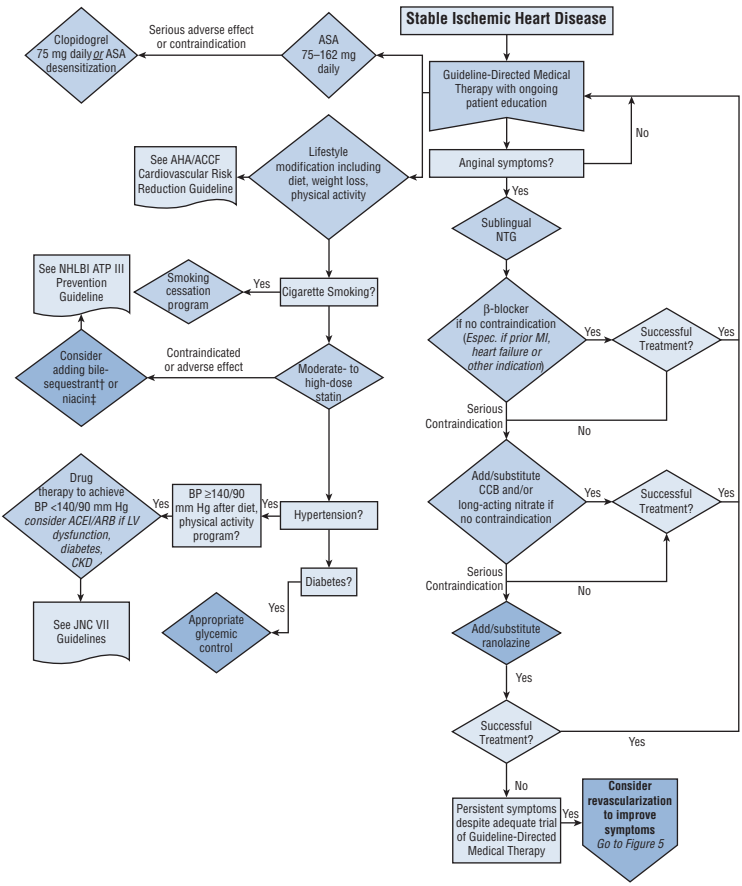
ACE, angiotensin-converting enzyme; ACS, acute coronary syndrome; ARB, angiotensin receptor blocker; CCBs, calcium channel blockers; CKD, chronic kidney disease, DM, diabetes mellitus; EF, ejection fraction; HF, heart failure; HTN, hypertension, LV, left ventricular; LVEF, left ventricular ejection fraction; MI, myocardial infarction.

[a]American College of Cardiology and American Heart Association Evidence Grading System Recommendation Class:
I = Conditions for which there is evidence or general agreement that a given procedure or treatment is useful and effective.
II = Conditions for which there is conflicting evidence or a divergence of opinion about the usefulness/efficacy of a given procedure or treatment.
IIa = Weight of evidence/opinion is in favor of usefulness or efficacy.

(*continued*)

TABLE 11–2 **Selected Evidence-Based Recommendations for Treatment of Stable Exertional Angina Pectoris (*Continued*)**

IIb = Usefulness/efficacy is less well established by evidence/opinion.
III = Conditions for which there is evidence or general agreement that a given procedure or treatment is not useful/effective and in some cases may be harmful.
Level of Evidence:
A = Data derived from multiple randomized clinical trials with large numbers of patients.
B = Data derived from a limited number of randomized trials with small numbers of patients, careful analyses of nonrandomized studies, or observational registries.
C = Expert consensus was the primary basis for the recommendation.



Algorithm for guideline-directed medical therapy for patients with SIHD.*
The algorithms do not represent a comprehensive list of recommendations.
†The use of bile acid sequestrant is relatively contraindicated when triglycerides are ≥200 mg/dL and is contraindicated when triglycerides are ≥500 mg/dL.
‡Dietary supplement niacin must not be used as a substitute for prescription niacin. ACCF indicates American College of Cardiology Foundation; ACEI, angiotensin-converting enzyme inhibitor; AHA, American Heart Association; ARB, angiotensin-receptor blocker; ASA, aspirin; ATP III, Adult Treatment Panel 3; BP, blood pressure; CCB, calcium channel blocker; CKD, chronic kidney disease; HDL-C, high-density lipoprotein cholesterol; JNC VII, Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure; LDL-C, low-density lipoprotein cholesterol; LV, left ventricular; MI, myocardial infarction; NHLBI, National Heart, Lung, and Blood Institute; and NTG, nitroglycerin.

FIGURE 11–1. Algorithm for guideline-directed medical therapy for patients with stable ischemic heart disease (IHD).

- **β-Blockers** may be preferable for chronic prophylaxis because of less frequent dosing and other desirable properties (eg, potential cardioprotective effects, antiarrhythmic effects, lack of tolerance, and antihypertensive efficacy). Patients most likely to respond well to β-blockade are those with a high resting HR and those with a relatively fixed anginal threshold.
- **CCBs** are as effective as β-blockers and are most useful in patients who have a variable threshold for exertional angina. Calcium antagonists may provide better skeletal muscle oxygenation, resulting in decreased fatigue and better exercise tolerance. They can be used safely in many patients with contraindications to β-blockers. Patients with conduction abnormalities and moderate to severe LV dysfunction (EF <35%) should not be treated with verapamil or diltiazem, whereas amlodipine may be used safely in many of these patients. Diltiazem has significant effects on the AV node and can produce heart block in patients with preexisting conduction disease or when other drugs with effects on conduction (eg, digoxin and β-blockers) are used concurrently. Nifedipine may cause excessive HR elevation, especially if the patient is not receiving a β-blocker, and this may offset its beneficial effect on MVo_2. The combination of CCBs and β-blockers is rational because the hemodynamic effect of calcium antagonists is complementary to β-blockade. However, combination therapy may not always be more effective than single-agent therapy.
- Chronic prophylaxis with long-acting forms of **nitroglycerin** (oral or transdermal), **ISDN**, **ISMN**, and **pentaerythritol tetranitrate** may be effective, but development of tolerance is a limitation. Monotherapy with nitrates should not be first-line therapy unless β-blockers and CCBs are contraindicated or not tolerated. A nitrate-free interval of 8 hours per day or longer should be provided to maintain efficacy.
- For prophylaxis when undertaking activities that predictably precipitate attacks, nitroglycerin 0.3 to 0.4 mg sublingually may be used approximately 5 minutes prior to the time of the activity. Nitroglycerin spray may be useful when inadequate saliva is produced to rapidly dissolve sublingual nitroglycerin or if a patient has difficulty opening the tablet container. The response usually lasts approximately 30 minutes.

TREATMENT OF CORONARY ARTERY SPASM AND VARIANT ANGINA PECTORIS

- All patients should be treated for acute attacks and maintained on prophylactic treatment for 6 to 12 months after the initial episode. Aggravating factors such as alcohol or cocaine use and cigarette smoking should be stopped.
- **Nitrates** are the mainstay of therapy, and most patients respond rapidly to sublingual **nitroglycerin** or **ISDN**. IV and intracoronary nitroglycerin may be useful for patients not responding to sublingual preparations.
- Because CCBs may be more effective, have few serious adverse effects, and can be given less frequently than nitrates, some authorities consider them the agents of choice for variant angina. **Nifedipine**, **verapamil**, and **diltiazem** are all equally effective as single agents for initial management. Patients unresponsive to CCBs alone may have nitrates added. Combination therapy with nifedipine plus diltiazem or nifedipine plus verapamil may be useful in patients unresponsive to single-drug regimens.
- β-Blockers have little or no role in the management of variant angina because they may induce coronary vasoconstriction and prolong ischemia.

EVALUATION OF THERAPEUTIC OUTCOMES

- Subjective measures of drug response include number of painful episodes, amount of rapid-acting nitroglycerin consumed, and symptomatic improvement in exercise capacity (ie, longer duration of exercise or fewer symptoms at the same exercise

level). Once patients have been optimized on medical therapy, symptoms should improve over 2 to 4 weeks and remain stable until the disease progresses.

- The Seattle Angina Questionnaire, Specific Activity Scale, and Canadian Cardiovascular Society classification system can be used to improve reproducibility of symptom assessment.
- If the patient is doing well, no other assessment may be necessary. Objective improvement may be assessed by increased exercise duration on ETT and absence of ischemic changes on ECG or deleterious hemodynamic changes. Limit use of echocardiography and cardiac imaging to patients not doing well to determine whether revascularization or other measures should be undertaken.
- Monitor for major adverse effects such as headache and dizziness with nitrates; fatigue and lassitude with β-blockers; and peripheral edema, constipation, and dizziness with CCBs.
- A comprehensive plan includes ancillary monitoring of lipid profiles, fasting plasma glucose, thyroid function tests, hemoglobin/hematocrit, and electrolytes.

See Chapter 6, Ischemic Heart Disease, authored by Robert L. Talbert, for a more detailed discussion of this topic.

CHAPTER 12

Shock

- *Shock* is an acute state of inadequate perfusion of critical organs that can lead to death if therapy is not optimal. Shock is defined as systolic blood pressure (SBP) less than 90 mm Hg or reduction of at least 40 mm Hg from baseline with perfusion abnormalities despite adequate fluid resuscitation.

PATHOPHYSIOLOGY

- Shock results in failure of the circulatory system to deliver sufficient oxygen (O_2) to tissues despite normal or reduced O_2 consumption. Shock may be caused by intravascular volume deficit (hypovolemic shock), myocardial pump failure (cardiogenic shock), or peripheral vasodilation (septic, anaphylactic, or neurogenic shock).
- Hypovolemic shock is characterized by acute intravascular volume deficiency due to external losses or internal redistribution of extracellular water. It can be precipitated by hemorrhage; burns; trauma; surgery; intestinal obstruction; and dehydration from considerable insensible fluid loss, overaggressive diuretic administration, and severe vomiting or diarrhea. Relative hypovolemia leading to hypovolemic shock occurs during significant vasodilation, which accompanies anaphylaxis, sepsis, and neurogenic shock.
- Fall in blood pressure (BP) is compensated by increased sympathetic outflow, activation of the renin–angiotensin system, and other factors that stimulate peripheral vasoconstriction. Compensatory vasoconstriction redistributes blood away from skin, skeletal muscles, kidneys, and gastrointestinal (GI) tract toward vital organs (eg, heart and brain) in attempt to maintain oxygenation, nutrition, and organ function.
- Severe lactic acidosis often develops secondary to tissue ischemia and causes localized vasodilation, which further exacerbates the impaired cardiovascular state.

CLINICAL PRESENTATION

- Patients with hypovolemic shock may have thirst, anxiousness, weakness, lightheadedness, dizziness, scanty urine output, and dark yellow urine.
- Signs of more severe volume loss include tachycardia (>120 beats/min), tachypnea (>30 breaths/min), hypotension (SBP <90 mm Hg), mental status changes or unconsciousness, agitation, and normal or low body temperature (in the absence of infection) with cold extremities and decreased capillary refill.
- Serum sodium and chloride concentrations are usually high with acute volume depletion. The blood urea nitrogen (BUN):creatinine ratio may be elevated initially, but the creatinine increases with renal dysfunction. Metabolic acidosis results in elevated base deficit and lactate concentrations with decreased bicarbonate and pH.
- Complete blood cell count (CBC) is normal in absence of infection. In hemorrhagic shock, the red cell count, hemoglobin, and hematocrit will decrease.
- Urine output is decreased to less than 0.5 to 1 mL/h. With more severe volume depletion, dysfunction of other organs may be reflected in laboratory testing (eg, elevated serum transaminases levels with hepatic dysfunction).

DIAGNOSIS AND MONITORING

- Noninvasive and invasive monitoring (**Table 12–1**) and evaluation of medical history, clinical presentation, and laboratory findings are important in establishing the diagnosis and assessing mechanisms responsible for shock. Findings include hypotension (SBP <90 mm Hg), depressed cardiac index (CI <2.2 L/min/m^2), tachycardia (heart rate >100 beats/min), and low urine output (<20 mL/h).

TABLE 12–1 Hemodynamic and Oxygen-Transport Monitoring Parameters

Parameter	Normal Value[a]
Blood pressure (systolic/diastolic)	100–130/70–85 mm Hg
Mean arterial pressure (MAP)	80–100 mm Hg
Pulmonary artery pressure (PAP)	25/10 mm Hg
Mean pulmonary artery pressure (MPAP)	12–15 mm Hg
Central venous pressure (CVP)	8–12 mm Hg
Pulmonary artery occlusion pressure (PAOP)	12–15 mm Hg
Heart rate (HR)	60–80 beats/min
Cardiac output (CO)	4–7 L/min
Cardiac index (CI)	2.8–3.6 L/min/m^2
Stroke volume index (SVI)	30–50 mL/m^2
Systemic vascular resistance index (SVRI)	1300–2100 dyne • sec/m^2 • cm^5
Pulmonary vascular resistance index (PVRI)	45–225 dyne • sec/m^2 • cm^5
Arterial O_2 saturation (Sao_2)	97% (range 95–100%)
Mixed venous O_2 saturation (Svo_2)	70–75%
Arterial O_2 content (Cao_2)	20.1 vol% (range 19–21%)
Venous O_2 content (Cvo_2)	15.5 vol% (range 11.5–16.5%)
O_2 content difference (C[a–v]o_2)	5 vol% (range 4%–6%)
O_2 consumption index (Vo_2)	131 mL/min/m^2 (range 100–180)
O_2 delivery index (Do_2)	578 mL/min/m^2 (range 370–730)
O_2 extraction ratio (O_2ER)	25% (range 22–30%)
Intramucosal pH (pHi)	7.40 (range 7.35–7.45)
Index (I)	Parameter indexed to body surface area

[a]Normal values may not be the same as values needed to optimize management of a critically ill patient.

- Pulmonary artery (Swan–Ganz) catheter can be used to determine central venous pressure (CVP), pulmonary artery pressure (PAP), cardiac output (CO), and pulmonary artery occlusion pressure (PAOP).
- Renal function can be assessed grossly by hourly measurements of urine output, but estimation of creatinine clearance based on isolated serum creatinine values may be inaccurate. Decreased renal perfusion and aldosterone release result in sodium retention and thus low urinary sodium (<30 mEq/L).
- In normal individuals, O_2 consumption (Vo_2) is dependent on O_2 delivery (Do_2) up to a certain critical level (Vo_2 flow dependency). At this point, tissue O_2 requirements have been satisfied, and further increases in Do_2 will not alter Vo_2 (flow independency). However, studies in critically ill patients show a continuous, pathologic dependence relationship of Vo_2 with Do_2. These indexed parameters are calculated as

$$Do_2 = CI \times (Cao_2) \text{ and } Vo_2 = CI \times (Cao_2 - Cvo_2)$$

  where CI = cardiac index, Cao_2 = arterial O_2 content, and Cvo_2 = mixed venous O_2 content.
- The Vo_2:Do_2 ratio (O_2 extraction ratio) can be used to assess adequacy of perfusion and metabolic response. Patients who can increase Vo_2 when Do_2 is increased are more likely to survive. However, low Vo_2 and O_2 extraction ratio values indicate poor O_2 utilization and lead to greater mortality.

TREATMENT

- Goals of Treatment: The goal during resuscitation from shock is to achieve and maintain mean arterial pressure (MAP) above 65 mm Hg while ensuring adequate perfusion to critical organs. The ultimate goals are to prevent further disease progression with subsequent organ damage and, if possible, to reverse organ dysfunction that has already occurred.

GENERAL APPROACH

- **Figures 12–1** and **12–2** contain algorithms for acute and ongoing management of adults with hypovolemia.
- Initiate supplemental O_2 at the earliest signs of shock, beginning with 4 to 6 L/min via nasal cannula or 6 to 10 L/min by face mask.
- Fluid resuscitation to maintain circulating blood volume is essential (see next section). If fluid administration does not achieve desired end points, pharmacologic support is necessary with inotropic and vasoactive drugs.
- Supportive care measures include assessment and management of pain, anxiety, agitation, and delirium.

FLUID RESUSCITATION FOR HYPOVOLEMIC SHOCK

- *Crystalloids*: Isotonic (or near isotonic) crystalloid solutions (**0.9% sodium chloride** or **lactated Ringer solution**) are the initial fluids of choice. The choice between normal saline and lactated Ringer solution is based on clinician preference and adverse effect concerns. Crystalloids can be rapidly and easily administered, are compatible with most drugs, and have low cost. Their disadvantages include the need to use large fluid volumes and the possibility that dilution of oncotic pressure may lead to pulmonary edema. Crystalloids are administered at a rate of 500 to 2000 mL/h, depending on severity of the deficit, degree of ongoing fluid loss, and tolerance to infusion volume. Usually 2 to 4 L of crystalloid normalizes intravascular volume.
- *Colloids*: **Hydroxyethyl starch**, **dextran**, and **albumin** possess the theoretical advantage of prolonged intravascular retention time compared with crystalloid solutions. However, colloids are expensive and have been associated with fluid overload, renal dysfunction, and bleeding. In 2013, the U.S. Food and Drug Administration (FDA) analyzed data from randomized controlled trials, meta-analyses, and observational studies and concluded that hydroxyethyl starch is associated with increased mortality and renal injury requiring renal replacement therapy in critically ill adult patients, including patients with sepsis and those admitted to the intensive care unit (ICU). The FDA concluded that the solutions should not be used in these patient populations and added a boxed warning to the labeling describing the risk of mortality and severe renal injury.
- *Blood products*: Some patients require blood products (**whole blood**, **packed red blood cells**, **fresh frozen plasma**, or **platelets**) to ensure maintenance of O_2-carrying capacity, as well as clotting factors and platelets for blood hemostasis. Blood products may be associated with transfusion-related reactions, virus transmission (rare), hypocalcemia resulting from added citrate, increased blood viscosity from supranormal hematocrit elevations, and hypothermia from failure to appropriately warm solutions before administration.

PHARMACOLOGIC THERAPY FOR SHOCK

- *Hypovolemic shock*: Inotropic agents and vasopressors are generally not indicated in initial treatment of hypovolemic shock (if fluid therapy is adequate), because the body's compensatory response is to increase CO and peripheral resistance to maintain BP. Use of vasopressors in lieu of fluids may exacerbate this resistance to the point that circulation is stopped. Therefore, vasoactive agents that dilate peripheral vasculature such as dobutamine are preferred if blood pressure is stable and high enough to tolerate the vasodilation. Vasopressors are only used as a temporizing measure or last resort when all other measures fail to maintain perfusion.

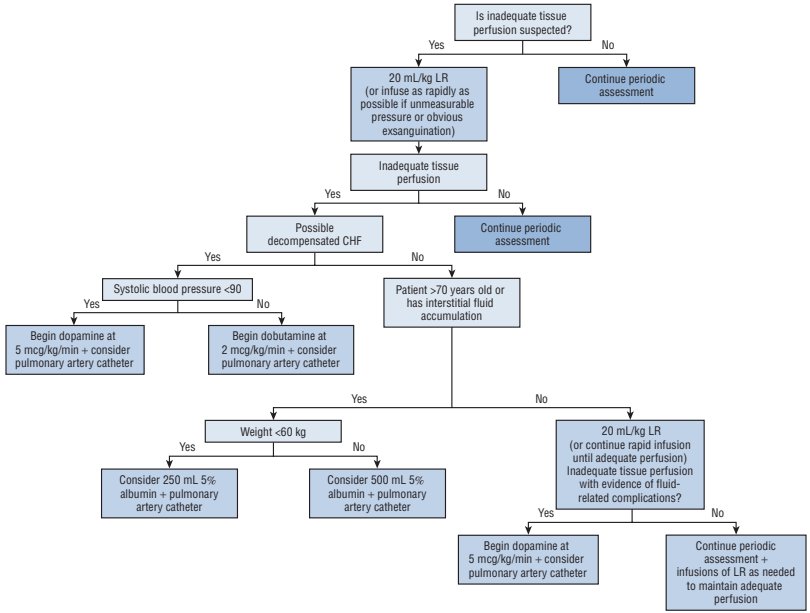


FIGURE 12–1. Hypovolemia protocol for adults. This protocol is not intended to replace or delay therapies such as surgical intervention or blood products for restoring O_2-carrying capacity or hemostasis. If available, some measurements may be used in addition to those listed in the algorithm, such as mean arterial pressure or pulmonary artery catheter recordings. The latter can be used to assist in medication choices (eg, agents with primary pressor effects may be desirable in patients with normal COs, whereas dopamine or dobutamine may be indicated in patients with suboptimal COs). Lower maximal doses of the medications in this algorithm should be considered when pulmonary artery catheterization is not available. (CHF, congestive heart failure; LR, lactated Ringer solution.)

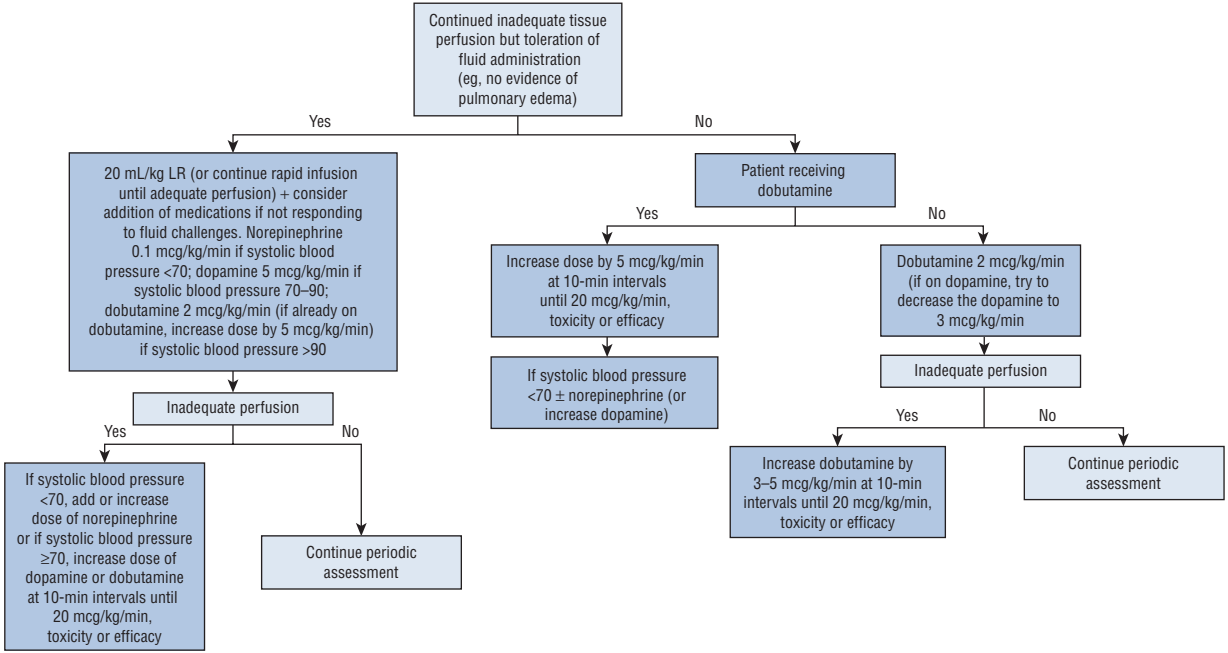


FIGURE 12–2. Ongoing management of inadequate tissue perfusion. (LR, lactated Ringer solution.)

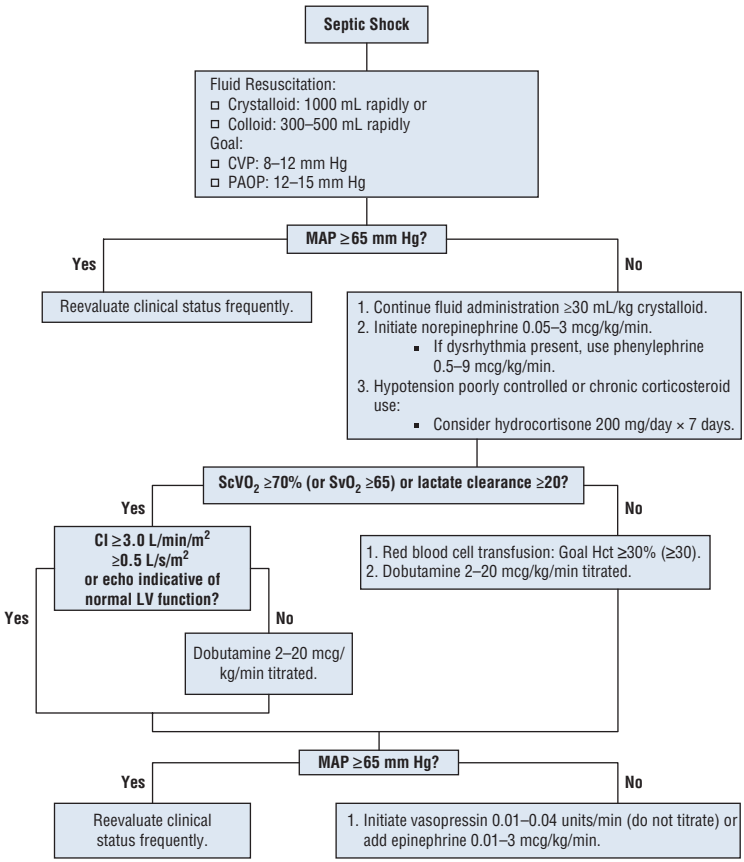


FIGURE 12–3. Algorithmic approach to resuscitative management of septic shock. Algorithmic approach is intended to be used in conjunction with clinical judgment, hemodynamic monitoring parameters, and therapy end points. (ACTH, adrenocorticotropic hormone; CI, cardiac index; CVP, central venous pressure; Hct, hematocrit; MAP, mean arterial pressure; PAOP, pulmonary artery occlusion pressure; $Scvo_2$, central venous O_2 saturation; Svo_2, mixed venous O_2 saturation.)

- *Septic shock*: An algorithm for use of fluid resuscitation, vasopressors, and inotropes in septic shock is shown in **Fig. 12–3**. Initial hemodynamic therapy for septic shock is administration of IV fluid (30 mL/kg of crystalloid), with the goal of attaining CVP 8 to 12 mm Hg or 15 mm Hg in mechanically ventilated patients or patients with abdominal distention or preexisting ventricular dysfunction. Crystalloids are preferred over colloids unless patients are at risk for adverse events from redistribution of IV fluids to extravascular tissues or are fluid restricted.

✓ **Norepinephrine** is the preferred initial vasopressor in septic shock not responding to fluid administration.

✓ **Epinephrine** may be added in cases where there is suboptimal hemodynamic response to norepinephrine.

✓ **Phenylephrine** may be tried as the initial vasopressor in cases of severe tachydysrhythmias.

TABLE 12–2 Receptor Pharmacology of Selected Inotropic and Vasopressor Agents Used in Septic Shock[a]

Agent	α_1	α_2	β_1	β_2	D
Dobutamine (0.5–4 mg/mL D_5W or NS)					
2–10 mcg/kg/min	+	0	++++	++	0
>10–20 mcg/kg/min	++	0	++++	+++	0
Dopamine (0.8–3.2 mg/mL D_5W or NS)					
1–3 mcg/kg/min	0	0	+	0	++++
3–10 mcg/kg/min	0/+	0	++++	++	++++
>10–20 mcg/kg/min	+++	0	++++	+	0
Epinephrine (0.008–0.016 mg/mL D_5W or NS)					
0.01–0.05 mcg/kg/min	++	++	++++	+++	0
>0.05–3 mcg/kg/min	++++	++++	+++	+	0
Norepinephrine (0.016–0.064 mg/mL D_5W)					
0.02–3 mcg/kg/min	+++	+++	+++	+/++	0
Phenylephrine (0.1–0.4 mg/mL D_5W or NS)					
0.5–9 mcg/kg/min	+++	+	+	0	0
Vasopressin (0.8 units/mL D_5W or NS)					
0.01–0.04 units/min	0	0	0	0	0

D, dopamine; D_5W, dextrose 5% in water; NS, normal saline.
[a]Activity ranges from no activity (0) to maximal (++++) activity.

✓ **Dobutamine** is used in low CO states despite adequate fluid resuscitation pressures.
✓ **Vasopressin** may be considered as adjunctive therapy in patients who are refractory to catecholamine vasopressors despite adequate fluid resuscitation.

Dosage titration and monitoring of vasopressor and inotropic therapy should be guided by clinical response, the goals of early goal-directed therapy, and lactate clearance. Vasopressor/inotrope therapy is continued until myocardial depression and vascular hyporesponsiveness (ie, blood pressure) of septic shock improve, usually measured in hours to days. Discontinuation of therapy should be executed slowly with careful monitoring.

- Receptor selectivities of vasopressors and inotropes are listed in **Table 12–2**. In general, these drugs act rapidly with short durations of action and are given as continuous infusions. Potent vasoconstrictors such as norepinephrine and phenylephrine should be given through central veins because of possibility of extravasation and tissue damage with peripheral administration. Careful monitoring and calculation of infusion rates are advised because dosing adjustments are made frequently, and varying admixture concentrations are used in volume-restricted patients.
- **Norepinephrine** is first-line therapy for septic shock because it effectively increases MAP. It has strong α_1-agonist activity and less potent β_1-agonist effects while maintaining weak vasodilatory effects of β_2-receptor stimulation. Norepinephrine infusions are initiated at 0.05 to 0.1 mcg/kg/min and rapidly titrated to preset goals of MAP (usually at least 65 mm Hg), improvement in peripheral perfusion (to restore urine production or decrease blood lactate), and/or achievement of desired oxygen-transport variables while not compromising cardiac index. Norepinephrine 0.01 to 2 mcg/kg/min improves hemodynamic parameters to "normal" values in most patients with septic shock. As with other vasopressors, norepinephrine dosages

exceeding those recommended by most references frequently are needed in critically ill patients with septic shock to achieve predetermined goals.

- **Phenylephrine** is a pure α_1-agonist; in sepsis, it improves MAP by increasing cardiac index through enhanced venous return to the heart (increase in CVP and stroke index) and by acting as a positive inotrope. Phenylephrine 0.5 to 9 mcg/kg/min, used alone or in combination with dobutamine or low doses of dopamine, improves blood pressure and myocardial performance in fluid-resuscitated septic patients. Adverse effects, such as tachydysrhythmias, are infrequent, particularly when it is used as a single agent or at higher doses, because it does not have β_1-adrenergic agonist activity. Phenylephrine may be a useful alternative in patients who cannot tolerate tachycardia or tachydysrhythmias from dopamine or norepinephrine and in patients who are refractory to dopamine or norepinephrine.
- **Epinephrine** has combined α- and β-agonist effects; it is an acceptable choice for hemodynamic support of septic shock because of its combined vasoconstrictor and inotropic effects, but it is associated with tachydysrhythmias and lactate elevation. As a result, it is considered an alternative agent. Infusion rates of 0.04 to 1 mcg/kg/min alone increase hemodynamic and oxygen-transport variables to supranormal values without adverse effects in septic patients without coronary artery disease. Large dosages (0.5–3 mcg/ kg/ min) often are required. Smaller dosages (0.10–0.50 mcg/kg/min) are effective when epinephrine is added to other vasopressors and inotropes. Younger patients appear to respond better to epinephrine, possibly because of greater β-adrenergic reactivity. Based on current evidence, epinephrine should not be used as initial therapy in patients with septic shock refractory to fluid administration. Although it effectively increases CO and Do_2, it has deleterious effects on the splanchnic circulation.
- **Dopamine** is generally not as effective as norepinephrine and epinephrine for achieving goal MAP in patients with septic shock. Dopamine doses of 5 to 10 mcg/kg/min increase cardiac index by improving contractility and heart rate, primarily from its β_1 effects. It increases MAP and SVR as a result of both increased CO and, at higher doses (>10 mcg/kg/min), its α_1 agonist effects. The clinical utility of dopamine is limited because large dosages are frequently necessary to maintain CO and MAP. At dosages exceeding 20 mcg/kg/min, further improvement in cardiac performance and regional hemodynamics is limited. Its clinical use frequently is hampered by tachycardia and tachydysrhythmias, which may lead to myocardial ischemia. Use dopamine with caution in patients with elevated preload because it may worsen pulmonary edema.
- **Dobutamine** is an inotrope with vasodilatory properties (an "inodilator"). It is used to increase the cardiac index, typically by 25% to 50%. Dobutamine should be started at dosages ranging from 2.5 to 5 mcg/kg/min. Although a dose response may be seen, dosages greater than 5 mcg/kg/min may provide limited beneficial effects on oxygen transport values and hemodynamics and may increase adverse cardiac effects. If given to patients who are intravascularly depleted, dobutamine will result in hypotension and a reflexive tachycardia.
- **Vasopressin** produces rapid and sustained improvement in hemodynamic parameters at dosages not exceeding 0.04 units/min. Doses above 0.04 units/min are associated with negative changes in CO and mesenteric mucosal perfusion. It should be used with extreme caution in septic shock patients with cardiac dysfunction. Cardiac ischemia appears to be a rare occurrence and may be related to administration of dosages 0.05 units/min or greater. In order to minimize adverse events and maximize beneficial effects, use vasopressin as add-on therapy to one or two catecholamine adrenergic agents rather than as first-line therapy or salvage therapy, and limit dosages to 0.04 units/min. Use vasopressin only if response to one or two adrenergic agents is inadequate or as a method for reducing the dosage of those therapies. Increased arterial pressure should be evident within the first hour of vasopressin therapy, at which time the dose(s) of adrenergic agent(s) should be reduced while maintaining goal MAP. Attempt to discontinue vasopressin when the dosage(s) of adrenergic agent(s) has been minimized (dopamine ≤5 mcg/kg/min, norepinephrine ≤0.1 mcg/kg/min, phenylephrine ≤1 mcg/kg/min, epinephrine ≤0.15 mcg/kg/min).

- **Corticosteroids** can be initiated in septic shock when adrenal insufficiency is suspected, when vasopressor dosages are escalating, or when weaning of vasopressor therapy proves futile. Adverse events are few because corticosteroids are administered for a short time, usually 7 days. Acutely, elevated BUN, white blood cell count, and glucose may occur. In general, treatment of septic shock with corticosteroids improves hemodynamic variables and lowers catecholamine vasopressor dosages with minimal to no adverse effect on patient safety.

EVALUATION OF THERAPEUTIC OUTCOMES

- Monitor patients with suspected volume depletion initially by vital signs, urine output, mental status, and physical examination.
- Placement of a CVP line provides a useful (although indirect and insensitive) estimate of the relationship between increased right atrial pressure and CO.
- Reserve pulmonary artery catheterization for complicated cases of shock not responding to conventional fluid and medication therapies. Complications related to catheter insertion, maintenance, and removal include damage to vessels and organs during insertion, arrhythmias, infections, and thromboembolic damage.
- Laboratory tests for ongoing monitoring of shock include electrolytes and renal function tests (BUN and serum creatinine); CBC to assess possible infection, O_2-carrying capacity of the blood, and ongoing bleeding; PT and aPTT to assess clotting ability; and lactate concentration and base deficit to detect inadequate tissue perfusion.
- Monitor cardiovascular and respiratory parameters continuously (see **Table 12–1**). Watch for trends, rather than specific CVP or PAOP numbers, because of interpatient variability in response.
- Successful fluid resuscitation should increase SBP (>90 mm Hg), CI (>2.2 L/min/m^2), and urine output (0.5–1 mL/kg/h) while decreasing SVR to the normal range. MAP of greater than 65 mm Hg should be achieved to ensure adequate cerebral and coronary perfusion pressure.
- Intravascular volume overload is characterized by high filling pressures (CVP >12–15 mm Hg, PAOP >20–24 mm Hg) and decreased CO (<3.5 L/min). If volume overload occurs, administer furosemide, 20 to 40 mg, by slow IV push to produce rapid diuresis of intravascular volume and "unload" the heart through venous dilation.
- Coagulation problems are primarily associated with low levels of clotting factors in stored blood, as well as dilution of endogenous clotting factors and platelets following administration of the blood. As a result, check a coagulation panel (PT, international normalized ratio [INR], and aPTT) in patients undergoing replacement of 50% to 100% of blood volume in 12 to 24 hours.

See Chapter 13, Use of Vasopressors and Inotropes in the Pharmacotherapy of Shock, authored by Robert MacLaren and Joseph F. Dasta, and Chapter 14, Hypovolemic Shock, authored by Brian L. Erstad, for a more detailed discussion of this topic.

Stroke

CHAPTER 13

- *Stroke* involves abrupt onset of focal neurologic deficit that lasts at least 24 hours and is presumed to be of vascular origin. Stroke can be either ischemic or hemorrhagic. Transient ischemic attacks (TIAs) are focal ischemic neurologic deficits lasting less than 24 hours and usually less than 30 minutes.

PATHOPHYSIOLOGY

ISCHEMIC STROKE

- Ischemic strokes (87% of all strokes) are due either to local thrombus formation or emboli occluding a cerebral artery. Cerebral atherosclerosis is a cause in most cases, but 30% are of unknown etiology. Emboli arise either from intra- or extracranial arteries. Twenty percent of ischemic strokes arise from the heart.
- Carotid atherosclerotic plaques may rupture, resulting in collagen exposure, platelet aggregation, and thrombus formation. The clot may cause local occlusion or dislodge and travel distally, eventually occluding a cerebral vessel.
- In cardiogenic embolism, stasis of blood flow in the atria or ventricles leads to formation of local clots that can dislodge and travel through the aorta to the cerebral circulation.
- Thrombus formation and embolism result in arterial occlusion, decreasing cerebral blood flow and causing ischemia and ultimately infarction distal to the occlusion.

HEMORRHAGIC STROKE

- Hemorrhagic strokes (13% of strokes) include subarachnoid hemorrhage (SAH), intracerebral hemorrhage, and subdural hematomas. SAH may result from trauma or rupture of an intracranial aneurysm or arteriovenous malformation (AVM). Intracerebral hemorrhage occurs when a ruptured blood vessel within the brain causes a hematoma. Subdural hematomas are usually caused by trauma.
- Blood in the brain parenchyma damages surrounding tissue through a mass effect and the neurotoxicity of blood components and their degradation products. Hemorrhagic stroke can result in abrupt increased intracranial pressure leading to herniation and death.

CLINICAL PRESENTATION

- Patients may be unable to provide a reliable history because of neurologic deficits. Family members or other witnesses may need to provide this information.
- Symptoms include unilateral weakness, inability to speak, loss of vision, vertigo, or falling. Ischemic stroke is not usually painful, but headache may occur in hemorrhagic stroke.
- Neurologic deficits on physical examination depend on the brain area involved. Hemi- or monoparesis and hemisensory deficits are common. Patients with posterior circulation involvement may have vertigo and diplopia. Anterior circulation strokes commonly result in aphasia. Patients may experience dysarthria, visual field defects, and altered levels of consciousness.

DIAGNOSIS

- Laboratory tests for hypercoagulable states should be done only when the cause cannot be determined based on presence of risk factors. Protein C, protein S, and antithrombin III are best measured in steady state rather than in the acute stage. Antiphospholipid antibodies are of higher yield but should be reserved for patients younger than 50 years and those who have had multiple venous or arterial thrombotic events or livedo reticularis.

- Computed tomography (CT) and magnetic resonance imaging (MRI) head scans can reveal areas of hemorrhage and infarction.
- Carotid Doppler (CD), electrocardiogram (ECG), transthoracic echocardiogram (TTE), and transcranial Doppler (TCD) studies can each provide valuable diagnostic information.

TREATMENT

- Goals of Treatment: The goals are to (1) reduce ongoing neurologic injury and decrease mortality and long-term disability, (2) prevent complications secondary to immobility and neurologic dysfunction, and (3) prevent stroke recurrence.

GENERAL APPROACH

- Ensure adequate respiratory and cardiac support and determine quickly from CT scan whether the lesion is ischemic or hemorrhagic.
- Evaluate ischemic stroke patients presenting within hours of symptom onset for reperfusion therapy.
- Elevated blood pressure (BP) should remain untreated in the acute period (first 7 days) after ischemic stroke to avoid decreasing cerebral blood flow and worsening symptoms. BP should be lowered if it exceeds 220/120 mm Hg or there is evidence of aortic dissection, acute myocardial infarction (MI), pulmonary edema, or hypertensive encephalopathy. If BP is treated in the acute phase, short-acting parenteral agents (eg, labetalol, nicardipine, nitroprusside) are preferred.
- Assess patients with hemorrhagic stroke to determine whether they are candidates for surgical intervention.
- After the hyperacute phase, focus on preventing progressive deficits, minimizing complications, and instituting secondary prevention strategies.

NONPHARMACOLOGIC THERAPY

- *Acute ischemic stroke*: Surgical decompression is sometimes necessary to reduce intracranial pressure. An interprofessional team approach that includes early rehabilitation can reduce long-term disability. In secondary prevention, carotid endarterectomy and stenting may be effective in reducing stroke incidence and recurrence in appropriate patients.
- *Hemorrhagic stroke*: In SAH, surgical intervention to clip or ablate the vascular abnormality reduces mortality from rebleeding. After primary intracerebral hemorrhage, surgical evacuation may be beneficial in some situations. Insertion of an external ventricular drain with monitoring of intracranial pressure is commonly performed in these patients.

PHARMACOLOGIC THERAPY OF ISCHEMIC STROKE

- Evidence-based recommendations for pharmacotherapy of ischemic stroke are given in **Table 13–1**.
- **Alteplase** (t-PA, tissue plasminogen activator) initiated within 4.5 hours of symptom onset reduces disability from ischemic stroke. Adherence to a strict protocol is essential to achieving positive outcomes: (1) activate the stroke team; (2) treat as early as possible within 4.5 hours of onset; (3) obtain CT scan to rule out hemorrhage; (4) meet all inclusion and no exclusion criteria (**Table 13–2**); (5) administer alteplase 0.9 mg/kg (maximum 90 mg) infused IV over 1 hour, with 10% given as initial bolus over 1 minute; (6) avoid anticoagulant and antiplatelet therapy for 24 hours; and (7) monitor the patient closely for elevated BP, response, and hemorrhage.
- **Aspirin** 160 to 325 mg/day started between 24 and 48 hours after completion of alteplase also reduces long-term death and disability.
- Secondary prevention of ischemic stroke:

  ✓ Use antiplatelet therapy in noncardioembolic stroke. **Aspirin**, **clopidogrel**, and **extended-release dipyridamole plus aspirin** are all first-line agents (see **Table 13–1**). **Cilostazol** is also a first-line agent, but its use has been limited by lack of data. Limit the combination of clopidogrel and ASA to select patients with a recent MI

TABLE 13–1 Recommendations for Pharmacotherapy of Ischemic Stroke

	Recommendation	Evidence[a]
Acute treatment	Alteplase 0.9 mg/kg IV (max 90 mg) over 1 h in select patients within 3 h of onset	IA
	Alteplase 0.9 mg/kg IV (max 90 mg) over 1 h between 3 and 4.5 h of onset	IB
	Aspirin 160–325 mg daily started within 48 h of onset	IA
Secondary prevention		
Noncardioembolic	Antiplatelet therapy	IA
	Aspirin 50–325 mg daily	IA
	Clopidogrel 75 mg daily	IIa B
	Aspirin 25 mg + extended-release dipyridamole 200 mg twice daily	IB
Cardioembolic (esp. atrial fibrillation)	Vitamin K antagonist (INR = 2.5)	IA
	Dabigatran 150 mg twice daily	2B
Atherosclerosis	Intense statin therapy	IB
All patients	BP reduction	IA

BP, blood pressure; INR, international normalized ratio.
[a]Classes of evidence: I, evidence or general agreement that treatment is useful and effective; II, conflicting evidence about usefulness; IIa, weight of evidence in favor of the treatment; IIb, usefulness less well established.
Levels of evidence: A, multiple randomized clinical trials; B, a single randomized trial or nonrandomized studies; C, expert consensus or case studies.

history or intracranial stenosis and only with ultra–low-dose ASA to minimize bleeding risk.

✓ Oral anticoagulation is recommended for atrial fibrillation and a presumed cardiac source of embolism. A vitamin K antagonist (**warfarin**) is first line, but other oral anticoagulants (eg, **dabigatran**) may be recommended for some patients.

- Treatment of elevated BP after ischemic stroke reduces risk of stroke recurrence. Treatment guidelines recommend BP reduction in patients with stroke or TIA after the acute period (first 7 days).
- **Statins** reduce risk of stroke by approximately 30% in patients with coronary artery disease and elevated plasma lipids. Treat ischemic stroke patients, regardless of baseline cholesterol, with high-intensity statin therapy to achieve a reduction of at least 50% in LDL for secondary stroke prevention.
- **Low-molecular-weight heparin** or **low-dose subcutaneous unfractionated heparin** (5000 units three times daily) is recommended for prevention of deep vein thrombosis in hospitalized patients with decreased mobility due to stroke and should be used in all but the most minor strokes.

PHARMACOLOGIC THERAPY OF HEMORRHAGIC STROKE

- There are no standard pharmacologic strategies for treating intracerebral hemorrhage. Follow medical guidelines for managing BP, increased intracranial pressure, and other medical complications in acutely ill patients in neurointensive care units.
- SAH due to aneurysm rupture is often associated with delayed cerebral ischemia in the 2 weeks after the bleeding episode. Vasospasm of the cerebral vasculature is thought to be responsible for the delayed ischemia and occurs between 4 and 21 days after the bleed. The calcium channel blocker **nimodipine** 60 mg every 4 hours for 21 days, along with maintenance of intravascular volume with pressor therapy, is recommended to reduce the incidence and severity of neurologic deficits resulting from delayed ischemia.

TABLE 13–2 Inclusion and Exclusion Criteria for Alteplase Use in Acute Ischemic Stroke

Inclusion Criteria (all YES boxes must be checked before treatment)

YES

- ❑ Age ≥18 years
- ❑ Clinical diagnosis of ischemic stroke causing a measurable neurologic deficit
- ❑ Time of symptom onset well established to be <4.5 h before treatment would begin

Exclusion Criteria (all NO boxes must be checked before treatment)

NO

- ❑ Evidence of intracranial hemorrhage on noncontrast head CT
- ❑ Only minor or rapidly improving stroke symptoms
- ❑ High clinical suspicion of SAH even with normal CT
- ❑ Active internal bleeding (eg, GI/GU bleeding within 21 days)
- ❑ Known bleeding diathesis, including, but not limited to, platelet count <100,000/mm^3 (<100 × 10^{12}/L)
- ❑ Patient has received heparin within 48 h and had an elevated aPTT
- ❑ Recent use of anticoagulant (eg, warfarin) and elevated PT (>15 s)/INR
- ❑ Intracranial surgery, serious head trauma, or previous stroke within 3 months
- ❑ Major surgery or serious trauma within 14 days
- ❑ Recent arterial puncture at noncompressible site
- ❑ Lumbar puncture within 7 days
- ❑ History of intracranial hemorrhage, AVM, or aneurysm
- ❑ Witnessed seizure at stroke onset
- ❑ Recent acute myocardial infarction
- ❑ SBP >185 mm Hg or DBP >110 mm Hg at time of treatment

Additional exclusion criteria if within 3–4.5 h of onset:

- ❑ Age >80 years
- ❑ Current treatment with oral anticoagulants
- ❑ NIH stroke scale >25 (severe stroke)
- ❑ History of both stroke and diabetes

[a]PTT, activated partial thromboplastin time; AVM, arteriovenous malformation; CT, computed tomography; DBP, diastolic blood pressure; GI, gastrointestinal; GU, genitourinary; INR, international normalized ratio; NIH, National Institutes of Health; PT, prothrombin time; SAH, subarachnoid hemorrhage; SBP, systolic blood pressure.

EVALUATION OF THERAPEUTIC OUTCOMES

- Monitor patients with acute stroke intensely for development of neurologic worsening (recurrence or extension), complications (thromboembolism, infection), and adverse treatment effects.
- The most common reasons for clinical deterioration in stroke patients include: (1) extension of the original lesion in the brain, (2) development of cerebral edema and raised intracranial pressure, (3) hypertensive emergency, (4) infection (eg, urinary and respiratory tract), (5) venous thromboembolism, (6) electrolyte abnormalities and rhythm disturbances, and (7) recurrent stroke. The approach to monitoring stroke patients is summarized in **Table 13–3**.

TABLE 13–3 Monitoring Hospitalized Acute Stroke Patients

	Treatment	Parameter(s)	Frequency
Ischemic stroke	Alteplase	BP, neurologic function, bleeding	Every 15 min × 1 h; every 0.5 h × 6 h; every 1 h × 17 h; every shift after
	Aspirin	Bleeding	Daily
	Clopidogrel	Bleeding	Daily
	ERDP/ASA	Headache, bleeding	Daily
	Warfarin	Bleeding, INR, Hb/Hct	INR daily × 3 days; weekly until stable; monthly
	Dabigatran	Bleeding	Daily
Hemorrhagic stroke		BP, neurologic function, ICP	Every 2 h in ICU
	Nimodipine (for SAH)	BP, neurologic function, fluid status	Every 2 h in ICU
All patients		Temperature, CBC	Temperature every 8 h; CBC daily
		Pain (calf or chest)	Every 8 h
		Electrolytes and ECG	Up to daily
	Heparins for DVT prophylaxis	Bleeding, platelets	Bleeding daily, platelets if suspected thrombocytopenia

BP, blood pressure; CBC, complete blood cell count; DVT, deep vein thrombosis; ECG, electrocardiogram; ERDP/ASA, extended-release dipyridamole plus aspirin; Hb, hemoglobin; Hct, hematocrit; ICP, intracranial pressure; ICU, intensive care unit; INR, international normalized ratio; SAH, subarachnoid hemorrhage.

See Chapter 10, Stroke, authored by Susan C. Fagan and David C. Hess, for a more detailed discussion of this topic.

CHAPTER 14

Venous Thromboembolism

- *Venous thromboembolism* (VTE) results from clot formation in the venous circulation and is manifested as deep vein thrombosis (DVT) and pulmonary embolism (PE).

PATHOPHYSIOLOGY

- Normal hemostasis (**Fig. 14–1**) maintains integrity of the circulatory system after blood vessel damage. Vascular injury allows components of the coagulation process to seal the breach through interaction of activated platelets and the clotting factor cascade initiated by tissue factor and culminating in formation of a fibrin clot.
- In contrast to physiologic hemostasis, pathologic venous thrombosis occurs in the absence of gross vein wall disruption and may be triggered by microparticles bearing tissue factor rather than the tissue factor expressed in vessel walls.
- Platelets are activated and contribute to thrombus formation by two pathways: (1) exposure of blood to subendothelial collagen after vascular injury; and (2) thrombin generation by tissue factor derived from the vessel wall or in blood. A platelet thrombus develops as activated platelets recruit unstimulated platelets. Platelet activation releases adenosine diphosphate (ADP), calcium ions, and P-selectin, an adhesion molecular that facilitates capture of microparticles bearing tissue factor. Accumulation of tissue factor in the platelet thrombus initiates fibrin clot formation via the coagulation cascade.
- The tissue factor pathway triggers coagulation by generating a small amount of thrombin, which converts factors VIII and V to their active cofactor forms (VIIIa, Va), which then stimulates the tenase and prothrombinase complexes to generate a large burst of thrombin.
- Finally, thrombin mediates conversion of fibrinogen to fibrin monomers, which precipitate and polymerize to form fibrin strands. Factor XIIIa covalently bonds these strands together. Fibrin deposition forms a meshwork that encases aggregated platelets to form a stabilized clot that seals the site of vascular injury and prevents blood loss.
- Hemostasis is controlled by antithrombotic substances secreted by intact endothelium adjacent to damaged tissue. Thrombomodulin modulates thrombin activity by converting protein C to its activated form (aPC), which joins with protein S to inactivate factors Va and VIIIa. This prevents coagulation reactions from spreading to uninjured vessel walls. In addition, circulating antithrombin inhibits thrombin and factor Xa. Heparan sulfate is secreted by endothelial cells and accelerates antithrombin activity. Heparin cofactor II also inhibits thrombin.
- The fibrinolytic system dissolves formed blood clots; plasminogen is converted to plasmin by tissue plasminogen activator and urokinase plasminogen activator. Plasmin degrades the fibrin mesh into soluble end products (fibrin split products or fibrin degradation products).
- Alterations in blood vessels, circulating elements in blood, and speed of blood flow can lead to pathologic clot formation (Virchow triad):
  - ✓ Vascular injury occurs with trauma (especially fractures of the pelvis, hip, or leg), orthopedic surgery (eg, knee and hip replacement), or indwelling venous catheters.
  - ✓ Hypercoagulable states include malignancy; activated protein C resistance; deficiency of protein C, protein S, or antithrombin; high concentrations of factor VIII, IX, and/or XI or fibrinogen; antiphospholipid antibodies; and estrogen use.
  - ✓ Stasis can result from damage to venous valves, vessel obstruction, prolonged immobility, or increased blood viscosity resulting from medical illness (eg, heart failure, myocardial infarction), surgery, paralysis (eg, stroke), polycythemia vera, obesity, or varicose veins.

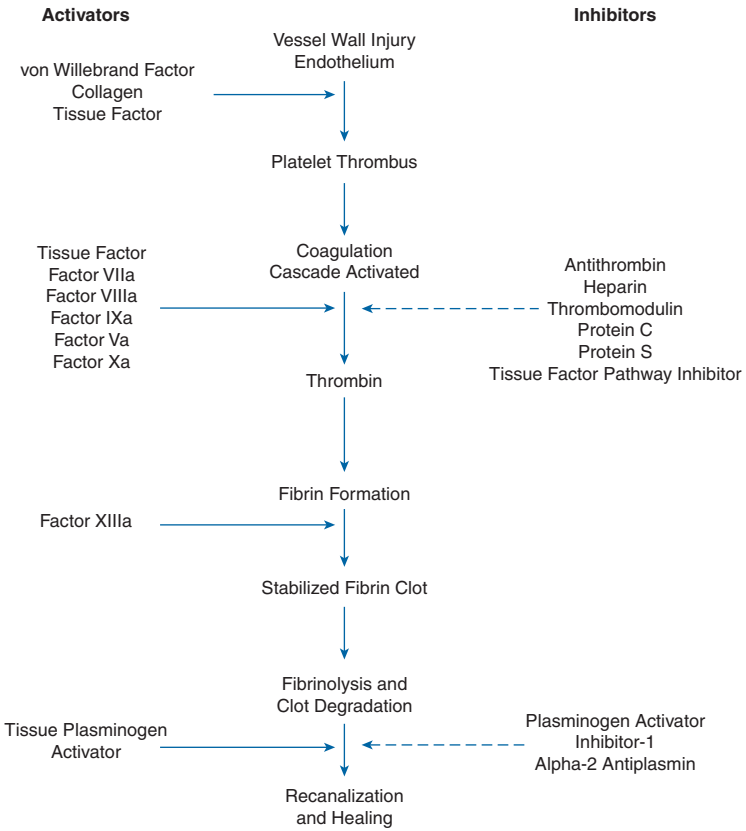


FIGURE 14–1. Hemostasis and thrombosis.

CLINICAL PRESENTATION

- Many patients never develop symptoms from the acute event.
- *Symptoms of DVT*: Unilateral leg swelling, pain, tenderness, erythema, and warmth. Physical signs may include a palpable cord and a positive Homan sign.
- *Symptoms of PE*: Cough, chest pain or tightness, shortness of breath palpitations, hemoptysis, dizziness, or lightheadedness. Signs of PE include tachypnea, tachycardia, diaphoresis, cyanosis, hypotension, shock, and cardiovascular collapse.
- Postthrombotic syndrome may produce chronic lower extremity swelling, pain, tenderness, skin discoloration, and ulceration.

DIAGNOSIS

- Assessment should focus on identifying risk factors (eg, increased age, major surgery, previous VTE, trauma, malignancy, hypercoagulable states, drug therapy).
- Radiographic contrast studies (venography, pulmonary angiography) are the most accurate and reliable method for VTE diagnosis. Noninvasive tests (eg, compression

ultrasound, computed tomography scan, ventilation-perfusion scan) are often used for initial evaluation of patients with suspected VTE.
- Elevated D-dimer blood levels occur in acute thrombosis but also with other conditions (eg, recent surgery or trauma, pregnancy, cancer). Therefore, a negative test can help exclude VTE, but a positive test is not conclusive evidence of the diagnosis.
- Clinical assessment checklists can be used to determine whether a patient has a high, moderate, or low probability of DVT or PE.

TREATMENT

- Goals of Treatment: The goals are to prevent development of PE and postthrombotic syndrome, reduce morbidity and mortality from the acute event, and minimize adverse effects and cost of treatment.

GENERAL APPROACH

- Anticoagulation is the primary treatment for VTE; DVT and PE are treated similarly (**Fig. 14–2**).
- After VTE is confirmed objectively, institute anticoagulant therapy as soon as possible. Anticoagulation is usually initiated with an injectable anticoagulant (unfractionated heparin [UFH], low-molecular-weight heparin [LMWH], or fondaparinux) and then transitioned to warfarin maintenance therapy. Injectable anticoagulants can be administered in the outpatient setting in most patients with DVT and in carefully selected hemodynamically stable patients with PE. Alternatively, oral rivaroxaban may be initiated in select patients.
- The acute phase (~7 days) requires rapidly-acting anticoagulants (UFH, LMWH, fondaparinux, rivaroxaban) to prevent thrombus extension and embolization.
- The early maintenance phase (7 days to 3 months) consists of continued anticoagulation to reduce risk of long-term sequelae (eg, postthrombotic syndrome) by allowing formed clot to be slowly dissolved by endogenous thrombolysis.
- Anticoagulation beyond 3 months is aimed at long-term secondary prevention of recurrent VTE.

NONPHARMACOLOGIC THERAPY

- Graduated compression stockings and intermittent pneumatic compression (IPC) devices improve venous blood flow and reduce risk of VTE.
- Inferior vena cava filters can provide short-term protection against PE in very high-risk patients with contraindications to anticoagulation therapy or in whom anticoagulant therapy has failed.
- Encourage patients to ambulate as much as symptoms permit.
- Consider thrombectomy in life- or limb-threatening DVT. For acute PE, catheter-based embolectomy might be suitable for patients who have contraindications to thrombolytic therapy, have failed thrombolytic therapy, or in whom death is likely before onset of thrombolysis. Reserve surgical embolectomy for massive PE and hemodynamic instability when thrombolysis is contraindicated, has failed, or will have insufficient time to take effect.

PHARMACOLOGIC THERAPY

Unfractionated Heparin

- **Unfractionated heparin (UFH)** prevents growth and propagation of a formed thrombus and allows endogenous thrombolytic systems to degrade the clot. Because some patients fail to achieve an adequate response, IV UFH has largely been replaced by LMWH or fondaparinux. UFH continues to have a role in patients with creatinine clearance less than 30 mL/min (<0.5 mL/s).
- When immediate and full anticoagulation is required, a weight-based IV bolus dose followed by a continuous IV infusion is preferred (**Table 14–1**). Fixed dosing

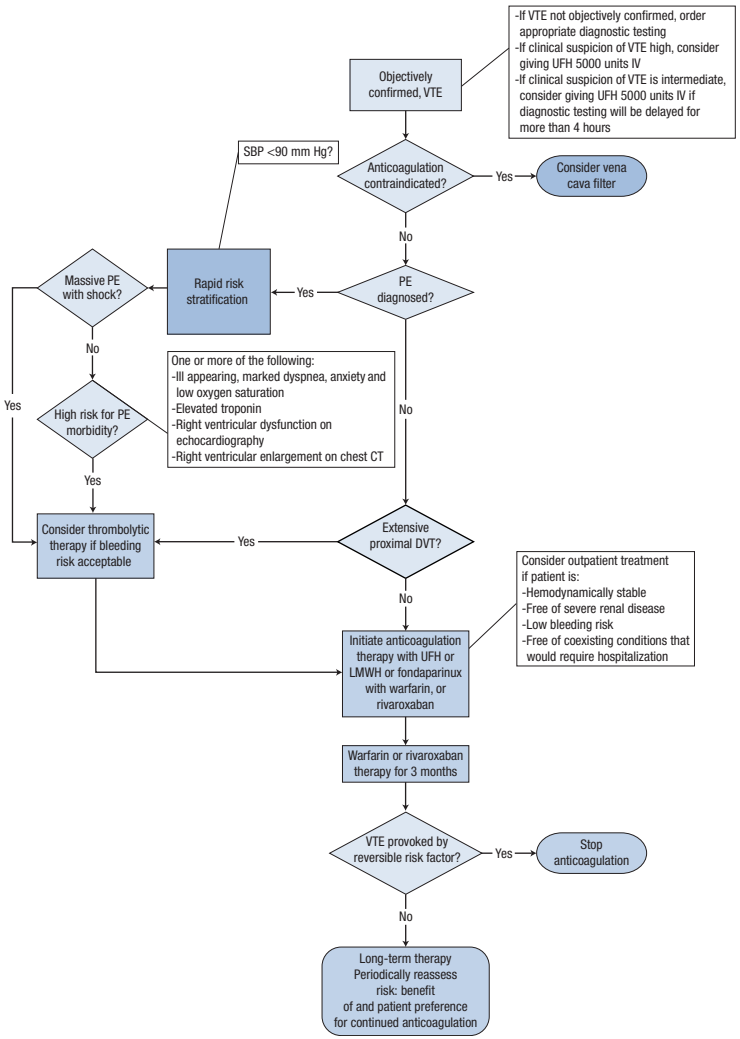


FIGURE 14–2. Treatment of venous thromboembolism (VTE). (CT, computed tomography; DVT, deep vein thrombosis; IV, intravenous; LMWH, low-molecular-weight heparin; PE, pulmonary embolism; SBP, systolic blood pressure; UFH, unfractionated heparin.)

(eg, 5000-unit bolus followed by 1000-units/h continuous infusion) produces similar clinical outcomes.

- Weight-based subcutaneous (SC) UFH (initial dose 333 units/kg SC followed by 250 units/kg every 12 hours) without coagulation monitoring is a less costly option for select patients; warfarin therapy is overlapped for at least 5 days and continued after UFH is discontinued.
- The activated partial thromboplastin time (aPTT) with a therapeutic range of 1.5 to 2.5 times the mean normal control value is generally used to determine the degree

TABLE 14–1 Weight-Based[a] Dosing for Unfractionated Heparin Administered by Continuous IV Infusion

Indication	Initial Loading Dose	Initial Infusion Rate
Deep vein thrombosis (DVT)/pulmonary embolism (PE)	80–100 units/kg Maximum = 10,000 units	17–20 units/kg/h Maximum = 2300 units/h
Activated Partial Thromboplastin Time (seconds)	**Maintenance Infusion Rate** ***Dose Adjustment***	
<37 (or anti–factor Xa <0.20 U/mL [<0.20 kU/L])	80 units/kg bolus, then increase infusion by 4 units/kg/h	
37–47 (or anti–factor Xa 0.20–0.29 U/mL [0.20–0.29 kU/L])	40 units/kg bolus, then increase infusion by 2 units/kg/h	
48–71 (or anti–factor Xa 0.30–0.70 U/mL [0.30–0.70 kU/L])	No change	
72–93 (or anti–factor Xa 0.71–1.00 U/mL [0.71–1.00 kU/L])	Decrease infusion by 2 units/kg/h	
>93 (or anti–factor Xa >1.00 U/mL [>1.00 kU/L])	Hold infusion for 1 h, then decrease by 3 units/kg/h	

[a]Use actual body weight for all calculations. Adjusted body weight may be used for obese patients (>130% of ideal body weight).

of therapeutic anticoagulation. Measure aPTT prior to initiation of therapy and 6 hours after the start of therapy or a dose change. Adjust the heparin dose promptly based on patient response.

- Bleeding is the primary adverse effect associated with anticoagulant drugs. The most common bleeding sites include the gastrointestinal (GI) tract, urinary tract, and soft tissues. Critical areas include intracranial, pericardial, and intraocular sites, and adrenal glands. Symptoms of bleeding include severe headache, joint pain, chest pain, abdominal pain, swelling, tarry stools, hematuria, or the passing of bright red blood through the rectum. Minor bleeding occurs frequently (eg, epistaxis, gingival bleeding, prolonged bleeding from cuts, bruising from minor trauma).
- If major bleeding occurs, discontinue UFH immediately and give IV **protamine sulfate** by slow IV infusion over 10 minutes (1 mg/100 units of UFH infused during the previous 4 hours; maximum 50 mg).
- Heparin-induced thrombocytopenia (HIT) is a serious immune-mediated problem that requires immediate intervention. Thrombocytopenia is the most common clinical manifestation, but serologic confirmation of heparin antibodies is required for making the diagnosis. Use of a clinical prediction rule, such as the four Ts score (*T*hrombocytopenia, *T*iming of platelet count fall or thrombosis, *T*hrombosis, o*T*her explanation for thrombocytopenia), can improve the value of platelet count monitoring and heparin antibody testing in predicting HIT. Discontinue all heparin if new thrombosis occurs in the setting of falling platelets in conjunction with a moderate or high four Ts score. Then initiate alternative anticoagulation with a parenteral direct thrombin inhibitor.
- Long-term UFH has been reported to cause alopecia, priapism, hyperkalemia, and osteoporosis.

Low-Molecular-Weight Heparin

- Advantages of LMWHs over UFH include: (1) predictable anticoagulation dose response, (2) improved SC bioavailability, (3) dose-independent clearance, (4) longer biologic half-life, (5) lower incidence of thrombocytopenia, and (6) less need for routine laboratory monitoring.
- LMWH given SC in fixed or weight-based doses is at least as effective as UFH given IV for VTE treatment. Efficacy and safety are similar with inpatient or outpatient

LMWH administration, once- or twice-daily dosing, and use of different LMWH preparations.

- Stable DVT patients who have normal vital signs, low bleeding risk, and no other comorbid conditions requiring hospitalization can be discharged early or treated entirely on an outpatient basis. Some patients with PE may also be managed safely as outpatients with LMWH or fondaparinux. Patients who are unsuitable candidates for outpatient treatment should be hospitalized.
- Recommended doses (based on actual body weight) of LMWH for treatment of DVT with or without PE include the following:
  - ✓ **Enoxaparin** (Lovenox): 1 mg/kg SC every 12 hours or 1.5 mg/kg every 24 hours
  - ✓ **Dalteparin** (Fragmin): 100 units/kg every 12 hours or 200 units/kg every 24 hours (not approved by the U.S. FDA [Food and Drug administration] for this indication)
  - ✓ **Tinzaparin** (Innohep): 175 units/kg SC every 24 hours
- Acute treatment with LMWH can be transitioned to long-term warfarin after 5 to 10 days.
- Because LMWH anticoagulant response is predictable when given SC, routine laboratory monitoring is unnecessary. Prior to initiating therapy, obtain a baseline complete blood cell count (CBC) with platelet count and serum creatinine. Check the CBC every 5 to 10 days during the first 2 weeks of LMWH therapy and every 2 to 4 weeks thereafter to monitor for occult bleeding. Measuring anti–factor Xa activity is the most widely used method to monitor LMWH; routine measurement is unnecessary in stable and uncomplicated patients.
- As with other anticoagulants, bleeding is the most common adverse effect of LMWH therapy, but major bleeding may be less common than with UFH. If major bleeding occurs, administer **protamine sulfate** IV, although it cannot neutralize the anticoagulant effect completely. The recommended dose of protamine sulfate is 1 mg per 1 mg of enoxaparin or 1 mg per 100 anti–factor Xa units of dalteparin or tinzaparin administered in the previous 8 hours. A second dose of 0.5 mg per 1 mg or 100 anti–factor Xa units can be given if bleeding continues. Smaller protamine doses can be used if the LMWH dose was given in the previous 8 to 12 hours. Protamine sulfate is not recommended if the LMWH was given more than 12 hours earlier.
- Thrombocytopenia can occur with LMWHs, but the incidence of HIT is three times lower than with UFH.

Fondaparinux

- **Fondaparinux sodium** (Arixtra) prevents thrombus generation and clot formation by indirectly inhibiting factor Xa activity through its interaction with antithrombin. It is approved for prevention of VTE following orthopedic (hip fracture, hip and knee replacement) or abdominal surgery and for the treatment of DVT and PE (in conjunction with warfarin).
- Fondaparinux is a safe and effective alternative to LMWH for treatment of DVT or PE.
- Fondaparinux is dosed once daily via weight-based subcutaneous injection: 5 mg if less than 50 kg, 7.5 mg if 50 to 100 kg, and 10 mg if greater than 100 kg. Fondaparinux is contraindicated if creatinine clearance is less than 30 mL/min (<0.5 mL/s).
- For VTE prevention, the dose is 2.5 mg SC once daily starting 6 to 8 hours after surgery.
- Patients receiving fondaparinux do not require routine coagulation testing. Measure CBC at baseline and periodically thereafter to detect occult bleeding. Monitor for signs and symptoms of bleeding daily. There is no specific antidote to reverse the antithrombotic activity of fondaparinux.

Direct Anti-Xa Inhibitors

- **Rivaroxaban** (Xarelto) and **apixaban** (Eliquis) are selective inhibitors of both free and clot-bound factor Xa that do not require antithrombin to exert their anticoagulant effect.
- Neither agent is FDA approved for VTE treatment in the United States, but rivaroxaban is approved for prevention of VTE following hip or knee replacement surgery; the

rivaroxaban dose is 10 mg orally once daily with or without food. Rivaroxaban should be initiated at least 6 to 10 hours after surgery once hemostasis has been established and continued for 12 days (knee replacement) or 35 days (hip replacement).

- Routine laboratory monitoring and dose adjustment are not required because of predictable pharmacokinetics. Bleeding is the most common adverse effect; patients should be observed closely for signs or symptoms of blood loss.

Warfarin

- **Warfarin** inhibits enzymes responsible for cyclic interconversion of vitamin K in the liver. Reduced vitamin K is a cofactor required for the carboxylation of the vitamin K–dependent coagulation proteins prothrombin (II); factors VII, IX, and X; and the endogenous anticoagulant proteins C and S. By reducing the supply of vitamin K, warfarin indirectly slows their rate of synthesis. By suppressing the production of clotting factors, warfarin prevents initial formation and propagation of thrombi. Warfarin has no direct effect on previously circulating clotting factors or previously formed thrombi. The time required to achieve its anticoagulant effect depends on the elimination half-lives of the coagulation proteins. Because prothrombin has a 2- to 3-day half-life, warfarin's full antithrombotic effect is not achieved for 8 to 15 days after initiation of therapy.
- Start warfarin concurrently with UFH or LMWH therapy. For patients with acute VTE, UFH, LMWH, or fondaparinux should be overlapped for at least 5 days, regardless of whether the target international normalized ratio (INR) was achieved earlier. The UFH or LMWH can then be discontinued once the INR is within the desired range for 2 consecutive days.
- Guidelines for initiating warfarin therapy are given in **Fig. 14–3**. The usual initial dose is 5 to 10 mg. Lower starting doses may be acceptable based on patient factors such as advanced age, malnutrition, liver disease, or heart failure. Starting doses greater than 10 mg should be avoided.
- Monitor warfarin therapy by the INR; for most indications, the target INR is 2.5, with an acceptable range of 2 to 3. After an acute thromboembolic event, measure the INR at least every 3 days during the first week of therapy. In general, do not make dose changes more frequently than every 3 days. Adjust doses by calculating the weekly dose and reducing or increasing it by 5% to 25%. The full effect of a dose changes may not become evident for 5 to 7 days. Once the patient's dose response is established, obtain an INR every 7 to 14 days until it stabilizes, then every 4 to 8 weeks thereafter.
- Hemorrhagic complications ranging from mild to severe and life-threatening can occur at any body site. The GI tract and nose are the most frequent sites of bleeding. Intracranial hemorrhage is the most serious complication and often results in permanent disability and death.
- Management of bleeding and excessive anticoagulation:
  - ✓ Most patients with asymptomatic INR elevations can be safely managed by withholding warfarin alone.
  - ✓ When the INR is greater than 4.5 without evidence of bleeding, the INR can be lowered by withholding warfarin, adjusting the dose of warfarin, and providing vitamin K to shorten the time to return to normal INR.
  - ✓ If the INR is 5 to 9, warfarin doses may be withheld or may be combined with a low dose of **oral phytonadione** (≤2.5 mg).
  - ✓ If the INR is between 4.5 and 10 without bleeding, routine use of vitamin K is not recommended because it has not been shown to affect the risk of developing subsequent bleeding or thromboembolism compared to simply withholding warfarin alone.
  - ✓ For INR is greater than 10 without evidence of bleeding, giving oral phytonadione 2.5 mg is suggested.
  - ✓ Use vitamin K with caution in patients at high risk of recurrent thromboembolism because of the possibility of INR overcorrection.
  - ✓ Patients with warfarin-associated major bleeding require supportive care and repletion of coagulation factors; 5 to 10 mg of vitamin K should be administered via slow IV injection.

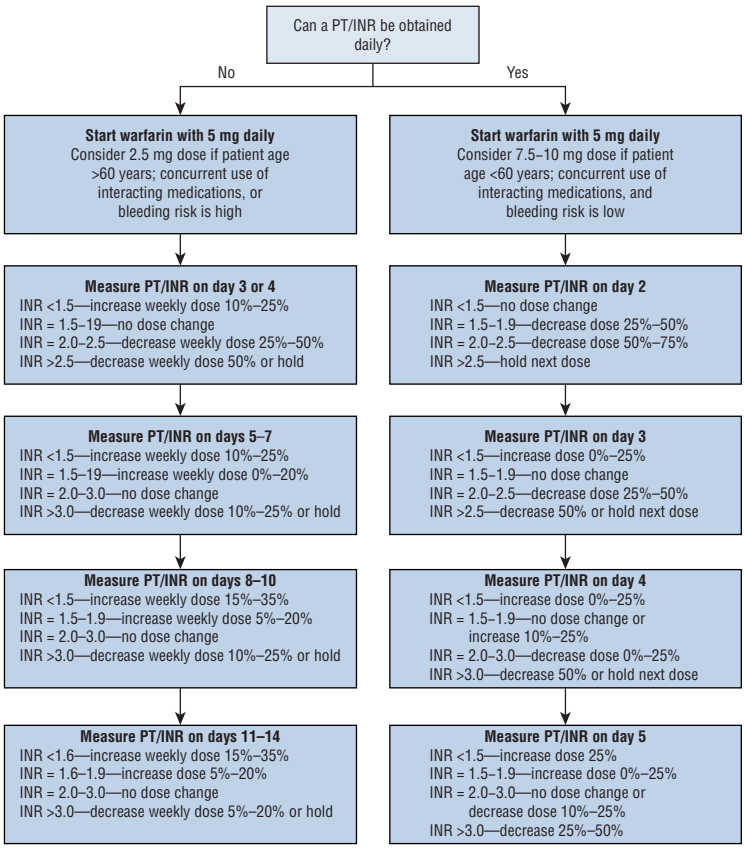


FIGURE 14–3. Initiation of warfarin therapy. (INR, international normalized ratio; PT, prothrombin time.)

- Nonhemorrhagic adverse effects of warfarin include the rare "purple toe" syndrome and skin necrosis.
- Because of the large number of food–drug and drug–drug interactions with warfarin, close monitoring and additional INR determinations may be indicated whenever other medications are initiated, or discontinued, or an alteration in consumption of vitamin K–containing foods is noted.

Thrombolytics

- Thrombolytic agents are proteolytic enzymes that enhance conversion of plasminogen to plasmin, which subsequently degrades the fibrin matrix.
- Removal of the occluding thrombus by fibrinolytic therapy (or surgical means) is rarely warranted. Patients who present within 14 days of symptom onset with extensive proximal DVT, good functional status, low bleeding risk, and a life expectancy of a year or more are candidates for thrombolysis.
- Patients with DVT that involves the iliac and common femoral veins are at highest risk for postthrombotic syndrome and may have the greatest potential to benefit from thrombus removal strategies.

- The risk of bleeding associated with catheter-directed drug administration appears to be less than systemic administration. For DVT, catheter-directed thrombolysis is preferred if appropriate expertise and resources are available. The same duration and intensity of anticoagulation therapy is recommended as for DVT patients who do not receive thrombolysis.
- For patients with massive PE manifested by shock and cardiovascular collapse (~5% of patients with PE), thrombolytic therapy is considered necessary in addition to aggressive interventions such as volume expansion, vasopressor therapy, intubation, and mechanical ventilation. Administer thrombolytic therapy in these patients without delay to reduce the risk of progression to multisystem organ failure and death. However, the risk of death from PE should outweigh the risk of serious bleeding associated with thrombolytic therapy.
- Dosage regimens of thrombolytic agents for treatment of DVT and/or PE:
  - ✓ **Alteplase** (Activase): For PE, 100 mg by IV infusion over 2 hours
  - ✓ **Streptokinase** (Streptase): 250,000 units IV over 30 minutes, followed by a continuous IV infusion of 100,000 units/h for 24 hours (PE) or 24 to 72 hours (DVT)
  - ✓ **Urokinase** (Abbokinase): For PE, 4400 IU/kg IV over 10 minutes, followed by 4400 IU/kg/h for 12 to 24 hours
- During thrombolytic therapy, IV UFH may be either continued or suspended; the most common practice in the United States is to suspend UFH. Measure the aPTT after completion of thrombolytic therapy. If the aPTT at that time is shorter than 80 seconds, start UFH infusion and adjust to maintain the aPTT in the therapeutic range. If the posttreatment aPTT is longer than 80 seconds, remeasure it every 2 to 4 hours and start a UFH infusion when the aPTT is shorter than 80 seconds.

PREVENTION

- Nonpharmacologic methods improve venous blood flow by mechanical means and include early ambulation, graduated compression stockings, IPC devices, and inferior vena cava filters.
- Pharmacologic options inhibit clotting factor activity or production. Appropriately selected therapy can significantly reduce the incidence of VTE after hip and knee replacement, hip fracture repair, general surgery, myocardial infarction, ischemic stroke, and in appropriately selected hospitalized medical patients.
- Refer to *Antithrombotic Therapy and Prevention of Thrombosis, 9th edition: Evidence-Based Clinical Practice Guidelines* published by the American College of Chest Physicians for detailed information on prophylaxis strategies based on the clinical situation and level of risk for VTE.

EVALUATION OF THERAPEUTIC OUTCOMES

- Monitor patients for resolution of symptoms, development of recurrent thrombosis, symptoms of the postthrombotic syndrome, and adverse effects from anticoagulants.
- Monitor hemoglobin, hematocrit, and blood pressure carefully to detect bleeding from anticoagulant therapy.
- Perform coagulation tests (aPTT, PT, and INR) prior to initiating therapy to establish the patient's baseline values and guide later anticoagulation.
- Ask outpatients taking warfarin about medication adherence and symptoms related to bleeding and thromboembolic complications. Any changes in concurrent medications should be carefully explored.

See Chapter 9, Venous Thromboembolism, authored by Daniel M. Witt and Nathan P. Clark for a more detailed discussion of this topic.

This page intentionally left blank

CHAPTER 15

Acne Vulgaris

- *Acne* is a common, usually self-limiting disease involving inflammation of the sebaceous follicles of the face and upper trunk.

PATHOPHYSIOLOGY

- Acne usually begins in the prepubertal period and progresses as androgen production and sebaceous gland activity increase with gonad development.
- Acne progresses through four stages: (1) increased follicular keratinization, (2) increased sebum production, (3) bacterial lipolysis of sebum triglycerides to free fatty acids, and (4) inflammation.
- Circulating androgens cause sebaceous glands to increase their size and activity. There is increased keratinization of epidermal cells and development of an obstructed sebaceous follicle, called a *microcomedone*. Cells adhere to each other, forming a dense keratinous plug. Sebum, produced in increasing amounts, becomes trapped behind the keratin plug and solidifies, contributing to open or closed comedone formation.
- Pooling of sebum in the follicle facilitates proliferation of the anaerobic bacterium *Propionibacterium acnes*, which generates a T-cell response resulting in inflammation. *P. acnes* produces a lipase that hydrolyzes sebum triglycerides into free fatty acids that may increase keratinization and lead to microcomedone formation.
- The closed comedone (whitehead) is the first visible lesion of acne. It is almost completely obstructed to drainage and has a tendency to rupture.
- An open comedone (blackhead) is formed as the plug extends to the upper canal and dilates its opening. Acne characterized by open and closed comedones is termed *noninflammatory acne*.
- Pus formation occurs due to recruitment of neutrophils into the follicle during the inflammatory process and release of *P. acnes*–generated chemokines. *P. acnes* also produces enzymes that increase permeability of the follicular wall, causing it to rupture, thereby releasing keratin, lipids, and irritating free fatty acids into the dermis. Inflammatory lesions that may form and lead to scarring include pustules, nodules, and cysts.

CLINICAL PRESENTATION

- Lesions usually occur on the face, back, upper chest, and shoulders. Severity varies from a mild comedonal form to severe inflammatory acne. The disease is categorized as mild, moderate, or severe, depending on the type and severity of lesions.
- Lesions may take months to heal completely, and fibrosis associated with healing may lead to permanent scarring.

DIAGNOSIS

- Diagnosis is established by patient assessment, which includes observation of lesions and excluding other potential causes (eg, drug-induced acne). Several different systems are in use to grade acne severity.

TREATMENT

- Goals of Treatment: The goals are to reduce the number and severity of lesions, slow disease progression, limit disease duration, prevent formation of new lesions, and prevent scarring and hyperpigmentation.

GENERAL APPROACH (FIG. 15–1)

- 2009 Global Alliance to Improve Outcomes in Acne consensus statements:

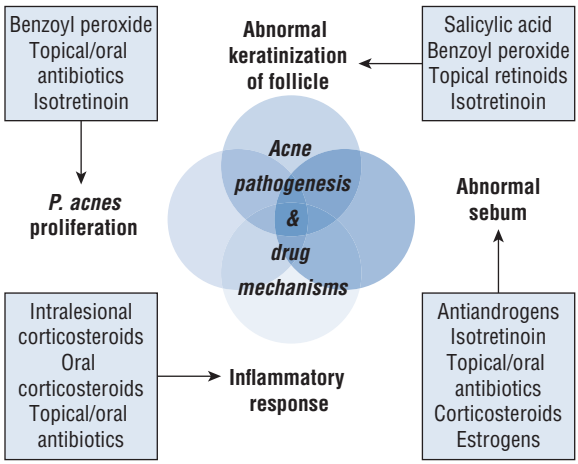
✓ Acne should be approached as a chronic disease.
✓ Strategies to limit antibiotic resistance are important in acne management.
✓ Combination retinoid-based therapy is first-line therapy.
✓ Topical retinoids should be first-line agents in maintenance therapy.
✓ Early, appropriate treatment is best to minimize potential for acne scars.
✓ Adherence should be assessed via verbal interview or use of a simple tool.

NONPHARMACOLOGIC THERAPY

- Encourage patients to avoid aggravating factors, maintain a balanced diet, and control stress.
- Patients should wash no more than twice daily with a mild, nonfragranced opaque or glycerin soap or a soapless cleanser. Scrubbing should be minimized to prevent follicular rupture.
- Comedone extraction results in immediate cosmetic improvement but has not been widely tested in clinical trials.

PHARMACOLOGIC THERAPY

- *Comedonal noninflammatory acne*: Select topical agents that target the increased keratinization by producing exfoliation. Topical retinoids (especially adapalene) are drugs of choice. Benzoyl peroxide or azelaic acid can be considered.
- *Mild to moderate papulopustular inflammatory acne*: It is important to reduce the population of *P. acnes*. Either the fixed-dose combination of adapalene and benzoyl peroxide or the fixed-dose combination of topical clindamycin and benzoyl peroxide is first choice therapy. As alternatives, a different topical retinoid used with a different topical antimicrobial agent could be used, with or without benzoyl peroxide. Azelaic acid or benzoyl peroxide can also be recommended.



© Debra Sibbald

FIGURE 15–1. Acne pathogenesis and drug mechanisms.

In more widespread disease, combination of a systemic antibiotic with adapalene is recommended for moderate papulopustular acne. If there are limitations in use of first-choice agents, alternatives include fixed-dose combination of erythromycin and tretinoin, fixed-dose combination of isotretinoin and erythromycin, or oral zinc. In cases of widespread disease, a combination of a systemic antibiotic with either benzoyl peroxide or adapalene in fixed combination with benzoyl peroxide can be considered.

- *Severe papulopustular or moderate nodular acne*: Oral isotretinoin monotherapy is first choice. Alternatives include systemic antibiotics in combination with adapalene, with the fixed-dose combination of adapalene and benzoyl peroxide or in combination with azelaic acid. If there are limitations to use of these agents, consider oral antiandrogens in combination with oral antibiotics or topical treatments, or systemic antibiotics in combination with benzoyl peroxide.
- *Nodular or conglobate acne*: Monotherapy with oral isotretinoin is first choice. An alternative is systemic antibiotics in combination with azelaic acid. If limitations exist to these agents, consider oral antiandrogens in combination with oral antibiotics, systemic antibiotics in combination with adapalene, benzoyl peroxide, or the adapalene-benzoyl peroxide fixed-dose combination.
- *Maintenance therapy for acne*: Topical retinoids are most commonly recommended (adapalene, tazarotene, or tretinoin). Topical azelaic acid is an alternative. Maintenance is usually begun after a 12-week induction period and continues for 3 to 4 months. A longer duration may be necessary to prevent relapse upon discontinuation. Long-term therapy with antibiotics is not recommended to minimize antibiotic resistance.

Exfoliants (Peeling Agents)

- Exfoliants induce continuous mild drying and peeling by irritation, damaging superficial skin layers and inciting inflammation. This stimulates mitosis, thickening the epidermis and increasing horny cells, scaling, and erythema. Decreased sweating results in a dry, less oily surface and may resolve pustular lesions.
- **Resorcinol** is less keratolytic than salicylic acid and, when used alone, is classified as the Food and Drug Administration (FDA) category II (not generally recognized as safe and effective). The FDA considers resorcinol 2% and resorcinol monoacetate 3% to be safe and effective when used in combination with sulfur 3% to 8%. Resorcinol is an irritant and sensitizer and should not be applied to large areas or on broken skin. It produces a reversible dark brown scale on some dark-skinned individuals.
- **Salicylic acid** is keratolytic, has mild antibacterial activity against *P. acnes*, and offers slight antiinflammatory activity at concentrations up to 5%. Salicylic acid is recognized by the FDA as safe and effective, but it may be less potent than benzoyl peroxide or topical retinoids. Salicylic acid products are often used as first-line therapy for mild acne because of their availability in concentrations up to 2% without a prescription. Concentrations of 5% to 10% can also be used by prescription, beginning with a low concentration and increasing as tolerance develops to the irritation. Salicylic acid is often used when patients cannot tolerate topical retinoids because of skin irritation.
- **Sulfur** is keratolytic and has antibacterial activity. It can quickly resolve pustules and papules, mask lesions, and produce irritation that leads to skin peeling. Sulfur is used in the precipitated or colloidal form in concentrations of 2% to 10%. Although it is often combined with salicylic acid or resorcinol to increase effect, use is limited by offensive odor and availability of more effective agents.

Topical Retinoids

- Retinoids reduce obstruction within the follicle and are useful for both comedonal and inflammatory acne. They reverse abnormal keratinocyte desquamation and are active keratolytics. They inhibit microcomedone formation, decreasing the number of mature comedones and inflammatory lesions.

- Topical retinoids are safe, effective, and economical for treating all but the most severe cases of acne. They should be the first step in moderate acne, alone or in combination with antibiotics and benzoyl peroxide, reverting to retinoids alone for maintenance once adequate results are achieved. Side effects include erythema, xerosis, burning, and peeling.
- Retinoids should be applied at night, a half hour after cleansing, starting with every other night for 1 to 2 weeks to adjust to irritation. Doses can be increased only after beginning with 4 to 6 weeks of the lowest concentration and least irritating vehicle.
- **Tretinoin** (retinoic acid and vitamin A acid) is available as 0.05% solution (most irritating); 0.01% and 0.025% gels; and 0.025%, 0.05%, and 0.1% creams (least irritating). Tretinoin should not be used in pregnant women because of risk to the fetus.
- **Adapalene** (Differin) is the topical retinoid of first choice for both treatment and maintenance therapy because it is as effective but less irritating than other topical retinoids. Adapalene is available as 0.1% gel, cream, alcoholic solution, and pledgets. A 0.3% gel formulation is also available.
- **Tazarotene** (Tazorac) is as effective as adapalene in reducing noninflammatory and inflammatory lesion counts when applied half as frequently. Compared with tretinoin, it is as effective for comedonal and more effective for inflammatory lesions when applied once daily. The product is available as a 0.05% and 0.1% gel or cream.

Topical Antibacterial Agents

- **Benzoyl peroxide** is bactericidal and also suppresses sebum production and reduces free fatty acids, which are comedogenic and inflammatory triggers. It is useful for both noninflammatory and inflammatory acne. It has a rapid onset and may decrease the number of inflamed lesions within 5 days. Used alone or in combination, benzoyl peroxide is the standard of care for mild to moderate papulopustular acne. It is often combined with topical retinoids or an antimicrobial. For maintenance therapy, benzoyl peroxide can be added to a topical retinoid.
- Soaps, lotions, creams, washes, and gels are available in concentrations of 1% to 10%. All single-agent preparations are available without prescription. Gel formulations are usually most potent, whereas lotions, creams, and soaps have weaker potency. Alcohol-based gel preparations generally cause more dryness and irritation.
- Therapy should be initiated with the weakest concentration (2.5%) in a water-based formulation or the 4% hydrophase gel. Once tolerance is achieved, the strength may be increased to 5% or the base changed to the acetone or alcohol gels, or to paste. It is important to wash the product off in the morning. A sunscreen should be applied during the day.
- Side effects of benzoyl peroxide include dryness, irritation, and, rarely, allergic contact dermatitis. It may bleach hair and clothing.
- **Topical erythromycin** and **clindamycin** have become less effective due to resistance by *P. acnes*. Addition of benzoyl peroxide or topical retinoids to the macrolide is more effective than antibiotic monotherapy. Clindamycin is preferred because of potent action and lack of systemic absorption. It is available as a single-ingredient topical preparation or in combination with benzoyl peroxide. Erythromycin is available alone and in combination with retinoic acid or benzoyl peroxide.
- **Azelaic acid** (Azelex) has antibacterial, antiinflammatory, and comedolytic activity. It is used for mild to moderate inflammatory acne but has limited efficacy compared with other therapies. It is an alternative to topical retinoids for maintenance therapy. Azelaic acid is well tolerated, with adverse effects of pruritus, burning, stinging, and tingling occurring in 1% to 5% of patients. Erythema, dryness, peeling, and irritation occur in fewer than 1% of patients. Azelaic acid is available in 20% cream and 15% gel formulations, which are usually applied twice daily (morning and evening) on clean, dry skin. Most patients experience improvement within 4 weeks, but treatment may be continued over several months if necessary.
- **Dapsone** 5% topical gel (Aczone) is a sulfone that has anti-inflammatory and antibacterial properties that improve both inflammatory and noninflammatory acne.

It may be useful for patients with sensitivities or intolerance to conventional antiacne agents and may be used in sulfonamide-allergic patients. Topical dapsone 5% gel has been used alone or in combination with adapalene or benzoyl peroxide but may be more irritating than other topical agents.

Oral Antibacterials

- Systemic antibiotics are standard therapy for moderate and severe acne and treatment-resistant inflammatory acne. Because of increasing bacterial resistance, patients with less severe forms should not be treated with oral antibiotics, and where possible duration of therapy should be limited (eg, 6–8 weeks).
- **Erythromycin** is effective, but because of bacterial resistance, its use should be limited to patients who cannot use a tetracycline derivative (eg, pregnant women and children <8 years old). **Ciprofloxacin**, **trimethoprim-sulfamethoxazole**, and **trimethoprim** alone are also effective in cases where other antibiotics cannot be used or are ineffective.
- **Tetracyclines** (**minocycline** and **doxycycline)** have antibacterial and anti-inflammatory effects. Tetracycline itself is no longer the drug of choice in this family due to diet-related effects on absorption and lower antibacterial and anti-inflammatory efficacy. Minocycline has been associated with pigment deposition in the skin, mucous membranes, and teeth; it may also cause dose-related dizziness, urticaria, hypersensitivity syndrome, autoimmune hepatitis, a systemic lupus erythematosus–like syndrome, and serum sickness–like reactions. Doxycycline is a photosensitizer, especially at higher doses.

Antisebum Agents

- **Isotretinoin** decreases sebum production, inhibits *P. acnes* growth, and reduces inflammation. It is approved for treatment of severe recalcitrant nodular acne. It is also useful for less severe acne that is treatment resistant or that produces either physical or psychological scarring. Isotretinoin is the only drug treatment for acne that produces prolonged remission.
- The approved dose is 0.5 to 2 mg/kg/day, usually given over a 20-week course. Drug absorption is greater when taken with food. Initial flaring can be minimized by starting with 0.5 mg/kg/day or less. Alternatively, lower doses can be used for longer periods, with a total cumulative dose of 120 to 150 mg/kg.
- Adverse effects are frequent and often dose related. Approximately 90% of patients experience mucocutaneous effects; drying of the mouth, nose, and eyes is most common. Cheilitis and skin desquamation occur in more than 80% of patients. Systemic effects include transient increases in serum cholesterol and triglycerides, increased creatine kinase, hyperglycemia, photosensitivity, pseudotumor cerebri, abnormal liver injury tests, bone abnormalities, arthralgias, muscle stiffness, headache, and a high incidence of teratogenicity. Patients should be counseled about and screened for depression during therapy, although a causal relationship to isotretinoin therapy is controversial.
- Because of teratogenicity, two different forms of contraception must be started in female patients of childbearing potential beginning 1 month before therapy, continuing throughout treatment, and for up to 4 months after discontinuation of therapy. All patients receiving isotretinoin must participate in the iPLEDGE program, which requires pregnancy tests and assurances by prescribers and pharmacists that they will follow required procedures.
- **Oral contraceptives** containing estrogen can be useful for acne in some women. Agents with FDA approval for this indication include **norgestimate with ethinyl estradiol** and **norethindrone acetate with ethinyl estradiol**; other estrogen-containing products may also be effective.
- **Spironolactone** in higher doses is an antiandrogenic compound. Doses of 50 to 200 mg have been shown to be effective in acne.
- **Cyproterone acetate** is an antiandrogen that may be effective for acne in females when combined with ethinyl estradiol (in the form of an oral contraceptive). No

cyproterone/estrogen–containing oral contraceptives are available in the United States.

- **Oral corticosteroids** in high doses used for short courses may be of temporary benefit in patients with severe inflammatory acne.

EVALUATION OF THERAPEUTIC OUTCOMES

- Provide patients with acne with a monitoring framework that includes specific parameters and frequency of monitoring. They should record the objective response to treatment in a diary. Contact patients within 2 to 3 weeks after the start of therapy to assess progress.
- Lesion counts should decrease by 10% to 15% within 4 to 8 weeks or by more than 50% within 2 to 4 months. Inflammatory lesions should resolve within a few weeks, and comedones should resolve by 3 to 4 months. If anxiety or depression is present at the outset, control or improvement should be achieved within 2 to 4 months.
- Long-term parameters should include no progression of severity, lengthening of acne-free periods throughout therapy, and no further scarring or pigmentation throughout therapy.
- Monitor patients regularly for adverse treatment effects, with appropriate dose reduction, alternative treatments, or drug discontinuation considered if these effects become intolerable.

See Chapter 77, Acne Vulgaris, authored by Debra J. Sibbald, for a more detailed discussion of this topic.

CHAPTER 16

Dermatologic Drug Reactions and Common Skin Conditions

- *Drug-induced skin reactions* can be irritant or allergic. Allergic drug reactions are classified into exanthematous, urticarial, blistering, and pustular eruptions. Skin disorders discussed include contact dermatitis, diaper dermatitis, and atopic dermatitis.

PATHOPHYSIOLOGY (FIG. 16–1)

- **Exanthematous** drug reactions include maculopapular rashes and drug hypersensitivity syndrome. **Urticarial** reactions include urticaria, angioedema, and serum sickness-like reactions. **Blistering** reactions include fixed drug eruptions, Stevens–Johnson syndrome, and toxic epidermal necrolysis. **Pustular** eruptions include acneiform drug reactions and acute generalized exanthematous pustulosis (AGEP) (**Fig. 16–1**).
- Drug-induced **hyperpigmentation** may be related to increased melanin (eg, hydantoins), direct deposition (eg, silver, mercury, tetracyclines, and antimalarials), or other mechanisms (eg, fluorouracil).
- Drug-induced photosensitivity reactions may be **phototoxic** (a nonimmunologic reaction) or **photoallergic** (an immunologic reaction). Medications associated with phototoxicity include amiodarone, tetracyclines, sulfonamides, psoralens, and coal tar. Common causes of photoallergic reactions include sulfonamides, sulfonylureas, thiazides, nonsteroidal antiinflammatory drugs (NSAIDs), chloroquine, and carbamazepine.
- **Contact dermatitis** is skin inflammation caused by irritants or allergic sensitizers. In **allergic contact dermatitis (ACD)**, an antigenic substance triggers an immunologic response, sometimes several days later. **Irritant contact dermatitis (ICD)** is caused by an organic substance that usually results in a reaction within a few hours of exposure.
- **Diaper dermatitis** (diaper rash) is an acute, inflammatory dermatitis of the buttocks, genitalia, and perineal region. It is a type of contact dermatitis resulting from direct fecal and moisture contact with the skin in an occlusive environment.
- **Atopic dermatitis** is an inflammatory condition with genetic, environmental, and immunologic mechanisms. Neuropeptides, irritation, or pruritus-induced scratching may cause release of proinflammatory cytokines from keratinocytes.

CLINICAL PRESENTATION

- **Maculopapular skin reaction** presents with erythematous macules and papules that may be pruritic. Lesions usually begin within 7 to 10 days after starting the offending medication and generally resolve within 7 to 14 days after drug discontinuation. Lesions may spread and become confluent. Common culprits include penicillins, cephalosporins, sulfonamides, and some anticonvulsants.
- **Drug hypersensitivity syndrome** is an exanthematous eruption accompanied by fever, lymphadenopathy, and multiorgan involvement (kidneys, liver, lung, bone marrow, heart, and brain). Signs and symptoms begin 1 to 4 weeks after starting the offending drug, and the reaction may be fatal if not promptly treated. Drugs implicated include allopurinol, sulfonamides, some anticonvulsants (barbiturates, phenytoin, carbamazepine, and lamotrigine), and dapsone.
- **Urticaria** and **angioedema** are simple eruptions that are caused by drugs in 5% to 10% of cases. Other causes are foods (most common) and physical factors such as cold or pressure, infections, and latex exposure. Urticaria may be the first sign of an emerging anaphylactic reaction characterized by hives, extremely pruritic red raised wheals, angioedema, and mucous membrane swelling that typically occurs within minutes to hours. Offending drugs include penicillins and related antibiotics, aspirin, sulfonamides, radiograph contrast media, and opioids.

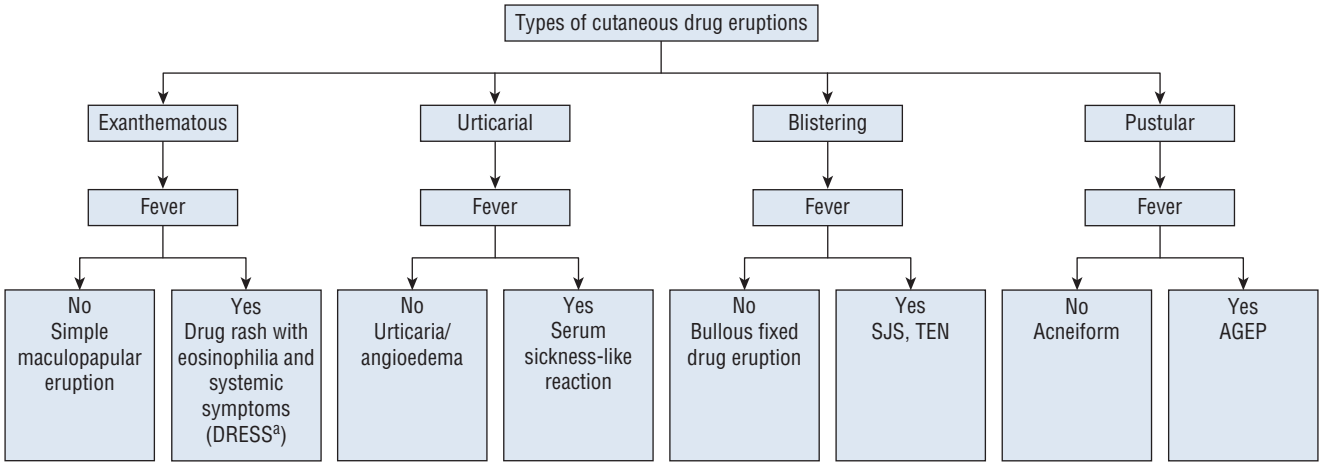


FIGURE 16–1. Types of cutaneous drug eruptions. (DRESS, drug rash with eosinophilia and systemic symptoms; SJS, Stevens-Johnson's syndrome; TEN, toxic epidermal necrolysis; AGEP, acute generalized exanthematous pustulosis.) (Adapted from Knowles S. Drug-induced skin reactions. In: Therapeutic Choices for Minor Ailments, Repchinsky Carol, ed. Ottawa (ON): Canadian Pharmacists Association; ©2013, with permission.)
[a]DRESS is also referred to as hypersensitivity syndrome reaction.

- **Serum sickness-like reactions** are complex urticarial eruptions presenting with fever, rash (usually urticarial), and arthralgias usually within 1 to 3 weeks after starting the offending drug.
- **Fixed drug eruptions** present as pruritic, red, raised lesions that may blister. Symptoms can include burning or stinging. Lesions may evolve into plaques. These so-called fixed eruptions recur in the same area each time the offending drug is given. Lesions appear and disappear within minutes to days, leaving hyperpigmented skin for months. Usual offenders include tetracyclines, barbiturates, sulfonamides, codeine, phenolphthalein, and NSAIDs.
- **Stevens–Johnson syndrome (SJS)** and **toxic epidermal necrolysis (TEN)** are blistering eruptions that are rare but severe and life-threatening. Onset occurs within 7 to 14 days after drug exposure. Patients present with generalized tender/painful bullous formation with fever, headache, and respiratory symptoms leading to rapid clinical deterioration. Lesions show rapid confluence and spread, resulting in extensive epidermal detachment and sloughing. This may result in marked fluid loss, hypotension, electrolyte imbalances, and secondary infections. Usual offending drugs include sulfonamides, penicillins, some anticonvulsants (hydantoins, carbamazepine, barbiturates, and lamotrigine), NSAIDs, and allopurinol.
- **Acneiform drug reactions** are pustular eruptions that induce acne. Onset is within 1 to 3 weeks. Common culprits include corticosteroids, androgenic hormones, some anticonvulsants, isoniazid, and lithium.
- **Acute generalized exanthematous pustulosis (AGEP)** has an acute onset (within days after starting the offending drug), fever, diffuse erythema, and many pustules. Generalized desquamation occurs 2 weeks later. Usual offending drugs include β-lactam antibiotics, macrolides, and calcium channel blockers.
- **Sun-induced skin reactions** appear similar to a sunburn and present with erythema, papules, edema, and sometimes vesicles. They appear in areas exposed to sunlight (eg, ears, nose, cheeks, forearms, and hands).
- **Diaper dermatitis** results in an erythematous rash, and severe cases may have vesicles and oozing erosions. The rash may be infected by *Candida* species and present with confluent red plaques, papules, and pustules.
- **Atopic dermatitis** presents differently depending on age. In infancy, an erythematous, patchy, pruritic, papular skin rash may first appear on the cheeks and chin and progress to red, scaling, oozing lesions. The rash affects the malar region of the cheeks, forehead, scalp, chin, and behind the ears while sparing the nose and paranasal creases. Over several weeks, lesions may spread to extensor surfaces of the lower legs (due to the infant's crawling), and eventually the entire body may be involved except for the diaper area and nose. In childhood, the skin is often dry, flaky, rough, and cracked; scratching may result in bleeding and lichenification. In adulthood, lesions are more diffuse with underlying erythema. The face is commonly involved and may be dry and scaly. Lichenification may be seen.

DIAGNOSIS

- A comprehensive patient history is important to obtain the following information:
  - ✓ Signs and symptoms (onset, progression, timeframe, lesion location and description, presenting symptoms, and previous occurrence
  - ✓ Urgency (severity, area, and extent of skin involvement; signs of a systemic/generalized reaction or disease condition)
  - ✓ Medication history
  - ✓ Differential diagnosis
- Lesion assessment includes identifying macules, papules, nodules, blisters, plaques, and lichenification. Some skin conditions cause more than one type of lesion.
- Inspect lesions for color, texture, size, and temperature. Areas that are oozing, erythematous, and warm to the touch may be infected.

TREATMENT

- Goals of Treatment: Relieve bothersome symptoms, remove precipitating factors, prevent recurrences, avoid adverse treatment effects, and improve quality of life.

DRUG-INDUCED SKIN REACTIONS

- If a drug-induced skin reaction is suspected, the most important treatment is discontinuing the suspected drug as quickly as possible and avoiding use of potential cross-sensitizers.
- The next step is to control symptoms (eg, pruritus). Signs or symptoms of a systemic or generalized reaction may require additional supportive therapy. For high fevers, acetaminophen is more appropriate than aspirin or another NSAID, which may exacerbate some skin lesions.
- Most maculopapular reactions disappear within a few days after discontinuing the agent, so symptomatic control of the affected area is the primary intervention. **Topical corticosteroids** and **oral antihistamines** can relieve pruritus. In severe cases, a short course of **systemic corticosteroids** may be warranted.
- Treatment of fixed drug reactions involves removal of the offending agent. Other therapeutic measures include **topical corticosteroids, oral antihistamines** to relieve itching, and perhaps cool water compresses on the affected area.
- Photosensitivity reactions typically resolve with drug discontinuation. Some patients benefit from **topical corticosteroids** and **oral antihistamines**, but these are relatively ineffective. **Systemic corticosteroids** (eg, **oral prednisone** 1 mg/kg/day tapered over 3 weeks) are more effective.
- For life-threatening SJS/TEN, supportive measures such as maintenance of adequate blood pressure, fluid and electrolyte balance, broad-spectrum antibiotics and vancomycin for secondary infections, and IV immunoglobulin (IVIG) may be appropriate. Corticosteroid use is controversial; if used, employ relatively high doses initially, followed by rapid tapering as soon as disease progression stops.
- Inform patients about the suspected drug, potential drugs to avoid in the future, and which drugs may be used instead. Give patients with photosensitivity reactions information about preventive measures, such as use of sunscreens and sun avoidance.

CONTACT DERMATITIS

- The first intervention involves identification, withdrawal, and avoidance of the offending agent.
- The second treatment is symptomatic relief while decreasing skin lesions. **Cold compresses** help soothe and cleanse the skin; they are applied to wet or oozing lesions, removed, remoistened, and reapplied every few minutes for a 20- to 30-minute period. If affected areas are already dry or hardened, wet dressings applied as soaks (without removal for up to 20–30 min) will soften and hydrate the skin; soaks should not be used on acute exudating lesions. **Calamine lotion** or **Burow solution (aluminum acetate)** may also be soothing.
- **Topical corticosteroids** help resolve the inflammatory process and are the mainstay of treatment. ACD responds better to topical corticosteroids than does ICD. Generally, use higher potency corticosteroids initially, switching to medium or lower potency corticosteroids as the condition improves (see Chap. 17, Table 17–1, for topical corticosteroid potencies).
- **Oatmeal baths** or oral **first-generation antihistamines** may provide relief for excessive itching.
- **Moisturizers** may be used to prevent dryness and skin fissuring.

DIAPER DERMATITIS

- Management involves frequent diaper changes, air drying (removing the diaper for as long as practical), gentle cleansing (preferably with nonsoap cleansers and lukewarm

water), and use of barrier products. **Zinc oxide** has astringent and absorbent properties and provides an effective barrier.

- Candidal (yeast) diaper rash should be treated with a topical antifungal agent and then covered by a barrier product. **Imidazoles** are the treatment of choice. The antifungal agents should be stopped once the rash subsides and the barrier product continued.
- In severe inflammatory diaper rashes, a very low potency topical corticosteroid **(hydrocortisone 0.5%–1%)** may be used for short periods (1–2 week).

ATOPIC DERMATITIS

- Nonpharmacologic measures for infants and children include the following:
  - ✓ Give lukewarm baths
  - ✓ Apply lubricants/moisturizers immediately after bathing
  - ✓ Use scent-free moisturizers liberally each day
  - ✓ Keep fingernails filed short
  - ✓ Select clothing made of soft cotton fabrics
  - ✓ Consider sedating oral antihistamines to reduce scratching at night
  - ✓ Keep the child cool; avoid situations that cause overheating
  - ✓ Learn to recognize skin infections and seek treatment promptly
  - ✓ Identify and remove irritants and allergens
- Topical corticosteroids are the drug treatment of choice. Low-potency agents (eg, **hydrocortisone 1%**) are suitable for the face, and medium-potency products (eg, **betamethasone valerate 0.1%**) may be used for the body. For longer-duration maintenance therapy, low-potency corticosteroids are recommended. Use midstrength and high-potency corticosteroids for short-term management of exacerbations. Reserve ultra-high and high-potency agents (eg, **betamethasone dipropionate 0.05%** and **clobetasone propionate 0.05%**) for short-term treatment (1–2 weeks) of lichenified lesions in adults. After lesions have improved significantly, use a lower-potency corticosteroid for maintenance when necessary. Avoid potent fluorinated corticosteroids on the face, genitalia, and intertriginous areas and in infants.
- The topical immunomodulators **tacrolimus** (Protopic) and **pimecrolimus** (Elidel) inhibit calcineurin, which normally initiates T-cell activation. Both agents are approved for atopic dermatitis in adults and children older than age 2. They can be used on all parts of the body for prolonged periods without producing corticosteroid-induced adverse effects. Tacrolimus ointment 0.03% (for moderate to severe atopic dermatitis in patients ages 2 and older) and 0.1% (for ages 16 and older) is applied twice daily. Pimecrolimus cream 1% is applied twice daily for mild to moderate atopic dermatitis in patients older than age 2. The most common adverse effect is transient burning at the site of application. Both drugs are recommended as second-line treatments due to concerns about a possible risk of cancer. For this reason, sun protection factor (SPF) 30 or higher is recommended on all exposed skin areas.
- Phototherapy may be recommended when the disease is not controlled by calcineurin inhibitors. It may also be steroid sparing, allowing for use of lower-potency corticosteroids, or even eliminating the need for corticosteroids in some cases.
- Coal tar preparations reduce itching and skin inflammation and are available as **crude coal tar** (1%–3%) or **liquor carbonis detergens** (5%–20%). They have been used in combination with topical corticosteroids, as adjuncts to permit effective use of lower corticosteroid strengths, and in conjunction with ultraviolet light therapies. Patients can apply the product at bedtime and wash it off in the morning. Factors limiting coal tar use include its strong odor and staining of clothing. Coal tar preparations should not be used on acute oozing lesions, which would result in stinging and irritation.
- Systemic therapies that have been used (but not FDA approved) for atopic dermatitis include corticosteroids, cyclosporine, interferon-γ, azathioprine, methotrexate, mycophenolate mofetil, IVIG, and biologic response modifiers.

EVALUATION OF THERAPEUTIC OUTCOMES

- Provide patients with information regarding causative factors, avoidance of substances that trigger skin reactions, and potential benefits and limitations of nondrug and drug therapy.
- Evaluate patients with chronic skin conditions periodically to assess disease control, the efficacy of current therapy, and the presence of possible adverse effects.

See Chapter W22, Dermatologic Drug Reactions and Common Skin Conditions, by Rebecca M. Law and David T.S. Law; and Chapter 79, Atopic Dermatitis, by Rebecca M. Law and Po Gin Kwa, for a more detailed discussion of these topics.

CHAPTER 17

Psoriasis

- *Psoriasis* is a chronic inflammatory disease characterized by recurrent exacerbations and remissions of thickened, erythematous, and scaling plaques.

PATHOPHYSIOLOGY

- Cutaneous inflammatory T-cell–mediated activation requires two signals mediated via cell–cell interactions by surface proteins and antigen-presenting cells, such as dendritic cells or macrophages: (1) interaction of the T-cell receptor with antigen, and (2) costimulation, which is mediated through various surface interactions.
- Activated T cells migrate from lymph nodes and the bloodstream into skin and secrete cytokines (eg, interferon-γ, interleukin 2 [IL-2]) that induce pathologic changes. Local keratinocytes and neutrophils produce other cytokines (eg, tumor necrosis factor-α [TNF-α], IL-8). T-cell production and activation results in keratinocyte proliferation.
- There is a significant genetic component. Studies of histocompatibility antigens show associations with human leukocyte antigens (HLA)-Cw6, TNF-α, and IL-3.

CLINICAL PRESENTATION

- Plaque psoriasis (psoriasis vulgaris) is seen in ~90% of psoriasis patients. Lesions are erythematous, red-violet in color, at least 0.5 cm in diameter, well demarcated, and typically covered with silver flaking scales. They may appear as single lesions at predisposed areas (eg, knees and elbows) or generalized over a wide body surface area (BSA).
- Pruritus may be severe and require treatment to minimize excoriations from frequent scratching. Lesions may be physically debilitating or socially isolating.
- Psoriatic arthritis involves both psoriatic lesions and inflammatory arthritis-like symptoms. Distal interphalangeal joints and adjacent nails are most commonly involved, but knees, elbows, wrists, and ankles may be affected.

DIAGNOSIS

- Diagnosis is based on physical examination findings of characteristic lesions. Skin biopsies are not diagnostic of psoriasis.
- Classification of psoriasis as mild, moderate, or severe is based on BSA and Psoriasis Area and Severity Index (PASI) measurements. A 2011 European classification system defines severity of plaque psoriasis as either mild or moderate-to-severe.

TREATMENT

- Goals of Treatment: Minimize or eliminate skin lesions, alleviate pruritus, reduce frequency of flare-ups, treat comorbid conditions, avoid adverse treatment effects, provide cost-effective treatment, provide appropriate counseling (eg, stress reduction), and maintain or improve quality of life.
- See **Figs. 17–1** and **17–2** for psoriasis treatment algorithms based on disease severity.

NONPHARMACOLOGIC THERAPY

- Stress reduction using guided imagery and stress management can improve extent and severity of psoriasis.
- Nonmedicated moisturizers help maintain skin moisture, reduce skin shedding, control scaling, and reduce pruritus.

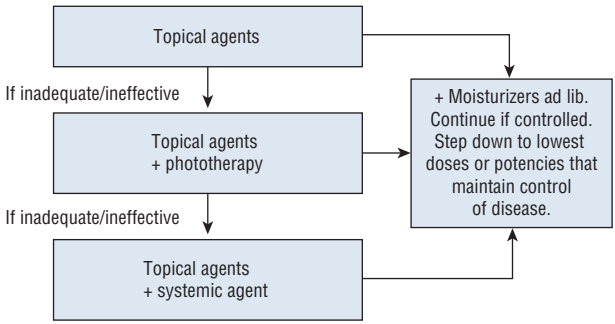


FIGURE 17–1. Treatment algorithm for mild to moderate psoriasis.

- Oatmeal baths further reduce pruritus, and regular use may reduce need for systemic antipruritic drugs. Harsh soaps and detergents should be avoided. Cleansing should involve tepid water, preferably with lipid- and fragrance-free cleansers.
- Sunscreens (preferably sun protection factor [SPF] 30 or higher) should be used when outdoors.

PHARMACOLOGIC THERAPY

Topical Therapies

- **Corticosteroids** (Table 17–1) have anti-inflammatory, anti-proliferative, immunosuppressive, and vasoconstrictive effects.
- Lower-potency products should be used for infants and for lesions on the face, intertriginous areas, and areas with thin skin. Mid- to high-potency agents are recommended as initial therapy for other areas of the body in adults. Reserve the highest potency corticosteroids for patients with very thick plaques or recalcitrant disease, such as plaques on the palms and soles. Use potency class I corticosteroids for only 2 to 4 weeks.
- Ointments are the most occlusive and most potent formulations because of enhanced penetration into the dermis. Patients may prefer the less greasy creams or lotions for daytime use.
- Adverse effects include skin atrophy, acne, contact dermatitis, hypertrichosis, folliculitis, hypopigmentation, perioral dermatitis, striae, telangiectasias, and traumatic purpura. Systemic adverse effects may occur with superpotent agents or with extended or

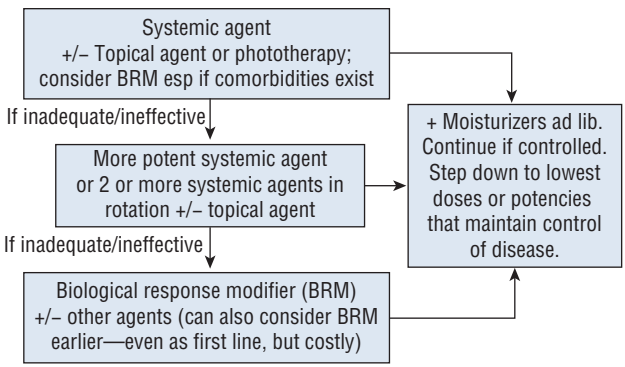


FIGURE 17–2. Treatment algorithm for moderate to severe psoriasis.

TABLE 17–1 Topical Corticosteroid Potency Chart

Potency Rating	Corticosteroid—Topical Preparations
Class 1: Superpotent	Betamethasone dipropionate 0.05% ointment (Diprolene and Diprosone ointment) Clobetasone propionate 0.05% lotion/spray/shampoo (Clobex lotion/spray/shampoo, OLUX foam) Clobetasone propionate 0.05% cream and ointment (Cormax, Temovate) Diflorasone diacetate 0.05% ointment (Florone, Psorcon) Halobetasol propionate 0.05% cream and ointment (Ultravate) Flurandrenolide tape 4 mcg/cm^2 (Cordran)
Class 2: Potent	Amcinonide 0.1% ointment (Cyclocort ointment) Betamethasone dipropionate 0.05% cream/gel (Diprolene cream, gel, and Diprosone cream) Desoximetasone 0.25% cream (Topicort) Fluocinonide 0.05% cream, gel, ointment (Lidex) Halcinonide 0.1% cream (Halog)
Class 3: Upper mid—strength	Amcinonide 0.1% cream (Cyclocort cream) Betamethasone valerate 0.1% ointment (Betnovate/Valisone ointment) Diflorasone diacetate 0.05% cream (Psorcon cream) Fluticasone propionate 0.005% ointment (Cutivate ointment) Mometasone furoate 0.1% ointment (Elocon ointment) Triamcinolone acetonide 0.5% cream and ointment (Aristocort)
Class 4: Mid—strength	Betamethasone valerate 0.12% foam (Luxiq) Clocortolone pivalate 0.1% cream (Cloderm) Desoximetasone 0.05% cream and gel (Topicort LP) Fluocinolone acetonide 0.025% ointment (Synalar ointment) Fluocinolone acetonide 0.2% cream (Synalar—HP) Hydrocortisone valerate 0.2% ointment (Westcort ointment) Mometasone furoate 0.1% cream (Elocon cream) Triamcinolone acetonide 0.1% ointment (Kenalog)
Class 5: Lower mid—strength	Betamethasone dipropionate 0.05% lotion (Diprosone lotion) Betamethasone valerate 0.1% cream and lotion (Betnovate/Valisone cream & lotion) Desonide 0.05% lotion (DesOwen) Fluocinolone acetonide 0.01% shampoo (Capex shampoo) Fluocinolone acetonide 0.01%, 0.025%, 0.03% cream (Synalar cream) Flurandrenolide 0.05% cream and lotion (Cordran) Fluticasone propionate 0.05% cream and lotion (Cutivate cream and lotion) Hydrocortisone butyrate 0.1% cream (Locoid) Hydrocortisone valerate 0.2% cream (Westcort cream) Prednicarbate 0.1% cream (Dermatop) Triamcinolone acetonide 0.1% cream and lotion (Kenalog cream and lotion)
Class 6: Mild	Alclometasone dipropionate 0.05% cream and ointment (Aclovate) Betamethasone valerate 0.05% cream and ointment Desonide 0.05% cream, ointment, gel (DesOwen, Desonate, Tridesilon) Desonide 0.05% foam (Verdeso) Fluocinonide acetonide 0.01% cream and solution (Synalar) Fluocinonide acetonide 0.01% FS oil (Derma—Smoothe)
Class 7: Least Potent	Hydrocortisone 0.5%, 1%, 2%, 2.5% cream, lotion, spray, and ointment (various brands)

Adapted from The National Psoriasis Foundation—Mild Psoriasis: Steroid potency chart, http://www.psoriasis.org/netcommunity/sublearn03_mild_potency. Rosso JD, Friedlander SF. Corticosteroids: Options in the era of steroid-sparing therapy. J Am Acad Dermatol 2005;53:S50–S58; and Leung DYM, Nicklas RA, Li JT, et al. Disease management of atopic dermatitis: An updated practice parameter. Ann Allergy Asthma Immunol 2004;93:S1–S17.

widespread use of midpotency agents. Such effects include hypothalamic-pituitary-adrenal axis suppression and less commonly Cushing's syndrome, osteonecrosis of the femoral head, cataracts, and glaucoma. All topical corticosteroids are pregnancy category C.

- **Calcipotriene** (Dovonex) is a synthetic vitamin D_3 analogue that binds to vitamin D receptors, which inhibits keratinocyte proliferation and enhances keratinocyte differentiation. Vitamin D_3 analogues also inhibit T-lymphocyte activity.
- For mild psoriasis, calcipotriene is more effective than anthralin and comparable to or slightly more effective than class 3 (upper mid-strength) topical corticosteroid ointments. Calcipotriene 0.005% cream, ointment, or solution is applied one or two times daily (no more than 100 g/wk).
- Adverse effects of calcipotriene include mild irritant contact dermatitis, burning, pruritus, edema, peeling, dryness, and erythema. Calcipotriene is pregnancy category C.
- **Tazarotene** (Tazorac) is a topical retinoid that normalizes keratinocyte differentiation, diminishes keratinocyte hyperproliferation, and clears the inflammatory infiltrate in psoriatic plaques. It is available as a 0.05% or 0.1% gel and cream and is applied once daily (usually in the evening).
- Adverse effects of tazarotene include a high incidence of dose-dependent irritation at application sites, resulting in burning, stinging, and erythema. Irritation may be reduced by using the cream formulation, lower concentration, alternate-day applications, or short-contact (30–60 min) treatment. Tazarotene is pregnancy category X and should not be used in women of childbearing potential unless effective contraception is being used.
- **Anthralin** has a direct anti-proliferative effect on epidermal keratinocytes, normalizing keratinocyte differentiation. Short-contact anthralin therapy (SCAT) is the preferred regimen, with ointment applied only to the thick plaque lesions for 2 hours or less and then wiped off. Zinc oxide ointment or nonmedicated stiff paste should be applied to the surrounding normal skin to protect it from irritation. Use anthralin with caution, if at all, on the face and intertriginous areas due to potential for severe irritation.
- Anthralin concentrations for SCAT range from 1% to 4% or as tolerated. Concentrations for continuous therapy vary from 0.05% to 0.4%.
- Anthralin may cause severe skin irritation, folliculitis, and allergic contact dermatitis. Anthralin is pregnancy category C.
- **Coal tar** is keratolytic and may have anti-proliferative and anti-inflammatory effects. Formulations include crude coal tar and tar distillates (liquor carbonis detergens) in ointments, creams, and shampoos. Coal tar is used infrequently due to limited efficacy and poor patient adherence and acceptance. It has a slower onset of action than calcipotriene, has an unpleasant odor, and stains clothing.
- Adverse effects include folliculitis, acne, local irritation, and phototoxicity. Risk of teratogenicity when used in pregnancy is low.
- **Salicylic acid** has keratolytic properties and has been used in shampoos or bath oils for scalp psoriasis. It enhances penetration of topical corticosteroids, thereby increasing corticosteroid efficacy. Systemic absorption and toxicity can occur, especially when applied to greater than 20% BSA or in patients with renal impairment. Salicylic acid should not be used in children. It may be used for limited and localized plaque psoriasis in pregnancy.

Phototherapy and Photochemotherapy

- Phototherapy consists of nonionizing electromagnetic radiation, either ultraviolet A (UVA) or ultraviolet B (UVB), as light therapy for psoriatic lesions. UVB is given alone as either broadband or narrowband (NB-UVB). Broadband UVB is also given as photochemotherapy with topical agents such as crude coal tar (Goeckerman regimen) or anthralin (Ingram regimen) for enhanced efficacy. UVA is generally given with a photosensitizer such as an oral psoralen to enhance efficacy; this regimen is called PUVA (psoralen + UVA treatment).

- Adverse effects of phototherapy include erythema, pruritus, xerosis, hyperpigmentation, and blistering. Patients must be provided with eye protection during and for 24 hours after PUVA treatments. PUVA therapy may also cause nausea or vomiting, which may be minimized by taking the oral psoralens with food or milk. Long-term PUVA use can lead to photoaging and cataracts. PUVA is also associated with a dose-related risk of carcinogenesis.

Systemic Therapies

- **Acitretin** (Soriatane) is a retinoic acid derivative and the active metabolite of etretinate. Retinoids may be less effective than methotrexate or cyclosporine when used as monotherapy. Acitretin is more commonly used in combination with topical calcipotriene or phototherapy. The initial recommended dose is 25 or 50 mg; therapy is continued until lesions have resolved. It is better tolerated when taken with meals. Adverse effects include hypertriglyceridemia and mucocutaneous effects such as dryness of the eyes, nasal and oral mucosa, chapped lips, cheilitis, epistaxis, xerosis, brittle nails, and burning skin. Less commonly, "retinoid dermatitis" may occur. Skeletal abnormalities occur rarely. All retinoids are teratogenic and are pregnancy category X. Acitretin should not be used in women of childbearing potential unless they use effective contraception for the duration of therapy and for 3 years after drug discontinuation.
- **Cyclosporine** is a systemic calcineurin inhibitor that is effective for inducing remission and for maintenance therapy of moderate to severe plaque psoriasis. It is also effective for pustular, erythrodermic, and nail psoriasis. Cyclosporine is significantly more effective than etretinate and has similar or slightly better efficacy than methotrexate. The usual dose is between 2.5 and 5 mg/kg/day given in two divided doses. After inducing remission, maintenance therapy using low doses (1.25–3 mg/kg/day) may prevent relapse. When discontinuing cyclosporine, a gradual taper of 1 mg/kg/day each week may prolong the time before relapse when compared with abrupt discontinuation. Because more than half of patients stopping cyclosporine relapse within 4 months, patients should be given appropriate alternative treatments shortly before or after discontinuing cyclosporine. Adverse effects include nephrotoxicity, hypertension, hypomagnesemia, hyperkalemia, hypertriglyceridemia, hypertrichosis, and gingival hyperplasia. The risk of skin cancer increases with the duration of treatment and with prior PUVA treatments.
- **Methotrexate** has antiinflammatory effects due to its effects on T-cell gene expression and also has cytostatic effects. It is more effective than acitretin and has similar or slightly less efficacy than cyclosporine. Methotrexate can be administered orally, subcutaneously, or intramuscularly. The starting dose is 7.5 to 15 mg once weekly, increased incrementally by 2.5 mg every 2 to 4 weeks until response; maximal doses are 25 mg weekly. Adverse effects include nausea, vomiting, stomatitis, macrocytic anemia, and hepatic and pulmonary toxicity. Nausea and macrocytic anemia may be reduced by giving oral folic acid 1 to 5 mg daily. Methotrexate should be avoided in patients with active infections and in those with liver disease. It is an abortifacient and teratogenic and is contraindicated in pregnancy (pregnancy category X).

Systemic Therapy with Biologic Response Modifiers

- Biologic response modifiers (BRMs) are considered for moderate to severe psoriasis when other systemic agents are inadequate or contraindicated. Cost considerations tend to limit their use as first-line therapy.
- **Adalimumab** (Humira) is a monoclonal TNF-α antibody that provides rapid control of psoriasis. It is indicated for psoriatic arthritis and treatment of adults with moderate to severe chronic plaque psoriasis who are candidates for systemic therapy or phototherapy. The recommended dose for psoriatic arthritis is 40 mg subcutaneously every other week. The recommended dose for adults with plaque psoriasis is an initial dose of 80 mg, followed by 40 mg every other week starting 1 week after the initial dose. The most common adverse reactions are infections (eg, upper respiratory and sinusitis), injection site reactions, headache, and rash.

- **Etanercept** (Enbrel) is a fusion protein that binds TNF-α, competitively interfering with its interaction with cell-bound receptors. Unlike the chimeric infliximab, etanercept is fully humanized, minimizing the risk of immunogenicity. Etanercept is FDA approved for reducing signs and symptoms and inhibiting the progression of joint damage in patients with psoriatic arthritis. It can be used in combination with methotrexate in patients who do not respond adequately to methotrexate alone. It is also indicated for adults with chronic moderate to severe plaque psoriasis. The recommended dose for psoriatic arthritis is 50 mg subcutaneously once per week. For plaque psoriasis, the dose is 50 mg subcutaneously twice weekly (administered 3 or 4 days apart) for 3 months, followed by a maintenance dose of 50 mg once weekly. Adverse effects include local reactions at the injection site (20% of patients), respiratory tract and GI infections, abdominal pain, nausea and vomiting, headaches, and rash. Serious infections (including tuberculosis) and malignancies are rare.
- **Infliximab** (Remicade) is a chimeric monoclonal antibody directed against TNF-α. It is indicated for psoriatic arthritis and chronic severe plaque psoriasis. The recommended dose is 5 mg/kg as an IV infusion at weeks 0, 2, and 6, then every 8 weeks thereafter. For psoriatic arthritis, it may be used with or without methotrexate. Adverse effects include headaches, fever, chills, fatigue, diarrhea, pharyngitis, and upper respiratory and urinary tract infections. Hypersensitivity reactions (urticaria, dyspnea, and hypotension) and lymphoproliferative disorders have been reported.
- **Alefacept** (Amevive) is a dimeric fusion protein that binds to CD2 on T cells to inhibit cutaneous T-cell activation and proliferation. It also produces a dose-dependent decrease in circulating total lymphocytes. Alefacept is approved for treatment of moderate to severe plaque psoriasis and is also effective for treatment of psoriatic arthritis. Significant response is usually achieved after about 3 months of therapy. The recommended dose is 15 mg intramuscularly once weekly for 12 weeks. Adverse effects are mild and include pharyngitis, flu-like symptoms, chills, dizziness, nausea, headache, injection site pain and inflammation, and nonspecific infection.
- **Ustekinumab** (Stelara) is an IL-12/23 monoclonal antibody approved for the treatment of psoriasis in adults 18 years or older with moderate to severe plaque psoriasis. The recommended dose for patients weighing 100 kg or less is 45 mg initially and 4 weeks later, followed by 45 mg every 12 weeks. For patients weighing 100 kg or more, the dose is 90 mg initially and 4 weeks later, followed by 90 mg every 12 weeks. Common adverse effects include upper respiratory infections, headache, and tiredness. Serious adverse effects include those seen with other BRMs, including tubercular, fungal, and viral infections and cancers. One case of reversible posterior leukoencephalopathy syndrome (RPLS) has been reported.

Combination Therapies

- Combination therapy may be used to enhance efficacy or minimize toxicity. Combinations can include two topical agents, a topical agent plus phototherapy, a systemic agent plus topical therapy, a systemic agent plus phototherapy, two systemic agents used in rotation, or a systemic agent and a BRM (see **Figs. 17–1** and **17–2**).
- The combination of a topical corticosteroid and a topical vitamin D_3 analogue is effective and safe with less skin irritation than monotherapy with either agent. The combination product containing calcipotriene and betamethasone dipropionate ointment (Taclonex) is effective for relatively severe psoriasis and may also be steroid sparing.
- The combination of retinoids with phototherapy (eg, tazarotene plus broadband UVB, acitretin plus broadband UVB or NB-UVB) also increases efficacy. Because retinoids may be photosensitizing and increase the risk of burning after UV exposure, doses of phototherapy should be reduced to minimize adverse effects. The combination of acitretin and PUVA (RE-PUVA) may be more effective than monotherapy with either treatment.
- Phototherapy has also been used with other topical agents, such as UVB with coal tar (Goeckerman regimen) to increase treatment response, because coal tar is also photosensitizing.

- BRMs used in combination with other therapies are being explored (eg, alefacept plus NB-UVB, infliximab plus methotrexate).

Alternative Drug Treatments

- **Mycophenolate mofetil** (CellCept) inhibits DNA and RNA synthesis and may have a lymphocyte anti-proliferative effect. Although not FDA approved for this indication, oral mycophenolate mofetil may be effective in some cases of moderate to severe plaque psoriasis. The usual dose is 500 mg orally four times daily, up to a maximum of 4 g daily. Common adverse effects include GI toxicity (diarrhea, nausea, and vomiting), hematologic effects (anemia, neutropenia, and thrombocytopenia), and viral and bacterial infections. Lymphoproliferative disease or lymphoma has been reported.
- **Hydroxyurea** inhibits cell synthesis in the S phase of the DNA cycle. It is sometimes used for patients with recalcitrant severe psoriasis, but BRMs may be a better option in these patients. The typical dose is 1 g daily, with a gradual increase to 2 g daily as needed and as tolerated. Adverse effects include bone marrow suppression, lesional erythema, localized tenderness, and reversible hyperpigmentation.

EVALUATION OF THERAPEUTIC OUTCOMES

- Help patients understand the general principles of therapy and the importance of adherence.
- A positive response involves normalization of involved areas of skin, as measured by reduced erythema and scaling, as well as reduction of plaque elevation.
- PASI is a uniform method to determine the extent of BSA affected, along with the degree of erythema, induration, and scaling. Severity scores are rated as less than 12 (mild), 12 to 18 (moderate), and more than 18 (severe).
- The Physician Global Assessment can also be used to summarize erythema, induration, scaling, and extent of plaques relative to baseline assessment.
- The National Psoriasis Foundation Psoriasis Score incorporates quality of life and the patient's perception of well-being, as well as induration, extent of involvement, the physician's static global assessment, and pruritus.
- Achievement of efficacy by any therapeutic regimen requires days to weeks. Initial dramatic response may be achieved with some agents, such as corticosteroids. However, sustained benefit with pharmacologically specific antipsoriatic therapy may require 2 to 8 weeks or longer for clinically meaningful response.

See Chapter 78, Psoriasis, authored by Rebecca M. Law and Wayne P. Gulliver, for a more detailed discussion of this topic.

This page intentionally left blank

Edited by Terry L. Schwinghammer

CHAPTER 18

Adrenal Gland Disorders

- Hyperfunction of the adrenal glands involves excess production of the adrenal hormones cortisol (resulting in Cushing syndrome) or aldosterone (resulting in hyperaldosteronism).
- Adrenal gland hypofunction is associated with primary (Addison disease) or secondary adrenal insufficiency.

CUSHING SYNDROME

PATHOPHYSIOLOGY

- Cushing syndrome results from effects of supraphysiologic glucocorticoid levels originating from either exogenous administration or endogenous overproduction by the adrenal gland (adrenocorticotropic hormone [ACTH]-dependent) or by abnormal adrenocortical tissues (ACTH-independent).
- ACTH-dependent Cushing syndrome (80% of all Cushing syndrome cases) is usually caused by overproduction of ACTH by the pituitary gland, causing adrenal hyperplasia. Pituitary adenomas account for ~85% of these cases (Cushing disease). Ectopic ACTH-secreting tumors and nonneoplastic corticotropin hypersecretion cause the remaining 20% of ACTH-dependent cases.
- Ectopic ACTH syndrome refers to excessive ACTH production resulting from an endocrine or nonendocrine tumor, usually of the pancreas, thyroid, or lung (eg, small-cell lung cancer).
- ACTH-independent Cushing syndrome is usually caused by adrenal adenomas and carcinomas.

CLINICAL PRESENTATION

- The most common findings in Cushing syndrome are central obesity and facial rounding (90% of patients). Peripheral obesity and fat accumulation occur in 50% of patients. Fat accumulation in the dorsocervical area (buffalo hump) is nonspecific, but increased supraclavicular fat pads are more specific for Cushing syndrome. Patients are often described as having moon facies and a buffalo hump.
- Other findings may include myopathy or muscular weakness, abdominal striae, hypertension, glucose intolerance, psychiatric changes, gonadal dysfunction, and amenorrhea and hirsutism in women.
- Up to 60% of patients develop Cushing-induced osteoporosis; ~40% present with back pain, and 20% progress to spinal compression fractures.

DIAGNOSIS

- Hypercortisolism can be established with a 24-hour urinary free cortisol (UFC), midnight plasma cortisol, late-night (11 PM) salivary cortisol, and/or low-dose dexamethasone suppression test (DST).
- Other tests to determine etiology are plasma ACTH test; adrenal vein catheterization; metyrapone stimulation test; adrenal, chest, or abdominal computed tomography (CT); corticotropin-releasing hormone (CRH) stimulation test; inferior petrosal sinus sampling; and pituitary magnetic resonance imaging (MRI).
- Adrenal nodules and masses are identified using high-resolution CT scanning or MRI.

TREATMENT

- Goals of Treatment: Limit morbidity and mortality and return the patient to a normal functional state by removing the source of hypercortisolism while minimizing pituitary or adrenal deficiencies.
- Treatment plans in Cushing syndrome based on etiology are included in **Table 18–1**.

Nonpharmacologic Therapy

- Treatment of choice for both ACTH-dependent and ACTH-independent Cushing syndrome is surgical resection of offending tumors. Transsphenoidal resection of the pituitary tumor is the treatment of choice for Cushing disease.
- Pituitary irradiation provides clinical improvement in ~50% of patients within 3 to 5 years, but improvement may not be seen for 6 to 12 months, and pituitary-dependent hormone deficiencies (hypopituitarism) can occur.
- Laparoscopic adrenalectomy may be preferred in patients with unilateral adrenal adenomas or for whom transsphenoidal surgery and pituitary radiotherapy have failed or cannot be used.

Pharmacologic Therapy

- Pharmacotherapy is generally used as secondary treatments in preoperative patients or as adjunctive therapy in postoperative patients awaiting response. Rarely, monotherapy is used as a palliative treatment when surgery is not indicated.

STEROIDOGENIC INHIBITORS

- **Metyrapone** inhibits 11 β-hydroxylase, thereby inhibiting cortisol synthesis. Initially, patients can demonstrate increased plasma ACTH concentrations because of a sudden drop in cortisol. This can increase androgenic and mineralocorticoid hormones, resulting in hypertension, acne, and hirsutism. Nausea, vomiting, vertigo, headache, dizziness, abdominal discomfort, and allergic rash have been reported after oral administration. Metyrapone is currently available through the manufacturer only for compassionate use.
- **Ketoconazole** inhibits cytochrome P-450 enzymes, including 11 β-hydroxylase and 17 α-hydroxylase. It is effective in lowering serum cortisol levels after several weeks of therapy. It also has antiandrogenic activity, which may be beneficial in women but can cause gynecomastia and decreased libido in men. The most common adverse effects are reversible elevation of hepatic transaminases, GI discomfort, and dermatologic reactions. Ketoconazole may be used concomitantly with metyrapone to achieve synergistic reduction in cortisol levels; in addition, ketoconazole's antiandrogenic actions may offset the androgenic potential of metyrapone.
- **Etomidate** is an imidazole derivative similar to ketoconazole that inhibits 11 β-hydroxylase. Because it is only available in a parenteral formulation, use is limited to patients with acute hypercortisolemia requiring emergency treatment.
- **Aminoglutethimide** inhibits cortisol synthesis by blocking conversion of cholesterol to pregnenolone early in the cortisol pathway. Side effects of severe sedation, nausea, ataxia, and skin rashes limit aminoglutethimide use in many patients. Other steroidogenesis inhibitors offer greater efficacy with fewer side effects; if aminoglutethimide is used, it should be coadministered with another steroidogenesis inhibitor (usually metyrapone) due to high relapse rates with aminoglutethimide monotherapy.

ADRENOLYTIC AGENTS

- **Mitotane** is a cytotoxic drug that inhibits the 11-hydroxylation of 11-desoxycortisol and 11-desoxycorticosterone in the adrenal cortex, reducing synthesis of cortisol and corticosterone. Similar to ketoconazole, mitotane takes weeks to months to exert beneficial effects. Sustained cortisol suppression occurs in most patients and may persist after drug discontinuation in up to one third of patients. Mitotane degenerates cells within the zona fasciculata and reticularis; the zona glomerulosa is minimally affected during acute therapy but can become damaged after long-term treatment. Mitotane can cause significant neurologic and GI side effects, and patients should be

TABLE 18–1 Treatment Options in Cushing Syndrome Based on Etiology

Etiology	Nondrug	Generic (Brand) Drug Name	Dosing		
			Initial	Usual	Maximum
Ectopic ACTH syndrome	Surgery, chemotherapy, irradiation	Metyrapone (Metopirone) 250 mg capsules	0.5–1 g/day, divided every 4 to 6 hours	1–2 g/day, divided every 4 to 6 hours	6 g/day
Pituitary-dependent	Surgery, irradiation	Cyproheptadine (Periactin) 2 mg/5 mL syrup or 4 mg tablets	4 mg twice daily	24–32 mg/day, divided four times daily	32 mg/day
		Mitotane (Lysodren) 500 mg tablets	0.5–1 g/day, increased by 0.5–1 g/day every 1 to 4 weeks	1–4 g daily, with food to decrease GI effects	12 g/day
		Metyrapone	See above	See above	See above
		Mifepristone (Korlym) 300 mg tablets	300 mg once daily, increased by 300 mg/day every 2 to 4 weeks	600–1200 mg/day	1200 mg/day
Adrenal adenoma	Surgery, postoperative replacement	Ketoconazole (Nizoral) 200 mg tablets	200 mg once or twice a day	200–1,200 mg/day, divided twice daily	1,600 mg/day divided four times daily
Adrenal carcinoma	Surgery	Mitotane	See above	See above	See above
		Metyrapone	See above	See above	See above
		Ketoconazole	See above	See above	See above
		Aminoglutethimide (Cytadren) 250 mg tablets	0.5–1 g/day, divided two to four times daily for 2 weeks	1 g/day, divided every 6 hours	2 g/day

ACTH, adrenocorticotropic hormone.

monitored carefully or hospitalized when initiating therapy. Nausea and diarrhea are common at doses greater than 2 g/day and can be avoided by gradually increasing the dose and/or administering it with food. Lethargy, somnolence, and other CNS effects are also common. Reversible hypercholesterolemia and prolonged bleeding times can occur.

NEUROMODULATORS OF ACTH RELEASE

- Pituitary secretion of ACTH is normally mediated by neurotransmitters such as serotonin, γ-aminobutyric acid (GABA), acetylcholine, and catecholamines. Although ACTH-secreting pituitary tumors (Cushing disease) self-regulate ACTH production to some degree, these neurotransmitters can still promote pituitary ACTH production. Consequently, agents that target these transmitters have been proposed for treatment of Cushing disease, including cyproheptadine, bromocriptine, cabergoline, valproic acid, octreotide, rosiglitazone, and tretinoin. None of these drugs have demonstrated consistent clinical efficacy for treating Cushing syndrome.
- **Cyproheptadine** can decrease ACTH secretion in some patients with Cushing disease. However, side effects such as sedation and weight gain significantly limit its use.
- **Pasireotide** is a somatostatin analogue that binds and activates somatostatin receptors, thereby inhibiting ACTH secretion, leading to decreased cortisol secretion. It is approved for treatment of adults with Cushing disease for whom pituitary surgery is not an option or has not been curative.

GLUCOCORTICOID-RECEPTOR BLOCKING AGENTS

- **Mifepristone** (RU-486) is a progesterone- and glucocorticoid-receptor antagonist that inhibits dexamethasone suppression and increases endogenous cortisol and ACTH levels in normal subjects. Evidence suggests that mifepristone is highly effective in reversing the manifestations of hypercortisolism. Its use for treatment of Cushing syndrome remains investigational.

EVALUATION OF THERAPEUTIC OUTCOMES

- Close monitoring of 24-hour UFC and serum cortisol levels is essential to identify adrenal insufficiency in patients with Cushing syndrome. Monitor steroid secretion with all drug therapy and give corticosteroid replacement if needed.

ADRENAL INSUFFICIENCY

PATHOPHYSIOLOGY

- Primary adrenal insufficiency (Addison disease) most often involves the destruction of all regions of the adrenal cortex. There are deficiencies of cortisol, aldosterone, and the various androgens, and levels of CRH and ACTH increase in a compensatory manner.
- Autoimmune dysfunction is responsible for 80% to 90% of cases in developed countries, whereas tuberculosis is the predominant cause in developing countries.
- Medications that inhibit cortisol synthesis (eg, ketoconazole) or accelerate cortisol metabolism (eg, phenytoin, rifampin, phenobarbital) can also cause primary adrenal insufficiency.
- Secondary adrenal insufficiency most commonly results from exogenous corticosteroid use, leading to suppression of the hypothalamic-pituitary-adrenal axis and decreased ACTH release, resulting in impaired androgen and cortisol production. Mirtazapine and progestins (eg, medroxyprogesterone acetate, megestrol acetate) have also been reported to induce secondary adrenal insufficiency. Secondary disease typically presents with normal mineralocorticoid concentrations.

CLINICAL PRESENTATION

- Weight loss, dehydration, hyponatremia, hyperkalemia, and elevated blood urea nitrogen are common in Addison disease.

- Hyperpigmentation is common in Addison disease and may involve exposed and nonexposed parts of the body. Hyperpigmentation is usually not seen in secondary adrenal insufficiency because of low amounts of melanocyte-stimulating hormone.

DIAGNOSIS

- The short cosyntropin stimulation test can be used to assess patients with suspected hypocortisolism. An increase to a cortisol level of 18 mcg/dL or more (500 nmol/L) rules out adrenal insufficiency.
- Patients with Addison disease have an abnormal response to the short cosyntropin stimulation test. Plasma ACTH levels are usually 400 to 2000 pg/mL (88 to 440 pmol/L) in primary insufficiency versus normal to low (5–50 pg/mL [1.1–11 pmol/L]) in secondary insufficiency. A normal cosyntropin-stimulation test does not rule out secondary adrenal insufficiency.
- Other tests include the insulin hypoglycemia test, the metyrapone test, and the CRH stimulation test.

TREATMENT

- Goals of Treatment: Limit morbidity and mortality, return the patient to a normal functional state, and prevent episodes of acute adrenal insufficiency.

Nonpharmacologic Therapy

- Inform patients of treatment complications, expected outcomes, proper medication administration and adherence, and possible side effects.

Pharmacotherapy

CORTICOSTEROIDS

- **Hydrocortisone, cortisone**, and **prednisone** are the glucocorticoids of choice, administered twice daily at the lowest effective dose while mimicking the normal diurnal adrenal rhythm of cortisol production.
- Recommended starting total daily doses are hydrocortisone 15 to 25 mg daily, which is approximately equivalent to cortisone acetate 25 to 37.5 mg, or prednisone 2.5 mg (Table 18–2). Two thirds of the dose is given in the morning, and one third is given 6 to 8 hours later.
- The patient's symptoms can be monitored every 6 to 8 weeks to assess proper glucocorticoid replacement.
- **Fludrocortisone acetate** 0.05 to 0.2 mg orally once daily can be used to replace mineralocorticoid loss. If parenteral therapy is needed, 2 to 5 mg of deoxycorticosterone trimethylacetate in oil can be administered intramuscularly every 3 to 4 weeks. The major reason for adding the mineralocorticoid is to minimize development of hyperkalemia.

TABLE 18–2 Relative Potencies of Glucocorticoids

Glucocorticoid	Anti-inflammatory Potency	Equivalent Potency (mg)	Approximate Half-Life (min)	Sodium-retaining Potency
Cortisone	0.8	25	30	2
Hydrocortisone	1	20	90	2
Prednisone	3.5	5	60	1
Prednisolone	4	5	200	1
Triamcinolone	5	4	300	0
Methylprednisolone	5	4	180	0
Betamethasone	25	0.6	100–300	0
Dexamethasone	30	0.75	100–300	0

- Because most adrenal crises occur because of glucocorticoid dose reductions or lack of stress-related dose adjustments, patients receiving corticosteroid replacement therapy should add 5 to 10 mg hydrocortisone (or equivalent) to their normal daily regimen shortly before strenuous activities, such as exercise. During times of severe physical stress (eg, febrile illnesses and after accidents), patients should be instructed to double their daily dose until recovery.
- Treatment of secondary adrenal insufficiency is identical to primary disease treatment, with the exception that mineralocorticoid replacement is usually not necessary.

Pharmacotherapy of Acute Adrenal Insufficiency

- Acute adrenal insufficiency (also known as adrenal crisis or addisonian crisis) represents a true endocrine emergency.
- Stressful situations, surgery, infection, and trauma are potential events that increase adrenal requirements, especially in patients with some underlying adrenal or pituitary insufficiency.
- The most common cause of adrenal crisis is abrupt withdrawal of exogenous glucocorticoids in patients receiving chronic treatment that resulted in hypothalamic-pituitary-adrenal-axis suppression.
- **Hydrocortisone** given parenterally is the corticosteroid of choice because of its combined glucocorticoid and mineralocorticoid activity. The starting dose is 100 mg IV by rapid infusion, followed by a continuous infusion (usually 10 mg/h) or intermittent bolus of 100 to 200 mg every 24 hours. IV administration is continued for 24 to 48 hours. If the patient is stable at that time, oral hydrocortisone can be started at a dose of 50 mg every 6 to 8 hours, followed by tapering to the individual's chronic replacement needs.
- **Fluid replacement** often is required and can be accomplished with IV dextrose 5% in normal saline solution at a rate to support blood pressure.
- If hyperkalemia is present after the hydrocortisone maintenance phase, additional mineralocorticoid supplementation can be achieved with **fludrocortisone acetate** 0.1 mg daily.
- Patients with adrenal insufficiency should carry a card or wear a bracelet or necklace that contains information about their condition. They should also have easy access to injectable hydrocortisone or glucocorticoid suppositories in case of an emergency or during times of physical stress, such as febrile illness or injury.

EVALUATION OF THERAPEUTIC OUTCOMES

- The end point of therapy for adrenal insufficiency is difficult to assess in most patients, but a reduction in excess pigmentation is a good clinical marker. Development of features of Cushing syndrome indicates excessive replacement.

See Chapter 59, Adrenal Gland Disorders, authored by Eric Dietrich, Steven M. Smith, and John G. Gums, for a more detailed discussion of this topic.

CHAPTER 19

Diabetes Mellitus

- *Diabetes mellitus* (DM) is a group of metabolic disorders characterized by hyperglycemia and abnormalities in carbohydrate, fat, and protein metabolism.

PATHOPHYSIOLOGY

- Type 1 DM (5%–10% of cases) usually develops in childhood or early adulthood and results from autoimmune-mediated destruction of pancreatic β-cells, resulting in absolute deficiency of insulin. The autoimmune process is mediated by macrophages and T lymphocytes with autoantibodies to β-cell antigens (eg, islet cell antibody, insulin antibodies).
- Type 2 DM (90% of cases) is characterized by a combination of some degree of insulin resistance and relative insulin deficiency. Insulin resistance is manifested by increased lipolysis and free fatty acid production, increased hepatic glucose production, and decreased skeletal muscle uptake of glucose.
- Uncommon causes of diabetes (1%–2% of cases) include endocrine disorders (eg, acromegaly, Cushing syndrome), gestational diabetes mellitus (GDM), diseases of the exocrine pancreas (eg, pancreatitis), and medications (eg, glucocorticoids, pentamidine, niacin, α-interferon).
- Microvascular complications include retinopathy, neuropathy, and nephropathy. Macrovascular complications include coronary heart disease, stroke, and peripheral vascular disease.

CLINICAL PRESENTATION

TYPE 1 DIABETES MELLITUS

- The most common initial symptoms are polyuria, polydipsia, polyphagia, weight loss, and lethargy accompanied by hyperglycemia.
- Individuals are often thin and are prone to develop diabetic ketoacidosis if insulin is withheld or under conditions of severe stress.
- Between 20% and 40% of patients present with diabetic ketoacidosis after several days of polyuria, polydipsia, polyphagia, and weight loss.

TYPE 2 DIABETES MELLITUS

- Patients are often asymptomatic and may be diagnosed secondary to unrelated blood testing.
- Lethargy, polyuria, nocturia, and polydipsia can be present. Significant weight loss is less common; more often, patients are overweight or obese.

DIAGNOSIS

- Criteria for diagnosis of DM include any one of the following:
  1. A1C of 6.5% or more
  2. Fasting (no caloric intake for at least 8 hours) plasma glucose of 126 mg/dL (7.0 mmol/L) or more
  3. Two-hour plasma glucose of 200 mg/dL (11.1 mmol/L) or more during an oral glucose tolerance test (OGTT) using a glucose load containing the equivalent of 75 g anhydrous glucose dissolved in water
  4. Random plasma glucose concentration of 200 mg/dL (11.1 mmol/L) or more with classic symptoms of hyperglycemia or hyperglycemic crisis

  In the absence of unequivocal hyperglycemia, criteria 1 through 3 should be confirmed by repeat testing.

TABLE 19–1 Glycemic Goals of Therapy

Biochemical Index	ADA	ACE and AACE
A1C	<7%[a] (<0.07)	≤6.5% (≤0.065)
Preprandial plasma glucose	70–130 mg/dL (3.9–7.2 mmol/L)	<110 mg/dL (<6.1 mmol/L)
Postprandial plasma glucose	<180 mg/dL[b] (<10 mmol/L)	<140 mg/dL (<7.8 mmol/L)

AACE, American Association of Clinical Endocrinologists; ACE, American College of Endocrinology; ADA, American Diabetes Association.
[a]More stringent glycemic goals may be appropriate if accomplished without significant hypoglycemia or adverse effects. Less stringent goals may also be appropriate in some situations.
[b]Postprandial glucose measurements should be made 1 to 2 hours after the beginning of the meal, generally the time of peak levels in patients with diabetes.

- Normal fasting plasma glucose (FPG) is less than 100 mg/dL (5.6 mmol/L).
- Impaired fasting glucose (IFG) is FPG 100 to 125 mg/dL (5.6–6.9 mmol/L).
- Impaired glucose tolerance (IGT) is diagnosed when the 2-hour postload sample of OGTT is 140 to 199 mg per dL (7.8–11.0 mmol/L).
- Pregnant women should undergo risk assessment for GDM at first prenatal visit and have glucose testing if at high risk (eg, positive family history, personal history of GDM, marked obesity, or member of a high-risk ethnic group).

TREATMENT

- Goals of Treatment: Ameliorate symptoms, reduce risk of microvascular and macrovascular complications, reduce mortality, and improve quality of life. Desirable plasma glucose and A1C levels are listed in **Table 19–1**.

GENERAL APPROACH

- Early treatment with near-normal glycemia reduces risk of microvascular disease complications, but aggressive management of cardiovascular risk factors (ie, smoking cessation, treatment of dyslipidemia, intensive blood pressure [BP] control, and antiplatelet therapy) is needed to reduce macrovascular disease risk.
- Appropriate care requires goal setting for glycemia, BP, and lipid levels; regular monitoring for complications; dietary and exercise modifications; appropriate self-monitoring of blood glucose (SMBG); and laboratory assessment.

NONPHARMACOLOGIC THERAPY

- Medical nutrition therapy is recommended for all patients. For type 1 DM, the focus is on physiologically regulating insulin administration with a balanced diet to achieve and maintain healthy body weight. The meal plan should be moderate in carbohydrates and low in saturated fat, with a focus on balanced meals. Patients with type 2 DM often require caloric restriction to promote weight loss.
- Aerobic exercise can improve insulin sensitivity and glycemic control and may reduce cardiovascular risk factors, contribute to weight loss or maintenance, and improve well-being.

PHARMACOLOGIC THERAPY: DRUG CLASS INFORMATION

Insulin (Tables 19-2, 19-3)

- **Regular insulin** has a relatively slow onset of action when given subcutaneously (SC), requiring injection 30 minutes prior to meals to achieve optimal postprandial glucose control and prevent delayed postmeal hypoglycemia.

TABLE 19–2 Available Insulins and Other Injectable Preparations

Generic Name	Analog[a]	Administration Options
Rapid-acting insulins		
Humalog (insulin lispro)	Yes	Insulin pen 3 mL, vial, and 3 mL pen cartridge
NovoLog (insulin aspart)	Yes	Insulin pen 3 mL, vial, or 3 mL pen cartridge
Apidra (insulin glulisine)	Yes	3 mL pen cartridge or OptiClik pen system
Short-acting insulins		
Humulin R (regular)	No	U-100, 10 mL vial; U-500, 20 mL vial
Novolin R (regular)	No	Insulin pen, vial, or 3 mL pen cartridge, and InnoLet
Intermediate-acting insulins (NPH)		
Humulin N	No	Vial, 3 mL prefilled pen
Novolin N	No	Vial, prefilled pen, and InnoLet
Long-acting insulins		
Lantus (insulin glargine)	Yes	Vial, 3 mL OptiClik pen system
Levemir (insulin detemir)	Yes	Vial, 3 mL pen cartridge and InnoLet
Premixed insulins		
Premixed insulin analog		
Humalog Mix 75/25 (75% neutral protamine lispro, 25% lispro)	Yes	Vial, prefilled pen
		Vial, prefilled pen, 3 mL pen cartridge
	Yes	3 mL pen
Novolog Mix 70/30 (70% aspart protamine suspension, 30% aspart)	Yes	
Humalog Mix 50/50 (50% neutral protamine lispro, 50% lispro)	Yes	
NPH-regular combinations		
Humulin 70/30	No	Vial, 3 mL prefilled pen
Novolin 70/30	No	Vial, pen cartridge, InnoLet
Other injectable preparations		
Exenatide (Byetta)	No	5 mcg/dose and 10 mcg/dose, 60 doses prefilled pen
Exenatide extended-release (Bydureon)	No	2-mg vial with separate diluent, single-use system
Liraglutide (Victoza)	Yes	3 mL pen, can deliver 0.6 mg, 1.2 mg, or 1.8 mg dose
Pramlintide (Symlin)	Yes	5 mL vial, 1.5 mL and 2.7 mL SymlinPen

NPH, neutral protamine Hagedorn.
[a]An insulin analog is a modified human insulin molecule that imparts particular pharmacokinetic advantages.

- **Lispro, aspart**, and **glulisine insulins** are analogs that are more rapidly absorbed, peak faster, and have shorter durations of action than regular insulin. This permits more convenient dosing within 10 minutes of meals (rather than 30 min prior), produces better efficacy in lowering postprandial blood glucose than regular insulin in type 1 DM, and minimizes delayed postmeal hypoglycemia.
- **Neutral protamine Hagedorn (NPH)** is intermediate-acting. Variability in absorption, inconsistent preparation by the patient, and inherent pharmacokinetic differences may contribute to a labile glucose response, nocturnal hypoglycemia, and fasting hyperglycemia.
- **Glargine** and **detemir** are long-acting "peakless" human insulin analogs that result in less nocturnal hypoglycemia than NPH insulin when given at bedtime.

TABLE 19–3 Pharmacokinetics of Various Insulins Administered Subcutaneously

Type of Insulin	Onset	Peak (hours)	Duration (hours)	Maximum Duration (hours)	Appearance
Rapid-acting					
Aspart	15–30 min	1–2	3–5	5–6	Clear
Lispro	15–30 min	1–2	3–4	4–6	Clear
Glulisine	15–30 min	1–2	3–4	5–6	Clear
Short-acting					
Regular	30–60 min	2–3	3–6	6–8	Clear
Intermediate-acting					
NPH	2–4 hours	4–6	8–12	14–18	Cloudy
Long-acting					
Detemir	2 hours	6–9	14–24	24	Clear
Glargine	4–5 hours	–	22–24	24	Clear

NPH, neutral protamine Hagedorn.

- In type 1 DM, the average daily insulin requirement is 0.5 to 0.6 units/kg. Requirements may fall to 0.1 to 0.4 units/kg in the honeymoon phase. Higher doses (0.5–1 unit/kg) are warranted during acute illness or ketosis. In type 2 DM, a dosage range of 0.7 to 2.5 units/kg is often required for patients with significant insulin resistance.
- Hypoglycemia and weight gain are the most common adverse effects of insulin. Treatment of hypoglycemia is as follows:
  - ✓ **Glucose** (10–15 g) given orally for conscious patients.
  - ✓ **Dextrose** IV may be required for unconscious patients.
  - ✓ **Glucagon**, 1 g intramuscularly, is preferred in unconscious patients when IV access cannot be established.

Glucagon-like Peptide 1 (GLP-1) Agonists

- **Exenatide** (Byetta, Bydureon) enhances insulin secretion and reduces hepatic glucose production. It also increases satiety, slows gastric emptying, and promotes weight loss. It significantly decreases postprandial glucose excursions but has only a modest effect on FPG. Average A1C reduction is ~0.9% with twice-daily exenatide.
  - ✓Byetta: Initial dose 5 mcg SC twice daily, titrated to 10 mcg twice daily in 1 month if needed and as tolerated. Inject 0 to 60 minutes before morning and evening meals.
  - ✓Bydureon: Extended-release product administered as 2 mg SC once weekly at any time of day, with or without meals.

The most common adverse effects are nausea, vomiting, and diarrhea. Injection site reactions (nodules, erythema) may occur with extended-release product.

- **Liraglutide** (Victoza) has pharmacologic and adverse effects similar to exenatide. Longer half-life permits once-daily dosing. Average A1C reduction is ~1.1%, and liraglutide lowers FPG and postprandial glucose levels by 25 to 40 mg/dL (1.4–2.2 mmol/L). Dosing: Begin with 0.6 mg SC once daily (independent of meals) for at least 1 week, then increase to 1.2 mg daily for at least 1 week. If necessary, increase to maximum dose of 1.8 mg daily after at least 1 week.

Amylinomimetic

- **Pramlintide** (Symlin) suppresses inappropriately high postprandial glucagon secretion, decreases prandial glucose excursions, increases satiety, and slows gastric emptying. It has little effect on FPG. Average A1C reduction is ~0.6%, but optimizing concurrent insulin may further decrease A1C. The most common adverse effects are

nausea, vomiting, and anorexia. It does not cause hypoglycemia when used alone but is indicated only in patients receiving insulin, so hypoglycemia can occur. If a prandial insulin dose is used, reduce it by 30% to 50% when pramlintide is started to minimize severe hypoglycemia. In type 2 DM, starting dose is 60 mcg SC prior to major meals; titrate up to 120 mcg per dose as tolerated and as warranted based on postprandial plasma glucose levels. In type 1 DM, start with 15 mcg prior to each meal, titrating up in 15 mcg increments to maximum 60 mcg prior to each meal if tolerated and warranted.

Sulfonylureas

- Sulfonylureas exert hypoglycemic action by stimulating pancreatic secretion of insulin. All sulfonylureas are equally effective in lowering blood glucose when administered in equipotent doses. On average, the A1C falls by 1.5% to 2% with FPG reductions of 60 to 70 mg/dL (3.3–3.9 mmol/L).
- The most common side effect is hypoglycemia, which is more problematic with long half-life drugs. Individuals at high risk include the elderly, those with renal insufficiency or advanced liver disease, and those who skip meals, exercise vigorously, or lose a substantial amount of weight. Weight gain is common; less common adverse effects include skin rash, hemolytic anemia, GI upset, and cholestasis. Hyponatremia is most common with chlorpropamide but has also been reported with tolbutamide.
- Recommended starting doses (**Table 19–4**) should be reduced in elderly patients who may have compromised renal or hepatic function. Dosage can be titrated as soon as every 2 weeks (longer interval with chlorpropamide) to achieve glycemic goals.

Short-acting Insulin Secretagogues (Meglitinides)

- Similar to sulfonylureas, meglitinides lower glucose by stimulating pancreatic insulin secretion, but insulin release is glucose dependent and diminishes at low blood glucose concentrations. Hypoglycemic risk appears to be less with meglitinides than with sulfonylureas. Average A1C reduction is 0.8% to 1%. These agents can be used to provide increased insulin secretion during meals (when needed) in patients who are close to glycemic goals. They should be administered before each meal (up to 30 minutes prior). If a meal is skipped, the medication should also be skipped.
  - ✓ **Repaglinide** (Prandin): Start with 0.5 to 2 mg orally with maximum 4 mg per meal (up to four meals daily or 16 mg/day).
  - ✓ **Nateglinide** (Starlix): 120 mg orally three times daily before each meal. Initial dose may be lowered to 60 mg per meal in patients who are near goal A1C.

Biguanides

- **Metformin** enhances insulin sensitivity of hepatic and peripheral (muscle) tissues, allowing for increased glucose uptake. It reduces A1C levels by 1.5% to 2%, FPG levels by 60 to 80 mg/dL (3.3–4.4 mmol/L), and retains ability to reduce FPG levels when very high (>300 mg/dL or >16.7 mmol/L). Metformin reduces plasma triglycerides and low-density lipoprotein (LDL) cholesterol by 8% to 15% and modestly increases high-density lipoprotein (HDL) cholesterol (2%). It does not induce hypoglycemia when used alone.
- Metformin is logical in overweight/obese type 2 DM patients (if tolerated and not contraindicated) because it is the only oral antihyperglycemic medication shown to reduce the risk of total mortality.
- The most common adverse effects are abdominal discomfort, stomach upset, diarrhea, and anorexia. These effects can be minimized by titrating the dose slowly and taking it with food. Extended-release metformin (Glucophage XR) may reduce GI side effects. Lactic acidosis occurs rarely and can be minimized by avoiding use in patients with renal insufficiency (serum creatinine of 1.4 mg/dL or more [≥124 μmol/L] in women and 1.5 mg/dL or more [≥133 μmol/L] in men), congestive heart failure, or conditions predisposing to hypoxemia or inherent lactic acidosis.
  - ✓ **Metformin immediate-release**: Start at 500 mg orally twice daily with the largest meals and increase by 500 mg weekly as tolerated until reaching glycemic goals or

TABLE 19–4 Oral Agents for the Treatment of Type 2 Diabetes Mellitus

Generic Name (generic version available? Y = yes, N = no)	Brand	Dosage Strengths (mg)	Recommended Starting Dosage (mg/day)		Maximum Dose (mg/day)	Metabolism or Therapeutic Notes
			Nonelderly	Elderly		
Sulfonylureas						
Acetohexamide (Y)	Dymelor	250, 500	250	125–250	1500	Hepatic metabolism; metabolite potency equal to parent compound; renally eliminated
Chlorpropamide (Y)	Diabinese	100, 250	250	100	500	Hepatic metabolism; also excreted unchanged renally
Tolazamide (Y)	Tolinase	100, 250, 500	100–250	100	1000	Hepatic metabolism; metabolite less active than parent compound; renally eliminated
Tolbutamide (Y)	Orinase	250, 500	1,000–2,000	500–1,000	3000	Hepatic metabolism to inactive metabolites excreted renally
Glipizide (Y)	Glucotrol	5, 10	5	2.5–5	40	Hepatic metabolism to inactive metabolites
Glipizide (Y)	Glucotrol XL	2.5, 5, 10, 20	5	2.5–5	20	Slow-release form; do not cut tablet
Glyburide (Y)	DiaBeta, Micronase	1.25, 2.5, 5	5	1.25–2.5	20	Hepatic metabolism; elimination one half renal, one half feces
Glyburide, micronized (Y)	Glynase	1.5, 3, 6	3	1.5–3	12	Equal control, but better absorption from micronized preparation
Glimepiride (Y)	Amaryl	1, 2, 4	1–2	0.5–1	8	Hepatic metabolism to inactive metabolites
Short-acting insulin secretagogues						
Nateglinide (N)	Starlix	60, 120	120 with meals	120 with meals	120 mg three times daily	Metabolized by cytochrome (CYP)-2C9 and -3A4 to weakly active metabolites; renally eliminated
Repaglinide (N)	Prandin	0.5, 1, 2	0.5–1 with meals	0.5–1 with meals	16	Metabolized by CYP-3A4 to inactive metabolites; excreted in bile

Biguanides						
Metformin (Y)	Glucophage	500, 850, 1000	500 mg twice daily	Assess renal function	2550	No metabolism; renally secreted and excreted
Metformin extended-release (Y)	Glucophage XR	500, 750, 1000	500–1,000 mg with evening meal	Assess renal function	2550	Take with evening meal or may split dose; may consider trial if intolerant to immediate-release
Metformin solution	Riomet	500 mg/5 mL	500 mg daily	Assess renal function	2000	
Thiazolidinediones						
Pioglitazone (N)	Actos	15, 30, 45	15	15	45	Metabolized by CYP-2C8 and -3A4; two metabolites have longer half-lives than parent compound
Rosiglitazone (N)	Avandia	2, 4, 8	2–4	2	8 mg/day or 4 mg twice daily	Metabolized by CYP-2C8 and -2C9 to inactive metabolites excreted renally
α-Glucosidase inhibitors						
Acarbose (N)	Precose	25, 50, 100	25 mg 1–3 times daily	25 mg 1–3 times daily	25–100 mg three times a day	Eliminated in bile
Miglitol (N)	Glyset	25, 50, 100	25 mg 1–3 times daily	25 mg 1–3 times daily	25–100 mg 3 times daily	Eliminated renally
Dipeptidyl peptidase-4 inhibitors (DPP-4 inhibitors)						
Sitagliptin (N)	Januvia	25, 50, 100	100 mg daily	25–100 mg daily based on renal function	100 mg daily	50 mg daily if CLcr >30 to <50 mL/min; 25 mg daily if CLcr <30 mL/min
Saxagliptin (N)	Onglyza	2.5, 5	5 mg daily	2.5–5 mg daily based on renal function	5 mg daily	2.5 mg daily if CLcr <50 mL/min or if on strong inhibitors of CYP-3A4/5
Linagliptin (N)	Tradjenta	5 mg	5 mg daily	5 mg daily	5 mg daily	Do not use with strong inducers of CYP3A4 or p-glycoprotein

TABLE 19–3 Oral Agents for the Treatment of Type 2 Diabetes Mellitus (*Continued*)

Generic Name (generic version available? Y = yes, N = no)	Brand	Dosage Strengths (mg)	Recommended Starting Dosage (mg/day)		Maximum Dose (mg/day)	Metabolism or Therapeutic Notes
			Nonelderly	Elderly		
Alogliptin (N)	Nesina	6.25, 12.5, 25 mg	25 mg daily	25 mg	25 mg daily	75% eliminated unchanged in urine
Example combination products						
Glyburide/metformin (Y)	Glucovance	1.25/250, 2.5/500, 5/500	2.5–5/500 mg twice daily	1.25/250 mg twice daily; assess renal function	20 mg of glyburide, 2000 mg of metformin	Used as initial therapy: 1.25/250 mg twice daily
Glipizide/metformin (N)	Metaglip	2.5/250, 2.5/500, 5/500	2.5–5/500 mg twice daily	2.5/250 mg; assess renal function	20 mg of glipizide, 2000 mg of metformin	Used as initial therapy: 2.5/250 mg twice daily
Rosiglitazone/metformin (N)	Avandamet	1/500, 2/500, 4/500, 2/1000, 4/1000	1–2/500 mg twice daily	1/500 mg twice daily; assess renal function	8 mg of rosiglitazone; 2000 mg of metformin	Can use as initial therapy

CLcr, creatinine clearance.

2500 mg/day. Metformin 850 mg can be dosed once daily and then increased every 1 to 2 weeks to maximum 850 mg three times daily (2550 mg/day).

✓ **Metformin extended-release** (Glucophage XR): Start with 500 mg orally with the evening meal and increase by 500 mg weekly as tolerated to maximum single evening dose of 2000 mg/day. Administration two or three times daily may reduce GI side effects and improve glycemic control. The 750 mg tablets can be titrated weekly to maximum dose of 2250 mg/day.

Thiazolidinediones (Glitazones)

- These agents enhance insulin sensitivity in muscle, liver, and fat tissues indirectly. Insulin must be present in significant quantities. When given for 6 months at maximal doses, pioglitazone and rosiglitazone reduce A1C by ~1.5% and FPG by 60 to 70 mg/dL (3.3–3.9 mmol/L). Maximum effects may not be seen until 3 to 4 months of therapy.
- Pioglitazone decreases plasma triglycerides by 10% to 20%, whereas rosiglitazone tends to have no effect. Pioglitazone does not cause significant increases in LDL cholesterol, whereas LDL cholesterol may increase by 5% to 15% with rosiglitazone.
- Fluid retention may occur, and peripheral edema is reported in 4% to 5% of patients. When used with insulin, incidence of edema is ~15%. Glitazones are contraindicated in patients with New York Heart Association class III or IV heart failure and should be used with caution in patients with class I or II heart failure or other underlying cardiac disease.
- Weight gain of 1.5 to 4 kg is not uncommon. Rarely, rapid gain of a large amount of weight may necessitate discontinuation of therapy. Glitazones have also been associated with liver injury, increased fractures, and a slightly increased risk of bladder cancer.
  - ✓ **Pioglitazone** (Actos): Start at 15 mg orally once daily; maximum dose 45 mg/day.
  - ✓ **Rosiglitazone** (Avandia): Initiate with 2 to 4 mg orally once daily; maximum dose 8 mg/day. A dose of 4 mg twice daily can reduce A1C by 0.2% to 0.3% more than 8 mg taken once daily.

α-Glucosidase Inhibitors

- These agents prevent breakdown of sucrose and complex carbohydrates in the small intestine, prolonging carbohydrate absorption. Net effect is reduction in postprandial glucose (40–50 mg/dL; 2.2–2.8 mmol/L) with relatively unchanged FBG (~10% reduction). Efficacy is modest, with average A1C reduction 0.3% to 1%. Good candidates for these drugs are patients who are near target A1C levels with near-normal FPG levels but high postprandial levels.
- The most common side effects are flatulence, bloating, abdominal discomfort, and diarrhea, which can be minimized by slow dosage titration. If hypoglycemia occurs when used in combination with a hypoglycemic agent (sulfonylurea or insulin), oral or parenteral glucose (dextrose) products or glucagon must be given because the drug will inhibit breakdown and absorption of more complex sugar molecules (eg, sucrose).
  - ✓ **Acarbose** (Precose) and **miglitol** (Glyset): Initiate therapy with very low dose (25 mg orally with one meal a day) and increase very gradually (over several months) to maximum 50 mg three times daily for patients weighing 60 kg or more, or 100 mg three times daily for patients above 60 kg. The drugs should be taken with the first bite of the meal so the drug is present to inhibit enzyme activity.

Dipeptidyl Peptidase-4 (DPP-4) Inhibitors

- DPP-4 inhibitors partially reduce the inappropriately elevated glucagon postprandially and stimulate glucose-dependent insulin secretion. Average A1C reduction 0.7% to 1% at maximum dose.
- The drugs are well tolerated, weight neutral, and do not cause GI side effects. Mild hypoglycemia may occur, but DPP-4 inhibitors do not increase risk of hypoglycemia as monotherapy or in combination with medications that have a low incidence of hypoglycemia. Urticaria and/or facial edema may occur in 1% of patients, and discontinuation is warranted. Rare cases of Stevens–Johnson syndrome have

been reported. Saxagliptin causes a dose-related reduction in absolute lymphocyte count; discontinuation should be considered if prolonged infection occurs.

✓ **Sitagliptin** (Januvia): Usual dose 100 mg orally once daily. Use 50 mg daily if CLcr 30 to 50 mL/min and 25 mg daily if CLcr less than 30 mL/min.

✓ **Saxagliptin** (Onglyza): Usual dose 5 mg orally daily. Reduce to 2.5 mg daily if CLcr less than 50 mL/min or strong CYP-3A4/5 inhibitors are used concurrently.

✓ **Linagliptin** (Tradjenta): 5 mg orally daily; dose adjustment not required in renal insufficiency or with concomitant drug therapy.

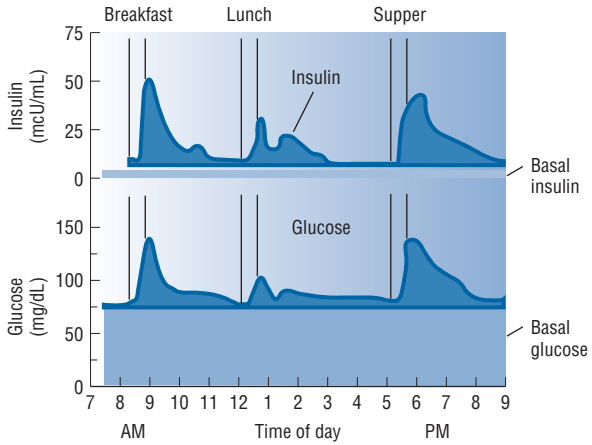
✓ **Alogliptin** (Nesina): Usual dose 25 mg once daily. Decrease to 12.5 mg daily when CLcr less than 60 mL/min and 6.25 mg when CLcr less than 30 mL/min.

Bile Acid Sequestrants

- **Colesevelam** (Welchol) binds bile acid in the intestinal lumen, decreasing the bile acid pool for reabsorption. Its mechanism in lowering plasma glucose levels is unknown.
- A1C reductions from baseline were ~0.4% when colesevelam 3.8 g/day was added to stable metformin, sulfonylureas, or insulin. FPG was modestly reduced by 5 to 10 mg/dL (0.3–0.6 mmol/L). Colesevelam may also reduce LDL cholesterol by 12% to 16% in patients with type 2 DM. Triglycerides may increase when combined with sulfonylureas or insulin, but not with metformin. Colesevelam is weight neutral.
- The most common side effects are constipation and dyspepsia; it should be taken with a large amount of water. Colesevelam has multiple absorption-related drug–drug interactions.
- Colesevelam dose for type 2 DM is six 625-mg tablets daily (total 3.75 g/day); may split into three tablets twice daily if desired. Administer each dose with meals because colesevelam binds to bile released during the meal.

PHARMACOTHERAPY OF TYPE 1 DIABETES MELLITUS

- All patients with type 1 DM require insulin, but the type and manner of delivery differ among patients and clinicians. Therapy should attempt to match carbohydrate intake with glucose-lowering processes (usually insulin) and exercise. Dietary intervention should allow the patient to live as normal a life as possible. All patients receiving insulin should have extensive education in recognition and treatment of hypoglycemia.
- Fig. 19–1 depicts the relationship between glucose concentrations and insulin secretion over the course of a day and how various insulin and amylinomimetic regimens may be given. The timing of insulin onset, peak, and duration of effect must match meal patterns and exercise schedules to achieve near-normal blood glucose values throughout the day.
- A regimen of two daily injections that may roughly approximate physiologic insulin secretion is split-mixed injections of a morning dose of intermediate-duration insulin (eg, NPH) and regular insulin before breakfast and again before the evening meal (see **Fig. 19–1**, no. 1). This assumes that the morning intermediate-acting insulin provides basal insulin for the day and covers the midday meal, the morning regular insulin covers breakfast, the evening intermediate-acting insulin gives basal insulin for the rest of the day, and the evening regular insulin covers the evening meal. Patients may be started on 0.6 units/kg/day, with two thirds given in the morning and one third in the evening. Intermediate-acting insulin (eg, NPH) should comprise two thirds of the morning dose and one half of the evening dose. However, most patients are not sufficiently predictable in their schedule and food intake to allow tight glucose control with this approach. If the fasting glucose in the morning is too high or hypoglycemia occurs in the early hours of sleep, the evening NPH dose may be moved to bedtime (now three total injections per day). This approach improves glycemic control and may reduce hypoglycemia sufficiently for patients unable to follow more intense regimens.



Intensive insulin therapy regimens

	7 AM (meal)	11 AM (meal)	5 PM (meal)	Bedtime
1. 2 doses,[a] R or rapid acting + N	R, L, A, GLU + N		R, L, A, GLU + N	
2. 3 doses, R or rapid acting + N	R, L, A, GLU + N	R, L, A, GLU	R, L, A, GLU + N	
3. 4 doses, R or rapid acting + N	R, L, A, GLU	R, L, A, GLU	R, L, A, GLU	N
4. 4 doses R or rapid acting + N	R, L, A, GLU + N	R, L, A, GLU	R, L, A, GLU	N
5. 4 doses,[b] R or rapid acting + long acting	R, L, A, GLU	R, L, A, GLU	R, L, A, GLU	G or D[b] (G may be given anytime every 24 hours)
	←	Adjusted basal	→	
6. CS-II pump	Bolus	Bolus	Bolus	
7. 3 doses pramlintide added to regimens above	P	P	P	

[a] Many clinicians may not consider this intensive insulin therapy
[b] May be given BID in type 1 DM = 5 doses

FIGURE 19–1. Relationship between insulin and glucose over the course of a day and how various insulin and amylinomimetic regimens could be given. (A, aspart; CS-II, continuous subcutaneous insulin infusion; D, detemir; G, glargine; GLU, glulisine; L, lispro; N, neutral protamine Hagedorn; P, pramlintide; R, regular.)

- The basal-bolus concept attempts to replicate normal insulin physiology by giving intermediate- or long-acting insulin as the basal component and rapid-acting insulin as the bolus or pre-meal portion (see **Fig. 19–1**, nos. 2, 3, 4, and 5). Intensive therapy using this approach is recommended for all adult patients at the time of diagnosis to reinforce the importance of glycemic control from the outset of treatment. Occasional patients with an extended honeymoon period may need less intensive therapy initially but should be converted to basal-bolus therapy at the onset of glycemic lability.
- The basal insulin component may be provided by once- or twice-daily **NPH** or **detemir**, or once-daily **insulin glargine**. Most type 1 DM patients require two injections of all insulins except insulin glargine. Insulin glargine and insulin detemir are the most feasible basal insulins for most patients with type 1 DM.
- The bolus or prandial insulin component is given before meals with **regular insulin, insulin lispro, insulin aspart,** or **insulin glulisine**. The rapid onset and short duration of rapid-acting insulin analogs more closely replicate normal physiology than regular insulin, allowing the patient to vary the amount of insulin injected based on the preprandial SMBG level, upcoming activity level, and anticipated carbohydrate intake. Most patients start with a prescribed dose of insulin preprandially that they vary based on an insulin algorithm. Carbohydrate counting is an effective tool for determining the amount of rapid-acting insulin to be injected preprandially.
- Approximately 50% of the total daily insulin dose should be basal insulin and 50% bolus insulin, divided into doses before meals. As an example, patients may begin on ~0.6 units/kg/day of insulin, with basal insulin 50% of the total dose and prandial insulin 20% of the total dose before breakfast, 15% before lunch, and 15% before dinner. Most patients require total daily doses between 0.5 and 1 unit/kg/day.
- Continuous subcutaneous insulin infusion pump therapy (generally using **insulin lispro** or **aspart** to diminish aggregation) is the most sophisticated form of insulin delivery (see **Fig. 19–1**, no. 6). The basal insulin dose may be varied, related to changes in insulin requirements throughout the day. In select patients, this feature of continuous subcutaneous insulin infusion allows greater glycemic control. However, it requires greater attention to detail and frequency of SMBG than a basal-bolus regimen with four injections daily.
- Pramlintide may be appropriate in type 1 DM patients who continue to have erratic postprandial control despite implementation of these strategies (see **Fig. 19–1**, no. 7). At initiation of therapy, each dose of prandial insulin should be reduced by 30% to 50% to prevent hypoglycemia. Pramlintide should be titrated based on GI adverse effects and postprandial glycemic goals.

PHARMACOTHERAPY OF TYPE 2 DIABETES MELLITUS

- Symptomatic patients may initially require insulin or combination oral therapy to reduce glucose toxicity (which may reduce β-cell insulin secretion and worsen insulin resistance).
- Patients with A1C 7% or less are usually treated with therapeutic lifestyle measures and an agent that will not cause hypoglycemia. Those with A1C greater than 7% but less than 8.5% could be initially treated with a single oral agent or combination therapy. Patients with higher initial A1C values may benefit from initial therapy with two oral agents or insulin. Patients with higher initial A1C values may benefit from initial therapy with two oral agents or even insulin.
- Obese patients (>120% ideal body weight) without contraindications should be started on metformin initially, titrated to ~2,000 mg/day. A glitazone may be used in patients intolerant of or having a contraindication to metformin.
- Near-normal-weight patients may be better treated with insulin secretagogues, although metformin will work in this population.

- When the disease progresses on metformin therapy, an insulin secretagogue such as a sulfonylurea is often added; however, better choices to sustain A1C reductions would be a glitazone or GLP-1 agonist, but each also has limitations.
- When initial therapy is no longer keeping the patient at the goal, adding one agent may be appropriate if the A1C is close to the goal. If the A1C is greater than 1% to 1.5% above the goal, multiple oral agents or insulin therapy may be appropriate.
- Triple therapy often consists of metformin, a sulfonylurea, and a glitazone or DPP-4 inhibitor. A logical alternative is metformin, a glitazone, and a GLP-1 agonist. A DPP-4 inhibitor may be an alternative to the GLP-1 agonist if an injectable product is not preferred.
- Insulin therapy should be considered if the A1C is greater than 8.5% to 9% on multiple therapies. Sulfonylureas are often stopped when insulin is added and insulin sensitizers are continued.
- Virtually all patients ultimately become insulinopenic and require insulin therapy. Patients are often transitioned to insulin by using a bedtime injection of an intermediate- or long-acting insulin with oral agents used primarily for glycemic control during the day. This results in less hyperinsulinemia during the day and less weight gain than starting prandial insulin or split-mix twice-daily insulin. Insulin sensitizers are commonly used with insulin because most patients are insulin resistant.
- When the combination of bedtime insulin plus daytime oral medications fails, a conventional multiple daily dose insulin regimen with an insulin sensitizer can be tried. If this is unsuccessful, a bolus injection can be given with the second largest meal of the day, for a total of three injections. After this, the standard basal-bolus model is followed. Other treatment options are also available.

TREATMENT OF COMPLICATIONS

Retinopathy

- Patients with established retinopathy should be examined by an ophthalmologist at least every 6 to 12 months. Early background retinopathy may reverse with improved glycemic control and optimized blood pressure (BP) control. More advanced disease will not fully regress with improved control, and aggressive glucose reduction may acutely worsen retinopathy. Laser photocoagulation has markedly improved sight preservation in diabetic patients.

Neuropathy

- Distal symmetrical peripheral neuropathy is the most common complication in patients with type 2 DM. Paresthesias, numbness, or pain may be predominant symptoms. The feet are involved far more often than the hands. Improved glycemic control is the primary treatment and may alleviate some symptoms. Pharmacologic therapy is symptomatic and empiric, including low-dose **tricyclic antidepressants,** anticonvulsants (eg, **gabapentin, pregabalin,** and rarely **carbamazepine**), **duloxetine, venlafaxine, topical capsaicin,** and various analgesics, including **tramadol** and **nonsteroidal anti-inflammatory drugs**.
- Gastroparesis can be severe and debilitating. Improved glycemic control, discontinuation of medications that slow gastric motility, and use of **metoclopramide** (preferably for only a few days at a time) or **erythromycin** may be helpful.
- Patients with orthostatic hypotension may require mineralocorticoids or adrenergic agonists.
- Diabetic diarrhea is commonly nocturnal and frequently responds to a 10- to 14-day course of an antibiotic such as **doxycycline** or **metronidazole**. **Octreotide** may be useful in unresponsive cases.
- Erectile dysfunction is common, and initial therapy should include a trial of an oral phosphodiesterase-5 inhibitor (eg, **sildenafil, vardenafil,** or **tadalafil**).

Nephropathy

- Glucose and BP control are most important for prevention of nephropathy, and BP control is most important for retarding the progression of established nephropathy.
- Angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers have shown efficacy in preventing the clinical progression of renal disease in patients with diabetes. Diuretics are frequently necessary due to volume-expanded states and are recommended second-line therapy.

Peripheral Vascular Disease and Foot Ulcers

- Claudication and nonhealing foot ulcers are common in type 2 DM. Smoking cessation, correction of dyslipidemia, and antiplatelet therapy are important treatment strategies.
- **Cilostazol** (Pletal) may be useful in select patients. Revascularization is successful with some patients.
- Local debridement and appropriate footwear and foot care are important in the early treatment of foot lesions. Topical treatments and other measures may be beneficial in more advanced lesions.

Coronary Heart Disease

- Multiple-risk-factor intervention (treatment of dyslipidemia and hypertension, smoking cessation, and antiplatelet therapy) reduces macrovascular events.
- The National Cholesterol Education Program Adult Treatment Panel III guidelines (see Chap. 8) classify DM as a coronary heart disease risk equivalent, and the goal LDL cholesterol is less than 100 mg/dL (<2.59 mmol/L). An optional LDL goal in high-risk patients is less than 70 mg/dL (<1.81 mmol/L). After the LDL goal is reached (usually with a **statin**), treatment of high triglycerides (≥200 mg/dL [<1.81 mmol/L]) is considered. The non-HDL goal for patients with DM is less than 130 mg/dL (<3.36 mmol/L). **Niacin** or a **fibrate** can be added to reach that goal if triglycerides are 201 to 499 mg/dL (2.27–5.64 mmol/L). Revised cholesterol treatment guidelines were released in late 2013.
- The American Diabetes Association recommends a goal BP less than 140/80 mm Hg in patients with DM. **ACE inhibitors** and **angiotensin receptor blockers** are generally recommended for initial therapy. Many patients require multiple agents, so **diuretics**, **calcium channel blockers**, and **β-blockers** are useful as second and third agents.

EVALUATION OF THERAPEUTIC OUTCOMES

- To follow long-term glycemic control for the previous 3 months, measure A1C at least twice a year in patients meeting treatment goals on a stable therapeutic regimen.
- Regardless of the insulin regimen chosen, make gross adjustments in the total daily insulin dose based on A1C measurements and symptoms such as polyuria, polydipsia, and weight gain or loss. Finer insulin adjustments can be determined on the basis of the results of frequent SMBG.
- Ask patients receiving insulin about the recognition of hypoglycemia at least annually. Document the frequency of hypoglycemia and the treatment required.
- Monitor patients receiving bedtime insulin for hypoglycemia by asking about nocturnal sweating, palpitations, and nightmares, as well as the results of SMBG.
- For patients with type 2 DM, obtain a routine urinalysis at diagnosis as the initial screening test for albuminuria. If positive, a 24-hour urine test for quantitative assessment will assist in developing a treatment plan. If the urinalysis is negative for protein, a test to evaluate the presence of microalbuminuria is recommended.
- Obtain fasting lipid profiles at each follow-up visit if not at goal, annually if stable and at goal, or every 2 years if the profile suggests low risk.

- Perform and document regular foot exams (each visit), urine albumin assessment (annually), and dilated ophthalmologic exams (yearly or more frequently with abnormalities).
- Administer an annual influenza vaccine and assess for administration of the pneumococcal vaccine and hepatitis B vaccine series along with management of other cardiovascular risk factors (eg, smoking and antiplatelet therapy).

See Chapter 57, Diabetes Mellitus, authored by Curtis L. Triplitt, Thomas Repas, and Carlos Alvarez, for a more detailed discussion of this topic.

Thyroid Disorders

20 CHAPTER

- *Thyroid disorders* involve thyroid hormone production or secretion and result in alterations in metabolic stability.

THYROID HORMONE PHYSIOLOGY

- Thyroid hormones; thyroxine (T_4) and triiodothyronine (T_3) are formed on thyroglobulin, a large glycoprotein synthesized within the thyroid cell. Inorganic iodide enters the thyroid follicular cell and is oxidized by thyroid peroxidase and covalently bound (organified) to tyrosine residues of thyroglobulin.
- Iodinated tyrosine residues monoiodotyrosine (MIT) and diiodotyrosine (DIT) combine (couple) to form iodothyronines in reactions catalyzed by thyroid peroxidase. Thus, two molecules of DIT combine to form T_4, and MIT and DIT join to form T_3.
- Proteolysis within thyroid cells releases thyroid hormone into the bloodstream. T_4 and T_3 are transported by thyroid-binding globulin (TBG), transthyretin, and albumin. Only the unbound (free) thyroid hormone can diffuse into cells, elicit biologic effects, and regulate thyroid-stimulating hormone (TSH) secretion from the pituitary.
- T_4 is secreted solely from the thyroid, but less than 20% of T_3 is produced there; most T_3 is formed from breakdown of T_4 catalyzed by the enzyme 5′-monodeiodinase in peripheral tissues. T_3 is five times more active than T_4. T_4 may also be acted on by 5′-monodeiodinase to form reverse T_3, which has no significant biologic activity.
- Thyroid hormone production is regulated by TSH secreted by the anterior pituitary, which in turn is under negative feedback control by the circulating level of free thyroid hormone and the positive influence of hypothalamic thyrotropin-releasing hormone (TRH). Thyroid hormone production is also regulated by extrathyroidal deiodination of T_4 to T_3, which can be affected by nutrition, nonthyroidal hormones, drugs, and illness.

THYROTOXICOSIS (HYPERTHYROIDISM)

PATHOPHYSIOLOGY

- Thyrotoxicosis results when tissues are exposed to excessive levels of T_4, T_3, or both. TSH-secreting pituitary tumors release biologically active hormone that is unresponsive to normal feedback control. The tumors may cosecrete prolactin or growth hormone; therefore, patients may present with amenorrhea, galactorrhea, or signs of acromegaly.
- In Graves disease, hyperthyroidism results from the action of thyroid-stimulating antibodies (TSAb) directed against the thyrotropin receptor on the surface of thyroid cell. These immunoglobulins bind to the receptor and activate the enzyme adenylate cyclase in the same manner as TSH.
- An autonomous thyroid nodule (toxic adenoma) is a thyroid mass whose function is independent of pituitary control. Hyperthyroidism usually occurs with larger nodules (>3 cm in diameter).
- In multinodular goiter, follicles with autonomous function coexist with normal or even nonfunctioning follicles. Thyrotoxicosis occurs when autonomous follicles generate more thyroid hormone than is required.
- Painful subacute (granulomatous or de Quervain) thyroiditis often develops after a viral syndrome, but rarely has a specific virus been identified in thyroid parenchyma.
- Painless (silent, lymphocytic, or postpartum) thyroiditis is a common cause of thyrotoxicosis; its etiology is not fully understood; autoimmunity may underlie most cases.
- Thyrotoxicosis factitia is produced by ingestion of exogenous thyroid hormone. This may occur when thyroid hormone is used for inappropriate indications, excessive

doses are used for accepted medical indications, there is accidental ingestion, or it is used surreptitiously.
- Amiodarone may induce thyrotoxicosis (2%–3% of patients) or hypothyroidism. It interferes with type I 5′-deiodinase, leading to reduced conversion of T_4 to T_3, and iodide release from the drug may contribute to iodine excess. Amiodarone also causes a destructive thyroiditis with loss of thyroglobulin and thyroid hormones.

CLINICAL PRESENTATION

- Symptoms of thyrotoxicosis include nervousness, anxiety, palpitations, emotional lability, easy fatigability, heat intolerance, weight loss concurrent with increased appetite, increased frequency of bowel movements, proximal muscle weakness (noted on climbing stairs or arising from a sitting position), and scanty or irregular menses in women.
- Physical signs include warm, smooth, moist skin and unusually fine hair; separation of the ends of the fingernails from the nail beds (onycholysis); retraction of the eyelids and lagging of the upper lid behind the globe upon downward gaze (lid lag); tachycardia at rest, widened pulse pressure, and systolic ejection murmur; occasional gynecomastia in men; fine tremor of the protruded tongue and outstretched hands; and hyperactive deep tendon reflexes.
- Graves disease is manifested by hyperthyroidism, diffuse thyroid enlargement, and extrathyroidal findings of exophthalmos, pretibial myxedema, and thyroid acropachy. In severe disease, a thrill may be felt and a systolic bruit may be heard over the gland.
- In subacute thyroiditis, patients have severe pain in the thyroid region, which often extends to the ear. Systemic symptoms include fever, malaise, myalgia, and signs and symptoms of thyrotoxicosis. The thyroid gland is firm and exquisitely tender on physical examination.
- Painless thyroiditis has a triphasic course that mimics painful subacute thyroiditis. Most patients present with mild thyrotoxic symptoms; lid retraction and lid lag are present, but exophthalmos is absent. The thyroid gland may be diffusely enlarged without tenderness.
- Thyroid storm is a life-threatening medical emergency characterized by decompensated thyrotoxicosis, high fever (often >39.4°C [103°F]), tachycardia, tachypnea, dehydration, delirium, coma, nausea, vomiting, and diarrhea. Precipitating factors include infection, trauma, surgery, radioactive iodine (RAI) treatment, and withdrawal from antithyroid drugs.

DIAGNOSIS

- Elevated 24-hour radioactive iodine uptake (RAIU) indicates true hyperthyroidism: the patient's thyroid gland is overproducing T_4, T_3, or both (normal RAIU 10%–30%). A low RAIU indicates that excess thyroid hormone is not a consequence of thyroid gland hyperfunction but is likely caused by thyroiditis or hormone ingestion.
- TSH-induced hyperthyroidism is diagnosed by evidence of peripheral hypermetabolism, diffuse thyroid gland enlargement, elevated free thyroid hormone levels, and elevated serum immunoreactive TSH concentrations. Because the pituitary gland is extremely sensitive to even minimal elevations of free T_4, a "normal" or elevated TSH level in any thyrotoxic patient indicates inappropriate production of TSH.
- TSH-secreting pituitary adenomas are diagnosed by demonstrating lack of TSH response to TRH stimulation, inappropriate TSH levels, elevated TSH α-subunit levels, and radiologic imaging.
- In thyrotoxic Graves disease, there is an increase in the overall hormone production rate with a disproportionate increase in T_3 relative to T_4 (**Table 20–1**). Saturation of TBG is increased due to elevated serum levels of T_4 and T_3, which is reflected in elevated T_3 resin uptake. As a result, concentrations of free T_4, free T_3, and the free T_4 and T_3 indices are increased to an even greater extent than the measured serum total T_4 and T_3 concentrations. The TSH level is undetectable due to negative feedback by elevated levels of thyroid hormone at the pituitary. In patients with manifest disease, measurement of serum free T_4 (or total T_4 and T_3 resin uptake), total T_3, and TSH will

TABLE 20–1 Thyroid Function Test Results in Different Thyroid Conditions

	Total T_4	Free T_4	Total T_3	T_3 Resin Uptake	Free Thyroxine Index	TSH
Normal	4.5–10.9 mcg/dL	0.8–2.7 ng/dL	60–181 ng/dL	22–34%	1.0–4.3 units	0.5–4.7 milli-international units/L
Hyperthyroid	↑↑	↑↑	↑↑↑	↑	↑↑↑	↓↓
Hypothyroid	↓↓	↓↓	↓	↓↓	↓↓↓	↑↑
Increased TBG	↑	Normal	↑	↓	Normal	Normal

TBG, thyroid-binding globulin; TSH, thyroid-stimulating hormone; T_3, triiodothyronine; T_4, thyroxine

confirm the diagnosis of thyrotoxicosis. If the patient is not pregnant, an increased 24-hour RAIU documents that the thyroid gland is inappropriately using iodine to produce more thyroid hormone when the patient is thyrotoxic.

- For toxic adenomas, because there may be isolated elevation of serum T_3 with autonomously functioning nodules, a T_3 level must be measured to rule out T_3 toxicosis if the T_4 level is normal. If autonomous function is suspected, but the TSH is normal, the diagnosis can be confirmed by failure of the autonomous nodule to decrease iodine uptake during exogenous T_3 administration sufficient to suppress TSH.
- In multinodular goiters, a thyroid scan shows patchy areas of autonomously functioning thyroid tissue.
- A low RAIU indicates the excess thyroid hormone is not a consequence of thyroid gland hyperfunction. This may be seen in painful subacute thyroiditis, painless thyroiditis, struma ovarii, follicular cancer, and factitious ingestion of exogenous thyroid hormone.
- In subacute thyroiditis, thyroid function tests typically run a triphasic course in this self-limited disease. Initially, serum T_4 levels are elevated due to release of preformed thyroid hormone. The 24-hour RAIU during this time is less than 2% because of thyroid inflammation and TSH suppression by the elevated T_4 level. As the disease progresses, intrathyroidal hormone stores are depleted, and the patient may become mildly hypothyroid with appropriately elevated TSH level. During the recovery phase, thyroid hormone stores are replenished, and serum TSH elevation gradually returns to normal.
- During the thyrotoxic phase of painless thyroiditis, the 24-hour RAIU is suppressed to less than 2%. Antithyroglobulin and antithyroid peroxidase antibody levels are elevated in more than 50% of patients.
- Thyrotoxicosis factitia should be suspected in a thyrotoxic patient without evidence of increased hormone production, thyroidal inflammation, or ectopic thyroid tissue. The RAIU is low because thyroid gland function is suppressed by exogenous thyroid hormone. Measurement of plasma thyroglobulin reveals presence of very low levels.

TREATMENT

- Goals of Treatment: Eliminate excess thyroid hormone; minimize symptoms and long-term consequences; and provide individualized therapy based on the type and severity of disease, patient age and gender, existence of nonthyroidal conditions, and response to previous therapy.

Nonpharmacologic Therapy

- Surgical removal of the thyroid gland should be considered in patients with a large gland (>80 g), severe ophthalmopathy, or lack of remission on antithyroid drug treatment.

- If thyroidectomy is planned, **propylthiouracil** (PTU) or **methimazole** is usually given until the patient is biochemically euthyroid (usually 6–8 weeks), followed by addition of **iodides** (500 mg/day) for 1–14 days before surgery to decrease vascularity of the gland. **Levothyroxine** may be added to maintain the euthyroid state while thionamides are continued.
- **Propranolol** has been used for several weeks preoperatively and 7 to 10 days after surgery to maintain pulse rate less than 90 beats/min. Combined pretreatment with propranolol and 10 to 14 days of **potassium iodide** also has been advocated.

Pharmacologic Therapy

THIOUREAS (THIONAMIDES)

- **PTU** and **methimazole** block thyroid hormone synthesis by inhibiting the peroxidase enzyme system of the thyroid, preventing oxidation of trapped iodide and subsequent incorporation into iodotyrosines and ultimately iodothyronine ("organification"); and by inhibiting coupling of MIT and DIT to form T_4 and T_3. PTU (but not methimazole) also inhibits peripheral conversion of T_4 to T_3.
- Usual initial doses include PTU 300 to 600 mg daily (usually in three or four divided doses) or methimazole 30 to 60 mg daily given in three divided doses. Evidence exists that both drugs can be given as a single daily dose.
- Improvement in symptoms and laboratory abnormalities should occur within 4 to 8 weeks, at which time a tapering regimen to maintenance doses can be started. Make dosage change monthly because the endogenously produced T_4 will reach a new steady-state concentration in this interval. Typical daily maintenance doses are PTU 50 to 300 mg and methimazole 5 to 30 mg. Continue therapy for 12 to 24 months to induce long-term remission.
- Monitor patients every 6 to 12 months after remission. If a relapse occurs, alternate therapy with RAI is preferred to a second course of antithyroid drugs, because subsequent courses are less likely to induce remission.
- Minor adverse reactions include pruritic maculopapular rashes, arthralgias, fever, and benign transient leukopenia (white blood cell count $<4000/mm^3$). The alternate thiourea may be tried in these situations, but cross-sensitivity occurs in ~50% of patients.
- Major adverse effects include agranulocytosis (with fever, malaise, gingivitis, oropharyngeal infection, and granulocyte count $<250/mm^3$), aplastic anemia, lupus-like syndrome, polymyositis, GI intolerance, hepatotoxicity, and hypoprothrombinemia. If it occurs, agranulocytosis usually develops in the first 3 months of therapy; routine monitoring is not recommended because of its sudden onset. Because of the risk of serious hepatotoxicity, PTU should not be considered first-line therapy except during the first trimester of pregnancy (when the risk of methimazole-induced embryopathy may exceed that of PTU-induced hepatotoxicity), intolerance to methimazole, and thyroid storm.

IODIDES

- **Iodide** acutely blocks thyroid hormone release, inhibits thyroid hormone biosynthesis by interfering with intrathyroidal iodide use, and decreases size and vascularity of the gland.
- Symptom improvement occurs within 2 to 7 days of initiating therapy, and serum T_4 and T_3 concentrations may be reduced for a few weeks.
- Iodides are often used as adjunctive therapy to prepare a patient with Graves disease for surgery, to acutely inhibit thyroid hormone release and quickly attain the euthyroid state in severely thyrotoxic patients with cardiac decompensation, or to inhibit thyroid hormone release after RAI therapy.
- **Potassium iodide** is available as a saturated solution (**SSKI,** 38 mg iodide per drop) or as **Lugol solution,** containing 6.3 mg of iodide per drop.
- Typical starting dose of SSKI is 3 to 10 drops daily (120–400 mg) in water or juice. When used to prepare a patient for surgery, it should be administered 7 to 14 days preoperatively.
- As an adjunct to RAI, SSKI should not be used before but rather 3 to 7 days after RAI treatment so the RAI can concentrate in the thyroid.

- Adverse effects include hypersensitivity reactions (skin rashes, drug fever, rhinitis, conjunctivitis), salivary gland swelling, "iodism" (metallic taste, burning mouth and throat, sore teeth and gums, symptoms of a head cold, and sometimes stomach upset and diarrhea), and gynecomastia.

ADRENERGIC BLOCKERS

- β-Blockers are used to ameliorate thyrotoxic symptoms such as palpitations, anxiety, tremor, and heat intolerance. They have no effect on peripheral thyrotoxicosis and protein metabolism and do not reduce TSAb or prevent thyroid storm. **Propranolol** and **nadolol** partially block conversion of T_4 to T_3, but this contribution to overall effect is small.
- β-Blockers are usually used as adjunctive therapy with antithyroid drugs, RAI, or iodides when treating Graves' disease or toxic nodules; in preparation for surgery; or in thyroid storm. The only conditions for which β-blockers are primary therapy for thyrotoxicosis are those associated with thyroiditis.
- **Propranolol** doses required to relieve adrenergic symptoms vary, but an initial dose of 20 to 40 mg orally four times daily is effective for most patients (heart rate <90 beats/min). Younger or more severely toxic patients may require 240 to 480 mg/day.
- β-Blockers are contraindicated in decompensated heart failure unless it is caused solely by tachycardia (high output). Other contraindications are sinus bradycardia, concomitant therapy with monoamine oxidase inhibitors or tricyclic antidepressants, and patients with spontaneous hypoglycemia. Side effects include nausea, vomiting, anxiety, insomnia, lightheadedness, bradycardia, and hematologic disturbances.
- Centrally acting sympatholytics (eg, **clonidine**) and calcium channel antagonists (eg, **diltiazem**) may be useful for symptom control when contraindications to β-blockade exist.

RADIOACTIVE IODINE

- **Sodium iodide–131** is an oral liquid that concentrates in the thyroid and initially disrupts hormone synthesis by incorporating into thyroid hormones and thyroglobulin. Over a period of weeks, follicles that have taken up RAI and surrounding follicles develop evidence of cellular necrosis and fibrosis of interstitial tissue.
- RAI is the agent of choice for Graves disease, toxic autonomous nodules, and toxic multinodular goiters. Pregnancy is an absolute contraindication to use of RAI.
- β-Blockers are the primary adjunctive therapy to RAI because they may be given anytime without compromising RAI therapy.
- Patients with cardiac disease and elderly patients are often treated with thionamides prior to RAI ablation because thyroid hormone levels transiently increase after RAI treatment due to release of preformed thyroid hormone.
- Antithyroid drugs are not routinely used after RAI because their use is associated with a higher incidence of posttreatment recurrence or persistent hyperthyroidism.
- If iodides are administered, they should be given 3 to 7 days after RAI to prevent interference with uptake of RAI in the thyroid gland.
- The goal of therapy is to destroy overactive thyroid cells, and a single dose of 4000 to 8000 rad results in a euthyroid state in 60% of patients at 6 months or sooner. A second dose of RAI should be given 6 months after the first RAI treatment if the patient remains hyperthyroid.
- Hypothyroidism commonly occurs months to years after RAI. The acute, short-term side effects include mild thyroidal tenderness and dysphagia. Long-term follow-up has not revealed an increased risk for development of thyroid carcinoma, leukemia, or congenital defects.

Treatment of Thyroid Storm

- Initiate the following therapeutic measures promptly: (1) suppression of thyroid hormone formation and secretion, (2) antiadrenergic therapy, (3) administration of corticosteroids, and (4) treatment of associated complications or coexisting factors that may have precipitated the storm (**Table 20–2**).

TABLE 20–2 Drug Dosages Used in the Management of Thyroid Storm

Drug	Regimen
Propylthiouracil	900–1200 mg/day orally in four or six divided doses
Methimazole	90–120 mg/day orally in four or six divided doses
Sodium iodide	Up to 2 g/day IV in single or divided doses
Lugol solution	5–10 drops three times daily in water or juice
Saturated solution of potassium iodide	1–2 drops three times daily in water or juice
Propranolol	40–80 mg every 6 hours
Dexamethasone	5–20 mg/day orally or IV in divided doses
Prednisone	25–100 mg/day orally in divided doses
Methylprednisolone	20–80 mg/day IV in divided doses
Hydrocortisone	100–400 mg/day IV in divided doses

- **Iodides,** which rapidly block the release of preformed thyroid hormone, should be administered after a thionamide is initiated to inhibit iodide utilization by the overactive gland.
- Antiadrenergic therapy with the short-acting agent **esmolol** is preferred because it can be used in patients with pulmonary disease or at risk for cardiac failure and because its effects can be rapidly reversed.
- **Corticosteroids** are generally recommended, but there is no convincing evidence of adrenocortical insufficiency in thyroid storm; their benefits may be attributed to their antipyretic action and stabilization of blood pressure (BP).
- General supportive measures, including **acetaminophen** as an antipyretic (aspirin or other nonsteroidal anti-inflammatory drugs may displace bound thyroid hormone), **fluid and electrolyte replacement, sedatives, digoxin, antiarrhythmics, insulin,** and **antibiotics** should be given as indicated.

EVALUATION OF THERAPEUTIC OUTCOMES

- After therapy (thionamides, RAI, or surgery) for hyperthyroidism has been initiated, evaluate patients monthly until they reach a euthyroid condition.
- Assess for clinical signs of continuing thyrotoxicosis or development of hypothyroidism.
- After T_4 replacement is initiated, the goal is to maintain both the free T_4 level and the TSH concentration in the normal range. Once a stable dose of T_4 is identified, monitor the patient every 6 to 12 months.

HYPOTHYROIDISM

PATHOPHYSIOLOGY

- The vast majority of patients have primary hypothyroidism due to thyroid gland failure from chronic autoimmune thyroiditis (Hashimoto's disease). Defects in suppressor T lymphocyte function lead to survival of a randomly mutating clone of helper T lymphocytes directed against antigens on the thyroid membrane. The resulting interaction stimulates B lymphocytes to produce thyroid antibodies.
- Iatrogenic hypothyroidism follows exposure to destructive amounts of radiation, after total thyroidectomy, or with excessive thionamide doses used to treat hyperthyroidism. Other causes of primary hypothyroidism include iodine deficiency, enzymatic defects within the thyroid, thyroid hypoplasia, and ingestion of goitrogens.
- Secondary hypothyroidism due to pituitary failure is uncommon. Pituitary insufficiency may be caused by destruction of thyrotrophs by pituitary tumors, surgical therapy, external pituitary radiation, postpartum pituitary necrosis (Sheehan syndrome), trauma, and infiltrative processes of the pituitary (eg, metastatic tumors, tuberculosis).

CLINICAL PRESENTATION

- Symptoms of hypothyroidism include dry skin, cold intolerance, weight gain, constipation, weakness, lethargy, fatigue, muscle cramps, myalgia, stiffness, and loss of ambition or energy. In children, thyroid hormone deficiency may manifest as growth or intellectual retardation.
- Physical signs include coarse skin and hair, cold or dry skin, periorbital puffiness, bradycardia, and slowed or hoarse speech. Objective weakness (with proximal muscles affected more than distal muscles) and slow relaxation of deep tendon reflexes are common. Reversible neurologic syndromes such as carpal tunnel syndrome, polyneuropathy, and cerebellar dysfunction may also occur.
- Most patients with secondary hypothyroidism due to inadequate TSH production have clinical signs of generalized pituitary insufficiency, such as abnormal menses and decreased libido, or evidence of a pituitary adenoma, such as visual field defects, galactorrhea, or acromegaloid features.
- Myxedema coma is a rare consequence of decompensated hypothyroidism manifested by hypothermia, advanced stages of hypothyroid symptoms, and altered sensorium ranging from delirium to coma. Mortality rates of 60% to 70% necessitate immediate and aggressive therapy.

DIAGNOSIS

- A rise in TSH level is the first evidence of primary hypothyroidism. Many patients have a free T_4 level within the normal range (compensated hypothyroidism) and few, if any, symptoms of hypothyroidism. As the disease progresses, the free T_4 drops below normal. The T_3 concentration is often maintained in the normal range despite low T_4. Antithyroid peroxidase antibodies and antithyroglobulin antibodies are usually elevated. The RAIU is not useful in evaluation of hypothyroidism because it can be low, normal, or elevated.
- Pituitary failure (secondary hypothyroidism) should be suspected in patients with decreased T_4 levels and inappropriately normal or low TSH levels.

TREATMENT OF HYPOTHYROIDISM

- Goals of Treatment: Restore thyroid hormone concentrations in tissue, provide symptomatic relief, prevent neurologic deficits in newborns and children, and reverse the biochemical abnormalities of hypothyroidism.
- **Levothyroxine** (L-thyroxine, T_4) is the drug of choice for thyroid hormone replacement and suppressive therapy because it is chemically stable, relatively inexpensive, free of antigenicity, and has uniform potency. Other commercially available thyroid preparations can be used but are not preferred therapy. Once a particular product is selected, therapeutic interchange is discouraged. Because T_3 (and not T_4) is the biologically active form, levothyroxine administration results in a pool of thyroid hormone that is readily and consistently converted to T_3.
- In patients with long-standing disease and older individuals without known cardiac disease start therapy with levothyroxine 50 mcg daily and increase after 1 month.
- The recommended initial dose for older patients with known cardiac disease is 25 mcg/day titrated upward in increments of 25 mcg at monthly intervals to prevent stress on the cardiovascular system.
- The average maintenance dose for most adults is ~125 mcg/day, but there is a wide range of replacement doses, necessitating individualized therapy and appropriate TSH monitoring to determine an appropriate dose.
- Although treatment of subclinical hypothyroidism is controversial, patients presenting with marked elevations in TSH (>10 mIU/L) and high titers of thyroid peroxidase antibody or prior treatment with sodium iodide–131 may be most likely to benefit from treatment.
- Levothyroxine is the drug of choice for pregnant women, and the goal is to decrease TSH to the normal reference range for pregnancy.
- Cholestyramine, calcium carbonate, sucralfate, aluminum hydroxide, ferrous sulfate, soybean formula, dietary fiber supplements, and espresso coffee may impair the

TABLE 20–3 Thyroid Preparations Used in the Treatment of Hypothyroidism

Drug/Dosage Form	Content	Relative Dose
Thyroid USP		
Armour Thyroid (T_4:T_3 ratio)	Desiccated beef or pork thyroid gland	1 grain (equivalent to 60 mcg of T_4)
9.5 mcg:2.25 mcg,		
19 mcg:4.5 mcg,		
38 mcg:9 mcg,		
57 mcg:13.5 mcg,		
76 mcg:18 mcg,		
114 mcg:27 mcg,		
152 mcg:36 mcg,		
190 mcg:45 mcg tablets		
Levothyroxine	Synthetic T_4	50–60 mcg
Synthroid, Levothroid, Levoxyl, Unithroid, and other generics 25, 50, 75, 88, 100, 112, 125, 137, 150, 175, 200, 300 mcg tablets; 200 and 500 mcg/vial injection		
Liothyronine	Synthetic T_3	15–37.5 mcg
Cytomel 5, 25, and 50 mcg tablets		
Liotrix		
Thyrolar ¼-, ½-, 1-, 2-, and 3-strength tablets	Synthetic T_4:T_3 in 4:1 ratio	50–60 mcg T_4 and 12.5–15 mcg T_3

T_3, triiodothyronine; T_4, thyroxine.

GI absorption of levothyroxine. Drugs that increase nondeiodinative T_4 clearance include rifampin, carbamazepine, and possibly phenytoin. Amiodarone may block conversion of T_4 to T_3.

- **Thyroid USP** (or desiccated thyroid) is usually derived from pig thyroid gland. It may be antigenic in allergic or sensitive patients. Inexpensive generic brands may not be bioequivalent.
- **Liothyronine** (synthetic T_3) has uniform potency but has a higher incidence of cardiac adverse effects, higher cost, and difficulty in monitoring with conventional laboratory tests.
- **Liotrix** (synthetic T_4:T_3 in a 4:1 ratio) is chemically stable, pure, and has a predictable potency but is expensive. It lacks therapeutic rationale because ~35% of T_4 is converted to T_3 peripherally.
- Excessive doses of thyroid hormone may lead to heart failure, angina pectoris, and myocardial infarction (MI). Hyperthyroidism leads to reduced bone density and increased risk of fracture.

TREATMENT OF MYXEDEMA COMA

- Immediate and aggressive therapy with IV bolus **levothyroxine**, 300 to 500 mcg, has traditionally been used. Initial treatment with IV **liothyronine** or a combination of both hormones has also been advocated because of impaired conversion of T_4 to T_3.
- Give glucocorticoid therapy with IV **hydrocortisone** 100 mg every 8 hours until coexisting adrenal suppression is ruled out.
- Consciousness, lowered TSH concentrations, and improvement in vital signs are expected within 24 hours.
- Maintenance levothyroxine doses are typically 75 to 100 mcg IV until the patient stabilizes and oral therapy is begun.
- Provide supportive therapy to maintain adequate ventilation, euglycemia, BP, and body temperature. Diagnose and treat underlying disorders such as sepsis and MI.

EVALUATION OF THERAPEUTIC OUTCOMES

- Serum TSH concentration is the most sensitive and specific monitoring parameter for adjustment of levothyroxine dose. Concentrations begin to fall within hours and are usually normalized within 2 to 6 weeks.
- Check both TSH and T_4 concentrations every 6 weeks until a euthyroid state is achieved. An elevated TSH level indicates insufficient replacement. Serum T_4 concentrations can be useful in detecting noncompliance, malabsorption, or changes in levothyroxine product bioequivalence. TSH may also be used to help identify noncompliance.
- In patients with hypothyroidism caused by hypothalamic or pituitary failure, alleviation of the clinical syndrome and restoration of serum T_4 to the normal range are the only criteria available for estimating the appropriate replacement dose of levothyroxine.

See Chapter 58, Thyroid Disorders, authored by Jacqueline Jonklaas and Robert L. Talbert, for a more detailed discussion of this topic.

CHAPTER 21

Cirrhosis and Portal Hypertension

CIRRHOSIS

- *Cirrhosis* is a diffuse injury to the liver characterized by fibrosis and a conversion of the normal hepatic architecture into structurally abnormal nodules. The end result is destruction of hepatocytes and their replacement by fibrous tissue.
- The resulting resistance to blood flow results in portal hypertension and the development of varices and ascites. Hepatocyte loss and intrahepatic shunting of blood result in diminished metabolic and synthetic function, which leads to hepatic encephalopathy (HE) and coagulopathy.
- Cirrhosis has many causes (**Table 21–1**). In the United States, excessive alcohol intake and chronic viral hepatitis (types B and C) are the most common causes.
- Cirrhosis results in elevation of portal blood pressure because of fibrotic changes within the hepatic sinusoids, changes in the levels of vasodilatory and vasoconstrictor mediators, and an increase in blood flow to the splanchnic vasculature. The pathophysiologic abnormalities that cause it result in the commonly encountered problems of ascites, portal hypertension and esophageal varices, HE, and coagulation disorders.
- **Portal hypertension** is characterized by hypervolemia, increased cardiac index, hypotension, and decreased systemic vascular resistance.
- Ascites is the pathologic accumulation of lymph fluid within the peritoneal cavity. It is one of the earliest and most common presentations of cirrhosis.
- The development of ascites is related to systemic arterial vasodilation that leads to the activation of the baroreceptors in the kidney and an activation of the renin–angiotensin–aldosterone system, activation of the sympathetic nervous system, and release of antidiuretic hormone in response to the arterial hypotension. These changes cause sodium and water retention.

PORTAL HYPERTENSION AND VARICES

- The most important sequelae of portal hypertension are the development of varices and alternative routes of blood flow resulting in acute variceal bleeding. Portal hypertension is defined by the presence of a gradient of greater than 5 mm Hg between the portal and central venous pressures.
- Progression to bleeding can be predicted by Child-Pugh score, size of varices, and the presence of red wale markings on the varices. First variceal hemorrhage occurs at an annual rate of about 15% and carries a mortality of 7% to 15%.

HEPATIC ENCEPHALOPATHY

- *Hepatic encephalopathy* (HE) is a metabolically induced functional disturbance of the brain that is potentially reversible.
- The symptoms of HE are thought to result from an accumulation of gut-derived nitrogenous substances in the systemic circulation as a consequence of shunting through portosystemic collaterals bypassing the liver. These substances then enter the central nervous system (CNS) and result in alterations of neurotransmission that affect consciousness and behavior.
- Altered ammonia, glutamate, benzodiazepine receptor agonists, aromatic amino acids, and manganese are potential causes of HE. An established correlation between blood ammonia levels and mental status does not exist.

TABLE 21–1 Etiology of Cirrhosis
Chronic alcohol consumption
Chronic viral hepatitis (types B and C)
Metabolic liver disease
Hemochromatosis, Wilson disease, α_1-antitrypsin deficiency, nonalcoholic steatohepatitis ("fatty liver"), cystic fibrosis
Immunologic disease
Autoimmune hepatitis, primary biliary cirrhosis
Vascular disease
Budd–Chiari syndrome, cardiac failure
Drugs
Isoniazid, methyldopa, amiodarone, dronedarone, methotrexate, tamoxifen, retinol (vitamin A), propylthiouracil, and didanosine

- Type A HE is induced by acute liver failure, type B results from portal-systemic bypass without intrinsic liver disease, and type C occurs with cirrhosis. HE may be classified as episodic, persistent, or minimal.

COAGULATION DEFECTS

- Complex coagulation derangements can occur in cirrhosis. These derangements include the reduction in the synthesis of coagulation factors, excessive fibrinolysis, disseminated intravascular coagulation, thrombocytopenia, and platelet dysfunction.
- Vitamin K–dependent clotting factor levels are decreased, with factor VII affected first because it has a short half-life. The net effect of these events is the development of bleeding diathesis.

CLINICAL PRESENTATION

- The range of presentation of patients with cirrhosis may be from asymptomatic, with abnormal laboratory or radiographic tests, to decompensated with ascites, spontaneous bacterial peritonitis, HE, or variceal bleeding.
- Some presenting characteristics with cirrhosis are anorexia, weight loss, weakness, fatigue, jaundice, pruritis, gastrointestinal (GI) bleeding, coagulopathy, increased abdominal girth with shifting flank dullness, mental status changes, and vascular spiders. **Table 21–2** describes the presenting signs and symptoms of cirrhosis.

TABLE 21–2 Clinical Presentation of Cirrhosis
Signs and symptoms
Asymptomatic
Hepatomegaly and splenomegaly
Pruritus, jaundice, palmar erythema, spider angiomata, and hyperpigmentation
Gynecomastia and reduced libido
Ascites, edema, pleural effusion, and respiratory difficulties
Malaise, anorexia, and weight loss
Encephalopathy
Laboratory tests
Hypoalbuminemia
Elevated prothrombin time (PT)
Thrombocytopenia
Elevated alkaline phosphatase (AST)
Elevated aspartate transaminase, alanine transaminase (ALT), and γ-glutamyl transpeptidase (GGT)

- A thorough history including risk factors that predispose patients to cirrhosis should be taken. Quantity and duration of alcohol intake should be determined. Risk factors for hepatitis B and C transmission should be determined.

LABORATORY ABNORMALITIES

- There are no laboratory or radiographic tests of hepatic function that can accurately diagnose cirrhosis. Routine liver assessment tests include alkaline phosphatase, bilirubin, aspartate transaminase (AST), alanine aminotransferase (ALT), and γ-glutamyl transpeptidase (GGT). Additional markers of hepatic synthetic activity include albumin and prothrombin time (PT).
- The aminotransferases, AST and ALT, are enzymes that have increased concentrations in plasma after hepatocellular injury. The highest concentrations are seen in acute viral infections and ischemic or toxic liver injury.
- Alkaline phosphatase levels and GGT are elevated in plasma with obstructive disorders that disrupt the flow of bile from hepatocytes to the bile ducts or from the biliary tree to the intestines in conditions such as primary biliary cirrhosis, sclerosing cholangitis, drug-induced cholestasis, bile duct obstruction, autoimmune cholestatic liver disease, and metastatic cancer of the liver.
- Elevations in serum conjugated bilirubin indicate that the liver has lost at least half its excretory capacity. When alkaline phosphatase is elevated and aminotransferase levels are normal, elevated conjugated bilirubin is a sign of cholestatic disease or possible cholestatic drug reactions.
- **Figure 21–1** describes a general algorithm for the interpretation of liver function tests.
- Albumin and coagulation factors are markers of hepatic synthetic activity and are used to estimate hepatocyte functioning in cirrhosis.
- Thrombocytopenia is a relatively common feature in chronic liver disease and is found in 15% to 70% of cirrhotic patients.
- The Child-Pugh classification system uses a combination of physical and laboratory findings to assess and define the severity of cirrhosis and is a predictor of patient survival, surgical outcome, and risk of variceal bleeding (**Table 21–3**).

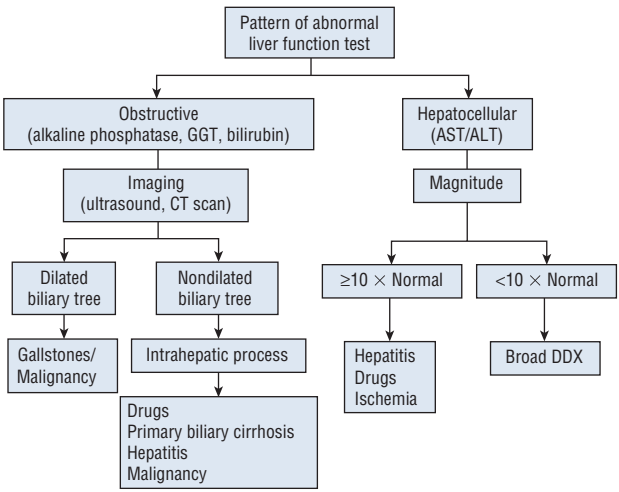


FIGURE 21–1. Interpretation of liver function tests. (ALT, alanine transaminase; AST, aspartate transaminase; CT, computed tomography; DDX, differential diagnosis; GGT, γ-glutamyl transpeptidase.)

TABLE 21–3 Criteria and Scoring for the Child–Pugh Grading of Chronic Liver Disease

Score	1	2	3
Total bilirubin (mg/dL)	1–2 (17.1–34.2 μmol/L)	2–3 (34.2–51.3 μmol/L)	>3 (>51.3 μmol/L)
Albumin (g/dL)	>3.5 (>35 g/L)	2.8–3.5 (28–35 g/L)	<2.8 (<28 g/L)
Ascites	None	Mild	Moderate
Encephalopathy (grade)	None	1 and 2	3 and 4
Prothrombin time (seconds prolonged)	1–4	4–6	>6

Grade A, <7 points; grade B, 7–9 points; grade C, 10–15 points. Data from reference 18.

- The model for end-stage liver disease (MELD) is a newer scoring system:

$$\text{MELD score} = 0.957 \times \log(\text{serum creatinine mg/dL}) + 0.378 \times \log(\text{bilirubin mg/dL}) + 1.120 \times \log(\text{INR}) + 0.643$$

where international normalized ratio (INR) is TK.

- In MELD, laboratory values less than 1 are rounded up to 1. The formula's score is multiplied by 10 and rounded to the nearest whole number.

TREATMENT

- Goals of Treatment: Treatment goals are clinical improvement or resolution of acute complications, such as variceal bleeding, and resolution of hemodynamic instability for an episode of acute variceal hemorrhage. Other goals are prevention of complications, adequate lowering of portal pressure with medical therapy using β-adrenergic blocker therapy, and support of abstinence from alcohol.

GENERAL APPROACH TO TREATMENT

- Approaches to treatment include the following:
  - ✓ Identify and eliminate the causes of cirrhosis (eg, alcohol abuse).
  - ✓ Assess the risk for variceal bleeding and begin pharmacologic prophylaxis where indicated, reserving endoscopic therapy for high-risk patients or acute bleeding episodes.
  - ✓ The patient should be evaluated for clinical signs of ascites and managed with pharmacologic treatment (eg, diuretics) and paracentesis. Spontaneous bacterial peritonitis (SBP) should be carefully monitored in patients with ascites who undergo acute deterioration.
  - ✓ HE is a common complication of cirrhosis and requires clinical vigilance and treatment with dietary restriction, elimination of CNS depressants, and therapy to lower ammonia levels.
  - ✓ Frequent monitoring for signs of hepatorenal syndrome, pulmonary insufficiency, and endocrine dysfunction is necessary.

MANAGEMENT OF PORTAL HYPERTENSION AND VARICEAL BLEEDING

- The management of varices involves three strategies: (1) primary prophylaxis to prevent rebleeding, (2) treatment of variceal hemorrhage, and (3) secondary prophylaxis to prevent rebleeding in patients who have already bled.

Primary Prophylaxis

- All patients with cirrhosis and portal hypertension should be screened for varices on diagnosis.
- The mainstay of primary prophylaxis is the use of a nonselective β-adrenergic blocking agent such as **propranolol** or **nadolol**. These agents reduce portal pressure by reducing portal venous inflow via two mechanisms: decrease in cardiac output and decrease in splanchnic blood flow.

- Therapy should be initiated with **propranolol**, 20 mg twice daily, or **nadolol**, 20 to 40 mg once daily, and titrated every 2 to 3 days to maximal tolerated dose to heart rate of 55 to 60 beats/min. β-Adrenergic blocker therapy should be continued indefinitely.
- Patients with contraindications to therapy with nonselective β-adrenergic blockers (ie, those with asthma, insulin-dependent diabetes with episodes of hypoglycemia, and peripheral vascular disease) or intolerance to β-adrenergic blockers should be considered for alternative prophylactic therapy with EVL.

ACUTE VARICEAL HEMORRHAGE

- **Figure 21–2** presents an algorithm for the management of variceal hemorrhage. Evidence-based recommendations for selected treatments are presented in **Table 21–4**.
- Initial treatment goals include (1) adequate blood volume resuscitation, (2) protection of the airway from aspiration of blood, (3) correction of significant coagulopathy and / or thrombocytopenia with fresh frozen plasma and platelets, (4) prophylaxis against SBP and other infections, (5) control of bleeding, (4) prevention of rebleeding, and (5) preservation of liver function.
- Prompt stabilization of blood volume to maintain hemoglobin of 8 g/dL with volume expansion to maintain systolic blood pressure of 90 to 100 mm Hg and heart rate of less than 100 beats/min is recommended. Airway management is critical. Fluid resuscitation involves colloids initially and subsequent blood products. Vigorous resuscitation with saline solution should generally be avoided.
- Combination pharmacologic therapy plus EVL or sclerotherapy (when EVL is not technically feasible) is the most rational approach to treatment of acute variceal bleeding.
- Vasoactive drug therapy (usually octreotide) to stop or slow bleeding is routinely used early in patient management to allow stabilization of the patient. Treatment with octreotide should be initiated early to control bleeding and facilitate endoscopy. Octreotide is administered as an IV bolus of 50 mcg followed by a continuous infusion of 50 mcg/h. It should be continued for 5 days after acute variceal bleeding. Patients should be monitored for hypo- or hyperglycemia.
- **Vasopressin**, alone or in combination with nitroglycerin, is not recommended as first-line therapy for the management of variceal hemorrhage. Vasopressin causes nonselective vasoconstriction and can result in myocardial ischemia or infarction, arrhythmias, mesenteric ischemia, ischemia of the limbs, or cerebrovascular accidents.
- Antibiotic therapy should be used early to prevent sepsis in patients with signs of infection or ascites. A short course (up to 7 days) of oral **norfloxacin** 400 mg twice daily or IV **ciprofloxacin** is recommended.
- EVL is the recommended form of endoscopic therapy for acute variceal bleeding, although endoscopic injection sclerotherapy (injection of 1–4 mL of a sclerosing agent into the lumen of the varices) may be used.
- If standard therapy fails to control bleeding, a salvage procedure such as balloon tamponade (with a Sengstaken-Blakemore tube) or transjugular intrahepatic portosystemic shunt (TIPS) is necessary.

Prevention of Rebleeding

- A nonselective β-adrenergic blocker along with EVL is the best treatment option for prevention of rebleeding.
- **Propranolol** may be given at 20 mg twice daily (or **nadolol**, 20–40 mg once daily) and titrated weekly to achieve a goal of heart rate 55 to 60 beats/min or the maximal tolerated dose. Patients should be monitored for evidence of heart failure, bronchospasm, or glucose intolerance.
- The combination therapy of a nonselective β-blocker with **isosorbide mononitrate** can be used in patients unable to undergo EVL.

ASCITES

- The therapeutic goals for patients with ascites are to control the ascites, prevent or relieve ascites-related symptoms (dyspnea and abdominal pain and distention), and prevent SBP and hepatorenal syndrome.

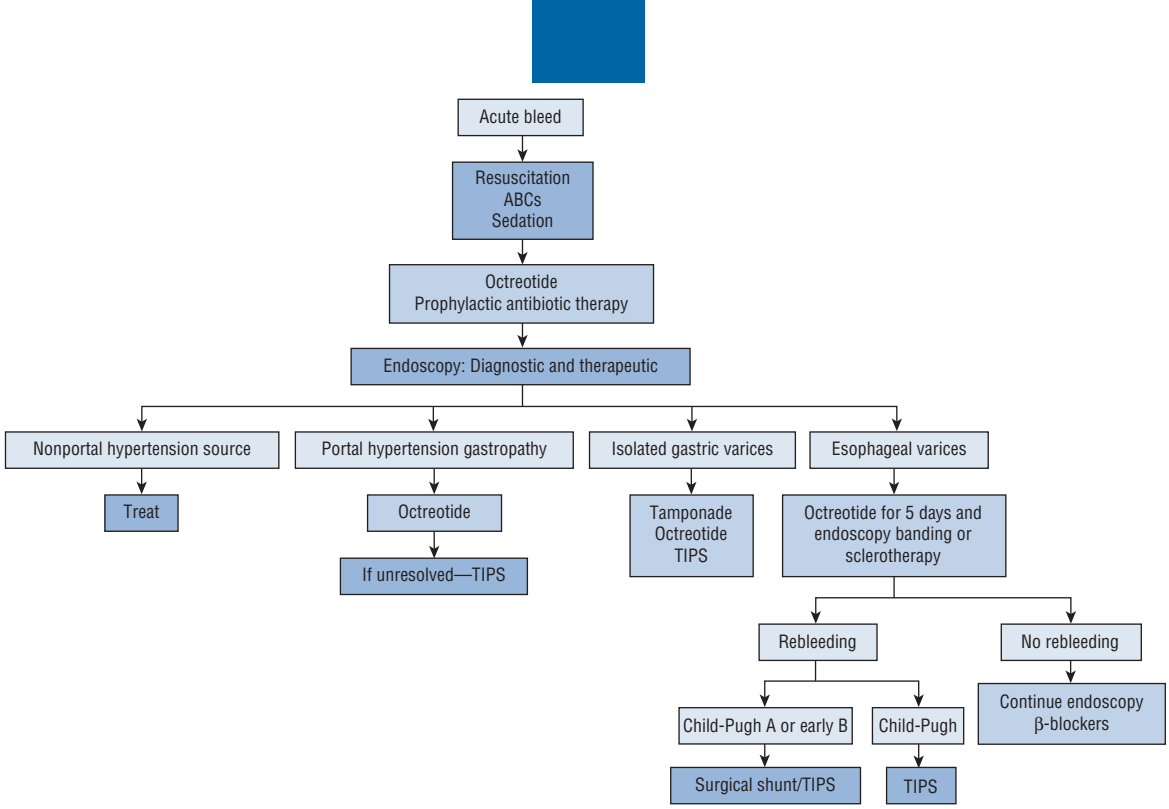


FIGURE 21–2. Management of acute variceal hemorrhage. (ABCs, airway, breathing, and circulation; TIPS, transjugular intrahepatic portosystemic shunt.)

TABLE 21–4 Evidence-Based Table of Selected Treatment Recommendations: Variceal Bleeding in Portal Hypertension

Recommendation	Grade
Prevention of variceal bleeding	
Nonselective β-blocker therapy should be initiated in:	
Patients with small varices and criteria for increased risk of hemorrhage	IIaC
Patients with medium/large varices without high risk of hemorrhage	IA
Endoscopic variceal ligation (EVL) should be offered to patients who have contraindications or intolerance to nonselective β-blockers	IA
EVL may be recommended for prevention in patients with medium/large varices at high risk of hemorrhage instead of nonselective β-blocker therapy	IA
Treatment of variceal bleeding	
Short-term antibiotic prophylaxis should be instituted upon admission	IA
Vasoactive drugs should be started as soon as possible, prior to endoscopy, and maintained for 3–5 days	IA
Endoscopy should be performed within 12 h to diagnose variceal bleeding and to treat bleeding with either sclerotherapy or EVL	IA
Secondary prophylaxis of variceal bleeding	
Nonselective β-blocker therapy plus EVL is the best therapeutic option for prevention of recurrent variceal bleeding	IA

Recommendation grading:
Class I—Conditions for which there is evidence and/or general agreement
Class II—Conditions for which there is conflicting evidence and/or a divergence of opinion
Class IIa—Weight of evidence/opinion is in favor of efficacy
Class IIb—Efficacy less well established
Class III—Conditions for which there is evidence and/or general agreement that treatment is not effective and/or potentially harmful
Level A—Data from multiple randomized trials or meta-analyses
Level B—Data derived from single randomized trial or nonrandomized studies
Level C—Only consensus opinion, case studies, or standard of care
Data from Garcia-Tsao G, Sanyal AJ, Grace ND, et al. Prevention and management of gastroesophageal varices and variceal hemorrhage in cirrhosis. Hepatology 2007;46(3):922–938.

- For patients with ascites, a serum–ascites albumin gradient should be determined. If the serum–ascites albumin gradient is greater than 1.1 g/dL (>11 g/L), the patient almost certainly has portal hypertension.
- The treatment of ascites secondary to portal hypertension includes abstinence from alcohol, sodium restriction (to 2 g/day), and diuretics. Fluid loss and weight change depend directly on sodium balance in these patients. A goal of therapy is to increase urinary excretion of sodium to greater than 78 mmol/day.
- Diuretic therapy should be initiated with single morning doses of **spironolactone**, 100 mg, and **furosemide**, 40 mg, titrated every 3 to 5 days, with a goal of 0.5 kg maximum daily weight loss. The dose of each can be increased together, maintaining the 100:40 mg ratio, to a maximum daily dose of 400 mg spironolactone and 160 mg furosemide.
- If tense ascites is present, paracentesis should be performed prior to institution of diuretic therapy and salt restriction.
- Liver transplant should be considered in patients with refractory ascites.

SPONTANEOUS BACTERIAL PERITONITIS

- Antibiotic therapy for prevention of spontaneous bacterial peritonitis (SBP) should be considered in all patients who are at high risk for this complication (those who experience a prior episode of SBP or variceal hemorrhage and those with low-protein ascites).
- Patients with documented or suspected SBP should receive broad-spectrum antibiotic therapy to cover *Escherichia coli, Klebsiella pneumoniae,* and *Streptococcus pneumoniae*.

TABLE 21–5 Treatment Goals: Episodic and Persistent Hepatic Encephalopathy

Episodic HE	Persistent HE
Control precipitating factor	Reverse encephalopathy
Reverse encephalopathy	Avoid recurrence
Hospital/inpatient therapy	Home/outpatient therapy
Maintain fluid and hemodynamic support	Manage persistent neuropsychiatric abnormalities
	Manage chronic liver disease
Expect normal mentation after recovery	High prevalence of abnormal mentation after recovery

- **Cefotaxime**, 2 g every 8 hours, or a similar third-generation cephalosporin for 5 days is considered the drug of choice. **Oral ofloxacin**, 400 mg every 12 hours for 8 days, is equivalent to IV cefotaxime.
- Patients who survive an episode of SBP should receive long-term antibiotic prophylaxis with daily norfloxacin 400 mg or double-strength trimethoprim-sulfamethoxazole.

Hepatic Encephalopathy

- Table 21–5 describes the treatment goals for hepatic encephalopathy (HE).
- The first approach to treatment of HE is to identify any precipitating causes. Precipitating factors and therapy alternatives are presented in Table 21–6.
- Treatment approaches include (1) reduction in blood ammonia concentrations by dietary restrictions, with drug therapy aimed at inhibiting ammonia production or enhancing its removal (lactulose and antibiotics); and (2) inhibition of γ-aminobutyric acid-benzodiazepine receptors by flumazenil.
- To reduce blood ammonia concentrations in patients with episodic HE, protein intake is limited or withheld (while maintaining caloric intake) until the clinical situation improves. Protein intake can be titrated back up based on tolerance to a total of 1 to 1.5 g/kg/day.

TABLE 21–6 Portosystemic Encephalopathy: Precipitating Factors and Therapy

Factor	Therapy Alternatives
GI bleeding	
Variceal	Band ligation/sclerotherapy Octreotide
Nonvariceal	Endoscopic therapy Proton pump inhibitors
Infection/sepsis	Antibiotics Paracentesis
Electrolyte abnormalities	Discontinue diuretics Fluid and electrolyte replacement
Sedative ingestion	Discontinue sedatives/tranquilizers Consider reversal (flumazenil/naloxone)
Dietary excesses	Limit daily protein Lactulose
Constipation	Cathartics Bowel cleansing/enema
Renal insufficiency	Discontinue diuretics Discontinue nonsteroidal anti-inflammatory drugs, nephrotoxic antibiotics Fluid resuscitation

TABLE 21–7 Drug Monitoring Guidelines

Drug	Adverse Drug Reaction	Monitoring Parameter	Comments
Nonselective β-adrenergic blocker	Heart failure, bronchospasm, glucose intolerance	BP, HR Goal HR: 55–60 beats/min or maximal tolerated dose	Nadolol or propranolol
Octreotide	Bradycardia, hypertension, arrhythmia, abdominal pain	BP, HR, EKG, abdominal pain	
Vasopressin	Myocardial ischemia/infarction, arrhythmia, mesenteric ischemia, ischemia of the limbs, cerebrovascular accident	EKG, distal pulses, symptoms of myocardial, mesenteric, or cerebrovascular ischemia/infarction	
Spironolactone/furosemide	Electrolyte disturbances, dehydration, renal insufficiency, hypotension	Serum electrolytes (especially potassium), SCr, blood urea nitrogen, BP Goal sodium excretion: >78 mmol/day	Spot urine sodium concentration greater than potassium concentration correlates well with daily sodium excretion >78 mmol/day
Lactulose	Electrolyte disturbances	Serum electrolytes Goal number of soft stools per day: 2–3	
Neomycin	Ototoxicity, nephrotoxicity	SCr, annual auditory monitoring	
Metronidazole	Neurotoxicity	Sensory and motor neuropathy	
Rifaximin	Nausea, diarrhea		

BP, blood pressure; HR, heart rate; beats/min, beats per minute; EKG, electrocardiogram; SCr, serum creatinine; mmol, millimole.

- To reduce blood ammonia concentrations in episodic HE, lactulose is initiated at 45 mL orally every hour (or 300 mL lactulose syrup with 700 mL water given as a retention enema held for 60 minutes) until catharsis begins. The dose is then decreased to 15 to 30 mL orally every 8 to 12 hours and titrated to produce two or three soft stools per day.
- Antibiotic therapy with **metronidazole** or **neomycin** is reserved for patients who have not responded to diet and lactulose. **Rifaximin** 550 mg twice daily plus lactulose can be used for patients with inadequate response to lactulose alone.
- Zinc acetate supplementation (220 mg twice daily) is recommended for long-term management in patients with cirrhosis who are zinc deficient.

EVALUATION OF THERAPEUTIC OUTCOMES

- **Table 21–7** summarizes the drug monitoring guidelines patients with cirrhosis and portal hypertension, including monitoring parameters and therapeutic outcomes.

See Chapter 24, Portal Hypertension and Cirrhosis, authored by Julie M. Sease, for a more detailed discussion of this topic.

Constipation

22 CHAPTER

- One definition of constipation is fewer than three stools per week for women and five for men despite a high-residue diet, or a period of more than 3 days without a bowel movement, straining at stool more than 25% of the time and/or two or fewer stools per week, and straining at defecation and less than one stool daily with minimal effort. The American Gastroenterological Association defines *constipation* as difficult or infrequent passage of stool, at times associated with straining or a feeling of incomplete defecation.

PATHOPHYSIOLOGY

- Constipation may be primary (occurs without an underlying identifiable cause) or secondary (the result of constipating drugs, lifestyle factors, or medical disorders). It is not a disease but a symptom of an underlying disease or problem.
- Constipation commonly results from a diet low in fiber, inadequate fluid intake, decreased physical activity, or from use of constipating drugs such as opiates. Constipation may sometimes be psychogenic in origin.
- Diseases or conditions that may cause constipation include the following:
  - ✓ Gastrointestinal (GI) disorders: Irritable bowel syndrome (IBS), diverticulitis, upper and lower GI tract diseases, hemorrhoids, anal fissures, ulcerative proctitis, tumors, hernia, volvulus of the bowel, syphilis, tuberculosis, lymphogranuloma venereum, and Hirschsprung disease
  - ✓ Metabolic and endocrine disorders: Diabetes mellitus with neuropathy, hypothyroidism, panhypopituitarism, pheochromocytoma, hypercalcemia, and enteric glucagon excess
  - ✓ Pregnancy
  - ✓ Cardiac disorders (eg, heart failure)
  - ✓ Neurogenic constipation: Head trauma, CNS tumors, spinal cord injury, cerebrospinal accidents, and Parkinson disease
  - ✓ Psychogenic causes
- Causes of drug-induced constipation are listed in **Table 22–1**. All opiate derivatives are associated with constipation, but the degree of intestinal inhibitory effects seems to differ among agents. Orally administered opiates appear to have greater inhibitory effect than parenterally administered agents; oral codeine is well known as a potent antimotility agent.

CLINICAL PRESENTATION

- **Table 22–2** shows the general clinical presentation of constipation.
- The patient should also be carefully questioned about usual diet and laxative regimens.
- General health status, signs of underlying medical illness (ie, hypothyroidism), and psychological status (eg, depression or other psychological illness) should also be assessed.
- Patients with alarm symptoms, a family history of colon cancer, or those older than 50 years with new symptoms may need further diagnostic evaluation.

TREATMENT

- Goals of Treatment: The major goals of treatment are to (a) relieve symptoms; (b) reestablish normal bowel habits; and (c) improve quality of life by minimizing adverse effects of treatment.

TABLE 22–1 Drugs Causing Constipation
Analgesics
Inhibitors of prostaglandin synthesis
Opiates
Anticholinergics
Antihistamines
Antiparkinsonian agents (eg, benztropine or trihexyphenidyl)
Phenothiazines
Tricyclic antidepressants
Antacids containing calcium carbonate or aluminum hydroxide
Barium sulfate
Calcium channel blockers
Clonidine
Diuretics (nonpotassium-sparing)
Ganglionic blockers
Iron preparations
Muscle blockers (D-tubocurarine, succinylcholine)
Nonsteroidal anti-inflammatory agents
Polystyrene sodium sulfonate

GENERAL APPROACH TO TREATMENT

- General measures believed to be beneficial in managing constipation include dietary modification to increase the amount of fiber consumed daily, exercise, adjustment of bowel habits so that a regular and adequate time is made to respond to the urge to defecate, and increased fluid intake.
- If an underlying disease is recognized as the cause of constipation, attempts should be made to correct it. GI malignancies may be removed through a surgical resection. Endocrine and metabolic derangements are corrected by the appropriate methods.
- If a patient is consuming medications known to cause constipation, consideration should be given to alternative agents. If no reasonable alternatives exist to the medication thought to be responsible for constipation, consideration should be given to lowering the dose. If a patient must remain on constipating medications, more attention must be given to general measures for prevention of constipation.
- The proper management of constipation will require a combination of nonpharmacologic and pharmacologic therapies.

DIETARY MODIFICATION AND BULK-FORMING AGENTS

- The most important aspect of the therapy for constipation is dietary modification to increase the amount of fiber consumed. Gradually increase daily fiber intake to 20 to 25 g, either through dietary changes or through fiber supplements. Fruits, vegetables, and cereals have the highest fiber content.
- A trial of dietary modification with high-fiber content should be continued for at least 1 month. Most patients begin to notice effects on bowel function 3 to 5 days after beginning a high-fiber diet.
- Abdominal distention and flatus may be particularly troublesome in the first few weeks, particularly with high bran consumption.

TABLE 22–2 Clinical Presentation of Constipation

Signs and symptoms
- Infrequent bowel movements (less than 3 per week)
- Stools that are hard, small, or dry
- Difficulty or pain of defecation
- Feeling of abdominal discomfort or bloating, incomplete evacuation, etc.

Alarm signs and symptoms
- Hematochezia
- Melena
- Family history of colon cancer
- Family history of inflammatory bowel disease
- Anemia
- Weight loss
- Anorexia
- Nausea and vomiting
- Severe, persistent constipation that is refractory to treatment
- New-onset or worsening constipation in elderly without evidence of primary cause

Physical examination
- Perform rectal exam for presence of anatomical abnormalities (such as fistulas, fissures, hemorrhoids, rectal prolapse) or abnormalities of perianal descent
- Digital examination of rectum to check for fecal impaction, anal stricture, or rectal mass

Laboratory and other diagnostic tests
- No routine recommendations for lab testing—as indicated by clinical discretion
- In patients with signs and symptoms suggestive of organic disorder, specific testing may be performed (i.e., thyroid function tests, electrolytes, glucose, complete blood count) based on clinical presentation
- In patients with alarm signs and symptoms or when structural disease is a possibility, select appropriate diagnostic studies:
  1. Protoscopy
  2. Sigmoidoscopy
  3. Colonoscopy
  4. Barium enema

PHARMACOLOGIC THERAPY

- The laxatives are divided into three classifications: (1) those causing softening of feces in 1 to 3 days (bulk-forming laxatives, **docusates**, and **lactulose**), (2) those resulting in soft or semifluid stool in 6 to 12 hours (**bisacodyl** and **senna**), and (3) those causing water evacuation in 1 to 6 hours (**saline cathartics**, **castor oil**, and **polyethylene glycol (PEG)–electrolyte lavage solution**).
- Other agents include a calcium channel activator, guanylate cyclase C agonist, and serotonergic agents.
- Dosage recommendations for laxatives and cathartics are provided in Table 22–3.

Recommendations

- The basis for treatment and prevention of constipation should consist of bulk-forming agents in addition to dietary modifications that increase dietary fiber.
- For most nonhospitalized persons with acute constipation, the infrequent use (less often than every few weeks) of most laxative products is acceptable; however, before more potent laxative or cathartics are used, relatively simple measures may be tried. For example, acute constipation may be relieved by the use of a **tap water enema** or a **glycerin** suppository; if neither is effective, the use of oral sorbitol, low doses of bisacodyl or senna, low-dose PEG solutions, or saline laxatives (eg, **milk of magnesia**) may provide relief.

TABLE 22–3 Dosage Recommendations for Laxatives and Cathartics

Agent	Recommended Dose
Agents that Cause Softening of Feces in 1–3 Days	
Bulk-forming agents/osmotic laxatives	
Methylcellulose	4–6 g/day
Polycarbophil	4–6 g/day
Psyllium	Varies with product
Polyethylene glycol 3350	17 g/dose
Emollients	
Docusate sodium	50–360 mg/day
Docusate calcium	50–360 mg/day
Docusate potassium	100–300 mg/day
Lactulose	15–30 mL orally
Sorbitol	30–50 g/day orally
Agents that Result in Soft or Semifluid Stool in 6–12 Hours	
Bisacodyl (oral)	5–15 mg orally
Senna	Dose varies with formulation
Magnesium sulfate (low dose)	<10 g orally
Agents that Cause Watery Evacuation in 1–6 Hours	
Magnesium citrate	18 g 300 mL water
Magnesium hydroxide	2.4–4.8 g orally
Magnesium sulfate (high dose)	10–30 g orally
Sodium phosphates	Varies with salt used
Bisacodyl	10 mg rectally
Polyethylene glycol–electrolyte preparations	4 L

- If laxative treatment is required for longer than 1 week, the person should be advised to consult a physician to determine whether there is an underlying cause of constipation that requires treatment with agents other than laxatives.
- For some bedridden or geriatric patients, or others with chronic constipation, bulk-forming laxatives remain the first line of treatment, but the use of more potent laxatives may be required relatively frequently. Agents that may be used in these situations include **sorbitol**, **lactulose**, low-dose PEG solutions, and milk of magnesia.
- In the hospitalized patient without GI disease, constipation may be related to the use of general anesthesia and/or opiate substances. Most orally or rectally administered laxatives may be used. For prompt initiation of a bowel movement, a **tap water enema** or glycerin suppository is recommended, or milk of magnesia.
- The approach to the treatment of constipation in infants and children should consider neurologic, metabolic, or anatomical abnormalities when constipation is a persistent problem. When not related to an underlying disease, the approach to constipation is similar to that in an adult. A high-fiber diet should be emphasized.

Emollient Laxatives (Docusates)

- These surfactant agents, **docusates** increase water and electrolyte secretion in the small and large bowel and result in a softening of stools within 1 to 3 days.
- Emollient laxatives are not effective in treating constipation but are used mainly to prevent constipation. They may be helpful in situations where straining at stool should be avoided, such as after recovery from myocardial infarction, with acute perianal disease, or after rectal surgery.

- It is unlikely that these agents are effective in preventing constipation if major causative factors (eg, heavy opiate use, uncorrected pathology, and inadequate dietary fiber) are not concurrently addressed.

Mineral Oil

- **Mineral oil** is the only lubricant laxative in routine use and acts by coating stool and allowing easier passage. Generally, the effect on bowel function is noted after 2 or 3 days of use.
- Mineral oil is helpful in situations similar to those suggested for docusates: to maintain a soft stool and avoid straining for relatively short periods of time (a few days to 2 weeks) but should be avoided in bedridden patients because of the risk of aspiration and lipoid pneumonia.
- Mineral oil may be absorbed systemically and cause a foreign-body reaction in lymphoid tissue.

Lactulose and Sorbitol

- **Lactulose** is generally not recommended as a first-line agent for the treatment of constipation because it is costly and may cause flatulence, nausea, and abdominal discomfort or bloating. It may be justified as an alternative for acute constipation and has been found to be particularly useful in elderly patients.
- **Sorbitol**, a monosaccharide, has been recommended as a primary agent in the treatment of functional constipation in cognitively intact patients. It is as effective as lactulose, may cause less nausea, and is much less expensive.

Saline Cathartics

- Saline cathartics are composed of relatively poorly absorbed ions such as magnesium, sulfate, phosphate, and citrate, which produce their effects primarily by osmotic action to retain fluid in the GI tract. These agents may be given orally or rectally.
- A bowel movement may result within a few hours of oral doses and in 1 hour or sooner after rectal administration.
- These agents should be used primarily for acute evacuation of the bowel, which may be necessary before diagnostic examinations, after poisonings, and in conjunction with some anthelmintics to eliminate parasites.
- Agents such as milk of magnesia (an 8% suspension of magnesium hydroxide) may be used occasionally (every few weeks) to treat constipation in otherwise healthy adults.
- Saline cathartics should not be used on a routine basis to treat constipation. With fecal impactions, the enema formulations of these agents may be helpful.

Glycerin

- This agent is usually administered as a 3-g suppository and exerts its effect by osmotic action in the rectum. As with most agents given as suppositories, the onset of action is usually less than 30 minutes. Glycerin is considered a safe laxative, although it may occasionally cause rectal irritation. Its use is acceptable on an intermittent basis for constipation, particularly in children.

Polyethylene Glycol–Electrolyte Lavage Solution

- Whole-bowel irrigation with polyethylene glycol (PEG)–electrolyte lavage solution has become popular for colon cleansing before diagnostic procedures or colorectal operations.
- Typically 4 L of this solution is administered over 3 hours to obtain complete evacuation of the GI tract. The solution is not recommended for the routine treatment of constipation, and its use should be avoided in patients with intestinal obstruction.
- Low doses of PEG solution (10–30 g or 17–34 g per 120–240 mL) once or twice daily may be used for treatment of constipation.

Lubiprostone and Linaclotide

- **Lubiprostone** (Amitiza) is approved for chronic idiopathic constipation and constipation-predominant IBS in adults. The dose is 24 mg capsule twice daily with food. Lubiprostone may cause headache, diarrhea, and nausea.
- **Linaclotide** (Linzess) is the newest agent approved for the treatment of constipation and IBS. It is approved in a 145-mcg dose and should not be used in patients younger than 18 years of age.

Opioid-Receptor Antagonists

- Alvimopan is an oral GI-specific μ-receptor antagonist for short-term use in hospitalized patients to accelerate recovery of bowel function after large or small bowel resection. It is given 12 mg (capsule) 30 minutes to 5 hours before surgery and then 12 mg twice daily for up to 7 days or until hospital discharge (maximum 15 doses).
- Methylnaltrexone is another μ-receptor antagonist approved for opioid-induced constipation in patients with advanced disease receiving palliative care or when response to laxative therapy has been insufficient.

Other Agents

- Tap water enemas may be used to treat simple constipation. The administration of 200 mL of water by enema to an adult often results in a bowel movement within 1.5 hours. Soapsuds are no longer recommended in enemas because their use may result in proctitis or colitis.

See Chapter 23, Diarrhea, Constipation, and Irritable Bowel Syndrome, authored by Patricia H. Fabel and Kayce M. Shealy, for a more detailed discussion of this topic.

Diarrhea

CHAPTER 23

- *Diarrhea* is an increased frequency and decreased consistency of fecal discharge as compared with an individual's normal bowel pattern. It is often a symptom of a systemic disease. Acute diarrhea is commonly defined as shorter than 14 days' duration, persistent diarrhea as longer than 14 days' duration, and chronic diarrhea as longer than 30 days' duration. Most cases of acute diarrhea are caused by infections with viruses, bacteria, or protozoa, and are generally self-limited.

PATHOPHYSIOLOGY

- Diarrhea is an imbalance in absorption and secretion of water and electrolytes. It may be associated with a specific disease of the gastrointestinal (GI) tract or with a disease outside the GI tract.
- Four general pathophysiologic mechanisms disrupt water and electrolyte balance, leading to diarrhea; (1) a change in active ion transport by either decreased sodium absorption or increased chloride secretion, (2) a change in intestinal motility, (3) an increase in luminal osmolarity, and (4) an increase in tissue hydrostatic pressure. These mechanisms have been related to four broad clinical diarrheal groups: secretory, osmotic, exudative, and altered intestinal transit.
- Secretory diarrhea occurs when a stimulating substance (eg, vasoactive intestinal peptide [VIP], laxatives, or bacterial toxin) increases secretion or decreases absorption of large amounts of water and electrolytes.
- Inflammatory diseases of the GI tract can cause exudative diarrhea by discharge of mucus, proteins, or blood into the gut. With **altered intestinal transit**, intestinal motility is altered by reduced contact time in the small intestine, premature emptying of the colon, or bacterial overgrowth.

CLINICAL PRESENTATION

- The clinical presentation of diarrhea is shown in **Table 23–1**. Most acute diarrhea is self-limiting, subsiding within 72 hours. However, infants, young children, the elderly, and debilitated persons are at risk for morbid and mortal events in prolonged or voluminous diarrhea.
- Many agents, including antibiotics and other drugs, cause diarrhea (**Table 23–2**). Laxative abuse for weight loss may also result in diarrhea.

TREATMENT

- Goals of Treatment: To manage the diet, prevent excessive water, electrolyte, and acid-base disturbances; provide symptomatic relief; treat curable causes of diarrhea; and manage secondary disorders causing diarrhea. Diarrhea, like a cough, may be a body defense mechanism for ridding itself of harmful substances or pathogens. The correct therapeutic response is not necessarily to stop diarrhea at all costs. If diarrhea is secondary to another illness, controlling the primary condition is necessary.

GENERAL APPROACH TO TREATMENT

- Management of the diet is a first priority for treatment of diarrhea (**Figs. 23–1** and **23–2**). Most clinicians recommend stopping solid foods for 24 hours and avoiding dairy products.
- When nausea or vomiting is mild, a digestible low-residue diet is administered for 24 hours.

TABLE 23–1 Clinical Presentation of Diarrhea

General

Usually, acute diarrheal episodes subside within 72 h of onset, whereas chronic diarrhea involves frequent attacks over extended time periods.

Signs and symptoms

Abrupt onset of nausea, vomiting, abdominal pain, headache, fever, chills, and malaise
Bowel movements are frequent and never bloody, and diarrhea lasts 12–60 h.
Intermittent periumbilical or lower right quadrant pain with cramps and audible bowel sounds is characteristic of small intestinal disease.
When pain is present in large intestinal diarrhea, it is a gripping, aching sensation with tenesmus (straining, ineffective, and painful stooling). Pain localizes to the hypogastric region, right or left lower quadrant, or sacral region.
In chronic diarrhea, a history of previous bouts, weight loss, anorexia, and chronic weakness are important findings.

Physical examination

Typically demonstrates hyperperistalsis with borborygmi and generalized or local tenderness.

Laboratory tests

Stool analysis studies include examination for microorganisms, blood, mucus, fat, osmolality, pH, electrolyte and mineral concentration, and cultures.
Stool test kits are useful for detecting GI viruses, particularly rotavirus.
Antibody serologic testing shows rising titers over a 3- to 6-day period, but this test is not practical and is nonspecific.
Occasionally, total daily stool volume is also determined.
Direct endoscopic visualization and biopsy of the colon may be undertaken to assess for the presence of conditions such as colitis or cancer.
Radiographic studies are helpful in neoplastic and inflammatory conditions.

- If vomiting is present and is uncontrollable with antiemetics, nothing is taken by mouth. As bowel movements decrease, a bland diet is begun. Feeding should continue in children with acute bacterial diarrhea.
- Rehydration and maintenance of water and electrolytes are the primary treatment measures until the diarrheal episode ends. If vomiting and dehydration are not

TABLE 23–2 Drugs Causing Diarrhea

Laxatives
Antacids containing magnesium
Antineoplastics
Auranofin (gold salt)
Antibiotics: Clindamycin, tetracyclines, sulfonamides, any broad-spectrum antibiotic
Antihypertensives: Reserpine, guanethidine, methyldopa, guanabenz, guanadrel, angiotensin-converting enzyme inhibitors
Cholinergics: Bethanechol, neostigmine
Cardiac agents: Quinidine, digitalis, digoxin
Nonsteroidal anti-inflammatory drugs
Misoprostol
Colchicine
Proton pump inhibitors
H_2-receptor blockers

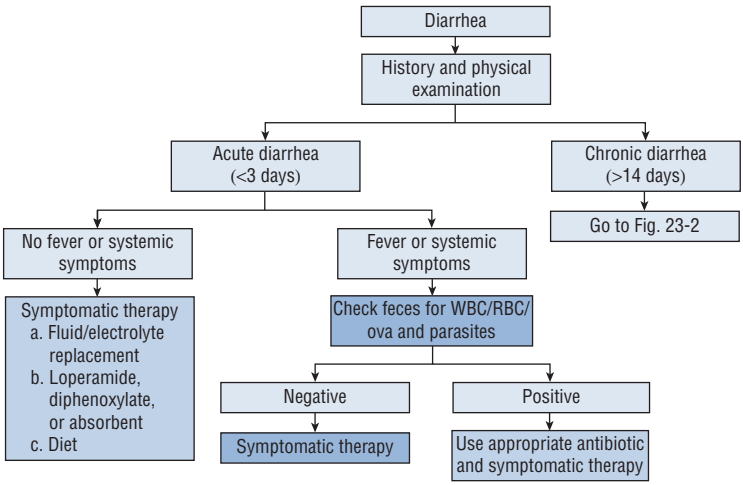


FIGURE 23–1. Recommendations for treating acute diarrhea. Follow these steps: (1) Perform a complete history and physical examination. (2) Is the diarrhea acute or chronic? If chronic diarrhea, go to Fig. 23–2. (3) If acute diarrhea, check for fever and/or systemic signs and symptoms (ie, toxic patient). If systemic illness (fever, anorexia, or volume depletion), check for an infectious source. If positive for infectious diarrhea, use the appropriate antibiotic/anthelmintic drug and symptomatic therapy. If negative for infectious cause, use only symptomatic treatment. (4) If no systemic findings, use symptomatic therapy based on severity of volume depletion, oral or parenteral fluid/electrolytes, antidiarrheal agents (see Table 23–4), and diet. (RBC, red blood cells; WBC, white blood cells.)

severe, enteral feeding is the less costly and preferred method. In the United States, many commercial oral rehydration preparations are available (**Table 23–3**).

PHARMACOLOGIC THERAPY

- Drugs used to treat diarrhea (**Table 23–4**) are grouped into several categories: antimotility, adsorbents, antisecretory compounds, antibiotics, enzymes, and intestinal microflora. Usually, these drugs are not curative but palliative.
- Opiates and opioid derivatives delay the transit of intraluminal content or increase gut capacity, prolonging contact and absorption. The limitations of the opiates are addiction potential (a real concern with long-term use) and worsening of diarrhea in selected infectious diarrheas.
- **Loperamide** is often recommended for managing acute and chronic diarrhea. Diarrhea lasting 48 hours beyond initiating loperamide warrants medical attention.
- Adsorbents (such as **kaolin-pectin**) are used for symptomatic relief (see **Table 23–4**). Adsorbents are nonspecific in their action; they adsorb nutrients, toxins, drugs, and digestive juices. Coadministration with other drugs reduces their bioavailability.
- **Bismuth subsalicylate** is often used for treatment or prevention of diarrhea (traveler's diarrhea) and has antisecretory, anti-inflammatory, and antibacterial effects. Bismuth subsalicylate contains multiple components that might be toxic if given in excess to prevent or treat diarrhea.
- ***Lactobacillus*** preparation is intended to replace colonic microflora. This supposedly restores intestinal functions and suppresses the growth of pathogenic microorganisms. However, a dairy product diet containing 200 to 400 g of lactose or dextrin is equally effective in recolonization of normal flora.

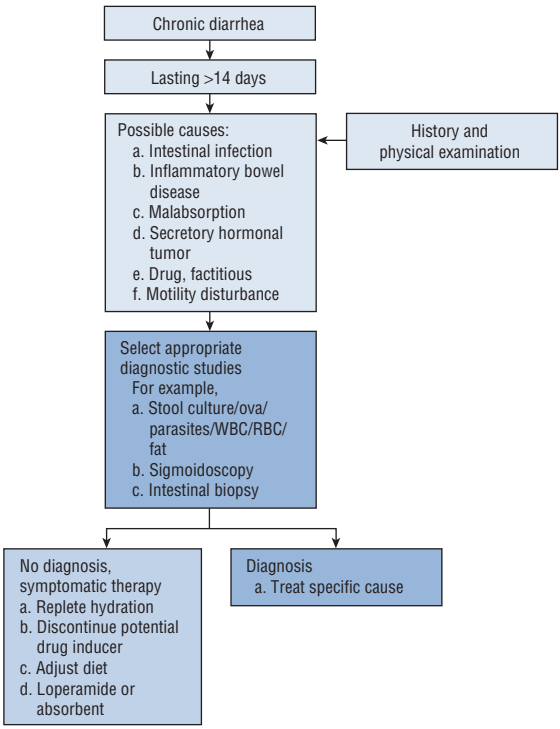


FIGURE 23–2. Recommendations for treating chronic diarrhea. Follow these steps: (1) Perform a careful history and physical examination. (2) The possible causes of chronic diarrhea are many. These can be classified into intestinal infections (bacterial or protozoal), inflammatory disease (Crohn disease or ulcerative colitis), malabsorption (lactose intolerance), secretory hormonal tumor (intestinal carcinoid tumor or vasoactive intestinal peptide [VIP]–secreting tumors), drug (antacid), factitious (laxative abuse), or motility disturbance (diabetes mellitus, irritable bowel syndrome, or hyperthyroidism). (3) If the diagnosis is uncertain, appropriate diagnostic studies should be ordered. (4) Once diagnosed, treatment is planned for the underlying cause with symptomatic antidiarrheal therapy. (5) If no specific cause can be identified, symptomatic therapy is prescribed. (RBC, red blood cells; WBC, white blood cells.)

- Anticholinergic drugs, such as **atropine**, block vagal tone and prolong gut transit time. Their value in controlling diarrhea is questionable and limited by side effects.
- **Octreotide**, a synthetic octapeptide analogue of endogenous somatostatin, is prescribed for the symptomatic treatment of carcinoid tumors and other peptide secreting tumors. The dosage range for managing diarrhea associated with carcinoid tumors is 100 to 600 mcg daily in two to four divided doses, subcutaneously, for 2 weeks. Octreotide is associated with adverse effects such as cholelithiasis, nausea, diarrhea, and abdominal pain.

EVALUATION OF THERAPEUTIC OUTCOMES

- Therapeutic outcomes are directed to key symptoms, signs, and laboratory studies. The constitutional symptoms usually improve within 24 to 72 hours. Elderly persons with chronic illness as well as infants may require hospitalization for parenteral

TABLE 23–3 Oral Rehydration Solutions

	WHO-ORS[a]	Pedialyte[b] (Ross)	CeraLyte (Cera Products)	Enfalyte (Mead Johnson)
Osmolality (mOsm/kg or mmol kg)	245	249	220	167
Carbohydrates[b] (g/L)	13.5	25	40[c]	30[c]
Calories (cal/L [J/L])	65 [272]	100 [418]	160 [670]	126 [527]
Electrolytes (mEq/L; mmol/L)				
Sodium	75	45	50–90	50
Potassium	20	20	20	25
Chloride	65	35	40–80	45
Citrate	—	30	30	34
Bicarbonate	30	—	—	—
Calcium	—	—	—	—
Magnesium	—	—	—	—
Sulfate	—	—	—	—
Phosphate	—	—	—	—

[a]World Health Organization reduced osmolarity oral rehydration solution.
[b]Carbohydrate is glucose.
[c]Rice syrup solids are carbohydrate source.

TABLE 23–4 Selected Antidiarrheal Preparations

	Dose Form	Adult Dose
Antimotility		
Diphenoxylate	2.5 mg/tablet 2.5 mg/5 mL	5 mg 4 times daily; do not exceed 20 mg/day
Loperamide	2 mg/capsule 2 mg/capsule	Initially 4 mg, then 2 mg after each loose stool; do not exceed 16 mg/day
Paregoric Opium tincture Difenoxin	2 mg/5 mL (morphine) 10 mg/mL (morphine) 1 mg/tablet	5–10 mL 1–4 times daily 0.6 mL 4 times daily 2 tablets, then 1 tablet after each loose stool; up to 8 tablets/day
Adsorbents		
Kaolin-pectin mixture	5.7 g kaolin + 130.2 mg pectin/30 mL	30–120 mL after each loose stool
Polycarbophil	500 mg/tablet	Chew 2 tablets 4 times daily or after each loose stool; do not exceed 12 tablets/day
Attapulgite	750 mg/15 mL 300 mg/7.5 mL 750 mg/tablet 600 mg/tablet 300 mg/tablet	1200–1500 mg after each loose bowel movement or every 2 h; up to 9000 mg/day

(*continued*)

TABLE 23–4 Selected Antidiarrheal Preparations (*Continued*)

	Dose Form	Adult Dose
Antisecretory		
Bismuth subsalicylate	1050 mg/30 mL 262 mg/15 mL 524 mg/15 mL 262 mg/tablet	Two tablets or 30 mL every 30 min to 1 h as needed up to 8 doses/day
Enzymes (lactase)	1250 neutral lactase units/4 drops 3300 FCC lactase units per tablet	3–4 drops taken with milk or dairy product
Bacterial replacement *(Lactobacillus acidophilus, Lactobacillus bulgaricus)*		2 tablets or 1 granule packet 3–4 times daily; give with milk, juice, or water
Octreotide	0.05 mg/mL 0.1 mg/mL 0.5 mg/mL	Initial: 50 mcg subcutaneously 1–2 times per day and titrate dose based on indication up to 600 mcg/day in 2–4 divided doses

rehydration and close monitoring. The frequency and character of bowel movements should be checked each day along with the vital signs and improving appetite.

- Monitor body weight, serum osmolality, serum electrolytes, complete blood cell count, urinalysis, and cultures (if appropriate). With an urgent or emergency situation, any change in the volume status of the patient is the most important outcome.
- Toxic patients (those with fever, dehydration, and hematochezia and those who are hypotensive) require hospitalization; they need IV electrolyte solutions and empiric antibiotics while awaiting cultures. With quick management, they usually recover within a few days.

See Chapter 23, Diarrhea, Constipation, and Irritable Bowel Syndrome, authored by Patricia H. Fabel and Kayce M. Shealy, for a more detailed discussion of this topic.

Gastroesophageal Reflux Disease

CHAPTER 24

- *Gastroesophageal reflux disease* (GERD) occurs when refluxed stomach contents lead to troublesome symptoms and/or complications. Episodic heartburn that is not frequent or painful enough to be bothersome is not included in the definition.

PATHOPHYSIOLOGY

- The key factor is abnormal reflux of gastric contents from the stomach into the esophagus. In some cases, reflux is associated with defective lower esophageal sphincter (LES) pressure or function. Patients may have decreased LES pressure from spontaneous transient LES relaxations, transient increases in intraabdominal pressure, or an atonic LES. Some foods and medications decrease LES pressure (**Table 24–1**).
- Problems with other normal mucosal defense mechanisms may contribute to development of GERD, including abnormal esophageal anatomy, improper esophageal clearance of gastric fluids, reduced mucosal resistance to acid, delayed or ineffective gastric emptying, inadequate production of epidermal growth factor, and reduced salivary buffering of acid.
- Esophagitis occurs when the esophagus is repeatedly exposed to refluxed gastric contents for prolonged periods. This can progress to erosion of the squamous epithelium of the esophagus (erosive esophagitis).
- Substances that promote esophageal damage upon reflux into the esophagus include gastric acid, pepsin, bile acids, and pancreatic enzymes. Composition and volume of the refluxate and duration of exposure are the primary determinants of the consequences of gastroesophageal reflux.
- Complications from long-term acid exposure include esophagitis, esophageal strictures, Barrett esophagus, and esophageal adenocarcinoma.

CLINICAL PRESENTATION

- Symptom-based GERD (with or without esophageal tissue injury) typically presents with heartburn, usually described as a substernal sensation of warmth or burning rising up from the abdomen that may radiate to the neck. It may be waxing and waning in character and aggravated by activities that worsen reflux (eg, recumbent position, bending-over, eating a high-fat meal). Other symptoms are water brash (hypersalivation), belching, and regurgitation. Alarm symptoms that may indicate complications include dysphagia, odynophagia, bleeding, and weight loss.
- Tissue injury–based GERD (with or without esophageal symptoms) may present with esophagitis, esophageal strictures, Barrett esophagus, or esophageal carcinoma. Alarm symptoms may also be present.
- Extraesophageal symptoms may include chronic cough, laryngitis, asthma, and dental enamel erosion.

DIAGNOSIS

- Clinical history is sufficient to diagnose GERD in patients with typical symptoms.
- Perform diagnostic tests in patients who do not respond to therapy or who present with alarm symptoms. Endoscopy is preferred for assessing mucosal injury and identifying Barrett esophagus and other complications.
- Ambulatory pH monitoring, esophageal manometry, combined impedance–pH monitoring, high-resolution esophageal pressure topography (HREPT), and an empiric trial of a proton pump inhibitor may be useful in some situations.

TABLE 24–1 Foods and Medications That May Worsen GERD Symptoms

Decreased lower esophageal sphincter (LES) pressure	
Foods	**Medications**
Fatty meal	Anticholinergics
Carminatives (peppermint and spearmint)	Barbiturates
Chocolate	Caffeine
Coffee, cola, and tea	Dihydropyridine calcium channel blockers
Garlic	Dopamine
Onions	Estrogen
Chili peppers	Ethanol
Alcohol (wine)	Nicotine
	Nitrates
	Progesterone
	Tetracycline
	Theophylline
Direct irritants to the esophageal mucosa	
Foods	**Medications**
Spicy foods	Aspirin
Orange juice	Bisphosphonates
Tomato juice	Nonsteroidal anti-inflammatory drugs
Coffee	Iron
Tobacco	Quinidine
	Potassium chloride

TREATMENT

- Goals of Treatment: The goals are to reduce or eliminate symptoms, decrease frequency and duration of gastroesophageal reflux, promote healing of injured mucosa, and prevent development of complications.

GENERAL APPROACH

- Therapy is directed toward decreasing acidity of the refluxate, decreasing the gastric volume available to be refluxed, improving gastric emptying, increasing LES pressure, enhancing esophageal acid clearance, and protecting the esophageal mucosa (Fig. 24–1).
- Treatment is determined by disease severity and includes the following:
  - ✓ Lifestyle changes and patient-directed therapy with **antacids** and/or nonprescription acid suppression therapy **(histamine 2–receptor antagonists [H_2RAs]** and/or **proton pump inhibitors [PPIs])**
  - ✓ Pharmacologic treatment with prescription-strength acid suppression therapy
  - ✓ Antireflux surgery
- The initial intervention depends in part on the patient's condition (symptom frequency, degree of esophagitis, and presence of complications). A step-up approach may be used, starting with lifestyle changes and patient-directed therapy and progressing to pharmacologic management or antireflux surgery. A step-down approach is also effective, starting with a PPI instead of an H_2RA, and then stepping down to the lowest dose of acid suppression needed to control symptoms (Table 24–2).

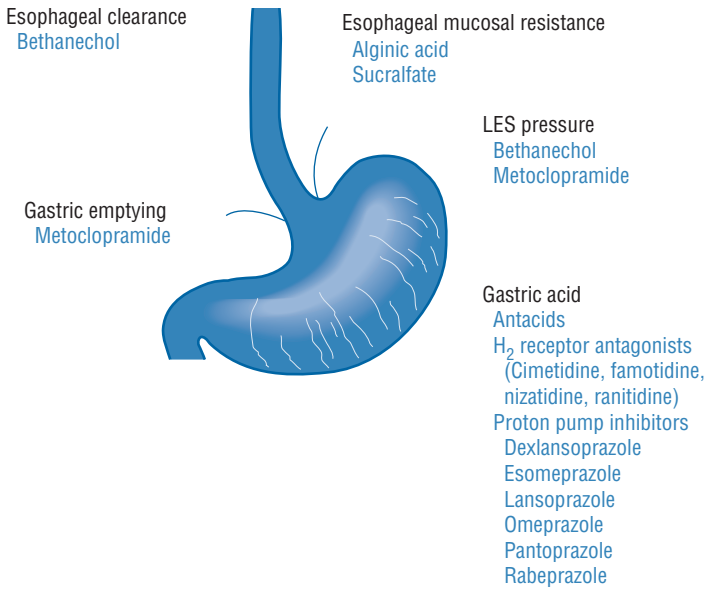


FIGURE 24–1. Therapeutic interventions in the management of gastroesophageal reflux disease (GERD). Pharmacologic interventions are targeted at improving defense mechanisms or decreasing aggressive factors. (LES, lower esophageal sphincter.)

TABLE 24–2 Therapeutic Approach to GERD in Adults

Patient Presentation	Recommended Treatment Regimen	Comments
Intermittent, mild heartburn	**Lifestyle modifications** **plus** **patient-directed therapy** Antacids • Maalox or Mylanta 30 mL as needed or after meals and at bedtime • Gaviscon 2 tablets or 15 mL after meals and at bedtime • Calcium carbonate 500 mg, 2–4 tablets as needed **and/or** Nonprescription H_2RA (taken up to twice daily) • Cimetidine 200 mg • Famotidine 10 mg • Nizatidine 75 mg • Ranitidine 75 mg **or** Nonprescription PPI (taken once daily) • Omeprazole 20 mg • Omeprazole 20 mg/sodium bicarbonate 1100 mg • Lansoprazole 15 mg	Individualize lifestyle modifications for each patient. If symptoms are unrelieved with lifestyle modifications and nonprescription medications after 2 weeks, patient should seek medical attention.

(*continued*)

TABLE 24–2 Therapeutic Approach to GERD in Adults (*Continued*)

Symptomatic relief of GERD	**Lifestyle modifications** **plus** **prescription-strength acid-suppression therapy** H_2RA (for 6–12 weeks) • Cimetidine 400 mg twice daily • Famotidine 20 mg twice daily • Nizatidine 150 mg twice daily • Ranitidine 150 mg twice daily **or** PPIs (for 4–8 weeks); all are given once daily • Dexlansoprazole 30 mg • Esomeprazole 20 mg • Lansoprazole 15–30 mg • Omeprazole 20 mg • Pantoprazole 40 mg • Rabeprazole 20 mg	For typical symptoms, treat empirically with prescription-strength acid suppression therapy. If symptoms recur, consider MT. ***Note***: Most patients require standard doses for MT. Mild GERD can usually be treated effectively with H_2RAs. Patients with moderate to severe symptoms should receive a PPI as initial therapy.
Healing of erosive esophagitis or treatment of patients with moderate to severe symptoms or complications	**Lifestyle modifications** **plus** **PPI for 4–16 weeks** • Dexlansoprazole 60 mg daily • Esomeprazole 20–40 mg daily • Lansoprazole 30 mg twice daily • Omeprazole 20 mg twice daily • Rabeprazole 20 mg twice daily • Pantoprazole 40 mg twice daily **or** High-dose H_2RA (for 8–12 weeks) • Cimetidine 400 mg 4 times daily or 800 mg twice daily • Famotidine 40 mg twice daily • Nizatidine 150 mg 4 times daily • Ranitidine 150 mg 4 times daily	For atypical or alarm symptoms, obtain endoscopy with biopsy to evaluate mucosa. Give a trial of a PPI. If symptoms are relieved, consider MT. PPIs are the most effective MT for patients with atypical symptoms, complications, and erosive disease. Patients not responding to pharmacologic therapy, including those with persistent atypical symptoms, should be evaluated via manometry or ambulatory reflux monitoring.
Interventional therapy	**Antireflux surgery**	

GERD, gastroesophageal reflux disease; H_2RA, histamine 2–receptor antagonist; MT, maintenance therapy; PPI, proton pump inhibitor.

- Patient-directed therapy (self-treatment with nonprescription medication) is appropriate for mild, intermittent symptoms. Patients with continuous symptoms lasting longer than 2 weeks should seek medical attention.

NONPHARMACOLOGIC THERAPY

- Potential lifestyle changes depending on the patient situation:
  - ✓ Elevate head of the bed by placing 6- to 8-in blocks under the headposts. Sleep on a foam wedge.

✓ Weight reduction for overweight or obese patients.
✓ Avoid foods that decrease LES pressure.
✓ Include protein-rich meals to augment LES pressure.
✓ Avoid foods with irritant effects on the esophageal mucosa.
✓ Eat small meals and avoid eating immediately prior to sleeping (within 3 hours if possible).
✓ Stop smoking.
✓ Avoid alcohol.
✓ Avoid tight-fitting clothes.
✓ For mandatory medications that irritate the esophageal mucosa, take in the upright position with plenty of liquid or food (if appropriate).

PHARMACOLOGIC THERAPY

Antacids and Antacid-Alginic Acid Products

- Antacids provide immediate symptomatic relief for mild GERD and are often used concurrently with acid suppression therapies. Patients who require frequent use for chronic symptoms should receive prescription-strength acid suppression therapy instead.
- An antacid with alginic acid (Gaviscon) is not a potent acid-neutralizing agent and does not enhance LES pressure, but it does form a viscous solution that floats on the surface of gastric contents. This serves as a protective barrier for the esophagus against reflux of gastric contents and reduces frequency of reflux episodes. The combination product may be superior to antacids alone in relieving GERD symptoms, but efficacy data indicating endoscopic healing are lacking.
- Antacids have a short duration, which necessitates frequent administration throughout the day to provide continuous acid neutralization. Taking antacids after meals can increase duration from approximately 1 to 3 hours; however, nighttime acid suppression cannot be maintained with bedtime doses.

Proton Pump Inhibitors

- PPIs (**dexlansoprazole**, **esomeprazole**, **lansoprazole**, **omeprazole**, **pantoprazole**, and **rabeprazole**) block gastric acid secretion by inhibiting hydrogen potassium adenosine triphosphatase in gastric parietal cells, resulting in profound and long-lasting antisecretory effects.
- PPIs are superior to H_2RAs in patients with moderate to severe GERD and should be given empirically to patients with troublesome symptoms. Twice-daily use is indicated in patients not responding to standard once-daily therapy.
- Adverse effects include headache, dizziness, somnolence, diarrhea, constipation, and nausea. Potential long-term adverse effects include enteric infections, vitamin B_{12} deficiency, hypomagnesemia, and bone fractures. PPIs can decrease the absorption of drugs such as **ketoconazole** and **itraconazole** that require an acidic environment for absorption. Inhibition of cytochrome P450 2C19 (CYP2C19) by PPIs (especially omeprazole) may decrease effectiveness of clopidogrel. Other drug interactions with PPIs also exist.
- PPIs degrade in acidic environments and are therefore formulated in delayed-release capsules or tablets. Dexlansoprazole, esomeprazole, lansoprazole, and omeprazole contain enteric-coated (pH-sensitive) granules in capsules. For patients unable to swallow the capsules, the contents can be mixed in applesauce or orange juice. In patients with nasogastric tubes, the contents can be mixed in 8.4% sodium bicarbonate solution. Esomeprazole granules can be dispersed in water. Esomeprazole, omeprazole, and pantoprazole are also available in a delayed-release oral suspension powder packet, and lansoprazole is available as a delayed-release, orally-disintegrating tablet. Patients taking pantoprazole or rabeprazole should be instructed not to crush, chew, or split the delayed-release tablets. Dexlansoprazole is available in a dual

delayed-release capsule, with the first release occurring 1 to 2 hours after the dose, and the second release occurring 4 to 5 hours after the dose.
- **Zegerid®** is a combination product containing omeprazole 20 or 40 mg with sodium bicarbonate in immediate-release oral capsules and powder for oral suspension. It should be taken on an empty stomach at least 1 hour before a meal. Zegerid offers an alternative to delayed-release capsules, powder for suspension, or IV formulation in adults with nasogastric tubes.
- **Lansoprazole**, **esomeprazole**, and **pantoprazole** are available in IV formulations for patients who cannot take oral medications, but they are not more effective than oral preparations and are significantly more expensive.
- Patients should take oral PPIs in the morning 15 to 30 minutes before breakfast or their largest meal of the day to maximize efficacy, because these agents inhibit only actively secreting proton pumps. Dexlansoprazole can be taken without regard to meals. If dosed twice daily, the second dose should be taken approximately 10 to 12 hours after the morning dose and prior to a meal or snack.

Histamine 2–Receptor Antagonists

- The histamine 2–receptor antagonists (H_2RAs) **cimetidine**, **ranitidine**, **famotidine**, and **nizatidine** in divided doses are effective for treating mild to moderate GERD. Low-dose nonprescription H_2RAs or standard doses given twice daily may be beneficial for symptomatic relief of mild GERD. Patients not responding to standard doses may be hypersecretors of gastric acid and require higher doses (see **Table 24–2**). The efficacy of H_2RAs for GERD treatment is highly variable and frequently lower than desired. Prolonged courses are frequently required.
- The most common adverse effects include headache, somnolence, fatigue, dizziness, and either constipation or diarrhea. Cimetidine may inhibit the metabolism of theophylline, warfarin, phenytoin, nifedipine, and propranolol, among other drugs.
- Because all H_2RAs are equally efficacious, selection of the specific agent should be based on differences in pharmacokinetics, safety profile, and cost.

Promotility Agents

- Promotility agents may be useful adjuncts to acid suppression therapy in patients with a known motility defect (eg, LES incompetence, decreased esophageal clearance, delayed gastric emptying). However, these agents are not as effective as acid suppression therapy and have undesirable side effects.
- **Metoclopramide**, a dopamine antagonist, increases LES pressure in a dose-related manner and accelerates gastric emptying. However, it does not improve esophageal clearance. Metoclopramide provides symptomatic improvement for some patients, but evidence supporting endoscopic healing is lacking. Tachyphylaxis and serious side effects (including extrapyramidal reactions and tardive dyskinesia) limit usefulness. Common adverse reactions include somnolence, nervousness, fatigue, dizziness, weakness, depression, diarrhea, and rash.
- **Bethanechol** has limited value because of side effects (eg, urinary retention, abdominal discomfort, nausea, flushing).

Mucosal Protectants

- **Sucralfate** is a nonabsorbable aluminum salt of sucrose octasulfate. It has limited value for treatment of GERD but may be useful for management of radiation esophagitis and bile or nonacid reflux GERD.

Combination Therapy

- Combination therapy with an acid-suppressing agent and a promotility agent or mucosal protectant seems logical, but data supporting such therapy are limited. This approach is not recommended unless a patient has GERD with motor dysfunction. Using the omeprazole-sodium bicarbonate immediate-release product

in addition to once daily PPI therapy offers an alternative for nocturnal GERD symptoms.

Maintenance Therapy

- Many patients with GERD relapse after medication is withdrawn, so maintenance treatment may be required. Consider long-term therapy to prevent complications and worsening of esophageal function in patients who have symptomatic relapse after discontinuation of therapy or dosage reduction, including patients with Barrett esophagus, strictures, or esophagitis.
- Most patients require standard doses to prevent relapses. H_2RAs may be effective maintenance therapy in patients with mild disease. PPIs are the drugs of choice for maintenance treatment of moderate to severe esophagitis or symptoms. Usual once-daily doses are omeprazole 20 mg, lansoprazole 30 mg, rabeprazole 20 mg, or esomeprazole 20 mg. Low doses of a PPI or alternate-day regimens may be effective in some patients with milder symptoms.
- "On-demand" maintenance therapy, by which patients take their PPI only when they have symptoms, may be effective for patients with endoscopy-negative GERD.

EVALUATION OF THERAPEUTIC OUTCOMES

- Monitor frequency and severity of GERD symptoms, and educate patients on symptoms that suggest presence of complications requiring immediate medical attention, such as dysphagia or odynophagia. Evaluate patients with persistent symptoms for presence of strictures or other complications.
- Monitor patients for adverse drug effects and the presence of atypical symptoms such as laryngitis, asthma, or chest pain. These symptoms require further diagnostic evaluation.

See Chapter 19, Gastroesophageal Reflux Disease, authored by Dianne B. May and Satish Rao, for a more detailed discussion of this topic.

CHAPTER 25

Hepatitis, Viral

- *Viral hepatitis* refers to the clinically important hepatotropic viruses responsible for hepatitis A (HAV), hepatitis B (HBV), delta hepatitis, hepatitis C (HCV), and hepatitis E.

HEPATITIS A

- HAV infection usually produces a self-limited disease and acute viral infection, with a low fatality rate, and confers lifelong immunity. International travel is a major risk factor for infection.
- HAV infection primarily occurs through transmission by the fecal-oral route, person-to-person, or by ingestion of contaminated food or water. The incidence of HAV correlates directly with low socioeconomic status, poor sanitary conditions, and overcrowding. Rates of HAV infection have increased among international travelers, injection drug users, and men who have sex with men.
- The disease exhibits three phases: incubation (averaging 28 days, range 15–50 days), acute hepatitis (generally lasting 2 months), and convalescence. Most patients have full clinical and biochemical recovery within 12 weeks. Nearly all individuals will have clinical resolution within 6 months of the infection. HAV does not lead to chronic infections.
- The clinical presentation of HAV infection is given in **Table 25–1**. Children younger than 6 years are typically asymptomatic.
- The diagnosis of acute HAV infection is based on clinical criteria of acute onset of fatigue, abdominal pain, loss of appetite, intermittent nausea and vomiting, jaundice or elevated serum aminotransferase levels, and serologic testing for immunoglobulin (Ig) M anti-HAV.

TREATMENT

- Goals of Treatment: Complete clinical resolution, including avoidance of complications, normalization of liver function, and reduction of infectivity and transmission. No specific treatment options exist for HAV. Management of HAV infection is primarily supportive. Steroid use is not recommended.

PREVENTION

- The spread of HAV can be best controlled by avoiding exposure. The most important measures to avoid exposure include good handwashing techniques and good personal hygiene practices.
- The current vaccination strategy in the United States includes vaccinating all children at 1 year of age. Groups who should receive HAV vaccine are shown in **Table 25–2**.
- Three inactivated virus vaccines are currently licensed in the United States: Havrix, Vaqta, and Twinrix. Approved dosing recommendations are shown in **Table 25–3**. Seroconversion rates of 94% or greater are achieved with the first dose.
- IG is used when pre- or postexposure prophylaxis against HAV infection is needed in persons for whom vaccination is not an option. It is most effective if given during the incubation phase of infection. A single dose of IG of 0.02 mL/kg is given intramuscularly for postexposure prophylaxis or short-term (≤5 months) preexposure prophylaxis. For lengthy stays, a single dose of 0.06 mL/kg is used. HAV vaccine may also be given with IG.
- For people recently exposed to HAV and not previously vaccinated, IG is indicated for
  - ✓ Those in close contact with an HAV-infected person; all staff and attendees of daycare centers when HAV is documented; those involved in a common source exposure (eg, a food-borne outbreak); classroom contacts of an index case patient; and schools, hospitals, and work settings where close personal contact occurred with the case patient.

TABLE 25–1 Clinical Presentation of Acute Hepatitis A

Signs and symptoms

- The preicteric phase brings nonspecific influenza-like symptoms consisting of anorexia, nausea, fatigue, and malaise
- Abrupt onset of anorexia, nausea, vomiting, malaise, fever, headache, and right upper quadrant abdominal pain with acute illness
- Icteric hepatitis is generally accompanied by dark urine, acholic (light-colored) stools, and worsening of systemic symptoms
- Pruritus is often a major complaint of icteric patients

Physical examination

- Icteric sclera, skin, and secretions
- Mild weight loss of 2–5 kg
- Hepatomegaly

Laboratory tests

- Positive serum immunoglobulin M anti–hepatitis A virus
- Mild elevations of serum bilirubin, γ-globulin, and hepatic transaminase (ALT [alanine transaminase] and aspartate transaminase [AST]) values to about twice normal in acute anicteric disease
- Elevations of alkaline phosphatase, γ-glutamyl transferase, and total bilirubin in patients with cholestatic illness

TABLE 25–2 Recommendations for Hepatitis A Vaccination

All children at 1 year of age
Children and adolescents ages 2–18 years who live in states or communities where routine hepatitis A vaccination has been implemented because of high disease incidence
Persons traveling to or working in countries that have high or intermediate endemicity of infection[a]
Men who have sex with men
Illegal-drug users
Persons who have occupational risk for infection (eg, persons who work with HAV-infected primates or HAV in a research laboratory setting)
Persons who have clotting factor disorders
Persons who have chronic liver disease (eg, persons with chronic liver disease caused by hepatitis B or C and persons awaiting liver transplants)
All previously unvaccinated persons anticipating close personal contact (eg, household contact or regular babysitter) with an international adoptee from a country of high or intermediate endemicity within the first 60 days following the arrival of the adoptee

HAV, hepatitis A virus.
[a]Travelers to Canada, Western Europe, Japan, Australia, or New Zealand are at no greater risk for HAV infection than they are while in the United States. All other travelers should be assessed for hepatitis A risk.
Source: Centers for Disease Control and Prevention. www.cdc.gov.

- Common vaccine side effects include soreness and warmth at the injection site, headache, malaise, and pain.

HEPATITIS B

- HBV is a leading cause of chronic hepatitis, cirrhosis, and hepatocellular carcinoma.
- Transmission of HBV occurs sexually, parenterally, and perinatally. In the United States, transmission occurs predominantly through sexual contact or injection-drug use. International travel is also an important risk factor.

TABLE 25–3 Recommended Dosing of Hepatitis A Vaccines

Vaccine	Vaccinee's Age (years)	Dose	Number of Doses	Schedule (months)
Havrix	1–18	720 ELISA units	2	0, 6–12
	≥19	1440 ELISA units	2	0, 6–12
Vaqta	1–18	25 units	2	0, 6–18
	≥19	50 units	2	0, 6–18
Twinrix	>18	720 ELISA units	3	0, 1, 6
	>18	720 ELISA units	4	0, 7 days
	(accelerated schedule)			21–30 days + 12 months

ELISA, enzyme-linked immunosorbent assay.
Source: Centers for Disease Control and Prevention. Prevention of hepatitis A through active or passive immunizations: recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR Morb Mortal Wkly Rep 2006;55(RR-7):1–23.

- Approximately 20% of patients with chronic HBV infection develop complications of decompensated cirrhosis, including hepatic insufficiency and portal hypertension as their compensated cirrhosis progresses to decompensated cirrhosis within a 5-year period. HBV is a risk factor for development of hepatocellular carcinoma.
- There are three phases of HBV infection. The incubation period for HBV is 4 to 10 weeks during which patients are highly infective. This is followed by a symptomatic phase with intermittent flares of hepatitis and marked increases in aminotransferase serum levels. The final phase is seroconversion to anti–hepatitis B core antigen (anti-HbcAg). Patients who continue to have detectable hepatitis B surface antigen (HbsAg) and HBcAg and a high serum titer of HBV DNA for longer than 6 months have chronic HBV.
- The interpretation of serologic markers for HBV is given in **Table 25–4**.
- The clinical presentation of chronic HBV is given in **Table 25–5**.

PREVENTION

- Prophylaxis of HBV can be achieved by vaccination or by passive immunity in post-exposure cases with HBV Ig.
- Two products are available for prevention of HBV infection: **HBV vaccine**, which provides active immunity, and **HBV Ig**, which provides temporary passive immunity.
- The goal of immunization against viral hepatitis is prevention of the short-term viremia that can lead to transmission of infection, clinical disease, and chronic HBV infection.
- Persons who should receive HBV vaccine are listed in **Table 25–6**.
- Side effects of the vaccines include soreness at the injection site, headache, fatigue, irritability, and fever.

TREATMENT

- **Goals of therapy:** The goals are to increase the likelihood of seroclearance of the virus, prevent disease progression to cirrhosis or hepatocellular carcinoma, and minimize further liver injury. Successful therapy is associated with loss of HBcAg status and seroconversion to anti-HBcAg.
- Some patients with chronic HBV infection should be treated. Recommendations for treatment consider the patient's age, serum HBV DNA and ALT levels, and histologic evidence and clinical progression of the disease. A suggested treatment algorithm for chronic HBV is shown for patients without (**Fig. 25–1**) and with cirrhosis (**Fig. 25–2**).
- All patients with chronic HBV infection should be counseled on preventing disease transmission, avoiding alcohol, and on being immunized against HBV.

TABLE 25–4 Interpretation of Serologic Tests in Hepatitis B Virus

Tests	Result	Interpretation
HBsAg	(–)	
Anti-HBC	(–)	Susceptible
Anti-HBs	(–)	
HBsAg	(–)	
Anti-HBc	(+)	Immune because of natural infection
Anti-HBs	(+)	
HBsAg	(–)	Immune because of vaccination (valid only if test performed 1–2 months after third vaccine dose)
Anti-HBc	(–)	
Anti-HBs	(+)	
HBsAg	(+)	
Anti-HBc	(+)	Acute infection
IgM anti-HBc	(+)	
HBsAg	(+)	
Anti-HBc	(+)	Chronic infection
IgM anti-HBc	(–)	
Anti-HBs	(–)	
HBsAg	(–)	Four interpretations possible:
Anti-HBc	(+)	1. Recovery from acute infection
Anti-HBs	(–)	2. Distant immunity and test not sensitive enough to detect low level of HBs in serum
		3. Susceptible with false-positive anti-HBc
		4. May have undetectable level of HBsAg in serum and be chronically infected

HBc, hepatitis B core; HBs, hepatitis B surface; HBsAg, hepatitis B surface antigen; IgM, immunoglobulin M.

Source: Centers for Disease Control and Prevention. Hepatitis B Serology. http://www.cdc.gov/ncidod/diseases/hepatitis/b/Bserology.htm.

- The immune-mediating agents approved as first-line therapy are interferon **(IFN)-alfa** and **pegylated (peg) IFN-alfa**. The antiviral agents **lamivudine**, **telbivudine**, **adefovir**, **entecavir**, and **tenofovir** are all approved as first-line therapy options for chronic HBV.
- For HBeAg-positive patients, treatment is recommended until HBeAg seroconversion and an undetectable HBV viral load are achieved and for 6 months of additional treatment. In HBeAg-negative patients, treatment should be continued until HBsAg clearance.

HEPATITIS C

- HCV is the most common blood-borne pathogen and is most often acquired through injection drug use. Screening for HCV infection is recommended in groups who are at high risk for infection (**Table 25–7**). The CDC recommends one-time screening of all patients born between 1945 and 1965.
- Transmission may occur by sexual contact; hemodialysis; or household, occupational, or perinatal exposure.
- In up to 85% of patients, acute HCV infection leads to chronic infection defined by persistently detectable HCV RNA for 6 months or more.

TABLE 25–5 Clinical Presentation of Chronic Hepatitis B[a]

Signs and symptoms

- Easy fatigability, anxiety, anorexia, and malaise
- Ascites, jaundice, variceal bleeding, and hepatic encephalopathy can manifest with liver decompensation
- Hepatic encephalopathy is associated with hyperexcitability, impaired mentation, confusion, obtundation, and eventually coma
- Vomiting and seizures

Physical examination

- Icteric sclera, skin, and secretions
- Decreased bowel sounds, increased abdominal girth, and detectable fluid wave
- Asterixis
- Spider angiomata

Laboratory tests

- Presence of hepatitis B surface antigen for >6 months
- Intermittent elevations of hepatic transaminase (alanine transaminase [ALT] and aspartate transaminase [AST]) and hepatitis B virus DNA >20,000 IU/mL (10^5 copies/mL or 10^8 copies/L)
- Liver biopsies for pathologic classification as chronic persistent hepatitis, chronic active hepatitis, or cirrhosis

[a]Chronic hepatitis B can be present even without all the signs, symptoms, and physical examination findings listed being apparent.

TABLE 25–6 Recommendations for HBV Vaccination

Infants
Adolescents, including all previously unvaccinated children <19 years old
All unvaccinated adults at risk for infection
All unvaccinated adults seeking vaccination (specific risk factor not required)
Men and women with a history of other sexually transmitted diseases and persons with a history of multiple sex partners (>1 partner/6 months)
Men who have sex with men
Injection-drug users
Household contacts and sex partners of persons with chronic HBV infection and healthcare and public safety workers with exposure to blood in the workplace
Clients and staff of institutions for the developmentally disabled
International travelers to regions with high or intermediate levels (HBsAg prevalence ≥2%) of endemic HBV infection
Recipients of clotting factor concentrates
Sexually transmitted disease clinic patients
HIV patient/HIV-testing patients
Drug abuse treatment and prevention clinic patients
Correctional facilities inmates
Chronic dialysis/ESRD patients
Persons with chronic liver disease

ESRD, end-stage renal disease; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; HIV, human immunodeficiency virus.

Source: Centers for Disease Control and Prevention. A comprehensive immunization strategy to eliminate transmission of hepatitis B virus infection in the United States: recommendations of the Advisory Committee on Immunization Practices (ACIP) Part 1: immunization of infants, children, and adolescents. MMWR Morb Mortal Wkly Rep 2005;54(RR-16):1–31.

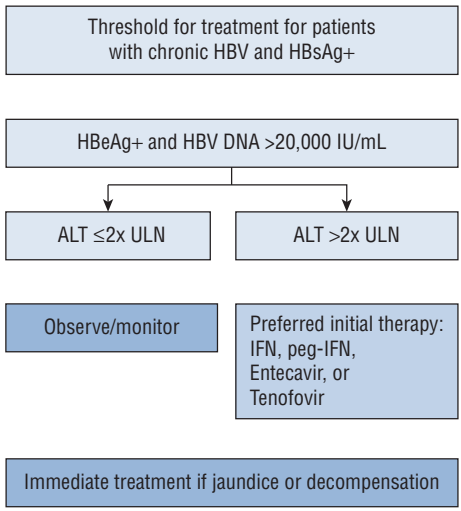


FIGURE 25–1. Suggested management algorithm for chronic hepatitis B virus infection without cirrhosis based on the recommendations of the American Association for the Study of Liver Diseases. (ALT, alanine transaminases; HBeAg, hepatitis B e antigen; peg-IFN, pegylated interferon; ULN, upper limit of normal.) (*Adapted from Lok ASF, McMahon BJ. AASLD practice guidelines: chronic hepatitis B. Hepatology 2001;34:1225–1241.*)

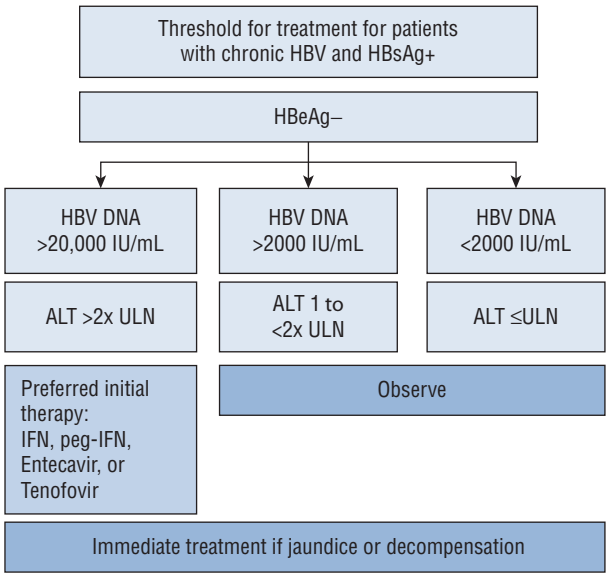


FIGURE 25–2. Suggested treatment algorithm for chronic hepatitis B virus infection with cirrhosis based on the recommendations of the American Association for the Study of Liver Diseases for chronic hepatitis B virus–infected patients with cirrhosis. (*Adapted from Lok ASF, McMahon BJ. AASLD practice guidelines: chronic hepatitis B. Hepatology 2001;34:1225–1241.*)

TABLE 25–7 Recommendations for Hepatitis C Virus (HCV) Screening
Anyone born between 1945 and 1965
Current or past use of injection-drug use
Coinfection with HIV
Received blood transfusions or organ transplantations before 1992
Received clotting factors before 1987
Patients who have ever been on hemodialysis
Patients with unexplained elevated ALT levels or evidence of liver disease
Healthcare and public safety workers after a needle-stick or mucosal exposure to HCV-positive blood
Children born to HCV-positive mothers
Sexual partners of HCV-positive patients

ALT, alanine transaminase; HIV, human immunodeficiency virus.

Data from reference 62.

- Patients with acute HCV are often asymptomatic and undiagnosed. One third of adults will experience some mild and nonspecific symptoms, including persistent fatigue. Additional symptoms include right upper quadrant pain, nausea, or poor appetite.
- An estimated 20% of patients with chronic HCV infection will develop cirrhosis, and half of those patients will progress to decompensated cirrhosis or hepatocellular carcinoma.
- The diagnosis of HCV infection is confirmed with a reactive enzyme immunoassay for anti-HCV. Serum transaminase values are elevated within 4 to 12 weeks after exposure.

TREATMENT

- Goals of Treatment: The goal is to eradicate HCV infection, which prevents the development of chronic HCV infection and sequelae.
- Treatment is indicated in patients previously untreated who have chronic HCV, circulating HCV RNA, increased ALT levels, evidence on biopsy of moderate to severe hepatic grade and stage, and compensated liver disease.
- Adherence to therapy is a crucial component in response, especially among genotype 1–infected patients. Patients who take at least 80% of their medications for at least 80% of the treatment time are more likely to successfully respond to therapy.
- The current standard of care for chronic HCV genotype 1 patients is a combination therapy of a once-weekly injection of peg-IFN, a daily oral dose of ribavirin, and either boceprevir or telaprevir. The PIs must be used in combination with peg-IFN and ribavirin to limit the development of resistance. For all other genotypes, the standard of care remains peg-IFN and ribavirin.
- All patients with chronic HCV infection should be vaccinated for HAV and HBV. Patients should be advised to maintain good overall health, stop smoking, and avoid alcohol and illicit drugs.
- Recommended treatment regimens for HCV infection are given in **Table 25–8**.

TABLE 25–8 Recommended Hepatitis C Virus Treatment Algorithm		
Genotype	**Therapeutic Regimen**	**Duration[a]**
1	Peg-IFN + ribavirin + boceprevir or telaprevir	Variable 24–48 weeks
2, 3, 4	Peg-IFN + ribavirin	24 weeks

[a]*Actual treatment duration may be different depending on virologic response.*

TABLE 25–9	Pegylated Interferon (Peg-IFN) Comparison	
	Pegasys	**PEG-Intron**
Interferon	Alpha-2a	Alpha-2b
Indications	HBV, HCV	HCV
PEG moiety (weight)	Branched (40 kDa)	Linear (12 kDa)
Distribution	8–12 L; highest concentration in liver, spleen, and kidneys	Body weight dependent: 1 L/kg; distributes throughout body
Metabolism	Liver	Liver
Excretion	Renal	Renal
Dosing	Fixed: 180 mcg/week subcutaneously	Weight dependent: 1.5 mcg/kg/week subcutaneously

HBV, hepatitis B virus; HCV, hepatitis C virus.

TABLE 25–10	Common Side Effects of peg-Interferon Therapy
Fatigue	Arthralgia
Fever	Musculoskeletal pain
Headache	Insomnia
Nausea	Depression
Anorexia	Anxiety/emotional lability
Rigors	Alopecia
Myalgia	Injection site reactions

- Two peg-IFNs are available: Pegasys and PEG-Intron (**Table 25–9**). It is unclear which is superior.
- Common side effects of peg-IFN are given in **Table 25–10**. Common side effects of ribavirin include fatigue, flu-like symptoms, neutropenia, thrombocytopenia, and anemia.

PREVENTION

- No HCV vaccine is currently available.

See Chapter 26, Viral Hepatitis, authored by Paulina Deming, for a more detailed discussion of this topic.

CHAPTER 26

Inflammatory Bowel Disease

- There are two forms of *inflammatory bowel disease* (IBD): ulcerative colitis (UC), a mucosal inflammatory condition confined to the rectum and colon, and Crohn disease, a transmural inflammation of gastrointestinal (GI) mucosa that may occur in any part of the GI tract. The etiologies of both conditions are unknown, but they may have a common pathogenetic mechanism.

PATHOPHYSIOLOGY

- Factors involved in cause of IBD include infectious agents, genetics, the environment, and the immune system. The microflora of the GI tract may provide an environmental trigger to activate inflammation and are highly implicated in the development of IBD. Several genetic markers and loci have been identified that occur more frequently in patients with IBD. The inflammatory response with IBD may indicate abnormal regulation of the normal immune response or an autoimmune reaction to self-antigens.
- Th1 cytokine activity is excessive in CD and increased expression of interferon-γ in the intestinal mucosa and production of IL-12 are features of the immune response in CD. Tumor necrosis factor-α (TNF-α) is a pivotal pro-inflammatory cytokine that is increased in the mucosa and intestinal lumen of patients with CD and UC.
- Antineutrophil cytoplasmic antibodies are found in a high percentage of patients with UC and less frequently with CD.
- Smoking appears to be protective for ulcerative colitis but associated with increased frequency of Crohn disease. The use of nonsteroidal anti-inflammatory drugs (NSAIDs) may trigger disease occurrence or lead to disease flares.
- UC and Crohn disease differ in two general respects: anatomical sites and depth of involvement within the bowel wall. There is, however, overlap between the two conditions, with a small fraction of patients showing features of both diseases (**Table 26–1**).

ULCERATIVE COLITIS

- UC is confined to the colon and rectum and affects primarily the mucosa and the submucosa. The primary lesion occurs in the crypts of the mucosa (crypts of Lieberkühn) in the form of a crypt abscess.
- Local complications (involving the colon) occur in the majority of patients with UC. Relatively minor complications include hemorrhoids, anal fissures, and perirectal abscesses.
- A major complication is toxic megacolon, a severe condition that occurs in up to 7.9% of UC patients admitted to hospitals. The patient with toxic megacolon usually has a high fever, tachycardia, distended abdomen, elevated white blood cell count, and a dilated colon.
- The risk of colonic carcinoma is much greater in patients with UC as compared with the general population.
- Approximately 11% of patients with UC have hepatobiliary complications, including fatty liver, pericholangitis, chronic active hepatitis, cirrhosis, sclerosing cholangitis, cholangiocarcinoma, and gallstones.
- Arthritis commonly occurs in patients with IBD and is typically asymptomatic and migratory. Arthritis typically involves one or a few large joints, such as the knees, hips, ankles, wrists, and elbows.
- Ocular complications (iritis, episcleritis, and conjunctivitis) occur in 2% to 29% of patients. Skin and mucosal lesions associated with IBD include erythema nodosum, pyoderma gangrenosum, aphthous ulceration, and Sweet syndrome.

TABLE 26–1 Comparison of the Clinical and Pathologic Features of Crohn Disease and Ulcerative Colitis

Feature	Crohn Disease	Ulcerative Colitis
Clinical		
Malaise, fever	Common	Uncommon
Rectal bleeding	Common	Common
Abdominal tenderness	Common	May be present
Abdominal mass	Common	Absent
Abdominal pain	Common	Unusual
Abdominal wall and internal fistulas	Common	Absent
Distribution	Discontinuous	Continuous
Aphthous or linear ulcers	Common	Rare
Pathologic		
Rectal involvement	Rare	Common
Ileal involvement	Very common	Rare
Strictures	Common	Rare
Fistulas	Common	Rare
Transmural involvement	Common	Rare
Crypt abscesses	Rare	Very common
Granulomas	Common	Rare
Linear clefts	Common	Rare
Cobblestone appearance	Common	Absent

CROHN DISEASE

- Crohn disease is a transmural inflammatory process. The terminal ileum is the most common site of the disorder, but it may occur in any part of the GI tract. Most patients have some colonic involvement. Patients often have normal bowel separating segments of diseased bowel; that is, the disease is often discontinuous.
- Complications of Crohn disease may involve the intestinal tract or organs unrelated to it. Small bowel stricture with subsequent obstruction is a complication that may require surgery. Fistula formation is common (20%–40% lifetime risk) and occurs much more frequently than with UC.
- Systemic complications of Crohn disease are common and similar to those found with UC. Arthritis, iritis, skin lesions, and liver disease often accompany Crohn disease.
- Nutritional deficiencies are common with Crohn disease (weight loss, iron deficiency anemia, vitamin B_{12} deficiency, folate deficiency, hypoalbuminemia, hypokalemia, and osteomalacia).

CLINICAL PRESENTATION

ULCERATIVE COLITIS

- There is a wide range of presentation in UC, ranging from mild abdominal cramping with frequent small-volume bowel movements to profuse diarrhea (**Table 26–2**). Many patients have disease confined to the rectum (proctitis).
- Most patients with UC experience intermittent bouts of illness after varying intervals of no symptoms.
- Mild disease, which afflicts two thirds of patients, has been defined as fewer than four stools daily, with or without blood, with no systemic disturbance and a normal erythrocyte sedimentation rate (ESR).
- Patients with moderate disease have more than four stools per day but with minimal systemic disturbance.

TABLE 26–2 Clinical Presentation of Ulcerative Colitis

Signs and symptoms
- Abdominal cramping
- Frequent bowel movements, often with blood in the stool
- Weight loss
- Fever and tachycardia in severe disease
- Blurred vision, eye pain, and photophobia with ocular involvement
- Arthritis
- Raised, tender red nodules that vary in size from 1 cm to several centimeters

Physical examination
- Hemorrhoids, fissures, or perirectal abscesses may be present.
- Iritis, uveitis, episcleritis, and conjunctivitis with ocular involvement
- Dermatologic findings with erythema nodosum, pyoderma gangrenosum, or aphthous ulceration

Laboratory tests
- Decreased hematocrit/hemoglobin
- Increased erythrocyte sedimentation rate
- Leukocytosis and hypoalbuminemia with severe disease
- (+) perinuclear antineutrophil cytoplasmic antibodies

- With severe disease, the patient has more than six stools per day with blood, with evidence of systemic disturbance as shown by fever, tachycardia, anemia, or ESR greater than 30.

CROHN DISEASE

- As with UC, the presentation of Crohn disease is highly variable (**Table 26–3**). A patient may present with diarrhea and abdominal pain or a perirectal or perianal lesion.
- The course of Crohn disease is characterized by periods of remission and exacerbation. Some patients may be free of symptoms for years, whereas others experience chronic problems despite medical therapy.
- The Crohn Disease Activity Index (CDAI) and the Harvey Bradshw Index are used to gauge response to therapy and determine remission. Disease activity may be assessed and correlated by evaluation of serum C-reactive protein concentrations.

TABLE 26–3 Clinical Presentation of Crohn Disease

Signs and symptoms
- Malaise and fever
- Abdominal pain
- Frequent bowel movements
- Hematochezia
- Fistula
- Weight loss and malnutrition
- Arthritis

Physical examination
- Abdominal mass and tenderness
- Perianal fissure or fistula

Laboratory tests
- Increased white blood cell count and erythrocyte sedimentation rate
- Anti–*Saccharomyces cerevisiae* antibodies

TREATMENT

- Goals of Treatment: Resolution of acute inflammatory processes, resolution of attendant complications (eg, fistulas or abscesses), alleviation of systemic manifestations (eg, arthritis), maintenance of remission from acute inflammation, or surgical palliation or cure.

NONPHARMACOLOGIC TREATMENT

- Protein–energy malnutrition and suboptimal weight is reported in up to 85% of patients with CD.
- The nutritional needs of the majority of patients can be adequately addressed with enteral supplementation. Parenteral nutrition is generally reserved for patients with severe malnutrition or those who fail enteral therapy or have a contraindication to receiving enteral therapy, such as perforation, protracted vomiting, short bowel syndrome, or severe intestinal stenosis.
- Probiotic formulas have been effective for inducing and maintaining remission in UC, but the data are not conclusive.
- For UC, colectomy may be indicated for patients with long-standing disease (>8 to 10 years), as a prophylactic measure against the development of CRC, and for patients with premalignant changes (severe dysplasia) on surveillance mucosal biopsies.
- The indications for surgery with Crohn disease are not as well established as they are for UC, and surgery is usually reserved for the complications of the disease. There is a high recurrence rate of Crohn disease after surgery.

PHARMACOLOGIC THERAPY

- The major types of drug therapy used in IBD are **aminosalicylates, glucocorticoids**, immunosuppressive agents (**azathioprine, mercaptopurine**, **cyclosporine**, and **methotrexate**), antimicrobials (**metronidazole** and **ciprofloxacin**), agents to inhibit tumor necrosis factor-α (TNF-α) (anti–TNF-α antibodies), and leukocyte adhesion and migration (**natalizumab**).
- **Sulfasalazine** combines a sulfonamide (sulfapyridine) antibiotic and mesalamine (5-aminosalicylic acid) in the same molecule. **Mesalamine**-based products are listed in **Table 26–4**.
- Corticosteroids and adrenocorticotropic hormone have been widely used for the treatment of UC and Crohn disease and are used in moderate to severe disease. Prednisone is most commonly used. Immunosuppressive agents such as azathioprine and mercaptopurine (a metabolite of azathioprine) are used in the long-term treatment of IBD. These agents are generally reserved for patients who fail mesalamine therapy or are refractory to or dependent on corticosteroids. Cyclosporine has been of short-term benefit in acute, severe UC when used in a continuous infusion.
- Methotrexate given 25 mg intramuscularly once weekly is useful for treatment and maintenance of Crohn disease.
- Antimicrobial agents, particularly metronidazole, are frequently used in attempts to control Crohn disease, particularly when it involves the perineal area or fistulas. Ciprofloxacin has also been used for treatment of Crohn disease.
- Infliximab is an anti-TNF antibody that is useful in moderate to severe active disease and steroid-dependent or fistulizing disease, but the cost far exceeds that of other regimens. Adalimumab is another anti-TNF antibody that is an option for patients with moderate to severe active Crohn disease or UC previously treated with infliximab who have lost response. Natalizumab is a leukocyte adhesion and migration inhibitor that is used for patients with Crohn disease who are unresponsive to other therapies.

TABLE 26–4 Agents for the Treatment of Inflammatory Bowel Disease

Drug	Brand Name	Initial Dose (g)	Usual Range
Sulfasalazine	Azulfidine Azulfidine EN	500 mg to 1 g 500 mg to 1 g	4–6 g/day 4–6 g/day
Mesalamine suppository	Rowasa	1 g	1 g daily to three times weekly
Mesalamine enema	Canasa	4 g	4 g daily to three times weekly
Mesalamine (oral)	Asacol Asacol HD Apriso Lialda Pentasa Delzicol	1.2 g/day 1.6 g/day 1.5 g/day 1.2–2.4 g/day 2 g/day 1.2 g/day	2.8–4.8 g/day 2.8–4.8 g/day 1.5 g/day once daily 1.2–4.8 g/day once daily 2–4 g/day 2.4–4.8 g/day
Olsalazine	Dipentum	1.5 g/day	1.5–3 g/day
Balsalazide	Colazal	2.25 g/day	2.25–6.75 g/day
Azathioprine	Imuran, Azasan	50–100 mg	1–2.5 mg/kg/day
Cyclosporine	Gengraf Neoral, Sandimmune	2–4 mg/kg/day IV 2–8 mg/kg/day oral	2–4 mg/kg/day IV
Mercaptopurine	Purinethol	50–100 mg	1–2.5 mg/kg/day
Methotrexate	Trexall	15–25 mg IM weekly	15–25 mg IM weekly
Adalimumab	Humira	160 mg SC day 1	80 mg SC 2 (day 15), and then 40 mg every 2 weeks
Certolizumab	Cimzia	400 mg SC	400 mg SC weeks 2 and 4, and then 400 mg SC monthly
Infliximab	Remicade	5 mg/kg IV	5 mg/kg weeks 2 and 6, 5–10 mg/kg every 8 weeks
Natalizumab	Tysabri	300 mg IV	300 mg IV every 4 weeks
Budesonide	Enterocort EC Uceris	9 mg	6–9 mg daily

SC, subcutaneous; IM, intramuscular.

Ulcerative Colitis

MILD TO MODERATE DISEASE

- Most patients with mild to moderate active UC can be managed on an outpatient basis with oral and/or topical mesalamine (**Fig. 26–1**). When given orally, usually 4 g/day to 6 g/day of sulfasalazine is required to attain control of active inflammation. Sulfasalazine therapy should be instituted at 500 mg/day and increased every few days up to 4 g/day or the maximum tolerated.
- Oral mesalamine derivatives (such as those listed in **Table 26–4**) are reasonable alternatives to sulfasalazine for treatment of UC as they are better tolerated.

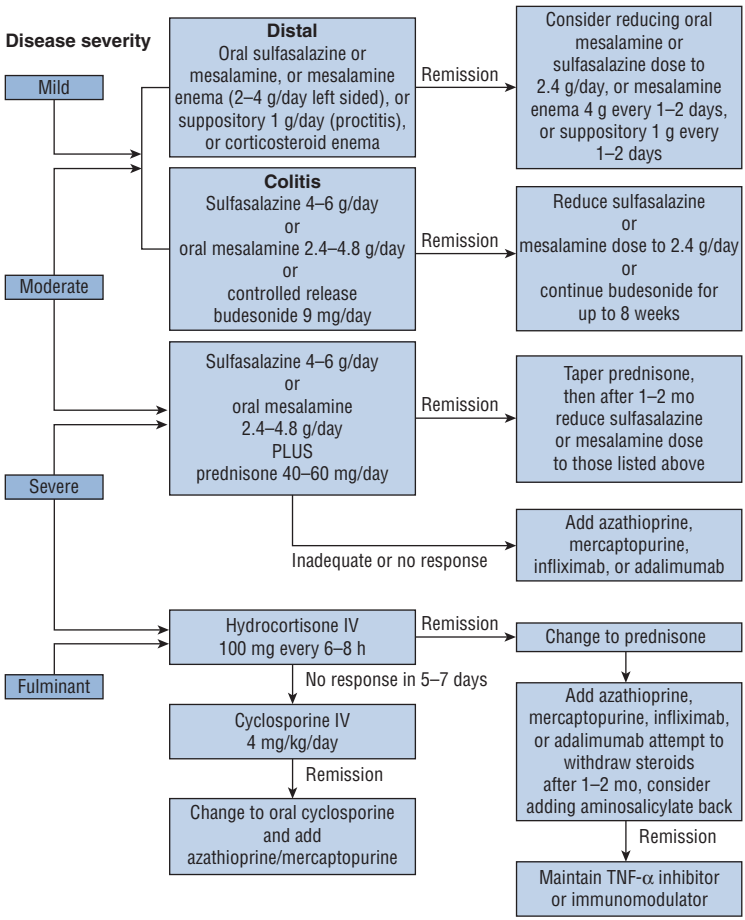


FIGURE 26–1. Treatment approaches for ulcerative colitis.

MODERATE TO SEVERE DISEASE

- Steroids have a place in the treatment of moderate to severe UC or in those who are unresponsive to maximal doses of oral and topical mesalamine. Oral **prednisone** 40 to 60 mg daily is recommended for adult.
- Infliximab is another viable option for patients with moderate to severe active UC who are unresponsive to steroids or other immunosuppressive agents.

SEVERE OR INTRACTABLE DISEASE

- Patients with uncontrolled severe colitis or incapacitating symptoms require hospitalization for effective management. Most medication is given by the parenteral route.
- IV hydrocortisone 300 mg daily in three divided doses or methylprednisolone 60 mg once daily is considered a first-line agent. A trial of steroids is warranted in most patients before proceeding to colectomy, unless the condition is grave or rapidly deteriorating.

- Patients who are unresponsive to parenteral corticosteroids after 3 to 7 days can receive cyclosporine or infliximab. A continuous IV infusion of cyclosporine 2 to 4 mg/kg/day is the typical dose range utilized and may delay the need for colectomy.

MAINTENANCE OF REMISSION

- Once remission from active disease has been achieved, the goal of therapy is to maintain the remission.
- Oral agents, including sulfasalazine, mesalamine, and balsalazide, are all effective options for maintenance therapy. The optimal dose to prevent relapse is 2 to 2.4 g/day of mesalamine equivalent, with rates of relapse over 6 to 12 months reported as 40%.
- Steroids do not have a role in the maintenance of remission with UC because they are ineffective. Steroids should be gradually withdrawn after remission is induced (over 2–4 weeks).

Crohn Disease

ACTIVE CROHN DISEASE

- Mesalamine derivatives have not demonstrated significant efficacy in CD. They are often tried as an initial therapy for mild to moderate CD given their favorable adverse effect profile.
- Mesalamine derivatives (e.g., **Pentasa** and **Asacol**) that release mesalamine in the small bowel may be more effective than sulfasalazine for ileal involvement.
- Oral **corticosteroids,** such as prednisone 40 to 60 mg/day, are generally considered first-line therapies and are frequently used for the treatment of moderate to severe Crohn disease. Budesonide (Entocort) at a dose of 9 mg daily is a viable first-line option for patients with mild to moderate ileal or right-sided (ascending colonic) disease.
- Metronidazole, given orally as 10 to 20 mg/kg/day in divided doses, may be useful in some patients with CD, particularly for patients with colonic or ileocolonic involvement, those with perineal disease, or those who are unresponsive to sulfasalazine.
- Azathioprine and mercaptopurine are not recommended to induce remission in moderate to severe CD; however, they are effective in maintaining steroid-induced remission and are generally limited to use for patients not achieving adequate response to standard medical therapy or in the setting of steroid dependency. The usual doses of azathioprine are 2 to 3 mg/kg/day, and for mercaptopurine 1 to 1.5 mg/kg/day. Starting doses are typically 50 mg/day and increased at 2-week intervals.
- Patients deficient in thiopurine S-methyltransferase (TPMT) are at greater risk of bone marrow suppression from azathioprine and mercaptopurine. Determination of TPMT or TPMT genotype is recommended to guide dosage.
- Cyclosporine is not recommended for Crohn disease except for patients with symptomatic and severe perianal or cutaneous fistulas. The dose of cyclosporine is important in determining efficacy. An oral dose of 5 mg/kg/day was not effective, whereas 7.9 mg/kg/day was effective. However, toxic effects limit application of the higher dosage. Dosage should be guided by cyclosporine whole-blood concentrations.
- Methotrexate, given as a weekly injection of 25 mg, has demonstrated efficacy for induction of remission in Crohn disease, as well as for maintenance therapy. The risks are bone marrow suppression, hepatotoxicity, and pulmonary toxicity.
- Infliximab is used for moderate to severe active Crohn disease in patients failing immunosuppressive therapy, in those who are corticosteroid dependent, and for treatment of fistulizing disease. A single, 5 mg/kg infusion is effective when given every day for 8 weeks. Additional doses at 2 and 6 weeks following the initial dose results in higher response rates. Patients may develop antibodies to infliximab, which can result in serious infusion reactions and loss of drug response.
- Adalimumab and certolizumab are effective in patients with moderate to severe Crohn disease who have lost response to infliximab. Natalizumab is reserved for patients who do not respond to steroids or the TNF inhibitors.

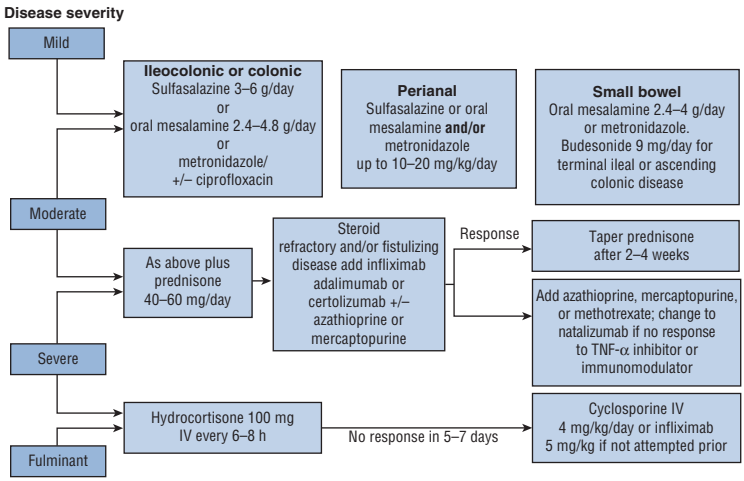


FIGURE 26–2. Treatment approaches for Crohn disease.

MAINTENANCE OF REMISSION

- Prevention of recurrence of disease is clearly more difficult with Crohn disease than with ulcerative colitis. Sulfasalazine and oral mesalamine derivatives are effective in preventing acute recurrences in quiescent Crohn disease (**Fig. 26-2**).
- Systemic steroids or budesonide also have no place in the prevention of recurrence of Crohn disease; these agents do not appear to alter the long-term course of the disease. Budesonide can be considered for maintenance therapy for up to 1 year, particularly in patients who have become corticosteroid dependent, for whom switching to budesonide is an option.
- Azathioprine and MP are effective in maintaining remission in CD in up to 70% of patients, particularly in infliximab- or steroid-induced remission, and therefore these drugs are generally considered first-line agents. There is evidence to suggest that, methotrexate, the TNF-α inhibitors are effective in maintaining remission in Crohn disease.

SELECTED COMPLICATIONS

Toxic Megacolon

- The treatment required for toxic megacolon includes general supportive measures to maintain vital functions, consideration for early surgical intervention, and antimicrobials.
- Aggressive fluid and electrolyte management are required for dehydration. When the patient has lost significant amounts of blood (through the rectum), blood replacement is also necessary.
- Steroids in high dosages (hydrocortisone 100 mg every 8 hours) should be administered IV to reduce acute inflammation.
- Broad-spectrum antimicrobials that include coverage for gram-negative bacilli and intestinal anaerobes should be used as preemptive therapy in the event that perforation occurs.

Systemic Manifestations

- For arthritis, aspirin or another NSAID may be beneficial, as are corticosteroids. However, NSAID use may exacerbate the underlying IBD and predispose patients to GI bleeding.
- Anemia secondary to blood loss from the GI tract can be treated with oral ferrous sulfate. Vitamin B_{12} or folic acid may also be required.

TABLE 26–5 Drug Monitoring Guidelines

Drug(s)	Adverse Drug Reaction	Monitoring Parameters	Comments
Sulfasalazine	Nausea, vomiting, headache Rash, anemia, pneumonitis Hepatotoxicity, nephritis Thrombocytopenia, lymphoma	Folate, complete blood count Liver function tests, Scr, BUN	Increase the dose slowly, over 1–2 weeks
Mesalamine	Nausea, vomiting, headache	GI disturbances	
Corticosteroids	Hyperglycemia, dyslipidemia	Blood pressure, fasting lipid panel	Avoid long-term use if possible or consider budesonide
	Osteoporosis, hypertension, acne	Glucose, vitamin D, bone density	
	Edema, infection, myopathy, psychosis		
Azathioprine/ mercaptopurine	Bone marrow suppression, pancreatitis	Complete blood count	Check TMPT activity
	Liver dysfunction, rash, arthralgia	Scr, BUN, liver function tests, genotype/ phenotype	
Methotrexate	Bone marrow suppression, pancreatitis	Complete blood count Scr, BUN	Check baseline pregnancy test
	Pneumonitis, pulmonary fibrosis, hepatitis	Liver function tests	Chest x-ray
Infliximab	Infusion-related reactions (infliximab), infection	Blood pressure/heart rate (infliximab)	Need negative PPD and viral serologies
Adalimumab	Heart failure, optic neuritis, demyelination, injection site reaction, signs of infection	Neurologic exam, mental status	
Certolizumab	Lymphoma	Trough concentrations (infliximab)	
Natalizumab	Infusion-related reactions	Brain MRI, mental status, progressive multifocal leukoencephalopathy	

EVALUATION OF THERAPEUTIC OUTCOMES

- See **Table 26-5** for drug monitoring guidelines.
- Patients receiving sulfasalazine should receive oral **folic acid** supplementation, as sulfasalazine inhibits folic acid absorption.
- The success of therapeutic regimens to treat IBDs can be measured by patient-reported complaints, signs and symptoms, direct physician examination (including endoscopy), history and physical examination, selected laboratory tests, and quality of life measures.
- To create more objective measures, disease-rating scales or indices have been created. The Crohn Disease Activity Index is a commonly used scale, particularly for evaluation of patients during clinical trials. The scale incorporates eight elements: (1) number of stools in the past 7 days, (2) sum of abdominal pain ratings from the past

7 days, (3) rating of general well-being in the past 7 days, (4) use of antidiarrheals, (5) body weight, (6) hematocrit, (7) finding of abdominal mass, and (8) a sum of symptoms present in the past week. Elements of this index provide a guide for those measures that may be useful in assessing the effectiveness of treatment regimens. The Perianal CD Activity Index is used for perianal Crohn disease.

- Standardized assessment tools have also been constructed for UC. Elements in these scales include (1) stool frequency; (2) presence of blood in the stool; (3) mucosal appearance (from endoscopy); and (4) physician's global assessment based on physical examination, endoscopy, and laboratory data.

See Chapter 21, Inflammatory Bowel Disease, authored by Brian A. Hemstreet, for a more detailed discussion of this topic.

CHAPTER 27

Nausea and Vomiting

- *Nausea* is usually defined as the inclination to vomit or as a feeling in the throat or epigastric region alerting an individual that vomiting is imminent. Vomiting is defined as the ejection or expulsion of gastric contents through the mouth, often requiring a forceful event.

ETIOLOGY AND PATHOPHYSIOLOGY

- Specific etiologies associated with nausea and vomiting are presented in **Table 27–1**.
- **Table 27–2** presents cytotoxic agents categorized by their emetogenic potential. Although some agents may have greater emetogenic potential than others, combinations of agents, high doses, clinical settings, psychological conditions, prior treatment experiences, and unusual stimuli to sight, smell, or taste may alter a patient's response to a drug treatment.
- The three consecutive phases of emesis are nausea, retching, and vomiting. Nausea, the imminent need to vomit, is associated with gastric stasis. Retching is the labored movement of abdominal and thoracic muscles before vomiting. The final phase of emesis is vomiting, the forceful expulsion of gastric contents due to GI retroperistalsis.
- Vomiting is triggered by afferent impulses to the vomiting center, a nucleus of cells in the medulla. Impulses are received from sensory centers, such as the chemoreceptor trigger zone (CTZ), cerebral cortex, and visceral afferents from the pharynx and GI tract. When excited, afferent impulses are integrated by the vomiting center, resulting in efferent impulses to the salivation center, respiratory center, and the pharyngeal, gastrointestinal (GI), and abdominal muscles, leading to vomiting.

CLINICAL PRESENTATION

- The clinical presentation of nausea and vomiting is given in **Table 27-3**. Nausea and vomiting may be classified as either simple or complex.

TREATMENT

- Goal of treatment: prevent or eliminate nausea and vomiting; ideally accomplished without adverse effects or with clinically acceptable adverse effects.

GENERAL APPROACH TO TREATMENT

- Treatment options for nausea and vomiting include drug and nondrug modalities and depend on associated medical conditions. For patients with simple complaints, perhaps related to food or beverage consumption, avoidance or moderation of dietary intake may be preferable. Patients with symptoms of systemic illness may improve dramatically as their underlying condition improves. Patients in whom these symptoms result from labyrinth changes produced by motion, may benefit quickly by assuming a stable physical position.
- Psychogenic vomiting may benefit from psychological interventions.

PHARMACOLOGIC MANAGEMENT

- Information concerning commonly available antiemetic preparations is compiled in **Table 27–4**. Treatment of simple nausea or vomiting usually requires minimal therapy.
- For most conditions, a single-agent antiemetic is preferred; however, for those patients not responding to such therapy and those receiving highly emetogenic chemotherapy, multiple-agent regimens are usually required.

TABLE 27–1 Specific Etiologies of Nausea and Vomiting

GI mechanisms	**Metabolic disorders**
Mechanical obstruction	Diabetes mellitus (diabetic ketoacidosis)
Gastric outlet obstruction	Addison's disease
Small bowel obstruction	Renal disease (uremia)
Functional GI disorders	**Psychiatric causes**
Gastroparesis	Psychogenic vomiting
Nonulcer dyspepsia	Anxiety disorders
Chronic intestinal pseudo-obstruction	Anorexia nervosa
Irritable bowel syndrome	**Therapy-induced causes**
Organic GI disorders	Cytotoxic chemotherapy
Peptic ulcer disease	Radiation therapy
Pancreatitis	Theophylline preparations
Pyelonephritis	Anticonvulsant preparations
Cholecystitis	Digitalis preparations
Cholangitis	Opiates
Hepatitis	Antibiotics
Acute gastroenteritis	Volatile general anesthetics
Viral	**Drug withdrawal**
Bacterial	Opiates
Cardiovascular diseases	Benzodiazepines
Acute myocardial infarction	**Miscellaneous causes**
Congestive heart failure	Pregnancy
Radiofrequency ablation	Noxious odors
Neurologic processes	Operative procedures
Increased intracranial pressure	
Migraine headache	
Vestibular disorders	

Source: Adapted from Hasler WL, Chey WD. Gastroenterol 2003;25:1860–1867.

- The treatment of simple nausea and vomiting usually requires minimal therapy. Both nonprescription and prescription drugs useful in the treatment of simple nausea and vomiting are usually effective in small, infrequently administered doses.

Drug Class Information

ANTACIDS

- Single or combination nonprescription antacid products, especially those containing magnesium hydroxide, aluminum hydroxide, and/or calcium carbonate, may provide sufficient relief from simple nausea or vomiting, primarily through gastric acid neutralization. Common antacid dosage regimens for the relief of nausea and vomiting include one or more 15 to 30 mL doses of single- or multiple-agent products.

TABLE 27–2 Emetic Risk of Agents Used in Oncology

Emetic Risk (If No Prophylactic Medication Is Administered)	Cytotoxic Agent (in Alphabetical Order)	Emetic Risk (If No Prophylactic Medication Is Administered)	Cytotoxic Agent (in Alphabetical Order)
High (>90%)	Combination of either doxorubicin or epirubicin + cyclophosphamide		Fluorouracil
	Carmustine		Gemcitabine
	Cisplatin (>50 mg/m^2)		Interferon alfa (<10 million units/m^2)
	Cyclophosphamide (≥1,500 mg/m^2)		Ixabepilone
	Dacarbazine		Lapatinib
	Ifosfamide (>10 g/m^2)		Methotrexate (<250 mg/m^2)
	Mechlorethamine		Mitomycin
	Streptozotocin		Mitoxantrone
Moderate (30–90%)	Aldesleukin (>12–15 million units/m^2)		Paclitaxel
	Amifostine (>300 mg/m^2)		Paclitaxel albumin
	Arsenic trioxide		Pemetrexed
	Azacitidine		Pentostatin
	Bendamustine		Romidepsin
	Busulfan		Sorafenib
	Carboplatin		Sunitinib
	Cisplatin (<50 mg/m^2)		Thiotepa
	Clofarabine		Topotecan
	Cytarabine (>200 mg/m^2)		Trastuzumab
	Cyclophosphamide (<1,500 mg/m^2)	Minimal (<10%)	Alemtuzumab
	Daunorubicin		Asparaginase
	Dactinomycin		Bevacizumab
	Doxorubicin		Bleomycin
	Epirubicin		Bortezomib
	Idarubicin		Cladribine
	Ifosfamide		Cytarabine (<200 mg/m^2)
	Interferon alfa (10 million units/m^2)		Decitabine
	Irinotecan		Denileukin diftitox
	Melphalan		Dexrazoxane
	Methotrexate (>250 mg/m^2)		Fludarabine
	Oxaliplatin		Ipilimumab
	Procarbazine		Nelarabine
	Temozolomide		Ofatumumab
Low (10–30%)	Cabazitaxel		Panitumumab
	Capecitabine		PEG-asparaginase
	Cetuximab		Rituximab
	Cytarabine (≤200 mg/m^2)		Temsirolimus
	Docetaxel		Trastuzumab
	Eribulin		Valrubicin
	Erlotinib		Vinblastine
	Etoposide		Vincristine
	Floxuridine		Vinorelbine

Adapted from reference 30. Adapted with permission from reference 2.

TABLE 27–3	Presentation of Nausea and Vomiting
General	
Depending on severity of symptoms, patients may present in mild to severe distress.	
Symptoms	
Simple: Self-limiting, resolves spontaneously and requires only symptomatic therapy	
Complex: Not relieved after administration of antiemetics; progressive deterioration of patient secondary to fluid–electrolyte imbalances; usually associated with noxious agents or psychogenic events	
Signs	
Simple: Patient complaint of queasiness or discomfort	
Complex: Weight loss, fever, and abdominal pain	
Laboratory tests	
Simple: None	
Complex: Serum electrolyte concentrations; upper/lower GI evaluation	
Other information	
Fluid input and output	
Medication history	
Recent history of behavioral or visual changes, headache, pain, or stress	
Family history positive for psychogenic vomiting	

HISTAMINE$_2$-RECEPTOR ANTAGONISTS

- Histamine$_2$-receptor antagonists (cimetidine, famotidine, nizatidine, and ranitidine) may be used in low doses to manage simple nausea and vomiting associated with heartburn or gastroesophageal reflux.

ANTIHISTAMINE-ANTICHOLINERGIC DRUGS

- Antiemetic drugs from the antihistaminic-anticholinergic category may be appropriate in the treatment of simple nausea and vomiting, especially associated with motion sickness.
- Adverse reactions that may be apparent with the use of the antihistaminic-anticholinergic agents primarily include drowsiness or confusion, blurred vision, dry mouth, urinary retention, and possibly tachycardia, particularly in elderly patients.

BENZODIAZEPINES

- Benzodiazepines are relatively weak antiemetics and are primarily used to prevent anxiety or anticipatory nausea and vomiting. Both alprazolam and lorazepam are used as adjuncts to other antiemetics in patients treated with cisplatin-containing regimens.

PHENOTHIAZINES

- **Phenothiazines** are most useful in patients with simple nausea and vomiting. Rectal administration is a reasonable alternative in patients in whom oral or parenteral administration is not feasible.
- Problems associated with these drugs are troublesome and potentially dangerous side effects, including extrapyramidal reactions, hypersensitivity reactions with possible liver dysfunction, marrow aplasia, and excessive sedation.

CORTICOSTEROIDS

- **Dexamethasone** is the most commonly used corticosteroid in the management of chemotherapy-induced nausea and vomiting (CINV) and postoperative nausea and

TABLE 27–4 Common Antiemetic Preparations and Adult Dosage Regimens

Drug	Adult Dosage Regimen	Dosage Form/Route	Availability	Adverse Drug Reactions	Monitoring Parameters	Comments
Antacids						
Antacids (various)	15–30 mL every 2–4 hours prn	Liquid/oral	OTC	Magnesium products: diarrhea Aluminum or calcium products: constipation	Assess for symptom relief	Useful with simple nausea/vomiting
Antihistaminic–Anticholinergic Agents						
Dimenhydrinate (Dramamine)	50–100 mg every 4–6 hours prn	Tab, chew tab, cap	OTC	Drowsiness, confusion, blurred vision, dry mouth, urinary retention	Assess for episodic relief of motion sickness or nausea/vomiting	Especially problematic in the elderly Increased risk of complications in patients with BPH, narrow angle glaucoma, or asthma
Diphenhydramine (Benadryl)	25–50 mg every 4–6 hours prn	Tab, cap, liquid	Rx/OTC	See above	See above	See above
	10–50 mg every 2–4 hours prn	IM, IV		See above	See above	See above
Hydroxyzine (Vistaril, Atarax)	25–100 mg every 4–6 hours prn	IM (unlabeled use)	Rx	See above	See above	See above
Meclizine (Bonine, Antivert)	12.5–25 mg 1 hour before travel; repeat every 12–24 hours prn	Tab, chew tab	Rx/OTC	See above	See above	See above

(*continued*)

TABLE 27–4 Common Antiemetic Preparations and Adult Dosage Regimens (*Continued*)

Drug	Adult Dosage Regimen	Dosage Form/Route	Availability	Adverse Drug Reactions	Monitoring Parameters	Comments
Scopolamine (Transderm Scop)	1.5 mg every 72 hours	Transdermal patch	Rx	See above	See above	See above
Trimethobenzamide (Tigan)	300 mg three to four times daily	Cap	Rx	See above	See above	See above
	200 mg three to four times daily	IM		See above	See above	See above
Benzodiazepines						
Alprazolam (Xanax)	0.5–2 mg three times daily prior to chemotherapy	Tab	Rx (C-IV)	Dizziness, sedation, appetite changes, memory impairment	Assess for episodes of ANV	Place in therapy: ANV
Lorazepam (Ativan)	0.5–2 mg on night before and morning of chemotherapy	Tab	Rx (C-IV)	See above	See above	See above
Butyrophenones						
Haloperidol (Haldol)	1–5 mg every 12 hours prn	Tab, liquid, IM, IV	Rx	Sedation, constipation, hypotension	Observe for additive sedation especially if used with narcotic analgesics	Place in therapy: palliative care
Droperidol (Inapsine)[a]	2.5 mg; additional 1.25 mg may be given	IM, IV	Rx	QT prolongation and/or torsade de pointes	12-Lead electrocardiogram prior to administration, followed by cardiac monitoring for 2–3 hours after administration	Limited use outside of clinical trials

Cannabinoids						
Dronabinol (Marinol)	5–15 mg/m^2 every 2–4 hours prn	Cap	Rx (C-III)	Euphoria, somnolence, xerostomia	Assess for symptom relief	May be useful with refractory CINV
Nabilone (Cesamet)	1–2 mg twice daily	Cap	Rx (C-II)	Somnolence, vertigo, xerostomia	See above	See above
Corticosteroids						
Dexamethasone	See Table 27–5 for CINV dosing and Table 27–6 for PONV dosing	Tab, IV	Rx	Insomnia, GI symptoms, agitation, appetite stimulation	Assess for efficacy as prophylactic agent: episodes of nausea/vomiting and hydration status	Useful as single-agent or combination therapy for prophylaxis of CINV and PONV
Cimetidine (Tagamet HB)	200 mg twice daily prn	Tab	OTC	Headache	Assess for symptom relief	Useful when nausea due to heartburn or GERD
Famotidine (Pepcid AC)	10 mg twice daily prn	Tab	OTC	Constipation, diarrhea	See above	See above
Nizatidine (Axid AR)	75 mg twice daily prn	Tab	OTC	Diarrhea, headache	See above	See above
Ranitidine (Zantac 75)	75 mg twice daily prn	Tab	OTC	Constipation, diarrhea	See above	See above
5-Hydroxytryptamine-3 Receptor Antagonists						
	See Table 27–5 for CINV dosing and Table 27–6 for PONV dosing	Tab, IV	Rx	Asthenia, constipation, headache	Assess for efficacy as prophylactic agent: episodes of nausea/vomiting and hydration status	Useful as single-agent or combination therapy for prophylaxis of CINV and PONV

(*continued*)

TABLE 27–4 Common Antiemetic Preparations and Adult Dosage Regimens (*Continued*)

Drug	Adult Dosage Regimen	Dosage Form/Route	Availability	Adverse Drug Reactions	Monitoring Parameters	Comments
Miscellaneous Agents						
Metoclopramide (Reglan)	10 mg four times daily	Tab	Rx	Asthenia, headache, somnolence	Assess for symptom relief	Prokinetic activity useful in diabetic gastroparesis
Olanzapine (Zyprexa)	2.5–5 mg twice daily	Tab	Rx	Sedation	Assess for decrease in episodes of nausea/vomiting	Use with caution in elderly. May be useful in breakthrough CINV
Phenothiazines						
Chlorpromazine (Thorazine)	10–25 mg every 4–6 hours prn	Tab, liquid	Rx	Constipation, dizziness, tachycardia, tardive dyskinesia	Assess for decrease in episodes of nausea/vomiting	Useful with simple nausea/vomiting
	25–50 mg every 4–6 hours prn	IM, IV		See above	See above	See above
Prochlorperazine (Compazine)	5–10 mg 3–4 times daily prn	Tab, liquid	Rx	Prolonged QT interval, sedation, tardive dyskinesia	Assess for decrease in episodes of nausea/vomiting	Useful with simple nausea/vomiting and for breakthrough CINV
	5–10 mg every 3–4 hours prn	IM		See above	See above	See above
	2.5–10 mg every 3–4 hours prn	IV	Rx	See above	See above	See above
	25 mg twice daily prn	Supp	Rx	See above	See above	See above

Promethazine (Phenergan)	12.5–25 mg every 4–6 hours prn	Tab, liquid, IM, IV, supp	Rx	Drowsiness, sedation	Assess for decreased nausea/vomiting episodes and improvement in hydration status	See above
Substance P/Neurokinin 1 Receptor Antagonist						
Aprepitant	See Table 27–5 for CINV dosing and Table 27–6 for PONV dosing	Cap, IV	Rx	Constipation, diarrhea, headache, hiccups	Assess for efficacy as prophylactic agent: episodes of nausea/vomiting and hydration status	Useful in combination therapy for prophylaxis of CINV and PONV

ANV, anticipatory nausea and vomiting; C-II, C-III, and C-IV, controlled substance schedule 2, 3, and 4, respectively; cap, capsule; chew tab, chewable tablet; CINV, chemotherapy-induced nausea and vomiting; GERD, gastroesophageal reflux disease; liquid, oral syrup, concentrate, or suspension; OTC, nonprescription; PONV, postoperative nausea and vomiting; Rx, prescription; supp, rectal suppository; tab, tablet.

[a]See text for current warnings.

vomiting (PONV), either as a single agent or in combination with 5-hydroxytriptamine-3 receptor antagonists (5-HT_3-RAs). For CINV, dexamethasone is effective in the prevention of both cisplatin-induced acute emesis and delayed nausea and vomiting with CINV when used alone or in combination.

METOCLOPRAMIDE

- **Metoclopramide** is used for its antiemetic properties in patients with diabetic gastroparesis and with dexamethasone for prophylaxis of delayed nausea and vomiting associated with chemotherapy administration.

CANNABINOIDS

- Oral **nabilone** and oral **dronabinol** are therapeutic options when CINV is refractory to other antiemetics; but are not indicated as first-line agents.

SUBSTANCE P/NEUROKININ 1 RECEPTOR ANTAGONISTS

- Substance P is a peptide neurotransmitter believed to be the primary mediator of the delayed phase of CINV and one of two mediators of the acute phase of CINV.
- **Aprepitant** and **fosaprepitant** (injectable form of aprepitant) are substance P/NK_1 receptor antagonists that are indicated as part of a multiple drug regimen for prophylaxis of nausea and vomiting associated with high-dose cisplatin-based chemotherapy.
- Numerous potential drug interactions are possible; clinically significant drug interactions with oral contraceptives, warfarin, and oral dexamethasone have been described.

5-HYDROXYTRIPTAMINE-3 RECEPTOR ANTAGONISTS

- 5-HT_3-RAs (**dolasetron, granisetron, ondansetron,** and **palonosetron**) are the standard of care in the management of CINV, PONV, and radiation-induced nausea and vomiting. The most common side effects associated with these agents are constipation, headache, and asthenia.

CHEMOTHERAPY-INDUCED NAUSEA AND VOMITING

- Nausea and vomiting that occur within 24 hours of chemotherapy administration are defined as acute; nausea and vomiting that starts more than 24 hours after chemotherapy administration are defined as delayed. The emetogenic potential of the chemotherapeutic agent or regimen (see **Table 27–2**) is the primary factor to consider when selecting an antiemetic for **prophylaxis** of CINV.
- Recommendations for antiemetics in patients receiving chemotherapy are presented in **Table 27–5**.

Prophylaxis of Chemotherapy-Induced Nausea and Vomiting

- Patients receiving chemotherapy that is classified as being of high emetic risk, should receive a combination antiemetic regimen containing three drugs on the day of chemotherapy administration (day 1)—a 5-HT_3-RA plus dexamethasone plus aprepitant or fosaprepitant.
- Patients receiving regimens that are classified as being of moderate emetic risk should receive a combination antiemetic regimen containing a 5-HT_3-RA plus dexamethasone on day 1 then dexamethasone on days 2 and 3.
- For prophylaxis of delayed CINV with high emetic risk, administration of aprepitant and dexamethasone on days 2 and 3 and dexamethasone with or without lorazepam on day 4 is recommended. For moderate emetic risk, one recommendation is to give aprepitant or any of the following: dexamethasone, a 5-HT_3-RA, and/or lorazepam, and or a histamine-2 blocker, or a proton pump inhibitor on days 2 and 3.

POSTOPERATIVE NAUSEA AND VOMITING

- A variety of pharmacologic approaches are available and may be prescribed as single or combination therapy for prophylaxis of PONV. See **Table 27–6** for doses of specific

TABLE 27–5 Dosage Recommendations for CINV for Adult Patients

Emetic Risk	Prophylaxis of Acute Phase of CINV (One Dose Administered Prior to Chemotherapy)	Prophylaxis of Delayed Phase of CINV
High (including the AC regimen[a])	5-HT_3 receptor antagonists (5-HT_3-RA):	
	Palonosetron 0.25 mg IV (preferred)	
	Dolasetron 100 mg orally	
	Granisetron 2 mg orally or 1 mg IV or 0.01 mg/kg IV or 34.3 mg transdermal patch	
	Ondansetron 16–24 mg orally or 8–12 mg IV (maximum 32 mg)	
	And dexamethasone 12 mg orally or IV	Dexamethasone 8 mg orally twice daily on days 2–4
	And Aprepitant 125 mg orally	Aprepitant 80 mg orally on days 2 and 3 after chemotherapy
	Or Fosaprepitant 115 mg IV ± Lorazepam 0.5–2 mg po or IV or SL every 4–6 hours on days 1–4 ± H_2 blocker or proton pump inhibitor	
Moderate	5-HT_3-RA:	
	Palonosetron 0.25 mg IV (preferred)	5-HT_3 -RA: dolasetron 100 mg orally daily[b]
	Dolasetron 100 mg orally	
	Granisetron 2 mg orally or 1 mg IV or 0.01 mg/kg IV or 34.3 mg transdermal patch	Granisetron 1–2 mg orally daily[b]
	Ondansetron 16–24 mg orally or 8–12 mg IV (maximum 32 mg)	Ondansetron 8 mg orally daily or twice daily[b]
	And Dexamethasone 8–12 mg orally or IV	Dexamethasone 8 mg orally twice daily[b]
	And in select patients[c] aprepitant 125 mg orally	Aprepitant 80 mg orally on days 2 and 3 if used on day 1
	Or Fosaprepitant 115 mg IV ± Lorazepam 0.5–2 mg po or IV or SL every 4–6 hours on days 1–4 ± H_2 blocker or proton pump inhibitor	

(*continued*)

TABLE 27–5 Dosage Recommendations for CINV for Adult Patients (*Continued*)

Emetic Risk	Prophylaxis of Acute Phase of CINV (One Dose Administered Prior to Chemotherapy)	Prophylaxis of Delayed Phase of CINV
Low	Dexamethasone 8–12 mg orally or IV	None
Minimal	None	None

Doses included in this table reflect the recommendations from published guidelines.[16, 24, 27] These doses may differ from manufacturer labeling; they reflect the consensus of the guideline participants. CINV, chemotherapy-induced nausea and vomiting.

[a]See reference 27.
[b]For 2–3 days following chemotherapy.
[c]Patients receiving other chemotherapies of moderate emetic risk, for example, carboplatin, cisplatin, doxorubicin, epirubicin, ifosfamide, irinotecan, or methotrexate.

TABLE 27–6 Recommended Prophylactic Doses of Selected Antiemetics for Postoperative Nausea and Vomiting in Adults and Postoperative Vomiting in Children

Drug	Adult Dose	Pediatric Dose (IV)	Timing of Dose[a]
Aprepitant[b]	40 mg orally	Not labeled for use in pediatrics	Within 3 h prior to induction
Dexamethasone	4–5 mg IV	150 mcg/kg up to 5 mg	At induction
Dimenhydrinate	1 mg/kg IV	0.5 mg/kg up to 25 mg	Not specified
Dolasetron	12.5 mg IV	350 mcg/kg up to 12.5 mg	At end of surgery
Droperidol[d]	0.625–1.25 mg IV	10–15 mcg/kg up to 1.25 mg	At end of surgery
Granisetron	0.35–1.5 mg IV	40 mcg/kg up to 0.6 mg	At end of surgery
Haloperidol	0.5–2 mg (IM or IV)	c	Not specified
Ondansetron	4 mg IV	50–100 mcg/kg up to 4 mg	At end of surgery
Palonosetron[b]	0.075 mg IV	Not labeled for patients <18 y	At induction
Prochlorperazine	5–10 mg IM or IV	c	At end of surgery
Promethazine[b]	6.25–25 mg IV	c	At induction
Scopolamine	Transdermal patch	c	Prior evening or 4 hours before surgery
Tropisetron	2 mg IV	0.1 mg/kg up to 2 mg	At end of surgery

[a]Based on recommendations from consensus guidelines may differ from manufacturer's recommendations.
[b]Labeled for use in PONV but not included in consensus guidelines.
[c]Pediatric dosing not included in consensus guidelines.
[d]See Food and Drug Administration (FDA) "black box" warning.
Gan TJ, Meyer TA, Apfel CC, et al. Society for ambulatory anesthesia guidelines for the management of postoperative nausea and vomiting. Anesth Analg 2007;105:1615–1628.

agents. PONV in adults occurs in 25% to 30% of patients and within 24 hours of undergoing anesthesia.
- Patients at low risk are unlikely to benefit from antiemetic prophylaxis. Patients at moderate risk of PONV should receive one or two prophylactic antiemetics, and those at high risk should receive two prophylactic antiemetics from different classes.

DISORDERS OF BALANCE

- Beneficial therapy for patients with nausea and vomiting associated with disorders of balance can reliably be found among the antihistaminic-anticholinergic agents. Neither the antihistaminic nor the anticholinergic potency appears to correlate well with the ability of these agents to prevent or treat the nausea and vomiting associated with motion sickness.
- Scopolamine (usually administered as a patch) is commonly used to prevent nausea or vomiting caused by motion.

ANTIEMETIC USE DURING PREGNANCY

- Initial management of nausea and vomiting of pregnancy (NVP) often involves dietary changes and/or lifestyle modifications.
- Pyridoxine (10–25 mg one to four times daily) is recommended as first-line therapy with or without doxylamine (12.5–20 mg one to four times daily). Patients with persistent NVP or who show signs of dehydration should receive IV fluid replacement with thiamine. Ondansetron 2 to 8 mg orally/IV every 8 hours as needed may alleviate NVP.

ANTIEMETIC USE IN CHILDREN

- For children receiving chemotherapy of high or moderate risk, a corticosteroid plus 5-HT_3-RAs should be administered. The best doses or dosing strategy has not been determined.
- For nausea and vomiting associated with pediatric gastroenteritis, there is greater emphasis on rehydration measures than on pharmacologic intervention.

See Chapter 22, Nausea and Vomiting, authored by Cecily V. DiPiro and Robert J. Ignoffo, for a more detailed discussion of this topic.

Pancreatitis

CHAPTER 28

- Acute pancreatitis (AP) is an inflammatory disorder of the pancreas characterized by upper abdominal pain and pancreatic enzyme elevations.
- Chronic pancreatitis (CP) is a progressive disease characterized by long-standing pancreatic inflammation leading to loss of pancreatic exocrine and endocrine function.

ACUTE PANCREATITIS

PATHOPHYSIOLOGY

- Gallstones and alcohol abuse account for most cases in the United States. A cause cannot be identified in some patients (idiopathic pancreatitis).
- Many medications have been implicated (**Table 28–1**), but a causal association is difficult to confirm because ethical and practical considerations prevent rechallenge.
- AP is initiated by premature activation of trypsinogen to trypsin within the pancreas, leading to activation of other digestive enzymes and autodigestion of the gland.
- Activated pancreatic enzymes released into the pancreas and surrounding tissues produce damage and necrosis to pancreatic tissue, surrounding fat, vascular endothelium, and adjacent structures. Lipase damages fat cells, producing noxious substances that cause further pancreatic and peripancreatic injury.
- Release of cytokines by acinar cells injures those cells and enhances the inflammatory response. Injured acinar cells liberate chemoattractants that attract neutrophils, macrophages, and other cells to the area of inflammation, causing systemic inflammatory response syndrome (SIRS). Vascular damage and ischemia cause release of kinins, which make capillary walls permeable and promote tissue edema.
- Pancreatic infection may result from increased intestinal permeability and translocation of colonic bacteria.
- Local complications in severe AP include acute fluid collection, pancreatic necrosis, infection, abscess, pseudocyst formation, and pancreatic ascites.
- Systemic complications include cardiovascular, renal, pulmonary, metabolic, hemorrhagic, and CNS abnormalities.

CLINICAL PRESENTATION

- Clinical presentation depends on severity of the inflammatory process and whether damage is confined to the pancreas or involves local and systemic complications.
- The initial presentation ranges from moderate abdominal discomfort to excruciating pain, shock, and respiratory distress. Abdominal pain occurs in 95% of patients and is usually epigastric, often radiating to the upper quadrants or back. Onset is usually sudden, and intensity is often described as "knife-like" or "boring." Pain usually reaches maximum intensity within 30 minutes and may persist for hours or days. Nausea and vomiting occur in 85% of patients and usually follow onset of pain.
- Signs associated with widespread pancreatic inflammation and necrosis include marked epigastric tenderness, abdominal distention, hypotension, tachycardia, and low-grade fever. In severe disease, bowel sounds are diminished or absent. Dyspnea and tachypnea are signs of acute respiratory complications.

DIAGNOSIS

- Diagnosis should be made within 48 hours based on characteristics of abdominal pain and elevation of amylase, lipase, or both to at least three times the upper limit of normal.

TABLE 28–1 Medications Associated with Acute Pancreatitis

Class I: Definite Association	Class II: Probable Association	Class III: Possible Association	
5-Aminosalicylic acid	Acetaminophen	Aldesleukin	Indomethacin
Asparaginase	Carbamazepine	Amiodarone	Infliximab
Azathioprine	Cisplatin	Calcium	Ketoprofen
Corticosteroids	Erythromycin	Celecoxib	Ketorolac
Cytarabine	Hydrochlorothiazide	Clozapine	Lipid emulsion
Didanosine	Interferon α_{2b}	Cholestyramine	Lisinopril
Enalapril	Lamivudine	Cimetidine	Mefenamic acid
Estrogens	Octreotide	Ciprofloxacin	Metformin
Furosemide	Sitagliptin	Clarithromycin	Methyldopa
Mercaptopurine		Clonidine	Metolazone
Opiates		Cyclosporine	Metronidazole
Pentamidine		Danazol	Nitrofurantoin
Pentavalent antimonials		Diazoxide	Omeprazole
Sulfasalazine		Etanercept	Ondansetron
Sulfamethoxazole and trimethoprim		Ethacrynic acid	Oxyphenbutazone
Sulindac		Exenatide	Paclitaxel
Tetracycline		Famciclovir	Pravastatin
Valproic acid/salts		Glyburide	Propofol
		Gold therapy	Propoxyphene
		Granisetron	Rifampin
		Ibuprofen	Sertraline
		Indinavir	Zalcitabine

- Contrast-enhanced computed tomography (CECT) of the abdomen may confirm the diagnosis; magnetic resonance imaging and ultrasonography are sometimes useful.
- AP may be associated with leukocytosis, hyperglycemia, and hypoalbuminemia. Hepatic transaminases, alkaline phosphatase, and bilirubin are usually elevated in gallstone pancreatitis and in patients with intrinsic liver disease. Marked hypocalcemia indicates severe necrosis and is a poor prognostic sign.
- Serum amylase usually rises 4 to 8 hours after symptom onset, peaks at 24 hours, and returns to normal over the next 8 to 14 days. Concentrations greater than three times the upper limit of normal are highly suggestive of AP.
- Serum lipase is specific to the pancreas, and concentrations are elevated and parallel the serum amylase elevations. Increases persist longer than serum amylase elevations and can be detected after the amylase has returned to normal.
- Hematocrit may be normal, but hemoconcentration results from multiple factors (eg, vomiting). Hematocrit greater than 47% predicts severe AP, and hematocrit less than 44% predicts mild disease.
- C-reactive protein levels greater than 150 mg/dL at 48 to 72 hours predict severe AP.
- Thrombocytopenia and increased international normalized ratio (INR) occur in some patients with severe AP and associated liver disease.

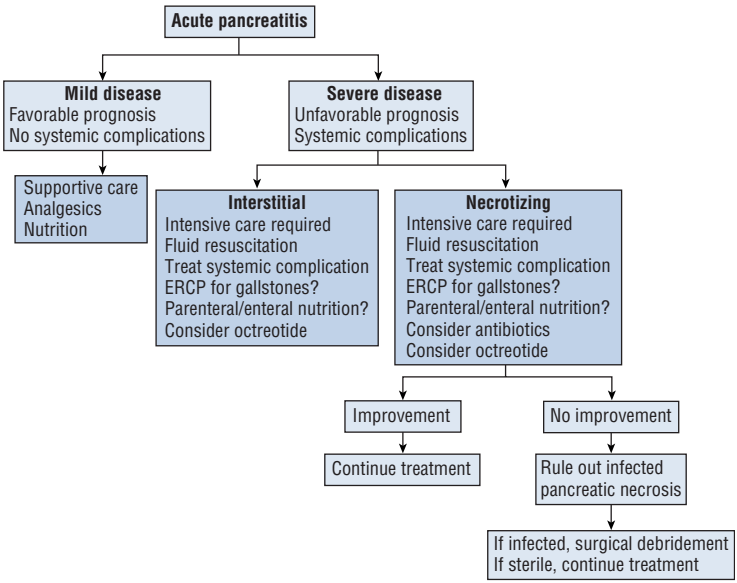


FIGURE 28–1. Algorithm of guidelines for evaluation and treatment of acute pancreatitis. (ERCP, endoscopic retrograde cholangiopancreatography.)

TREATMENT

- Goals of Treatment: Relieve abdominal pain and nausea; replace fluids; correct electrolyte, glucose, and lipid abnormalities; minimize systemic complications; and prevent pancreatic necrosis and infection.

Nonpharmacologic Therapy

- **Nutritional support** is important because AP creates a catabolic state that promotes nutritional depletion. Patients with mild AP can begin oral feeding when bowel sounds have returned, and pain has resolved. Nutritional support should begin when it is anticipated that oral nutrition will be withheld for longer than 1 week. Enteral feeding is preferred over parenteral nutrition (PN) in severe AP, if it can be tolerated. If enteral feeding is not possible or is inadequate, PN should be implemented before protein and calorie depletion become advanced.
- **Endoscopic retrograde cholangiopancreatography (ERCP)** is performed to remove any biliary tract stones.
- **Surgery** is indicated in patients with pancreatic pseudocyst or abscess or to drain the pancreatic bed if hemorrhagic or necrotic material is present.

Pharmacologic Therapy

- Patients with AP often require IV antiemetics for nausea. Patients with severe AP should be treated with antisecretory agents to prevent stress-related mucosal bleeding. Appropriate fluid resuscitation and pain management are also necessary.
- Vasodilation from the inflammatory response, vomiting, and nasogastric suction contribute to hypovolemia and fluid and electrolyte abnormalities, necessitating replacement. Because there is a lack of objective data, treatment guidelines call for

rapid replacement of fluid without details on the optimal rate or type of fluid. Some patients require aggressive fluid resuscitation, whereas others may require gradual fluid administration.

- Parenteral opioid analgesics are used to control abdominal pain. **Morphine** is often used, and patient-controlled analgesia should be considered in patients who require frequent opioid dosing (eg, every 2–3 hours). Meperidine is no longer recommended as a first-line agent because of adverse effects (eg, seizures) and dosing limitations.
- There are insufficient data to support routine use of somatostatin or octreotide for treatment of AP.
- Prophylactic antibiotics offer no benefit in mild AP or when there is no necrosis. Use of antibiotics in severe AP (with or without necrosis) but without infection is not supported by controlled trials. Use of antibiotics in necrotizing AP is only recommended in the presence of known or suspected infection. Surgical debridement is required once infection develops in patients with necrotic AP. Because the source of bacterial contamination in AP is most likely the colon, broad-spectrum antibiotics that cover enteric aerobic gram-negative bacilli and anaerobic organisms should be started within 48 hours and continued for 2 to 3 weeks when infection is present. **Imipenem–cilastatin** (500 mg IV every 8 hours) has been widely used but has been replaced on many formularies by newer carbapenems (eg, meropenem). A fluoroquinolone (eg, **ciprofloxacin** or **levofloxacin**) combined with **metronidazole** should be considered for penicillin-allergic patients.

EVALUATION OF THERAPEUTIC OUTCOMES

- In patients with mild AP, assess pain control, fluid and electrolyte status, and nutrition periodically depending on the degree of abdominal pain and fluid loss.
- Transfer patients with severe AP to an intensive care unit for close monitoring of vital signs, fluid and electrolyte status, white blood cell count, blood glucose, lactate dehydrogenase, aspartate aminotransferase, serum albumin, hematocrit, blood urea nitrogen, serum creatinine, and INR. Continuous hemodynamic and arterial blood gas monitoring is essential. Serum lipase, amylase, and bilirubin require less frequent monitoring. Monitor for signs of infection, relief of abdominal pain, and adequate nutritional status. Severity of disease and patient response should be assessed using an evidence-based method such as APACHE II.

CHRONIC PANCREATITIS

PATHOPHYSIOLOGY

- CP results from long-standing pancreatic inflammation and leads to irreversible destruction of pancreatic tissue with fibrin deposition and loss of exocrine and endocrine function.
- Chronic ethanol consumption accounts for about 70% of cases in Western society; 10% result from other causes, and 20% are idiopathic.
- The exact pathogenesis is unknown. Activation of pancreatic stellate cells by toxins, oxidative stress, and/or inflammatory mediators appears to be the cause of fibrin deposition.
- Abdominal pain may be caused in part by increased pancreatic parenchymal pressure from obstruction, inflammation, and necrosis. Compression of pancreatic nerve fibers after a meal, along with continuous firing of peripheral and central neurons, may explain the burning and shooting pain of CP.
- Malabsorption of protein and fat occurs when capacity for enzyme secretion is reduced by 90%. A minority of patients develop complications, including pancreatic pseudocyst, abscess, and ascites or common bile duct obstruction, leading to cholangitis or secondary biliary cirrhosis.

CLINICAL PRESENTATION

- The main features of CP are abdominal pain, malabsorption, weight loss, and diabetes. Jaundice occurs in ~10% of patients.
- Patients typically report deep, penetrating epigastric or abdominal pain that may radiate to the back. Pain often occurs with meals and at night and may be associated with nausea and vomiting.
- Steatorrhea and azotorrhea occur in most patients. Steatorrhea is often associated with diarrhea and bloating. Weight loss may occur.
- Pancreatic diabetes is a late manifestation commonly associated with pancreatic calcification.

DIAGNOSIS

- Diagnosis is based primarily on clinical presentation and either imaging or pancreatic function studies. Noninvasive imaging includes abdominal ultrasound, computed tomography (CT), and magnetic resonance cholangiopancreatography (MRCP). Invasive imaging includes endoscopic ultrasonography (EUS) and ERCP.
- Serum amylase and lipase are usually normal or only slightly elevated but may be increased in acute exacerbations.
- Total bilirubin, alkaline phosphatase, and hepatic transaminases may be elevated with ductal obstruction. Serum albumin and calcium may be low with malnutrition.
- Pancreatic function tests include
  - ✓ Serum trypsinogen (<20 ng/mL is abnormal)
  - ✓ Fecal elastase (<200 mcg/g of stool is abnormal)
  - ✓ Fecal fat estimation (>7 g/day is abnormal; stool must be collected for 72 hours)
  - ✓ Secretin stimulation (evaluates duodenal bicarbonate secretion)
  - ✓ ^{13}C-mixed triglyceride breath test

TREATMENT

- Goals of Treatment: Goals for uncomplicated CP are to relieve abdominal pain, treat complications of malabsorption and glucose intolerance, and improve quality of life.

Nonpharmacologic Therapy

- Lifestyle modifications should include abstinence from alcohol and smoking cessation.
- Advise patients with steatorrhea to eat smaller, more frequent meals and reduce dietary fat intake.
- Patients who do not consume adequate calories from their normal diet may be given whole protein or peptide-based oral nutritional supplements.
- Invasive procedures and surgery are used primarily to treat uncontrolled pain and the complications of chronic pancreatitis.

Pharmacologic Therapy

- Pain management should begin with oral nonopioid analgesics such as **acetaminophen** or a **nonsteroidal antiinflammatory drug** administered on a scheduled basis before meals to help decrease postprandial pain.
- A trial of **pancreatic enzyme supplementation** for pain relief may be given prior to adding opioids.
- If these measures fail, add low-potency oral opioids (eg, **hydrocodone**) to nonopioid analgesics. **Tramadol** has also been used. Severe pain unresponsive to these therapies necessitates use of other opioids (eg, **codeine, morphine sulfate, oxycodone,** or **hydromorphone**). Unless contraindicated, use oral opioids before parenteral,

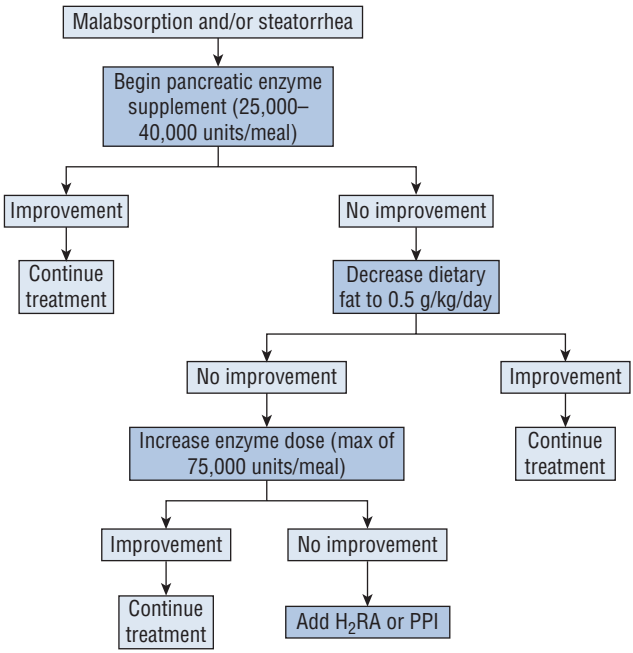


FIGURE 28–2. Algorithm for the treatment of malabsorption and steatorrhea in chronic pancreatitis. (H_2RA, histamine$_2$ receptor antagonist; PPI, proton pump inhibitor.)

transdermal, or other dosage forms. In patients with pain that is difficult to manage, consider nonopioid modulators of chronic pain (eg, **pregabalin**, **selective serotonin reuptake inhibitors** and **tricyclic antidepressants**).

- Pancreatic enzyme supplementation and reduction in dietary fat intake are the primary treatments for malabsorption due to CP (**Fig. 28–2**). This combination enhances nutritional status and reduces steatorrhea. The enzyme dose required to minimize malabsorption is 25,000 to 40,000 units of lipase administered with each meal. The dose may be increased to a maximum of 75,000 units per meal. Products containing enteric-coated microspheres or minimicrospheres may be more effective than other dosage forms (**Table 28–2**).
- Adverse effects from pancreatic enzyme supplements are generally benign, but high doses can lead to nausea, diarrhea, and intestinal upset. A more serious but uncommon adverse effect is fibrosing colonopathy. Deficiencies in fat-soluble vitamins have been reported, and appropriate monitoring (especially of vitamin D) is warranted.
- Addition of an H_2RA or PPI may increase the effectiveness of pancreatic enzyme therapy by increasing gastric and duodenal pH.

EVALUATION OF THERAPEUTIC OUTCOMES

- Assess the severity and frequency of abdominal pain periodically to determine efficacy of the analgesic regimen. Patients receiving opioids should be prescribed scheduled bowel regimens and be monitored for constipation.

TABLE 28–2 Commercially Available Pancreatic Enzyme (Pancrelipase) Preparations

	Enzyme Content per Unit Dose (USP Units)		
Product	*Lipase*	*Amylase*	*Protease*
Tablets			
Viokace™ 10,440 lipase units	10,440	39,150	39,150
Viokace™ 20,880 lipase units	20,880	78,300	78,300
Enteric-coated beads			
Zenpep® 3000 lipase units	3000	16,000	10,000
Zenpep® 5000 lipase units	5000	27,000	17,000
Zenpep® 10,000 lipase units	10,000	55,000	34,000
Zenpep® 15,000 lipase units	15,000	82,000	51,000
Zenpep® 20,000 lipase units	20,000	109,000	68,000
Zenpep® 25,000 lipase units	25,000	136,000	85,000
Enteric-coated microspheres with bicarbonate buffer	8000	30,250	28,750
Pertzye™ 8000 lipase units	16,000	60,500	57,500
Pertzye™ 16,000 lipase units			
Enteric-coated minimicrospheres			
Creon® 3000 lipase units	3000	15,000	9,500
Creon® 6000 lipase units	6000	30,000	19,000
Creon® 12,000 lipase units	12,000	60,000	38,000
Creon® 24,000 lipase units	24,000	120,000	76,000
Enteric-coated minitablets/microtablets			
Pancreaze® 4200 lipase units	4200	17,500	10,000
Pancreaze® 10,500 lipase units	10,500	43,750	25,000
Pancreaze® 16,800 lipase units	16,800	70,000	40,000
Pancreaze® 21,000 lipase units	21,000	61,000	37,000
Ultresa™ 13,800 lipase units	13,800	27,600	27,600
Ultresa™ 20,700 lipase units	20,700	41,400	41,400
Ultresa™ 23,000 lipase units	23,000	46,000	46,000

USP, United States Pharmacopeia.

- For patients receiving pancreatic enzymes for malabsorption, monitor body weight and stool frequency and consistency periodically.
- Monitor blood glucose carefully in diabetic patients.

See Chapter 25, Pancreatitis, authored by Scott Bolesta and Patricia A. Montgomery, for a more detailed discussion of this topic.

CHAPTER 29

Peptic Ulcer Disease

- *Peptic ulcer disease* (PUD) refers to a group of ulcerative disorders of the upper gastrointestinal (GI) tract that require acid and pepsin for their formation.

PATHOPHYSIOLOGY

- Pathogenesis of duodenal and gastric ulcers involves pathophysiologic abnormalities and environmental and genetic factors.
- Most peptic ulcers occur in presence of acid and pepsin when *Helicobacter pylori* (HP), nonsteroidal anti-inflammatory drugs (NSAIDs), or other factors disrupt normal mucosal defense and healing mechanisms. Increased gastric acid secretion may occur with duodenal ulcers, but patients with gastric ulcers usually have normal or reduced rates of acid secretion.
- Normal mucosal defense and repair mechanisms include mucus and bicarbonate secretion, intrinsic epithelial cell defense, and mucosal blood flow. Maintenance of mucosal integrity and repair is mediated by endogenous prostaglandin production.
- HP infection causes gastric mucosal inflammation in all infected individuals, but only a minority develop an ulcer or gastric cancer. Mucosal injury is produced by elaborating bacterial enzymes (urease, lipases, and proteases), adherence, and HP virulence factors. HP induces gastric inflammation by altering the host inflammatory response and damaging epithelial cells.
- Nonselective NSAIDs (including aspirin) cause gastric mucosal damage by two mechanisms: (1) a direct or topical irritation of the gastric epithelium, and (2) systemic inhibition of endogenous mucosal prostaglandin synthesis.
- Use of corticosteroids alone does not increase risk of ulcer or complications, but ulcer risk is doubled in corticosteroid users taking NSAIDs concurrently.
- Epidemiologic evidence links cigarette smoking to PUD, impaired ulcer healing, and ulcer-related GI complications. Risk is proportional to amount smoked per day.
- Although clinical observation suggests that ulcer patients are adversely affected by stressful life events, controlled studies have not documented a cause-and-effect relationship.
- Coffee, tea, cola beverages, beer, milk, and spices may cause dyspepsia but do not increase PUD risk. Ethanol ingestion in high concentrations is associated with acute gastric mucosal damage and upper GI bleeding but is not clearly the cause of ulcers.

CLINICAL PRESENTATION

- Abdominal pain is the most frequent PUD symptom. Pain is often epigastric and described as burning but can present as vague discomfort, abdominal fullness, or cramping. Nocturnal pain may awaken patients from sleep, especially between 12 AM and 3 AM.
- Pain from duodenal ulcers often occurs 1 to 3 hours after meals and is usually relieved by food, whereas food may precipitate or accentuate ulcer pain in gastric ulcers. Antacids provide rapid pain relief in most ulcer patients.
- Heartburn, belching, and bloating often accompany pain. Nausea, vomiting, and anorexia are more common in gastric than duodenal ulcers.
- Severity of symptoms varies among patients and may be seasonal, occurring more frequently in spring or fall.
- Presence or absence of epigastric pain does not define an ulcer. Ulcer healing does not necessarily render the patient asymptomatic. Conversely, absence of pain does not preclude an ulcer diagnosis, especially in the elderly who may present with a "silent" ulcer complication.
- Ulcer complications include upper GI bleeding, perforation into the peritoneal cavity, penetration into an adjacent structure (eg, pancreas, biliary tract, or liver), and gastric

outlet obstruction. Bleeding may be occult or present as melena or hematemesis. Perforation is associated with sudden, sharp, severe pain, beginning first in the epigastrium but quickly spreading over the entire abdomen. Symptoms of gastric outlet obstruction typically occur over several months and include early satiety, bloating, anorexia, nausea, vomiting, and weight loss.

DIAGNOSIS

- Physical examination may reveal epigastric tenderness between the umbilicus and the xiphoid process that less commonly radiates to the back.
- Routine laboratory tests are not helpful in establishing a diagnosis of PUD. Hematocrit, hemoglobin, and stool guaiac tests are used to detect bleeding.
- Diagnosis of HP infection can be made using endoscopic or nonendoscopic (urea breath test [UBT], serologic antibody detection, and stool antigen) tests. Testing for HP is recommended only if eradication therapy is planned. If endoscopy is not planned, serologic antibody testing is reasonable to determine HP status. The UBT is the preferred nonendoscopic method to verify HP eradication but must be delayed at least 4 weeks after completion of treatment to avoid confusing bacterial suppression with eradication.
- Diagnosis of PUD depends on visualizing the ulcer crater either by upper GI radiography or endoscopy. Endoscopy has largely replaced radiography because it provides a more accurate diagnosis and permits direct visualization of the ulcer.

TREATMENT

- Goals of Treatment: Relieve ulcer pain, heal the ulcer, prevent ulcer recurrence, and reduce ulcer-related complications. In HP-positive patients with an active ulcer, previously documented ulcer, or history of an ulcer-related complication, goals are to eradicate the organism, heal the ulcer, and cure the disease with a cost-effective drug regimen.

NONPHARMACOLOGIC TREATMENT

- Patients with PUD should eliminate or reduce psychological stress, cigarette smoking, and use of NSAIDs (including aspirin). If possible, alternative agents such as **acetaminophen** or a nonacetylated salicylate (eg, **salsalate**) should be used for pain relief.
- Although there is no need for a special diet, patients should avoid foods and beverages that cause dyspepsia or exacerbate ulcer symptoms (eg, spicy foods, caffeine, and alcohol).
- Elective surgery is rarely performed because of highly effective medical management. Emergency surgery may be required for bleeding, perforation, or obstruction.

PHARMACOLOGIC TREATMENT

- **Figure 29–1** depicts an algorithm for evaluation and management of a patient with dyspeptic or ulcer-like symptoms.
- Indications for treatment of HP include gastric or duodenal ulcer, mucosa-associated lymphoid tissue (MALT) lymphoma, postendoscopic resection of gastric cancer, and uninvestigated dyspepsia. Treatment should be effective, well tolerated, convenient, and cost-effective.
- First-line therapy to eradicate HP infection is usually initiated with a proton pump inhibitor (PPI)–based, three-drug regimen for 10 to 14 days. If a second treatment course is required, the regimen should contain different antibiotics, or a four-drug regimen with a bismuth salt, metronidazole, tetracycline, and a PPI should be used (**Table 29–1**).
- Bismuth-based quadruple therapy is recommended as an alternative for patients allergic to penicillin. All medications except the PPI should be taken with meals and at bedtime.
- In sequential therapy, the antibiotics are administered in a sequence rather than all together. The rationale is to treat initially with antibiotics that rarely promote

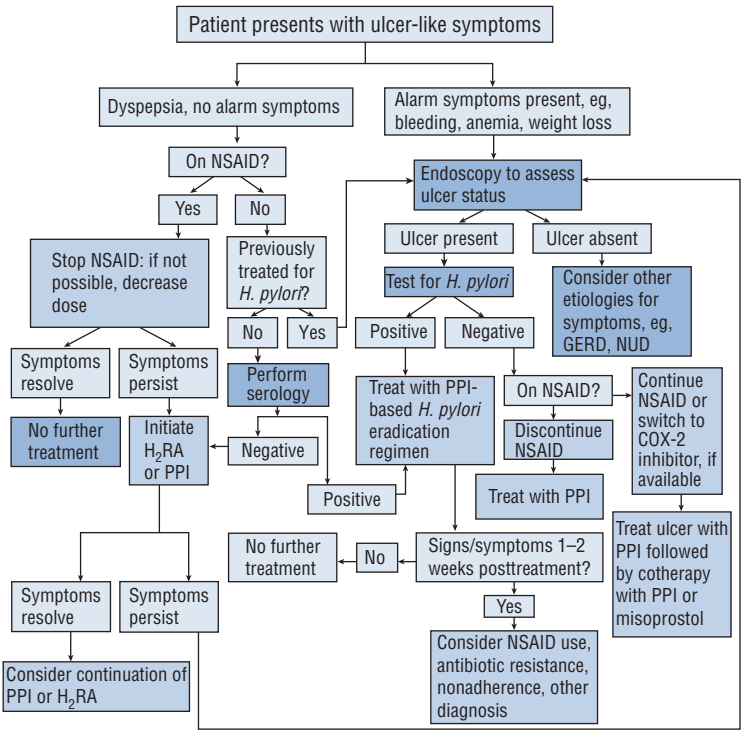


FIGURE 29–1. Guidelines for the evaluation and management of a patient who presents with dyspeptic or ulcer-like symptoms. (COX-2, cyclooxygenase-2; GERD, gastroesophageal reflux disease; *H. pylori, Helicobacter pylori;* H_2RA, histamine$_2$-receptor antagonist; NSAID, nonsteroidal antiinflammatory drug; NUD, nonulcer dyspepsia; PPI, proton pump inhibitor.)

resistance (eg, amoxicillin) to reduce bacterial load and preexisting resistant organisms and then to follow with different antibiotics (eg, clarithromycin and metronidazole) to kill the remaining organisms. The potential advantage of superior eradication rates requires confirmation in the United States before this regimen can be recommended as first-line therapy.

- If initial treatment fails to eradicate HP, second-line (salvage) treatment should: (1) use antibiotics that were not included in the initial regimen, (2) use antibiotics that are not associated with resistance, (3) use a drug that has a topical effect (eg, bismuth), and (4) extend the treatment duration to 14 days. A 14-day course of the PPI-based quadruple regimen is the most commonly used second-line therapy after failure of a PPI–amoxicillin–clarithromycin regimen.
- Patients with NSAID-induced ulcers should be tested to determine HP status. If HP positive, start treatment with a PPI-based three-drug regimen. If HP negative, discontinue the NSAID and treat with either a PPI, H_2RA, or sucralfate (**Table 29–2**). If the NSAID must be continued despite ulceration, initiate treatment with a PPI (if HP negative) or a PPI-based three-drug regimen (if HP positive). Cotherapy with a PPI or misoprostol or switching to a selective cyclooxygenase-2 (COX-2) inhibitor is recommended for patients at risk of developing an ulcer-related complication.

TABLE 29–1 Drug Regimens to Eradicate *Helicobacter pylori*

Drug #1	Drug #2	Drug #3	Drug #4
Proton pump inhibitor–based triple therapy[a]			
PPI once or twice daily[b]	Clarithromycin 500 mg twice daily	Amoxicillin 1 g twice daily *or* metronidazole 500 mg twice daily	
Bismuth-based quadruple therapy[a]			
PPI or H_2RA once or twice daily[b,c]	Bismuth subsalicylate[d] 525 mg 4 times daily	Metronidazole 250–500 mg 4 times daily	Tetracycline 500 mg 4 times daily
Sequential therapy[e]			
PPI once or twice daily on days 1–10[b]	Amoxicillin 1 g twice daily on days 1–5	Metronidazole 250–500 mg twice daily on days 6–10	Clarithromycin 250–500 mg twice daily on days 6–10
Second-line (salvage) therapy for persistent infections			
PPI or H_2RA once or twice daily[b,c]	Bismuth subsalicylate[d] 525 mg 4 times daily	Metronidazole 250–500 mg 4 times daily	Tetracycline 500 mg 4 times daily
PPI once or twice daily[b,f]	Amoxicillin 1 g twice daily	Levofloxacin 250 mg twice daily	

H_2RA, H_2-receptor antagonist; PPI, proton pump inhibitor.
[a]Although treatment is minimally effective if used for 7 days, 1–14 days is recommended. The antisecretory drug may be continued beyond antimicrobial treatment for patients with a history of a complicated ulcer (eg, bleeding) or in heavy smokers.
[b]Standard PPI peptic ulcer healing dosages given once or twice daily (see Table 29–2).
[c]Standard H_2RA peptic ulcer healing dosages may be used in place of a PPI (see Table 29–2).
[d]Bismuth subcitrate potassium (biskalcitrate) 140 mg, as the bismuth salt, is contained in a prepackaged capsule (Pylera), along with metronidazole 125 mg and tetracycline 125 mg; three capsules are taken with each meal and at bedtime; a standard PPI dosage is added to the regimen and taken twice daily. All medications are taken for 10 days.
[e]Requires validation as first-line therapy in the United States.
[f]Requires validation as rescue therapy in the United States.

- Limit maintenance therapy with a PPI or H_2RA (see **Table 29–2**) to high-risk patients with ulcer complications, patients who fail HP eradication, and those with HP-negative ulcers.
- Patients with ulcers refractory to treatment should undergo upper endoscopy to confirm a nonhealing ulcer, exclude malignancy, and assess HP status. HP-positive patients should receive eradication therapy. In HP-negative patients, higher PPI doses (eg, omeprazole 40 mg/day) heal the majority of ulcers. Continuous PPI treatment is often necessary to maintain healing. Patients with refractory gastric ulcer may require surgery because of the possibility of malignancy.

EVALUATION OF THERAPEUTIC OUTCOMES

- Monitor patients for symptomatic relief of ulcer pain, potential adverse drug effects, and drug interactions.
- Ulcer pain typically resolves in a few days when NSAIDs are discontinued and within 7 days upon initiation of antiulcer therapy. Most patients with uncomplicated PUD will be symptom free after treatment with any of the recommended antiulcer regimens.

TABLE 29–2 Oral Drug Regimens Used to Heal Peptic Ulcers and Maintain Ulcer Healing

Generic Name	Prescription Brand Name	Duodenal or Gastric Ulcer Healing (mg/dose)	Maintenance of Ulcer Healing (mg/dose)
Proton pump inhibitors			
Omeprazole	Prilosec, various	20–40 daily	20–40 daily
Omeprazole sodium bicarbonate	Zegerid	20–40 daily	20–40 daily
Lansoprazole	Prevacid, various	15–30 daily	15–30 daily
Rabeprazole	Aciphex	20 daily	20 daily
Pantoprazole	Pantoprazole, various	40 daily	40 daily
Esomeprazole	Nexium	20–40 daily	20–40 daily
Dexlansoprazole	Dexilant	30–60 daily	30 daily
H_2-receptor antagonists			
Cimetidine	Tagamet, various	300 four times daily 400 twice daily 800 at bedtime	400–800 at bedtime
Famotidine	Pepcid, various	20 twice daily 40 at bedtime	20–40 at bedtime
Nizatidine	Axid, various	150 twice daily 300 at bedtime	150–300 at bedtime
Ranitidine	Zantac, various	150 twice daily 300 at bedtime	150–300 at bedtime
Mucosal protectant			
Sucralfate	Carafate, various	1 g 4 times daily 2 g twice daily	1–2 g twice daily 1 g 4 times daily

- Persistence or recurrence of symptoms within 14 days after the end of treatment suggests failure of ulcer healing or HP eradication, or an alternative diagnosis such as gastroesophageal reflux disease.
- Most patients with uncomplicated HP-positive ulcers do not require confirmation of ulcer healing or HP eradication.
- Monitor patients taking NSAIDs closely for signs and symptoms of bleeding, obstruction, penetration, and perforation.
- Follow-up endoscopy is justified in patients with frequent symptomatic recurrence, refractory disease, complications, or suspected hypersecretory states.

See Chapter 20, Peptic Ulcer Disease, authored by Bryan L. Love and Matthew N. Thoma, for a more detailed discussion of this topic.

This page intentionally left blank

CHAPTER 30

Contraception

- *Contraception* is the prevention of pregnancy by inhibiting sperm from reaching a mature ovum or by preventing a fertilized ovum from implanting in the endometrium.

THE MENSTRUAL CYCLE

- The median length of the menstrual cycle is 28 days (range 21–40 days). The first day of menses is day 1. Ovulation usually occurs on day 14. After ovulation, the luteal phase lasts until the beginning of the next cycle.
- The hypothalamus secretes gonadotropin-releasing hormone, which stimulates the anterior pituitary to secrete gonadotropins, follicle-stimulating hormone (FSH), and luteinizing hormone (LH).
- In the follicular phase, FSH levels increase and cause recruitment of a small group of follicles for continued growth. Between days 5 and 7, one of these becomes the dominant follicle, which later ruptures to release the oocyte. The dominant follicle develops, increasing amounts of estradiol and inhibin, providing a negative feedback on the secretion of gonadotropin-releasing hormone and FSH.
- The dominant follicle continues to grow and synthesizes estradiol, progesterone, and androgen. Estradiol stops the menstrual flow from the previous cycle, thickens the endometrial lining, and produces thin, watery cervical mucus. FSH regulates aromatase enzymes that induce conversion of androgens to estrogens in the follicle.
- The pituitary releases a midcycle LH surge that stimulates the final stages of follicular maturation and ovulation. Ovulation occurs 24 to 36 hours after the estradiol peak and 10 to 16 hours after the LH peak.
- The LH surge is the most clinically useful predictor of approaching ovulation. Conception is most successful when intercourse takes place from 2 days before ovulation to the day of ovulation.
- After ovulation, the remaining luteinized follicles become the corpus luteum, which synthesizes androgen, estrogen, and progesterone (**Fig. 30–1**).
- If pregnancy occurs, human chorionic gonadotropin prevents regression of the corpus luteum and stimulates continued production of estrogen and progesterone. If pregnancy does not occur, the corpus luteum degenerates, progesterone declines, and menstruation occurs.

TREATMENT

- Goal of Treatment: the prevention of pregnancy following sexual intercourse.

NONPHARMACOLOGIC THERAPY

- A comparison of methods of nonhormonal contraception is shown in **Table 30–1**.
- The abstinence (rhythm) method is associated with relatively high pregnancy rates.

Barrier Techniques

- Diaphragms are effective because they are barriers and because of the spermicide placed in the diaphragm before insertion. It should be inserted up to 6 hours before intercourse and must be left in place for at least 6 hours after. It should not be left in place for more than 24 hours because of the risk of toxic shock syndrome (TSS).

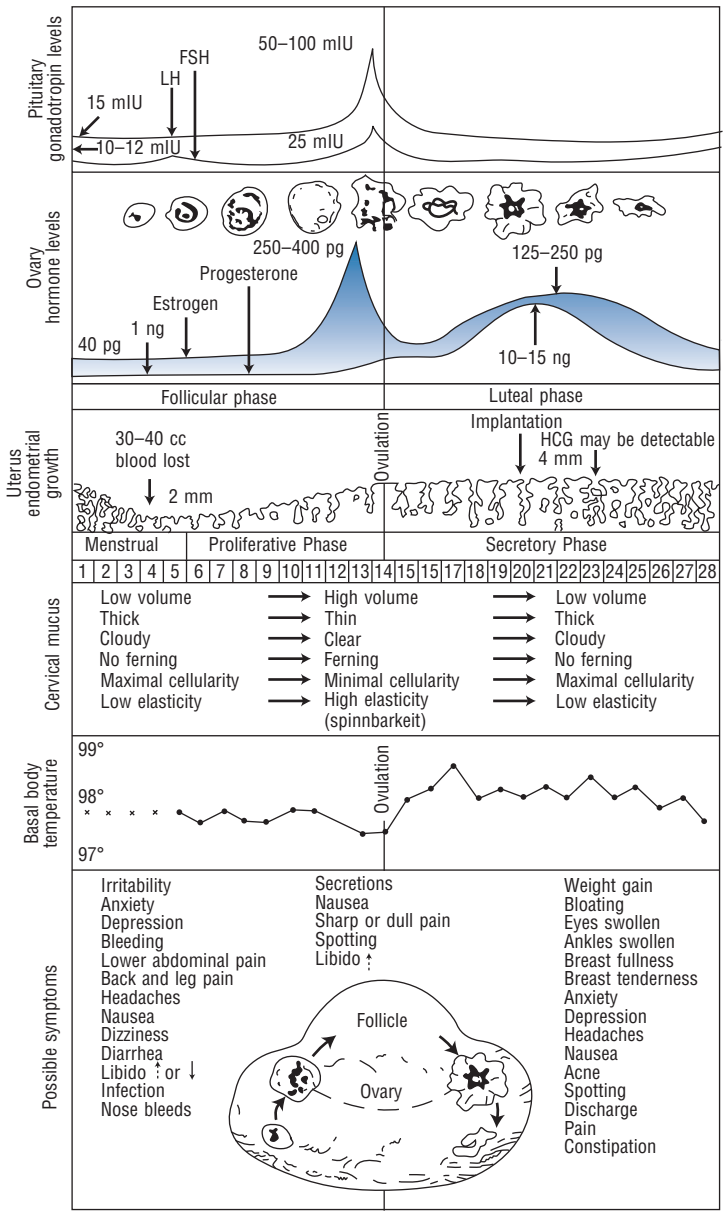


FIGURE 30–1. Menstrual cycle events, idealized 28-day cycle. (FSH, follicle-stimulating hormone; HCG, human chorionic gonadotropin; LH, luteinizing hormone.) LH: 15 mIU/mL = 15 IU/L; 50 to 100 IU/mL = 50 to 100 IU/L. FSH: 10 to 12 mIU/mL = 10 to 12 IU/L; 25 mIU/mL = 25 IU/L. Estrogen: 40 pg/mL = ~150 pmol/L; 250 to 400 pg/mL = ~920 to 1470 pmol/L; 125 to 250 pg/mL = ~460 to 920 pmol/L. Progesterone: 1 ng/mL = 3 nmol/L; 10 to 15 ng/mL = ~30 to 50 nmol/L. Temperatures: 99° F = 37.2° C; 98° F = 36.7° C; 97° F = 36.1° C.

TABLE 30–1 Comparison of Methods of Nonhormonal Contraception

Method	Absolute Contraindications	Advantages	Disadvantages	Percent of Women with Pregnancy[a]	
				Perfect Use	Typical Use
Condoms, male	Allergy to latex or rubber	Inexpensive STD protection, including HIV (latex only)	High user failure rate Poor acceptance Possibility of breakage Efficacy decreased by oil-based lubricants Possible allergic reactions to latex in either partner	2	15
Condoms, female	Allergy to polyurethane History of TSS	Can be inserted just before intercourse or ahead of time STD protection, including HIV	High user failure rate Dislike ring hanging outside vagina Cumbersome	5	21
Diaphragm with spermicide	Allergy to latex, rubber, or spermicide Recurrent UTIs History of TSS Abnormal gynecologic anatomy	Low cost Decreased incidence of cervical neoplasia Some protection against STDs	High user failure rate Decreased efficacy with increased frequency of intercourse Increased incidence of vaginal yeast UTIs, TSS Efficacy decreased by oil-based lubricants Cervical irritation	6	12

(*continued*)

TABLE 30–1 Comparison of Methods of Nonhormonal Contraception (*Continued*)

Method	Absolute Contraindications	Advantages	Disadvantages	Percent of Women with Pregnancy[a]	
				Perfect Use	Typical Use
Cervical cap (FemCap)	Allergy to spermicide History of TSS Abnormal gynecologic anatomy Abnormal papanicolaou smear	Low cost Latex-free Some protection against STDs FemCap reusable for up to 2 years	High user failure rate Decreased efficacy with parity Cannot be used during menses	9	16[b]
Spermicides alone	Allergy to spermicide	Inexpensive	High user failure rate Must be reapplied before each act of intercourse May enhance HIV transmission No protection against STDs	18	28
Sponge (Today)	Allergy to spermicide Recurrent UTIs History of TSS Abnormal gynecologic anatomy	Inexpensive	High user failure rate Decreased efficacy with parity Cannot be used during menses No protection against STDs	9[c]	12[d]

HIV, human immunodeficiency virus; STD, sexually transmitted disease; TSS, toxic shock syndrome; UTI, urinary tract infection.

[a]Failure rates in the United States during first year of use.
[b]Failure rate with FemCap reported to be 24% per package insert.
[c]Failure rate with Today sponge reported to be 20% in parous women.
[d]Failure rate with Today sponge reported to be 32% in parous women.

- The cervical cap can be inserted 6 hours prior to intercourse, and should not remain in place for longer than 48 hours to reduce the risk of TSS. A condom should also be used to protect against sexually transmitted diseases (STDs) including human immunodeficiency virus (HIV).
- Most condoms made in the United States are latex, which is impermeable to viruses, but ~5% are made from lamb intestine, which is not impermeable to viruses. Mineral oil–based vaginal drug formulations (eg, Cleocin vaginal cream, Premarin vaginal cream, Vagistat 1, Femstat, and Monistat vaginal suppositories) can decrease the barrier strength of latex. Condoms with spermicides are not recommended, as they provide no additional protection against pregnancy or STDs and may increase vulnerability to HIV.
- The female condom (Reality) covers the labia, as well as the cervix. However, the pregnancy rate is higher than with male condoms.

PHARMACOLOGIC THERAPY

- **Table 30-2** compares unintended pregnancy rates and continuation rates for pharmacologic contraceptive methods.

Spermicides and Spermicide Implanted Barrier Techniques

- Most spermicides contain nonoxynol-9, surfactants that destroy sperm cell walls and block entry into the cervical os. They offer no protection against STDs, and when used more than twice daily, nonoxynol-9 may increase the transmission of HIV.
- The **vaginal contraceptive sponge (Today)** contains nonoxynol-9 and provides protection for 24 hours. After intercourse, the sponge must be left in place for at least 6 hours before removal. It should not be left in place for more than 24 to 30 hours to reduce the risk of TSS. It is available without a prescription.

Hormonal Contraception

COMPOSITION AND FORMULATIONS

- Hormonal contraceptives contain either a combination of synthetic estrogen and synthetic progestin or a progestin alone.

TABLE 30–2 Comparison of Unintended Pregnancy and Continuation Rates for Pharmacologic Contraceptive Methods

Method	Percent of Women with Pregnancy with Typical Use[a]	Percent of Women with Pregnancy with Perfect Use[a]	Percent of Women Continuing Use[b]
Combined oral contraceptive and progestin-only oral contraceptive	8	0.3	68
Combined hormonal transdermal contraceptive patch	8	0.3	68
Combined hormonal vaginal contraceptive ring	8	0.3	68
Depo-medroxyprogesterone acetate	3	0.3	56
Copper IUD	0.8	0.6	78
Levonorgestrel IUD	0.2	0.2	80
Progestin-only implant	0.05	0.05	84

[a]Failure rates in the United States during first year of use.
[b]Continuation rate in the United States at the end of the first year of use.

- Progestins thicken cervical mucus, delay sperm transport, and induce endometrial atrophy. They also block the LH surge and thus inhibit ovulation. Estrogens suppress FSH release (which may contribute to blocking the LH surge) and also stabilize the endometrial lining and provide cycle control.

COMPONENTS

- **Table 30–3** lists available oral contraceptives (OCs) by brand name and hormonal composition. Mestranol must be converted to ethinyl estradiol (EE) in the liver to be active. It is ~50% less potent than EE.
- Progestins vary in their progestational activity and differ with respect to inherent estrogenic, antiestrogenic, and androgenic effects. Their estrogenic and antiestrogenic properties occur because progestins are metabolized to estrogenic substances. Androgenic activity depends on the presence of sex hormone (testosterone) binding globulin and the androgen-to-progesterone activity ratio. If sex hormone binding globulin decreases, free testosterone levels increase, and androgenic side effects are more prominent.

CONSIDERATIONS WITH USE OF COMBINED HORMONAL CONTRACEPTIVES (CHC)

- Obtain a medical history and blood pressure measurement, and discuss the risks, benefits, and adverse effects with the patient before prescribing a CHC.
- Noncontraceptive benefits of OCs include decreased menstrual cramps and ovulatory pain; decreased menstrual blood loss; improved menstrual regularity; decreased iron deficiency anemia; reduced risk of ovarian and endometrial cancer; and reduced risk of ovarian cysts, ectopic pregnancy, pelvic inflammatory disease, endometriosis, uterine fibroids, and benign breast disease.
- Serious symptoms that may be associated with CHCs and monitoring of hormonal contraception are shown in **Tables 30–4** and **30-5**, respectively.
- The main safety concern about CHCs is their lack of protection against STDs. Encourage use of condoms to prevent STDs.
- **Table 30–6** shows graded eligibility criteria for contraceptive use.

Women over 35 Years of Age

- Use of CHCs containing less than 50 mcg estrogen may be considered in healthy nonsmoking women older than 35 years.
- CHCs are not recommended for women older than 35 years with migraine, uncontrolled hypertension, smoking or diabetes with vascular disease.
- Studies have not demonstrated an increased risk of cardiovascular disease with low-dose CHCs in healthy, nonobese women.

Women Who Smoke

- Women older than 35 years who smoke and take OCs have an increased risk of myocardial infarction; therefore, clinicians should prescribe CHCs with caution, if at all, in this group. Smoking 15 or more cigarettes per day by women over 35 years is a contraindication to the use of CHCs, and the risks generally outweigh the benefits even in those who smoke fewer than 15 cigarettes per day. Progestin-only methods should be considered in this group.

Hypertension

- CHCs, regardless of estrogen dose, can cause small increases in blood pressure (6–8 mm Hg). In women with hypertension, OCs have been associated with an increased risk of myocardial infarction (MI) and stroke. Use of low-dose CHCs is acceptable in women younger than 35 years with well-controlled and monitored hypertension. Hypertensive women with end-organ disease or who smoke should not use CHCs.
- Systolic blood pressure greater than or equal to 160 mm HG or diastolic blood pressure greater than or equal to 100 mm Hg is a contraindication to use of CHCs.

TABLE 30–3 Composition of Commonly Prescribed Oral Contraceptives[a]

Product	Estrogen	Micrograms[b]	Progestin	Milligrams[b]	Spotting and Breakthrough Bleeding
50 mcg Estrogen					
Necon 1/50, Norinyl 1+50	Mestranol	50	Norethindrone	1	10.6
Ovcon 50	Ethinyl estradiol	50	Norethindrone	1	11.9
Ogestrel 0.5/50	Ethinyl estradiol	50	Norgestrel	0.5	4.5
Zovia 1/50	Ethinyl estradiol	50	Ethynodiol diacetate	1	13.9
Sub-50 mcg Estrogen Monophasic					
Aviane, Falmina, Lessina, Levlite, Lutera, Orsythia, Sronyx	Ethinyl estradiol	20	Levonorgestrel	0.1	26.5
Brevicon, Modicon, Necon 0.5/35, Nortrel 0.5/35 Wera	Ethinyl estradiol	35	Norethindrone	0.5	24.6
Zovia 1/35, Kelnor	Ethinyl estradiol	37.4	Ethynodiol diacetate	1	37.4
Apri, Desogen, Emoquette, Ortho-Cept, Reclipsen, Solia	Ethinyl estradiol	30	Desogestrel	0.15	13.1
Levora, Nordette, Portia, Altavera, Kurvelo, Marlissa	Ethinyl estradiol	30	Levonorgestrel	0.15	14
Gildess Fe 1/20, Junel 1/20, Junel Fe 1/20, Loestrin 1/20; Fe 1/20, Microgestin 1/20; Fe 1/20	Ethinyl estradiol	20	Norethindrone 1mg	1	26.5
Gildess Fe 1.5/30, Junel 1.5/30, Junel Fe 1.5/30, Loestrin Fe 1.5/30, Microgestin 1.5/30, Microgestin Fe 1.5/30	Ethinyl estradiol	30	Norethindrone acetate	1.5	25.2
Cryselle, Elinest, Lo-Ovral, Low-Ogestrel	Ethinyl estradiol	30	Norgestrel	0.3	9.6
Necon 1/35, Norinyl 1+35, Nortrel 1/35, Ortho-Novum 1/35, Alyacen 1/35, Cyclafem 1/35, Dasetta 1/35	Ethinyl estradiol	35	Norethindrone	1	14.7

(*continued*)

TABLE 30–3 Composition of Commonly Prescribed Oral Contraceptives[a] (*Continued*)

Product	Estrogen	Micrograms[b]	Progestin	Milligrams[b]	Spotting and Breakthrough Bleeding
Ortho-Cyclen, Mononessa, Mono-Linyah, Previfem, Sprintec	Ethinyl estradiol	35	Norgestimate	0.25	14.3
Ovcon-35, Balziva, Femcon Fe chewable, Zenchent, Briellyn, Gildagia, Philith, Zeosa chewable	Ethinyl estradiol	35	Norethindrone	0.4	11
Yasmin, Ocella, Safyral, Syeda, Zarah	Ethinyl estradiol	30	Drospirenone	3	14.5
Sub-50 mcg Estrogen Monophasic Extended Cycle					
Loestrin-24 FE[c]	Ethinyl estradiol	20	Norethindrone	1	50[e]
Lybrel, Amethyst	Ethinyl estradiol	20	Levonorgestrel	0.09	52[e]
Introvale, Seasonale, Jolessa, Quasense[d]	Ethinyl estradiol	30	Levonorgestrel	0.15	58.5[e]
Beyaz, Gianvi, Loryna, Vestura, Yaz[c]	Ethinyl estradiol	20	Drospirenone	3	52.5[e]
Sub-50 mcg Estrogen Multiphasic					
Caziant, Cyclessa, Cesia, Velivet	Ethinyl estradiol	25 (7) 25 (7) 25 (7)	Desogestrel	0.1 (7) 0.125 (7) 0.15 (7)	11.1
Estrostep Fe, Tilia Fe, Tri-Legest Fe	Ethinyl estradiol Ethinyl estradiol Ethinyl estradiol	20 (5) 30 (7) 35 (9)	Norethindrone acetate Norethindrone acetate Norethindrone acetate	1 (5) 1 (7) 1 (9)	21.7
Kariva, Mircette, Azurette, Viorele	Ethinyl estradiol Ethinyl estradiol	20 (21) 10 (5)	Desogestrel Desogestrel	0.15 (21)	19.7
Necon 10/11	Ethinyl estradiol Ethinyl estradiol	35 (10) 35 (11)	Norethindrone Norethindrone	0.5 (10) 1 (11)	17.6

Ortho-Novum 7/7/7, Nortrel 7/7/7, Necon 7/7/7, Alyacen 7/7/7, Cyclafem 7/7/7, Dasetta 7/7/7	Ethinyl estradiol	35 (7)	Norethindrone	0.5 (7)	14.5
	Ethinyl estradiol Ethinyl estradiol	35 (7) 35 (7)	Norethindrone Norethindrone	0.75 (7) 1 (7)	
Ortho Tri-Cyclen, Trinessa, Tri-Previfem, Tri-Sprintec, Tri-Estarylla, Tri-Linyah	Ethinyl estradiol	35 (7)	Norgestimate	0.18 (7)	17.7
	Ethinyl estradiol Ethinyl estradiol	35 (7) 35 (7)	Norgestimate Norgestimate	0.215 (7) 0.25 (7)	
Ortho Tri-Cyclen Lo, Tri Lo Sprintec	Ethinyl estradiol Ethinyl estradiol Ethinyl estradiol	25 (7) 25 (7) 25 (7)	Norgestimate Norgestimate Norgestimate	0.18 (7) 0.215 (7) 0.25 (7)	11.5
Aranelle, Leena, Tri-Norinyl	Ethinyl estradiol Ethinyl estradiol Ethinyl estradiol	35 (7) 35 (9) 35 (5)	Norethindrone Norethindrone Norethindrone	0.5 (7) 1 (9) 0.5 (5)	25.5
Enpresse, Trivora, Levonest Myzilra	Ethinyl estradiol Ethinyl estradiol Ethinyl estradiol	30 (6) 40 (5) 30 (10)	Levonorgestrel Levonorgestrel Levonorgestrel	0.05 (6) 0.075 (5) 0.125 (10)	
Natazia	Estradiol valerate	3 (2) 2 (22) 1 (2)	Dienogest	0 (2) 2 (5) 3 (17) 0 (4)	

(*continued*)

TABLE 30–3 Composition of Commonly Prescribed Oral Contraceptives[a] (*Continued*)

Product	Estrogen	Micrograms[b]	Progestin	Milligrams[b]	Spotting and Breakthrough Bleeding
Sub-50 mcg Estrogen Multiphasic Extended Cycle					
Amethia, Seasonique	Ethinyl estradiol Ethinyl estradiol	30 (84) 10 (7)	Levonorgestrel' Levonorgestrel	0.15 (84) 0.15 (7)	42.5[e]
Progestin Only					
Camila, Errin, Heather, Jolivette, Micronor, Nor-QD, Nora-BE	Ethinyl estradiol	–	Norethindrone	0.35	42.3

[a]28-day regimens (21-day active pills, then 7-day pill-free interval) unless otherwise noted.
[b]Number in parentheses refers to the number of days the dose is received in multiphasic oral contraceptives.
[c]28-day regimen (24-day active pills, then 4-day pill-free interval).
[d]91-day regimen (84-day active pills, then 7-day pill-free interval).
[e]Percent reporting after 6 to 12 months of use.

TABLE 30–4 Serious Symptoms That May Be Associated with Combined Hormonal Contraception

Serious Symptoms	Possible Underlying Problem
Blurred vision, diplopia, flashing lights, blindness, papilledema	Stroke, hypertension, temporary vascular problem of many possible sites, retinal artery thrombosis
Numbness, weakness, tingling in extremities, slurred speech	Hemorrhagic or thrombotic stroke
Migraine headaches	Vascular spasm, stroke
Breast mass, pain, or swelling	Breast cancer
Chest pain (radiating to left arm or neck), shortness of breath, coughing up blood	Pulmonary embolism, myocardial infarction
Abdominal pain, hepatic mass or tenderness, jaundice, pruritus	Gallbladder disease, hepatic adenoma, pancreatitis, thrombosis of abdominal artery or vein
Excessive spotting, breakthrough bleeding	Endometrial, cervical, or vaginal cancer
Severe leg pain (calf, thigh), tenderness, swelling, warmth	Deep-vein thrombosis

Diabetes

- The new progestins are believed to have little, if any, effect on carbohydrate metabolism. Women younger than 35 years with diabetes but no vascular disease who do not smoke can safely use CHCs. Diabetic women with vascular disease or diabetics of more than 20 years' duration should not use CHCs.

Dyslipidemia

- Generally, synthetic progestins decrease high-density lipoprotein (HDL) and increase low-density lipoprotein (LDL). Estrogens decrease LDL but increase HDL and may moderately increase triglycerides. Most low-dose CHCs (with the possible exception of levonorgestrel pills, which may reduce HDL levels in some patients) have no significant impact on HDL, LDL, triglycerides, or total cholesterol.
- The mechanism for the increased cardiovascular disease in CHC users is believed to be thromboembolic and thrombotic changes, not atherosclerosis.
- Women with controlled dyslipidemias can use low-dose CHCs, with monitoring of fasting lipid profiles. Women with uncontrolled dyslipidemia (LDL >160 mg/dL [4.14 mmol/L], HDL <35 mg/dL [0.91 mmol/L], triglycerides >250 mg/dL [2.83 mmol/L]) and additional risk factors (eg, coronary artery disease, diabetes, hypertension, smoking, or a positive family history) should use an alternative method of contraception.

Thromboembolism

- Estrogens have a dose-related effect in the development of venous thromboembolism (VTE) and pulmonary embolism, especially in women with underlying hypercoagulable states or who have acquired conditions (eg, obesity, pregnancy, immobility, trauma, surgery, and certain malignancies) that predispose them to coagulation abnormalities.
- The risk of VTE in women using low-dose OCs (<50 mcg EE) was four times the risk in nonusers. However, this risk is less than the risk of thromboembolic events during pregnancy. OCs containing desogestrel, drospirenone, and norgestimate have slightly increased risk of thrombosis.
- The transdermal patch and vaginal ring expose women to higher estrogen and are associated with increased thromboembolic risk.

TABLE 30–5 Drug Monitoring Table for Hormonal Contraception

Drug (or Drug Class)	Adverse Drug Reactions	Monitoring Parameter	Comments
Combined hormonal contraception	Nausea/vomiting	Patient symptoms	Typically improves after two to three cycles; consider changing to lower estrogenic
	Breast tenderness	Patient symptoms	
	Weight gain	Weight	
	Acne, oily skin	Visual inspection	Consider changing to lower androgenic
	Depression, fatigue	Depression screening	Data are limited and conflicting
	Breakthrough bleeding/spotting	Menstrual symptoms	Consider changing to higher estrogenic
	Application site reaction (transdermal)	Visual inspection	
	Vaginal irritation (vaginal ring)	Patient symptoms	
Depo-medroxyprogesterone acetate	Menstrual irregularities	Menstrual symptoms	
	Weight gain	Weight	
	Acne	Visual inspection	
	Hirsutism	Visual inspection	
	Depression	Depression screening	Data are limited and conflicting
	Decreased bone density	BMD	Do not routinely screen with DXA
Levonorgestrel IUD	Menstrual irregularities	Menstrual symptoms	Typically spotting, amenorrhea
	Insertion-related complications	Cramping, pain	Prophylactic NSAIDs or local anesthetic may reduce occurrence

	Expulsion	Cramping, pain, spotting, dyspareunia, missing strings	IUD strings should be checked regularly by women to ensure IUD properly placed
	Pelvic inflammatory disease	Lower abdominal pain, unusual vaginal discharge, fever	Overall risk of developing is rare, but counseling on STD prevention is important
Copper IUD	See levonorgestrel IUD above	See levonorgestrel IUD above	Menstrual irregularities are typically heavier menses with copper IUD
Progestin-only implant	Menstrual irregularities Insertion-site reactions	Menstrual symptoms Pain, bruising, skin irritation, erythema, pus, fever	Typically well-tolerated and resolve without treatment, infection is rare

TABLE 30–6 U.S. Medical Eligibility Criteria for Contraceptive Use: Classifications for Combined Hormonal Contraceptives

Category 4: Unacceptable health risk (method not to be used)

- Breast-feeding or non-breastfeeding <21 days postpartum
- Current breast cancer
- Severe (decompensated) cirrhosis
- History/risk of or current deep venous thrombosis/pulmonary embolism (not on anticoagulant therapy); thrombogenic mutations
- Major surgery with prolonged immobilization
- Migraines with aura, any age
- Systolic blood pressure ≥160 mm Hg or diastolic ≥100 mm Hg
- Current and history of ischemic heart disease
- Benign hepatocellular adenoma or malignant liver tumor
- Moderately or severely impaired cardiac function; normal or mildly impaired cardiac function <6 months
- Smoking ≥15 cigarettes per day and age ≥35
- Complicated solid organ transplantation
- History of cerebrovascular accident
- SLE; positive or unknown antiphospholipid antibodies
- Complicated valvular heart disease

Category 3: Theoretical or proven risks usually outweigh the advantages

- Breast-feeding 21–30 days postpartum with or without risk factors for VTE
- Breast-feeding 30–42 days postpartum with other risk factors for VTE
- Non-breastfeeding 21–42 days postpartum with other risk factors for VTE
- Past breast cancer and no evidence of disease for 5 years
- History of DVT/PE (not on anticoagulant therapy), but lower risk for recurrent DVT/PE
- Current gallbladder disease, symptomatic and medically treated
- Migraines without aura, age ≥35 *(category 4 with continued use)*
- History of bariatric surgery; malabsorptive procedures
- History of cholestasis, past COC-related
- Hypertension; systolic blood pressure 140–159 mm Hg or diastolic 90–99 mm Hg
- Normal or mildly impaired cardiac function ≥6 months
- Postpartum 21 to 42 days with other risk factors for VTE
- Smoking <15 cigarettes per day and age ≥35
- Use of ritonavir-boosted protease inhibitors
- Use of certain anticonvulsants (phenytoin, carbamazepine, barbiturates, primidone, topiramate, oxcarbazepine, and lamotrigine)
- Use of rifampicin or rifabutin therapy
- Diabetes with vascular disease or >20 years duration (*possibly category 4 depending upon severity*)
- Multiple risk factors for arterial cardiovascular disease (older age, smoking, diabetes, and hypertension) (*possibly category 4 depending on category and severity*)

Category 2: Advantages generally outweigh theoretical or proven risks

- Age ≥40 (in the absence of other comorbid conditions that increase CVD risk)
- Sickle-cell disease
- Undiagnosed breast mass
- Cervical cancer and awaiting treatment; cervical intraepithelial neoplasia
- Family history (first-degree relatives) of DVT/PE
- Major surgery without prolonged immobilization
- Diabetes mellitus (type 1 or type 2)
- Gallbladder disease; symptomatic and treated by cholecystectomy or asymptomatic
- Migraines without aura, age <35 (*category 3 with continued use*)
- History of pregnancy-related cholestasis
- History of high blood pressure during pregnancy
- Benign liver tumors; focal nodular hyperplasia
- Obesity
- Breast-feeding 30–42 days postpartum without risk factors for VTE

- Breast-feeding >42 days postpartum
- Non-breastfeeding 21–42 days postpartum without risk factors for VTE
- Rheumatoid arthritis on or off immunosuppressive therapy
- Smoking and <35 years old
- Uncomplicated sold organ transplantation
- Superficial thrombophlebitis
- SLE and severe thrombocytopenia or immunosuppressive treatment
- Unexplained vaginal bleeding before evaluation
- Uncomplicated valvular heart disease
- Use of nonnucleoside reverse transcriptase inhibitors
- Hyperlipidemia (*possibly category 3 based upon type, severity, and other risk factors*)
- Inflammatory bowel disease (*possibly category 3 for those with increased risk of VTE*)

Category 1: No restriction (method can be used)

- Thalassemia, iron deficiency anemia
- Mild compensated cirrhosis
- Minor surgery without immobilization
- Depression
- Gestational diabetes mellitus
- Endometrial cancer/hyperplasia, endometriosis
- Epilepsy
- Gestational trophoblastic disease
- Nonmigrainous headaches
- History of bariatric surgery; restrictive procedures
- History of pelvic surgery
- HIV infected or high risk
- Malaria
- Ovarian cancer
- Past ectopic pregnancy
- PID
- Postabortion
- Non-breastfeeding >42 days postpartum
- Severe dysmenorrhea
- Sexually transmitted infections
- Varicose veins
- Thyroid disorders
- Tuberculosis
- Uterine fibroids
- Use of nucleoside reverse transcriptase inhibitors
- Use of broad-spectrum antibiotics, antifungals, and antiparasitics

CHC, combined hormonal contraception; HIV, human immunodeficiency virus; VTE, venous thromboembolism; PE, pulmonary embolism; CVD, cardiovascular disease; PID, pelvic infl ammatory disease.

- For women at increased risk of thromboembolism (older than 35 years, obesity, smoking, personal or family history of venous thrombosis, prolonged immobilization), consider low-dose oral estrogen contraceptives containing older progestins or progestin-only methods.
- Emergency contraception (EC) has not been associated with an increased risk of thromboembolic events.

Migraine Headache

- Women with migraines may experience a decreased or increased frequency of migraines when using CHCs. CHCs may be considered for healthy, nonsmoking women with migraines without aura. Women of any age who have migraine with aura and women over 35 years with any type of migraine should not use CHCs. Women who develop migraines (with or without aura) while receiving CHCs should immediately discontinue their use and consider a progestin-only option.

Breast Cancer

- The choice to use CHCs should not be influenced by the presence of benign breast disease or a family history of breast cancer with either BRCA1 or BRCA2 mutation, but women with a current or past history of breast cancer should not use CHCs.

Systemic Lupus Erythematosus

- OCs do not increase the risk of flare among women with stable systemic lupus erythematosus (SLE) and without antiphospholipid/anticardiolipin antibodies. CHCs should be avoided in women with SLE if they have antiphospholipid antibodies or vascular complications. Progestin-only contraceptives can be used in these women.

Obesity

- OCs have lower efficacy in obese women, and low-dose OCs may be especially problematic. Obese women are at increased risk for VTE. The American Congress of Obstetrics and Gynecology recommends that the transdermal contraceptive patches should not be used as a first choice in women weighing greater than 90 kg (198 lb), and that progestin-only contraception may be better for obese women over 35 years.

GENERAL CONSIDERATIONS FOR ORAL CONTRACEPTIVES

- With perfect use, their efficacy is more than 99%, but with typical use, up to 8% of women may experience unintended pregnancy.
- Monophasic OCs contain a constant amount of estrogen and progestin for 21 days, followed by 7 days of placebo. Biphasic and triphasic pills contain variable amounts of estrogen and progestin for 21 days and are followed by a 7-day placebo phase.
- Extended-cycle pills and continuous combination regimens may offer some side effect and convenience benefits. One particular extended-cycle OC increases the number of hormone-containing pills from 21 to 84 days, followed by a 7-day placebo phase, resulting in four menstrual cycles per year. Another product provides hormone-containing pills daily throughout the year. Continuous combination regimens provide OCs for 21 days, then very-low-dose estrogen and progestin for an additional 4 to 7 days.
- Third-generation OCs contain newer progestins (eg, desogestrel, drospirenone, gestodene, and norgestimate). These potent progestins have no estrogenic effects and are less androgenic than levonorgestrel, and thus are thought to have fewer side effects (eg, less likelihood or severity of acne). Drospirenone may also cause less weight gain compared with levonorgestrel.
- The progestin-only "minipills" tend to be less effective than combination OCs, and they are associated with irregular and unpredictable menstrual bleeding. They must be taken every day of the menstrual cycle at approximately the same time of day to maintain contraceptive efficacy. They are associated with more ectopic pregnancies than other hormonal contraceptives.
- In the "quick start" method for initiating OCs, the woman takes the first pill on the day of her office visit (after a negative urine pregnancy test). In the first-day start

method, women take the first pill on the first day of the next menstrual cycle. The Sunday start method was used for many years, whereby the first pill was taken on the first Sunday after starting the menstrual cycle.
- The World Health Organization's Selected Practice Recommendations for Contraceptive Use can be used for guidance when instructing women what to do if a pill is missed.

CHOICE OF AN ORAL CONTRACEPTIVE

- In women without coexisting medical conditions, an OC containing 35 mcg or less of EE and less than 0.5 mg of norethindrone is recommended.
- Adolescents, underweight women (<50 kg [110 lb]), women older than 35 years, and those who are perimenopausal may have fewer side effects with OCs containing 20 to 25 mcg of EE. However, these low-estrogen OCs are associated with more breakthrough bleeding and an increased risk of contraceptive failure if doses are missed.

MANAGING SIDE EFFECTS

- Many symptoms occurring in the first cycle of OC use (eg, breakthrough bleeding, nausea, and bloating), improve by the third cycle of use. Table 30-5 shows side effect monitoring of hormonal contraceptives.
- Table 30–4 shows symptoms of a serious or potentially serious nature associated with CHC.
- Instruct women to immediately discontinue CHCs if they experience warning signs referred to by the mnemonic ACHES (*a*bdominal pain, *c*hest pain, *h*eadaches, *e*ye problems, and *s*evere leg pain).

DRUG INTERACTIONS

- Tell women to use an alternative method of contraception if there is a possibility of a drug interaction compromising OC efficacy.
- Rifampin reduces the efficacy of OCs. Advise women to use an additional nonhormonal contraceptive agent during the course of rifampin therapy.
- Tell women about the small risk of interaction with other antibiotics, and that additional nonhormonal contraceptives can be considered if desired. If there is breakthrough bleeding in women taking concomitant antibiotics and OCs, an alternate method of contraception should be used during the time of concomitant use.
- **Phenobarbital, carbamazepine,** and **phenytoin** potentially reduce the efficacy of OCs, and many anticonvulsants are known teratogens. Intrauterine devices (IUDs), injectable medroxyprogesterone, or nonhormonal options may be considered for women taking these drugs.

DISCONTINUATION OF THE ORAL CONTRACEPTIVE, RETURN OF FERTILITY

- Traditionally, women are advised to allow two or three normal menstrual periods after discontinuing CHCs before becoming pregnant. However, in several studies, infants conceived in the first month after an OC was discontinued had no greater chance of miscarriage or a birth defect than those born in the general population.

EMERGENCY CONTRACEPTION (EC)

- Oral EC will not disrupt the fertilized egg after implantation has occurred.
- A progestin-only formulation containing levonorgestrel (available in **Plan B One-Step** and **Next Choice**) is approved for EC in the United States.
- Plan B One-Step is one tablet containing 1.5 mg levonorgestrel which is taken within 72 hours of unprotected intercourse. It is available for women and girls of all ages in the United States without a prescription. Next Choice is two tablets, each containing 0.75 mg levonorgestrel. The first tablet is taken within 72 hours of unprotected intercourse (the sooner, the more effective); the second dose is taken 12 hours later.
- Evidence suggests that the levonorgestrel containing products can be moderately effective up to 120 hours after unprotected intercourse.

- Ulpristal is a selective progesterone receptor modulator available by prescription as a single dose of 30 mg taken within 120 hours of unprotected intercourse. It is considered noninferior to levonorgestrel containing ECs.
- Use of higher doses of CHCs can be used for EC, but they may not be as effective, and they may cause more side effects.
- Nausea and vomiting occur significantly less often with progestin-only and progesterone receptor modulator EC.
- Backup barrier methods should be used after EC for at least 7 days.

TRANSDERMAL CONTRACEPTIVES

- A combination contraceptive is available as a transdermal patch **(Ortho Evra)**, which may have improved adherence compared with OCs. Efficacy seems to be compromised in women more than 90 kg (198 lb). The patch should be applied to the abdomen, buttocks, upper torso, or upper arm at the beginning of the menstrual cycle and replaced every week for 3 weeks.
- Women using the patch are exposed to ~60% more estrogen than if they were taking an OC containing 35 mg of EE, possibly leading to increased thromboembolic risk.

VAGINAL RINGS

- **NuvaRing** releases ~15 mcg/day of EE and 120 mcg/day of etonogestrel over a 3-week period. On first use, the ring should be inserted on or prior to the fifth day of the cycle, remain in place for 3 weeks, then be removed. One week should lapse before the new ring is inserted on the same day of the week as it was for the last cycle. A second form of contraception should be used for the first 7 days of ring use or if the ring has been expelled for more than 3 hours.

LONG-ACTING INJECTABLE AND IMPLANTABLE CONTRACEPTIVES

- Women who particularly benefit from progestin-only methods, including minipills, are those who are breast-feeding, intolerant of estrogens, and those with concomitant medical conditions in which estrogen is not recommended. Injectable and implantable contraceptives are also beneficial for women with adherence issues. Pregnancy failure rates with long-acting progestin contraception are lower than with CHC.

Injectable Progestins

- Depot medroxyprogesterone acetate **(DMPA)** 150 mg is administered by deep intramuscular injection in the gluteal or deltoid muscle within 5 days of onset of menstrual bleeding, and the dose should be repeated every 12 weeks. Another formulation contains 104 mg of DMPA (Depo-SubQ Provera 104), which is injected subcutaneously into the thigh or abdomen. Exclude pregnancy in women more than 1 week late for repeat injection of the intramuscular formulation or 2 weeks late for repeat injection of the subcutaneous formulation. Return of fertility may be delayed after discontinuation.
- DMPA can be given immediately postpartum in women who are not breast-feeding, but in women, who are breast-feeding, delay administration for 6 weeks.
- Women using DMPA have a lower incidence of *Candida* vulvovaginitis, ectopic pregnancy, pelvic inflammatory disease, and endometrial and ovarian cancer compared with women using no contraception. The median time to conception from the first omitted dose is 10 months.
- The most frequent adverse effect of DMPA is menstrual irregularities, which decrease after the first year. Breast tenderness, weight gain, and depression occur less frequently.
- DMPA is associated with a reduction in bone mineral density (BMD), but it is not associated with the development of osteoporosis or fractures. BMD loss may slow after 1 to 2 years of DMPA use, and effects on BMD may not be completely reversible upon discontinuation. DMPA should not be continued beyond 2 years unless other contraceptive methods are inadequate.

Subdermal Progestin Implants

- **Nexplanon**, an etonogestrel implant which is radiopaque, is replacing **Implanon**. It is a 4 cm implant, containing 68 mg of etonogestrel that is placed under the skin of the upper arm. It releases 60 mcg daily for the first month, decreasing gradually to 30 mcg/day at the end of the 3 years of recommended use. With perfect use, efficacy exceeds 99%, but it may be less in women more than 130% of their ideal body weight.
- The major adverse effect is irregular menstrual bleeding. Other side effects are headache, vaginitis, weight gain, acne, and breast and abdominal pain. It does not appear to decrease BMD. Fertility returns within 30 days of removal.

INTRAUTERINE DEVICES

- IUDs cause low-grade intrauterine inflammation and increased prostaglandin formation. Also, endometrial suppression is caused by progestin-releasing IUDs. Efficacy rates are greater than 99%.
- The risk of pelvic inflammatory disease among users, highest during the first 20 days after insertion, ranges from 1% to 2.5%.
- **ParaGard** (copper) can be left in place for 10 years. A disadvantage of ParaGard is increased menstrual blood flow and dysmenorrhea.
- **Mirena** and **Skyla** release levonorgestrel. They must be replaced after 5 years (Mirena) and 3 years (Skyla). They cause a reduction in menstrual blood loss.

EVALUATION OF THERAPEUTIC OUTCOMES

- Monitor blood pressure annually in all CHC users.
- Monitor glucose levels closely when CHCs are started or stopped in women with a history of glucose intolerance or diabetes mellitus.
- For all contraceptive users do annual cytologic screening (more often if they are at risk for STDs), pelvic and breast examination, and well woman consultation. Also, regularly evaluate for problems that may relate to the CHCs (eg, breakthrough bleeding, amenorrhea, weight gain, and acne).
- Annually monitor women using Nexplanon for menstrual cycle disturbances, weight gain, local inflammation or infection at the implant site, acne, breast tenderness, headaches, and hair loss.
- Evaluate women using DMPA every 3 months for weight gain, menstrual cycle disturbances, and fractures.
- Monitor women with IUDs at 1 to 3 month intervals for proper positioning of the IUD, changes in menstrual bleeding patterns, upper genital tract infection, and protection against STDs.

See Chapter 62, Contraception, authored by Sarah P. Shrader and Kelly R. Ragucci, for a more detailed discussion of this topic.

Menopausal, Perimenopausal, and Postmenopausal Hormone Therapy

CHAPTER 31

- *Menopause* is the permanent cessation of menses following the loss of ovarian follicular activity. Perimenopause begins with the onset of menstrual irregularity and ends 12 months after the last menstrual period.

PHYSIOLOGY

- The hypothalamic-pituitary-ovarian axis controls reproductive physiology. Follicle-stimulating hormone (FSH) and luteinizing hormone (LH), produced by the pituitary in response to gonadotropin-releasing hormone from the hypothalamus, regulate ovarian function. Gonadotropins are also influenced by negative feedback from the sex steroids estradiol (produced by the dominant follicle) and progesterone (produced by the corpus luteum). Other sex steroids are androgens, primarily testosterone and androstenedione, secreted by the ovarian stroma.
- Physiologic changes of menopause result from loss of ovarian follicular activity.
- As women age, circulating FSH progressively rises and ovarian inhibin-B and anti-Mullerian hormone declines. In menopause there is a 10- to 15-fold increase in circulating FSH, a four- to fivefold increase in LH, and a greater than 90% decrease in circulating estradiol concentrations.

CLINICAL PRESENTATION

- Symptoms of perimenopause and menopause include vasomotor symptoms (hot flushes and night sweats), sleep disturbances, depression, anxiety, poor concentration and memory, vaginal dryness and dyspareunia, headache, sexual dysfunction, and arthralgia.
- Signs include urogenital atrophy in menopause and dysfunctional uterine bleeding in perimenopause. Other potential causes of dysfunctional uterine bleeding should be ruled out.
- Additionally, loss of estrogen production results in metabolic changes; increase in central abdominal fat; and effects on lipids, vascular function, and bone metabolism.

DIAGNOSIS

- Menopause is determined retrospectively after 12 consecutive months of amenorrhea. FSH on day 2 or 3 of the menstrual cycle greater than 10 to 12 IU/L indicates diminished ovarian reserve.
- The diagnosis of menopause should include a comprehensive medical history and physical examination, complete blood count, and measurement of serum FSH. When ovarian function has ceased, serum FSH concentrations exceed 40 IU/L. Altered thyroid function and pregnancy must be excluded.

TREATMENT

- Goals of Treatment: The goals are to relieve symptoms, improve quality of life, and minimize medication adverse effects.
- Mild vasomotor and/or vaginal symptoms can often be alleviated by lowering the room temperature; decreasing intake of caffeine, spicy foods, and hot beverages; smoking cessation; exercise; and a healthy diet.
- Mild vaginal dryness can sometimes be relieved by nonestrogenic vaginal creams, but significant vaginal dryness often requires local or systemic estrogen therapy.
- **Figure 31–1** outlines the pharmacologic treatment of women with menopausal symptoms. Food and Drug Administration (FDA)-approved indications and contraindications for menopausal hormone therapy are shown in **Table 31–1**.

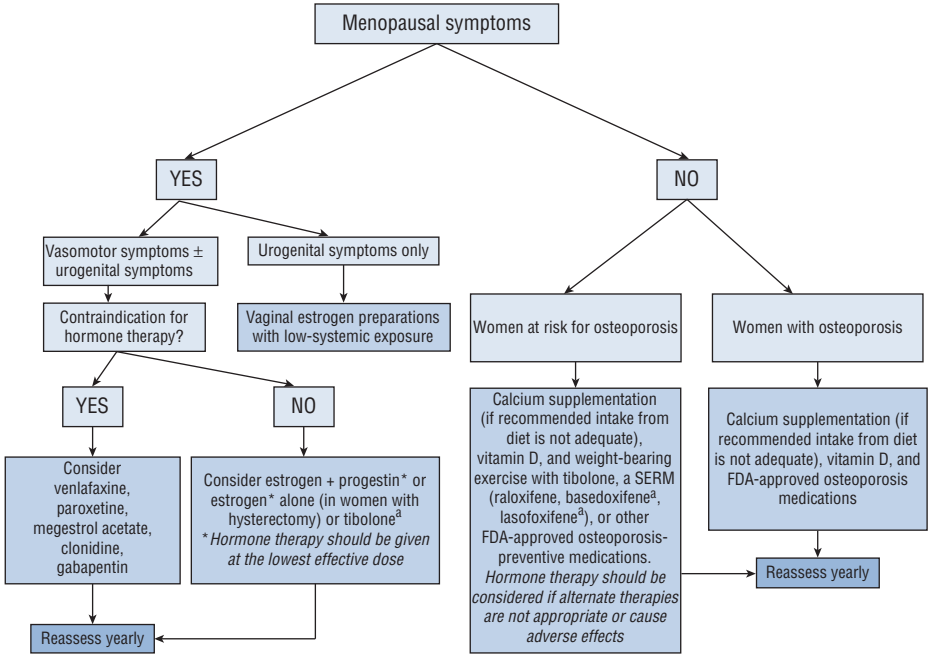


FIGURE 31–1. Algorithm for pharmacologic management of menopause symptoms. [a]Currently not available in the United States.

TABLE 31–1	FDA Indications and Contraindications for Menopausal Hormone Therapy with Estrogens and Progestins
Indications	
For systemic use	Treatment of moderate to severe vasomotor symptoms (i.e., moderate to severe hot flushes)
For intravaginal use (low systemic exposure)	Treatment of moderate to severe symptoms of vulvar and vaginal atrophy (i.e., moderate to severe vaginal dryness, dyspareunia, and atrophic vaginitis)
Contraindications	
Absolute contraindications	Undiagnosed abnormal genital bleeding Known, suspected, or history of cancer of the breast Known or suspected estrogen- or progesterone-dependent neoplasia Active deep vein thrombosis, pulmonary embolism, or a history of these conditions Active or recent (e.g., within the past year) arterial thromboembolic disease (e.g., stroke, myocardial infarction) Liver dysfunction or disease
Relative contraindications	Elevated blood pressure Hypertriglyceridemia Impaired liver function and past history of cholestatic jaundice Hypothyrodism Fluid retention Severe hypocalcemia Ovarian cancer Exacerbation of endometriosis Exacerbation of asthma, diabetes mellitus, migraine, systemic lupus erythematosus, epilepsy, porphyria, and hepatic hemangioma

- For women with hypertriglyceridemia, liver disease, or gallbladder disease, transdermal estrogen can be used, but oral estrogen should be avoided.
- Use hormone therapy at the lowest effective dose and for the shortest duration needed for symptom control.
- Approved indications for hormone therapy are vasomotor symptoms and urogenital atrophy. It is also indicated for prevention of osteoporotic fracture in postmenopausal women younger than 60 years who are at increased fracture risk when alternative therapies are contraindicated or cause adverse effects (see Chap. 3).
- As new data are continuously published, the most current guidelines should always be consulted.

HORMONE THERAPY

- Evidence-based guidelines for hormone therapy for menopausal symptoms are shown in **Table 31–2**.
- Systemic hormone therapy is the most effective treatment for moderate to severe vasomotor symptoms. For urogenital symptoms, such as vaginal dryness and dyspareunia, intravaginal estrogen cream, tablet, or ring should be considered before oral therapy. Ospemifene is another option. Intravaginal estrogen reduces the risk of recurrent urinary tract infections and may improve urge incontinence and overactive bladder.
- In women with an intact uterus, hormone therapy consists of an estrogen plus a progestogen. In women who have undergone hysterectomy, estrogen therapy is given unopposed by a progestogen. Most women with vasomotor symptoms need hormone treatment for less than 5 years. Concomitant progestogen therapy is unnecessary with low-dose micronized 17β-estradiol or estriol cream.

TABLE 31–2 Evidence-Based Hormone Therapy Guidelines for Menopausal Symptom Management

Recommendation	Recommendation Grade[a]
In the absence of contraindications, estrogen-based postmenopausal hormone therapy should be used for treatment of moderate to severe vasomotor symptoms	A1
Systemic or vaginal estrogen therapy should be used for treatment of urogenital symptoms and vaginal atrophy	A1
Postmenopausal women taking estrogen-based therapy should be followed up every year, taking into account findings from new clinical trials	A1
Postmenopausal women taking estrogen-based therapy should be informed about potential risks	A1
Safety and tolerability may vary substantially with the type and regimen of hormone therapy	B2
Breast cancer risk increases after use of continuous combined hormone therapy for longer than 5 years	A1
Breast cancer risk does not increase after long-term estrogen-only therapy (6.8 years) in postmenopausal women with hysterectomy	A1
Hormone therapy should not be used for primary or secondary prevention of coronary heart disease	A1
Oral hormone therapy increases risk of venous thromboembolism	A1
Nonoral hormone therapy may be safer for postmenopausal women at risk for venous thromboembolism who choose to take hormone therapy	B2
Oral hormone therapy increases risk of ischemic stroke	A1
Although hormone therapy decreases risk of osteoporotic fractures, it cannot be recommended as a first-line therapy for the treatment of osteoporosis	A1
Potential harm (cardiovascular disease, breast cancer, and thromboembolism) from long-term hormone therapy (use greater than 5 years) outweighs potential benefits	A1
Young women with primary ovarian insufficiency have severe menopausal symptoms and increased risk for osteoporosis and cardiovascular disease. Decisions on whether and how these young women must be treated should not be based on studies of hormone therapy in women older than 50 years	B3

Quality of evidence: 1, evidence from more than one properly randomized controlled trial; 2, evidence from more than one well-designed clinical trial with randomization from cohort or case-controlled analytic studies or multiple time series, or dramatic results from uncontrolled experiments; 3, evidence from opinions of respected authorities based on clinical experience, descriptive studies, or reports of expert communities.

[a] ***Strength of recommendations***: A, good evidence to support recommendation; B, moderate evidence to support recommendation; C, poor evidence to support recommendation.

- The **continuous combined oral estrogen–progestogen** arm of the Women's Health Initiative (WHI) study was terminated after a mean of 5.2-years follow-up because of the occurrence of a prespecified level of invasive breast cancer. This study also found increased coronary disease events, stroke, and pulmonary embolism. Beneficial effects included decreases in hip, spine, and wrist fracture and colorectal cancer.
- The oral estrogen-alone arm was stopped after a mean of 7-years follow-up. Estrogen-only therapy caused no increase in coronary heart disease risk or breast cancer risk, but the risk of stroke and hip fracture was increased.
- Women with vasomotor symptoms taking hormone therapy have better mental health and fewer depressive symptoms compared with those taking placebo, but hormone therapy may worsen quality of life in women without vasomotor symptoms.
- The WHI study found that postmenopausal women 65 years or older taking **estrogen plus progestogen** therapy had twice the rate of dementia, including Alzheimer's disease. Combined therapy did not prevent mild cognitive impairment.

Estrogens

- Estrogen products and doses for hormone therapy are shown in **Table 31–3**. The oral and transdermal routes are used most frequently. There is no evidence that one estrogen compound is more effective than another in relieving menopausal symptoms or preventing osteoporosis.
- **Conjugated equine estrogens** are composed of **estrone sulfate** (50%–60%) and other estrogens such as **equilin** and **17α-dihydroequilin**.
- **Estradiol** is the predominant and most active form of endogenous estrogens. Given orally, it is metabolized by the intestinal mucosa and liver (10% reaches the circulation as free estradiol), and resultant estrone concentrations are three to six times those of estradiol.
- **Ethinyl estradiol** is a semisynthetic estrogen that has similar activity following administration by the oral and parenteral routes.
- **Nonoral estrogens**, including transdermal, intranasal, and vaginal products, avoid first-pass metabolism and result in a more physiologic estradiol:estrone ratio (ie, estradiol concentrations greater than estrone concentrations). Transdermal estrogen is also less likely to affect sex hormone–binding globulin, circulating lipids, coagulation parameters, or C-reactive protein levels.
- Variability in absorption is common with the **percutaneous preparations** (gels, creams, and emulsions).
- **Estradiol pellets** contain pure **crystalline 17β-estradiol** and are placed subcutaneously into the anterior abdominal wall or buttock. They are difficult to remove.
- **Vaginal creams**, **tablets**, and **rings** are used for treatment of urogenital atrophy. Systemic estrogen absorption is lower with the vaginal tablets and rings (Estring), compared with the vaginal creams.
- New evidence indicates that lower doses of estrogens are effective in controlling postmenopausal symptoms and reducing bone loss. Lower doses of hormone therapy (conjugated estrogen equine 0.4 mg/day and medroxyprogesterone acetate 1.5 mg/day) showed equivalent symptom relief and bone density preservation without an increase in endometrial hyperplasia. Even ultralow doses of 17β-estradiol delivered by vaginal ring improved serum lipid profiles and prevented bone loss in elderly women.
- Adverse effects of **estrogen** include nausea, headache, breast tenderness, and heavy bleeding. More serious adverse effects include increased risk for coronary heart disease, stroke, venous thromboembolism, breast cancer, and gallbladder disease. Transdermal estrogen is less likely than oral estrogen to cause breast tenderness, gallbladder disease, and deep vein thrombosis.
- Current data suggest that phytoestrogens are no more effective than placebo for hot flushes or other menopausal symptoms. Further study is needed to clarify the effects of phytoestrogens on the breast, bone, and endometrium.

TABLE 31–3 Estrogen Products for Hormone Therapy

Drug	Brand Name[a]	Initial Dose/ Low Dose	Usual Dose Range	Comments
Systemic Estrogen Products (for the treatment of moderate and severe vasomotor symptoms ± urogenital symptoms)				
Oral estrogens[b]				
Conjugated equine estrogens	Premarin (once daily)	0.3 or 0.45 mg	0.3–1.25 mg	Dosage form available as 0.3, 0.45, 0.625, 0.9, 1.25 mg
Synthetic conjugated estrogens	Cenestin, Enjuvia (once daily)	0.3 mg	0.3–1.25 mg	Dosage form available as 0.3, 0.45, 0.625, 0.9, 1.25 mg
Esterified estrogens (75–85% estrone + 6–15% equilin)	Menest (once daily)	0.3 mg	0.3–2.5 mg	Administer 3 weeks on and 1 week off Dosage form available as 0.3, 0.625, 1.25, 2.5 mg
Estropipate (piperazine estrone sulfate)	Ogen, Ortho-Est, Generics (once daily)	0.75 mg	0.75–6 mg	Dosage form available as 0.75, 1, 5, 3, 6 mg
Estradiol acetate	Femtrace (once daily)	0.45 mg	0.45–1.8 mg	Dosage form available as 0.45, 0.9, 1.8 mg
Micronized 17 β-estradiol	Estrace Generics (once daily)	1 mg	1 or 2 mg	Administer 3 weeks on and 1 week off Dosage form available as 1, 2 mg
Transdermal estrogens patches				
17 β-estradiol	Alora (patch applied twice weekly)[c]	0.025 mg/day	0.025–0.1 mg/day	Dosage form available as 0.025, 0.05, 0.075, 0.1 mg/day
	Climara (patch applied once weekly)[c]	0.025 mg/day	0.025–0.1 mg/day	Dosage form available as 0.025, 0.0375, 0.05, 0.06, 0.075, 0.1 mg/day

(*continued*)

TABLE 31–3 Estrogen Products for Hormone Therapy (*Continued*)

Drug	Brand Name[a]	Initial Dose/ Low Dose	Usual Dose Range	Comments
	Menostar (patch applied once weekly)[c,d]	0.014 mg/day	0.014 mg/day	
	Estraderm (patch applied twice weekly)[c]	–	0.05 or 0.1 mg/day	Dosage form available as 0.05, 0.1 mg/day
	Vivelle, Vivelle Dot (patch applied twice weekly)[c]	0.025 mg/day	0.025–0.1 mg/day, 0.05 is standard dose	Dosage form available as 0.025, 0.0375, 0.05 (standard dose), 0.075, 0.1 mg/day
Other topical forms of estrogen				
17 β-estradiol topical emulsion	Estrasorb 0.25% emulsion (topical once daily)	–	Two pouches (which delivers 0.05 mg of estradiol per day)	Apply to legs
17 β-estradiol topical gel	EstroGel 0.06% metered-dose pump (topical once daily)	–	1.25 g/day (contains 0.75 mg estradiol)	Apply from wrist to shoulder
	Elestrin 0.06% metered-dose pump (topical once daily)		1–2 unit doses (1 unit dose: 0.87 g, which dose: 0.87 g, which contains 0.52 mg estradiol)	Apply to upper arm
	Divigel 0.1% (topical once daily)	0.25 g	0.25–1 g (provides 0.25–1 mg of estradiol)	Apply to upper thigh. Dosage form available as 0.25, 0.5, 1 g
17 β-estradiol transdermal spray	Evamist (topical once daily)	1 spray	2–3 sprays (1.53 mg of estradiol per spray)	Apply to inner surface of forearm
Implanted estrogens[e]				
Implanted 17 β-estradiol	Estradiol pellets implanted subcutaneously every 6 months	25 mg	50–100 mg	

Vaginal estrogens			
Estradiol acetate vaginal ring	Femring (intravaginally; replaced every 3 months)	12.4 mg ring	12.4, 24.8 mg ring (delivers 0.05 or 0.1 mg estradiol/day)
Intravaginal Estrogen Products (for the treatment of urogenital symptoms only/low systemic exposure)			
Conjugated equine estrogens (CEE) vaginal cream	Premarin		0.5–2 g/day (contains 0.625 mg CEE per g)
17 β-estradiol vaginal cream	Estrace		1 g/day (contains 0.1 mg estradiol per g)
17 β-estradiol vaginal ring	Estring (intravaginally; replaced every 90 days)		2 mg ring (delivers 0.0075 mg/day)
Estradiol hemihydrate vaginal tablet	Vagifem (intravaginally; twice weekly)	10 mcg	10 or 25 mcg

[a]United States brand names.
[b]Orally administered estrogens stimulate synthesis of hepatic proteins and increase circulating concentrations of sex hormone-binding globulin, which in turn may compromise the bioavailability of androgens and estrogens. Women with elevated triglyceride concentrations or significant liver function abnormalities are candidates for nonoral estrogen therapy.
[c]Do not apply estrogen patches on or near breasts. Avoid waistline as patch may rub off with tight-fitting clothing.
[d]FDA-approved for prevention of postmenopausal osteoporosis only.
[e]Not available in the United States.

TABLE 31–4 Progestogen Doses for Endometrial Protection (Oral Cyclic Administration)

Progestogen	Brand Name	Dosage
Dydrogesterone[a]	Duphaston	10–20 mg/day for 12–14 days per calendar month (oral dosage form available as 10 mg tablets)
Medroxyprogesterone acetate	Provera	5–10 mg/day for 12–14 days per calendar month (oral dosage form available as 2.5, 5, 10 mg tablets)
Micronized progesterone	Prometrium	200 mg/day for 12–14 days per calendar month (oral dosage form available as 100 and 200 mg tablets)
Norethindrone acetate	Aygestin[b]	5 mg/day for 12–14 days per calendar month (oral dosage form available as 2.5, 5 mg tablets)

[a]Not available in the United States.
[b]Not approved for postmenopausal hormone therapy in the United States.

Progestogens

- In women who have not undergone hysterectomy, a **progestogen** should be added because estrogen monotherapy is associated with endometrial hyperplasia and cancer.
- The most commonly used oral progestogens are **medroxyprogesterone acetate**, **micronized progesterone**, and **norethindrone** (also known as **norethisterone) acetate**.
- Several progestogen regimens to prevent endometrial hyperplasia are shown in **Table 31–4**. Four **combination estrogen–progestogen** regimens are shown in **Table 31–5**. Methods of administration include the following:
  - ✓ **Continuous-cyclic (sequential)** results in scheduled vaginal withdrawal bleeding in approximately 90% of women.
  - ✓ **Continuous-combined** prevents monthly bleeding. It may initially cause unpredictable spotting or bleeding.
  - ✓ **Continuous long-cycle (cyclic withdrawal)** reduces monthly bleeding. Estrogen is given daily, and progestogen is given six times yearly (every other month) for 12 to 14 days, resulting in six periods per year.
  - ✓ **Intermittent-combined (continuous-pulsed)** lowers the incidence of uterine bleeding. It consists of 3 days of estrogen therapy alone, followed by 3 days of combined estrogen and progestogen, which is then repeated without interruption. It causes fewer side effects than regimens with higher progestogen doses.
- Adverse effects of progestogens include irritability, headache, mood swings, fluid retention, and sleep disturbance.

ALTERNATIVE DRUG TREATMENTS

- Alternatives to estrogen treatment of hot flashes are shown in **Table 31–6**.
- For women with contraindications to hormone therapy, selective serotonin reuptake inhibitors and venlafaxine may be used, but lack of long-term efficacy and drug interactions may be problematic.

Androgens

- The therapeutic use of **testosterone** in women (**Table 31–7**), although controversial, is becoming more widespread, even in the absence of androgen deficiency. Testosterone, with or without estrogen, may improve the quality of the sexual experience in postmenopausal women.

TABLE 31–5 Common Combination Postmenopausal Hormone Therapy Regimens

Regimen	Brand Name	Dosage
Oral Regimens		
Conjugated equine estrogen (CEE) + medroxyprogesterone acetate (MPA)	Prempro (continuous)	0.625 mg/2.5 MPA, 0.625 mg/5 mg daily Low dose: 0.3 mg/1.5 mg, 0.45 mg/1.5 mg daily
	Premphase (continuous sequential)	0.625 mg CEE daily only in the first 2 weeks of a 4-week cycle then 0.625 mg daily CEE + 5 mg MPA daily in the last 2 weeks of a 4-week cycle
Ethinyl estradiol (EE) + norethindrone acetate (NETA)	Generic, Femhrt (continuous)	5 mcg EE/1 mg NETA daily Low dose (Femhrt only): 2.5 mcg EE/0.5 mg NETA daily
Estradiol (E) + drospirenone (DRSP)	Angeliq (continuous)	1 mg E/5 mg DRSP daily Low dose: 0.5 mg E/0.25 mg DRSP daily
Estradiol (E) + norgestimate	Prefest (estrogen/intermittent progestogen)	1 mg E daily for first 3 days then 1 mg E/0.09 mg norgestimate daily for next 3 days; this pattern is repeated continuously
Estradiol (E) + norethindrone acetate (NETA)	Activella (continuous)	1 mg E/0.5 mg NETA daily Low-dose: 0.5 mg E/0.1 mg NETA daily
	Mimvey (continuous)	1 mg E/0.5 mg NETA daily
Transdermal Regimens		
Estradiol + norethindrone acetate patch	CombiPatch (continuous)	Continuous: 0.05/0.14 mg, 0.05/0.25 mg (apply 1 patch twice weekly)
	CombiPatch (continuous sequential)	Continuous sequential: 0.05 mg of an estradiol only patch (apply 1 patch twice weekly) in the first 2 weeks of a 4-week cycle then either dose of the CombiPatch (apply 1 patch twice weekly) in the last 2 weeks of a 4-week cycle
Estradiol (E) + levonorgestrel patch	Climara Pro (continuous)	0.045 mg E/0.015 mg/day (apply 1 patch once weekly)

CEE, conjugated equine estrogen; DRSP, drospirenone; E, estradiol; EE, ethinyl estradiol; NETA, norethindrone acetate; MPA, medroxyprogesterone acetate.

- Absolute contraindications to androgen therapy include pregnancy or lactation and known or suspected androgen-dependent neoplasia. Relative contraindications include concurrent use of conjugated equine estrogens (for parenteral testosterone therapy), low sex hormone–binding globulin level, moderate to severe acne, clinical hirsutism, and androgenic alopecia.
- Adverse effects from excessive dosage include virilization, fluid retention, and potentially adverse lipoprotein lipid effects, which are more likely with oral administration. Long-term safety of testosterone in women is undetermined.

TABLE 31–6 Alternatives to Estrogen for Treatment of Hot Flushes[a]

Drug	Brand Name[b]	Initial Dose	Usual Dose Range	Comments
Tibolone[c]	Livial (not available in the United States)	2.5 mg	2.5 mg/day	Tibolone is not recommended during the perimenopause period because it may cause irregular bleeding
Venlafaxine	Effexor, Effexor XR	37.5 mg	37.5–150 mg/day	Adverse effects include nausea, headache, somnolence, dizziness, insomnia, nervousness, xerostomia, anorexia, constipation, diaphoresis, weakness, and hypertension
Desvenlafaxine	Pristiq	100–150 mg	100–150 mg/day	Adverse effects include nausea, headache, somnolence, dizziness, insomnia, xerostomia, anorexia, constipation, diaphoresis, and weakness
Paroxetine, paroxetine CR[d]	Brisdelle,e Paxil, Paxil CR, Pexeva	17.5 mg/day (paroxetine),[e] 10 mg/day (paroxetine), or 12.5 mg/day (paroxetine CR)	7.5 mg/day,[e] 10–20 mg/day or 12.5–25 mg/day	Adverse effects include nausea, somnolence, insomnia, headache, dizziness, xerostomia, constipation, diarrhea, weakness, and diaphoresis

Megestrol acetate	Megace	20 mg/day	20–40 mg/day	Progesterone may be linked to breast cancer etiology; also, there is concern regarding the safety of progestational agents in women with preexisting breast cancer
Clonidine	Catapres and generic tablets (oral) Catapres-TTS (transdermal) Kapvay tablets (extended release; oral)	0.1 mg/day	0.1 mg/day	Adverse effects include drowsiness, dizziness, hypotension, and dry mouth, especially with higher doses
Gabapentin	Gralise, Neurontin	300 mg at bedtime	900 mg/day (divided in three daily doses), doses up to 2,400 mg/day (divided in three daily doses) have been studied	Adverse effects include somnolence and dizziness; these symptoms often can be obviated with a gradual increase in dosing

CR, controlled release.

[a]Treatment of postmenopausal hot flushes is an off-label indication in the United States for all medications listed except for one formulation of paroxetine.
[b]United States brand names.
[c]Not available in the United States.
[d]Other selective serotonin reuptake inhibitors (e.g., citalopram, escitalopram, fluoxetine, and sertraline) have also been studied may also be used for the treatment of hot flushes.
[e]The brand Brisdelle contains 7.5 mg of paroxetine and is FDA-approved to treat moderate to severe vasomotor symptoms of menopause. This specific product is not FDA-approved for treating psychiatric conditions.

TABLE 31–7 Androgen Regimens Used for Women

Regimen	Brand Name	Usual Dose	Frequency	Comments
Methyltestosterone in combination with esterified estrogens	Covaryx	2.5 mg methyltestosterone + 1.25 mg esterified estrogens daily	Daily	Oral
	Covaryx HS	1.25 mg methyltestosterone + 0.625 mg esterified estrogens daily Both regimens given 3 weeks on and 1 week off		
Testosterone pellets[b]	Testopel	50 mg[c]	Every 6 months	Subcutaneous (implanted)
Transdermal testosterone system[a]	Intrinsa	150 or 300 mcg/day	Every 3–4 days	Transdermal patch

[a]Not available in the United States.
[b]Not approved for use in women in the United States.
[c]Only 75 mg pellets available in the United States.

Selective Estrogen Receptor Modulators

- These are nonsteroidal compounds that act as estrogen agonists in some tissues such as bone and as estrogen antagonists in other tissues such as breast through high-affinity binding to the estrogen receptor.
- **Tamoxifen** is an antagonist in breast tissue and an agonist on the bone and endometrium (see Chap. 60).
- **Raloxifene** is approved for prevention and treatment of postmenopausal osteoporosis and reduction in risk of invasive breast cancer in postmenopausal women with osteoporosis. The dose is 60 mg once daily. Third-generation selective estrogen receptor modulators (SERMs), bazedoxifene, and lasofoxifene have a similar efficacy and adverse effect profile. SERMs may worsen vasomotor symptoms and increase the risk of venous thromboembolism (see Chap. 3). Raloxifene use is associated with a lower incidence of breast cancer than placebo. It is as effective as tamoxifen in reducing risk of invasive breast cancer and has a lower risk of thromboembolic events.
- Ospemifene is recently approved for moderate to severe dyspareunia from menopausal vulvar and vaginal atrophy. It has a boxed warning for increased risk of endometrial cancer in women with a uterus who use estrogens without a progestin to reduce endometrial hyperplasia. It also increases risk of stroke and deep vein thrombosis in postmenopausal women who receive daily oral conjugated estrogens alone.

Tibolone

- **Tibolone** (unavailable in the United States) has combined estrogenic, progestogenic, and androgenic activity. Tibolone improves mood, libido, menopausal symptoms, and vaginal atrophy. It protects against bone loss and reduces the risk of vertebral fractures. It reduces total cholesterol, triglyceride, lipoprotein (a), but may decrease high-density lipoprotein concentrations. It decreases the risk of breast and colon cancer in women ages 60 to 85 years.

- Adverse effects include weight gain and bloating. It may increase the risk of stroke in elderly women. It is associated with breast cancer recurrence, and it may increase endometrial cancer risk.

RISKS OF HORMONE THERAPY

- Do not use postmenopausal hormone therapy to reduce the risk of coronary heart disease.
- The WHI trial showed an overall increase in the risk of coronary heart disease in healthy postmenopausal women ages 50 to 79 years taking **estrogen–progestogen therapy** compared with those taking placebo. The estrogen-alone arm of the WHI showed no effect (either increase or decrease) in the risk of coronary heart disease. Women who started hormone therapy 10 years or more after the time of menopause tended to have increased coronary heart disease risk compared with women who started therapy within 10 years of menopause.
- Women taking estrogen have a twofold increased risk for thromboembolic events, and oral administration increases the risk of venous thromboembolism compared to transdermal administration. Norpregnane progestogens appear to be thrombogenic. Avoid hormone therapy in women at high risk for thromboembolic events.
- In the WHI study, **estrogen plus progestogen therapy** had an increased risk for invasive breast cancer (appearing after 3 years of study participation), with a trend toward increasing risk with increasing duration of therapy. The estrogen-only arm of the WHI showed no increase in risk for breast cancer during the 7-year follow-up which persisted after discontinuation. The Million Women Study reported that current use of hormone therapy increased breast cancer risk and breast cancer mortality. Increased incidence was observed for **estrogen only**, **estrogen plus progestogen**, and **tibolone**. In a reanalysis of 51 studies, less than 5 years of therapy with **combined estrogen–progestogen** was associated with a 15% increase in risk for breast cancer, and the risk increased with greater duration of treatment. Five years after discontinuation of hormone replacement therapy, the risk of breast cancer was no longer increased. The addition of progestogen to estrogen may increase breast cancer risk beyond that observed with estrogen alone.
- **Estrogen alone** given to women with an intact uterus increases uterine cancer risk; this increased risk begins within 2 years of start of treatment and persists for many years after discontinuation. The sequential addition of **progestin** to estrogen for at least 10 days of the cycle or continuous combined estrogen–progestogen does not increase the risk of endometrial cancer. A 4-year trial of **raloxifene** in women with osteoporosis showed no increased risk of endometrial cancer.
- It appears that **combined hormone therapy** does not increase the risk of ovarian cancer, but the risk for postmenopausal women taking estrogen-only therapy for more than 10 years may be increased.
- Women taking **estrogen** or **combined estrogen–progestogen** hormone therapy are at increased risk for cholecystitis, cholelithiasis, and cholecystectomy. Transdermal estrogen is an alternative to oral therapy for women at high risk for cholelithiasis.

EVALUATION OF THERAPEUTIC OUTCOMES

- After initiating hormone therapy, follow-up at 6 weeks is advisable to assess efficacy, side effects, and patterns of withdrawal bleeding.
- With estrogen-based therapy, there should be yearly breast examinations, monthly breast self-examinations, and periodic mammograms. Women on hormone therapy should undergo annual monitoring, including pelvic examination, blood pressure checks, and routine endometrial cancer surveillance.
- Bone mineral density should be measured in women older than 65 years and in women younger than 65 years with risk factors for osteoporosis. Repeat testing should be done as clinically indicated.

- *Sequential therapy*: Perform transvaginal ultrasound, and where indicated an endometrial biopsy, if vaginal bleeding occurs at an unexpected time or when heavier or more prolonged withdrawal bleeding occurs.
- *Continuous combined therapy*: Consider endometrial evaluation when irregular bleeding persists for more than 6 months after initiating therapy.

See Chapter 65, Hormone Therapy in Women, authored by Sophia N. Kalantaridou, Devra K. Dang, and Karim Anton Calis, for a more detailed discussion of this topic.

CHAPTER 32

Pregnancy and Lactation: Therapeutic Considerations

- Resources on the use of drugs in pregnancy and lactation include the Food and Drug Administration (FDA) categorization system, the primary literature, tertiary compendia, textbooks, and computerized databases (eg, www.motherisk.org and www.toxnet.nlm.nih.gov).

PHYSIOLOGIC AND PHARMACOKINETIC FACTORS

- The duration of pregnancy is approximately 280 days (measured from the first day of the last menstrual period to birth). Pregnancy is divided into three periods of 3 calendar months (ie, trimesters).
- Drug absorption during pregnancy may be altered by delayed gastric emptying and vomiting. An increased gastric pH may affect absorption of weak acids and bases. Hepatic perfusion increases. Higher estrogen and progesterone levels may alter liver enzyme activity and increase elimination of some drugs but cause accumulation of others.
- Maternal plasma volume, cardiac output, and glomerular filtration increase by 30% to 50% or higher during pregnancy, possibly lowering the plasma concentration of renally cleared drugs. Body fat increases; thus volume of distribution of fat-soluble drugs may increase. Plasma albumin concentrations decrease; thus volume of distribution of highly protein bound drugs may increase. However, there may be little change in serum concentration, as these unbound drugs are more rapidly cleared by the liver and kidneys.
- The placenta is the organ of exchange between the mother and fetus for drugs. Drugs with molecular weights less than 500 Da transfer readily, drugs with molecular weights from 600 to 1000 Da cross more slowly, and drugs with molecular weights greater than 1000 Da (eg, insulin and heparin) do not cross in significant amounts.
- Lipophilic drugs (eg, opiates and antibiotics) cross more easily than do water-soluble drugs. Certain protein-bound drugs may achieve higher plasma concentrations in the fetus than in the mother.

DRUG SELECTION DURING PREGNANCY

- The incidence of congenital malformation is approximately 3% to 5%, and it is estimated that 1% of all birth defects are caused by medication exposure.
- Adverse effects on the fetus depend on drug dosage, route of administration, concomitant exposure to other agents, and stage of pregnancy when the exposure occurred.
- Fetal exposure to a teratogen in the first 2 weeks after conception may have an "all or nothing" effect (ie, could destroy the embryo or have no ill effect). Exposure during organogenesis (18–60 days postconception) may cause structural anomalies (eg, **methotrexate**, **cyclophosphamide**, **diethylstilbestrol**, **lithium**, **retinoids**, **thalidomide**, some **antiepileptic drugs [AEDs]**, and **coumarin derivatives**).
- Exposure after this point may result in growth retardation, central nervous system (CNS) or other abnormalities, or death. **Nonsteroidal anti-inflammatory drugs (NSAIDs)** and **tetracycline derivatives** are more likely to exhibit effects in the second or third trimester.
- Principles for drug use during pregnancy include (1) selecting drugs that have been used safely for a long time; (2) prescribing doses at the lower end of the dosing range; (3) eliminating nonessential medication and discouraging self-medication; and (4) avoiding medications known to be harmful.

PRECONCEPTION PLANNING

- Folic acid supplementation between 0.4 and 0.9 mg daily is recommended throughout the reproductive years to reduce the risk for neural tube defects in offspring. Women at high risk (eg, those who take certain seizure medications or who have had a previously affected pregnancy) should take 4 mg/day.
- Reduction in the use of alcohol, tobacco, and other substances prior to pregnancy improves outcomes. For smoking cessation, behavioral interventions are preferred. Use of **nicotine replacement therapy** during pregnancy is controversial; if used, intermittent delivery formulations (eg, gum) are preferred over patches. If patches are used, 16-hour patches are preferred over 24-hour patches.

PREGNANCY-INFLUENCED ISSUES

GASTROINTESTINAL TRACT

- Constipation commonly occurs during pregnancy. Institute education, physical exercise, and increased intake of dietary fiber and fluid. If additional therapy is warranted, give **supplemental fiber** and/or a stool softener. **Polyethylene glycol**, **lactulose**, **sorbitol**, and **magnesium** and **sodium salts** can be used intermittently short term. **Senna** and **bisacodyl** can be used occasionally. **Avoid castor oil** and **mineral oil**.
- Therapy for gastroesophageal reflux disease includes lifestyle and dietary modifications, for example, small, frequent meals; alcohol, tobacco, and caffeine avoidance; food avoidance 3 hours before bedtime; and elevation of the head of the bed. If necessary, initiate **aluminum**, **calcium**, or **magnesium antacids**; **sucralfate**; or **cimetidine** or **ranitidine**. Proton pump inhibitors are options if response to histamine 2 (H_2)–receptor blockers is inadequate. Avoid **sodium bicarbonate** and **magnesium trisilicate**.
- Therapy for hemorrhoids includes high intake of dietary fiber, adequate oral fluid intake, and use of sitz baths. If response is inadequate, laxatives and stool softeners can be used. Topical anesthetics, skin protectants, and astringents may help irritation and pain. Topical hydrocortisone may reduce inflammation and pruritus.
- Nonpharmacologic treatments for nausea and vomiting include eating small, frequent meals; avoiding fatty foods; and acupressure. Pharmacotherapy may include antihistamines (eg, **doxylamine**), **pyridoxine**, and **dopamine antagonists** (eg, **metoclopramide**). **Ondansetron** can be used when other agents have failed, and **ginger** is considered safe and effective. **Dexamethasone** and **prednisolone** have been effective for hyperemesis gravidarum (ie, severe nausea and vomiting causing weight loss >5% of prepregnancy weight, dehydration, and ketonuria), but the risk of oral clefts is increased.

GESTATIONAL DIABETES MELLITUS

- First-line therapy for all women with gestational diabetes mellitus (GDM) includes dietary modification and caloric restrictions for obese women. Daily self-monitoring of blood glucose is required. If nutritional intervention fails to achieve fasting plasma glucose levels of less than 90 to 99 mg/dL (5–5.5 mmol/L), 1-hour postprandial plasma glucose concentrations of 140 mg/dL or less (7.8 mmol/L), or 2-hour postprandial levels of less than 120 to 127 mg/dL (6.7–7 mmol/L), therapy with **recombinant human insulin** should be instituted; **glyburide** may be considered an alternative. Metformin may also be considered, but it crosses the placenta and is less studied.

HYPERTENSION

- Hypertension (HTN) during pregnancy includes gestational HTN (ie, HTN without proteinuria developing after 20 weeks' gestation), preeclampsia (ie, HTN with proteinuria), chronic HTN (preexisting HTN or developing before 20 weeks' gestation), and preeclampsia superimposed on chronic HTN. Eclampsia, a medical emergency, is preeclampsia with seizures. HTN in pregnancy is a diastolic blood pressure of 90 mm Hg or more based on the average of two or more measurements from the same arm.

- For women at risk for preeclampsia, low-dose **aspirin** (75–81 mg/day) after 12 weeks' gestation reduces the risk for preeclampsia by 17%. Aspirin also reduces the risk of preterm birth by 8% and fetal and neonatal death by 14%. **Calcium**, 1 to 2 g/day, decreases the relative risk of HTN by 30% and preeclampsia by 48%. Calcium, 1 g/day, is appropriate for all pregnant women.
- Antihypertensive drug therapy is discussed later under Chronic Illnesses in Pregnancy.
- **Magnesium sulfate** is used to decrease the risk of progression of preeclampsia to eclampsia and to treat eclamptic seizures. Avoid **diazepam** and **phenytoin**.

THYROID ABNORMALITIES

- Gestational transient thyrotoxicosis usually resolves by 20 weeks' gestation. Antithyroid medication is usually not needed.

VENOUS THROMBOEMBOLISM

- For treatment of acute thromboembolism during pregnancy, **low-molecular-weight heparin** is preferred over **unfractionated heparin**. Continue treatment throughout pregnancy and for 6 weeks after delivery. Duration of therapy should not be less than 3 months. Avoid **warfarin** because it may cause fetal bleeding, malformations of the nose, stippled epiphyses, or CNS anomalies.

ACUTE CARE ISSUES IN PREGNANCY

HEADACHE

- For tension and migraine headaches during pregnancy, first-line therapies are nonpharmacologic, including relaxation, stress management, and biofeedback.
- For tension headache, **acetaminophen** or **ibuprofen** can be used if necessary. All NSAIDs are contraindicated in the third trimester because of the potential for closure of the ductus arteriosus. Avoid aspirin in the third trimester, as it may also cause closure of the ductus arteriosus, maternal and fetal bleeding, and decreased uterine contractility. Opioids are rarely used.
- For migraine headache, acetaminophen and ibuprofen can be used. Opioids have been used, but they can contribute to nausea, and long-term use can cause neonatal withdrawal. For nonresponsive migraines, sumatriptan can be used. **Ergotamine** and **dihydroergotamine** are contraindicated. For migraine-associated nausea, promethazine, prochlorperazine, and metoclopramide can be used.
- For pregnant women with severe headaches (usually migraine) not responsive to other treatments, propranolol, at the lowest effective dose, can be used as preventive treatment. Alternatives include amitriptyline or nortriptyline, 10 to 25 mg daily by mouth.

URINARY TRACT INFECTION

- The principal infecting organism is *Escherichia coli*, but *Proteus mirabilis*, *Klebsiella pneumoniae*, and group B *Streptococcus* cause some infections. Untreated bacteriuria may result in pyelonephritis, preterm labor, preeclampsia, transient renal failure, and low birth weight.
- Treatment of asymptomatic bacteriuria is necessary to reduce the risk of pyelonephritis and premature delivery. Treatment for 7 to 14 days is common. Repeat urine cultures are recommended monthly for the remainder of gestation.
- **Cephalexin** is considered safe and effective for asymptomatic bacteriuria. *E. coli* resistance to ampicillin and amoxicillin is problematic. **Nitrofurantoin** is not active against *Proteus* and should not be used after week 37 due to concern for hemolytic anemia in the newborn. **Sulfa-containing drugs** may increase the risk for kernicterus in the newborn and should be avoided during the last weeks of gestation. **Folate antagonists**, such as **trimethoprim**, are relatively contraindicated during the first trimester because of their association with cardiovascular malformations.

Regionally, increased rates of *E. coli* resistance to trimethoprim-sulfa limit its use. **Fluoroquinolones** and **tetracyclines** are contraindicated.

SEXUALLY TRANSMITTED DISEASES

- Pharmacotherapy for selected sexually transmitted infections is shown in **Table 32–1**.
- Complications of *Chlamydia trachomatis* include pelvic inflammatory disease, ectopic pregnancy, and infertility. *Chlamydia* infection can be transmitted at birth to the neonate and cause conjunctivitis and a subacute, afebrile pneumonia.
- **Penicillin** is the drug of choice for syphilis, and it is effective for preventing transmission to the fetus and treating the already infected fetus.
- *Neisseria gonorrhoeae* is a risk factor for pelvic inflammatory disease and preterm delivery. Symptoms in the neonate (eg, rhinitis, vaginitis, urethritis, ophthalmia neonatorum, and sepsis) usually start within 2 to 5 days of birth. Blindness can occur.
- The overriding concern with genital herpes is transmission of the virus to the neonate during birth. Maternal use of **acyclovir** during the first trimester is not associated with an increased risk of birth defects. **Valacyclovir** is an alternative. For **famciclovir**, safety data are more limited.
- Bacterial vaginosis is a risk factor for premature rupture of membranes, preterm labor, preterm birth, intraamniotic infection, and postpartum endometritis.
- Data are conflicting concerning treating women at low risk for preterm labor.

CHRONIC ILLNESSES IN PREGNANCY

ALLERGIC RHINITIS AND ASTHMA

- Diagnosis and staging of asthma during pregnancy is the same as in nonpregnant women, but more frequent follow-up is necessary. The risks of medication use to the fetus are lower than the risks of untreated asthma.
- Treatment follows a six-step approach. As step 1, all pregnant patients with asthma should have access to a short-acting inhaled **β_2-agonist** (**albuterol** is the preferred agent).
- For persistent asthma (step 2 or higher), low, medium, or high doses of controller corticosteroids are foundational. Budesonide is preferred, but corticosteroids used before pregnancy can be continued. Long-acting **β_2-agonists** are safe.
- **Cromolyn**, **leukotriene receptor antagonists**, and **theophylline** are considered alternative agents, but they are not preferred.
- For patients with the most severe disease, systemic corticosteroids are recommended.
- First-line medications for allergic rhinitis during pregnancy include intranasal **corticosteroids**, **nasal cromolyn**, and first-generation antihistamines (eg, **chlorpheniramine** and **hydroxyzine**). **Intranasal corticosteroids** are the most effective treatment and have a low risk for systemic effect. **Beclomethasone** and **budesonide** have been used most. **Loratadine** and **cetirizine** do not appear to increase fetal risk, but they have not been extensively studied.
- Use of an external nasal dilator, short-term **topical oxymetazoline**, or **inhaled corticosteroids** may be preferred over oral decongestants, especially during early pregnancy.

DIABETES

- **Insulin** is the drug of choice for patients with type 1 or 2 diabetes during pregnancy. Switch women receiving insulin glargine or detemir to NPH insulin. **Glyburide** and **metformin** may be alternatives but are not recommended by the American Diabetic Association.
- Goals for self-monitoring of blood glucose are the same as for GDM.

EPILEPSY

- Major malformations are two to three times more likely in children born to women taking AEDs than to those who do not, but the risks of untreated epilepsy to the fetus are considered to be greater than those associated with the AEDs.

TABLE 32–1 Management of Sexually Transmitted Diseases in Pregnancy

STI	Drug Name (Brand Name)	Usual Dose	Monitoring	Comments
Bacterial vaginosis	*Recommended:* Metronidazole (Flagyl) *OR* Clindamycin (Cleocin)	 • 500 mg by mouth two times daily × 7 days • 250 mg by mouth three times daily × 7 days • 300 mg by mouth two times daily × 7 days	Follow-up testing not required if symptoms resolve	Vaginal preparations are not recommended because of the risk for subclinical upper-genital tract infection Intravaginal clindamycin during second half of pregnancy has caused low birth weight and neonatal infection
Chancroid	*Recommended:* Azithromycin (Zithromax) *OR* Ceftriaxone (Rocephin) *OR* Erythromycin base (Ery-Tab)	1 g by mouth × 1 dose 250 mg IM × 1 dose 500 mg by mouth three times daily × 7 days	Re-examine after 3 to 7 days; ulcer improvement should be noticeable by 3 days. Complete healing depends on the ulcer size	Test for HIV when chancroid is diagnosed. If negative, serologic testing for syphilis and HIV should occur 3 months after chancroid diagnosis
Chlamydia	*Recommended:* Azithromycin (Zithromax) *OR* Amoxicillin (Amoxil) *Alternatives*[a]*:* Erythromycin base Erythromycin ethylsuccinate	 1 g by mouth × 1 dose 500 mg by mouth three times daily × 7 days	Test-of-cure at 3 weeks after therapy completion (except if in first trimester, then retest after 3 months)	Gonorrheal coinfection common; both are treated concurrently Chlamydial infection is asymptomatic in men and women Women below age 25 years and those at high risk (e.g., multiple partners) should be retested in the third trimester
Gonorrhea	*Recommended:* Ceftriaxone (Rocephin) *PLUS* Azithromycin (Zithromax) *Alternative:* Cefixime (Suprax) *PLUS* Azithromycin (Zithromax)	 250 mg IM × 1 dose 1 g by mouth × 1 dose 400 mg by mouth × 1 dose 1 g by mouth × 1 dose	Because of high reinfection rate, repeat testing for gonorrhea 3 months after treatment. For alternative regimen, test-of-cure required in 1 week	Chlamydial coinfection common; both are treated concurrently Use alternative regimen only if ceftriaxone not available

(*continued*)

TABLE 32–1 Management of Sexually Transmitted Diseases in Pregnancy (*Continued*)

STI	Drug Name (Brand Name)	Usual Dose	Monitoring	Comments
Syphilis[b]				
Primary, secondary, early latent	*Recommended:* Benzathine penicillin G (Bicillin L-A)	2.4 million units IM × 1 dose	Nontreponemal serologic evaluation[c] at 6 and 12 months	For treatment failure or reinfection, use same drug and dose but increase to 3 weekly injections unless neurosyphilis is present
Tertiary, late latent	*Recommended:* Benzathine penicillin G (Bicillin L-A)	2.4 million units IM × 3 doses at 1-week intervals	Nontreponemal serologic evaluation[c] at 6, 12, and 24 months. CSF examination may be required	Use this regimen for late latent or latent syphilis of unknown duration
Neurosyphilis	*Recommended:* Aqueous penicillin G (Pfizerpen) *Alternative:* Procaine penicillin (Wycillin, Pfizerpen-AS) *PLUS* Probenecid	Three to four million units IV every 4 hours or continuous IV × 10-14 days 2.4 million units IM daily × 10-14 days 500 mg by mouth four times daily × 10-14 days	If initial elevation of leukocytes in CSF, repeat CSF every 6 months until normalization	Consider repeat treatment if CSF leukocytes or protein do not normalize after 2 years Use alternative regimen only if compliance can be ensured
Trichomoniasis	*Recommended:* Metronidazole	2 g by mouth × 1 dose	Consider rescreening patients at 3 months because of high reinfection rate	While tinidazole is an alternative for nonpregnant women, safe use during pregnancy is not well-studied

CSF, cerebrospinal fluid; IM, intramuscular; STI, sexually transmitted infection.
[a] Refer to reference 47 for specific dosing recommendations.
[b] Pregnant women with history of penicillin allergy should undergo penicillin desensitization as no proven alternatives exist.
[c] Nontreponemal evaluation consists of VDRL (Venereal Disease Research Laboratory) and RPR (rapid plasma regain).

- Major malformations with valproic acid therapy are dose related and range from 6.2% to 10.7%. When possible, avoid **valproic acid** during pregnancy to minimize the risk of neural tube defects, facial clefts, and cognitive teratogenicity.
- Rates of major malformations associated with monotherapy of other AEDs are 2.9% to 3.6%. Polytherapy is associated with higher rates.
- **Carbamazepine** and **lamotrigine** may be the safest AEDs for use in pregnancy.
- **Phenytoin**, **lamotrigine**, and **carbamazepine** may cause cleft palate, and **phenobarbital** may cause cardiac malformations.
- Drug therapy should be optimized prior to conception, and AED monotherapy is recommended when possible.
- If drug withdrawal is planned, it should be done at least 6 months prior to conception.
- All women with epilepsy should take **folic acid**, 4 to 5 mg daily, starting before pregnancy and continuing through at least the first trimester. The American Academy of Pediatrics recommends that all neonates receive vitamin K at delivery.

HUMAN IMMUNODEFICIENCY VIRUS INFECTION

- Pregnant women infected with human immunodeficiency virus (HIV) should receive antiretroviral (ARV) therapy to decrease the risk of perinatal transmission of HIV. ARV therapy is selected from those recommended for nonpregnant adults (with consideration given to the teratogenic profiles of each drug). Women already taking ARV therapy should continue their regimen when possible.
- Women taking **efavirenz** should continue it, as neural tube defects usually occur through weeks 5 to 6 of gestation, and pregnancy often is not recognized until weeks 4 to 6.
- For ARV-naïve women, use of a three-drug combination regimen is recommended and usually contains two nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs) with high transplacental passage (preferred: zidovudine, lamivudine; alternatives: emtricitabine, tenofovir, abacavir) along with a protease inhibitor (preferred: atazanavir plus low-dose ritonavir, lopinavir/ritonavir; alternative: darunavir or saquinavir, both with low-dose ritonavir). Nevirapine, a nonnucleoside reverse transcriptase inhibitor (NNRTI), can be used as an alternative to a protease inhibitor but is associated with severe rash and life-threatening or fatal hepatotoxicity.
- Some women who do not require immediate therapy may choose to delay ARV therapy until after the first trimester to avoid potential teratogenicity.
- For women with HIV, cesarean section before the onset of labor (usually at 39 weeks' gestation) is recommended to reduce the risk of perinatal HIV transmission. If maternal viral load is 400 copies/mL or more (400×10^3/L or greater) or not known, IV zidovudine should be initiated with a 1-hour loading dose (2 mg/kg) followed by a continuous infusion (1 mg/kg) for 2 hours (cesarean) or until delivery (for vaginal delivery). Zidovudine IV should still be administered in the presence of resistance to oral zidovudine. Women with a viral load below 400 copies/mL (400×10^3/L or less) near delivery do not require zidovudine IV but should continue their ARV regimen.

HYPERTENSION

- Severe HTN (systolic blood pressure [sBP] = ≥160 mm Hg or diastolic blood pressure [dBP] ≥ 110 mm Hg) can cause maternal complications, hospital admission, and potential premature delivery. Drug therapy is indicated for women with BP of 160/110 mm Hg or more. BP should be lowered by a maximum of 25% in the first minutes to 1 hour with further reduction to below 160/100 mm Hg over a period of hours. Commonly used agents are labetalol and hydralazine, but hydralazine causes more fetal adverse effects. Oral nifedipine may also be used.
- Treatment of nonsevere HTN (sBP 140–159 mm Hg or dBP 90–109 mm Hg) reduces risks of severe HTN by 50% but does not substantially affect fetal outcomes. In the United States, treatment is started at BPs of 150 to 160/100 to

110 mm Hg, with a goal of BP of less than 150/100 mm Hg. In Canada and the United Kingdom, the target goal is lower. No evidence exists for the superior efficacy of one antihypertensive agent versus another, but drugs commonly used include labetalol, methyldopa, and calcium channel blockers. β-Antagonists can be used except atenolol.

- **ACE inhibitors**, **angiotensin receptor antagonists**, and **renin inhibitors** are contraindicated throughout pregnancy.
- **Thiazide diuretics** can be used in women who were treated with them before pregnancy

DEPRESSION

- In general, monotherapy is preferred over polytherapy even if higher doses are required. If antidepressants are used, the lowest possible dose should be used for the shortest possible time to minimize adverse fetal and maternal pregnancy outcomes.
- In one study, pregnant women who stopped taking antidepressants were more likely to relapse than women who completed treatment.
- The **selective serotonin reuptake inhibitors (SSRIs)** are not considered major teratogens. **The serotonin/norepinephrine reuptake inhibitors (SNRIs)** are less well defined. Use of SSRIs and SNRIs in the latter part of pregnancy is associated with persistent pulmonary HTN of the newborn and prenatal antidepressant exposure syndrome (ie, cardiac, respiratory, neurologic, gastrointestinal [GI], and metabolic complications from drug toxicity or withdrawal of drug therapy). Tricyclic antidepressants are not considered major teratogens but have been associated with neonatal withdrawal syndrome when used late in pregnancy An epidemiologic study suggests that first-trimester use of **paroxetine** may be associated with a 1.5- to 2-fold increased risk for cardiac defects in the infant.

THYROID DISORDERS

- For hypothyroidism, give levothyroxine to attain a thyroid-stimulating hormone (TSH) of 0.1 to 2.5, 0.2 to 3, and 0.3 to 3 mIU/L in the first, second, and third trimesters, respectively. It can be started at 0.1 mg/day. Women receiving thyroid replacement therapy before pregnancy may require increased dosage during pregnancy. Monitor TSH levels every 4 weeks during the first half of pregnancy and at least once between 26 and 32 weeks of pregnancy to allow for dose titration.
- Hyperthyroidism therapy includes the thioamides (ie, methimazole, propylthiouracil [PTU]). Dose reductions are possible after attaining a euthyroid state. Some support a switch to PTU during the first trimester because of potential risks with methimazole followed by a subsequent switch to methimazole for the second and third trimesters to prevent hepatotoxicity from PTU. Iodine-131 is contraindicated. The goal of therapy is to attain free thyroxine concentrations near the upper limit of normal.

LABOR AND DELIVERY

PRETERM LABOR

- Preterm labor is labor that occurs between 20 and 37 weeks of gestation.

Tocolytic Therapy

- The goals of tocolytic therapy are to postpone delivery long enough to allow for maximum effect of antenatal steroids, for transportation of the mother to a facility equipped to deal with high-risk deliveries, and to prolong pregnancy when there are underlying self-limited conditions that can cause labor. Tocolytics can be started when there are regular uterine contractions with cervical change. Do not use them in cases of intrauterine fetal demise, a lethal fetal anomaly, intrauterine infection, fetal distress, severe preeclampsia, vaginal bleeding, or maternal hemodynamic instability.
- There are four classes of tocolytics: β-agonists (terbutaline and ritodrine [not available in the United States], **magnesium sulfate**, **NSAIDs**, and **calcium channel blockers**.

Prolongation of pregnancy with tocolytics is not associated with significant reduction in rates of respiratory distress syndrome or neonatal death.

- β-Agonists have a higher risk for maternal side effects. Terbutaline doses range from 250 to 500 mcg subcutaneously every 3 to 4 hours. The FDA cautions that **injectable terbutaline** should not be used to prevent preterm labor or treat it beyond 48 to 72 hours because of the risk for maternal death and heart problems, including cardiac arrhythmias, myocardial infarction, pulmonary edema, and tachycardia. Do not use terbutaline outside of the hospital. **Do not use oral terbutaline** for the prevention or treatment of preterm labor, as it has the same risks as the injectable form but has not been shown to be effective.
- A Cochrane review does not support the effectiveness of magnesium sulfate.
- **Nifedipine** is associated with fewer side effects than magnesium or β-agonists. Five to 10 mg nifedipine may be administered sublingually every 15 to 20 minutes for three doses. Once stabilized, 10 to 20 mg may be administered orally every 4 to 6 hours for preterm contractions. It can cause hypotension and a change in uteroplacental blood flow.
- Indomethacin, 50 to 100 mg orally or rectally, followed by 25 to 50 mg orally every 6 hours has been used. Premature constriction of the ductus arteriosus has been reported.

Antenatal Glucocorticoids

- A Cochrane review shows the benefit of antenatal **corticosteroids** for fetal lung maturation to prevent respiratory distress syndrome, intraventricular hemorrhage, and death in infants delivered prematurely.
- Current recommendations are **betamethasone**, 12 mg IM every 24 hours for two doses, or **dexamethasone**, 6 mg IM every 12 hours for four doses, to pregnant women between 26 and 34 weeks' gestation who are at risk for preterm delivery within the next 7 days. Benefits from antenatal glucocorticoid administration are believed to begin within 24 hours.

GROUP B *STREPTOCOCCUS* INFECTION

- Prenatal screening (vaginal/rectal cultures) for group B *Streptococcus* colonization of all pregnant women at 35 to 37 weeks' gestation is recommended. If cultures are positive, or if the woman had a previous infant with invasive group B *Streptococcus* disease, or if the woman had group B *Streptococcus* bacteriuria, antibiotics are given.
- The currently recommended regimen for group B *Streptococcus* disease is **penicillin G**, 5 million units IV, followed by 2.5 million units IV every 4 hours until delivery. Alternatives include **ampicillin**, 2 g IV, followed by 1 g IV every 4 hours; **cefazolin**, 2 g IV, followed by 1 g every 8 hours; **clindamycin**, 900 mg IV every 8 hours; or **erythromycin**, 500 mg IV every 6 hours. In penicillin-allergic women in whom sensitivity testing shows resistance to clindamycin and erythromycin, **vancomycin**, 1 g IV every 12 hours until delivery, can be used.

CERVICAL RIPENING AND LABOR INDUCTION

- Prostaglandin E_2 analogues (eg, **dinoprostone [Prepidil gel** and **Cervidil vaginal insert]**) are commonly used for cervical ripening. Fetal heart rate monitoring is required when Cervidil is used. **Misoprostol**, a prostaglandin E_1 analogue, is effective and inexpensive, but it has been associated with uterine rupture.
- **Oxytocin** is the most commonly used agent for labor induction after cervical ripening.

LABOR ANALGESIA

- The IV or IM administration of narcotics is commonly used for pain associated with labor. Compared with epidural analgesia, parenteral opioids are associated with lower rates of oxytocin augmentation, shorter stages of labor, and fewer instrumental deliveries.
- Epidural analgesia involves administering an opioid and/or an anesthetic (eg, fentanyl and/or bupivacaine) through a catheter into the epidural space to provide pain relief. Epidural analgesia is associated with longer stages of labor, more instrumental

deliveries, and maternal fever compared to parenteral narcotic analgesia. Patient-controlled epidural analgesia results in a lower total dose of local anesthetic. Complications of epidural analgesia include hypotension, nausea, vomiting, itching, and urinary retention.
- Other options for labor analgesia include spinal analgesia and nerve blocks.

LACTATION ISSUES

DRUG USE DURING LACTATION

- Medications enter breast milk via passive diffusion of nonionized and non–protein-bound medication. Drugs with high molecular weights, lower lipid solubility, and higher protein binding are less likely to cross into breast milk, or they transfer more slowly or in smaller amounts. The higher the maternal serum concentration of drug, the higher the concentration will be in breast milk. Drugs with longer half-lives are more likely to maintain higher levels in breast milk. The timing and frequency of feedings and the amount of milk ingested by the infant are also important.
- Strategies for reducing infant risk from drugs transferred into breast milk include selecting medications for the mother that would be considered safe for use in the infant and choosing medications with shorter half-lives, higher protein binding, lower bioavailability, and lower lipid solubility.

RELACTATION

- For relactation use **metoclopramide**, 10 mg three times daily for 7 to 14 days only if nondrug therapy is ineffective.

See Chapter 61, Pregnancy and Lactation: Therapeutic Considerations, authored by Kristina E. Ward and Barbara M. O'Brien, for a more detailed discussion of this topic.

Edited by Cecily V. DiPiro

CHAPTER 33

Anemias

- *Anemias* are a group of diseases characterized by a decrease in hemoglobin (Hb) or red blood cells (RBCs), resulting in decreased oxygen-carrying capacity of blood. The World Health Organization defines anemia as Hb less than 13 g/dL (<130 g/L; <8.07 mmol/L) in men or less than 12 g/dL (<120 g/L; <7.45 mmol/L) in women.

PATHOPHYSIOLOGY

- The functional classification of anemias is found in **Fig. 33–1**. The most common anemias are included in this chapter.
- Morphologic classifications are based on cell size. Macrocytic cells are larger than normal and are associated with deficiencies of vitamin B_{12} or folic acid. Microcytic cells are smaller than normal and are associated with iron deficiency, whereas normocytic anemia may be associated with recent blood loss or chronic disease.
- Iron-deficiency anemia (IDA) can be caused by inadequate dietary intake, inadequate gastrointestinal (GI) absorption, increased iron demand (eg, pregnancy), blood loss, and chronic diseases.
- Vitamin B_{12}– and folic acid–deficiency anemias can be caused by inadequate dietary intake, decreased absorption, and inadequate utilization. Deficiency of intrinsic factor causes decreased absorption of vitamin B_{12} (ie, pernicious anemia). Folic acid–deficiency anemia can be caused by hyperutilization due to pregnancy, hemolytic anemia, myelofibrosis, malignancy, chronic inflammatory disorders, long-term dialysis, or growth spurt. Drugs can cause anemia by reducing absorption of folate (eg, **phenytoin**) or through folate antagonism (eg, **methotrexate**).
- Anemia of inflammation (AI) is a newer term used to describe both anemia of chronic disease and anemia of critical illness. AI is a hypoproliferative anemia that traditionally has been associated with infectious or inflammatory processes, tissue injury, and conditions associated with release of proinflammatory cytokines. See **Table 33–1** for diseases associated with AI. For information on anemia of chronic kidney disease, see Chap. 74.
- Age-related reductions in bone marrow reserve can render elderly patients more susceptible to anemia caused by multiple minor and often unrecognized diseases (eg, nutritional deficiencies) that negatively affect erythropoiesis.
- Pediatric anemias are often due to a primary hematologic abnormality. The risk of IDA is increased by rapid growth spurts and dietary deficiency.

CLINICAL PRESENTATION

- Signs and symptoms depend on rate of development and age and cardiovascular status of the patient. Acute-onset anemia is characterized by cardiorespiratory symptoms such as tachycardia, light-headedness, and breathlessness. Chronic anemia is characterized by weakness, fatigue, headache, symptoms of heart failure, vertigo, faintness, cold sensitivity, pallor, and loss of skin tone.
- IDA is characterized by glossal pain, smooth tongue, reduced salivary flow, pica (compulsive eating of nonfood items), and pagophagia (compulsive eating of ice) seen when Hb concentration is less than 9 g/dL (<90 g/L; <5.59 mmol/L).
- Neurologic effects (eg, numbness and ataxia) of vitamin B_{12} deficiency may occur in absence of anemia. Psychiatric findings, including irritability, depression, and

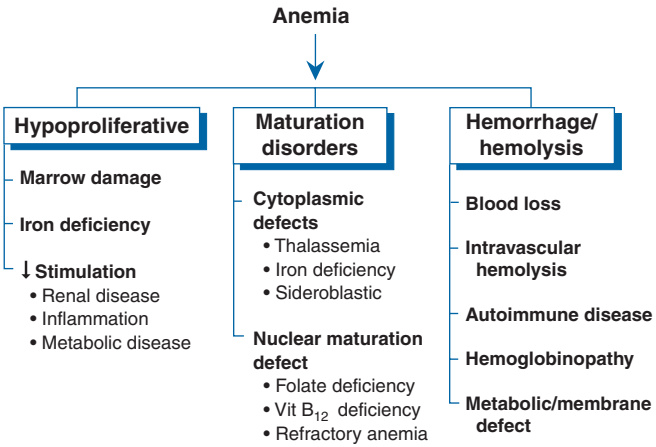


FIGURE 33–1. Functional classification of anemia. Each of the major categories of anemia (hypoproliferative, maturation disorders, and hemorrhage/hemolysis) can be further subclassified according to the functional defect in the several components of normal erythropoiesis.

TABLE 33–1 Diseases Causing Anemia of Inflammation

Common causes
Chronic infections
Tuberculosis
Other chronic lung infections (e.g., lung abscess, bronchiectasis)
Human immunodeficiency virus
Subacute bacterial endocarditis
Osteomyelitis
Chronic urinary tract infections
Chronic inflammation
Rheumatoid arthritis
Systemic lupus erythematosus
Inflammatory bowel disease
Inflammatory osteoarthritis
Gout
Other (collagen vascular) diseases
Chronic inflammatory liver diseases
Malignancies
Carcinoma
Lymphoma
Leukemia
Multiple myeloma
Less common causes
Alcoholic liver disease
Congestive heart failure
Thrombophlebitis
Chronic obstructive pulmonary disease
Ischemic heart disease

memory impairment, may also occur with vitamin B_{12} deficiency. Anemia with folate deficiency is not associated with neurologic or psychiatric symptoms.

DIAGNOSIS

- Rapid diagnosis is essential because anemia is often a sign of underlying pathology.
- Initial evaluation of anemia involves a complete blood cell count (CBC), reticulocyte index, and examination of the stool for occult blood. **Figure 33–2** shows a broad, general algorithm for the diagnosis of anemia based on laboratory data.
- The earliest and most sensitive laboratory change for IDA is decreased serum ferritin (storage iron), which should be interpreted in conjunction with decreased transferrin saturation and increased total iron-binding capacity (TIBC). Hb, hematocrit (Hct), and RBC indices usually remain normal until later stages of IDA.
- In macrocytic anemias, mean corpuscular volume is usually elevated to greater than 100 fL. Vitamin B_{12} and folate concentrations can be measured to differentiate between the two deficiency anemias. A vitamin B_{12} value less than 150 pg/mL (<111 pmol/L), together with appropriate peripheral smear and clinical symptoms, is diagnostic of vitamin B_{12}–deficiency anemia. A decreased RBC folate concentration (<150 ng/mL [<340 nmol/L]) appears to be a better indicator of folate-deficiency anemia than a decreased serum folate concentration (<3 ng/mL [<7 nmol/L]).

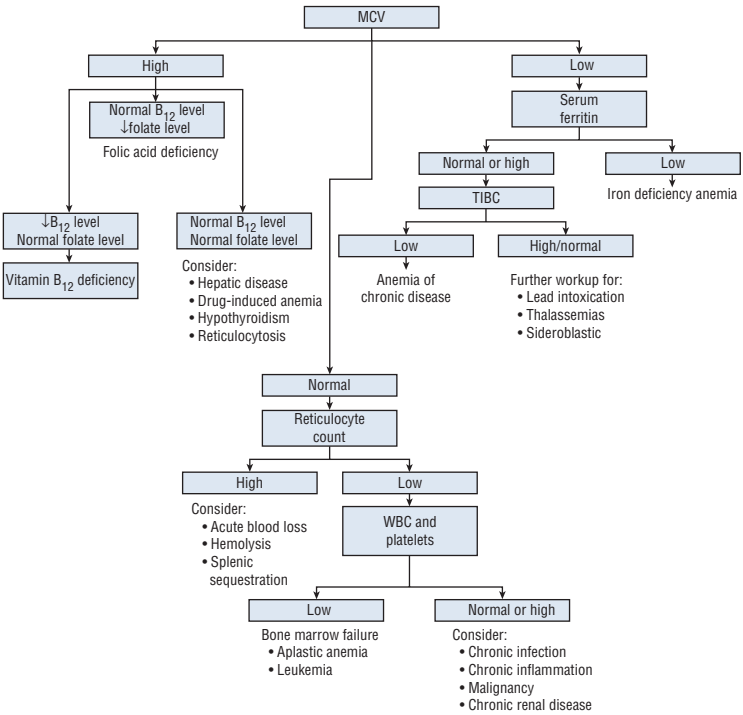


FIGURE 33–2. General algorithm for diagnosis of anemias. (↓, decreased; MCV, mean corpuscular volume; TIBC, total iron-binding capacity; WBC, white blood cells.)

- The diagnosis of AI is usually one of exclusion, with consideration of coexisting iron and folate deficiencies. Serum iron is usually decreased, but, unlike IDA, serum ferritin is normal or increased, and TIBC is decreased. The bone marrow reveals an abundance of iron; the peripheral smear reveals normocytic anemia.
- Elderly patients with symptoms of anemia should undergo a CBC with peripheral smear and reticulocyte count and other laboratory studies as needed to determine the etiology of anemia.
- The diagnosis of anemia in pediatric populations requires use of age- and gender-adjusted norms for laboratory values.

TREATMENT

- Goals of Treatment: The goals are to alleviate signs and symptoms, correct the underlying etiology (eg, restore substrates needed for RBC production), replace body stores, and prevent recurrence of anemia.

IRON-DEFICIENCY ANEMIA

- **Oral iron** therapy with soluble ferrous iron salts, which are not enteric coated and not slow- or sustained-release, is recommended at a daily dosage of 200 mg elemental iron in two or three divided doses (**Table 33–2**).
- Iron is poorly absorbed from vegetables, grain products, dairy products, and eggs, and best absorbed from meat, fish, and poultry. Administer iron at least 1 hour before meals because food interferes with absorption, but administration with food may be needed to improve tolerability.
- Consider **parenteral iron** for patients with iron malabsorption, intolerance of oral iron therapy, or noncompliance. Parenteral administration, however, does not hasten the onset of hematologic response. The replacement dose depends on the etiology of anemia and Hb concentration (**Table 33–3**).
- **Iron dextran**, **sodium ferric gluconate**, **ferumoxytol**, and **iron sucrose** are available parenteral iron preparations with similar efficacy but different molecular size, pharmacokinetics, bioavailability, and adverse effect profiles (**Table 33–4**).

VITAMIN B_{12}–DEFICIENCY ANEMIA

- Oral vitamin B_{12} supplementation appears to be as effective as parenteral, even in patients with pernicious anemia, because the alternate vitamin B_{12} absorption pathway is independent of intrinsic factor. Initiate oral **cobalamin** at 1 to 2 mg daily for 1 to 2 weeks, followed by 1 mg daily.
- Parenteral therapy acts more rapidly than oral therapy and is recommended if neurologic symptoms are present. A popular regimen is IM **cyanocobalamin**, 1000 mcg

TABLE 33–2 Oral Iron Products

Iron Salt	Percent Elemental Iron	Common: Formulations and Elemental Iron Provided
Ferrous sulfate	20	60–65 mg/324–325 mg tablet 60 mg/5 mL syrup 44 mg/5 mL elixir 15 mg/1 mL
Ferrous sulfate (exsiccated)	30	65 mg/200 mg tablet 50 mg/160 mg tablet
Ferrous gluconate	12	38 mg/325 mg tablet 28–29 mg/240–246 mg tablet
Ferrous fumarate	33	66 mg/200 mg tablet 106 mg/324–325 mg tablet

TABLE 33–3 Equations for Calculating Doses of Parenteral Iron

In patients with IDA

Adults and children >15 kg (33 lb)

Dose (mL) = 0.0442 (desired Hb − observed Hb) × LBW + (0.26 × LBW)

LBW males = 50 kg + (2.3 × [inches over 5 ft])

LBW females = 45.5 kg + (2.3 × [inches over 5 ft])

Children 5–15 kg (11–33 lb)

Dose (mL) = 0.0442 (desired Hb − observed Hb) × W + (0.26 × W)

In patients with anemia secondary to blood loss (hemorrhagic diathesis or long-term dialysis)

mg of iron = blood loss × Hct

where blood loss is in milliliters and Hct is expressed as a decimal fraction

Hb, hemoglobin; Hct, hematocrit; IDA, iron-deficiency anemia; LBW, lean body weight; W, weight.

daily for 1 week, then weekly for 1 month, and then monthly. Initiate daily oral administration after symptoms resolve.

FOLATE-DEFICIENCY ANEMIA

- Oral **folate**, 1 mg daily for 4 months, is usually sufficient for treatment of folic acid–deficiency anemia, unless the etiology cannot be corrected. If malabsorption is present, a dose of 1 to 5 mg daily may be necessary.

ANEMIA OF INFLAMMATION

- Treatment of anemia of inflammation (AI) is less specific than that of other anemias and should focus on correcting reversible causes. Reserve iron therapy for an established IDA; iron is not effective when inflammation is present. RBC transfusions are effective but should be limited to episodes of inadequate oxygen transport and Hb of 8 to 10 g/dL (80–100 g/L; 4.97–6.21 mmol/L).
- **Erythropoiesis-stimulating agents (ESAs)** can be considered, but response can be impaired in patients with AI (off-label use). The initial dosage for **epoetin alfa** is 50 to 100 units/kg three times weekly and **darbepoetin alfa** 0.45 mcg/kg once weekly. ESA use may result in iron deficiency. Many practitioners routinely supplement ESA therapy with oral iron therapy.
- Potential toxicities of exogenous ESA administration include increases in blood pressure, nausea, headache, fever, bone pain, and fatigue. Hb must be monitored during ESA therapy. An increase in Hb greater than 12 g/dL (>120 g/L; >7.45 mmol/L) with treatment or a rise of greater than 1 g/dL (>10 g/L; >0.62 mmol/L) every 2 weeks has been associated with increased mortality and cardiovascular events.
- In patients with anemia of critical illness, parenteral iron is often used but is associated with a theoretical risk of infection. Routine use of ESAs or RBC transfusions is not supported by clinical studies.

ANEMIA IN PEDIATRIC POPULATIONS

- Anemia of prematurity is usually treated with RBC transfusions. ESA use is controversial because it has not been shown to clearly reduce transfusion requirements.
- Infants aged 9 to 12 months: administer iron sulfate 3 mg/kg (elemental iron) once or twice daily between meals for 4 weeks. Continue for 2 additional months in responders to replace storage iron pools. The dose and schedule of vitamin B_{12} should be titrated according to the clinical and laboratory response. The daily dose of folate is 1 to 3 mg.

TABLE 33–4 Comparison of Parenteral Iron Preparations

Drug	Brand Name/ Molecular Weight	Amount of Elemental Iron	Usual Adult Dose	Indication	IM Injection	Common Adverse Effects
Ferumoxytol	Feraheme: 750,000 Da	30 mg/mL	Initial 510 mg IV followed by 510 mg IV 3–8 days later (rate 30 mg/s)	Treatment of IDA for adults with chronic kidney disease	No	Hypersensitivity reactions, diarrhea, constipation, nausea, dizziness, hypotension, and peripheral edema
Iron dextran	InFeD: 165,000 Da Dexferrum: 265,000 Da	50 mg/mL	See Table 33–3; Daily dosages should be limited to 100 mg iron (rate not to exceed 50 mg/min) Must administer 0.5 mL test dose and observe 1 hour	Treatment of iron deficiency when oral therapy is infeasible or ineffective	Yes—Z track method	Black box warning: anaphylactic reactions Pain and brown staining at injection site, flushing, hypotension, fever, chills, myalgia, anaphylaxis
Iron sucrose	Venofer: 34,000– 60,000 Da	20 mg/mL	Hemodialysis: 100 mg during consecutive dialysis session to 1,000 mg (10 doses) Nondialysis: 200 mg on five different occasions within 14 days (total dose 1000 mg) See the package insert for specific rates Monitor during and at least 30 minutes postdose for anaphylactic reactions	Treatment of IDA for patients with chronic kidney, nondialysis and dialysis dependent	No	Anaphylactic reactions, hypotension, hypertension, nausea, muscle cramps, headaches, upper respiratory infection, edema, dizziness
Sodium ferric gluconate	Ferrlecit: 289,000–444,000 Da	12.5 mg/mL	125 mg elemental iron per dialysis session Most require cumulative dose of 1 g over the eight dialysis session for a favorable response Monitor during and at least 30 minutes postdose for anaphylactic reactions	Treatment of IDA in patients undergoing hemodialysis in conjunction with erythropoietin therapy	No	Hypersensitivity reactions (including anaphylactic reactions), hypotension, hypertension, headache, dizziness, nausea, vomiting, diarrhea, injection site reactions, muscle cramps, dyspnea, chest pain

EVALUATION OF THERAPEUTIC OUTCOMES

- IDA: Positive response to oral iron therapy characterized by modest reticulocytosis in a few days with an increase in Hb seen at 2 weeks. Reevaluate the patient if reticulocytosis does not occur. Hb should return to normal after 2 months; continue iron therapy until iron stores are replenished and serum ferritin normalized (up to 12 months).
- Megaloblastic anemia: Signs and symptoms usually improve within a few days after starting vitamin B_{12} or folate therapy. Neurologic symptoms can take longer to improve or can be irreversible, but should not progress during therapy. Reticulocytosis should occur within 3 to 5 days. Hb begins to rise a week after starting vitamin B_{12} therapy and should normalize in 1 to 2 months. Hct should rise within 2 weeks after starting folate therapy and should normalize within 2 months.
- ESAs: Reticulocytosis should occur within a few days. Monitor iron, TIBC, transferrin saturation, and ferritin levels at baseline and periodically during therapy. The optimal form and schedule of iron supplementation are unknown. Discontinue ESAs if a clinical response does not occur after 8 weeks.
- Pediatrics: Monitor Hb, Hct, and RBC indices 6 to 8 weeks after initiation of iron therapy. Monitor Hb or Hct weekly in premature infants.

See Chapter 80, Anemias, authored by Kristen Cook, and William L. Lyons, for a more detailed discussion of this topic.

Sickle Cell Disease

CHAPTER 34

- *Sickle cell syndromes*, which can be divided into sickle cell trait (SCT) and sickle cell disease (SCD), are hereditary conditions characterized by the presence of sickle hemoglobin (HbS) in red blood cells (RBCs).
- SCT is the heterozygous inheritance of one normal β-globin gene producing hemoglobin A (HbA) and one sickle gene producing HbS (HbAS) gene. Individuals with SCT are asymptomatic.
- SCD can be of homozygous or compounded heterozygous inheritance. Homozygous HbS (HbSS) has historically been referred to as sickle cell anemia (SCA).

PATHOPHYSIOLOGY

- Clinical manifestations of SCD are due to impaired circulation, RBC destruction, and stasis of blood flow attributed to disturbances in RBC polymerization and to membrane damage. Additional contributing factors include functional asplenia (and increased risk of bacterial infection), deficient opsonization, and coagulation abnormalities.
- Polymerization allows deoxygenated hemoglobin to exist as a semisolid gel that protrudes into the cell membrane, distorting RBCs into sickle shapes. Sickle-shaped RBCs increase blood viscosity and encourage sludging in the capillaries and small vessels, leading to local tissue hypoxia that accentuates the pathologic process.
- Repeated cycles of sickling, upon deoxygenation, and unsickling, upon oxygenation, damage the RBC membrane and cause irreversible sickling. Rigid, sickled RBCs are easily trapped, resulting in shortened circulatory survival and chronic hemolysis.

CLINICAL PRESENTATION

- SCD involves multiple organ systems. Clinical manifestations depend on the genotype (**Table 34–1**).
- Cardinal features of SCD are hemolytic anemia and vasoocclusion. Symptoms are delayed until 4 to 6 months of age when HbS replaces fetal hemoglobin (HbF). Common findings include pain with fever, pneumonia, splenomegaly, and, in infants, pain and swelling of the hands and feet (eg, hand-and-foot syndrome or dactylitis).
- Usual clinical signs and symptoms of SCD include chronic anemia; fever; pallor; arthralgia; scleral icterus; abdominal pain; weakness; anorexia; fatigue; enlarged liver, spleen, and heart; and hematuria.
- Acute complications of SCD include fever and infection (eg, sepsis caused by encapsulated pathogens such as *Streptococcus pneumoniae*), stroke, acute chest syndrome, and priapism. Acute chest syndrome is characterized by pulmonary infiltration, respiratory symptoms, and equivocal response to antibiotic therapy.
- Sickle cell crisis can be precipitated by infection, dehydration, stresses, and sudden temperature changes. The most common type is vasoocclusive crisis, which is manifested by pain over the involved areas without change in Hb. Aplastic crisis is characterized by acute decrease in Hb with decreased reticulocyte count manifested as fatigue, dyspnea, pallor, and tachycardia. Splenic sequestration crisis is a massive enlargement of the spleen, leading to hypotension, shock, and sudden death in young children. Repeated infarctions lead to autosplenectomy; therefore, incidence declines as adolescence approaches.
- Chronic complications involve many organs and include pulmonary hypertension, bone and joint destruction, ocular problems, cholelithiasis, cardiovascular abnormalities, depression, and hematuria and other renal complications. Children experience delayed growth and sexual maturation.
- Patients with SCT are usually asymptomatic, except for rare painless hematuria.

TABLE 34–1 Clinical Features of SCT and Common Types of SCD

Type	Clinical Features
SCT	Rare painless hematuria; normal Hb level; heavy exercise under extreme conditions can provoke gross hematuria and complications
SCA-HbSS	Pain crises, microvascular disruption of organs (spleen, liver, bone marrow, kidney, brain, and lung), gallstones, priapism, leg ulcers, anemia (Hb 7–10 g/dL [70–100 g/L; 4.34–6.21 mmol/L])
HbSC	Painless hematuria and rare aseptic necrosis of bone; vasoocclusive crises are less common and occur later in life; other complications are ocular disease and pregnancy-related problems; mild anemia (Hb 10–12 g/dL [100–120 g/L; 6.21–7.45 mmol/L])
HbSβ^+-thal	Rare crises; milder severity than SCD because of production of HbA; Hb 10–14 g/dL (100–140 g/L; 6.21–8.69 mmol/L) with microcytosis
HbSβ^0-thal	No HbA production; severity similar to SCA; Hb 7–10 g/dL (70–100 g/L; 4.34–6.21 mmol/L) with microcytosis

Hb, hemoglobin; HbA, hemoglobin A; HbSβ^+-thal, sickle cell β^+-thalassemia; HbSβ^0-thal, sickle cell β^0-thalassemia; HbSC, sickle cell hemoglobin C; HbSS, homozygous sickle cell hemoglobin; SCA, sickle cell anemia; SCD, sickle cell disease; SCT, sickle cell trait.

DIAGNOSIS

- SCD is usually identified by routine neonatal screening programs using isoelectric focusing, high-performance liquid chromatography, or electrophoresis.
- Laboratory findings include low hemoglobin; increased reticulocyte, platelet, and white blood cell counts; and sickle forms on the peripheral smear.

TREATMENT

- Goals of Treatment: The goals are to reduce hospitalizations, complications, and mortality.

GENERAL PRINCIPLES

- Patients with SCD require lifelong multidisciplinary care. Interventions include general measures, preventive strategies, and treatment of complications and acute crises.
- Routine immunizations plus influenza, meningococcal, and pneumococcal vaccinations are recommended.
- Prophylactic **penicillin** is recommended until 5 years of age. Beginning at age 2 months or earlier, the dosage is penicillin V potassium, 125 mg orally twice daily until 3 years of age and then 250 mg twice daily until age 5 years, or benzathine penicillin, 600,000 units intramuscularly every 4 weeks from age 6 months to 6 years.
- **Folic acid**, 1 mg daily, is recommended in adult patients, pregnant women, and patients of all ages with chronic hemolysis.

FETAL HEMOGLOBIN INDUCERS

- HbF directly effects polymer formation. Increases in HbF correlate with decreased RBC sickling and adhesion. Patients with low HbF levels have more frequent crises and higher mortality.
- **Hydroxyurea**, a chemotherapeutic agent, has many effects on blood cells, including the stimulation of HbF production. It is indicated for patients with frequent painful episodes, severe symptomatic anemia, acute chest syndrome, or other severe vasoocclusive complications. The starting dose is 15 mg/kg as a single daily dose (**Fig. 34–1**).

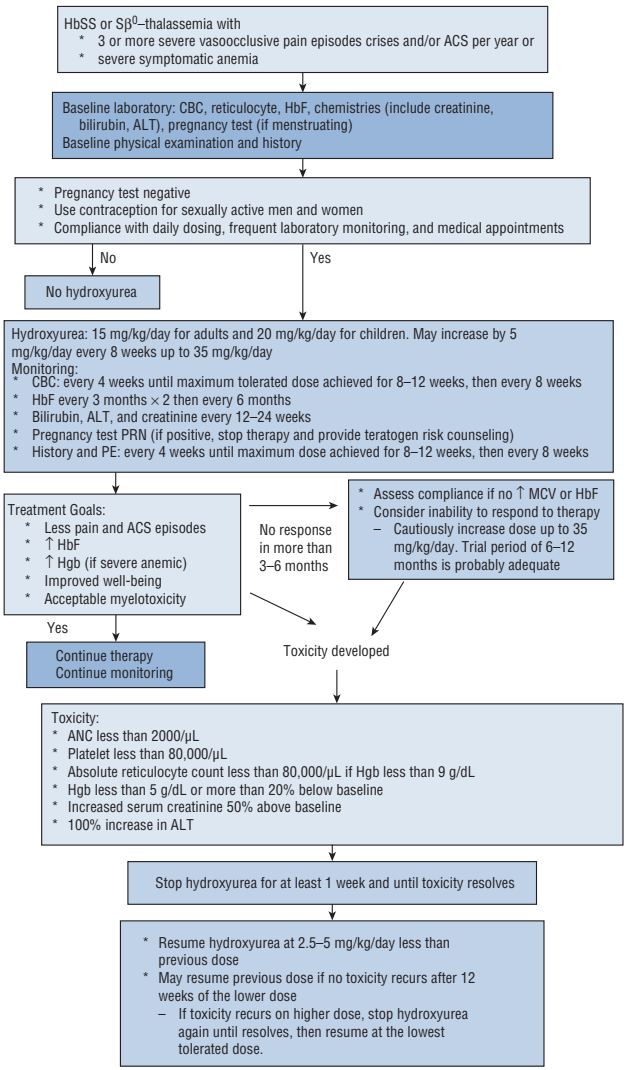


FIGURE 34–1. Hydroxyurea use in sickle cell disease (SCD). (ACS, acute chest syndrome; ALT, alanine aminotransferase; ANC, absolute neutrophil count; CBC, complete blood cell count; Hb, hemoglobin; HbF, fetal hemoglobin; HbSS, homozygous sickle cell hemoglobin; HbSSβ^0, sickle cell β^0-thalassemia; MCV, mean corpuscular volume; PE, physical examination; PRN, as needed; RBC, red blood cell.) (*From McCavit TL. Sickle cell disease. Pediatr Rev 2012;33:195–204, quiz 5–6; Ware RE, Argun B. Hematology. Am Soc Hematol Educ Program 2009;2009:62–69; Wang WC, Ware RE, Miller ST, et al. Hydroxycarbamide in very young children with sickle-cell anaemia: a multicentre, randomised, controlled trial (BABY HUG). Lancet 2011;377:1663–1672; Ballas SK, McCarthy WF, Guo N, et al. Exposure to hydroxyurea and pregnancy outcomes in patients with sickle cell anemia. J Natl Med Assoc 2009;101:1046–1051; and Heeney MM, Ware RE. Hydroxyurea for children with sickle cell disease. Hematol Oncol Clin North Am 2010;24:199–214.*)

- The use of **5-aza-2-deoxycytidine (decitabine)** is being investigated in adults who do not respond to hydroxyurea.
- Chronic transfusions are indicated for primary and secondary stroke prevention in children. Transfusions are usually given every 3 to 4 weeks or as needed to maintain desired HbS levels. The optimal duration is unknown. Risks include alloimmunization, hyperviscosity, viral transmission (requiring hepatitis A and B vaccination), volume and iron overload, and transfusion reactions.
- Allogeneic hematopoietic stem cell transplantation is the only curative therapy for SCD. The best candidates are younger than 16 years, have severe complications, and have human leukocyte antigen–matched donors. Risks must be carefully considered and include mortality, graft rejection, and secondary malignancies.

TREATMENT OF COMPLICATIONS

- Educate patients to recognize conditions that require urgent evaluation. Balanced fluid status and oxygen saturation of at least 92% are important to avoid exacerbation during acute illness.
- RBC transfusions are indicated for acute exacerbation of baseline anemia (eg, aplastic crisis, hepatic or splenic sequestration, or severe hemolysis), severe vasoocclusive episodes, and procedures requiring general anesthesia or ionic contrast. Transfusions can be useful in patients with complicated obstetric problems, refractory leg ulcers, or refractory and protracted painful episodes.
- Promptly evaluate fever of 38.5°C (101.3°F) or higher. Empiric antibiotic therapy should provide coverage against encapsulated organisms (eg, **ceftriaxone** for outpatients and **cefotaxime** for inpatients).
- Initiate incentive spirometry; appropriate fluid therapy; broad-spectrum antibiotics, including a **macrolide** or **quinolone**; and, for hypoxia or acute distress, oxygen therapy in acute chest syndrome. Steroids and nitric oxide are being evaluated.
- Priapism has been treated with analgesics, antianxiety agents, and vasoconstrictors to force blood out of the corpus cavernosum (eg, **phenylephrine** and **epinephrine**), and vasodilators to relax smooth muscle (eg, **terbutaline** and **hydralazine**).

TREATMENT OF SICKLE CELL CRISIS

- Treatment of *aplastic crisis* is primarily supportive. Blood transfusions may be indicated for severe or symptomatic anemia.
- Treatment options for *splenic sequestration* include observation alone, especially for adults because they tend to have milder episodes; chronic transfusion to delay splenectomy; and splenectomy after a life-threatening crisis, after repetitive episodes, or for chronic hypersplenism.
- Hydration and analgesics are mainstays of treatment for *vasoocclusive (painful) crisis*. Administer fluids IV or orally at 1 to 1.5 times the maintenance requirement; monitor closely to avoid volume overload. Consider an infectious etiology and initiate empiric therapy if indicated.
- Tailor analgesic therapy to the individual because of the variable frequency and severity of pain. Pain scales should be used to quantify the degree of pain.
- Use **nonsteroidal anti-inflammatory drugs (NSAIDs)** or **acetaminophen** for mild to moderate pain. Manage mild to moderate pain in the outpatient setting with weak opioids such as **codeine** or **hydrocodone**.
- Treat severe pain aggressively with an opioid, such as **morphine**, **hydromorphone**, **fentanyl**, or **methadone**. **Meperidine** should be avoided because accumulation of the normeperidine metabolite can cause neurotoxicity, especially in patients with impaired renal function.
- Treat severe pain with an IV opioid titrated to pain relief and then administered on a scheduled basis with as-needed dosing for breakthrough pain. Patient-controlled analgesia is commonly utilized.

- Suspicion of addiction commonly leads to suboptimal pain control. Factors that minimize dependence include aggressive pain control, frequent monitoring, and tapering medication according to response.

EVALUATION OF THERAPEUTIC OUTCOMES

- Evaluate patients on a regular basis to establish baseline symptoms, monitor changes, and provide age-appropriate education.
- Evaluate CBC and reticulocyte counts every 3 to 6 months up to 2 years of age, then every 6 to 12 months. Screen HbF level annually. Evaluate renal, hepatobiliary, and pulmonary function annually. Screen patients for retinopathy.
- Assess efficacy of hydroxyurea by monitoring the number, severity, and duration of sickle cell crises.

See Chapter 82, Sickle Cell Disease, authored by C. Y. Jennifer Chan and Melissa Frei-Jones, for a more detailed discussion of this topic.

CHAPTER 35

Antimicrobial Regimen Selection

- A systematic approach to the selection and evaluation of an antimicrobial regimen is shown in **Table 35–1**. An "empiric" antimicrobial regimen is begun before the offending organism is identified and sometimes before the documentation of the presence of infection, whereas a "definitive" regimen is instituted when the causative organism is known.

CONFIRMING THE PRESENCE OF INFECTION

FEVER

- *Fever* is defined as a controlled elevation of body temperature above the expected 37°C (98.6°F) (measured orally) and is a manifestation of many disease states other than infection.
- Many drugs have been identified as causes of fever. Drug-induced fever is defined as persistent fever in the absence of infection or other underlying condition. The fever must coincide temporally with the administration of the offending agent and disappear promptly upon its withdrawal, after which the temperature remains normal.

SIGNS AND SYMPTOMS

White Blood Cell Count

- Most infections result in elevated white blood cell (WBC) counts (leukocytosis) because of the mobilization of granulocytes and/or lymphocytes to destroy invading microbes. Normal values for WBC counts are between 4000 and 10,000 cells/mm^3.
- Bacterial infections are associated with elevated granulocyte counts (neutrophils and basophils), often with increased numbers of immature forms (band neutrophils) seen in peripheral blood smears (left-shift). With infection, peripheral leukocyte counts may be high, but they are rarely higher than 30,000 to 10,000 cells/mm^3 (4×10^9 and 10×10^9/L). Low neutrophil counts (neutropenia) after the onset of infection indicate an abnormal response and are generally associated with a poor prognosis for bacterial infection.
- Relative lymphocytosis, even with normal or slightly elevated total WBC counts, is generally associated with tuberculosis and viral or fungal infections. Many types of infections, however, may be accompanied by a completely normal WBC count and differential.

Pain and Inflammation

- Pain and inflammation may accompany infection and are sometimes manifested by swelling, erythema, tenderness, and purulent drainage. Unfortunately, these signs may be apparent only if the infection is superficial or in a bone or joint.
- The manifestations of inflammation with deep-seated infections such as meningitis, pneumonia, endocarditis, and urinary tract infection must be ascertained by examining tissues or fluids. For example, the presence of polymorphonuclear leukocytes (neutrophils) in spinal fluid, lung secretions (sputum), and urine is highly suggestive of bacterial infection.

TABLE 35–1	Systematic Approach for Selection of Antimicrobials
Confirm the presence of infection	
	Careful history and physical
	Signs and symptoms
	Predisposing factors
Identify the pathogen	
	Collection of infected material
	Stains
	Serologies
	Culture and sensitivity
Select the presumptive therapy considering every infected site	
	Host factors
	Drug factors
Monitor therapeutic response	
	Clinical assessment
	Laboratory tests
	Assess therapeutic failure

IDENTIFICATION OF THE PATHOGEN

- Infected body materials must be sampled, if at all possible or practical, before the institution of antimicrobial therapy. A Gram stain of the material may reveal bacteria, or an acid-fast stain may detect mycobacteria or actinomycetes. A delay in obtaining infected fluids or tissues until after therapy is started may result in false-negative culture results or alterations in the cellular and chemical composition of infected fluids.
- Blood cultures should be performed in the acutely ill, febrile patient. Less accessible fluids or tissues are obtained when needed to assess localized signs or symptoms (eg, spinal fluid in meningitis and joint fluid in arthritis). Abscesses and cellulitic areas should also be aspirated.
- Caution must be used in the evaluation of positive culture results from normally sterile sites (eg, blood, cerebrospinal fluid [CSF], and joint fluid). The recovery of bacteria normally found on the skin in large quantities (eg, coagulase-negative staphylococci and diphtheroids) from one of these sites may be a result of contamination of the specimen rather than a true infection.

SELECTION OF PRESUMPTIVE THERAPY

- A variety of factors must be considered to select rational antimicrobial therapy, including the severity and acuity of the disease, host factors, factors related to the drugs used, and the necessity for use of multiple agents.
- The drugs of choice for the treatment of most pathogens are compiled from a variety of sources and are intended as guidelines rather than specific rules for antimicrobial use (**Table 35–2**).
- When antimicrobial regimens are selected, local susceptibility data should be considered whenever possible rather than information published by other institutions or national compilations.

HOST FACTORS

- When a patient for initial or empiric therapy is evaluated, the following factors should be considered:
  - ✓ Allergy or history of adverse drug reactions.
  - ✓ Age of patient.

TABLE 35–2 Drugs of Choice, First Choice, and Alternative(s)

GRAM-POSITIVE COCCI

Enterococcus faecalis (generally not as resistant to antibiotics as *Enterococcus faecium*)

- Serious infection (endocarditis, meningitis, pyelonephritis with bacteremia)
  - Ampicillin (or penicillin G) + (gentamicin or streptomycin)
  - Vancomycin + (gentamicin or streptomycin), daptomycin, linezolid, telavancin, tigecycline[a]
- Urinary tract infection
  - Ampicillin, amoxicillin
  - *Fosfomycin* or *nitrofurantoin*

E. faecium (generally more resistant to antibiotics than *E. faecalis*)

- Recommend consultation with infectious disease specialist.
  - Linezolid, quinupristin/dalfopristin, daptomycin, tigecycline[a]

Staphylococcus aureus / *Staphylococcus epidermidis*

- Methicillin (oxacillin)-sensitive
  - Nafcillin or oxacillin
  - FGC,[b,c] *trimethoprim–sulfamethoxazole, clindamycin, BL/BLI*[d]
- Hospital-acquired methicillin (oxacillin)–resistant
  - Vancomycin ± (gentamicin or rifampin)
  - *Daptomycin, linezolid, telavancin, tigecycline, trimethoprim–sulfamethoxazole , or quinupristin–dalfopristin*
- Community-acquired methicillin (oxacillin)–resistant
  - Clindamycin, trimethoprim–sulfamethoxazole, doxycycline[a]
  - *Daptomycin, linezolid, telavancin, tigecycline,[a] or vancomycin*

Streptococcus (groups A, B, C, G, and *Streptococcus bovis*)

- Penicillin G or V or ampicillin
- *FGC,[b,c] erythromycin, azithromycin, clarithromycin*

Streptococcus pneumoniae

- Penicillin-sensitive (minimal inhibitory concentration [MIC] <0.1 mcg/mL [mg/L])
  - Penicillin G or V or ampicillin
  - *FGC,[b,c] doxycycline,[a] azithromycin, clarithromycin, erythromycin*
- Penicillin intermediate (MIC 0.1 to 1 mcg/mL [mg/L])
  - High-dose penicillin (12 million units/day for adults) or ceftriaxone c or cefotaxime[c]
  - *Levofloxacin,[a] moxifl oxacin,[a] gemifl oxacin,[a] or vancomycin*
- Penicillin-resistant (MIC ≥1.0 mcg/mL [mg/L])
  - Recommend consultation with infectious disease specialist.
    - *Vancomycin ± rifampin*
    - *Per sensitivities: cefotaxime, ceftriaxone,[c] levofloxacin,[a] moxifloxacin,[a] or gemifloxacin[a]*

Streptococcus, viridans group

- Penicillin G ± gentamicin[e]
- *Cefotaxime,[c] ceftriaxone,[c] erythromycin, azithromycin, clarithromycin, or vancomycin ± gentamicin*

GRAM-NEGATIVE COCCI

Moraxella (Branhamella) catarrhalis

- Amoxicillin–clavulanate, ampicillin–sulbactam
- *Trimethoprim–sulfamethoxazole, erythromycin, azithromycin, clarithromycin, doxycycline,[a] SGC,[c,f] cefotaxime,[c] ceftriaxone,[c] or TGCPO*[c,g]

(continued)

TABLE 35–2 Drugs of Choice, First Choice, and Alternative(s) (*Continued*)

Neisseria gonorrhoeae (also give concomitant treatment for Chlamydia trachomatis)
- Disseminated gonococcal infection
  - Ceftriaxone[c] or cefotaxime[c]
  - *Oral follow-up: cefpodoxime,[c] ciprofloxacin,[a] or levofloxacin[a]*
- Uncomplicated infection
  - Ceftriaxone,[c] cefotaxime,[c] or cefpodoxime[c]
  - *Ciprofloxacin[a] or levofloxacin[a]*

Neisseria meningitides
- Penicillin G
- *Cefotaxime[c] or ceftriaxone[c]*

GRAM-POSITIVE BACILLI

Clostridium perfringens
- Penicillin G ± clindamycin
- *Metronidazole,[a] clindamycin, doxycycline,[a] cefazolin,[c] carbapenem[h,i]*

Clostridium difficile
- Oral metronidazole[a]
- Oral *vancomycin*

GRAM-NEGATIVE BACILLI

Acinetobacter spp.
- Doripenem, imipenem, or meropenem ± aminoglycoside[j] (amikacin usually most effective)
- *Ampicillin–sulbactam, colistin,[i] or tigecycline[a]*

Bacteroides fragilis (and others)
- *Metronidazole[a]*
- *BL/BLI,[d] clindamycin, cefoxitin,[c] cefotetan,[c] or carbapenem[h,i]*

Enterobacter spp.
- Carbapenem[h] or cefepime ± aminoglycoside[j]
- *Ciprofloxacin,[a] levofl oxacin,[a] piperacillin–tazobactam, ticarcillin–clavulanate*

Escherichia coli
- Meningitis
  - Cefotaxime,[c] ceftriaxone,[c] meropenem
- Systemic infection
  - Cefotaxime[c] or ceftriaxone[c]
  - *BL/BLI,[d] fluoroquinolone,[a,k] carbapenem[h,i]*
- Urinary tract infection
  - Most oral agents: check sensitivities
  - Ampicillin, amoxicillin–clavulanate, doxycycline,[a] or cephalexin[c]
  - *Aminoglycoside,[j] FGC,[b,c] nitrofurantoin, fluoroquinolone[a,k]*

Gardnerella vaginalis
- Metronidazole[a]
- *Clindamycin*

Haemophilus influenzae
- Meningitis
  - Cefotaxime[c] or ceftriaxone[c]
  - *Meropenem[i]*
- Other infections
  - BL/BLI,[d] or if β-lactamase-negative, ampicillin or amoxicillin
  - *Trimethoprim–sulfamethoxazole, cefuroxime,[c] azithromycin, clarithromycin, or fluoroquinolone[a,k]*

TABLE 35–2 Drugs of Choice, First Choice, and Alternative(s) (*Continued*)

Klebsiella pneumoniae
- BL/BLI,[d] cefotaxime,[c] ceftriaxone,[c] cefepime[c]
- Carbapenem,[h,i] fluoroquinolone[a,k]

Legionella spp.
- Azithromycin, erythromycin ± rifampin, or fluoroquinolone[a,k]
- Trimethoprim–sulfamethoxazole, clarithromycin, or doxycycline[a]

Pasteurella multocida
- Penicillin G, ampicillin, amoxicillin
- *Doxycycline, a BL/BLI,[d] trimethoprim–sulfamethoxazole or ceftriaxone[c]*

Proteus mirabilis
- Ampicillin
- *Trimethoprim–sulfamethoxazole*

Proteus (indole-positive) (including *Providencia rettgeri* , *Morganella morganii* , and *Proteus vulgaris*)
- Cefotaxime,[c] ceftriaxone,[c] or fluoroquinolone[a,k]
- *BL/BLI,[d] aztreonam,[l] aminoglycosides,[j] carbapenem[h,i]*

Providencia stuartii
- Amikacin, cefotaxime,[c] ceftriaxone,[c] fluoroquinolone[a,k]
- *Trimethoprim–sulfamethoxazole, aztreonam,[l] carbapenem[h,i]*

Pseudomonas aeruginosa
- Urinary tract infection only
  - Aminoglycoside[j]
  - Ciprofloxacin,[a] levofloxacin[a]
- Systemic infection
  - Cefepime,[c] ceftazidime,[c] doripenem,[i] imipenem,[i] meropenem,[i] piperacillin–tazobactam, or ticarcillin–clavulanate + aminoglycoside[j]
  - *Aztreonam,[l] ciprofloxacin,[a] levofloxacin,[a] colistin[j]*

Salmonella typhi
- Ciprofloxacin,[a] levofloxacin,[c] ceftriaxone,[c] cefotaxime[c]
- *Trimethoprim–sulfamethoxazole*

Serratia marcescens
- Ceftriaxone,[c] cefotaxime,[c] cefepime,[c] ciprofloxacin,[a] levofloxacin[a]
- *Aztreonam,[l] carbapenem,[h,i] piperacillin–tazobactam, ticarcillin– clavulanate*

Stenotrophomonas (Xanthomonas) maltophilia (generally very resistant to all antimicrobials)
- Trimethoprim–sulfamethoxazole.
- *Check sensitivities to ceftazidime,[c] doxycycline,[a] minocycline,[a] and ticarcillin–clavulanate.*

MISCELLANEOUS MICROORGANISMS

Chlamydia pneumoniae
- Doxycycline[a]
- *Azithromycin, clarithromycin, erythromycin, or fluoroquinolone[a,k]*

C. trachomatis
- Azithromycin or doxycycline[a]
- *Levofloxacin,[a] erythromycin*

Mycoplasma pneumoniae
- Azithromycin, clarithromycin, erythromycin, fluoroquinolone[a,k]
- *Doxycycline[a]*

(*continued*)

TABLE 35–2 Drugs of Choice, First Choice, and Alternative(s) (*Continued*)

SPIROCHETES

Treponema pallidum
- Neurosyphilis
  - Penicillin G
  - *Ceftriaxone*[c]
- *Primary or secondary*
  - Benzathine, penicillin G
  - *Ceftriaxone*[c] *or doxycycline*[a]

Borrelia burgdorferi (choice depends on stage of disease)
- Ceftriaxone[c] or cefuroxime axetil,[c] doxycycline,[a] amoxicillin
- *High-dose penicillin, cefotaxime*[c]

[a]Not for use in pregnant patients or children.
[b]First-generation cephalosporins—IV: cefazolin; orally: cephalexin, cephradine, or cefadroxil.
[c]Some penicillin-allergic patients may react to cephalosporins.
[d]β-Lactam/β-lactamase inhibitor combination—IV: ampicillin–sulbactam, piperacillin–tazobactam, and ticarcillin–clavulanate; orally: amoxicillin–clavulanate.
[e]Gentamicin should be added if tolerance or moderately susceptible (MIC > 0.1 mcg/mL [mg/L]) organisms are encountered; streptomycin is used but can be more toxic.
[f]Second-generation cephalosporins—IV: cefuroxime; orally: cefaclor, cefditoren, cefprozil, cefuroxime axetil, and loracarbef.
[g]Third-generation cephalosporins—orally: cefdinir, cefixime, cefetamet, cefpodoxime proxetil, and ceftibuten.
[h]Carbapenem: doripenem, ertapenem, imipenem/cilastatin, and meropenem.
[i]Reserve for serious infection.
[j]Aminoglycosides: gentamicin, tobramycin, and amikacin; use per sensitivities.
[k]Fluoroquinolones IV/orally: ciprofloxacin, levofloxacin, and moxifloxacin.
[l]Generally reserved for patients with hypersensitivity reactions to penicillin

- ✓ Pregnancy.
- ✓ Metabolic or genetic variation.
- ✓ *Renal and hepatic function*: Patients with diminished renal and/or hepatic function will accumulate certain drugs unless the dosage is adjusted.
- ✓ *Concomitant drug therapy*: Any concomitant therapy the patient is receiving may influence the selection of drug therapy, the dose, and monitoring. A list of selected drug interactions involving antimicrobials is provided in **Table 35–3**.
- ✓ Concomitant disease states.

DRUG FACTORS

- Integration of both pharmacokinetic and pharmacodynamic properties of an agent is important when choosing antimicrobial therapy to ensure efficacy and prevent resistance. Antibiotics may demonstrate concentration-dependent (aminoglycosides and fluoroquinolones) or time-dependent (β-lactams) bactericidal effects.
- The importance of tissue penetration varies with the site of infection. The central nervous system (CNS) is one body site where the importance of antimicrobial penetration is relatively well defined, and correlations with clinical outcomes are established. Drugs that do not reach significant concentrations in CSF should either be avoided or instilled directly when treating meningitis.
- Apart from the bloodstream, other body fluids in which drug concentration data are clinically relevant are urine, synovial fluid, and peritoneal fluid.
- Pharmacokinetic parameters such as area under the concentration-time curve (AUC) and maximal plasma concentration can be predictive of treatment outcome when

TABLE 35–3 Major Drug Interactions With Antimicrobials

Antimicrobial	Other Agent(s)	Mechanism of Action/Effect	Clinical Management
Aminoglycosides	Neuromuscular blocking agents	Additive adverse effects	Avoid
	Nephrotoxins (N) or ototoxins (O) (eg, amphotericin B [N]), cisplatin (N/O), cyclosporine (N), furosemide (O), NSAIDs (N), radio contrast (N), vancomycin (N)	Additive adverse effects	Monitor aminoglycoside SDC and renal function
Amphotericin B	Nephrotoxins (eg, aminoglycosides, cidofovir, cyclosporine, foscarnet, pentamidine)	Additive adverse effects	Monitor renal function
Azoles	See Chap. 38		
Chloramphenicol	Phenytoin, tolbutamide, ethanol	Decreased metabolism of other agents	Monitor phenytoin SDC, blood glucose
Foscarnet	Pentamidine IV	Increased risk of severe nephrotoxicity/hypocalcemia	Monitor renal function/serum calcium
Isoniazid	Carbamazepine, phenytoin	Decreased metabolism of other agents (nausea, vomiting, nystagmus, ataxia)	Monitor drug SDC
Macrolides/azalides	Digoxin	Decreased digoxin bioavailability and metabolism	Monitor digoxin SDC; avoid if possible
	Theophylline	Decreased metabolism of theophylline	Monitor theophylline SDC
Metronidazole	Ethanol (drugs containing ethanol)	Disulfiram-like reaction	Avoid
Penicillins and cephalosporins	Probenecid, aspirin	Blocked excretion of β-lactams	Use if prolonged high concentration of β-lactam desirable
Ciprofloxacin/norfloxacin	Theophylline	Decreased metabolism of theophylline	Monitor theophylline
Quinolones	Classes Ia and III Antiarrhythmics	Increased QT interval	Avoid
	Multivalent cations (antacids, iron, sucralfate, zinc, vitamins, dairy, citric acid) didanosine	Decreased absorption of quinolone	Separate by 2 h

(*continued*)

TABLE 35–3 Major Drug Interactions With Antimicrobials (*Continued*)

Antimicrobial	Other Agent(s)	Mechanism of Action/Effect	Clinical Management
Rifampin	Azoles, cyclosporine, methadone propranolol, PIs, oral contraceptives, tacrolimus, warfarin	Increased metabolism of other agent	Avoid if possible
Sulfonamides	Sulfonylureas, phenytoin, warfarin	Decreased metabolism of other agent	Monitor blood glucose, SDC, PT
Tetracyclines	Antacids, iron, calcium, sucralfate	Decreased absorption of tetracycline	Separate by 2 h
	Digoxin	Decreased digoxin bioavailability and metabolism	Monitor digoxin SDC; avoid if possible

PI, protease inhibitor; PT, prothrombin time; SDC, serum drug concentrations.
Azalides: azithromycin; azoles: fluconazole, itraconazole, ketoconazole, and voriconazole; macrolides: erythromycin, clarithromycin; protease inhibitors: amprenavir, indinavir, lopinavir/ritonavir, nelfinavir, ritonavir, and saquinavir; quinolones: ciprofloxacin, gemifloxacin, levofloxacin, moxifloxacin.

specific ratios of AUC or maximal plasma concentration to the minimum inhibitory concentration (MIC) are achieved. For some agents, the ratio of AUC to MIC, peak-to-MIC ratio, or the time that the drug concentration is above the MIC may predict efficacy.

- The most important pharmacodynamic relationship for antimicrobials that display time-dependent bactericidal effects (such as penicillins and cephalosporins) is the duration that drug concentrations exceed the MIC.

COMBINATION ANTIMICROBIAL THERAPY

- Combinations of antimicrobials are generally used to broaden the spectrum of coverage for empiric therapy, achieve synergistic activity against the infecting organism, and prevent the emergence of resistance.
- Increasing the coverage of antimicrobial therapy is generally necessary in mixed infections in which multiple organisms are likely to be present, such as intra-abdominal and female pelvic infections in which a variety of aerobic and anaerobic bacteria may produce disease. Another clinical situation in which increased spectrum of activity is desirable is with nosocomial infection.

Synergism

- The achievement of synergistic antimicrobial activity is advantageous for infections caused by gram-negative bacilli in immunosuppressed patients.
- Traditionally, combinations of aminoglycosides and β-lactams have been used because these drugs together generally act synergistically against a wide variety of bacteria. However, the data supporting superior efficacy of synergistic over nonsynergistic combinations are weak.
- Synergistic combinations may produce better results in infections caused by *Pseudomonas aeruginosa*, as well as in certain infections caused by *Enterococcus* spp.
- The use of combinations to prevent the emergence of resistance is widely applied but not often realized. The only circumstance in which this has been clearly effective is in the treatment of tuberculosis.

Disadvantages of Combination Therapy

- Although there are potentially beneficial effects from combining drugs, there are also potential disadvantages, including increased cost, greater risk of drug toxicity, and superinfection with even more resistant bacteria.
- Some combinations of antimicrobials are potentially antagonistic. For example, agents that are capable of inducing β-lactamase production in bacteria (eg, cefoxitin) may antagonize the effects of enzyme-labile drugs such as penicillins or imipenem.

MONITORING THERAPEUTIC RESPONSE

- After antimicrobial therapy has been instituted, the patient must be monitored carefully for a therapeutic response. Culture and sensitivity reports from specimens collected must be reviewed.
- Use of agents with the narrowest spectrum of activity against identified pathogens is recommended.
- Patient monitoring should include a variety of parameters, including WBC count, temperature, signs and symptoms of infection, appetite, radiologic studies as appropriate, and determination of antimicrobial concentrations in body fluids.
- As the patient improves, the route of antibiotic administration should be reevaluated. Switching to oral therapy is an accepted practice for many infections. Criteria favoring the switch to oral therapy include the following:
  - ✓ Overall clinical improvement
  - ✓ Lack of fever for 8 to 24 hours
  - ✓ Decreased WBC
  - ✓ A functioning gastrointestinal (GI) tract

FAILURE OF ANTIMICROBIAL THERAPY

- A variety of factors may be responsible for the apparent lack of response to therapy. It is possible that the disease is not infectious or nonbacterial in origin, or there is an undetected pathogen. Other factors include those directly related to drug selection, the host, or the pathogen. Laboratory error in identification and/or susceptibility testing errors are rare.

Failures Caused by Drug Selection

- Factors directly related to the drug selection include an inappropriate selection of drug, dosage, or route of administration. Malabsorption of a drug product due to GI disease (eg, short-bowel syndrome) or a drug interaction (eg, complexation of fluoroquinolones with multivalent cations resulting in reduced absorption) may lead to potentially subtherapeutic serum concentrations.
- Accelerated drug elimination is also a possible reason for failure and may occur in patients with cystic fibrosis or during pregnancy, when more rapid clearance or larger volumes of distribution may result in low serum concentrations, particularly for aminoglycosides.
- A common cause of failure of therapy is poor penetration into the site of infection. This is especially true for the so-called privileged sites, such as the CNS, the eye, and the prostate gland.

Failures Caused by Host Factors

- Patients who are immunosuppressed (eg, granulocytopenia from chemotherapy and acquired immunodeficiency syndrome) may respond poorly to therapy because their own defenses are inadequate to eradicate the infection despite seemingly adequate drug regimens.
- Other host factors are related to the necessity for surgical drainage of abscesses or removal of foreign bodies and/or necrotic tissue. If these situations are not corrected, they result in persistent infection and, occasionally, bacteremia, despite adequate antimicrobial therapy.

Failures Caused by Microorganisms

- Factors related to the pathogen include the development of drug resistance during therapy. Primary resistance refers to the intrinsic resistance of the pathogens producing the infection. However, acquisition of resistance during treatment has become a major problem as well.
- The increase in resistance among pathogenic organisms is believed to be due, in large part, to continued overuse of antimicrobials in the community, as well as in hospitals, and the increasing prevalence of immunosuppressed patients receiving long-term suppressive antimicrobials for the prevention of infections.

See Chapter 83, Antimicrobial Regimen Selection, authored by David S. Burgess, for a more detailed discussion of this topic.

CHAPTER 36

Central Nervous System Infections

- Central Nervous System (CNS) infections include a wide variety of clinical conditions and etiologies: meningitis, meningoencephalitis, encephalitis, brain and meningeal abscesses, and shunt infections. The focus of this chapter is meningitis.

PATHOPHYSIOLOGY

- Central nervous system infections are the result of hematogenous spread from a primary infection site, seeding from a parameningeal focus, reactivation from a latent site, trauma, or congenital defects in the CNS.
- Passive and active exposure to cigarette smoke and the presence of a cochlear implant that includes a positioner, both increase the risk of bacterial meningitis.
- CNS infections may be caused by a variety of bacteria, fungi, viruses, and parasites. The most common causes of bacterial meningitis are *Streptococcus pneumoniae,* group B *Streptococcus*, *Neisseria meningitidis, Haemophilus influenzae,* and *Listeria monocytogenes,*
- The critical first step in the acquisition of acute bacterial meningitis is nasopharyngeal colonization of the host by the bacterial pathogen. The bacteria first attach themselves to nasopharyngeal epithelial cells and are then phagocytized into the host's bloodstream.
- A common characteristic of most CNS bacterial pathogens (eg, *H. influenzae, Escherichia coli,* and *N. meningitidis*) is the presence of an extensive polysaccharide capsule that is resistant to neutrophil phagocytosis and complement opsonization.
- The neurologic sequelae of meningitis occur due to the activation of host inflammatory pathways. Bacterial cell death causes the release of cell wall components such as lipopolysaccharide, lipid A (endotoxin), lipoteichoic acid, teichoic acid, and peptidoglycan, depending on whether the pathogen is gram-positive or gram-negative. These cell wall components cause capillary endothelial cells and CNS macrophages to release cytokines (interleukin-1, tumor necrosis factor, and other inflammatory mediators). Proteolytic products and toxic oxygen radicals cause an alteration of the blood–brain barrier, whereas platelet-activating factor activates coagulation, and arachidonic acid metabolites stimulate vasodilation. These events lead to cerebral edema, elevated intracranial pressure, cerebrospinal fluid (CSF) pleocytosis, decreased cerebral blood flow, cerebral ischemia, and death.

CLINICAL PRESENTATION

- Meningitis causes CSF fluid changes, and these changes can be used as diagnostic markers of infection (**Table 36–1**).
- Clinical presentation varies with age; generally, the younger the patient, the more atypical and the less pronounced is the clinical picture.
- Patients may receive antibiotics before a diagnosis of meningitis is made, delaying presentation to the hospital. Prior antibiotic therapy may cause the Gram stain and CSF culture to be negative, but the antibiotic therapy rarely affects CSF protein or glucose.
- Classic signs and symptoms include fever, nuchal rigidity, altered mental status, chills, vomiting, photophobia, and severe headache. Kernig and Brudzinski signs may be present but are poorly sensitive and frequently absent in children.
- Clinical signs and symptoms in young children may include bulging fontanelle, apneas, purpuric rash, and convulsions, in addition to those just mentioned.

TABLE 36–1 Mean Values of the Components of Normal and Abnormal Cerebrospinal Fluid

Type	Normal	Bacterial	Viral	Fungal	Tuberculosis
WBC (cells/mm^3 or •10^6/L)	<5 (<30 in newborns)	1,000–5,000	5–500	100–400	25–500
Differential[a]	Monocytes	Neutrophils	Lymphocytes	Lymphocytes	Variable
Protein (mg/dL)	<50 (<500 mg/L)	Elevated	Mild elevation	Elevated	Elevated
Glucose (mg/dL)	45–80 (2.5–4.4 mmol/L)	Low	Normal	Low	Low
CSF: blood glucose ratio	50–60%	Decreased	Normal	Decreased	Decreased

[a]Initial cerebrospinal fluid (CSF) and while blood cell (WBC) count may reveal a predominance of polymorphonuclear leukocytes (PMNs).

SIGNS AND SYMPTOMS AND LABORATORY TESTS

- Purpuric and petechial skin lesions typically indicate meningococcal involvement, although the lesions may be present with *H. influenzae* meningitis. Rashes rarely occur with pneumococcal meningitis.
- *Bacterial Meningitis Score is a validated clinical decision tool aimed to identify children older than 2 months with CSF pleocytosis who are at low risk of ABM. This tool incorporates clinical features such as positive CSF Gram stain, presence of seizure, serum absolute neutrophil count of 10,000 cells/mm^3 or more (≥10 × 10^9/L), CSF protein ≥80 mg/dL (≥800 mg/L), and CSF neutrophil count ≥1000 cells/mm^3 (≥1 × 10^9/L). Treatment is recommended when one or more criteria are present.* An elevated CSF protein of 50 mg/dL or more and a CSF glucose concentration less than 50% of the simultaneously obtained peripheral value suggest bacterial meningitis (see **Table 36–1**).
- The values for CSF glucose, protein, and WBC concentrations found with bacterial meningitis overlap significantly with those for viral, tuberculous, and fungal meningitis (see **Table 36–1**) and cannot always distinguish the different etiologies of meningitis.
- Gram stain and culture of the CSF are the most important laboratory tests performed for bacterial meningitis. When performed before antibiotic therapy is initiated, Gram stain is both rapid and sensitive and can confirm the diagnosis of bacterial meningitis in 75% to 90% of cases.
- Polymerase chain reaction (PCR) techniques can be used to diagnose meningitis caused by *N. meningitidis, S. pneumoniae,* and *H. influenzae* type b (Hib). Latex fixation, latex coagglutination, and enzyme immunoassay tests provide for the rapid identification of several bacterial causes of meningitis, including *S. pneumoniae, N. meningitidis,* and Hib. The rapid antigen tests should be used in situations in which the Gram stain is negative.
- Diagnosis of tuberculosis meningitis employs acid-fast staining, culture, and PCR of the CSF.

TREATMENT

- Goals of Treatment: Eradication of infection with amelioration of signs and symptoms preventing morbidity and mortality, initiating appropriate antimicrobials, providing supportive care, and preventing disease through timely introduction of vaccination and chemoprophylaxis.
- The administration of fluids, electrolytes, antipyretics, analgesia, and other supportive measures are particularly important for patients presenting with acute bacterial meningitis.

PHARMACOLOGIC TREATMENT

- Empiric antimicrobial therapy should be instituted as soon as possible to eradicate the causative organism (**Table 36–2**). Antimicrobial therapy should last at least 48 to 72 hours or until the diagnosis of bacterial meningitis can be ruled out. Continued therapy should be based on the assessment of clinical improvement, cultures, and susceptibility testing results. Once a pathogen is identified, antibiotic therapy should be tailored to the specific pathogen. The first dose of antibiotic should not be withheld even when lumbar puncture is delayed or neuroimaging is being performed.
- With increased meningeal inflammation, there will be greater antibiotic penetration (**Table 36–3**). Problems of CSF penetration were traditionally overcome by direct instillation of antibiotics intrathecally, intracisternally, or intraventricularly. Advantages of direct instillation, however, must be weighed against the risks of invasive CNS procedures. Intrathecal administration of antibiotics is unlikely to produce therapeutic concentrations in the ventricles possibly owing to the unidirectional flow of CSF.
- **Table 36–4** for antimicrobial agents of first choice and alternatives for treatment of meningitis caused by gram-positive and gram-negative microorganisms.

Dexamethasone as an Adjunctive Treatment for Meningitis

- In addition to antibiotics, **dexamethasone** is a commonly used therapy for the treatment of pediatric meningitis.
- Current recommendations call for the use of adjunctive dexamethasone in infants and children with *H. influenzae* meningitis. The recommended IV dose is 0.15 mg/kg every 6 hours for 2 to 4 days, initiated 10 to 20 minutes prior to or concomitant with,

TABLE 36–2 Bacterial Meningitis: Most Likely Pathogens and Empirical Therapy by Age Group

Age	Most Likely Organisms	Empirical Therapy[a]
<1 month	*S. agalactiae* Gram-negative enterics[b] *L. monocytogenes*	Ampicillin + cefotaxime *or* ampicillin + aminoglycoside
1–23 months	*S. pneumoniae* *N. meningitidis* *H. influenzae* *S. agalactiae*	Vancomycin[c] + third-generation cephalosporin (cefotaxime *or* ceftriaxone)
2–50 years	*N. meningitidis* *S. pneumoniae*	Vancomycin[c] + third-generation cephalosporin (cefotaxime *or* ceftriaxone)
>50 years	*S. pneumoniae* *N. meningitidis* Gram-negative enterics[b] *L. monocytogenes*	Vancomycin[c] + ampicillin + third-generation cephalosporin (cefotaxime *or* ceftriaxone)

Strength of recommendation: (A) Good evidence to support a recommendation for use; should always be offered. (B) Moderate evidence to support a recommendation for use; should generally be offered.

Quality of evidence: (I) Evidence from ≥1 properly randomized, controlled trial. (II) Evidence from ≥1 well-designed clinical trial, without randomization; from cohort or case–control analytic studies (preferably from ≥1 center) or from multiple time series. (III) Evidence from opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees.[19]

[a]All recommendations are A-III.

[b]*E. coli*, *Klebsiella* spp., and *Enterobacter* spp. common.

[c]Vancomycin use should be based on local incidence of penicillin-resistant *S. pneumoniae* and until cefotaxime or ceftriaxone minimum inhibitory concentration results are available.

TABLE 36–3 Penetration of Antimicrobial Agents into the Cerebrospinal Fluid (CSF)[a]

Therapeutic Levels in CSF With or Without Inflammation	
Acyclovir	Levofloxacin
Chloramphenicol	Linezolid
Ciprofloxacin	Metronidazole
Fluconazole	Moxifloxacin
Flucytosine	Pyrazinamide
Foscarnet	Rifampin
Fosfomycin	Sulfonamides
Ganciclovir	Trimethoprim
Isoniazid	Voriconazole
Therapeutic Levels in CSF with Inflammation of Meninges	
Ampicillin ± sulbactam	Imipenem
Aztreonam	Meropenem
Cefepime	Nafcillin
Cefotaxime	Ofloxacin
Ceftazidime	Penicillin G
Ceftriaxone	Piperacillin/tazobactam[b]
Cefuroxime	Pyrimethamine
Colistin	Quinupristin/dalfopristin
Daptomycin	Ticarcillin ± clavulanic acid[b]
Ethambutol	Vancomycin
Nontherapeutic Levels in CSF With or Without Inflammation	
Aminoglycosides	Cephalosporins (second generation)[c]
Amphotericin B	Doxycycline[d]
β-Lactamase inhibitors[e]	Itraconazole[f]
Cephalosporins (first generation)	

CSF, cerebrospinal fluid.

[a]Using recommended CNS dosing and compared with MIC of target pathogens.
[b]May not achieve therapeutic levels against organisms with higher MIC, as in *P. aeruginosa.* Tazobactam does not penetrate blood–brain barrier.
[c]Cefuroxime is an exception.
[d]Documented effectiveness for *Borrelia burgdorferi*
[e]Includes clavulanic acid, sulbactam, and tazobactam.
[f]Achieves therapeutic concentrations for *Cryptococcus neoformans* therapy.

but not after, the first dose of antimicrobials. Clinical outcome is unlikely to improve if dexamethasone is given after the first dose of antimicrobial and should therefore be avoided. If adjunctive dexamethasone is used, careful monitoring of signs and symptoms of gastrointestinal (GI) bleeding and hyperglycemia should be employed.

Neisseria Meningitidis (Meningococcus)

- The presence of petechiae may be the primary clue that the underlying pathogen is *N. meningitidis*. Approximately 60% of adults and up to 90% of pediatric patients with meningococcal meningitis have purpuric lesions, petechiae, or both. *N. meningitidis* meningitis is the leading cause of bacterial meningitis in children and young adults in the United States and around the world. Most cases occur in the winter or spring, at a time when viral meningitis is relatively uncommon.
- Approximately 10 to 14 days after the onset of the disease and despite successful treatment, the patient develops a characteristic immunologic reaction of fever, arthritis (usually involving large joints), and pericarditis. The synovial fluid is characterized by a large number of polymorphonuclear cells, elevated protein concentrations, normal glucose concentrations, and sterile cultures.

TABLE 36–4 Antimicrobial Agents of First Choice and Alternative Choice for Treatment of Meningitis Caused by Gram-Positive and Gram-Negative Microorganisms

Organism	Antibiotics of First Choice	Alternative Antibiotics	Recommended Duration of Therapy
Gram-positive Organisms			
Streptococcus pneumoniae[a]			10–14 days
Penicillin susceptible MIC ≤0.06 mcg/mL (mg/L)	Penicillin G or ampicillin (A-III)	Cefotaxime (A-III), ceftriaxone (A-III), cefepime (B-II), or meropenem (B-II)	
Penicillin resistant MIC >0.06 mcg/mL (mg/L)	Vancomycin[b, c] + cefotaxime or ceftriaxone (A-III)	Moxifloxacin (B-II)	
Ceftriaxone resistant MIC >0.5 mcg/mL (mg/L)	Vancomycin[b, c] + cefotaxime or ceftriaxone (A-III)	Moxifloxacin (B-II)	
Staphylococcus aureus			14–21 days
Methicillin susceptible	Nafcillin or oxacillin (A-III)	Vancomycin (A-III) or meropenem (B-III)	
Methicillin resistant	Vancomycin[b, c] (A-III)	Trimethoprim-sulfamethoxazole or linezolid (B-III)	
Group B *Streptococcus*	Penicillin G or ampicillin (A-III) ± gentamicin[b, c]	Ceftriaxone or cefotaxime (B-III)	14–21 days
S. epidermidis	Vancomycin[b, c] (A-III)	Linezolid (B-III)	14–21 days
L. monocytogenes	Penicillin G or ampicillin ± gentamicin[b, c, e] (A-III)	Trimethoprim sulfamethoxazole (A-III), meropenem (B-III)	≥ 21 days
Gram-negative Organisms			
Neisseria meningitidis			7–10 days
Penicillin susceptible	Penicillin G or ampicillin (A-III)	Cefotaxime or ceftriaxone (A-III)	
Penicillin resistant	Cefotaxime or ceftriaxone (A-III)	Meropenem or moxifloxacin (A-III)	

(*continued*)

TABLE 36–4 Antimicrobial Agents of First Choice and Alternative Choice for Treatment of Meningitis Caused by Gram-Positive and Gram-Negative Microorganisms (*Continued*)

Organism	Antibiotics of First Choice	Alternative Antibiotics	Recommended Duration of Therapy
Haemophilus influenzae			7–10 days
β-Lactamase negative	Ampicillin (A-III)	Cefotaxime (A-III), ceftriaxone (A-III), cefepime (A-III), or moxifloxacin (A-III)	
β-Lactamase positive	Cefotaxime or ceftriaxone (A-I)	Cefepime (A-I) or moxifloxacin (A-III)	
Enterobacteriaceae[f]	Cefotaxime or ceftriaxone (A-II)	Cefepime (A-III), moxifloxacin (A-III), meropenem (A-III), or aztreonam (A-III)	21 days
Pseudomonas aeruginosa	Cefepime or ceftazidime (A-II) ± tobramycin[b,c] (A-III)	Ciprofloxacin (A-III), meropenem (A-III), piperacillin plus tobramycin[a,b] (A-III), colistin sulfomethate[g] (B-III), aztreonam (A-III)	21 days

[a]European guidelines recommend considering the addition of rifampin to vancomycin therapy.
[b]Direct CNS administration may be considered if failed conventional treatment.
[c]Monitor serum drug levels.
[d]Based on clinical experience; no clear recommendations.
[e]European guidelines recommend adding gentamicin for the first 7 days of treatment.
[f]Includes *E. coli and Klebsiella* spp.
[g]Should be reserved for multidrug-resistant pseudomonal or *Acinetobacter* infections for which all other therapeutic options have been exhausted.

See Table 84-2 footnotes for rating scale of evidence.
Strength of recommendation: A, good evidence to support a recommendation for use; should always be offered; B, moderate evidence to support a recommendation for use; should generally be offered. Quality of evidence: I, evidence from 1 or more properly randomized, controlled trial; II, evidence from 1 or less well-designed clinical trial, without randomization; from cohort or case-controlled analytic studies (preferably from >1 center) or from multiple time-series; III, evidence from opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees.

- Deafness unilaterally, or more commonly bilaterally, may develop early or late in the disease course.

TREATMENT AND PREVENTION

- Aggressive, early intervention with **high-dose IV crystalline penicillin G**, 50,000 units/kg every 4 hours, is usually recommended for treatment of *N. meningitidis* meningitis (see **Table 36-4**).
- Close contacts of patients contracting *N. meningitidis* meningitis are at an increased risk of developing meningitis. Prophylaxis of contacts should be started only after consultation with the local health department.
- In general, rifampin, ceftriaxone, ciprofloxacin, or azithromycin is given for prophylaxis. For regions with reported ciprofloxacin resistance, one dose of azithromycin 500 mg is recommended for prophylaxis.

Streptococcus Pneumoniae (Pneumococcus or Diplococcus)

- *S. pneumoniae* is the leading cause of meningitis in patients 2 months of age or older in the United States.
- Neurologic complications, such as coma and seizures, are common.
- The treatment of choice until susceptibility of the organism is known is the combination of **vancomycin** plus **ceftriaxone.** Penicillin may be used for drug-susceptible isolates with minimum inhibitory concentrations of 0.06 mcg/mL or less, but for intermediate isolates ceftriaxone is used, and for highly drug-resistant isolates a combination of ceftriaxone and vancomycin should be used. A high percent of *S. pneumoniae* is either intermediately or highly resistant to penicillin. Meropenem is recommended as an alternative to a third-generation cephalosporin in penicillin nonsusceptible isolates. IV linezolid and daptomycin have emerged as therapeutic options for treating multidrug-resistant gram-positive infections.
- VA heptavalent conjugate vaccine is available for use in infants between 2 months and 9 years of age. Current recommendations are for all healthy infants younger than 2 years of age to be immunized with the heptavalent vaccine at 2, 4, 6, and 12 to 15 months.
- The Centers for Disease Control and Prevention (CDC) recommends use of 23-valent pneumococcal vaccine (PPV 23) for persons over 65 years of age; persons 2 to 64 years of age who have achronic illness, who live in high-risk environments, and who lack a functioning spleen; and immunocompromised persons over 2 years, including those with human immunodeficiency virus (HIV) infection. All healthy infants younger than 2 years of age to be immunized with the 13-valent pneumococcal conjugate vaccine (PCV13) at 2, 4, 6, and 12 to 15 months.

Haemophilus Influenzae

- In the past, *H. influenzae* was the most common cause of meningitis in children 6 months to 3 years of age, but this has declined dramatically since the introduction of effective vaccines.
- Because approximately 20% of *H. influenzae* are ampicillin resistant, many clinicians use a third-generation cephalosporin (**cefotaxime** or **ceftriaxone**) for initial antimicrobial therapy. Once bacterial susceptibilities are available, ampicillin may be used if the isolate proves ampicillin sensitive. Cefepime and fluoroquinolones are suitable alternatives regardless of β-lactamase activity.
- Prophylaxis of close contacts should be started only after consultation with the local health department and the CDC.
- Vaccination with Hib conjugate vaccines is usually begun in children at 2 months. The vaccine should be considered in patients older than 5 years with sickle cell disease, asplenia, or immunocompromising diseases.

TABLE 36–5 Dosing of Antimicrobial Agents by Age Group

Agent	Infants and Children	Adults	Monitoring/Comments
Antibacterial			
Ampicillin	75 mg/kg every 6 hours	2 g every 4 hours	
Aztreonam	—	2 g every 6–8 hours	Alternative for penicillin allergy
Cefepime	50 mg/kg every 8 hours	2 g every 8 hours	Consider prolonged infusion
Cefotaxime	75 mg/kg every 6–8 hours	2 g every 4–6 hours	Preferred in neonates
Ceftazidime	50 mg/kg every 8 hours	2 g every 8 hours	
Ceftriaxone	100 mg/kg daily	2 g every 12 hours	Avoid in neonates
Ciprofloxacin	10 mg/kg every 8 hours	400 mg every 8–12 hours	Consider higher doses for *P. aeruginosa*
Colistin	5 mg/kg/day	5 mg/kg/day	Consider intraventricular doses Only for MDR organisms Monitor renal function
Gentamicin	2.5 mg/kg every 8 hours	2 mg/kg every 8 hours *or* 5–7 mg/kg daily	TDM is recommended Monitor renal function
Levofloxacin	—	750 mg daily	May prolong QTc
Linezolid	10 mg/kg every 8 hours	600 mg every 12 hours	May cause thrombocytopenia and peripheral neuropathy
Meropenem	40 mg/kg every 8 hours	2 g every 8 hours	Consider prolonged infusion
Moxifloxacin	—	400 mg daily	May prolong QTc
Oxacillin/nafcillin	50 mg/kg every 6 hours	2 g every 4 hours	Nafcillin preferred if renal dysfunction
Penicillin G	0.05 million units/kg every 4 hours	4 million units every 4 hours	
Polymyxin B	—	1.25–1.5 mg/kg every 12 hours	Only for MDR organisms No data in pediatric patients
Tobramycin	2.5 mg/kg every 8 hours	2.5 mg/kg every 8 hours *or* 5–7 mg/kg daily	TDM is recommended Monitor renal function
Trimethoprim–sulfamethoxazole	5 mg/kg every 6–12 hours	5 mg/kg every 6–12 hours	Dose based on trimethoprim
Vancomycin	15 mg/kg every 6 hours	15–20 mg/kg every 8–12 hours	TDM is recommended Monitor renal function

Antimycobacterials			
Isoniazid	10–15 mg/kg daily	5 mg/kg daily	Supplemental vitamin B_6 is recommended
Rifampin	10–20 mg/kg daily (maximum 600 mg daily)	600 mg daily	Many drug–drug interactions
Pyrazinamide	15–30 mg/kg daily	15–30 mg/kg daily	Rarely causes hepatotoxicity
Ethambutol	15–25 mg/kg daily	15–25 mg/kg daily	May cause neutropenia
Antifungals			
Amphotericin B	1 mg/kg daily	0.7–1 mg/kg daily	Monitor renal function Maintain adequate hydration
Lipid amphotericin B	5 mg/kg once daily	3–4 mg/kg daily	Monitor renal function Maintain adequate hydration
Flucytosine	25 mg/kg every 6 hours	25 mg/kg every 6 hours	Consider TDM to avoid bone marrow suppression
Fluconazole	6–12 mg/kg daily	800–1,200 mg daily	Monitor liver function
Itraconazole	—	200 mg every 12 hours	Consider TDM Suspension form is preferred
Posaconazole	—	400 mg every 12 hours	Variable absorption No data in pediatric patients
Voriconazole	7 mg/kg every 12 hours	6 mg/kg every 12 hours × 2 doses, and then 4 mg/kg every 12 hours	Consider TDM Many drug–drug interactions Monitor liver function
Antivirals			
Acyclovir	10–20 mg/kg every 8 hours	10–20 mg/kg every 8 hours	Monitor renal function Maintain adequate hydration
Ganciclovir	—	5 mg/kg every 12 hours	Monitor renal function
Foscarnet	—	60 mg/kg every 8 hours *or* 90 mg/kg every 12 hours	Monitor renal function Maintain adequate hydration

TDM, therapeutic drug monitoring; MDR, multidrug resistant.

Listeria Monocytogenes

- *L. monocytogenes* is a gram-positive, diphtheroid-like organism and is responsible for 10% of all reported cases of meningitis in those older than 65 years.
- The combination of **penicillin G** or **ampicillin** with an aminoglycoside results in a bactericidal effect. Patients should be treated a minimum of 3 weeks. Combination therapy is given for at least 10 days with the remainder completed with penicillin G or ampicillin alone.
- **Trimethoprim–sulfamethoxazole** and **meropenem** may be an effective alternative because adequate CSF penetration is achieved with these agents.

Gram-Negative Bacillary Meningitis

- Elderly debilitated patients are at an increased risk of gram-negative meningitis but typically lack the classic signs and symptoms of the disease.
- Optimal antibiotic therapies for gram-negative bacillary meningitis have not been fully defined. Meningitis caused by *Pseudomonas aeruginosa* is initially treated with an extended-spectrum β-lactam such as ceftazidime or cefepime (A-II), or alternatively aztreonam, ciprofloxacin, or meropenem. The addition of an aminoglycoside—usually tobramycin—to one of the above agents should also be considered (see **Table 36–4**).
- If the pseudomonad is suspected to be antibiotic resistant or becomes resistant during therapy, an intraventricular aminoglycoside (preservative-free) should be considered along with IV aminoglycoside.
- Gram-negative organisms, other than *P. aeruginosa,* that cause meningitis can be treated with a third- or fourth-generation cephalosporin such as **cefotaxime, ceftriaxone, ceftazidime,** or **cefepime**
- Therapy for gram-negative meningitis is continued for a minimum of 21 days. CSF cultures may remain positive for several days or more on a regimen that will eventually be curative.

See Chapter 84, Central Nervous System Infections, authored by Ramy H. Elshaboury, Elizabeth D. Hermsen, Isaac F. Mitropoulos, and John C. Rotschafer, for a more detailed discussion of this topic.

CHAPTER 37

Endocarditis

- *Endocarditis* is an inflammation of the endocardium, the membrane lining the chambers of the heart and covering the cusps of the heart valves. *Infective endocarditis* (IE) refers to infection of the heart valves by microorganisms, primarily bacteria.
- Endocarditis is often referred to as either acute or subacute depending on the clinical presentation. Acute bacterial endocarditis is a fulminating infection associated with high fevers, systemic toxicity, and death within days to weeks if untreated. Subacute infectious endocarditis is a more indolent infection, usually occurring in a setting of prior valvular heart disease.

ETIOLOGY

- Most patients with IE have risk factors, such as preexisting cardiac valve abnormalities. Many types of structural heart disease resulting in turbulence of blood flow will increase the risk for IE. Some of the most important risk factors include the following:
  - ✓ Highest risk: presence of a prosthetic valve or previous endocarditis
  - ✓ Congenital heart disease, chronic intravenous access, diabetes mellitus, healthcare-related exposure, acquired valvular dysfunction (eg, rheumatic heart disease), hypertrophic cardiomyopathy, mitral valve prolapse with regurgitation, and intravenous (IV) drug abuse.
- Three groups of organisms cause most cases of IE: streptococci, staphylococci, and enterococci (**Table 37–1**).

CLINICAL PRESENTATION

- The clinical presentation of patients with IE is highly variable and nonspecific (**Table 37–2**). Fever is the most common finding. The mitral and aortic valves are most often affected.
- Important clinical signs, especially prevalent in subacute illness, may include the following peripheral manifestations ("stigmata") of endocarditis: Osler nodes, Janeway lesions, splinter hemorrhages, petechiae, clubbing of the fingers, Roth's spots, and emboli.
- Without appropriate antimicrobial therapy and surgery, IE is usually fatal. With proper management, recovery can be expected in most patients.
- Factors associated with increased mortality include the following: congestive heart failure, culture-negative endocarditis, endocarditis caused by resistant organisms such as fungi and gram-negative bacteria, left-sided endocarditis caused by *Staphylococcus aureus,* prosthetic valve endocarditis (PVE).
- Ninety percent to 95% of patients with IE have a positive blood culture when three samples are obtained during a 24-hour period. Anemia, leukocytosis, and thrombocytopenia may be present.
- Transesophageal echocardiography is important in identifying and localizing valvular lesions in patients suspected of having IE. It is more sensitive for detecting vegetations (90%–100%), compared with transthoracic echocardiography (58%–63%).
- The Modified Duke criteria, encompassing major findings of persistent bacteremia and echocardiographic findings and other minor findings, are used to categorize patients as "definite IE" or "possible IE."

TREATMENT

- Goals of Treatment: relieve the signs and symptoms of disease. Decrease morbidity and mortality associated with infection. Eradicate the causative organism with minimal drug exposure. Provide cost-effective antimicrobial therapy. Prevent IE in high-risk patients with appropriate prophylactic antimicrobials.

TABLE 37–1 Etiologic Organisms in Infective Endocarditis[a]

Agent	Percentage of Cases
Staphylococci	30–70
Coagulase positive	20–68
Coagulase negative	3–26
Streptococci	9–38
Viridans streptococci	10–28
Other streptococci	3–14
Enterococci	5–18
Gram-negative aerobic bacilli	1.5–13
Fungi	1–9
Miscellaneous bacteria	<5
Mixed infections	1–2
"Culture negative"	<5–17

[a]Values encompass community-acquired, healthcare-associated, native valve, and prosthetic valve infective endocarditis.

Data from references 3, 11, and 16.

TABLE 37–2 Clinical Presentation of Infective Endocarditis

General
The clinical presentation of infective endocarditis is highly variable and nonspecific.
Symptoms
Fever, chills, weakness, dyspnea, night sweats, weight loss, and/or malaise.
Signs
Fever is common, as well as a heart murmur (sometimes new or changing). The patient may or may not have embolic phenomenon, splenomegaly, or skin manifestations (eg, Osler nodes or Janeway lesions).
Laboratory tests
White blood cell count may be normal or only slightly elevated.
Nonspecific findings include anemia (normocytic or normochromic), thrombocytopenia, an elevated erythrocyte sedimentation rate or C-reactive protein, and altered urinary analysis (proteinuria/microscopic hematuria).
The hallmark laboratory finding is continuous bacteremia; three sets of blood cultures should be collected over 24 hours.
Other diagnostic tests
An electrocardiogram, chest radiograph, and echocardiogram are commonly performed. Echocardiography to determine the presence of valvular vegetations plays a key role in the diagnosis of infective endocarditis; it should be performed in all suspected cases.

- The most important approach to treatment of IE is isolation of the infecting pathogen and determination of antimicrobial susceptibilities, followed by high-dose, bactericidal antibiotics for an extended period.
- Treatment usually is started in the hospital, but in select patients, it may be completed in the outpatient setting as long as defervescence has occurred and followup blood cultures show no growth.
- Large doses of parenteral antimicrobials usually are necessary to achieve bactericidal concentrations within vegetations. An extended duration of therapy is required, even for susceptible pathogens, because microorganisms are enclosed within valvular vegetations and fibrin deposits.
- Drug dosing for treatment of IE is given in **Table 37–3**.

NONPHARMACOLOGIC THERAPY

- Surgery is an important adjunct to management of endocarditis in certain patients. In most cases, valvectomy and valve replacement are performed to remove infected tissues and restore hemodynamic function. Indications for surgery include heart failure, persistent bacteremia, persistent vegetation, an increase in vegetation size, or recurrent emboli despite prolonged antibiotic treatment, valve dysfunction, paravalvular extension (eg, abscess), or endocarditis caused by resistant organisms.

STREPTOCOCCAL ENDOCARDITIS

- Streptococci are a common cause of IE, with most isolates being viridans streptococci.
- Most viridans streptococci are exquisitely sensitive to penicillin G with minimum inhibitory concentrations (MICs) of 0.12 mcg/mL or less. The MIC should be determined for all viridans streptococci and the results used to guide therapy. Approximately 10% to 20% are moderately susceptible (MIC 0.12–0.5 mcg/mL).
- Recommended therapy in the uncomplicated case caused by fully susceptible strains in native valves is 4 weeks of either high-dose **penicillin G** or **ceftriaxone**, or 2 weeks of combined or penicillin G or ceftriaxone therapy plus **gentamicin** (**Table 37–4**).
- The following conditions should all be present to consider a 2-week treatment regimen:
  - ✓ The isolate is penicillin sensitive (MIC ≤0.1 mcg/mL).
  - ✓ There are no cardiovascular risk factors such as heart failure, aortic insufficiency, or conduction abnormalities.
  - ✓ No evidence of thromboembolic disease
  - ✓ Native valve infection
  - ✓ No vegetation greater than 5 mm diameter on echocardiogram.
  - ✓ Clinical response is evident within 7 days.
- Vancomycin is effective and is the drug of choice for the patient with a history of immediate-type hypersensitivity reaction to penicillin. When vancomycin is used, the addition of gentamicin is not recommended.
- For patients with complicated infection (eg, extracardiac foci) or when the organism is relatively resistant (MIC = 0.12–0.5 mcg/mL), combination therapy with an aminoglycoside and penicillin (higher dose) or ceftriaxone for the first 2 weeks is recommended followed by penicillin or ceftriaxone alone for an additional 2 weeks.
- In patients with endocarditis of prosthetic valves or other prosthetic material caused by viridans streptococci and *Streptococcus bovis*, treatment courses are extended to 6 weeks (**Table 37–5**).

STAPHYLOCOCCAL ENDOCARDITIS

- *S. aureus* has become more prevalent as a cause of endocarditis because of increased IV drug abuse, frequent use of peripheral and central venous catheters, and valve replacement surgery. Coagulase-negative staphylococci (usually *S. epidermidis*) are prominent causes of PVE.

TABLE 37–3 Drug Dosing for Treatment of IE[a]

Drug	Brand Name	Recommended Dose	Pediatric (Ped) Dose[b]	Additional Information
Ampicillin	NA	2 g IV every 4 hours	50 mg/kg every 4 hours or 75 mg/kg every 6 hours	24-hour total dose may be administered as a continuous infusion: 12 g IV every 24 hours
Ampicillin–sulbactam	Unasyn®	2 g IV every 4 hours	50 mg/kg every 4 hours or 75 mg/kg every 6 hours	
Aqueous crystalline penicillin G sodium	NA			24-hour total dose may be administered as a continuous infusion: 12–18 million units IV every 24 hours (Ped: 200,000 units/kg IV/24 hours)
• MIC <0.12 mcg/mL (mg/L) (native valve only)		3 million units IV every 4 hours or every 6 hours	50,000 units/kg IV every 6 hours	
• All other indications		4 million units IV every 4 hours or 6 million units IV every 6 hours	50,000 units/kg IV every 4 hours or 75,000 units/kg IV every 6 hours	24 million units IV every 24 hours (Ped: 300,000 units/kg IV every 24 hours)
Cefazolin	Ancef®	2 g IV every 8 hours	33 mg/kg IV every 8 hours	
Cefepime	Maxipime®	2 g IV every 8 hours	50 mg/kg IV every 8 hours	
Ceftriaxone sodium	Rocephin®	2 g IV or IM every 24 hours 2 g IV or IM every 12 hours (*E. faecalis only*)	100 mg/kg IV or IM every 24 hours	
Ciprofloxacin	Cipro®	400 mg IV every 12 hours or 500 mg po every 12 hours	20–30 mg/kg IV or po every 12 hours	Avoid use if possible in patients <18 years of age
Daptomycin	Cubicin®	6 mg/kg IV every 24 hours		Doses as high as 8–10 mg/kg IV every 24 hours have been used in adults; doses should be calculated using actual body weight
Doxycline	Vibramycin ®	100 mg IV or po every 12 hours	1–2 mg/kg IV or po every 12 hours	

Gentamicin sulfate	NA	1 mg/kg IV or IM every 8 hours	1 mg/kg IV or IM every 8 hours	Doses should be calculated using ideal body weight or adjusted body weight if >120% of ideal body weight; may also be administered as a single dose of 3 mg/kg of actual body weight
Imipenem–cilastatin	Primaxin®	500 mg IV every 6 hours	15–25 mg/kg IV every 6 hours	
Linezolid	Zyvox®	600 mg IV or po every 12 hours	10 mg/kg IV every 8 hours	
Nafcillin or oxacillin	NA	2 g IV every 4 hours	50 mg/kg IV every 6 hours	
Quinupristin–dalfopristin	Synercid®	7.5 mg/kg IV every 8 hours	7.5 mg/kg IV every 8 hours	
Rifampin	Rifadin®	300 mg IV or po every 8 hours	5–7 mg/kg IV or po every 8 hours	
Streptomycin	NA	15 mg/kg IV or IM every 12 hours		
Vancomycin	Vancocin®	15–20 mg/kg IV every 8 hours or every 12 hours	15 mg/kg IV every 6 hours	A loading dose of 25–30 mg/kg may be administered in adults; doses should be calculated using actual body weight; single doses should not exceed 2 g

[a]All doses assume normal renal function.
[b]Should not exceed adult dosage.

TABLE 37–4 Therapy of Native Valve Endocarditis Caused by Viridans Group Streptococci, *Streptococcus bovis*, and *Staphylococci*

Agent[a]	Duration	Strength of Recommendation	Comments
Highly Penicillin-Susceptible (MIC ≤0.12 mcg/mL [mg/L]) Viridans Group Streptococci and *Streptococcus Bovis*			
Aqueous crystalline penicillin G sodium	4 weeks	1A	2-Week regimens are not intended for the following patients: • Most patients >65 years of age • Impairment of the eighth cranial nerve function • Renal function with a creatinine clearance <20 mL/min (<0.33 mL/s) • Known cardiac or extracardiac abscess • Infection with *Abiotrophia, Granulicatella*, or *Gemalla* species
Ceftriaxone	4 weeks	1A	
Aqueous crystalline penicillin G sodium plus gentamicin	2 weeks	1B	
Ceftriaxone plus gentamicin	2 weeks	1B	
Vancomycin	4 weeks	1B	Recommended only for patients unable to tolerate penicillin or ceftriaxone
Viridans Group Streptococci and *S. Bovis* Relatively Resistant to Penicillin (MIC >0.12 to ≤0.5 mcg/mL [mg/L])			
Aqueous crystalline penicillin G sodium	4 weeks	1B	
plus gentamicin	2 weeks		
Ceftriaxone	4 weeks	1B	
plus gentamicin	2 weeks		
Vancomycin	4 weeks	1B	Recommended only for patients unable to tolerate penicillin or ceftriaxone
Oxacillin-Susceptible Staphylococci[b]			
Nafcillin or oxacillin	6 weeks	1A	Aqueous crystalline penicillin G sodium may be used as an alternative if the strain is highly penicillin susceptible (MIC ≤0.1 mcg/mL [mg/L]) and does not produce β-lactamase; use similar dosing as streptococci relatively resistant to penicillin
Optional: gentamicin sulfate[c]	3–5 days		

Cefazolin	6 weeks	1B	For use in patients with nonanaphylactoid-type penicillin allergies; patients with an unclear history of immediate-type hypersensitivity to penicillin should be considered for skin testing
Optional: gentamicin sulfate[c]	3–5 days		
Vancomycin	6 weeks	1B	For use in patients with anaphylactoid-type hypersensitivity to penicillin and/or cephalosporins
Oxacillin-Resistant Staphylococci			
Vancomycin	6 weeks	1B	
Daptomycin	6 weeks	1A	

Please refer to Table 89-6 for treatment of NVE caused by enterococci.

[a]See Tables 89-8 and 89-9 for appropriate dosing, administration, and monitoring information.
[b]Regimens indicate treatment for left-sided endocarditis or complicated right-sided endocarditis; uncomplicated right-sided endocarditis may be treated for shorter durations and is described in the text.
[c]The clinical benefit of synergistic aminoglycoside therapy is discussed briefly in the text.

Data from references 4 and 20.

TABLE 37–5 Therapy for Prosthetic Valve Endocarditis Caused by Viridans Group Streptococci, *Streptococcus bovis*, and Staphylococci

Agent[a]	Duration (weeks)	Strength of Recommendation	Comments
Highly Penicillin-Susceptible (MIC ≤0.12 mcg/mL [mg/L]) Viridans Group Streptococci and *Streptococcus Bovis*			
Aqueous crystalline penicillin G sodium	6	1B	Combination therapy with gentamicin has not demonstrated superior cure rates compared with monotherapy with a penicillin or cephalosporin and should be avoided in patients with CrCl <30 mL/min (<0.50 mL/s)
with or without gentamicin	2		
Ceftriaxone	6	1B	
with or without gentamicin	2		
Vancomycin	2	1B	Recommended only for patients unable to tolerate penicillin or ceftriaxone
Relatively Resistant or Fully Resistant (MIC >0.12 mcg/mL [mg/L]) Viridans Group Streptococci and *S. Bovis*			
Aqueous crystalline penicillin G sodium	6	1B	
plus gentamicin			
Ceftriaxone plus gentamicin	6	1B	
Vancomycin	6	1B	Recommended only for patients unable to tolerate penicillin or ceftriaxone
Oxacillin-Susceptible Staphylococci			
Nafcillin or oxacillin	≥6	1B	Aqueous crystalline penicillin G sodium may be used as an alternative if the strain is highly penicillin susceptible (MIC ≤0.1 mcg/mL [mg/L]) and does not produce β-lactamase; use similar dosing as streptococci relatively resistant to penicillin; cefazolin may be substituted for nafcillin or oxacillin in patient with nonimmediate-type hypersensitivity
plus rifampin	≥6		
plus gentamicin	2		

Vancomycin	≥6	1B	Recommended only for patients with anaphylactoid-type hypersensitivity to penicillin and/or cephalosporins
plus rifampin	≥6		
plus gentamicin	2		
Oxacillin-Resistant Staphylococci			
Vancomycin	≥6	1B	
plus rifampin	≥6		
plus gentamicin	2		

Please refer to Table 89-6 for treatment of PVE caused by enterococci.

[a]See Tables 89-8 and 89-9 for appropriate dosing, administration, and monitoring information.

Data from references 4 and 20.

- The recommended therapy for patients with left-sided IE caused by methicillin-sensitive *S. aureus* (MSSA) is 6 weeks of **nafcillin** or **oxacillin**, often combined with a short course of gentamicin (see **Table 37–4**).
- If a patient has a mild, delayed allergy to penicillin, **first-generation cephalosporins** are effective alternatives but should be avoided in patients with an immediate-type hypersensitivity reaction.
- In a patient with a positive penicillin skin test or a history of immediate hypersensitivity to penicillin, **vancomycin** is the agent of choice. Vancomycin, however, kills *S. aureus* slowly and is generally regarded as inferior to penicillinase-resistant penicillins for MSSA. Penicillin-allergic patients who fail on vancomycin therapy should be considered for penicillin desensitization. **Daptomycin** (at a dose of 6 mg/kg/day) was approved by the FDA in 2006 for the treatment of *S. aureus* bacteremia associated with right-sided native valve endocarditis (NVE) and is now a recommended alternative.
- **Vancomycin** is the drug of choice for methicillin-resistant staphylococci because most methicillin-resistant *S. aureus* (MRSA) and most coagulase-negative staphylococci are susceptible. Reports of *S. aureus* strains resistant to vancomycin are emerging.

Treatment of *Staphylococcus* Endocarditis in IV Drug Abusers

- IE in IV drug abusers is most frequently (60%–70%) caused by *S. aureus,* although other organisms may be more common in certain geographic locations.
- Standard treatment for MSSA consists of 4 weeks of therapy with a **penicillinase-resistant penicillin**.
- A 2-week course of **nafcillin** or **oxacillin** plus an aminoglycoside may be effective. Short-course vancomycin, in place of nafcillin or oxacillin, appears to be ineffective.

Treatment of Staphylococcal Prosthetic Valve Endocarditis

- PVE that occurs within 2 months of cardiac surgery is usually caused by staphylococci implanted at the time of surgery. Methicillin-resistant organisms are common. Vancomycin is the cornerstone of therapy.
- Because of the high morbidity and mortality associated with PVE and refractoriness to therapy, combinations of antimicrobials are usually recommended.
- For methicillin-resistant staphylococci (both MRSA and coagulase-negative staphylococci), **vancomycin** is used with rifampin for 6 weeks or more (see **Table 37–5**). An **aminoglycoside** is added for the first 2 weeks if the organism is susceptible.
- For methicillin-susceptible staphylococci, a **penicillinase-stable penicillin** is used in place of vancomycin. If an organism is identified other than staphylococci, the treatment regimen should be guided by susceptibilities and should be at least 6 weeks in duration.

ENTEROCOCCAL ENDOCARDITIS

- Enterococci cause 5% to 18% of endocarditis cases and are noteworthy for the following reasons: (1) no single antibiotic is bactericidal; (2) MICs to penicillin are relatively high (1–25 mcg/mL); (3) they are intrinsically resistant to all cephalosporins and relatively resistant to aminoglycosides (ie, "low-level" aminoglycoside resistance); (4) combinations of a cell wall–active agent, such as a penicillin or vancomycin, plus an aminoglycoside are necessary for killing; and (5) resistance to all available drugs is increasing.
- Enterococcal endocarditis ordinarily requires 4 to 6 weeks of high-dose **penicillin G** or **ampicillin**, plus **gentamicin** for cure (**Table 37–6**). A 6-week course is recommended for patients with symptoms lasting longer than 3 months and those with PVE.

TABLE 37–6 Treatment Options for Native Valve or Prosthetic Valve Endocarditis Caused Enterococci

Agent[a]	Duration[b] (Weeks)	Strength of Recommendation	Comments
Ampicillin-, Penicillin-, and Vancomycin-Susceptible Strains			
Ampicillin plus gentamicin	4–6	1A	Symptoms present for <3 months: use 4-week regimen
			Symptoms present for >3 months: use 6-week regimen
Aqueous crystalline penicillin G sodium plus gentamicin	4–6	1A	
Vancomycin plus gentamicin	6	1B	Recommended only for patients unable to tolerate penicillin or ampicillin
Gentamicin-Resistant Strains			
If susceptible, use streptomycin in place of gentamicin in the regimens listed above			
Penicillin-Resistant Strains			
Ampicillin–sulbactam plus gentamicin (β-lactamase–producing strain)	6	IIaC	Treatment with ampicillin–sulbactam for >6 weeks will be needed if strain is also gentamicin resistant
Vancomycin plus gentamicin (intrinsic penicillin resistance[c])	6	IIaC	May also use in patients with β-lactamase–producing strains who have known intolerance to ampicillin–sulbactam
***Enterococcus Faecium* Strains Resistant to Penicillin, Aminoglycosides, and Vancomycin[c]**			
Linezolid	≥ 8	IIaC	Antimicrobial cure rates may be <50%; bacteriologic cure may only be achieved with cardiac valve replacement
Quinupristin–dalfopristin	≥8	IIaC	
***Enterococcus Faecalis* Strains Resistant to Penicillin, Aminoglycosides, and Vancomycin[c]**			
Imipenem–cilastatin plus ampicillin	≥8	IIbC	
Ceftriaxone plus ampicillin	≥8	IIbC	

[a]See Tables 89-8 and 89-9 for appropriate dosing, administration, and monitoring information.
[b]All patients with prosthetic valves should be treated for at least 6 weeks.
[c]Infectious disease consult highly recommended.

Data from reference 4.

TABLE 37–7 Provides drug monitoring for selected agents

Drug	Major Adverse Drug Reactions	Monitoring Parameters	Comments
Daptomycin	Myopathy, rhabdomyolysis	Creatinine phosphokinase (CPK) at least weekly; monitor for signs and symptoms of muscle pain	More frequent monitoring may be warranted in patients with renal dysfunction or receiving concomitant therapy with HMG-CoA reductase inhibitors; discontinue if symptomatic and CPK >5 times the upper limit of normal (ULN) or if CPK ≥10 times ULN
Gentamicin	Nephrotoxicity, ototoxicity, neuromuscular blockade	When dosed three times daily: • Target peak serum concentrations of 3–4 mcg/mL (mg/L; 6.3–8.4 µmol/L) and trough serum concentrations of <1 mcg/mL (mg/L; <2.1 µmol/L)	Avoid concomitant use of other nephrotoxic agents such as diuretics, nonsteroidal antiinflammatory drugs, and radiocontrast media. Avoid rapid IV administration
Linezolid	Thrombocytopenia, optic, or peripheral neuropathy	Platelet counts at baseline and weekly, visual changes	More common with prolonged therapy (≥2 weeks for thrombocytopenia, >28 days for visual symptoms); avoid concomitant myelosuppressive agents
Quinupristin–dalfopristin	Phlebitis (peripheral administration), myalgias, arthralgias, hyperbilirubinemia	Signs and symptoms of joint or muscle pain	Venous irritation may be alleviated by increasing the infusion volume from 250 to 500 or 750 mL; alternatively administer via a central line
Rifampin	Hepatotoxicity	Baseline liver function tests, and then at least every 2–4 weeks during therapy	Avoid concomitant medications that cause hepatotoxicity; may cause red or orange discoloration of bodily secretions (urine, sweat, tears)
Vancomycin	Nephrotoxicity, red man syndrome	Target trough concentrations of 15–20 mcg/mL[a] (mg/L; 10–14 µmol/L)	Red man syndrome may be managed by prolonging the infusion time from 1 to 2 hours; administration of an antihistamine prior to loading or maintenance doses may also be considered

[a]Measuring peak serum vancomycin concentrations is no longer recommended.

- In addition to isolates with high-level aminoglycoside resistance, β-lactamase-producing enterococci (especially *Enterococcus faecium*) are increasingly reported. If these organisms are discovered, use of vancomycin or ampicillin–sulbactam in combination with gentamicin should be considered.

EVALUATION OF THERAPEUTIC OUTCOMES

- The evaluation of patients treated for IE includes assessment of signs and symptoms, blood cultures, microbiologic tests (eg, MIC, minimum bactericidal concentration [MBC], or serum bactericidal titers), serum drug concentrations, and other tests to evaluate organ function.
- Persistence of fever beyond 1 week may indicate ineffective antimicrobial therapy, emboli, infections of intravascular catheters, or drug reactions. In some patients, low-grade fever may persist even with appropriate antimicrobial therapy.
- With effective therapy, blood cultures should be negative within a few days, although microbiologic response to vancomycin may be unusually slower. After the initiation of therapy, blood cultures should be rechecked until they are negative. During the remainder of the therapy, frequent blood culturing is not necessary.
- If bacteria continue to be isolated from blood beyond the first few days of therapy, it may indicate that the antimicrobials are inactive against the pathogen or that the doses are not producing adequate concentrations at the site of infection.
- For all isolates from blood cultures, MICs (not MBCs) should be determined.
- Serum concentrations of the antimicrobial should generally exceed the MBC of the organism; however, in practice this principle is usually not helpful in monitoring patients with endocarditis.

TABLE 37–8 Antibiotic Regimens for Prophylaxis of Endocarditis With a Dental Procedure

Highest Risk Cardiac Conditions	Presence of a prosthetic heart valve Prior diagnosis of infective endocarditis Cardiac transplantation with subsequent valvulopathy Congenital heart disease (CHD)[a]	
Types of procedures	Any that require perforation of the oral mucosa or manipulation of the periapical region of the teeth of gingival tissue	
Antimicrobial Options	**Adult Doses[b]**	**Pediatric Doses[b] (mg/kg)**
Oral amoxicillin	2 g	50
IM or IV ampicillin[c]	2 g	50
IM or IV cefazolin or ceftriaxone[c, d, e]	1 g	50
Oral cephalexin[d, e, f]	2 g	50
Oral clindamycin[e]	600 mg	20
Oral azithromycin or clarithromycin[e]	500 mg	15
IV or IM clindamycin[c, e]	600 mg	20

[a]Includes only the following: unrepaired cyanotic CHD, prophlyaxis within the first 6 months of implanting prosthetic material to repair a congenital heart defect, and repaired CHD with residual defects at or adjacent to prosthetic material.
[b]All one-time doses administered 30–60 minutes prior to initiation of the procedure.
[c]For patients unable to tolerate oral medication.
[d]Should be avoided in patients with immediate-type hypersensitivity reaction to penicillin or ampicillin (e.g., anaphylaxis, urticaria, or angioedema).
[e]Option for patients with nonimmediate hypersensitivity reaction to penicillin or ampicillin.
[f]May substitute with an alternative first- or second-generation cephalosporin at an equivalent dose.

Data from reference 18.

PREVENTION OF ENDOCARDITIS

- Antimicrobial prophylaxis is used to prevent IE in patients believed to be at high risk.
- The use of antimicrobials for this purpose requires consideration of the types of patients who are at risk; the procedures causing bacteremia; the organisms that are likely to cause endocarditis; and the pharmacokinetics, spectrum, cost, and ease of administration of available agents. The objective of prophylaxis is to diminish the likelihood of IE in high-risk individuals who are undergoing procedures that cause transient bacteremia.
- Endocarditis prophylaxis is recommended for all dental procedures that involve manipulation of the gingival tissue of the periapical region of teeth or perforation of the oral mucosa.
- Antibiotic regimens for a dental procedure are given in **Table 37–8**.

See Chapter 89, Infective Endocarditis, authored by Angie Veverka, Michael A. Crouch, and Brian L. Odle, for a more detailed discussion of this topic.

CHAPTER 38

Fungal Infections, Invasive

SPECIFIC FUNGAL INFECTIONS

HISTOPLASMOSIS

- *Histoplasmosis* is caused by inhalation of dust-borne microconidia of the dimorphic fungus *Histoplasma capsulatum*. In the United States, most disease is localized along the Ohio and Mississippi river valleys.

Clinical Presentation and Diagnosis

- In the vast majority of patients, low-inoculum exposure to *H. capsulatum* results in mild or asymptomatic pulmonary histoplasmosis. The course of disease is generally benign, and symptoms usually abate within a few weeks of onset. Patients exposed to a higher inoculum during a primary infection or reinfection may experience an acute, self-limited illness with flu-like pulmonary symptoms, including fever, chills, headache, myalgia, and nonproductive cough.
- Chronic pulmonary histoplasmosis generally presents as an opportunistic infection imposed on a preexisting structural abnormality, such as lesions resulting from emphysema. Patients demonstrate chronic pulmonary symptoms and apical lung lesions that progress with inflammation, calcified granulomas, and fibrosis. Progression of disease over a period of years, seen in 25% to 30% of patients, is associated with cavitation, bronchopleural fistulas, extension to the other lung, pulmonary insufficiency, and often death.
- In patients exposed to a large inoculum and in immunocompromised hosts, progressive illness, disseminated histoplasmosis, occurs. The clinical severity of the diverse forms of disseminated histoplasmosis (**Table 38–1**) generally parallels the degree of macrophage parasitization observed.
- Acute (infantile) disseminated histoplasmosis is seen in infants and young children and (rarely) in adults with Hodgkin disease or other lymphoproliferative disorders. It is characterized by unrelenting fever; anemia; leukopenia or thrombocytopenia; enlargement of the liver, spleen, and visceral lymph nodes; and GI symptoms, particularly nausea, vomiting, and diarrhea. Untreated disease is uniformly fatal in 1 to 2 months
- Most adults with disseminated histoplasmosis demonstrate a mild, chronic form of the disease. Untreated patients are often ill for 10 to 20 years, with long asymptomatic periods interrupted by relapses characterized by weight loss, weakness, and fatigue.
- Adult patients with acquired immunodeficiency syndrome (AIDS) demonstrate an acute form of disseminated disease that resembles the syndrome seen in infants and children. Progressive disseminated histoplasmosis can occur as the direct result of initial infection or because of reactivation of dormant foci.
- In most patients, serologic evidence remains the primary method in the diagnosis of histoplasmosis. Results obtained from complement fixation, immunodiffusion, and latex antigen agglutination antibody tests are used alone or in combination.
- In the AIDS patient with progressive disseminated histoplasmosis, the diagnosis is best established by bone marrow biopsy and culture, which yield positive cultures in 90% of patients.

Treatment

- Recommended therapy for the treatment of histoplasmosis is summarized in **Table 38–1**.
- Asymptomatic or mildly ill patients and patients with sarcoid-like disease generally do not benefit from antifungal therapy. Therapy may be helpful in symptomatic patients whose conditions have not improved during the first month of infection.

TABLE 38–1 Clinical Manifestations and Therapy of Histoplasmosis

Type of Disease and Common Clinical Manifestations	Approximate Frequency (%)[a]	Therapy/Comments
Nonimmunosuppressed Host		
Acute pulmonary histoplasmosis		
Asymptomatic or mild to moderate disease	50–99	*Asymptomatic, mild, or symptoms <4 weeks:* No therapy generally required. Itraconazole (200 mg three times daily for 3 days and then 200 mg once or twice daily for 6–12 weeks) is recommended for patients who continue to have symptoms for 11 months Symptoms >4 weeks: Itraconazole 200 mg once daily × 6–12 weeks[b]
Self-limited disease	1–50	*Self-limited disease:* Amphotericin B[c] 0.3–0.5 mg/kg/day × 2–4 weeks (total dose 500 mg) or ketoconazole 400 mg orally daily × 3–6 months can be beneficial in patients with severe hypoxia following inhalation of large inocula; antifungal therapy generally not useful for arthritis or pericarditis; NSAIDs or corticosteroids can be useful in some cases
Mediastinal granulomas	1–50	Most lesions resolve spontaneously; surgery or antifungal therapy with amphotericin B 40–50 mg/day × 2–3 weeks or itraconazole 400 mg/day orally × 6–12 months can be beneficial in some severe cases; mild to moderate disease can be treated with itraconazole for 6–12 months
Moderately severe to severe diffuse pulmonary disease		Lipid amphotericin B 3–5 mg/kg/day followed by itraconazole 200 mg twice daily for 3 days then twice daily for a total of 12 weeks of therapy; alternatively, in patients at low risk for nephrotoxicity, amphotericin B deoxycholate 0.7–1 mg/kg/day can be utilized; methylprednisolone (0.5–1 mg/kg daily IV) during the first 1–2 weeks of antifungal therapy is recommended for patients who develop respiratory complications, including hypoxemia or significant respiratory distress
Inflammatory/fibrotic disease	0.02	*Fibrosing mediastinitis:* The benefit of antifungal therapy (itraconazole 200 mg twice daily × 3 months) is controversial but should be considered, especially in patients with elevated ESR or CF titers ≤1:32; surgery can be of benefit if disease is detected early; late disease cannot respond to therapy *Sarcoid-like:* NSAIDs or corticosteroids[d] can be of benefit for some patients *Pericarditis:* Severe disease: corticosteroids 1 mg/kg/day or pericardial drainage procedure

TABLE 38–1 Clinical Manifestations and Therapy of Histoplasmosis (*Continued*)

Type of Disease and Common Clinical Manifestations	Approximate Frequency (%)[a]	Therapy/Comments
Chronic cavitary pulmonary histoplasmosis	0.05	Antifungal therapy generally recommended for all patients to halt further lung destruction and reduce mortality *Mild–moderate disease:* Itraconazole (200 mg three times daily for 3 days and then one or two times daily for at least 1 year; some clinicians recommend therapy for 18–24 months due to the high rate of relapse; itraconazole plasma concentrations should be obtained after the patient has been receiving this agent for at least 2 weeks *Severe disease*: Amphotericin B 0.7 mg/kg/day for a minimum total dose of 25–35 mg/kg is effective in 59–100% of cases and should be used in patients who require hospitalization or are unable to take itraconazole because of drug interactions, allergies, failure to absorb drug, or failure to improve clinically after a minimum of 12 weeks of itraconazole therapy
Histoplasma endocarditis		Amphotericin B (lipid formulations may be preferred, due to their lower rate of renal toxicity) plus a valve replacement is recommended; if the valve cannot be replaced, lifelong suppression with itraconazole is recommended
CNS histoplasmosis		Amphotericin B should be used as initial therapy (lipid formulations at 5 mg/kg/day, for a total dosage of 175 mg/kg may be preferred, due to their lower rate of renal toxicity) for 4–6 weeks, followed by an oral azole (fluconazole or itraconazole 200 mg two or three times daily) for at least a year; some patients may require lifelong therapy; response to therapy should be monitored by repeat lumbar punctures to assess *Histoplasma* antigen levels, WBC, and CF antibody titers; blood levels of itraconazole should be obtained to ensure adequate drug exposure
Immunosuppressed Host		
Disseminated histoplasmosis	0.02–0.05	*Disseminated histoplasmosis:* Untreated mortality 83–93%; relapse 5–23% in non-AIDS patients; therapy is recommended for all patients
Acute (Infantile)		*Nonimmunosuppressed patients:* Ketoconazole 400 mg/day orally × 6–12 months or Amphotericin B 0.7 to 1.0 mg/kg daily IV for 4–6 weeks

(*continued*)

TABLE 38–1 Clinical Manifestations and Therapy of Histoplasmosis (*Continued*)

Type of Disease and Common Clinical Manifestations	Approximate Frequency (%)[a]	Therapy/Comments
Subacute		*Immunosuppressed patients (non-AIDS) or endocarditis or CNS disease:* Amphotericin B 0.7 to 1.0 mg/kg daily IV for 3 months followed by fluconazole or itraconazole 200 mg orally twice daily × 12 months
Progressive histoplasmosis (immunocompetent patients and immunosuppressed patients without AIDS)		*Moderately severe to severe:* Liposomal amphotericin B (3 mg/kg daily), amphotericin B lipid complex (ABLC, 5 mg/kg daily), or deoxycholate amphotericin B (0.7–1 mg/kg daily) for 1–2 weeks, followed by itraconazole (200 mg twice daily for at least 12 months) *Mild to moderate:* Itraconazole (200 mg twice daily for at least 12 months)
Progressive disease of AIDS	25–50[e]	Amphotericin B 0.7 to 1.0 mg/kg daily IV for 3 months[f] or itraconazole 200 mg three times daily for 3 days then twice daily for 12 weeks, followed by lifelong suppressive therapy with itraconazole 200–400 mg orally daily; although patients receiving secondary prophylaxis (chronic maintenance therapy) might be at low risk for recurrence of systemic mycosis when their CD4+ T-lymphocyte counts increase to >100 cells/μL (>100 × 10^6/L) in response to HAART, the number of patients who have been evaluated is insufficient to warrant a recommendation to discontinue prophylaxis

AIDS, acquired immunodeficiency syndrome; CF, complement fixation; ESR, erythrocyte sedimentation rate; HAART, highly active antiretroviral therapy; NSAIDs, nonsteroidal antiinflammatory drugs; PO, orally.

[a]As a percentage of all patients presenting with histoplasmosis.

[b]Itraconazole plasma concentrations should be measured during the second week of therapy to ensure that detectable concentrations have been achieved. If the concentration is below 1 mcg/mL (mg/L; 1.4 μmol/L), the dose may be insufficient or drug interactions can be impairing absorption or accelerating metabolism, requiring a change in dosage. If plasma concentrations are greater than 10 mcg/mL (mg/L; 14 μmol/L), the dosage can be reduced.

[c]Deoxycholate amphotericin B.

[d]Effectiveness of corticosteroids is controversial.

[e]As a percentage of AIDS patients presenting with histoplasmosis as the initial manifestation of their disease.

[f]Liposomal amphotericin B (AmBisome) may be more appropriate for disseminated disease.

- **Amphotericin B** dosages of 50 mg/day (up to 1 mg/kg per day) should be administered intravenously (IV) to a cumulative dose of 15 to 35 mg/kg (1 to 2 g) in patients who require hospitalization. Amphotericin B can be replaced with **itraconazole** 200 mg orally twice daily when the patient no longer requires hospitalization or IV therapy to complete a 12-week total course of induction therapy. In patients who do not require hospitalization, itraconazole therapy for 12 weeks can be used.
- Response to therapy should be measured by resolution of radiologic, serologic, and microbiologic parameters and improvement in signs and symptoms of infection.

- Once the initial course of therapy for histoplasmosis is completed, lifelong suppressive therapy with oral azoles or amphotericin B (1–1.5 mg/kg weekly or biweekly) is recommended, because of the frequent recurrence of infection.
- Relapse rates in AIDS patients not receiving preventive maintenance are 50% to 90%.

BLASTOMYCOSIS

- North American *blastomycosis* is a systemic fungal infection caused by *Blastomyces dermatitidis*. Pulmonary disease probably occurs by inhalation conidia, which convert to the yeast forms in the lungs. It may be acute or chronic and can mimic infection with tuberculosis (TB), pyogenic bacteria, other fungi, or malignancy.
- Blastomycosis can disseminate to virtually every other body organ, including skin, bones, and joints, or the genitourinary tract, without any evidence of pulmonary disease.

Clinical Presentation and Diagnosis

- Acute pulmonary blastomycosis is generally an asymptomatic or self-limited disease characterized by fever, shaking chills, and a productive, purulent cough, with or without hemoptysis in immunocompetent individuals.
- Sporadic pulmonary blastomycosis may present as a more chronic or subacute disease, with low-grade fever, night sweats, weight loss, and a productive cough resembling that of TB rather than bacterial pneumonia. Chronic pulmonary blastomycosis is characterized by fever, malaise, weight loss, night sweats, chest pain, and productive cough.
- The simplest and most successful method of diagnosing blastomycosis is by direct microscopic visualization of the large, multinucleated yeast with single, broad-based buds in sputum or other respiratory specimens, following digestion of cells and debris with 10% potassium hydroxide. Histopathologic examination of tissue biopsies and culture of secretions should be used to identify *B. dermatitidis*.

Treatment

- In the immunocompetent host, acute pulmonary blastomycosis can be mild and self-limited and may not require treatment. However, consideration should be given to treating all infected individuals to prevent extrapulmonary dissemination. All individuals with moderate to severe pneumonia, disseminated infection, or those who are immunocompromised require antifungal therapy (**Table 38–2**).
- Some authors recommend azole therapy for the treatment of self-limited pulmonary disease, with the hope of preventing late extrapulmonary disease.
- **Itraconazole**, 200 to 400 mg/day, demonstrated 90% efficacy as a first-line agent in the treatment of non-life-threatening, non-CNS blastomycosis and 95% success rate for compliant patients who completed at least 2 months of therapy.
- All patients with disseminated blastomycosis and those with extrapulmonary disease require therapy.
- Patients infected with human immunodeficiency virus (HIV) should receive induction therapy with amphotericin B and chronic suppressive therapy with an oral azole antifungal.

COCCIDIOIDOMYCOSIS

- *Coccidioidomycosis* is caused by infection with *Coccidioides immitis*. The endemic regions encompass the semiarid areas of the southwestern United States from California to Texas, known as the Lower Sonoran Zone. It encompasses a spectrum of illnesses ranging from primary uncomplicated respiratory tract infection that resolves spontaneously to progressive pulmonary or disseminated infection.

Clinical Presentation and Diagnosis

- Approximately 60% of those infected are asymptomatic or have nonspecific symptoms that are often indistinguishable from those of ordinary upper respiratory infections, including fever, cough, headache, sore throat, myalgias, and fatigue.

TABLE 38–2 Therapy of Blastomycosis

Type of Disease	Preferred Treatment
Pulmonary[a]	
Moderately severe to severe disease	Lipid formulation of amphotericin B 3–5 mg/kg IV daily or amphotericin B[b] 0.7–1 mg/kg IV daily (total dose 1.5–2.5 g) × 1–2 weeks or until improvement is noted, followed by itraconazole[c,d] 200 mg orally three times daily for 3 days, then 200 mg twice daily, × total of 6–12 months
Mild to moderate disease	Itraconazole[c,d] 200 mg orally three times daily for 3 days, then 200 mg twice daily, for a total of 6 months[c]
CNS disease	*Induction:* Lipid formulation of amphotericin B 5 mg/kg IV daily × 4–6 weeks, followed by an oral azole as consolidation therapy *Consolidation:* Fluconazole[d] 800 mg orally daily, or itraconazole[d] 200 mg two or three times orally daily, or voriconazole[d] 200–400 mg orally twice daily, for ≥12 months and until resolution of CSF abnormalities
Disseminated or Extrapulmonary Disease	
Moderately severe to severe disease	Lipid formulation of amphotericin B 3–5 mg/kg IV daily or amphotericin B[b] 0.7–1 mg/kg IV daily × 1–2 weeks or until improvement is noted, followed by itraconazole[c,d] 200 mg orally three times daily for 3 days, then 200 mg twice daily × 6–12 months. Treat osteoarticular disease with 12 months of antifungal therapy Most clinicians prefer to step-down to itraconazole[d] therapy once the patient's condition improves
Mild to moderate	Itraconazole[c,d] 200 mg orally three times daily for 3 days, then 200 mg once or twice daily × ≥12 months. Treat osteoarticular disease with 12 months of antifungal therapy
Immunocompromised Host (Including Patients with AIDS, Transplants, or Receiving Chronic Glucocorticoid Therapy)	
Acute disease	Lipid formulation of amphotericin B 3–5 mg/kg IV daily or amphotericin B[b] 0.7–1 mg/kg IV daily × 1–2 weeks or until improvement is noted, then give suppressive therapy for a total of at least 12 months of therapy
Suppressive therapy	Itraconazole[c,d] 200 mg orally three times daily for 3 days, then 200 mg twice daily for a total of at least 12 months of therapy; lifelong suppressive therapy with oral itraconazole[d] 200 mg daily may be required for immunosuppressed patients in whom immunosuppression cannot be reversed, and in patients who experience relapse despite appropriate therapy

AIDS, acquired immunodeficiency syndrome.

[a]In the immunocompetent host, acute pulmonary blastomycosis can be mild and self-limited and may not require treatment.

[b]Desoxycholate amphotericin B.

[c]Serum levels of itraconazole should be determined after the patient has received itraconazole for ≥2 weeks, to ensure adequate drug exposure.

[d]Azoles should not be used during pregnancy.

A fine, diffuse rash may appear during the first few days of illness. Chronic, persistent pneumonia or persistent pulmonary coccidioidomycosis (primary disease lasting >6 weeks) is complicated by hemoptysis, pulmonary scarring, and the formation of cavities or bronchopleural fistulas.

- Disseminated infection occurs in less than 1% of infected patients. Dissemination may occur to the skin, lymph nodes, bone, meninges, spleen, liver, kidney, and adrenal gland. CNS infection occurs in ~16% of patients with disseminated infection.
- The diagnoses of coccidioidomycosis generally utilize identification or recovery of *Coccidioides* spp. from clinical specimens and detection of specific anticoccidioidal antibodies in serum or other body fluids.

Treatment

- Therapy of coccidioidomycosis is difficult, and the results are unpredictable. Only 5% of infected persons require therapy.
- Azole antifungals, primarily fluconazole and itraconazole, have replaced amphotericin B as initial therapy for most chronic pulmonary or disseminated infections. Specific antifungals (and their usual dosages) for the treatment of coccidioidomycosis include amphotericin B IV (0.5–1.5 mg/kg/day), **ketoconazole** (400 mg orally daily), IV or oral **fluconazole** (usually 400–800 mg daily, although dosages as high as 1200 mg/day have been used without complications), and itraconazole (200–300 mg orally twice daily as either capsules or solution). If itraconazole is used, measurement of serum concentrations may be helpful to ascertain whether oral bioavailability is adequate.
- Amphotericin B is generally preferred as initial therapy in patients with rapidly progressive disease, whereas azoles are generally preferred in patients with subacute or chronic presentations. Lipid formulations of amphotericin B have not been extensively studied for coccidioidomycosis but can offer a means of giving more drugs with less toxicity. Treatments for primary respiratory diseases (mainly symptomatic patients) are 3- to 6-month courses of therapy.
- Patients with disease outside the lungs should be treated with 400 mg/day of an oral azole. For meningeal disease, fluconazole 400 mg/day orally should be used; however, some clinicians initiate therapy with 800 or 1000 mg/day, and itraconazole doses of 400 to 600 mg/day are comparable.

CRYPTOCOCCOSIS

- *Cryptococcosis* is a noncontagious, systemic mycotic infection caused by the ubiquitous encapsulated soil yeast *Cryptococcus neoformans*.

Clinical Presentation and Diagnosis

- Primary cryptococcosis in humans almost always occurs in the lungs. Symptomatic infections are usually manifested by cough, rales, and shortness of breath that generally resolve spontaneously.
- Disease may remain localized in the lungs or disseminate to other tissues, particularly the CNS, although the skin can also be affected.
- In the non-AIDS patient, the symptoms of cryptococcal meningitis are nonspecific. Headache, fever, nausea, vomiting, mental status changes, and neck stiffness are generally observed. In AIDS patients, fever and headache are common, but meningismus and photophobia are much less common than in non-AIDS patients.
- Examination of cerebrospinal fluid (CSF) in patients with cryptococcal meningitis generally reveals an elevated opening pressure, CSF pleocytosis (usually lymphocytes), leukocytosis, a decreased CSF glucose, an elevated CSF protein, and a positive cryptococcal antigen.
- Antigens to *C. neoformans* can be detected by latex agglutination. *C. neoformans* can be detected in ~60% of patients by India ink smear of CSF and cultured in more than 96% of patients.

TABLE 38–3 Therapy of Cryptococcosis[a,b]

Type of Disease and Common Clinical Manifestations	Therapy/Comments
Nonimmunocompromised Patients (Non-HIV-Infected, Nontransplant)	
Meningoencephalitis *without* neurological complications, in patients in whom CSF yeast cultures are negative after 2 weeks of therapy	*Induction*: Amphotericin B[c] IV 0.7–1 mg/kg/day plus flucytosine 100 mg/kg/day orally in four divided doses × ≥4 weeks A lipid formulation of amphotericin B may be substituted for amphotericin B in the second 2 weeks
Follow all regimens with suppressive therapy	*Consolidation:* Fluconazole 400–800 mg orally daily × 8 weeks *Maintenance:* Fluconazole 200 mg orally daily × 6–12 months
Meningoencephalitis with neurological complications	*Induction:* Same as for patients without neurologic complications, but consider extending the induction therapy for a total of 6 weeks. A lipid formulation of amphotericin B may be given for the last 4 weeks of the prolonged induction period *Consolidation:* Fluconazole 400 mg orally daily × 8 weeks
Mild-to-moderate pulmonary disease (Nonmeningeal disease)	Fluconazole 400 mg orally daily × 6–12 months
Severe pulmonary cryptococcosis	*Same as CNS disease × 12 months*
Cryptococcemia (nonmeningeal, nonpulmonary disease)	*Same as CNS disease × 12 months*
Immunocompromised Patients	
Severe pulmonary cryptococcosis	Same as CNS disease × 12 months
HIV-infected Patients	
Primary therapy; induction and consolidation[g]	*Preferred regimen:* *Induction:* Amphotericin B[d] IV 0.7–1 mg/kg IV daily plus flucytosine 100 mg/kg/day orally in four divided doses for ≥ 2 weeks
Follow all regimens with suppressive therapy	*Consolidation:* Fluconazole 400 mg [6 mg/kg] orally daily × ≥8 weeks Liposomal amphotericin B 3–4 mg/kg IV daily, or amphotericin B lipid complex (ABLC) 5 mg/kg IV daily, for ≥2 weeks can be substituted for amphotericin B[d] in patients with or at risk for renal dysfunction *Alternative regimens, in order of preference:* Amphotericin B[d] IV 0.7–1 mg/kg IV daily × 4–6 weeks or liposomal amphotericin B 3–4 mg/kg IV daily[f] × 4–6 weeks or ABLC 5 mg/kg IV daily × 4–6 weeks *or* Amphotericin B[d] IV 0.7 mg/kg IV daily, plus fluconazole 800 mg (12 mg/kg) orally daily × 2 weeks, followed by fluconazole 800 mg [12 mg/kg] orally daily × ≥8weeks *or* Fluconazole ≥800 mg (1,200 mg/day is preferred) orally daily plus flucytosine 100 mg/kg/day orally in four divided doses × 6 weeks

TABLE 38–3 Therapy of Cryptococcosis[a,b] (*Continued*)

Type of Disease and Common Clinical Manifestations	Therapy/Comments
	or Fluconazole 800–1,200 mg/day orally daily × 10–12 weeks (a dosage ≥1,200 mg/day is preferred when fluconazole is used alone)[e] *or* Itraconazole 200 mg orally twice daily × 10–12 weeks (use of itraconazole, which produces minimal concentrations of active drug in the CSF is discouraged)[i]
Suppressive/maintenance therapy[h]	Preferred: Fluconazole 200 mg orally daily × ≥1 *year* *or* Itraconazole[i]: 200 mg orally twice daily × ≥1 year *or* Amphotericin B[j] IV 1 mg/kg weekly × ≥1 year
Organ Transplant Recipients	
Mild–moderate non-CNS disease or mild-to-moderate symptoms without diffuse pulmonary infiltrates	Fluconazole 400 mg (6 mg/kg) orally daily × 6–12 months
CNS disease, moderately severe or severe CNS disease or disseminated disease without CNS disease, or severe pulmonary disease without evidence of extrapulmonary or disseminated disease	*Induction:* Liposomal amphotericin B 3–4 mg/kg IV daily,[f] or ABLC 5 mg/kg IV daily *plus* flucytosine 100 mg/kg/day orally in four divided doses × ≥2 weeks If induction therapy does not include flucytosine, consider a lipid formulation of amphotericin B for ≥4–6 weeks of induction therapy. Consider the use of a lipid formulation of amphotericin B lipid formulation (6 mg/kg IV daily) in patients with a high-fungal burden disease or relapse of disease. *Consolidation:* Fluconazole 400–800 mg (6–12 mg/kg) per day orally for 8 weeks *Maintenance*: Fluconazole 200–400 mg per day orally for 6–12 months

HIV, human immunodeficiency virus; IT, intrathecal.

[a]When more than one therapy is listed, they are listed in order of preference.
[b]See the text for definitions of induction, consolidation, suppressive/maintenance therapy, and prophylactic therapy.
[c]Deoxycholate amphotericin B.
[d]In patients with significant renal disease, lipid formulations of amphotericin B can be substituted for deoxycholate amphotericin B during the induction.
[e]Or until cerebrospinal fluid (CSF) cultures are negative.
[f]Liposomal amphotericin B has been given safely up to 6 mg/kg daily; could be considered in treatment failure or in patients with a high fungal burden.
[g]Initiate HAART therapy 2–10 weeks after commencement of initial antifungal treatment.
[h]Consider discontinuing suppressive therapy during HAART in patients with a CD4 cell count ≥100 cells/μL (≥100 × 106/L) and an undetectable or very low HIV RNA level sustained for ≥3 months (with a minimum of 12 months of antifungal therapy). Consider reinstitution of maintenance therapy if the CD4 cell count decreases to <100 cells/μL (<100 × 106/L).
[i]Drug level monitoring is strongly advised.
[j]Use is discouraged except in azole intolerant patients, since it is less effective than azole therapy, and is associated with a risk of IV catheter-related infections.

TABLE 38–4 Antifungal Therapy of Invasive Candidiasis

Type of Disease and Common Clinical Manifestations	Therapy/Comments
Prophylaxis of Candidemia	
Nonneutropenic patients[a]	Not recommended except for severely ill/high-risk patients in whom fluconazole IV/PO 400 mg daily should be used (see the text)
Neutropenic patients[a]	The optimal duration of therapy is unclear but at a minimum should include the period at risk for neutropenia: Fluconazole IV/PO 400 mg daily or itraconazole solution 2.5 mg/kg every 12 hours PO *or* micafungin 50 mg (1 mg/kg in patients under 50 kg) IV daily
Solid-organ transplantation, liver transplantation	*Patients with two or more key risk factors*[b]: Amphotericin B IV 10–20 mg daily or liposomal amphotericin B (AmBisome) 1 mg/kg/day or fluconazole 400 mg orally daily
Empirical (Preemptive) Antifungal Therapy	
Suspected disseminated candidiasis in febrile nonneutropenic patients	None recommended; data are lacking defining subsets of patients who are appropriate for therapy (see the text)
Initial Antifungal Therapy (Documented Candidemia with Unknown Candida Species)	
Febrile neutropenic patients with prolonged fever despite 4–6 days of empirical antibacterial therapy	*Treatment duration:* Until resolution of neutropenia An echinocandin[d] is a reasonable alternative; voriconazole can be used in selected situations (see the text)
Less critically ill patients with no recent azole exposure	An echinocandin[d] or fluconazole (loading dose of 800 mg [12 mg/kg], then 400 mg [6 mg/kg] daily)
Additional mold coverage is desired	Voriconazole
Antifungal Therapy of Documented Candidemia and Acute Hematogenously Disseminated Candidiasis, Unknown Species	
Nonimmunocompromised host[c]	*Treatment duration:* 2 weeks after the last positive blood culture and resolution of signs and symptoms of infection *Remove existing central venous catheters when feasible plus fluconazole (loading dose of 800 mg [12 mg/kg], then 400 mg [6 mg/kg] daily) or an echinocandin*[d]
Patients with recent azole exposure, moderately severe or severe illness, or who are at high risk of infection due to *C. glabrata* or *C. krusei*	*An echinocandin*[d] Transition from an echinocandin to fluconazole is recommended for patients who are clinically stable and have isolates (e.g., *C. albicans*) likely to be susceptible to fluconazole

TABLE 38–4 Antifungal Therapy of Invasive Candidiasis (Continued)

Type of Disease and Common Clinical Manifestations	Therapy/Comments
Patients who are less critically ill and who have had no recent azole exposure	Fluconazole
Antifungal Therapy of Specific Pathogens	
C. albicans, C. tropicalis, and C. parapsilosis	Fluconazole IV/PO 6 mg/kg/day or an echinocandin[d] or amphotericin B IV 0.7 mg/kg/day *plus* fluconazole IV/PO 800 mg/day; amphotericin B deoxycholate 0.5–1 mg/kg daily or a lipid formulation of amphotericin B (3–5 mg/kg daily) are alternatives in patients who are intolerant to other antifungals; transition from amphotericin B deoxycholate or a lipid formulation of amphotericin B to fluconazole is recommended in patients who are clinically stable and whose isolates are likely to be susceptible to fluconazole (e.g., *C. albicans*); voriconazole (400 mg [6 mg/kg] twice daily × two doses then 200 mg [3 mg/kg] twice daily thereafter) is efficacious, but offers little advantage over fluconazole; it may be utilized as step-down oral therapy for selected cases of candidiasis due to *C. krusei* or voriconazole-susceptible *C. glabrata* *Patients intolerant or refractory to other therapy*[e]*:* Amphotericin B lipid complex IV 5 mg/kg/day Liposomal amphotericin B IV 3–5 mg/kg/day Amphotericin B colloid dispersion IV 2–6 mg/kg/day
C. krusei	Amphotericin B IV ≤1 mg/kg/day or an echinocandin[d]
C. lusitaniae	Fluconazole IV/PO 6 mg/kg/day
C. glabrata	An echinocandin[d] (transition to fluconazole or voriconazole therapy is not recommended without confirmation of isolate susceptibility)
Neutropenic host[f]	*Treatment duration:* Until resolution of neutropenia *Remove existing central venous catheters when feasible, plus:* or Amphotericin B IV 0.7–1 mg/kg/day (total dosages 0.5–1 g) or *Patients failing therapy with traditional amphotericin B:* Lipid formulation of amphotericin B IV 3–5 mg/kg/day
Chronic disseminated candidiasis (hepatosplenic candidiasis)	*Treatment duration:* Until calcification or resolution of lesions *Stable patients:* Fluconazole IV/PO 6 mg/kg/day Acutely ill or refractory *patients:* Amphotericin B IV 0.6–0.7 mg/kg/day

(*continued*)

TABLE 38–4 Antifungal Therapy of Invasive Candidiasis (Continued)

Type of Disease and Common Clinical Manifestations	Therapy/Comments
Urinary candidiasis	*Asymptomatic disease:* Generally no therapy is required *Symptomatic or high-risk patients*[g]: Removal of urinary tract instruments, stents, and Foley catheters, +7–14 days therapy with fluconazole 200 mg orally daily or amphotericin B IV 0.3–1 mg/kg/day

PO, orally.

[a]Patients at significant risk for invasive candidiasis include those receiving standard chemotherapy for acute myelogenous leukemia, allogeneic bone marrow transplants, or high-risk autologous bone marrow transplants. However, among these populations, chemotherapy or bone marrow transplant protocols do not all produce equivalent risk, and local experience should be used to determine the relevance of prophylaxis.

[b]Risk factors include retransplantation, creatinine of more than 2 mg/dL (177 µmol/L), choledochojejunostomy, intraoperative use of 40 units or more of blood products, and fungal colonization detected within the first 3 days after transplantation.

[c]Therapy is generally the same for acquired immunodeficiency syndrome (AIDS)/non-AIDS patients except where indicated and should be continued for 2 weeks after the last positive blood culture and resolution of signs and symptoms of infection. All patients should receive an ophthalmologic examination. Amphotericin B can be switched to fluconazole (IV or oral) for the completion of therapy. Susceptibility testing of the infecting isolate is a useful adjunct to species identification during selection of a therapeutic approach because it can be used to identify isolates that are unlikely to respond to fluconazole or amphotericin B. However, this is not currently available at most institutions.

[d]Echinocandin = caspofungin 70 mg loading dose, then 50 mg IV daily maintenance dose, or micafungin 100 mg daily, or anidulafungin 200 mg loading dose, then 100 mg daily maintenance dose.

[e]Often defined as failure of ≥500 mg amphotericin B, initial renal insufficiency (creatinine ≥2.5 mg/dL [≥221 µmol/L] or creatinine clearance <25 mL/min [< 0.42 mL/s]), a significant increase in creatinine (to 2.5 mg/dL [221 µmol/L] for adults or 1.5 mg/dL [133 µmol/L] for children), or severe acute administration-related toxicity.

[f]Patients who are neutropenic at the time of developing candidemia should receive a recombinant cytokine (granulocyte colony-stimulating factor or granulocyte–monocyte colony-stimulating factor) that accelerates recovery from neutropenia.

[g]Patients at high risk for dissemination include neutropenic patients, low-birth-weight infants, patients with renal allografts, and patients who will undergo urologic manipulation.

Treatment

- Treatment of cryptococcosis is detailed in **Table 38–3**. For asymptomatic, immunocompetent persons with isolated pulmonary disease and no evidence of CNS disease, careful observation may be warranted. With symptomatic infection, **fluconazole** or **amphotericin B** is warranted.
- The use of intrathecal **amphotericin B** is not recommended for the treatment of cryptococcal meningitis except in very ill patients or in those with recurrent or progressive disease despite aggressive IV amphotericin B therapy. The dosage of amphotericin B employed is usually 0.5 mg administered via the lumbar, cisternal, or intraventricular (via an Ommaya reservoir) route two or three times weekly.
- **Amphotericin B** with **flucytosine** is the initial treatment of choice for acute therapy of cryptococcal meningitis in AIDS patients. Many clinicians will initiate therapy with amphotericin B, 0.7 to 1 mg/kg/day IV (with flucytosine, 100 mg/kg/day). After 2 weeks, consolidation therapy with **fluconazole** 400 mg/day orally can be administered for 8 weeks or until CSF cultures are negative.

- Relapse of *C. neoformans* meningitis occurs in ~50% of AIDS patients after completion of primary therapy. HIV-infected patients requiring chronic suppressive therapy of cryptococcal meningitis can receive **Fluconazole** (200 mg daily) for chronic suppressive therapy.

CANDIDA INFECTIONS

- Eight species of *Candida* are regarded as clinically important pathogens in human disease: *C. albicans, C. tropicalis, C. parapsilosis, C. krusei, C. stellatoidea, C. guilliermondii, C. lusitaniae*, and *C. glabrata*.

HEMATOGENOUS CANDIDIASIS

- Hematogenous candidiasis describes the clinical circumstances in which hematogenous seeding to deep organs such as the eye, brain, heart, and kidney occurs.
- *Candida* is generally acquired via the gastrointestinal (GI) tract, although organisms may also enter the bloodstream via indwelling IV catheters. Immunosuppressed patients, including those with lymphoreticular or hematologic malignancies, diabetes, immunodeficiency diseases, or those receiving immunosuppressive therapy with high-dose corticosteroids, immunosuppressants, antineoplastic agents, or broad-spectrum antimicrobial agents are at high risk for invasive fungal infections. Major risk factors include the use of central venous catheters, total parenteral nutrition, receipt of multiple antibiotics, extensive surgery and burns, renal failure and hemodialysis, mechanical ventilation, and prior fungal colonization.
- No test has demonstrated reliable accuracy in the clinical setting for diagnosis of disseminated *Candida* infection. Blood cultures are positive in only 25% to 45% of neutropenic patients with disseminated candidiasis. Fluorescence in situ hybridization has excellent sensitivity and specificity in the identification of *C. albicans* from blood.
- Treatment of candidiasis is presented in **Table 38–4**.

ASPERGILLUS INFECTIONS

- Of more than 300 species of *Aspergillus*, three are most commonly pathogenic: *A. fumigatus*, *A. flavus*, and *A. niger*.
- Aspergillosis is generally acquired by inhalation of airborne conidia that are small enough (2.5–3 mm) to reach the alveoli or the paranasal sinuses.
- Superficial or locally invasive infections of the ear, skin, or appendages can often be managed with topical antifungal therapy.

Allergic Bronchopulmonary Aspergillosis

- Allergic manifestations of *Aspergillus* range in severity from mild asthma to allergic bronchopulmonary aspergillosis characterized by severe asthma with wheezing, fever, malaise, weight loss, chest pain, and a cough productive of blood-streaked sputum.
- Therapy is aimed at minimizing the quantity of antigenic material released in the tracheobronchial tree.
- Antifungal therapy is generally not indicated in the management of allergic manifestations of aspergillosis, although some patients have demonstrated a decrease in their glucocorticoid dose following therapy with itraconazole. Itraconazole 200 mg twice daily for 16 weeks resulted in reduced corticosteroid dose and improvement in exercise tolerance and pulmonary function.

Aspergilloma

- In the nonimmunocompromised host, *Aspergillus* infections of the sinuses most commonly occur as saprophytic colonization (aspergillomas, or "fungus balls") of previously abnormal sinus tissue. Treatment consists of removal of the aspergilloma. Therapy with glucocorticoids and surgery is generally successful.
- Although IV amphotericin B is generally not useful in eradicating aspergillomas, intracavitary instillation of amphotericin B has been employed successfully in a limited number of patients. Hemoptysis generally ceases when the aspergilloma is eradicated.

Invasive Aspergillosis

- Patients often present with classic signs and symptoms of acute pulmonary embolus: pleuritic chest pain, fever, hemoptysis, a friction rub, and a wedge-shaped infiltrate on chest radiographs.
- Demonstration of *Aspergillus* by repeated culture and microscopic examination of tissue provides the most firm diagnosis.
- In the immunocompromised host, aspergillosis is characterized by vascular invasion leading to thrombosis, infarction, and necrosis of tissue.

Treatment

- Antifungal therapy should be instituted in any of the following conditions: (1) persistent fever or progressive sinusitis unresponsive to antimicrobial therapy; (2) an eschar over the nose, sinuses, or palate; (3) the presence of characteristic radiographic findings, including wedge-shaped infarcts, nodular densities, or new cavitary lesions; or (4) any clinical manifestation suggestive of orbital or cavernous sinus disease or an acute vascular event associated with fever. Isolation of *Aspergillus* spp. from nasal or respiratory tract secretions should be considered confirmatory evidence in any of the previously mentioned clinical settings.
- Voriconazole is the drug of choice for primary therapy of most patients with aspergillosis as it provided improved survival and fewer side effects.
- In patients who cannot tolerate voriconazole, amphotericin B can be used. Full doses (1–1.5 mg/kg/day) are generally recommended, with response measured by defervescence and radiographic clearing. The lipid-based formulations may be preferred as initial therapy in patients with marginal renal function or in patients receiving other nephrotoxic drugs. The optimal duration of treatment is unknown.
- **Caspofungin** is indicated for treatment of invasive aspergillosis in patients who are refractory to or intolerant of other therapies such as amphotericin B.
- The use of prophylactic antifungal therapy to prevent primary infection or reactivation of aspergillosis during subsequent courses of chemotherapy is controversial.

See Chapter 99 Invasive Fungal Infections, authored by Peggy L. Carver, for a more detailed discussion of this topic.

CHAPTER 39

Gastrointestinal Infections

INTRODUCTION

- *Gastrointestinal* (GI) infections are among the more common causes of morbidity and mortality around the world. Most are caused by viruses, and some are caused by bacteria or other organisms. In underdeveloped and developing countries, acute gastroenteritis involving diarrhea is the leading cause of mortality in infants and children younger than 5 years of age. In the United States, there are 179 million episodes of acute gastroenteritis each year, causing over 600,000 hospitalizations and over 5000 deaths.
- Public health measures such as clean water supply and sanitation facilities, as well as quality control of commercial products are important for the control of most enteric infections. Sanitary food handling and preparation practices significantly decrease the incidence of enteric infections.

REHYDRATION, ANTIMOTILITY, AND PROBIOTIC THERAPY

- Treatment of dehydration includes rehydration, replacement of ongoing losses, and continuation of normal feeding. Fluid replacement is the cornerstone of therapy for diarrhea regardless of etiology.
- Initial assessment of fluid loss is essential for rehydration. Weight loss is the most reliable means of determining the extent of water loss. Clinical signs such as changes in skin turgor, sunken eyes, dry mucous membranes, decreased tearing, decreased urine output, altered mentation, and changes in vital signs can be helpful in determining approximate deficits (**Table 39–1**).
- The necessary components of oral rehydration solution (ORS) include glucose, sodium, potassium chloride, and water (**Table 39–2**). ORS should be given in small frequent volumes (5 mL every 2–3 min) in a teaspoon or oral syringe.
- Severely dehydrated patients should be resuscitated initially with lactated Ringer solution or normal intravenous (IV) saline.
- Early refeeding as tolerated is recommended. Age-appropriate diet may be resumed as soon as dehydration is corrected. Early initiation of feeding shortens the course of diarrhea. Initially, easily digested foods, such as bananas, applesauce, and cereal may be added as tolerated. Foods high in fiber, sodium, and sugar should be avoided.
- Antimotility drugs such as **diphenoxylate** and **loperamide** offer symptomatic relief in patients with watery diarrhea by reducing the number of stools. Antimotility drugs are not recommended in patients with many toxin-mediated dysenteric diarrheas (ie, enterohemorrhagic *Escherichia coli* [EHEC], pseudomembranous colitis, shigellosis).
- Several systematic reviews and meta-analyses have shown an overall reduction in the duration of diarrhea by approximately 17 to 30 hours with the use of probiotics. The data do not clearly define type, dose, or duration of probiotic treatment that would result in clinical benefit.

BACTERIAL INFECTIONS

- Antibiotics are not essential in the treatment of most mild diarrheas, and empirical therapy for acute GI infections may result in unnecessary antibiotic courses. Antibiotic choices for bacterial infections are given in **Table 39–3.**

ENTEROTOXIGENIC (CHOLERA-LIKE) DIARRHEA

- *Vibrio cholerae* 01 is the serogroup that most often causes human epidemics and pandemics. Four mechanisms for transmission have been proposed: animal reservoirs, chronic carriers, asymptomatic or mild disease victims, and water reservoirs.

TABLE 39–1 Clinical Assessment of Degree of Dehydration in Children Based on Percentage of Body Weight Loss[a]

Variable	Minimal or No Dehydration (<3% Loss of Body Weight)	Mild-to-Moderate (3–9% Loss of Body Weight)	Severe (≥10% Loss of Body Weight)
Blood pressure	Normal	Normal	Normal to reduced
Quality of pulses	Normal	Normal or slightly decreased	Weak, thready, or not palpable
Heart rate	Normal	Normal to increased	Increased (bradycardia in severe cases)
Breathing	Normal	Normal to fast	Deep
Mental status	Normal	Normal to listless	Apathetic, lethargic, or comatose
Eyes	Normal	Sunken orbits/decreased tears	Deeply sunken orbits/absent tears
Mouth and tongue	Moist	Dry	Parched
Thirst	Normal	Eager to drink	Drinks poorly; too lethargic to drink
Skin fold	Normal	Recoil in <2 seconds	Recoil in >2 seconds
Extremities	Warm, normal capillary refill	Cool, prolonged capillary refill	Cold, mottled, cyanotic, prolonged capillary refill
Urine output	Normal to decreased	Decreased	Minimal
Hydration therapy	None	ORS 50–100 mL/kg over 3–4 hours	Lactated Ringer's solution or normal saline 20 mL/kg in 15–30 minutes intravenously until mental status or perfusion improve; followed by 5% dextrose ½ normal saline intravenously at twice maintenance rates or ORS 100 mL/kg over 4 hours.
Replacement of ongoing losses	<10 kg body weight: 60–120 mL ORS per >10 kg body weight: 120–240 mL ORS per diarrheal stool or emesis	Same	If unable to tolerate ORS, administer through nasogastric tube or administer 5% dextrose ½ normal saline with 20 mEq/L potassium chloride intravenously

ORS, oral rehydration solution.

[a]Percentages vary among authors for each dehydration category; hemodynamic and perfusion status is most important; when unsure of category, therapy for more severe category is recommended.

Data from King CK, Glass R, Bresee JS, Duggan C. Managing acute gastroenteritis among children: oral rehydration, maintenance, and nutritional therapy. MMWR Recomm Rep. 2003;52(RR-16):1–16; and World Health Organization. The treatment of diarrhoea: a manual for physicians and other senior health workers http://whqlibdoc.who. int/publications/2005/9241593180.pdf. Geneva, Switzerland: World Health Organization; 2005.

TABLE 39–2 Comparison of Common Solutions Used in Oral Rehydration and Maintenance

Product	Na (mEq/L)	K (mEq/L)	Base (mEq/L)	Carbohydrate (mmol/L)	Osmolality (mOsm/L)
WHO/UNICEF (2002)	75	20	30	75	245
Naturalyte	45	20	48	140	265
Pedialyte	45	20	30	140	250
Infalyte	50	25	30	70	200
Rehydralyte	75	20	30	140	250
Cola	2	0	13	700	750
Apple juice[a]	5	32	0	690	730
Chicken broth[a]	250	8	0	0	500
Sports beverage[a]	20	3	3	255	330

WHO/UNICEF, World Health Organization/United Nations (International) Children's Fund.
[a]These solutions should be avoided in dehydration.

TABLE 39–3 Recommendations for Antibiotic Therapy

Pathogen	Children	Adults
Watery Diarrhea		
Vibrio cholerae O1	Erythromycin 30 mg/kg/day divided every 8 hours orally × 3 days; azithromycin 10 mg/kg/day given orally once daily × 3 days	Doxycycline 300 mg orally × 1 day Alternatives: tetracycline 500 mg orally four times daily × 3 days; erythromycin 250 mg orally every 8 hours × 3 days; azithromycin 500 mg orally once daily × 3 days
Enterotoxigenic *Escherichia coli*	Azithromycin 10 mg/kg/day given orally once daily × 3 days; ceftriaxone 50 mg/kg/day given IV once daily × 3 days	Ciprofloxacin 750 mg orally once daily × 1–3 days. Alternatives: rifaximin 200 mg orally three times daily × 3 days; azithromycin 1,000 mg orally × 1 day or 500 mg orally daily × 3 days
Dysenteric Diarrhea		
Shigella species[a]	Azithromycin 10 mg/kg/day given orally once daily × 3 days; ceftriaxone 50 mg/kg/day given IV once daily × 3 days	Ciprofloxacin 750 mg orally once daily × 3 days; levofloxacin 500 mg orally once daily × 3 days Alternatives: azithromycin 500 mg orally once daily × 3 days
Salmonella		
Nontyphoidal[a]	Ceftriaxone 100 mg/kg/day divided IV every 12 hours × 7–10 days; azithromycin 20 mg/kg/day orally once daily × 7 days	Ciprofloxacin 750 mg orally once daily × 7–10 days; levofloxacin 500 mg orally once daily × 7–10 days Alternatives: azithromycin 500 mg orally once daily × 7 days For immunocompromised patients, duration should be increased to 14 days for both fluoroquinolones and azithromycin

(*continued*)

TABLE 39–3 Recommendations for Antibiotic Therapy (Continued)

Pathogen	Children	Adults
Campylobacter[a]	Azithromycin 10 mg/kg/day given orally once daily × 3–5 days; erythromycin 30 mg/kg/day divided into two to four doses orally × 3–5 days	Azithromycin 500 mg orally once daily × 3 days; erythromycin 500 mg orally every 6 hours × 3 days
Yersinia species[a]	Treat as shigellosis	Treat as shigellosis
Clostridium difficile	Metronidazole 7.5 mg/kg (maximum: 500 mg) orally or IV every 8 hours × 10–14 days; vancomycin 10 mg/kg (maximum: 125 mg) orally every 6 hours × 10–14 days	Mild-to-moderate disease: metronidazole 500 mg orally or IV every 8 hours daily × 10–14 days Severe disease: vancomycin 125 mg orally every 6 hours × 10–14 days Alternatives: rifaximin 400 mg orally every 6 hours × 10–14 days; fidaxomicin 200 mg orally every 12 hours × 10–14 days
Traveler's Diarrhea		
Prophylaxis[a]		Norfloxacin 400 mg or ciprofloxacin 750 mg orally daily; rifaximin 200 mg one to three times daily up to 2 weeks
Treatment		Ciprofloxacin 750 mg orally × 1 day or 500 mg orally every 12 hours × 3 days; levofloxacin 1,000 mg orally × 1 day or 500 mg orally daily × 3 days; rifaximin 200 mg three times daily × 3 days; azithromycin 1,000 mg orally × 1 day or 500 mg orally daily × 3 days

[a]For high-risk patients only. See the preceding text for the high-risk patients in each infection.

- Most pathology of cholera is thought to result from an enterotoxin that increases cyclic adenosine monophosphate–mediated secretion of chloride ion into the intestinal lumen, which results in isotonic secretion (primarily in the small intestine) exceeding the absorptive capacity of the intestinal tract (primarily the colon).
- The incubation period of *V. cholerae* is 1 to 3 days.
- Cholera is characterized by a spectrum from the asymptomatic state to the most severe typical cholera syndrome. Patients may lose up to 1 L of isotonic fluid every hour. The onset of diarrhea is abrupt and is followed rapidly or sometimes preceded by vomiting. Fever occurs in less than 5% of patients. In the most severe state, this disease can progress to death in a matter of 2 to 4 hours if not treated.
- The goal of treatment is rapid restoration of fluid losses, correction of metabolic acidosis, and replacement of potassium deficiency. The mainstay of treatment for cholera consists of fluid and electrolyte replacement with ORS to restore fluid and electrolyte losses. Rice-based rehydration formulations are the preferred ORS for cholera patients. In patients who cannot tolerate ORS, IV therapy with Ringer lactate can be used.
- Antibiotics are not necessary in most cholera cases. In severe cases, antibiotics shorten the duration of diarrhea, decrease the volume of fluid lost, and shorten the duration of the carrier state (see **Table 39–4**). A single dose of oral **doxycycline** is the

TABLE 39–4 Characteristics of Acute Bacterial Gastroenteritis

Bacteria	Incubation Period	Duration	Mode of Transmission	Common Symptoms
Watery Diarrhea				
Vibrio cholerae	2–3 days	1–3 days	Contaminated food or water with human feces usually in areas of inadequate treatment of sewage and drinking water	Profuse watery diarrhea, vomiting, and leg cramps Death can occur within hours without treatment
Enterotoxigenic *E. coli*	1–3 days	3–4 days	Contaminated food or water with animal or human feces	Watery diarrhea and abdominal cramping
Enteropathogenic *E. coli*	9–12 hours	NR	Contaminated food or water with animal or human feces	Acute onset of profuse watery diarrhea, vomiting, and low-grade fever in young children (<2 years of age) in the developing world
Enteroaggregative *E. coli*	NR	NR	Contaminated food or water with animal or human feces	Chronic, watery, mucoid, secretory diarrhea with low-grade fever in immunocompromised persons (HIV infections)
Enteroinvasive *E. coli*	10–18 hours	NR	Contaminated food or water with animal or human feces	Watery diarrhea in young children in the developing world
Dysentery Diarrhea				
Shigella	1–3 days	1–7 days	Fecal–oral Contaminated food or water with infected human feces	Watery or bloody diarrhea (8–10 stools/day), severe abdominal pain, fever, and malaise
Enterohemorrhagic *E. coli*	3–4 days	5–7 days	Contaminated food (particularly cattle) or water with animal or human feces	Severe stomach cramps, diarrhea (often bloody), and vomiting Approximately 5–10% develop hemolytic uremic syndrome
Campylobacter jejuni	2–5 days	5–7 days	Contaminated food (particularly poultry), water, or contact with infected animals	Diarrhea (often bloody), cramping, abdominal pain, and fever
Nontyphoid *Salmonella*	12–36 hours	1–5 days	Contaminated food, water, or contact with infected animals	Diarrhea (sometimes bloody), fever, and abdominal cramps
Yersinia	4–7 days	1–3 weeks	Contaminated food or water	Fever, abdominal pain, and diarrhea (often bloody)

NR, not reported.

TABLE 39–5 Characteristics of Agents Responsible for Acute Viral Gastroenteritis

Virus	Peak Age of Onset	Time of Year	Duration	Mode of Transmission	Common Symptoms
Rotavirus	6 months to 2 years	October to April	3–7 days	Fecal–oral, water, food	Nausea, vomiting, diarrhea, fever, abdominal pain, lactose intolerance
Norovirus	All age groups	Peak in winter	2–3 days	Fecal–oral, food, water, environment	Nausea, vomiting, diarrhea, abdominal cramps, myalgia
Astrovirus	<7 years	Winter	1–4 days	Fecal–oral, water, shellfish	Diarrhea, headache, malaise, nausea
Enteric adenovirus	<2 years	Year-round	7–9 days	Fecal–oral	Diarrhea, respiratory symptoms, vomiting, fever
Pestivirus	<2 years	NR	3 days	NR	Mild
Coronavirus-like particles	<2 years	Fall and early winter	7 days	NR	Respiratory disease
Enterovirus	NR	NR	NR	NR	Mild diarrhea, secondary organ damage

NR, not reported.

preferred agent. In children and pregnant women, **erythromycin** and **azithromycin** may be used. In areas of high tetracycline resistance, fluoroquinolones are effective.

TRAVELER'S DIARRHEA

- Traveler's diarrhea describes the clinical syndrome caused by contaminated food or water that is manifested by malaise, anorexia, and abdominal cramps followed by the sudden onset of diarrhea that incapacitates many travelers.
- The most common pathogens are bacterial in nature and include enterotoxigenic *Escherichia coli* (ETEC) (20%–72%), Shigella (3%–25%), Campylobacter (3%–17%), and Salmonella (3%–7%). Viruses (up to 30%) are also potential causes, as are parasites.
- Although the efficacy of prophylactic antibiotics has been documented, their use is not recommended for most travelers due to the potential side effects of antibiotics. Prophylactic antibiotics are recommended only in high-risk individuals or in situations in which short-term illness could ruin the purpose of the trip, such as a military mission. A fluoroquinolone is the drug of choice when traveling to most areas of the world.
- The goals of treatment are to avoid dehydration, reduce the severity and duration of symptoms, and prevent interruption to planned activities.
- Fluid and electrolyte replacement should be initiated at the onset of diarrhea.
- Antibiotics used for treatment are found in **Table 39–4**.
- For symptom relief, **loperamide** (preferred because of its quicker onset and longer duration of relief relative to bismuth) may be taken (4 mg orally initially and then 2 mg with each subsequent loose stool to a maximum of 16 mg/day in patients without bloody diarrhea and fever). Loperamide should be discontinued if symptoms persist for more than 48 hours. Other symptomatic therapy in mild diarrhea includes

bismuth subsalicylate 524 mg every 30 minutes for up to eight doses. There is insufficient evidence to warrant the recommendation of probiotics.

CLOSTRIDIUM DIFFICILE

- *C. difficile* is the most common cause of infectious diarrhea in hospitalized patients in North America and Europe. It is associated most often with broad-spectrum antimicrobials, including clindamycin, ampicillin, cephalosporins, and fluoroquinolones.
- Pseudomembranous colitis may result in a spectrum of disease, from mild diarrhea to life-threatening toxic megacolon and pseudomembranous enterocolitis. *C. difficile* infection (CDI) should be suspected in patients experiencing diarrhea with a recent history of antibiotic use (within the previous 3 months) or in those whose diarrhea began 72 hours after hospitalization.
- Diagnosis is established by detection of toxin A or B in the stool, stool culture for *C. difficile,* or endoscopy.
- Initial therapy should include discontinuation of the offending agent. The patient should be supported with fluid and electrolyte replacement.
- Both vancomycin and metronidazole are effective, but **metronidazole,** 250 mg orally four times daily or 500 mg three times daily, is the drug of choice for mild to moderate CDI. In patients with severe disease, contraindication or intolerance to metronidazole, and inadequate response to metronidazole, oral vancomycin, or fidaxomicin is recommended.
- Relapse can occur in 20% of patients. Management of a first relapse is identical to the primary episode. The optimal management of multiple relapses is not clear. Fecal transplantation is sometimes used.
- Drugs that inhibit peristalsis, such as **diphenoxylate**, are contraindicated.

VIRAL INFECTIONS

- Viruses are now recognized as the leading cause of diarrhea in the world.
- In infants and children rotavirus, a double-stranded, wheel-shaped RNA virus is the most common cause of diarrhea worldwide and 1 million people die annually from the infection.
- In the United States, routine rotavirus vaccination is recommended for all infants beginning at age 2 months. There are two vaccines, RotaTeq (RV5) and Rotarix (RV1) available for reducing rotaviral gastroenteritis.

See Chapter 91, Gastrointestinal Infections and Enterotoxigenic Poisonings, authored by Steven Martin and Rose Jung, for a more detailed discussion of this topic.

Human Immunodeficiency Virus Infection

CHAPTER 40

- **Tables 40–1** and **40–2** present the case definition for adult, adolescent, and children, respectively, for *human immunodeficiency virus* (HIV) infection.

ETIOLOGY AND PATHOGENESIS

- Infection with HIV occurs through three primary modes: sexual, parenteral, and perinatal. Sexual intercourse, primarily anal and vaginal intercourse, is the most common vehicle for transmission. The probability of HIV transmission from receptive anorectal intercourse is 0.5% to 3% per sexual contact and lower for receptive vaginal intercourse. Condom use reduces the risk of transmission by ~20-fold. Individuals with genital ulcers or sexually transmitted diseases, such as syphilis, chancroid, herpes, gonorrhea, *Chlamydia,* and trichomoniasis are at great risk for contracting HIV.
- The use of contaminated needles or other injection-related paraphernalia by drug abusers has been the main cause of parenteral transmissions of HIV.
- Healthcare workers have a small risk of occupationally acquiring HIV, mostly through accidental injury, most often percutaneous needlestick injury.
- Perinatal infection, or vertical transmission, is the most common cause of pediatric HIV infection. The risk of mother-to-child transmission is ~25% in the absence of breast-feeding or antiretroviral therapy. Breast-feeding can also transmit HIV.

CLINICAL PRESENTATION AND DIAGNOSIS

- Clinical presentations of primary HIV infection vary, but patients often have a viral syndrome or mononucleosis-like illness with fever, pharyngitis, and adenopathy (**Table 40–3**). Symptoms may last for 2 weeks.
- The probability of progression to AIDS is related to RNA viral load; in one study, 5-year mortality rates were 5% for those with a viral load less than 4530 and 49% for those greater than 36,270.
- Most children born with HIV are asymptomatic. On physical examination, they often present with unexplained physical signs such as lymphadenopathy, hepatomegaly, splenomegaly, failure to thrive, weight loss or unexplained low birth weight, and fever of unknown origin. Laboratory findings include anemia, hypergammaglobulinemia, altered mononuclear cell function, and altered T-cell subset ratios. The normal range for CD4 cell counts in children is much different than for adults (see **Table 40–2**).
- Clinical presentations of the opportunistic infections are presented in Infectious Complications of HIV below.
- The preferred method for diagnosing HIV is an enzyme-linked immunosorbent assay, which detects antibodies against HIV-1 and is both highly sensitive and specific. False-positives can occur in multiparous women; in recent recipients of hepatitis B, HIV, influenza, or rabies vaccine; following multiple blood transfusions; and in those with liver disease or renal failure or undergoing chronic hemodialysis. False-negatives may occur if the patient is newly infected and the test is performed before antibody production is adequate. The minimum time to develop antibodies is 3 to 4 weeks from initial exposure.
- Positive enzyme-linked immunosorbent assays are repeated in duplicate and if one or both tests are reactive, a confirmatory test is performed for final diagnosis. Western blot assay is the most commonly used confirmatory test, although an indirect immunofluorescence assay is available.
- The viral load test quantifies viremia by measuring the amount of viral RNA. There are several methods used for determining the amount of HIV RNA: reverse transcriptase–coupled polymerase chain reaction, branched DNA, and nucleic acid

TABLE 40–1 Surveillance Case Definition for HIV Infection Among Adults and Adolescents (≥13 years) – United States, 2008

Stage	Laboratory evidence (laboratory-confirmed HIV infection *plus*)	Clinical evidence
Stage 1	$CD4^+$ cell count ≥500 cells/mm^3 (500 × 10^6/L) or $CD4^+$ percentage ≥29	None required (but no AIDS-defining condition)
Stage 2	$CD4^+$ cell count 200–499 cells/mm^3 (200–499 × 10^6/L) or $CD4^+$ percentage 14–28	None required (but no AIDS-defining condition)
Stage 3 (AIDS)	$CD4^+$ cell count <200 cells/mm^3 (<200 × 10^6/L) or $CD4^+$ percentage <14	Or documentation of an AIDS-defining condition (with laboratory-confirmed HIV infection)
Stage unknown	No information on $CD4^+$ counts	And no information on presence of AIDS-defining conditions
AIDS indicator conditions		
Candidiasis of bronchi, trachea, or lungs	Lymphoma, Burkitt	
Candidiasis, esophageal	Lymphoma, immunoblastic	
Cervical cancer, invasive	Lymphoma, primary, for brain	
Coccidioidomycosis, disseminated or extrapulmonary	*Mycobacterium avium* complex or *Mycobacterium kansasii*, disseminated or extrapulmonary	
Cryptococcosis, extrapulmonary	*Mycobacterium tuberculosis,* any site (pulmonary or extrapulmonary)	
Cryptosporidiosis, chronic intestinal (duration >1 month)	*Mycobacterium*, other species or unidentified species, disseminated or extrapulmonary	
Cytomegalovirus disease (other than liver, spleen, or nodes)	*Pneumocystis jirovecii* pneumonia	
Cytomegalovirus retinitis (with loss of vision)	Pneumonia, recurrent	

(*continued*)

TABLE 40–1 Surveillance Case Definition for HIV Infection Among Adults and Adolescents (≥13 years) – United States, 2008 (*Continued*)

Stage	Laboratory evidence (laboratory-confirmed HIV infection *plus*)	Clinical evidence
Encephalopathy, HIV related	Progressive multifocal leukoencephalopathy	
Herpes simplex: chronic ulcer(s) (duration >1 month); or bronchitis, pneumonitis, or esophagitis	*Salmonella* septicemia, recurrent	
Histoplasmosis, disseminated or extrapulmonary	Toxoplasmosis of brain	
Isosporiasis, chronic intestinal (duration >1 month)	Wasting syndrome due to HIV	
Kaposi sarcoma		

Data from Schneider E, Whitmore S, Glynn KM, Dominguez K, et al. Revised surveillance case definitions for HIV infection among adults, adolescents, and children aged <18 months and for HIV infection and AIDS among children aged 18 months to <13 years–United States, 2008. MMWR Recomm Rep 2008;57(RR-10):1–12.

TABLE 40–2 Centers for Disease Control and Prevention 1994 Revised Classification System for HIV Infection in Children Younger Than 13 Years

Immunologic Categories	12 Months cells/μL or 10^6/L (%)[a]	1–5 Years cells/μL or 10^6/L (%)[a]	6–12 Years cells/μL or 10^6/L (%)[a]
1. No evidence of suppression	≥1500 (≥25%)	≥1000 (≥25%)	≥500 (≥25%)
2. Evidence of moderate suppression	750–1499 (15–24%)	500–999 (15–24%)	200–499 (15–24%)
3. Severe suppression	<750 (<15%)	<500 (<15%)	<200 (<15%)

Immunologic Categories	N: No Signs/ Symptoms	A: Mild Signs/ Symptoms	B: Moderate Signs/ Symptoms	C: Severe Signs/ Symptoms
1. No evidence of suppression	N1	A1	B1	C1
2. Evidence of moderate suppression	N2	A2	B2	C2
3. Severe suppression	N3	A3	B3	C3

HIV, human immunodeficiency virus.

[a]Percentage of total lymphocytes.

sequence–based assay. Each assay has its own lower limit of sensitivity, and results can vary from one assay method to the other; therefore, it is recommended that the same assay method be used consistently within patients.

- Viral load can be used as a prognostic factor to monitor disease progression and the effects of treatment.
- The number of CD4 lymphocytes in the blood is a surrogate marker of disease progression. The normal adult CD4 lymphocyte count ranges between 500 and 1600 cells/mm^3 (500 and 1600 × 10^6/L), or 40% to 70% of all lymphocytes.

TABLE 40–3 Clinical Presentation of Primary HIV Infection in Adults

Symptoms
Fever, sore throat, fatigue, weight loss, and myalgia
40%–80% of patients will also exhibit a morbilliform or maculopapular rash usually involving the trunk
Diarrhea, nausea, and vomiting
Lymphadenopathy, night sweats
Aseptic meningitis (fever, headache, photophobia, and stiff neck) may be present in one fourth of presenting case
Other
High viral load (may exceed 1 million copies/mL)
Persistent decrease in CD4 lymphocytes

HIV, human immunodeficiency virus.

TREATMENT

- Goal of Treatment: The central goal of antiretroviral therapy is to decrease morbidity and mortality, improve quality of life, restore and preserve immune function, and prevent further transmission through maximum suppression of HIV replication (HIV RNA level that is undetectable).

GENERAL APPROACH

- Regular, periodic measurement of plasma HIV RNA levels and CD4 cell counts is necessary to determine the risk of disease progression in an HIV-infected individual and to determine when to initiate or modify antiretroviral treatment regimens.
- Treatment decisions should be individualized by the level of risk indicated by plasma HIV RNA levels and CD4 counts.
- The use of potent combination antiretroviral therapy to suppress HIV replication to below the levels of detection of sensitive plasma HIV RNA assays limits the potential for selection of antiretroviral-resistant HIV variants, the major factor limiting the ability of antiretroviral drugs to inhibit virus replication and delay disease progression.
- The most effective means to accomplish durable suppression of HIV replication is the simultaneous initiation of combinations of effective anti-HIV drugs with which the patient has not been previously treated and that are not cross-resistant with antiretroviral agents with which the patient has been treated previously. Each of the antiretroviral drugs used in combination therapy regimens should always be used according to optimum schedules and dosages.
- Women should receive optimal antiretroviral therapy regardless of pregnancy status.
- The same principles of antiretroviral therapy apply to both HIV-infected children and adults, although the treatment of HIV-infected children involves unique pharmacologic, virologic, and immunologic considerations.
- Persons with acute primary HIV infections should be treated with combination antiretroviral therapy to suppress virus replication to levels below the limit of detection of sensitive plasma HIV RNA assays.
- HIV-infected persons, even those with viral loads below detectable limits, should be considered infectious and should be counseled to avoid sexual and drug-use behaviors that are associated with transmission or acquisition of HIV and other infectious pathogens.
- An excellent source for information on treatment guidelines can be found at *http://aidsinfo.nih.gov/*.
- Treatment is recommended for all HIV-infected persons with a CD4 lymphocyte count below 500 cells/mm^3 (500 × 10^6/L). Many clinicians would also favor starting therapy in asymptomatic patients with CD4 counts above 500 cells/mm^3 (500 × 10^6/L). Other indications for therapy at any CD4 count include pregnancy, history of AIDS-defining illness, HIV-associated nephropathy, or HIV/hepatitis B virus coinfection (**Table 40–4**).

PHARMACOLOGIC THERAPY

Antiretroviral Agents

- Inhibiting viral replication with a combination of potent antiretroviral therapy has been the most clinically successful strategy in the treatment of HIV infection. There have been four primary groups of drugs used: entry inhibitors, reverse transcriptase inhibitors, integrase strand transfer inhibitors (InSTIs), and HIV protease inhibitors (PIs) (**Table 40–5**).
- Reverse transcriptase inhibitors are of two types: those that are derivatives of purine- and pyrimidine-based nucleosides and nucleotides (NRTIs) and those that are not nucleoside- or nucleotide-based (NNRTIs).
- Current recommendations for initial treatment of HIV infection advocate a minimum of three active antiretroviral agents: **tenofovir disoproxil fumarate** plus **emtricitabine** with either a ritonavir-enhanced PI (**darunavir** or **atazanavir**), the NNRTI **efavirenz**, or

TABLE 40–4 Treatment of Human Immunodeficiency Virus Infection: Antiretroviral Regimens Recommended in Antiretroviral-Naïve Persons

	Preferred Regimens	Limitation
NNRTI-based	Efavirenz + tenofovir+ emtricitabine (AI)	Not recommended in the first trimester of pregnancy or in women without adequate contraception
HIV PI-based	Darunavir + ritonavir + tenofovir + emtricitabine (AI)	Rash (darunavir has sulfonamide moiety)
	Atazanavir + ritonavir + tenofovir + emtricitabine (AI)	Not with high doses of proton-pump inhibitors, unconjugated hyperbilirubinemia
InSTI-based	Raltegravir + tenofovir + emtricitabine (AI)	Twice daily (not once daily)
Alternative Regimens (Some Potential Disadvantages vs. Preferred Regimens)		
NNRTI-based	Efavirenz + abacavir + lamivudine (BI)	Possible reduced efficacy for high viral loads (abacavir)
	Rilpivirine + tenofovir + emtricitabine (BI)	Possible reduced efficacy for high viral loads; no proton-pump inhibitors (rilpivirine)
	Rilpivirine + abacavir + lamivudine (BIII)	See above
HIV PI-based	Atazanavir + ritonavir + abacavir + lamivudine (BI)	See above
	Darunavir + ritonavir + abacavir + lamivudine (BII)	See above
	Lopinavir–ritonavir (once or twice daily) either with abacavir + lamivudine or tenofovir + emtricitabine (BI)	GI intolerance, lipids
	Fosamprenavir/ritonavir (once or twice daily) either with abacavir + lamivudine or tenofovir + emtricitabine (BI)	Rash
InSTI-based	Raltegravir + abacavir + lamivudine (BIII)	See above
	Elvitegravir + cobicistat + tenofovir + emtricitabine (BI)	Should not be used when creatinine clearance <70 mL/min (<1.17 mL/s)

(*continued*)

TABLE 40–4 Treatment of Human Immunodeficiency Virus Infection: Antiretroviral Regimens Recommended in Antiretroviral-Naïve Persons (*Continued*)

	Preferred Regimens	Limitation
Acceptable Regimens (Potential Additional Disadvantages or Pending Additional Data)		
NNRTI-based	Efavirenz + zidovudine + lamivudine (CI)	Nausea, anemia, lipoatrophy (zidovudine)
	Nevirapine + zidovudine + lamivudine or tenofovir + emtricitabine (CI)	Not in moderate/severe hepatic impairment; not in women with pre-ART CD4 count >250 cells/mm^3 (> 250 × 106/L) and men with pre-ART CD4 count >400 cells/mm^3 (> 400 × 106/L)
	Nevirapine + abacavir + lamivudine (CIII)	See above
	Rilpivirine + zidovudine + lamivudine (CIII)	See above
HIV PI-based	Atazanavir + (abacavir or zidovudine) + lamivudine (CI)	Lower atazanavir concentrations compared with atazanavir–ritonavir
	(Fosamprenavir + ritonavir or atazanavir + ritonavir) + zidovudine + lamivudine (CI)	See above
	(Darunavir + ritonavir or lopinavir + ritonavir) + zidovudine + lamivudine (CIII)	See above
CCR5-inhibitor-based	Maraviroc + zidovudine + lamivudine (CI)	Lower virologic activity versus efavirenz, need tropism test
	Maraviroc + (tenofovir + emtricitabine or abacavir + lamivudine) (CIII)	See above
InSTI-based	Raltegravir + zidovudine + lamivudine (CIII)	See above
Regimens or Components that should not be used as Initial Therapy		
Regimen or Component		**Comment**
Any all NRTI regimen (DI)		Inferior virologic efficacy
Lamivudine (or emtricitabine) + didanosine (DIII)		Inferior virologic efficacy
Didanosine + tenofovir (DII)		Inferior virologic efficacy, CD4 declines
Stavudine (DI)		Toxicity including subcutaneous fat loss, peripheral neuropathy, and lactic acidosis

Darunavir, fosamprenavir, saquinavir, or tipranavir without ritonavir (DI-DIII)	Insufficient plasma concentrations and efficacy or not studied
Delavirdine (DIII)	Inferior virologic efficacy and inconvenient dosing
Enfuvirtide (DIII)	Not studied in naïve patients, inconvenient injections
Etravirine (DIII)	Insufficient data in naïve patients
Indinavir with or without ritonavir (DIII)	Nephrolithiasis, fluid requirements and inconvenient
Nelfinavir (without ritonavir) (DI)	Inferior virologic efficacy
Ritonavir at virologic doses (DIII)	GI intolerance
Tipranavir–ritonavir (DI)	Inferior virologic efficacy

Tenofovir, tenofovir disoproxil fumarate.
Evidence-based rating definition.
Rating strength of recommendation:
A: Both strong evidence for efficacy and substantial clinical benefit support recommendation for use; should always be offered.
B: Moderate evidence for efficacy or strong evidence for efficacy but only limited clinical benefit, supports recommendation for use; should usually be offered.
C: Evidence for efficacy is insufficient to support a recommendation for or against use, or evidence for efficacy might not outweigh adverse consequences (e.g., drug toxicity, drug interactions) or cost of treatment under consideration; use is optional.
D: Moderate evidence for lack of efficacy or for adverse outcome supports recommendation against use; should usually not be offered.
E: Good evidence for lack of efficacy or for adverse outcome supports a recommendation against use; should never be offered.
Rating Quality of Evidence Supporting the Recommendation:
I: Evidence from at least one correctly randomized, controlled trial with clinical outcomes and/or validated laboratory endpoints.
II: Evidence from at least one well-designed clinical trial without randomization or observational cohorts with long-term clinical outcomes.
III: Evidence from opinions of respected authorities based on clinical experience, descriptive studies, or reports of consulting committees.
Lamivudine and emtricitabine are considered interchangeable.

Adapted from Department of Health and Human Services (DHHS) Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the use of antiretroviral agents in HIV-1 infected adults and adolescents. Updated March 27, 2012. http://AIDSinfo.NIH.gov. From reference 30.

TABLE 40–5 Selected Pharmacologic Characteristics of Antiretroviral Compounds

Drug	*F* (%)	$t_{1/2}$ (h)[a]	Adult Dose[b] (doses/day)	Plasma C_{max}/C_{min} (μM)	Distinguishing Adverse Effect
Integrase Inhibitors (InSTI)					
Elvitegravir (coformulated with cobicistat)	?	13	150 mg (1)	3.8/1	Diarrhea, nausea, headache
Raltegravir	?	9	400 mg (2)	1.74/0.22	Increased creatine phosphokinase
Nucleoside (Nucleotide) Reverse Transcriptase Inhibitors (NtRTIs)					
Abacavir	83	1.5/20	300 mg (2) *or* 600 mg (1)	5.2/0.03 7.4[c]	Hypersensitivity
Didanosine	42	1.4/24	200 mg (2) *or* 400 mg (1)	2.8/0.03 5.6[c]	Peripheral neuropathy, pancreatitis
Emtricitabine	93	10/39	200 mg (1)	7.3/0.04	Pigmentation on soles and palms in non-whites
Lamivudine	86	5/22	150 mg (2) *or* 300 mg (1)	6.3/1.6 10.5/0.5	Headache, pancreatitis (children)
Stavudine	86	1.4/7	40 mg (2)	2.4/0.04	Lipoatrophy, peripheral neuropathy
Tenofovir disoproxil fumarate	40	17/150	300 mg (1)	1.04/0.4	Renal toxicity (proximal tubulopathy)
Zidovudine	85	2/7	200 mg (3) *or* 300 mg (2)	0.2 3[c]	Anemia, neutropenia, myopathy
Nonnucleoside Reverse Transcriptase Inhibitors (NNRTIs)					
Delavirdine	85	5.8	400 mg (3) *or* 600 mg (2)	35/14	Rash, elevated liver function tests

Efavirenz	43	48	600 mg (1)	12.9/5.6	CNS disturbances and potential teratogenicity
Etravirine	?	41	200 mg (2)	1.69/0.86	Rash, nausea
Nevirapine	93	25	200 mg (2)[d]	22/14	Potentially serious rash and hepatotoxicity
Rilpivirine	?	50	25 mg (1)	0.7/0.3	Possibly depression
Protease Inhibitors (PIs)					
Fosamprenavir[e]			1400 mg (1)[e,f]	14.3/2.9	Rash
Atazanavir	68	7	400 mg (1) *or* 300 mg (1)[f]	3.3/0.23 6.2/0.9	Unconjugated hyperbilirubinemia
Darunavir	82	15	800 mg (1)[f] *or* 600 mg (2)[f]	11.9/6.5	Hepatitis, rash
Indinavir	60	1.5	800 mg (3) *or* 400–800 mg (2)[f]	13/0.25	Nephrolithiasis
Lopinavir[g]	?	5.5	800 mg (1) *or* 400 mg (2)	13.6/7.5	Hyperlipidemia/GI intolerance
Nelfinavir	?	2.6	750 mg (3) *or* 1250 mg (2)	5.3/1.76 7/1.2	Diarrhea

(*continued*)

TABLE 40–5 Selected Pharmacologic Characteristics of Antiretroviral Compounds (*Continued*)

Drug	*F* (%)	$t_{1/2}$ (h)[a]	Adult Dose[b] (doses/day)	Plasma C_{max}/C_{min} (μM)	Distinguishing Adverse Effect
Ritonavir	60	3–5	600 mg (2)[d] *or* "Boosting doses"	16/5	GI intolerance
Saquinavir	4	3	1,000 mg (2)[f]	3.9/0.55	QT prolongation
Tipranavir	?	6	500 mg (2)[f]	77.6/35.6	Hepatotoxicity, intracranial hemorrhage
Entry Inhibitors—Fusion Inhibitor					
Enfuvirtide	84	3.8	90 mg (2)	1.1/0.73	Injection-site reactions
Coreceptor Inhibitor					
Maraviroc	33	15	300 mg (2)	1.2/0.066	Hepatitis, allergic reaction

C_{max}, maximum plasma concentration; C_{min}, minimum plasma concentration; *F*, bioavailability; $t_{1/2}$, elimination half-life.
[a]NtRTIs: Plasma NtRTI $t_{1/2}$/intracellular (peripheral blood mononuclear cells) NtRTI-triphosphate $t_{1/2}$; plasma $t_{1/2}$ only for other classes.
[b]Dose adjustment may be required for weight, renal or hepatic disease, and drug interactions.
[c]C_{min} concentration typically below the limit of quantification.
[d]Initial dose escalation recommended to minimize side effects.
[e]Fosamprenavir is a tablet phosphate prodrug of amprenavir. Amprenavir is no longer available.
[f]Must be boosted with low doses of ritonavir (100 to 200 mg).
[g]Available as coformulation 4:1 lopinavir to ritonavir.

Adapted from Department of Health and Human Services (DHHS) Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the use of antiretroviral agents in HIV-1 infected adults and adolescents. Updated March 27, 2012. http://AIDSinfo.NIH.gov and product information for agents.

the InSTI, **raltegravir**. Multiple alternative regimens are also safe and effective, but have one or two disadvantages compared with the preferred regimens such as lack of long-term follow-up, weaker virologic responses with high viral loads, lower tolerability, or greater risk of long-term toxicities such as subcutaneous fat loss.

- Significant drug interactions can occur with many antiretroviral agents. The latest information on drug interactions of antiretroviral drugs should be consulted.
  - ✓ **Ritonavir** is a potent inhibitor of cytochrome P450 enzyme 3A and is used to reduce clearance of other PIs. **Rifampin** may substantially reduce the concentrations of PIs and is contraindicated with the use of most PIs. Saint John's wort is a potent inducer of metabolism and is contraindicated with PIs, NNRTIs, and **maraviroc**.

TREATMENT DURING PREGNANCY

- In general, pregnant women should be treated like nonpregnant adults with some exceptions. Efavirenz should be avoided when possible in pregnant women during the first trimester or in women trying to conceive because of potential teratogenicity. Drugs that cross the placental barrier should be avoided, such as **abacavir**, emtricitabine, **lamivudine**, tenofovir, or **zidovudine.**
- Intravenous (IV) zidovudine is recommended intrapartum depending on the mother's viral load, based on early studies demonstrating clear prophylactic effectiveness as well as extensive familiarity with the side effect profile. Infants also receive zidovudine (± several doses of **nevirapine**) prophylaxis for 6 weeks after birth.

POSTEXPOSURE PROPHYLAXIS

- Postexposure prophylaxis with a triple-drug regimen consisting of two NRTIs and a boosted PI is recommended for percutaneous blood exposure involving significant risk (ie, large-bore needle or large volume of blood or blood from patients with advanced AIDS).
- Two NRTIs may be offered to healthcare workers with lower risk of exposure such as that involving either the mucous membrane or skin. Treatment is not necessary if the source of exposure is urine or saliva.
- The optimal duration of treatment is unknown, but at least 4 weeks of therapy is advocated. Ideally, treatment should be initiated within 1 to 2 hours of exposure, but treatment is recommended for up to 72 hours postexposure.

EVALUATION OF THERAPEUTIC OUTCOMES

- Following the initiation of therapy, patients are usually monitored at 3-month intervals with immunologic (ie, CD4 count), virologic (HIV RNA), and clinical assessments.
- There are two general indications to change therapy: significant toxicity and treatment failure.
- Specific criteria to indicate treatment failure have not been established through controlled clinical trials. As a general guide, the following events should prompt consideration for changing therapy:
  - ✓ Less than a 1 $\log_{10}$ reduction in HIV RNA 1 to 4 weeks after the initiation of therapy, or a failure to achieve less than 200 copies/mL ($<200 \times 10^3$/L) by 24 weeks or less than 50 copies/mL ($<50 \times 10^3$/L) by 48 weeks
  - ✓ After HIV RNA suppression, repeated detection of HIV-RNA
  - ✓ Clinical disease progression, usually the development of a new opportunistic infection

THERAPEUTIC FAILURE

- The most important measure of therapeutic failure is suboptimal suppression of viral replication.

- Therapeutic failure may be the result of nonadherence to medication, development of drug resistance, intolerance to one or more medications, adverse drug–drug interactions, or pharmacokinetic–pharmacodynamic variability.
- Patients should be treated with at least two (preferably three) fully active antiretroviral drugs based on medication history, resistance tests, and new mechanistic drug classes (eg, maraviroc and raltegravir). The goal of therapy is to suppress HIV-RNA to less than 50 copies/mL ($<50 \times 10^3$/L). In cases when less than 50 copies/mL ($<50 \times 10^3$/L) cannot be attained, maintenance on the regimen is preferred over drug discontinuation so as to prevent rapid immunological and clinical decline.

INFECTIOUS COMPLICATIONS OF HUMAN IMMUNODEFICIENCY VIRUS

- The development of certain opportunistic infections is directly or indirectly related to the level of CD4 lymphocytes. The principle in the management of opportunistic infections (OIs) is treating HIV infection to enable CD4 cells to recover and be maintained above safe levels. Other important principles are:
  - ✓ Preventing exposure to opportunistic pathogens
  - ✓ Using vaccinations to prevent first episodes of disease
  - ✓ Initiating primary chemoprophylaxis at certain CD4 thresholds to prevent first episodes of disease
  - ✓ Treating emergent OIs
  - ✓ Initiating secondary chemoprophylaxis to prevent disease recurrence
  - ✓ Discontinuing prophylaxis with sustained immune recovery
- The spectrum of infectious diseases observed in HIV-infected individuals and recommended first-line therapies are shown in **Table 40–6.**

Pneumocystis carinii (Pneumocystis jiroveci)

- *P. jiroveci* pneumonia is the most common life-threatening opportunistic infection in patients with AIDS. The taxonomy of the organism is unclear, having been classified as both protozoan and fungal.

CLINICAL PRESENTATION

- Characteristic symptoms include fever and dyspnea; clinical signs are tachypnea, with or without rales or rhonchi, and a nonproductive or mildly productive cough. Chest radiographs may show florid or subtle infiltrates or may occasionally be normal, although infiltrates are usually interstitial and bilateral. Arterial blood gases may show minimal hypoxia (partial pressure of oxygen [PaO_2] 80 to 95 mm Hg [10.6–12.6 kPa]) but in more advanced disease may be markedly abnormal.
- The onset of *P. carinii* pneumonia (PCP) is often insidious, occurring over a period of weeks. Clinical signs are tachypnea with or without rales or rhonchi and a nonproductive or mildly productive cough occurring over a period of weeks, although more fulminant presentations can occur.

TREATMENT

- Treatment with **trimethoprim–sulfamethoxazole** or parenteral pentamidine is associated with a 60% to 100% response rate. Trimethoprim–sulfamethoxazole is the regimen of choice for treatment and subsequent prophylaxis of PCP in patients with and without HIV.
- Trimethoprim–sulfamethoxazole is given in doses of 15 to 20 mg/kg/day (based on the trimethoprim component) as three or four divided doses for the treatment of PCP. Treatment duration is typically 21 days but must be based on clinical response.
- Trimethoprim–sulfamethoxazole is usually initiated by the IV route, although oral therapy (as oral absorption is high) may suffice in mildly ill and reliable patients or to complete a course of therapy after a response has been achieved with IV administration.
- The more common adverse reactions seen with trimethoprim–sulfamethoxazole are rash (including Stevens–Johnson syndrome), fever, leukopenia, elevated serum

TABLE 40–6 Therapies for Common Opportunistic Pathogens in HIV-Infected Individuals

Clinical Disease	Preferred Initial Therapies for Acute Infection in Adults (Strength of Recommendation in Parentheses)	Common Drug- or Dose-Limiting Adverse Reactions
Fungi		
Candidiasis, oral	Fluconazole 100 mg orally for 7–14 days (AI)	Elevated liver function tests, hepatotoxicity, nausea, and vomiting
	or	
	Nystatin 500,000 units oral swish (~5 mL) four times daily for 7–14 days (BII)	Taste, patient acceptance
Candidiasis, esophageal	Fluconazole 100–400 mg orally or IV daily for 14–21 days (AI)	Same as above
	or	
	Itraconazole 200 mg/day orally for 14–21 days (AI)	Elevated liver function tests, hepatotoxicity, nausea, and vomiting
Pneumocystis jirovecii pneumonia	Trimethoprim–sulfamethoxazole IV or orally 15–20 mg/kg/day as trimethoprim component in three to four divided doses for 21 days[a] (AI)	Skin rash, fever, leucopenia Thrombocytopenia
	Moderate or severe therapy should be started IV	
	or	
	Pentamidine IV 4 mg/kg/day for 21 days[a] (AI)	Azotemia, hypoglycemia, hyperglycemia, arrhythmias
	Mild episodes	
	Atovaquone suspension 750 mg (5 mL) orally twice daily with meals for 21 days[a] (BI)	Rash, elevated liver enzymes, diarrhea
Cryptococcal meningitis	Amphotericin B 0.7 mg/kg/day IV for a minimum of 2 weeks with flucytosine 100 mg/kg/day orally in four divided doses (AI) followed by	Nephrotoxicity, hypokalemia, anemia, fever, chills
		Bone marrow suppression
		Elevated liver enzymes

(*continued*)

TABLE 40–6 Therapies for Common Opportunistic Pathogens in HIV-Infected Individuals (*Continued*)

Clinical Disease	Preferred Initial Therapies for Acute Infection in Adults (Strength of Recommendation in Parentheses)	Common Drug- or Dose-Limiting Adverse Reactions
	Fluconazole 400 mg/day, orally for 8 weeks or until CSF cultures are negative (AI)[a]	Same as above
Histoplasmosis	Liposomal amphotericin B 3 mg/kg/day IV for 2 weeks (AI) *followed by* Itraconazole 200 mg orally thrice daily for 3 days then twice daily, for 12 months (AII)[a]	Same as above
Coccidioidomycosis	Amphotericin B 0.7–1 mg/kg/day IV until clinical improvement (usually after 500–1,000 mg) then switch to azole (AII)[a]	Same as above
	or	
	Fluconazole 400–800 mg once daily (meningeal disease) (AII)[a]	Same as above
Protozoa		
Toxoplasmic encephalitis	Pyrimethamine 200 mg orally once, then 50–75 mg/day	Bone marrow suppression
	plus	
	Sulfadiazine 1–1.5 g orally four times daily	Allergy, rash, drug fever
	and	
	Leucovorin 10–25 mg orally daily for 6 weeks (AI)[a]	
Isosporiasis	Trimethoprim and sulfamethoxazole: 160 mg trimethoprim and 800 mg sulfamethoxazole orally or IV four times daily for 10 days (AII)[a]	Same as above
Bacteria		
Mycobacterium avium complex	Clarithromycin 500 mg orally twice daily	GI intolerance, optic neuritis, peripheral neuritis
	plus	
	ethambutol 15 mg/kg/day orally (AI)	Rash, GI intolerance
	and	
	For advanced disease, rifabutin 300 mg/day (dose may need adjustment with ART) (AI)[a]	Neutropenia, discolored urine, uveitis

Salmonella enterocolitis or bacteremia	Ciprofloxacin 500–750 mg orally (or 400 mg IV) twice daily for 14 days (longer duration for bacteremia or advanced HIV) (AIII)	GI intolerance
Campylobacter enterocolitis	Ciprofloxacin 500 mg orally twice daily *or* Azithromycin 500 mg orally daily for 7 days (or 14 days with bacteremia) (BIII)	Same as above
Shigella enterocolitis	Ciprofloxacin 500 mg orally twice daily for 5 days (or 14 days for bacteremia) (AIII)	Same as above
Viruses		
Mucocutaneous herpes simplex	Acyclovir 5 mg/kg IV every 8 hours until lesions regress, then acyclovir 400 mg orally three times daily until complete healing (famciclovir or valacyclovir is alternative) (AII)	GI intolerance, crystalluria
Primary varicella-zoster	Acyclovir 10–15 mg/kg every 8 hours IV for 7–10 days, then switch to oral acyclovir 800 mg five times daily after defervescence (famciclovir or valacyclovir is alternative) (AIII)	Obstructive nephropathy, CNS symptoms
Cytomegalovirus (retinitis)	Ganciclovir intraocular implant *plus* valganciclovir 900 mg twice daily for 14–21 days then once daily until immune recovery from ART (AI)[a]	Neutropenia, thrombocytopenia
Cytomegalovirus esophagitis or colitis	Ganciclovir 5 mg/kg IV every 12 hours for 21 to 28 days (BII)	Same as above

ART, antiretroviral therapy; CSF, cerebrospinal fluid; HIV, human immunodefi ciency virus.

[a]Maintenance therapy is recommended.

See Table 103-4 for levels of evidence-based recommendations. .

TABLE 40–7 Therapies for Prophylaxis of First-Episode Opportunistic Diseases in Adults and Adolescents

Pathogen	Indication	First Choice (Strength of Recommendation in Parentheses)
I. Standard of care		
Pneumocystis jirovecii	CD4$^+$ count <200/mm^3 (<200 × 10^6/L) or oropharyngeal candidiasis	Trimethoprim–sulfamethoxazole, one double-strength tablet orally once daily (AI) or one single-strength tablet orally once daily (AI)
Mycobacterium tuberculosis		
Isoniazid-sensitive	(Active TB should be ruled out): + test for latent TB infection with no prior TB treatment history *or* – test for latent TB infection, but close contact with case of active tuberculosis *or* history of untreated or inadequately treated healed TB regardless of latent TB infection test results	Isoniazid 300 mg orally plus pyridoxine, 50 mg orally once daily for 9 months (AII) *or* Isoniazid 900 mg orally twice weekly (BII) plus pyridoxine 50 mg orally daily for 9 months (BIII)
For exposure to drug-resistant TB	Consult public health authorities	
Toxoplasma gondii	Immunoglobulin G antibody to *Toxoplasma* and CD^4+ count <100/mm^3 (<100 × 10^6/L)	Trimethoprim–sulfamethoxazole one double-strength tablet orally once daily (AII)
Mycobacterium avium complex	CD4$^+$ count <50/mm^3 (<50 × 10^6/L)	Azithromycin 1,200 mg orally once weekly (AI) or 600 mg orally twice weekly (BIII) or clarithromycin 500 mg orally twice daily (AI)
Varicella zoster virus (VZV)	Preexposure: CD4 ≥200/mm^3 (≥200 × 10^6/L), no history of varicella infection, or, if available, negative antibody to VZV Postexposure: Significant exposure to chicken pox or shingles for patients who have no history of either condition or, if available, negative antibody to VZV	Varicella vaccination; two doses, 3 months apart (CIII) Varicella-zoster immune globulin, 125 IU per 10 kg (maximum of 625 IU) IM, within 96 hours after exposure to a person with active varicella or herpes zoster (AIII)

Streptococcus pneumoniae	CD4 count ≥200 cells/mm^3 (≥200 × 10^6/L) or no receipt of vaccination in past 5 years. Consider for those with CD4 <200/mm^3 (<200 × 10^6/L) and those with an CD4 increase to > 200/mm^3 (>200 × 10^6/L) on ART (CIII)	23-valent polysaccharide vaccine, 0.5 mL intramuscularly (BII) revaccination every 5 years may be considered (CIII)
Hepatitis B virus	All susceptible patients	Hepatitis B vaccine, three doses (AII) Anti-HBs should be obtained 1 month after the vaccine series completion (BIII)
Influenza virus	All patients (annually, before influenza season)	Inactivated trivalent influenza virus vaccine (annual): 0.5 mL intramuscularly (AIII)
Hepatitis A virus	All susceptible (anti-hepatitis A virus–negative) patients at increased risk for hepatitis A infection (e.g., chronic liver disease, illegal drug users, men who have sex with men)	Hepatitis A vaccine: two doses (AII) antibody response should be assessed 1 month after vaccination; with revaccination as needed (BIII)
Human papillomavirus (HPV) infection	15–26 year old women	HPV quadravalent vaccine months 0, 2, and 6 (CIII)
Histoplasma capsulatum	CD4$^+$ count <150/mm^3 (<150 × 10^6/L) endemic geographic area and high risk for exposures	Fluconazole 100–200 mg orally once daily (CI)

See Table 103–4 for levels of evidence-based recommendations.

transaminases, and thrombocytopenia. The incidence of these adverse reactions is higher in HIV-infected individuals than in those not infected with HIV.
- For pentamidine, side effects include hypotension, tachycardia, nausea, vomiting, severe hypoglycemia or hyperglycemia, pancreatitis, irreversible diabetes mellitus, elevated transaminases, nephrotoxicity, leukopenia, and cardiac arrhythmias.
- The early addition of adjunctive glucocorticoid therapy to anti-PCP regimens has been shown to decrease the risk of respiratory failure and improve survival in patients with AIDS and moderate to severe PCP (PaO_2 ≤70 mm Hg [≤9.3 kPa]or [alveolar–arterial] gradient greater than or equal to 35 mm Hg [≥4.7 kPa]).

PROPHYLAXIS

- Currently, PCP prophylaxis is recommended for all HIV-infected individuals who have already had previous PCP. Prophylaxis is also recommended for all HIV-infected persons who have a CD4 lymphocyte count less than 200 cells/mm^3 (ie, their CD4 cells are <14% of total lymphocytes) or a history of oropharyngeal candidiasis.
- Trimethoprim–sulfamethoxazole is the preferred therapy for both primary and secondary prophylaxis of PCP in adults and adolescents. The recommended dose in adults and adolescents is one double-strength tablet daily.

See Chapter 103, Human Immunodeficiency Virus Infection, authored by Peter L. Anderson, Thomas N. Kakuda, and Courtney V. Fletcher, for a more detailed discussion of this topic.

CHAPTER 41

Influenza

- *Influenza* is a viral illness associated with high mortality and high hospitalization rates among persons younger than age 65 years. Seasonal influenza epidemics result in 25 million to 50 million influenza cases, ~200,000 hospitalizations, and more than 30,000 deaths each year in the United States. Overall, more people die of influenza than of any other vaccine-preventable illness.
- The route of influenza transmission is person-to-person via inhalation of respiratory droplets, which can occur when an infected person coughs or sneezes. The incubation period for influenza ranges between 1 and 7 days, with an average incubation of 2 days. Adults are considered infectious from the day before their symptoms begin through 7 days after the onset of illness, whereas children can be infectious for longer than 10 days after the onset of illness. Viral shedding can persist for weeks to months in severely immunocompromised people.

CLINICAL PRESENTATION

- The presentation of influenza is similar to a number of other respiratory illnesses.
- The clinical course and outcome are affected by age, immunocompetence, viral characteristics, smoking, comorbidities, pregnancy, and the degree of preexisting immunity.
- Complications of influenza may include exacerbation of underlying comorbidities, primary viral pneumonia, secondary bacterial pneumonia or other respiratory illnesses (eg, sinusitis, bronchitis, and otitis), encephalopathy, transverse myelitis, myositis, myocarditis, pericarditis, and Reye syndrome.

SIGNS AND SYMPTOMS

- Classic signs and symptoms of influenza include rapid onset of fever, myalgia, headache, malaise, nonproductive cough, sore throat, and rhinitis.
- Nausea, vomiting, and otitis media are also commonly reported in children.
- Signs and symptoms typically resolve in 3 to 7 days, although cough and malaise may persist for more than 2 weeks.

LABORATORY TESTS

- The gold standard for diagnosis of influenza is viral culture.
- Rapid antigen and point-of-care tests, direct fluorescence antibody test, and the reverse transcription polymerase chain reaction assay may be used for rapid detection of virus.
- Chest radiograph should be obtained if pneumonia is suspected.
- Rapid tests have allowed for prompt diagnosis and initiation of antiviral therapy and decreased inappropriate use of antibiotics.

PREVENTION

- The best means to decrease the morbidity and mortality associated with influenza is to prevent infection through vaccination. Appropriate infection control measures, such as hand hygiene, basic respiratory etiquette (cover your cough and throw tissues away), and contact avoidance, are also important in preventing the spread of influenza.
- Annual vaccination is recommended for all persons age 6 months or older and caregivers (eg, parents, teachers, babysitters, nannies) of children less than 6 months of age.
- Vaccination is also recommended for those who live with and/or care for people who are at high risk, including household contacts and healthcare workers.

- The Advisory Committee on Immunization Practices (ACIP) has made the following recommendations regarding the vaccinations of persons with reports of egg allergy: (a) vaccination with trivalent influenza vaccine (TIV) rather than with live-attenuated influenza vaccine (LAIV) for persons with a history of egg allergy that involves only hives. Vaccination should be done by a healthcare provider who is familiar with possible manifestations of egg allergy and the recipient should be observed for at least 30 minutes after dose. (b) Persons with severe allergic reactions such as angioedema, respiratory distress, light-headedness, or recurrent emesis or required epinephrine after an egg exposure should be referred to a physician with expertise in the management of allergic reactions for the receipt of an influenza vaccination. (c) Severe allergic reaction to influenza vaccine is a contraindication to receiving future vaccinations.
  - ✓ The ideal time for vaccination is October or November to allow for the development and maintenance of immunity during the peak of the influenza season.
  - ✓ The two vaccines currently available for prevention of influenza are the TIV and the LAIV. The specific strains included in the vaccine each year change based on antigenic drift.
  - ✓ TIV is FDA approved for use in people over 6 months of age, regardless of their immune status. Of note, several commercial products are available and are approved for different age groups (**Table 41–1**).
  - ✓ Adults older than 65 years benefit from influenza vaccination, including prevention of complications and decreased risk of influenza-related hospitalization and death. However, people in this population may not generate a strong antibody response to the vaccine and may remain susceptible to infection.
  - ✓ The most frequent adverse effect associated with TIV is soreness at the injection site that lasts for less than 48 hours. TIV may cause fever and malaise in those who have not previously been exposed to the viral antigens in the vaccine. Allergic-type reactions (hives and systemic anaphylaxis) rarely occur after influenza vaccination and are likely a result of a reaction to residual egg protein in the vaccine.
  - ✓ Vaccination should be avoided in persons who are not at high risk for influenza complications and who have experienced Guillain–Barré syndrome within 6 weeks of receiving a previous influenza vaccine.
  - ✓ LAIV is made with live, attenuated viruses and is approved for intranasal administration in healthy people between 2 and 49 years of age (**Table 41–2**). Advantages of LAIV include its ease of administration, intranasal rather than intramuscular administration, and the potential induction of broad mucosal and systemic immune response.
  - ✓ LAIV is only approved for children over the age of 2 years in part because of data showing an increase in asthma or reactive airway disease in those younger than 5 years.
  - ✓ The adverse effects typically associated with LAIV administration include runny nose, congestion, sore throat, and headache.
  - ✓ LAIV should not be given to immunosuppressed patients or given by healthcare workers who are severely immunocompromised.

POSTEXPOSURE PROPHYLAXIS

- Antiviral drugs available for prophylaxis of influenza should be considered adjuncts but are not replacements for annual vaccination.
- **Amantadine** and **rimantadine** are currently not recommended for prophylaxis or treatment in the United States because of the rapid emergence of resistance.
- The neuraminidase inhibitors **oseltamivir** and **zanamivir** are effective prophylactic agents against influenza in terms of preventing laboratory-confirmed influenza when used for seasonal prophylaxis and preventing influenza illness among persons exposed to a household contact who were diagnosed with influenza. **Table 41–3** gives dosing recommendations.
- In those patients who did not receive the influenza vaccination and are receiving an antiviral drug for prevention of disease during the influenza season, the

TABLE 41–1 Approved Influenza Vaccines for Different Age Groups—United States, 2010–2011 Season

Vaccine	Trade Name	Manufacturer	Dose/Presentation	Thimerosal Mercury Content (mcg Hg/0.5 mL dose)	Age Group	Number of Doses
TIV	Fluzone	Sanofi Pasteur	0.25-mL prefilled syringe 0.5-mL prefilled syringe 0.5-mL vial 5-mL multidose vial	0 0 0 0	6–35 months ≥36 months ≥36 months ≥6 months	1 or 2[a] 1 or 2[a] 1 or 2[a] 1 or 2[a]
TIV	Agriflu	Novartis Vaccines	0.5-mL prefilled syringe	0	≥18 years	1
TIV	Fluvirin	Novartis Vaccines	0.5-mL prefilled syringe 5-mL multidose vial	<1 25	≥4 years ≥4 years	1 or 2[a] 1 or 2[a]
TIV	Fluarix	GlaxoSmithKline	0.5-mL prefilled syringe	0	≥3 years	1
TIV	FluLaval	ID Biomedical Corporation	5-mL multidose vial	<25	≥18 years	1
TIV	Afluria	CSL Biotherapies	0.5-mL prefilled syringe 5-mL multidose vial	0 24.5	≥9 years ≥9 years	1
TIV High Dose	Fluzone HD	Sanofi Pasteur	0.5-mL prefilled syringe	0	65 years	1
TIV intradermal	Fluzone Intradermal	Sanofi Pasteur	0.1-mL prefilled microinjection system	0	18–64 years	1[b]
LAIV	FluMist[c]	MedImmune	0.2-mL sprayer	0	2–49 years	1 or 2[d]

LAIV, live-attenuated influenza vaccine; TIV, trivalent influenza vaccine.

[a] Two doses administered at least 1 month apart are recommended for children aged 6 months to less than 9 years who are receiving influenza vaccine for the first time or received one dose in first year of vaccination during the previous influenza season.

[b] *Given intradermally*. A 0.1-mL dose contains 9 mcg of each vaccine antigen (27 mcg total).

[c] The new quadrivalent formulation of FluMist approved in 2012 will replace currently available seasonal trivalent LAIV formulation beginning 2013–2014 season.

[d] Two doses administered 4 weeks apart are recommended for children aged 2 to less than 9 years who are receiving influenza vaccine for the first time.

TABLE 41–2 Comparison of Trivalent Influenza Vaccine (TIV) and Live-Attenuated Influenza Vaccine (LAIV)

Characteristic	TIV	LAIV
Age groups approved for use	>6 months	5 to 49 years
Immune status requirements	Immunocompetent or immunocompromised	Immunocompetent
Viral properties	Inactivated (killed) influenza A (H3N2), A (H1N1), and B viruses	Live-attenuated influenza A (H3N2), A (H1N1), and B viruses
Route of administration	Intramuscular	Intranasal
Immune system response	High serum IgG antibody response	Lower IgG response and high serum IgA mucosal response

Ig, immunoglobulin.

medication should optimally be taken for the entire duration of influenza activity in the community.

- Prophylaxis should be considered during influenza season for the following groups of patients:
  - ✓ Persons at high risk of serious illness and/or complications who cannot be vaccinated
  - ✓ Persons at high risk of serious illness and/or complications who are vaccinated after influenza activity has begun in their community because the development of sufficient antibody titers after vaccination takes ~2 weeks
  - ✓ Unvaccinated persons who have frequent contact with those at high risk
  - ✓ Persons who may have an inadequate response to vaccination (eg, advanced human immunodeficiency virus disease)
  - ✓ Long-term care facility residents, regardless of vaccination status, when an outbreak has occurred in the institution
  - ✓ Unvaccinated household contacts of someone who was diagnosed with influenza
- LAIV should not be administered until 48 hours after influenza antiviral therapy has stopped, and influenza antiviral drugs should not be administered for 2 weeks after the administration of LAIV because the antiviral drugs inhibit influenza virus replication.
- Pregnant women, regardless of trimester, should receive annual influenza vaccination with TIV but not with LAIV.
- The adamantanes and neuraminidase inhibitors are not recommended during pregnancy because of concerns regarding the effects of the drugs on the fetus.
- Immunocompromised hosts should receive annual influenza vaccination with TIV but not LAIV.

TREATMENT

- Goals of Therapy: The four primary goals of therapy of influenza are as follows: 1) control symptoms, 2) prevent complications, 3) decrease work and/or school absenteeism, 4) prevent the spread of infection.
- Antiviral drugs are most effective if started within 48 hours of the onset of illness. Adjunct agents, such as acetaminophen for fever or an antihistamine for rhinitis, may be used concomitantly with the antiviral drugs.

TABLE 41–3 Recommended Daily Dosage of Influenza Antiviral Medications for Treatment and Prophylaxis— United States

Drug	Adult Treatment	Adult Prophylaxis[a]	Pediatric Treatment[b]	Pediatric Prophylaxis[c]
Oseltamivir	75-mg capsule twice daily for 5 days	75-mg capsule daily	≤3 months[d]: 12 mg twice daily 3–5 months[d]: 20 mg twice daily 6–11 months[d]: 25 mg twice daily ≥1 year ≤15 kg: 30 mg twice daily 16–23 kg: 45 mg twice daily 23–40 kg: 60 mg twice daily >40 kg: 75 mg twice daily All for 5 days	≤3 months. Not recommended; situation judged critical due to limited data in this group 3–5 months[d]: 20 mg daily 6–11 months[d]: 25 mg daily ≥1 year ≤15 kg: 30 mg daily 16–23 kg: 45 mg daily 23–40 kg: 60 mg daily >40 kg: 75 mg daily
Zanamivir	2 inhalations twice daily × 5 days	2 inhalations daily	2 inhalations twice daily × 5 days for ≥7 years old	2 inhalations daily for ≥5 years old
Rimantadine[e]	200 mg/day in one to two doses × 7 days	200 mg/day in one to two doses	1–9 years old or <40 kg: 6.6 mg/kg/day divided twice daily (maximum 150 mg/day) ≥10 years old: 200 mg/day in one to two doses Treat 5–7 days	1–9 years old: 5 mg/kg daily (maximum 150 mg/day) ≥10 years old: 200 mg/day in one to two doses

(continued)

TABLE 41–3 Recommended Daily Dosage of Influenza Antiviral Medications for Treatment and Prophylaxis— United States (*Continued*)

Drug	Adult Treatment	Adult Prophylaxis[a]	Pediatric Treatment[b]	Pediatric Prophylaxis[c]
Amantadine[e]	200 mg/day in one to two doses until 24–48 hours after symptom resolution	Same as treatment doses	>12 years old: same as adult 1–9 years old: 5 mg/kg/day in one to two doses; maximum 150 mg/day ≥10–12 years old: 100 mg orally twice daily	Same as treatment doses

[a]If influenza vaccine is administered, prophylaxis can generally be stopped 14 days after vaccination for noninstitutionalized persons. When prophylaxis is being administered following an exposure, prophylaxis should be continued for 10 days after the last exposure. In persons at high risk for complications from influenza for whom vaccination is contraindicated or expected to be ineffective, chemoprophylaxis should be continued for the duration that influenza viruses are circulating in the community during influenza season.
[b]Alternate dosing by IDSA/PIDS (2011) is: infants and premature—1 mg/kg/dose q 12 h; 0–8 months—3 mg/kg/dose q 12 h; 9–23 months—3.5 mg/kg/dose q 12 h.
[c]Alternate dosing by IDSA/PIDS (2011) is: 3–8 months—3 mg/kg/dose daily; 9–23 months—3.5 mg/kg/dose daily.
[d]Unlabeled dosing.
[e]Note: Although amantadine and rimantadine have been used historically for the treatment and prophylaxis of influenza A viruses, due to high resistance, the CDC no longer recommends the use of these agents for the treatment and/or prophylaxis of influenza.

- Patients suffering from influenza should get adequate sleep and maintain a low level of activity. They should stay home from work and/or school in order to rest and prevent the spread of infection. Appropriate fluid intake should be maintained. Cough/throat lozenges, warm tea, or soup may help with symptom control (cough and sore throat).

PHARMACOLOGIC THERAPY

- The neuraminidase inhibitors are the only antiviral drugs available for treatment and prophylaxis of influenza and are oseltamivir and zanamivir. IV **peramivir** is another NA inhibitor under investigation for treatment of influenza. The adamantanes (amantadine and rimantadine) are no longer recommended due to high resistance among influenza viruses.
- Oseltamivir and zanamivir are neuraminidase inhibitors that have activity against both influenza A and influenza B viruses. When administered within 48 hours of the onset of illness, oseltamivir and zanamivir may reduce the duration of illness by ~1 day versus placebo. Benefits are highly dependent on the timing of initiation of treatment, ideally being within 12 hours of illness onset.
- Oseltamivir is approved for treatment in those older than 1 year; zanamivir is approved for treatment in those older than 7 years. The recommended dosages vary by agent and age (see **Table 41–3**), and the recommended duration of treatment for both agents is 5 days.
- Neuropsychiatric complications consisting of delirium, seizures, hallucinations, and self-injury in pediatric patients have been reported following treatment with oseltamivir.
- Oseltamivir and zanamivir have been used in pregnancy, but solid clinical safety data are lacking. Both the adamantanes and the neuraminidase inhibitors are excreted in breast milk and should be avoided by mothers who are breast-feeding their infants. More studies are needed in these populations who are at high risk for serious disease and complications from influenza.

EVALUATION OF THERAPEUTIC OUTCOMES

- Patients should be monitored daily for resolution of signs and symptoms associated with influenza, such as fever, myalgia, headache, malaise, nonproductive cough, sore throat, and rhinitis. These signs and symptoms will typically resolve within ~1 week. If the patient continues to exhibit signs and symptoms of illness beyond 10 days or a worsening of symptoms after 7 days, a physician visit is warranted, as this may be an indication of a secondary bacterial infection.

See Chapter 87, Influenza, authored by Jessica C. Njoku and Elizabeth D. Hermsen, for a more detailed discussion of this topic.

Intraabdominal Infections

42 CHAPTER

- Intraabdominal infections are those contained within the peritoneum or retroperitoneal space. Two general types of intraabdominal infections are discussed throughout this chapter: peritonitis and abscess.
- Peritonitis is defined as the acute, inflammatory response of peritoneal lining to microorganisms, chemicals, irradiation, or foreign body injury. It may be classified as either primary or secondary. With primary peritonitis, an intraabdominal focus of disease may not be evident. In secondary peritonitis, a focal disease process is evident within the abdomen.
- An abscess is a purulent collection of fluid separated from surrounding tissue by a wall consisting of inflammatory cells and adjacent organs. It usually contains necrotic debris, bacteria, and inflammatory cells.

PATHOPHYSIOLOGY

- **Table 42–1** summarizes many of the potential causes of bacterial peritonitis. Appendicitis is the most frequent cause of abscess. Intraabdominal infection results from entry of bacteria into the peritoneal or retroperitoneal spaces or from bacterial collections within intraabdominal organs. When peritonitis results from peritoneal dialysis, skin surface flora are introduced via the peritoneal catheter.
- In primary peritonitis, bacteria may enter the abdomen via the bloodstream or the lymphatic system, by transmigration through the bowel wall, through an indwelling peritoneal dialysis catheter, or via the fallopian tubes in female patients.
- In secondary peritonitis, bacteria most often enter the peritoneum or retroperitoneum as a result of disruption of the integrity of the gastrointestinal (GI) tract caused by diseases or traumatic injuries.
- When bacteria become dispersed throughout the peritoneum, the inflammatory process involves the majority of the peritoneal lining. Fluid and protein shift into the abdomen (called "third spacing") may decrease circulating blood volume and cause shock.
- Peritonitis often results in death because of the effects on major organ systems. Fluid shifts and endotoxins may cause hypotension and shock.
- An abscess begins by the combined action of inflammatory cells (eg, neutrophils), bacteria, fibrin, and other inflammatory components. Within the abscess, oxygen tension is low, and anaerobic bacteria thrive.

MICROBIOLOGY

- Primary bacterial peritonitis is often caused by a single organism. In children, the pathogen is usually group A *Streptococcus, Streptococcus pneumoniae, Escherichia coli,* or *Bacteroides* species. When peritonitis occurs in association with cirrhotic ascites, *E. coli* is isolated most frequently.
- Peritonitis in patients undergoing peritoneal dialysis is most often caused by common skin organisms: *Staphylococcus epidermidis, Staphylococcus aureus,* streptococci, and diphtheroids. Gram-negative bacteria associated with peritoneal dialysis infections include *E. coli, Klebsiella,* and *Pseudomonas.*
- Secondary intraabdominal infections are often polymicrobial. The mean number of isolates of microorganisms from infected intraabdominal sites has ranged from 2.9 to 3.7, including an average of 1.3 to 1.6 aerobes and 1.7 to 2.1 anaerobes. The frequencies with which specific bacteria were isolated in intraabdominal infections are given in **Table 42–2.**
- The combination of aerobic and anaerobic organisms appears to greatly increase pathogenicity. In intraabdominal infections, facultative bacteria may provide an environment conducive to the growth of anaerobic bacteria.

TABLE 42–1 Causes of Bacterial Peritonitis
Primary bacterial peritonitis
Peritoneal dialysis
Cirrhosis with ascites
Nephrotic syndrome
Secondary bacterial peritonitis
Miscellaneous causes
Diverticulitis
Appendicitis
Inflammatory bowel diseases
Salpingitis
Biliary tract infections
Necrotizing pancreatitis
Neoplasms
Intestinal obstruction
Perforation
Mechanical GI problems
Any cause of small bowel obstruction (adhesions and hernia)
Vascular causes
Mesenteric arterial or venous occlusion (atrial fibrillation)
Mesenteric ischemia without occlusion
Trauma
Blunt abdominal trauma with rupture of intestine
Penetrating abdominal trauma
Iatrogenic intestinal perforation (endoscopy)
Intraoperative events
Peritoneal contamination during abdominal operation
Leakage from GI anastomosis

- Aerobic enteric bacteria and anaerobic bacteria are both pathogens in intraabdominal infection. Aerobic bacteria, particularly *E. coli*, appear responsible for the early mortality from peritonitis, whereas anaerobic bacteria are major pathogens in abscesses, with *Bacteroides fragilis* predominating.
- The role of *Enterococcus* as a pathogen is not clear. Enterococcal infection occurs more commonly in postoperative peritonitis, in the presence of specific risk factors indicating failure of the host defenses, or with the use of broad-spectrum antibiotics.

CLINICAL PRESENTATION

- Intraabdominal infections have a wide spectrum of clinical features often depending on the specific disease process, the location and the magnitude of bacterial contamination, and concurrent host factors. Patients with primary and secondary peritonitis present quite differently (**Table 42–3**).
- If peritonitis continues untreated, the patient may experience hypovolemic shock from fluid loss into the peritoneum, bowel wall, and lumen. This may be accompanied by generalized sepsis. Intraabdominal abscess may pose a diagnostic challenge, as the symptoms are neither specific nor dramatic.

TABLE 42–2 Pathogens Isolated from Patients with Intraabdominal Infection

	Secondary Peritonitis	Community-Acquired Infection	Nosocomial Infection
Gram-negative bacteria			
Escherichia coli	32%–61%	29%	22.5%
Enterobacter	8%–26%	5.2%	8.0%
Klebsiella	6%–26%	2.8%	4.5%
Proteus	4%–23%	1.7%	2.4%
Gram-positive bacteria			
Enterococcus	18%–24%	10.6%	18%
Streptococcus	6%–55%	13.7%	10%
Staphylococcus	6%–16%	3.1%	4.8%
Anaerobic bacteria			
Bacteroides	25%–80%	13.7%	10.3%
Clostridium	5%–18%	3.5%	3.4%
Fungi	2%–5%	3%	4%

Data from Marshall JC, Innes M. Intensive care unit management of intraabdominal infection. Crit Care Med 2003;31:2228–2237; and Montravers P, Lepape A, Dubreuil L, et al. Clinical and microbiological profiles of community-acquired and nosocomial infections: Results of the French prospective, observational EBIIA study. J Antimicrob Chemother. 2009;63:785–794.

- The overall outcome from intraabdominal infection depends on five key factors: inoculum size, virulence of the organisms, the presence of adjuvants within the peritoneal cavity that facilitate infection, the adequacy of host defenses, and the adequacy of initial treatment.

TREATMENT

- The goals of treatment are the correction of intraabdominal disease processes or injuries that have caused infection and the drainage of collections of purulent material (eg, abscess). A secondary objective is to achieve resolution of infection without major organ system complications or adverse treatment effects.
- The three major modalities for the treatment of intraabdominal infection are prompt surgical drainage of the infected site, hemodynamic resuscitation and support of vital functions, and early administration of appropriate antimicrobial therapy to treat infection not removed by surgery.
- Antimicrobials are an important adjunct to drainage procedures in the treatment of intraabdominal infections; however, the use of antimicrobial agents without surgical intervention is usually inadequate. For most cases of primary peritonitis, drainage procedures may not be required, and antimicrobial agents become the mainstay of therapy.
- In the early phase of serious intraabdominal infections, attention should be given to the maintenance of organ system functions. With generalized peritonitis, large volumes of IV fluids are required to restore vascular volume, to improve cardiovascular function, and to maintain adequate tissue perfusion and oxygenation.

TABLE 42–3 Clinical Presentation of Peritonitis
Primary Peritonitis
The patient may not be in acute distress, particularly with peritoneal dialysis.
Signs and symptoms
The patient may complain of nausea, vomiting (sometimes with diarrhea), and abdominal tenderness.
Temperature may be only mildly elevated or not elevated in patients undergoing peritoneal dialysis.
Bowel sounds are hypoactive.
The cirrhotic patient may have worsening encephalopathy.
Cloudy dialysate fluid with peritoneal dialysis
Laboratory tests
The patient's WBC count may be only mildly elevated.
Ascitic fluid usually contains >250 leukocytes/mm^3 (>250 × 10^6/L), and bacteria may be evident on Gram stain of a centrifuged specimen.
In 60% to 80% of patients with cirrhotic ascites, the Gram stain is negative.
Other diagnostic tests
Culture of peritoneal dialysate or ascitic fluid should be positive.
Secondary Peritonitis
Signs and symptoms
Generalized abdominal pain
Tachypnea
Tachycardia
Nausea and vomiting
Temperature is normal initially, then increases to 37.7 to 38.8°C (100–102°F) within the first few hours; it may continue to rise for the next several hours.
Hypotension and shock if volume is not restored
Decreased urine output due to vascular volume depletion
Physical examination
Voluntary abdominal guarding changing to involuntary guarding and a "board-like" abdomen
Abdominal tenderness and distention
Faint bowel sounds that cease over time
Laboratory tests
Leukocytosis (15,000–20,000 WBC/mm^3 [15-20 × 10^9/L]), with neutrophils predominating and an elevated percentage of immature neutrophils (bands)
Elevated hematocrit and BUN because of dehydration
Patient progresses from early alkalosis because of hyperventilation and vomiting to acidosis and lactic acidemia.
Other diagnostic tests
Abdominal radiographs may be useful because free air in the abdomen (indicating intestinal perforation) or distention of the small or large bowel is often evident.

BUN, blood urea nitrogen; WBC, white blood cell.

TABLE 42–4 Recommended Agents for the Treatment of Community-acquired, Complicated Intraabdominal Infections

Agents Recommended for Mild-to-Moderate Infections	Agents Recommended for High Risk or High Severity Infections
Single Agent	
Cefoxitin[a]	Piperacillin–tazobactam
Ticarcillin–clavulanate	
Moxifloxacin[b]	Imipenem–cilastatin,[c] Meropenem,[c]
Ertapenem[c]	Doripenem[c]
Combination Regimens	
Cefazolin,[a] cefuroxime,[a] ceftriaxone, cefotaxime each in combination with metronidazole	Cefepime or ceftazidime each in combination with metronidazole
Ciprofloxacin[b] or levofloxacin[b] each in combination with metronidazole	Ciprofloxacin[b] or levofloxacin[b] each in combination with metronidazole

[a]Empiric first- and second-generation cephalosporin use should be avoided unless local antibiograms show >80% to 90% susceptibility of *E. coli* to these agents.
[b]Use of quinolones may be associated with treatment failure due to increasing resistance of enteric pathogens including *E. coli*. Empiric quinolone use should be avoided unless local antibiograms show >80% to 90% susceptibility of *E. coli* to quinolones.
[c]Carbapenems should typically be reserved for settings where there is a high risk of resistance to other agents.

Adapted from Solomkin et al.[39]

NONPHARMACOLOGIC TREATMENT

- Secondary peritonitis is treated surgically; this is called "source control," which refers to the physical measures undertaken to eradicate the focus of infection. Abdominal laparotomy may be used to correct the cause of peritonitis.
- Aggressive fluid repletion and management are required for the purposes of achieving or maintaining proper intravascular volume to ensure adequate cardiac output, tissue perfusion, and correction of acidosis.
- In the initial hour of treatment, a large volume of IV solution (lactated Ringer solution) may need to be administered to restore intravascular volume. This may be followed by up to 1 L/h until fluid balance is restored in a few hours.
- In patients with significant blood loss (hematocrit ≤25%), blood should be given. This is generally in the form of packed red blood cells.
- Enteral or parenteral nutrition facilitates improved immune function and wound healing to ensure recovery.

PHARMACOLOGIC THERAPY

- The goals of antimicrobial therapy are to control bacteremia and to establish the metastatic foci of infection, to reduce suppurative complications after bacterial contamination, and to prevent local spread of existing infection.
- An empiric antimicrobial regimen should be started as soon as the presence of intraabdominal infection is suspected on the basis of likely pathogens.

Recommendations

- **Table 42–4** presents recommended and alternative regimens for community-acquired complicated intraabdominal infections. Guidelines for initial antimicrobial treatment of specific intraabdominal infections are presented in **Table 42–5**.
- Evidence-based treatment principles for complicated intraabdominal infections are given in **Table 42–6**.

TABLE 42–5 Guidelines for Initial Antimicrobial Agents for Intraabdominal Infections

	Primary Agents	Alternatives
Primary (Spontaneous) Bacterial Peritonitis		
Cirrhosis	Ceftriaxone, cefotaxime	1. Piperacillin–tazobactam, carbapenems 2. Aztreonam combined with an agent active against *Streptococcus* spp. (e.g., vancomycin) or quinolones with significant *Streptococcus* spp. activity (levofloxacin, moxifloxacin)
Peritoneal dialysis	Initial empiric regimens should be active against both Gram-positive (including *S. aureus*) and Gram-negative pathogens: Gram-positive agent (first-generation cephalosporin or vancomycin) plus a Gram-negative agent (third-generation cephalosporin or aminoglycoside)	1. Cefepime or carbapenems may be used alone 2. Aztreonam or an aminoglycoside may be used in place of ceftazidime or cefepime as long as combined with a Gram-positive agent 3. Quinolones may be used in place of Gram-negative agents if local susceptibilities allow
	1. Staphylococcus spp.:oxacillin/nafcillin or first-generation cephalosporin	1. Vancomycin should be used if concern for methicillin-resistant *Staphylococcus* spp. 2. Add rifampin for 5–7 days with vancomycin for methicillin-resistant *Staphylococcus aureus*
	2. *Streptococcus* or *Enterococcus*: ampicillin	1. An aminoglycoside may be added for *Enterococcus* spp. 2. Linezolid, daptomycin, or quinupristin/dalfopristin should be used to treat vancomycin-resistant *Enterococcus* spp. not susceptible to ampicillin
	3. Aerobic Gram-negative bacilli: ceftazidime or cefepime	1. The regimen should be based on in vitro sensitivity tests
	4. *Pseudomonas aeruginosa*: two agents with differing mechanisms of action, such as an oral quinolone plus ceftazidime, cefepime, tobramycin, or piperacillin	

(*continued*)

TABLE 42–5 Guidelines for Initial Antimicrobial Agents for Intraabdominal Infections (*Continued*)

	Primary Agents	Alternatives
Secondary Bacterial Peritonitis		
Perforated peptic ulcer	First-generation cephalosporins	1. Ceftriaxone, cefotaxime, or antianaerobic cephalosporins[a]
Other	Third- or fourth-generation cephalosporin with metronidazole, piperacillin–tazobactam or ticarcillin–clavulanate, carbapenem	1. Ciprofloxacin[b] or levofloxacin[b] each with metronidazole or *moxifloxacin*[b] alone 2. Aztreonam with vancomycin and metronidazole 3. Antianaerobic cephalosporins[a]
Abscess		
General	Third- or fourth-generation cephalosporin with metronidazole, piperacillin–tazobactam, or ticarcillin–clavulanate	1. Imipenem–cilastatin, meropenem, doripenem, or ertapenem 2. Ciprofloxacin b or levofloxacin b each with metronidazole or moxifloxacin alone
Liver	As above	Use metronidazole if amoebic liver abscess is suspected
Spleen	Ceftriaxone or cefotaxime	Moxifloxacin[b] or levofloxacin[b]
Other Intraabdominal Infections		
Appendicitis	Same management as for community-acquired complicated intraabdominal infections as listed in Table 92-6[39]	
Community-acquired	Ceftriaxone or cefotaxime	Severe infection, piperacillin/tazobactam, antipseuodomonal acute cholecystitis carbapenem, aztreonam with metronidazole
Cholangitis	Ceftriaxone or cefotaxime each with or without metronidazole	Vancomycin with aztreonam with or without metronidazole
Acute contamination from abdominal trauma	Antianaerobic cephalosporins[a] or metronidazole with either ceftriaxone or cefotaxime	1. Piperacillin/tazobactam or a carbapenem 2. Ciprofloxacin[b] or levofloxacin[b] each with metronidazole or moxifloxacin alone

[a]Cefoxitin or ceftizoxime; these agents should be avoided empirically unless local antibiograms show >80% to 90% susceptibility of *E. coli* to these agents.
[b]Use of quinolones may be associated with treatment failure due to increasing resistance of enteric pathogens including *E. coli*. Empiric quinolone use should be avoided unless local antibiograms show >80% to 90% susceptibility of *E. coli* to quinolones.

TABLE 42–6 Evidence-based Recommendations for Treatment of Complicated Intraabdominal Infections

	Grade of Recommendation[a]
Elements of Appropriate Intervention	
An appropriate source control procedure to drain infected foci, control ongoing peritoneal contamination by diversion or resection, and restore anatomic and physiological function to the extent feasible is recommended for nearly all patients with intraabdominal infection	B-2
Community-Acquired Infections of Mild-to-Moderate Severity in Adults	
Antibiotics used for empiric treatment of community-acquired intraabdominal infections should be active against enteric Gram-negative aerobic and facultative bacilli and enteric Gram-positive streptococci	A-1
For patients with mild-to-moderate community-acquired infections, the use of ticarcillin–clavulanate, cefoxitin, ertapenem, moxifloxacin, or tigecycline as single-agent therapy or combinations of metronidazole with cefazolin, cefuroxime, ceftriaxone, cefotaxime, levofloxacin, or ciprofloxacin are preferable to regimens with substantial anti-pseudomonal activity (Table 92-6)	A-1
Empiric coverage of *Enterococcus* is not necessary in patients with mild-to-moderate severity community-acquired intraabdominal infection	A-1
The use of agents listed as appropriate for higher-severity community-acquired infection and healthcare-associated infection is not recommended for patients with mild-to-moderate community-acquired infection, because such regimens may carry a greater risk of toxicity and facilitate acquisition of more resistant organisms	B-2
High-Risk or High-Severity Community-Acquired Infections in Adults[b]	
The empiric use of antimicrobial regimens with broad-spectrum activity against Gram-negative organisms, including meropenem, imipenem–cilastatin, doripenem, piperacillin–tazobactam, ciprofloxacin or levofloxacin in combination with metronidazole, or ceftazidime or cefepime in combination with metronidazole, is recommended for patients with high-severity community-acquired intraabdominal infection	A-1
Aztreonam plus metronidazole is an alternative, but addition of an agent effective against Gram-positive cocci is recommended	B-3
Healthcare-Associated Infections in Adults	
Empiric antibiotic therapy for healthcare-associated intraabdominal infection should be driven by local microbiologic results	A-2
To achieve empiric coverage of likely pathogens, multidrug regimens that include agents with expanded spectra of activity against Gram-negative aerobic and facultative bacilli may be needed. These agents include meropenem, imipenem–cilastatin, doripenem, piperacillin–tazobactam, or ceftazidime or cefepime in combination with metronidazole. Aminoglycosides or colistin may be required	B-3

(*continued*)

TABLE 42–6 Evidence-based Recommendations for Treatment of Complicated Intraabdominal Infections (*Continued*)

	Grade of Recommendation[a]
Antimicrobial Agents Not Recommended	
Ampicillin–sulbactam is not recommended for use because of high rates of resistance to this agent among community-acquired *E. coli*	B-2
Quinolone-resistant *E. coli* have become common in some communities, and quinolones should not be used unless hospital surveys indicate 90% susceptibility of *E. coli* to quinolones	A-2
Cefotetan and clindamycin are not recommended for use because of increasing prevalence of resistance to these agents among the *Bacteroides fragilis* group	B-2
Because of the availability of less toxic agents demonstrated to be at least equally effective, aminoglycosides are not recommended for routine use in adults with community-acquired intraabdominal infection	B-2
Oral Completion Therapy	
For adults recovering from intraabdominal infection, completion of the antimicrobial course with oral forms of moxifloxacin, ciprofloxacin plus metronidazole, levofloxacin plus metronidazole, an oral cephalosporin with metronidazole, or amoxicillin– clavulanic acid is acceptable in patients able to tolerate an oral diet and in patients in whom susceptibility studies do not demonstrate resistance	B-2
Duration of Therapy	
Antimicrobial therapy of established infection should be limited to 4–7 days, unless it is difficult to achieve adequate source control. Longer durations of therapy have not been associated with improved outcome	B-3
For acute stomach and proximal jejunum perforations, in the absence of acid-reducing therapy or malignancy and when source control is achieved within 24 hours, prophylactic antiinfective therapy directed at aerobic Gram-positive cocci for 24 hours is adequate	B-2
Bowel injuries attributable to penetrating, blunt, or iatrogenic trauma that are repaired within 12 hours and any other intraoperative contamination of the operative field by enteric contents should be treated with antibiotics for ≤24 hours	A-1
Acute appendicitis without evidence of perforation, abscess, or local peritonitis requires only prophylactic administration of narrow spectrum regimens active against aerobic and facultative and obligate anaerobes; treatment should be discontinued within 24 hours	A-1
The administration of prophylactic antibiotics to patients with severe necrotizing pancreatitis prior to the diagnosis of infection is not recommended	A-1

Anaerobic Coverage	
Coverage for obligate anaerobic bacilli should be provided for distal small bowel, appendiceal, and colon-derived infection and for more proximal GI perforations in the presence of obstruction or paralytic ileus	A-1
Antifungal Therapy	
Antifungal therapy for patients with severe community-acquired or healthcare-associated infection is recommended if *Candida* is grown from intraabdominal cultures	B-2
Anti-MRSA Therapy	
Empiric antimicrobial coverage directed against MRSA should be provided to patients with healthcare-associated intraabdominal infection who are known to be colonized with the organism or who are at risk of having an infection due to this organism because of prior treatment failure and significant antibiotic exposure	B-2
Vancomycin is recommended for treatment of suspected or proven intraabdominal infection due to MRSA	A-3
Antienterococcal Therapy	
Antimicrobial therapy for enterococci should be given when enterococci are recovered from patients with healthcare-associated infection	B-III
Empiric antienterococcal therapy is recommended for patients with high-risk community-acquired infections and healthcare-associated intraabdominal infections, particularly those with postoperative infection, those who have previously received cephalosporins or other antimicrobial agents selecting for *Enterococcus* species, immunocompromised patients, and those with valvular heart disease or prosthetic intravascular materials	B-II
Initial empiric antienterococcal therapy should be directed against Enterococcus faecalis. Antibiotics that can potentially be used against this organism, on the basis of susceptibility testing of the individual isolate, include ampicillin, piperacillin/tazobactam, and vancomycin	B-III
Empiric therapy directed against vancomycin-resistant *Enterococcus faecium* is not recommended unless the patient is at very high risk for an infection due to this organism, such as a liver transplant recipient with an intraabdominal infection originating in the hepatobiliary tree or a patient known to be colonized with vancomycin-resistant *E. faecium*	B-III

[a]Strength of recommendations: A, B, C = good, moderate, and poor evidence to support recommendation, respectively. Quality of evidence: 1 = Evidence from ≥1 properly randomized, controlled trial. 2 = Evidence from ≥1 well-designed clinical trial without randomization, from cohort or case-controlled analytic studies; from multiple time series, or from dramatic results from uncontrolled experiments. 3 = Evidence from opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert communities.

[b]Criteria for high risk or high severity community-acquired infection: APACHE II score ≥15, delay in initial intervention (>24 hours), advanced age, comorbidity and degree of organ dysfunction, low albumin level, poor nutritional status, degree of peritoneal involvement or diffuse peritonitis, inability to achieve adequate debridement or control of drainage, and presence of malignancy.

From Solomkin et al.[39]

- The selection of a specific agent or combination should be based on culture and susceptibility data for peritonitis that occurs from chronic peritoneal dialysis. If microbiologic data are unavailable, empiric therapy should be initiated.
- For established intraabdominal infections, most patients are adequately treated with 5 to 7 days of antimicrobial therapy.
- Intraperitoneal administration of antibiotics is preferred over IV therapy in the treatment of peritonitis that occurs in patients undergoing continuous ambulatory peritoneal dialysis. Initial antibiotic regimens should be effective against both gram-positive and gram-negative organisms.
- Suitable antibiotics for initial empiric treatment of continuous ambulatory peritoneal dialysis–associated peritonitis are **cefazolin** (loading dose [LD] 500 mg/L; maintenance dose [MD] 125 mg/L) or **vancomycin** (LD 1000 mg/L; MD 25 mg/L) in cases of high prevalence of methicillin-resistant *Staphylococcus aureus* (MRSA) or β-lactam allergy may be utilized for Gram-positive coverage. One of these Gram-positive agents should be combined with a Gram-negative agent such as **ceftazidime** (LD 500 mg/L; MD 125 mg/L) or **cefepime** (LD 500 mg/L; MD 125 mg/L) or an aminoglycoside (**gentamicin** or **tobramycin** LD 8 mg/L; MD 4 mg/L).
- Antimicrobial therapy should be continued for at least 1 week after the dialysate fluid is clear and for a total of at least 14 days.

EVALUATION OF THERAPEUTIC OUTCOMES

- The patient should be continually reassessed to determine the success or failure of therapies.
- Once antimicrobials are initiated and other important therapies described earlier in the Treatment section are used, most patients should show improvement within 2 to 3 days. Usually, temperature will return to near normal, vital signs should stabilize, and the patient should not appear in distress, with the exception of recognized discomfort and pain from incisions, drains, and nasogastric tube.
- At 24 to 48 hours, aerobic bacterial culture results should return. If a suspected pathogen is not sensitive to the antimicrobial agents being given, the regimen should be changed if the patient has not shown sufficient improvement.
- If the isolated pathogen is susceptible to one antimicrobial, and the patient is progressing well, concurrent antimicrobial therapy may often be deescalated.
- With present anaerobic culturing techniques and the slow growth of these organisms, anaerobes are often not identified until 4 to 7 days after culture, and sensitivity information is difficult to obtain. For this reason, there are usually few data with which to alter the antianaerobic component of the antimicrobial regimen.
- Superinfection in patients being treated for intraabdominal infection is often due to *Candida*; however, enterococci or opportunistic gram-negative bacilli such as *Pseudomonas* or *Serratia* may be involved.
- Treatment regimens for intraabdominal infection can be judged successful if the patient recovers from the infection without recurrent peritonitis or intraabdominal abscess and without the need for additional antimicrobials. A regimen can be considered unsuccessful if a significant adverse drug reaction occurs, if reoperation is necessary, or if patient improvement is delayed beyond 1 or 2 weeks.

See Chapter 92, Intraabdominal Infections, authored by Keith M. Olsen, Alan E. Gross, and Joseph T. DiPiro, for a more detailed discussion of this topic.

CHAPTER 43

Respiratory Tract Infections, Lower

BRONCHITIS

ACUTE BRONCHITIS

- *Bronchitis* refers to an inflammatory condition of the large elements of the tracheobronchial tree that is usually associated with a generalized respiratory infection. The inflammatory process does not extend to include the alveoli. The disease entity is frequently classified as either acute or chronic. Acute bronchitis occurs in all ages, whereas chronic bronchitis primarily affects adults.
- Acute bronchitis most commonly occurs during the winter months. Cold, damp climates and/or the presence of high concentrations of irritating substances such as air pollution or cigarette smoke may precipitate attacks.
- Respiratory viruses are by far the most common infectious agents associated with acute bronchitis. The common cold viruses including rhinovirus and coronavirus and lower respiratory tract pathogens including influenza virus, adenovirus, and respiratory syncytial virus, account for the majority of cases. *Mycoplasma pneumoniae* also appears to be a frequent cause of acute bronchitis. Other bacterial causes are *Chlamydia pneumoniae* and *Bordetella pertussis*.
- Infection of the trachea and bronchi causes hyperemic and edematous mucous membranes and an increase in bronchial secretions. Destruction of respiratory epithelium can range from mild to extensive and may affect bronchial mucociliary function. In addition, the increase in bronchial secretions, which can become thick and tenacious, further impairs mucociliary activity. Recurrent acute respiratory infections may be associated with increased airway hyperreactivity and possibly the pathogenesis of chronic obstructive lung disease.

Clinical Presentation

- Acute bronchitis usually begins as an upper respiratory infection. The patient typically has nonspecific complaints, such as malaise and headache, coryza, and sore throat.
- Cough is the hallmark of acute bronchitis. It occurs early and will persist despite the resolution of nasal or nasopharyngeal complaints. Frequently, the cough is initially nonproductive but progresses, yielding mucopurulent sputum.
- Chest examination may reveal rhonchi and coarse, moist rales bilaterally. Chest radiographs, when performed, are usually normal.
- Bacterial cultures of expectorated sputum are generally of limited utility because of the inability to avoid normal nasopharyngeal flora by the sampling technique. Viral antigen detection tests can be used when a specific diagnosis is necessary. Cultures, polymerase chain reaction (PCR), or serologic diagnosis of *M. pneumoniae* and culture, direct fluorescent antibody detection, or PCR for *B. pertussis* should be obtained in prolonged or severe cases when epidemiologic considerations would suggest their involvement.

Treatment

- **Goals of Therapy:** The goal is to provide comfort to the patient and, in the unusually severe case, to treat associated dehydration and respiratory compromise.
- The treatment of acute bronchitis is symptomatic and supportive in nature. Reassurance and antipyretics alone are often sufficient. Bed rest and mild analgesic-antipyretic therapy are often helpful in relieving the associated lethargy, malaise, and fever. Patients should be encouraged to drink fluids to prevent dehydration and possibly decrease the viscosity of respiratory secretions.
- **Aspirin** or **acetaminophen** (650 mg in adults or 10–15 mg/kg per dose in children with a maximum daily adult dose of <4 g and 60 mg/kg for children) or **ibuprofen**

(200–800 mg in adults or 10 mg/kg per dose in children with a maximum daily dose of 3.2 g for adults and 40 mg/kg for children) is administered every 4 to 6 hours.
- In children, aspirin should be avoided and acetaminophen used as the preferred agent because of the possible association between aspirin use and the development of Reye syndrome.
- Mist therapy and/or the use of a vaporizer may further promote the thinning and loosening of respiratory secretions. In otherwise healthy patients, no meaningful benefits have been described with the use of oral or aerosolized β_2-receptor agonists and/or oral or aerosolized corticosteroids.
- Persistent, mild cough, which may be bothersome, may be treated with **dextromethorphan**; more severe coughs may require intermittent **codeine** or other similar agents.
- Routine use of antibiotics in the treatment of acute bronchitis is discouraged; however, in patients who exhibit persistent fever or respiratory symptomatology for more than 4 to 6 days, the possibility of a concurrent bacterial infection should be suspected.
- When possible, antibiotic therapy is directed toward anticipated respiratory pathogen(s) (ie, *Streptococcus pneumoniae*).
- *M. pneumoniae,* if suspected by history or if confirmed by culture, serology, or PCR may be treated with **azithromycin.** Also, a fluoroquinolone with activity against these pathogens (**levofloxacin**) may be used in adults.
- See Chap. 42 for recommendations to treat influenza.

CHRONIC BRONCHITIS

- Chronic bronchitis is a result of several contributing factors, including cigarette smoking; exposure to occupational dusts, fumes, and environmental pollution; host factors [eg, genetic factors]; and bacterial or viral infections.
- Chronic bronchitis is defined clinically as the presence of a chronic cough productive of sputum lasting more than 3 consecutive months of the year for 2 consecutive years without an underlying etiology of bronchiectasis or tuberculosis.

Clinical Presentation

- The hallmark of chronic bronchitis is a cough that may range from a mild to severe, incessant coughing productive of purulent sputum. Expectoration of the largest quantity of sputum usually occurs upon arising in the morning, although many patients expectorate sputum throughout the day. The expectorated sputum is usually tenacious and can vary in color from white to yellow-green. The diagnosis of chronic bronchitis is based primarily on clinical assessment and history.
- An increased number of polymorphonuclear granulocytes in sputum often suggests continual bronchial irritation, whereas an increased number of eosinophils may suggest an allergic component. The most common bacterial isolates (expressed in percentages of total cultures) identified from sputum culture in patients experiencing an acute exacerbation of chronic bronchitis are given in **Table 43–1.**

TABLE 43–1 Common Bacterial Isolates in Chronic Bronchitis

Bacteria	Percentage of Total Cultures
Haemophilus influenzae[a]	45%
Moraxella catarrhalis[a]	30%
Streptococcus pneumoniae[b]	20%
Escherichia coli, Enterobacter species, *Klebsiella,* and *Pseudomonas aeruginosa*	5%

[a]Often β-lactamase positive.
[b]Up to 25% of strains may have intermediate or high resistance to penicillin.

TABLE 43–2 Clinical Presentation of Chronic Bronchitis
Signs and symptoms
Excessive sputum expectoration
Cyanosis (advanced disease)
Physical examination
Chest auscultation usually reveals inspiratory and expiratory rales, rhonchi, and mild wheezing with an expiratory phase that is frequently prolonged.
Hyperresonance on percussion with obliteration of the area of cardiac dullness.
Normal vesicular breathing sounds are diminished.
Clubbing of digits (advanced disease)
Obesity
Chest radiograph
Increase in the anteroposterior diameter of the thoracic cage (observed as a barrel chest)
Depressed diaphragm with limited mobility
Laboratory tests
Erythrocytosis (advanced disease)
Pulmonary function tests
Decreased vital capacity
Prolonged expiratory flow

- With the exception of pulmonary findings, the physical examination of patients with mild to moderate chronic bronchitis is usually unremarkable (**Table 43–2**).

Treatment

- **Goals of Therapy**: The goal is to reduce the severity of symptoms, to ameliorate acute exacerbations, and to achieve prolonged infection-free intervals.
- A complete occupational/environmental history for the determination of exposure to noxious and irritating gases, as well as cigarette smoking must be assessed. Exposure to bronchial irritants should be reduced.
- Attempts should be made with the patient to reduce or eliminate cigarette smoking.
- Humidification of inspired air may promote the hydration (liquefaction) of tenacious secretions, allowing for more effective sputum production. The use of mucolytic aerosols (eg, N-acetylcysteine and deoxyribonuclease) is of questionable therapeutic value. Mucolytic was associated with a small reduction in acute exacerbations and did not cause any harm, improve quality of life, or slow the decline of lung function.
- For patients with moderate to severe chronic obstructive pulmonary disease (COPD), combination therapy with a long-acting β_2-agonist and inhaled corticosteroid led to decreased exacerbations and rescue medication use while it also improved quality of life, lung function, and symptom scores compared with long-acting β_2–agonist monotherapy.

PHARMACOLOGIC THERAPY

- Oral or aerosolized bronchodilators (eg, **albuterol** aerosol) may be of benefit to some patients during acute pulmonary exacerbations. For patients who consistently demonstrate limitations in airflow, a therapeutic change of β-agonist bronchodilator should be considered. Chronic inhalation of the salmeterol/fluticasone combination has been associated with improved pulmonary function and quality of life.
- Long-term inhalation of **ipratropium** (or **tiotropium**) decreases the frequency of cough, severity of cough, and volume of expectorated sputum.
- Use of antimicrobials for treatment of chronic bronchitis has been controversial but is becoming more accepted. Agents should be selected that are effective against likely pathogens, have the lowest risk of drug interactions, and can be administered in a manner that promotes compliance (see **Fig. 43–1**).

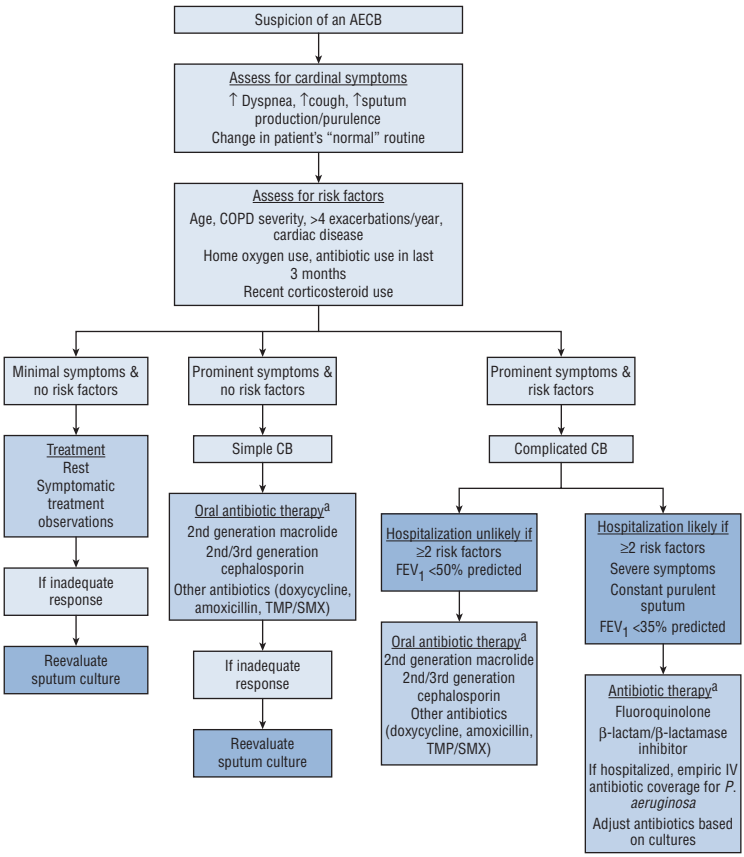


FIGURE 43–1. Clinical algorithm for the diagnosis and treatment of chronic bronchitic patients with an acute exacerbation incorporating the principles of the clinical classification system (AECB, acute exacerbation of chronic bronchitis; COPD, chronic obstructive pulmonary disease; CB, chronic bronchitis; TMP/SMX, trimethoprim/sulfamethoxazole). [a]See Table 43–9 for commonly used antibiotics and doses.

- The Anthonisen criteria can be used to determine if antibiotic therapy is indicated. The patient will most likely benefit from antibiotic therapy if two or three of the following are present: (1) increase of shortness of breath, (2) increase in sputum volume, or (3) production of purulent sputum.
- Selection of antibiotics should consider that up to 30% to 40% of *H. influenzae* and 95% to 100% of *M. catarrhalis* are β-lactamase producers; up to 40% of *S. pneumoniae* demonstrate penicillin resistance, with 20% being highly resistant.
- Antibiotics commonly used in the treatment of these patients and their respective adult starting doses are outlined in **Table 43–3.** Duration of symptom-free periods may be enhanced by antibiotic regimens using the upper limit of the recommended daily dose for 5 to 7 days.

BRONCHIOLITIS

- Bronchiolitis is an acute viral infection of the lower respiratory tract of infants that affects ~50% of children during the first year of life and 100% by 3 years.

TABLE 43–3 Oral Antibiotics Commonly Used for the Treatment of Acute Respiratory Exacerbations in Chronic Bronchitis

Antibiotic	Usual Adult Dose (g)	Dose Schedule (doses/day)
Preferred drugs		
Ampicillin	0.25–0.5	4
Amoxicillin	0.5–0.875	3-2
Amoxicillin–clavulanate	0.5–0.875	3-2
Ciprofloxacin	0.5–0.75	2
Levofloxacin	0.5–0.75	1
Moxifloxacin	0.4	1
Doxycycline	0.1	2
Minocycline	0.1	2
Tetracycline HCl	0.5	4
Trimethoprim–sulfamethoxazole	1 DS[a]	2
Supplemental drugs		
Azithromycin	0.25–0.5	1
Erythromycin	0.5	4
Clarithromycin	0.25–0.5	2
Cephalexin	0.5	4

[a] DS, double-strength tablet (160 mg trimethoprim/800 mg sulfamethoxazole).

- Respiratory syncytial virus is the most common cause of bronchiolitis, accounting for up to 75% of all cases. Parainfluenza viruses are the second most common cause. Bacteria serve as secondary pathogens in only a small minority of cases.

Clinical Presentation

- The most common clinical signs of bronchiolitis are found in **Table 43–4.** A prodrome suggesting an upper respiratory tract infection, usually lasting from 2 to 8 days, precedes the onset of clinical symptoms. As a result of limited oral intake due to coughing combined with fever, vomiting, and diarrhea, infants are frequently dehydrated.
- The diagnosis of bronchiolitis is based primarily on history and clinical findings. Identification of *respiratory syncytial virus (*RSV) by PCR should be available routinely from most clinical laboratories, but its relevance to the clinical management of bronchiolitis remains obscure.

TABLE 43–4 Clinical Presentation of Bronchiolitis

Signs and symptoms
Prodrome with irritability, restlessness, and mild fever
Cough and coryza
Vomiting, diarrhea, noisy breathing, and an increase in respiratory rate as symptoms progress
Labored breathing with retractions of the chest wall, nasal flaring, and grunting
Physical examination
Tachycardia and respiratory rate of 40–80/min in hospitalized infants
Wheezing and inspiratory rales
Mild conjunctivitis in one-third of patients
Otitis media in 5% to 10% of patients
Laboratory examinations
Peripheral white blood cell count normal or slightly elevated
Abnormal arterial blood gases (hypoxemia and, rarely, hypercarbia)

Treatment

- Bronchiolitis is a self-limiting illness and usually requires no therapy (other than reassurance, antipyretics, and adequate fluid intake) unless the infant is hypoxic or dehydrated. Otherwise healthy infants can be treated for fever, provided generous amounts of oral fluids, and observed closely.
- In severely affected children, the mainstays of therapy for bronchiolitis are oxygen therapy and intravenous (IV) fluids.
- Aerosolized β-adrenergic therapy appears to offer little benefit for the majority of patients but may be useful in the child with a predisposition toward bronchospasm.
- Because bacteria do not represent primary pathogens in the etiology of bronchiolitis, antibiotics should not be routinely administered. However, many clinicians frequently administer antibiotics initially while awaiting culture results because the clinical and radiographic findings in bronchiolitis are often suggestive of a possible bacterial pneumonia.
- **Ribavirin** may be considered for bronchiolitis caused by respiratory syncytial virus in a subset of patients (severely ill patients, especially those with chronic lung disease, congenital heart disease, prematurity, and immunodeficiency (especially severe combined immunodeficiency and human immunodeficiency virus [HIV] infection).). Use of the drug requires special equipment (small-particle aerosol generator) and specifically trained personnel for administration via oxygen hood or mist tent.

PNEUMONIA

- Pneumonia is the most common infectious cause of death in the United States. It occurs in persons of all ages, although the clinical manifestations are most severe in the very young, the elderly, and the chronically ill. **Table 43–5** presents the classification of pneumonia and risk factors

PATHOPHYSIOLOGY

- Microorganisms gain access to the lower respiratory tract by three routes: they may be inhaled as aerosolized particles, they may enter the lung via the bloodstream from an extrapulmonary site of infection, or aspiration of oropharyngeal contents may occur.
- Lung infections with viruses suppress the bacterial clearing activity of the lung by impairing alveolar macrophage function and mucociliary clearance, thus setting the stage for secondary bacterial pneumonia.
- The vast majority of pneumonia cases acquired in the community by otherwise healthy adults are due to *S. pneumoniae* (up to 75% of all cases). Other common bacterial causes are *M. pneumoniae, Legionella* species*, C. pneumoniae,* and *H. influenzae* and a variety of viruses.
- Healthcare-associated pneumonia (HCAP) is a classification used to distinguish nonhospitalized patients at risk for multi drug-resistant (MDR) pathogens (eg, *P. aeruginosa*, Acinetobacter species, and methicillin-resistant *Staphylococcus aureus* [MRSA]) from those with community-acquired pneumonia.
- Gram-negative aerobic bacilli and *S. aureus* and MDR pathogens are also the leading causative agents in hospital-acquired pneumonia.
- Anaerobic bacteria are the most common etiologic agents in pneumonia that follows the gross aspiration of gastric or oropharyngeal contents.
- In the pediatric age group, most pneumonias are due to viruses, especially respiratory syncytial virus, parainfluenza, and adenovirus. *S. pneumoniae* is the most common bacterial cause, followed by group *A Streptococcus, S. aureus*, and *H. influenzae* type b

TABLE 43–5 Pneumonia Classifications and Risk Factors

Type of Pneumonia	Definition	Risk Factors
Community acquired (CAP)	Pneumonia developing in patients with no contact to a medical facility	• Age >65 years • Diabetes mellitus • Asplenia • Chronic cardiovascular, pulmonary, renal and/or liver disease • Smoking and/or alcohol abuse
Healthcare associated (HCAP)	Pneumonia developing in patients not in an acute care medical facility but two or more risk factors for MDR pathogens	• Recent hospitalization ≥2 days within past 90 days • Nursing home or long-term care facility resident • Recent (past 30 days) antibiotic use, chemotherapy, wound care or infusion therapy at either a healthcare facility or home • Hemodialysis patients • Contact with a family member with infection caused by MDR pathogen
Hospital-acquired (HAP)	Pneumonia developing >48 hours after hospital admission	• Witnessed aspiration • COPD, ARDS, or coma • Administration of antacids, H_2-antagonists, or proton pump inhibitor • Supine position • Enteral nutrition, nasogastric tube • Reintubation, tracheostomy, or patient transport • Prior antibiotic exposure • Head trauma, ICP monitoring • Age >60 years • See health care associated for MDR risk factors
Ventilator associated (VAP)	Pneumonia developing >48 hours after intubation and mechanical ventilation	• Same as hospital acquired

ARDS, adult respiratory distress syndrome; CAP, community-acquired pneumonia; COPD, chronic obstructive pulmonary disease; HAP, hospital-acquired pneumonia; HCAP, healthcare-associated pneumonia; ICP, intracranial pressure; MDR, multidrug resistant; VAP, ventilator-associated pneumonia.

CLINICAL PRESENTATION

Gram-Positive and Gram-Negative Bacterial Pneumonia

- The clinical presentation of pneumonia is found in **Table 43–6**.
- The chest radiograph and sputum examination and culture are the most useful diagnostic tests for gram-positive and gram-negative bacterial pneumonia. Typically, the chest radiograph reveals a dense lobar or segmental infiltrate.

TABLE 43–6	Clinical Presentation of Pneumonia
Signs and symptoms	
Abrupt onset of fever, chills, dyspnea, and productive cough	
Rust-colored sputum or hemoptysis	
Pleuritic chest pain	
Physical examination	
Tachypnea and tachycardia	
Dullness to percussion	
Increased tactile fremitus, whispered pectoriloquy, and egophony	
Chest wall retractions and grunting respirations	
Diminished breath sounds over the affected area	
Inspiratory crackles during lung expansion	
Chest radiograph	
Dense lobar or segmental infiltrate	
Laboratory examination	
Leukocytosis with a predominance of polymorphonuclear cells	
Low oxygen saturation on arterial blood gas or pulse oximetry	

- Substantial changes in a patient's mental status, often out of proportion to the degree of fever, are seen in approximately one fourth of patients. Obtundation, hallucinations, grand mal seizures, and focal neurologic findings have also been associated with this illness.
- Laboratory findings include leukocytosis with predominance of mature and immature granulocytes in 50% to 75% of patients.

Anaerobic Pneumonia

- The course of anaerobic pneumonia is typically indolent with cough, low-grade fever, and weight loss, although an acute presentation may occur. Putrid sputum, when present, is highly suggestive of the diagnosis. Chest radiographs reveal infiltrates typically located in dependent lung segments, and lung abscesses develop in 20% of patients 1 to 2 weeks into the course of the illness.

Mycoplasma pneumoniae

- *M. pneumoniae* pneumonia presents with a gradual onset of fever, headache, and malaise, with the appearance 3 to 5 days after the onset of illness of a persistent, hacking cough that initially is nonproductive. Sore throat, ear pain, and rhinorrhea are often present. Lung findings are generally limited to rales and rhonchi; findings of consolidation are rarely present.
- Nonpulmonary manifestations are extremely common and include nausea, vomiting, diarrhea, myalgias, arthralgias, polyarticular arthritis, skin rashes, myocarditis and pericarditis, hemolytic anemia, meningoencephalitis, cranial neuropathies, and Guillain–Barré syndrome. Systemic symptoms generally clear in 1 to 2 weeks, whereas respiratory symptoms may persist up to 4 weeks.
- Radiographic findings include patchy or interstitial infiltrates, which are most commonly seen in the lower lobes.
- Sputum Gram stain may reveal mononuclear or polymorphonuclear leukocytes, with no predominant organism. Although *M. pneumoniae* can be cultured from respiratory secretions using specialized medium, 2 to 3 weeks may be necessary for culture identification.

Viral Pneumonia

- The clinical pictures produced by respiratory viruses are sufficiently variable and overlap to such a degree that an etiologic diagnosis cannot confidently be made on clinical grounds alone. Serologic tests for virus-specific antibodies are often used in the diagnosis of viral infections. The diagnostic fourfold rise in titer between acute

and convalescent phase sera may require 2 to 3 weeks to develop; however, same-day diagnosis of viral infections is now possible through the use of indirect immunofluorescence tests on exfoliated cells from the respiratory tract.

- Radiographic findings are nonspecific and include bronchial wall thickening and perihilar and diffuse interstitial infiltrates.

Hospital-acquired Pneumonia

- The strongest predisposing factor for hospital-acquired pneumonia (HAP) is mechanical ventilation. Factors predisposing patients to HAP include severe illness, long duration of hospitalization, supine positioning, witnessed aspiration, coma, acute respiratory distress syndrome, patient transport, and prior antibiotic exposure.
- The diagnosis of nosocomial pneumonia is usually established by the presence of a new infiltrate on chest radiograph, fever, worsening respiratory status, and the appearance of thick, neutrophil-laden respiratory secretions.

TABLE 43–7 Evidence-Based Empiric Antimicrobial Therapy for Pneumonia in Adults

Clinical Setting	Usual Pathogens	Empirical Therapy
Outpatient/Community Acquired		
Previously healthy	*S. pneumoniae, M. pneumoniae, H. influenzae, C. pneumoniae, M. catarrhalis*	Macrolide/azalide,[b] or tetracycline[c]
	viral	Oseltamivir or zanamivir if <48° from onset of symptoms
Comorbidities (diabetes, heart/lung/liver/renal disease, alcoholism)		Fluoroquinolone[d] or β-lactam + macrolide[b]
Elderly	*S. pneumoniae*, gram-negative bacilli	Piperacillin/tazobactam or cephalosporin[e] or carbapenem[f] Fluoroquinolone[d] or β-lactam + macrolide[b]/tetracycline
Inpatient/Community Acquired		
Non-ICU	*S. pneumoniae, H. influenzae, M. pneumoniae, C. pneumoniae, Legionella* sp.	Fluoroquinolone[d] or β-lactam + macrolide[b]/tetracycline
ICU	*S. pneumoniae, S. aureus, Legionella* sp., gram-negative bacilli, H. *influenzae*	β-Lactam + macrolide[b]/fluoroquinolone[d]
	If *P. aeruginosa* suspected	Piperacillin/tazobactam or meropenem or cefepime + fluoroquinolone[d]/AMG/azithromycin; or β-lactam + AMG + azithromycin/respiratory fluoroquinolone[d]
	If MRSA suspected	Above + vancomycin or linezolid
	Viral	Oseltamivir or zanamivir ± antibiotics for 2° infection

(*Continued*)

TABLE 43–7 Evidence-Based Empiric Antimicrobial Therapy for Pneumonia in Adults (*Continued*)

Clinical Setting	Usual Pathogens	Empirical Therapy
Hospital Acquired, Ventilator Associated, or Healthcare Associated		
No risk factors for MDR pathogens	*S. pneumoniae, H. influenzae*, MSSA enteric gram-negative bacilli	Ceftriaxone or fluoroquinolone[d] or ampicillin/sulbactam or ertapenem or doripenem
Risk factors for MDR pathogen	*P. aeruginosa, K. pneumoniae* (ESBL), *Acinetobacter* sp.	Antipseudomonal cephalosporin[e] or antipseudomonal carbapenem or β-lactam/β-lactamase + antipseudomonal fluoroquinolone[d] or AMG[g]
	If MRSA or *Legionella* sp. suspected	Above + vancomycin or linezolid
Aspiration	*S. aereus*, enteric gram-negative bacilli	Penicillin or clindamycin or piperacillin/tazobactam + AMG[g]
	Anaerobes	Clindamycin, β-lactam/β-lactamase, or carbapenem
Atypical Pneumonia[h]		
Legionella pneumophilia		Fluoroquinolone,[d] doxycycline, or azithromycin
Mycoplasma pneumonia		Fluoroquinolone,[d] doxycycline, or azithromycin
Chlamydophila pneumonia		Fluoroquinolone[d] doxycycline, or azithromycin
SARS		Fluoroquinolone[d] or macrolides[b]
Avian influenza		Oseltamivir
H1N1 influenza		Oseltamivir

MRSA, methicillin-resistant *Staphylococcus aureus*; AMG, aminoglycoside; SARS, severe acute respiratory syndrome; ESBL, extended-spectrum β-lactamases; MDR, multidrug resistant; MSSA, methicillin-sensitive *Staphylococcus aureus*.

[a]See the section Selection of Antimicrobial Agents.
[b]Macrolide/azalide: erythromycin, clarithromycin, and azithromycin.
[c]Tetracycline: tetracycline, HC1, and doxycycline.
[d]Fluoroquinolone: ciprofloxacin, levofloxacin, and moxifloxacin.
[e]Antipseudomonal cephalosporin: cefepime and ceftazidime.
[f]Antipseudomonal carbapenem: imipenem and meropenem.
[g]Aminoglycoside: amikacin, gentamicin, and tobramycin.
[h]For tuberculosis, see Chapter 90.

Data from references 5, 7, and 52.

TREATMENT

- Eradication of the offending organism and complete clinical cure are the primary objectives. Associated morbidity should be minimized (eg, renal, pulmonary, or hepatic dysfunction).
- The first priority on assessing the patient with pneumonia is to evaluate the adequacy of respiratory function and to determine whether there are signs of systemic illness, specifically dehydration, or sepsis with resulting circulatory collapse.

- The supportive care of the patient with pneumonia includes the use of humidified oxygen for hypoxemia, fluid resuscitation, administration of bronchodilators (albuterol) when bronchospasm is present, and chest physiotherapy with postural drainage if there is evidence of retained secretions.
- Important therapeutic adjuncts include adequate hydration (by IV route if necessary), optimal nutritional support, and fever control.
- The treatment of bacterial pneumonia initially involves the empiric use of a relatively broad-spectrum antibiotic (or antibiotics) effective against probable pathogens after appropriate cultures and specimens for laboratory evaluation have been obtained. Therapy should be narrowed to cover specific pathogens once the results of cultures are known.
- Appropriate empiric choices for the treatment of bacterial pneumonias relative to a patient's underlying disease are shown in **Table 43–7** for adults and **Table 43–8** for children. Dosages for antibiotics to treat pneumonia are provided in **Table 43–9.**
- Antibiotic concentrations in respiratory secretions in excess of the pathogen minimum inhibitory concentration (MIC) are necessary for successful treatment of pulmonary infections.
- The benefit of antibiotic aerosols or direct endotracheal instillation has not been consistently demonstrated.

TABLE 43–8 Empirical Antimicrobial Therapy for Pneumonia in Pediatric Patients [a]

Clinical Setting	Usual Pathogen(s)	Empirical Therapy
Outpatient/Community Acquired		
<1 month	Group B *Streptococcus, H. influenzae* (nontypeable), *E. coli*, *S. aureus*, *Listeria*	Ampicillin/sulbactam, cephalosporin,[b] carbapenem[c]
	CMV, RSV, adenovirus	Ribavirin for RSV[d]
1–3 months	*C. pneumoniae*, possibly *Ureaplasma*, CMV, *Pneumocystis carinii* (afebrile pneumonia syndrome)	Macrolide/azalide,[e] trimethoprim–sulfamethoxazole
	S. pneumoniae, *S. aureus*	Semisynthetic penicillin[f] or cephalosporin[g]
Preschool-aged children	Viral (rhinovirus, RSV, influenza A and B, parainfluenzae, adenovirus, human metapneumovirus, coronavirus)	Antimicrobial therapy not routinely required
Previously healthy, fully immunized infants and preschool children with suspected mild–moderate bacterial CAP	*S. pneumoniae*, *M. pneumoniae*, other atypical	Amoxicillin, cephalosporin[b,g] Macrolide/azalide or fluoroquinolone
Previously healthy, fully immunized school-aged children and adolescents with mild–moderate CAP	*S. pneumoniae*	Amoxicillin, cephalosporin,[b,g] or fluoroquinolone
	M. pneumoniae, other atypical	Macrolide/azalide, fluoroquinolone, or tetracycline
Moderate–severe CAP during influenza virus outbreak	Influenza A and B, other viruses	Oseltamivir or zanamivir

(*continued*)

TABLE 43–8 Empirical Antimicrobial Therapy for Pneumonia in Pediatric [a]

Clinical Setting	Usual Pathogen(s)	Empirical Therapy
Inpatient/Community Acquired		
Fully immunized infants and school-aged children	*S. pneumoniae*	Ampicillin, penicillin G, cephalosporin[b]
	CA-MRSA	β-Lactam + vancomycin/clindamycin
	M. pneumoniae, *C. pneumoniae*	β-Lactam + macrolide/fluoroquinolone/doxycycline
Not fully immunized infants and children; regions with invasive penicillin-resistant pneumococcal strains; patients with life-threatening infections	*S. pneumoniae*, *PCN resistant*	Cephalosporin[b]
	MRSA	Add vancomycin/clindamycin
	M. pneumoniae, other atypical pathogens	Macrolide/azalide[e] + β-lactam/doxycycline/fluoroquinolone

CMV, cytomegalovirus; RSV, respiratory syncytial virus; CAP, community-acquired pneumonia; MRSA, methicillin resistant *S. aureus*.
[a]See the section Selection of Antimicrobial Agents.
[b]Third-generation cephalosporin: ceftriaxone and cefotaxime. Note that cephalosporins are not active against *Listeria*.
[c]Carbapenem: imipenem–cilastatin and meropenem.
[d]See text for details regarding possible ribavirin treatment for RSV infection.
[e]Macrolide/azalide: erythromycin and clarithromycin/azithromycin.
[f]Semisynthetic penicillin: nafcillin and oxacillin.
[g]Second-generation cephalosporin: cefuroxime and cefprozil.

Data from reference 6.

TABLE 43–9 Antibiotic Doses for the Treatment of Bacterial Pneumonia

			Daily Antibiotic Dose[a]	
Antibiotic Class	**Antibiotic**	**Brand Name**	**Pediatric**	**Adult (Total Dose/Day)**
Penicillin	Ampicillin ± sulbactam	Unasyn®	150–200 mg/kg/day	6–12 g
	Amoxicillin ± clavulanate[b]	Augmentin®	45–100 mg/kg/day	0.75–1 g
	Piperacillin/tazobactam	Zosyn®	200–300 mg/kg/day	12–18 g
	Penicillin		100,000–250,000 units/kg/day	12–18 million units
Extended-spectrum cephalosporins	Ceftriaxone	Rocephin®	50–75 mg/kg/day	1–2 g
	Cefotaxime	Claforan®	150 mg/kg/day	2–12 g
	Ceftazidime	Fortaz®/Tazicef®	90–150 mg/kg/day	4–6 g
	Cefepime	Maxipime®	100–150 mg/kg/day	2–6 g

(*continued*)

TABLE 43–9 Antibiotic Doses for the Treatment of Bacterial Pneumonia

			Daily Antibiotic Dose[a]	
Antibiotic Class	**Antibiotic**	**Brand Name**	**Pediatric**	**Adult (Total Dose/Day)**
Macrolide/azalide	Clarithromycin	Biaxin®	15 mg/kg/day	0.5–1 g
	Erythromycin	Ery-Tab®	30–50 mg/kg/day	1–2 g
	Azithromycin	Zithromax®	10 mg/kg × 1 day, and then 5 mg/kg/day × 4 days	500 mg day 1, and then 250 mg/day × 4 days
Fluoroquinolones[c]	Moxifloxacin	Avelox®	—	400 mg
	Gemifloxacin	Factive®	—	320 mg
	Levofloxacin	Levaquin®	8–20 mg/kg/day	750 mg
	Ciprofloxacin	Cipro®	30 mg/kg/day	1.2 g
Tetracycline[d]	Doxycycline	Monodox®/ Doxy 100™	2–5 mg/kg/day	100–200 mg
	Tetracycline HCl		25–50 mg/kg/day	1–2 g
Aminoglycosides	Gentamicin		7.5–10 mg/kg/day	7.5 mg/kg
	Tobramycin		7.5–10 mg/kg/day	7.5 mg/kg
Carbapenems	Imipenem	Primaxin®	60–100 mg/kg/day	2–4 g
	Meropenem	Merrem®	30–60 mg/kg/day	1–3 g
Other	Vancomycin	Zyvox®	45–60 mg/kg/day	2–3 g
	Linezolid	Cleocin®	20–30 mg/kg/day	1.2 g
	Clindamycin		30–40 mg/kg/day	1.8 g

[a]Doses can be increased for more severe disease and may require modification for patients with organ dysfunction.
[b]Higher-dose amoxicillin and amoxicillin/clavulanate (e.g., 90 mg/kg/day) are used for penicillin-resistant *S. pneumoniae*.
[c]Fluoroquinolones have been avoided for pediatric patients because of the potential for cartilage damage; however, they have been used for MDR bacterial infection safely and effectively in infants and children (see text).
[d]Tetracyclines are rarely used in pediatric patients, particularly in those younger than 8 years because of tetracycline-induced permanent tooth discoloration.

EVALUATION OF THERAPEUTIC OUTCOMES

- With community-acquired pneumonia, time for resolution of cough, sputum production, and presence of constitutional symptoms (eg, malaise, nausea or vomiting, and lethargy) should be assessed. Progress should be noted in the first 2 days, with complete resolution in 5 to 7 days.
- With nosocomial pneumonia, the above parameters should be assessed along with white blood cell counts, chest radiograph, and blood gas determinations.

See Chapter 85, Lower Respiratory Tract Infections, authored by Martha G. Blackford, Mark L. Glover, and Michael D. Reed for a more detailed discussion of this topic.

Respiratory Tract Infections, Upper

CHAPTER 44

OTITIS MEDIA

- *Otitis media* is an inflammation of the middle ear. There are three subtypes of otitis media: acute otitis media, otitis media with effusion, and chronic otitis media. The three are differentiated by (a) acute signs of infection, (b) evidence of middle ear inflammation, and (c) presence of fluid in the middle ear.
- There are more than 709 million cases of otitis media worldwide each year; half of these cases occur in children under 5 years of age.
- Otitis media is most common in infants and children. The risk factors for amoxicillin-resistant bacteria in acute otitis media include attendance at a child care center, recent receipt of antibiotic treatment (past 30 days), and age younger than 2 years.

PATHOPHYSIOLOGY

- Approximately 40% to 75% of acute otitis media cases are caused by viral pathogens. *Streptococcus pneumoniae* is the most common bacterial cause of acute otitis media (35%–40%). Nontypable strains of *Haemophilus influenzae* and *Moraxella catarrhalis* are each responsible for 30% to 35% and 15% to 18% of cases, respectively.
- Acute bacterial otitis media usually follows a viral upper respiratory tract infection that causes eustachian tube dysfunction and mucosal swelling in the middle ear.
- Up to 40% of *S. pneumonia* isolates in the United States are penicillin nonsusceptible, and up to half of these have high-level penicillin resistance. Approximately 30% to 40% of *H. influenzae* and greater than 90% of *M. catarrhalis* isolates from the upper respiratory tract produce β–lactamases.

CLINICAL PRESENTATION

- Irritability and tugging on the ear are often the first clues that a child has acute otitis media.
- A diagnosis of acute otitis media requires the following three criteria: (a) acute signs of infection, (b) evidence of middle ear inflammation, and (c) presence of fluid in the middle ear. The latter two criteria must be determined by otoscopic exam. The signs of infection must be acute and may be nonspecific, including fever (<25% of patients) and otalgia (>75% of patients). Younger children may be irritable, tug on the involved ear, and have difficulty sleeping.
- Signs and symptoms of middle ear inflammation include erythema of the tympanic membrane and otalgia. Middle ear effusion is indicated by any of the following: fullness or bulging of the tympanic membrane (most important sign), limited or absent mobility of the tympanic membrane, and otorrhea.

TREATMENT

- Goals of Treatment: The goals are pain management, prudent antibiotic use, and secondary disease prevention. Acute otitis media should first be differentiated from otitis media with effusion or chronic otitis media.
- Primary prevention of acute otitis media with vaccines should be considered. The seven-valent pneumococcal conjugate vaccine reduced the occurrence of acute otitis media by 6% to 7% during infancy. The vaccine did not benefit older children with a history of acute otitis media.
- Pain of otitis media should be addressed with oral analgesics. **Acetaminophen** or a nonsteroidal antiinflammatory agent, such as **ibuprofen**, should be offered early

to relieve pain of acute otitis media. Decongestants or antihistamines should not be recommended for acute otitis media because they provide minimal benefit.

- A brief observation period should be considered to determine whether the patient requires immediate antibiotic therapy because of disease severity or patient characteristics.
- Antimicrobial therapy is used to treat otitis media; however, a high percentage of children will be cured with symptomatic treatment alone.
- Delayed antibiotic treatment (48–72 hours) may be considered in children 6 months to 2 years of age if symptoms are not severe and the diagnosis is uncertain, and in children 2 years of age or older with an uncertain diagnosis. Delayed treatment decreases antibiotic adverse effects and minimizes bacterial resistance.
- High-dose **amoxicillin** (80–90 mg/kg/day) is the drug of choice for acute otitis media. If β-lactamase-producing pathogens are suspected or known, amoxicillin should be given with **clavulanate** (90 mg/kg/day of amoxicillin with 6.4 mg/kg/day of clavulanate in two divided doses). Treatment recommendations for acute otitis media are found in **Table 44–1.**

TABLE 44–1 Antibiotics for Acute Otitis Media

Antibiotic	Brand Name	Dose	Comments[a]
Initial Diagnosis			
Amoxicillin	Amoxil®	80-90 mg/kg/day divided twice daily	First-line (nonsevere)
Amoxicillin clavulanate[b]	Augmentin®	90 mg/kg/day of amoxicillin plus 6.4 mg/kg/day of clavulanate divided twice daily	First-line (severe)
Cefdinir, cefuroxime, cefpodoxime	Omnicef ®, Ceftin®, Vantin ®		Non–type 1 allergy (nonsevere)
Ceftriaxone (1–3 days)	Rocephin®		Non–type 1 allergy (severe)
Azithromycin, clarithromycin	Zithromax® , Biaxin®		Type 1 allergy (nonsevere)
Failure at 48–72 Hours			
Amoxicillin clavulanate[b]	Augmentin®	90 mg/kg/day of amoxicillin plus 6.4 mg/kg/day of clavulanate divided twice daily	First-line (nonsevere)
Ceftriaxone (1–3 days)	Rocephin®		First-line (severe) and non–type 1 allergy (nonsevere)
Clindamycin	Cleocin®		Non–type 1 allergy (severe) and type 1 allergy (nonsevere and severe)

[a]Severe: temperature greater than or equal to 39°C (102°F) and/or severe otalgia.
[b]Amoxicillin–clavulanate 90:6.4 or 14:1 ratio is available in the United States; 7:1 ratio is available in Canada (use amoxicillin 45 mg/kg for one dose, amoxicillin 45 mg/kg with clavulanate 6.4 mg/kg for second dose).

From reference 6.

- If treatment failure occurs with amoxicillin, an agent should be chosen with activity against β-lactamase-producing *H. influenzae* and *M. catarrhalis,* as well as drug-resistant *S. pneumoniae,* such as high-dose amoxicillin–clavulanate (recommended) or cefuroxime, cefdinir, cefpodoxime, cefprozil, or intramuscular ceftriaxone.
- In children at least 6 years old who have mild to moderate acute otitis media, a 5- to 7-day course of antibiotics may be used. Some experts have speculated that patients can be treated for as little as 3 to 5 days but short-course treatment is not recommended in children younger than 2 years of age.
- Surgical insertion of tympanostomy tubes (T tubes) is an effective method for the prevention of recurrent otitis media. Patients with acute otitis media should be reassessed after 3 days, with most children being asymptomatic at 7 days.

ANTIBIOTIC PROPHYLAXIS OF RECURRENT INFECTIONS

- Recurrent otitis media is defined as at least three episodes in 6 months or at least four episodes in 12 months. Recurrent infections are of concern because patients younger than 3 years are at high risk for hearing loss and language and learning disabilities. Data from studies generally do not favor prophylaxis.

PHARYNGITIS

- *Pharyngitis* is an acute infection of the oropharynx or nasopharynx that results in 1% to 2% of all outpatient visits. Although viral causes are most common, group A β-hemolytic *Streptococcus* (GABHS), or *Streptococcus pyogenes,* is the primary bacterial cause.
- Viruses (eg, rhinovirus, coronavirus, and adenovirus) cause most of the cases of acute pharyngitis. A bacterial etiology for acute pharyngitis is far less likely. Of all of the bacterial causes, GABHS is the most common (15%–30% of cases in pediatric patients and 5%–15% in adults).
- Nonsuppurative complications of GABHS pharyngitis include acute rheumatic fever, acute glomerulonephritis, reactive arthritis, peritonsillar abscess, retropharyngeal abscess cervical lymphadenitis, mastoiditis, otitis media, rhinosinusitis, and necrotizing fasciitis.

CLINICAL PRESENTATION

- The most common symptom of pharyngitis is sore throat. The clinical presentation of group A streptococcal pharyngitis is presented in **Table 44–2**. Evidence-based principles for diagnosis of Group *A Streptococcus* is found in **Table 44–3**.

TREATMENT

- Goals of Treatment: The goal is to improve clinical signs and symptoms, minimize adverse drug reactions, prevent transmission to close contacts, and prevent acute rheumatic fever and suppurative complications such as peritonsillar abscess, cervical lymphadenitis, and mastoiditis.
- Antimicrobial therapy should be limited to those who have clinical and epidemiologic features of GABHS pharyngitis, preferably with a positive laboratory test.
- Because pain is often the primary reason for visiting a physician, emphasis on analgesics such as **acetaminophen** and nonsteroidal anti-inflammatory drugs (NSAIDs) to aid in pain relief is strongly recommended.
- Penicillin and amoxicillin are the treatments of choice. Antimicrobial treatment should be limited to those who have clinical and epidemiologic features of GABHS pharyngitis with a positive laboratory test. (**Table 44–4**). **Table 44–5** presents dosing guidelines for recurrent infections. **Table 44–6** presents evidence-based principles for diagnosis of group A *Streptococcus* pharyngitis. The duration of therapy for GABHS pharyngitis is 10 days, except for benzathine penicillin and azithromycin, to maximize bacterial eradication.

TABLE 44–2 Clinical Presentation and Diagnosis of Group A Streptococcal Pharyngitis
General
A sore throat of sudden onset that is mostly self-limited
Fever and constitutional symptoms resolving in 3 to 5 days
Clinical signs and symptoms are similar for viral and nonstreptococcal bacterial causes.
Signs and symptoms of GABHS pharyngitis
Sore throat
Pain on swallowing
Fever
Headache, nausea, vomiting, and abdominal pain (especially in children)
Erythema/inflammation of the tonsils and pharynx with or without patchy exudates
Enlarged, tender lymph nodes
Red swollen uvula, petechiae on the soft palate, and a scarlatiniform rash
Several symptoms that are not suggestive of group A *Streptococcus* are cough, conjunctivitis, and coryza.
Laboratory tests
Throat swab and culture
Rapid antigen detection testing

TABLE 44–3 Evidence-Based Principles for Diagnosis of Group A *Streptococcus*	
Recommendations	**Level**
Selective use of diagnostic testing only in those with clinical features suggestive of group A *Streptococcus* will increase the proportion of positive tests as well as results of those truly infected, not carriers	A-II
Clinical diagnosis cannot be made with certainty even by the most experienced clinician; bacteriologic confirmation is required	A-II
Throat culture remains the diagnostic standard, with a sensitivity of 90–95% for detection of group A *Streptococcus* if done correctly	A-II
Rapid identification and treatment of patients with disease can reduce transmission, allow patients to return to work or school earlier, and reduce the acute morbidity of the disease	A-II
The majority of rapid antigen-detection tests available have a specificity >95% (minimizes overprescribing to those without disease) and a sensitivity of 80–90% compared with culture	A-II
Early initiation of antibiotic therapy results in faster resolution of signs and symptoms. Delays in therapy (if awaiting cultures) can be made safely for up to 9 days after symptom onset and still prevent major complications such as rheumatic fever	A-I

These guidelines provide a systematic weighting of the strength of the recommendation (A, good; B, moderate; and C, poor) and quality of evidence (I, at least one randomized controlled trial; II, at least one well-designed clinical trial, not randomized, or a cohort or case–control analytical study, or from multiple time series, or from dramatic results of an uncontrolled trial; and III, expert opinion).

From Bisno AL, Gerber MA, Gwaltney JM Jr, et al. Practice guidelines for the diagnosis and management of group A streptococcal pharyngitis: Infectious Diseases Society of America. Clin Infect Dis 2002;35(2):113–125.

TABLE 44–4 Antibiotics and Doses for Group A β-Hemolytic Streptococcal Pharyngitis

Antibiotic	Brand Name	Dose	Duration	Rating
Preferred Antibiotics				
Penicillin V	Pen-V®	Children: 250 mg twice daily or three times daily orally	10 days	IB
		Adult: 250 mg four times daily or 500 mg twice daily orally		
Penicillin G benzathine	Bicillin L-A®	Less than 27 kg: 0.6 million units; 27 kg or greater: 1.2 million units intramuscularly	One dose	IB
Amoxicillin[a]	Amoxil®	50 mg/kg once daily (maximum 1,000 mg); 25 mg/kg (maximum 500 mg) twice daily	10 days	IB
Penicillin Allergy				
Cephalexin	Keflex®	20 mg/kg/dose orally twice daily (maximum 500 mg/dose)	10 days	IB
Cefadroxil	Duricef®	30 mg/kg orally once daily (maximum 1 g)	10 days	IB
Clindamycin	Cleocin®	7 mg/kg/dose orally thrice daily (maximum 300 mg/dose)	10 days	IIaB
Azithromycin[b]	Zithromax®	12 mg/kg orally once daily (maximum 500 mg)	5 days	IIaB
Clarithromycin[b]	Biaxin®	15 mg/kg orally per day divided in two doses (maximum 250 mg twice daily)	10 days	IIaB

These guidelines provide a systematic weighting of the strength of the recommendation (Class I, conditions for which there is evidence and/or general agreement that a given procedure or treatment is beneficial, useful, and effective; Class II, conditions for which there is conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of a procedure or treatment; Class IIa, weight of evidence/opinion is in favor of usefulness/efficacy; Class IIb, usefulness/efficacy is less well established by evidence/opinion; Class III, conditions for which there is evidence and/or general agreement that a procedure/treatment is not useful/effective and in some cases may be harmful) and quality of evidence (A, data derived from multiple randomized clinical trials or meta-analyses; B, data derived from a single randomized trial or nonrandomized studies; C, only consensus opinion of experts, cases studies, or standard of care).

[a]Standard formulation, not extended release.

[b]Resistance of GABHS to these agents may vary and local susceptibilities should be considered with these agents.

From reference 47.

- The duration of therapy for group A streptococcal pharyngitis is 10 days to maximize bacterial eradication.
- Most cases of pharyngitis are self-limited; however, antimicrobial therapy will hasten resolution when given early to proven cases of GABHS. Symptoms generally resolve by 3 or 4 days even without therapy. Follow-up testing is generally not necessary for index cases or in asymptomatic contacts of the index patient.

ACUTE BACTERIAL RHINOSINUSITIS

- *Sinusitis* is an inflammation and/or infection of the paranasal sinus mucosa. The term *rhinosinusitis* is used by some specialists, because sinusitis typically also involves the nasal mucosa. The majority of these infections are viral in origin. It is important

TABLE 44–5 Antibiotics and Doses for Eradication of Group A β-Hemolytic Streptococcal Pharyngitis in Chronic Carriers

Antibiotic	Brand Name	Dose
Clindamycin	Cleocin®	20–30 mg/kg/day orally in three divided doses (maximum 300 mg/dose)
Amoxicillin–clavulanate	Augmentin®	40 mg/kg/day orally in three divided doses (maximum 2,000 mg/day of amoxicillin)
Penicillin V and rifampin	Pen-V®, Rifadin®	Penicillin V: 50 mg/kg/day in four doses × 10 days (maximum 2,000 mg/day); *and* rifampin: 20 mg/kg/day in one dose × last 4 days of treatment (maximum 600 mg/day)
Penicillin G benzathine and rifampin	Bicillin L-A®, Rifadin®	Penicillin G benzathine: less than 27 kg—0.6 million units; 27 kg or greater—1.2 million units intramuscularly; *and* rifampin: 20 mg/kg/day orally in two doses during last 4 days of treatment with penicillin (maximum 600 mg/day)

From reference 47.

TABLE 44–6 Evidence-based Principles for Diagnosis of Group A *Streptococcus*

Recommendations	Level
Selective use of diagnostic testing in only those with clinical features suggestive of group A *Streptococcus* will increase the proportion of positive tests, as well as results of those truly infected, not carriers.	A-II
Clinical diagnosis cannot be made with certainty even by the most experienced clinician; bacteriologic confirmation is required.	A-II
Throat culture remains the diagnostic standard, with a sensitivity of 90% to 95% for detection of group A *Streptococcus* if done correctly.	A-II
Rapid identification and treatment of patients with disease can reduce transmission, allow patients to return to work or school earlier, and reduce the acute morbidity of the disease.	A-II
The majority of rapid antigen detection tests available have a specificity >95% (minimizes overprescription to those without disease) and a sensitivity of 80% to 90% compared with culture.	A-II
Early initiation of antimicrobial therapy results in faster resolution of signs and symptoms. Delays in therapy (if awaiting cultures) can be made safely for up to 9 days after symptom onset and still prevent major complications such as rheumatic fever.	A-I

Rating:
Strength of recommendation—A to E
Evidence to support use: A, good; B, moderate; C, poor
Evidence against use: D, moderate; E, good
Quality of evidence—I, II, or III
I: At least one randomized controlled trial
II: At least one well-designed clinical trial, not randomized, or a cohort or case-controlled analytical study, or from multiple time series, or from dramatic results of an uncontrolled trial
III: Opinions of respected authorities

Data from Bisno AL, Gerber MA, Gwaltney JM, et al. Practice guidelines for the diagnosis and management of group A streptococcal pharyngitis (IDSA guidelines). Clin Infect Dis 2002;35:113–125.

TABLE 44–7	Clinical Presentation and Diagnosis of Bacterial Rhinosinusitis
General	
There are 3 clinical presentations that are most consistent with acute bacterial versus viral rhinosinusitis: • Onset with *persistent* signs or symptoms compatible with acute rhinosinusitis, lasting for ≥10 days without any evidence of clinical improvement (strong, low–moderate) • Onset with *severe* signs or symptoms of high fever (≥39°C [102°F]) and purulent nasal discharge or facial pain lasting for at least 3 to 4 consecutive days at the beginning of illness (strong, low–moderate) • Onset with *worsening* signs or symptoms characterized by new-onset fever, headache, or increase in nasal discharge following a typical viral URI that lasted 5 to 6 days and were initially improving ("double sickening") (strong, low–moderate)	
Signs and symptoms	
• Purulent anterior nasal discharge, purulent or discolored posterior nasal discharge, nasal congestion or obstruction, facial congestion or fullness, facial pain or pressure, fever, headache, ear pain/pressure/fullness, halitosis, dental pain, cough, and fatigue	

to differentiate between viral and bacterial sinusitis to aid in optimizing treatment decisions.

- Acute bacterial sinusitis is most often caused by the same bacteria implicated in acute otitis media: *S. pneumoniae* and *H. influenzae.* These organisms are responsible for ~50% to 70% of bacterial causes of acute sinusitis in both adults and children.

CLINICAL PRESENTATION

- The typical clinical presentation of bacterial sinusitis is presented in **Table 44–7.**

TREATMENT

- Goals of Treatment: reduce signs and symptoms, achieving and maintaining patency of the ostia, limiting antimicrobial treatment to those who may benefit, eradicating bacterial infection with appropriate antimicrobial therapy, minimizing the duration of illness, preventing complications, and preventing progression from acute disease to chronic disease.
- Nasal decongestant sprays such as **phenylephrine** and **oxymetazoline** that reduce inflammation by vasoconstriction are often used in nonbacterial rhinosinusitis. Use should be limited to the recommended duration of the product (no more than 3 days) to prevent rebound congestion. Oral decongestants may also aid in nasal or sinus patency. Irrigation of the nasal cavity with saline and steam inhalation may be used to increase mucosal moisture, and mucolytics (eg, guaifenesin) may be used to decrease the viscosity of nasal secretions. Antihistamines and oral decongestants should not be used for acute bacterial sinusitis in view of their anticholinergic effects that can dry mucosa and disturb clearance of mucosal secretions.
- Antimicrobial therapy is superior to placebo in reducing or eliminating symptoms, although the benefit is small.
- **Amoxicillin** is first-line treatment for acute bacterial sinusitis. It is cost effective in acute uncomplicated disease, and initial use of newer broad-spectrum agents is not justified. The approach to treating acute bacterial rhinosinusitis in children and adults is given in **Table 44–8.**

TABLE 44–8 Antibiotics and Doses for Acute Bacterial Rhinosinusitis

Antibiotic	Brand Name	Dose	Comments
Children			
Initial Empirical Therapy			
Amoxicillin–clavulanate	Augmentin®	45 mg/kg/day po twice daily	First-line
Amoxicillin–clavulanate	Augmentin®	90 mg/kg/day po twice daily	Second-line
β-Lactam Allergy			
Clindamycin plus cefixime or cefpodoxime	Cleocin®, Suprax®, Vantin®	Clindamycin (30–40 mg/kg/day po three times daily) plus cefixime (8 mg/kg/day po twice daily) or cefpodoxime (10 mg/kg/day po twice daily)	Non–type 1 allergy
Levofloxacin	Levaquin®	10–20 mg/kg/day po every 12–24 hours	Type 1 allergy
Risk for Antibiotic Resistance or Failed Initial Therapy			
Amoxicillin–clavulanate	Augmentin®	90 mg/kg/day po twice daily	
Clindamycin plus cefixime or cefpodoxime	Cleocin®, Suprax®, Vantin®	Clindamycin (30–40 mg/kg/day po three times daily) plus cefixime (8 mg/kg/day po twice daily) or cefpodoxime (10 mg/kg/day po twice daily)	
Levofloxacin	Levaquin®	10–20 mg/kg/day po every 12–24 hours	
Severe Infection Requiring Hospitalization			
Ampicillin–sulbactam	Unasyn®	200–400 mg/kg/day IV every 6 hours	
Ceftriaxone	Rocephin®	50 mg/kg/day IV every 12 hours	
Cefotaxime	Claforan®	100–200 mg/kg/day IV every 6 hours	
Levofloxacin	Levaquin®	10–20 mg/kg/day IV every 12–24 hours	
Adults			
Initial Empirical Therapy			
Amoxicillin–clavulanate	Augmentin®	500 mg/125 mg po three times daily, or 875 mg/125 mg po twice daily	First-line
Amoxicillin–clavulanate	Augmentin®	2,000 mg/125 mg po twice daily	Second-line
Doxycycline		100 mg po twice daily or 200 mg po once daily	Second-line
β-Lactam Allergy			
Doxycycline		100 mg po twice daily or 200 mg po once daily	
Levofloxacin	Levaquin®	500 mg po once daily	
Moxifloxacin	Avelox®	400 mg po once daily	

(*continued*)

TABLE 44–8 Antibiotics and Doses for Acute Bacterial Rhinosinusitis (*Continued*)

Antibiotic	Brand Name	Dose	Comments
Risk for Antibiotic Resistance or Failed Initial Therapy			
Amoxicillin–clavulanate	Augmentin®	2,000 mg/125 mg po twice daily	
Levofloxacin	Levaquin®	500 mg po once daily	
Moxifloxacin	Avelox®	400 mg po once daily	
Severe Infection Requiring Hospitalization			
Ampicillin–sulbactam	Unasyn®	1.5–3 g IV every 6 hours	
Levofloxacin	Levaquin®	500 mg po once daily	
Moxifloxacin	Avelox®	400 mg po once daily	
Ceftriaxone	Rocephin®	1–2 g IV every 12–24 hours	
Cefotaxime	Claforan®	2 g IV every 4–6 hours	

po, orally.

- The duration of antimicrobial therapy for the treatment of acute bacterial rhinosinusitis is not well established. Most trials have used 10- to 14-day antibiotic courses for uncomplicated rhinosinusitis. For adults, the recommended duration is 5 to 7 days.

See Chapter 86, Upper Respiratory Tract Infections, authored by Christopher Frei and Bradi Frei, for a more detailed discussion of this topic.

CHAPTER 45

Sepsis and Septic Shock

- The definitions of terms related to *sepsis* are given in **Table 45–1**. Physiologically similar systemic inflammatory response syndrome can be seen even in the absence of identifiable infection.

ETIOLOGY AND PATHOPHYSIOLOGY

- The sites of infections that most frequently lead to sepsis are the respiratory tract (39%–50%), urinary tract (5%–37%), and intra-abdominal space (8%–16%). Sepsis may be caused by gram-negative (52% of sepsis) or gram-positive bacteria (37%), as well as by fungi (5%) or other microorganisms.
- *Escherichia coli, Klebsiella species,* and *Pseudomonas aeruginosa* are the most commonly isolated gram-negative pathogens in sepsis. Other common gram-negative pathogens are *Serratia* spp., *Enterobacter* spp., and *Proteus* spp. *P. aeruginosa* is the most frequent cause of sepsis fatality. Common gram-positive pathogens are *Staphylococcus aureus, Streptococcus pneumoniae,* coagulase-negative staphylococci, and *Enterococcus* species.
- *Candida* species (particularly *Candida albicans*) are common fungal etiologic agents of bloodstream infections. The crude 12-week mortality rate for sepsis due to candidemia was 35.2%.
- The pathophysiologic focus of gram-negative sepsis has been on the lipopolysaccharide (endotoxin) component of the gram-negative cell wall. Lipid A is a part of the endotoxin molecule from the gram-negative bacterial cell wall that is highly immunoreactive and is responsible for most of the toxic effects. Endotoxin first associates with a protein called lipopolysaccharide-binding protein in plasma. This complex then engages a specific receptor (CD14) on the surface of the macrophage, which activates it and causes release of inflammatory mediators.
- Sepsis involves a complex interaction of proinflammatory (eg, tumor necrosis factor-α [TNF-α]; interleukin [IL]-1, IL-6) and anti-inflammatory mediators (eg, IL-1 receptor antagonist, IL-4, and IL-10). IL-8, platelet-activating factor, leukotrienes, and thromboxane A_2 are also important.
- TNF-α is considered the primary mediator of sepsis. Concentrations are elevated early in the inflammatory response during sepsis, and there is a correlation with the severity of sepsis. TNF-α release leads to activation of other cytokines associated with cellular damage, and it stimulates release of arachidonic acid metabolites that contribute to endothelial cell damage.
- Anti-inflammatory mediators including IL-1 receptor antagonist, IL-4, and IL-10 are also produced in sepsis and inhibit production of proinflammatory cytokines. The net effect can vary depending on the state of activation of the target cell, and the ability of the target cell to release can augment or inhibit the primary mediator.
- A primary mechanism of injury with sepsis is through endothelial cells. With inflammation, endothelial cells allow circulating cells (eg, granulocytes) and plasma constituents to enter inflamed tissues, which may result in organ damage.
- Endotoxin activates complement, which then augments the inflammatory response through stimulation of leukocyte chemotaxis, phagocytosis and lysosomal enzyme release, increased platelet adhesion and aggregation, and production of toxic superoxide radicals.
- A key endogenous substance involved in inflammation of sepsis is activated protein C, which enhances fibrinolysis and inhibits inflammation. Levels of protein C are reduced in patients with sepsis.
- Shock is the most ominous complication associated with gram-negative sepsis and causes death in about one half of patients. Another complication is disseminated intravascular coagulation (DIC), which occurs in up to 38% of patients with

TABLE 45–1 Definitions Related to Sepsis

Condition	Definition
Bacteremia (fungemia)	Presence of viable bacteria (fungi) in the bloodstream
Infection	Inflammatory response to invasion of normally sterile host tissue by the microorganisms
Systemic inflammatory response syndrome	Systemic inflammatory response to a variety of clinical insults, which can be infectious or noninfectious. The response is manifested by two or more of the following conditions: temperature >38°C or <36°C; HR >90 beats/min; RR >20 breaths/min or $PaCO_2$<32 mmHg (<4.3 kPa); WBC >12,000 cells/mm^3 (>12 × 10^9/L), <4000 cells/mm^3 (4 × 10^9/L), or >10% (>0.10) immature (band) forms; positive fluid balance (>20 mL/kg over 24 h); hyperglycemia; plasma; arterial hypotension; CI >3.5 L/min (>0.058 L/s); arterial hypoxemia; acute oliguria; creatinine increase >0.5 mg/dL (>0.44 µmol/L); coagulation abnormalities; ileus, platelets <100,000/mm^3 (>100 × 10^9/L); bilirubin >4 mg/dL (>68 µmol/L); hyperlactatemia; decreased capillary refill
Sepsis	Systemic inflammatory response syndrome secondary to infection
Severe sepsis	Sepsis associated with organ dysfunction, hypoperfusion, or hypotension. Hypoperfusion and perfusion abnormalities may include, but are not limited to, lactic acidosis, oliguria, or acute alteration in mental status.
Septic shock	Sepsis with hypotension, despite fluid resuscitation, along with the presence of perfusion abnormalities. Patients who are on inotropic or vasopressor agents may not be hypotensive at the time perfusion abnormalities are measured.
Refractory septic shock	Persistent septic shock, requiring dopamine >15 mcg/kg/min or norepinephrine >0.25 mcg/kg/min to maintain mean arterial blood pressure
Multiple-organ dysfunction syndrome	Presence of altered organ function requiring intervention to maintain homeostasis

CI, confidence interval; HR, heart rate; $Paco_2$, partial pressure of carbon dioxide; RR, respiratory rate; SD; standard deviation; WBC, white blood cell (count).

septic shock. DIC is the inappropriate activation of the clotting cascade that causes formation of microthrombi, resulting in consumption of coagulation factors, organ dysfunction, and bleeding. Acute respiratory distress syndrome (ARDS) is another common complication of sepsis.

- The hallmark of the hemodynamic effect of sepsis is the hyperdynamic state characterized by high cardiac output and an abnormally low systemic vascular resistance.

TABLE 45–2 Signs and Symptoms Associated With Sepsis

Early Sepsis	Late Sepsis
Fever or hypothermia	Lactic acidosis
Rigors, chills	Oliguria
Tachycardia	Leukopenia
Tachypnea	DIC
Nausea, vomiting	Myocardial depression
Hyperglycemia	Pulmonary edema
Myalgias	Hypotension (shock)
Lethargy, malaise	Hypoglycemia
Proteinuria	Azotemia
Hypoxia	Thrombocytopenia
Leukocytosis	ARDS
Hyperbilirubinemia	GI hemorrhage
	Coma

ARDS, acute respiratory distress syndrome; DIC, disseminated intravascular coagulation; GI, gastrointestinal.

CLINICAL PRESENTATION

- The signs and symptoms of early sepsis are variable and include fever, chills, and a change in mental status. Hypothermia may occur instead of fever. The patient may be hypoxic. Signs and symptoms of early and late sepsis are found in **Table 45–2**.
- Progression of uncontrolled sepsis leads to evidence of organ dysfunction, which may include oliguria, hemodynamic instability with hypotension or shock, lactic acidosis, hyperglycemia or hypoglycemia, possibly leukopenia, DIC, thrombocytopenia, ARDS, GI (gastrointestinal) hemorrhage, or coma.

TREATMENT

- The primary goals for treatment of sepsis are as follows: timely diagnosis and identification of the pathogen, rapid elimination of the source of infection, early initiation of aggressive antimicrobial therapy, interruption of the pathogenic sequence leading to septic shock, and avoidance of organ failure.
- Evidence-based treatment recommendations for sepsis and septic shock from the *Surviving Sepsis* campaign are presented in **Table 45–3**.

ANTIMICROBIAL THERAPY

- Early antimicrobial therapy is critical in the management of septic patients. The regimen selected should be based on the suspected site of infection, likely pathogens and the local antibiotic susceptibility patterns, whether the organism was acquired from the community or a hospital, and the patient's immune status.
- The antibiotics that may be used for empiric treatment of sepsis are listed in **Table 45–4**
- If *P. aeruginosa* is suspected, or with sepsis from hospital-acquired infections, an antipseudomonal cephalosporin (**ceftazidime** or **cefepime**), antipseudomonal fluoroquinolone (**ciprofloxacin** or **levofloxacin**), or an aminoglycoside should be included in the regimen.
- The antimicrobial regimen should be reassessed after 48 to 72 hours based on microbiologic and clinical data.

TABLE 45–3 Evidence-based Treatment Recommendations for Sepsis and Septic Shock

Recommendations	Recommendation Grades[a]
Initial resuscitation (first 6 hours)	
Early goal-directed goals, including CVP 8–12 mm Hg, MAP ≥65 mm Hg, central venous oxygen saturation ≥70%	1C
Antibiotic therapy	
IV broad-spectrum antibiotic within 1 h of diagnosis of septic shock and severe sepsis against likely bacterial/fungal pathogens	1B
Reassess antibiotic therapy daily with microbiology and clinical data to narrow coverage	1C
Fluid therapy	
No clinical outcome difference between colloids and crystalloids	1B
Fluid challenges of 1000 mL of crystalloids or 300–500 mL of colloids over 30 min	1D
Vasopressors	
Norepinephrine and dopamine are the initial choices	1C
Maintain MAP ≥ 65 mm Hg	1C
Inotropic therapy	
Use dobutamine when cardiac output remains low despite fluid resuscitation and combined inotropic/vasopressor therapy	1C
Glucose control	
Use IV insulin to keep blood glucose ≤150 mg/dL	2C
Steroids	
IV hydrocortisone for septic shock when hypotension remains poorly responsive to adequate fluid resuscitation and vasopressors	2C
Hydrocortisone dose should be <300 mg/day	1A
Recombinant human activated protein C (drotrecogin)	
Consider in sepsis-induced organ dysfunction with high risk of death (typically APACHE II ≥25 or multiple organ failure) in the absence of contraindications	2B
Deep vein thrombosis prophylaxis	
Use either low-molecular-weight heparin or low-dose unfractionated heparin in preventing deep vein thrombosis	1A
Stress ulcer prophylaxis	
H2 receptor blocker or proton pump inhibitor is effective	1A, 1B

CVP, central venous pressure; IV, intravenous; MAP, mean arterial pressure.

[a]Grades of Recommendation, Assessment, Development, and Evaluation (GRADE) system: a structured system for rating quality of evidence and grading strength of recommendation in clinical practice. Quality of evidence: high (grade A), moderate (grade B), low (grade C), or very low (grade D). Strength of recommendation: strong (grade 1) or weak (grade 2).

Adapted from Dellinger RP, Levy MM, Carlet JM, et al. Surviving sepsis campaign: International guidelines for management of severe sepsis and septic shock: 2008. Crit Care Med 2008;36:296–327.

- When *S. aureus* is likely to be methicillin-resistant, linezolid may be preferred to vancomycin because of the poor penetration of vancomycin into the lungs, as well as the worldwide emergence of glycopeptide intermediately resistant *S. aureus*.
- The average duration of antimicrobial therapy in the normal host with sepsis is 7 to 10 days, and fungal infections can require 10 to 14 days.

TABLE 45–4 Empiric Antimicrobial Regimens in Sepsis

Infection (Site or Type)	Antimicrobial Regimen		
	Community-acquired	Hospital-acquired	
Urinary tract	Ceftriaxone or ciprofloxacin/levofloxacin	Ciprofloxacin/levofloxacin or ceftriaxone or ceftazidime	
Respiratory tract	Levofloxacin[a]/moxifloxacin or ceftriaxone + clarithromycin/azithromycin	Piperacillin/tazobactam or ceftazidime or cefipime + levofloxacin/ciprofloxacin or aminoglycoside	
Intraabdominal	Piperacillin/tazobactam or ciprofloxacin + metronidazole	Piperacillin/tazobactam or carbapenem[b]	
Skin/soft tissue	Vancomycin or linezolid or daptomycin	Vancomycin + piperacillin/tazobactam	
Catheter-related		Vancomycin	
Unknown		Piperacillin/ tazobactam or ceftazidime/cefipime or imipenem/meropenem	+/– Vancomycin not gentamicin.

[a]750 mg orally once daily.
[b]Imipenem, meropenem, doripenem.

- Treatment of invasive candidiasis involves amphotericin B-based preparations, azole antifungal agents, and echinocandin antifungal agents, or combinations. The choice depends on the clinical status of the patient, the fungal species and its susceptibility, relative drug toxicity, presence of organ dysfunction that would affect drug clearance, and the patient's prior exposure to antifungal agents. In general, suspected systemic mycotic infection leading to sepsis in nonneutropenic patients should be treated empirically with parenteral fluconazole, caspofungin, anidulafungin, or micafungin.

HEMODYNAMIC SUPPORT

- Maintenance of adequate tissue oxygenation is important in the treatment of sepsis and is dependent on adequate perfusion and adequate oxygenation of the blood.
- Rapid fluid resuscitation is the best initial therapeutic intervention for treatment of hypotension in sepsis. The goal is to maximize cardiac output by increasing the left ventricular preload, which will ultimately restore tissue perfusion.
- Fluid administration should be titrated to clinical end points such as heart rate, urine output, blood pressure (BP), and mental status. Isotonic crystalloids, such as 0.9% sodium chloride or lactated Ringer solution, are commonly used for fluid resuscitation.
- Iso-oncotic colloid solutions (plasma and plasma protein fractions), such as 5% albumin and 6% hetastarch, offer the advantage of more rapid restoration of intravascular volume with less volume infused, however, synthetic colloids cause dose-related renal impairment and increased bleeding. Crystalloid solutions require two to four times more volume than colloids, they are generally recommended for fluid resuscitation because of the lower cost. However, colloids can be preferred, especially when the serum albumin is less than 2 g/dL (20 g/L).

INOTROPE AND VASOACTIVE DRUG SUPPORT

- When fluid resuscitation is insufficient to maintain tissue perfusion, the use of inotropes and vasoactive drugs is necessary. Selection and dosage are based on the

TABLE 45–5 Receptor Activity of Cardiovascular Agents Commonly Used in Septic Shock

Agent	α_1	α_2	β_1	β_2	Dopaminergic
Dopamine	++/+++	?	++++	++	++++
Dobutamine	+	+	++++	++	0
Norepinephrine	+++	+++	+++	+/++	0
Phenylephrine	++/+++	+	?	0	0
Epinephrine	++++	++++	++++	+++	0

α_1, α_1-adrenergic receptor; α_2, α_2-adrenergic receptor; β_1, β_1-adrenergic receptor; β_2, β_2-adrenergic receptor; 0, no activity; ++++, maximal activity; ?, unknown activity.

pharmacologic properties of various catecholamines and how they influence hemodynamic parameters (Table 45–5).

Suggested Protocol for the Use of Inotropes and Vasoactive Agents

- **Norepinephrine** is a potent α-adrenergic agent (0.01–3 mcg/kg/min) that is useful as a vasopressor to restore adequate BP after failure to restore adequate BP and organ perfusion with appropriate fluid resuscitation.
- **Dopamine** in doses >5 mcg/kg/min increases mean arterial pressure and cardiac output.
- **Dobutamine** (2–20 mcg/kg/min) is an α-adrenergic inotropic agent that many clinicians prefer for improving cardiac index. Dobutamine should be considered in severely septic patients with adequate filling pressures and BP but low confidence interval (CI).
- **Epinephrine** (0.1–0.5 mcg/kg/min) increases CI and produces peripheral vasoconstriction. It is reserved for patients who fail to respond to traditional therapies to maintain blood pressure.

Early Goal-Directed Therapy

- Initial resuscitation of a patient in severe sepsis or sepsis induced tissue hypoperfusion should begin as soon as the syndrome is recognized. The goals during the first 6 hours included CVP of 8 to 12 mm Hg, MAP of 65 mm Hg or more, urine output of 0.5 mL/kg/h or more, and a central venous or mixed venous oxygen saturation of 70% or more (≥0.70). Compliance with the goals of early goal-directed group was closely correlated with the overall mortality rate.

Adjunctive Therapy

- Cortisol levels vary widely in patients with septic shock, and some studies have suggested increased mortality associated with both low and high serum cortisol levels. An adrenocorticotropic hormone (ACTH) stimulation test has been used to identify those patients who have a relative adrenal insufficiency who should then receive supplemental steroid.

See Chapter 97, Severe Sepsis and Septic Shock, authored by S. Lena Kang-Birken, for a more detailed discussion of this topic.

CHAPTER 46

Sexually Transmitted Diseases

- The spectrum of sexually transmitted diseases (STDs) includes the classic venereal diseases—gonorrhea, syphilis, chancroid, lymphogranuloma venereum, and granuloma inguinale—as well as a variety of other pathogens known to be spread by sexual contact (**Table 46–1**). Common clinical syndromes associated with STDs are listed in **Table 46–2.** The most current information on epidemiology, diagnosis, and treatment of STDs provided by the Centers for Disease Control and Prevention (CDC) can be found at *www.cdc.gov.*

GONORRHEA

- *Neisseria gonorrhoeae* is a gram-negative diplococcus estimated to cause up to 600,000 infections per year in the United States. Humans are the only known host of this intracellular parasite.

CLINICAL PRESENTATION

- Infected individuals may be symptomatic or asymptomatic, have complicated or uncomplicated infections, and have infections involving several anatomical sites.
- The most common clinical features of gonococcal infections are presented in **Table 46–3.** Approximately 15% of women with gonorrhea develop pelvic inflammatory disease. Left untreated, pelvic inflammatory disease can be an indirect cause of infertility and ectopic pregnancies.
- In 0.5% to 3% of patients with gonorrhea, the gonococci invade the bloodstream and produce disseminated disease. The usual clinical manifestations of disseminated gonococcal infection are tender necrotic skin lesions, tenosynovitis, and monoarticular arthritis.
- Diagnosis of gonococcal infections can be made by gram-stained smears, culture (the most reliable method), or newer methods based on the detection of cellular components of the gonococcus (eg, enzymes, antigens, DNA, or lipopolysaccharide) in clinical specimens.
- Although culture of infected fluids is not the most sensitive of diagnostic tests for gonorrhea, it is still the diagnostic test of choice because of the high specificity.
- Alternative methods of diagnosis include enzyme immunoassay, DNA probes, and nucleic acid amplification techniques.

TREATMENT

- Parenteral **ceftriaxone** is the only agent recommended for gonorrhea treatment. (**Table 46–4**).
- Coexisting chlamydial infection, which is documented in up to 50% of women and 20% of men with gonorrhea, constitutes the major cause of postgonococcal urethritis, cervicitis, and salpingitis in patients treated for gonorrhea. As a result, concomitant treatment with **doxycycline** or **azithromycin** is recommended in all patients treated for gonorrhea. A single dose of azithromycin (2 g) is highly effective against chlamydia.
- Pregnant women infected with *N. gonorrhoeae* should be treated with **ceftriaxone**. For presumed *Chlamydia trachomatis* infection, azithromycin or amoxicillin is the preferred treatment.
- Treatment of gonorrhea during pregnancy is essential to prevent ophthalmia neonatorum. The CDC recommends that erythromycin (0.5%) ophthalmic ointment be instilled in each conjunctival sac immediately postpartum to prevent ophthalmia neonatorum.

TABLE 46–1 Sexually Transmitted Diseases

Disease	Associated Pathogens
Bacterial	
Gonorrhea	*Neisseria gonorrhoeae*
Syphilis	*Treponema pallidum*
Chancroid	*Haemophilus ducreyi*
Granuloma inguinale	*Calymmatobacterium granulomatis*
Enteric disease	*Salmonella* spp., *Shigella* spp., *Campylobacter fetus*
Campylobacter infection	*Campylobacter jejuni*
Bacterial vaginosis	*Gardnerella vaginalis, Mycoplasma hominis, Bacteroides* spp., *Mobiluncus* spp.
Group B streptococcal infections	Group B *Streptococcus*
Chlamydial	
Nongonococcal urethritis	*Chlamydia trachomatis*
Lymphogranuloma venereum	*C. trachomatis*, type L
Viral	
Acquired immunodeficiency syndrome	Human immunodeficiency virus
Herpes genitalis	Herpes simplex virus, types I and II
Viral hepatitis	Hepatitis A, B, C, and D viruses
Condylomata acuminata	Human papillomavirus
Molluscum contagiosum	Poxvirus
Cytomegalovirus infection	Cytomegalovirus
Mycoplasmal	
Nongonococcal urethritis	*Ureaplasma urealyticum*
Protozoal	
Trichomoniasis	*Trichomonas vaginalis*
Amebiasis	*Entamoeba histolytica*
Giardiasis	*Giardia lamblia*
Fungal	
Vaginal candidiasis	*Candida albicans*
Parasitic	
Scabies	*Sarcoptes scabiei*
Pediculosis pubis	*Phthirus pubis*
Enterobiasis	*Enterobius vermicularis*

SYPHILIS

- The causative organism of syphilis is *Treponema pallidum,* a spirochete.
- Syphilis is usually acquired by sexual contact with infected mucous membranes or cutaneous lesions, although on rare occasions it can be acquired by nonsexual personal contact, accidental inoculation, or blood transfusion.

TABLE 46–2 Selected Syndromes Associated With Common Sexually Transmitted Pathogens

Syndrome	Commonly Implicated Pathogens	Common Clinical Manifestations[a]
Urethritis	*Chlamydia trachomatis*, herpes simplex virus, *Neisseria gonorrhoeae, Trichomonas vaginalis, Ureaplasma urealyticum*	Urethral discharge, dysuria
Epididymitis	*C. trachomatis, N. gonorrhoeae*	Scrotal pain, inguinal pain, flank pain, urethral discharge
Cervicitis/ vulvovaginitis	*C. trachomatis, Gardnerella vaginalis*, herpes simplex virus, human papillomavirus, *N. gonorrhoeae, T. vaginalis*	Abnormal vaginal discharge, vulvar itching/ irritation, dysuria, dyspareunia
Genital ulcers (painful)	*Haemophilus ducreyi*, herpes simplex virus	Usually multiple vesicular/pustular (herpes) or papular/pustular (*H. ducreyi*) lesions that may coalesce; painful, tender lymphadenopathy[b]
Genital ulcers (painless)	*Treponema pallidum*	Usually single papular lesion
Genital/anal warts	Human papillomavirus	Multiple lesions ranging in size from small papular warts to large exophytic condylomas
Pharyngitis	*C. trachomatis* (?), herpes simplex virus, *N. gonorrhoeae*	Symptoms of acute pharyngitis, cervical lymphadenopathy, fever[c]
Proctitis	*C. trachomatis*, herpes simplex virus, *N. gonorrhoeae, T. pallidum*	Constipation, anorectal discomfort, tenesmus, mucopurulent rectal discharge
Salpingitis	*C. trachomatis, N. gonorrhoeae*	Lower abdominal pain, purulent cervical or vaginal discharge, adnexal swelling, fever[d]

[a]For some syndromes, clinical manifestations may be minimal or absent.
[b]Recurrent herpes infection may manifest as a single lesion.
[c]Most cases of pharyngeal gonococcal infection are asymptomatic.
[d]Salpingitis increases the risk of subsequent ectopic pregnancy and infertility.

CLINICAL PRESENTATION

- The clinical presentation of syphilis is varied, with progression through multiple stages possible in untreated or inadequately treated patients (**Table 46–5**).

Primary Syphilis

- Primary syphilis is characterized by the appearance of a chancre on cutaneous or mucocutaneous tissue. Chancres persist only for 1 to 8 weeks before spontaneously disappearing.

Secondary Syphilis

- The secondary stage of syphilis is characterized by a variety of mucocutaneous eruptions, resulting from widespread hematogenous and lymphatic spread of *T. pallidum.*
- Signs and symptoms of secondary syphilis disappear in 4 to 10 weeks; however, in untreated patients, lesions may recur at any time within 4 years.

TABLE 46–3 Presentation of Gonorrhea Infections

	Men	Women
General	Incubation period 1–14 days Symptom onset in 2–8 days	Incubation period 1–14 days Symptom onset in 10 days
Site of infection	Most common—urethra Others—rectum (usually due to rectal intercourse in men who have sex with men), oropharynx, eye	Most common—endocervical canal Others—urethra, rectum (usually due to perineal contamination), oropharynx, eye
Symptoms	May be asymptomatic or minimally symptomatic Urethral infection—dysuria and urinary frequency Anorectal infection—asymptomatic to severe rectal pain Pharyngeal infection asymptomatic to mild pharyngitis	May be asymptomatic or minimally symptomatic Endocervical infection—usually asymptomatic or mildly symptomatic Urethral infection—dysuria, urinary frequency Anorectal and pharyngeal infection—symptoms same as for men
Signs	Purulent urethral or rectal discharge can be scant to profuse Anorectal—pruritus, mucopurulent discharge, bleeding	Abnormal vaginal discharge or uterine bleeding; purulent urethral or rectal discharge can be scant to profuse
Complications	Rare (epididymitis, prostatitis, inguinal lymphadenopathy, urethral stricture) Disseminated gonorrhea	Pelvic inflammatory disease and associated complications (ie, ectopic pregnancy, infertility) Disseminated gonorrhea (3 times more common than in men)

Latent Syphilis

- Persons with a positive serologic test for syphilis but with no other evidence of disease have latent syphilis.
- Most untreated patients with latent syphilis have no further sequelae; however, ~25% to 30% progress to either neurosyphilis or late syphilis with clinical manifestations other than neurosyphilis.

Tertiary Syphilis and Neurosyphilis

- Forty percent of patients with primary or secondary syphilis exhibit CNS infection.

DIAGNOSIS

- Because *T. pallidum* is difficult to culture in vitro, diagnosis is based primarily on dark-field or direct fluorescent antibody microscopic examination of serous material from a suspected syphilitic lesion or on results from serologic testing.
- Serologic tests are the mainstay in the diagnosis of syphilis and are categorized as nontreponemal or treponemal. Common nontreponemal tests include the Venereal Disease Research Laboratory (VDRL) slide test, rapid plasma reagin (RPR) card test, unheated serum reagin (USR) test, and the toluidine red unheated serum test. (TRUST).
- Treponemal tests are more sensitive than nontreponemal tests and are used to confirm the diagnosis (ie, the fluorescent treponemal antibody absorption).

TABLE 46–4 Treatment of Gonorrhea

Type of Infection	Recommended Regimens[a]	Alternative Regimens[a]
Uncomplicated infections of the cervix, urethra, and rectum in adults	Ceftriaxone 250 mg IM once *plus* Azithromycin 1 g PO once, or doxycycline 100 mg PO twice daily for 7 days[b]	Cefixime 400 mg PO once *plus* Azithromycin 1 g PO once, or doxycycline 100 mg PO twice daily for 7 days (plus test of cure in 1 week)[c,d,e]
Uncomplicated infections of the pharynx	Ceftriaxone 250 mg IM once *plus* Azithromycin 1 g PO once, or doxycycline 100 mg PO twice daily for 7 days	Consult with infectious disease expert
Disseminated gonococcal infection in adults (>45 kg)	Ceftriaxone 1 g IM or IV every 24 hours[f]	Cefotaxime 1 g IV every 8 hours[f] or ceftizoxime 1 g IV every 8 hours[f]
Uncomplicated infections of the cervix, urethra, and rectum in children (≤45 kg)	Ceftriaxone 125 mg IM once	
Gonococcal conjunctivitis in adults	Ceftriaxone 1 g IM once[g]	
Ophthalmia neonatorum	Ceftriaxone 25–50 mg/kg IV or IM once (not to exceed 125 mg)	
Infants born to mothers with gonococcal infection (prophylaxis)	Erythromycin (0.5%) ophthalmic ointment in a single application[h]	Ceftriaxone 25–50 mg/kg IM or IV once (not to exceed 125 mg)

CDC, Centers for Disease Control and Prevention; *C. trachomatis, Chlamydia trachomatis;* NAAT, Nucleic Acid Amplification Test; PO, orally.

[a]Recommendations are those of the CDC.
[b]Tetracyclines are contraindicated during pregnancy. Pregnant women should be treated with recommended cephalosporin-based combination therapy. Women who cannot tolerate a cephalosporin should receive azithromycin 2 g PO once and have a test of cure 1 week later.
[c]Ideally performed using culture; if culture is not available, use a NAAT for *N. gonorrhoeae.*
[d]Patients who are treatment failures with alternative regimens should be treated with ceftriaxone 250 mg IM once plus azithromycin 2 g PO once in consultation with an infectious disease expert.
[e]For patients with severe cephalosporin allergy, azithromycin 2 g PO once is recommended plus a test of cure in a week.
[f]Parenteral treatment regimens should be continued for 24–48 hours after improvement begins; at this time therapy can be switched to cefixime 400 mg PO twice daily (tablet or suspension) to complete a 7-day course of treatment.
[g]A single lavage of the infected eye with normal saline should be considered; empiric therapy for *C. trachomatis* is recommended.
[h]Efficacy in preventing chlamydial ophthalmia is unclear.

TABLE 46–5	Presentation of Syphilis Infections
General	
Primary	Incubation period 10 to 90 days (mean 21 days)
Secondary	Develops 2 to 8 weeks after initial infection in untreated or inadequately treated individuals
Latent	Develops 4 to 10 weeks after secondary stage in untreated or inadequately treated individuals
Tertiary	Develops in ~30% of untreated or inadequately treated individuals 10 to 30 years after initial infection
Site of infection	
Primary	External genitalia, perianal region, mouth, and throat
Secondary	Multisystem involvement secondary to hematogenous and lymphatic spread
Latent	Potentially multisystem involvement (dormant)
Tertiary	CNS, heart, eyes, bones, and joints
Signs and symptoms	
Primary	Single, painless, indurated lesion (chancre) that erodes, ulcerates, and eventually heals (typical); regional lymphadenopathy is common; multiple, painful, purulent lesions possible but uncommon
Secondary	Pruritic or nonpruritic rash, mucocutaneous lesions, flu-like symptoms, lymphadenopathy
Latent	Asymptomatic
Tertiary	Cardiovascular syphilis (aortitis or aortic insufficiency), neurosyphilis (meningitis, general paresis, dementia, tabes dorsalis, eighth cranial nerve deafness, blindness), gummatous lesions involving any organ or tissue

TREATMENT

- Treatment recommendations from the CDC for syphilis are presented in **Table 46–6.** Parenteral **penicillin G** is the treatment of choice for all stages of syphilis. Benzathine penicillin G is the only penicillin effective for single-dose therapy.
- Patients with abnormal cerebrospinal fluid findings should be treated as having neurosyphilis.
- For pregnant patients, penicillin is the treatment of choice at the dosage recommended for that particular stage of syphilis. To ensure treatment success and prevent transmission to the fetus, some experts advocate an additional intramuscular dose of benzathine penicillin G, 2.4 million units, 1 week after completion of the recommended regimen.
- Most patients treated for primary and secondary syphilis experience the Jarisch–Herxheimer reaction after treatment, characterized by flu-like symptoms such as transient headache, fever, chills, malaise, arthralgia, myalgia, tachypnea, peripheral vasodilation, and aggravation of syphilitic lesions. The Jarisch–Herxheimer reaction should not be confused with penicillin allergy. Most reactions can be managed symptomatically with analgesics, antipyretics, and rest.
- CDC recommendations for serologic follow-up of patients treated for syphilis are given in Table 46–6**.**
- For women treated during pregnancy, monthly, quantitative, nontreponemal tests are recommended in those at high risk of reinfection.

TABLE 46–6 Drug Therapy and Follow-up of Syphilis

Stage/Type of Syphilis	Recommended Regimens[a,b]	Follow-up Serology
Non-penicillin allergic patients		
Primary, secondary, or early latent syphilis (<1 year's duration)	Benzathine penicillin G 2.4 million units IM in a single dose[c]	Quantitative nontreponemal tests at 6 and 12 months for primary and secondary syphilis; at 6, 12, and 24 months for early latent syphilis[d]
Late latent syphilis (>1 year's duration) or latent syphilis of unknown duration	Benzathine penicillin G 2.4 million units IM once a week for 3 successive weeks (7.2 million units total)	Quantitative nontreponemal tests at 6, 12, and 24 months[e]
Neurosyphilis	Aqueous crystalline penicillin G 18–24 million units IV (3–4 million units every 4 hours or by continuous infusion) for 10–14 days[f] *or* Aqueous procaine penicillin G 2.4 million units IM daily plus probenecid 500 mg orally four times daily, both for 10–14 days[f]	CSF examination every 6 months until the cell count is normal; if it has not decreased at 6 months or is not normal by 2 years, retreatment should be considered
Congenital syphilis (infants with proven or highly probable disease)	Aqueous crystalline penicillin G 50,000 units/kg IV every 12 h during the first 7 days of life and every 8 h thereafter for a total of 10 days *or* Procaine penicillin G 50,000 units/kg IM daily for 10 days	Serologic follow-up only recommended if antimicrobials other than penicillin are used
Penicillin-allergic patients[g]		
Primary, secondary, or early latent syphilis	Doxycycline 100 mg orally 2 times daily for 14 days[g,h] *or* Tetracycline 500 mg orally 4 times daily for 14 days[h] Ceftriaxone 1 g IM or IV daily for 8–10 days	Same as for non–penicillin-allergic patients

(*continued*)

CHLAMYDIA

- Infections caused by *C. trachomatis* are believed to be the most common STD in the United States. *C. trachomatis* is an obligate intracellular parasite that has some similarities to viruses and bacteria.

TABLE 46–6 Drug Therapy and Follow-up of Syphilis (*Continued*)

Stage/Type of Syphilis	Recommended Regimens[a,b]	Follow-up Serology
Penicillin-allergic patients[g]		
Late latent syphilis (>1 year's duration) or syphilis of unknown duration	Doxycycline 100 mg orally twice a day for 28 days[h,i] *or* Tetracycline 500 mg orally 4 times daily for 28 days[h,i]	Same as for non–penicillin-allergic patients

CDC, Centers for Disease Control and Prevention; CSF, cerebrospinal fluid; IM, intramuscular/intramuscularly.
[a]Recommendations are those of the CDC.
[b]The CDC recommends that all patients diagnosed with syphilis be tested for HIV infection.
[c]Some experts recommend multiple doses of benzathine penicillin G or other supplemental antibiotics in addition to benzathine penicillin G in HIV-infected patients with primary or secondary syphilis; HIV-infected patients with early latent syphilis should be treated with the recommended regimen for latent syphilis of more than 1 year's duration.
[d]More frequent follow-up (ie, 3, 6, 9, 12, and 24 months) recommended for HIV-infected patients.
[e]More frequent follow-up (ie, 6, 12, 18, and 24 months) recommended for HIV-infected patients.
[f]Some experts administer benzathine penicillin G 2.4 million units IM once per week for up to 3 weeks after completion of the neurosyphilis regimens to provide a total duration of therapy comparable to that used for late syphilis in the absence of neurosyphilis.
[g]For nonpregnant patients; pregnant patients should be treated with penicillin after desensitization.
[h]Pregnant patients allergic to penicillin should be desensitized and treated with penicillin.
[i]Limited data suggest that ceftriaxone my be effective, although the optimal dosage and treatment duration are unclear.

CLINICAL PRESENTATION

- In comparison with gonorrhea, chlamydial genital infections are more frequently asymptomatic, and when present, symptoms tend to be less noticeable. **Table 46–7** summarizes the usual clinical presentation of chlamydial infections.
- Similar to gonorrhea, chlamydia may be transmitted to an infant during contact with infected cervicovaginal secretions. Nearly two thirds of infants acquire chlamydial infection after endocervical exposure, with the primary morbidity associated with seeding of the infant's eyes, nasopharynx, rectum, or vagina.
- Culture of endocervical or urethral epithelial cell scrapings is the most specific method (close to 100%) for detection of chlamydia, but sensitivity is as low as 70%. Between 3 and 7 days are required for results.
- Tests that allow rapid identification of chlamydial antigens and nucleic acid provide more rapid results, are technically less demanding, are less costly, and in some situations have greater sensitivity than culture. Commonly used nonculture tests for detection of *C. trachomatis* are the enzyme immunosorbent assay (EIA), DNA hybridization probe, and nucleic acid amplification tests (NAATs).

TREATMENT

- Recommended regimens for treatment of chlamydial infections are given in **Table 46–8.** Single-dose **azithromycin** and 7-day **doxycycline** are the agents of choice.
- Treatment of chlamydial infections with the recommended regimens is highly effective; therefore, posttreatment cultures are not routinely recommended.
- Infants with pneumonitis should receive follow-up testing because erythromycin is only 80% effective.

TABLE 46–7 Presentation of *Chlamydia* Infections

	Men	Women
General	Incubation period—35 days Symptom onset—7 to 21 days	Incubation period—7 to 35 days Usual symptom onset—7 to 21 days
Site of infection	Most common—urethra Others—rectum (receptive anal intercourse), oropharynx, eye	Most common—endocervical canal Others—urethra, rectum (usually due to perineal contamination), oropharynx, eye
Symptoms	More than 50% of urethral and rectal infections are asymptomatic Urethral infection—mild dysuria, discharge Pharyngeal infection—asymptomatic to mild pharyngitis	More than 66% of cervical infections are asymptomatic Urethral infection—usually subclinical; dysuria and frequency uncommon Rectal and pharyngeal infection—symptoms same as for men
Signs	Scant to profuse, mucoid to purulent urethral or rectal discharge Rectal infection—pain, discharge, bleeding	Abnormal vaginal discharge or uterine bleeding; purulent urethral or rectal discharge can be scant to profuse
Complications	Epididymitis, Reiter's syndrome (rare)	Pelvic inflammatory disease and associated complications (ie, ectopic pregnancy, infertility) Reiter syndrome (rare)

GENITAL HERPES

- The term ***herpes*** is used to describe two distinct but antigenically related serotypes of herpes simplex virus (HSV). HSV type 1 (HSV-1) is most commonly associated with oropharyngeal disease; type 2 (HSV-2) is most closely associated with genital disease.

CLINICAL PRESENTATION

- A summary of the clinical presentation of genital herpes is provided in **Table 46–9.**
- Tissue culture is the most specific (100%) and sensitive method (80%–90%) of confirming the diagnosis of first-episode genital herpes; however, culture is relatively insensitive in detecting HSV in ulcers in the latter stages of healing and in recurrent infections.

TREATMENT

- Goals of Treatment: to relieve symptoms and to shorten the clinical course, prevent complications and recurrences, and to decrease disease transmission.
- Palliative and supportive measures are the cornerstone of therapy for patients with genital herpes. Pain and discomfort usually respond to warm saline baths or the use of analgesics, antipyretics, or antipruritics.
- Specific treatment recommendations are given in **Table 46–10.**
- Oral **acyclovir, valacyclovir**, and **famciclovir** are the treatments of choice for outpatients with first-episode genital herpes. Treatment does not prevent latency or alter the subsequent frequency and severity of recurrences.
- Suppressive oral antiviral therapy reduces the frequency and the severity of recurrences in 70% to 80% of patients experiencing frequent recurrences.

TABLE 46–8 Treatment of Chlamydial Infections

Infection	Recommended Regimens[a]	Alternative Regimen
Uncomplicated urethral, endocervical, or rectal infection in adults	Azithromycin 1 g orally once *or* doxycycline 100 mg orally twice daily for 7 days	Ofloxacin 300 mg orally twice daily for 7 days, *or* levofloxacin 500 mg orally once daily for 7 days, *or* erythromycin base 500 mg orally four times daily for 7 days, *or* erythromycin ethyl succinate 800 mg orally four times daily for 7 days
Urogenital infections during pregnancy	Azithromycin 1 g orally as a single dose *or* amoxicillin 500 mg orally three times daily for 7 days	Erythromycin base 500 mg orally four times daily for 7 days, *or* erythromycin base 250 mg orally four times daily for 14 days, *or* erythromycin ethyl succinate 800 mg orally four times daily for 7 days (*or* 400 mg orally four times daily for 14 days)
Conjunctivitis of the newborn or pneumonia in infants	Erythromycin base 50 mg/kg/day orally in four divided doses for 14 days[b]	—

[a] Recommendations are those of the Centers for Disease Control and Prevention.
[b] Topical therapy alone is inadequate and is unnecessary when systemic therapy is administered.

- Acyclovir, valacyclovir, and famciclovir have been used to prevent reactivation of infection in patients seropositive for HSV who undergo transplantation procedures or induction chemotherapy for acute leukemia.
- The safety of **acyclovir, famciclovir, and valacyclovir** therapy during pregnancy is not established, although there is no evidence of teratogenic effects of acyclovir in humans.

TRICHOMONIASIS

- Trichomoniasis is caused by *Trichomonas vaginalis,* a flagellated, motile protozoan that is responsible for 3 million to 5 million cases per year in the United States.
- Coinfection with other STDs (eg, gonorrhea) is common in patients diagnosed with trichomoniasis.

CLINICAL PRESENTATION

- The typical presentation of trichomoniasis in men and women is presented in **Table 46–11.**
- *T. vaginalis* produces nonspecific symptoms also consistent with bacterial vaginosis; thus, laboratory diagnosis is required.
- The simplest and most reliable means of diagnosis is a wet-mount examination of the vaginal discharge. Trichomoniasis is confirmed if characteristic pear-shaped, flagellating organisms are observed. Newer diagnostic tests such as monoclonal antibody or DNA probe techniques, as well as polymerase chain reaction tests, are highly sensitive and specific.

TREATMENT

- **Metronidazole** and **tinidazole** are the only antimicrobial agents available in the United States that are consistently effective in *T. vaginalis* infections.
- Treatment recommendations for *Trichomonas* infections are given in **Table 46–12.**

TABLE 46–9 Presentation of Genital Herpes Infections	
General	Incubation period 2–14 days (mean 4 days) Can be caused by either HSV-1 or HSV-2
Classification of infection	
First-episode primary	Initial genital infection in individuals lacking antibody to either HSV-1 or HSV-2
First-episode nonprimary	Initial genital infection in individuals with clinical or serologic evidence of prior HSV (usually HSV-1) infection
Recurrent	Appearance of genital lesions at some time following healing of first-episode infection
Signs and symptoms	
First-episode infections	Most primary infections are asymptomatic or minimally symptomatic Multiple painful pustular or ulcerative lesions on external genitalia developing over a period of 7–10 days; lesions heal in 2–4 weeks (mean, 21 days) Flu-like symptoms (eg, fever, headache, malaise) during first few days after appearance of lesions Others—local itching, pain, or discomfort; vaginal or urethral discharge, tender inguinal adenopathy, paresthesias, urinary retention Severity of symptoms greater in women than in men Symptoms are less severe (eg, fewer lesions, more rapid lesion healing, fewer or milder systemic symptoms) with nonprimary infections Symptoms more severe and prolonged in the immunocompromised On average, viral shedding lasts ~11 or 12 days for primary infections and 7 days for nonprimary infections
Recurrent	Prodrome seen in ~50% of patients prior to appearance of recurrent lesions; mild burning, itching, and tingling are typical prodromal symptoms Compared with primary infections, recurrent infections associated with (1) fewer lesions that are more localized, (2) shorter duration of active infection (lesions heal within 7 days), and (3) milder symptoms Severity of symptoms greater in women than in men Symptoms more severe and prolonged in the immunocompromised On average, viral shedding lasts ~4 days Asymptomatic viral shedding is more frequent during the first year after infection with HSV
Therapeutic implications of HSV-1 versus HSV-2 genital infection	Primary infections due to HSV-1 and HSV-2 virtually indistinguishable Recurrence rate is greater after primary infection with HSV-1 Recurrent infections with HSV-2 tend to be more severe
Complications	Secondary infection of lesions; extragenital infection due to autoinoculation; disseminated infection (primarily in immunocompromised patients); meningitis or encephalitis; neonatal transmission

HSV, herpes simplex virus.

TABLE 46–10 Treatment of Genital Herpes

Type of Infection	Recommended Regimens[a,b]	Alternative Regimen
First clinical episode of genital herpes[c]	Acyclovir 400 mg PO three times daily for 7–10 days,[d] *or* Acyclovir 200 mg PO five times daily for 7–10 days,[d] *or* Famciclovir 250 mg PO three times daily for 7–10 days,[d] *or* Valacyclovir 1 g PO twice daily for 7–10 days[d]	Acyclovir 5–10 mg/kg IV every 8 hours for 2–7 days or until clinical improvement occurs, followed by oral therapy to complete at least 10 days of total therapy[e]
Recurrent infection		
Episodic therapy	Acyclovir 400 mg PO three times daily for 5 days,[f] *or* Acyclovir 800 mg PO twice daily for 5 days,[f] *or* Acyclovir 800 mg PO three times daily for 2 days,[f] *or* Famciclovir 125 mg PO twice daily for 5 days,[f] *or* Famciclovir 1 g PO twice daily for 1 day,[f] *or* Famciclovir 500 mg PO once, followed by 250 mg PO twice daily for 2 days,[f] *or* Valacyclovir 500 mg PO twice daily for 3 days,[f] *or* Valacyclovir 1 g PO once daily for 5 days[f]	
Suppressive therapy	Acyclovir 400 mg PO twice daily, *or* Famciclovir 250 mg PO twice daily, *or* Valacyclovir 500 mg or 1,000 mg PO once daily[g]	

CDC, Centers for Disease Control and Prevention; HIV, human immunodeficiency virus; PO, orally.

[a]Recommendations are those of the CDC.
[b]HIV-infected patients can require more aggressive therapy.
[c]Primary or nonprimary first episode.
[d]Treatment duration can be extended if healing is incomplete after 10 days.
[e]Only for patients with severe symptoms or complications that necessitate hospitalization.
[f]Requires initiation of therapy within 24 hours of lesion onset or during the prodrome that precedes some outbreaks.
[g]Valacyclovir 500 mg appears less effective than other valacyclovir and acyclovir regimens in patients with 10 or more recurrences per year.

TABLE 46–11 Presentation of *Trichomonas* Infections

	Men	Women
General	Incubation period 3–28 days Organism may be detectable within 48 hours after exposure to infected partner	Incubation period 3–28 days
Site of infection	Most common—urethra Others—rectum (usually due to rectal intercourse in men who have sex with men), oropharynx, eye	Most common—endocervical canal Others—urethra, rectum (usually due to perineal contamination), oropharynx, eye
Symptoms	May be asymptomatic (more common in men than women) or minimally symptomatic Urethral discharge (clear to mucopurulent) Dysuria, pruritus	May be asymptomatic or minimally symptomatic Scant to copious, typically malodorous vaginal discharge (50%–75%) and pruritus (worsen during menses) Dysuria, dyspareunia
Signs	Urethral discharge	Vaginal discharge Vaginal pH 4.5–6 Inflammation/erythema of vulva, vagina, and/or cervix Urethritis
Complications	Epididymitis and chronic prostatitis (uncommon) Male infertility (decreased sperm motility and viability)	Pelvic inflammatory disease and associated complications (ie, ectopic pregnancy, infertility) Premature labor, premature rupture of membranes, and low-birth-weight infants (risk of neonatal infections is low) Cervical neoplasia

TABLE 46–12 Treatment of Trichomoniasis

Type	Recommended Regimen[a]	Alternative Regimen
Symptomatic and asymptomatic infections	Metronidazole 2 g orally in a single dose[b] *or* Tinidazole 2 g orally in a single dose	Metronidazole 500 mg orally two times daily for 7 days[c] *or* Tinidazole 2 g orally in a single dose[d]
Treatment in pregnancy	Metronidazole 2 g orally in a single dose[e]	

CDC, Centers for Disease Control and Prevention.

[a]Recommendations are those of the CDC.

[b]Treatment failures should be treated with metronidazole 500 mg orally twice daily for 7 days. Persistent failures should be managed in consultation with an expert. Metronidazole or tinidazole 2 g orally daily for 5 days has been effective in patients infected with *T. vaginalis* strains mildly resistant to metronidazole, but experience is limited; higher doses also have been used.

[c]Metronidazole labeling approved by the FDA does not include this regimen. Dosage regimens for treatment of trichomoniasis included in the product labeling are the single 2 g dose, 250 mg three times daily for 7 days, and 375 mg twice daily for 7 days. The 250 mg and 375 mg dosage regimens are currently not included in the CDC recommendations.

[d]For treatment failures with metronidazole 2 g as a single dose.

[e]Metronidazole is pregnancy category B, and tinidazole is pregnancy category C; both drugs are contraindicated in the first trimester of pregnancy. Some clinicians recommend deferring metronidazole treatment in asymptomatic pregnant women until after 37 weeks' gestation.

- GI complaints (eg, anorexia, nausea, vomiting, and diarrhea) are the most common adverse effects with the single 2 g dose of metronidazole or tinidazole, occurring in 5% to 10% of treated patients. Some patients complain of a bitter, metallic taste in the mouth.
- Patients intolerant of the single 2 g dose because of GI adverse effects usually tolerate the multidose regimen.
- To achieve maximal cure rates and prevent relapse with the single 2 g dose of metronidazole, simultaneous treatment of infected sexual partners is necessary.
- Patients who fail to respond to an initial course usually respond to a second course of metronidazole or tinidazole therapy.
- Patients taking metronidazole should be instructed to avoid alcohol ingestion during therapy and for 1 or 2 days after completion of therapy because of a possible disulfiram-like effect.
- At present no satisfactory treatment is available for pregnant women with *Trichomonas* infections. Metronidazole and tinidazole are contraindicated during the first trimester of pregnancy.
- Follow-up is considered unnecessary in patients who become asymptomatic after treatment with metronidazole.
- When patients remain symptomatic, it is important to determine if reinfection has occurred. In these cases, a repeat course of therapy, as well as identification and treatment or retreatment of infected sexual partners, is recommended.

OTHER SEXUALLY TRANSMITTED DISEASES

- Several STDs other than those previously discussed occur with varying frequency in the United States and throughout the world. Although an in-depth discussion of these diseases is beyond the scope of this chapter, recommended treatment regimens are given in **Table 46–13**.

TABLE 46–13 Treatment Regimens for Miscellaneous Sexually Transmitted Diseases

Infection	Recommended Regimen[a]	Alternative Regimen
Chancroid (*Haemophilus ducreyi*)	Azithromycin 1 g PO in a single dose, *or* Ceftriaxone 250 mg IM in a single dose, *or* Ciprofloxacin 500 mg PO twice daily for 3 days,[b] *or* Erythromycin base 500 mg PO four times daily for 7 days	
Lymphogranuloma venereum	Doxycycline 100 mg PO twice daily for 21 days[c]	Erythromycin base 500 mg PO four times daily for 21 days[d]
Human papillomavirus (HPV) infection		
External genital/perianal warts	*Provider-Administered Therapies:* Cryotherapy (e.g., liquid nitrogen or cryoprobe); repeat weekly as necessary, *or* Podophyllin resin 10–25% in compound tincture of benzoin applied to lesions; repeat weekly as necessary,[e,f] *or* Trichloroacetic acid (TCA) 80–90% *or* bichloracetic acid (BCA) 80–90% applied to warts; repeat weekly as necessary, *or*	Intralesional interferon *or* Photodynamic therapy *or*

TABLE 46–13 Treatment Regimens for Miscellaneous Sexually Transmitted Diseases (*Continued*)

Infection	Recommended Regimen[a]	Alternative Regimen
	Surgical removal (tangential scissor excision, tangential shave excision, curettage, or electrosurgery) *Patient-Applied Therapies:* Podofilox 0.5% solution or gel applied twice daily for 3 days, followed by 4 days of no therapy; cycle is repeated as necessary for up to four cycles,[f] *or* Imiquimod 5% cream applied at bedtime three times weekly for up to 16 weeks,[f] *or* Sinecatechins 15% ointment applied three times daily for up to 16 weeks	Topical cidofovir
Vaginal and anal warts	Cryotherapy with liquid nitrogen, or TCA or BCA 80–90% as for external HPV warts; repeat weekly as necessary[g] Surgical removal (not for vaginal or urethral meatus warts)	
Urethral meatus warts	Cryotherapy with liquid nitrogen, or podophyllin resin 10–25% in compound tincture of benzoin applied at weekly intervals[f,h]	
Prevention	Gardasil® (human papillomavirus quadrivalent [types 6, 11, 16, and 18]) recombinant vaccine 0.5 mL IM on day 1; a second and third dose are administered 2 and 6 months following the first dose[i,j,k] Cervarix® (human papillomavirus bivalent [types 16 and 18]) recombinant vaccine 0.5 mL IM on day 1; a second and third dose are administered 1 and 6 months following the first dose[i,l]	

[a]Recommendations are those of the Centers for Disease Control and Prevention (CDC).
[b]Ciprofloxacin is contraindicated for pregnant and lactating women and for persons aged <18 years.
[c]Azithromycin 1 g PO once weekly for 3 weeks can be effective.
[d]Pregnant patients should be treated with erythromycin.
[e]Some experts recommended washing podophyllin off after 1–4 hours to minimize local irritation.
[f]Safety during pregnancy is not established.
[g]Surgical removal of anal warts is also a recommended treatment.
[h]Some specialists recommend the use of podofilox and imiquimod for treating distal meatal warts.
[i]CDC recommendations: vaccination is recommended in girls 11–12 years of age, and in females aged 13–26 years who either were not previously vaccinated, or who did not complete the vaccination series.
[j]FDA approved labeling for Gardasil®: indicated in girls and women 9 through 26 years of age for the prevention of cervical, vulvar, vaginal, and anal cancer caused by HPV types 16 and 18, genital warts (condyloma acuminata) caused by HPV types 6 and 11, and precancerous or dysplastic lesions caused by HPV types 6, 11, 16, and 18.
[k]Vaccination is recommended in males aged 9–26 years to prevent genital warts and anal cancer.
[l]FDA approved labeling for Cervarix®: indicated in females 9 through 25 years of age for the prevention of cervical cancer, cervical intraepithelial neoplasia grade 2 or worse, adenocarcinoma in situ, and cervical intraepithelial neoplasia grade 1 caused by HPV types 16 and 18.

See Chapter 95, Sexually Transmitted Diseases, authored by Leroy C. Knodel, for a more detailed discussion of this topic.

Skin and Soft-Tissue Infections 47 CHAPTER

- Bacterial infections of the skin can be classified as primary or secondary (**Table 47–1**). Primary bacterial infections are usually caused by a single bacterial species and involve areas of generally healthy skin (eg, impetigo and erysipelas). Secondary infections, however, develop in areas of previously damaged skin and are frequently polymicrobic.
- The conditions that may predispose a patient to the development of skin and soft-tissue infections (SSTIs) include (1) a high concentration of bacteria; (2) excessive moisture of the skin; (3) inadequate blood supply; (4) availability of bacterial nutrients; and (5) damage to the corneal layer, allowing for bacterial penetration.
- The majority of SSTIs are caused by gram-positive organisms and, less commonly, gram-negative bacteria present on the skin surface. *Staphylococcus aureus* and *Streptococcus pyogenes* account for the majority of SSTIs. Community-associated methicillin-resistant *S. aureus* (CA-MRSA) has emerged and is often isolated in otherwise healthy patients.

ERYSIPELAS

- *Erysipelas* (Saint Anthony's fire) is an infection of the superficial layers of the skin and cutaneous lymphatics. The infection is almost always caused by β-hemolytic streptococci, with *S. pyogenes* (group A *streptococci*) responsible for most infections.
- The lower extremities are the most common sites for erysipelas. Patients often experience flu-like symptoms (fever and malaise) prior to the appearance of the lesions. The infected area is painful, often a burning pain. Erysipelas lesions are bright red and edematous with lymphatic streaking and clearly demarcated raised margins. Leukocytosis is common, and C-reactive protein is generally elevated.
- Mild to moderate cases of erysipelas in adults are treated with intramuscular **procaine penicillin G** or **penicillin VK**. For more serious infections, aqueous penicillin G, 2 million to 8 million units daily, should be administered intravenously (IV). Penicillin-allergic patients can be treated with clindamycin or erythromycin.
- Evidence-based recommendations for treatment of SSTIs are found in **Table 47–2**, and recommended drugs and dosing regimens for outpatient treatment of mild to moderate SSTIs are found in **Table 47–3** and **Table 47–4**.

IMPETIGO

- *Impetigo* is a superficial skin infection that is seen most commonly in children. It is highly communicable and spreads through close contact. Most cases are caused by *S. pyogenes*, but *S. aureus* either alone or in combination with *S. pyogenes* has emerged as a principal cause of impetigo.

CLINICAL PRESENTATION

- Exposed skin, especially the face, is the most common site for impetigo.
- Pruritus is common, and scratching of the lesions may further spread infection through excoriation of the skin. Other systemic signs of infection are minimal.
- Weakness, fever, and diarrhea are sometimes seen with bullous impetigo.
- Nonbullous impetigo manifests initially as small, fluid-filled vesicles. These lesions rapidly develop into pus-filled blisters that readily rupture. Purulent discharge from the lesions dries to form golden yellow crusts that are characteristic of impetigo.
- In the bullous form of impetigo, the lesions begin as vesicles and turn into bullae containing clear yellow fluid. Bullae soon rupture, forming thin, light brown crusts.
- Regional lymph nodes may be enlarged.

TABLE 47–1 Bacterial Classification of Important Skin and Soft-Tissue Infections

Primary infections	
Erysipelas	Group A streptococci
Impetigo	*Staphylococcus aureus,* group A streptococci
Lymphangitis	Group A streptococci; occasionally *S. aureus*
Cellulitis	Group A streptococci, *S. aureus*; occasionally other gram-positive cocci, gram-negative bacilli, and/or anaerobes
Necrotizing fasciitis	
Type I	Anaerobes (*Bacteroides* spp., *Peptostreptococcus* spp.) and facultative bacteria (streptococci, Enterobacteriaceae)
Type II	Group A streptococci
Type III	*Clostridium perfringens*
Secondary infections	
Diabetic foot infections	*S. aureus,* streptococci, Enterobacteriaceae, *Bacteroides* spp., *Peptostreptococcus* spp., *Pseudomonas aeruginosa*
Pressure sores	*S. aureus,* streptococci, Enterobacteriaceae, *Bacteroides* spp., *Peptostreptococcus* spp., *P. aeruginosa*
Bite wounds	
Animal	*Pasteurella multocida, S. aureus,* streptococci, *Bacteroides* spp.
Human	*Eikenella corrodens, S. aureus,* streptococci, *Corynebacterium* spp., *Bacteroides* spp., *Peptostreptococcus* spp.
Burn wounds	*P. aeruginosa,* Enterobacteriaceae, *S. aureus,* streptococci

TREATMENT

- Penicillinase-resistant penicillins (eg, **dicloxacillin**) are the agents of first choice because of the increased isolation of *S. aureus*. First-generation cephalosporins (eg, cephalexin) are also effective (see **Table 47–3**). **Penicillin** may be used for impetigo caused by *S. pyogenes*. It may be administered as either a single intramuscular dose of benzathine penicillin G (300,000–600,000 units in children, 1.2 million units in adults) or as oral penicillin VK given for 7 to 10 days. Penicillin-allergic patients can be treated with oral **clindamycin**. Recommended doses for antimicrobials are found in **Table 47–4.**
- **Mupirocin ointment** and antimicrobials (except penicillin and erythromycin) are equally effective.

CELLULITIS

- Cellulitis is an acute, spreading infectious process that initially affects the epidermis and dermis and may subsequently spread within the superficial fascia. This process is characterized by inflammation but with little or no necrosis or suppuration of soft tissue.
- Cellulitis is most often caused by *S. pyogenes* or *S. aureus* (see **Table 47–1**).
- *S. aureus* is the most common pathogen isolated from injection drug users; the incidence of MRSA is also rising. Anaerobic bacteria, especially oropharyngeal anaerobes, are also found commonly, particularly in polymicrobic infections.

TABLE 47–2 Evidence-Based Recommendations for Treatment of Skin and Soft-Tissue Infections

Recommendations	Recommendation Grade
Folliculitis, Furuncles, Carbuncles	
Folliculitis and small furuncles can be treated with moist heat; large furuncles and carbuncles require incision and drainage. Antimicrobial therapy is unnecessary unless extensive lesions or fever are present	A-II for nondrug management; E-III for recommendation against antibiotics
Erysipelas	
Most infections are caused by *Streptococcus pyogenes*. Penicillin (oral or IV depending on clinical severity) is the drug of choice	A-I
If *Staphylococcus aureus* is suspected, a penicillinase-resistant penicillin or first-generation cephalosporin should be used	A-I
Impetigo	
S. aureus accounts for the majority of infections; consequently, a penicillin-resistant penicillin or first-generation cephalosporin is recommended	A-I
Topical therapy with mupirocin is equivalent to oral therapy	A-I
Cellulitis	
Empiric antibiotics for outpatients with purulent cellulitis should provide activity against community-associated MRSA; coverage of β-hemolytic streptococci is likely not required. Mild–moderate infections can generally be treated with oral agents (dicloxacillin, cephalexin, clindamycin) unless resistance is high in the community	A-II
Empiric antibiotics for outpatients with nonpurulent cellulitis should provide activity against β-hemolytic streptococci; coverage for community-associated MRSA may be considered for patients with systemic toxicity or those who have not responded to β-lactam therapy alone	A-II
Recommended antibiotics for empiric coverage of community-associated MRSA in outpatients include orally administered trimethoprim–sulfamethoxazole, doxycycline, minocycline, clindamycin, and linezolid	A-II for all listed options
If coverage of both β-hemolytic streptococci and community-associated MRSA is desired, empiric antibiotic regimens for outpatient therapy include orally administered clindamycin alone; linezolid alone; or trimethoprim–sulfamethoxazole, doxycycline, or minocycline in combination with amoxicillin	A-II for all listed options

Hospitalized patients with complicated or purulent cellulitis should receive IV antibiotics with activity against MRSA pending culture data. Antibiotic options include vancomycin, linezolid, daptomycin, telavancin, and clindamycin	A-I for all except clindamycin; clindamycin A-III
A *β*-lactam antibiotic (e.g., cefazolin) may be considered for empiric treatment of nonpurulent cellulitis in hospitalized patients. Antibiotics should be modified to include MRSA coverage if unfavorable clinical response	A-II
In the treatment of *S. aureus* infections, trough serum vancomycin concentrations should always be maintained >10 mg/L (>7 μmol/L) to avoid development of resistance	B-III
Necrotizing Fasciitis	
Early and aggressive surgical debridement of all necrotic tissue is essential	A-III
Necrotizing fasciitis caused by *S. pyogenes* should be treated with the combination of clindamycin and penicillin	A-II
In the treatment of necrotizing fasciitis caused by methicillin-resistant *S. aureus* infections, trough serum vancomycin concentrations of 15–20 mg/L (10–14 μmol/L) are recommended	B-II
Clostridial gas gangrene (myonecrosis) should be treated with clindamycin and penicillin	B-III
Diabetic Foot Infections	
Clinically uninfected wounds should not be treated with antibiotics	A-III
Empiric antibiotic regimens should be selected based on severity of infection and likely pathogens	A-III
Antibiotic therapy should target only aerobic gram-positive cocci in patients with mild to moderate infection who have not received antibiotics within the previous month	C-III
Broad-spectrum empiric antibiotic therapy should be initiated in most patients with severe infections, until culture and susceptibility data are available	A-III
Empiric antibiotics directed against *Pseudomonas aeruginosa* are usually unnecessary except in patients with specific risk factors for infection with this pathogen: patient has been soaking feet, patient has failed previous antibiotic therapy with nonpseudomonal agents, or clinically severe infection	A-III

(*Continued*)

TABLE 47–2 Evidence-Based Recommendations for Treatment of Skin and Soft-Tissue Infections (*Continued*)

Recommendations	Recommendation Grade
Empiric antibiotics directed against MRSA should be considered in patients with specific risk factors, including: prior history of infection or colonization with MRSA, high local prevalence of MRSA (e.g., ≥50% for mild infections, ≥30% for severe infection), or clinically severe infection	C-III
Oral agents with high bioavailability may be used in the treatment of most mild, and many moderate, infections	A-II
Parenteral therapy is initially preferred for all severe, and some moderate, infections. After initial response, step-down therapy to oral agents can be considered	C-III
Definitive therapy should be based on results of appropriately collected cultures and sensitivities, as well as clinical response to empiric antimicrobial agents	A-III
Appropriate wound care, in addition to appropriate antimicrobial therapy, is often necessary for healing of infected wounds	A-III
Antibiotic therapy should only be continued until resolution of signs/symptoms of infection, but not necessarily until the wound is fully healed. The duration of therapy should initially be 1–2 weeks for mild infections and 2–3 weeks for moderate to severe infection	C-III
Animal Bites	
Many bite wounds can be treated on an outpatient basis with amoxicillin–clavulanic acid	B-II
Serious infections requiring IV antimicrobial therapy can be treated with a β-lactam/β-lactamase inhibitor combination or second-generation cephalosporin with activity against anaerobes (e.g., cefoxitin)	B-II
Penicillinase-resistant penicillins, first-generation cephalosporins, macrolides, and clindamycin should not be used for treatment of infected wounds because of their poor activity against *Pasteurella multocida*	D-III
Human Bites	
Antimicrobial therapy should provide coverage against *Eikenella corrodens*, *S. aureus*, and β-lactamase–producing anaerobes	B-III

Strength of recommendation: A, good evidence for use; B, moderate evidence for use; C, poor evidence for use, optional; D, moderate evidence to support not using; E, good evidence to support not using. *Quality of evidence*: I, evidence from ≥1 properly randomized controlled trials; II, evidence from ≥1 well-designed clinical trials without randomization, case–control analytic studies, multiple time series, or dramatic results from uncontrolled experiments; III, evidence from expert opinion, clinical experience, descriptive studies, or reports of expert committees.

TABLE 47–3 Recommended Oral Drugs or Outpatient Treatment of Mild–Moderate Skin and Soft-Tissue Infections

Infection	Adults	Children
Folliculitis	None; warm saline compresses usually sufficient	
Furuncles and carbuncles	Dicloxacillin Cephalexin Clindamycin[a] Trimethoprim–sulfamethoxazole[b]	Dicloxacillin Cephalexin Clindamycin[a,b] Trimethoprim–sulfamethoxazole[b]
Erysipelas	Procaine penicillin G Penicillin VK Clindamycin[a] Erythromycin[a]	Penicillin VK Clindamycin[a] Erythromycin[a]
Impetigo	Dicloxacillin Cephalexin Cefadroxil Clindamycin[a] Mupirocin ointment[a] Retapamulin ointment[a] Trimethoprim–sulfamethoxazole[b]	Dicloxacillin Cephalexin Cefadroxil Clindamycin[a,b] Mupirocin ointment[a] Retapamulin ointment[a] Trimethoprim–sulfamethoxazole[b]
Lymphangitis	Initial IV therapy, followed by penicillin VK Clindamycin[a]	Initial IV therapy, followed by penicillin VK Clindamycin[a]
Diabetic foot infections	Dicloxacillin Clindamycin Cephalexin Amoxicillin–clavulanate Levofloxacin ± metronidazole or clindamycin[a,c] Ciprofloxacin ± metronidazole or clindamycin[a,c] Moxifloxacin	
Bite wounds (animal or human)	Amoxicillin–clavulanate Doxycycline[a] Moxifloxacin[a] Trimethoprim–sulfamethoxazole + metronidazole or clindamycin[a] Levofloxacin or ciprofloxacin + metronidazole or clindamycin[a] Cefuroxime axetil + metronidazole or clindamycin Dicloxacillin + penicillin VK	Amoxicillin–clavulanate Trimethoprim–sulfamethoxazole + metronidazole or clindamycin[a] Cefuroxime axetil + metronidazole or clindamycin Dicloxacillin + penicillin VK

[a]Recommended for patients with penicillin allergy.
[b]Recommended if CA-MRSA is suspected.
[c]Fluoroquinolone alone may be suitable for mild infections, while addition of drugs with antianaerobic activity may be recommended for more severe infections.

TABLE 47–4 Drug Dosing Table

Drug	Brand Name	Initial Dose	Usual Range	Special Population Dose	Other
Oral Agents					
Amoxicillin–clavulanate	Augmentin®	875/125 mg orally two times daily	875/125 mg orally two times daily	Pediatric: 40 mg/kg (of the amoxicillin component) orally in two divided doses	
Cefaclor	Ceclor®	500 mg orally every 8 hours	500 mg orally every 8 hours	Pediatric: 20–40 mg/kg/day (not to exceed 1 g) orally in three divided doses	
Cefadroxil	Duricef®	500 mg orally every 12 hours	250–500 mg orally every 12 hours	Pediatric: 30 mg/kg orally in two divided doses	
Cefuroxime axetil	Ceftin®	500 mg orally every 12 hours	250–500 mg orally every 12 hours	Pediatric: 20–30 mg/kg orally in two divided doses	
Cephalexin	Keflex®	250–500 mg orally every 6 hours	250–500 mg orally every 6 hours	Pediatric: 25–50 mg/kg orally in four divided doses	
Ciprofloxacin	Cipro®	500 mg orally every 12 hours	500–750 mg orally every 12 hours		
Clindamycin	Cleocin®	300–600 mg orally every 6–8 hours	300–600 mg orally every 6–8 hours	Pediatric: 10–30 mg/kg/day orally in three to four divided doses[4]	
Dicloxacillin	Dynapen®	250–500 mg orally every 6 hours	250–500 mg orally every 6 hours	Pediatric: 25–50 mg/kg orally in four divided doses	
Doxycycline	Vibramycin®	100–200 mg orally every 12 hours	100–200 mg orally every 12 hours		May be used for oral treatment of MRSA infection
Erythromycin	E-Mycin® Erythrocin®	250–500 mg orally every 6 hours	250–500 mg orally every 6 hours	Pediatric: 30–50 mg/kg orally in four divided doses[a]	

Levofloxacin	Levaquin®	500–750 mg orally once daily	500–750 mg orally once daily		
Metronidazole	Flagyl®	250–500 mg orally every 8 hours	250–500 mg orally every 8 hours	Pediatric: 30 mg/kg orally in three to four divided doses	
Moxifloxacin	Avelox®	400 mg orally once daily	400 mg orally once daily		
Mupirocin ointment	Bactroban®	Apply to affected areas ointment every 8 hours	Apply to affected areas ointment every 8 hours	Pediatric: apply to affected areas ointment every 8 hours	
Penicillin VK	Veetids® Pen-V®	250–500 mg orally every 6 hours	250–500 mg orally every 6 hours	Pediatric: 25,000–90,000 units/kg orally in four divided doses	
Retapamulin ointment	Altabax®	Apply to affected area every 12 hours	Apply to affected area every 12 hours	Pediatric: apply to affected area every 12 hours	
Trimethoprim–sulfamethoxazole	Bactrim® Septra® Cotrimoxazole®	160/800 mg orally every 12 hours	160 /800 mg orally every 12 hours	Pediatric: 4–6 mg/kg (of the trimethoprim component) orally every 12 hours	Up to double the usual dose may be considered for oral treatment of MRSA infection
Parenteral Agents					
Ampicillin	Omnipen® Polycillin® Principen®	2 g IV every 6 hours	1–2 g IV every 4–6 hours	Pediatric: 200–300 mg/kg/day IV in four to six divided doses	
Aztreonam	Azactam®	1 g IV every 6 hours	1 g IV every 6 hours	Pediatric: 100–150 mg/kg/day IV in four divided doses	
Cefazolin	Ancef® Kefzol®	1 g IV every 8 hours	1 g IV every 6–8 hours	Pediatric: 75 mg/kg/day IV in three divided doses	

(*Continued*)

TABLE 47–4 Drug Dosing Table (*Continued*)

Drug	Brand Name	Initial Dose	Usual Range	Special Population Dose	Other
Cefepime	Maxipime®	2 g IV every 12 hours	1–2 g IV every 12 hours	Pediatric: 100 mg/kg/day IV in two divided doses	
Cefotaxime	Claforan®	2 g IV every 6 hours	1–2 g IV every 6 hours	150–200 mg/kg/day in three to four divided doses	
Cefoxitin	Mefoxin®	1–2 g IV every 6 hours	1–2 g IV every 6 hours	Pediatric: 30–40 mg/kg/day IV in four divided doses	
Ceftazidime	Fortaz®	2 g IV every 8 hours	1–2 g IV every 8 hours	Pediatric: 150 mg/kg/day IV in three divided doses	
Ceftriaxone	Rocephin®	1 g IV once daily	1 g IV once daily		
Cefuroxime	Zinacef®	1.5 g IV every 8 hours	0.75–1.5 g IV every 8 hours	Pediatric: 150 mg/kg/day IV in three divided doses	
Ciprofloxacin	Cipro®	400 mg IV every 8–12 hours	400 mg IV every 8–12 hours		
Clindamycin	Cleocin®	300–600 mg IV every 6–8 hours	300–600 mg IV every 6–8 hours; 600–900 mg IV every 6–8 hours for necrotizing fasciitis	Pediatric: 30–50 mg/kg/day IV in three to four divided doses	
Daptomycin	Cubicin®	4 mg/kg IV once daily	4 mg/kg IV once daily		For MRSA infection
Doripenem	Doribax®	500 mg IV every 8 hours	500 mg IV every 8 hours		
Ertapenem	Invanz®	1 g IV once daily	1 g IV once daily	Pediatric: 30 mg/kg/day IV in one to two divided doses	

Gentamicin	Garamycin®	Traditional: 2 mg/kg loading dose, followed by 1.5 mg/kg IV every 8 hours. Alternative: 5–7 mg/kg IV once daily	Traditional dosing: guided by measured serum concentrations	Pediatric: 5–7 mg/kg/day IV in three divided doses; doses guided by serum concentrations	
Imipenem–cilastatin	Primaxin®	500 mg IV every 6 hours	250–500 mg IV every 6–8 hours	Pediatric: 40–80 mg/kg/day IV in four divided doses	
Levofloxacin	Levaquin®	750 mg IV once daily	500–750 mg IV once daily		
Linezolid	Zyvox®	600 mg IV or orally every 12 hours	600 mg IV or orally every 12 hours	Pediatric: 20–30 mg/kg/day IV in two to three divided doses	For MRSA infection
Meropenem	Merrem®	1 g IV every 8 hours	1 g IV every 8 hours	Pediatric: 60 mg/kg/day IV in three divided doses	
Metronidazole	Flagyl®	500 mg IV every 8 hours	500 mg IV every 8 hours	Pediatric: 30–50 mg/kg/day IV in three divided doses	
Moxifloxacin	Avelox®	400 mg IV once daily	400 mg IV once daily		
Nafcillin	Nafcil®	2 g IV every 6 hours	1–2 g IV every 4–6 hour	Pediatric: 100–200 mg/kg/day IV in four to six equally divided doses	
Penicillin G	Pfizerpen® Bicillin® Wycillin®	1–2 million units IV every 4–6 hours	1–2 million units IV every 4–6 hours	Pediatric: 100,000–200,000 units/kg/day IV in four divided doses[a]	

(*Continued*)

TABLE 47–4 Drug Dosing Table (*Continued*)

Drug	Brand Name	Initial Dose	Usual Range	Special Population Dose	Other
Piperacillin–tazobactam	Zosyn®	4.5 g IV every 6 hours	3.375–4.5 g IV every 6 hours	Pediatric: 250–350 mg/kg/day IV in three to four divided doses	
Procaine penicillin G	Bicillin C-R®	600,000 units IM every 12 hours	600,000–1.2 million units IM every 12 hours	Pediatric: 25,000–50,000 units/kg (maximum 1.2 million units) IM once daily	
Tigecycline	Tigacil®	100 mg IV once, and then 50 mg IV every 12 hours	100 mg IV once, and then 50 mg IV every 12 hours		
Tobramycin	Nebcin®	Traditional: 2 mg/kg loading dose, followed by 1.5 mg/kg IV every 8 hours. Alternative: 5–7 mg/kg IV once daily	Traditional dosing: guided by measured serum concentrations	Pediatric: 5–7 mg/kg/day IV in three divided doses; doses guided by serum concentrations	
Vancomycin	Vancocin®	30–40 mg/kg/day IV in two divided doses	Dosing guided by serum concentrations to achieve trough of 15–20 mg/L	Pediatric: 40–60 mg/kg/day IV in three to four divided doses; doses guided by serum concentrations	For MRSA infection

IM, intramuscularly; MRSA, methicillin-resistant *S. aureus.*
[a]Dosing guidelines in patients with normal renal function.

CLINICAL PRESENTATION

- Cellulitis is characterized by erythema and edema of the skin. The lesion, which may be extensive, is painful and nonelevated and has poorly defined margins. Tender lymphadenopathy associated with lymphatic involvement is common. Malaise, fever, and chills are also commonly present. There is usually a history of an antecedent wound from minor trauma, an ulcer, or surgery.
- A Gram stain of a smear obtained by injection and aspiration of 0.5 mL of saline (using a small-gauge needle) into the advancing edge of the erythematous lesion may help in making the microbiologic diagnosis but often yields negative results. Blood cultures are useful, as bacteremia may be present in 30% of cases.

TREATMENT

- **Goal of treatment:** The goal for acute bacterial cellulitis is rapid eradication of the infection and prevention of further complications. Antimicrobial therapy of bacterial cellulitis is directed toward the type of bacteria either documented to be present or suspected. Local care of cellulitis includes elevation and immobilization of the involved area to decrease local swelling. Incision and drainage is the primary therapy for infections such as small abscesses and furuncles, and in otherwise uncomplicated patients with mild infections. Systemic antibiotic therapy is often unnecessary in such cases.
- Antibiotic therapy is recommended along with incision and drainage in patients with more complicated abscesses associated with the following: severe or extensive disease involving multiple sites of infection; rapidly progressive infection in the presence of associated cellulitis; signs and symptoms of systemic illness; complicating factors such as extremes of age, comorbidities, or immunosuppression; abscesses in areas that are difficult to drain, such as hands, face, and genitalia; or lack of response to previous drainage alone.
- As streptococcal cellulitis is indistinguishable clinically from staphylococcal cellulitis, administration of a semisynthetic penicillin (**dicloxacillin**) or first-generation cephalosporin (**cephalexin**) is recommended until a definitive diagnosis, by skin or blood cultures, can be made (**Table 47–5**).
- The usual duration of therapy for cellulitis is 5 to 10 days.

DIABETIC FOOT INFECTIONS

- Three key factors are involved in the causation of diabetic foot problems: neuropathy, ischemia, and immunologic defects. Any of these disorders can occur in isolation; however, they frequently occur together.
- There are three major types of diabetic foot infections: deep abscesses, cellulitis of the dorsum, and mal perforans ulcers of the sole of the foot. Osteomyelitis may occur in 30% to 40% of infections.
- Mild cases of diabetic foot infections (DFI) are often monomicrobial. However, more severe infections are typically polymicrobic; up to 60% of hospitalized patients have polymicrobial infections. Staphylococci and streptococci are the most common pathogens, although gram-negative bacilli and anaerobes occur in 50% of cases.
- Patients with peripheral neuropathy often do not experience pain but seek medical attention for swelling or erythema. Lesions vary in size and clinical features. A foul-smelling odor suggests anaerobic organisms. Temperature may be mildly elevated or normal.

TREATMENT

- **Goal of treatment:** The goal is preservation of as much normal limb function as possible while preventing infectious complications. Most infections can be successfully treated on an outpatient basis with wound care and antibiotics.
- Necrotic tissue must be thoroughly debrided with wound drainage and amputation as required.
- Diabetic glycemic control should be maximized to ensure optimal healing.

TABLE 47–5 Initial Treatment Regimens for Cellulitis and Necrotizing Fasciitis

Antibiotic	Adult Dose and Route	Pediatric Dose and Route
Cellulitis		
Staphylococcal or unknown gram-positive infection		
Mild to moderate nonpurulent infection	Dicloxacillin or cephalexin orally[a]	Dicloxacillin or cephalexin orally[a]
Mild to moderate purulent infection with suspected CA-MRSA	Trimethoprim–sulfamethoxazole, doxycycline, minocycline, or clindamycin orally	Trimethoprim–sulfamethoxazole or clindamycin orally
Severe nonpurulent infection	IV cefazolin or nafcillin[b]	IV cefazolin or nafcillin[b]
Severe purulent infection	IV vancomycin, linezolid, or daptomycin	IV vancomycin or linezolid
Streptococcal (documented)		
Mild to moderate infection	Penicillin VK orally[a] or IM procaine penicillin G[a]	Penicillin VK orally or IM procaine penicillin G[a]
Severe infection	IV aqueous penicillin G[a]	IV aqueous penicillin G[a]
Gram-negative bacilli		
Mild to moderate infection	Cefaclor or cefuroxime axetil orally[c]	Cefaclor or cefuroxime axetil orally
Severe infection	IV aminoglycoside[d] or IV cephalosporin (first- or second-generation depending on severity of infection or susceptibility pattern)[c]	IV aminoglycoside[d] or IV cephalosporin (first- or second-generation depending on severity of infection or susceptibility pattern)
Polymicrobic infection without anaerobes		
	IV aminoglycoside[e] + IV penicillin G, nafcillin, or vancomycin depending on isolation of staphylococci or streptococci and risk for MRSA infection	IV aminoglycoside[e] + IV penicillin G, nafcillin, or vancomycin depending on isolation of staphylococci or streptococci and risk for MRSA infection

Polymicrobic infection with anaerobes		
Mild to moderate infection	Amoxicillin/clavulanate orally. *Or* ciprofloxacin or levofloxacin + clindamycin or metronidazole orally. *Or* moxifloxacin orally	Amoxicillin/clavulanate orally
Severe infection	IV aminoglycoside[e] + IV clindamycin or metronidazole. *Or* IV second- or third-generation cephalosporin + IV clindamycin or metronidazole. *Or* IV antianaerobic second-generation cephalosporin. *Or* IV imipenem–cilastatin, meropenem, ertapenem, doripenem, or piperacillin–tazobactam	IV aminoglycoside[e] + IV clindamycin or metronidazole. *Or* IV second- or third-generation cephalosporin + IV clindamycin or metronidazole. *Or* IV antianaerobic second-generation cephalosporin. *Or* IV imipenem–cilastatin, meropenem, ertapenem, or piperacillin–tazobactam
Necrotizing fasciitis		
Type I	IV ampicillin–sulbactam or piperacillin–tazobactam + IV clindamycin + IV ciprofloxacin. *Or* IV cefotaxime + IV clindamycin or metronidazole. *Or* IV imipenem/cilastatin, meropenem, or ertapenem	
Type II	IV penicillin G + IV clindamycin[d]	
Type III	IV penicillin G + IV clindamycin[d]	

CA-MRSA, community-associated methicillin-resistant *Staphylococcus aureus;* IM, intramuscularly.

[a]For penicillin-allergic patients, use clindamycin.
[b]For penicillin-allergic patients, use vancomycin.
[c]For penicillin-allergic adults, use a fluoroquinolone (ciprofloxacin, levofloxacin, or moxifloxacin).
[d]May consider initially adding vancomycin for CA-MRSA coverage if suspicions of staphylococcal involvement (see text).
[e]A fluoroquinolone (adults only) or aztreonam may be used in place of the aminoglycoside in patients with severe renal dysfunction or other relative contraindications to aminoglycoside use.

- The patient should initially be restricted to bed rest, leg elevation, and control of edema, if present.
- Suggested antibiotic regimens for empiric treatment of diabetic foot infections are found in **Table 47–6**.

INFECTED PRESSURE ULCERS

- A pressure sore is also called a "decubitus ulcer" or "bed sore." A classification system for pressure sores is presented in **Table 47–7**. Many factors are thought to predispose patients to the formation of pressure ulcers: paralysis, paresis, immobilization, malnutrition, anemia, infection, and advanced age. Four factors thought to be most critical to their formation are pressure, shearing forces, friction, and moisture; however, there is still debate as to the exact pathophysiology of pressure sore formation. The areas of highest pressure are generated over the bony prominences.
- Most pressure sores are colonized by bacteria; however, bacteria frequently infect healthy tissue. A large variety of aerobic gram-positive and gram-negative bacteria, as well as anaerobes, are frequently isolated.

CLINICAL PRESENTATION

- Most pressure sores are in the pelvic region and lower extremities. The most common sites are the sacral and coccygeal areas, ischial tuberosities, and greater trochanter.
- Clinical infection is recognized by the presence of redness, heat, and pain. Purulent discharge, foul odor, and systemic signs (fever and leukocytosis) may be present.
- Pressure sores vary greatly in their severity, ranging from an abrasion to large lesions that can penetrate into the deep fascia involving both bone and muscle.

PREVENTION AND TREATMENT

- **Goal of treatment:** The goal is to clean and decontaminate the ulcer to promote wound healing by permitting the formation of healthy granulation tissue or to prepare the wound for an operative procedure. The main factors to be considered for successful wound care are (1) relief of pressure; (2) debridement of necrotic tissue; (3) wound cleansing; (4) dressing selection; and (5) prevention, diagnosis, and treatment of infection.
- Prevention is the single most important aspect in the management of pressure sores. Friction and shearing forces can be minimized by proper positioning. Skin care and prevention of soilage are important, with the intent being to keep the surface relatively free from moisture. Relief of pressure (even for 5 min once every 2 h) is probably the single most important factor in preventing pressure sore formation.
- Medical management is generally indicated for lesions that are of moderate size and of relatively shallow depth (stage 1 or 2 lesions) and are not located over a bony prominence.
- Debridement can be accomplished by surgical or mechanical means (wet-to-dry dressing changes). Other effective therapies are hydrotherapy, wound irrigation, and dextranomer. Pressure sores should be cleaned with normal saline.
- See **Table 47–3** for systemic treatment of an infected pressure sore. A short, 2-week trial of topical antibiotic (**silver sulfadiazine** or **triple antibiotic**) is recommended for a clean ulcer that is not healing or is producing a moderate amount of exudate despite appropriate care.

INFECTED BITE WOUNDS

DOG BITES

- Patients at risk of acquiring an infection after a bite have had a puncture wound, have not sought medical attention within 8 hours of injury, and are older than 50 years.
- The infected dog bite is usually characterized by a localized cellulitis and pain at the site of injury. The cellulitis usually spreads proximally from the initial site of injury. If *Pasteurella multocida* is present, a rapidly progressing cellulitis is observed within 24 to 48 hours of initial injury.

TABLE 47–6 Suggested Antibiotic Regimens for Empiric Treatment of Diabetic Foot Infections

Severity of Infection	Probable Pathogens	Drug(s)[a]	Duration of Therapy
Mild	*Staphylococcus aureus* (MSSA) *Streptococcus* spp. *S. aureus* (MRSA) • Patients with history of MRSA infection or colonization in past year • Prevalence of MRSA ≥50% in local geographic area • Recent hospitalization	Amoxicillin–clavulanate Cephalexin Dicloxacillin Clindamycin Levofloxacin Moxifloxacin[b]	1–2 weeks; may increase up to 4 weeks if infection slow to resolve
Moderate to severe (initially oral or IV antibiotics for moderately severe infections, IV antibiotics for severe infections)	MSSA *Streptococcus* spp. Enterobacteriaceae Obligate anaerobes	Ampicillin/sulbactam Cefoxitin Ceftriaxone Imipenem/cilastatin Ertapenem Levofloxacin Moxifloxacin Tigecycline Levofloxacin or ciprofloxacin + clindamycin	Moderately severe infection: 1–3 weeks; severe infection: 2–4 weeks
	MRSA • Patients with history of MRSA infection or colonization in past year • Prevalence of MRSA ≥30% in local geographic area • Recent hospitalization • Infection severe enough that not empirically covering MRSA poses unacceptable risk of treatment failure	Add to one of the above regimens: • Vancomycin • Linezolid • Daptomycin	
	Pseudomonas aeruginosa • Patient has been soaking feet • Patient has previously failed therapy with nonpseudomonal antibiotic regimen • Severe infection	Piperacillin/tazobactam	
	Mixed infections potentially including all of the above	Cefepime, ceftazidime, or aztreonam + metronidazole or clindamycin + vancomycin[c] *Or* piperacillin–tazobactam or imipenem–cilastatin or meropenem[b] + vancomycin[c]	

MRSA, methicillin-resistant *S. aureus*; MSSA, methicillin-susceptible *S. aureus*.

[a]Agents not shown in any particular order of preference.
[b]Not specifically recommended in IDSA guidelines but may be appropriate treatment option.
[c]Linezolid or daptomycin may be used in place of vancomycin.

TABLE 47–7	Pressure Sore Classification
Suspected deep tissue injury	Area of discolored intact skin or blood-filled blister due to damage of underlying soft tissue from pressure and/or shear. Area may be preceded by tissue that is painful, firm, mushy, boggy, warmer, or cooler as compared with adjacent tissue.
Stage 1	Pressure sore is generally reversible, is limited to the epidermis, and resembles an abrasion. Intact skin with nonblanchable redness of a localized area, usually over a bony prominence. The area may be painful, firm, soft, warmer, or cooler as compared with adjacent tissue.
Stage 2	A stage 2 sore also may be reversible; partial thickness loss of dermis presenting as a shallow open ulcer with a red pink wound bed. May also present as an intact or open/ruptured serum-filled blister or as a shiny or dry shallow ulcer.
Stage 3[a]	Full thickness tissue loss. Subcutaneous fat may be visible, but bone, tendon, or muscles are not exposed. May include undermining and tunneling. Depth of the ulcer varies by anatomical location; may range from shallow to extremely deep over areas of significant adiposity.
Stage 4[a]	Full thickness tissue loss with exposed bone, tendon, or muscle; can extend into muscle and/or supporting structures (eg, fascia, tendon, or joint capsule) making osteomyelitis possible. Often include undermining and tunneling; depth of the ulcer varies by anatomical location.
Unstageable[a]	Full thickness tissue loss in which the base of the ulcer is covered by slough (yellow, tan, gray, green, or brown) and/or eschar (tan, brown, or black) in the wound bed. True depth, and therefore stage, cannot be determined.

[a]Stage 3, Stage 4, and unstageable lesions are unlikely to resolve on their own and often require surgical intervention.

Data from Black J, Baharestani M, Cuddigan J, et al. National Pressure Ulcer Advisory Panel's updated pressure ulcer staging system. Derm Nursing 2007;19:343–349.

- Most infections are polymicrobial. Pasteurella is the most frequent isolate from both dog and cat bites.
- Wounds should be thoroughly irrigated with a sterile saline solution. Proper irrigation will reduce the bacterial count in the wound.
- The role of antimicrobials for non-infected dog bite wounds remains controversial. However, prophylactic antibiotics are generally advised unless the wound is very superficial and easily cleaned, or unless the patient presents 72 hours or more after injury and has no clinical signs of infection. Prophylaxis is more strongly recommended in patients with moderate to severe wounds, or if the wound is considered at high risk for infection.
- **Amoxicillin–clavulanic** acid is commonly recommended for oral outpatient therapy. Alternative oral agents include **moxifloxacin** or **doxycycline** alone, or **trimethoprim–sulfamethoxazole, levofloxacin, ciprofloxacin**, or a second- or third-generation cephalosporin in combination with metronidazole or clindamycin to provide activity against oropharyngeal anaerobes.
- Treatment options for patients requiring IV therapy include β-lactam–β-lactamase inhibitors (**ampicillin–sulbactam** and **piperacillin–tazobactam**), second-generation

cephalosporins with antianaerobic activity (**cefoxitin**), and **ertapenem**. Therapy should generally be continued from 7 to 14 days.

- If the immunization history of a patient with anything other than a clean minor wound is not known, tetanus/diphtheria toxoids should be administered. Both tetanus/diphtheria toxoids and tetanus immunoglobulin should be administered to patients who have never been immunized.
- If a patient has been exposed to rabies, the treatment objectives consist of thorough irrigation of the wound, tetanus prophylaxis, antibiotic prophylaxis (if indicated), and immunization. Postexposure prophylaxis immunization consists of both passive antibody administration and vaccine administration.

CAT BITES

- Approximately 20% of cat bites become infected. These infections are frequently caused by *P. multocida,* which has been isolated in the oropharynx of 50% to 70% of healthy cats.
- The management of cat bites is similar to that discussed for dog bites. Antibiotic therapy is as described for dog bites.

HUMAN BITES

- Infections can occur in 10% to 50% of patients with human bites.
- Infections caused by these injuries are most often caused by the normal oral flora, which includes both aerobic and anaerobic microorganisms. Human bite wounds are notable for potential involvement of *Eikenella corrodens* in approximately 30% of infections.
- Management of bite wounds consists of aggressive irrigation and topical wound dressing, surgical debridement, and immobilization of the affected area. Primary closure for human bites is not generally recommended. Tetanus toxoid and antitoxin may be indicated.
- Patients with noninfected bite injuries should be given prophylactic antibiotic therapy for 3 to 5 days. **Amoxicillin–clavulanic** acid (500 mg every 8 h) is commonly recommended. Alternatives for penicillin-allergic patients include fluoroquinolones or **trimethoprim–sulfamethoxazole** in combination with **clindamycin** or **metronidazole**.
- Patients with serious injuries or clenched-fist injuries should be started on IV antibiotics. Treatment options for patients requiring IV therapy include β-lactam–β-lactamase inhibitor combinations (**ampicillin–sulbactam, piperacillin–tazobactam**), second-generation cephalosporins with antianaerobic activity (eg, **cefoxitin**), and ertapenem.

See Chapter 88, Skin and Soft-Tissue Infections, authored by Douglas N. Fish and Susan L. Pendland, for a more detailed discussion of this topic.

Surgical Prophylaxis

CHAPTER 48

- Antibiotics administered before contamination of previously sterile tissues or fluids are considered prophylactic. The goal of prophylactic antibiotics is to prevent an infection from developing.
- Presumptive antibiotic therapy is administered when an infection is suspected but not yet proven. Therapeutic antibiotics are required for established infection.
- *Surgical-site infections* (SSIs) are classified as either incisional (eg, cellulitis of the incision site) or involving an organ or space (eg, with meningitis). Incisional SSIs may be superficial (skin or subcutaneous tissue) or deep (fascial and muscle layers). Both types, by definition, occur by postoperative day 30. This period extends to 1 year in the case of deep infection, associated with prosthesis implantation.

RISK FACTORS FOR SURGICAL WOUND INFECTION

- The traditional classification system developed by the National Research Council (NRC) stratifying surgical procedures by infection risk is reproduced in **Table 48–1**. The NRC wound classification for a specific procedure is determined intraoperatively and is the primary determinant of whether antibiotic prophylaxis is warranted.
- The Study on the Efficacy of Nosocomial Infection Control (SENIC) analyzed more than 100,000 surgery cases and identified abdominal operations, operations lasting more than 2 hours, contaminated or dirty procedures, and more than three underlying medical diagnoses as factors associated with an increased incidence of SSI. When the NRC classification described in **Table 48–1** was stratified by the number of SENIC risk factors present, the infection rates varied by as much as a factor of 15 within the same operative category.
- The SENIC risk assessment technique has been modified to include the American Society of Anesthesiologists preoperative assessment score (**Table 48–2**). An American Society of Anesthesiologists score greater than or equal to three was associated with increased SSI risk.

BACTERIOLOGY

- Bacteria involved in SSI are acquired either from the patient's normal flora (endogenous) or from contamination during the surgical procedure (exogenous).
- Loss of protective flora via antibiotics can upset the balance and allow pathogenic bacteria to proliferate and increase infectious risk.
- Normal flora can become pathogenic when translocated to a normally sterile tissue site or fluid during surgical procedures.
- According to the National Nosocomial Infections Surveillance System, the five most common pathogens encountered in surgical wounds are *Staphylococcus aureus*, coagulase-negative staphylococci, Enterococci, *Escherichia coli*, and *Pseudomonas aeruginosa*.
- Impaired host defenses, vascular occlusive states, traumatized tissues, and the presence of a foreign body greatly decrease the number of bacteria required to cause an SSI.

ANTIBIOTIC ISSUES

SCHEDULING ANTIBIOTIC ADMINISTRATION

- The following principles must be considered when providing antimicrobial surgical prophylaxis:
  - ✓ Antimicrobials should be delivered to the surgical site prior to the initial incision. They should be administered with anesthesia, just prior to initial incision. Antibiotics should not be prescribed to be given "on-call to the OR [operating room]."

TABLE 48–1 National Research Council Wound Classification, Risk of Surgical-Site Infection (SSI), and Indication for Antibiotics

Classification	SSI Rate (%)		Criteria	Antibiotics
	Preoperative Antibiotics	No Preoperative Antibiotics		
Clean	5.1	0.8	No acute inflammation or transection of GI, oropharyngeal, genitourinary, biliary, or respiratory tracts. Elective case, no technique break.	Not indicated unless high-risk procedure[a]
Clean-contaminated	10.1	1.3	Controlled opening of aforementioned tracts with minimal spillage/minor technique break. Clean procedures performed emergently or with major technique breaks.	Prophylactic antibiotics indicated
Contaminated	21.9	10.2	Acute, nonpurulent inflammation present. Major spillage/technique break during clean-contaminated procedure.	Prophylactic antibiotics indicated
Dirty	N/A	N/A	Obvious preexisting infections present (abscess, pus, or necrotic tissue present).	Therapeutic antibiotics required

N/A, not applicable.

[a]High-risk procedures include implantation of prosthetic materials and other procedures in which surgical-site infection is associated with high morbidity.

✓ Bactericidal antibiotic tissue concentrations should be maintained throughout the surgical procedure.

- Strategies to ensure appropriate antimicrobial prophylaxis use are described in **Table 48–3**.

ANTIMICROBIAL SELECTION

- The choice of the prophylactic antimicrobial depends on the type of surgical procedure, most likely pathogenic organisms, safety and efficacy of the antimicrobial, current literature evidence supporting its use and cost.

TABLE 48–2 American Society of Anesthesiologists Physical Status Classification

Class	Description
1	Normal healthy patient
2	Mild systemic disease
3	Severe systemic disease that is not incapacitating
4	Incapacitating systemic disease that is a constant threat to life
5	Not expected to survive 24 h with or without operation

- Typically, gram-positive coverage is included in the choice of surgical prophylaxis because organisms such as *S. aureus* and *S. epidermidis* are common skin flora.
- Parenteral antibiotic administration is favored because of its reliability in achieving suitable tissue concentrations.
- First-generation cephalosporins (particularly cefazolin) are the preferred choice, particularly for clean surgical procedures. Antianaerobic cephalosporins (eg, cefoxitin or cefotetan) are appropriate choices when broad-spectrum anaerobic and gram-negative coverage is desired.
- Vancomycin may be considered for prophylactic therapy in surgical procedures involving implantation of a prosthetic device in which the rate of methicillin-resistant *S. aureus* (MRSA) is high. If the risk of MRSA is low and a β-lactam hypersensitivity exists, clindamycin can be used instead of cefazolin in order to limit vancomycin use.

RECOMMENDATIONS FOR SPECIFIC TYPES OF SURGERIES

- Specific recommendations are summarized in **Table 48–4**.

GASTRODUODENAL SURGERY

- The risk of infection rises with conditions that increase gastric pH and subsequent bacterial overgrowth, such as obstruction, hemorrhage, malignancy, and acid-suppression therapy (clean-contaminated).

TABLE 48–3 Strategies for Implementing an Institutional Program to Ensure the Appropriate Use of Antimicrobial Prophylaxis in Surgery

1. Educate
Develop an educational program that enforces the importance and rationale of timely antimicrobial prophylaxis.
Make this educational program available to all healthcare practitioners involved in the patient's care.
2. Standardize the ordering process
Establish a protocol (eg, a preprinted order sheet) that standardizes antibiotic choice according to current published evidence, formulary availability, institutional resistance patterns, and cost.
3. Standardize the delivery and administration process
Use a system that ensures that antibiotics are prepared and delivered to the holding area in a timely fashion.
Standardize the administration time to <1 h preoperatively.
Designate responsibility and accountability for antibiotic administration.
Provide visible reminders to prescribe or administer prophylactic antibiotics (eg, checklists).
Develop a system to remind surgeons or nurses to readminister antibiotics intraoperatively during long procedures.
4. Provide feedback
Follow up with regular reports of compliance and infection rates.

TABLE 48–4 Most Likely Pathogens and Specific Recommendations for Surgical Prophylaxis

Type of Operation	Likely Pathogens	Recommended Prophylaxis Regimen[a]	Comments	Grade of Recommendation[b]
GI Surgery				
Gastroduodenal	Enteric gram-negative bacilli, gram-positive cocci, oral anaerobes	Cefazolin 1 g × 1 (see the text for recommendations for percutaneous endoscopic gastrostomy)	High-risk patients only (obstruction, hemorrhage, malignancy, acid suppression therapy, morbid obesity)	IA
Cholecystectomy	Enteric gram-negative bacilli, anaerobes	Cefazolin 1 g × 1 for high-risk patients Laparoscopic: none	High-risk patients only (acute cholecystitis, common duct stones, previous biliary surgery, jaundice, age >60 years, obesity, diabetes mellitus)	IA
Transjugular intrahepatic portosystemic shunt (TIPS)	Enteric gram-negative bacilli, anaerobes	Ceftriaxone 1 g × 1	Longer-acting cephalosporins preferred	IA
Appendectomy	Enteric gram-negative bacilli, anaerobes	Cefoxitin or cefotetan 1 g × 1	Second intraoperative dose of cefoxitin may be required if procedure lasts longer than 3 hours	IA
Colorectal	Enteric gram-negative bacilli, anaerobes	Orally: neomycin 1 g + erythromycin base 1 g at 1, 2, and 11 PM 1 day preoperatively plus mechanical bowel preparation IV: cefoxitin or cefotetan 1 g × 1	Benefits of oral plus IV is controversial except for colostomy reversal and rectal resection	IA
GI endoscopy	Variable, depending on procedure, but typically enteric gram-negative bacilli, gram-positive cocci, oral anaerobes	Orally: amoxicillin 2 g × 1 IV: ampicillin 2 g × 1 or cefazolin 1 g × 1	Recommended only for high-risk patients undergoing high-risk procedures (see the text)	IA

(*continued*)

TABLE 48–4 Most Likely Pathogens and Specific Recommendations for Surgical Prophylaxis (*Continued*)

Type of Operation	Likely Pathogens	Recommended Prophylaxis Regimen[a]	Comments	Grade of Recommendation[b]
Urologic Surgery				
Prostate resection, shock-wave lithotripsy, ureteroscopy	*Escherichia coli*	Ciprofloxacin 500 mg orally *or* Trimethoprim–sulfamethoxazole 1 DS tablet	All patients with positive preoperative urine cultures should receive a course of antibiotic treatment	IA–IB
Removal of external urinary catheters, cystography, urodynamic studies, simple cystourethroscopy	*E. coli*	Ciprofloxacin 500 mg orally *or* Trimethoprim–sulfamethoxazole 1 DS tablet	Should be considered only in patients with risk factors (see the text)	IB
Gynecological Surgery				
Cesarean section	Enteric gram-negative bacilli, anaerobes, group B streptococci, enterococci	Cefazolin 2 g × 1	Can be given before initial incision or after cord is clamped	IA
Hysterectomy	Enteric gram-negative bacilli, anaerobes, group B streptococci, enterococci	Vaginal: cefazolin 1 g × 1 Abdominal: cefotetan 1 g × 1 or cefazolin 1 g × 1	Metronidazole 1 g IV × 1 is recommended alternative for penicillin allergy	IA
Head and Neck Surgery				
Maxillofacial surgery	*Staphylococcus aureus,* streptococci oral anaerobes	Cefazolin 2 g or clindamycin 600 mg	Repeat intraoperative dose for operations longer than 4 hours	IA

Head and neck cancer resection	*S. aureus,* streptococci oral anaerobes	Clindamycin 600 mg at induction and every 8 hours × 2 more doses	Add gentamicin for clean–contaminated procedures	IA
Cardiothoracic Surgery				
Cardiac surgery	*S. aureus, Staphylococcus epidermidis, Corynebacterium*	Cefazolin 1 g every 8 hours × 48 hours	Patients >80 kg (176 lb) should receive 2 g of cefazolin instead; in areas with high prevalence of *S. aureus* resistance, vancomycin should be considered	IA
Thoracic surgery	*S. aureus, S. epidermidis, Corynebacterium,* enteric gram-negative bacilli	Cefuroxime 750 mg IV every 8 hours × 48 hours	First-generation cephalosporins are deemed inadequate, and shorter durations of prophylaxis have not been adequately studied	IA
Vascular Surgery				
Abdominal aorta and lower extremity vascular surgery	*S. aureus, S. epidermidis,* enteric gram-negative bacilli	Cefazolin 1 g at induction and every 8 hours × 2 more doses	Although complications from infections may be infrequent, graft infections are associated with significant morbidity	IB
Orthopedic Surgery				
Joint replacement	*S. aureus, S. epidermidis*	Cefazolin 1 g × 1 preoperatively, then every 8 hours × 2 more doses	Vancomycin reserved for penicillin-allergic patients or where institutional prevalence of methicillin-resistant *S. aureus* warrants use	IA
Hip fracture repair	*S. aureus, S. epidermidis*	Cefazolin 1 g × 1 preoperatively, then every 8 hours for 48 hours	Compound fractures are treated as if infection is presumed	IA
Open/compound fractures	*S. aureus, S. epidermidis,* gram-negative bacilli, polymicrobial	Cefazolin 1 g × 1 preoperatively, then every 8 hours for a course of presumed infection	Gram-negative coverage (i.e., gentamicin) often indicated for severe open fractures	IA

(*continued*)

TABLE 48–4 Most Likely Pathogens and Specific Recommendations for Surgical Prophylaxis (*Continued*)

Type of Operation	Likely Pathogens	Recommended Prophylaxis Regimen[a]	Comments	Grade of Recommendation[b]
Neurosurgery				
CSF shunt procedures	*S. aureus, S. epidermidis*	Cefazolin 1 g every 8 h × 3 doses or ceftriaxone 2 g × 1	No agents have been shown to be better than cefazolin in randomized comparative trials	IA
Spinal surgery	*S. aureus, S. epidermidis*	Cefazolin 1 g × 1	Limited number of clinical trials comparing different treatment regimens	IB
CSF shunt procedures	*S. aureus, S. epidermidis*	Cefazolin 1 g every 8 h × 3 doses or ceftriaxone 2 g × 1	No agents have been shown to be better than cefazolin in randomized comparative trials	IA
Craniotomy	*S. aureus, S. epidermidis*	Cefazolin 1 g × 1 or cefotaxime 1 g × 1	IV × 1 can be substituted for patients with penicillin allergy Trimethoprim–sulfamethoxazole (160/800 mg)	IA

CSF, cerebrospinal fluid; DS, double strength.

[a]One-time doses are optimally infused at induction of anesthesia except as noted. Repeat doses may be required for long procedures. See the text for references.
[b]Strength of recommendations:
Category IA: Strongly recommended and supported by well-designed experimental, clinical, or epidemiologic studies.
Category IB: Strongly recommended and supported by some experimental, clinical, or epidemiologic studies and strong theoretical rationale.
Category II: Suggested and supported by suggestive clinical or epidemiologic studies or theoretical rationale.

- A single dose of intravenous (IV) **cefazolin** will provide adequate prophylaxis for most cases. Oral **ciprofloxacin** may be used for patients with β-lactam hypersensitivity.
- Postoperative therapeutic antibiotics may be indicated if perforation is detected during surgery, depending on whether an established infection is present.

BILIARY TRACT SURGERY

- Antibiotic prophylaxis has been proven beneficial for surgery involving the biliary tract.
- Most frequently encountered organisms include *E. coli, Klebsiella,* and Enterococci. Single-dose prophylaxis with **cefazolin** is currently recommended. **Ciprofloxacin** and **levofloxacin** are alternatives for patients with β-lactam hypersensitivity.
- For low-risk patients undergoing elective laparoscopic cholecystectomy, antibiotic prophylaxis is of no benefit and is not recommended.
- Some surgeons use presumptive antibiotics for cases of acute cholecystitis or cholangitis and defer surgery until the patient is afebrile, in an attempt to decrease infection rates further, but this practice is controversial.
- Detection of an active infection during surgery (gangrenous gallbladder or suppurative cholangitis) is an indication for therapeutic postoperative antibiotics.

COLORECTAL SURGERY

- Anaerobes and gram-negative aerobes predominate in SSIs (see **Table 48–4**), although gram-positive aerobes are also important. Therefore, the risk of an SSI in the absence of an adequate prophylactic regimen is substantial.
- Reducing bacteria load with a thorough bowel preparation regimen (4 L of polyethylene glycol solution or 90 mL of sodium phosphate solution administered orally the day before surgery) is controversial, even though it is used by most surgeons.
- The combination of 1 g of **neomycin** and 1 g of **erythromycin base** given orally 19, 18, and 9 hours preoperatively is the most commonly used oral regimen in the United States.
- Whether perioperative parenteral antibiotics, in addition to the standard preoperative oral antibiotic regimen, will lower SSI rates further is controversial. Patients who cannot take oral medications should receive parenteral antibiotics.
- Postoperative antibiotics are unnecessary in the absence of any untoward events or findings during surgery.

APPENDECTOMY

- A cephalosporin with antianaerobic activity such as **cefoxitin** or **cefotetan** is currently recommended as a first-line agent. Cefotetan may be superior for longer operations because of its longer duration of action.
- Single-dose therapy with cefotetan is adequate. Intraoperative dosing of cefoxitin may be required if the procedure extends beyond 3 hours.

UROLOGIC PROCEDURES

- As long as the urine is sterile preoperatively, the risk of SSI after urologic procedures is low, and the benefit of prophylactic antibiotics in this setting is controversial. *E. coli* is the most frequently encountered organism.
- Antibiotic prophylaxis is warranted for all patients undergoing transurethral resection of the prostate or bladder tumors, shock wave lithotripsy, percutaneous renal surgery, or ureteroscopy.
- Specific recommendations are listed in **Table 48–4**.
- Urologic procedures requiring an abdominal approach such as a nephrectomy or cystectomy require prophylaxis appropriate for a clean-contaminated abdominal procedure.

CESAREAN SECTION

- Antibiotics are efficacious to prevent SSIs for women undergoing cesarean section regardless of underlying risk factors.

- **Cefazolin**, 2 g IV, remains the drug of choice. Providing a broader spectrum by using cefoxitin against anaerobes or piperacillin for better coverage against *Pseudomonas* or enterococci, for example, does not lower postoperative infection rates any further in comparative studies.
- The timing of antibiotic administration is controversial, as some advocate administration just after the umbilical cord is clamped, avoiding exposure of the infant to the drug, whereas others advocate administration before the initial incision.

HYSTERECTOMY

- Vaginal hysterectomies are associated with a high rate of postoperative infection when performed without the benefit of prophylactic antibiotics.
- A single preoperative dose of **cefazolin** or **cefoxitin** is recommended for vaginal hysterectomy. For patients with β-lactam hypersensitivity, a single preoperative dose of **metronidazole** or **doxycycline** is effective.
- Abdominal hysterectomy SSI rates are correspondingly lower than vaginal hysterectomy rates. However, prophylactic antibiotics are still recommended regardless of underlying risk factors.
- Both cefazolin and antianaerobic cephalosporins (eg, **cefoxitin** and **cefotetan**) have been studied extensively for abdominal hysterectomy. Single-dose cefotetan is superior to single-dose cefazolin. The antibiotic course should not exceed 24 hours in duration.

HEAD AND NECK SURGERY

- Use of prophylactic antibiotics during head and neck surgery depends on the procedure type. Clean procedures, such as parotidectomy or a simple tooth extraction, are associated with low rates of SSI. Head and neck procedures involving an incision through a mucosal layer carry a high risk of SSI.
- Specific recommendations for prophylaxis are listed in **Table 48–4**.
- Although typical doses of **cefazolin** are ineffective for anaerobic infections, the recommended 2 g dose produces concentrations high enough to be inhibitory to these organisms. A 24-hour duration has been used in most studies, but single-dose therapy may also be effective.
- For most head and neck cancer resections, 24 hours of clindamycin is appropriate.

CARDIAC SURGERY

- Although most cardiac surgeries are technically clean procedures, prophylactic antibiotics have been shown to lower rates of SSI.
- The usual pathogens are skin flora (see **Table 48–4**) and, rarely, gram-negative enteric organisms.
- Risk factors for developing an SSI after cardiac surgery include obesity, renal insufficiency, connective tissue disease, reexploration for bleeding, and poorly timed administration of antibiotics.
- **Cefazolin** has been extensively studied and is currently considered the drug of choice. Patients weighing more than 80 kg should receive 2 g cefazolin rather than 1 g. Doses should be administered no earlier than 60 minutes before the first incision and no later than the beginning of induction of anesthesia.
- Extending antibiotic administration beyond 48 hours does not lower SSI rates.
- **Vancomycin** use may be justified in hospitals with a high incidence of SSI with MRSA or when sternal wounds are to be explored for possible mediastinitis.

NONCARDIAC VASCULAR SURGERY

- Prophylactic antibiotics are beneficial, especially in procedures involving the abdominal aorta and the lower extremities.
- Twenty-four hours of prophylaxis with IV **cefazolin** is adequate. For patients with β-lactam allergy, 24 hours of oral **ciprofloxacin** is effective.

ORTHOPEDIC SURGERY

- Prophylactic antibiotics are beneficial in cases involving implantation of prosthetic material (pins, plates, and artificial joints).
- The most likely pathogens mirror those of other clean procedures and include staphylococci and, infrequently, gram-negative aerobes.
- **Cefazolin** is the best-studied antibiotic and is thus the drug of choice. For hip fracture repairs and joint replacements, it should be administered for 24 hours. **Vancomycin** is not recommended unless a patient has a history of β-lactam hypersensitivity or the propensity for MRSA infection at the institution necessitates its use.

NEUROSURGERY

- The use of prophylactic antibiotics in neurosurgery is controversial.
- Single doses of **cefazolin** or, where required, **vancomycin** appears to lower SSI risk after craniotomy.

MINIMALLY INVASIVE AND LAPAROSCOPIC SURGERY

- The role of prophylactic antimicrobials depends on the type of procedure performed and preexisting risk factors for infection. There are insufficient clinical trials to provide general recommendations.
- Patients undergoing ERCP do not need antimicrobial prophylaxis unless biliary obstruction is evident. In these situations, a single 1 g dose of cefazolin will suffice.

See Chapter 101, Antimicrobial Prophylaxis in Surgery, authored by Salmaan Kanji, for a more detailed discussion of this topic.

Tuberculosis

CHAPTER 49

- *Tuberculosis* (TB) is a communicable infectious disease caused by *Mycobacterium tuberculosis*. It can produce silent, latent infection, as well as progressive, active disease. Globally, 2 billion people are infected and roughly 2 million people die from TB each year.
- *M. tuberculosis* is transmitted from person to person by coughing or sneezing. Close contacts of TB patients are most likely to become infected.
- Human immunodeficiency virus (HIV) is the most important risk factor for active TB, especially among people 25 to 44 years of age. An HIV-infected individual with TB infection is over 100-fold more likely to develop active disease than an HIV-seronegative patient.
- Approximately 90% of patients who experience primary disease have no further clinical manifestations other than a positive skin test either alone or in combination with radiographic evidence of stable granulomas. Tissue necrosis and calcification of the originally infected site and regional lymph nodes may occur, resulting in the formation of a radiodense area referred to as a *Ghon complex*.
- Approximately 5% of patients (usually children, the elderly, or the immunocompromised) experience progressive primary disease at the site of the primary infection (usually the lower lobes) and frequently by dissemination, leading to meningitis and often to involvement of the upper lobes of the lung as well.
- Approximately 10% of patients develop reactivation disease, which arises subsequent to the hematogenous spread of the organism. In the United States, most cases of TB are believed to result from reactivation.
- Occasionally, a massive inoculum of organisms may be introduced into the bloodstream, causing widely disseminated disease and granuloma formation known as *miliary TB*.

CLINICAL PRESENTATION AND DIAGNOSIS

- The classic presentation of pulmonary TB is nonspecific, indicative only of a slowly evolving infectious process (**Table 49–1**). The onset of TB may be gradual. Physical examination is nonspecific but suggestive of progressive pulmonary disease.
- Clinical features associated with extrapulmonary TB vary depending on the organ system(s) involved but typically consist of slowly progressive decline of organ function with low-grade fever and other constitutional symptoms.
- Patients with HIV may have atypical presentation. HIV-positive patients are less likely to have positive skin tests, cavitary lesions, or fever. They have a higher incidence of extrapulmonary TB and are more likely to present with progressive primary disease.
- TB in the elderly is easily confused with other respiratory diseases. It is far less likely to present with positive skin tests, fevers, night sweats, sputum production, or hemoptysis. TB in children may present as typical bacterial pneumonia and is called **progressive primary TB**.
- The most widely used screening method for tuberculous infection is the tuberculin skin test, which uses purified protein derivative (PPD). Populations most likely to benefit from skin testing are listed in **Table 49–2**.
- The Mantoux method of PPD administration consists of the intracutaneous injection of PPD containing five tuberculin units. The test is read 48 to 72 hours after injection by measuring the diameter of the zone of induration.
- Some patients may exhibit a positive test 1 week after an initial negative test; this is referred to as a *booster effect*.
- Confirmatory diagnosis of a clinical suspicion of TB must be made via chest radiograph and microbiologic examination of sputum or other infected material to rule out active disease.

TABLE 49–1 Clinical Presentation of Tuberculosis

Signs and symptoms
Patients typically present with weight loss, fatigue, a productive cough, fever, and night sweats
Frank hemoptysis
Physical examination
Dullness to chest percussion, rales, and increased vocal fremitus are observed frequently on auscultation
Laboratory tests
Moderate elevations in the white blood cell count with a lymphocyte predominance
Diagnostic Considerations
Positive sputum smear
Fiber-optic bronchoscopy (if sputum tests are inconclusive and suspicion is high)
Chest radiograph
Patchy or nodular infiltrates in the apical area of the upper lobes or the superior segment of the lower lobes
Cavitation that may show air–fluid levels as the infection progresses

TABLE 49–2 Criteria for Tuberculin Skin Test Positivity, by Risk Group

Reaction ≥5 mm of Induration	Reaction ≥10 mm of Induration	Reaction ≥15 mm of Induration
HIV-positive persons Recent contacts of TB case patients	Recent immigrants (ie, within the last 5 years) from high-prevalence countries Injection drug users	Persons with no risk factors for TB
Fibrotic changes on chest radiograph consistent with prior TB	Residents and employees[a] of the following high-risk congregate settings: prisons and jails, nursing homes and other long-term care facilities for the elderly, hospitals and other healthcare facilities, residential facilities for patients with AIDS, and homeless shelters	
Patients with organ transplants and other immunosuppressed patients (receiving the equivalent of prednisone for ≥1 month)[b]	Mycobacteriology laboratory personnel Persons with the following clinical conditions that place them at high risk: silicosis, diabetes mellitus, chronic renal failure, some hematologic disorders (eg, leukemias and lymphomas), other specific malignancies (eg, carcinoma of the head or neck and lung), weight loss ≥10% of ideal body weight, gastrectomy, and jejunoileal bypass Children younger than 4 years or infants, children, and adolescents exposed to adults at high risk	

AIDS, acquired immunodeficiency syndrome; HIV, human immunodeficiency virus; TB, tuberculosis.

[a]For persons who are otherwise at low risk and are tested at the start of employment, a reaction ≥15 mm induration is considered positive.

[b]Risk of TB in patients treated with corticosteroids increases with higher dose and longer duration.

Adapted from Centers for Disease Control and Prevention. Screening for tuberculosis and tuberculosis infection in high-risk populations: Recommendations of the Advisory Council for the Elimination of Tuberculosis. MMWR 1995;44(No. RR-11):19–34.

- When active TB is suspected, attempts should be made to isolate *M. tuberculosis* from the infected site. Daily sputum collection over three consecutive days is recommended.
- Tests to measure release of interferon-γ in the patient's blood in response to TB antigens may provide quick and specific results for identifying *M. tuberculosis*.

TREATMENT

- Goals of Treatment: The goals are prompt resolution of signs and symptoms of disease, achievement of a noninfectious state, thus ending isolation, adherence to the treatment regimen by the patient, and cure as quickly as possible (generally with at least 6 months of treatment)
- Drug treatment is the cornerstone of TB management. A minimum of two drugs, and generally three or four drugs, must be used simultaneously. Directly observed therapy (DOT) by a healthcare worker is a cost effective way to ensure completion of treatment and is considered the standard of care.
- Drug treatment is continued for at least 6 months and up to 2 to 3 years for some cases of multidrug-resistant TB (MDR-TB).
- Patients with active disease should be isolated to prevent spread of the disease.
- Public health departments are responsible for preventing the spread of TB, finding where TB has already spread using contact investigation.
- Debilitated patients may require therapy for other medical conditions, including substance abuse and HIV infection, and some may need nutritional support.
- Surgery may be needed to remove destroyed lung tissue, space-occupying lesions, and some extrapulmonary lesions.

PHARMACOLOGIC TREATMENT

Latent Infection

- As described in **Table 49–3**, chemoprophylaxis should be initiated in patients to reduce the risk of progression to active disease.
- **Isoniazid**, 300 mg daily in adults, is the preferred treatment for latent TB in the United States, generally given for 9 months.
- **Rifampin**, 600 mg daily for 4 months, can be used when isoniazid resistance is suspected or when the patient cannot tolerate isoniazid. Rifabutin, 300 mg daily, may be substituted for rifampin for patients at high risk of drug interactions.
- The CDC recommends the 12-week isoniazid/**rifapentine** regimen as an equal alternative to 9 months of daily isoniazid for treating latent tuberculosis infection (LTBI) in otherwise healthy patients aged 12 years or older who have a predictive factor for greater likelihood of TB developing, which included recent exposure to contagious TB, conversion from negative to positive on an indirect test for infection (ie, interferon-gamma release assays [IGRA] or tuberculin skin test), and radiographic findings of healed pulmonary TB.
- Pregnant women, alcoholics, and patients with poor diets who are treated with isoniazid should receive pyridoxine, 10 to 50 mg daily, to reduce the incidence of central nervous system (CNS) effects or peripheral neuropathies.

Treating Active Disease

- **Table 49–4** lists options for treatment of culture-positive pulmonary TB caused by drug-susceptible organisms. Doses of antituberculosis drugs are given in **Table 49–5**. Other sources should be consulted for treatment recommendations when TB is concurrent with HIV infection. The standard TB treatment regimen is isoniazid, rifampin, pyrazinamide, and ethambutol for 2 months, followed by isoniazid and rifampin for 4 months. Ethambutol can be stopped if susceptibility to isoniazid, rifampin, and pyrazinamide is shown.
- Appropriate samples should be sent for culture and susceptibility testing prior to initiating therapy for all patients with active TB. The data should guide the initial drug selection for the new patient. If susceptibility data are not available, the drug resistance pattern in the area where the patient likely acquired TB should be used.

TABLE 49–3 Recommended Drug Regimens for Treatment of Latent Tuberculosis (TB) Infection in Adults

Drug	Interval and Duration	Comments	Rating[a] (Evidence)[b] HIV−	HIV+
Isoniazid	Daily for 9 months[c,d]	In HIV-infected patients, isoniazid may be administered concurrently with nucleoside reverse transcriptase inhibitors, protease inhibitors, or nonnucleoside reverse transcriptase inhibitors	A (II)	A (II)
	Twice weekly for 9 months[c,d]	Directly observed therapy must be used with twice-weekly dosing	B (II)	B (II)
Isoniazid	Daily for 6 months[d]	Not indicated for HIV-infected persons, those with fibrotic lesions on chest radiographs, or children	B (I)	C (I)
	Twice weekly for 6 months[d]	Directly observed therapy must be used with twice-weekly dosing	B (II)	B (III)
Rifampin	Daily for 4 months	For persons who are contacts of patients with isoniazid-resistant, rifampin-susceptible TB who cannot tolerate pyrazinamide	B (II)	C (I)

HIV, human immunodeficiency virus; −, negative; +, positive.

[a]Strength of recommendation: A, preferred; B, acceptable alternative; C, offer when A and B cannot be given.

[b]Quality of evidence: I, randomized clinical trial data; II, data from clinical trials that are not randomized or were conducted in other populations; III, expert opinion.

[c]Recommended regimen for children younger than 18 years.

[d]Recommended regimens for pregnant women. Some experts would use rifampin and pyrazinamide for 2 months as an alternative regimen in HIV-infected pregnant women, although pyrazinamide should be avoided during the first trimester.

Adapted from Centers for Disease Control and Prevention. Targeted tuberculin testing and treatment of latent tuberculosis infection. MMWR 2000;49(RR-6):31.

- If the patient is being evaluated for the retreatment of TB, it is imperative to know what drugs were used previously and for how long.
- Patients must complete 6 months or more of treatment. HIV-positive patients should be treated for an additional 3 months and at least 6 months from the time that they convert to smear and culture negativity. When isoniazid and rifampin cannot be used, treatment duration becomes 2 years or more, regardless of immune status.
- Patients who are slow to respond, those who remain culture positive at 2 months of treatment, those with cavitary lesions on chest radiograph, and HIV-positive patients should be treated for 9 months and for at least 6 months from the time they convert to smear and culture negativity.

DRUG RESISTANCE

- If the organism is drug resistant, the aim is to introduce two or more active agents that the patient has not received previously. With MDR-TB, no standard regimen

TABLE 49–4 Drug Regimens for Culture-Positive Pulmonary Tuberculosis Caused by Drug-Susceptible Organisms

Initial Phase			Continuation Phase				Rating[a] (Evidence)[b]	
Regimen	Drugs	Interval and Doses[c] (Minimal Duration)	Regimen	Drugs	Interval and Doses[c,d] (Minimal Duration)	Range of Total Doses (Minimal Duration)	HIV–	HIV+
1	Isoniazid, rifampin, pyrazinamide, ethambutol	Seven days per week for 56 doses (8 weeks) or 5 days/week for 40 doses (8 weeks)[c]	1a	Isoniazid/rifampin	Seven days per week for 126 doses (18 weeks) or 5 days/week for 90 doses (18 weeks)[c]	182–130 (26 weeks)	A (I)	A (II)
			1b	Isoniazid/rifampin	Twice weekly for 36 doses (18 weeks)	92–76 (26 weeks)	A (I)	A (II)[f]
			1c[g]	Isoniazid/rifapentine	Once weekly for 18 doses (18 weeks)	74–58 (26 weeks)	B (I)	E (I)
2	Isoniazid, rifampin, pyrazinamide, ethambutol	Seven days per week for 14 doses (2 weeks), then twice weekly for 12 doses (6 weeks) or 5 days/week for 10 doses (2 weeks)[e] then twice weekly for 12 doses (6 weeks)	2a	Isoniazid/rifampin	Twice weekly for 36 doses (18 weeks)	62–58 (26 weeks)	A (II)	B (II)[f]
			2b[g]	Isoniazid/rifapentine	Once weekly for 18 doses (18 weeks)	44–40 (26 weeks)	B (I)	E (I)

3	Isoniazid, rifampin, pyrazinamide, ethambutol	Three times weekly for 24 doses (8 weeks)	3a	Isoniazid/rifampin	Three times weekly for 54 doses (18 weeks)	78 (26 weeks)	B (I)	B (II)
4	Isoniazid, rifampin, ethambutol	Seven days per week for 56 doses (8 weeks) or 5 days/week for 40 doses (8 weeks)[c]	4a	Isoniazid/rifampin	Seven days per week for 217 doses (31 weeks) or 5 days/week for 155 doses (31 weeks)[e]	273–195 (39 weeks)	C (I)	C (II)
			4b	Isoniazid/rifampin	Twice weekly for 62 doses (31 weeks)	118–102 (39 weeks)	C (I)	C (II)

HIV, human immunodeficiency virus.

[a]Ratings: A, preferred; B, acceptable alternative; C, offer when A and B cannot be given; E, should never be given.
[b]Evidence ratings: I, randomized clinical trial; II, data from clinical trials that were not randomized or were conducted in other populations; III, expert opinion.
[c]When directly observed therapy is used, drugs may be given 5 days per week and the necessary number of doses adjusted accordingly. Although there are no studies that compare five with seven daily doses, extensive experience indicates this would be an effective practice.
[d]Patients with cavitation on initial chest radiograph and positive cultures at completion of 2 months of therapy should receive a 7-month (31-weeks; either 217 doses [daily] or 62 doses [twice weekly]) continuation phase.
[e]Five-day-a-week administration is always given by directly observed therapy. Rating for 5-day-per-week regimens is A (III).
[f]Not recommended for HIV-infected patients with $CD4^+$ cell counts less than 100 cells/μL [$<100 \times 10^6$/L].
[g]Options 1c and 2b should be used only in HIV-negative patients who have negative sputum smears at the time of completion of 2 months of therapy and who do not have cavitation on initial chest radiograph. For patients started on this regimen and found to have a positive culture from the 2-month specimen, treatment should be extended an extra 3 months.

From Centers for Disease Control and Prevention. Treatment of tuberculosis. MMWR 2003;52(RR-11).

TABLE 49–5 Doses[a] of Antituberculosis Drugs for Adults and Children[b]

Drug	Preparation	Adults/Children	Doses			
			Daily	1 × per week	2 × per week	3 × per week
First-line drugs						
Isoniazid	Tablets (50 mg, 100 mg, 300 mg); elixir (50 mg/5 mL); aqueous solution (100 mg/mL) for intravenous or intramuscular injection	Adults (max) Children (max)	5 mg/kg (300 mg) 10–15 mg/kg (300 mg)	15 mg/kg (900 mg) –	15 mg/kg (900 mg) 20–30 mg/kg (300 mg)	15 mg/kg (900 mg) –
Rifampin	Capsule (150 mg, 300 mg); powder may be suspended for oral administration; aqueous solution for intravenous injection	Adults[c] (max) Children (max)	10 mg/kg (600 mg) 10–20 mg/kg (600 mg)	– –	10 mg/kg (600 mg) 10–20 mg/kg (600 mg)	10 mg/kg (600 mg) –
Rifabutin	Capsule (150 mg)	Adults[c] (max) Children	5 mg/kg (300 mg) Appropriate dosing for children is unknown	– Appropriate dosing for children is unknown	5 mg/kg (300 mg) Appropriate dosing for children is unknown	5 mg/kg (300 mg) Appropriate dosing for children is unknown
Rifapentine	Tablet (150 mg, film coated)	Adults	–	10 mg/kg (continuation phase) (600 mg usual adult dose)	–	–
		Children	The drug is not approved for use in children	The drug is not approved for use in children	The drug is not approved for use in children	The drug is not approved for use in children

Pyrazinamide	Tablet (500 mg, scored)	Adults	1000 mg (40–55 kg) 1500 mg (56–75 kg) 2000 mg (76–90 kg)[j]	– – –	2000 mg (40–55 kg) 3000 mg (56–75 kg) 4000 mg (76–90 kg)[j]	1500 mg (40–55 kg) 2500 mg (56–75 kg) 3000 mg (76–90 kg)[j]
		Children (max)	15–30 mg/kg (2 g)	–	50 mg/kg (2 g)	–
Ethambutol	Tablet (100 mg, 400 mg)	Adults	800 mg (40–55 kg) 1200 mg (56–75 kg) 1600 mg (76–90 kg)[j]	– – –	2000 mg (40–55 kg) 2800 mg (56–75 kg) 4000 mg (76–90 kg)[j]	1200 mg (40–55 kg) 2000 mg (56–75 kg) 2400 mg (76–90 kg)[j]
		Children[d] (max)	15–20 mg/kg daily (1 g)	–	50 mg/kg (2.5 g)	–
Second-line drugs						
Cycloserine	Capsule (250 mg)	Adults (max)	10–15 mg/kg/day (1 g in 2 doses), usually 500–750 mg/day in 2 doses	There are no data to support intermittent administration	There are no data to support intermittent administration	There are no data to support intermittent administration
		Children (max)	10–15 mg/kg/day (1 g/day)	–	–	–
Ethionamide	Tablet (250 mg)	Adults[f] (max)	15–20 mg/kg/day (1 g/day), usually 500–750 mg/day in a single daily dose or two divided doses[f]	There are no data to support intermittent administration	There are no data to support intermittent administration	There are no data to support intermittent administration
		Children (max)	15–20 mg/kg/day (1 g/day)	There are no data to support intermittent administration	There are no data to support intermittent administration	There are no data to support intermittent administration

(*continued*)

TABLE 49–5 Doses[a] of Antituberculosis Drugs for Adults and Children[b]

			Doses			
Drug	**Preparation**	**Adults/Children**	**Daily**	**1 × per week**	**2 × per week**	**3 × per week**
Second-line drugs						
Streptomycin	Aqueous solution (1-g vials) for intravenous or intramuscular administration	Adults (max) Children (max)	g 20–40 mg/kg/day (1 g)	g –	g 20 mg/kg	g –
Amikacin/ kanamycin	Aqueous solution (500 mg and 1 g vials) for intravenous or intramuscular administration	Adults (max) Children (max)	g 15–30 mg/kg/day (1 g) intravenous or intramuscular as a single daily dose	g –	g 15–30 mg/kg	g –
Capreomycin	Aqueous solution (1 g vials) for intravenous or intramuscular administration	Adults (max) Children (max)	g 15–30 mg/kg/day (1 g) as a single daily dose	g –	15–30 mg/kg	g –
p-Amino-salicylic acid (PAS)	Granules (4 g packets) can be mixed with food; tablets (500 mg) are still available in some countries, but not in the United States; a solution for intravenous administration is available in Europe	Adults	8–12 g/day in 2 or 3 doses	There are no data to support intermittent administration	There are no data to support intermittent administration	There are no data to support intermittent administration

		Children (max)	200–300 mg/kg/day in 2–4 divided doses (10 g)	There are no data to support intermittent administration	There are no data to support intermittent administration	There are no data to support intermittent administration
Moxifloxacin[h]	Tablets (400 mg); aqueous solution (400 mg/250 mL) for intravenous injection	Adults	400 mg daily	There are no data to support intermittent administration	There are no data to support intermittent administration	There are no data to support intermittent administration

[a]Dose per weight is based on ideal body weight. Children weighing more than 40 kg should be dosed as adults.
[b]For purposes of this document, adult dosing begins at age 15 years.
[c]Dose may need to be adjusted when there is concomitant use of protease inhibitors or nonnucleoside reverse transcriptase inhibitors.
[d]The drug can likely be used safely in older children but should be used with caution in children less than 5 years of age, in whom visual acuity cannot be monitored. In younger children, ethambutol at the dose of 15 mg/kg per day can be used if there is suspected or proven resistance to isoniazid or rifampin.
[e]It should be noted that although this is the dose recommended generally, most clinicians with experience using cycloserine indicate that it is unusual for patients to be able to tolerate this amount. Serum concentration measurements are often useful in determining the optimal dose for a given patient.
[f]The single daily dose can be given at bedtime or with the main meal.
[g]Dose: 15 mg/kg per day (1 g) but 10 mg/kg in persons older than 59 years of age (750 mg). Usual dose: 750–1000 mg administered intramuscularly or intravenously, given as a single dose 5–7 days/week and reduced to two or three times per week after the first 2–4 months or after culture conversion, depending on the efficacy of the other drugs in the regimen.
[h]The long-term (more than several weeks) use of moxifloxacin in children and adolescents has not been approved because of concerns about effects on bone and cartilage growth. The optimal dose is not known.

Data from American Thoracic Society, Centers for Disease Control and Prevention, Infectious Diseases Society of America. Treatment of tuberculosis. MMWR Recomm Rep 2003;52(RR-11):1–77.

can be proposed. It is critical to avoid monotherapy or adding only a single drug to a failing regimen.
- Drug resistance should be suspected in the following situations:
  - ✓ Patients who have received prior therapy for TB
  - ✓ Patients from geographic areas with a high prevalence of resistance (South Africa, Mexico, Southeast Asia, the Baltic countries, and the former Soviet states)
  - ✓ Patients who are homeless, institutionalized, IV drug abusers, and/or infected with HIV
  - ✓ Patients who still have acid-fast bacilli–positive sputum smears after 2 months of therapy
  - ✓ Patients who still have positive cultures after 2 to 4 months of therapy
  - ✓ Patients who fail therapy or relapse after retreatment
  - ✓ Patients known to be exposed to MDR-TB cases

SPECIAL POPULATIONS

Tuberculous Meningitis and Extrapulmonary Disease

- In general, **isoniazid, pyrazinamide, ethionamide,** and **cycloserine** penetrate the cerebrospinal fluid readily. Patients with CNS TB are often treated for longer periods (9–12 months). Extrapulmonary TB of the soft tissues can be treated with conventional regimens. TB of the bone is typically treated for 9 months, occasionally with surgical debridement.

Children

- TB in children may be treated with regimens similar to those used in adults, although some physicians still prefer to extend treatment to 9 months. Pediatric doses of drugs should be used.

Pregnant Women

- The usual treatment of pregnant women is isoniazid, rifampin, and ethambutol for 9 months.
- Women with TB should be cautioned against becoming pregnant, as the disease poses a risk to the fetus as well as to the mother. Isoniazid or ethambutol is relatively safe when used during pregnancy. Supplementation with B vitamins is particularly important during pregnancy. **Rifampin** has been rarely associated with birth defects, but those seen are occasionally severe, including limb reduction and CNS lesions. **Pyrazinamide** has not been studied in a large number of pregnant women, but anecdotal information suggests that it may be safe. **Ethionamide** may be associated with premature delivery, congenital deformities, and Down syndrome when used during pregnancy, so it cannot be recommended in pregnancy. **Streptomycin** has been associated with hearing impairment in the newborn, including complete deafness and must be reserved for critical situations where alternatives do not exist. **Cycloserine** is not recommended during pregnancy. Fluoroquinolones should be avoided in pregnancy and during nursing.

Renal Failure

- In nearly all patients, isoniazid and rifampin do not require dose modifications in renal failure. Pyrazinamide and ethambutol typically require a reduction in dosing frequency from daily to three times weekly (**Table 49–6**).

EVALUATION OF THERAPEUTIC OUTCOMES AND PATIENT MONITORIG

- The most serious problem with TB therapy is nonadherence to the prescribed regimen. The most effective way to ensure adherence is with directly observed therapy.
- Patients who are who are AFB smear positive should have sputum samples sent for acid-fast bacilli stains every 1 to 2 weeks until two consecutive smears are negative. Once on maintenance therapy, patients should have sputum cultures performed monthly until negative, which generally occurs over 2 to 3 months. If sputum cultures continue to be positive after 2 months, drug susceptibility testing should be repeated, and serum drug concentrations should be checked.

TABLE 49–6 Dosing Recommendations for Adult Patients with Reduced Renal Function and for Adult Patients Receiving Hemodialysis

Drug	Change in Frequency?	Recommended Dose and Frequency for Patients with Creatinine Clearance <30 mL/min or for Patients Receiving Hemodialysis
Isoniazid	No change	300 mg once daily, or 900 mg 3 times weekly
Rifampin	No change	600 mg once daily, or 600 mg 3 times weekly
Pyrazinamide	Yes	25–35 mg/kg per dose 3 times weekly (not daily)
Ethambutol	Yes	15–25 mg/kg per dose 3 times weekly (not daily)
Levofloxacin	Yes	750–1000 mg per dose 3 times weekly (not daily)
Cycloserine	Yes	250 mg once daily, or 500 mg/dose 3 times weekly[a]
Ethionamide	No change	250–500 mg per dose daily
p-Aminosalicylic acid	No change	4 g per dose twice daily
Streptomycin	Yes	12–15 mg/kg per dose 2 or 3 times weekly (not daily)
Capreomycin	Yes	12–15 mg/kg per dose 2 or 3 times weekly (not daily)
Kanamycin	Yes	12–15 mg/kg per dose 2 or 3 times weekly (not daily)
Amikacin	Yes	12–15 mg/kg per dose 2 or 3 times weekly (not daily)

Note: Standard doses are given unless there is intolerance.

The medications should be given after hemodialysis on the day of hemodialysis. Monitoring of serum drug concentrations should be considered to ensure adequate drug absorption, without excessive accumulation, and to assist in avoiding toxicity. Data currently are not available for patients receiving peritoneal dialysis. Until data become available, begin with doses recommended for patients receiving hemodialysis and verify adequacy of dosing using serum concentration monitoring.

[a]The appropriateness of 250 mg daily doses has not been established. There should be careful monitoring for evidence of neurotoxicity.

Adapted from American Thoracic Society, Centers for Disease Control and Prevention, Infectious Diseases Society of America. Treatment of tuberculosis. MMWR Recomm Rep 2003;52(RR-11):1–77.

- Patients should have blood urea nitrogen, serum creatinine, aspartate transaminase or alanine transaminase, and a complete blood count determined at baseline and periodically, depending on the presence of other factors that may increase the likelihood of toxicity (advanced age, alcohol abuse, and possibly pregnancy). Hepatotoxicity should be suspected in patients whose transaminases exceed five times the upper limit of normal or whose total bilirubin exceeds 3 mg/dL (51.3 μmol/L). At this point, the offending agent(s) should be discontinued and alternatives selected.

See **Table 49–7** for drug monitoring recommendations.

TABLE 49–7 Antituberculosis Drug Monitoring Table

Drug	Adverse Effects	Monitoring
Isoniazid	Asymptomatic elevation of aminotransferases, clinical hepatitis, fatal hepatitis, peripheral neurotoxicity, CNS effects, lupus-like syndrome, hypersensitivity, monoamine poisoning, diarrhea	LFT monthly in patients who have preexisting liver disease or who develop abnormal liver function that does not require discontinuation of drug; dosage adjustments may be necessary in patients receiving anticonvulsants or warfarin
Rifampin	Cutaneous reactions, GI reactions (nausea, anorexia, abdominal pain), flu-like syndrome, hepatotoxicity, severe immunologic reactions, orange discoloration of bodily fluids (sputum, urine, sweat, tears), drug interactions due to induction of hepatic microsomal enzymes	Liver enzymes and interacting drugs as needed (e.g., warfarin)
Rifabutin	Hematologic toxicity, uveitis, GI symptoms, polyarthralgias, hepatotoxicity, pseudojaundice (skin discoloration with normal bilirubin), rash, flu-like syndrome, orange discoloration of bodily fluids (sputum, urine, sweat, tears)	Drug interactions are less problematic than rifampin
Rifapentine	Similar to those associated with rifampin	Drug interactions are being investigated and are likely similar to rifampin
Pyrazinamide	Hepatotoxicity, GI symptoms (nausea, vomiting), nongouty polyarthralgia, asymptomatic hyperuricemia, acute gouty arthritis, transient morbilliform rash, dermatitis	Serum uric acid can serve as a surrogate marker for adherence; LFTs in patients with underlying liver disease
Ethambutol	Retrobulbar neuritis, peripheral neuritis, cutaneous reactions	Baseline visual acuity testing and testing of color discrimination; monthly testing of visual acuity and color discrimination in patients taking >15–20 mg/kg, having renal insufficiency, or receiving the drug for >2 months
Streptomycin	Ototoxicity, neurotoxicity, nephrotoxicity	Baseline audiogram, vestibular testing, Romberg's testing, and SCr Monthly assessments of renal function and auditory or vestibular symptoms
Amikacin/kanamycin	Ototoxicity, nephrotoxicity	Baseline audiogram, vestibular testing, Romberg's testing, and SCr; monthly assessments of renal function and auditory or vestibular symptoms

TABLE 49–7 Antituberculosis Drug Monitoring Table (*Continued*)

Drug	Adverse Effects	Monitoring
Capreomycin	Nephrotoxicity, ototoxicity	Baseline audiogram, vestibular testing, Romberg's testing, and SCr Monthly assessments of renal function and auditory or vestibular symptoms Baseline and monthly serum K^+ and Mg^{2+}
p-Aminosalicylic acid	Hepatotoxicity, GI distress, malabsorption syndrome, hypothyroidism, coagulopathy	Baseline LFTs and TSH TSH every 3 months
Moxifloxacin	GI disturbance, neurologic effects, cutaneous reactions	No specific monitoring recommended

LFT, liver function test; TSH, thyroid-stimulating hormone.

Adapted from American Thoracic Society, Centers for Disease Control and Prevention, Infectious Diseases Society of America. Treatment of tuberculosis. MMWR Recomm Rep 2003;52(RR-11):1–77.

See Chapter 90, Tuberculosis, authored by Rocsanna Namdar, Michael Lauzardo, and Charles A. Peloquin, for a more detailed discussion of this topic.

Urinary Tract Infections

CHAPTER 50

- Infections of the urinary tract represent a wide variety of clinical syndromes including urethritis, cystitis, prostatitis, and pyelonephritis.
- A *urinary tract infection* (UTI) is defined as the presence of microorganisms in the urine that cannot be accounted for by contamination. The organisms have the potential to invade the tissues of the urinary tract and adjacent structures.
- Lower tract infections include cystitis (bladder), urethritis (urethra), prostatitis (prostate gland), and epididymitis. Upper tract infections involve the kidney and are referred to as *pyelonephritis*.
- Uncomplicated UTIs are not associated with structural or neurologic abnormalities that may interfere with the normal flow of urine or the voiding mechanism. Complicated UTIs are the result of a predisposing lesion of the urinary tract, such as a congenital abnormality or distortion of the urinary tract, stone, indwelling catheter, prostatic hypertrophy, obstruction, or neurologic deficit that interferes with the normal flow of urine and urinary tract defenses.
- Recurrent UTIs, two or more UTIs occurring within 6 months or three or more within 1 year, are characterized by multiple symptomatic episodes with asymptomatic periods occurring between these episodes. These infections are due to reinfection or to relapse. Reinfections are caused by a different organism and account for the majority of recurrent UTIs. Relapse represents the development of repeated infections caused by the same initial organism.

ETIOLOGY

- The most common cause of uncomplicated UTIs is *E. coli,* accounting for more than 80% to 90% of community-acquired infections. Additional causative organisms are *Staphylococcus saprophyticus* (coagulase-negative staphylococcus), *Klebsiella pneumoniae, Proteus* spp., *Pseudomonas aeruginosa,* and *Enterococcus* spp.
- The urinary pathogens in complicated or nosocomial infections may include *E. coli,* which accounts for less than 50% of these infections, *Proteus* spp., *K. pneumoniae, Enterobacter* spp., *P. aeruginosa,* staphylococci, and enterococci. Enterococci represent the second most frequently isolated organisms in hospitalized patients.
- Most UTIs are caused by a single organism; however, in patients with stones, indwelling urinary catheters, or chronic renal abscesses, multiple organisms may be isolated.

CLINICAL PRESENTATION

- The typical symptoms of lower and upper UTIs are presented in **Table 50–1**.
- Symptoms alone are unreliable for the diagnosis of bacterial UTIs. The key to the diagnosis of a UTI is the ability to demonstrate significant numbers of microorganisms present in an appropriate urine specimen to distinguish contamination from infection.
- Elderly patients frequently do not experience specific urinary symptoms, but they will present with altered mental status, change in eating habits, or gastrointestinal (GI) symptoms.
- A standard urinalysis should be obtained in the initial assessment of a patient. Microscopic examination of the urine should be performed by preparation of a Gram stain of unspun or centrifuged urine. The presence of at least one organism per oil-immersion field in a properly collected uncentrifuged specimen correlates with greater than 100,000 colony-forming units (CFU)/mL (10^5 CFU/mL) (>10^8 CFU/L) of urine.
- Criteria for defining significant bacteriuria are listed in **Table 50–2**.
- The presence of pyuria (>10 white blood cells/mm^3 [10×10^6/L]) in a symptomatic patient correlates with significant bacteriuria.

TABLE 50–1 Clinical Presentation of Urinary Tract Infections (UTIs) in Adults

Signs and symptoms
Lower UTI: dysuria, urgency, frequency, nocturia, suprapubic heaviness
Gross hematuria
Upper UTI: flank pain, fever, nausea, vomiting, malaise
Physical examination
Upper UTI: costovertebral tenderness
Laboratory tests
Bacteriuria
Pyuria (WBC >10/mm^3)[>10 x 10^6/L]
Nitrite-positive urine (with nitrite reducers)
Leukocyte esterase-positive urine
Antibody-coated bacteria (upper UTI)

WBC, white blood cell count.

TABLE 50–2 Diagnostic Criteria for Significant Bacteriuria

≥10^2 CFU coliforms/mL [>10^5 CFU/L] or ≥10^5 CFU [>10^8 CFU/L] noncoliforms/mL in a symptomatic female patient
≥10^3 CFU bacteria/mL [>10^6 CFU/L] in a symptomatic male patient
≥10^5 CFU bacteria/mL [>10^8 CFU/L] in asymptomatic individuals on two consecutive specimens
Any growth of bacteria on suprapubic catheterization in a symptomatic patient
≥10^2 CFU bacteria/mL [>10^5 CFU/L] in a catheterized patient</tb>

CFU, colony-forming unit.

- The nitrite test can be used to detect the presence of nitrate-reducing bacteria in the urine (eg, *E. coli*). The leukocyte esterase test is a rapid dipstick test to detect pyuria.
- The most reliable method of diagnosing UTIs is by quantitative urine culture. Patients with infection usually have more than 10^5 bacteria/mL [10^8/L] of urine, although as many as one third of women with symptomatic infection have less than 10^5 bacteria/mL [10^8/L].

TREATMENT

- The goals of treatment for UTIs are to eradicate the invading organisms, prevent or treat systemic consequences of infection, and prevent recurrence of infection.
- The management of a patient with a UTI includes initial evaluation, selection of an antibacterial agent and duration of therapy, and follow-up evaluation.
- The initial selection of an antimicrobial agent for the treatment of UTI is primarily based on the severity of the presenting signs and symptoms, the site of infection, and whether the infection is determined to be complicated or uncomplicated.

PHARMACOLOGIC TREATMENT

- The ability to eradicate bacteria from the urinary tract is directly related to the sensitivity of the organism and the achievable concentration of the antimicrobial agent in the urine.
- The therapeutic management of UTIs is best accomplished by first categorizing the type of infection: acute uncomplicated cystitis, symptomatic abacteriuria, asymptomatic bacteriuria, complicated UTIs, recurrent infections, or prostatitis.

- **Table 50–3** lists the most common agents used in the treatment of UTIs, along with comments concerning their general use.
- **Table 50–4** presents an overview of various therapeutic options for outpatient therapy for UTI.
- **Table 50–5** describes empiric treatment regimens for specific clinical situations.

Acute Uncomplicated Cystitis

- These infections are predominantly caused by *E. coli,* and antimicrobial therapy should be directed against this organism initially. Because the causative organisms and their susceptibilities are generally known, a cost-effective approach to management is recommended that includes a urinalysis and initiation of empiric therapy without a urine culture (**Fig. 50–1**).
- Short-course therapy (3-day therapy) with **trimethoprim–sulfamethoxazole** or a **fluoroquinolone** (eg, **ciprofloxacin** or **levofloxacin,** but not moxifloxacin) is superior to single-dose therapy for uncomplicated infection. Fluoroquinolones should be reserved for patients with suspected or possible pyelonephritis due to the collateral damage risk. Instead, a 3-day course of trimethoprim–sulfamethoxazole, a 5-day course of nitrofurantoin, or a one-time dose of fosfomycin should be considered as first-line therapy. In areas where there is more than 20% resistance of *E. coli* to trimethoprim–sulfamethoxazole, nitrofurantoin or fosfomycin should be utilized. Amoxicillin or ampicillin is not recommended because of the high incidence of resistant *E. coli*. Follow-up urine cultures are not necessary in patients who respond.

Complicated Urinary Tract Infections

ACUTE PYELONEPHRITIS

- The presentation of high-grade fever (>38.3°C [100.9°F]) and severe flank pain should be treated as acute pyelonephritis, and aggressive management is warranted. Severely ill patients with pyelonephritis should be hospitalized and IV drugs administered initially. Milder cases may be managed with oral antibiotics in an outpatient setting.
- At the time of presentation, a Gram stain of the urine should be performed, along with urinalysis, culture, and sensitivities.
- In the mild to moderately symptomatic patient for whom oral therapy is considered, an effective agent should be administered for 7 to 14 days, depending on the agent used. Fluoroquinolones (ciprofloxacin or levofloxacin) orally for 7 to 10 days are the first-line choice in mild to moderate pyelonephritis. Other options include trimethoprim–sulfamethoxazole for 14 days. If a Gram stain reveals gram-positive cocci, *Streptococcus faecalis* should be considered and treatment directed against this pathogen (**ampicillin**).
- In the seriously ill patient, the traditional initial therapy is an IV **fluoroquinolone**, an **aminoglycoside** with or without **ampicillin**, or an extended-spectrum **cephalosporin** with or without an aminoglycoside.
- If the patient has been hospitalized in the last 6 months, has a urinary catheter, or is in a nursing home, the possibility of *P. aeruginosa* and *enterococci* infection, as well as multiple-resistant organisms, should be considered. In this setting, **ceftazidime, ticarcillin–clavulanic acid, piperacillin, aztreonam, meropenem,** or **imipenem,** in combination with an **aminoglycoside**, is recommended. If the patient responds to initial combination therapy, the aminoglycoside may be discontinued after 3 days.
- Follow-up urine cultures should be obtained 2 weeks after the completion of therapy to ensure a satisfactory response and to detect possible relapse.

URINARY TRACT INFECTIONS IN MEN

- The conventional view is that therapy in men requires prolonged treatment (**Fig. 50–2**).
- A urine culture should be obtained before treatment, because the cause of infection in men is not as predictable as in women.
- If gram-negative bacteria are presumed, **trimethoprim–sulfamethoxazole** or a **fluoroquinolone** is a preferred agent. Initial therapy is for 10 to 14 days. For recurrent

TABLE 50–3 Commonly Used Antimicrobial Agents in the Treatment of Urinary Tract Infections

Drug	Brand Name	Adverse Drug Reactions	Monitoring Parameters	Comments
Oral Therapy				
Trimethoprim–sulfamethoxazole	Bactrim®, Septra®	Rash, Stevens–Johnson Syndrome, renal failure, photosensitivity, hematologic (neutropenia, anemia, etc.)	Serum creatinine, BUN, electrolytes, signs of rash, and CBC	This combination is highly effective against most aerobic enteric bacteria except *P. aeruginosa*. High urinary tract tissue concentrations and urine concentrations are achieved, which may be important in complicated infection treatment. Also effective as prophylaxis for recurrent infections
Nitrofurantoin	Macrobid®	GI intolerance, neuropathies, and pulmonary reactions	Baseline serum creatinine and BUN	This agent is effective as both therapeutic and prophylactic agents in patients with recurrent UTIs. Main advantage is the lack of resistance even after long courses of therapy
Fosfomycin	Monurol®	Diarrhea, headache, and angioedema	No routine tests recommended	Single-dose therapy for uncomplicated infections, low levels of resistance, use with caution in patients with hepatic dysfunction
Fluoroquinolones				
Ciprofloxacin Levofloxacin	Cipro® Levaquin®	Hypersensitivity, photosensitivity, GI symptoms, dizziness, confusion, and tendonitis (black box warning)	CBC, baseline serum creatinine, and BUN	The fluoroquinolones have a greater spectrum of activity, including *P. aeruginosa*. These agents are effective for pyelonephritis and prostatitis. Avoid in pregnancy and children. Moxifloxacin should not be used owing to inadequate urinary concentrations
Penicillins				
Amoxicillin–clavulanate	Augmentin®	Hypersensitivity (rash, anaphylaxis), diarrhea, superinfections, and seizures	CBC, signs of rash, or hypersensitivity	Due to increasing *E. coli* resistance, amoxicillin–clavulanate is the preferred penicillin for uncomplicated cystitis

(*continued*)

TABLE 50–3 Commonly Used Antimicrobial Agents in the Treatment of Urinary Tract Infections (*Continued*)

Drug	Brand Name	Adverse Drug Reactions	Monitoring Parameters	Comments
Cephalosporins				
Cefdnir	Omnicef®	Hypersensitivity (rash, anaphylaxis), diarrhea, superinfections, and seizures	CBC, signs of rash, or hypersensitivity	There are no major advantages of these agents over other agents in the treatment of UTIs, and they are more expensive. These agents are not active against enterococci
Cefpodoxime-proxetil	Vantin®			
Parenteral Therapy				
Aminoglycosides				
Gentamicin	Garamycin®	Ototoxicity, nephrotoxicity	Serum creatinine and BUN, serum drug concentrations, and individual pharmacokinetic monitoring	These agents are renally excreted and achieve good concentrations in the urine. Amikacin generally is reserved for multidrug-resistant bacteria
Tobramycin	Nebcin®			
Amikacin	Amikin®			
Penicillins				
Ampicillin–sulbactam	Unasyn®	Hypersensitivity (rash, anaphylaxis), diarrhea, superinfections, and seizures	CBC, signs of rash, or hypersensitivity	These agents generally are equally effective for susceptible bacteria. The extended-spectrum penicillins are more active against *P. aeruginosa* and *enterococci* and often are preferred over cephalosporins. They are very useful in renally impaired patients or when an aminoglycoside is to be avoided
Piperacillin–tazobactam	Zosyn®			
Cephalosporins				
Ceftriaxone	Rocephin®	Hypersensitivity (rash, anaphylaxis), diarrhea, superinfections, and seizures	CBC, signs of rash, or hypersensitivity	Second- and third-generation cephalosporins have a broad spectrum of activity against gram-negative bacteria, but are not active against *enterococci* and have limited activity against *P. aeruginosa*. Ceftazidime and cefepime are active against *P. aeruginosa*. They are useful for nosocomial infections and urosepsis due to susceptible pathogens
Ceftazidime	Fortaz®			
Cefepime	Maxipime®			

Carbapenems/Monobactams				
Imipenem–cilistatin	Primaxin®	Hypersensitivity (rash, anaphylaxis), diarrhea, superinfections, and seizures	CBC, signs of rash, or hypersensitivity	Carbapenems have a broad spectrum of activity, including gram-positive, gram-negative, and anaerobic bacteria. Imipenem, meropenem, and doripenem are active against *P. aeruginosa* and enterococci, but ertapenem is not. Aztreonam is a monobactam that is only active against gram-negative bacteria, including some strains of *P. aeruginosa*. Generally useful for nosocomial infections when aminoglycosides are to be avoided and in penicillin-sensitive patients
Meropenem	Merrem®			
Doripenem	Doribax®			
Ertapenem	Invanz®			
Aztreonam	Azactam®			
Fluoroquinolones				
Ciprofloxacin	Cipro®	Hypersensitivity, photosensitivity, GI symptoms, dizziness, confusion, and tendonitis (black box warning)	CBC, baseline serum creatinine, and BUN	These agents have broad-spectrum activity against both gram-negative and gram-positive bacteria. They provide urine and high-tissue concentrations and are actively secreted in reduced renal function
Levofloxacin	Levaquin®			

TABLE 50–4 Overview of Outpatient Antimicrobial Therapy for Lower Tract Infections in Adults

Indications	Antibiotic	Dose[a]	Interval	Duration
Lower tract infections				
Uncomplicated	Trimethoprim–sulfamethoxazole	1 DS tablet	Twice a day	3 days
	Nitrofurantoin monohydrate	100 mg	Twice a day	5 days
	Fosfomycin	3 g	Single dose	1 day
	Ciprofloxacin	250 mg	Twice a day	3 days
	Levofloxacin	250 mg	Once a day	3 days
	Amoxicillin–clavulanate	500 mg	Every 8 hours	5–7 days
Complicated	Trimethoprim–sulfamethoxazole	1 DS tablet	Twice a day	7–10 days
	Ciprofloxacin	250–500 mg	Twice a day	7–10 days
	Levofloxacin	250 mg	Once a day	10 days
		750 mg	Once a day	5 days
	Amoxicillin–clavulanate	500 mg	Every 8 hours	7–10 days
Recurrent infections	Nitrofurantoin	50 mg	Once a day	6 months
	Trimethoprim–sulfamethoxazole	1/2 SS tablet	Once a day	6 months
Acute pyelonephritis	Trimethoprim–sulfamethoxazole	1 DS tablet	Twice a day	14 days
	Ciprofloxacin	500 mg	Twice a day	14 days
		1000 mg ER	Once a day	7 days
	Levofloxacin	250 mg	Once a day	10 days
		750 mg	Once a day	5 days
	Amoxicillin–clavulanate	500 mg	Every 8 hours	14 days

DS, double strength; SS, single strength.

[a]Dosing intervals for normal renal function.

infections in men, cure rates are much higher with a 6-week regimen of **trimethoprim– sulfamethoxazole**.

Recurrent Infections

- Recurrent episodes of UTI (reinfections and relapses) account for a significant portion of all UTIs. These patients are most commonly women and can be divided into two groups: those with fewer than two or three episodes per year and those who develop more frequent infections.
- In patients with infrequent infections (ie, fewer than three infections per year), each episode should be treated as a separately occurring infection. Short-course therapy should be used in symptomatic female patients with lower tract infection.
- In patients who have frequent symptomatic infections, long-term prophylactic antimicrobial therapy may be instituted (see **Table 50–4**). Therapy is generally given for 6 months, with urine cultures followed periodically.
- In women who experience symptomatic reinfections in association with sexual activity, voiding after intercourse may help prevent infection. Also, self-administered,

TABLE 50–5 Evidence-Based Empirical Treatment of Urinary Tract Infections and Prostatitis

Diagnosis	Pathogens	Treatment Recommendation	Comments
Acute uncomplicated cystitis	*Escherichia coli*, *Staphylococcus saprophyticus*	1. Nitrofurantoin × 5 days (A, I)[a] 2. Trimethoprim–sulfamethoxazole × 3 days (A, I)[a] 3. Fosfomycin × 1 dose (A, I)[a] 4. Fluoroquinolone × 3 days (A, I)[a] 5. β-Lactams × 3–7 days (B, I)[a]	Short-course therapy more effective than single dose Reserve fluoroquinolones as alternatives to development of resistance (A-III)[a] *β*-Lactams as a group are not as effective in acute cystitis then trimethoprim–sulfamethoxazole or the fluoroquinolones, do not use amoxicillin or ampicillin[a]
Pregnancy	As above	1. Amoxicillin–clavulanate × 7 days 2. Cephalosporin × 7 days 3. Trimethoprim–sulfamethoxazole × 7 days	Avoid trimethoprim–sulfamethoxazole during the third trimester
Acute pyelonephritis			
Uncomplicated	*E. coli*	1. Quinolone × 7 days (A, I)[a] 2. Trimethoprim–sulfamethoxazole (if susceptible) × 14 days (A, I)[a]	Can be managed as outpatient
Complicated	Gram-positive bacteria *E. coli* *P. mirabilis* *K. pneumoniae* *P. aeruginosa* *Enterococcus faecalis*	1. Amoxicillin or amoxicillin–clavulanic acid × 14 days 2. Quinolone × 14 days 3. Extended-spectrum penicillin plus aminoglycoside	Severity of illness will determine duration of IV therapy; culture results should direct therapy Oral therapy may complete 14 days of therapy
Prostatitis	*E. coli* *K. pneumoniae* *Proteus* spp. *P. aeruginosa*	1. Trimethoprim–sulfamethoxazole × 4–6 weeks 2. Quinolone × 4–6 weeks	Acute prostatitis may require IV therapy initially Chronic prostatitis may require longer treatment periods or surgery

[a]Strength of recommendations: A, good evidence for; B, moderate evidence for; C, poor evidence for and against; D, moderate against; E, good evidence against. Quality of evidence: I, at least one proper randomized, controlled study; II, one well-designed clinical trial; III, evidence from opinions, clinical experience, and expert committees.

Data from reference 1.

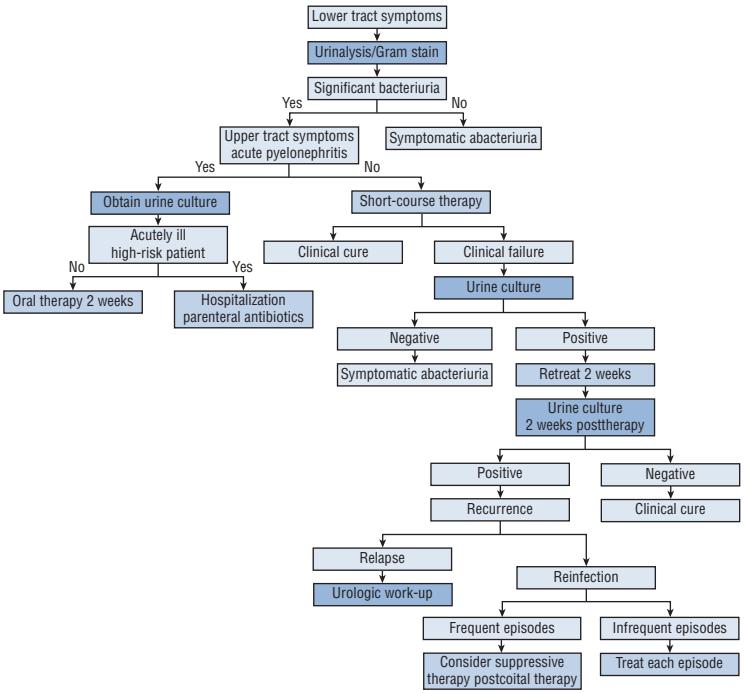


FIGURE 50–1. Management of urinary tract infections in women.

single-dose prophylactic therapy with **trimethoprim–sulfamethoxazole** taken after intercourse significantly reduces the incidence of recurrent infection in these patients.

- Women who relapse after short-course therapy should receive a 2-week course of therapy. In patients who relapse after 2 weeks, therapy should be continued for another 2 to 4 weeks. If relapse occurs after 6 weeks of treatment, urologic examination should be performed, and therapy for 6 months or even longer may be considered.

SPECIAL CONDITIONS

Urinary Tract Infection in Pregnancy

- In patients with significant bacteriuria, symptomatic or asymptomatic treatment is recommended to avoid possible complications during the pregnancy. Therapy should consist of an agent with a relatively low adverse-effect potential (**cephalexin, amoxicillin, or amoxicillin/clavulanate**) administered for 7 days.
- Tetracyclines should be avoided because of teratogenic effects and sulfonamides should not be administered during the third trimester because of the possible development of kernicterus and hyperbilirubinemia. Also, the fluoroquinolones should not be given because of their potential to inhibit cartilage and bone development in the newborn.

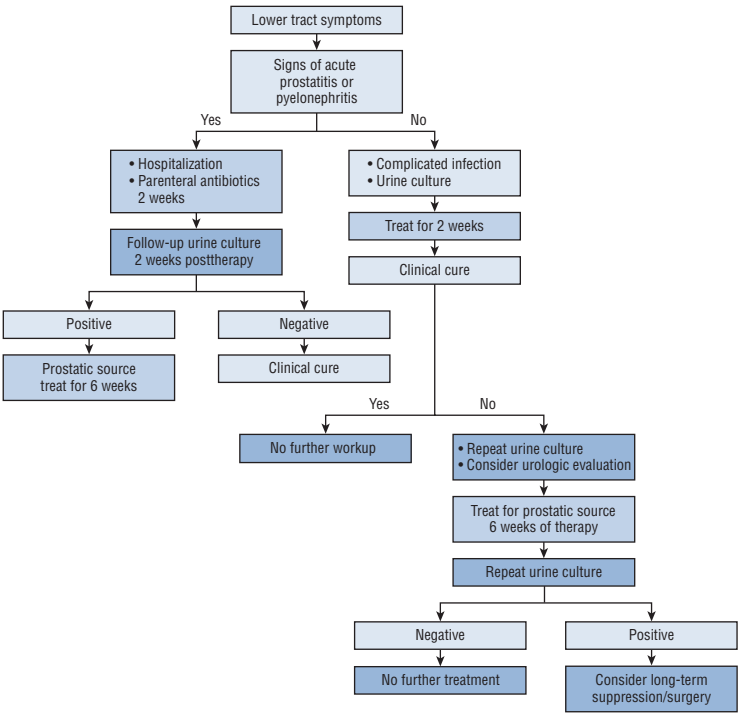


FIGURE 50–2. Management of urinary tract infections in men.

Catheterized Patients

- When bacteriuria occurs in the asymptomatic, short-term catheterized patient (<30 days), the use of systemic antibiotic therapy should be withheld and the catheter removed as soon as possible. If the patient becomes symptomatic, the catheter should again be removed, and treatment as described for complicated infections should be started.
- The use of prophylactic systemic antibiotics in patients with short-term catheterization reduces the incidence of infection over the first 4 to 7 days. In long-term catheterized patients, however, antibiotics only postpone the development of bacteriuria and lead to emergence of resistant organisms.

See Chapter 94, Urinary Tract Infections and Prostatitis, authored by Elizabeth A. Coyle and Randall A. Prince, for a more detailed discussion of this topic.

Vaccines, Toxoids, and Other Immunobiologics

51 CHAPTER

- *Vaccines* are substances administered to generate a protective immune response. They can be live attenuated or killed.
- *Toxoids* are inactivated bacterial toxins. They retain the ability to stimulate the formation of antitoxins, which are antibodies directed against the bacterial toxin.
- *Adjuvants* are inert substances, such as aluminum salts (ie, alum), which enhance vaccine antigenicity by prolonging antigen absorption.
- *Immune sera* are sterile solutions containing antibody derived from human (immunoglobulin [Ig]) or equine (antitoxin) sources.

VACCINE AND TOXOID RECOMMENDATIONS

- The recommended schedules for routine immunization of children (and adolescents) and adults are shown in **Tables 51–1** and **51–2**, respectively. The catch-up schedule for persons 4 months to 18 years of age is shown in **Table 51–3**.
- In general, killed vaccines can be administered simultaneously at separate sites. Killed and live-attenuated vaccines may be administered simultaneously at separate sites. If they cannot be administered simultaneously, they can be administered at any interval between doses with the exception of cholera (killed) and yellow fever (live) vaccines, which should be given at least 3 weeks apart. If live vaccines are not administered simultaneously, their administration should be separated by at least 4 weeks.
- Administration of live vaccines, such as rubella or varicella, are deferred until postpartum and are routinely recommended for new mothers who do not have evidence of immunity prior to hospital discharge. These live vaccines can be administered without regard to administration of Rho(D) Ig (RDIg) in the postpartum period. Additionally, Tdap is recommended for all new mothers who have not received a Tdap before because household contacts are frequently implicated as the source of pertussis infection in a young infant.
- In general, severely immunocompromised individuals should not receive live vaccines.
- Patients with chronic conditions that cause limited immunodeficiency (eg, renal disease, diabetes, liver disease, and asplenia) and who are not receiving immunosuppressants may receive live-attenuated and killed vaccines, as well as toxoids.
- Patients with active malignant disease may receive killed vaccines or toxoids but should not be given live vaccines. Live virus vaccines may be administered to persons with leukemia who have not received chemotherapy for at least 3 months.
- If a person has been receiving high-dose corticosteroids or has had a course lasting longer than 2 weeks, then at least 1 month should pass before immunization with live virus vaccines.
- Responses to live and killed vaccines generally are suboptimal for human immunodeficiency virus (HIV)–infected patients and decrease as the disease progresses.
- General contraindications to vaccine administration include a history of anaphylactic reaction to a previous dose or an unexplained encephalopathy occurring within 7 days of a dose of pertussis vaccine. Immunosuppression and pregnancy are temporary contraindications to live vaccines.
- Whenever possible, transplant patients should be immunized before transplantation. Live vaccines generally are not given after transplantation.

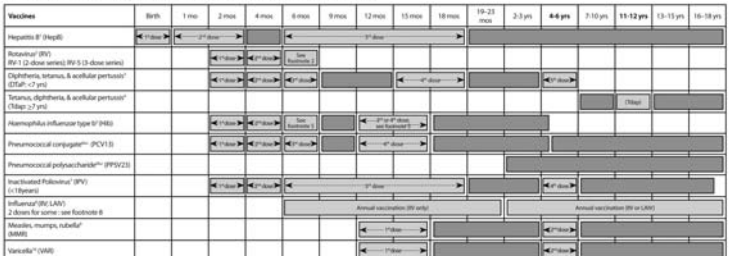
DIPHTHERIA TOXOID ADSORBED AND DIPHTHERIA ANTITOXIN

- Two strengths of diphtheria toxoid are available: pediatric (D) and adult, which contains less antigen. Primary immunization with D is indicated for children

TABLE 51–1 2012 Childhood and Adolescent Immunization Schedule

Figure 1. Recommended immunization schedule for persons aged 0 through 18 years—2013.
(FOR THOSE WHO FALL BEHIND OR START LATE, SEE THE CATCH-UP SCHEDULE (FIGURE 2)).

These recommendations must be read with the footnotes that follow. For those who fall behind or start late, provide catch-up vaccination at the earliest opportunity as indicated by the green bars in Figure 1. To determine minimum intervals between doses, see the catch-up schedule (Figure 2). School entry and adolescent vaccine age groups are in bold.



This schedule includes recommendations in effect as of January 1, 2013. Any dose not administered at the recommended age should be administered at a subsequent visit, when indicated and feasible. The use of a combination vaccine generally is preferred over separate injections of its equivalent component vaccines. Vaccination providers should consult the relevant Advisory Committee on Immunization Practices (ACIP) statement for detailed recommendations, available online at http://www.cdc.gov/vaccines/pubs/acip-list.htm. Clinically significant adverse events that follow vaccination should be reported to the Vaccine Adverse Event Reporting System (VAERS) online (http://www.vaers.hhs.gov) or by telephone (800-822-7967). Suspected cases of vaccine-preventable diseases should be reported to the state or local health department. Additional information, including precautions and contraindications for vaccination, is available from CDC online (http://www.cdc.gov/vaccines) or by telephone (800-CDC-INFO [800-232-4636]).

This schedule is approved by the Advisory Committee on Immunization Practices (http://www.cdc.gov/vaccines/acip/index.html), the American Academy of Pediatrics (http://www.aap.org), the American Academy of Family Physicians (http://www.aafp.org), and the American College of Obstetricians and Gynecologists (http://www.acog.org).

NOTE: The above recommendations must be read along with the footnotes of this schedule.

Footnotes — Recommended immunization schedule for persons aged 0 through 18 years—United States, 2013

For further guidance on the use of the vaccines mentioned below, see: http://www.cdc.gov/vaccines/pubs/acip-list.htm.

1. **Hepatitis B (HepB) vaccine. (Minimum age: birth)**
   Routine vaccination:
   At birth
   - Administer monovalent HepB vaccine to all newborns before hospital discharge.
   - For infants born to hepatitis B surface antigen (HBsAg)–positive mothers, administer HepB vaccine and 0.5 mL of hepatitis B immune globulin (HBIG) within 12 hours of birth. These infants should be tested for HBsAg and antibody to HBsAg (anti-HBs) 1 to 2 months after completion of the HepB series, at age 9 through 18 months (preferably at the next well-child visit).
   - If mother's HBsAg status is unknown, within 12 hours of birth administer HepB vaccine to all infants regardless of birth weight. For infants weighing <2,000 grams, administer HBIG in addition to HepB within 12 hours of birth. Determine mother's HBsAg status as soon as possible and, if she is HBsAg-positive, also administer HBIG for infants weighing ≥2,000 grams (no later than age 1 week).

   Doses following the birth dose
   - The second dose should be administered at age 1 or 2 months. Monovalent HepB vaccine should be used for doses administered before age 6 weeks.
   - Infants who did not receive a birth dose should receive 3 doses of a HepB-containing vaccine on a schedule of 0, 1 to 2 months, and 6 months starting as soon as feasible. See Figure 2.
   - The minimum interval between dose 1 and dose 2 is 4 weeks and between dose 2 and 3 is 8 weeks. The final (third or fourth) dose in the HepB vaccine series should be administered no earlier than age 24 weeks, and at least 16 weeks after the first dose.
   - Administration of a total of 4 doses of HepB vaccine is recommended when a combination vaccine containing HepB is administered after the birth dose.

   Catch-up vaccination:
   - Unvaccinated persons should complete a 3-dose series.
   - A 2-dose series (doses separated by at least 4 months) of adult formulation Recombivax HB is licensed for use in children aged 11 through 15 years.
   - For other catch-up issues, see Figure 2.
2. **Rotavirus (RV) vaccines. (Minimum age: 6 weeks for both RV-1 [Rotarix] and RV-5 [RotaTeq]).**
   Routine vaccination:
   - Administer a series of RV vaccine to all infants as follows:
     1. If RV-1 is used, administer a 2-dose series at 2 and 4 months of age.
     2. If RV-5 is used, administer a 3-dose series at ages 2, 4, and 6 months.
     3. If any dose in series was RV-5 or vaccine product is unknown for any dose in the series, a total of 3 doses of RV vaccine should be administered.

   Catch-up vaccination:
   - The maximum age for the first dose in the series is 14 weeks, 6 days.
   - Vaccination should not be initiated for infants aged 15 weeks 0 days or older.
   - The maximum age for the final dose in the series is 8 months, 0 days.
   - If RV-1 (Rotarix) is administered for the first and second doses, a third dose is not indicated.
   - For other catch-up issues, see Figure 2.
3. **Diphtheria and tetanus toxoids and acellular pertussis (DTaP) vaccine. (Minimum age: 6 weeks)**
   Routine vaccination:
   - Administer a 5-dose series of DTaP vaccine at ages 2, 4, 6, 15–18 months, and 4 through 6 years. The fourth dose may be administered as early as age 12 months, provided at least 6 months have elapsed since the third dose.

   Catch-up vaccination:
   - The fifth (booster) dose of DTaP vaccine is not necessary if the fourth dose was administered at age 4 years or older.
   - For other catch-up issues, see Figure 2.
4. **Tetanus and diphtheria toxoids and acellular pertussis (Tdap) vaccine. (Minimum age: 10 years for Boostrix, 11 years for Adacel).**
   Routine vaccination:
   - Administer 1 dose of Tdap vaccine to all adolescents aged 11 through 12 years.
   - Tdap can be administered regardless of the interval since the last tetanus and diphtheria toxoid-containing vaccine.
   - Administer one dose of Tdap vaccine to pregnant adolescents during each pregnancy (preferred during 27 through 36 weeks gestation) regardless of number of years from prior Td or Tdap vaccination.

   Catch-up vaccination:
   - Persons aged 7 through 10 years who are not fully immunized with the childhood DTaP vaccine series, should receive Tdap vaccine as the first dose in the catch-up series; if additional doses are needed, use Td vaccine. For these children, an adolescent Tdap vaccine should not be given.
   - Persons aged 11 through 18 years who have not received Tdap vaccine should receive a dose followed by tetanus and diphtheria toxoids (Td) booster doses every 10 years thereafter.
   - An inadvertent dose of DTaP vaccine administered to children aged 7 through 10 years can count as part of the catch-up series. This dose can count as the adolescent Tdap dose, or the child can later receive a Tdap booster dose at age 11–12 years.
   - For other catch-up issues, see Figure 2.
5. ***Haemophilus influenzae* type b (Hib) conjugate vaccine. (Minimum age: 6 weeks)**
   Routine vaccination:
   - Administer a Hib vaccine primary series and a booster dose to all infants. The primary series doses should be administered at 2, 4, and 6 months of age; however, if PRP-OMP (PedvaxHIB or Comvax) is administered at 2 and 4 months of age, a dose at age 6 months is not indicated. One booster dose should be administered at age 12 through15 months.
   - Hiberix (PRP-T) should only be used for the booster (final) dose in children aged 12 months through 4 years, who have received at least 1 dose of Hib.

   Catch-up vaccination:
   - If dose 1 was administered at ages 12-14 months, administer booster (as final dose) at least 8 weeks after dose 1.
   - If the first 2 doses were PRP-OMP (PedvaxHIB or Comvax), and were administered at age 11 months or younger, the third (and final) dose should be administered at age 12 through 15 months and at least 8 weeks after the second dose.
   - If the first dose was administered at age 7 through 11 months, administer the second dose at least 4 weeks later and a final dose at age 12 through 15 months, regardless of Hib vaccine (PRP-T or PRP-OMP) used for first dose.
   - For unvaccinated children aged 15 months or older, administer only 1 dose.

older than 6 weeks. Generally, D is given along with tetanus and acellular pertussis (DTaP) vaccines at 2, 4, and 6 months of age, and then at 15 to 18 months and 4 to 6 years of age.

- For nonimmunized adults, a complete three-dose series of diphtheria toxoid should be administered, with the first two doses given at least 4 weeks apart and the third dose 6 to 12 months after the second. One dose in the series should be Tdap. The combined preparation, tetanus–diphtheria (Td), is recommended in adults because it contains less diphtheria toxoid than DTaP, with fewer reactions seen from the diphtheria preparation. Booster doses are given every 10 years.

TABLE 51–1 2012 Childhood and Adolescent Immunization Schedule (*Continued*)



For further guidance on the use of the vaccines mentioned below, see: http://www.cdc.gov/vaccines/pubs/acip-list.htm.

- For other catch-up issues, see Figure 2.

Vaccination of persons with high-risk conditions:

- Hib vaccine is not routinely recommended for patients older than 5 years of age. However one dose of Hib vaccine should be administered to unvaccinated or partially vaccinated persons aged 5 years or older who have leukemia, malignant neoplasms, anatomic or functional asplenia (including sickle cell disease), human immunodeficiency virus (HIV) infection, or other immunocompromising conditions.

6a. Pneumococcal conjugate vaccine (PCV). (Minimum age: 6 weeks)

Routine vaccination:

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

Catch-up vaccination:

- Administer 1 dose of PCV13 to all healthy children aged 24 through 59 months who are not completely vaccinated for their age.
- For other catch-up issues, see Figure 2.

Vaccination of persons with high-risk conditions:

- For children aged 24 through 71 months with certain underlying medical conditions (see footnote 6c), administer 1 dose of PCV13 if 3 doses of PCV were received previously, or administer 2 doses of PCV13 at least 8 weeks apart if fewer than 3 doses of PCV were received previously.
- A single dose of PCV13 may be administered to previously unvaccinated children aged 6 through 18 years who have anatomic or functional asplenia (including sickle cell disease), HIV infection or an immunocompromising condition, cochlear implant or cerebrospinal fluid leak. See MMWR 2010;59 (No. RR-11), available at http://www.cdc.gov/mmwr/pdf/rr/rr5911.pdf.
- Administer PPSV23 at least 8 weeks after the last dose of PCV to children aged 2 years or older with certain underlying medical conditions (see footnotes 6b and 6c).

6b. Pneumococcal polysaccharide vaccine (PPSV23). (Minimum age: 2 years)

Vaccination of persons with high-risk conditions:

- Administer PPSV23 at least 8 weeks after the last dose of PCV to children aged 2 years or older with certain underlying medical conditions (see footnote 6c). A single revaccination with PPSV should be administered after 5 years to children with anatomic or functional asplenia (including sickle cell disease) or an immunocompromising condition.

6c. Medical conditions for which PPSV23 is indicated in children aged 2 years and older and for which use of PCV13 is indicated in children aged 24 through 71 months:

- Immunocompetent children with chronic heart disease (particularly cyanotic congenital heart disease and cardiac failure); chronic lung disease (including asthma if treated with high-dose oral corticosteroid therapy); diabetes mellitus; cerebrospinal fluid leaks; or cochlear implant.
- Children with anatomic or functional asplenia (including sickle cell disease and other hemoglobinopathies, congenital or acquired asplenia, or splenic dysfunction).
- Children with immunocompromising conditions: HIV infection, chronic renal failure and nephrotic syndrome, diseases associated with treatment with immunosuppressive drugs or radiation therapy, including malignant neoplasms, leukemias, lymphomas and Hodgkin disease; or solid organ transplantation, congenital immunodeficiency.

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

Routine vaccination:

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

Catch-up vaccination:

- In the first 6 months of life, minimum age and minimum intervals are only recommended if the person is at risk for imminent exposure to circulating poliovirus (ie, travel to a polio-endemic region or during an outbreak).
- If 4 or more doses are administered before age 4 years, an additional dose should be administered at age 4 through 6 years.
- A fourth dose is not necessary if the third dose was administered at age 4 years or older and at least 6 months after the previous dose.
- If both OPV and IPV were administered as part of a series, a total of 4 doses should be administered, regardless of the child's current age.
- IPV is not routinely recommended for U.S. residents aged 18 years or older.
- For other catch-up issues, see Figure 2.

8. Influenza vaccines. (Minimum age: 6 months for inactivated influenza vaccine [IIV]; 2 years for live, attenuated influenza vaccine [LAIV])

Routine vaccination:

- Administer influenza vaccine annually to all children beginning at age 6 months. For most healthy, nonpregnant persons aged 2 through 49 years, either LAIV or IIV may be used. However, LAIV should NOT be administered to some persons, including 1) those with asthma, 2) children 2 through 4 years who had wheezing in the past 12 months, or 3) those who have any other underlying medical conditions that predispose them to influenza complications. For all other contraindications to use of LAIV see MMWR 2010; 59 (No. RR-8), available at http://www.cdc.gov/mmwr/pdf/rr/rr5908.pdf.
- Administer 1 dose to persons aged 9 years and older.

For children aged 6 months through 8 years:

- For the 2012–13 season, administer 2 doses (separated by at least 4 weeks) to children who are receiving influenza vaccine for the first time. For additional guidance, follow dosing guidelines in the 2012 ACIP influenza vaccine recommendations, MMWR 2012;61:613–618, available at http://www.cdc.gov/mmwr/pdf/wk/mm6132.pdf.
- For the 2013–14 season, follow dosing guidelines in the 2013 ACIP influenza vaccine recommendations.

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

Routine vaccination:

- Administer the first dose of MMR vaccine at age 12 through 15 months, and the second dose at age 4 through 6 years. The second dose may be administered before age 4 years, provided at least 4 weeks have elapsed since the first dose.
- Administer 1 dose of MMR vaccine to infants aged 6 through 11 months before departure from the United States for international travel. These children should be revaccinated with 2 doses of MMR vaccine, the first at age 12 through 15 months (12 months if the child remains in an area where disease risk is high), and the second dose at least 4 weeks later.
- Administer 2 doses of MMR vaccine to children aged 12 months and older, before departure from the United States for international travel. The first dose should be administered on or after age 12 months and the second dose at least 4 weeks later.

Catch-up vaccination:

- Ensure that all school-aged children and adolescents have had 2 doses of MMR vaccine; the minimum interval between the 2 doses is 4 weeks.

10. Varicella (VAR) vaccine. (Minimum age: 12 months)

Routine vaccination:

- Administer the first dose of VAR vaccine at age 12 through 15 months, and the second dose at age 4 through 6 years. The second dose may be administered before age 4 years, provided at least 3 months have elapsed since the first dose. If the second dose was administered at least 4 weeks after the first dose, it can be accepted as valid.

Catch-up vaccination:

- Ensure that all persons aged 7 through 18 years without evidence of immunity (see MMWR 2007;56 (No. RR-4), available at http://www.cdc.gov/mmwr/pdf/rr/rr5604.pdf) have 2 doses of varicella vaccine. For children aged 7 through 12 years the recommended minimum interval between doses is 3 months (if the second dose was administered at least 4 weeks after the first dose, it can be accepted as valid); for persons aged 13 years and older, the minimum interval between doses is 4 weeks.

11. Hepatitis A vaccine (HepA). (Minimum age: 12 months)

Routine vaccination:

- Initiate the 2-dose HepA vaccine series for children aged 12 through 23 months; separate the 2 doses by 6 to 18 months.
- Children who have received 1 dose of HepA vaccine before age 24 months, should receive a second dose 6 to 18 months after the first dose.
- For any person aged 2 years and older who has not already received the HepA vaccine series, 2 doses of HepA vaccine separated by 6 to 18 months may be administered if immunity against hepatitis A virus infection is desired.

Catch-up vaccination:

- The minimum interval between the two doses is 6 months.

Special populations:

- Administer 2 doses of Hep A vaccine at least 6 months apart to previously unvaccinated persons who live in areas where vaccination programs target older children, or who are at increased risk for infection.

12. Human papillomavirus (HPV) vaccines. (HPV4 [Gardasil] and HPV2 [Cervarix]). (Minimum age: 9 years)

Routine vaccination:

- Administer a 3-dose series of HPV vaccine on a schedule of 0, 1–2, and 6 months to all adolescents aged 11–12 years. Either HPV4 or HPV2 may be used for females, and only HPV4 may be used for males.
- The vaccine series can be started beginning at age 9 years.
- Administer the second dose 1 to 2 months after the first dose and the third dose 6 months after the first dose (at least 24 weeks after the first dose).

Catch-up vaccination:

- Administer the vaccine series to females (either HPV2 or HPV4) and males (HPV4) at age 13 through 18 years if not previously vaccinated.
- Use recommended routine dosing intervals (see above) for vaccine series catch-up.

13. Meningococcal conjugate vaccines (MCV). (Minimum age: 6 weeks for Hib-MenCY, 9 months for Menactra [MCV4-D], 2 years for Menveo [MCV4-CRM]).

Routine vaccination:

- Administer MCV4 vaccine at age 11–12 years, with a booster dose at age 16 years.
- Adolescents aged 11 through 18 years with human immunodeficiency virus (HIV) infection should receive a 2-dose primary series of MCV4, with at least 8 weeks between doses. See MMWR 2011; 60:1018–1019 available at: http://www.cdc.gov/mmwr/pdf/wk/mm6030.pdf.
- For children aged 9 months through 10 years with high-risk conditions, see below.

Catch-up vaccination:

- Administer MCV4 vaccine at age 13 through 18 years if not previously vaccinated.
- If the first dose is administered at age 13 through 15 years, a booster dose should be administered at age 16 through 18 years with a minimum interval of at least 8 weeks between doses.
- If the first dose is administered at age 16 years or older, a booster dose is not needed.
- For other catch-up issues, see Figure 2.

Vaccination of persons with high-risk conditions:

- For children younger than 19 months of age with anatomic or functional asplenia (including sickle cell disease), administer an infant series of Hib-MenCY at 2, 4, 6, and 12–15 months.
- For children aged 2 through 18 months with persistent complement component deficiency, administer either an infant series of Hib-MenCY at 2, 4, 6, and 12 through 15 months or a 2-dose primary series of MCV4-D starting at 9 months, with at least 8 weeks between doses. For children aged 19 through 23 months with persistent complement component deficiency who have not received a complete series of Hib-MenCY or MCV4-D, administer 2 primary doses of MCV4-D at least 8 weeks apart.
- For children aged 24 months and older with persistent complement component deficiency or anatomic or functional asplenia (including sickle cell disease), who have not received a complete series of Hib-MenCY or MCV4-D, administer 2 primary doses of either MCV4-D or MCV4-CRM. If MCV4-D (Menactra) is administered to a child with asplenia (including sickle cell disease), do not administer MCV4-D until 2 years of age and at least 4 weeks after the completion of all PCV13 doses. See MMWR 2011;60:1391–2, available at http://www.cdc.gov/mmwr/pdf/wk/mm6040.pdf.
- For children aged 9 months and older who are residents of or travelers to countries in the African meningitis belt or to the Hajj, administer an age-appropriate formulation and series of MCV4 for protection against serogroups A and W-135. Prior receipt of Hib-MenCY is not sufficient for children traveling to the meningitis belt or the Hajj. See MMWR 2011;60:1391–2, available at http://www.cdc.gov/mmwr/pdf/wk/mm6040.pdf.
- For children who are present during outbreaks caused by a vaccine serogroup, administer or complete an age-and formulation-appropriate series of Hib-MenCY or MCV4.
- For booster doses among persons with high-risk conditions refer to http://www.cdc.gov/vaccines/pubs/acip-list.htm#mening.

Additional information

- For contraindications and precautions to use of a vaccine and for additional information regarding that vaccine, vaccination providers should consult the relevant ACIP statement available online at http://www.cdc.gov/vaccines/pubs/acip-list.htm.
- For the purposes of calculating intervals between doses, 4 weeks = 28 days. Intervals of 4 months or greater are determined by calendar months.
- Information on travel vaccine requirements and recommendations is available at http://wwwnc.cdc.gov/travel/page/vaccinations.htm.
- For vaccination of persons with primary and secondary immunodeficiencies, see Table 13, "Vaccination of persons with primary and secondary immunodeficiencies," in General Recommendations on Immunization (ACIP), available at http://www.cdc.gov/mmwr/preview/mmwrhtml/rr6002a1.htm; and American Academy of Pediatrics. Passive immunization. In: Pickering LK, Baker CJ, Kimberlin DW, Long SS eds. Red book: 2012 report of the Committee on Infectious Diseases. 29th ed. Elk Grove Village, IL: American Academy of Pediatrics.

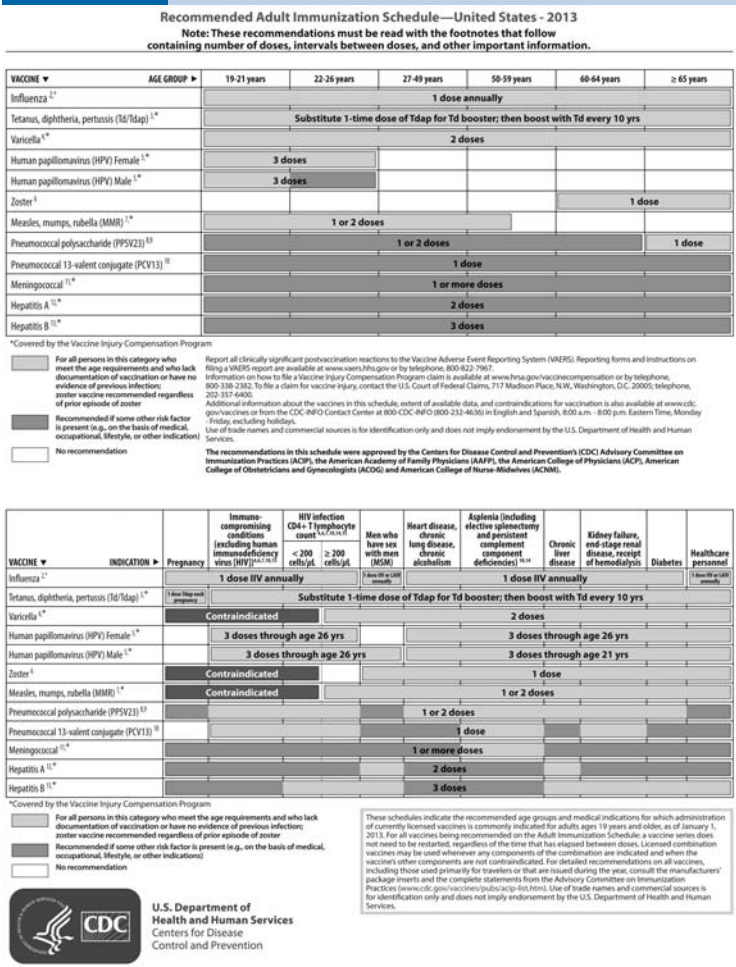
U.S. Department of Health and Human Services
Centers for Disease Control and Prevention

- Adverse effects to diphtheria toxoid include mild to moderate tenderness, erythema, and induration at the injection site.

TETANUS TOXOID, TETANUS TOXOID ADSORBED, AND TETANUS IMMUNOGLOBULIN

- In children, primary immunization against tetanus is usually done in conjunction with diphtheria and pertussis vaccination using DTaP or a combination vaccine that includes other antigens. A 0.5-mL dose is recommended at 2, 4, 6, and 15 to 18 months of age, but the first dose can be administered as early as age 6 weeks.
- In children 7 years and older and in adults who have not been previously immunized, a series of three 0.5 mL doses of Td are administered intramuscularly (IM) initially. The first two doses are given 1 to 2 months apart and the third dose 6 to 12 months later. Boosters are recommended every 10 years.

TABLE 51–2 2012 Adult Immunization Schedule



- Tetanus toxoid may be given to immunosuppressed patients if indicated.
- Tetanus Ig (TIg) is used to provide passive tetanus immunization after the occurrence of traumatic wounds in nonimmunized or suboptimally immunized persons (**Table 51–4**). A dose of 250 to 500 units is administered IM. When administered with tetanus toxoid, separate sites for administration should be used.
- TIg also used for the treatment of tetanus. In this setting, a single dose of 3000 to 6000 units is administered IM.

HAEMOPHILUS INFLUENZAE TYPE B VACCINES

- *Haemophilus influenzae* type b (Hib) vaccines currently in use are conjugate products, consisting of either a polysaccharide or oligosaccharide of polyribosylribitol phosphate (PRP) covalently linked to a protein carrier.

TABLE 51–2 2012 Adult Immunization Schedule (*Continued*)

Footnotes — Recommended Immunization Schedule for Adults Aged 19 Years and Older—United States, 2013

1. Additional information

- Additional guidance for the use of the vaccines described in this supplement is available at http://www.cdc.gov/vaccines/pubs/acip-list.htm.
- Information on vaccination recommendations when vaccination status is unknown and other general immunization information can be found in the General Recommendations on Immunization at http://www.cdc.gov/mmwr/preview/mmwrhtml/rr6002a1.htm.
- Information on travel vaccine requirements and recommendations (e.g., for hepatitis A and B, meningococcal, and other vaccines) are available at http://wwwnc.cdc.gov/travel/page/vaccinations.htm.

2. Influenza vaccination

- Annual vaccination against influenza is recommended for all persons aged 6 months and older.
- Persons aged 6 months and older, including pregnant women, can receive the inactivated influenza vaccine (IIV).
- Healthy, nonpregnant persons aged 2–49 years without high-risk medical conditions can receive either intranasally administered live, attenuated influenza vaccine (LAIV) (FluMist), or IIV. Health-care personnel who care for severely immunocompromised persons (i.e., those who require care in a protected environment) should receive IIV rather than LAIV.
- The intramuscularly or intradermally administered IIV are options for adults aged 18–64 years.
- Adults aged 65 years and older can receive the standard dose IIV or the high-dose IIV (Fluzone High-Dose).

3. Tetanus, diphtheria, and acellular pertussis (Td/Tdap) vaccination

- Administer one dose of Tdap vaccine to pregnant women during each pregnancy (preferred during 27–36 weeks' gestation), regardless of number of years since prior Td or Tdap vaccination.
- Administer Tdap to all other adults who have not previously received Tdap or for whom vaccine status is unknown. Tdap can be administered regardless of interval since the most recent tetanus or diphtheria-toxoid-containing vaccine.
- Adults with an unknown or incomplete history of completing a 3-dose primary vaccination series with Td-containing vaccines should begin or complete a primary vaccination series including a Tdap dose.
- For unvaccinated adults, administer the first 2 doses at least 4 weeks apart and the third dose 6–12 months after the second.
- For incompletely vaccinated (i.e., less than 3 doses) adults, administer remaining doses.
- Refer to the Advisory Committee on Immunization Practices (ACIP) statement for recommendations for administering Td/Tdap as prophylaxis in wound management (see footnote #1).

4. Varicella vaccination

- All adults without evidence of immunity to varicella (as defined below) should receive 2 doses of single-antigen varicella vaccine or a second dose if they have received only 1 dose.
- Special consideration for vaccination should be given to those who have close contact with persons at high risk for severe disease (e.g., health-care personnel and family contacts of persons with immunocompromising conditions) or are at high risk for exposure or transmission (e.g., teachers; child care employers; residents and staff members of institutional settings, including correctional institutions; college students; military personnel; adolescents and adults living in households with children; nonpregnant women of childbearing age; and international travelers).
- Pregnant women should be assessed for evidence of varicella immunity. Women who do not have evidence of immunity should receive the first dose of varicella vaccine upon completion or termination of pregnancy and before discharge from the health-care facility. The second dose should be administered 4–8 weeks after the first dose.
- Evidence of immunity to varicella in adults includes any of the following:
  - documentation of 2 doses of varicella vaccine at least 4 weeks apart;
  - U.S.-born before 1980 except health-care personnel and pregnant women;
  - history of varicella based on diagnosis or verification of varicella disease by a health-care provider;
  - history of herpes zoster based on diagnosis or verification of herpes zoster disease by a health-care provider; or
  - laboratory evidence of immunity or laboratory confirmation of disease.

5. Human papillomavirus (HPV) vaccination

- Two vaccines are licensed for use in females, bivalent HPV vaccine (HPV2) and quadrivalent HPV vaccine (HPV4), and one HPV vaccine for use in males (HPV4).
- For females, either HPV4 or HPV2 is recommended in a 3-dose series for routine vaccination at age 11 or 12 years, and for those aged 13 through 26 years, if not previously vaccinated.
- For males, HPV4 is recommended in a 3-dose series for routine vaccination at age 11 or 12 years, and for those aged 13 through 21 years, if not previously vaccinated. Males aged 22 through 26 years may be vaccinated.
- HPV4 is recommended for men who have sex with men (MSM) through age 26 years for those who did not get any or all doses when they were younger.
- Vaccination is recommended for immunocompromised persons (including those with HIV infection) through age 26 years for those who did not get any or all doses when they were younger.
- A complete series for either HPV4 or HPV2 consists of 3 doses. The second dose should be administered 1–2 months after the first dose; the third dose should be administered 6 months after the first dose (at least 24 weeks after the first dose).
- HPV vaccines are not recommended for use in pregnant women. However, pregnancy testing is not needed before vaccination. If a woman is found to be pregnant after initiating the vaccination series, no intervention is needed; the remainder of the 3-dose series should be delayed until completion of pregnancy.
- Although HPV vaccination is not specifically recommended for health-care personnel (HCP) based on their occupation, HCP should receive the HPV vaccine as recommended (see above).

6. Zoster vaccination

- A single dose of zoster vaccine is recommended for adults aged 60 years and older regardless of whether they report a prior episode of herpes zoster. Although the vaccine is licensed by the Food and Drug Administration (FDA) for use among and can be administered to persons aged 50 years and older, ACIP recommends that vaccination begins at age 60 years.
- Persons aged 60 years and older with chronic medical conditions may be vaccinated unless their condition constitutes a contraindication, such as pregnancy or severe immunodeficiency.
- Although zoster vaccination is not specifically recommended for HCP, they should receive the vaccine if they are in the recommended age group.

7. Measles, mumps, rubella (MMR) vaccination

- Adults born before 1957 generally are considered immune to measles and mumps. All adults born in 1957 or later should have documentation of 1 or more doses of MMR vaccine unless they have a medical contraindication to the vaccine, or laboratory evidence of immunity to each of the three diseases. Documentation of provider-diagnosed disease is not considered acceptable evidence of immunity for measles, mumps, or rubella.

Measles component:

- A routine second dose of MMR vaccine, administered a minimum of 28 days after the first dose, is recommended for adults who
  - are students in postsecondary educational institutions;
  - work in a health-care facility; or
  - plan to travel internationally.
- Persons who received inactivated (killed) measles vaccine or measles vaccine of unknown type during 1963–1967 should be revaccinated with 2 doses of MMR vaccine.

Mumps component:

- A routine second dose of MMR vaccine, administered a minimum of 28 days after the first dose, is recommended for adults who
  - are students in a postsecondary educational institution;
  - work in a health-care facility; or
  - plan to travel internationally.
- Persons vaccinated before 1979 with either killed mumps vaccine or mumps vaccine of unknown type who are at high risk for mumps infection (e.g., persons who are working in a health-care facility) should be considered for revaccination with 2 doses of MMR vaccine.

Rubella component:

- For women of childbearing age, regardless of birth year, rubella immunity should be determined. If there is no evidence of immunity, women who are not pregnant should be vaccinated. Pregnant women who do not have evidence of immunity should receive MMR vaccine upon completion or termination of pregnancy and before discharge from the health-care facility.

HCP born before 1957:

- For unvaccinated health-care personnel born before 1957 who lack laboratory evidence of measles, mumps, and/or rubella immunity or laboratory confirmation of disease, health-care facilities should consider vaccinating personnel with 2 doses of MMR vaccine at the appropriate interval for measles and mumps or 1 dose of MMR vaccine for rubella.

8. Pneumococcal polysaccharide (PPSV23) vaccination

- Vaccinate all persons with the following indications:
  - all adults aged 65 years and older;
  - adults younger than age 65 years with chronic lung disease (including chronic obstructive pulmonary disease, emphysema, and asthma); chronic cardiovascular diseases; diabetes mellitus; chronic renal failure; nephrotic syndrome; chronic liver disease (including cirrhosis); alcoholism; cochlear implants; cerebrospinal fluid leaks; immunocompromising conditions; and functional or anatomic asplenia (e.g., sickle cell disease and other hemoglobinopathies, congenital or acquired asplenia, splenic dysfunction, or splenectomy [if elective splenectomy is planned, vaccinate at least 2 weeks before surgery]).
  - residents of nursing homes or long-term care facilities; and
  - adults who smoke cigarettes.
- Persons with immunocompromising conditions and other selected conditions are recommended to receive PCV13 and PPSV23 vaccines. See footnote #10 for information on timing of PCV13 and PPSV23 vaccinations.
- Persons with asymptomatic or symptomatic HIV infection should be vaccinated as soon as possible after their diagnosis.
- When cancer chemotherapy or other immunosuppressive therapy is being considered, the interval between vaccination and initiation of immunosuppressive therapy should be at least 2 weeks. Vaccination during chemotherapy or radiation therapy should be avoided.
- Routine use of PPSV23 is not recommended for American Indians/Alaska Natives or other persons younger than age 65 years unless they have underlying medical conditions that are PPSV23 indications. However, public health authorities may consider recommending PPSV23 for American Indians/Alaska Natives who are living in areas where the risk for invasive pneumococcal disease is increased.
- When indicated, PPSV23 should be administered to patients who are uncertain of their vaccination status and there is no record of previous vaccination. When PCV13 is also indicated, a dose of PCV13 should be given first (see footnote #10).

9. Revaccination with PPSV23

- One-time revaccination 5 years after the first dose is recommended for persons aged 19 through 64 years with chronic renal failure or nephrotic syndrome; functional or anatomic asplenia (e.g., sickle cell disease or splenectomy); and for persons with immunocompromising conditions.
- Persons who received 1 or 2 doses of PPSV23 before age 65 years for any indication should receive another dose of the vaccine at age 65 years or later if at least 5 years have passed since their previous dose.
- No further doses are needed for persons vaccinated with PPSV23 at or after age 65 years.

10. Pneumococcal conjugate 13-valent vaccination (PCV13)

- Adults aged 19 years or older with immunocompromising conditions (including chronic renal failure and nephrotic syndrome), functional or anatomic asplenia, CSF leaks or cochlear implants, and who have not previously received PCV13 or PPSV23 should receive a single dose of PCV13 followed by a dose of PPSV23 at least 8 weeks later.
- Adults aged 19 years or older with the aforementioned conditions who have previously received one or more doses of PPSV23 should receive a dose of PCV13 one or more years after the last PPSV23 dose was received. For those that require additional doses of PPSV23, the first such dose should be given no sooner than 8 weeks after PCV13 and at least 5 years since the most recent dose of PPSV23.
- When indicated, PCV13 should be administered to patients who are uncertain of their vaccination status history and there is no record of previous vaccination.
- Although PCV13 is licensed by the Food and Drug Administration (FDA) for use among and can be administered to persons aged 50 years and older, ACIP recommends PCV13 for adults aged 19 years and older with the specific medical conditions noted above.

11. Meningococcal vaccination

- Administer 2 doses of meningococcal conjugate vaccine quadrivalent (MCV4) at least 2 months apart to adults with functional asplenia or persistent complement component deficiencies.
- HIV-infected persons who are vaccinated also should receive 2 doses.
- Administer a single dose of meningococcal vaccine to microbiologists routinely exposed to isolates of Neisseria meningitidis, military recruits, and persons who travel to or live in countries in which meningococcal disease is hyperendemic or epidemic.
- First-year college students up through age 21 years who are living in residence halls should be vaccinated if they have not received a dose on or after their 16th birthday.
- MCV4 is preferred for adults with any of the preceding indications who are aged 55 years and younger; meningococcal polysaccharide vaccine (MPSV4) is preferred for adults aged 56 years and older.
- Revaccination with MCV4 every 5 years is recommended for adults previously vaccinated with MCV4 or MPSV4 who remain at increased risk for infection (e.g., adults with anatomic or functional asplenia or persistent complement component deficiencies).

12. Hepatitis A vaccination

- Vaccinate any person seeking protection from hepatitis A virus (HAV) infection and persons with any of the following indications:
  - men who have sex with men and persons who use injection or noninjection illicit drugs;
  - persons working with HAV-infected primates or with HAV in a research laboratory setting;
  - persons with chronic liver disease and persons who receive clotting factor concentrates;
  - persons travelling to or working in countries that have high or intermediate endemicity of hepatitis A; and
  - unvaccinated persons who anticipate close personal contact (e.g., household or regular babysitting) with an international adoptee during the first 60 days after arrival in the United States from a country with high or intermediate endemicity. (See footnote #1 for more information on travel recommendations). The first dose of the 2-dose hepatitis A vaccine series should be administered as soon as adoption is planned, ideally 2 or more weeks before the arrival of the adoptee.
- Single-antigen vaccine formulations should be administered in a 2-dose schedule at either age 0 and 6–12 months (Havrix), or age 0 and 6–18 months (Vaqta). If the combined hepatitis A and hepatitis B vaccine (Twinrix) is used, administer 3 doses at 0, 1, and 6 months; alternatively, a 4-dose schedule may be used, administered on days 0, 7, and 21–30, followed by a booster dose at month 12.

13. Hepatitis B vaccination

- Vaccinate persons with any of the following indications and any person seeking protection from hepatitis B virus (HBV) infection:
  - sexually active persons who are not in a long-term, mutually monogamous relationship (e.g., persons with more than one sex partner during the previous 6 months); persons seeking evaluation or treatment for a sexually transmitted disease (STD); current or recent injection-drug users; and men who have sex with men;
  - health-care personnel and public-safety workers who are potentially exposed to blood or other infectious body fluids;
  - persons with diabetes younger than age 60 years as soon as feasible after diagnosis; persons with diabetes who are age 60 years or older at the discretion of the treating clinician based on increased need for assisted blood glucose monitoring in long-term care facilities, likelihood of acquiring hepatitis B infection, its complications or chronic sequelae, and likelihood of immune response to vaccination;
  - persons with end-stage renal disease, including patients receiving hemodialysis; persons with HIV infection; and persons with chronic liver disease;
  - household contacts and sex partners of hepatitis B surface antigen–positive persons; clients and staff members of institutions for persons with developmental disabilities; and international travelers to countries with high or intermediate prevalence of chronic HBV infection; and
  - all adults in the following settings: STD treatment facilities; HIV testing and treatment facilities; facilities providing drug-abuse treatment and prevention services; health-care settings targeting services to injection-drug users or men who have sex with men; correctional facilities; end-stage renal disease programs and facilities for chronic hemodialysis patients; and institutions and nonresidential daycare facilities for persons with developmental disabilities.
- Administer a 3-dose series to complete a 3-dose series of hepatitis B vaccine to those persons not vaccinated or not completely vaccinated. The second dose should be administered 1 month after the first dose; the third dose should be given at least 2 months after the second dose (and at least 4 months after the first dose). If the combined hepatitis A and hepatitis B vaccine (Twinrix) is used, give 3 doses at 0, 1, and 6 months; alternately, a 4-dose Twinrix schedule, administered on days 0, 7, and 21–30 followed by a booster dose at month 12 may be used.
- Adult patients receiving hemodialysis or with other immunocompromising conditions should receive 1 dose of 40 µg/mL (Recombivax HB) administered on a 3-dose schedule at 0, 1, and 6 months or 2 doses of 20 µg/mL (Engerix-B) administered simultaneously on a 4-dose schedule at 0, 1, 2, and 6 months.

14. Selected conditions for which Haemophilus influenzae type b (Hib) vaccine may be used

- 1 dose of Hib vaccine should be considered for persons who have sickle cell disease, leukemia, or HIV infection, or who have anatomic or functional asplenia if they have not previously received Hib vaccine.

15. Immunocompromising conditions

- Inactivated vaccines generally are acceptable (e.g., pneumococcal, meningococcal, and influenza [inactivated influenza vaccine]), and live vaccines generally are avoided in persons with immune deficiencies or immunocompromising conditions. Information on specific conditions is available at http://www.cdc.gov/vaccines/pubs/acip-list.htm.

- Hib conjugate vaccines are indicated for routine use in all infants and children younger than 5 years.
- The primary series of Hib vaccination consists of 0.5-mL IM doses at 2, 4, and 6 months of age. If PRP-OMP (PRP conjugated to an outer membrane protein) is used, it should be given at ages 2 and 4 months. A booster dose is recommended at age 12 to 15 months.
- For infants 7 to 11 months of age who have not been vaccinated, three doses of Hib vaccine should be given: two doses spaced 4 weeks apart and then a booster dose at age 12 to 15 months (but at least 8 weeks since the second dose). For unvaccinated children ages 12 to 14 months, two doses should be given, with an interval of 2 months between doses. In a child older than 15 months, a single dose of any of the four conjugate vaccines is indicated.

TABLE 51–3 Children and Adult Catch-up Schedule

FIGURE 2. Catch-up immunization schedule for persons aged 4 months through 18 years who start late or who are more than 1 month behind — United States, 2013

The figure below provides catch-up schedules and minimum intervals between doses for children whose vaccinations have been delayed. A vaccine series does not need to be restarted, regardless of the time that has elapsed between doses. Use the section appropriate for the child's age. Always use this table in conjunction with Figure 1 and the footnotes that follow.

Vaccine	Minimum Age for Dose 1	Minimum Interval Between Doses			
		Dose 1 to dose 2	Dose 2 to dose 3	Dose 3 to dose 4	Dose 4 to dose 5
Persons aged 4 months through 6 years					
Hepatitis B[1]	Birth	4 weeks	8 weeks and at least 16 weeks after first dose; minimum age for the final dose is 24 weeks.		
Rotavirus[2]	6 weeks	4 weeks	4 weeks[2]		
Diphtheria, tetanus, pertussis[3]	6 weeks	4 weeks	4 weeks	6 months	6 months[3]
Haemophilus influenzae type b[4]	6 weeks	4 weeks if first dose administered at younger than age 12 months 8 weeks (as final dose) if first dose administered at age 12–14 months No further doses needed if first dose administered at age 15 months or older	4 weeks[4] if current age is younger than 12 months 8 weeks (as final dose)[4] if current age is 12 months or older and first dose administered at younger than age 12 months and second dose administered at younger than 15 months No further doses needed if previous dose administered at age 15 months or older	8 weeks (as final dose) This dose only necessary for children aged 12 through 59 months who received 3 doses before age 12 months	
Pneumococcal[5]	6 weeks	4 weeks if first dose administered at younger than age 12 months 8 weeks (as final dose for healthy children) if first dose administered at age 12 months or older or current age 24 through 59 months No further doses needed for healthy children if first dose administered at age 24 months or older	4 weeks if current age is younger than 12 months 8 weeks (as final dose for healthy children) if current age is 12 months or older No further doses needed for healthy children if previous dose administered at age 24 months or older	8 weeks (as final dose) This dose only necessary for children aged 12 through 59 months who received 3 doses before age 12 months or for children at high risk who received 3 doses at any age	
Inactivated poliovirus[7]	6 weeks	4 weeks	4 weeks	6 months[7] minimum age 4 years for final dose	
Meningococcal[8]	6 weeks	8 weeks[13]	see footnote 13	see footnote 13	
Measles, mumps, rubella[9]	12 months	4 weeks			
Varicella[10]	12 months	3 months			
Hepatitis A[11]	12 months	6 months			
Persons aged 7 through 18 years					
Tetanus, diphtheria; tetanus, diphtheria, pertussis[3]	7 years[3]	4 weeks	4 weeks if first dose administered at younger than age 12 months 6 months if first dose administered at 12 months or older	6 months if first dose administered at younger than age 12 months	
Human papillomavirus[12]	9 years	Routine dosing intervals are recommended[12]			
Hepatitis A[11]	12 months	6 months			
Hepatitis B[1]	Birth	4 weeks	8 weeks (and at least 16 weeks after first dose)		
Inactivated poliovirus[7]	6 weeks	4 weeks	4 weeks[7]	6 months[7]	
Meningococcal[8]	6 weeks	8 weeks[13]			
Measles, mumps, rubella[9]	12 months	4 weeks			
Varicella[10]	12 months	3 months if person is younger than age 13 years 4 weeks if person is aged 13 years or older			

NOTE: The above recommendations must be read along with the footnotes of this schedule.

Footnotes — Recommended immunization schedule for persons aged 0 through 18 years — United States, 2013

For further guidance on the use of the vaccines mentioned below, see: http://www.cdc.gov/vaccines/pubs/acip-list.htm.

1. **Hepatitis B (HepB) vaccine. (Minimum age: birth)**
   Routine vaccination:
   At birth
   - Administer monovalent HepB vaccine to all newborns before hospital discharge.
   - For infants born to hepatitis B surface antigen (HBsAg)–positive mothers, administer HepB vaccine and 0.5 mL of hepatitis B immune globulin (HBIG) within 12 hours of birth. These infants should be tested for HBsAg and antibody to HBsAg (anti-HBs) 1 to 2 months after completion of the HepB series, at age 9 through 18 months (preferably at the next well-child visit).
   - If mother's HBsAg status is unknown, within 12 hours of birth administer HepB vaccine to all infants regardless of birth weight. For infants weighing <2,000 grams, administer HBIG in addition to HepB within 12 hours of birth. Determine mother's HBsAg status as soon as possible and, if she is HBsAg-positive, also administer HBIG for infants weighing ≥2,000 grams (no later than age 1 week).

   Doses following the birth dose
   - The second dose should be administered at age 1 or 2 months. Monovalent HepB vaccine should be used for doses administered before age 6 weeks.
   - Infants who did not receive a birth dose should receive 3 doses of a HepB-containing vaccine on a schedule of 0, 1 to 2 months, and 6 months starting as soon as feasible. See Figure 2.
   - The minimum interval between dose 1 and dose 2 is 4 weeks and between dose 2 and 3 is 8 weeks. The final (third or fourth) dose in the HepB vaccine series should be administered no earlier than age 24 weeks, and at least 16 weeks after the first dose.
   - Administration of a total of 4 doses of HepB vaccine is recommended when a combination vaccine containing HepB is administered after the birth dose.

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

2. **Rotavirus (RV) vaccines. (Minimum age: 6 weeks for both RV-1 [Rotarix] and RV-5 [RotaTeq]).**
   Routine vaccination:
   - Administer a series of RV vaccine to all infants as follows:
     1. If RV-1 is used, administer a 2-dose series at 2 and 4 months of age.
     2. If RV-5 is used, administer a 3-dose series at ages 2, 4, and 6 months.
     3. If any dose in series was RV-5 or vaccine product is unknown for any dose in the series, a total of 3 doses of RV vaccine should be administered.

   Catch-up vaccination:
   - The maximum age for the first dose in the series is 14 weeks, 6 days.
   - Vaccination should not be initiated for infants aged 15 weeks 0 days or older.
   - The maximum age for the final dose in the series is 8 months, 0 days.
   - If RV-1 (Rotarix) is administered for the first and second doses, a third dose is not indicated.
   - For other catch-up issues, see Figure 2.

3. **Diphtheria and tetanus toxoids and acellular pertussis (DTaP) vaccine. (Minimum age: 6 weeks)**
   Routine vaccination:
   - Administer a 5-dose series of DTaP vaccine at ages 2, 4, 6, 15–18 months, and 4 through 6 years. The fourth dose may be administered as early as age 12 months, provided at least 6 months have elapsed since the third dose.

   Catch-up vaccination:
   - The fifth (booster) dose of DTaP vaccine is not necessary if the fourth dose was administered at age 4 years or older.
   - For other catch-up issues, see Figure 2.

4. **Tetanus and diphtheria toxoids and acellular pertussis (Tdap) vaccine. (Minimum age: 10 years for Boostrix, 11 years for Adacel).**
   Routine vaccination:
   - Administer 1 dose of Tdap vaccine to all adolescents aged 11 through 12 years.
   - Tdap can be administered regardless of the interval since the last tetanus and diphtheria toxoid-containing vaccine.

HEPATITIS VACCINES

- Information on hepatitis vaccines can be found in Chap. 25.

HUMAN PAPILLOMAVIRUS VACCINE

- Bivalent (Cervarix) and quadrivalent (Gardisil) vaccines are available. Both vaccines are recommended as a three-dose series (0, 2, and 6 months) for all female patients 11 to 12 years old and ages 13 to 26 years. The quadrivalent vaccine is licensed for prevention of genital warts in female patients 9 to 26 years of age.
- The vaccine is well tolerated, with injection site reactions and headache and fatigue occurring as commonly as in placebo groups.

TABLE 51–3 Children and Adult Catch-up Schedule (Continued)

For further guidance on the use of the vaccines mentioned below, see: http://www.cdc.gov/vaccines/pubs/acip-list.htm.

- Administer one dose of Tdap vaccine to pregnant adolescents during each pregnancy (preferred during 27 through 36 weeks gestation) regardless of number of years from prior Td or Tdap vaccination.

Catch-up vaccination:

- Persons aged 7 through 10 years who are not fully immunized with the childhood DTaP vaccine series should receive Tdap vaccine as the first dose in the catch-up series; if additional doses are needed, use Td vaccine. For these children, an adolescent Tdap vaccine should not be given.
- Persons aged 11 through 18 years who have not received Tdap vaccine should receive a dose followed by tetanus and diphtheria toxoids (Td) booster doses every 10 years thereafter.
- An inadvertent dose of DTaP vaccine administered to children aged 7 through 10 years can count as part of the catch-up series. This dose can count as the adolescent Tdap dose, or the child can later receive a Tdap booster dose at age 11–12 years.
- For other catch-up issues, see Figure 2.

5. Haemophilus influenzae type b (Hib) conjugate vaccine. (Minimum age: 6 weeks)

Routine vaccination:

- Administer a Hib vaccine primary series and a booster dose to all infants. The primary series doses should be administered at 2, 4, and 6 months of age; however, if PRP-OMP (PedvaxHIB or Comvax) is administered at 2 and 4 months of age, a dose at age 6 months is not indicated. One booster dose should be administered at age 12 through 15 months.
- Hiberix (PRP-T) should only be used for the booster (final) dose in children aged 12 months through 4 years, who have received at least 1 dose of Hib.

Catch-up vaccination:

- If dose 1 was administered at ages 12-14 months, administer booster (as final dose) at least 8 weeks after dose 1.
- If the first 2 doses were PRP-OMP (PedvaxHIB or Comvax), and were administered at age 11 months or younger, the third (and final) dose should be administered at age 12 through 15 months and at least 8 weeks after the second dose.
- If the first dose was administered at age 7 through 11 months, administer the second dose at least 4 weeks later and a final dose at age 12 through 15 months, regardless of Hib vaccine (PRP-T or PRP-OMP) used for first dose.
- For unvaccinated children aged 15 months or older, administer only 1 dose.
- For other catch-up issues, see Figure 2.

Vaccination of persons with high-risk conditions:

- Hib vaccine is not routinely recommended for patients older than 5 years of age. However one dose of Hib vaccine should be administered to unvaccinated or partially vaccinated persons aged 5 years or older who have leukemia, malignant neoplasms, anatomic or functional asplenia (including sickle cell disease), human immunodeficiency virus (HIV) infection, or other immunocompromising conditions.

6a. Pneumococcal conjugate vaccine (PCV). (Minimum age: 6 weeks)

Routine vaccination:

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

Catch-up vaccination:

- Administer 1 dose of PCV13 to all healthy children aged 24 through 59 months who are not completely vaccinated for their age.
- For other catch-up issues, see Figure 2.

Vaccination of persons with high-risk conditions:

- For children aged 24 through 71 months with certain underlying medical conditions (see footnote 6c), administer 1 dose of PCV13 if 3 doses of PCV were received previously, or administer 2 doses of PCV13 at least 8 weeks apart if fewer than 3 doses of PCV were received previously.
- A single dose of PCV13 may be administered to previously unvaccinated children aged 6 through 18 years who have anatomic or functional asplenia (including sickle cell disease), HIV infection or an immunocompromising condition, cochlear implant or cerebrospinal fluid leak. See MMWR 2010;59 (No. RR-11); available at http://www.cdc.gov/mmwr/pdf/rr/rr5911.pdf.
- Administer PPSV23 at least 8 weeks after the last dose of PCV to children aged 2 years or older with certain underlying medical conditions (see footnotes 6b and 6c).

6b. Pneumococcal polysaccharide vaccine (PPSV23). (Minimum age: 2 years)

Vaccination of persons with high-risk conditions:

- Administer PPSV23 at least 8 weeks after the last dose of PCV to children aged 2 years or older with certain underlying medical conditions (see footnote 6c). A single revaccination with PPSV should be administered after 5 years to children with anatomic or functional asplenia (including sickle cell disease) or an immunocompromising condition.

6c. Medical conditions for which PPSV23 is indicated in children aged 2 years and older and for which use of PCV13 is indicated in children aged 24 through 71 months:

- Immunocompetent children with chronic heart disease (particularly cyanotic congenital heart disease and cardiac failure); chronic lung disease (including asthma if treated with high-dose oral corticosteroid therapy), diabetes mellitus; cerebrospinal fluid leaks; or cochlear implant.
- Children with anatomic or functional asplenia (including sickle cell disease and other hemoglobinopathies, congenital or acquired asplenia, or splenic dysfunction).
- Children with immunocompromising conditions: HIV infection, chronic renal failure and nephrotic syndrome, diseases associated with treatment with immunosuppressive drugs or radiation therapy, including malignant neoplasms, leukemias, lymphomas and Hodgkin disease; or solid organ transplantation, congenital immunodeficiency.

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

Routine vaccination:

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

Catch-up vaccination:

- In the first 6 months of life, minimum age and minimum intervals are only recommended if the person is at risk for imminent exposure to circulating poliovirus (i.e., travel to a polio-endemic region or during an outbreak).
- If 4 or more doses are administered before age 4 years, an additional dose should be administered at age 4 through 6 years.
- A fourth dose is not necessary if the third dose was administered at age 4 years or older and at least 6 months after the previous dose.
- If both OPV and IPV were administered as part of a series, a total of 4 doses should be administered, regardless of the child's current age.
- IPV is not routinely recommended for U.S. residents aged 18 years or older.
- For other catch-up issues, see Figure 2.

8. Influenza vaccines. (Minimum age: 6 months for inactivated influenza vaccine [IIV]; 2 years for live, attenuated influenza vaccine [LAIV])

Routine vaccination:

- Administer influenza vaccine annually to all children beginning at age 6 months. For most healthy, nonpregnant persons aged 2 through 49 years, either LAIV or IIV may be used. However, LAIV should NOT be administered to some persons, including 1) those with asthma, 2) children 2 through 4 years who had wheezing in the past 12 months, or 3) those who have any other underlying medical conditions that predispose them to influenza complications. For all other contraindications to use of LAIV see MMWR 2010; 59 (No. RR-8), available at http://www.cdc.gov/mmwr/pdf/rr/rr5908.pdf.

Additional Information

- For contraindications and precautions to use of a vaccine and for additional information regarding that vaccine, vaccination providers should consult the relevant ACIP statement available online at http://www.cdc.gov/vaccines/pubs/acip-list.htm.
- For the purposes of calculating intervals between doses, 4 weeks = 28 days. Intervals of 4 months or greater are determined by calendar months.
- Information on travel vaccine requirements and recommendations is available at http://wwwnc.cdc.gov/travel/page/vaccinations.htm.
- For vaccination of persons with primary and secondary immunodeficiencies, see Table 13, "Vaccination of persons with primary and secondary immunodeficiencies," in General Recommendations on Immunization (ACIP), available at http://www.cdc.gov/mmwr/preview/mmwrhtml/rr6002a1.htm; and American Academy of Pediatrics. Passive immunization. In: Pickering LK, Baker CJ, Kimberlin DW, Long SS, eds. Red book: 2012 report of the Committee on Infectious Diseases. 29th ed. Elk Grove Village, IL: American Academy of Pediatrics.

- Administer 1 dose to persons aged 9 years and older.

For children aged 6 months through 8 years:

- For the 2012–13 season, administer 2 doses (separated by at least 4 weeks) to children who are receiving influenza vaccine for the first time. For additional guidance, follow dosing guidelines in the 2012 ACIP influenza vaccine recommendations, MMWR 2012; 61: 613–618, available at http://www.cdc.gov/mmwr/pdf/wk/mm6132.pdf.
- For the 2013–14 season, follow dosing guidelines in the 2013 ACIP influenza vaccine recommendations.

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

Routine vaccination:

- Administer the first dose of MMR vaccine at age 12 through 15 months, and the second dose at age 4 through 6 years. The second dose may be administered before age 4 years, provided at least 4 weeks have elapsed since the first dose.
- Administer 1 dose of MMR vaccine to infants aged 6 through 11 months before departure from the United States for international travel. These children should be revaccinated with 2 doses of MMR vaccine, the first at age 12 through 15 months (12 months if the child remains in an area where disease risk is high), and the second dose at least 4 weeks later.
- Administer 2 doses of MMR vaccine to children aged 12 months and older, before departure from the United States for international travel. The first dose should be administered on or after age 12 months and the second dose at least 4 weeks later.

Catch-up vaccination:

- Ensure that all school-aged children and adolescents have had 2 doses of MMR vaccine; the minimum interval between the 2 doses is 4 weeks.

10. Varicella (VAR) vaccine. (Minimum age: 12 months)

Routine vaccination:

- Administer the first dose of VAR vaccine at age 12 through 15 months, and the second dose at age 4 through 6 years. The second dose may be administered before age 4 years, provided at least 3 months have elapsed since the first dose. If the second dose was administered at least 4 weeks after the first dose, it can be accepted as valid.

Catch-up vaccination:

- Ensure that all persons aged 7 through 18 years without evidence of immunity (see MMWR 2007;56 (No. RR-4); available at http://www.cdc.gov/mmwr/pdf/rr/rr5604.pdf.) have 2 doses of varicella vaccine. For children aged 7 through 12 years the recommended minimum interval between doses is 3 months (if the second dose was administered at least 4 weeks after the first dose, it can be accepted as valid); for persons aged 13 years and older, the minimum interval between doses is 4 weeks.

11. Hepatitis A vaccine (HepA). (Minimum age: 12 months)

Routine vaccination:

- Initiate the 2-dose HepA vaccine series for children aged 12 through 23 months; separate the 2 doses by 6 to 18 months.
- Children who have received 1 dose of HepA vaccine before age 24 months should receive a second dose 6 to 18 months after the first dose.
- For any person aged 2 years and older who has not already received the HepA vaccine series, 2 doses of HepA vaccine separated by 6 to 18 months may be administered if immunity against hepatitis A virus infection is desired.

Catch-up vaccination:

- The minimum interval between the two doses is 6 months.

Special populations:

- Administer 2 doses of Hep A vaccine at least 6 months apart to previously unvaccinated persons who live in areas where vaccination programs target older children, or who are at increased risk for infection.

12. Human papillomavirus (HPV) vaccines. (HPV4 [Gardasil] and HPV2 [Cervarix]). (Minimum age: 9 years)

Routine vaccination:

- Administer 3 3-dose series of HPV vaccine on a schedule of 0, 1–2, and 6 months to all adolescents aged 11–12 years. Either HPV4 or HPV2 may be used for females, and only HPV4 may be used for males.
- The vaccine series can be started beginning at age 9 years.
- Administer the second dose 1 to 2 months after the first dose and the third dose 6 months after the first dose (at least 24 weeks after the first dose).

Catch-up vaccination:

- Administer the vaccine series to females (either HPV2 or HPV4) and males (HPV4) at age 13 through 18 years if not previously vaccinated.
- Use recommended routine dosing intervals (see above) for vaccine series catch-up.

13. Meningococcal conjugate vaccines (MCV). (Minimum age: 6 weeks for Hib-MenCY; 9 months for Menactra [MCV4-D], 2 years for Menveo [MCV4-CRM]).

Routine vaccination:

- Administer MCV4 vaccine at age 11–12 years, with a booster dose at age 16 years.
- Adolescents aged 11 through 18 years with human immunodeficiency virus (HIV) infection should receive a 2-dose primary series of MCV4, with at least 8 weeks between doses. See MMWR 2011; 60:1018–1019 available at: http://www.cdc.gov/mmwr/pdf/wk/mm6030.pdf.
- For children aged 9 months through 10 years with high-risk conditions, see below.

Catch-up vaccination:

- Administer MCV4 vaccine at age 13 through 18 years if not previously vaccinated.
- If the first dose is administered at age 13 through 15 years, a booster dose should be administered at age 16 through 18 years with a minimum interval of at least 8 weeks between doses.
- If the first dose is administered at age 16 years or older, a booster dose is not needed.
- For other catch-up issues, see Figure 2.

Vaccination of persons with high-risk conditions:

- For children younger than 19 months of age with anatomic or functional asplenia (including sickle cell disease), administer an infant series of Hib-MenCY at 2, 4, 6, and 12–15 months.
- For children aged 2 through 18 months with persistent complement component deficiency, administer either an infant series of Hib-MenCY at 2, 4, 6, and 12 through 15 months or a 2-dose primary series of MCV4-D starting at 9 months, with at least 8 weeks between doses. For children aged 19 through 23 months with persistent complement component deficiency who have not received a complete series of Hib-MenCY or MCV4-D, administer 2 primary doses of MCV4-D at least 8 weeks apart.
- For children aged 24 months and older with persistent complement component deficiency or anatomic or functional asplenia (including sickle cell disease), who have not received a complete series of Hib-MenCY or MCV4-D, administer 2 primary doses of either MCV4-D or MCV4-CRM. If MCV4-D (Menactra) is administered to a child with asplenia (including sickle cell disease), do not administer MCV4-D until 2 years of age and at least 4 weeks after the completion of all PCV13 doses. See MMWR 2011;60:1391–2, available at http://www.cdc.gov/mmwr/pdf/wk/mm6040.pdf.
- For children aged 9 months and older who are residents of or travelers to countries in the African meningitis belt or to the Hajj, administer an age-appropriate formulation and series of MCV4 for protection against serogroups A and W-135. Prior receipt of Hib-MenCY is not sufficient for children traveling to the meningitis belt or the Hajj. See MMWR 2011;60:1391–2, available at http://www.cdc.gov/mmwr/pdf/wk/mm6040.pdf.
- For children who are present during outbreaks caused by a vaccine serogroup, administer or complete an age and formulation-appropriate series of Hib-MenCY or MCV4.
- For booster doses among persons with high-risk conditions refer to http://www.cdc.gov/vaccines/pubs/acip-list.htm#mening.



U.S. Department of Health and Human Services
Centers for Disease Control and Prevention

TABLE 51–4 Tetanus Prophylaxis

	Clean, Minor		All Other	
Vaccination History	**Td**	**TIg**	**Tda**	**TIg**
Unknown or fewer than three doses	Yes	No	Yes	Yes
Greater than or equal to three doses	No[a,b]	No	No[a,c]	No

Td, tetanus–diphtheria; TIg, tetanus immunoglobulin.

[a]A single dose of diphtheria, tetanus toxoids, and acellular pertussis should be used for the next dose of Td toxoid.

[b]Yes if >10 years since last dose.

[c]Yes if >5 years since last dose.

INFLUENZA VIRUS VACCINE

- See Chap. 41 for information regarding influenza vaccination.

MEASLES VACCINE

- Measles vaccine is a live-attenuated vaccine that is administered for primary immunization to persons 12 to 15 months of age or older, usually as a combination of measles, mumps, and rubella (MMR). A second dose is recommended at 4 to 6 years of age.
- The vaccine should not be given to immunosuppressed patients (except those infected with HIV) or pregnant women. HIV-infected persons who have never had measles or have never been vaccinated should be given measles-containing vaccine unless there is evidence of severe immunosuppression.
- The vaccine should not be given within 1 month of any other live vaccine unless the vaccine is given on the same day (as with the MMR vaccine).
- Measles vaccine is indicated in all persons born after 1956 or in those who lack documentation of wild virus infection by either history or antibody titers.

MENINGOCOCCAL POLYSACCHARIDE VACCINE

- There are two meningococcal conjugate vaccines: Menactra is licensed for individuals 9 months to 55 years old and Menveo for those 12 to 55 years old. They are recommended for all children 11 to 12 years old with a second dose at 16 years of age. The vaccine is indicated in high-risk populations such as those exposed to the disease, those in the midst of uncontrolled outbreaks, travelers to an area with epidemic hyperendemic meningococcal disease, and individuals who have terminal complement deficiencies or asplenia. Reimmunization at 5-year intervals is recommended for individuals who are at high risk. The polysaccharide vaccine should be reserved for those older than 55 years who require immunization.
- The polysaccharide vaccine is administered subcutaneously as a single 0.5-mL dose, and the conjugate vaccine is administered by IM injection.

MUMPS VACCINE

- The vaccine (usually given in conjunction with measles and rubella, MMR) is given beginning at age 12 to 15 months, with a second dose prior to entry into elementary school.
- Two doses of mumps vaccine are recommended for school-age children, international travelers, college students, and healthcare workers born after 1956.
- Postexposure vaccination is of no benefit.
- Mumps vaccine should not be given to pregnant women or immunosuppressed patients. The vaccine should not be given within 6 weeks (preferably 3 months) of administration of Ig.

PERTUSSIS VACCINE

- Acellular pertussis vaccine is usually administered in combination with diphtheria and tetanus toxoids (as DTaP).
- The primary immunization series for pertussis vaccine consists of four doses given at ages 2, 4, 6, and 15 to 18 months. A booster dose is recommended at age 4 to 6 years. Pertussis vaccine is administered in combination with diphtheria and tetanus (DTaP). Administration of an acellular pertussis-containing vaccine is also recommended for adolescents once between ages 11 and 18 years. In addition, adolescents should receive a pertussis-containing vaccine with their next dose of Td toxoids.

- Systemic reactions, such as moderate fever, occur in 3% to 5% of those receiving vaccines. Very rarely, high fever, febrile seizures, persistent crying spells, and hypotonic hyporesponsive episodes occur after vaccination.
- There are only two contraindications to pertussis administration: (1) an immediate anaphylactic reaction to a previous dose and (2) encephalopathy within 7 days of a previous dose, with no evidence of other cause.

PNEUMOCOCCAL VACCINES

- Pneumococcal polysaccharide vaccine is a mixture of capsular polysaccharides from 23 of the 83 most prevalent types of *Streptococcus pneumoniae* seen in the United States.
- Pneumococcal vaccine is recommended for the following immunocompetent persons:
  - ✓ Persons 65 years or older. If an individual received vaccine more than 5 years earlier and was younger than 65 at the time of administration, revaccination should be given.
  - ✓ Persons ages 2 to 64 years with chronic illness
  - ✓ Persons ages 2 to 64 years with functional or anatomical asplenia. When splenectomy is planned, pneumococcal vaccine should be given at least 2 weeks before surgery.
  - ✓ Persons ages 2 to 64 years living in environments where the risk of invasive pneumococcal disease or its complications is increased. This does not include daycare center employees and children.
- Pneumococcal vaccination is recommended for immunocompromised persons 2 years of age or older with
  - ✓ HIV infection
  - ✓ Leukemia, lymphoma, Hodgkin disease, or multiple myeloma
  - ✓ Generalized malignancy
  - ✓ Chronic renal failure of nephritic syndrome
  - ✓ Patients receiving immunosuppressive therapy
  - ✓ Organ or bone marrow transplant recipients
- Because children younger than 2 years do not respond adequately to the pneumococcal polysaccharide vaccine, a heptavalent pneumococcal conjugate vaccine (PCV) was created that can be administered at 2, 4, and 6 months of age and between 12 and 15 months of age.
- PCV 13 valent, (PCV13) is administered as a 0.5-mL IM injection at 2, 4, and 6 months of age and between 12 and 15 months of age. A single dose of PCV13 should be administered to children aged 6 to 18 years with sickle cell disease or splenic dysfunction, HIV infection, immunocompromising conditions, cochlear implant, or cerebral spinal fluid leak should be immunized. It is also licensed for individuals aged 50 years and older.

POLIOVIRUS VACCINES

- Two types of trivalent poliovirus vaccines are currently licensed for distribution in the United States: an enhanced inactivated poliovirus vaccine (IPV) and a live-attenuated, oral poliovirus vaccine (OPV). IPV is the recommended vaccine for the primary series and booster dose for children in the United States, whereas OPV is recommended in areas of the world that have circulating poliovirus.
- IPV is given to children ages 2, 4, and 6 to 18 months and 4 to 6 years. Primary poliomyelitis immunization is recommended for all children and young adults up to age 18 years. Allergies to any component of IPV, including streptomycin, polymyxin B, and neomycin, are contraindications to vaccine use.
- The routine use of OPV in the United States has been discontinued. OPV is not recommended for persons who are immunodeficient or for normal individuals

who reside in a household where another person is immunodeficient. It should not be given during pregnancy because of the small but theoretical risk to the fetus.

RUBELLA VACCINE

- The vaccine is given with measles and mumps vaccines (MMR) at 12 to 15 months of age, then at 4 to 6 years.
- The vaccine should not be given to immunosuppressed individuals, although MMR vaccine should be administered to young children with HIV without severe immunosuppression as soon as possible after their first birthday. The vaccine should not be given to individuals with anaphylactic reaction to neomycin.
- Although the vaccine has not been associated with congenital rubella syndrome, its use in pregnancy is contraindicated. Women should be counseled not to become pregnant for 4 weeks after vaccination.

VARICELLA VACCINE

1. Varicella virus vaccine is recommended for all children 12 to 18 months of age, with a second dose prior to entering school between 4 and 6 years of age. It is also recommended for persons above this age if they have not had chickenpox. Persons ages 13 years and older should receive two doses separated by 4 to 8 weeks.

- The vaccine is contraindicated in immunosuppressed or pregnant patients.
- Children with asymptomatic or mildly symptomatic HIV should receive two doses of varicella vaccine 3 months apart.

VARICELLA ZOSTER VACCINE

1. The zoster vaccine is recommended for immunocompetent individuals older than 60 years. It should not be used in immunocompromised individuals, including those with HIV or malignancies or in pregnant women.

- Administration of varicella zoster Ig is by the IM route (never IV).

IMMUNOGLOBULIN

1. Ig is available as both IM (IGIM) and IV (IGIV) preparations.

- **Table 51–5** lists the suggested dosages for IGIM in various disease states.
- The uses for IGIV are as follows:
  - ✓ Primary immunodeficiency states, including both antibody deficiencies and combined deficiencies
  - ✓ Idiopathic thrombocytopenic purpura

TABLE 51–5 Indications and Dosage of Intramuscular Immunoglobulin in Infectious Diseases

Primary immunodeficiency states	1.2 mL/kg IM, then 0.6 mL/kg every 2–4 weeks
Hepatitis A exposure	0.02 mL/kg IM within 2 weeks if <1 year or >39 years of age
Hepatitis A prophylaxis	0.02 mL/kg IM for exposure <3 months' duration
	0.06 mL/kg IM for exposure up to 5 months' duration
Hepatitis B exposure	0.06 mL/kg (hepatitis B immunoglobulin preferred in known exposures)
Measles exposure	0.25 mL/kg (maximum dose 15 mL) as soon as possible
	0.5 mL/kg (maximum dose 15 mL) as soon as possible for immunocompromised individuals
Varicella exposure	0.6–1.2 mL/kg as soon as possible when varicella zoster immunoglobulin is not available

✓ Chronic lymphocytic leukemia in patients who have had a serious bacterial infection
✓ Kawasaki disease (mucocutaneous lymph node syndrome)
✓ Bone marrow transplant
✓ Varicella zoster

RHO(D) IMMUNOGLOBULIN

1. Rho(D) Ig (RDIg) suppresses the antibody response and formation of anti-Rho(D) in Rho(D)-negative, D^u-negative women exposed to Rho(D)-positive blood and prevents the future chance of erythroblastosis fetalis in subsequent pregnancies with a Rho(D)-positive fetus.

- RDIg, when administered IM within 72 hours of delivery of a full-term infant, reduces active antibody formation from 12% to between 1% and 2%.
- RDIg is also used in the case of a premenopausal woman who is Rho(D) negative and has inadvertently received Rho(D)-positive blood or blood products.
- RDIg may be used after abortion, miscarriage, amniocentesis, or abdominal trauma.

See Chapter 102, Vaccines, Toxoids, and Other Immunobiologics, authored by Mary S. Hayney, for a more detailed discussion of this topic.

CHAPTER 52

Alzheimer's Disease

- *Alzheimer's disease* (AD) is a progressive and eventually fatal dementia of unknown cause characterized by loss of cognitive and physical functioning, commonly with behavior symptoms.

PATHOPHYSIOLOGY

- Dominantly inherited forms of AD are fewer than 1% of cases. More than half of young-onset, dominantly inherited cases are attributed to alterations on chromosomes 1, 14, or 21. Genetic susceptibility to late-onset AD is primarily linked to the apolipoprotein E (APOE) genotype, but an interaction of multiple genes with the environment may be at play.
- Risk factors associated with AD include age, decreased reserve capacity of the brain, head injury, Down syndrome, depression, mild cognitive impairment, and risk factors for vascular disease, including hypertension, elevated low-density lipoprotein cholesterol, low high-density lipoprotein cholesterol, and diabetes.
- Signature findings include intracellular neurofibrillary tangles (NFTs), extracellular amyloid plaques in the cortex and medial temporal lobe, and degeneration of neurons and synapses and cortical atrophy. Density of NFTs correlates with severity of dementia.
- Proposed mechanisms for these changes include (1) β-amyloid protein aggregation, leading to formation of plaques; (2) hyperphosphorylation of tau protein, leading to NFTs; (3) synaptic failure and depletion of neurotrophin and neurotransmitters; (4) mitochondrial dysfunction; and (5) oxidative stress.
- Of neurotransmitter deficits, loss of cholinergic activity is most prominent, and it correlates with AD severity. Cholinergic cell loss seems to be a consequence of AD pathology, not the cause of it.
- Other neurotransmitter considerations include the following: (1) Serotonergic neurons of the raphe nuclei and noradrenergic cells of the locus ceruleus are lost; (2) monoamine oxidase type B activity is increased; (3) glutamate pathways of the cortex and limbic structures are abnormal; and (4) excitatory neurotransmitters, including glutamate, may be neurotoxic in AD.

CLINICAL PRESENTATION

- Cognitive decline is gradual and includes memory loss, aphasia, apraxia, agnosia, disorientation, and impaired executive function. Other symptoms include depression, psychotic symptoms, aggression, motor hyperactivity, uncooperativeness, wandering, and combativeness. Patients become increasingly unable to care for themselves. **Table 52–1** shows the stages of AD.

DIAGNOSIS

- The diagnostic criteria of the National Institute on Aging and the Alzheimer's Association view AD as a spectrum beginning with an asymptomatic preclinical

TABLE 52–1	Stages of Alzheimer's Disease
Mild (MMSE score 26–18)	Patient has difficulty remembering recent events. Ability to manage finances, prepare food, and carry out other household activities declines. May get lost while driving. Begins to withdraw from difficult tasks and to give up hobbies. May deny memory problems
Moderate (MMSE score 17–10)	Patient requires assistance with activities of daily living. Frequently disoriented with regard to time (date, year, and season). Recall for recent events is severely impaired. May forget some details of past life and names of family and friends. Functioning may fluctuate from day to day. Patient generally denies problems. May become suspicious or tearful. Loses ability to drive safely. Agitation, paranoia, and delusions are common
Severe (MMSE score 9–0)	Patient loses ability to speak, walk, and feed self. Incontinent of urine and feces. Requires care 24 hours a day, 7 days a week

MMSE, Mini-Mental Status Examination.

phase progressing to the symptomatic preclinical phase and then to the dementia phase. AD is a clinical diagnosis, based largely on identified symptoms and difficulty with activities of daily living revealed by patient and caregiver interviews.

- In the future, improved brain imaging and validated biomarkers of disease will enable a more sophisticated diagnosis with identified cognitive strengths and weaknesses and neuroanatomic localization of deficits.
- Patients with suspected AD should have a history and physical examination with appropriate laboratory tests (serum B_{12}, folate, thyroid panel, blood cell counts, serum electrolytes, and liver function tests), and computed tomography or magnetic resonance imaging may aid diagnosis. To exclude other diagnoses, cerebrospinal fluid analysis or an electroencephalogram can occasionally be justified.
- Obtain information on medication use; alcohol or other substance use; family medical history; and history of trauma, depression, or head injury. Rule out medication use (eg, anticholinergics, sedatives, hypnotics, opioids, antipsychotics, and anticonvulsants) as contributors to dementia symptoms. Rule out medications that could contribute to delirium (eg, digoxin, nonsteroidal anti-inflammatory drugs [NSAIDs], histamine 2 [H_2] receptor antagonists, amiodarone, antihypertensives, and corticosteroids).
- The Folstein Mini-Mental State Examination (MMSE) can help establish a history of deficits in two or more areas of cognition at baseline against which to evaluate change in severity over time. The average expected decline in an untreated patient is 2 to 4 points per year.

TREATMENT

- Goals of Treatment: The goal of treatment in AD is to maintain functioning as long as possible, with a secondary goal to treat the psychiatric and behavioral sequelae.
- For mild to moderate AD, consider use of a cholinesterase inhibitor, and titrate to maintenance dose. For moderate to severe AD, consider adding memantine, and titrate to maintenance dose. Alternatively, consider memantine or cholinesterase inhibitor alone. Treat behavior symptoms with support and behavior interventions, and use pharmacological management only if necessary.

NONPHARMACOLOGIC THERAPY

- Sleep disturbances, wandering, urinary incontinence, agitation, and aggression should be managed with behavioral and environmental interventions whenever possible.

- On initial diagnosis, the patient and caregiver should be educated on the course of illness, available treatments, legal decisions, changes in lifestyle that will become necessary, and other quality-of-life issues.

PHARMACOTHERAPY OF COGNITIVE SYMPTOMS

- Managing blood pressure, cholesterol, and blood sugar may reduce the risk of developing AD.
- Reasonable expectations of treatment may be a slowed decline in abilities and delayed long-term care placement.
- Those who respond to treatment may lose the benefits when medication is stopped.

Cholinesterase Inhibitors

- Table 52–2 summarizes dosing of the cholinesterase inhibitors and **memantine**. When switching from one cholinesterase inhibitor to another, 1 week washout is generally sufficient.
- No comparative trials have assessed the effectiveness of one agent over another. **Donepezil**, **rivastigmine**, and **galantamine** are indicated in mild to moderate AD; donepezil is also indicated for severe AD.
- If the decline in MMSE score is more than 2 to 4 points after treatment for 1 year with the initial agent, it is reasonable to change to a different cholinesterase inhibitor. Otherwise, treatment should be continued with the initial medication throughout the course of the illness. The three cholinesterase inhibitors have similar efficacy in mild to moderate AD, and duration of benefit lasts 3 to 12 months. Because of their short half-lives, if rivastigmine or galantamine treatment is interrupted for several days or longer, retitrate starting at the lowest dose.
- The most frequent adverse effects include mild to moderate gastrointestinal (GI) symptoms (nausea, vomiting, and diarrhea), urinary incontinence, dizziness, headache, syncope, bradycardia, muscle weakness, salivation, and sweating. Abrupt discontinuation can cause worsening of cognition and behavior in some patients. Table 52–3 shows side effects and monitoring parameters.

Other Drugs

- **Memantine** (Namenda) blocks glutamatergic neurotransmission by antagonizing *N*-methyl-D-aspartate receptors, which may prevent excitotoxic reactions. It is used as monotherapy and in combination with a cholinesterase inhibitor. It is indicated for treatment of moderate to severe AD, but not for mild AD. It is not metabolized by the liver but is primarily excreted unchanged in the urine. Dosing must be adjusted in patients with renal impairment. It is usually well tolerated; side effects include constipation, confusion, dizziness, and headache.
- Guidelines recommend low-dose **aspirin** in AD patients with significant brain vascular disease.
- Trials do not support the use of **estrogen** to prevent or treat dementia.
- **Vitamin E** is under investigation for prevention of AD and is not recommended for treatment of AD.
- Because of the incidence of side effects and a lack of supporting evidence, neither **NSAIDs** nor **prednisone** is recommended for treatment or prevention of AD.
- Trials of ***statin*** drugs have not shown significant benefit in prevention or treatment of AD.
- Because of limited efficacy data, the potential for adverse effects (eg, nausea, vomiting, diarrhea, headache, dizziness, restlessness, weakness, and hemorrhage), and poor standardization of herbal products, ginkgo biloba is not recommended for prevention or treatment of AD.
- Do not use ginkgo biloba in individuals taking anticoagulants or antiplatelet drugs, and use cautiously in those taking **NSAIDs**.
- **Huperzine A** has not been adequately evaluated and is not currently recommended for treatment of AD.

TABLE 52–2 Dosing of Drugs Used for Cognitive Symptoms

Drug	Brand Name	Initial Dose	Usual Range	Special Population Dose	Other
Cholinesterase Inhibitors					
Donepezil	Aricept®, Aricept® ODT®	5 mg daily in the evening	5–10 mg daily in mild to moderate AD 10–23 mg daily in moderate to severe AD		Available as: tablet, orally disintegrating tablet (ODT) Can be taken with or without food Weight loss associated with 23 mg daily dose
Rivastigmine	Exelon®, Exelon® Patch	1.5 mg twice daily (capsule, oral solution) 4.6 mg/day (transdermal patch)	3–6 mg twice a day (capsule, oral solution) 9.5–13.3 mg/day (transdermal patch)	Moderate to severe renal impairment, mild to moderate hepatic impairment, or low body weight (<50 kg [110 lb]): consider maximum daily dose of 4.6 mg every 24 hours (transdermal patch)	Available as: capsule, oral solution, transdermal patch Take with meals Also indicated for dementia associated with Parkinson's disease Application of multiple transdermal patches at same time associated with hospitalization and death
Galantamine	Razadyne®, Razdyne® ER	4 mg twice daily (tablet, oral solution) 8 mg daily in the morning (extended-release capsule)	8–12 mg twice a day (tablet, oral solution) 16–24 mg (extended-release capsule)	Moderate renal or hepatic impairment: maximum daily dose of 16 mg Severe renal or hepatic impairment: not recommended	Available as: tablet, oral solution, extended-release capsule Take with meals
***N*-Methyl-d-Aspartate (NMDA) Receptor Antagonist**					
Memantine	Namenda®, Namenda® XR	5 mg daily 7 mg daily (extended-release capsule)	10 mg twice daily 28 mg daily (extended-release capsule)	Severe renal impairment: target maintenance dose of 5 mg twice daily (tablet, oral solution) or 14 mg daily (extended-release capsule)	Available as: tablet, oral solution, extended-release capsule Can be taken with or without food

ODT, orally disintegrating tablet.

TABLE 52–3 Monitoring Drug Therapy for Cognitive Symptoms

Drug	Adverse Drug Reaction	Monitoring Parameter	Comments
Cholinesterase inhibitors	Dizziness, syncope, bradycardia, atrial arrhythmias, myocardial infarction, angina, seizures, sinoatrial and atrioventricular block	Report of dizziness or falls, pulse, blood pressure, and postural blood pressure change	Dizziness is usually mild, transient, and not related to cardiovascular problems Routine pulse checks at baseline, monthly during titration, and every 6 months thereafter
Cholinesterase inhibitors	Nausea, vomiting, diarrhea, anorexia, and weight loss	Weight and GI complaints	Take with food to decrease GI upset Usually transient, dose-related GI adverse effects seen with drug initiation, dosage titration, or drug switch Debilitated patients or those weighing <55 kg (121 lb) may be more likely to experience GI adverse effects and significant weight loss, particularly when rivastigmine is prescribed or when titrating to donepezil 23 mg GI adverse effects less prominent with transdermal versus oral rivastigmine
Cholinesterase inhibitors	Peptic ulcer disease, GI bleeding	Signs or symptoms of active or occult GI bleeding	Of particular concern for patients at increased risk of developing ulcers, such as those with a history of ulcer disease or concurrently taking NSAIDs
Cholinesterase inhibitors	Insomnia, vivid/abnormal dreams, nightmares	Complaints of sleep disturbances, daytime drowsiness	Donepezil can be taken in the morning to decrease risk of sleep disturbances
Memantine	Headache, confusion, dizziness, hallucinations	Report of dizziness or falls, hallucinations	Confusion may be observed during dose titration and is usually transient Memantine may mitigate GI adverse effects associated with cholinesterase inhibitor therapy
Memantine	Constipation	GI complaints	

NSAIDs, nonsteroidal antiinflammatory drugs.

PHARMACOTHERAPY OF NONCOGNITIVE SYMPTOMS

- Pharmacotherapy for noncognitive symptoms targets psychotic symptoms, inappropriate or disruptive behavior, and depression. Medications and recommended doses are shown in Table 52–4.
- General guidelines include the following: (1) Use environmental interventions first and pharmacotherapy only when necessary; (2) identify and correct underlying causes of disruptive behaviors when possible; (3) start with reduced doses and titrate slowly; (4) monitor closely; (5) periodically attempt to taper and discontinue medication; and (6) document carefully.
- Avoid anticholinergic psychotropic medications as they may worsen cognition.

Cholinesterase Inhibitors and Memantine

- **Cholinesterase inhibitors** and **memantine** have shown modest improvement of behavioral symptoms over time but may not significantly reduce acute agitation.

Antipsychotics

- Antipsychotic medications have traditionally been used for disruptive behaviors and neuropsychiatric symptoms, but the risks and benefits must be carefully weighed.
- A meta-analysis found that only 17% to 18% of dementia patients showed a modest treatment response with atypical antipsychotics. Adverse events (eg, somnolence, extrapyramidal symptoms, abnormal gait, worsening cognition, cerebrovascular events, and increased risk of death [see black-box warning]) offset advantages. Another systematic review and meta-analysis found small but significant improvement in behavioral symptom scores in patients treated with **aripiprazole**, **olanzapine**, and **risperidone**.
- Typical antipsychotics may also produce a small increased risk of death, and more severe extrapyramidal effects and hypotension than the atypicals.
- Antipsychotic treatment in AD patients should rarely be continued beyond 12 weeks.

TABLE 52–4 Medications Used for Noncognitive Symptoms of Dementia

Drugs	Starting Dose (mg)	Maintenance Dose in Dementia (mg/day)	Target Symptoms
Antipsychotics			
Aripiprazole	10–15	30 (maximum)	Psychosis: hallucinations, delusions, suspiciousness Disruptive behaviors: agitation, aggression
Olanzapine	2.5	5–10	
Quetiapine	25	100–400	
Risperidone	0.25	0.5–2	
Antidepressants			
Citalopram	10	10–20	Depression: poor appetite, insomnia, hopelessness, anhedonia, withdrawal, suicidal thoughts, agitation, anxiety
Escitalopram	5	10 (maximum)	
Fluoxetine	10	10–20	
Paroxetine	10	10–40	
Sertraline	12.5	150 (maximum)	
Mirtazapine	15	15–30	
Trazodone	25	75–150	
Anticonvulsants			
Carbamazepine	100	300–600	Agitation or aggression
Valproic acid	125	500–1,500	

Antidepressants

- Depression and dementia share many symptoms, and the diagnosis of depression can be difficult, especially later in the course of AD.
- **A selective serotonin reuptake inhibitor** (SSRI) is usually given to depressed patients with AD, and the best evidence is for **sertraline** and **citalopram**. **Tricyclic antidepressants** are usually avoided.

Miscellaneous Therapies

- Use of **benzodiazepines is** not advised except on an "as needed" basis for infrequent episodes of agitation.
- **Carbamazepine**, **valproic acid**, and **gabapentin** may be alternatives, but evidence is conflicting.

EVALUATION OF THERAPEUTIC OUTCOMES

- At baseline interview both patient and caregiver, identify target symptoms; define therapeutic goals; and document cognitive status, physical status, functional performance, mood, thought processes, and behavior.
- MMSE for cognition, Physical Self-Maintenance Scale for activities of daily living, and Neuropsychiatric Inventory Questionnaire for assessment of behavioral disturbances should be used to quantify changes in symptoms and functioning.
- Observe the patient carefully for potential side effects. The specific side effects to be monitored and the method and frequency of monitoring should be documented.
- Assess for drug effectiveness, side effects, adherence to regimen, and need for dosage adjustment or change in treatment at least monthly. Several months to 1 year of treatment may be required to determine whether therapy is beneficial.

See Chapter 38, Alzheimer's Disease, authored by Patricia W. Slattum, Emily P. Peron, and Angela Massey Hill, for a more detailed discussion of this topic.

Epilepsy

CHAPTER 53

- *Epilepsy* is defined by the occurrence of at least two unprovoked seizures with or without convulsions (ie, violent, involuntary contraction[s] of the voluntary muscles) separated by at least 24 hours. A seizure results from an excessive discharge of cortical neurons and is characterized by changes in electrical activity as measured by the electroencephalogram (EEG).

PATHOPHYSIOLOGY

- Seizures result from excessive excitation or from disordered inhibition of neurons. Initially, a small number of neurons fire abnormally. Normal membrane conductances and inhibitory synaptic currents then break down, and excitability spreads locally (focal seizure) or more widely (generalized seizure).
- Mechanisms that may contribute to synchronous hyperexcitability include (1) alterations of ion channels in neuronal membranes, (2) biochemical modifications of receptors, (3) modulation of second messaging systems and gene expression, (4) changes in extracellular ion concentrations, (5) alterations in neurotransmitter uptake and metabolism in glial cells, (6) modification in the ratio and function of inhibitory circuits, and (7) local imbalances between the main neurotransmitters (eg, glutamate, γ-aminobutyric acid [GABA]) and neuromodulators (eg, acetylcholine, norepinephrine, and serotonin)
- Prolonged seizures and continued exposure to glutamate can result in neuronal injury, functional deficits, and rewiring of neuronal circuitry.

CLINICAL PRESENTATION

- The International Classification of Epileptic Seizures (**Table 53–1**) classifies epilepsy on the basis of clinical description and electrophysiologic findings.
- Many patients, particularly those with complex partial or generalized tonic-clonic (GTC) seizures, are amnestic to the actual seizure event.

SYMPTOMS AND SIGNS

- Symptoms depend on seizure type. Although seizures can vary between patients, they tend to be stereotyped within an individual.
- Partial (focal) seizures begin in one hemisphere of the brain and, unless they become secondarily generalized, result in an asymmetric seizure. Partial seizures manifest as alterations in motor functions, sensory or somatosensory symptoms, or automatisms. Patients may have memory loss or aberrations of behavior. A partial seizure that becomes generalized is termed a *secondarily generalized seizure.* In complex partial seizures, there is impairment of consciousness and no memory of the event.
- Absence seizures generally occur in young children or adolescents and exhibit a sudden onset, interruption of ongoing activities, a blank stare, and possibly a brief upward rotation of the eyes. There is only a very brief (seconds) period of altered consciousness. Absence seizures have a characteristic two to four cycles per second spike and slow-wave EEG pattern.
- GTC seizures are major convulsive episodes and are always associated with a loss of consciousness. Motor symptoms are bilateral. GTC seizures may be preceded by premonitory symptoms (ie, an aura). A tonic-clonic seizure that is preceded by an aura is likely a partial seizure that is secondarily generalized. Tonic-clonic seizures begin with a short tonic contraction of muscles followed by a period of rigidity and clonic movements. The patient may lose sphincter control, bite the tongue, or become cyanotic. The episode is frequently followed by a deep sleep.

TABLE 53–1 International Classification of Epileptic Seizures

I. Partial seizures (seizures begin locally)
A. Simple (without impairment of consciousness)
1. With motor symptoms
2. With special sensory or somatosensory symptoms
3. With psychic symptoms
B. Complex (with impairment of consciousness)
1. Simple partial onset followed by impairment of consciousness—with or without automatisms
2. Impaired consciousness at onset—with or without automatisms
C. Secondarily generalized (partial onset evolving to generalized tonic–clonic seizures)
II. Generalized seizures (bilaterally symmetrical and without local onset)
A. Absence
B. Myoclonic
C. Clonic
D. Tonic
E. Tonic–clonic
F. Atonic
G. Infantile spasms
III. Unclassified seizures
IV. Status epilepticus

- Interictally (between seizure episodes), there are typically no objective, pathognomonic signs of epilepsy.
- Myoclonic jerks are brief shock-like muscular contractions of the face, trunk, and extremities. They may be isolated events or rapidly repetitive.
- In atonic seizures, there is a sudden loss of muscle tone that may be described as a head drop, dropping of a limb, or slumping to the ground.

DIAGNOSIS

- Ask the patient and family to characterize the seizure for frequency, duration, precipitating factors, time of occurrence, presence of an aura, ictal activity, and postictal state.
- Physical and neurologic examination and laboratory examination may identify an etiology.

LABORATORY TESTS

- In some cases, particularly following GTC (or perhaps complex partial) seizures, serum prolactin levels may be transiently elevated. A serum prolactin level obtained within 10 to 20 minutes of a tonic-clonic seizure can help differentiate seizure activity from pseudoseizure activity but not from syncope.
- Laboratory tests (SMA-20 [sequential multichannel analysis], complete blood cell count, urinalysis, and special blood chemistries) may be done to rule out treatable causes of seizures (hypoglycemia, altered serum electrolyte concentrations, infections, etc) that do not represent epilepsy. A lumbar puncture may be indicated if there is fever.

OTHER DIAGNOSTIC TESTS

- EEG is very useful in the diagnosis of various seizure disorders, but epileptiform activity is found in only about 50% of patients with epilepsy.
- Although magnetic resonance imaging is very useful (especially imaging of the temporal lobes), computed tomography typically is not helpful except in the initial evaluation for a brain tumor or cerebral bleeding.

TREATMENT

- Goals of Treatment: The goals are to control or reduce the frequency and severity of seizures, minimize side effects, and ensure compliance, allowing the patient to live as normal a life as possible. Complete suppression of seizures must be balanced against tolerability of side effects, and the patient should be involved in defining the balance. Side effects and comorbidities (eg, anxiety, depression) as well as social issues (eg, driving, job security, relationships, social stigma) have significant impact on quality of life.

GENERAL APPROACH

- Drug selection depends on the type of epilepsy (**Table 53–2**), drug-specific adverse effects, and patient preferences. **Figure 53–1** is a suggested algorithm for treatment of epilepsy.
- Begin with monotherapy. About 65% of patients can be maintained on one antiepileptic drug (AED) and be well controlled, although not necessarily seizure free.
- Up to 60% of patients with epilepsy are noncompliant; this is the most common reason for treatment failure.
- Drug therapy may not be indicated in patients who have had only one seizure or those whose seizures have minimal impact on their lives. Patients who have had two or more seizures should generally be started on AEDs.
- Factors favoring successful withdrawal of AEDs include a seizure-free period of 2 to 4 years, complete seizure control within 1 year of onset, an onset of seizures after age 2 years and before age 35 years, and a normal EEG and neurologic examination. Poor prognostic factors include a history of a high frequency of seizures, repeated episodes of status epilepticus, a combination of seizure types, and development of abnormal mental functioning. A 2-year, seizure-free period is suggested for absence and rolandic epilepsy, whereas a 4-year, seizure-free period is suggested for simple partial, complex partial, and absence associated with tonic-clonic seizures. According to the American Academy of Neurology Guidelines, discontinuation of AEDs may be considered in patients seizure free for 2 to 5 years, if there is a single type of partial seizure or primary GTC seizures, if the neurologic examination and IQ are normal, and if the EEG normalized with treatment. Always withdraw AEDs gradually.

MECHANISM OF ACTION

- The mechanism of action of most AEDs includes effects on ion channel (sodium and Ca) kinetics, augmentation of inhibitory neurotransmission (increasing CNS GABA), and modulation of excitatory neurotransmission (decreasing or antagonizing glutamate and aspartate). AEDs effective against GTC and partial seizures probably work by delaying recovery of sodium channels from activation. Drugs that reduce corticothalamic T-type Ca currents are effective against generalized absence seizures.

SPECIAL CONSIDERATIONS IN THE FEMALE PATIENT

- Estrogen has a seizure-activating effect, whereas progesterone has a seizure-protective effect. Enzyme-inducing AEDs (eg, phenobarbital, phenytoin, carbamazepine, topiramate, oxcarbazepine, and perhaps rufinamide, lamotrigine, clobazam, and felbamate) may cause treatment failures in women taking **oral contraceptives**; a supplemental form of birth control is advised if breakthrough bleeding occurs.
- For catamenial epilepsy (seizures just before or during menses) or seizures that occur at the time of ovulation, conventional AEDs should be tried first, but intermittent

TABLE 53–2 Drugs of Choice for Specific Seizure Disorders

Seizure Type	First-Line Drugs	Alternative Drugs[a]	Comments
Partial seizures (newly diagnosed)			
U.S. guidelines	*Adults and adolescents:*		*FDA approved:*
	Carbamazepine		Carbamazepine
	Gabapentin		Lacosamide
	Oxcarbazepine		Phenobarbital
	Phenobarbital		Phenytoin
	Phenytoin		Topiramate
	Topiramate		Valproic acid
	Valproic acid		
U.K. guidelines	Carbamazepine	Levetiracetam	
	Lamotrigine	Oxcarbazepine	
		Valproic acid	
ILAE guidelines	*Adults:*	*Adults:*	
	Carbamazepine	Gabapentin	
	Phenytoin	Lamotrigine	
	Valproic acid	Oxcarbazepine	
		Phenobarbital	
		Topiramate	
	Children:	*Children:*	
	Oxcarbazepine	Phenobarbital	
		Phenytoin	
		Topiramate	
		Valproic acid	
	Elderly:	*Elderly:*	
	Gabapentin	Carbamazepine	
	Lamotrigine		
U.S. Expert Panel 2005	Carbamazepine	Levetiracetam	
	Lamotrigine		
	Oxcarbazepine		
Partial seizures (refractory monotherapy)			
U.S. guidelines	Lamotrigine		*FDA approved:*
	Oxcarbazepine		Carbamazepine
	Topiramate		Lamotrigine
			Oxcarbazepine
			Phenobarbital
			Phenytoin
			Topiramate
			Valproic acid

(*continued*)

TABLE 53–2 Drugs of Choice for Specific Seizure Disorders (*Continued*)

Seizure Type	First-Line Drugs	Alternative Drugs[a]	Comments
U.K. guidelines	Lamotrigine Oxcarbazepine Topiramate		
Partial seizures (refractory adjunct)			
U.S. guidelines	*Adults:* Gabapentin Lamotrigine Levetiracetam Oxcarbazepine Tiagabine Topiramate Zonisamide *Children*: Gabapentin Lamotrigine Oxcarbazepine Topiramate		*FDA approved:* Carbamazepine Gabapentin Lamotrigine Levetiracetam Oxcarbazepine Phenobarbital Phenytoin Pregabalin Tiagabine Valproic acid Vigabatrin Zonisamide
U.K. guidelines	Carbamazepine Clobazam Gabapentin Lamotrigine Levetiracetam Oxcarbazepine Valproic acid Topiramate	Lacosamide Phenobarbital Phenytoin Pregabalin Tiagabine Vigabatrin Zonisamide	
Generalized seizures absence (newly diagnosed)			
U.S. guidelines	Lamotrigine		*FDA approved:* Ethosuximide Valproic acid
U.K. guidelines	Ethosuximide Lamotrigine Valproic Acid	Clobazam Clonazepam Levetiracetam Topiramate Zonisamide	
ILAE guidelines	None	Ethosuximide Lamotrigine Valproic acid	
U.S. Expert Panel 2005	Ethosuximide Valproic acid	Lamotrigine	

TABLE 53–2 Drugs of Choice for Specific Seizure Disorders (*Continued*)

Seizure Type	First-Line Drugs	Alternative Drugs[a]	Comments
Primary generalized (tonic–clonic)			
U.S. guidelines	Topiramate		*FDA approved:* Lamotrigine Levetiracetam Topiramate
U.K. guidelines	In following order: Valproic acid Lamotrigine Carbamazepine Oxcarbazepine	Clobazam Levetiracetam Topiramate	
ILAE guidelines	None	*Adults:* Carbamazepine Lamotrigine Oxcarbazepine Phenobarbital Phenytoin Topiramate Valproic acid *Children:* Carbamazepine Phenobarbital Phenytoin Topiramate Valproic acid	
U.S. Expert Panel 2005	Valproic acid	Lamotrigine Topiramate	
Juvenile myoclonic epilepsy			
			FDA approved: Levetiracetam (myoclonic seizures)
U.K. guidelines	Ethosuximide Lamotrigine Valproic acid	Clobazam Clonazepam Levetiracetam Topiramate Zonisamide	

(*continued*)

TABLE 53–2 Drugs of Choice for Specific Seizure Disorders (*Continued*)

Seizure Type	First-Line Drugs	Alternative Drugs[a]	Comments
ILAE	None	Clonazepam	
		Lamotrigine	
		Levetiracetam	
		Topiramate	
		Valproic acid	
		Zonisamide	
U.S. Expert Panel 2005	Valproic acid	Levetiracetam	
		Topiramate	
		Zonisamide	

ILAE, International League Against Epilepsy.
[a]Includes possibly effective drugs.

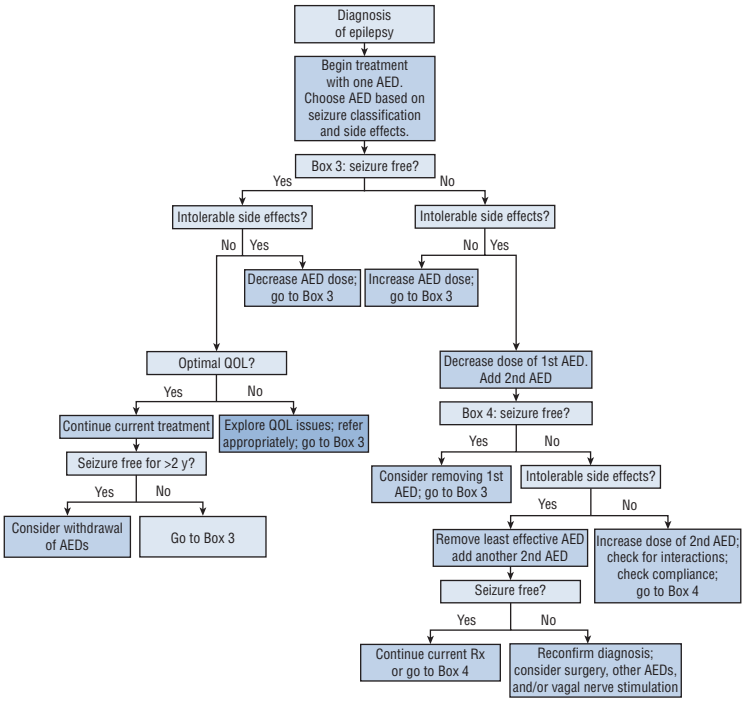


FIGURE 53–1. Algorithm for the treatment of epilepsy. (AED, antiepileptic drug; QOL, quality of life.)

supplementation with higher-dose AEDs or benzodiazepines should be considered. **Acetazolamide** has been used with limited success. **Progestational agents** may also be effective.

- About 25% to 30% of women have increased seizure frequency during pregnancy, and a similar percentage have decreased frequency.
- AED monotherapy is preferred in pregnancy. Clearance of **phenytoin**, **carbamazepine**, **phenobarbital**, **ethosuximide**, **lamotrigine**, **oxcarbazepine**, **levetiracetam**, **topiramate**, and **clorazepate** increases during pregnancy, and protein binding may be reduced. There is a higher incidence of adverse pregnancy outcomes in women with epilepsy, and the risk of congenital malformations is 4% to 6% (twice as high as in nonepileptic women).
- **Barbiturates** and **phenytoin** are associated with congenital heart malformations and facial clefts. **Carbamazepine** has a 0.5% to 1% risk for spina bifida and hypospadias. Topiramate may have a negative effect on birth weight and increase the risk for oral cleft and hypospadias.
- **Valproic acid** has a 1% to 2% risk of neural tube defects and an increased risk of neurodevelopmental deficits, reduced verbal abilities, and poorer attentional tasks. Teratogenicity can occur at lower doses, but the risk for major congenital malformations significantly increases at doses of 600 mg/day and largest risk is seen at doses greater than 1000 mg/day.
- Other adverse outcomes of maternal seizures are growth, psychomotor, and mental retardation. Some teratogenic events can be prevented by adequate **folate** intake; **prenatal vitamins with folic acid** (~0.4–5 mg/day) should be given to women of childbearing potential who are taking AEDs. Higher folate doses should be used in women with a history of a previous pregnancy with a neural tube defect or taking valproic acid. **Vitamin K**, 10 mg/day orally, given to the mother during the last month before delivery can prevent neonatal hemorrhagic disorder. Alternatively, parenteral vitamin K can be given to the newborn at delivery.

PHARMACOKINETICS AND SPECIAL POPULATIONS

- AED pharmacokinetic data are summarized in **Table 53–3**. For populations known to have altered plasma protein binding, measure free rather than total serum concentrations if the AED is highly protein bound. Conditions altering AED protein binding include chronic renal failure, liver disease, hypoalbuminemia, burns, pregnancy, malnutrition, displacing drugs, and age (neonates and the elderly). Unbound concentration monitoring is especially useful for **phenytoin**.
- Neonates and infants display decreased efficiency in renal elimination and may metabolize drugs more slowly, but by age 2 or 3 years children may metabolize drugs more rapidly than adults. Thus, neonates and infants require lower doses of AED, but children require higher doses of many AEDs than adults. Lower doses of AEDs are often required in the elderly. Some elderly patients have increased receptor sensitivity to CNS drugs, making the accepted therapeutic range invalid.

THE ROLE OF SERUM CONCENTRATION MONITORING

- **Table 53–4** shows dosing and target serum concentration ranges for AEDs. Seizure control may occur before the "minimum" of the therapeutic serum range is reached, and some patients may need serum concentrations beyond the "maximum." The therapeutic range for AEDs may be different for different seizure types (eg, higher for complex partial seizures than for GTC seizures). Clinicians should determine the optimal serum concentration for each patient. Serum concentration determinations can be useful to document lack of or loss of efficacy, establish noncompliance, and guide therapy in patients with renal and/or hepatic disease and patients taking multiple drugs, as well as in women who are pregnant or taking **oral contraceptives**.

TABLE 53–3 Antiepileptic Drug Pharmacokinetic Data

AED	$t_{1/2}$ (Hours)	Time to Steady State (Days)	Unchanged (%)	V_D (L/kg)	Clinically Important Metabolite	Protein Binding (%)
Carbamazepine	12 M; 5–14 Co	21–28 for completion of autoinduction	<1	1–2	10,11-epoxide	40–90
Clobazam	36–42	7–14	3	1.4	*N*-desmethyl clobazam	80–90
Ethosuximide	A 60; C 30	6–12	10–20	0.67	No	0
Ezogabine	7–11	3–4	36%	2–3	*n*-Acetylmetabolite	80
Felbamate	16–22	5–7	50	0.73–0.82	No	~25
Gabapentin[a]	5–40[b]	1–2	100	0.65–1.04	No	0
Lacosamide	13	3	40	0.6	No	<15
Lamotrigine	25.4 M	3–15	0	1.28	No	40–50
Levetiracetam	7–10	2		0.7	No	<10
Oxcarbazepine	3–13	2		0.7	10-Hydroxy-carbazepine	40
Phenobarbital	A 46–136; C 37–73	14–21	20–40	0.6	No	50
Phenytoin	A 10–34; C 5–14	7–28	<5	0.6–8.0	No	90
Pregabalin	A 6–7[b]	1–2	90	0.5	No	0
Primidone	A 3.3–19; C 4.5–11	1–4	40	0.43–1.1	PB	80
Rufinamide	6–10	2	4	0.8-1.2	No	26–35
Tiagabine	5–13		Negligible		No	95

Topiramate	18–21	4–5	50–70	0.55–0.8 (male); 0.23–0.4 (female)	No	15
Valproic acid	A 8–20; C 7–14	1–3	<5	0.1–0.5	May contribute to toxicity	90–95 binding saturates
Vigabatrin	5–8	N/A	<2	0.8	No	0
Zonisamide	24–60	5–15		0.8–1.6	No	40–60

A, adult; AED, antiepileptic drug; C, child; Co, combination therapy; M, monotherapy; N/A, not applicable since effect depends on inhibiting enzyme; PB, phenobarbital; V_D, volume of distribution.

[a]The bioavailability of gabapentin is dose-dependent.
[b]Half-life depends on renal function.

TABLE 53–4 Antiepileptic Drugs Dosing and Target Serum Concentration Ranges

Drug	Brand Name	Initial or Starting Dose	Usual Range or Maximum Dose	Comments Target Serum Concentration Range
Barbiturates				
Phenobarbital	Various	1–3 mg/kg/day (10–20 mg/kg LD)	180–300 mg	10–40 mcg/mL (43–172 µmol/L)
Primidone	Mysoline	100–125 mg/day	750–2,000 mg	5–10 mcg/mL (23-46 µmol/L)
Benzodiazepines				
Clobazam	Onfi	≤30 kg 5 mg/day; >30 kg 10 mg/day	≤30 kg up to 20 mg; >30 kg up to 40 mg	0.03–0.3 ng/mL (0.1–1.0 nmol/L)
Clonazepam	Klonopin	1.5 mg/day	20 mg	20–70 ng/mL (0.06–0.22 µmol/L)
Diazepam	Valium	PO: 4–40 mg IV: 5–10 mg	PO: 4–40 mg IV: 5–30 mg	100–1,000 ng/mL (0.4–3.5 µmol/L)
Lorazepam	Ativan	PO: 2–6 mg IV: 0.05 mg/kg IM: 0.05 mg/kg	PO: 10 mg IV: 0.05 mg/kg	10–30 ng/mL (31–93 nmol/L)
Hydantoin				
Phenytoin	Dilantin	PO: 3–5 mg/kg (200–400 mg) (15–20 mg/kg LD)	PO: 500–600 mg	Total: 10–20 mcg/mL (40–79 µmol/L) Unbound: 0.5–3 mcg/mL (2–12 µmol/L)
Succinimide				
Ethosuximide	Zarontin	500 mg/day	500–2,000 mg	40–100 mcg/mL (282–708 µmol/L)
Other				
Carbamazepine	Tegretol	400 mg/day	400–2,400 mg	4–12 mcg/mL (17–51 µmol/L)

Ezogabine	Potiga	300 mg/day	1,200 mg	Not defined
Felbamate	Felbatol	1,200 mg/day	3,600 mg	30–60 mcg/mL (126–252 µmol/L)
Gabapentin	Neurontin	300–900 mg/day	4,800 mg	2–20 mcg/mL (12–117 µmol/L)
Lacosamide	Vimpat	100 mg/day	400 mg	Not defined
Lamotrigine	Lamictal	25 mg every other day if on VPA; 25–50 mg/day if not on VPA	100–150 mg if on VPA; 300–500 mg if not on VPA	4–20 mcg/mL (16–78 µmol/L)
Levetiracetam	Keppra Keppra XR	500–1,000 mg/day	3,000–4,000 mg	12–46 mcg/mL (70–270 µmol/L)
Oxcarbazepine	Trileptal	300–600 mg/day	2,400–3,000 mg	3–35 mcg/mL (MHD) (12–139 µmol/L)
Pregabalin	Lyrica	150 mg/day	600 mg	Not defined
Rufinamide	Banzel	400–800 mg/day	3,200 mg	Not defined
Tiagabine	Gabitril	4–8 mg/day	80 mg	0.02–0.2 mcg/mL (0.05–0.5 µmol/L)
Topiramate	Topamax	25–50 mg/day	200–1,000 mg	5–20 mcg/mL (15–59 µmol/L)
Valproic acid	Depakene Depakene SR Depakote Depakote ER Depacon	15 mg/kg (500–1,000 mg)	60 mg/kg (3,000–5,000 mg)	50–100 mcg/mL (347–693 µmol/L)
Vigabatrin	Sabril	1,000 mg/day	3,000 mg	0.8–36 mcg/mL (6–279 µmol/L)
Zonisamide	Zonegran	100–200 mg/day	600 mg	10–40 mcg/mL (47–188 µmol/L)

IM, intramuscular; LD, loading does; MHD, 10-monohydroxy-derivative; PO, orally; VPA, valproic acid.

EFFICACY

- The traditional treatment of tonic-clonic seizures is **phenytoin** or **phenobarbital**, but **carbamazepine** and **valproic acid** use is increasing, as efficacy is equal and side effects are more favorable.
- In a landmark Veterans Affairs study, **carbamazepine** and **valproic acid** had equal retention rates for tonic-clonic seizures, but **carbamazepine** was superior for partial seizures and **valproic acid** caused slightly more adverse effects.
- In the United States, **carbamazepine** and **phenytoin** are the most commonly prescribed AEDs for partial seizures.
- Studies suggest that as monotherapy for partial seizures, **lamotrigine** is as effective as **carbamazepine** and **phenytoin**; lamotrigine may be better tolerated in the elderly. Clinical data suggest that **oxcarbazepine** is as effective as **phenytoin**, **valproic acid**, and **immediate-release carbamazepine**, with perhaps fewer side effects. **Levetiracetam** was found to have equal efficacy and tolerability with controlled-release carbamazepine.
- The newer AEDs were first approved as adjunctive therapy for refractory partial seizures. To date, **lamotrigine**, **topiramate**, **oxcarbazepine**, and **felbamate** have the Food and Drug Administration (FDA) approval as monotherapy in patients with partial seizures, but felbamate causes significant side effects.
- Absence seizures are best treated with **ethosuximide**, **valproic acid**, and perhaps **lamotrigine**. For a combination of absence and other generalized or partial seizures, **valproic acid** or lamotrigine is preferred. If valproic acid is ineffective in treating a mixed seizure disorder that includes absence, **ethosuximide** should be used in combination with another AED.

ADVERSE EFFECTS

- AED side effects and monitoring are shown in **Table 53–5**. Concentration-dependent side effects can often be alleviated by decreasing the dose or avoided by increasing the dose very slowly.
- When acute organ failure occurs, it usually happens within the first 6 months of AED therapy.
- Patients of Southeast Asian heritage who are to receive **carbamazepine** or possibly **phenytoin** can be screened for HLA-B*1502 antigen, which places them at higher risk for Stevens–Johnson syndrome as well as toxic epidermal necrolysis. Also, the HLA genotype HLA-A*3101 is associated with carbamazepine-induced skin reactions in Chinese, Japanese, and European people.
- Any patient taking AEDs who complains of lethargy, vomiting, fever, or rash should have a laboratory assessment, including white blood cell counts and liver function tests.
- **Valproic acid** may cause less cognitive impairment than **phenytoin** and **phenobarbital**. Some of the newer agents (eg, **gabapentin** and **lamotrigine**) likely cause fewer cognitive impairments than the older agents (eg, **carbamazepine**). **Topiramate** may cause substantial cognitive impairment.
- **Phenytoin**, **carbamazepine**, **phenobarbital**, **oxcarbazepine**, **felbamate**, and **valproic acid** may interfere with vitamin D metabolism, causing asymptomatic high-turnover bone disease with normal bone mineral density (BMD) or decreased BMD and osteoporosis. Laboratory tests may reveal elevated bone-specific alkaline phosphatase and decreased serum Ca and 25-OH vitamin D, as well as intact parathyroid hormone. Patients taking these drugs should get supplemental vitamin D and calcium and BMD testing if other risk factors for osteoporosis are present.

DRUG–DRUG INTERACTIONS

- **Table 53–6** shows AED elimination pathways and major effects on hepatic enzymes. Use caution when AEDs are added or discontinued.
- **Phenobarbital**, **phenytoin**, **primidone**, and **carbamazepine** are potent inducers of cytochrome P450 (CYP450), epoxide hydrolase, and uridine diphosphate

TABLE 53–5 Antiepileptic Drug Side Effects and Monitoring

	Adverse Drug Reaction Acute Side Effects		
Drug	**Concentration Dependent**	**Idiosyncratic**	**Chronic Side Effects**
Carbamazepine	Diplopia Dizziness Drowsiness Nausea Unsteadiness Lethargy	Blood dyscrasias Rash (HLA antigen testing may be relevant to avoid Stevens–Johnson or toxic epidermal necrolysis)	Hyponatremia Metabolic bone disease (monitor vit D and serum calcium)
Clobazam	Somnolence Sedation Pyrexia Ataxia	Drooling Aggression Irritability Constipation	
Ethosuximide	Ataxia Drowsiness GI distress (avoid by multiple daily dosing) Unsteadiness Hiccoughs	Blood dyscrasias Rash	Behavior changes Headache

(*continued*)

TABLE 53–5 Antiepileptic Drug Side Effects and Monitoring (*Continued*)

	Adverse Drug Reaction Acute Side Effects		
Drug	**Concentration Dependent**	**Idiosyncratic**	**Chronic Side Effects**
Ezogabine	Dizziness Somnolence Fatigue Confusion Vertigo Tremors Blurred vision	Urinary retention QT prolongation (get baseline EKG and during treatment) Euphoria	Not established
Felbamate	Anorexia Nausea Vomiting Insomnia Headache	Aplastic anemia (follow CBC) Acute hepatic failure (follow liver enzymes)	Not established
Gabapentin	Dizziness Fatigue Somnolence Ataxia	Pedal edema	Weight gain
Lacosamide	Dizziness Vertigo	Liver enzyme elevation	Not established

	Headache Nausea Vomiting PR interval increase (get baseline EKG and during treatment)		
Lamotrigine	Diplopia Dizziness Unsteadiness Headache	Rash (slower titration of dose may decrease chance of occurrence)	Not established
Levetiracetam	Sedation Behavioral disturbance	Psychosis (rare but more common in elderly or persons with mental illness)	Not established
Oxcarbazepine	Sedation Dizziness Ataxia Nausea	Rash	Hyponatremia
Phenobarbital	Ataxia Hyperactivity Headache Unsteadiness Sedation Nausea	Blood dyscrasias Rash	Behavior changes Connective tissue disorders Intellectual blunting Metabolic bone disease Mood change Sedation

(*continued*)

TABLE 53–5 Antiepileptic Drug Side Effects and Monitoring (*Continued*)

	Adverse Drug Reaction Acute Side Effects		
Drug	**Concentration Dependent**	**Idiosyncratic**	**Chronic Side Effects**
Phenytoin	Ataxia	Blood dyscrasias	Behavior changes
	Nystagmus	Rash (HLA antigen testing may be relevant to avoid Stevens–Johnson or toxic epidermal necrolysis)	Cerebellar syndrome (occurs high serum levels)
	Behavior changes		
	Dizziness	Immunologic reaction	Connective tissue changes
	Headache		Skin thickening
	Incoordination		Folate deficiency
	Sedation		Gingival hyperplasia
	Lethargy		Hirsutism
	Cognitive impairment		Coarsening of facial features
	Fatigue		Acne
	Visual blurring		Cognitive impairment
			Metabolic bone disease (monitor vit D and serum calcium)
			Sedation
Pregabalin	Dizziness	Pedal edema	Weight gain
	Somnolence	Creatine kinase elevation	
	Incoordination	Decrease platelets	
	Dry mouth		
	Blurred vision		

Primidone	Behavior changes Headache Nausea Sedation Unsteadiness	Blood dyscrasias Rash	Behavior change Connective tissue disorders Cognitive impairment Sedation
Rufinamide	Dizziness Nausea Vomiting Somnolence	Multiorgan hypersensitivity Status epilepticus Leukopenia QT shortening	Not established
Tiagabine	Dizziness Fatigue Difficulties concentrating Nervousness Tremor Blurred vision Depression Weakness	Spike-wave stupor	Not established
Topiramate	Difficulties concentrating Psychomotor slowing Speech or language problems	Metabolic acidosis Acute angle glaucoma Oligohydrosis	Kidney stones Weight loss

(*continued*)



TABLE 53–5 Antiepileptic Drug Side Effects and Monitoring (*Continued*)

	Adverse Drug Reaction Acute Side Effects		
Drug	**Concentration Dependent**	**Idiosyncratic**	**Chronic Side Effects**
	Somnolence, fatigue Dizziness Headache		
Valproic acid	GI upset Sedation Unsteadiness Tremor Thrombocytopenia	Acute hepatic failure Acute pancreatitis Alopecia	Polycystic ovary-like syndrome (increase incidence in females <20 years or overweight) Weight gain Hyperammonemia Menstrual cycle irregularities
Vigabatrin	Permanent vision loss Fatigue Somnolence Weight gain Tremor Blurred vision	Abnormal MRI brain signal changes (infants with infantile spasms) Peripheral neuropathy Anemia	Permanent vision loss (greater frequency, adults vs. children vs. infants)
Zonisamide	Sedation Dizziness Cognitive impairment Nausea	Rash (is a sulfa drug) Metabolic acidosis Oligohydrosis	Kidney stones Weight loss

TABLE 53–6 Antiepileptic Drugs Elimination Pathways and Major Effects on Hepatic Enzymes

Antiepileptic Drugs	Major Hepatic Enzymes	Renal Elimination (%)	Induced	Inhibited
Carbamazepine	CYP3A4; CYP1A2; CYP2C8	<1	CYP1A2; CYP2C; CYP3A; GT	None
Clobazam	CYP3A4; CYP2C19; CYP2B6	0	CYP3A4 (weak)	CYP2D6
Ethosuximide	CYP3A4	12–20	None	None
Ezogabine	GT; acetylation	85	None	None
Felbamate	CYP3A4; CYP2E1; other	50	CYP3A4	CYP2C19; β-oxidation
Gabapentin	None	Almost completely	None	None
Lacosamide	CYP2C19	70	None	None
Lamotrigine	GT	10	GT	None
Levetiracetam	None (undergoes nonhepatic hydrolysis)	66	None	None
Oxcarbazepine (MHD is active oxcarbazepine metabolite)	Cytosolic system	1	CYP3A4; CYP3A5; GT	CYP2C19
		(27 as MHD)		
Phenobarbital	CYP2C9; other	25	CYP3A; CYP2C; GT	None
Phenytoin	CYP2C9; CYP2C19	5	CYP3A; CYP2C; GT	
Pregabalin	None	100	None	None
Rufinamide	Hydrolysis	2	CYP3A4 (weak)	CYP2E1 (weak)
Tiagabine	CYP3A4	2	None	None
Topiramate	Not known	70	CYP3A (dose dependent)	CYP2C19
Valproate	GT; β-oxidation	2	None	CYP2C9; GT epoxide hydrolase
Vigabatrin	None	Almost completely	CYP2C9	None
Zonisamide	CYP3A4	35	None	None

CYP, cytochrome P450 isoenzyme system; GT, glucuronyltransferase.

glucuronosyltransferase enzyme systems. **Valproic acid** inhibits many hepatic enzyme systems and displaces some drugs from plasma albumin.
- **Felbamate** and **topiramate** can act as inducers with some isoforms and inhibitors with others.
- Except for **levetiracetam** and **gabapentin**, which are eliminated mostly unchanged by the renal route, AEDs are metabolized wholly or in part by hepatic enzymes.

CLINICAL APPLICATION

- AED dosing is shown in **Table 53–4**. **Tables 53–3**, **53–5**, and **53–6** show AED pharmacokinetics, side effects and monitoring, and elimination pathways, respectively.
- Usually dosing is initiated at one-fourth to one-third of the anticipated maintenance dose and gradually increased over 3 or 4 weeks to an effective dose.

Carbamazepine

- Food may enhance the bioavailability of **carbamazepine**.
- Controlled- and sustained-release preparations dosed every 12 hours are bioequivalent to immediate-release preparations dosed every 6 hours. The sustained-release capsule can be opened and sprinkled on food.
- Hyponatremia occurs less frequently than with oxcarbazepine, but periodic serum sodium concentrations are recommended, especially in the elderly.
- Leukopenia is the most common hematologic side effect (up to 10%) but is usually transient. It may be persistent in 2% of patients. Carbamazepine may be continued unless the white blood cell count drops to less than 2500/mm^3 (2.5×10^9/L) and the absolute neutrophil count drops to less than 1000/mm^3 (1×10^9/L).
- Rashes may occur in 10% of patients. Other side effects include nausea, hepatitis, osteomalacia, cardiac conduction defects, and lupus-like reactions.
- Carbamazepine may interact with other drugs by inducing their metabolism. **Valproic acid** increases concentrations of the 10,11-epoxide metabolite without affecting the concentration of carbamazepine. The interaction of **erythromycin** and **clarithromycin** (CYP3A4 inhibition) with carbamazepine is particularly significant.
- Loading doses are used only in critically ill patients.
- Although some patients, especially those on monotherapy, may be maintained on twice-a-day dosing, most patients, especially children, will require dosing two to four times daily. Larger doses can be given at bedtime. Dose increases can be made every 2 to 3 weeks.

Clobazam

- Abrupt discontinuation can cause a withdrawal syndrome (eg, behavioral disorder, tremor, anxiety, dysphoria, insomnia, convulsions, psychosis).
- As an inducer of CYP3A4, clobazam may lower serum levels of some oral contraceptives. In the elderly and poor metabolizers of CYP2C19, initiate dosing as in patients weighing less than 30 kg. Many patients develop some tolerance.
- It is more effective than clonazepam for Lennox–Gastaut syndrome but less effective than clonazepam for myoclonic jerks and absence seizures. It is adjunctive treatment for seizures of Lennox–Gastaut syndrome.

Ethosuximide

- No loading dose is needed; titration over 1 to 2 weeks to maintenance doses of 20 mg/kg/day usually produces therapeutic serum concentrations. It is usually given in two equal doses daily.
- There is some evidence for nonlinear metabolism at higher serum concentrations.
- Valproic acid may inhibit metabolism of **ethosuximide**, but only if the metabolism of ethosuximide is near saturation.

Ezogabine

- Dose reduction is recommended in the elderly.
- It can cause urinary retention and QT prolongation.

- Alcohol may increase systemic exposure to **ezogabine** with an increase in side effects.
- It may cause falsely elevated results on urine and serum bilirubin laboratory tests.
- It must be taken three times daily.

Felbamate

- **Felbamate** is approved for atonic seizures in patients with Lennox–Gastaut syndrome and is effective for partial seizures as well. Because of reports of aplastic anemia (1 in 3000 patients) and hepatitis (1 in 10,000 patients), felbamate is recommended only for patients refractory to other AEDs. Risk factors for aplastic anemia may include a history of cytopenia, AED allergy or toxicity, viral infection, and/or immunologic problems.

Gabapentin

- **Gabapentin** is a second-line agent for patients with partial seizures who have failed initial treatment. It may also have a role in patients with less severe seizure disorders, such as new-onset partial epilepsy, especially in elderly patients.
- Bioavailability decreases with increasing doses (ie, is a saturable process). It is eliminated exclusively renally, and dosage adjustment is necessary in patients with impaired renal function.
- Dosing is initiated at 300 mg at bedtime and increased to 300 mg twice daily on the second day and 300 mg three times daily on the third day. Further titrations are then made. The manufacturer recommends usual maintenance doses from 1800 to 2400 mg/day.

Lacosamide

- **Lacosamide** is a schedule V controlled substance.
- There is a linear relationship between daily doses and serum concentrations up to 800 mg/day. Moderate hepatic and renal impairment both increase systemic drug exposure by up to 40%.
- Lacosamide can cause a small increase in the median PR interval.
- The starting dose is 100 mg/day in two divided doses, with dose increase by 100 mg/day every week until a daily dose of 200 mg to 400 mg has been reached.

Lamotrigine

- **Lamotrigine** is useful as both adjunctive therapy for partial seizures and as monotherapy. It may also be a useful alternative for primary generalized seizures, such as absence and as adjunctive therapy for primary GTC seizures.
- Rashes are usually generalized, erythematous, and morbilliform, but Stevens–Johnson reaction has also occurred. The incidence of the more serious rashes appears to be increased in patients who are also receiving **valproic acid** and who have rapid dosage titration. Valproic acid substantially inhibits the metabolism of lamotrigine and alters dosing (see **Table 53–4**).

Levetiracetam

- Renal elimination of unchanged drug accounts for 66% of **levetiracetam** clearance, and the dose should be adjusted for impaired renal function. It has linear pharmacokinetics and is metabolized in blood by nonhepatic enzymatic hydrolysis.
- It is effective in the adjunctive treatment of partial seizures in adults who have failed initial therapy.
- Adverse effects include sedation, fatigue, coordination difficulties, agitation, irritability, and lethargy. A slight decline in red and white blood cells was noted in clinical trials.
- The recommended initial dose is 500 mg orally twice daily. In some intractable seizure patients, the oral dose has been titrated rapidly over 3 days up to 3000 mg/day (1500 mg twice daily).

Oxcarbazepine

- Patients with significant renal impairment may require dose adjustment. The relationship between dose and serum concentration is linear. It does not autoinduce its own metabolism.
- It is indicated for use as monotherapy or adjunctive therapy for partial seizures in adults and children as young as 4 years of age. It is also a potential first-line drug for patients with primary, generalized convulsive seizures.
- It generally has fewer side effects than **phenytoin**, **valproic acid**, or **carbamazepine**. Hyponatremia is reported in up to 25% of patients and is more likely in the elderly. About 25% to 30% of patients who have had a rash with carbamazepine will have a similar reaction with oxcarbazepine.
- Concurrent use of oxcarbazepine with **ethinyl estradiol** and **levonorgestrel**-containing contraceptives may render these agents less effective. Oxcarbazepine may increase serum concentrations of **phenytoin** and decrease serum concentrations of **lamotrigine** (induction of uridine diphosphate glucuronosyltransferase).
- In patients converted from carbamazepine, the typical maintenance doses of oxcarbazepine are 1.5 times the carbamazepine dose or less if patients are on larger carbamazepine doses. See manufacturer's recommendations for dosing by weight.

Phenobarbital

- Phenobarbital, a potent enzyme inducer, interacts with many drugs. Diuretics and urinary alkalinizers increase the amount of phenobarbital excreted renally.
- Phenobarbital impairs cognitive performance. In children, paradoxical hyperactivity can occur.
- **Ethanol** increases phenobarbital metabolism, but **valproic acid**, **cimetidine**, and **chloramphenicol** inhibit its metabolism.
- Phenobarbital can usually be dosed once daily, and bedtime dosing may minimize daytime sedation.

Phenytoin

- **Phenytoin** is a first-line AED for primary generalized convulsive seizures and for partial seizures.
- Absorption may be saturable at higher doses. Do not change brands without careful monitoring. Food may slow absorption. The intramuscular route is best avoided, as absorption is erratic. Fosphenytoin can safely be administered IV and intramuscularly, and it is ordered in phenytoin equivalents. Equations are available to normalize the phenytoin concentration in patients with hypoalbuminemia or renal failure.
- Zero-order kinetics occurs within the usual therapeutic range, so any change in dose may produce disproportional changes in serum concentrations.
- In nonacute situations, phenytoin may be initiated in adults at oral doses of 5 mg/kg/day and titrated upward. Subsequent dosage adjustments should be done cautiously because of nonlinearity in elimination. Most adult patients can be maintained on a single-daily dose, but children often require more frequent administration. Only extended-release preparations should be used for single-daily dosing.
- One author suggested that if the phenytoin serum concentration is less than 7 mcg/mL (28 μmol/L), the daily dose should be increased by 100 mg; if the concentration is 7 to 12 mcg/mL (28 to 48 μmol/L), the daily dose can be increased by 50 mg; and if the concentration is greater than 12 mcg/mL (48 μmol/L), the daily dose can be increased by 30 mg or less.
- At concentrations greater than 50 mcg/mL (200 μmol/L), phenytoin can exacerbate seizures.
- Phenytoin is prone to many drug interactions. If protein-binding interactions are suspected, free rather than total phenytoin serum concentrations are a better therapeutic guide.
- Phenytoin decreases **folic acid** absorption, but folic acid replacement enhances phenytoin clearance and can result in loss of efficacy. Phenytoin tablets and suspension contain phenytoin acid, whereas the capsules and parenteral solution are phenytoin

sodium. One hundred mg of phenytoin acid is equal to 92 mg of phenytoin sodium. Caution: There are two different strengths of phenytoin suspension and capsules.

Pregabalin

- **Pregabalin**, a schedule V controlled substance, is a second-line agent for patients with partial seizures who have failed initial treatment.
- It is eliminated unchanged primarily by renal excretion; dosage adjustment is required in patients with significant renal dysfunction.
- Drug interactions are unlikely.

Rufinamide

- **Rufinamide** is an adjunctive agent used for Lennox–Gastaut syndrome in patients who have failed valproic acid, topiramate, and lamotrigine.
- Children may have a higher clearance of rufinamide than adults.
- It is dosed twice daily because of slow absorption and a short half-life.
- Multiorgan hypersensitivity has occurred within 4 weeks of dose initiation in children younger than 12 years.

Tiagabine

- **Tiagabine** is considered second-line therapy for patients with partial seizures who have failed initial therapy.
- Side effects are usually transient and can be diminished by taking it with food.
- Tiagabine is displaced from protein by **naproxen**, **salicylates**, and **valproate**.
- Minimal effective adult dosing level is 30 mg/day.

Topiramate

- **Topiramate** is a first-line AED for patients with partial seizures as an adjunct or for monotherapy. It is also approved for tonic-clonic seizures in primary generalized epilepsy.
- Approximately 50% of the dose is excreted renally, and tubular reabsorption may be prominently involved.
- Nephrolithiasis occurs in 1.5% of patients. It has also been associated with acute narrow-angle glaucoma, word-finding difficulties, oligohidrosis, and metabolic acidosis.
- Enzyme inducers may decrease topiramate serum levels. It increases the clearance of ethinyl estradiol.
- Dose increments may occur every 1 or 2 weeks. For patients on other AEDs, doses greater than 600 mg/day do not appear to lead to improved efficacy and may increase side effects.

Valproic Acid and Divalproex Sodium

- The free fraction may increase as the total serum concentration increases, and monitoring free concentrations may be more useful than total concentrations, especially at higher serum concentrations and in patients with hypoalbuminemia.
- At least 10 metabolites have been identified, and some may be active. One may account for hepatotoxicity (4-*ene*-valproic acid), and it is increased by enzyme-inducing drugs. Most hepatotoxicity deaths were in mentally retarded children younger than 2 years who were receiving multiple drug therapy.
- It is first-line therapy for primary generalized seizures, such as absence, myoclonic, and atonic seizures, and is approved for adjunctive and monotherapy treatment of partial seizures. It can also be useful in mixed seizure disorders.
- GI complaints may be minimized with the enteric-coated formulation or by giving with food. Thrombocytopenia is common but is responsive to a decrease in dose. Pancreatitis is rare.
- Although **carnitine** administration may partially ameliorate hyperammonemia, it is expensive and only limited data support routine supplementation in patients taking valproic acid.
- Valproic acid is an enzyme inhibitor that increases serum concentrations of concurrently administered **phenobarbital**, **carbamazepine 10,11-epoxide** (without

affecting concentrations of the parent drug), and **lamotrigine**. Carbapenems and combination oral contraceptives may lower serum levels of valproic acid.
- Twice-daily dosing is reasonable, but children and patients taking enzyme inducers may require three- or four-times-daily dosing.
- The enteric-coated tablet **divalproex sodium** causes fewer GI side effects. It is metabolized in the gut to valproic acid. When switching from Depakote to Depakote-ER, the dose should be increased by 14% to 20%. Depakote ER may be given once daily.

Vigabatrin

- **Vigabatrin** is first-line for infantile spasms and a third-line adjunctive agent for refractory partial epilepsy.
- It is excreted unchanged in the urine; dosage adjustment is necessary in renally impaired patients.
- It can cause permanent bilateral concentric visual field constriction and reduce visual acuity. Vision should be checked at baseline and every 3 months for up to 6 months after discontinuation. It may aggravate myoclonic and absence seizures.
- Vigabatrin induces CYP2C and decreases phenytoin plasma levels by ~20%.

Zonisamide

- **Zonisamide**, a broad-spectrum **sulfonamide** AED, is approved as adjunctive therapy for partial seizures, but it is potentially effective in a variety of partial and primary generalized seizure types.
- Word-finding difficulties can occur. Symptomatic kidney stones may occur in 2.6% of patients. As hypersensitivity reactions may occur in 0.02% of patients, use it cautiously (if at all) in patients with a history of sulfonamide allergy. Monitoring of renal function may be advisable in some patients.
- Start dosing in adults at 100 mg/day and increase by 100 mg/day every 2 weeks until a response is seen. It is suitable for once- or twice-daily dosing, but once-daily dosing may cause more side effects.

EVALUATION OF THERAPEUTIC OUTCOMES

- Monitor long term for seizure control, side effects, social adjustment, including quality of life, drug interactions, compliance, and side effects. Clinical response is more important than serum drug concentrations.
- Screen periodically for psychiatric disorders (eg, anxiety, depression).
- Ask patients and caregivers to record severity and frequency of seizures.

See Chapter 40, Epilepsy, authored by Susan J. Rogers and Jose E. Cavazos, for a more detailed discussion of this topic.

CHAPTER 54

Headache: Migraine and Tension-Type

MIGRAINE HEADACHE

- *Migraine*, a common, recurrent, primary headache of moderate to severe intensity, interferes with normal functioning and is associated with gastrointestinal (GI), neurologic, and autonomic symptoms. In migraine with aura, focal neurologic symptoms precede or accompany the attack.

PATHOPHYSIOLOGY

- Activation of trigeminal sensory nerves triggers the release of vasoactive neuropeptides, including calcitonin gene-related peptide, neurokinin A, and substance P from perivascular axons. Vasodilation of dural blood vessels may occur with extravasation of dural plasma resulting in inflammation.
- Twin studies suggest 50% heritability of migraine, with a multifactorial polygenic basis. Migraine triggers may be modulators of the genetic set point that predisposes to migraine headache.
- Specific populations of serotonin (5-HT) receptors appear to be involved in the pathophysiology and treatment of migraine headache. **Ergot alkaloids** and **triptan** derivatives are agonists of vascular and neuronal 5-HT_1 receptors, resulting in vasoconstriction and inhibition of vasoactive neuropeptide release.

CLINICAL PRESENTATION AND DIAGNOSIS

- Migraine headache is characterized by recurring episodes of throbbing head pain, frequently unilateral.
- Approximately 12% to 79% of migraineurs have premonitory symptoms (not to be confused with aura) in the hours or days before headache onset. Neurologic symptoms (phonophobia, photophobia, hyperosmia, and difficulty concentrating) are most common, but psychological (anxiety, depression, euphoria, irritability, drowsiness, hyperactivity, and restlessness), autonomic (eg, polyuria, diarrhea, and constipation), and constitutional (eg, stiff neck, yawning, thirst, food cravings, and anorexia) symptoms may also occur.
- A migraine aura is experienced by approximately 25% of migraineurs. Aura evolves over 5 to 20 minutes and lasts less than 60 minutes. Headache usually occurs within 60 minutes of the end of the aura. Visual auras can include both positive features (eg, scintillations, photopsia, teichopsia, and fortification spectrum) and negative features (eg, scotoma and hemianopsia). Sensory and motor symptoms such as paresthesias or numbness of the arms and face, dysphasia or aphasia, weakness, and hemiparesis may also occur.
- Migraine headache may occur at any time but usually occurs in the early morning. Pain is usually gradual in onset, peaking in intensity over minutes to hours and lasting 4 to 72 hours. Pain is typically in the frontotemporal region and is moderate to severe. Headache is usually unilateral and throbbing with GI symptoms (eg, nausea and vomiting) almost invariably accompanying the headache. Other systemic symptoms include anorexia, constipation, diarrhea, abdominal cramps, nasal stuffiness, blurred vision, diaphoresis, facial pallor, and localized facial, scalp, or periorbital edema. Sensory hyperacuity (photophobia, phonophobia, or osmophobia) is frequent. Many patients seek a dark, quiet place.
- Once the headache pain wanes, a resolution phase characterized by exhaustion, malaise, and irritability ensues.
- A comprehensive headache history is essential and includes age at onset; frequency, timing, and duration of attacks; possible triggers; ameliorating factors; description and characteristics of symptoms; associated signs and symptoms; treatment history; and family and social history.

- Neuroimaging should be considered in patients with unexplained abnormal neurologic examination or atypical headache history.
- Onset of migraine headaches after age 50 suggests an organic etiology, such as a mass lesion, cerebrovascular disease, or temporal arteritis.

TREATMENT

- Goals of Treatment: The goal is to achieve consistent, rapid headache relief with minimal adverse effects and symptom recurrence, and minimal disability and emotional distress, thereby enabling the patient to resume normal daily activities. Ideally, patients should be able to manage their headaches effectively without emergency department or physician office visits.
- Limit use of acute migraine therapies to fewer than 10 days per month to avoid development of medication-misuse headache.

Nonpharmacologic Treatment

- Apply ice to the head and recommend periods of rest or sleep, usually in a dark, quiet environment.
- Identify and avoid triggers of migraine attacks (Table 54–1).
- Behavioral interventions (relaxation therapy, biofeedback, and cognitive therapy) may help patients who prefer nondrug therapy or when drug therapy is ineffective or not tolerated.

TABLE 54–1 Commonly Reported Triggers of Migraine

Food triggers
Alcohol
Caffeine/caffeine withdrawal
Chocolate
Fermented and pickled foods
Monosodium glutamate (e.g., in Chinese food, seasoned salt, and instant foods)
Nitrate-containing foods (e.g., processed meats)
Saccharin/aspartame (e.g., diet foods or diet sodas)
Tyramine-containing foods
Environmental triggers
Glare or flickering lights
High altitude
Loud noises
Strong smells and fumes
Tobacco smoke
Weather changes
Behavioral–physiologic triggers
Excess or insufficient sleep
Fatigue
Menstruation, menopause
Sexual activity
Skipped meals
Strenuous physical activity (e.g., prolonged overexertion)
Stress or post stress

Pharmacologic Treatment of Acute Migraine

- Administer acute migraine therapies (Table 54–2) at the onset of migraine. (See algorithm in Fig. 54–1.)
- Pretreatment with an antiemetic (eg, **metoclopramide**, **chlorpromazine**, or **prochlorperazine**) 15 to 30 minutes before oral or nonoral migraine treatments (rectal suppositories, nasal spray, or injections) may be advisable when nausea and vomiting are severe. In addition to its antiemetic effects, metoclopramide helps reverse gastroparesis and enhances absorption of oral medications.
- Frequent or excessive use of acute migraine medications can result in increasing headache frequency and drug consumption known as medication-overuse headache. This occurs commonly with overuse of simple or combination analgesics, **opiates**, **ergotamine tartrate**, and **triptans**. Limit use of acute migraine therapies to 2 or 3 days per week.

ANALGESICS AND NONSTEROIDAL ANTIINFLAMMATORY DRUGS

- **Simple analgesics** and **nonsteroidal anti-inflammatory drugs (NSAIDs)** are first-line treatments for mild to moderate migraine attacks; some severe attacks are also responsive. **Aspirin**, **diclofenac**, **ibuprofen**, **ketorolac**, **naproxen sodium**, **tolfenamic acid**, and the combination of **acetaminophen** plus **aspirin** and **caffeine** are effective.
- NSAIDs appear to prevent neurogenically mediated inflammation in the trigeminovascular system by inhibiting prostaglandin synthesis.
- In general, NSAIDs with a long half-life are preferred, as less frequent dosing is needed. Rectal suppositories and intramuscular (IM) **ketorolac** are options for patients with severe nausea and vomiting.
- The combination of **acetaminophen**, **aspirin**, and **caffeine** is approved in the United States for relieving migraine pain.
- Aspirin and acetaminophen are also available by prescription in combination with a short-acting barbiturate (**butalbital**). No randomized, placebo-controlled studies support the efficacy of butalbital-containing formulations for migraine.
- **Midrin**, a **proprietary** combination of **acetaminophen**, **isometheptene mucate** (a sympathomimetic amine), and **dichloralphenazone** (a chloral hydrate derivative), may be an alternative for patients with mild to moderate migraine attacks.

ERGOT ALKALOIDS AND DERIVATIVES

- **Ergot alkaloids** are useful for moderate to severe migraine attacks. They are nonselective $5HT_1$ receptor agonists that constrict intracranial blood vessels and inhibit the development of neurogenic inflammation in the trigeminovascular system. Venous and arterial constriction occurs. They also have activity at dopaminergic receptors.
- **Ergotamine tartrate** is available for oral, sublingual, and rectal administration. Oral and rectal preparations contain caffeine to enhance absorption and potentiate analgesia. Titrate to an effective dose that is not nauseating.
- **Dihydroergotamine (DHE)** is available for intranasal and parenteral (IM, IV, or subcutaneous [SC]) administration. Patients can self-administer IM or SC DHE.
- Nausea and vomiting are common with ergotamine derivatives, so consider antiemetic pretreatment. Other common side effects include abdominal pain, weakness, fatigue, paresthesias, muscle pain, diarrhea, and chest tightness. Symptoms of severe peripheral ischemia (ergotism) include cold, numb, painful extremities; continuous paresthesias; diminished peripheral pulses; and claudication. Gangrenous extremities, myocardial infarction (MI), hepatic necrosis, and bowel and brain ischemia have occurred rarely with ergotamine. Do not use **ergotamine derivatives** and **triptans** within 24 hours of each other.
- Contraindications to use of ergot derivatives include renal and hepatic failure; coronary, cerebral, or peripheral vascular disease; uncontrolled hypertension; sepsis; and women who are pregnant or nursing.
- DHE does not appear to cause rebound headache, but dosage restrictions for ergotamine tartrate should be strictly observed to prevent this complication.

TABLE 54–2 Dosing of Acute Migraine Therapies[a]

Drug	Dose	Usual Range/Comments
Analgesics		
Acetaminophen (Tylenol)	1,000 mg at onset; repeat every 4–6 hours as needed	Maximum daily dose is 4 g
Acetaminophen 250 mg/aspirin 250 mg/caffeine 65 mg (Excedrin Migraine)	2 tablets at onset and every 6 hours	Available as nonprescription medication as Excedrin Migraine
Nonsteroidal Antiinflammatory Drugs		
Aspirin	500–1,000 mg every 4–6 hours	Maximum daily dose is 4 g
Ibuprofen (Motrin)	200–800 mg every 6 hours	Avoid doses >2.4 g/day
Naproxen sodium (Aleve, Anaprox)	550–825 mg at onset; can repeat 220 mg in 3–4 hours	Avoid doses >1.375 g/day
Diclofenac (Cataflam, Voltaren)	50–100 mg at onset; can repeat 50 mg in 8 hours	Avoid doses >150 mg/day
Ergotamine Tartrate		
Oral tablet (1 mg) with caffeine 100 mg (Cafergot)	2 mg at onset; then 1–2 mg every 30 minutes as needed	Maximum dose is 6 mg/day or 10 mg/wk; consider pretreatment with an antiemetic
Sublingual tablet (2 mg) (Ergomar)		
Rectal suppository (2 mg) with caffeine 100 mg (Cafergot, Migergot)	Insert 0.5 to 1 suppository at onset; repeat after 1 hour as needed	Maximum dose is 4 mg/day or 10 mg/wk; consider pretreatment with an antiemetic

Dihydroergotamine		
Injection 1 mg/mL (D.H.E. 45)	0.25–1 mg at onset IM, IV, or subcutaneous; repeat every hour as needed	Maximum dose is 3 mg/day or 6 mg/wk
Nasal spray 4 mg/mL (Migranal)	One spray (0.5 mg) in each nostril at onset; repeat sequence 15 minutes later (total dose is 2 mg or four sprays)	Maximum dose is 3 mg/day; prime sprayer four times before using; do not tilt head back or inhale through nose while spraying; discard open ampules after 8 hours
Serotonin Agonists (Triptans)		
Sumatriptan (Imitrex)		
Injection	6 mg subcutaneous at onset; can repeat after 1 hour if needed	Maximum daily dose is 12 mg
Oral tablets	25, 50, 85, or 100 mg at onset; can repeat after 2 hours if needed	Optimal dose is 50–100 mg; maximum daily dose is 200 mg; combination product with naproxen, 85/500 mg
Nasal spray	5, 10, or 20 mg at onset; can repeat after 2 hours if needed	Optimal dose is 20 mg; maximum daily dose is 40 mg; single-dose device delivering 5 or 20 mg; administer one spray in one nostril
Zolmitriptan (Zomig, Zomig-ZMT)		
Oral tablets	2.5 or 5 mg at onset as regular or orally disintegrating tablet; can repeat after 2 hours if needed	Optimal dose is 2.5 mg; maximum dose is 10 mg/day
		Do not divide ODT dosage form
Nasal spray	5 mg (one spray) at onset; can repeat after 2 hours if needed	Maximum daily dose is 10 mg/day
Naratriptan (Amerge)	1 or 2.5 mg at onset; can repeat after 4 hours if needed	Optimal dose is 2.5 mg; maximum daily dose is 5 mg

(*continued*)

TABLE 54–2 Dosing of Acute Migraine Therapies[a] (*Continued*)

Drug	Dose	Usual Range/Comments
Rizatriptan (Maxalt, Maxalt-MLT)	5 or 10 mg at onset as regular or orally disintegrating tablet; can repeat after 2 hours if needed	Optimal dose is 10 mg; maximum daily dose is 30 mg; onset of effect is similar with standard and orally disintegrating tablets; use 5-mg dose (15 mg/day maximum) in patients receiving propranolol
Almotriptan (Axert)	6.25 or 12.5 mg at onset; can repeat after 2 hours if needed	Optimal dose is 12.5 mg; maximum daily dose is 25 mg
Frovatriptan (Frova)	2.5 or 5 mg at onset; can repeat in 2 hours if needed	Optimal dose 2.5–5 mg; maximum daily dose is 7.5 mg (three tablets)
Eletriptan (Relpax)	20 or 40 mg at onset; can repeat after 2 hours if needed	Maximum single dose is 40 mg; maximum daily dose is 80 mg
Miscellaneous		
Metoclopramide (Reglan)	10 mg IV at onset	Useful for acute relief in the office or emergency department setting
Prochlorperazine (Compazine)	10 mg IV or IM at onset	Useful for acute relief in the office or emergency department setting

ODT, orally disintegrating tablet.

[a]Limit use of symptomatic medications to fewer than 10 days/mo when possible to avoid medication-misuse headache.

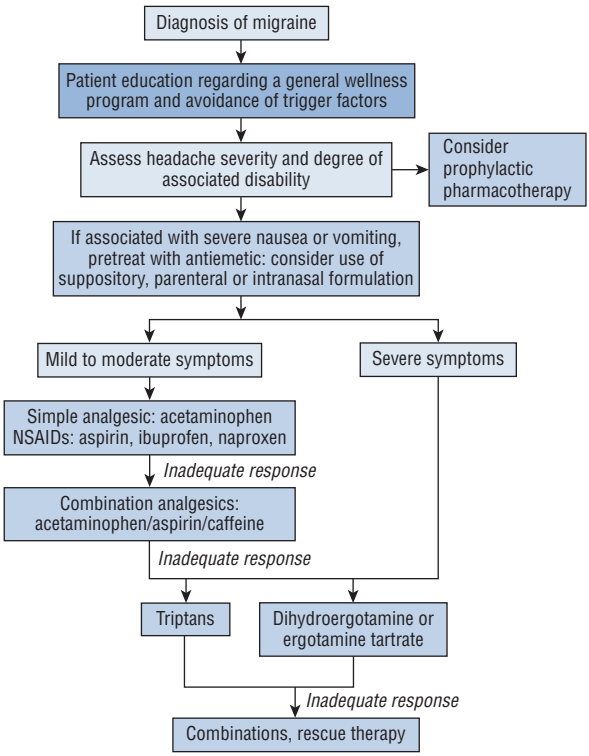


FIGURE 54–1. Treatment algorithm for migraine headaches.

SEROTONIN RECEPTOR AGONISTS (TRIPTANS)

- The **triptans (Table 54–3)** are appropriate first-line therapies for patients with mild to severe migraine or as rescue therapy when nonspecific medications are ineffective.
- They are selective agonists of the $5HT_{1B}$ and $5HT_{1D}$ receptors. Relief of migraine headache results from (1) normalization of dilated intracranial arteries, (2) inhibition of vasoactive peptide release, and (3) inhibition of transmission through second-order neurons ascending to the thalamus.
- **Sumatriptan** SC injection is packaged as an autoinjector device for self-administration. Compared with the oral formulation, SC administration offers enhanced efficacy and more rapid onset of action. Intranasal sumatriptan also has a faster onset of effect than the oral formulation and produces similar rates of response.
- Second-generation triptans (all except sumatriptan) have higher oral bioavailability and longer half-lives than oral sumatriptan, which could theoretically reduce headache recurrence. However, comparative clinical trials are necessary to determine their relative efficacy.
- Pharmacokinetic characteristics of the triptans are shown in **Table 54–3**.
- Lack of response to one triptan does not preclude effective therapy with another triptan.
- Side effects of triptans include paresthesias, fatigue, dizziness, flushing, warm sensations, and somnolence. Minor injection site reactions are reported with SC use, and taste perversion and nasal discomfort may occur with intranasal administration.

TABLE 54–3 Pharmacokinetic Characteristics of Triptans

Drug	Half-Life (Hours)	Time to Maximal Concentration (t_{max})	Bioavailability (%)	Elimination
Almotriptan	3–4	1.4–3.8 hours	80	MAO-A, CYP3A4, CYP2D6
Eletriptan	4–5	1–2 hours	50	CYP3A4
Frovatriptan	25	2–4 hours	24–30	Mostly unchanged, CYP1A2
Naratriptan	5–6	2–3 hours	63–74	Largely unchanged, CYP450 (various isoenzymes)
Rizatriptan	2–3		45	MAO-A
Oral tablets		1–1.2 hours		
Disintegrating		1.6–2.5 hours		
Sumatriptan	2			MAO-A
SC injection		12–15 minutes	97	
Oral tablets		2.5 hours	14	
Nasal spray		1–2.5 hours	17	
Zolmitriptan	3		40–48	CYP1A2, MAO-A
Oral		2 hours		
Disintegrating		3.3 hours		
Nasal		4 hours		

CYP, cytochrome P450; MAO-A, monoamine oxidase type A.

Up to 25% of patients report chest tightness; pressure; heaviness; or pain in the chest, neck, or throat. The mechanism of these symptoms is unknown, but a cardiac source is unlikely in most patients. Isolated cases of MI and coronary vasospasm with ischemia have been reported.

- Contraindications include ischemic heart disease, uncontrolled hypertension, cerebrovascular disease, hemiplegic and basilar migraine, and pregnancy. Do not give triptans within 24 hours of ergotamine derivative administration or within 2 weeks of therapy with monoamine oxidase inhibitors. Concomitant use of triptans with selective serotonin reuptake inhibitors or serotonin–norepinephrine reuptake inhibitors can cause serotonin syndrome, a potentially life-threatening condition.
- Use triptans cautiously in patients at risk for unrecognized coronary artery disease. Do a cardiovascular assessment before giving triptans to postmenopausal women, men over 40 years of age, and patients with uncontrolled risk factors, and administer the first dose under medical supervision.

OPIOIDS

- Reserve opioids and derivatives (eg, **meperidine**, **butorphanol**, **oxycodone**, and **hydromorphone**) for patients with moderate to severe infrequent headaches in whom conventional therapies are contraindicated or as rescue medication after failure to respond to conventional therapies. Closely supervise opioid therapy.

Pharmacologic Prophylaxis of Migraine

- Prophylactic therapies (Table 54–4) are administered daily to reduce the frequency, severity, and duration of attacks, and to increase responsiveness to acute therapies. (See algorithm in Fig. 54–2.)

TABLE 54–4 Dosing of Prophylactic Migraine Therapies

Drug	Initial Dose	Usual Range	Comments
***β*-Adrenergic Antagonists**			
Atenolol[a] (Tenormin)	50 mg/day	50–200 mg/day	
Metoprolol[b] (Toprol, Toprol XL)	100 mg/day in divided doses	100–200 mg/day in divided doses	Dose short-acting four times a day and long-acting two times a day; available as extended release
Nadolol[a] (Corgard)	40–80 mg/day	80–240 mg/day	
Propranolol[b] (Inderal, Inderal LA)	40 mg/day in divided doses	40–160 mg/day in divided doses	Dose short-acting two to three times a day and long-acting one to two times a day; available as extended release
Timolol[b] (Blocadren)	20 mg/day in divided doses	20–60 mg/day in divided doses	
Antidepressants			
Amitriptyline[a] (Elavil)	10 mg at bedtime	20–50 mg at bedtime	
Venlafaxine[a] (Effexor, Effexor XR)	37.5 mg/day	75–150 mg/day	Available as extended release; increase dose after 1 week
Anticonvulsants			
Topiramate[b] (Topamax)	25 mg/day	50–200 mg/day in divided doses	As effective as amitriptyline, propranolol, or valproate; increase by 25 mg/wk
Valproic acid/divalproex sodium[b] (Depakene, Depakote, Depakote ER)	250–500 mg/day in divided doses, or daily for extended release	500–1,500 mg/day in divided doses, or daily for extended release	Monitor levels if compliance is an issue
Nonsteroidal Antiinflammatory Drugs			
Ibuprofen[a] (Motrin)	400–1,200 mg/day in divided doses	Same as initial dose	Use intermittently, such as for menstrual migraine prevention; daily or prolonged use may lead to medication-overuse headache and is limited by potential toxicity

(*continued*)

TABLE 54–4 Dosing of Prophylactic Migraine Therapies (*Continued*)

Drug	Initial Dose	Usual Range	Comments
Ketoprofen[a] (Orudis)	150 mg/day in divided doses	Same as initial dose	
Naproxen sodium[a] (Aleve, Anaprox)	550–1,100 mg/day in divided doses	Same as initial dose	
Serotonin Agonists (Triptans)			
Frovatriptan[b] (Frova)	2.5 or 5 mg/day in divided doses	Same as initial dose	Taken in the perimenstrual period to prevent menstrual migraine
Naratriptan[a] (Amerge)	2 mg/day in divided doses	Same as initial dose	
Zolmitriptan[a] (Zomig)	5–7.5 mg/day in divided doses	Same as initial dose	
Miscellaneous			
Histamine[a] (Histatrol)	1–10 ng two times per week	Same as initial dose	May cause transient itching and burning at injection site
Magnesium[a]	400 mg/day	800 mg/day in divided doses	May be more helpful in migraine with aura and menstrual migraine
MIG-99[a] (feverfew)	10–100 mg/day in divided doses	Same as initial dose	Withdrawal may be associated with increased headaches
Petasites[b]	100–150 mg/day in divided doses	150 mg/day in divided doses	Use only commercial preparations; plant is carcinogenic
Riboflavin[a]	400 mg/day in divided doses	400 mg/day in divided doses	Benefit only after 3 months

[a]Level B—probably effective (one Class I or two Class II studies).
[b]Level A—established efficacy (≥2 Class I studies).

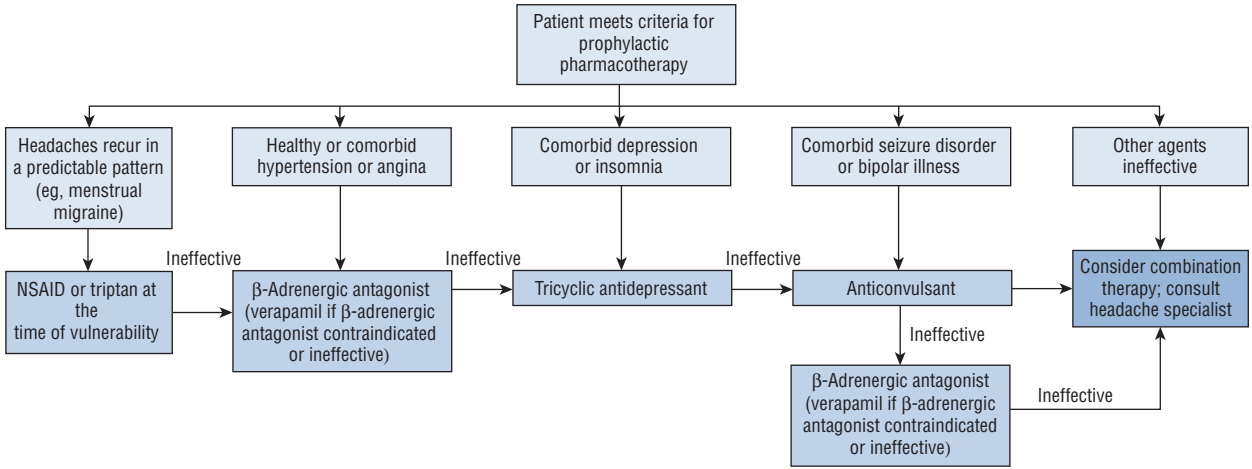


FIGURE 54–2. Treatment algorithm for prophylactic management of migraine headaches. (NSAID, nonsteroidal anti-inflammatory drug.)

- Consider prophylaxis in the setting of recurring migraines that produce significant disability; frequent attacks requiring symptomatic medication more than twice per week; symptomatic therapies that are ineffective, contraindicated, or produce serious side effects; uncommon migraine variants that cause profound disruption or risk of neurologic injury; and patient preference to limit the number of attacks.
- Preventive therapy may also be given intermittently when headaches recur in a predictable pattern (eg, exercise-induced or menstrual migraine).
- Because efficacy of various prophylactic agents appears to be similar, drug selection is based on side effect profiles and comorbid conditions. Response to an agent is unpredictable, and a 2- to 3-month trial is necessary to judge efficacy.
- Only **propranolol**, **timolol**, **divalproex sodium**, and **topiramate** are Food and Drug Administration (FDA) approved for migraine prevention.
- Initiate prophylaxis with low doses, and advance slowly until a therapeutic effect is achieved or side effects become intolerable.
- Continue prophylaxis for at least 6 to 12 months after headache frequency and severity have diminished, and then gradual tapering or discontinuation may be reasonable.

β-ADRENERGIC ANTAGONISTS

- **Propranolol**, **timolol**, and **metoprolol** reduce the frequency of migraine attacks by 50% in more than 50% of patients. Atenolol and **nadolol** are probably also effective. β-Blockers with intrinsic sympathomimetic activity are ineffective.
- Bronchoconstrictive and hyperglycemic effects can be minimized with β_1-selective β-blockers.
- Side effects include drowsiness, fatigue, sleep disturbances, vivid dreams, memory disturbance, depression, sexual dysfunction, bradycardia, and hypotension.
- Use with caution in patients with heart failure, peripheral vascular disease, atrioventricular conduction disturbances, asthma, depression, and diabetes.

ANTIDEPRESSANTS

- The tricyclic antidepressants (TCA) **amitriptyline** and **venlafaxine** are probably effective for migraine prophylaxis. There are insufficient data to support or refute the efficacy of other antidepressants.
- Their beneficial effects in migraine prophylaxis are independent of antidepressant activity and may be related to downregulation of central $5HT_2$ and adrenergic receptors.
- TCAs are usually well tolerated at the doses used for migraine prophylaxis, but anticholinergic effects may limit use, especially in elderly patients or those with benign prostatic hyperplasia or glaucoma. Evening doses are preferred because of sedation. Increased appetite and weight gain can occur. Orthostatic hypotension and slowed atrioventricular conduction are occasionally reported.
- **Phenelzine** has been used for refractory headache, but its complex side-effect profile and dietary and medication restrictions limit its use.

ANTICONVULSANTS

- **Valproic acid**, **divalproex sodium** (a 1:1 molar combination of valproate sodium and valproic acid), and **topiramate** can reduce the frequency, severity, and duration of headaches.
- Side effects of valproic acid and divalproex sodium include nausea (less common with divalproex sodium and gradual dosing titration), tremor, somnolence, weight gain, hair loss, and hepatotoxicity (the risk of hepatotoxicity appears to be low in patients older than 10 years on monotherapy). The extended-release formulation of divalproex sodium is administered once daily and is better tolerated than the enteric-coated formulation. Valproate is contraindicated in pregnancy and patients with a history of pancreatitis or chronic liver disease.
- Fifty percent of patients respond to **topiramate**. Paresthesias (~50% of patients) and weight loss (9%–12% of patients) are common. Other side effects include fatigue,

anorexia, diarrhea, difficulty with memory, language problems, taste perversions, and nausea. Kidney stones, acute myopia, acute angle-closure glaucoma, and oligohidrosis have been infrequently reported.

NONSTEROIDAL ANTIINFLAMMATORY DRUGS

- **Nonsteroidal anti-inflammatory drugs (NSAIDs)** are modestly effective for reducing the frequency, severity, and duration of migraine attacks, but potential GI and renal toxicity limit daily or prolonged use.
- They may be used intermittently to prevent headaches that recur in a predictable pattern (eg, menstrual migraine). Treatment should be initiated 1 or 2 days before the time of headache vulnerability and continued until vulnerability is passed.
- For migraine prevention, evidence for efficacy is strongest for naproxen and weakest for aspirin.

OTHER DRUGS

- **Verapamil** has been widely used, but evidence for efficacy is inadequate.
- **Frovatriptan** is effective for prophylaxis of menstrual migraine, and **naratriptan** and **zolmitriptan** are probably effective.
- Other medications that may be effective include **Petasites**, **riboflavin** (**vitamin B_2**), **extract of feverfew**, subcutaneous **histamine**, **lisinopril**, **candesartan**, **clonidine**, **guanfacine**, and **coenzyme Q10**, but additional research is needed to confirm efficacy.

TENSION-TYPE HEADACHE

- Tension-type headache, the most common type of primary headache, is more common in women than men. Pain is usually mild to moderate and nonpulsatile. Episodic headaches may become chronic in some patients.

PATHOPHYSIOLOGY

- Pain is thought to originate from myofascial factors and peripheral sensitization of nociceptors. Central mechanisms are also involved. Mental stress, nonphysiologic motor stress, a local myofascial release of irritants, or a combination of these may be the initiating stimulus.

CLINICAL PRESENTATION

- Premonitory symptoms and aura are absent, and pain is usually mild to moderate, bilateral, nonpulsatile, and in the frontal and temporal areas, but occipital and parietal areas can also be affected.
- Mild photophobia or phonophobia may occur. Pericranial or cervical muscles may have tender spots or localized nodules in some patients.

TREATMENT

- Nonpharmacologic therapies include reassurance and counseling, stress management, relaxation training, and biofeedback. Physical therapeutic options (eg, heat or cold packs, ultrasound, electrical nerve stimulation, massage, acupuncture, trigger point injections, and occipital nerve blocks) have performed inconsistently.
- **Simple analgesics** (alone or in combination with caffeine) and **NSAIDs** are the mainstay of acute therapy. **Acetaminophen**, **aspirin**, **diclofenac**, **ibuprofen**, **naproxen**, **ketoprofen**, and **ketorolac** are effective.
- High-dose NSAIDs and the combination of aspirin or acetaminophen with **butalbital**, or rarely, **codeine** are effective options. Avoid the use of butalbital and codeine combinations when possible.
- Give acute medication for episodic headache no more often than 3 days (butalbital-containing), 9 days (combination analgesics), or 15 days (NSAIDs) per month to prevent the development of chronic tension-type headache.

- There is no evidence to support the efficacy of muscle relaxants.
- Consider preventive treatment if headache frequency is more than two per week, duration is longer than 3 to 4 hours, or severity results in medication overuse or substantial disability.
- The **TCAs** are used most often for prophylaxis of tension headache, but **venlafaxine**, **mirtazapine**, **gabapentin**, and **topiramate** may also be effective.

EVALUATION OF THERAPEUTIC OUTCOMES

- Monitor for frequency, intensity, and duration of headaches and for any change in the headache pattern. Encourage patients to keep a headache diary to document frequency, duration, and severity of headaches, headache response, and potential triggers of migraine headaches.
- Monitor patients taking abortive therapy for frequency of use of prescription and nonprescription medications and for side effects.
- Document patterns of abortive medication used to establish the need for prophylactic therapy. Monitor prophylactic therapies closely for adverse reactions, abortive therapy needs, adequate dosing, and compliance.

See Chapter 45, Headache Disorders, authored by Deborah S. Minor and Marion R. Wofford, for a more detailed discussion of this topic.

CHAPTER 55

Pain Management

- *Pain* is a subjective, unpleasant, sensory, and emotional experience associated with actual or potential tissue damage or described in terms of such damage. It may be classified as acute, chronic, or cancer pain.

PATHOPHYSIOLOGY

NOCICEPTIVE PAIN

- Nociceptive pain is either somatic (arising from skin, bone, joint, muscle, or connective tissue) or visceral (arising from internal organs, eg, the large intestine).
- Stimulation of free nerve endings (*nociceptors*) leads to the sensation of pain. These receptors, found in both somatic and visceral structures, are activated by mechanical, thermal, and chemical impulses. Release of bradykinins, prostaglandins, histamine, interleukins, tumor necrosis factor α (TNF-α), serotonin, and substance P may sensitize and/or activate nociceptors. Receptor activation leads to action potentials that continue from the site of noxious stimuli to the dorsal horn of the spinal cord and then ascend to higher centers. The thalamus may act as a relay station and pass the impulses to central structures where pain is processed further.
- The endogenous opiate system consists of neurotransmitters (eg, enkephalins, dynorphins, and β-endorphins) and receptors (eg, μ, δ, and κ) that are found throughout the central and peripheral nervous systems (CNS and PNS). Endogenous opioids bind to opioid receptors and modulate the transmission of pain impulses.
- A descending CNS system also controls pain transmission. This system originates in the brain and can inhibit synaptic pain transmission at the dorsal horn. Important neurotransmitters here include endogenous opioids, serotonin, norepinephrine, and γ-aminobutyric acid.

PATHOPHYSIOLOGIC PAIN

- Pathophysiologic pain (eg, postherpetic neuralgia, diabetic neuropathy, fibromyalgia, irritable bowel syndrome, chronic headaches, and some noncardiac chest pain) is often described in terms of chronic pain. It results from damage or abnormal functioning of nerves in the CNS or PNS. Pain circuits sometimes rewire themselves anatomically and biochemically.

CLINICAL PRESENTATION

GENERAL

- Patients may be in acute distress or display no noticeable suffering.

SYMPTOMS

- Acute pain can be sharp or dull, burning, shock-like, tingling, shooting, radiating, fluctuating in intensity, varying in location, and occurring in a temporal relationship with an obvious noxious stimulus. Chronic pain can present similarly and often occurs without a temporal relationship with a noxious stimulus. Over time, the chronic pain presentation may change (eg, sharp to dull, obvious to vague).

SIGNS

- Acute pain can cause hypertension, tachycardia, diaphoresis, mydriasis, and pallor. These signs are seldom present in chronic pain.
- In acute pain, outcomes of treatment are generally predictable. In chronic pain, comorbid conditions are often present, and outcomes of treatment are often unpredictable.

- Neuropathic pain is often chronic, not well described, and not easily treated with conventional analgesics. There may be exaggerated painful responses to normally noxious stimuli (hyperalgesia) or painful responses to normally nonnoxious stimuli (allodynia).

DIAGNOSIS

- Pain is always subjective; thus pain is best diagnosed based on patient description, history, and physical examination. A baseline description of pain can be obtained by assessing PQRST characteristics (***p***alliative and ***p***rovocative factors, ***q***uality, ***r***adiation, ***s***everity, and ***t***emporal factors). Mental factors may lower the pain threshold (eg, anxiety, depression, fatigue, anger, and fear). Behavioral, cognitive, social, and cultural factors may also affect the pain experience.

TREATMENT

- Goals of Treatment: The goals are to minimize pain, maximize functioning, and provide reasonable comfort and quality of life at the lowest effective analgesic dose. With chronic pain, goals may include rehabilitation and resolution of psychosocial issues.
- The elderly and the young are at higher risk for undertreatment of pain because of communication limitations. **Figures 55–1** and **55–2** are algorithms for management of acute pain and pain in oncology patients, respectively.

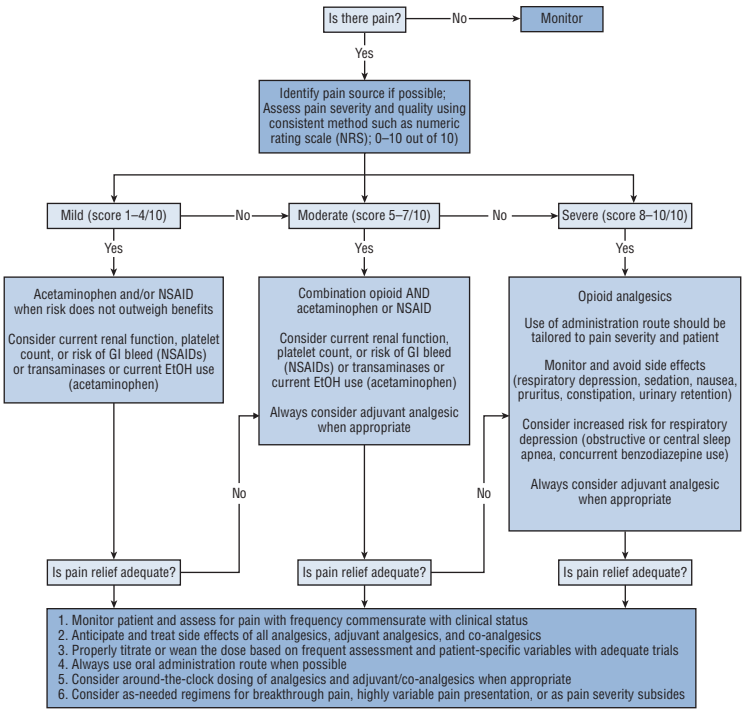


FIGURE 55–1. Algorithm for management of acute pain.

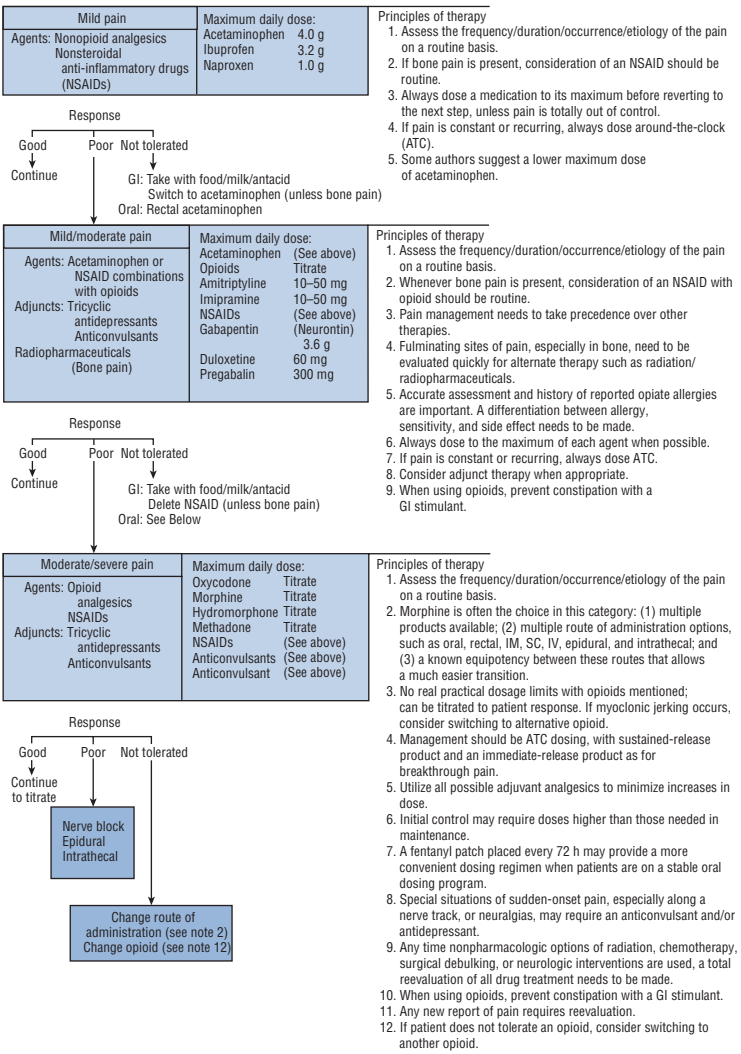


FIGURE 55–2. Algorithm for pain management in oncology patients.

NONOPIOID AGENTS

- Initiate treatment with the most effective analgesic with the fewest side effects. See **Table 55–1** for adult dosages of Food and Drug Administration (FDA)–approved nonopioid analgesics.
- The nonopioids are often preferred over the opioids for mild to moderate pain. The salicylates and nonsteroidal anti-inflammatory drugs (NSAIDs) reduce prostaglandins, thereby decreasing the number of pain impulses received by the CNS.
- **NSAIDs** may be particularly useful for cancer-related bone pain and chronic low back pain.

TABLE 55–1 Adult Dosing of FDA-Approved Nonopioid Analgesics

Class and Generic Name	Brand Name	Initial Dose (mg)	Usual Dose Range in mg and (Maximal Dose in mg/day)	Special Population	Other
Salicylates					
Acetylsalicylic acid[a]—aspirin	Various	325–1,000	325–1,000 every 4–6 hours (4,000)		
Choline and magnesium trisalicylate	Various	500–1,500	500–1,500 every 8–12 hours (4,500)	750 every 8 hours (elderly)	
Diflunisal	Various	500–1,000	250–500 every 8–12 hours (1,500)		
Acetaminophen					
	Oral—Tylenol, various	325–1,000	325–1,000 every 4–6 hours (4,000[b])		
	Parenteral—Ofirmev	1,000	1,000 every 6 hours (4,000[b])	If <50 kg, 15 mg/kg every 6 hours, 750 mg maximum single dose	
Anthranilic Acids					
Meclofenamate	Various	50–100	50–100 every 4–6 hours (400)		
Mefenamic acid	Ponstel	500	250 every 6 hours (1,000[c])		Maximum 7 days
Indolacetic Acid					
Etodolac (immediate release)	Various	200–400	200–400 every 6–8 hours (1,000)		
Phenylacetic Acids					
Diclofenac potassium	Cataflam, various	25–50, in some patients, initial 100	Capsule-25 four times daily; Tablet 50 three times a day (150[d])		
Diclofenac epolamine (patch)	Flector (patch)	One patch	Patch to be applied twice daily to painful area		Intact skin only

Diclofenac sodium (gel, solution)	Voltaren, Pennsaid			Gel and solution dosing joint specific for osteoarthritis and actinic keratoses	
Propionic Acids					
Ibuprofen[a]	Motrin, Advil, various	200–400	200–400 every 4–6 hours (1,200[e]) (2,400[f])		
	Caldolor (parenteral)	400–800	(3,200[f]) Injectable, 400–800 every 6 hours (3,200[f])		Infused over 30 minutes
Fenoprofen	Nalfon, various	200	200 every 4–6 hours (3,200)		
Ketoprofen	Various	25	25–50 every 6–8 hours (300)		
Naproxen	Naprosyn, various	250–500	250–500 every 12 hours (1,000)	For osteoarthritis	
Naproxen sodium[a]	Aleve, Anaprox, various	275–550	550 every 12 hours or 275 every 6–8 hours (1,100[g])	For acute pain	
Pyrrolacetic Acids					
Ketorolac—parenteral	Various (parenteral)	30[h]–60 (single IM dose only) 15[h]–30 (single IV dose only)	15[h]–30 IV every 6 hours (60[h]–120)		Maximum 5 days
Ketorolac—oral	Various	10[h]–20	10 every 4–6 hours (40)		Maximum 5 days, which includes parenteral doses. Indicated for continuation with parenteral only

(*continued*)

TABLE 55–1 Adult Dosing of FDA-Approved Nonopioid Analgesics (*Continued*)

Class and Generic Name	Brand Name	Initial Dose (mg)	Usual Dose Range in mg and (Maximal Dose in mg/day)	Special Population	Other
Ketorolac—nasal spray	Various	One spray in one[h] or each nostril	One spray, that is, 15.75 mg in each nostril every 6–8 hours (63[h]–126)	Elderly and weight <50 kg one spray (15.75 mg) in one nostril every 6–8 hours	Maximum 5 days
Cox-2 Selective					
Celecoxib	Celebrex	Initial 400 12 hours later followed by another 200 on first day	200 twice daily (400)		Note some recommend maintenance doses of 200 mg/day due to cardiac concerns

FDA, Food and Drug Administration; IM, intramuscular.

[a]Available both as an over-the-counter preparation and as a prescription drug.
[b]Some experts believe 4,000 mg may be too high. OTC max dose 3,000 mg daily.
[c]Up to 1,250 mg on the first day.
[d]Up to 200 mg on the first day.
[e]Over-the-counter dose.
[f]Some individuals may respond better to 3,200 mg as opposed to 2,400 mg, although well-controlled trials show no better response; consider risk versus benefits when using 3,200 mg/day, parenteral maximum daily dose = 3,200 mg.
[g]Initial daily dose may go to 1,375 mg.
[h]Dose for elderly and those under 50 kg (110 lbs).

- **The salicylate salts** cause fewer gastrointestinal (GI) side effects than aspirin and do not inhibit platelet aggregation.
- Do not give aspirin-like compounds to children or teenagers with viral illnesses (eg, influenza or chickenpox), as Reye syndrome may result.
- **Acetaminophen** has analgesic and antipyretic activity but little anti-inflammatory action. It is highly hepatotoxic on overdose.

OPIOID AGENTS

- The onset of action of oral **opioids** is about 45 minutes, and peak effect usually is seen in about 1 to 2 hours.
- Addiction is characterized by impaired control over drug use, compulsive use, continued use despite harm, and craving. For definitions of physical dependence, substance abuse, substance dependence, tolerance, and withdrawal, see Chap. 71.
- Equianalgesic doses, histamine-releasing characteristics, and dosing guidelines are shown in **Tables 55–2** and **55–3**. Equianalgesic doses are only a guide, and doses must be individualized. Analgesic drug monitoring is summarized in **Table 55–4**.
- Partial agonists and antagonists (eg, **pentazocine**) compete with agonists for opioid receptor sites and exhibit mixed agonist–antagonist activity. They may have selectivity for analgesic receptor sites and cause fewer side effects than opioids.
- Initially give analgesics around the clock for acute pain. As the painful state subsides, as-needed schedules can be used. Around-the-clock administration is also useful for management of chronic pain.
- Patients with severe pain may receive high doses of opioids with no unwanted side effects, but as pain subsides, patients may not tolerate even low doses.
- Most opioid-related itching or rash is due to histamine release and mast cell degranulation, and is not a true allergic response.
- When opioid allergies occur, an opioid from a different structural class may be cautiously tried. For these purposes, the mixed agonist–antagonist class behaves most like the morphine-like agonists.
- With patient-controlled analgesia, patients self-administer preset amounts of IV opioids via a syringe pump electronically interfaced with a timing device; thus patients can balance pain control with sedation.
- Administration of opioids directly into the CNS (**Table 55–5**; epidural and intrathecal/subarachnoid routes) is common for acute pain, chronic noncancer pain, and cancer pain. These methods require careful monitoring because of reports of marked sedation, respiratory depression, pruritus, nausea, vomiting, urinary retention, and hypotension. **Naloxone** is used to reverse respiratory depression, but continuous infusion may be required. Monitor respiratory function for 24 hours after a single dose of intrathecal or epidural morphine.
- Intrathecal and epidural opioids are often administered by continuous infusion or patient-controlled analgesia. They are safe and effective when given simultaneously with intrathecal or epidural local anesthetics such as **bupivacaine**. All agents administered directly into the CNS should be preservative-free.

Morphine and Congeners (Phenanthrenes)

- Many clinicians consider **Morphine** to be the first-line agent for moderate to severe pain. Morphine is often considered the opioid of choice to treat pain associated with myocardial infarction, as it decreases myocardial oxygen demand.
- Respiratory depression often manifests as decreased respiratory rate. The cough reflex is also depressed. Patients with underlying pulmonary dysfunction are at risk for increased respiratory compromise. Respiratory depression can be reversed by **naloxone**.
- Combining opioid analgesics with alcohol or other CNS depressants amplifies CNS depression and is potentially lethal.
- **Morphine** may cause orthostatic hypotension, and hypovolemic patients are at particular risk.

TABLE 55–2 Opioid Analgesics, Central Analgesics, Opioid Antagonist

Class and Generic Name (Brand Name)	Chemical Source	Relative Histamine Release	Route	Equianalgesic Dose in Adults (mg)	Approximate Onset (minutes)/Half-Life (hours)
Phenanthrenes (Morphine-Like Agonists)					
Morphine (various)	Naturally occurring	+++	IM	10	10–20[a]/2–4
			PO	30	
Hydromorphone (Dilaudid, Exalgo, various)	Semisynthetic	+	IM	1.5	10–20[a]/2–3
			PO	7.5	
Oxymorphone (Opana, various)	Semisynthetic	+	IM	1	10–20[a]/2
			PO	10	
Levorphanol (various)	Semisynthetic	+	PO	Variable	30–60/12–15
Codeine (various)	Naturally occurring	+++	IM	15–30[b]	
			PO	15–30[b]	10–30/3
Hydrocodone (available as combination)	Semisynthetic	N/A	PO	30	30–60/4
Oxycodone (OxyContin, Oxecta, Roxicodone, various)	Semisynthetic	+	PO	20	30–60[a]/2–3
Phenylpiperidines (Meperidine-Like Agonists)					
Meperidine (Demerol, various)	Synthetic	+++	IM	100	10–20/2–6
			PO	300[c]	

Fentanyl (Sublimaze, Duragesic, Lazanda, Abstral, Fentora, Subsys, Actiq, Onsolis, various)	Synthetic	+	IM	0.1	7–15[a]/3–4
			Transdermal	Variable[d]	
			Buccal, transmucosal, sublingual, nasal inhaled	Variable[e]	
Diphenylheptanes					
Methadone	Synthetic	+	IM/IV	Variable[f] (acute)	
(Dolophine, various)			PO	Variable[f] (acute)	30–60/8–59
			IM	Variable[f] (chronic)	
			PO	Variable[f] (chronic)	
Agonist–Antagonist or Partial Agonists					
Pentazocine (Talwin)	Synthetic	N/A	IM	Not recommended	
			PO	50[b]	15–30/2–3
Butorphanol (various)	Synthetic	N/A	IM	2[b]	10–20/3–4
			Intranasal	1[b] (one spray)	
Nalbuphine (various)	Synthetic	N/A	IM	10[b]	<15/5
Buprenorphine (Buprenex, Butrans, Subutex, various)	Synthetic	N/A	IM	0.3	10–20/2–6
			Transdermal	Variable	
			Sublingual	0.4	

(*continued*)

TABLE 55–2 Opioid Analgesics, Central Analgesics, Opioid Antagonist (*Continued*)

Class and Generic Name (Brand Name)	Chemical Source	Relative Histamine Release	Route	Equianalgesic Dose in Adults (mg)	Approximate Onset (minutes)/Half-Life (hours)
Antagonist					
Naloxone (Narcan, various)	Synthetic	N/A	IV	0.4–2[g]	1–2 (IV)/2–5 (IM) onset slightly longer than IV and if no response within 5 minutes repeat dose/0.05–1.5
Central Analgesics					
Tramadol (Ultram, Rybix, Ryzolt, ConZip, various)	Synthetic	N/A	PO	120	<60[a]/5–7
Tapentadol (Nucynta)	Synthetic	N/A	PO	N/A	Within 60[a]/4

IM, intramuscular; N/A, not available; PO, oral.

[a]Onset of action may differ for long-acting formulations.
[b]Starting dose only (equianalgesia not shown).
[c]Not recommended.
[d]Equivalent PO morphine dose = variable.
[e]For breakthrough pain only. Equianalgesic dose conversion should be avoided for Transmucosal Immediate Release Fentanyl (TIRF) products.
[f]The equianalgesic dose of methadone when compared with other opioids will decrease progressively the higher the previous opioid dose. Caution should be exercised when initiating in opioid naïve patients.
[g]Starting doses to be used in cases of opioid overdose.

TABLE 55–3 Dosing Guidelines

Drug(s)	Initial Dose and Usual Range (Use lowest effective dose, titrate up or down based on patient response, opioid-tolerant patients may need dose modification)	Comments
NSAIDs/ acetaminophen/ aspirin	LOWEST effective dose should be used for the SHORTEST period of time with judicious evaluation of risk factors (see Table 55–1).	• Used in mild-to-moderate pain • May use in conjunction with opioid agents to decrease doses of each • Regular alcohol use with acetaminophen use may result in liver toxicity • Care must be exercised to avoid overdose when combination products containing these agents are used • With NSAIDs underlying renal impairment, hypovolemia, and CHF may predispose to nephrotoxicity
Morphine	PO 5–30 mg every 4 hours[a] IM 5–10 mg every 4 hours[a] IV 2–5 mg every 3–4 hours[a] SR 15–30 mg every 12 hours (may need to be every 8 hours in some patients) Rectal 10–20 mg every 4 hours[a]	• Drug of choice in severe pain • May use immediate-release product with controlled release product to control breakthrough pain in cancer pain • Typical patient-controlled analgesia IV dose is 1 mg with a 10-minute lockout interval • Every 24-hour products available (Avinza should not exceed doses of 1,600 mg/day) • Morphine liposomal (DepoDur) at 10, 15 mg/mL is available for epidural administration

(*continued*)

TABLE 55–3 Dosing Guidelines (*Continued*)

Drug(s)	Initial Dose and Usual Range (Use lowest effective dose, titrate up or down based on patient response, opioid-tolerant patients may need dose modification)	Comments
Hydromorphone	PO 2–4 mg every 4–6 hours[a] IM 0.8–1 mg every 4–6 hours[a] IV 0.2–0.6 mg every 2–3 hours[a] Rectal 3 mg every 6–8 hours[a]	• Use in severe pain • More potent than morphine; otherwise, no advantages • Typical patient-controlled analgesia IV dose is 0.2 mg with a 10-minute lockout interval • Every 24-hour product (Exalgo) available but only through a REMS program
Oxymorphone	IM/SQ 1–1.5 mg every 4–6 hours[a] IV 0.5 mg initial dose PO immediate-release 5–10 mg every 4–6 hours[a] PO extended-release 5–10 mg every 12 hours	• Use in severe pain • May use immediate-release product with controlled release product to control breakthrough pain in cancer pain • Extended-release reformulated to deter misuse
Levorphanol	PO 2 mg every 6–8 hours	• Use in severe pain • Extended half-life useful in cancer patients • In chronic pain, wait 3 days between dosage adjustments
Codeine	PO 15–30 mg every 4–6 hours[a] Maximum 360 mg day IM 15–30 mg every 4 hours[a]	• Use in mild to moderate pain • Weak analgesic; use with NSAIDs, aspirin, or acetaminophen, analgesic prodrug • Should not be used in children

Hydrocodone	PO 5–10 mg every 4–6 hours[a]	• Use in moderate/severe pain • Most effective when used with NSAIDs, aspirin, or acetaminophen
Oxycodone	PO 5–15 mg every 4–6 hours[a] Controlled release 10 mg every 12 hours	• Use in moderate/severe pain • Most effective when used with NSAIDs, aspirin, or acetaminophen • May use immediate-release product with controlled release product to control breakthrough pain in cancer pain • CR reformulated to deter misuse
Meperidine	IM 50–100 mg every 3–4 hours[a] IV 5–10 mg every 5 minutes as needed[a]	• Use in severe pain • Oral not recommended • Do not use in renal failure • May precipitate tremors, myoclonus, and seizures • Use with monoamine oxidase inhibitors can induce hyperpyrexia and/or seizures or opioid overdose symptoms
Fentanyl	IV 25–50 mcg/h IM 50–100 mcg every 1–2 hours[a] Transdermal 25 mcg/h every 72 hours Transmucosal (Actiq lollipop) 200 mcg. Must wait 4 hours prior to redosing. However, at any time during therapy may repeat previous dose × 1, 30 minutes after start of previous dose for that episode of breakthrough pain. Transmucosal (Onsolis buccal film) 200 mcg. Must wait 2 hours prior to redosing.	• Used in severe pain • Do not use transdermal in acute pain • With transmucosal, intranasal, sublingual dosing, always start with lowest dose despite daily opioid intake. Product-specific titration and maximum dose recommendations exist • Transmucosal, intranasal, sublingual for breakthrough cancer pain in patients already receiving or tolerant to opioids • Transmucosal, intranasal, sublingual fentanyl dosage forms are only available through a REMS program.

(*continued*)

TABLE 55–3 Dosing Guidelines (*Continued*)

Drug(s)	Initial Dose and Usual Range (Use lowest effective dose, titrate up or down based on patient response, opioid-tolerant patients may need dose modification)	Comments
	Transmucosal (Fentora Buccal Tablet) 100 mcg. Must wait 4 hours prior to redosing. However, at any time during therapy may repeat previous dose × 1, 30 minutes after dose for that episode of breakthrough pain. Intranasal (Lazanda Spray) 100 mcg (one spray) in one nostril. Wait 2 hours prior to redosing. Sublingual (Subsys Spray) 100 mcg (one spray). Must wait 4 hours prior to redosing. However, at any time during therapy may repeat previous dose × 1, 30 minutes after dose for that episode of breakthrough pain. Sublingual (Abstral Tablet,) 100 mcg. Must wait 2 hours prior to redosing. However, at any time during therapy may repeat previous dose × 1, 30 minutes after dose for that episode of breakthrough pain.	
Methadone	PO 2.5–10 mg every 8–12 hours IM 2.5–10 mg every 8–12 hours	• Effective in severe chronic pain • Sedation can be major problem • Some chronic pain patients can be dosed every 12 hours • Equianalgesic dose of methadone when compared with other opioids will decrease progressively the higher the previous opioid dose. • Avoid dose titrations more frequently than every 2 weeks
Pentazocine	IM, IV 30 mg every 3–4 hours[b] (maximum 360 mg day) PO 50–100 mg every 3–4 hours[b] (maximum 600 mg daily, for those 50 mg tablet containing 0.5 mg of naloxone) PO 25 mg every 4 hours[b] (maximum 150 mg daily, for those 25 mg tablet containing 650 mg of acetaminophen)	• Third-line agent for moderate-to-severe pain • May precipitate withdrawal in opiate-dependent patients • Parenteral doses not recommended

Butorphanol	IM 1–4 mg every 3–4 hours[b] IV 0.5–2 mg every 3–4 hours[b] Intranasal 1 mg (one spray) every 3–4 hours[b] If inadequate relief after initial spray, may repeat in other nostril × 1 in 60–90 minutes. Maximum two sprays (one per nostril) every 3–4 hours[b]	• Second-line agent for moderate-to-severe pain • May precipitate withdrawal in opiate-dependent patients
Nalbuphine	IM, IV 10 mg every 3–6 hours[b] (maximum 20 mg dose, 160 mg daily)	• Second-line agent for moderate-to-severe pain • May precipitate withdrawal in opiate-dependent patients
Buprenorphine	IM 0.3 mg every 6 hours[b] May repeat × 1, 30–60 minutes after initial dose IM 0.6 mg single dose may be given Slow IV 0.3 mg every 6 hours[b] May repeat × 1, 30–60 minutes after initial dose Transdermal delivery systems (5, 10, 20 mcg/h) available for every 7 day administration	• Second-line agent for moderate-to-severe pain • May precipitate withdrawal in opiate-dependent patients • Detailed manufacturer dosing conversion recommendations exist • Naloxone may not be effective in reversing respiratory depression • Infuse IV dose over at least 2 minutes
Naloxone	IV 0.4–2 mg may repeat × 1, 30–60 minutes after initial dose	• When reversing opiate side effects in patients needing analgesia, dilute and titrate (0.1–0.2 mg every 2–3 minutes) so as not to reverse analgesia • Duration of action of some opioids may outlast duration of naloxone; in these cases we may need to repeat doses
Tramadol	PO 50–100 mg every 4–6 hours[a] If rapid onset not required, start 25 mg/day and titrate over several days Extended-release PO 100 mg every 24 hours	• Maximum dose for nonextended-release, 400 mg/24 h, if more than 75 years old 300 mg/24 h, if creatinine clearance less than 30 mL/min 200 mg/24 h; maximum for extended-release, 300 mg/24 h • Decrease dose in patient with renal impairment and in the elderly

(*continued*)

TABLE 55–3 Dosing Guidelines (*Continued*)

Drug(s)	Initial Dose and Usual Range (Use lowest effective dose, titrate up or down based on patient response, opioid-tolerant patients may need dose modification)	Comments
Tapentadol	PO 50–100 mg every 4–6 hours[a] Extended-release PO 50 mg every 12 hours	• First day of therapy may administer second dose after the first as soon as 1 hour after the first dose • Maximum dose first day 700 mg, maximum dose thereafter 600 mg (maximum dose for CR 500 mg) • REMS required

CHF, congestive heart failure; CR, Controlled Release; HCL, hydrochloride; IM, intramuscular; NSAID, nonsteroidal antiinflammatory drug; PO, oral; REMS, risk evaluation and mitigation strategies; SQ, subcutaneous; SR, sustained release.

[a]May start with an around-the-clock regimen and switch to as needed if/when the painful signal subsides or is episodic.
[b]Limited analgesic effect.

TABLE 55–4 Analgesic Drug Monitoring

Drug (class)	Adverse Reaction	Monitoring Parameter	Comments
Opioids	Respiratory depression	Respiratory rate OR end-tidal capnography	Capnography considered more sensitive; however, equipment may be expensive to incorporate.
			Higher risk—Obstructive sleep apnea, chronic obstructive pulmonary disease
	Constipation	Bowel movement frequency and consistency	Constipation may be assessed using Bristol Scale
	Sedation	Sedation scale	Will decrease over time
	Nausea, vomiting	Nausea, vomiting	Will decrease over time
	Tolerance	Regular efficacy monitoring	With chronic use, may lead to need for larger doses
	Dependence	Regular efficacy monitoring	Will develop with chronic use
	Addiction/abuse	Regular efficacy monitoring	Seldom problem with acute pain. In chronic pain use specified time trials with opioids, targeted functional end points, screening tools, and frequent monitoring
	Histamine release	Monitor for urticaria, pruritus, bronchospasm	Incidence varies among agents
	Increase in sphincter tone	Monitor for biliary spasm, urinary retention	Incidence varies among agents
	Hypogonadism	Monitor fatigue, depression, sexual dysfunction, amenorrhea (women)	Problem with chronic use
NSAIDs	Upper GI bleeding	Complete blood count, stool guaiac (if symptoms such as black tarry stools, warrant)	One of leading causes of hospitalizations due to drug-related adverse effects in the United States
	Acute renal failure	Serum creatinine	
Acetaminophen	Hepatotoxicity	Serum transaminases (ALT/AST) Liver synthesis tests (PT/INR, albumin) Acetaminophen serum concentration	Elevated transaminases may occur even at doses less than 4000 mg daily

NSAIDs, nonsteroidal antiinflammatory drugs; ALT/AST, alanine transaminase/aspartate transaminase; PT/INR, prothrombin time/International normalized ratio.

TABLE 55–5 Intraspinal Opioids

Agent	Single Dose (mg)	Onset of Pain Relief (minutes)	Duration of Pain Relief—Single Dose (hours)	Continual Infusion Dose (mg/h)
Epidural Route				
Morphine	1–6	30	6–24	0.1–1
Hydromorphone	0.8–2	5–15	4–16	0.1–0.3
Fentanyl	0.025–0.1	5	2–8	0.025–0.1
Sufentanil	0.01–0.06	5	2–4	0.01–0.05
Subarachnoid Route (Intrathecal)				
Morphine	0.1–0.3	15	8–34	N/A
Fentanyl	0.005–0.025	5	3–6	N/A

Note: Doses above should not be interpreted as equianalgesic doses for conversion to or from the specific opioid or route of administration.

- Opioid side effects and monitoring are summarized in **Table 55–4**. In patients with head trauma who are not ventilated, morphine-induced respiratory depression can increase intracranial pressure and cloud the neurologic examination results.

Meperidine and Congeners (Phenylpiperidines)

- **Meperidine** is less potent and has a shorter duration of action than morphine.
- With high doses or in patients with renal failure, the metabolite normeperidine accumulates, causing tremor, muscle twitching, and possibly seizures. In most settings, it offers no advantages over morphine. Do not use it long term, and avoid its use in the elderly and in those with renal dysfunction.
- Do not combine meperidine with monoamine oxidase inhibitors because severe respiratory depression or excitation, delirium, hyperpyrexia, and convulsions may occur.
- **Fentanyl** is often used as an adjunct to general anesthesia. It is more potent and faster acting than meperidine. Transdermal fentanyl can be used for chronic pain requiring opioid analgesics. After a patch is applied, optimal analgesic effect requires 12 to 24 hours, and analgesia may last 72 hours. It may take 6 days after increasing a dose to achieve new steady-state levels. Thus, do not use the fentanyl patch for acute pain. Various dosage forms are available for breakthrough cancer pain (see **Table 55–3**).

Methadone and Congeners (Diphenylheptanes)

- **Methadone** has extended duration of action and ability to suppress withdrawal symptoms in heroin addicts. With repeated doses, its analgesic duration of action is prolonged, but excessive sedation may result. Although effective for acute pain, it is used for chronic cancer pain and increasingly for chronic noncancer pain.
- There are a growing number of methadone-related deaths, and cardiac arrhythmias may occur, especially with higher doses. The equianalgesic dose of methadone may decrease with higher doses of the previous opioid.

Opioid Agonist–Antagonist Derivatives

- This analgesic class may cause less respiratory depression than opioids and may have lower abuse potential than morphine. However, psychotomimetic responses (eg, hallucinations and dysphoria with **pentazocine**), a limited analgesic effect, and the propensity to initiate withdrawal in opioid-dependent patients have limited their use.

Opioid Antagonists

- **Naloxone**, a pure opioid antagonist that binds competitively to opioid receptors, does not produce an analgesic response or opioid side effects. It is used to reverse the toxic effects of agonist and agonist–antagonist opioids.

Central Analgesic

- **Tramadol** and **tapentadol** are centrally acting analgesics. Tramadol, indicated for moderate to moderately severe pain, binds to μ opiate receptors and inhibits norepinephrine and serotonin reuptake. Tapentadol, for moderate to severe acute pain and diabetic peripheral neuropathy, binds to the same receptor and inhibits norepinephrine.
- They have side-effect profiles similar to those of other opioid analgesics. They may also increase the risk of seizures. Tramadol may be useful for treating chronic pain, especially neuropathic pain. Tapentadol, a schedule II controlled substance, may be useful for acute pain.

ADJUVANT ANALGESICS

- Chronic pain with a neuropathic component often requires adjuvant analgesic therapy (Table 55–6), such as antidepressants, anticonvulsants, or topically applied local anesthetics. For cancer bone pain, **strontium-89**, **samarium**, **corticosteroids**, and bisphosphonates are useful adjuvants.

TABLE 55–6 Pharmacologic Management of Chronic Noncancer Pain

Type of Pain	Nonopioids	Opioids	Other Medications	Comments
Chronic low back pain	Acetaminophen NSAIDs (long-term use evidence weak)	Short-term use for mild-to-moderate flare-ups Not first line	Tramadol, TCAs, AEDs	Acetaminophen, NSAIDs first; tramadol or opioids in selected patients; AEDs or TCAs may be considered if neuropathic symptoms (evidence weak)
Fibromyalgia	Acetaminophen	Not recommended	Tramadol, AEDs (pregabalin), SNRIs (duloxetine, milnacipran)	Acetaminophen considered first (evidence weak); tramadol (evidence weak) AEDs, SNRIs (stronger evidence)
Neuropathic pain	Acetaminophen NSAIDs are rarely effective	Considered second-line therapy, are tried after AEDs, SNRIs, and/or TCAs	TCAs, AEDs, SNRIs, central analgesics, topical (e.g., 5% lidocaine patch, capsaicin)	TCAs, SNRIs, AEDs, 5% lidocaine patch considered first line; central analgesics, and opioids considered second-line agents; capsaicins considered third line

AED, antiepileptic drug; NSAIDs, nonsteroidal antiinflammatory drugs; SNRI, serotonin–norepinephrine reuptake inhibitor; TCA, tricyclic antidepressant.

TABLE 55–7 Injectable Local Anesthetics[a]

Agent (Brand Name)	Onset (minutes)	Duration (hours)
Esters		
Procaine (Novocain)	2–5	0.25–1
Chloroprocaine (Nesacaine, various)	6–12	0.5
Tetracaine (Pontocaine, various)	≤15	2–3
Amides		
Articaine[b] (Septicaine)	1–6	1
Mepivacaine (Polocaine, various)	3–5	0.75–1.5
Bupivacaine (Marcaine, various)	5	2–4
Bupivacaine liposomal (Exparel—local infiltration only)	Variable	24 local 96 systemic
Lidocaine (Xylocaine, various)	<2	0.5–1
Prilocaine (Citanest, various)	<2	≥1
Ropivacaine[c] (Naropin)	10–30	0.5–6

[a]Unless otherwise indicated, values are for infiltrative anesthesia.
[b]Product contains epinephrine.
[c]Epidural administration.

REGIONAL ANALGESIA

- Regional analgesia with **local anesthetics** (Table 55–7) is useful for both acute and chronic pain. Anesthetics can be positioned by injection (ie, in the joints, epidural or intrathecal space, nerve plexus, or along nerve roots) or applied topically.
- High plasma concentrations of local anesthetics can cause dizziness, tinnitus, drowsiness, disorientation, muscle twitching, seizures, and respiratory arrest. Cardiovascular effects include myocardial depression, heart block, and hypotension. Skillful technical application, frequent administration, and specialized follow-up are required.

SPECIAL CONSIDERATIONS IN CANCER PAIN

- Pharmacologic therapies (as summarized in **Fig. 55–2**) should be coupled with psychological, surgical, and supportive therapies using an interdisciplinary approach. Individualization of therapy and continuous assessment of pain response, side effects, and behavior are required.

SPECIAL CONSIDERATIOINS IN CHRONIC NONCANCER PAIN

- As pain becomes more chronic, hypertension, tachycardia, and diaphoresis become less evident, and depression, sleep disturbances, anxiety, irritability, employment problems, and family instability tend to dominate.
- An integrated, interdisciplinary, systematic approach (eg, pain clinic) is preferred. Maximal benefit may take months to years.
- Although commonly used, limited data support using opioids for chronic noncancer pain (see **Table 55–6**).

EVALUATION OF THERAPEUTIC OUTCOMES

- Pain intensity, pain relief, and medication side effects must be assessed regularly. The timing and frequency of assessment depend on the type of pain, analgesic used, route of administration, and concomitant medications. Postoperative pain and acute exacerbations of cancer pain may require hourly assessment, whereas chronic non-malignant pain may need only daily (or less frequent) monitoring. Quality of life must be assessed regularly in all patients.
- The four A's (eg, ***a***nalgesia, ***a***ctivity, ***a***berrant drug behavior, and ***a***dverse effects) are key assessment measures for patients with chronic pain.
- The best management of opioid-induced constipation is prevention. Patients should be counseled on proper intake of fluids and fiber, and a stimulant laxative should be added with chronic opioid use.

See Chapter 44, Pain Management, authored by Terry J. Baumann, Chris M. Herndon, and Jennifer M. Strickland, for a more detailed discussion of this topic.

Parkinson's Disease

CHAPTER 56

- *Parkinson's disease* (PD) has highly characteristic neuropathologic findings and a clinical presentation, including motor deficits and, in some cases, mental deterioration.

PATHOPHYSIOLOGY

- Two hallmark features in the substantia nigra pars compacta are loss of neurons and presence of Lewy bodies. The degree of nigrostriatal dopamine loss correlates positively with severity of motor symptoms.
- Reduced activation of dopamine$_1$ and dopamine$_2$ receptors results in greater inhibition of the thalamus and reduced activation of the motor cortex. Clinical improvement may be tied to restoring activity more at the dopamine$_2$ receptor than at the dopamine 1 receptor.

CLINICAL PRESENTATION

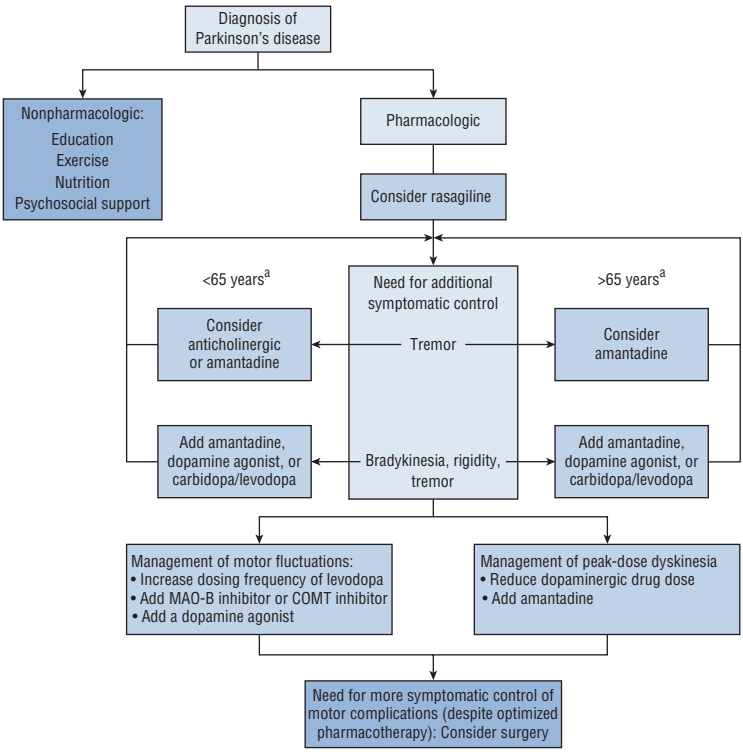
- PD develops insidiously and progresses slowly. It is relatively asymptomatic until profound depletion (70%–80%) of substantia nigra pars compacta neurons has occurred.
- Initial symptoms may be sensory, but as the disease progresses, one or more classic primary features presents (eg, resting tremor, rigidity, bradykinesia, and postural instability that may lead to falls).
- Resting tremor is often the sole presenting complaint. However, only two thirds of PD patients have tremor on diagnosis, and some never develop this sign. Tremor is present most commonly in the hands, often begins unilaterally, and sometimes has a characteristic "pill-rolling" quality. Resting tremor is usually abolished by volitional movement and is absent during sleep.
- Muscular rigidity involves increased muscular resistance to passive range of motion and can be cogwheel in nature. It commonly affects both upper and lower extremities, and facial muscles may be affected.
- Intellectual deterioration is not inevitable, but some patients deteriorate in a manner indistinguishable from Alzheimer's disease.

DIAGNOSIS

- A diagnosis of PD can be made with a high level of confidence when there is bradykinesia (along with resting tremor and/or rigidity), prominent asymmetry, and a positive response to dopaminergic medication.
- Other symptoms may include: decreased dexterity, difficulty arising from a chair, postural instability, festinating gait, dysarthria, difficulty swallowing, reduced facial expression, freezing at initiation of movement, hypophonia, micrographia, bladder disturbances, constipation, blood pressure changes, dementia, anxiety, depression, sleepiness, insomnia, obstructive sleep apnea.
- Several other conditions must be excluded, such as medication-induced Parkinsonism (eg, induced by antipsychotics, phenothiazine antiemetics, or metoclopramide), essential tremor, corticobasal ganglionic degeneration, multiple system atrophy, and progressive supranuclear palsy.

TREATMENT

- Goals of Treatment: The goals of treatment are to minimize symptoms, disability, and side effects while maintaining quality of life. Education of patients and caregivers, exercise, and proper nutrition are essential.



[a]Age is not the sole determinant for drug choice. Other factors such as cognitive function and overall safety and tolerability of drug (especially in the elderly) should be considered.

FIGURE 56–1. General approach to the management of early to advanced Parkinson's disease.

PHARMACOLOGIC THERAPY

General Approach

- An algorithm for management of early to advanced PD is shown in Fig. 56–1. Table 56–1 is a summary of available antiparkinson medications and their dosing, and Table 56–2 shows side effect monitoring.
- Monotherapy usually begins with a **monoamine oxidase-B (MAO-B) inhibitor**.
- Consider addition of a **catechol-*O*-methyltransferase (COMT) inhibitor** if motor fluctuations develop to extend **L-dopa** duration of activity. Alternatively, consider addition of an MAO-B inhibitor or **dopamine agonist**.
- For management of L-dopa-induced peak-dose dyskinesias, consider addition of **amantadine**.

Anticholinergic Medications

- Anticholinergic drugs can improve tremor and sometimes dystonic features in some patients, but they rarely substantially improve bradykinesia or other disabilities. They can be used as monotherapy or in conjunction with other antiparkinson drugs.
- Anticholinergic side effects include dry mouth, blurred vision, constipation, and urinary retention. More serious reactions include forgetfulness, confusion, sedation,

TABLE 56–1 Dosing of Drugs Used in Parkinson's Disease[a]

Generic Name	Trade Name	Starting Dose[b] (mg/day)	Maintenance Dose[b] (mg/day)	Dosage Forms (mg)
Anticholinergic Drugs				
Benztropine	Cogentin	0.5–1	1–6	0.5, 1, 2
Trihexyphenidyl	Artane	1–2	6–15	2, 5, 2/5 mL
Carbidopa/Levodopa Products				
Carbidopa/L-dopa	Sinemet	100–300[c]	300–1,000[c]	10/100, 25/100, 25/250
Carbidopa/L-dopa ODT	Parcopa	100–300[c]	300–1,000[c]	10/100, 25/100, 25/250
Carbidopa/L-dopa CR	Sinemet CR	200–400[c]	400–1,000[c]	25/100, 50/200
Carbidopa/L-dopa/ entacapone	Stalevo	200–600[d]	600–1,600[d]	12.5/50/200, 18.75/75/200, 25/100/200, 31.25/125/200, 37.5/150/200, 50/200/200
Carbidopa	Lodosyn	25	25–75	25
Dopamine Agonists				
Apomorphine	Apokyn	1–3	3–12	30/3 mL
Bromocriptine	Parlodel	2.5–5	15–40	2.5, 5
Pramipexole	Mirapex	0.125	1.5–4.5	0.125, 0.25, 0.5, 1, 1.5
Pramipexole ER	Mirapex ER	0.375	1.5–4.5	0.375, 0.75, 1.5, 3, 4.5
Ropinirole	Requip	0.75	9–24	0.25, 0.5; 1, 2, 3, 4, 5
Ropinirole XL	Requip XL	2	8–24	2, 4, 6, 8, 12
Rotigotine	Neupro	2	2–8	1, 2, 3, 4, 6, 8
COMT Inhibitors				
Entacapone	Comtan	200–600	200–1,600	200
Tolcapone	Tasmar	300	300–600	100, 200
MAO-B Inhibitors				
Rasagiline	Azilect	0.5–1	0.5–1	0.5, 1
Selegiline	Eldepryl	5–10	5–10	5
Selegiline ODT	Zelapar	1.25	1.25–2.5	1.25, 2.5
Miscellaneous				
Amantadine	Symmetrel	100	200–300	100, 50/5 mL

COMT, catechol-O-methyltransferase; CR, controlled release; MAO, monoamine oxidase; ODT, orally disintegrating tablet.

[a]Marketed in the United States for Parkinson's disease.
[b]Dosages may vary beyond stated range.
[c]Dosages expressed as L-dopa component.
[d]Dosages expressed as entacapone component.

TABLE 56–2 Monitoring of Potential Adverse Reactions to Drug Therapy for Parkinson's Disease

Generic Name	Adverse Drug Reaction	Monitoring Parameter	Comments
Amantadine	Confusion	Mental status; renal function	Reduce dosage; adjust dose for renal impairment
	Livedo reticularis	Lower extremity examination; ankle edema	Reversible upon drug discontinuation
Benztropine	Anticholinergic effects, confusion, sedation	Dry mouth, mental status, constipation, urinary retention	Reduce dosage; avoid in elderly; history of constipation, memory impairment, urinary retention
Trihexyphenidyl	See benztropine	See benztropine	See benztropine
Carbidopa/L-dopa	Drowsiness	Daytime drowsiness	Reduce dose
	Dyskinesias	Abnormal involuntary movements	Reduce dose; add amantadine
	Nausea	Nausea	Take with food
COMT Inhibitors			
Entacapone	Augmentation of L-dopa side effects; also diarrhea	See carbidopa/L-dopa; also bowel movements	Reduce dose of L-dopa; antidiarrheal agents
Tolcapone	See entacapone; also liver toxicity	See carbidopa/L-dopa; also ALT/AST	See carbidopa/L-dopa; also at start of therapy and for every dose increase, ALT and AST levels at baseline and every 2–4 weeks for the first 6 months of therapy; afterward monitor based on clinical judgment.
Dopamine agonists			
Apomorphine	Drowsiness	Mental status	Reduce dose
	Nausea	Nausea	Premedicate with trimethobenzamide
	Orthostatic hypotension	Blood pressure, dizziness upon standing	Reduce dose
Bromocriptine	Confusion	Mental status	Reduce dose
	Drowsiness	Mental status	Reduce dose

(*continued*)

TABLE 56–2 Monitoring of Potential Adverse Reactions to Drug Therapy for Parkinson's Disease (*Continued*)

Generic Name	Adverse Drug Reaction	Monitoring Parameter	Comments
	Hallucinations/delusions	Mental status	Reduce dose
	Nausea	Nausea	Titrate dose upward slowly; take with food
	Orthostatic hypotension	Blood pressure, dizziness upon standing	Reduce dose
	Pulmonary fibrosis	Chest radiograph	Chest radiograph at baseline and once yearly
Pramipexole	Confusion	Mental status	Reduce dose
	Drowsiness	Mental status	Reduce dose
	Hallucinations/delusions	Mental status	Reduce dose
	Impulsivity	Behavior	Reduce dose
	Nausea	Nausea	Titrate dose upward slowly; take with food
	Orthostatic hypotension	Blood pressure, dizziness upon standing	Reduce dose
Ropinirole	See pramipexole	See pramipexole	See pramipexole
Rotigotine	See pramipexole; also skin irritation at site of patch application	See pramipexole; also skin examination	See pramipexole; rotate patch application site
MAO-B inhibitors			
Rasagiline	Nausea	Nausea	Take with food
Selegiline	Confusion	Mental status	Reduce dose
	Insomnia	Mental status	Administer dose earlier in day
	Hallucinations	Mental status	Reduce dose
	Orthostatic hypotension	Blood pressure, dizziness upon standing	Reduce dose

ALT, alanine aminotransferase; AST, aspartate aminotransferase; COMT, catechol-*O*-methyltransferase; MAO, monoamine oxidase.

depression, and anxiety. Patients with preexisting cognitive deficits and the elderly are at greater risk for central anticholinergic side effects.

Amantadine

- Amantadine often provides modest benefit for tremor, rigidity, and bradykinesia. It may also decrease dyskinesia.
- Adverse effects include sedation, dry mouth, hallucinations, dizziness, and confusion. Livedo reticularis (a diffuse mottling of the skin in the upper or lower extremities) is a common but reversible side effect.
- Doses should be reduced in patients with renal dysfunction (100 mg/day with creatinine clearances of 30–50 mL/min [0.50–0.84 mL/s], 100 mg every other day for creatinine clearances of 15–29 mL/min [0.25–0.49 mL/s], and 200 mg every 7 days for creatinine clearances less than 15 mL/min [0.25 mL/s]) and those on hemodialysis.

Levodopa and Carbidopa/Levodopa

- **L-dopa**, the most effective drug available, is a precursor of dopamine. Unlike **dopamine**, **carbidopa**, and **benserazide**, it crosses the blood-brain barrier. Ultimately, all PD patients will require L-dopa.
- When to start L-dopa (eg, right after diagnosis or when symptoms compromise social, occupational, or psychological well-being) is controversial.
- In the central nervous system (CNS) and peripherally, L-dopa is converted by L-amino acid decarboxylase (L-AAD) to dopamine. In the periphery, carbidopa or benserazide can block L-AAD, thus increasing CNS penetration of administered L-dopa and decreasing dopamine adverse effects (eg, nausea, cardiac arrhythmias, postural hypotension, and vivid dreams). Benserazide is unavailable in the United States.
- Initially L-dopa 300 mg/day (in divided doses) combined with carbidopa often achieves adequate relief. The usual maximal dose of L-dopa is 800 to 1000 mg/day.
- About 75 mg of carbidopa is required to effectively block peripheral L-AAD, but some patients need more. Carbidopa/L-dopa is most widely used in a 25/100 mg tablet, but 25/250 mg and 10/100 mg dosage forms are available. Controlled-release preparations of carbidopa/L-dopa are available in 50/200 mg and 25/100 mg strengths. For patients with difficulty swallowing, an orally disintegrating tablet is available.
- After oral L-dopa, time to peak plasma concentrations varies intra- and inter-subject. Meals delay gastric emptying, but antacids promote gastric emptying. L-dopa is absorbed primarily in the proximal duodenum via a saturable large neutral amino acid transport system, thus high-protein meals can interfere with bioavailability.
- L-dopa is not bound to plasma proteins, and the elimination half-life is approximately 1 hour. Adding carbidopa or benserazide can extend the half-life to 1.5 hours, and adding a COMT inhibitor (eg, **entacapone**) can extend it to approximately 2 to 2.5 hours.
- Long-term, L-dopa-associated motor complications can be disabling. The most common of these are "end-of-dose wearing off" and "peak-dose dyskinesias." The risk of developing motor fluctuations or dyskinesias is approximately 10% per year of L-dopa therapy. However, motor complications can occur 5 to 6 months after starting L-dopa, especially when excessive doses are used initially. **Table 56–3** shows these motor complications and suggests management strategies.
- "End-of-dose wearing off" is related to the increasing loss of neuronal dopamine storage capability and the short half-life of L-dopa. Bedtime administration of a dopamine agonist or a sustained-release formulation product (eg, carbidopa/L-dopa CR, **ropinirole XL**, **rotigotine transdermal patch**, or **pramipexole ER**) may help reduce nighttime off episodes and improve morning functioning.
- "Delayed-on" or "no-on" can result from delayed gastric emptying or decreased absorption in the duodenum. Crushing carbidopa/L-dopa tablets and taking with a glass of water or using the orally disintegrating tablet on an empty stomach may help. Subcutaneous apomorphine may be used as rescue therapy.

TABLE 56–3 Common Motor Complications and Possible Initial Treatments

Effect	Possible Treatments
End-of-dose "wearing off" (motor fluctuation)	Increase frequency of carbidopa/L-dopa doses; add either COMT inhibitor or MAO-B inhibitor or dopamine agonist
"Delayed on" or "no on" response	Give carbidopa/L-dopa on empty stomach; use carbidopa/L-dopa ODT; avoid carbidopa/L-dopa CR; use apomorphine subcutaneous
Start hesitation ("freezing")	Increase carbidopa/L-dopa dose; add a dopamine agonist or MAO-B inhibitor; utilize physical therapy along with assistive walking devices or sensory cues (e.g., rhythmic commands, stepping over objects)
Peak-dose dyskinesia	Provide smaller doses of carbidopa/L-dopa; add amantadine

COMT, catechol-*O*-methyltransferase; CR, controlled release; MAO, monoamine oxidase; ODT, orally disintegrating tablet.

- "Freezing," episodic inhibition of lower extremity motor function, may be worsened by anxiety and may increase falls.
- Dyskinesias, involuntary choreiform movements usually involving the neck, trunk, and extremities, are usually associated with peak striatal dopamine levels. Less commonly, dyskinesias can develop during the rise and fall of L-dopa effects (the dyskinesias-improvement-dyskinesias or diphasic pattern of response).
- "Off-period dystonia," muscle contractions most commonly in distal lower extremities (eg, feet or toes) occurs often in the early morning. Consider bedtime administration of sustained-release products, use of baclofen, or selective denervation with botulinum toxin.

Monoamine Oxidase B Inhibitors

- At therapeutic doses, **selegiline** and **rasagiline**, selective, irreversible inhibitors of MAO-B, are unlikely to induce a "cheese reaction" (hypertension, headache) unless excessive amounts of dietary tyramine are ingested. However, combining MAO-B inhibitors with meperidine and other opioid analgesics is contraindicated because of a small risk of serotonin syndrome.
- Selegiline blocks dopamine breakdown and can extend the duration of action of L-dopa up to 1 hour. It often permits reduction of the L-dopa dose by as much as one half.
- Selegiline also increases the peak effects of L-dopa and can worsen preexisting dyskinesias or psychiatric symptoms, such as delusions. Metabolites of selegiline are l-methamphetamine and L-amphetamine. The oral disintegrating tablet may provide improved response and fewer side effects than the conventional formulation.
- Rasagiline also enhances L-dopa effects and is modestly beneficial as monotherapy. Early initiation may be associated with better long-term outcomes.
- Rasagiline may provide 1 hour of extra "on" time during the day. It is considered a first-line agent (as is entacapone) for managing motor fluctuations of L-dopa.
- There is no firm evidence that selegiline or rasagiline slow neurodegeneration.

Catechol-O-Methyltransferase Inhibitors

- **Tolcapone** and **entacapone** are used in conjunction with carbidopa/L-dopa to prevent the peripheral conversion of L-dopa to dopamine (increasing the area under the curve of L-dopa by approximately 35%). Thus, "on" time is increased by approximately 1 to 2 hours, and dosage requirements of L-dopa are decreased. Avoid concomitant use of nonselective MAO inhibitors to prevent inhibition of the pathways for normal catecholamine metabolism.

- COMT inhibition is more effective than controlled-release carbidopa/L-dopa in providing consistent extension of effect.
- Tolcapone's use is limited by the potential for fatal liver toxicity. Strict monitoring of liver function is required. Reserve tolcapone for patients with fluctuations unresponsive to other therapies.
- Because entacapone has a shorter half-life, 200 mg is given with each dose of carbidopa/L-dopa up to eight times a day. Dopaminergic adverse effects may occur and are managed by reducing the carbidopa/L-dopa dose. Brownish orange urine discoloration may occur (as with tolcapone), but hepatotoxicity is not reported with entacapone.

Dopamine Agonists

- The ergot derivative **bromocriptine** and the nonergots **pramipexole**, **rotigotine**, and **ropinirole** are beneficial adjuncts in patients experiencing fluctuation in response to L-dopa. They decrease the frequency of "off" periods and provide an L-dopa-sparing effect.
- Titrate the dose of dopamine agonists slowly to enhance tolerance and find the least dose that provides optimal benefit (see **Table 56–1**).
- The nonergots are safer and are effective as monotherapy in mild to moderate PD and as adjuncts to L-dopa in patients with motor fluctuations.
- There is less risk of developing motor complications from monotherapy with dopamine agonists than from L-dopa. Because younger patients are more likely to develop motor fluctuations, dopamine agonists are preferred in this population. Older patients are more likely to experience psychosis and orthostatic hypotension from dopamine agonists; therefore, carbidopa/L-dopa may be the best initial medication in elderly patients, particularly if cognitive problems or dementia is present.
- Common side effects of dopamine agonists are shown in **Table 56–2**. Other side effects include vivid dreams, sleep attacks, and impulsive behaviors. Hallucinations and delusions can be managed using a stepwise approach (**Table 56–4**). When added to L-dopa, dopamine agonists may worsen dyskinesias.

TABLE 56–4 Stepwise Approach to Management of Drug-Induced Hallucinosis and Psychosis in Parkinson's Disease

1. General measures such as evaluating for electrolyte disturbance (especially hypercalcemia or hyponatremia), hypoxemia, or infection (especially encephalitis, sepsis, or urinary tract infection)
2. Simplify the antiparkinsonian regimen as much as possible by discontinuing or reducing the dosage of medications with the highest risk-to-benefit ratio first[a]
(a) Discontinue anticholinergics, including other nonparkinsonian medications with anticholinergic activity such as antihistamines or tricyclic antidepressants
(b) Taper and discontinue amantadine
(c) Discontinue monoamine oxidase-B inhibitor
(d) Taper and discontinue dopamine agonist
(e) Consider reduction of L-dopa (especially evening doses) and discontinuation of catechol-*O*-methyltransferase inhibitors
3. Consider atypical antipsychotic medication if disruptive hallucinosis or psychosis persists
(a) Quetiapine 12.5–25 mg at bedtime; gradually increase by 25 mg each week if necessary, until hallucinosis or psychosis improved or
(b) Clozapine 12.5–50 mg at bedtime; gradually increase by 25 mg each week if necessary until hallucinosis or psychosis improved (requires frequent monitoring for leukopenia)

[a]If dosage reduction or medication discontinuation is either infeasible or undesirable, go to step 3.

- **Bromocriptine** is not commonly used because of a risk of pulmonary fibrosis and less efficacy than the other agonists.
- **Pramipexole** is primarily renally excreted, and the initial dose must be adjusted in renal insufficiency. A once-daily extended-release formulation is available.
- **Ropinirole** is metabolized by cytochrome P4501A2; fluoroquinolones and smoking may alter ropinirole clearance. A once-daily formulation is available.
- **Rotigotine** patch provides continuous release over 24 hours, and disposition is not affected by hepatic or renal impairment.
- **Apomorphine** is a nonergot dopamine agonist given as a subcutaneous "rescue" injection. For patients with advanced PD with intermittent "off" episodes despite optimized therapy, subcutaneous apomorphine triggers an "on" response within 20 minutes, and duration of effect is up to 100 minutes. Most patients require 0.06 mg/kg. Prior to injection, patients should be premedicated with the antiemetic trimethobenzamide. It is contraindicated with the serotonin-3-receptor blockers (eg, ondansetron).

EVALUATION OF THERAPEUTIC OUTCOMES

- Educate patients and caregivers about recording medication doses and administration times and duration of "on" and "off" periods.
- Monitor symptoms, side effects, and activities of daily living, and individualize therapy. Concomitant medications that may worsen motor symptoms, memory, falls, or behavioral symptoms should be discontinued if possible.

See Chapter 43, Parkinson's Disease, authored by Jack J. Chen and David M. Swope, for a more detailed discussion of this topic.

CHAPTER 57

Status Epilepticus

- *Status epilepticus* (SE) is any seizure lasting more than 30 minutes, whether or not consciousness is impaired, or recurrent seizures without an intervening period of consciousness. SE is a medical emergency, and aggressive treatment of seizures that last 5 minutes or more is strongly recommended. **Table 57–1** shows the classification of SE. This chapter focuses on generalized convulsive status epilepticus (GCSE), the most common and severe form.

PATHOPHYSIOLOGY

- Seizure initiation is likely caused by an imbalance between excitatory (eg, glutamate, calcium, sodium, substance P, and neurokinin B) and inhibitory (γ-aminobutyric acid [GABA], adenosine, potassium, neuropeptide Y, opioid peptides, and galanin) neurotransmission.
- Seizure maintenance is largely caused by glutamate acting on postsynaptic *N*-methyl-D-aspartate (NMDA) and α-amino-3-hydroxy-5-methylisoxazole-4-propionate (AMPA)/kainate receptors. Sustained depolarization can result in neuronal death.
- $GABA_A$ receptors may become less responsive to endogenous GABA and GABA antagonists.
- During phase I of GCSE, each seizure produces marked increases in plasma epinephrine, norepinephrine, and steroid concentrations that may cause hypertension, tachycardia, and cardiac arrhythmias. Muscle contractions and hypoxia can cause acidosis, hypotension, shock, rhabdomyolysis, and secondary hyperkalemia, and acute tubular necrosis may ensue.
- In phase II, beginning 30 minutes into the seizure, the patient begins to decompensate and may become hypotensive with compromised cerebral blood flow. Serum glucose may be normal or decreased, and hyperthermia, respiratory deterioration, hypoxia, and ventilatory failure may develop.
- In prolonged seizures, motor activity may cease, but electrical seizures may persist.

MORBIDITY AND MORTALITY

- Younger children, the elderly, and those with preexisting epilepsy have a higher propensity for sequelae.
- Recent estimates suggest a mortality rate up to 16% in children, 20% in adults, and 38% in the elderly. Neonates have a higher mortality and more neurologic sequelae.
- Variables affecting outcome are (1) the time between onset of GCSE and the initiation of treatment and (2) the duration of the seizure. The mortality rate is 2.6%, 19%, and 32% for those with seizures lasting 10 to 29 minutes, longer than 30 minutes, and longer than 60 minutes, respectively.

CLINICAL PRESENTATION

- Symptoms: impaired consciousness (eg, ranging from lethargy to coma); disorientation (once GCSE is controlled); and pain associated with injuries.
- Early signs: generalized convulsions; acute injuries or central nervous system (CNS) insults that cause extensor or flexor posturing; hypothermia or fever suggestive of intercurrent illnesses (eg, sepsis or meningitis); incontinence; normal blood pressure or hypotension; and respiratory compromise.
- Late signs: clinical seizures may or may not be apparent; pulmonary edema with respiratory failure; cardiac failure (dysrhythmias, arrest, or cardiogenic shock); hypotension or hypertension; disseminated intravascular coagulation or multi-system organ failure; rhabdomyolysis; and hyperpyrexia.

TABLE 57–1 International Classification of Status Epilepticus

Convulsive		Nonconvulsive	
International	**Traditional Terminology**	**International**	**Traditional Terminology**
Generalized SE • Tonic–clonic[a,b] • Tonic[c] • Clonic[c] • Myoclonic[b] • Erratic[d]	Grand mal, epilepticus convulsivus	Absence[c]	Petit mal, spike-and-wave stupor, spike-and-slow-wave or 3/s spike-and-wave, epileptic fugue, epilepsia minora continua, epileptic twilight, minor SE
Secondary generalized SE[a,b] • Tonic • Partial seizures with secondary generalization		Partial SE[a,b] Simple partial Somatomotor Dysphasic Other types Complex partial	Focal motor, focal sensory, epilepsia partialis continua, adversive SE Elementary Temporal lobe, psychomotor, epileptic fugue state, prolonged epileptic stupor, prolonged epileptic confusional state, continuous epileptic twilight state

SE, status epilepticus.

[a]Most common in older children.
[b]Most common in adolescents and adults.
[c]Most common in infants and young children.
[d]Most common in neonates.

DIAGNOSIS

- Assess: language; cognitive abilities; motor, sensory, and reflex abnormalities; pupillary response; injuries; asymmetry; and posturing.
- Initial laboratory tests: complete blood count (CBC) with differential; serum chemistry profile (eg, electrolytes, calcium, magnesium, glucose, serum creatinine, alanine aminotransferase [ALT], and aspartate aminotransferase [AST]); urine drug/alcohol screen; albumin, hepatic function; renal function; blood cultures; arterial blood gases (ABGs); and serum drug concentrations if previous anticonvulsant use is suspected or known.
- Other potential diagnostic tests: spinal tap if CNS infection suspected; electroencephalograph (EEG) should be obtained immediately and once clinical seizures are controlled; computed tomography (CT) with and without contrast; magnetic resonance imaging (MRI); and radiograph if indicated to diagnose fractures.

TREATMENT

- Goals of Treatment: 1) identify GCSE subtype and precipitating factors; 2) terminate clinical and electrical seizure activity as soon as possible and preserve cardiorespiratory function, 3) minimize side effects, 4) prevent recurrent seizures, and 5) avoid pharmacoresistant epilepsy and/or neurologic sequelae.
- For any tonic-clonic seizure that does not stop automatically or when doubt exists regarding the diagnosis, treatment of GCSE should begin during the diagnostic workup. **Figure 57–1** is an algorithm for treatment of GCSE. **Table 57–2** shows doses used in the pharmacologic management of GCSE, and **Table 57–3** shows the adverse drug reactions and monitoring of these drugs.

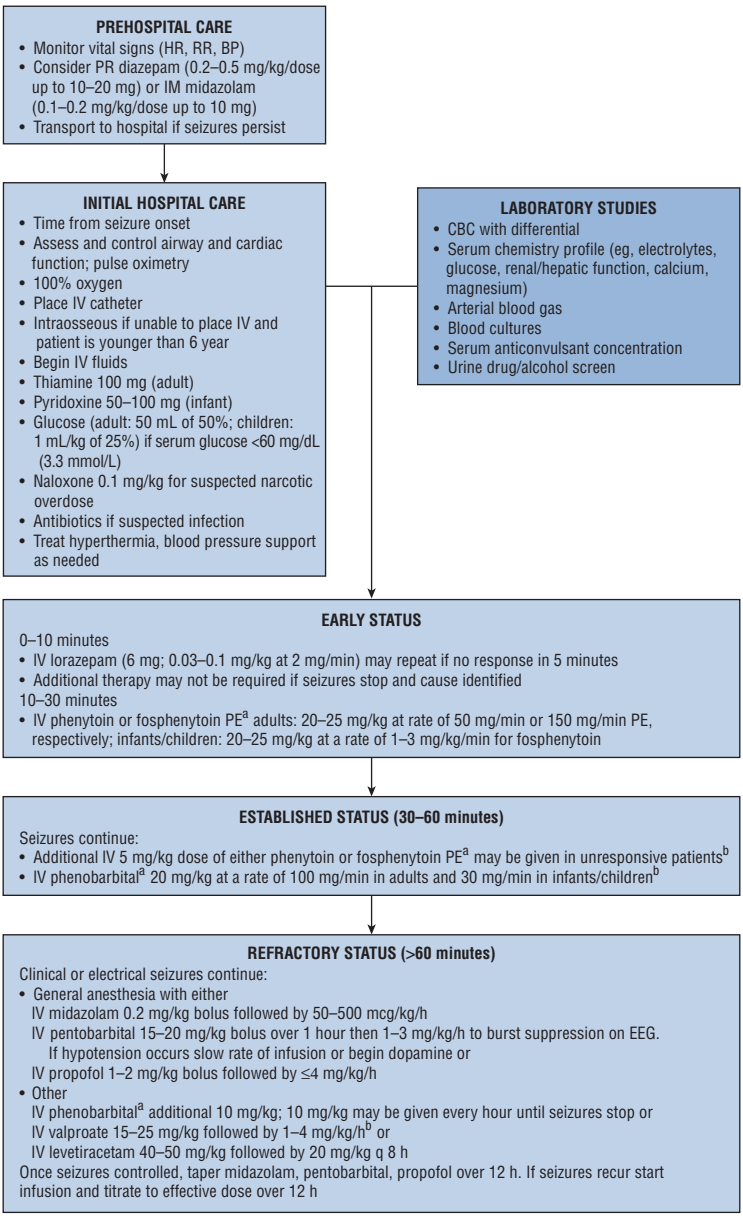


FIGURE 57–1. Algorithm for the treatment of generalized convulsive status epilepticus (GCSE). (BP, blood pressure; CBC, complete blood count; EEG, electroencephalogram; GCSE, generalized convulsive status epilepticus; HR, heart rate; PR, per rectum; RR, respiratory rate.) [a]Because variability exists in dosing, monitor serum concentration. [b]If seizure is controlled, begin maintenance doses and optimize using serum concentration monitoring.

TABLE 57–2 Dosing of Medications Used in the Initial Treatment of GCSE

Drug (Route)	Brand Name	Initial Dose (Maximum Dose)	Maintenance Dose	Comments
Diazepam (IV)	Valium plus generic			
Adult		0.25 mg/kg[a,b,c] (20 mg)	Not used	Given IV at a rate not to exceed 5 mg/min
Pediatric		0.25–0.5 mg/kg[a,c] (20 mg)	Not used	
Fosphenytoin (IV)	Cerebyx plus generic			
Adult		20–25 mg PE/kg	4–5 mg PE/kg/day	Given IV at a rate not to exceed 150 mg PE/min in adults and 3 mg PE/kg/min in pediatric patients
Pediatric		20–25 mg PE/kg	5–10 mg PE/kg/day	
Lorazepam (IV)	Ativan plus generic			
Adult		4 mg[b,c] (6 mg)	Not used	Given IV at a rate not to exceed 2 mg/min in adult and pediatric patients
Pediatric		0.1 mg/kg[a,c] (6 mg)	Not used	
Midazolam (IV, IM)	Versed plus generic			
Adult		200 mcg/kg[a,d]	50–500 mcg/kg/h[e]	Given IV at a rate 0.5–1 mg/min in adults and over 2–3 minutes in pediatric patients
Pediatric		150 mcg/kg[a,d]	60–120 mcg/kg/h[e]	
Phenobarbital (IV)	Generic			
Adult		10–20 mg/kg[e]	1–4 mg/kg/day[e]	Given IV at a rate not to exceed 100 mg/min in adults and 30 mg/min in pediatric patients
Pediatric		15–20 mg/kg[e]	3–5 mg/kg/day[e]	
Phenytoin (IV)	Dilantin plus generic			
Adult		20–25 mg/kg[f]	4–5 mg/kg/day[e]	Given IV at a rate not to exceed 50 mg/min[g] in adults and 3 mg/kg/min (max 50 mg/min) in pediatric patients
Pediatric		20–25 mg/kg[f]	5–10 mg/kg/day[e]	

GCSE, generalized convulsive status epilepticus; PE, phenytoin equivalents.

[a]Doses can be repeated every 10 to 15 minutes until the maximum dosage is given.
[b]Initial doses in the elderly are 2 to 5 mg.
[c]Larger doses can be required if patients chronically on a benzodiazepine (e.g., clonazepam).
[d]Can be given by the intramuscular, rectal, or buccal routes.
[e]Titrate dose as needed.
[f]Administer additional loading dose based on serum concentration.
[g]The rate should not exceed 25 mg/min in elderly patients and those with known atherosclerotic cardiovascular disease.

TABLE 57–3 Adverse Drug Reactions and Monitoring of Patients Receiving Drugs for GCSE

Drug	Adverse Drug Reaction	Monitoring Parameters	Comments
Diazepam	Hypotension and cardiac arrhythmias	Vital signs and electrocardiogram (ECG) during administration	Propylene glycol causes hypotension and cardiac arrhythmias when administered too rapidly; hypotension may occur with large doses
Fosphenytoin	Hypotension and cardiac arrhythmias; paresthesia, pruritus	Vital signs and ECG during administration	Hypotension is less than that noted with phenytoin, as this product does not contain propylene glycol; pruritus generally involves the face and groin areas, is dose and rate related, and subsides 5–10 minutes after infusion
Lidocaine	Fasciculations, visual disturbances, tinnitus, seizures		Occur at serum concentrations between 6 and 8 mg/L (25.6–34.1 µmol/L); seizures >8 mg/L (34.1 µmol/L)
Lorazepam	Apnea, hypotension, bradycardia, cardiac arrest, respiratory depression, metabolic acidosis, and renal toxicity	Vital signs and ECG during administration; HCO_3 and serum creatinine; cumulative dose of propylene glycol	Accumulation of propylene glycol during prolong continuous infusions may cause acidosis
Pentobarbital	Hypotension	Vital signs and ECG during administration	Rate of infusion should be slower or dopamine should be added if hypotension occurs
Phenytoin	Hypotension and cardiac arrhythmia; nystagmus	Vital signs and ECG during administration	Propylene glycol causes hypotension and cardiac arrhythmias when administered too rapidly. Large loading doses are generally not given to elderly individuals with preexisting cardiac disease or in critically ill patients with marginal blood pressure. The infusion rate should be slowed if the QT interval widens or if hypotension or arrhythmias develop; horizontal nystagmus suggests serum concentration above the reference range and toxicity; if a serum phenytoin concentration validates this, the dose should be decreased

(*continued*)

TABLE 57–3 Adverse Drug Reactions and Monitoring of Patients Receiving Drugs for GCSE (*Continued*)

Drug	Adverse Drug Reaction	Monitoring Parameters	Comments
Phenobarbital	Hypotension, respiratory, and CNS depression	Vital signs and mental status; EEG if used in anesthesia doses	Contains propylene glycol; if hypotension occurs, slow the rate of administration or begin dopamine; apnea and hypopnea can be more profound in patients treated initially with benzodiazepines
Propofol	Progressive metabolic acidosis, hemodynamic instability, and bradyarrhythmias	Vital signs, ECG, osmolar gap; EEG if used in anesthesia doses	Referred to as propofol infusion related syndrome, which can be fatal
Topiramate	Metabolic acidosis	Acid base status (serum bicarbonate)	Extremely rare

CNS, central nervous system; ECG, electrocardiogram; EEG, electroencephalogram.

- Maintain normal to high blood pressure. Aggressively treat hyperthermia (eg, rectal acetaminophen; cooling blankets).
- Give **thiamine** (100 mg IV) prior to IV glucose (see **Fig. 57–1**).
- Assess metabolic and/or respiratory acidosis with frequent ABG measurements to determine pH, partial pressure of oxygen (Pao_2), partial pressure of carbon dioxide ($Paco_2$), and HCO_3. If pH is less than 7.2 secondary to metabolic acidosis, give sodium bicarbonate. Use assisted ventilation to correct respiratory acidosis.

BENZODIAZEPINES

- Give a **benzodiazepine** as soon as possible if the patient is actively seizing. Generally, one or two IV doses stops seizures within 2 to 3 minutes. Diazepam, lorazepam, and midazolam are equally effective. If seizures have stopped, give a longer-acting anticonvulsant.
- IV **diazepam** is extremely lipophilic and quickly distributed into the brain, but it redistributes rapidly into body fat, causing a very short duration of effect (<0.5 h). Therefore, give a longer-acting anticonvulsant (eg, **phenytoin** or **phenobarbital**) immediately after the diazepam. The initial dose of diazepam can be repeated if the patient does not respond within 10 to 15 minutes.
- IV **lorazepam** is currently considered the benzodiazepine of choice by most practitioners. It takes longer to reach peak brain levels than diazepam but has a longer duration of action (12–24 h). Propylene glycol, which is in the vehicle of diazepam and lorazepam, can cause dysrhythmia and hypotension if administered too rapidly. They are also irritating to veins and must be diluted with an equal volume of compatible diluent before administration.
- IV **midazolam** is water soluble and diffuses rapidly into the CNS but has a very short half-life. Maintenance doses must be given by continuous infusion. There is increasing interest in giving it buccally, intramuscularly, and intranasally when IV access cannot be obtained readily. Buccal midazolam may be more effective than rectal diazepam in children.
- With benzodiazepine administration, a brief period of cardiorespiratory depression (<1 min) may occur and can necessitate assisted ventilation or require intubation, especially if the benzodiazepine is used with a barbiturate. Hypotension may occur with high doses of benzodiazepines.

PHENYTOIN

- **Phenytoin** has a 20 to 36 hour half-life, but it cannot be delivered fast enough to be a first-line agent. It takes longer to control seizures than the benzodiazepines because it enters the brain more slowly. It causes less respiratory depression and sedation than the **benzodiazepines** or **phenobarbital**, but its vehicle (propylene glycol) is associated with administration-related hypotension and cardiac arrhythmias, which are more likely with large loading doses and in critically ill patients with marginal blood pressure.
- Phenytoin should be diluted to 5 mg/mL or less in normal saline. See **Table 57–2 and 57–3** for dosing, rates of administration, cautions, and monitoring. Maintenance doses should be started within 12 to 24 hours of the loading dose.
- In determining a loading dose, consider if the patient was taking phenytoin prior to admission and the phenytoin serum concentration if known. A larger loading dose is required in obese patients.
- Phenytoin is associated with pain and burning during infusion. Phlebitis may occur with chronic infusion, and tissue necrosis is likely on infiltration. Intramuscular administration is not recommended.

FOSPHENYTOIN

- **Fosphenytoin,** the water-soluble phosphate ester of phenytoin, is a phenytoin prodrug. See **Table 57–3** for adverse effects and monitoring.
- The dose of fosphenytoin sodium is expressed as phenytoin sodium equivalents (PE). Do not give the loading dose intramuscularly (IM) unless IV access is impossible.

- Serum phenytoin concentrations should not be obtained for at least 2 hours after IV and 4 hours after IM administration.

PHENOBARBITAL

- The Working Group on Status Epilepticus recommends that **phenobarbital** be given after a benzodiazepine plus phenytoin has failed.
- Estimated lean body mass should be used to calculate dose in obese patients.
- Peak brain concentrations occur 12 to 60 minutes after IV dosing. Usually, seizures are controlled within minutes of the loading dose.
- See **Table 57–2** for dosing and **Table 57–3** for adverse effects, cautions, and monitoring. If the initial loading dose does not stop the seizures within 20 to 30 minutes, an additional 10 to 20 mg/kg dose may be given. If seizures continue, a third 10 mg/kg load may be given. When necessary, larger loading doses (eg, 30 mg/kg) have been used in neonates. There is no maximum dose beyond which further doses are likely to be ineffective. Once seizures are controlled, start the maintenance dose within 12 to 24 hours.

REFRACTORY GENERALIZED CONVULSIVE STATUS EPILEPTICUS

- When adequate doses of a benzodiazepine, hydantoin, or phenobarbital have failed, the condition is termed refractory. Approximately 10% to 15% of patients will develop refractory GCSE. Doses of agents used to treat refractory GCSE are given in **Table 57–4**.
- Most clinicians recommend anesthetic doses of midazolam, pentobarbital, or propofol, but other options include continuous infusion of a benzodiazepine, valproate, lacosamide, levetiracetam, topiramate, or lidocaine.
- A meta-analysis showed that among patients with refractory GCSE, response rates were: pentobarbital (92%), midazolam (80%), and propofol (73%). Seizure recurrence was least common with pentobarbital (12%), compared with propofol (15%) and midazolam (51%). Pentobarbital caused more hypotension.

Benzodiazepines

- Some clinicians recommend anesthetic doses of **midazolam** as the first-line treatment for refractory GCSE (see **Table 57–4**). Most patients respond within an hour. Successful discontinuation is enhanced by maintaining serum **phenytoin** concentrations greater than 20 mg/L (79 µmol/L) and **phenobarbital** concentrations greater than 40 mg/L (172 µmol/L). Hypotension and poikilothermia can occur and may require supportive therapies.
- Large-dose, continuous infusion **lorazepam** has also been used, but adverse reactions due to propylene glycol can occur.

Pentobarbital

- If response to high doses of **midazolam** is inadequate, anesthetizing is recommended. Intubation and respiratory support are mandatory during **barbiturate** coma, and continuous EEG and monitoring of vital signs are essential. A short-acting barbiturate (eg, **pentobarbital** or **thiopental**) is preferred (see **Fig. 57–1**).
- Give a loading dose of **Pentobarbital** to provide serum concentration (40 mg/L; 177 µmol/L) sufficient to induce an isoelectric EEG. Follow the loading dose immediately with an infusion (see **Table 57–4**), increasing gradually until there is burst suppression on the EEG or adverse effects occur. Usual duration of coma is 2 to 3 days. To avoid complications, discontinue pentobarbital as soon as possible. Other anticonvulsants should be at therapeutic levels before pentobarbital is withdrawn. As pentobarbital is a hepatic enzyme inducer, maintenance doses of most anticonvulsants need to be higher than usual.

Valproate

- For dosing see **Table 57–4**. The IV dosage form is not FDA approved for GCSE.
- One study suggested that the maintenance infusion rate should be adjusted as follows: 1) if no metabolic enzyme inducers are present, infuse at 1 mg/kg/hour; 2) if one or

TABLE 57–4 Dosing of Medications Used to Treat Refractory GCSE

Drug (Brand Name)	Initial Dose (Maximum Dose)	Maintenance Dose	Comments
Lacosamide (Vimpat)			
Adult	200–400 mg	200 mg bid	Administer IV over 15 minutes
Pediatric	2.5–3 mg/kg	6–8 mg/kg/day, given twice a day	
Levetiracetam (Keppra plus generics)			
Adult	2,000–3,000 mg	1,000 mg thrice a day	Administer IV over 5–15 minutes
Pediatric	40–60 mg/kg	40–60 mg/kg/day	
Lidocaine (generics)			
Adult	50–100 mg	1.5–3.5 mg/kg/h	Administer IV in ≤2 minutes
Pediatric	1 mg/kg (maximum 3–5 mg/kg in the first hour)	1.2–3 mg/kg/h	
Midazolam (Versed plus generic)			
Adult	200 mcg/kg[a]	50–500 mcg/kg/h[b]	Initial dose may be given IM; administer IV over 0.5–1 mg/min; continuous-infusion rate should be increased every 15 minutes in those who do not respond and should be guided by EEG response; development of tachyphylaxis can require frequent increases in dose; decrease dose by 1 mcg/kg/min every 2 hours once GCSE is controlled
Pediatric	150 mcg/kg[a]	60–120 mcg/kg/h[b]	
Pentobarbital (generics)			
Adult	10–20 mg/kg	1–5 mg/kg/h[b]	Over 1–2 hours, rate of infusion should be slowed or dopamine should be added if hypotension occurs; gradually titrate dose upward until there is evidence of burst suppression on EEG (i.e., isoelectric EEG) or prohibitive adverse effects occur. Twelve hours after a burst suppression is obtained, the rate should be titrated downward every 2–4 hours
Pediatric	15–20 mg/kg	1–5 mg/kg/h[b]	

(*continued*)

TABLE 57–4 Dosing of Medications Used to Treat Refractory GCSE (*Continued*)

Drug (Brand Name)	Initial Dose (Maximum Dose)	Maintenance Dose	Comments
Propofol (Diprivan plus generic)			
Adult	2 mg/kg	5–10 mg/kg/h[b]	Over 10 seconds in adults and 20–30 seconds in pediatric patients
Pediatric	3 mg/kg	2–18 mg/kg/h[c]	
Topiramate (Topamax plus generic)			
Adult	300–500 mg	400–1,600 mg/day	Given orally in divided dose every 12 hours. Doses as large as 25 mg/kg/day for 2–5 days have been used in children
Pediatric	5–10 mg/kg	5–10 mg/kg/day	
Valproate (Depacon plus generic)			
Adult	15–30 mg/kg	1–4 mg/kg/h[b]	Administer at 3 mg/kg/min; and follow by a continuous or intermittent infusion; larger doses may be required in those on hepatic enzyme inducers
Pediatric	20–25 mg/kg	1–4 mg/kg/h[b]	

EEG, electroencephalogram; GCSE, generalized convulsive status epilepticus; IM, intramuscular; IV, intravenous.

[a]Doses can be repeated twice at 10 to 15 minute intervals until the maximum dosage is given.
[b]Titrate dose as needed.
[c]Generally recommended not to exceed a dose of 4 mg/kg/h and a duration of 48 hours.

more inducers are present (eg, phenobarbital or phenytoin), infuse at 2 mg/kg/hour; and 3) if inducers and pentobarbital coma are present, infuse at 4 mg/kg/hour.
- There are no reports of respiratory depression; hemodynamic instability is rare, but vital signs should be monitored closely during the loading dose.

Propofol

- **Propofol** is very lipid soluble and has a large volume of distribution and a rapid onset of action. It has comparable efficacy to midazolam for refractory GCSE. Adverse effects and monitoring are shown in **Table 57–3**.
- An adult dose (see **Table 57–4**) can provide greater than 1000 cal/day as lipid and cost over $800/day.

Other Agents

- **Topiramate** tablets can be crushed, dissolved in a small amount of water, and given orally. Response tends to be delayed hours to days.
- IV **levetiracetam** is not hepatically metabolized and is minimally protein bound. Doses above 3000 mg/day do not add additional efficacy.
- IV **lidocaine** is not recommended unless other agents have failed. **Table 57–4** shows recommended dosing, and **Table 57–3** shows adverse effects and monitoring.

EVALUATION OF THERAPEUTIC OUTCOMES

- An EEG allows practitioners to determine when abnormal electrical activity has ceased and may assist in determining which anticonvulsant was effective. Monitor vital signs during the infusion. Assess the infusion site for evidence of infiltration before and during administration of phenytoin.

See Chapter 41, Status Epilepticus, authored by Stephanie J. Phelps and James W. Wheless, for a more detailed discussion of this topic.

This page intentionally left blank

Edited by Cecily V. DiPiro

CHAPTER 58

Obesity

- *Obesity* occurs when there is an imbalance between energy intake and energy expenditure over time, resulting in increased energy storage.

PATHOPHYSIOLOGY

- The etiology of obesity is usually unknown, but it is likely multifactorial and related to varying contributions from genetic, environmental, and physiologic factors.
- Genetic factors appear to be the primary determinants of obesity in some individuals, whereas environmental factors are more important in others. Identification of the total number of contributing genes is an area of extensive research.
- Environmental factors include reduced physical activity or work, abundant food supply, relatively sedentary lifestyles, increased availability of high-fat foods, and cultural factors and religious beliefs.
- Medical conditions including Cushing disease and growth hormone deficiency or genetic syndromes such as Prader–Willi syndrome can be associated with weight gain.
- Medications associated with weight gain include insulin, corticosteroids, some antidepressants, antipsychotics, and several anticonvulsants.
- Many neurotransmitters and neuropeptides stimulate or depress the brain's appetite network, impacting total calorie intake.
- The degree of obesity is determined by the net balance of energy ingested relative to energy expended over time. The single largest determinant of energy expenditure is metabolic rate, which is expressed as *resting energy expenditure* or *basal metabolic rate.* Physical activity is the other major factor that affects total energy expenditure.
- Major types of adipose tissue are (1) white adipose tissue, which manufactures, stores, and releases lipid; and (2) brown adipose tissue, which dissipates energy via uncoupled mitochondrial respiration. Adrenergic stimulation activates lipolysis in fat cells and increases energy expenditure in adipose tissue and skeletal muscle.

CLINICAL PRESENTATION

- Obesity is associated with serious health risks and increased mortality. Central obesity reflects high levels of intraabdominal or visceral fat that is associated with the development of hypertension, dyslipidemia, type 2 diabetes, and cardiovascular disease. Other obesity comorbidities are osteoarthritis and changes in the female reproductive system.
- Body mass index (BMI) and waist circumference (WC) are recognized, acceptable markers of excess body fat that independently predict disease risk (**Table 58–1**).
- BMI is calculated as weight (kg) divided by the square of the height (m^2).
- WC, the most practical method of characterizing central adiposity, is the narrowest circumference between the last rib and the top of the iliac crest.

TREATMENT

- Goals of Treatment: Weight management goals may include losing a predefined amount of weight, decreasing the rate of weight gain, or maintaining a weight-neutral status, depending on the clinical situation.

TABLE 58–1 Classification of Overweight and Obesity by Body Mass Index (BMI), Waist Circumference (WC), and Associated Disease Risk

			Disease Risk[a] (Relative to Normal Weight and Waist Circumference)	
	BMI (kg/m²)	Obesity Class	Men ≤40 in (≤102 cm) Women ≤35 in (≤89 cm)	>40 in (>102 cm) >35 in (>89 cm)
Underweight	<18.5		—	—
Normal weight[b]	18.5–24.9		—	High
Overweight	25–29.9		Increased	High
Obesity	30–34.9	I	High	Very high
	35–39.9	II	Very high	Very high
Extreme obesity	≥40	III	Extremely high	Extremely high

[a]Disease risk for type 2 diabetes, hypertension, and cardiovascular disease.
[b]Increased waist circumference can also be a marker for increased risk even in persons of normal weight.

Adapted from Preventing and Managing the Global Epidemic of Obesity: Report of the World Health Organization Consultation on Obesity. Geneva: World Health Organization; 1997. Reprinted with permission from National Institutes of Health, National Heart, Lung and Blood Institute. 1997, http://www.nhlbi.nih.gov/guidelines/obesity/ob_home.htm.

GENERAL APPROACH

- Successful obesity treatment plans incorporate reduced caloric intake, exercise, behavior modification with or without pharmacologic therapy, and/or surgery (**Fig. 58–1**). Weight loss of 5% to 10% of initial weight is a reasonable goal for most obese patients. Measures of success not only include pounds lost but also improvement in comorbid conditions, including blood pressure, blood glucose, and lipids.
- Many diets exist to aid weight loss. Regardless of the program, energy consumption must be less than energy expenditure. A reasonable goal is loss of 0.5 to 1 kg per week with a diet balanced in fat, carbohydrate, and protein intake.
- Increased physical activity combined with reduced calorie intake and behavior modification can augment weight loss and improve obesity-related comorbidities and cardiovascular risk factors.
- The primary aim of behavior modification is to help patients choose lifestyles conducive to safe and sustained weight loss. Behavioral therapy is based on principles of human learning, which use stimulus control and reinforcement to substitute desirable behaviors for learned, undesirable habits.
- Bariatric surgery, which reduces the stomach volume or absorptive surface of the alimentary tract, remains the most effective intervention for obesity. Surgery should be reserved for those with BMI above 35 or 40 kg/m² and significant comorbidities due to the morbidity and mortality associated with the surgical procedures.

PHARMACOLOGIC THERAPY

- The debate regarding the role of pharmacotherapy remains heated, fueled by the need to treat a growing epidemic and by the fallout from the removal of several agents from the market because of adverse reactions.
- Long-term pharmacotherapy may have a role for patients who have no contraindications to approved drug therapy (**Table 58–2**). The National Institutes of Health guidelines recommend consideration of pharmacotherapy in adults with BMI ≥30 kg/m² and/or WC ≥40 in (102 cm) for men or 35 in (89 cm) for women, or BMI of

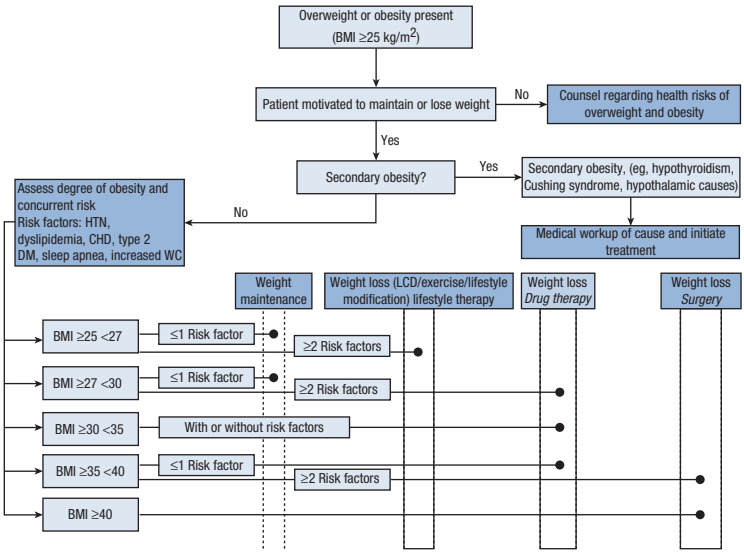


FIGURE 58–1. Treatment algorithm. Candidates for pharmacotherapy are selected on the basis of body mass index (BMI) and waist circumference (WC) criteria, along with consideration of concurrent risk factors. Medication therapy is always used as an adjunct to a comprehensive weight-loss program that includes diet, exercise, and behavioral modification. CHD, coronary heart disease; DM, diabetes mellitus, HTN, hypertension; LCD, low-calorie diet; WC, ≥40 in [≥102 cm] for men and ≥35 in [≥89 cm] for women.

27 to 30 kg/m^2 with at least two concurrent risk factors if 6 months of diet, exercise, and behavioral modification failed to achieve weight loss.

- **Orlistat** (180 or 360 mg in 3 divided doses/day) is a lipase inhibitor that induces weight loss by lowering dietary fat absorption; it also improves lipid profiles, glucose control, and other metabolic markers. Soft stools, abdominal pain or colic, flatulence, fecal urgency, and/or incontinence occur in 80% of individuals using prescription strength, are mild to moderate in severity, and improve after 1 to 2 months of therapy. Orlistat is approved for long-term use. It interferes with the absorption of fat-soluble vitamins, **cyclosporine**, **levothyroxine**, and **oral contraceptives**. A nonprescription formulation is also available.
- **Lorcaserin** is a selective serotonin receptor agonist (5-HT$_{2c}$) approved for chronic weight management. Activation of central 5-HT$_{2c}$ receptors results in appetite suppression leading to modest weight loss as compared with placebo. Discontinue lorcaserin if 5% weight loss is not achieved by week 12. Common adverse effects include headache, dizziness, constipation, fatigue, and dry mouth.
- **Phentermine** in combination with **topiramate extended release** is indicated for chronic weight management. Doses are gradually titrated from phentermine 3.75 to 15 mg and topiramate 23 to 92 mg over 4 months but the drug should be stopped after 12 weeks if 5% weight loss is not achieved. Common adverse effects include constipation, dry mouth, paraesthesia, dysgeusia, and insomnia.
- **Phentermine** and **diethylpropion** are each more effective than placebo in achieving short-term weight loss. Neither should be used in patients with severe hypertension or significant cardiovascular disease. Short-term therapy is not consistent with current national guidelines for chronic management of obesity.

TABLE 58–2 Pharmacotherapeutic Agents for Weight Loss

Drug	Brand Name	Initial Dose	Usual Range	Special Population Dose	Comment
Gastrointestinal Lipase Inhibitor					
Orlistat	Xenical	120 mg three times daily with each main meal containing fat	120 mg three times daily with each main meal containing fat		Approved for long-term use Take during or up to 1 hour after the meal Omit dose if meal is occasionally missed or contains no fat
Orlistat	Alli[a]	60 mg three times daily with each main meal containing fat	60 mg three times daily with each main meal containing fat		Same as Xenical
Serotonin 2C Receptor Agonist					
Lorcaserin	Belviq	10 mg twice daily	10 mg twice daily	Use with caution in moderate renal impairment and severe hepatic impairment; not recommended in patients with end state renal disease	Approved for long-term use Controlled substance: C–IV
Phentermine–Topiramate Combination					
Phentermine and topiramate extended release	Qsymia	3.75 mg of phentermine and 23 mg of topiramate once daily for 14 days; then increase to 7.5 mg of phentermine and 46 mg of topiramate once daily	7.5 mg of phentermine and 46 mg of topiramate once daily to a maximum dose of phentermine 15 mg and topiramate 92 mg	Maximum dose for patients with moderate or severe renal impairment or patients with moderate hepatic impairment is 7.5 mg of phentermine and 46 mg of topiramate	Approved for long-term use Take dose in the morning to avoid insomnia Controlled substance: C–IV

Noradrenergic Agents					
Phendimetrazine	Bontril PDM; Bontril Slow-Release	Conventional tablet: start at 17.5 mg two or three times daily, given 1 hour before meals Extended-release capsule: 105 mg once daily 30–60 minutes before morning meal	70–105 mg/day	Use caution in patients with renal impairment	Approved for short-term monotherapy Controlled substance: C–III Prescriptions should be written for the smallest quantity to minimize possibility of overdose
Phentermine	Adipex-P, Suprenza	Orally disintegrating tablet: 15 or 30 mg once every morning Phentermine hydrochloride: 15–37.5 mg/day given in one or two divided doses; administer before breakfast or 1–2 hours after breakfast	Orally disintegrating tablet: 15 or 30 mg once every morning Phentermine hydrochloride: 15–37.5 mg/day given in one or two divided doses; administer before breakfast or 1–2 hours after breakfast	Use with caution in patients with renal impairment	Approved for short-term monotherapy Controlled substance: C–IV Prescriptions should be written for the smallest quantity to minimize possibility of overdose Individualize to achieve adequate response with lowest effective dose
Diethylpropion	Tenuate, Tenuate Dospan	Immediate release: 25 mg three times daily administered 1 hour before meals Controlled release: 75 mg once daily administered at midmorning	75 mg/day	Use with caution in patients with renal impairment	Approved for short-term monotherapy Dose should not be administered in the evening or at bedtime Controlled substance: C–IV

[a]Available without a prescription.

- **Amphetamines** should generally be avoided because of their powerful stimulant effects and addictive potential.
- Many complementary and alternative therapy products are promoted for weight loss. Regulation of dietary supplements is less rigorous than that of prescription and over-the-counter drug products; manufacturers do not have to prove safety and effectiveness prior to marketing.

EVALUATION OF THERAPEUTIC OUTCOMES

- Assess progress once or twice monthly for 1 to 2 months, then monthly. Each encounter should document weight, WC, BMI, blood pressure, medical history, and patient assessment of tolerability of drug therapy.
- Discontinue medication therapy after 3 to 4 months if the patient has failed to demonstrate weight loss or maintenance of prior weight.
- Diabetic patients require more intense medical monitoring and self-monitoring of blood glucose. Weekly healthcare visits for 1 to 2 months may be necessary until the effects of diet, exercise, and weight loss medication become more predictable.
- Monitor patients with hyperlipidemia or hypertension to assess effects of weight loss on appropriate end points.

See Chapter 121, Obesity, authored by Amy Heck Sheehan, Judy T. Chen, Jack A. Yanovski, and Karim Anton Calis, for a more detailed discussion of this topic.

CHAPTER 59

Nutrition Evaluation and Support

- Malnutrition is a consequence of nutrient imbalance resulting from inadequate intake, absorption, or utilization of protein and energy. Undernutrition can result in changes in subcellular, cellular, or organ function that increase the individual's risks of morbidity and mortality.
- For information on overnutrition or obesity, see Chap. 58.
- Nutrition screening provides a systematic way to identify individuals in any care environment who need a detailed nutrition assessment.
- Nutrition assessment is the first step in developing a nutrition care plan. Goals of nutrition assessment are to identify the presence of factors associated with an increased risk of developing undernutrition and complications, estimate nutrition needs, and establish baseline parameters for assessing the outcome of therapy.
- This assessment should include a nutrition-focused history, a physical exam including anthropometrics, and laboratory measurements.

CLINICAL EVALUATION

- Medical and dietary history should include weight changes within 6 months, dietary intake changes, gastrointestinal (GI) symptoms, functional capacity, and disease states.
- Physical examination should focus on assessment of lean body mass (LBM) and physical findings of vitamin, trace element, and essential fatty acid deficiencies.

ANTHROPOMETRIC MEASUREMENTS

- Anthropometric measurements are physical measurements of the size, weight, and proportions of the human body used to compare an individual with normative population standards. The most common measurements are weight, stature, head circumference (for children younger than 3 years of age) waist circumference, and measurements of limb size (eg, skinfold thickness and midarm muscle and wrist circumferences), along with bioelectrical impedance analysis (BIA).
- Interpretation of actual body weight (ABW) should consider ideal weight (IBW) for height, usual body weight (UBW), fluid status, and age. Change over time can be calculated as the percentage of UBW. Unintentional weight loss >10% in 6 months increases risk of poor clinical outcome in adults.
- The best indicator of adequate nutrition in children is appropriate growth. Weight, stature, and head circumference should be plotted on the appropriate growth curve and compared with usual growth velocities. Average weight gain for newborns is 10 to 20 g/kg/day (24 to 35 g/day for term infants and 10 to 25 g/day for preterm infants).
- Body mass index (BMI) is another index of weight-for-height that is highly correlated with body fat. Interpretation of BMI should include consideration of gender, frame size, and age. BMI values greater than 25 kg/m^2 are indicative of overweight, and values less than 18.5 kg/m^2 are indicative of undernutrition. BMI is calculated as follows:

$$\text{Body weight (kg)}/[\text{height (m)}]^2$$

- Measurements of skinfold thickness estimate subcutaneous fat, midarm muscle circumference estimates skeletal muscle mass, and waist circumference estimates abdominal fat content.
- BIA is a simple, noninvasive, and relatively inexpensive way to measure LBM. It is based on differences between fat tissue and lean tissue's resistance to conductivity. Fluid status should be considered in interpretation of BIA results.

TABLE 59–1 Visceral Proteins Used for Assessment of Lean Body Mass

Serum Protein	Half-Life (Days)	Function	Factors Resulting in Increased Values	Factors Resulting in Decreased Values
Albumin	18–20	Maintains plasma oncotic pressure; transports small molecules	Dehydration, anabolic steroids, insulin, infection	Overhydration; edema; kidney dysfunction; nephrotic syndrome; poor dietary intake; impaired digestion; burns; congestive heart failure; cirrhosis; thyroid, adrenal, or pituitary hormones; trauma; sepsis
Transferrin	8–9	Binds Fe in plasma; transports Fe to bone	Fe deficiency, pregnancy, hypoxia, chronic blood loss, estrogens	Chronic infection, cirrhosis, burns, enteropathies, nephrotic syndrome, cortisone, testosterone
Prealbumin	2–3	Binds T_3 and, to a lesser extent, T_4; retinol-binding protein carrier	Kidney dysfunction	Cirrhosis, hepatitis, stress, surgery, inflammation, hyperthyroidism, cystic fibrosis, burns, kidney dysfunction, zinc deficiency

T_3, triiodothyronine; T_4, thyroxine.

BIOCHEMICAL AND IMMUNE FUNCTION STUDIES

- LBM can be assessed by measuring serum visceral proteins (**Table 59–1**). They are best for assessing uncomplicated semistarvation and recovery, and less useful for assessing status during acute stress. Interpret visceral proteins relative to overall clinical status because they are affected by factors other than nutrition.
- Nutrition affects immune status both directly and indirectly. Total lymphocyte count and delayed cutaneous hypersensitivity reactions are immune function tests useful in nutrition assessment, but their lack of specificity limits their usefulness as nutrition status markers.
- Delayed cutaneous hypersensitivity is commonly assessed using antigens to which the patient has been previously sensitized. The recall antigens used most frequently are mumps and *Candida albicans*. Anergy is associated with severe malnutrition, and immune response is restored with nutrition repletion.

SPECIFIC NUTRIENT DEFICIENCIES

- Biochemical assessment of trace element, vitamin, and essential fatty acid deficiencies should be based on the nutrient's function, but few practical methods are available. Therefore, most assays measure serum concentrations of the individual nutrient.
- Clinical syndromes are associated with deficiencies of the following trace elements: zinc, copper, manganese, selenium, chromium, iodine, fluoride, molybdenum, and iron.
- Single vitamin deficiencies are uncommon; multiple vitamin deficiencies more commonly occur with undernutrition. For information on iron deficiency and other anemias, see Chap. 33.

- Essential fatty acid deficiency is rare but can occur with prolonged lipid-free parenteral nutrition, very-low-fat enteral formulas or diets, severe fat malabsorption, or severe malnutrition. The body can synthesize all fatty acids except for linoleic and linolenic acid.
- Carnitine can be synthesized from lysine and methionine, but synthesis is decreased in premature infants. Low carnitine levels can occur in premature infants receiving parenteral nutrition or carnitine-free diets.

ASSESSMENT OF NUTRIENT REQUIREMENTS

- Assessment of nutrient requirements must be made in the context of patient-specific factors (eg, age, gender, size, disease state, clinical condition, nutrition status, and physical activity).
- To replace recommended dietary allowances, the Food and Nutrition Board created the dietary reference intakes made up of seven nutrient groups.

ENERGY REQUIREMENTS

- Adults should consume 45% to 65% of total calories from carbohydrates, 20% to 35% from fat, and 10% to 35% from protein. Recommendations are similar for children, except that infants should consume 40% to 50% of total calories from fat.
- Energy requirements of individuals can be estimated using published, validated equations or directly measured, depending on factors including severity of illness and resources available. The simplest method is to use population estimates of calories required per kilogram of body weight.
- Healthy adults with normal nutrition status and minimal illness severity require an estimated 20 to 25 kcal ABW/kg/day (84–105 kJ ABW/kg/day). Daily energy requirements for children are approximately 150% of basal metabolic rate with additional calories to support activity and growth. Consult references for equations used to estimate energy expenditure in adults and children.
- Energy requirements for all ages increase with fever, sepsis, major surgery, trauma, burns, long-term growth failure, and chronic conditions (eg, bronchopulmonary dysplasia, congenital heart disease, and cystic fibrosis).

PROTEIN, FLUID, AND MICRONUTRIENT REQUIREMENTS

Protein

- Protein requirements are based on age, gender, nutrition status, disease state, and clinical condition. The usual recommended daily protein allowances are 0.8 g/kg for adults, 1 to 1.5 g/kg for adults over 60 years of age, 1.5 to 2 g/kg for patients with metabolic stress (eg, infection, trauma, and surgery), and 2.5 to 3 g/kg for patients with burns.

Fluid

- Daily adult fluid requirements are approximately 30 to 35 mL/kg, 1 mL/kcal (or per every 4.19 kJ) ingested, or 1500 mL/m^2.
- Daily fluid requirements for children and preterm infants who weigh less than 10 kg are at least 100 mL/kg. An additional 50 mL/kg should be provided for each kilogram of body weight between 11 and 20 kg, and 20 mL/kg for each kilogram greater than 20 kg.
- Examples of factors that result in increased fluid requirements include gastrointestinal (GI) losses, fever, sweating, and increased metabolism, whereas kidney or cardiac failure and hypoalbuminemia with starvation are examples of factors that result in decreased fluid requirements.
- Assess fluid status by monitoring urine output and specific gravity, serum electrolytes, and weight changes. An hourly urine output of at least 1 mL/kg for children and 40 to 50 mL for adults is needed to ensure tissue perfusion.

Micronutrients

- Requirements for micronutrients (ie, electrolytes, trace elements, and vitamins) vary with age, gender, route of administration, and underlying clinical conditions.

- Sodium, potassium, magnesium, and phosphorus requirements are typically decreased in patients with kidney failure, whereas calcium requirements are increased (see Chaps. 74 and 75).

DRUG–NUTRIENT INTERACTIONS

- Concomitant drug therapy can alter serum concentrations of vitamins (**Table 59–2**), minerals, and electrolytes.
- Some drug delivery systems contain nutrients. For example, the vehicle for propofol is 10% lipid emulsion, and most IV therapies include dextrose or sodium.

TABLE 59–2 Drug and Vitamin Interactions

Drug	Effect
Antacids	Thiamine deficiency
Antibiotics	Vitamin K deficiency
Aspirin	Folic acid deficiency; increased vitamin C excretion
Cathartics	Increased requirements for vitamins D, C, and B_6
Cholestyramine	Vitamins A, D, E, and K and β-carotene malabsorption
Colestipol	Vitamins A, D, E, and K and β-carotene malabsorption
Corticosteroids	Decreased vitamins A, D, and C
Diuretics (loop)	Thiamine deficiency
Efavirenz	Vitamin D deficiency caused by increased metabolism of 25(OH)-vitamin D and $1,25(OH)_2$-vitamin D
$Histamine_2$ antagonists	Vitamin B_{12} malabsorption (reduced acid results in impaired release of B_{12} from food)
Isoniazid	Vitamin B_6 and niacin deficiency
Isotretinoin	Vitamin A increases toxicity
Mercaptopurine	Niacin deficiency
Methotrexate	Folic acid inhibits effect
Orlistat	Vitamins A, D, E, and K malabsorption caused by fat malabsorption
Pentamidine	Folic acid deficiency
Phenobarbital	Increased vitamin D metabolism
Phenytoin	Increased vitamin D metabolism; folic acid concentrations decrease
Primidone	Folic acid deficiency
Protease inhibitors	Vitamin D deficiency (impaired renal hydroxylation)
Proton pump inhibitors	Vitamin B_{12} malabsorption (reduced acid results in impaired release of B_{12} from food)
Sulfasalazine	Folic acid malabsorption
Trimethoprim	Folic acid depletion
Warfarin	Vitamin K inhibits effect; vitamins A, C, and E may affect prothrombin time
Zidovudine	Folic acid and B_{12} deficiencies increase myelosuppression

NUTRITION SUPPORT

- The primary objective of nutrition support therapy is to promote positive clinical outcomes of an illness and improve quality of life.

ENTERAL NUTRITION

- Enteral nutrition (EN) delivers nutrients by tube or mouth into the GI tract; we will focus on delivery through a feeding tube.
- EN is indicated for the patient who cannot or will not eat enough to meet nutritional requirements and who has a functioning GI tract and a method of enteral access. Potential indications include neoplastic disease, organ failure, hypermetabolic states, GI disease, and neurologic impairment.
- Distal mechanical intestinal obstruction and necrotizing enterocolitis are the only absolute contraindications to EN. Conditions that challenge the success of EN include severe diarrhea, protracted vomiting, enteric fistulas, severe GI hemorrhage, and intestinal dysmotility.
- EN has replaced parenteral nutrition (PN) as the preferred method for the feeding of critically ill patients requiring specialized nutrition support. Advantages of EN over PN include maintaining GI tract structure and function; fewer metabolic, infectious, and technical complications; and lower costs.
- The optimal time to initiate EN is controversial. Early initiation within 24 to 72 hours of hospitalization is recommended for critically ill patients because this approach appears to decrease infectious complications and reduce mortality. If patients are only mildly to moderately stressed and well nourished, EN initiation can be delayed until oral intake is inadequate for 7 to 14 days.

ACCESS

- EN can be administered through four routes, which have different indications, tube placement options, advantages, and disadvantages (**Table 59–3**). The choice depends on the anticipated duration of use and the feeding site (ie, stomach vs small bowel).
- The stomach is generally the least expensive and least labor-intensive access site; however, patients who have impaired gastric emptying are at risk for aspiration and pneumonia.
- Long-term access should be considered when EN is anticipated for more than 4 to 6 weeks.

ADMINISTRATION METHODS

- EN can be administered by continuous, cyclic, bolus, and intermittent methods. The choice depends on the feeding tube location, patient's clinical condition, intestinal function, residence environment, and tolerance to tube feeding.
- Continuous EN is preferred for initiation and has the advantage of being well tolerated. Disadvantages include cost and inconvenience associated with pump and administration sets.
- Cyclic EN has the advantage of allowing breaks from the infusion system, thereby increasing mobility, especially if EN is administered nocturnally.
- Bolus EN is most commonly used in long-term care residents who have a gastrostomy. Advantages include short administration time (eg, 5–10 min) and minimal equipment (eg, a syringe). Bolus EN has the potential disadvantages of causing cramping, nausea, vomiting, aspiration, and diarrhea.
- Intermittent EN is similar to bolus EN except that the feeding is administered over 20 to 60 minutes, which improves tolerability but requires more equipment (eg, reservoir bag and infusion pump). Like bolus EN, intermittent EN mimics normal eating patterns.
- Protocols outlining initiation and advancement criteria are a useful strategy to optimize achievement of nutrient goals based on GI tolerance. Clinical signs of intolerance include abdominal distention or cramping, high gastric residual volumes, aspiration, and diarrhea.

TABLE 59–3 Options and Considerations in the Selection of Enteral Access

Access	EN Duration/Patient Characteristics	Tube Placement Options	Advantages	Disadvantages
Nasogastric or orogastric	Short term Intact gag reflex Normal gastric emptying	Manually at bedside	Ease of placement Allows for all methods of administration Inexpensive Multiple commercially available tubes and sizes	Potential tube displacement Potential increased aspiration risk
Nasoduodenal or nasojejunal	Short term Impaired gastric motility or emptying High risk of GER or aspiration	Manually at bedside Fluoroscopically Endoscopically	Potential reduced aspiration risk Allows for early postinjury or postoperative feeding Multiple commercially available tubes and sizes	Manual transpyloric passage requires greater skill Potential tube displacement or clogging Bolus or intermittent feeding not tolerated
Gastrostomy	Long term Normal gastric emptying	Surgically Endoscopically Radiologically Laparoscopically	Allows for all methods of administration Low-profile buttons available Large-bore tubes less likely to clog Multiple commercially available tubes and sizes	Attendant risks associated with each type of procedure Potential increased aspiration risk Risk of stoma site complications
Jejunostomy	Long term Impaired gastric motility or gastric emptying High risk of GER or aspiration	Surgically Endoscopically Radiologically Laparoscopically	Allows for early postinjury or postoperative feeding Potential reduced aspiration risk Multiple commercially available tubes and sizes Low-profile buttons available	Attendant risks associated with each type of procedure Bolus or intermittent feeding not tolerated Risk of stoma site complications

EN, enteral nutrition; GER, gastroesophageal reflux.

- Continuous EN feedings are typically started in adults at 20 to 50 mL/hour and advanced by 10 to 25 mL/hour every 4 to 8 hours until the goal is achieved. Intermittent EN feedings are started at 120 mL every 4 hours and advanced by 30 to 60 mL every 8 to 12 hours.
- EN feedings are typically started in children at 1 to 2 mL/kg/hour for continuous feeding or 2 to 4 mL/kg per bolus with advancement by similar amounts every 4 to 24 hours. Feedings are started at lower rates or volumes in premature infants, usually 10 to 20 mL/kg/day.

FORMULATIONS

- Historically, EN formulations were created to provide essential nutrients, including macronutrients (eg, carbohydrates, fats, and proteins) and micronutrients (eg, electrolytes, trace elements, vitamins, and water).
- Over time, formulations have been enhanced to improve tolerance and meet specific patient needs. For example, nutraceuticals or pharmaconutrients are added to modify the disease process or improve clinical outcome; however, these health claims are not regulated by the FDA.
- The molecular form of the protein source determines the amount of digestion required for absorption within the small bowel. The carbohydrate component usually provides the major source of calories; polymeric entities are preferred over elemental sugars. Vegetable oils are the most common sources of fat in EN formulations.
- Soluble and insoluble fiber has been added to several EN formulations. Potential benefits of soluble fiber include trophic effects on colonic mucosa, promotion of sodium and water absorption, and regulation of bowel function.
- Osmolality is a function of the size and quantity of ionic and molecular particles primarily related to protein, carbohydrate, electrolyte, and mineral content. The osmolality of EN formulations for adults ranges from 300 to 900 mOsm/kg (300–900 mmol/kg), and an osmolality less than 450 mOsm/kg (450 mmol/kg) is recommended for children. Osmolality is commonly thought to affect GI tolerability, but there is a lack of supporting evidence.

CLASSIFICATION OF ENTERAL FEEDING FORMULATIONS

- EN formulations are classified by their composition and intended patient population (**Table 59–4**). Formularies should focus on clinically significant characteristics of available products, avoid duplicate formulations, and include only specialty formulations with evidence-based indications.

COMPLICATIONS AND MONITORING

- Monitor patients for metabolic, GI, and mechanical complications of EN (**Table 59–5**).
- Metabolic complications associated with EN are analogous to those of parenteral nutrition (PN), but the occurrence is lower.
- GI complications include nausea, vomiting, abdominal distention, cramping, aspiration, diarrhea, and constipation. Gastric residual volume is thought to increase the risk of vomiting and aspiration.
- Mechanical complications include tube occlusion or malposition and nasopulmonary intubation. Techniques for clearing occluded tubes include pancreatic enzymes in sodium bicarbonate and using a declogging device. Techniques for maintaining patency include flushing with at least 30 mL of water before and after medication administration and intermittent feedings and at least every 8 hours during continuous feeding.

DRUG DELIVERY VIA FEEDING TUBE

- Administering drugs via tube feeding is a common practice. If the drug is a solid that can be crushed (eg, *not* a sublingual, sustained-release, or enteric-coated formulation) or is a capsule, mix with 15 to 30 mL of water or other appropriate solvent and administer. Otherwise, a liquid dosage preparation should be used. Administer

TABLE 59–4 Adult Enteral Feeding Formulation Classification System

Category	Features	Indications
Standard polymeric	Isotonic	Designed to meet the needs of the majority of patients
	1–1.2 kcal/mL (4.2–5 kJ/mL)	Patients with functional GI tract
	NPC:N 125:1 to 150:1	Not suitable for oral use
	May contain fiber	
High protein	NPC:N <125:1	Patients with protein requirements >1.5 g/kg/day, such as trauma patients and those with burns, pressure sores, or wounds
	May contain fiber	Patients receiving propofol
High caloric density	1.5–2 kcal/mL (6.3–8.4 kJ/mL)	Patients requiring fluid and/or electrolyte restriction, such as kidney insufficiency
	Lower electrolyte content per calorie	
	Hypertonic	
Elemental	High proportion of free amino acids	Patients who require low fat
	Low in fat	Use has generally been replaced by peptide-based formulations
Peptide-based	Contains dipeptides and tripeptides	Indications/benefits not clearly established
	Contains MCTs	Trial may be warranted in patients who do not tolerate intact protein due to malabsorption
Disease-specific		
Kidney	Caloric dense	Alternative to high caloric density formulations, but generally more expensive
	Protein content varies	
	Low electrolyte content	

Liver	Increased branched-chain and decreased aromatic amino acids	Patients with hepatic encephalopathy
Lung	High fat, low carbohydrate Antiinflammatory lipid profile and antioxidants	Patients with ARDS and severe ALI
Diabetes mellitus	High fat, low carbohydrate	Alternative to standard, fiber-containing formulation in patients with uncontrolled hyperglycemia
Immune-modulating	Supplemented with glutamine, arginine, nucleotides, and/or omega-3 fatty acids	Patients undergoing major elective GI surgery, trauma, burns, head and neck cancer, and critically ill patients on mechanical ventilation Use with caution in patients with sepsis Select nutrients may be beneficial or harmful in subgroups of critically ill patients
Oral supplement	Sweetened for taste Hypertonic	Patients who require supplementation to an oral diet

ALI, acute lung injury; ARDS, acute respiratory distress syndrome; MCT, medium-chain triglyceride; NPC:N, nonprotein calorie-to-nitrogen ratio.

TABLE 59–5 Suggested Monitoring for Patients on Enteral Nutrition

Parameter	During Initiation of EN Therapy	During Stable EN Therapy
Vital signs	Every 4–6 hours	As needed with suspected change (i.e., fever)
Clinical assessment		
Weight	Daily	Weekly
Length/height (children)	Weekly–monthly	Monthly
Head circumference (<3 years of age)	Weekly–monthly	Monthly
Total intake/output	Daily	As needed with suspected change in intake/output
Tube-feeding intake	Daily	Daily
Enterostomy tube site assessment	Daily	Daily
GI tolerance		
Stool frequency/volume	Daily	Daily
Abdomen assessment	Daily	Daily
Nausea or vomiting	Daily	Daily
Gastric residual volumes	Every 4–8 hours (varies)	As needed when delayed gastric emptying suspected
Tube placement	Prior to starting, then ongoing	Ongoing
Laboratory		
Electrolytes, blood urea nitrogen/serum creatinine, glucose	Daily	Every 1–3 months
Calcium, magnesium, phosphorus	3–7 times/week	Every 1–3 months
Liver function tests	Weekly	Every 1–3 months
Trace elements, vitamins	If deficiency/toxicity suspected	If deficiency/toxicity suspected

EN, enteral nutrition.

multiple medications separately, each followed by flushing the tube with 5 to 15 mL of water.

- Mixing of liquid medications with EN formulations can cause physical incompatibilities that inhibit drug absorption and clog small-bore feeding tubes. Incompatibility is more common with formulations containing intact (vs hydrolyzed) protein and medications formulated as acidic syrups. Mixing of liquid medications and EN formulations should be avoided whenever possible.
- The most significant drug–nutrient interactions result in reduced bioavailability and suboptimal pharmacologic effect (**Table 59–6**). Continuous feeding requires interruption for drug administration, and medications should be spaced between bolus feedings.

PARENTERAL NUTRITION

- Parenteral nutrition (PN) provides macro- and micronutrients by central or peripheral venous access to meet specific nutritional requirements of the patient.

TABLE 59–6 Medications with Special Considerations for Enteral Feeding Tube Administration

Drug	Interaction	Comments
Phenytoin	Reduced bioavailability in the presence of tube feedings Possible phenytoin binding to calcium caseinates or protein hydrolysates in enteral feeding	To minimize interaction, holding tube feedings 1–2 hours before and after phenytoin has been suggested; this has no proven benefit Adjust tube-feeding rate to account for time held for phenytoin administration Monitor phenytoin serum concentration and clinical response closely Consider switching to IV phenytoin if unable to reach therapeutic serum concentration
Fluoroquinolones Tetracyclines	Potential for reduced bioavailability because of complexation of drug with divalent and trivalent cations found in enteral feeding	Consider holding tube feeding 1 hour before and after administration Avoid jejunal administration of ciprofloxacin Monitor clinical response
Warfarin	Decreased absorption of warfarin because of enteral feeding; therapeutic effect antagonized by vitamin K in enteral formulations	Adjust warfarin dose based on INR Anticipate need to increase warfarin dose when enteral feedings are started and decrease dose when enteral feedings are stopped Consider holding tube feeding 1 hour before and after administration
Omeprazole Lansoprazole	Administration via feeding tube complicated by acid-labile medication within delayed-release, base-labile granules	Granules become sticky when moistened with water and may occlude small-bore tubes Granules should be mixed with acidic liquid when given via a gastric feeding tube An oral liquid suspension can be extemporaneously prepared for administration via a feeding tube

INR, International Normalized Ratio.

- PN should be considered when a patient cannot meet nutritional requirements through use of the GI tract. Consider PN after suboptimal nutritional intake for 1 day in preterm infants, 2 to 3 days in term infants, 3 to 5 days in critically injured children, 5 to 7 days in other children, and 7 to 14 days in older children and adults.

COMPONENTS OF PARENTERAL NUTRITION

- Macronutrients (ie, water, protein, dextrose, and IV fat emulsion [IVFE]) are used for energy (dextrose, fat) and as structural substrates (protein and fats).
- Protein is provided as crystalline amino acids (CAAs). When oxidized, 1 g of protein yields 4 calories (~17 J). Including the caloric contribution from protein in calorie calculations is controversial; therefore, PN calories can be calculated as either total or nonprotein calories.
- Standard CAA products contain a balanced profile of essential, semiessential, and nonessential L-amino acids and are designed for patients with "normal" organ function and nutritional requirements. Standard CAA products differ in amino acid, total nitrogen, and electrolyte content but have similar effects on protein markers.
- The primary energy source in PN solutions is carbohydrate, usually as dextrose monohydrate which is available in concentrations ranging from 5% to 70%. When oxidized, 1 g of hydrated dextrose provides 3.4 kcal (14.2 kJ).
- Commercially available intravenous fat emulsions (IVFEs) provide calories and essential fatty acids. These products differ in triglyceride source, fatty acid content, and essential fatty acid concentration.
- When oxidized, 1 g of fat yields 9 kcal (38 kJ). Because of the caloric contribution from egg phospholipid and glycerol, caloric content of IVFE is 1.1 kcal/mL (4.6 kJ/mL) for the 10%, 2 kcal/mL (8.4 kJ/mL) for the 20%, and 3 kcal/mL (12.6 kJ/mL) for the 30% emulsions.
- Essential fatty acid deficiency can be prevented by giving IVFE, 0.5 to 1 g/kg/day for neonates and infants and 100 g/wk for adults.
- IVFE 10% and 20% products can be administered by a central or peripheral vein, added directly to PN solution as a total nutrient admixture (TNA) or three-in-one system (lipids, protein, glucose, and additives), or piggybacked with a CAA and dextrose solution, commonly referred to as a two-in-one solution. IVFE 30% is approved only for TNA preparation.
- Micronutrients (ie, vitamins, trace elements, and electrolytes) are required to support metabolic activities for cellular homeostasis such as enzyme reactions, fluid balance, and regulation of electrophysiologic processes.
- Multivitamin products have been formulated to comply with guidelines for adults, children, and infants. These products contain 13 essential vitamins, including vitamin K.
- Requirements for trace elements depend on the patient's age and clinical condition. Examples include using higher doses of zinc in patients with high-output ostomies or diarrhea; restricting or withholding manganese and copper in patients with cholestatic liver disease; and restricting or withholding chromium, molybdenum, and selenium in patients with renal failure.
- Chromium, copper, manganese, selenium, and zinc are considered essential and available as single- or multiple-entity products for addition to PN solutions.
- Sodium, potassium, calcium, magnesium, phosphorus, chloride, and acetate are necessary components of PN for maintenance of numerous cellular functions.
- Electrolyte requirements depend on the patient's age, disease state, organ function, drug therapy, nutrition status, and extrarenal losses.

SPECIFICS OF PARENTERAL NUTRITION

- The patient's clinical condition determines whether PN is administered through a peripheral or central vein.
- Peripheral parenteral nutrition (PPN) candidates do not have large nutritional requirements, are not fluid restricted, and are expected to regain GI tract function within 10 to 14 days. Solutions for PPN have lower final concentrations of amino acid

(3–5%), dextrose (5%–10%), and micronutrients as compared with central parenteral nutrition (CPN).

- Primary advantages of PPN include a lower risk of infectious, metabolic, and technical complications.
- CPN is useful in patients who require PN for more than 7 to 14 days and who have large nutrient requirements, poor peripheral venous access, or fluctuating fluid requirements.
- CPN solutions are highly concentrated hypertonic solutions that must be administered through a large central vein. The choice of venous access site depends on factors including patient age and anatomy. Peripherally inserted central catheters (PICCs) are often used for both short- and long-term central venous access in acute or home care settings.
- Disadvantages include risks associated with catheter insertion, use, and care. Central venous access has a greater potential for infection.
- PN regimens for adults can be based on formulas computer programs, or standardized order forms. Order forms are popular because they help educate practitioners and foster cost-efficient nutrition support by minimizing errors in ordering, compounding, and administering.
- Pediatric PN regimens typically require an individualized approach because practice guidelines often recommend nutrient intake based on weight. Labeling should reflect "amount per day" and also "amount per kilogram per day."

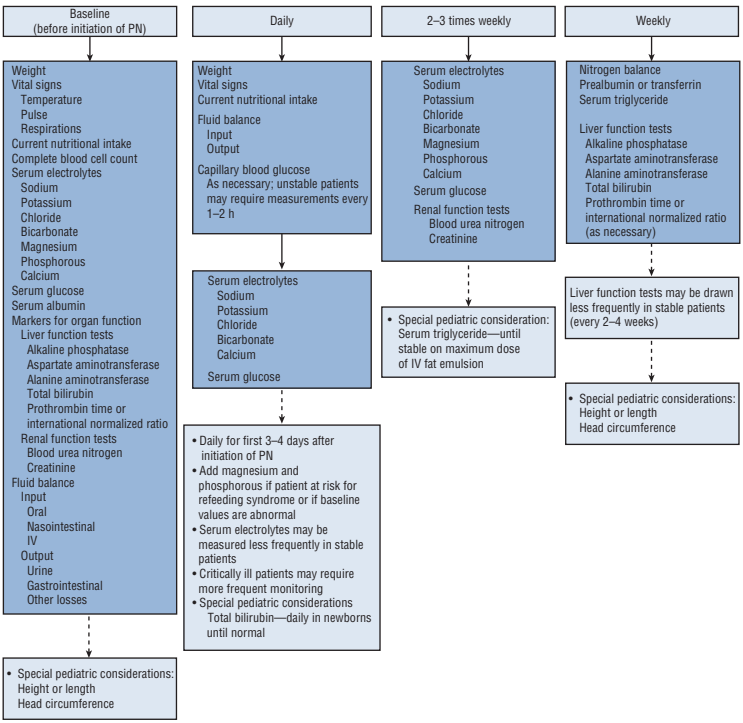


FIGURE 59–1. Monitoring strategy for patients receiving parenteral nutrition (PN).

EVALUATION OF THERAPEUTIC OUTCOMES

- Assessing the outcome of EN includes monitoring objective measures of body composition, protein and energy balance, and subjective outcome for physiologic muscle function and wound healing.
- Measures of disease-related morbidity include length of hospital stay, infectious complications, and patient's sense of well-being. Ultimately, the successful use of EN avoids the need for PN.
- Outcomes with PN are determined through routine assessment of the clinical condition of the patient, with a focus on nutritional and metabolic effects of the PN regimen.
- Biochemical and clinical parameters should be monitored routinely in patients receiving PN (**Fig. 59–1**).

See Chapter 118, Assessment of Nutrition Status and Nutrition Requirements, authored by Katherine Hammond Chessman and Vanessa J. Kumpf; Chapter 119, Parenteral Nutrition, authored by Todd W. Mattox and Catherine M. Crill; and Chapter 120, Enteral Nutrition, authored by Vanessa J. Kumpf and Katherine Hammond Chessman, for a more detailed discussion of this topic.

CHAPTER 60

Breast Cancer

- *Breast cancer* is a malignancy originating from breast tissue. Disease confined to a localized breast lesion is referred to as *early, primary, localized,* or *curable.* Disease detected clinically or radiologically in sites distant from the breast is referred to as *advanced* or *metastatic breast cancer* (MBC), which is usually incurable.

EPIDEMIOLOGY

- Two variables most strongly associated with occurrence of breast cancer are gender and advancing age. Additional risk factors include endocrine factors (eg, early menarche, nulliparity, late age at first birth, and hormone replacement therapy), genetic factors (eg, personal and family history, mutations of tumor suppresser genes [*BRCA1* and *BRCA2*]), and environmental and lifestyle factors (eg, radiation exposure).
- Breast cancer cells often spread undetected by contiguity, lymph channels, and through the blood early in the course of the disease, resulting in metastatic disease after local therapy. The most common metastatic sites are lymph nodes, skin, bone, liver, lungs, and brain.

CLINICAL PRESENTATION

- A painless lump is the initial sign of breast cancer in most women. The typical malignant mass is solitary, unilateral, solid, hard, irregular, and nonmobile. Nipple changes are less commonly seen. More advanced cases present with prominent skin edema, redness, warmth, and induration.
- Symptoms of MBC depend on the site of metastases but may include bone pain, difficulty breathing, abdominal pain or enlargement, jaundice, and mental status changes.
- Many women first detect some breast abnormalities themselves, but it is increasingly common for breast cancer to be detected during routine screening mammography in asymptomatic women.

DIAGNOSIS

- Initial workup should include a careful history, physical examination of the breast, three-dimensional mammography, and, possibly, other breast imaging techniques, such as ultrasound and magnetic resonance imaging (MRI).
- Breast biopsy is indicated for a mammographic abnormality that suggests malignancy or for a palpable mass on physical examination.

STAGING

- Stage (anatomical extent of disease) is based on primary tumor extent and size (T_{1-4}), presence and extent of lymph node involvement (N_{1-3}), and presence or absence of distant metastases (M_{0-1}). The staging system determines prognosis and assists with treatment decisions. Simplistically stated, these stages may be represented as follows:
  - ✓ *Early Breast Cancer*
    - Stage 0: Carcinoma in situ or disease that has not invaded the basement membrane
    - Stage I: Small primary invasive tumor without lymph node involvement
    - Stage II: Involvement of regional lymph nodes
  - ✓ *Locally Advanced Breast Cancer*

- Stage III: Usually a large tumor with extensive nodal involvement in which the node or tumor is fixed to the chest wall; also includes inflammatory breast cancer, which is rapidly progressive

✓ *Advanced or Metastatic Breast Cancer*

- Stage IV: Metastases in organs distant from the primary tumor

PATHOLOGIC EVALUATION

- Development of malignancy is a multistep process involving preinvasive (or noninvasive) and invasive phases. The goal of treatment for noninvasive carcinomas is to prevent the development of invasive disease.
- Pathologic evaluation of breast lesions establishes the histologic diagnosis and confirms the presence or absence of prognostic factors.
- Most breast carcinomas are adenocarcinomas and are classified as ductal or lobular.

PROGNOSTIC FACTORS

- The ability to predict prognosis is used to design treatment recommendations to maximize quantity and quality of life.
- Age at diagnosis and ethnicity are patient characteristics that may affect prognosis.
- Tumor size and presence and number of involved axillary lymph nodes are primary factors in assessing the risk for breast cancer recurrence and subsequent metastatic disease. Other disease characteristics that provide prognostic information are histologic subtype, nuclear or histologic grade, lymphatic and vascular invasion, and proliferation indices.
- Hormone receptors [estrogen (ER) and progesterone (PR)] are not strong prognostic markers but are used clinically to predict response to endocrine therapy.
- HER2/*neu* (HER2) overexpression is associated with transmission of growth signals that control aspects of normal cell growth and division. Overexpression of HER2 is associated with increased tumor aggressiveness, rates of recurrence, and mortality.
- Genetic profiling tools provide additional prognostic information to aid in treatment decisions for subgroups of patients with otherwise favorable prognostic features.

TREATMENT

- Goals of Treatment: Adjuvant therapy for early and locally advanced breast cancer is administered with curative intent. Treatment of MBC is done to improve symptoms and quality of life, and to prolong survival.
- Treatment is rapidly evolving. Specific information regarding the most promising interventions can be found only in the primary literature.
- Treatment can cause substantial toxicity, which differs depending on the individual agent, administration method, and combination regimen. A comprehensive review of toxicities is beyond the scope of this chapter; consult appropriate references.

EARLY BREAST CANCER

Local-Regional Therapy

- Surgery alone can cure most patients with in situ cancers and approximately one half of those with stage II cancers.
- Breast-conserving therapy (BCT) is often primary therapy for stage I and II disease; it is preferable to modified radical mastectomy because it produces equivalent survival rates with cosmetically superior results. BCT includes removal of part of the breast, surgical evaluation of axillary lymph nodes, and radiation therapy (RT) to prevent local recurrence.
- RT is administered to the entire breast over 4 to 6 weeks to eradicate residual disease after BCT. Reddening and erythema of the breast tissue with subsequent shrinkage of total breast mass are minor complications associated with RT.
- Simple or total mastectomy involves removal of the entire breast without dissection of underlying muscle or axillary nodes. This procedure is used for carcinoma in situ where the incidence of axillary node involvement is only 1% or with local recurrence following BCT.

- Axillary lymph nodes should be sampled for staging and prognostic information. Lymphatic mapping with sentinel lymph node biopsy is a less invasive alternative to axillary dissection; however, the procedure is controversial in certain patient populations.

Systemic Adjuvant Therapy

- Systemic adjuvant therapy is the administration of systemic therapy following definitive local therapy (surgery, radiation, or both) when there is no evidence of metastatic disease but a high likelihood of disease recurrence. The goal of such therapy is cure.
- Administration of chemotherapy, endocrine therapy, or both results in improved disease-free survival (DFS) and/or overall survival (OS) for all treated patients.
- The National Comprehensive Cancer Network (NCCN) practice guidelines are updated at least annually and should be consulted for treatment recommendations.
- Genetic tests are being prospectively validated as decision-support tools for adjuvant chemotherapy in ER-positive, node-negative breast cancer to identify primary tumor characteristics that may predict for the likelihood of distant recurrence and/or death.

ADJUVANT CHEMOTHERAPY

- Early administration of effective combination chemotherapy at a time of low tumor burden should increase the likelihood of cure and minimize emergence of drug-resistant tumor cell clones. Combination regimens have historically been more effective than single-agent chemotherapy (**Table 60–1**).
- Anthracycline-containing regimens (eg, **doxorubicin** and **epirubicin**) reduce the rate of recurrence and death as compared with regimens that contain **cyclophosphamide**, **methotrexate**, and **fluorouracil**.
- The addition of taxanes, **docetaxel** and **paclitaxel**, to adjuvant regimens comprised of the drugs listed above resulted in reduced risk of distant recurrence, any recurrence, and overall mortality compared with a nontaxane regimen in node-positive breast cancer patients. The use of taxane-containing regimens in node-negative patients remains controversial.
- Initiate chemotherapy within 12 weeks of surgical removal of the primary tumor. Optimal duration of adjuvant treatment is unknown but appears to be 12 to 24 weeks, depending on the regimen used.
- *Dose intensity* refers to the amount of drug administered per unit of time, which can be achieved by increasing dose, decreasing time between doses, or both. *Dose density* is one way of achieving dose intensity by decreasing time between treatment cycles.
- Dose-dense adjuvant regimens for node-positive breast cancer resulted in prolonged DFS and OS. No benefit in DFS or OS was shown for sequential versus concurrent chemotherapy but sequential therapy appears to be less toxic.
- Concomitant or sequential administration of a taxane with an anthracycline-based regimen is standard of care in node-positive breast cancer.
- Dose increases in standard regimens appears to not be beneficial and may be harmful.
- Avoid dose reductions in standard regimens unless necessitated by severe toxicity.
- Short-term toxicities of adjuvant chemotherapy are generally well tolerated, especially with the availability of serotonin-antagonist and substance P/neurokinin 1–antagonist antiemetics and myeloid growth factors.
- Survival benefit for adjuvant chemotherapy in stage I and II breast cancer is modest. The absolute reduction in mortality at 10 years is 5% in node-negative and 10% in node-positive disease.

ADJUVANT BIOLOGIC THERAPY

- **Trastuzumab** in combination with adjuvant chemotherapy is indicated in patients with early stage, HER2-positive breast cancer. The risk of recurrence was reduced up to 50% in clinical trials.
- Unanswered questions with the use of adjuvant trastuzumab include optimal concurrent chemotherapy, optimal dose, schedule and duration of therapy, and use of other concurrent therapeutic modalities.

TABLE 60–1 Selected Adjuvant Chemotherapy Regimens for Breast Cancer

AC	**TC**
Doxorubicin 60 mg/m^2 IV, day 1	Docetaxel 75 mg/m^2 IV, day 1
Cyclophosphamide 600 mg/m^2 IV, day 1	Cyclophosphamide 600 mg/m^2 IV, day 1
Repeat cycles every 21 days for 4 cycles	Repeat cycles every 21 days for 4 cycles
FAC	**TAC**
Fluorouracil 500 mg/m^2 IV, days 1 and 4	Docetaxel 75 mg/m^2 IV, day 1
Doxorubicin 50 mg/m^2 IV continuous infusion over 72 hours	Doxorubicin 50 mg/m^2 IV bolus, day 1
Cyclophosphamide 500 mg/m^2 IV, day 1	Cyclophosphamide 500 mg/m^2 IV, day 1 (doxorubicin should be given first)
Repeat cycles every 21–28 days for 6 cycles	Repeat cycles every 21 days for 6 cycles (must be given with growth factor support)
AC → Paclitaxel	**Paclitaxel → FAC**
Doxorubicin 60 mg/m^2 IV, day 1	Paclitaxel 80 mg/m^2 per week IV over 1 hour every week for 12 weeks
Cyclophosphamide 600 mg/m^2 IV, day 1	Followed by:
Repeat cycles every 21 days for 4 cycles	Fluorouracil 500 mg/m^2 IV, days 1 and 4
Followed by:	Doxorubicin 50 mg/m^2 IV continuous infusion over 72 hours
Paclitaxel 80 mg/m^2 IV weekly	Cyclophosphamide 500 mg/m^2 IV, day 1
Repeat cycles every 7 days for 12 cycles	Repeat cycles every 21–28 days for 4 cycles[g]
FEC	**CEF**
Fluorouracil 500 mg/m^2 IV, day 1	Cyclophosphamide 75 mg/m^2 per day orally on days 1–14
Epirubicin 100 mg/m^2 IV bolus, day 1	Epirubicin 60 mg/m^2 IV, days 1 and 8
Cyclophosphamide 500 mg/m^2 IV, day 1	Fluorouracil 600 mg/m^2 IV, days 1 and 8
Repeat cycle every 21 days for 6 cycles	Repeat cycles every 21 days for 6 cycles (requires prophylactic antibiotics or growth factor support)
CMF	**Dose-Dense AC → Paclitaxel**
Cyclophosphamide 100 mg/m^2 per day orally, days 1–14	Doxorubicin 60 mg/m^2 IV bolus, day 1
Methotrexate 40 mg/m^2 IV, days 1 and 8	Cyclophosphamide 600 mg/m^2 IV, day 1

Fluorouracil 600 mg/m^2 IV, days 1 and 8 Repeat cycles every 28 days for 6 cycles *Or* Cyclophosphamide 600 mg/m^2 IV, day 1 Methotrexate 40 mg/m^2 IV, day 1 Fluorouracil 600 mg/m^2 IV, days 1 and 8 Repeat cycles every 21 days for 6 cycles	Repeat cycles every 14 days for 4 cycles (must be given with growth factor support) Followed by: Paclitaxel 175 mg/m^2 IV over 3 hours Repeat cycles every 14 days for 4 cycles (must be given with growth factor support)

AC, Adriamycin (doxorubicin), Cytoxan (cyclophosphamide); CAF, Cytoxan (cyclophosphamide), Adriamycin (doxorubicin), 5-fluorouracil; CEF, cyclophosphamide, epirubicin, 5-fluorouracil; CMF, cyclophosphamide, methotrexate, 5-flourouracil; FAC, 5-fluorouracil, Adriamycin (doxorubicin), cyclophosphamide; FEC, 5-fluorouracil, epirubicin, cyclophosphamide; TAC, Taxotere (docetaxel), Adriamycin (doxorubicin), cyclophosphamide; TC, Taxotere (docetaxel), cyclophosphamide.

ADJUVANT ENDOCRINE THERAPY

- **Tamoxifen**, **toremifene**, oophorectomy, ovarian irradiation, luteinizing hormone–releasing hormone (LHRH) agonists, and aromatase inhibitors (AI) are hormonal therapies used in the treatment of primary or early-stage breast cancer. Tamoxifen was the gold standard adjuvant hormonal therapy for three decades and is generally considered the adjuvant hormonal therapy of choice for premenopausal women. It has both estrogenic and antiestrogenic properties, depending on the tissue and gene in question.
- Tamoxifen 20 mg daily, beginning soon after completing chemotherapy and continuing for 5 years, reduces the risk of recurrence and mortality. It is usually well-tolerated however, symptoms of estrogen withdrawal (hot flashes and vaginal bleeding) may occur but decrease in frequency and intensity over time. Tamoxifen reduces the risk of hip radius and spine fractures. It increases the risks of stroke, pulmonary embolism, deep vein thrombosis, and endometrial cancer, particularly in women age 50 years or older.
- Premenopausal women benefit from ovarian ablation with LHRH agonists (eg, **goserelin**) in the adjuvant setting, either with or without concurrent tamoxifen. Trials are ongoing to further define the role of LHRH agonists.
- Guidelines recommend incorporation of AIs into adjuvant hormonal therapy for postmenopausal, hormone-sensitive breast cancer. Experts believe that **anastrozole**, **letrozole**, and **exemestane** have similar antitumor efficacy and toxicity profiles. Adverse effects with AIs include bone loss/osteoporosis, hot flashes, myalgia/arthralgia, vaginal dryness/atrophy, mild headaches, and diarrhea.
- The optimal drug, dose, sequence, and duration of administration of AIs in the adjuvant setting are not known.

LOCALLY ADVANCED BREAST CANCER (STAGE III)

- Neoadjuvant or primary chemotherapy is the initial treatment of choice. Benefits include rendering inoperable tumors resectable and increasing the rate of BCT.
- Primary chemotherapy with an anthracycline- and taxane-containing regimen is recommended. The use of trastuzumab with chemotherapy is appropriate for patients with HER2-positive tumors.
- Surgery followed by chemotherapy and adjuvant RT should be administered to minimize local recurrence.
- Cure is the primary goal of therapy for most patients with stage III disease.

METASTATIC BREAST CANCER (STAGE IV)

- The choice of therapy for MBC is based on the site of disease involvement and the presence or absence of certain characteristics, as described below.

Endocrine Therapy

- Endocrine therapy is the treatment of choice for patients who have hormone receptor–positive metastases in soft tissue, bone, pleura, or, if asymptomatic, viscera. Compared with chemotherapy, endocrine therapy has an equal probability of response and a better safety profile.
- Patients are sequentially treated with endocrine therapy until their tumors cease to respond, at which time chemotherapy can be given.
- No one endocrine therapy has clearly superior survival benefit. Choice of agent is based primarily on mechanism of action, toxicity and patient preference (**Table 60–2**).
- AIs are generally first line therapy in postmenopausal women. AIs reduce circulating and target organ estrogens by blocking peripheral conversion from an androgenic precursor, the primary source of estrogens in postmenopausal women. The third-generation aromatase inhibitors anastrozole, letrozole, and exemestane are more selective and potent than the prototype, **aminoglutethimide.** When compared with tamoxifen, patients receiving AIs had similar response rates as well as lower incidence of thromboembolic events and vaginal bleeding.

TABLE 60–2 Endocrine Therapies Used for Metastatic Breast Cancer

Drug	Brand Name	Initial Dose	Usual Range	Special Population Dose	Comments
Aromatase Inhibitors: Nonsteroidal					
Anastrozole	Arimidex, generic	1 mg orally daily			
Letrozole	Femara, generic	2.5 mg orally daily		Caution in severe liver impairment[a]	
Aromatase Inhibitor: Steroidal					
Exemestane	Aromasin	25 mg orally daily			Take after meals
Antiestrogens: SERMs					
Tamoxifen	Nolvadex, generic	20 mg orally daily		See text regarding CYP2D6	See text regarding CYP2D6
Toremifene	Fareston	60 mg orally daily			
Antiestrogen: SERD					
Fulvestrant	Faslodex	500 mg IM every 28 days (after loading days 1, 15, 29)	250–500 mg (see text for details)	Moderate liver impairment[a] administer 250 mg IM every 28 days (after loading days 1, 15, 29)	
LHRH Agonists					
Goserelin	Zoladex	3.6 mg SC every 28 days		Premenopausal women only	
Leuprolide	Lupron (IM), generic	3.75 mg IM (SC) every 28 days	Other formulations and doses are not used for breast cancer	Premenopausal women only	Not FDA approved for breast cancer; other formulations are administered differently
Triptorelin	Trelstar	3.75 mg IM every 28 days		Premenopausal women only	Not FDA-approved for breast cancer

(*continued*)

TABLE 60–2 Endocrine Therapies Used for Metastatic Breast Cancer (*Continued*)

Drug	Brand Name	Initial Dose	Usual Range	Special Population Dose	Comments
Progestins					
Megestrol acetate	Megace, generic	40 mg orally 4 times a day	80 mg twice daily also appropriate		Absorption may be increased when taken with food
Medroxyprogesterone	DepoProvera, generic	400 mg IM every week	400–1000 mg IM every week	May need to decrease dose in severe liver impairment[a]	
Androgens					
Fluoxymesterone	Androxy, generic	10 mg orally twice a day	10–20/day in divided doses	Avoid in severe renal or liver impairment[a]	
Estrogens					
Ethinyl estradiol	Multiple generics	1 mg orally 3 times a day	Lower doses not effective	Avoid in jaundice or "marked" liver disease	Take with food
Conjugated estrogens	Premarin	2.5 mg orally 3 times a day	Lower doses not effective	Avoid in jaundice or "marked" liver disease	Take with food

IM, intramuscular; LHRH, luteinizing hormone-releasing hormone; SC, subcutaneous; SERD, selective estrogen receptor downregulator SERM, selective estrogen receptor modulator.
[a]Severe liver impairment: Child-Pugh class C; moderate liver impairment: Child-Pugh class B.

- Tamoxifen, a selective estrogen receptor modulator (SERM) is the preferred initial agent when metastases are present in premenopausal women except when metastases occur within 1 year of adjuvant tamoxifen. In addition to the side effects described for adjuvant therapy, tumor flare or hypercalcemia occurs in approximately 5% of patients with MBC.
- **Toremifene**, also a SERM, has similar efficacy and tolerability as tamoxifen and is an alternative to tamoxifen in postmenopausal patients. **Fulvestrant** is a second-line intramuscular agent with similar efficacy and safety when compared with anastrozole or exemestane in patients who progressed on tamoxifen.
- Surgical or chemical ovarian ablation is considered by some to be the endocrine therapy of choice in premenopausal women and produces similar overall response rates as tamoxifen. Medical castration with an LHRH analogue (**goserelin**, **leuprolide**, or **triptorelin**) is a reversible alternative to surgery. If used as first-line therapy for MBC, combination therapy with tamoxifen is recommended.
- Progestins are generally reserved for third-line therapy. They cause weight gain, fluid retention, and thromboembolic events.

Chemotherapy

- Chemotherapy is used as initial therapy for women with hormone receptor–negative tumors; with rapidly progressive or symptomatic lung, liver, or bone marrow involvement; and after failure of endocrine therapy.
- The choice of treatment depends on patient characteristics, expected toxicities, and previous exposure to chemotherapy. Single agents are associated with lower response rates than combination therapy, but time to progression and OS are similar. Single agents are better tolerated, an important consideration in the palliative metastatic setting (**Table 60–3**).
- Treatment with sequential single agents is recommended over combination regimens unless the patient has rapidly progressive disease, life-threatening visceral disease, or the need for rapid symptom control.
- Combination regimens produce objective responses in approximately 60% of patients previously unexposed to chemotherapy, but complete responses occur in less than 10% of patients. The median duration of response is 5 to 12 months; the median survival is 14 to 33 months. A specific chemotherapy regimen is continued until there is unequivocal evidence of progressive disease or intolerable side effects.
- **Anthracyclines** and **taxanes** produce response rates of 50% to 60% when used as first-line therapy for MBC. Single-agents **capecitabine**, **vinorelbine**, and **gemcitabine** have response rates of 20% to 25% when used after an anthracycline and a taxane.
- **Ixabepilone**, a microtubule stabilizing agent, is indicated as monotherapy or in combination with capecitabine. **Eribulin** is a second antimicrotubule agent approved as monotherapy in patients who have received at least two prior chemotherapy regimens for MBC.

Biologic or Targeted Therapy

- Three anti-HER2 agents are available: trastuzumab, **lapatinib**, and **pertuzumab**. The majority of data supporting the role of these agents in MBC focuses on trastuzumab. Trastuzumab produces response rates of 15% to 20% when used as a single agent and increases response rates, time to progression, and OS when combined with chemotherapy. It has been studied in doublet (**taxane–trastuzumab** and **vinorelbine–trastuzumab**) and triplet (**trastuzumab–taxane–platinum**) combinations, but the optimum regimen is unknown.
- Trastuzumab is well tolerated, but the risk of cardiotoxicity is 5% with single-agent trastuzumab and unacceptably high in combination with an anthracycline.
- Lapatinib is an oral tyrosine kinase inhibitor that targets both HER2 and the epidermal growth factor receptor. It demonstrated improved response rates and time to progression in combination with capecitabine, as compared with capecitabine alone,

TABLE 60–3 Selected Chemotherapy Regimens for Metastatic Breast Cancer

Single-Agent Chemotherapy

Paclitaxel
Paclitaxel 175 mg/m^2 IV over 3 hours
Repeat cycles every 21 days
or
Paclitaxel 80 mg/m^2/week IV over 1 hour
Repeat dose every 7 days

Docetaxel
Docetaxel 60–100 mg/m^2 IV over 1 hour
Repeat cycles every 21 days
or
Docetaxel 30–35 mg/m^2/week IV over 30 minutes
Repeat dose every 7 days

Protein-Bound Paclitaxel
Protein-bound Paclitaxel 260 mg/m^2 IV over 30 minutes
Repeat cycles every 21 days
or
Protein-bound paclitaxel 100–150 mg/m^2 IV over 30 minutes on days 1, 8, and 15
Repeat cycle every 28 days

Capecitabine
Capecitabine 2,000–2,500 mg/m^2 per day orally, divided twice daily for 14 days
Repeat cycles every 21 days

Vinorelbine
Vinorelbine 30 mg/m^2 IV, days 1 and 8
Repeat cycles every 21 days
or
Vinorelbine 25–30 mg/m^2/week IV
Repeat cycles every 7 days (adjust dose based on absolute neutrophil count; see product information)

Gemcitabine
Gemcitabine 600–1,000 mg/m^2/week IV, days 1, 8, and 15
Repeat cycles every 28 days (may need to hold day 15 dose based on blood counts)[q]

Ixabepilone
Ixabepilone 40 mg/m^2 IV over 3 hours
Repeat cycles every 21 days

Eribulin
Eribulin 1.4 mg/m^2/dose IV over 2–5 minutes on days 1 and 8
Repeat dose every 21 days

Liposomal Doxorubicin
Liposomal doxorubicin 30–50 mg/m^2 IV over variable duration
Repeat cycles every 28 days

Combination Chemotherapy Regimens	
Docetaxel + Capecitabine Docetaxel 75 mg/m^2 IV over 1 hour, day 1 Capecitabine 2,000–2,500 mg/m^2 per day orally divided twice daily for 14 days Repeat cycles every 21 days	**Paclitaxel + Gemcitabine** Paclitaxel 175 mg/m^2 IV over 3 hours, day 1 Gemcitabine 1250 mg/m^2 IV days 1 and 8 Repeat cycles every 21 days
Ixabepilone + Capecitabine Ixabepilone 40 mg/m^2 IV over 3 hours, day 1 Capecitabine 1,750–2,000 mg/m^2/day orally divided twice daily for 14 days Repeat cycles every 21 days	**Paclitaxel + Bevacizumab** Paclitaxel 90 mg/m^2 IV over 1 hour, days 1, 8, and 15 Bevacizumab 10 mg/kg IV over 30–90 minutes, days 1 and 15 Repeat cycles every 28 days

in patients previously treated with an anthracycline, taxane, and trastuzumab. The most common adverse events were rash and diarrhea.
- Pertuzumab is a monoclonal antibody that binds to a different HER2 domain as compared with trastuzumab. The NCCN guidelines include pertuzumab in combination with trastuzumab plus a taxane.

Radiation Therapy

- Commonly used to treat painful bone metastases or other localized sites of disease, including brain and spinal cord lesions. Pain relief is seen in approximately 90% of patients who receive RT.

PREVENTION OF BREAST CANCER

- SERMs and AIs are being studied for pharmacologic risk reduction of breast cancer.
- The most clinical information is available for the SERMs, tamoxifen and **raloxifene**, which reduce the rates of invasive breast cancer in women at high risk for developing the disease. Rates of endometrial cancer and deep vein thromboses are higher in patients receiving tamoxifen, but the overall quality of life is similar between the two agents.
- Exemestane taken for 5-years significantly reduced the rates of invasive breast cancers with tolerable adverse events. Clinical trials with other AIs are underway.

EVALUATION OF THERAPEUTIC OUTCOMES

EARLY BREAST CANCER

- The goal of adjuvant therapy in early-stage disease is cure. Because there is no clinical evidence of disease when adjuvant therapy is administered, assessment of this goal cannot be fully evaluated for years after initial diagnosis and treatment.
- Adjuvant chemotherapy can cause significant toxicity. Optimize supportive care measures such as antiemetics and growth factors to maintain dose intensity.

LOCALLY ADVANCED BREAST CANCER

- The goal of neoadjuvant chemotherapy in locally advanced breast cancer is cure. Complete pathologic response, determined at the time of surgery, is the desired end point.

METASTATIC BREAST CANCER

- Optimizing quality of life is the therapeutic end point in the treatment of patients with MBC. Valid and reliable tools are available for objective assessment of quality of life in patients with breast cancer.
- The least toxic therapies are used initially, with increasingly aggressive therapies applied in a sequential manner that does not significantly compromise quality of life.
- Tumor response is measured by changes in laboratory tests, diagnostic imaging or physical examination.

See Chapter 105, Breast Cancer, authored by Chad M. Barnett, Laura Boehnke Michaud, and Francisco J. Esteva, for a more detailed discussion of this topic.

CHAPTER 61

Colorectal Cancer

- *Colorectal cancer* (CRC) is a malignant neoplasm involving the colon, rectum, and anal canal.

PATHOPHYSIOLOGY

- Development of a colorectal neoplasm is a multistep process of genetic and phenotypic alterations of normal bowel epithelium structure and function leading to dysregulated cell growth, proliferation, and tumor development.
- Features of colorectal tumorigenesis include genomic instability, activation of oncogene pathways, mutational inactivation or silencing of tumor-suppressor genes, and activation of growth factor pathways.
- Adenocarcinomas account for more than 90% of tumors of the large intestine.

PREVENTION AND SCREENING

- Primary prevention is aimed at preventing CRC in an at-risk population. Trials with celecoxib in people with familial adenomatous polyposis (FAP) showed reduction in size and number of polyps after 6 to 9 months of treatment, but there is a lack of long-term benefit.
- Secondary prevention is aimed at preventing malignancy in a population that has already manifested an initial disease process. Secondary prevention includes procedures ranging from colonoscopic removal of precancerous polyps detected during screening colonoscopy to total colectomy for high-risk individuals (eg, FAP)
- Current US guidelines for average-risk individuals include annual occult fecal blood testing starting at age 50 years and examination of the colon every 5 or 10 years, depending on the procedure.

CLINICAL MANIFESTATIONS

- Signs and symptoms of CRC can be extremely varied, subtle, and nonspecific. Early-stage CRC is often asymptomatic and detected by screening procedures.
- Blood in the stool is the most common sign; however, any change in bowel habits, vague abdominal discomfort, or abdominal distention may be a warning sign. Less common signs and symptoms include nausea, vomiting, and, if anemia is severe, fatigue.
- Twenty percent of patients present with metastatic disease most commonly in the liver, lung, and bones.

DIAGNOSIS

- Perform a physical examination and obtain a careful personal and family history. Evaluate entire large bowel by colonoscopy.
- Obtain baseline laboratory tests: complete blood cell count, international normalized ratio (INR), activated partial thromboplastin time, liver and renal function tests, and serum carcinoembryonic antigen (CEA). Serum CEA serves as a marker for monitoring CRC response to treatment, but it is too insensitive and nonspecific to be used as a screening test for early-stage CRC.
- Radiographic imaging studies may include chest radiographs, bone scan, chest and abdominal computed tomography scans, positron emission tomography, ultrasonography, and magnetic resonance imaging.

- Determine CRC stage at diagnosis to predict prognosis and develop treatment options. Stage is based on size of the primary tumor (T_{1-4}), presence and extent of lymph node involvement (N_{0-2}), and presence or absence of distant metastases (M).
  - ✓ Stage I disease involves tumor invasion of the submucosa (T_1) or muscularis propria (T_2) and negative lymph nodes.
  - ✓ Stage II disease involves tumor invasion through the muscularis propria into pericolorectal tissues (T_3), or penetration to the surface of the visceral peritoneum (T_{4a}), or directly invades or is adherent to other organs or structures (T_{4b}), and negative lymph nodes.
  - ✓ Stage III disease includes T_{1-4} and positive regional lymph nodes.
  - ✓ Stage IV disease includes any T, any N, and distant metastasis.

PROGNOSIS

- Stage at diagnosis is the most important independent prognostic factor for survival and disease recurrence. Five-year relative survival is approximately 91% for those with localized tumor as compared with 12% for those with metastatic disease.
- Poor prognostic clinical factors at diagnosis include bowel obstruction or perforation, high preoperative CEA level, distant metastases, and location of the primary tumor in the rectum or rectosigmoid area.
- Molecular markers, particularly MSI, 18q/*DCC* mutation or LOH, *BRAF* V600E mutation, and *KRAS* mutations are also associated with CRC prognosis.

TREATMENT

- Goals of Treatment: The goals include cure for stages I, II, and III; the intent is to eradicate micrometastatic disease. Most stage IV disease is incurable; palliative treatment is given to control cancer growth, reduce symptoms, improve quality of life, and extend survival. Twenty to thirty percent of patients with metastatic disease may be cured if their metastases are resectable.
- Treatment modalities are surgery, radiation therapy (RT), chemotherapy, and biomodulators.

OPERABLE DISEASE

Surgery

- Complete surgical resection of the primary tumor with regional lymphadenectomy is a curative approach for patients with operable CRC.
- The preferred surgical procedure for rectal cancer is a total excision of the mesorectum that includes tissue containing perirectal fat and draining lymph nodes.
- Common complications of colorectal surgery include infection, anastomotic leakage, obstruction, adhesions, sexual dysfunction, and malabsorption syndromes.

Adjuvant Therapy for Colon Cancer

- Adjuvant therapy is administered after complete tumor resection to eliminate residual micrometastatic disease. Adjuvant therapy is not indicated for stage I CRC because more than 90% of patients are cured by surgical resection alone.
- Results of adjuvant chemotherapy studies in patients with stage II disease are conflicting. Despite a lack of consensus among practitioners, the approach to treatment of high-risk stages II and III disease is similar.
- Adjuvant chemotherapy is the standard of care for stage III colon cancer.

Adjuvant Radiation Therapy

- Adjuvant radiation therapy (RT) has a limited role in colon cancer because most recurrences are extrapelvic and occur in the abdomen.

Adjuvant Chemotherapy

- Standard adjuvant regimens include a fluoropyrimidine (**fluorouracil** [with **leucovorin**] or **capecitabine**) as a single agent or in combination with **oxaliplatin**. Leucovorin enhances cytotoxic activity of fluorouracil.
- Administration method affects clinical activity and toxicity. In most common combination regimens, fluorouracil is administered by both IV bolus injection and by continuous IV infusion. No one treatment schedule is superior for overall patient survival.
- Continuous IV infusion of fluorouracil is generally well tolerated but is associated with palmar-plantar erythrodysesthesia (hand–foot syndrome) and stomatitis. IV bolus administration is associated with leukopenia, which is dose limiting and can be life threatening. Both administration methods are associated with a similar incidence of mucositis, diarrhea, nausea and vomiting, and alopecia.
- In rare cases, patients deficient in dihydropyrimidine dehydrogenase, responsible for the catabolism of fluorouracil, develop severe toxicity, including death, after fluorouracil administration.
- National guidelines recommend oxaliplatin-based regimens as the first-line option for patients with stage III colon cancer who can tolerate combination therapy. It is commonly administered with fluorouracil/leucovorin. Oxaliplatin is associated with both acute and persistent neuropathies, including rare, acute pharyngolaryngeal dysesthesia, neutropenia, and gastrointestinal (GI) toxicity.
- Selection of an adjuvant regimen (**Table 61–1**) is based on patient-specific factors, including performance status, comorbid conditions, and patient preference based on lifestyle factors. Age should also be considered as subset analysis of large clinical trials has shown that patients older than 70 years may not benefit from adjuvant oxaliplatin.
- Fluorouracil/leucovorin regimens currently have limited use but are acceptable options in patients who cannot receive oxaliplatin and are unable to tolerate oral capecitabine.

Adjuvant Therapy for Rectal Cancer

- Rectal cancer is more difficult to resect with wide margins, so local recurrences are more frequent than with colon cancer. Adjuvant RT plus chemotherapy is considered the standard of care for stages II and III rectal cancer.
- RT reduces the risk of local tumor recurrence in patients undergoing surgery for rectal cancer. RT is given prior to surgery to decrease tumor size, making it more resectable.
- Preoperative (neoadjuvant) chemoradiation shrinks rectal tumors prior to surgical resection, improving sphincter preservation. Preoperative infusional fluorouracil-based regimens or oral capecitabine plus RT are recommended. Patients should receive adjuvant chemotherapy following surgery to total 6 months of chemotherapy.

METASTATIC DISEASE

Initial Therapy

- Patients with metastatic colorectal cancer (MCRC) are considered to have resectable, potentially resectable, or unresectable metastatic disease. Multimodality therapy is indicated for resectable or potentially resectable metastases. Chemotherapy is for disseminated disease and the primary treatment modality for unresectable MCRC.
- Determine mutation status with tumor *KRAS* genotyping at diagnosis. Epidermal growth factor receptor (EGFR) inhibitors should be considered only in patients with tumors with wild-type *KRAS*.

RESECTABLE OR POTENTIALLY RESECTABLE MCRC

- Surgical resection of metastases with curative intent is the primary goal. Five-year overall survival (OS) rates are improved to 20% to 50% with resection. Best candidates are patients with no significant medical risk factors, fewer than four hepatic

TABLE 61–1 Chemotherapy Regimens for the Adjuvant Treatment of Colorectal Cancer

Regimen	Agents	Comments
FOLFOX4	Oxaliplatin 85 mg/m^2 IV day 1 Leucovorin 200 mg/m^2 per day IV over 2 hours days 1 and 2 Fluorouracil 400 mg/m^2 IV bolus, after leucovorin, then 600 mg/m^2 CIV over 22 hours days 1 and 2 Repeat every 14 days	Improved OS and DFS as compared with infusional fluorouracil-leucovorin–based regimens.
mFOLFOX6	Oxaliplatin 85 mg/m^2 IV on day 1 Leucovorin 400 mg/m^2 IV on day 1 Fluorouracil 400 mg/m^2 IV bolus, after leucovorin on day 1, then 1200 mg/m^2/day × 2 days CIV (total 2,400 mg/m^2 over 46–48 hours) Repeat every 14 days	Sensory neuropathy, neutropenia; easier administration as compared to FOLFOX4.
FLOX	Oxaliplatin 85 mg/m^2 IV administered on weeks 1, 3, and 5 Fluorouracil 500 mg/m^2 IV bolus weekly × 6 Folinic acid 500 mg/m^2 IV weekly × 6 Each cycle lasts 8 weeks and is repeated for 3 cycles	Improved DFS as compared with bolus fluorouracil-leucovorin–based regimens. Increased toxicity compared to FOLFOX4.
Capecitabine	Capecitabine 1250 mg/m^2 PO twice daily on days 1 through 14 Each cycle lasts 14 days and is repeated every 21 days	Equivalent DFS as compared with the Mayo Clinic regimen with improved tolerability.
CapOx	Oxaliplatin 130 mg/m^2 IV day 1 Capecitabine 850–1000 mg/m^2 twice daily orally for 14 days Each cycle lasts 14 days and is repeated every 21 days	Improved DFS in patients with stage III colon cancer compared to capecitabine alone.
Fluorouracil-Based Regimens		
Roswell Park regimen	Fluorouracil 600 mg/m^2 IV day 1 Leucovorin 500 mg/m^2 IV day 1 over 2 hours Repeat weekly for 6 of 8 weeks	
Mayo Clinic regimen	Fluorouracil 425 mg/m^2 per day IV, days 1–5 Leucovorin 20 mg/m^2 per day IV, days 1–5 Repeat every 4 to 5 weeks	
de Gramont regimen	Fluorouracil 400 mg/m^2 per day IV bolus, followed by 600 mg/m^2 CIV over 22 hours, days 1 and 2 for 2 consecutive days Leucovorin 200 mg/m^2 per day IV over 2 hours, days 1 and 2 Repeat every 2 weeks	Improved safety as compared with the Mayo Clinic regimen.

CIV, continuous intravenous infusion; DFS, disease-free survival; OS, overall survival; PO, by mouth.

lesions, CEA less than 200 ng/mL, small tumor size, lack of extrahepatic tumor, and adequate surgical margins. Adjuvant systemic chemotherapy is recommended.

- Neoadjuvant or conversional chemotherapy is administered to increase complete resection rates with resectable and potentially resectable liver or lung lesions (Table 61–2). Chemotherapy with or without biologic agents is given over 2 to 3 months pre-op. Adjuvant chemotherapy is always administered.
- Consider hepatic-directed therapy in addition to or as an alternative to surgical resection in patients with liver-only or liver-predominant MCRC. Hepatic artery infusion (HAI) delivers chemotherapy (eg, **floxuridine** and **fluorouracil**) through the hepatic artery directly into the liver. Tumor ablation uses radiofrequency ablation or microwave energy to generate heat to destroy tumor cells. Cryoablation is also used. These strategies are less successful than surgical interventions.

UNRESECTABLE MCRC

- Systemic chemotherapy palliates symptoms and improves survival in patients with unresectable disease. RT may control localized symptoms. Most MCRCs are incurable; however, randomized trials confirm that chemotherapy prolongs life and improves quality of life.
- Consider goals of therapy, history of prior chemotherapy, tumor *KRAS* mutation status, and risk of drug-related toxicities to determine a management strategy. Regimens are the same for metastatic cancer of the colon and rectum.
- Accepted initial chemotherapy regimens consist of oxaliplatin-containing regimens (FOLFOX, CapOx), **irinotecan**-containing regimens (FOLFIRI), oxaliplatin plus irinotecan plus fluorouracil plus leucovorin (FOLFOXIRI), infusional fluorouracil plus leucovorin alone, and capecitabine alone (**Table 61–2**).
- Irinotecan is a topoisomerase I inhibitor. Tumor response rates, time to progression, and OS are improved when irinotecan is administered with fluorouracil plus leucovorin as initial therapy. Early- and late-onset diarrhea and neutropenia are dose-limiting toxicities of irinotecan.
- Oxaliplatin in combination with infusional fluorouracil plus leucovorin results in higher response rates and improved progression-free survival (PFS), with variable effects on OS. It is approved for first-line and salvage therapy.
- **Capecitabine** monotherapy is suitable for first-line therapy in patients not likely to tolerate IV chemotherapy. Available for oral administration, it is converted to fluorouracil and is a suitable replacement for infusional fluorouracil in combination with oxaliplatin (CapOx).
- Guidelines recommend addition of **bevacizumab** to FOLFOX or FOLFIRI, as appropriate. Bevacizumab is a humanized monoclonal antibody directed against vascular endothelial growth factor (VEGF). Addition of bevacizumab to fluorouracil-based regimens increases PFS and OS as compared to chemotherapy alone.
- Bevacizumab is associated with hypertension, which is easily managed with oral antihypertensive agents. Other safety concerns include bleeding, thrombocytopenia, and proteinuria. GI perforation is a rare but potentially fatal complication necessitating prompt evaluation of abdominal pain associated with vomiting or constipation.
- **Cetuximab** is an EGFR inhibitor indicated for use in patients with wild-type *KRAS* tumors in combination with FOLFIRI. A large phase III trial failed to confirm the benefit of adding cetuximab to FOLFOX and is not included in practice guidelines. Common adverse events include acne-like skin rash, asthenia, lethargy, malaise, and fatigue.
- **Panitumumab**, an EGFR inhibitor, can be combined with either FOLFOX or FOLFIRI in patients with wild-type *KRAS* tumors.
- Patients may receive consecutive regimens; the sequence of drugs appears less important than exposure to all active agents in the course of chemotherapy treatments.

Second-Line Therapy

- The selection of second-line chemotherapy is primarily based on the type of prior therapy received, as well as the response to prior treatments, site and extent of disease,

TABLE 61–2 Chemotherapeutic Regimens for Metastatic Colorectal Cancer

Regimen	Agents	Major Dose-Limiting Toxicities	Comments
Oxaliplatin-Containing Regimens			
Oxaliplatin plus bimonthly infusional fluorouracil/leucovorin; FOLFOX4	See Table 61–1	Sensory neuropathy, neutropenia	
Modified oxaliplatin plus bimonthly infusional fluorouracil/leucovorin; mFOLFOX6	See Table 61–1	Sensory neuropathy, neutropenia; easier administration as compared to FOLFOX4	
FOLFOX plus bevacizumab	Bevacizumab 5 mg/kg IV day 1 before mFOLFOX6 Repeat cycle every 2 weeks	Hypertension, thrombosis, proteinuria from bevacizumab added to toxicities of FOLFOX	
FOLFOX plus panitumumab	Panitumumab 6 mg/kg IV day 1 before mFOLFOX6 Repeat cycle every 2 weeks	Rash, diarrhea, hypomagnesemia added to toxicities of FOLFOX	Only *KRAS* wild-type tumor.
Oxaliplatin plus capecitabine; CapOx	Oxaliplatin 130 mg/m^2 IV day 1 Capecitabine 850 mg/m^2 orally twice a day, days 1–14 Repeat cycle every 3 weeks	Diarrhea, hand–foot syndrome, neuropathies	
CapOx plus bevacizumab	Bevacizumab 7.5 mg/kg IV day 1 Capecitabine 850 mg/m^2 orally twice a day, days 1–14 Repeat cycle every 3 weeks	Hypertension, thrombosis, proteinuria from bevacizumab added to toxicities of CapOx	Reduced capecitabine dose better tolerated.

Irinotecan-Containing Regimens			
Irinotecan plus infusional fluorouracil/ leucovorin; FOLFIRI	Irinotecan 180 mg/m^2 IV day 1 Leucovorin 400 mg/m^2 IV day 1 Fluorouracil 400 mg/m^2 IV bolus, after leucovorin on day 1, then 1200 mg/m^2/day × 2 days CIV (total 2,400 mg/m^2 over 46–48 hours) Repeat cycle every 14 days	Diarrhea, mucositis, neutropenia	
FOLFIRI plus bevacizumab	Bevacizumab 5 mg/kg IV day prior to FOLFIRI Repeat cycle every 2 weeks	Hypertension, thrombosis, proteinuria from bevacizumab added to toxicities of FOLFIRI	
FOLFIRI plus ziv-aflibercept	Ziv-aflibercept 4 mg/kg IV prior to FOLFIRI Repeat cycle every 2 weeks	Hypertension, hemorrhage, thrombosis, proteinuria from ziv-aflibercept added to toxicities of FOLFIRI, with increased incidence of diarrhea, asthenia, and neutropenia	
FOLFIRI plus cetuximab	Cetuximab (weekly or biweekly) IV before FOLFIRI Repeat cycle every 2 weeks	Toxicities from cetuximab added to toxicities of FOLFIRI	Only *KRAS* wild-type tumor.
FOLFIRI plus panitumumab	Panitumumab 6 mg/kg IV day 1 before FOLFIRI Repeat cycle every 2 weeks	Toxicities from panitumumab added to toxicities of FOLFIRI	Only *KRAS* wild-type tumor.
FOLFOXIRI	Irinotecan 165 mg/m^2 IV day 1 prior to oxaliplatin Oxaliplatin 85 mg/m^2 IV prior to leucovorin day 1 Leucovorin 400 mg/m^2 IV day 1 prior to fluorouracil Fluorouracil 1600 mg/m^2/day × 2 days CIV (total 3,200 mg/m^2 over 48 hours) Repeat cycle every 2 weeks	Neutropenia, diarrhea, stomatitis, peripheral neurotoxicity, thrombocytopenia	More neutropenia and peripheral neurotoxicity compared to FOLFIRI.

(*continued*)

TABLE 61–2 Chemotherapeutic Regimens for Metastatic Colorectal Cancer (*Continued*)

Regimen	Agents	Major Dose-Limiting Toxicities	Comments
IROX	Oxaliplatin 85 mg/m^2 IV day 1 prior to irinotecan Irinotecan 200 mg/m^2 IV day 1 Repeat cycle every 3 weeks	Neutropenia, diarrhea, sensory disturbances	
Irinotecan Regimens			
Weekly irinotecan	Irinotecan 125 mg/m^2 IV every week for 4 of 6 weeks	Neutropenia, diarrhea	
Biweekly irinotecan	Irinotecan 180 mg/m^2 IV every 2 weeks	Neutropenia, diarrhea	
Every 3-week irinotecan	Irinotecan 350 mg/m^2 IV every 3 weeks	Neutropenia, diarrhea (less-than-weekly irinotecan)	
Cetuximab plus irinotecan	Cetuximab (weekly or biweekly) prior to irinotecan continued as previously dosed or as above	Asthenia, diarrhea, nausea, papulopustular and follicular rash	Only *KRAS* wild-type tumor. Cetuximab added to irinotecan following disease progression with irinotecan regimen.
Panitumumab plus irinotecan	Panitumumab 6 mg/kg IV day 1 prior to irinotecan Irinotecan 180 mg/m^2 IV day 1 Repeat cycle every 2 weeks	Asthenia, diarrhea, nausea, papulopustular and follicular rash	Only *KRAS* wild-type tumor. Panitumumab added to irinotecan following disease progression with irinotecan regimen.
Fluoropyrimidine Regimens			
Simplified bolus plus infusional fluorouracil/leucovorin; (sLV5FU2)	Fluorouracil 400 mg/m^2 IV bolus, after leucovorin on day 1, then 1200 mg/m^2/day × 2 days CIV (total 2,400 mg/m^2 over 46–48 hours)	Neutropenia, mucositis	Easier to administer compared to de Gramont regimen.

	Repeat cycle every 14 days		
Bolus fluorouracil plus leucovorin; Roswell Park regimen	See Table 61–1	Neutropenia, diarrhea	
Bevacizumab plus fluorouracil/ leucovorin	Bevacizumab 5 mg/kg IV day 1 prior to fluorouracil and leucovorin, repeat every 2 weeks	Hypertension, bleeding, proteinuria, diarrhea, neutropenia	Infusional fluorouracil/ leucovorin regimen preferred to bolus fluorouracil regimen.
Capecitabine	Capecitabine 850–1250 mg/m^2 orally twice a day, days 1–14, repeated every 3 weeks	Hand-foot syndrome, diarrhea, hyperbilirubinemia	
Capecitabine plus bevacizumab	Bevacizumab 7.5 mg/kg IV day 1 Capecitabine 850–1250 mg/m^2 orally twice a day, days 1–14 Repeat cycle every 3 weeks	Hypertension, thrombosis, proteinuria, hand–foot syndrome, diarrhea, asthenia	
EGFR-Inhibitors			
Cetuximab Biweekly cetuximab	Cetuximab 400 mg/m^2 IV loading dose, then cetuximab 250 mg/m^2 IV weekly thereafter Cetuximab 500 mg/m^2 IV every 2 weeks	Papulopustular and follicular rash, asthenia, constipation, diarrhea, allergic reactions, hypomagnesemia	Only *KRAS* wild-type tumor.
Panitumumab	6 mg/kg IV over 60 minutes every 2 weeks	Rash, hypomagnesemia, rare allergic reactions	Only *KRAS* wild-type tumor.
Regorafenib	Regorafenib 160 mg orally once daily, days 1–21 Repeat cycle every 4 weeks	Hand-foot syndrome, fatigue, diarrhea, hypertension, rash	Can be given without regard to tumor *KRAS* genotype.

CIV, continuous intravenous; EGFR, epidermal growth factor receptor.

and patient factors and treatment preferences. The optimal sequence of regimens has not been established (**Table 61–3**).

- Administer EGFR inhibitors in combination with irinotecan or as single agents *except* bevacizumab and **ziv-aflibercept** that are only used in combination.
- Cetuximab, either alone or in combination with irinotecan, can be used in patients with disease progression on irinotecan. Response rates are greater with combination therapy.
- Panitumumab monotherapy or in combination with chemotherapy regimens is recommended in current guideline. Use of panitumumab should be limited to patients with wild-type *KRAS* tumors only.
- Neither panitumumab nor cetuximab should be used in the second-line setting if used in the initial regimen.
- Bevacizumab is used in the second-line setting if not used in initial treatment and is approved after progression on first-line treatment.
- Ziv-aflibercept is a soluble recombinant fusion protein designed to block the angiogenic process used in second-line setting with FOLFIRI. **Regorafenib** is an oral angiogenesis inhibitor approved for third- or fourth-line treatment of MCRC.
- No conclusive survival advantage has been demonstrated for palliative HAI.

Personalized Pharmacotherapy

- Tumor and patient pharmacogenetic factors and molecular markers assist with drug therapy individualization, and may predict prognosis and/or response to therapies.

TABLE 61–3 Second-Line and Salvage Chemotherapy Regimens for MCRC[a]

Disease Progression with Prior Regimen	Comments
Oxaliplatin-Based Regimen	
Options	
1. Single agent cetuximab or panitumumab	Only if *KRAS* wild-type; cetuximab improved OS compared to best supportive care
2. Panitumumab + FOLFIRI	Only if *KRAS* wild-type; increased PFS compared to FOLFIRI alone
3. Ziv-aflibercept + irinotecan	
Irinotecan-Based Regimen	
Options	
1. FOLFOX or CapOx ± bevacizumab	Bevacizumab FDA-approved to continue with second-line options
2. FOLFOX or CapOx ± cetuximab or panitumumab	Only if *KRAS* wild-type
3. Cetuximab ± irinotecan	Only if *KRAS* wild-type; response rates with combination greater than cetuximab monotherapy
4. Single-agent panitumumab	Only if *KRAS* wild-type
Therapy after second progression or third progression	
1. Regorafenib	

CapOx, capecitabine plus oxaliplatin; FOLFIRI, fluorouracil plus leucovorin plus irinotecan; FOLFOX, fluorouracil plus leucovorin plus oxaliplatin.

[a]Single-agent fluoropyrimidine-based therapy or clinical trials are also acceptable options depending on patient-specific factors.

- Test tumors for *KRAS* mutations at diagnosis of stage IV disease; patients with mutations on codons 12 and 13 on chromosome 12 are not candidates for EGFR inhibitors.
- High-frequency microsatellite instability (MSI-H) confers a good prognosis for stage II CRC and these patients do not benefit from adjuvant fluorouracil.

Evaluation of Therapeutic Outcomes

- Goals of monitoring are to evaluate benefit of treatment and detect recurrence.
- Patients who undergo curative surgical resection, with or without adjuvant therapy, require routine follow-up. Consult practice guidelines for specifics.
- Evaluate patients for anticipated side effects such as loose stools or diarrhea, nausea or vomiting, mouth sores, fatigue, and fever.
- Patients should be closely monitored for side effects that require prompt intervention, such as irinotecan-induced diarrhea, bevacizumab-induced GI perforation, hypertension and proteinuria, oxaliplatin-induced neuropathy, and cetuximab and panitumumab-induced skin rash.
- Fewer than one half of patients develop symptoms of recurrence, such as pain syndromes, changes in bowel habits, rectal or vaginal bleeding, pelvic masses, anorexia, and weight loss. Recurrences in asymptomatic patients may be detected because of increased serum CEA levels.
- Monitor quality-of-life indices, especially in patients with metastatic disease.

See Chapter 107, Colorectal Cancer, authored by Lisa E. Davis, Weijing Sun, and Patrick J. Medina, for a more detailed discussion of this topic.

Lung Cancer

CHAPTER 62

- *Lung cancer* is a solid tumor originating from the bronchial epithelial cells. This chapter distinguishes between non–small cell lung cancer (NSCLC) and small cell lung cancer (SCLC) because they have different natural histories and responses to therapy.

PATHOPHYSIOLOGY

- Lung carcinomas arise from normal bronchial epithelial cells that have acquired multiple genetic lesions and are capable of expressing a variety of phenotypes.
- Activation of protooncogenes, inhibition or mutation of tumor suppressor genes, and production of autocrine growth factors contribute to cellular proliferation and malignant transformation. Molecular changes, such as overexpression of c-KIT in SCLC and epidermal growth factor receptor (EGFR) in NSCLC, also affect disease prognosis and response to therapy.
- Cigarette smoking is responsible for approximately 80% of lung cancer cases. Other risk factors are exposure to environmental respiratory carcinogens (eg, asbestos, benzene, and arsenic), genetic risk factors, and history of other lung diseases (eg, chronic obstructive pulmonary disease [COPD] and asthma).
- The major cell types are SCLC (~15% of all lung cancers), adenocarcinoma (~50%), squamous cell carcinoma (<30%), and large cell carcinoma. The last three types are grouped together and referred to as NSCLC.

CLINICAL PRESENTATION

- The most common initial signs and symptoms are cough, dyspnea, chest pain, or discomfort, with or without hemoptysis. Many patients also exhibit systemic symptoms such as anorexia, weight loss, and fatigue.
- Disseminated disease can cause neurologic deficits from CNS metastases, bone pain or pathologic fractures secondary to bone metastases, or liver dysfunction from hepatic involvement.
- Paraneoplastic syndromes may be the first sign of an underlying malignancy; examples include cachexia, hypercalcemia, syndrome of inappropriate antidiuretic hormone secretion, and Cushing syndrome.

DIAGNOSIS

- Chest radiographs, endobronchial ultrasound, computed tomography (CT) scan, and positron emission tomography (PET) scan are the most valuable diagnostic tests. Integrated CT–PET technology appears to improve diagnostic accuracy in staging NSCLC over CT or PET alone.
- Pathologic confirmation is established by examination of sputum cytology and/or tumor biopsy by bronchoscopy, mediastinoscopy, percutaneous needle biopsy, or open-lung biopsy.
- All patients must have a thorough history and physical examination to detect signs and symptoms of the primary tumor, regional spread of the tumor, distant metastases, paraneoplastic syndromes, and ability to withstand aggressive surgery or chemotherapy.

STAGING

- The World Health Organization has established a TNM staging classification for lung cancer based on primary tumor size and extent (T), regional lymph node involvement (N), and presence or absence of distant metastases (M).

- A simpler system is commonly used to compare treatments. Stage I includes tumors confined to the lung without lymphatic spread, stage II includes large tumors with ipsilateral peribronchial or hilar lymph node involvement, stage III includes other lymph node and regional involvement, and stage IV includes any tumor with distant metastases.
- A two-stage classification is widely used for SCLC. Limited disease is confined to one hemithorax and can be encompassed by a single radiation port. All other disease is classified as extensive.

TREATMENT

NON–SMALL CELL LUNG CANCER

- Goals of Treatment: Definitive cure is the desired outcome with early stage disease. Prolongation of survival is desired in patients with advanced stage disease.
- The stage of NSCLC and the patient's comorbidities and performance status (ie, the ability to perform activities of daily living) determine which treatment modalities will be used. The intent of treatment—curative or palliative—influences the aggressiveness of therapy.

Recommendations for Chemotherapy, Radiation Therapy, and Surgery

- Local disease (stages IA and IB) is associated with a favorable prognosis. Surgery is the mainstay of treatment and may be used alone or with radiation therapy (RT) and/or chemotherapy. The adjuvant treatment regimen of choice is not clear.
- Stages IIA and IIB disease is primarily treated with surgery followed by adjuvant chemotherapy (**Table 62–1**). Chemoradiotherapy is recommended for stage II medically inoperable patients. Combination of **cisplatin** and **etoposide** is preferred and should be given concurrently rather than sequentially with RT.
- Optimal outcomes with resectable stage IIIA disease are achieved with chemotherapy plus either radiation or surgery, depending on patient and tumor features.
- A majority of patients present with unresectable stage IIIB or IV NSCLC. Chemotherapy is administered to select patients with intent to palliate symptoms, improve quality of life, and increase duration of survival.
- Four to six cycles of doublet chemotherapy with **cisplatin** or **carboplatin** plus **docetaxel, gemcitabine, paclitaxel, pemetrexed,** or **vinorelbine** (**Table 62–1**) are recommended as first-line palliative chemotherapy for patients with unresectable stage III or IV disease. Cisplatin-based doublets improve survival and quality of life in this patient population as compared with best supportive care or single-agent chemotherapy. No combination was found to be superior; tolerance of expected toxicities may contribute to the decision.
- Non–platinum-based combination regimens (eg, **gemcitabine–paclitaxel** and **gemcitabine–docetaxel**) are recommended as first-line therapy of advanced NSCLC in patients with a contraindication to a platinum (cisplatin or carboplatin) agent.
- **Docetaxel, pemetrexed,** and an oral EGFR inhibitor, **erlotinib,** are options for second-line therapy in patients with good performance status who progress during or after first-line therapy. Patients with squamous histology should not receive pemetrexed or erlotinib.
- Pemetrexed maintenance therapy prolongs overall survival in patient with nonsquamous histology. Best results were seen in patients with adenocarcinoma.
- Standard of care for advanced-stage squamous cell lung cancer is a platinum doublet described previously. Addition of **cetuximab,** a monoclonal antibody that binds to the extracellular portion of the EGFR receptor, to cisplatin and vinorelbine prolonged median overall survival.
- Genetic testing is recommended for patients with advanced nonsquamous disease to determine the treatment plan. Patients with a mutation in the EGFR receptor should receive first-line erlotinib and those with an ALK rearrangement should be treated with **crizotinib,** an ALK tyrosine kinase inhibitor.

TABLE 62–1 Common Chemotherapy Regimens Used to Treat Lung Cancer

Non–small cell lung carcinoma[a]	
Carboplatin/paclitaxel/bevacizumab	Carboplatin AUC 6 mg/mL/min IV on day 1 Paclitaxel 200 mg/m^2 IV on day 1 Bevacizumab 15 mg/kg IV on day 1 Repeat cycle every 3 weeks. Continue bevacizumab until progression
Carboplatin/pemetrexed	Carboplatin AUC 5 mg/mL/min IV on day 1 Pemetrexed 500 mg/m^2 IV on day 1 Repeat cycle every 3 weeks
Cetuximab/cisplatin/vinorelbine	Cetuximab 400 mg/m^2 IV first dose on day 1, then 250 mg/m^2 IV weekly Cisplatin 80 mg/m^2 IV on day 1 Vinorelbine 25 mg/m^2 IV on days 1 and 8 Repeat cycle every 3 weeks
Cisplatin/paclitaxel (CP)	Cisplatin 75 mg/m^2 IV on day 1 Paclitaxel 175 mg/m^2 over 24 h IV on day 1 Repeat cycle every 21 days *or* Cisplatin 80 mg/m^2 IV on day 1 Paclitaxel 175 mg/m^2 IV over 3 h on day 1 Repeat cycle every 21 days
Gemcitabine/cisplatin (GC)	Gemcitabine 1000 mg/m^2 IV on days 1, 8, and 15 Cisplatin 100 mg/m^2 IV on day 1 Repeat cycle every 28 days
Gemcitabine/cisplatin (GCq21)	Gemcitabine 1200 mg/m^2 on days 1 and 8 Cisplatin 80 mg/m^2 IV on day 1 Repeat cycle every 21 days *or* Gemcitabine 1250 mg/m^2 on days 1 and 8 Cisplatin 80 mg/m^2 IV on day 1 Repeat cycle every 21 days
Docetaxel/cisplatin (DC)	Docetaxel 75 mg/m^2 IV on day 1 Cisplatin 75 mg/m^2 IV on day 1 Repeat cycle every 21 days
Paclitaxel/carboplatin (PCb)	Paclitaxel 225 mg/m^2 over 3 hours IV on day 1 Carboplatin AUC 6 mg/mL/min IV on day 1 Repeat cycle every 21 days *or* Paclitaxel 175 mg/m^2 IV over 3 h on day 1 Carboplatin AUC 6 mg/mL/min IV on day 1 Repeat cycle every 21 days for 6 cycles
Vinorelbine/cisplatin (VC)	Vinorelbine 25 mg/m^2 IV weekly Cisplatin 100 mg/m^2 IV on day 1 Repeat cycle every 28 days *or* Vinorelbine 30 mg/m^2 IV on days 1 and 8 Cisplatin 80 mg/m^2 IV on day 1 Repeat cycle every 21 days
Etoposide/cisplatin (EP)	Etoposide 100 mg/m^2 IV on days 1–3 Cisplatin 100 mg/m^2 IV on day 1 Repeat cycle every 28 days

TABLE 62–1 Common Chemotherapy Regimens Used to Treat Lung Cancer (*Continued*)	
Vinorelbine/gemcitabine (VG)	Vinorelbine 25 mg/m^2 IV on days 1 and 8 Gemcitabine 1000 mg/m^2 on days 1 and 8 Repeat cycle every 21 days
Paclitaxel/gemcitabine (PG)	Paclitaxel 175 mg/m^2 IV over 3 h on day 1 Gemcitabine 1250 mg/m^2 on days 1 and 8 Repeat cycle every 21 days
Gemcitabine/docetaxel (GD)	Gemcitabine 1000 mg/m^2 IV on days 1 and 8 Docetaxel 100 mg/m^2 IV on day 8 Repeat cycle every 21 days
Paclitaxel/vinorelbine (PV)	Paclitaxel 135 mg/m^2 IV on day 1 Vinorelbine 25 mg/m^2 IV on day 1 Repeat cycle every 14 days for 9 cycles
Small cell lung carcinoma[b]	
Etoposide/cisplatin (EP)	Cisplatin 80 mg/m^2 IV on day 1 Etoposide 100 mg/m^2 IV on days 1–3 Repeat cycle every 3 weeks *or* Cisplatin 60 mg/m^2 IV on day 1 Etoposide 120 mg/m^2 IV on days 1–3 Repeat cycle every 3 weeks
Cisplatin/irinotecan (IP)	Cisplatin 60 mg/m^2 IV on day 1 Irinotecan 60 mg/m^2 IV on days 1, 8, and 15 Repeat cycle every 4 weeks *or* Cisplatin 30 mg/m^2 IV on day 1 Irinotecan 65 mg/m^2 IV on days 1 and 8 Repeat cycle every 3 weeks

AUC, area under the curve; IV, intravenous/intravenously.

[a]NCCN Clinical Practice Guidelines in Oncology: Non–Small Cell Lung Cancer. In: National Comprehensive Cancer Network Inc; V1.2013.
[b]NCCN Clinical Practice Guidelines in Oncology: Small Cell Lung Cancer. V.q.2013.

- **Bevacizumab,** a recombinant, humanized monoclonal antibody, neutralizes vascular endothelial growth factor. NCCN guidelines recommend addition of bevacizumab to carboplatin–paclitaxel in advanced NSCLC of nonsquamous cell histology in patients with no history of hemoptysis and no CNS metastasis who are not receiving therapeutic anticoagulation. Initiate maintenance therapy in patients who have stable disease after or respond to four to six cycles of doublet therapy with or without bevacizumab.

SMALL CELL LUNG CANCER

- Goals of Treatment: The goals include cure or prolonged survival, which requires aggressive combination chemotherapy.

Surgery and Radiation Therapy

- Use of surgery in SCLC is limited to solitary nodules without evidence of metastasis to lymph nodes.
- SCLC is very radiosensitive. Radiation is always combined with chemotherapy (EP is preferred regimen) to treat limited disease SCLC. Concurrent radiotherapy is not used routinely in extensive disease.
- Radiotherapy is used to prevent and treat brain metastases, a frequent occurrence with SCLC. Prophylactic cranial irradiation (PCI) is used in patients with limited or extensive disease to reduce the risk of brain metastases.

- Chemotherapy with concurrent radiation is recommended for limited-stage SCLC.
- The most frequently used regimen for limited- and extensive-stage SCLC is **cisplatin** or **carboplatin** combined with **etoposide** (EP). **Irinotecan** in combination with cisplatin has also been shown to be active (**Table 62–1**).
- Recurrent SCLC is usually less sensitive to chemotherapy. Topotecan (IV and oral) is the only FDA-approved second-line therapy for SCLC. If recurrence occurs in more than 3 months, national guidelines recommend single-agent topotecan, **gemcitabine**, irinotecan, paclitaxel, docetaxel, CAV (**cyclophosphamide, doxorubicin,** and **vincristine**), and **vinorelbine**.
- Patients with SCLC that recurs within 3 months of first-line chemotherapy are considered refractory to chemotherapy and unlikely to respond to a second-line regimen.

EVALUATION OF THERAPEUTIC OUTCOMES

- Evaluate tumor response to chemotherapy for NSCLC at the end of the second or third cycle and at the end of every second cycle thereafter. Patients with stable disease, objective response, or measurable decrease in tumor size should continue treatment until four to six cycles have been administered. Consider maintenance therapy with pemetrexed in responding patients with nonsquamous histology.
- Evaluate efficacy of first-line therapy for SCLC after two or three cycles of chemotherapy. If there is no response or progressive disease, therapy can be discontinued or changed to a non–cross-resistant regimen. If responsive to chemotherapy, the induction regimen should be administered for four to six cycles. Responding patients benefit from the addition of PCI following initial therapy.
- Intensive therapeutic monitoring is required for all patients with lung cancer to avoid drug-related and radiotherapy-related toxicities. These patients frequently have numerous concurrent medical problems requiring close attention.
- References should be consulted for management of common toxicities associated with the aggressive chemotherapy regimens used for lung cancer.

See Chapter 106, Lung Cancer, authored by Val R. Adams and Susanne M. Arnold, for a more detailed discussion of this topic.

CHAPTER 63

Lymphomas

- *Lymphomas* are a heterogeneous group of malignancies that arise from immune cells residing predominantly in lymphoid tissues. Differences in histology have led to the classification of Hodgkin and non-Hodgkin lymphoma (HL and NHL, respectively), which are addressed separately in this chapter.

HODGKIN LYMPHOMA

PATHOPHYSIOLOGY

- B-cell transcriptional processes are disrupted during malignant transformation, preventing expression of B-cell surface markers and production of immunoglobulin messenger RNA. Alterations in the normal apoptotic pathways favor cell survival and proliferation.
- Malignant Reed–Sternberg cells overexpress nuclear factor-κ B, which is associated with cell proliferation and antiapoptotic signals. Infections with viral and bacterial pathogens upregulate nuclear factor-κ B. Epstein–Barr virus is found in many, but not all, HL tumors.

CLINICAL PRESENTATION

- Most patients with HL present with a painless, rubbery, enlarged lymph node in the supradiaphragmatic area and commonly have mediastinal nodal involvement. Asymptomatic adenopathy of the inguinal and axillary regions may also be present.
- Constitutional, or "B," symptoms (eg, fever, drenching night sweats, and weight loss) are present at diagnosis in approximately 25% of patients with HL.

DIAGNOSIS AND STAGING

- Diagnosis requires the presence of Reed–Sternberg cells in the lymph node biopsy.
- Staging is performed to provide prognostic information and to guide therapy. Clinical staging is based on noninvasive procedures such as history, physical examination, laboratory tests, and radiography, including positron emission tomography (PET). Pathologic staging is based on biopsy findings of strategic sites (eg, muscle, bone, skin, spleen, and abdominal nodes) using an invasive procedure (eg, laparoscopy).
- At diagnosis, approximately half of patients have localized disease (stages I, II, and IIE) and the others have advanced disease, of which 10% to 15% is stage IV.
- Prognosis predominantly depends on age and tumor stage; patients older than 65 to 70 years have a lower cure rate than younger patients. Patients with limited stage disease (stages I and II) have a 90% to 95% cure rate, whereas those with advanced disease (stages III and IV) have a 60% to 80% cure rate.

TREATMENT

- Goals of Treatment: The goal is to maximize curability while minimizing short- and long-term treatment-related complications.
- Treatment options include radiation therapy (RT), chemotherapy, or both (combined-modality therapy). The therapeutic role of surgery is limited, regardless of stage.
- RT is an integral part of treatment and can be used alone for select patients with early-stage disease, although most patients will receive chemotherapy and radiation. *Involved-field radiation* targets a single field of HL. *Extended-field* or *subtotal nodal radiation* targets the involved field and an uninvolved area. Total nodal radiation targets all areas.
- Long-term complications of RT, chemotherapy, and chemoradiotherapy include gonadal dysfunction, secondary malignancies (eg, lung, breast, and GI tract, as well as leukemia), and cardiac disease.

Initial Chemotherapy

- Two to eight cycles of chemotherapy should be administered, depending on the stage of disease and the presence of risk factors (Tables 63–1 and 63–2).

Salvage Chemotherapy

- Response to salvage therapy depends on the extent and site of recurrence, previous therapy, and duration of first remission. Choice of salvage therapy should be guided by response to initial therapy and a patient's ability to tolerate therapy.
- Patients who relapse after an initial complete response can be treated with the same regimen, a non–cross-resistant regimen, RT, or high-dose chemotherapy and autologous hematopoietic stem cell transplantation (HSCT).
- Lack of complete remission after initial therapy or relapse within 1 year after completing initial therapy is associated with a poor prognosis. Patients with these prognostic factors are candidates for high-dose chemotherapy and HSCT.

NON-HODGKIN LYMPHOMA

PATHOPHYSIOLOGY

- NHLs are derived from monoclonal proliferation of malignant B or T lymphocytes and their precursors. Current classification schemes characterize NHLs according to cell of origin, clinical features, and morphologic features.

TABLE 63–1 General Treatment Recommendations for Hodgkin Lymphoma

Early-stage disease	
Favorable disease (stage IA or IIA with no risk factors)	2 cycles of Stanford V or 4 cycles of ABVD followed by involved-field radiation
Unfavorable disease (stage IA or IIA with risk factors [eg, B symptoms, extranodal disease, bulky disease, 3 or more sites of nodal involvement, or an ESR >50 mm/h; ≥13.9 μm/s])	2–4 cycles of ABVD plus involved-field radiation; if radiation is omitted, 6 cycles of ABVD are recommended
Advanced-stage disease	
Favorable disease (stage III or IV)	6–8 cycles of ABVD plus radiation to residual disease sites
Unfavorable prognosis (stage III or IV with 4 or more poor prognostic factors [eg, low serum albumin, low hemoglobin, male gender, age ≥45 years, high WBC, lymphocytopenia])	6–8 cycles of escalated-dose BEACOPP plus radiation to residual disease sites
Relapsed disease	
Relapse after radiation	6–8 cycles of chemotherapy with or without radiation (treat as if this were primary advanced disease)
Relapse after primary chemotherapy[a]	Salvage chemotherapy at conventional doses or high-dose chemotherapy and autologous hematopoietic stem cell transplantation

ABVD, doxorubicin (Adriamycin), bleomycin, vinblastine, and dacarbazine; BEACOPP, bleomycin, etoposide, doxorubicin (Adriamycin), cyclophosphamide, vincristine (Oncovin), procarbazine, and prednisone; ESR, erythrocyte sedimentation rate; WBC, white blood cell count.

[a]A standard regimen or approach does not exist. See **Table 63–2** for details of chemotherapy regimens.

TABLE 63–2 Combination Chemotherapy Regimens for Hodgkin Lymphoma

Drug	Dosage (mg/m²)	Route	Days
MOPP			
Mechlorethamine	6	IV	1, 8
Vincristine	1.4	IV	1, 8
Procarbazine	100	Oral	1–14
Prednisone	40	Oral	1–14
Repeat every 21 days			
ABVD			
Doxorubicin (Adriamycin®)	25	IV	1, 15
Bleomycin	10	IV	1, 15
Vinblastine	6	IV	1, 15
Dacarbazine	375	IV	1, 15
Repeat every 28 days			
MOPP/ABVD			
Alternating months of MOPP and ABVD			
MOPP/ABV hybrid			
Mechlorethamine	6	IV	1
Vincristine	1.4	IV	1
Procarbazine	100	Oral	1–7
Prednisone	40	Oral	1–14
Doxorubicin	35	IV	8
Bleomycin	10	IV	8
Vinblastine	6	IV	8
Repeat every 28 days			
Stanford V			
Doxorubicin	25	IV	Weeks 1, 3, 5, 7, 9, 11
Vinblastine	6	IV	Weeks 1, 3, 5, 7, 9, 11
Mechlorethamine	6	IV	Weeks 1, 5, 9
Etoposide	60	IV	Weeks 3, 7, 11
Vincristine	1.4[a]	IV	Weeks 2, 4, 6, 8, 10, 12
Bleomycin	5	IV	Weeks 2, 4, 6, 8
Prednisone	40	Oral	Every other day for 12 weeks; begin tapering at week 10
One course (12 weeks)			
BEACOPP (standard-dose)			
Bleomycin	10	IV	8
Etoposide	100	IV	1–3
Adriamycin (doxorubicin)	25	IV	1

(*continued*)

TABLE 63–2 Combination Chemotherapy Regimens for Hodgkin Lymphoma (*Continued*)

Drug	Dosage (mg/m²)	Route	Days
Cyclophosphamide	650	IV	1
Oncovin® (vincristine)	1.4[a]	IV	8
Procarbazine	100	Oral	1–7
Prednisone	40	Oral	1–14
Repeat every 21 days			
BEACOPP (escalated-dose)			
Bleomycin	10	IV	8
Etoposide	200	IV	1–3
Adriamycin (doxorubicin)	35	IV	1
Cyclophosphamide	1250	IV	1
Oncovin® (vincristine)	1.4[a]	IV	8
Procarbazine	100	Oral	1–7
Prednisone	40	Oral	1–14
Granulocyte colony-stimulating factor		Subcutaneously	8+
Repeat every 21 days			

[a]Vincristine dose capped at 2 mg.

- World Health Organization (WHO) classification uses *grade* to refer to histologic parameters such as cell and nuclear size, density of chromatin, and proliferation fraction, and *aggressiveness* to denote clinical behavior of a tumor.

CLINICAL PRESENTATION

- Patients present with a variety of symptoms, which depend on site of involvement and whether it is nodal or extranodal.
- Adenopathy can be localized or generalized. Involved nodes are painless, rubbery, and discrete and usually located in the cervical and supraclavicular regions. Mesenteric or GI involvement can cause nausea, vomiting, obstruction, abdominal pain, palpable abdominal mass, or GI bleeding. Bone marrow involvement can cause symptoms related to anemia, neutropenia, or thrombocytopenia.
- Forty percent of patients with NHL present with B symptoms—fever, drenching night sweats, and weight loss.

DIAGNOSIS AND STAGING

- Diagnosis is established by biopsy of an involved lymph node. Diagnostic workup of NHL is generally similar to that of HL.
- NHL classification systems continue to evolve. Slow-growing or indolent lymphomas are favorable (untreated survival measured in years), whereas rapid-growing or aggressive lymphomas are unfavorable (untreated survival measured in weeks to months).
- Prognosis depends on histologic subtype and clinical risk factors (eg, age >60 years, performance status of 2 or more, abnormal lactate dehydrogenase, extranodal involvement, and stage III or IV disease). These risk factors are used to calculate the International Prognostic Index (IPI) that is most useful in patients with aggressive lymphomas.
- A newer prognostic index for patients with indolent (follicular) lymphomas uses similar risk factors except that poor performance status is replaced with low hemoglobin

(<12 g/dL [<120 g/L; 7.45 mmol/L]). Current research is focused on prognostic importance of phenotypic and molecular characteristics of NHL.

TREATMENT

- Goals of Treatment: The goals are to relieve symptoms and, whenever possible, cure the patient of disease while minimizing the risk of serious toxicity.

General Principles

- Appropriate therapy for NHL depends on many factors, including patient age, histologic type, stage and site of disease, presence of adverse prognostic factors, and patient preference.
- Treatment is divided into two categories: limited disease (eg, localized disease; Ann Arbor stages I and II) and advanced disease (eg, Ann Arbor stage III or IV and stage II patients with poor prognostic features).
- Treatment options include RT, chemotherapy, and biologic agents. RT is used for remission induction with early stage, localized disease and, more commonly, as a palliative measure in advanced disease.
- Effective chemotherapy ranges from single-agent therapy for indolent lymphomas to aggressive, complex combination regimens for aggressive disease.

Indolent Lymphomas

- Follicular lymphomas occur in older adults, with a majority having advanced disease that includes the chromosomal translocation t(14;18). Clinical course is generally indolent, with median survival of 8 to 10 years. The natural history of follicular lymphoma is unpredictable, with spontaneous regression of objective disease seen in 20% to 30% of patients.

LOCALIZED FOLLICULAR LYMPHOMA

- Options for stage I and II follicular lymphoma include locoregional RT and immunotherapy (ie, **rituximab**) with or without chemotherapy or RT.
- RT is the standard treatment and is usually curative. Chemotherapy is not recommended, unless the patient has high-risk, stage II disease.

ADVANCED FOLLICULAR LYMPHOMA

- Management of stages III and IV indolent lymphoma is controversial because standard approaches are not curative. Median time to relapse is only 18 to 36 months. After relapse, response can be reinduced; however, response rates and durations decrease with each retreatment.
- Therapeutic options are diverse and include watchful waiting, RT, single-agent therapy, combination chemotherapy, biologic therapy, radioimmunotherapy, and combined-modality therapy. Immediate aggressive therapy does not improve survival compared with conservative therapy (ie, watchful waiting followed by single-agent chemotherapy, **rituximab,** or RT, when treatment is needed).
- Oral alkylating agents **chlorambucil** or **cyclophosphamide,** used alone or in combination with **prednisone,** are the mainstay of treatment. These single agents are as effective as combination regimens and produce minimal toxicity, but secondary acute leukemia is a concern. **Bendamustine** is an IV alkylating agent approved for relapsed or refractory indolent NHL.
- Two adenosine analogues, **fludarabine** and **cladribine,** produce high response rates in previously untreated and relapsed advanced follicular lymphoma. Their use is associated with prolonged myelosuppression and profound immunosuppression, increasing risk of opportunistic infections.
- Rituximab, a chimeric monoclonal antibody directed at the CD20 molecule on B cells, is one of the most widely used therapies for follicular lymphoma. It is approved for first-line therapy either alone or combined with chemotherapy and as maintenance therapy for patients with stable disease or with partial or complete response following induction chemotherapy.

- The most common chemotherapy regimen used with rituximab is the CHOP regimen (Table 63–3). Practice guidelines list rituximab maintenance for up to 2 years as an option in both first- and second-line therapy.
- Rituximab adverse effects are usually infusion related, especially after the first infusion of rituximab, and consist of fever, chills, respiratory symptoms, fatigue, headache, pruritus, and angioedema. Pretreatment with oral **acetaminophen**, 650 mg, and **diphenhydramine**, 50 mg, 30 minutes before the infusion is recommended.
- Anti-CD20 radioimmunoconjugates are mouse antibodies linked to radioisotopes (eg, ^{131}**I-tositumomab** and ^{90}**Y-ibritumomab tiuxetan**). They have the advantage of delivering radiation to tumor cells expressing the CD20 antigen and to adjacent tumor cells that do not express it. They have the disadvantage of damaging adjacent normal tissue (eg, bone marrow).
- Radioimmunotherapy was initially used as salvage therapy and is being evaluated as first-line therapy in combination with CHOP.
- Radioimmunotherapy is generally well tolerated. Toxicities include infusion-related reactions, myelosuppression, and possibly myelodysplastic syndrome or acute myelogenous leukemia. ^{131}I-tositumomab can cause thyroid dysfunction.
- High-dose chemotherapy followed by HSCT is an option for relapsed follicular lymphoma. The recurrence rate is lower after allogeneic than after autologous HSCT, but the benefit is offset by increased treatment-related mortality.

Aggressive Lymphomas

- Diffuse large B-cell lymphomas (DLBCLs) are the most common lymphoma in patients of all ages but most commonly seen in the seventh decade. Extranodal disease is present at diagnosis in 30% to 40% of patients. IPI score correlates with prognosis. Diffuse aggressive lymphomas are sensitive to chemotherapy, with cure achieved in some patients.

TREATMENT OF LOCALIZED DISEASE

- Stage I and nonbulky stage II should be treated with three or four cycles of rituximab and CHOP (R-CHOP) (**Table 63–3**) followed by locoregional RT.
- Patients with at least one adverse risk factor should receive six cycles of R-CHOP followed by locoregional RT.

TREATMENT OF ADVANCED DISEASE

- Bulky stage II and stages III and IV lymphoma should be treated with R-CHOP or rituximab and CHOP-like chemotherapy until achieving complete response (usually four cycles). Two or more additional cycles should be given following complete response for a total of six to eight cycles. Maintenance therapy following a complete response does not improve survival.
- Consider high-dose chemotherapy with autologous HSCT in high-risk patients who respond to standard chemotherapy and meet HSCT criteria.

TABLE 63–3 Combination Chemotherapy for Non-Hodgkin Lymphoma (CHOP)[a,b]

Drug	Dose (mg/m^2)	Route	Days
Cyclophosphamide	750	IV	1
Doxorubicin	50	IV	1
Vincristine	1.4[c]	IV	1
Prednisone	100	Oral	1–5

[a]Cycle should be repeated every 21 days.
[b]Rituximab 375 mg/m^2 on day 1 is commonly added (R-CHOP).
[c]Vincristine dose capped at 2 mg.

- Although historically elderly adults have lower complete response and survival rates than younger patients, full-dose R-CHOP is recommended as initial treatment for aggressive lymphoma in the elderly.

TREATMENT OF REFRACTORY OR RELAPSED DISEASE

- Approximately one third of patients with aggressive lymphoma will require salvage therapy at some point. Salvage therapy is more likely to induce response if the response to initial chemotherapy was complete (chemosensitivity) than if it was primarily or partially resistant to chemotherapy.
- High-dose chemotherapy with autologous HSCT is the therapy of choice for younger patients with chemosensitive relapse.
- Salvage regimens incorporate drugs not used as initial therapy. Commonly used regimens include DHAP (**dexamethasone**, **cytarabine**, and **cisplatin**), ESHAP (**etoposide**, **methylprednisolone**, cytarabine, and cisplatin), and MINE (**mesna, ifosfamide, mitoxantrone,** and **etoposide**). None is clearly superior to the others.
- ICE (ifosfamide, **carboplatin,** and etoposide) appears to be better tolerated than cisplatin-containing regimens, especially in elderly adults.
- Rituximab is being evaluated in combination with many salvage regimens.

NON-HODGKIN LYMPHOMA IN ACQUIRED IMMUNODEFICIENCY SYNDROME

- Patients with AIDS have more than a 100-fold increased risk of developing NHL, which is usually aggressive (eg, Burkitt or DLBCL).
- Treatment of AIDS-related lymphoma is difficult because underlying immunodeficiency increases the risk of treatment-related myelosuppression.
- Standard combination regimens (eg, CHOP) yield disappointing results. Newer approaches, including dose-adjusted EPOCH (etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin), appear promising. The role of rituximab in the treatment of AIDS-related DLBCL is not clear.
- Prophylactic antibiotics should be continued during chemotherapy, but the optimal timing for highly active antiretroviral therapy (HAART) is not clear in patients with AIDS-related lymphoma.

EVALUATION OF THERAPEUTIC OUTCOMES

- The primary outcome to be identified is tumor response, which is based on physical examination, radiologic evidence, PET/computed tomography (CT) scanning, and other baseline findings.
- Patients are evaluated for response at the end of four cycles or, if treatment is shorter, at the end of treatment.

See Chapter 109, Lymphomas, authored by Alexandre Chan and Gary C. Yee, for a more detailed discussion of this topic.

Prostate Cancer

CHAPTER 64

- *Prostate cancer* is a malignant neoplasm that arises from the prostate gland. Prostate cancer has an indolent course; localized prostate cancer is curable by surgery or radiation therapy, but advanced prostate cancer is not yet curable.

PATHOPHYSIOLOGY

- The normal prostate is composed of acinar secretory cells that are altered when invaded by cancer. The major pathologic cell type is adenocarcinoma (>95% of cases).
- Prostate cancer can be graded. Well-differentiated tumors grow slowly, whereas poorly differentiated tumors grow rapidly and have a poor prognosis.
- Metastatic spread can occur by local extension, lymphatic drainage, or hematogenous dissemination. Skeletal metastases from hematogenous spread are the most common sites of distant spread. The lung, liver, brain, and adrenal glands are the most common sites of visceral involvement, but these organs are not usually involved initially.
- The rationale for hormone therapy is based on the effect of androgens on the growth and differentiation of the normal prostate (**Fig. 64–1**).
- The testes and the adrenal glands are the major sources of androgens, specifically dihydrotestosterone (DHT).
- Luteinizing hormone–releasing hormone (LHRH) from the hypothalamus stimulates the release of luteinizing hormone (LH) and follicle-stimulating hormone (FSH) from the anterior pituitary gland.
- LH complexes with receptors on the Leydig cell testicular membrane and stimulates the production of testosterone and small amounts of estrogen.
- FSH acts on testicular Sertoli cells to promote maturation of LH receptors and produce an androgen-binding protein.
- Circulating testosterone and estradiol influence the synthesis of LHRH, LH, and FSH by a negative-feedback loop at the hypothalamic and pituitary level.

CHEMOPREVENTION

- The risk of prostate cancer was reduced approximately 25% in patients taking **finasteride** for treatment of benign prostatic hypertrophy (BPH), but prostate cancer diagnosed in patients on finasteride is more aggressive.
- Current guidelines do not recommend the use of finasteride or **dutasteride** for prostate cancer chemoprevention. Although finasteride reduces the prevalence of prostate cancer, the impact on prostate cancer morbidity or mortality has not been demonstrated.

SCREENING

- Screening for prostate cancer is controversial. The current approach involves offering a baseline prostate-specific antigen (PSA) and digital rectal examination (DRE) at age 40 with annual evaluations beginning at age 50 for men of normal risk. Earlier testing is recommended for men at higher risk for prostate cancer.
- Advantages of DRE include specificity, low cost, safety, and ease of performance; disadvantages include relative insensitivity and interobserver variability.
- PSA is a glycoprotein produced and secreted by prostate epithelial cells. Acute urinary retention, acute prostatitis, and BPH influence PSA, thereby limiting the usefulness of PSA alone for early detection, but it is a useful marker for monitoring response to therapy.

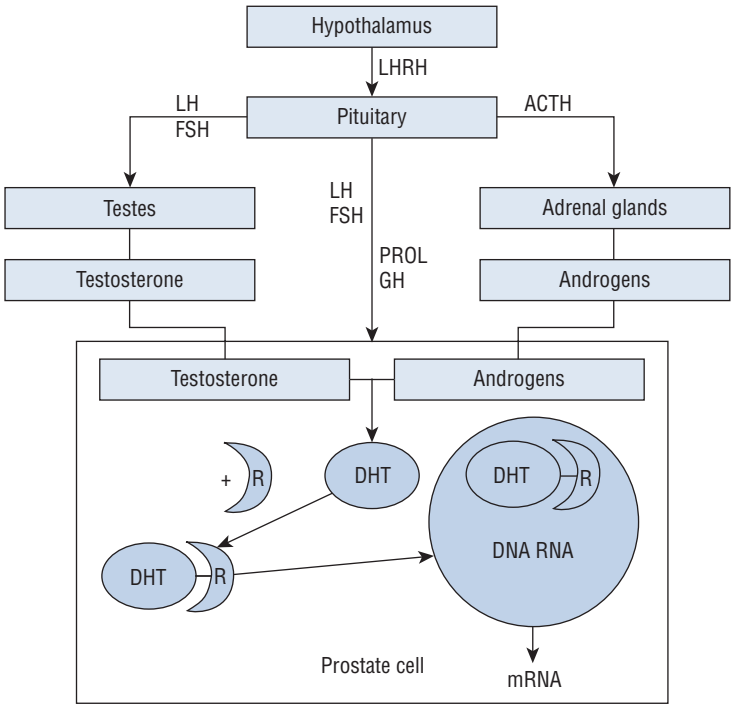


FIGURE 64–1. Hormonal regulation of the prostate gland. (ACTH, adrenocorticotropic hormone; DHT, dihydrotestosterone; FSH, follicle-stimulating hormone; GH, growth hormone; LH, luteinizing hormone; LHRH, luteinizing hormone–releasing hormone; mRNA, messenger RNA; PROL, prolactin; R, receptor.)

CLINICAL PRESENTATION

- Localized prostate cancer is usually asymptomatic.
- Locally invasive prostate cancer is associated with ureteral dysfunction or impingement, such as alterations in micturition (eg, urinary frequency, hesitancy, and dribbling).
- Advanced disease commonly presents with back pain and stiffness due to osseous metastases. Untreated spinal cord lesions can lead to cord compression. Lower extremity edema can occur as a result of lymphatic obstruction. Anemia and weight loss are nonspecific signs of advanced disease.

TREATMENT

- Goals of Treatment: In early-stage prostate cancer, the goal is to minimize morbidity and mortality. Surgery and radiation therapy are curative but also associated with significant morbidity and mortality. In advanced prostate cancer, treatment focuses on providing symptom relief and maintaining quality of life.

GENERAL APPROACH

- Initial treatment depends on disease stage, Gleason score, presence of symptoms, and patient's life expectancy. The most appropriate therapy for early-stage prostate cancer is unknown. See **Table 64–1** for management recommendations based on risk of recurrence.

TABLE 64–1 Initial Management of Prostate Cancer Based on Expected Survival and Recurrence Risk

Recurrence Risk	Expected Survival (Years)	Initial Therapy
Very Low		
T_{1c}	Less than 20	Observation
T_{1c}	20 or more	Observation *or* Radical prostatectomy with or without pelvic lymph node dissection *or* Radiation therapy
Low		
T_1–T_{2a} and Gleason 2–6 and PSA less than 10 ng/mL (10 mcg/L) and less than 5% tumor in specimen	10 or more	Observation *or* Radical prostatectomy with or without pelvic lymph node dissection or radiation therapy
	Less than 10	Observation
Intermediate		
T_{2b}–T_{2c} or Gleason 7 or PSA 10–20 ng/mL (10–20 mcg/L)	10 or less	Observation *or* Radical prostatectomy with pelvic lymph node dissection *or* Radiation therapy with or without 4–6 months of neoadjuvant androgen deprivation therapy with or without brachytherapy
T_{2b}–T_{2c} or Gleason 7 or PSA 10–20 ng/mL (10–20 mcg/L)	10 or more	Radical prostatectomy with pelvic lymph node dissection *or* Radiation therapy with or without 4–6 months of neoadjuvant androgen deprivation therapy with or without brachytherapy

High	
T_{3a}, Gleason 8–10, PSA greater than 20 ng/mL (20 mcg/L)	Radiation therapy and ADT[a] (2–3 years) with or without brachytherapy or Radical prostatectomy and pelvic lymph node dissection
Very High	
T_{3b}–T_4	Radiation therapy and ADT (2–3 years) with or without brachytherapy or Radical prostatectomy and pelvic lymph node dissection or ADT
Very High	
Any T, N_1	ADT (2–3 years) or Radiation therapy and ADT (2–3 years)
Any T, Any N, M_1	ADT with Orchiectomy or LHRH agonist[b] + 7 days antiandrogen therapy or LHRH agonist + antiandrogen or LHRH agonist

ADT, androgen deprivation therapy; LHRH, luteinizing hormone-releasing hormone; PSA, prostate-specific antigen.
[a]Androgen deprivation therapy to achieve serum testosterone levels less than 50 ng/dL (1.7 nmol/L)
[b]LHRH agonist, medical castrations, or surgical are equivalent.

- Initial treatment modality for advanced prostate cancer is androgen ablation (eg, orchiectomy or LHRH agonists with or without antiandrogens). After disease progression, secondary hormonal manipulations, cytotoxic chemotherapy, and supportive care are used.

NONPHARMACOLOGIC THERAPY

Observation

- Observation or watchful waiting involves monitoring the course of disease and initiating treatment if the cancer progresses. PSA and DRE are performed every 6 months.
- Advantages include avoiding adverse effects of definitive therapies and minimizing risk of unnecessary therapies. The major disadvantage is the risk of cancer progression requiring more intense therapy.

Surgery and Radiation Therapy

- Bilateral orchiectomy rapidly reduces circulating androgens to castrate levels. Many patients are not surgical candidates due to advanced age, and other patients find this procedure psychologically unacceptable. Orchiectomy is the preferred initial treatment for patients with impending spinal cord compression or ureteral obstruction.
- Radical prostatectomy and radiation therapy are potentially curative therapies but are associated with complications that must be weighed against expected benefit. Consequently, many patients postpone therapy until symptoms develop.
- Complications of radical prostatectomy include blood loss, stricture formation, incontinence, lymphocele, fistula formation, anesthetic risk, and impotence. Nerve-sparing techniques facilitate return of sexual potency after prostatectomy.
- Acute complications of radiation therapy include cystitis, proctitis, hematuria, urinary retention, penoscrotal edema, and impotence.
- Chronic complications of radiation therapy include proctitis, diarrhea, cystitis, enteritis, impotence, urethral stricture, and incontinence.

PHARMACOLOGIC THERAPY

Drug Treatments of First Choice

LUTEINIZING HORMONE–RELEASING HORMONE AGONISTS

- LHRH agonists are a reversible method of androgen ablation and are as effective as orchiectomy.
- There are no comparative trials of LHRH agonists, so the choice is usually based on cost and patient and physician preference for a dosing schedule (**Table 64–2**). **Leuprolide acetate**, **leuprolide depot, leuprolide implant, triptorelin depot, triptorelin implant,** and **goserelin acetate implant** are currently available. Dosing intervals range from once monthly to every 16 weeks. Leuprolide implant is a mini-osmotic pump that delivers daily doses for 1 year.
- The most common adverse effects of LHRH agonists include disease flare-up during the first week of therapy (eg, increased bone pain or urinary symptoms), hot flashes, erectile impotence, decreased libido, and injection-site reactions. Use of an antiandrogen (eg, **flutamide, bicalutamide,** or **nilutamide**) prior to initiation of LHRH therapy and for 2 to 4 weeks after is a strategy to minimize initial tumor flare.
- Decreases in bone mineral density complicate androgen deprivation therapy (ADT), resulting in increased risk of osteoporosis, osteopenia, and skeletal fractures. Calcium and vitamin D supplements and a baseline bone mineral density are recommended.

GONADOTROPIN-RELEASING HORMONE ANTAGONISTS

- The gonadotropin-releasing hormone (GnRH) antagonist **degarelix** binds reversibly to GnRH receptors in the pituitary gland, reducing the production of testosterone to castrate levels in 7 days or less. A major advantage of degarelix over LHRH agonists is the lack of tumor flare.

- Degarelix is administered as a subcutaneous injection every 28 days. Injection site reactions are the most frequently reported adverse effects and include pain, erythema, swelling, induration, and nodules.

ANTIANDROGENS

- Monotherapy with **flutamide, bicalutamide,** and **nilutamide** is no longer recommended due to decreased efficacy as compared with patients treated with LHRH agonist therapy. Antiandrogens are indicated for advanced prostate cancer only when combined with an LHRH agonist (flutamide and bicalutamide]) or orchiectomy (nilutamide). In combination, antiandrogens can reduce the LHRH agonist–induced flare.
- **Enzalutamide** is approved as a single agent in metastatic hormone-resistant prostate cancer patients who have previously received **docetaxel**.
- Adverse effects of antiandrogens are summarized in Table 64–2.

COMBINED ANDROGEN BLOCKADE

- The role of combined androgen blockade (CAB), also referred to as *maximal androgen deprivation* or *total androgen blockade*, continues to be evaluated. The combination of LHRH agonists or orchiectomy with antiandrogens is the CAB approach most extensively studied.
- Some investigators consider CAB to be the initial hormone therapy of choice for newly diagnosed patients because the major benefit is seen in patients with minimal disease. Some argue that treatment should not be delayed because combined androgen deprivation trials demonstrate a survival advantage for young patients with good performance status and minimal disease who were initially treated with hormone therapy.
- Until definitive trials are published, it is appropriate to use either LHRH agonist monotherapy or CAB as initial therapy for metastatic prostate cancer.

ALTERNATIVE DRUG TREATMENTS

- Selection of salvage therapy depends on what was used as initial therapy. Radiotherapy can be used after radical prostatectomy. Androgen ablation can be used after radiation therapy or radical prostatectomy.
- If testosterone levels are not suppressed (ie, >20 ng/dL [0.7 nmol/L]) after initial LHRH agonist therapy, an antiandrogen or orchiectomy may be indicated. If testosterone levels are suppressed, the disease is considered androgen independent and should be treated with palliative therapy.
- If initial therapy consists of an LHRH agonist and antiandrogen, androgen withdrawal should be attempted. Mutations of the androgen receptor may allow antiandrogens to become agonists. Withdrawal produces responses lasting 3 to 14 months in up to 35% of patients.
- Androgen synthesis inhibitors provide symptomatic but brief relief in approximately 50% of patients. **Aminoglutethimide** causes adverse effects in 50% of patients, such as lethargy, ataxia, dizziness, and self-limiting rash. The adverse effects of **ketoconazole** include GI intolerance, transient increases in liver and renal function tests, and hypoadrenalism. **Abiraterone** targets CYP17A1 resulting in decreased circulating levels of testosterone (Table 64–2). Review medication profiles because abiraterone is an inhibitor of CYP2D6.

CHEMOTHERAPY

- **Docetaxel,** 75 mg/m^2 every 3 weeks, combined with **prednisone,** 5 mg twice daily, improves survival in castrate-refractory prostate cancer. The most common adverse events include nausea, alopecia, and myelosuppression.
- **Cabazitaxel** 25 mg/m^2 every 3 weeks with prednisone 10 mg daily significantly improves progression-free and overall survival. Neutropenia, febrile neutropenia, neuropathy, and diarrhea are the most significant toxicities.

TABLE 64–2 Hormonal Therapies for Prostate Cancer

Drug (Brand Name)	Usual Dose	Toxicities	Hepatic/Renal Adjustments	Monitoring Parameters	Drug Interactions	Administration
Antiandrogens						
Flutamide (Eulexin)	750 mg/day	Gynecomastia Hot flashes Gastrointestinal disturbances (diarrhea) Loss of libido LFT abnormalities Breast tenderness Methemoglobinemia	Contraindicated in patients with hepatic impairment No dosage adjustment necessary in chronic renal impairment	Serum transaminases should be monitored prior to start of therapy and monthly for first 4 months, then periodically thereafter. Monitor for tumor reduction, testosterone/estrogen, and phosphatase serum levels.	Substrate of CYP1A2 and CYP3A4	Administered orally in three divided doses. Capsule may be opened into applesauce, pudding, or other soft foods.
Bicalutamide (Casodex)	50 mg/day (up to 150 mg/day—unlabeled use)	Gynecomastia Hot flashes Gastrointestinal disturbances (diarrhea) Decrease libido LFT abnormalities Breast tenderness	Discontinue if ALT >2 times upper limit of normal or patient develops jaundice	Serum transaminases should be monitored prior to start of therapy and monthly for first 4 months, then periodically thereafter. Periodic monitoring of CBC, EKG, echocardiograms, serum testosterone, luteinizing hormone, and PSA.	Inhibits CYP3A4 May increase concentration of vitamin K antagonists.	May be taken with or without food.

Nilutamide (Nilandron)	300 mg/day for first month then 150 mg/day	Gynecomastia Hot flashes Gastrointestinal disturbances (constipation) LFT abnormalities Breast tenderness Visual disturbances (impaired dark adaptation) Alcohol intolerance Interstitial pneumonitis	Contraindicated in patients with hepatic impairment Discontinue if ALT >2 times upper limit of normal or patient develops jaundice	Serum transaminases should be monitored prior to start of therapy and monthly for first 4 months, then periodically thereafter. Chest x-ray at baseline and consideration of pulmonary function testing (at baseline)	Substrate of CYP2C19 and weak inhibitor of CYP2C19	May be taken with or without food.
Enzalutamide (Xtandi)	160 mg/day	Gastrointestinal disturbances (diarrhea) Musculoskeletal disorders (back pain, arthralgias, muscle pain, weakness) Asthenia Peripheral edema CNS (headache, dizziness) Seizures LFT abnormalities	No adjustment necessary for renal or hepatic impairment	Complete blood counts baseline and periodically. LFTs baseline and periodically.	Strong CYP3A4 and moderate CYP2C9 and CYP2C19 inducer. Avoid CYP3A4, CYP2C9 and CYP2C19 sensitive substrates. CYP2C8 substrate, avoid strong inducers and inhibitors of CYP2C8 If vitamin K antagonists necessary, conduct additional INR monitoring.	May be taken with or without food.

(*continued*)

TABLE 64–2 Hormonal Therapies for Prostate Cancer (*Continued*)

Drug (Brand Name)	Usual Dose	Toxicities	Hepatic/Renal Adjustments	Monitoring Parameters	Drug Interactions	Administration
Androgen Synthesis Inhibitor						
Abiraterone acetate (Zytiga)	1000 mg/day + prednisone 5 mg BID	Gastrointestinal disturbances (diarrhea) Edema Hypokalemia Hypophosphatemia LFT abnormalities Hypertriglyceridemia	250 mg daily for Child Pugh Class B. Avoid use in Child Pugh Class C. Withhold treatment if LFTs >5 times the ULN or bilirubin >3 ULN	Serum transaminases should be monitored prior to start of therapy, every 2 weeks for 3 months, then monthly thereafter. Monitor for signs and symptoms of adrenocorticoid insufficiency; monthly for hypertension, hypokalemia, and fluid retention.	Substrate of CYP3A4. Use with caution with CYP3A4 inhibitors and inducers. Inhibits CYP1A2, CYP2C19, CYP2C8, CYP2C9, CYP2D6, CYP3A4, and P-glycoprotein. Use sensitive substrates with caution.	Administer on an empty stomach, at least 1 hour before and 2 hours after food.
Luteinizing-Hormone Agonists						
Leuprolide (Lupron)	7.5 mg IM every month 22.5 mg IM every 3 months 30 mg IM every 4 months 45 mg IM every 6 months	Hot flashes Decreased libido Gynecomastia Osteoporosis Fatigue Weight gain	No adjustment necessary for renal or hepatic impairment	Serum testosterone ~4 weeks after initiation, PSA, blood glucose, and $HgbA_{1c}$ prior to initiation and periodically thereafter.	May diminish the effects of antidiabetic agents.	Vary injection site.

Goserelin (Zoladex)	3.6 mg SQ implant every month 10.8 mg SQ implant every 3 months	Hot flashes Decreased libido Gynecomastia Osteoporosis Fatigue Weight gain	No adjustment necessary for renal or hepatic impairment	Monitor bone mineral density, serum calcium, and cholesterol/lipids.	May diminish the effects of antidiabetic agents.	Vary injection site.
Triptorelin (Trelstar)	3.75 mg IM every month 11.25 mg IM every 3 months 22.5 mg IM every 6 months	Hot flashes Decreased libido Gynecomastia Osteoporosis Fatigue Weight gain	No adjustment necessary for renal or hepatic impairment	Monitor serum testosterone levels and prostate specific antigen.	May diminish the effects of antidiabetic agents.	Vary injection site.
Gonadotropin-Releasing Hormone Antagonists						
Degarelix (Firmagon)	240 mg SQ loading dose 80 mg SQ every 28 days (following 28 days after loading dose)	Hot flashes Decreased libido Gynecomastia Osteoporosis Fatigue Weight gain	Use in caution with CL_{cr} <50 mL/min Do not use in patients with severe hepatic impairment	Prostate-specific antigen periodically, serum testosterone monthly until castration achieved then every other month, LFTs at baseline in addition to serum electrolytes and bone mineral density.	Use with caution with agents that may increase QTC interval.	Vary injection site.

ALT, alanine aminotransferase; BID, twice daily; CBC, complete blood count; CL_{cr}, creatinine clearance; CNS, central nervous system; CYP, cytochrome P450; EKG, electrocardiogram; $HgbA_{1c}$, hemoglobin A1c; IM, intramuscular injection; INR, international normalized ratio; LFT, liver function test; PSA, prostate-specific antigen; SQ, subcutaneous injection; ULN, upper limit of normal.

IMMUNOTHERAPY

- **Sipuleucel-T** is a novel autologous cellular immunotherapy indicated for minimally symptomatic prostate cancer. Use is controversial because trials have not been done to compare it to standard second-line hormonal interventions.

EVALUATION OF THERAPEUTIC OUTCOMES

- Monitor primary tumor size, involved lymph nodes, and tumor marker response such as PSA with definitive, curative therapy. PSA level is checked every 6 months for the first 5 years, then annually.
- With metastatic disease, clinical benefit can be documented by evaluating performance status, weight, quality of life, analgesic requirements, and PSA or DRE at 3-month intervals.

See Chapter 108, Prostate Cancer, authored by Leann B. Norris and Jill M. Kolesar, for a more detailed discussion of this topic.

Edited by Cecily V. DiPiro

CHAPTER 65

Glaucoma

- *Glaucomas* are ocular disorders that lead to an optic neuropathy characterized by changes in the optic nerve head (optic disc) that is associated with loss of visual sensitivity and field.

PATHOPHYSIOLOGY

- There are two major types of glaucoma: primary open-angle glaucoma (POAG) or ocular hypertension, which accounts for most cases and is therefore the focus of this chapter, and closed-angle glaucoma (CAG). Either type can be a primary inherited disorder, congenital, or secondary to disease, trauma, or drugs.
- In POAG, the specific cause of optic neuropathy is unknown. Increased intraocular pressure (IOP) was historically considered to be the sole cause. Additional contributing factors include increased susceptibility of the optic nerve to ischemia, excitotoxicity, autoimmune reactions, and other abnormal physiologic processes.
- Although IOP is a poor predictor of which patients will have visual field loss, the risk of visual field loss increases with increasing IOP. IOP is not constant; it changes with pulse, blood pressure, forced expiration or coughing, neck compression, and posture. IOP demonstrates diurnal variation with a minimum pressure around 6 PM and a maximum pressure upon awakening.
- The balance between the inflow and outflow of aqueous humor determines IOP. Inflow is increased by β-adrenergic agents and decreased by α_2- and β-adrenergic blockers, dopamine blockers, carbonic anhydrase inhibitors (CAIs), and adenylate cyclase stimulators. Outflow is increased by cholinergic agents, which contract the ciliary muscle and open the trabecular meshwork, and by prostaglandin analogues and β- and α_2-adrenergic agonists, which affect uveoscleral outflow.
- Secondary OAG has many causes, including exfoliation syndrome, pigmentary glaucoma, systemic diseases, trauma, surgery, ocular inflammatory diseases, and drugs. Secondary glaucoma can be classified as pretrabecular (normal meshwork is covered and prevents outflow of aqueous humor), trabecular (meshwork is altered or material accumulates in the intertrabecular spaces), or posttrabecular (episcleral venous blood pressure is increased).
- Many drugs can increase IOP (**Table 65–1**). The potential to induce or worsen glaucoma depends on the type of glaucoma and on whether it is adequately controlled.
- CAG occurs when there is a physical blockage of the trabecular meshwork, resulting in increased IOP.

CLINICAL PRESENTATION

- POAG is slowly progressive and is usually asymptomatic until onset of substantial visual field loss. Central visual acuity is maintained, even in late stages.
- Patients with CAG typically experience intermittent prodromal symptoms (eg, blurred or hazy vision with halos around lights and, occasionally, headache). Acute episodes produce symptoms associated with a cloudy, edematous cornea; ocular pain; nausea, vomiting, and abdominal pain; and diaphoresis.

TABLE 65–1	Drugs That May Induce or Potentiate Increased Intraocular Pressure
Open-angle glaucoma	
	Ophthalmic corticosteroids (high risk)
	Systemic corticosteroids
	Nasal/inhaled corticosteroids
	Fenoldopam
	Ophthalmic anticholinergics
	Succinylcholine
	Vasodilators (low risk)
	Cimetidine (low risk)
Closed-angle glaucoma	
	Topical anticholinergics
	Topical sympathomimetics
	Systemic anticholinergics
	Heterocyclic antidepressants
	Low-potency phenothiazines
	Antihistamines
	Ipratropium
	Benzodiazepines (low risk)
	Theophylline (low risk)
	Vasodilators (low risk)
	Systemic sympathomimetics (low risk)
	CNS stimulants (low risk)
	Selective serotonin reuptake inhibitors
	Imipramine
	Venlafaxine
	Topiramate
	Tetracyclines (low risk)
	Carbonic anhydrase inhibitors (low risk)
	Monoamine oxidase inhibitors (low risk)
	Topical cholinergics (low risk)

DIAGNOSIS

- POAG is confirmed by the presence of characteristic optic disc changes and visual field loss, with or without increased IOP. *Normal tension glaucoma* refers to disc changes, visual field loss, and IOP less than 21 mm Hg (2.8 kPa). *Ocular hypertension* refers to IOP greater than 21 mm Hg (2.8 kPa) without disc changes or visual field loss.
- CAG is usually visualized by gonioscopy. IOP is generally markedly elevated (eg, 40–90 mm Hg [5.3–12 kPa]) when symptoms are present. Additional signs include hyperemic conjunctiva, cloudy cornea, shallow anterior chamber, and occasionally edematous and hyperemic optic disc.

TREATMENT OF OCULAR HYPERTENSION AND OPEN-ANGLE GLAUCOMA

- Goal of Treatment: The goal is to preserve visual function by reducing IOP to a level at which no further optic nerve damage occurs.
- Treat ocular hypertension if the patient has a significant risk factor such as IOP greater than 25 mm Hg (3.3 kPa), vertical cup:disc ratio greater than 0.5, or central corneal thickness less than 555 µm. Additional risk factors to be considered include family history of glaucoma, black race, severe myopia, and presence of only one eye. The goal of therapy is to lower IOP by 20% to 30% from baseline to decrease the risk of optic nerve damage.
- Treat all patients with elevated IOP and characteristic optic disc changes or visual field defects. An initial target IOP reduction of 30% is desired in patients with POAG.
- Initiate drug therapy in a stepwise manner (**Fig. 65–1**), starting with lower concentrations of a single well-tolerated topical agent (**Table 65–2**). Historically, β-blockers (eg, **timolol**) were the treatment of choice provided no contraindications existed.
- Newer agents are also suitable for first-line therapy. Prostaglandin analogs (eg, **latanoprost, bimatoprost,** and **travoprost**) offer once-daily dosing, better IOP reduction, good tolerance, and, recently, availability of lower-cost generics. **Brimonidine** and topical CAIs are also suitable for first-line therapy.
- **Pilocarpine** and **dipivefrin**, a prodrug of **epinephrine**, are used as third-line therapies because of adverse events or reduced efficacy as compared with newer agents.
- **Carbachol**, topical cholinesterase inhibitors, and oral CAIs (eg, **acetazolamide**) are used as last-resort options after failure of less toxic options.
- Optimal timing of laser trabeculoplasty or surgical trabeculectomy is controversial, ranging from initial therapy to after failure of third- or fourth-line drug therapy. Antiproliferative agents such as **fluorouracil** and **mitomycin C** are used to modify the healing process and maintain patency.

TREATMENT OF CLOSED-ANGLE GLAUCOMA

- Acute CAG with high IOP requires rapid reduction in IOP. Iridectomy is the definitive treatment producing a hole in the iris that permits aqueous humor flow to move directly from the posterior to the anterior chamber.
- Drug therapy of an acute attack typically consists of an osmotic agent and secretory inhibitor (eg, β-blocker, α_2-agonist, **latanoprost**, or CAI), with or without pilocarpine.
- Osmotic agents are used to rapidly decrease IOP. Examples include **glycerin**, 1 to 2 g/kg orally, and **mannitol**, 1 to 2 g/kg IV.
- Although traditionally the drug of choice, pilocarpine use is controversial as initial therapy. Once IOP is controlled, pilocarpine should be given every 6 hours until iridectomy is performed.
- Topical corticosteroids can be used to reduce ocular inflammation and synechiae.

EVALUATION OF THERAPEUTIC OUTCOMES

- Successful outcomes require identifying an effective, well-tolerated regimen; closely monitoring therapy; and patient adherence. Whenever possible, therapy for open-angle glaucoma should be started as a single agent in one eye to facilitate evaluation of drug efficacy and tolerance. Many drugs or combinations may need to be tried before the optimal regimen is identified.
- Monitoring therapy for POAG should be individualized. Assess IOP response every 4 to 6 weeks initially, every 3 to 4 months after IOPs become acceptable, and more frequently if therapy is changed. Visual field and disc changes are monitored annually, unless glaucoma is unstable or worsening.
- Monitor patients for loss of control of IOP (tachyphylaxis), especially with β-blockers or **apraclonidine**. Treatment can be temporarily discontinued to monitor benefit.

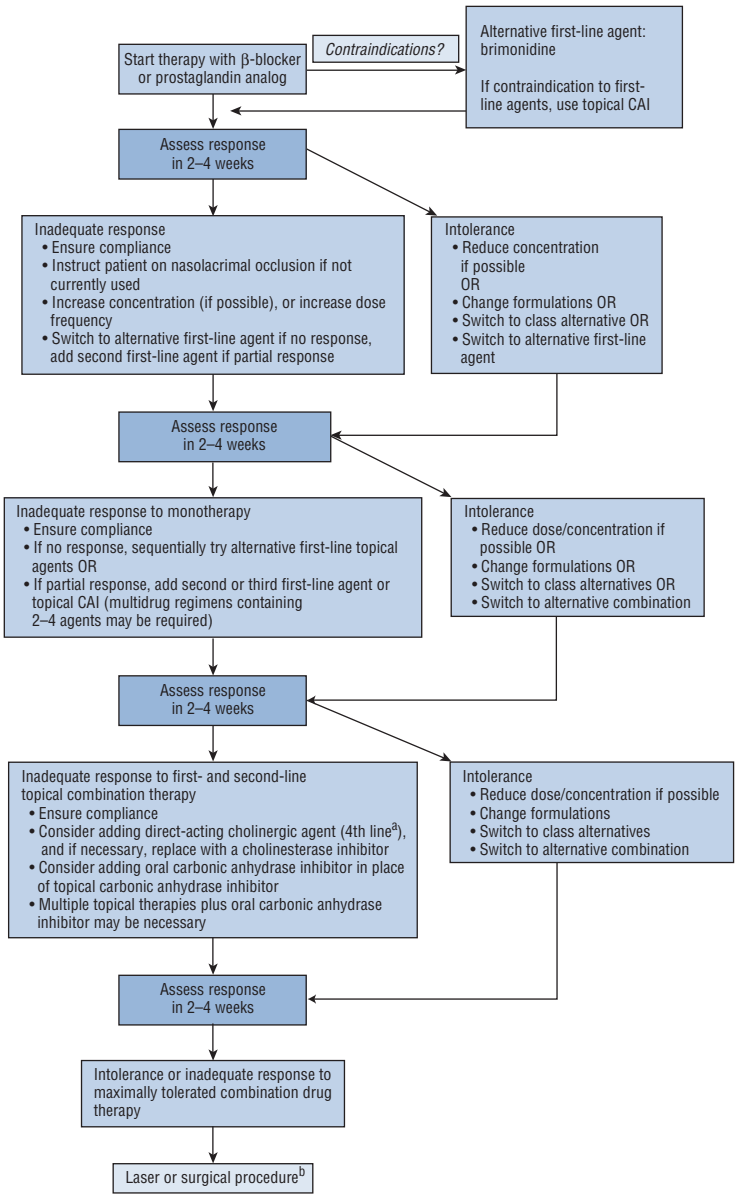


FIGURE 65–1. Algorithm for the pharmacotherapy of open-angle glaucoma. [a]Fourth-line agents not commonly used any longer. [b]Most clinicians believe the laser procedure should be performed earlier (eg, after three-drug maximum or with a poorly adherent patient). (CAI, carbonic anhydrase inhibitor.)

TABLE 65–2 Topical Drugs Used in the Treatment of Open-Angle Glaucoma

Drug	Pharmacologic Properties	Common Brand Names	Dose Form	Strength (%)	Usual Dose[a]	Mechanism of Action
β-Adrenergic Blocking Agents						
Betaxolol	Relative β_1-selective	Generic	Solution	0.5	One drop twice a day	All reduce aqueous production of ciliary body
		Betoptic-S	Suspension	0.25	One drop twice a day	
Carteolol	Nonselective, intrinsic sympathomimetic activity	Generic	Solution	1	One drop twice a day	
Levobunolol	Nonselective	Betagan	Solution	0.25, 0.5	One drop twice a day	
Metipranolol	Nonselective	OptiPranolol	Solution	0.3	One drop twice a day	
Timolol	Nonselective	Timoptic, Betimol, Istalol	Solution	0.25, 0.5	One drop every day—one to two times a day	
		Timoptic-XE	Gelling solution	0.25, 0.5	One drop every day[a]	
Nonspecific Adrenergic Agonists						
Dipivefrin	Epinephrine prodrug	Propine	Solution	0.1	One drop twice a day	Increased aqueous humor outflow
α_2-Adrenergic Agonists						
Apraclonidine	Specific α_2-agonists	Iopidine	Solution	0.5, 1	One drop two to three times a day	Both reduce aqueous humor production; brimonidine known to also increase uveoscleral outflow; only brimonidine has primary indication

(*continued*)

TABLE 65–2 Topical Drugs Used in the Treatment of Open-Angle Glaucoma (*Continued*)

Drug	Pharmacologic Properties	Common Brand Names	Dose Form	Strength (%)	Usual Dose[a]	Mechanism of Action
Brimonidine		Alphagan P	Solution	0.15, 0.1	One drop two to three times a day	
Cholinergic Agonists Direct Acting						
Carbachol	Irreversible	Carboptic, Isopto Carbachol	Solution	1.5, 3	One drop two to three times a day	All increase aqueous humor outflow through trabecular meshwork
Pilocarpine	Irreversible	Isopto Carpine, Pilocar	Solution	0.25, 0.5, 1, 2, 4, 6, 8, 10	One drop two to three times a day	
					One drop four times a day	
		Pilopine HS	Gel	4	Every 24 hours at bedtime	
Cholinesterase Inhibitors						
Echothiophate		Phospholine Iodide	Solution	0.125	Once or twice a day	
Carbonic Anhydrase Inhibitors						
Topical						
Brinzolamide	Carbonic anhydrase type II inhibition	Azopt	Suspension	1	Two to three times a day	All reduce aqueous humor production of ciliary body
Dorzolamide		Trusopt Generic	Solution	2	Two to three times a day	

Systemic						
Acetazolamide		Generic	Tablet	125 mg, 250 mg	125–250 mg two to four times a day	
		Injection	500 mg/vial	250–500 mg		
		Diamox Sequels	Capsule	500 mg	500 mg twice a day	
Methazolamide		Generic	Tablet	25 mg, 50 mg	25–50 mg two to three times a day	
Prostaglandin Analogs						
Latanoprost	Prostanoid agonist	Xalatan	Solution	0.005	One drop every night	Increases aqueous uveoscleral outflow and to a lesser extent trabecular outflow
Bimatoprost	Prostamide agonist	Lumigan	Solution	0.01, 0.03	One drop every night	
Travoprost	Prostanoid agonist	Travatan Z	Solution	0.004	One drop every night	
Tafluprost	Prostanoid agonist	Zioptan	Preservative free solution	0.0015%	One drop every night	
Combinations						
Timolol–dorzolamide		Cosopt Generic	Solution	Timolol 0.5% dorzolamide 2%	One drop twice daily	
Timolol–brimonidine		Combigan	Solution	Timolol 0.5% brimonide 0.2%	One drop twice daily	
Brinzolamide–brimonidine		Simrinza		Brinzolamide 1% brimonidine 0.2%	One drop three times daily	

[a]The use of nasolacrimal occlusion will increase the number of patients successfully treated with longer dosage intervals.

- There is no specific target IOP because the correlation between IOP and optic nerve damage is poor. Typically, a reduction of 25% to 30% is desired.
- The target IOP also depends on disease severity and is generally less than 21 mm Hg (2.8 kPa) for early visual field loss or optic disc changes, with progressively lower targets for greater damage. Targets as low as less than 10 mm Hg (1.3 kPa) are desired for very advanced disease, continued damage at higher IOPs, normal-tension glaucoma, and pretreatment pressures in the low to midteens.
- Monitor medication adherence because it is commonly inadequate and a cause of therapy failure.

See Chapter 75, Glaucoma, authored by Richard G. Fiscella, Timothy S. Lesar, and Deepak P. Edward, for a more detailed discussion of this topic.

CHAPTER 66

Anxiety Disorders

- In anxiety disorders the most prominent features are anxiety and avoidance which are irrational or impair functioning.

PATHOPHYSIOLOGY

- *Noradrenergic model.* This model suggests that the autonomic nervous system of anxious patients is hypersensitive and overreacts to various stimuli. The locus ceruleus may have a role in regulating anxiety, as it activates norepinephrine release and stimulates the sympathetic and parasympathetic nervous systems. Chronic noradrenergic overactivity downregulates α_2-adrenoreceptors in patients with generalized anxiety disorder (GAD) and posttraumatic stress disorder (PTSD). Patients with social anxiety disorder (SAD) appear to have a hyperresponsive adrenocortical response to psychological stress.
- γ-*Aminobutyric acid (GABA) receptor model.* GABA is the major inhibitory neurotransmitter in the central nervous system (CNS). Many antianxiety drugs target the $GABA_A$ receptor. **Benzodiazepines** enhance the inhibitory effects of GABA, which regulates or inhibits serotonin (5-hydroxytroptamine; 5-HT), norepinephrine, and dopamine activity. Anxiety symptoms may be linked to underactivity of GABA systems or downregulated central benzodiazepine receptors. In patients with GAD, benzodiazepine binding in the left temporal lobe is reduced. Abnormal sensitivity to antagonism of the benzodiazepine-binding site and decreased binding occurs in panic disorder. In generalized SAD there may be abnormal central $GABA_B$ receptor function. Abnormalities of GABA inhibition may lead to increased response to stress in PTSD.
- *5-HT model.* GAD symptoms may reflect excessive 5-HT transmission or overactivity of the stimulatory 5-HT pathways. Patients with SAD have greater prolactin response to **buspirone** challenge, indicating an enhanced central serotonergic response. The role of 5-HT in panic disorder is unclear, but it may be involved with development of anticipatory anxiety. 5-HT and dopamine systems may also be involved in the pathophysiology of generalized SAD.
- Patients with PTSD hypersecrete corticotropin-releasing factor, but have subnormal levels of cortisol at the time of trauma and chronically. Dysregulation of the hypothalamic-pituitary-adrenal axis may be a risk factor for eventual development of PTSD.
- Neuroimaging studies support the role of the amygdala, anterior cingulate cortex, and insula in the pathophysiology of anxiety. In GAD, there is an abnormal increase in the brain's fear circuitry and increased activity in the prefrontal cortex. Patients with panic disorder have abnormalities of midbrain structures. Patients with SAD have greater activity in the amygdala and insula. In PTSD, the amygdala plays a role in the persistence of traumatic memory.

CLINICAL PRESENTATION

GENERALIZED ANXIETY DISORDER

- The diagnosis of GAD requires excessive anxiety and worry most days about a number of matters for at least 6 months. Symptoms are at least three of the following:

TABLE 66–1 Clinical Presentation of Generalized Anxiety Disorder

Psychological and Cognitive Symptoms	Physical Symptoms
• Excessive anxiety	• Restlessness
• Worries that are difficult to control	• Fatigue
• Feeling keyed up or on edge	• Muscle tension
• Poor concentration or mind going blank	• Sleep disturbance
	• Irritability

restlessness; easily fatigued; difficulty concentrating; irritability; muscle tension; and sleep disturbance (**Table 66–1**).

- Significant distress or impairment in functioning is present, and the disturbance is not caused by a substance or another medical condition.
- Women are twice as likely as men to have GAD. The illness has a gradual onset at an average age of 21 years. The course is chronic, with multiple exacerbations and remissions.

PANIC DISORDER

- Recurrent unexpected panic attacks. At least one attack has been followed by at least one month of one: 1) persistent worry about additional panic attacks or 2) change in behavior related to the attacks.
- Symptoms of a panic attack are shown in **Table 66–2**. During an attack, there must be at least four physical symptoms in addition to intense fear or discomfort. Symptoms reach a peak within 10 minutes and usually last no more than 20 or 30 minutes.
- Up to 70% of patients eventually develop agoraphobia, which is avoidance of specific situations (eg, being in crowded places or crossing bridges) where they fear a panic attack might occur. Patients may become homebound.

SOCIAL ANXIETY DISORDER

- SAD is a chronic disorder with an intense fear or anxiety about one or more social situations in which there is scrutiny by others which may result in negative evaluation and rejection. Exposure to the feared situation(s) almost always provokes fear or anxiety, and the situations are avoided or endured with intense anxiety. Symptoms of SAD are shown in **Table 66–3**. The fear or avoidance lasts for at least 6 months and causes significant impairment in functioning.

TABLE 66–2 Clinical Presentation of a Panic Attack

Psychological Symptoms	• Feeling of choking
• Depersonalization	• Hot flushes
• Derealization	• Palpitations
• Fear of losing control, going crazy, or dying	• Nausea
	• Paresthesias
Physical Symptoms	• Shortness of breath
• Abdominal distress	• Sweating
• Chest pain or discomfort	• Tachycardia
• Chills	• Trembling or shaking
• Dizziness or light-headedness	

TABLE 66–3 Clinical Presentation of Social Anxiety Disorder

Fears of Being

- Scrutinized by others
- Embarrassed
- Humiliated

Some Feared Situations

- Eating or writing in front of others
- Interacting with authority figures
- Speaking in public
- Talking with strangers
- Use of public toilets

Physical Symptoms

- Blushing
- "Butterflies in the stomach"
- Diarrhea
- Sweating
- Tachycardia
- Trembling

Types

- Generalized: fear and avoidance extend to a wide range of social situations
- Nongeneralized: fear limited to one or two situations

POSTTRAUMATIC STRESS DISORDER

- In adults and children older than 6, there is exposure to actual or threatened death, serious injury, or sexual violence, either directly, or by witnessing the event(s) happening to others, learning about the event(s) happening to someone close, or experiencing repeated or extreme exposure to details of the event(s).
- Duration of intrusive, avoidance, cognitive, and arousal/reactivity symptoms (**Table 66–4**) must be present longer than 1 month and cause significant distress or impairment. PTSD co-occurs with mood, anxiety, and substance use disorders.

TABLE 66–4 Clinical Presentation of Posttraumatic Stress Disorder

Reexperiencing Symptoms

- Recurrent, intrusive distressing memories of the trauma
- Recurrent, disturbing dreams of the event
- Feeling that the traumatic event is recurring (eg dissociative flashbacks)
- Physiologic reaction to reminders of the trauma

Avoidance Symptoms

- Avoidance of conversations about the trauma
- Avoidance of thoughts or feelings about the trauma
- Avoidance of activities that are reminders of the event
- Avoidance of people or places that arouse recollections of the trauma
- Inability to recall an important aspect of the trauma
- Anhedonia
- Estrangement from others
- Restricted affect
- Sense of a foreshortened future (e.g., does not expect to have a career, marriage)

Hyperarousal Symptoms

- Decreased concentration
- Easily startled
- Hypervigilance
- Insomnia
- Irritability or anger outbursts

Subtypes

- Acute: duration of symptoms is less than 3 months
- Chronic: symptoms last for longer than 3 months
- With delayed onset: onset of symptoms is at least 6 months posttrauma

TABLE 66–5 Common Medical Illnesses Associated with Anxiety Symptoms
Cardiovascular
Angina, arrhythmias, cardiomyopathy, congestive heart failure, hypertension, ischemic heart disease, myocardial infarction
Endocrine and metabolic
Cushing's disease, diabetes, hyperparathyroidism, hyperthyroidism, hypothyroidism, hypoglycemia, hyponatremia, hyperkalemia, pheochromocytoma, vitamin B_{12} or folate deficiencies
Neurologic
Migraine, seizures, stroke, neoplasms, poor pain control
Respiratory system
Asthma, chronic obstructive pulmonary disease, pulmonary embolism, pneumonia
Others
Anemias, cancer, systemic lupus erythematosus, vestibular dysfunction

DIAGNOSIS

- Evaluation of the anxious patient requires a physical and mental status examination; complete psychiatric diagnostic exam; appropriate laboratory tests; and a medical, psychiatric, and drug history.
- Anxiety symptoms may be associated with medical illnesses (Table 66–5) or drug therapy (Table 66–6), and they may be present in several major psychiatric illnesses (eg, mood disorders, schizophrenia, organic mental syndromes, and substance withdrawal).

TABLE 66–6 Drugs Associated with Anxiety Symptoms
Anticonvulsants: carbamazepine, phenytoin
Antidepressants: selective serotonin reuptake inhibitors, bupropion, serotonin–norepinephrine reuptake inhibitors
Antihypertensives: clonidine, felodipine
Antibiotics: quinolones, isoniazid
Bronchodilators: albuterol, theophylline
Corticosteroids: prednisone
Dopamine agonists: amantadine, levodopa
Herbals: ma huang, ginseng, ephedra
Illicit substances: ecstasy, marijuana
Nonsteroidal antiinflammatory drugs: ibuprofen, indomethacin
Stimulants: amphetamines, methylphenidate, nicotine, caffeine, cocaine
Sympathomimetics: pseudoephedrine, phenylephrine
Thyroid hormones: levothyroxine
Toxicity: anticholinergics, antihistamines, digoxin

TREATMENT

GENERALIZED ANXIETY DISORDER

- Goals of Treatment: The goals are to reduce severity, duration, and frequency of symptoms and improve functioning. The long-term goal is minimal or no anxiety symptoms, no functional impairment, prevention of recurrence, and improved quality of life.
- Nonpharmacologic modalities include psychotherapy, short-term counseling, stress management, cognitive therapy, meditation, supportive therapy, and exercise. Ideally, patients with GAD should have psychological therapy, alone or in combination with antianxiety drugs. Cognitive behavioral therapy (CBT), though not widely available, is the most effective psychological therapy. Patients should avoid caffeine, stimulants, excessive alcohol, and diet pills.
- Drug choices for GAD, panic disorder, and SAD are shown in **Table 66–7**, and nonbenzodiazepine antianxiety agents for GAD and their dosing are shown in **Table 66–8**.
- **Hydroxyzine**, often used in primary care, is considered a second-line agent.
- **Pregabalin** produced anxiolytic effects similar to **lorazepam, alprazolam,** and **venlafaxine** in acute trials. Sedation and dizziness were the most common adverse effects, and the dose should be tapered over 1 week to discontinue. Quetiapine extended release, 150 mg/day was superior to placebo and as effective as paroxetine 20 mg/day and escitalopram 10 mg/day, but with earlier onset of action.
- The Food and Drug Administration (FDA) has established a link between antidepressant use and suicidality (suicidal thinking and behaviors) in children, adolescents, and young adults up to 24 years old. All antidepressants carry a black box warning advising caution in using antidepressants in this population, and the FDA also recommends specific monitoring parameters (consult the FDA-approved labeling or the FDA website).

TABLE 66–7 Drug Choices for Anxiety Disorders

Anxiety Disorder	First-Line Drugs	Second-Line Drugs	Alternatives
Generalized anxiety disorder	Duloxetine Escitalopram Paroxetine Sertraline Venlafaxine XR	Benzodiazepines Buspirone Imipramine Pregabalin	Hydroxyzine Quetiapine
Panic disorder	SSRIs Venlafaxine XR	Alprazolam Citalopram Clomipramine Clonazepam Imipramine	Phenelzine
Social anxiety disorder	Escitalopram Fluvoxamine CR Paroxetine Sertraline Venlafaxine XR	Clonazepam Citalopram	Gabapentin Phenelzine Pregabalin

CR, controlled-release; SSRI, selective serotonin reuptake inhibitor; XR, extended-release.

TABLE 66–8 Nonbenzodiazepine Antianxiety Agents for Generalized Anxiety Disorder

Drug	Brand Name	Initial Dose	Usual Range (mg/day)[a]	Comments
Antidepressants				
Duloxetine	Cymbalta	30 or 60 mg/day	60–120	FDA-approved
Escitalopram	Lexapro	10 mg/day	10–20	FDA-approved, available generically
Imipramine	Tofranil	50 mg/day	75–200	Available generically
Paroxetine	Paxil Pexeva	20 mg/day	20–50	FDA-approved, available generically, avoid in pregnancy
Sertraline	Zoloft	50 mg/day	50–200	Available generically
Venlafaxine XR	Effexor XR	37.5 or 75 mg/day	75–225[b]	FDA-approved, available generically
Azapirone				
Buspirone	BuSpar	7.5 mg twice daily	15–60[b]	FDA-approved, available generically
Diphenylmethane				
Hydroxyzine	Vistaril	25 or 50 mg four times daily	200–400	FDA-approved, available generically, approved in children for anxiety and tension in divided daily doses of 50–100 mg
Anticonvulsant				
Pregabalin	Lyrica	50 mg three times daily	150–600	Dosage adjustment required in renal impairment
Atypical antipsychotic				
Quetiapine XR	Seroquel XR	50 mg at bedtime	150–300	

XR, extended-release.

[a]Elderly patients are usually treated with approximately one half of the dose listed.
[b]No dosage adjustment is required in elderly patients.

Antidepressants

- Antidepressants are efficacious for acute and long-term management of GAD (see Table 66–7). They are the treatment of choice for long-term management of chronic anxiety, especially in the presence of depressive symptoms. Antianxiety response requires 2 to 4 weeks. See Chap. 68 for additional information on antidepressants.
- **Selective serotonin reuptake inhibitors (SSRIs), extended-release venlafaxine,** and **duloxetine** are effective in acute therapy (response rates of 60%–68%).
- Common side effects and monitoring parameters for medications used for anxiety disorders are shown in Table 66–9. **Tricyclic antidepressants** (**TCAs**) commonly cause sedation, orthostatic hypotension, anticholinergic effects, and weight gain, and they are very toxic on overdose.

Benzodiazepine Therapy

- The benzodiazepines are the most effective and frequently prescribed drugs for the treatment of acute anxiety (Table 66–10). About 65% to 75% of patients with GAD

TABLE 66–9 Monitoring of Adverse Effects Associated with Medications Used in the Treatment of Anxiety Disorders

Medication Class/Drug	Adverse Drug Reaction	Monitoring Parameter	Comments
Selective Serotonin Reuptake Inhibitors			
	Jitteriness syndrome	Patient interview	
	Suicidality	Patient interview	Monitor weekly in first few weeks in patients with comorbid depression and patients under age 25
	Nausea, diarrhea	Patient interview	Typically transient
	Headache	Patient interview	Typically transient
	Weight gain	Body weight, BMI, waist circumference	Paroxetine may be more likely to cause weight gain
	Sexual dysfunction	Patient interview	Significant reason for nonadherence
	Hyponatremia	Basic metabolic panel	Monitor at baseline and periodically thereafter. More frequent monitoring required in high-risk groups, especially the elderly (>65 years)
	Thrombocytopenia	Complete blood count	Reported with citalopram
	Teratogenicity	Pregnancy test at baseline	Avoid paroxetine in pregnancy; Pregnancy Category D
	QT prolongation	ECG	Before starting citalopram, consider ECG and measurement of QT interval in patients with cardiac disease
	Discontinuation syndrome	Patient interview	Avoid abrupt discontinuation in all but fluoxetine

(*continued*)

TABLE 66–9 Monitoring of Adverse Effects Associated with Medications Used in the Treatment of Anxiety Disorders (*Continued*)

Medication Class/Drug	Adverse Drug Reaction	Monitoring Parameter	Comments
Serotonin–Norepinephrine Reuptake Inhibitors			
	Jitteriness syndrome	Patient interview	
	Suicidality	Patient interview	Monitor weekly in first few weeks in patients with comorbid depression and patients under age 25
	Nausea, diarrhea	Patient interview	Typically transient
	Headache	Patient interview	Typically transient
	Elevated blood pressure	Blood pressure	Monitor blood pressure on initiation and regularly during treatment
	Sexual dysfunction	Patient interview	Significant reason for nonadherence
	Discontinuation syndrome	Patient interview	Avoid abrupt discontinuation
Tricyclic Antidepressants			
	Jitteriness syndrome	Patient interview	
	Suicidality	Patient interview	Monitor weekly in first few weeks in patients with comorbid depression and patients under age 25
	Anticholinergic effects	Patient interview	Contraindicated with narrow-angle glaucoma, prostatic hypertrophy, and urinary retention
	Weight gain	Body weight, BMI, waist circumference	
	Sexual dysfunction	Patient interview	Significant reason for nonadherence
	Sedation	Patient interview	Administer dosage at bedtime when feasible
	Arrhythmia	ECG	At baseline and periodically in children and patients >40 years of age
	Orthostatic hypotension	Blood pressure with position changes	
	Cholinergic rebound	Patient interview	Avoid abrupt discontinuation; taper doses

Benzodiazepines			
	Drowsiness, fatigue	Patient interview	Avoid operating large machinery; tolerance to sedation develops after repeated dosing
	Anterograde amnesia and memory impairment	Patient interview	Risk of anterograde amnesia is worsened with concomitant intake of alcohol
	Dependence	Patient interview; Prescription Monitoring Program	Monitor for early refills or escalation of dosage
	Withdrawal symptoms	Physical examination; patient interview	Taper doses on discontinuation
	Respiratory depression	Respiratory rate	Avoid administering with other CNS depressants (ie, opioids, alcohol)
	Psychomotor impairment	Physical examination	Increased risk of falls
	Paradoxical disinhibition	Physical examination; family report	Increase in anxiety, irritability, or agitation may be seen in the elderly or children
Other Drugs			
Buspirone	Nausea, abdominal pain	Patient interview	Typically transient
	Drowsiness, dizziness	Patient interview	Typically transient
Phenelzine	Jitteriness syndrome	Patient interview	
	Suicidality	Patient interview	Monitor weekly in first few weeks in patients with comorbid depression and patients under age 25
	Hypertensive crisis	Blood pressure	Tyramine-free diet and avoidance of drug interactions required
	Orthostatic hypotension	Blood pressure with position changes	

(*continued*)

TABLE 66–9 Monitoring of Adverse Effects Associated with Medications Used in the Treatment of Anxiety Disorders (*Continued*)

Medication Class/Drug	Adverse Drug Reaction	Monitoring Parameter	Comments
Pregabalin	Dizziness, somnolence	Patient interview	
	Peripheral edema	Physical examination	
	Thrombocytopenia	Complete blood count	
	Weight gain	Body weight	
Quetiapine	Sedation	Patient interview	
	Metabolic syndrome	Body weight, BMI, waist circumference, fasting lipids and glucose	Fasting labs at baseline and then periodically
	Akathisia	Patient interview	
	Tardive dyskinesia	Abnormal Involuntary Movement Scale	
	Orthostatic hypotension	Blood pressure with position changes	

ECG, electrocardiogram; BMI, body mass index.

TABLE 66–10 Benzodiazepine Antianxiety Agents

Drug	Brand Name	Approved Dosage Range (mg/day)	Maximum Dosage for Geriatric Patients (mg/day)	Approximate Equivalent Dose (mg)	Comments
Alprazolam[a]	Niravam,[b] Xanax	0.75–4	2	0.5	Associated with interdose rebound anxiety
	Xanax XR	1–10[c]			
Chlordiazepoxide[a]	Librium	25–400	40	10	
Clonazepam[a]	Klonopin	1–4[c]	3	0.25–0.5	
	Klonopin Wafer[b]				
Clorazepate[a]	Tranxene	7.5–60	30	7.5	
Diazepam[a]	Valium	2–40	20	5	
Lorazepam[a]	Ativan	0.5–10	3	1	Preferred in elderly
Oxazepam[a]	Serax	30–120	60	30	Preferred in elderly

XR, extended-release.

[a]Available generically.
[b]Orally disintegrating formulation.
[c]Panic disorder dose.

have a marked to moderate response, and most of the improvement occurs in the first 2 weeks of therapy. They are more effective for somatic and autonomic symptoms of GAD, whereas antidepressants are more effective for the psychic symptoms (eg, apprehension and worry).

- Theoretically, benzodiazepines ameliorate anxiety through potentiation of GABA activity, but other neurotransmitters may also be involved.
- The dose must be individualized. The elderly are more sensitive to benzodiazepines and may experience falls when taking them.

PHARMACOKINETICS

- Benzodiazepine pharmacokinetic properties are shown in **Table 66–11**. **Diazepam** and **clorazepate** have high lipophilicity and are rapidly absorbed and distributed into the CNS. They have rapid antianxiety effects, but a shorter duration of effect after a single dose than would be predicted based on half-life, as they are rapidly distributed to the periphery.
- **Lorazepam** and **oxazepam** are less lipophilic, have a slower onset, but a longer duration of action. They are not recommended for immediate relief of anxiety.
- **Avoid intramuscular (IM) diazepam** and **chlordiazepoxide** because of variability in rate and extent of absorption. **IM lorazepam** provides rapid and complete absorption.
- **Clorazepate**, a prodrug, is converted to **desmethyldiazepam** in the stomach through a pH-dependent process that may be impaired by concurrent antacid use. Several other benzodiazepines are also converted to desmethyldiazepam, which has a long half-life and can accumulate, especially in the elderly and others with impaired oxidation.
- Intermediate- or short-acting benzodiazepines are preferred for chronic use in the elderly and those with liver disorders because of minimal accumulation and achievement of steady state within 1 to 3 days.

TABLE 66–11 Pharmacokinetics of Benzodiazepine Antianxiety Agents

Drug	Time to Peak Plasma Level (Hours)	Elimination Half-Life, Parent (Hours)	Metabolic Pathway	Clinically Significant Metabolites	Protein Binding (%)
Alprazolam	1–2	12–15	Oxidation	—	80
Chlordiazepoxide	1–4	5–30	*N*-Dealkylation	Desmethylchlordiazepoxide	96
			Oxidation	Demoxepam	
				DMDZ[a]	
Clonazepam	1–4	30–40	Nitroreduction	—	85
Clorazepate	1–2	Prodrug	Oxidation	DMDZ	97
Diazepam	0.5–2	20–80	Oxidation	DMDZ	98
				Oxazepam	
Lorazepam	2–4	10–20	Conjugation	—	85
Oxazepam	2–4	5–20	Conjugation	—	97

[a]Desmethyldiazepam (DMDZ) half-life 50–100 hours.

ADVERSE EVENTS

- The most common side effect of benzodiazepines is CNS depression. Tolerance usually develops to this effect. Other side effects are disorientation, psychomotor impairment, confusion, aggression, excitement, and anterograde amnesia (see **Table 66–9**).

ABUSE, DEPENDENCE, WITHDRAWAL, AND TOLERANCE

- Those with a history of drug abuse should not receive benzodiazepines. Those with GAD and panic disorder are at high risk for dependence because of the chronicity of the illnesses.
- Benzodiazepine dependence is defined by appearance of a withdrawal syndrome (ie, anxiety, insomnia, agitation, muscle tension, irritability, nausea, diaphoresis, nightmares, depression, hyperreflexia, tinnitus, delusions, hallucinations, and seizures) upon abrupt discontinuation.

BENZODIAZEPINE DISCONTINUATION

- After benzodiazepines are abruptly discontinued, three events can occur: 1) Rebound symptoms are an immediate but transient return of original symptoms with an increased intensity compared with baseline; 2) Recurrence or relapse is the return of original symptoms at the same intensity as before treatment; or 3) Withdrawal is the emergence of new symptoms and a worsening of preexisting symptoms.
- The onset of withdrawal symptoms is within 24 to 48 hours after discontinuation of short-elimination half-life benzodiazepines and 3 to 8 days after discontinuation of long-elimination half-life drugs.
- Discontinuation strategies include:
  - ✓ A 25% per week reduction in dosage until 50% of the dose is reached, then reduce by one eighth every 4 to 7 days. If therapy duration exceeds 8 weeks, a taper over 2 to 3 weeks is recommended, but if duration of treatment is 6 months, a taper over 4 to 8 weeks should ensue. Longer durations of treatment may require a 2- to 4-month taper.
  - ✓ Adjunctive use of **carbamazepine** or **pregabalin** can help to reduce withdrawal symptoms during the benzodiazepine taper.

DRUG INTERACTIONS

- Combining **benzodiazepines** with **alcohol** or other **CNS depressants** may be fatal.
- Addition of nefazodone, ritonavir, or ketoconazole can increase the blood levels of **alprazolam** and **diazepam.**

DOSING AND ADMINISTRATION

- Start with low doses, and adjust weekly (see **Table 66–10**).
- Treatment of acute anxiety generally should not exceed 4 weeks. Manage persistent symptoms with antidepressants.
- Long half-life benzodiazepines may be dosed once daily at bedtime, providing nighttime hypnotic and next day anxiolytic effects.
- Use low doses of short-elimination half-life agents in the elderly.

Buspirone Therapy

- **Buspirone** is a 5-HT_{1A} partial agonist that lacks anticonvulsant, muscle relaxant, sedative-hypnotic, motor impairment, and dependence-producing properties.
- It is a second-line agent for GAD because of inconsistent reports of long-term efficacy, delayed onset of effect, and lack of efficacy for potentially comorbid depressive and anxiety disorders. It is an option for patients who fail other anxiolytic therapies or patients with a history of alcohol or substance abuse. It does not provide rapid or "as needed" antianxiety effects.
- It has a mean $t_{1/2}$ of 2.5 hours, and it is dosed two to three times daily (see **Table 66–8**).

DRUG INTERACTIONS

- **Buspirone** may elevate blood pressure in patients taking a monoamine oxidase inhibitor (MAOI).

- **Verapamil, itraconazole,** and **fluvoxamine** can increase buspirone levels, and **rifampin** reduces buspirone blood levels 10-fold.

DOSING AND ADMINISTRATION

- Buspirone can be titrated in increments of 5 mg/day every 2 or 3 days as needed.
- The onset of anxiolytic effects requires 2 weeks or more; maximum benefit may require 4 to 6 weeks.
- It may be less effective in patients who have previously taken benzodiazepines.

Evaluation of Therapeutic Outcomes

- Initially, monitor anxious patients every two weeks for reduction in anxiety symptoms, improvement in functioning, and side effects. The Hamilton Rating Scale for Anxiety or the Sheehan Disability Scale can help measure drug response.

PANIC DISORDER

- Goals of Treatment: The goals are complete resolution of panic attacks, marked reduction in anticipatory anxiety, elimination of phobic avoidance, and resumption of normal activities.

General Approach

- SSRIs are first-line agents for panic disorder (Table 66–12). An algorithm for drug therapy of panic disorder is shown in Fig. 66–1.
- Most patients without agoraphobia improve with pharmacotherapy alone, but if agoraphobia is present, CBT typically is initiated concurrently. Patients treated with CBT are less likely to relapse than those treated with **imipramine** alone. For patients who cannot or will not take medications, CBT alone is indicated.
- Educate patient to avoid **caffeine**, nicotine, alcohol, drugs of abuse, and stimulants.
- If pharmacotherapy is used, antidepressants, especially the SSRIs, are preferred in elderly patients and youth. The benzodiazepines are second line in these patients because of potential problems with disinhibition.
- Usually patients are treated for 12 to 24 months before discontinuation is attempted over 4 to 6 months. Many patients require long-term therapy. Single weekly doses of **fluoxetine** have been used for maintenance.

Antidepressants

- Stimulatory side effects (eg, anxiety, insomnia, jitteriness) can occur in **TCA**- and **SSRI**-treated patients. This may hinder compliance and dose escalation. Low initial doses and gradual dose titration may eliminate these effects (see **Table 66–9**).
- **Imipramine** blocks panic attacks within 4 weeks in 75% of patients, but reducing anticipatory anxiety and phobic avoidance requires 8 to 12 weeks.
- 25% of panic disorder patients discontinue **TCAs** because of side effects.
- **SSRIs** eliminate panic attacks in 60% to 80% of patients within about 4 weeks, but some patients require 8 to 12 weeks.
- Approximately 54% to 60% of patients became panic-free on extended-release venlafaxine, 75 mg or 150 mg.

Benzodiazepines

- **Benzodiazepines** are second-line agents for panic disorder except when rapid response is essential. Avoid benzodiazepine monotherapy in patients with panic disorder who are depressed or have a history of depression. Avoid benzodiazepines in patients with a history of **alcohol** or drug abuse. They are often used concomitantly with antidepressants in the first 4 to 6 weeks to achieve a more rapid antipanic response.
- Relapse rates of 50% or higher are common despite slow drug tapering.
- **Alprazolam** and **clonazepam** are the most frequently used benzodiazepines. Therapeutic response typically occurs within 1 to 2 weeks. With alprazolam, there may be breakthrough symptoms between doses. The use of extended-release alprazolam or clonazepam avoids this problem.

TABLE 66–12 Drugs Used in the Treatment of Panic Disorder

Class/Generic Name	Brand Name	Starting Dose	Antipanic Dosage Range (mg)	Comments
Selective Serotonin Reuptake Inhibitors				
Citalopram	Celexa	10 mg/day	20–40	Dosage used in clinical trials; maximum dose limited by QT prolongation; available generically
Escitalopram	Lexapro	5 mg/day	10–20	Dosage used in clinical trials; available generically
Fluoxetine	Prozac	5 mg/day	10–30	Available generically
Fluvoxamine	Luvox	25 mg/day	100–300	Available generically
Paroxetine	Paxil	10 mg/day	20–60	FDA-approved; available generically
	Pexeva			
	Paxil CR	12.5 mg/day	25–75	
Sertraline	Zoloft	25 mg/day	50–200	FDA-approved; available generically
Serotonin–Norepinephrine Reuptake Inhibitor				
Venlafaxine XR	Effexor XR	37.5 mg/day	75–225	FDA-approved; available generically
Benzodiazepines				
Alprazolam	Xanax	0.25 mg three times a day	4–10	FDA-approved; available generically
	Xanax XR	0.5–1 mg/day	1–10	
Clonazepam	Klonopin	0.25 mg once or twice per day	1–4	FDA-approved; available generically
Diazepam	Valium	2–5 mg three times a day	5–20	Dosage used in clinical trials; available generically
Lorazepam	Ativan	0.5–1 mg three times a day	2–8	Dosage used in clinical trials; available generically
Tricyclic Antidepressant				
Imipramine	Tofranil	10 mg/day	75–250	Dosage used in clinical trials; available generically
Monoamine Oxidase Inhibitor				
Phenelzine	Nardil	15 mg/day	45–90	Dosage used in clinical trials

DOSING AND ADMINISTRATION

- The starting dose of **clonazepam** is 0.25 mg twice daily, with a dose increase to 1 mg by the third day. Increases by 0.25 to 0.5 mg every 3 days to 4 mg/day can be made if needed.
- The starting dose of **alprazolam** is 0.25 to 0.5 mg three times daily (or 0.5 mg once daily of extended-release alprazolam), slowly increasing over several weeks as needed. Most patients require 3 to 6 mg/day.

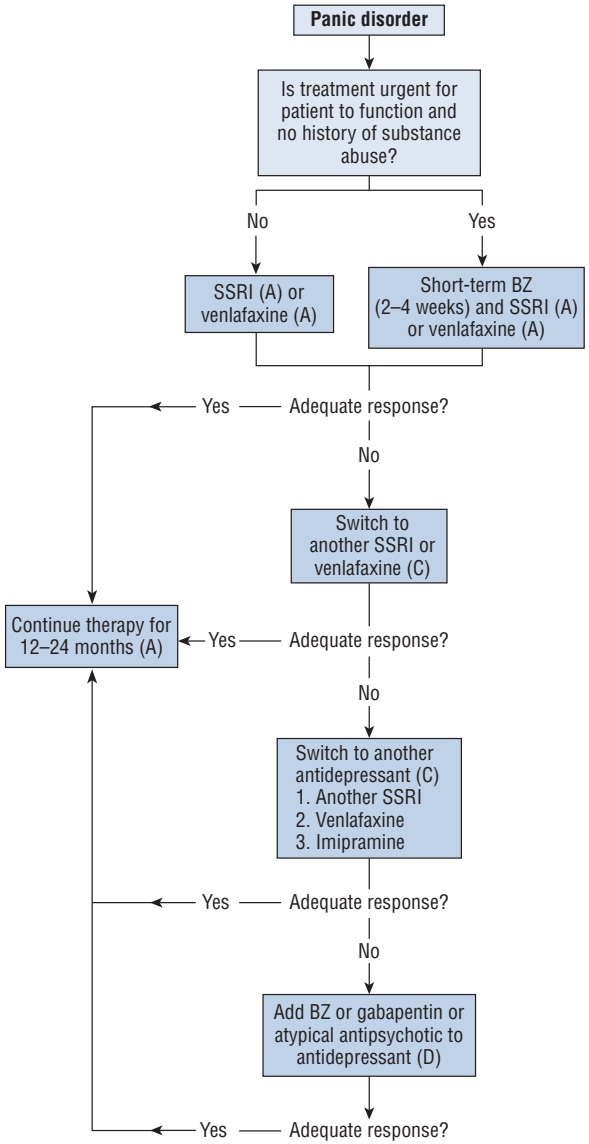


FIGURE 66–1. Algorithm for the pharmacotherapy of panic disorder. Strength of recommendations: A, directly based on category I evidence (i.e., meta-analysis of randomized controlled trials [RCT] or at least one RCT); B, directly based on category II evidence (i.e., at least one controlled study without randomization or one other type of quasi-experimental study); C, directly based on category III evidence (i.e., nonexperimental descriptive studies); D, directly based on category IV evidence (i.e., expert committee reports or opinions and/or clinical experience of respected authorities). (BZ, benzodiazepine; SSRI, selective serotonin reuptake inhibitor.)

EVALUATION OF THERAPEUTIC OUTCOMES

- Evaluate patients with panic disorder every 1 to 2 weeks during the first few weeks to fine-tune dosing and to monitor side effects. Once stabilized, they can be seen every 2 months. The Panic Disorder Severity Scale (with a remission goal of three or less with no or mild agoraphobic avoidance, anxiety, disability, or depressive symptoms) and the Sheehan Disability Scale (with a goal of less than or equal to one on each item) can be used to measure disability. During drug discontinuation, the frequency of appointments should be increased.

SOCIAL ANXIETY DISORDER

- Goals of Treatment: The goals are to reduce the physiologic symptoms and phobic avoidance, increase participation in desired social activities, and improve quality of life.
- Patients with SAD often respond more slowly and less completely than patients with other anxiety disorders.
- After improvement, at least 1 year of maintenance treatment is recommended. Long-term treatment may be needed for patients with unresolved symptoms, comorbidity, an early onset of disease, or a prior history of relapse.
- CBT (exposure therapy, cognitive restructuring, relaxation training, and social skills training) and pharmacotherapy are considered equally effective in SAD, but CBT can lead to a greater likelihood of maintaining response after treatment termination. Even after response, most patients continue to experience more than minimal residual symptoms.
- CBT and social skills training are effective in children with SAD. SSRIs and serotonin norepinephrine reuptake inhibitors are effective in children 6 to 17 years of age. Individuals up to 24 years of age should be closely monitored for increased risk of suicide.
- An algorithm for treatment of SAD is shown in **Fig. 66–2**
- **Paroxetine, sertraline, extended-release fluvoxamine,** and **extended-release venlafaxine** are first-line agents (**Table 66–13**).

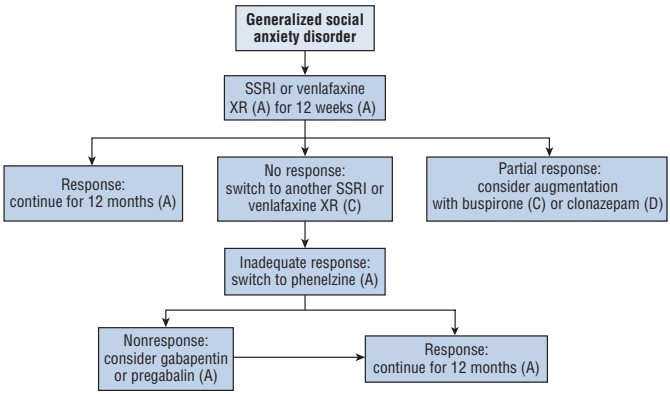


FIGURE 66–2. Algorithm for the pharmacotherapy of generalized social anxiety disorder. Strength of recommendations: A, directly based on category I evidence (i.e., meta-analysis of randomized controlled trials [RCT] or at least one RCT); B, directly based on category II evidence (i.e., at least one controlled study without randomization or one other type of quasi-experimental study); C, directly based on category III evidence (i.e., nonexperimental descriptive studies); D, directly based on category IV evidence (i.e., expert committee reports or opinions and/or clinical experience of respected authorities). (SSRI, selective serotonin reuptake inhibitor.)

TABLE 66–13 Drugs Used in the Treatment of Generalized Social Anxiety Disorder

Drug	Brand Name	Initial Dose	Usual Range (mg/day)	Comments
Selective Serotonin Reuptake Inhibitors				
Citalopram	Celexa	20 mg/day	20–40	Dosage used in clinical trials; maximum dose of 40 mg limited by QT prolongation; available generically
Escitalopram	Lexapro	5 mg/day	10–20	Dosage used in clinical trials; available generically
Fluvoxamine CR	Luvox CR	100 mg	100–300	FDA-approved; available generically
Paroxetine	Paxil	10 mg/day	10–60	FDA-approved; available generically
Paroxetine CR	Paxil CR	12.5 mg/day	12.5–37.5	FDA-approved; available generically
Sertraline	Zoloft	25–50 mg/day	50–200	FDA-approved; available generically
Serotonin–Norepinephrine Reuptake Inhibitor				
Venlafaxine XR	Effexor XR	75 mg/day	75–225	FDA-approved; available generically
Benzodiazepine				
Clonazepam	Klonopin	0.25 mg/day	1–4	Dosage used in clinical trials; used as augmenting agent; available generically
Monoamine Oxidase Inhibitor				
Phenelzine	Nardil	15 mg at bedtime	60–90	Dosage used in clinical trials
Alternative Agents				
Buspirone	BuSpar	10 mg twice per day	45–60	Dosage used in clinical trials; used as augmenting agent; available generically
Gabapentin	Neurontin	100 mg three times a day	900–3,600	Dosage used in clinical trials; dosage adjustment required in renal impairment
Pregabalin	Lyrica	100 mg three times a day	600	Dosage used in clinical trials
Quetiapine	Seroquel	25 mg at bedtime	25–400	Dosage used in clinical trials

XR, extended-release; CR, controlled-release.

- With **SSRI** treatment, the onset of effect is delayed 4 to 8 weeks, and maximum benefit is often not observed until 12 weeks or longer.
- The TCAs are not effective for SAD. Mixed results have been reported for **fluoxetine**.
- **SSRIs** are initiated at doses similar to those used for depression. If there is comorbid panic disorder, the **SSRI** dose should be started at one fourth to one half the usual starting doses of antidepressants. The dose should be tapered slowly (monthly) during discontinuation to decrease the risk of relapse.
- Efficacy with **extended-release venlafaxine is well established**.
- Reserve **benzodiazepines** for patients at low risk of substance abuse, those who require rapid relief, or those who have not responded to other therapies. **Clonazepam** is the most extensively studied benzodiazepine for treatment of generalized SAD. It should be tapered not faster than 0.25 mg every 2 weeks.
- **Gabapentin** was effective for SAD, with an onset of effect of 2 to 4 weeks. **Pregabalin** was superior to placebo at a dose of 600 mg/day.
- *β*-**Blockers** blunt the peripheral autonomic symptoms of arousal (eg, rapid heart rate, sweating, blushing, and tremor) and are often used to decrease anxiety in performance-related situations. For specific SAD, 10 to 80 mg of **propranolol** or 25 to 100 mg of **atenolol** can be taken 1 hour before the performance. A test dose should be taken at home before the performance to be sure adverse effects will not be problematic.
- **Phenelzine**, **a MAOI**, is effective but is reserved for treatment-resistant patients because of dietary restrictions, potential drug interactions, and adverse effects.
- Monitor patients with SAD for symptom response, adverse effects, overall functionality, and quality of life. Evaluate patients weekly during dosage titration and monthly once stabilized. Ask patients to keep a diary to record symptoms and their severity and side effects. The clinician-related Liebowitz Social Anxiety Scale and the patient-rated Social Phobia Inventory can be used to monitor severity of symptoms and symptom change.

POSTTRAUMATIC STRESS DISORDER

- Goals of Treatment: The goals are to decrease core symptoms, disability, and comorbidity and improve quality of life.
- Immediately after the trauma, patients should receive treatment individualized to their presenting symptoms (eg, **nonbenzodiazepine hypnotic** or short courses of CBT). Brief courses of CBT in close proximity to the trauma can help prevent PTSD.
- If symptoms persist for 3 to 4 weeks, and there is social or occupational impairment, patients should receive pharmacotherapy or psychotherapy, or both.
- Psychotherapies for PTSD include stress management, eye movement desensitization and reprocessing (EMDP), and psychoeducation. Trauma-focused CBT (TFCBT) and EMDP are more effective than stress management or group therapy to reduce PTSD symptoms.
- **Figure 66–3** shows an algorithm for the pharmacotherapy of PTSD.
- The **SSRIs** and **venlafaxine** are first-line pharmacotherapy for PTSD (**Table 66–14**).
- **Sertraline** and **paroxetine** are approved for acute treatment of PTSD, and sertraline is approved for long-term management.
- Antiadrenergics and atypical antipsychotics can be used as augmenting agents.
- The **SSRIs** are believed to be more effective for numbing symptoms than other drugs. About 60% of sertraline-treated patients showed improvement in arousal and avoidance/numbing symptoms.
- **Mirtazapine** was effective in doses up to 45 mg/day and is a second-line agent. **Amitriptyline and imipramine,** are also second-line drugs. **Phenelzine** is a third-line drug.
- If there is no improvement in the acute stress response 3 to 4 weeks following trauma, SSRIs should be started in a low dose with slow titration upward toward antidepressant doses. Eight to 12 weeks is an adequate duration of treatment to determine response.

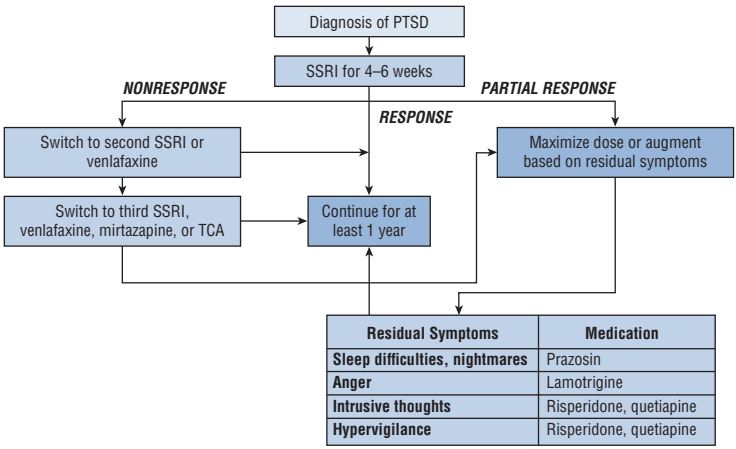


FIGURE 66–3. Algorithm for the pharmacotherapy of posttraumatic stress disorder.

TABLE 66–14 Dosing of Antidepressants in the Treatment of Posttraumatic Stress Disorder

Drug	Brand Name	Initial Dose	Usual Range (mg/day)	Comments
Selective Serotonin Reuptake Inhibitors				
Fluoxetine[a]	Prozac®	10 mg/day	10–40[b]	
Paroxetine[a]	Paxil®, Pexeva®	10–20 mg/day	20–40[b]	Maximum dose is 50 mg/day[c]
Sertraline[a]	Zoloft®	25 mg/day	50–100	Maximum dose is 200 mg/day[c]
Other Agents				
Amitriptyline[a]	Elavil®	25 or 50 mg/day	75–200[b]	
Imipramine[a]	Tofranil®	25 or 50 mg/day	75–200[b]	
Mirtazapine[a]	Remeron®	15 mg/night	30–60[b]	
Phenelzine[a]	Nardil®	15 or 30 mg every night	45–90[b]	
Venlafaxine extended-release[a]	Effexor XR®	37.5 mg/day	75–225[b]	

[a]Available generically.
[b]Dosage used in clinical trials but not FDA-approved.
[c]Dosage is FDA-approved.

- Responders to drug therapy should continue treatment for at least 12 months. When discontinued, drug therapy should be tapered slowly over 1 month or more to reduce the likelihood of relapse.
- **Prazosin**, in daily doses of 1 to 4 mg, can be useful in some patients with PTSD.
- **Risperidone, quetiapine**, α_1-adrenergic antagonists, antidepressants, mood stabilizers, and anticonvulsants may be used as augmenting agents in partial responders.
- See patients frequently for the first 3 months, then monthly for 3 months. In months 6 to 12, patients can be seen every 2 months. Monitor for symptom response, suicidal ideation, disability, side effects, and treatment adherence.

See Chapter 53, Anxiety Disorders I, authored by Sarah T. Melton and Cynthia K. Kirkwood, and Chapter 54, Anxiety Disorders II, authored by Cynthia K. Kirkwood, Sarah T. Melton, and Barbara G. Wells, for a more detailed discussion of this topic.

Bipolar Disorder

CHAPTER 67

- *Bipolar I disorder*: at least one manic episode, which may have been preceded by and may be followed by hypomanic or major depressive episodes.
- *Bipolar II disorder*: at least one hypomanic episode and a current or past major depressive episode.

PATHOPHYSIOLOGY

- Medical conditions, medications, and treatments that may induce mania are shown in **Table 67–1**.
- Bipolar disorder is influenced by developmental, genetic, neurobiological, and psychological factors. Probably multiple gene loci are involved in heredity.
- Environmental or psychosocial stressors and immunologic factors are associated with bipolar disorder.

CLINICAL PRESENTATION

- Different types of episodes may occur sequentially with or without a period of normal mood (euthymia) between. There can be mood fluctuations that continue for months or after one episode, there can be years without recurrence of any type of mood episode (**Table 67–2**).

MAJOR DEPRESSIVE EPISODE

- Delusions, hallucinations, and suicide attempts are more common in bipolar depression than in unipolar depression.

MANIC EPISODE

- Acute mania usually begins abruptly, and symptoms increase over several days. Bizarre behavior, hallucinations, and paranoid or grandiose delusions may occur. There is marked impairment in functioning.
- Manic episodes may be precipitated by stressors, sleep deprivation, antidepressants, central nervous system (CNS) stimulants, or bright light.

HYPOMANIC EPISODE

- There is no marked impairment in social or occupational functioning, no delusions, and no hallucinations. Some patients may be more productive than usual, but 5% to 15% of patients may rapidly switch to a manic episode.

DIAGNOSIS

- The *Diagnostic and Statistical Manual of Mental Disorders,* 4th ed., text revision, classifies bipolar disorders as (1) bipolar I, (2) bipolar II, (3) cyclothymic disorder, and (4) bipolar disorder not otherwise specified. See Table 67–2 for diagnostic criteria.
- A medical, psychiatric, and medication history; physical examination; and laboratory testing are necessary to rule out organic causes of mania or depression.

COURSE OF ILLNESS

- Childhood onset is associated with more mood episodes, rapid cycling, and comorbid psychiatric conditions.
- Rapid cyclers, 20% of bipolar patients, have four or more episodes per year (major depressive, manic, or hypomanic). Rapid-cycling is associated with frequent and severe episodes of depression and a poorer long-term prognosis.

TABLE 67–1 Secondary Causes of Mania

Medical conditions that induce mania
• CNS disorders (brain tumor, strokes, head injuries, subdural hematoma, multiple sclerosis, systemic lupus erythematosus, temporal lobe seizures, Huntington's disease)
• Infections (encephalitis, neurosyphilis, sepsis, human immunodeficiency virus)
• Electrolyte or metabolic abnormalities (calcium or sodium fluctuations, hyperglycemia or hypoglycemia)
• Endocrine or hormonal dysregulation (Addison's disease, Cushing's disease, hyperthyroidism or hypothyroidism, menstrual-related or pregnancy-related or perimenopausal mood disorders)
Medications or drugs that induce mania
• Alcohol intoxication
• Drug withdrawal states (alcohol, α_2-adrenergic agonists, antidepressants, barbiturates, benzodiazepines, opiates)
• Antidepressants (MAOIs, TCAs, 5-HT and/or NE and/or DA reuptake inhibitors, 5-HT antagonists)
• DA-augmenting agents (CNS stimulants: amphetamines, cocaine, sympathomimetics; DA agonists, releasers, and reuptake inhibitors)
• Hallucinogens (LSD, PCP)
• Marijuana intoxication precipitates psychosis, paranoid thoughts, anxiety, and restlessness
• NE-augmenting agents (α_2-adrenergic antagonists, β-agonists, NE reuptake inhibitors)
• Steroids (anabolic, adrenocorticotropic hormone, corticosteroids)
• Thyroid preparations
• Xanthines (caffeine, theophylline)
• Nonprescription weight loss agents and decongestants (ephedra, pseudoephedrine)
• Herbal products (St. John's wort)
Somatic therapies that induce mania
• Bright light therapy
• Deep brain stimulation
• Sleep deprivation

DA, dopamine; 5-HT, serotonin; LSD, lysergic acid diethylamide; MAOI, monoamine oxidase inhibitor; NE, norepinephrine; PCP, phencyclidine; TCA, tricyclic antidepressant.

- Women are more likely to have increased depressive symptoms, older age of onset, better adherence, and thyroid abnormalities. Men may have more manic episodes and substance use.
- Suicide attempts occur in up to 50% of patients with bipolar disorder, and ~10% to 19% of individuals with bipolar I disorder commit suicide.
- Episodes may become longer in duration and more frequent with aging.

TREATMENT

- Goals of Treatment: **Table 67–3.**

GENERAL APPROACH

- **Table 67–4** shows the approach to treating acute episodes in adults.
- Adherence to treatment is the most important factor in achieving goals.

TABLE 67–2 Evaluation and Diagnosis of Mood Episodes

Diagnosis Episode	Impairment of Functioning or Need for Hospitalization[a]	*DSM-IV-TR* Criteria[b]
Major depressive	Yes	>2-Week period of either depressed mood or loss of interest or pleasure in normal activities, associated with at least five of the following symptoms: • Depressed, sad mood (adults); can be irritable mood in children • Decreased interest and pleasure in normal activities • Decreased appetite, weight loss • Insomnia or hypersomnia • Psychomotor retardation or agitation • Decreased energy or fatigue • Feelings of guilt or worthlessness • Impaired concentration and decision making • Suicidal thoughts or attempts
Manic	Yes	>1-Week period of abnormal and persistent elevated mood (expansive or irritable), associated with at least three of the following symptoms (four if the mood is only irritable): • Inflated self-esteem (grandiosity) • Decreased need for sleep • Increased talking (pressure of speech) • Racing thoughts (flight of ideas) • Distractible (poor attention) • Increased activity (socially, at work, or sexually) or increased motor activity or agitation • Excessive involvement in activities that are pleasurable but have a high risk for serious consequences (buying sprees, sexual indiscretions, poor judgment in business ventures)
Hypomanic	No	At least 4 days of abnormal and persistent elevated mood (expansive or irritable), associated with at least three of the following symptoms (four if the mood is only irritable): • Inflated self-esteem (grandiosity) • Decreased need for sleep • Increased talking (pressure of speech) • Racing thoughts (flight of ideas) • Increased activity (socially, at work, or sexually) or increased motor activity or agitation • Excessive involvement in activities that are pleasurable but have a high risk for serious consequences (buying sprees, sexual indiscretions, poor judgment in business ventures)

(*continued*)

TABLE 67–2 Evaluation and Diagnosis of Mood Episodes (*Continued*)

Diagnosis Episode	Impairment of Functioning or Need for Hospitalization[a]	*DSM-IV-TR* Criteria[b]
Mixed	Yes	Criteria for both a major depressive episode and a manic episode (except for duration) occur nearly every day for at least a 1-week period
Rapid cycling	Yes	>4 major depressive or manic episodes (manic, mixed, or hypomanic) in 12 months

[a]Impairment in social or occupational functioning; need for hospitalization because of potential self-harm, harm to others, or psychotic symptoms.
[b]The disorder is not caused by a medical condition (eg hypothyroidism) or substance-induced disorder (eg antidepressant treatment, medications, electroconvulsive therapy).

- Bipolar patients should remain on a mood stabilizer (eg, lithium, valproate, carbamazepine) lifelong. During acute episodes, medications can be added and then tapered after stabilization.

NONPHARMACOLOGIC THERAPY

- Nonpharmacologic approaches include: 1) psychotherapy (eg, individual, group, and family), interpersonal therapy, and/or cognitive behavioral therapy, 2) stress

TABLE 67–3 General Principles for the Management of Bipolar Disorder

Goals of treatment

- Eliminate mood episode with complete remission of symptoms (ie, acute treatment)
- Prevent recurrences or relapses of mood episodes (ie, continuation phase treatment)
- Return to complete psychosocial functioning
- Maximize adherence with therapy
- Minimize adverse effects
- Use medications with the best tolerability and fewest drug interactions
- Treat comorbid substance use and abuse
- Eliminate alcohol, marijuana, cocaine, amphetamines, and hallucinogens
- Minimize nicotine use and stop caffeine intake at least 8 hours prior to bedtime
- Avoidance of stressors or substances that precipitate an acute episode

Monitor for

- Mood episodes: document symptoms on a daily mood chart (document life stressors, type of episode, length of episode, and treatment outcome); monthly and yearly life charts are valuable for documenting patterns of mood cycles
- Medication adherence (missing doses of medications is a primary reason for nonresponse and recurrence of episodes)
- Adverse effects, especially sedation and weight gain (manage rapidly and vigorously to avoid noncompliance)
- Suicidal ideation or attempts (suicide completion rates with bipolar I disorder are 10–15%; suicide attempts are primarily associated with depressive episodes, mixed episodes with severe depression, or presence of psychosis)

TABLE 67–4 Algorithm and Guidelines for the Acute Treatment of Mood Episodes in Patients with Bipolar I Disorder

Acute Manic or Mixed Episode		Acute Depressive Episode	
General Guidelines		**General Guidelines**	
Assess for secondary causes of mania or mixed states (eg alcohol or drug use) Discontinue antidepressants Taper off stimulants and caffeine if possible Treat substance abuse Encourage good nutrition (with regular protein and essential fatty acid intake), exercise, adequate sleep, stress reduction, and psychosocial therapy		Assess for secondary causes of depression (eg alcohol or drug use) Taper off antipsychotics, benzodiazepines, or sedative–hypnotic agents if possible Treat substance abuse Encourage good nutrition (with regular protein and essential fatty acid intake), exercise, adequate sleep, stress reduction, and psychosocial therapy	
Hypomania	**Mania**	**Mild to Moderate Depressive Episode**	**Severe Depressive Episode**
First, optimize current mood stabilizer or initiate mood-stabilizing medication: lithium,[a] valproate,[a] carbamazepine,[a] or SGAs Consider adding a benzodiazepine (lorazepam or clonazepam) for short-term adjunctive treatment of agitation or insomnia if needed Alternative medication treatment options: oxcarbazepine	**First**, two- or three-drug combinations (lithium,[a] valproate,[a] or SGA) **plus** a benzodiazepine (lorazepam or clonazepam) and/or antipsychotic for short-term adjunctive treatment of agitation or insomnia; lorazepam is recommended for catatonia Do not combine antipsychotics Alternative medication treatment options: carbamazepine[a]; if patient does not respond or tolerate, consider oxcarbazepine	**First**, initiate and/or optimize mood-stabilizing medication: lithium[a] or quetiapine Alternative anticonvulsants: lamotrigine,[b] valproate[a]; antipsychotics: fluoxetine/olanzapine combination	**First**, optimize current mood stabilizer or initiate mood-stabilizing medication: lithium[a] or quetiapine Alternative fluoxetine/olanzapine combination If psychosis is present, initiate an antipsychotic in combination with above Do not combine antipsychotics Alternative anticonvulsants: lamotrigine,[b] valproate[a]

Second, if response is inadequate, consider a two-drug combination: • Lithium[a] **plus** an anticonvulsant or an SGA • Anticonvulsant **plus** an anticonvulsant or SGA	**Second**, if response is inadequate, consider a three-drug combination: • Lithium[a] **plus** an anticonvulsant **plus** an antipsychotic • Anticonvulsant **plus** an anticonvulsant **plus** an antipsychotic **Third**, if response is inadequate, consider ECT for mania with psychosis or catatonia,[d] or add clozapine for treatment-refractory illness	**Second**, if response is inadequate, consider carbamazepine[a] or adding antidepressant **Third**, if response is inadequate, consider a three-drug combination: • Lithium **plus** lamotrigine[b] **plus** an antidepressant • Lithium **plus** quetiapine **plus** antidepressant[c] **Fourth**, if response is inadequate, consider ECT for treatment-refractory illness and depression with psychosis or catatonia[d]

ECT, electroconvulsive therapy; SGA, second-generation antipsychotic.

[a]Use standard therapeutic serum concentration ranges if clinically indicated; if partial response or breakthrough episode, adjust dose to achieve higher serum concentrations without causing intolerable adverse effects; valproate is preferred over lithium for mixed episodes and rapid cycling; lithium and/or lamotrigine is preferred over valproate for bipolar depression.

[b]Lamotrigine is not approved for the acute treatment of depression, and the dose must be started low and slowly titrated up to decrease adverse effects if used for maintenance therapy of bipolar I disorder. Lamotrigine may be initiated during acute treatment with plans to transition to this medication for long-term maintenance. A drug interaction and a severe dermatologic rash can occur when lamotrigine is combined with valproate (ie lamotrigine doses must be halved from standard dosing titration).

[c]Controversy exists concerning the use of antidepressants, and they are often considered third line in treating acute bipolar depression, except in patients with no recent history of severe acute mania or potentially in bipolar II patients.

[d]ECT is used for severe mania or depression during pregnancy and for mixed episodes; prior to treatment, anticonvulsants, lithium, and benzodiazepines should be tapered off to maximize therapy and minimize adverse effects.

reduction techniques, relaxation therapy, massage, and yoga, 3) sleep (regular bedtime and awake schedule; avoid alcohol or caffeine intake prior to bedtime), 4) nutrition (regular intake of protein-rich foods or drinks and essential fatty acids; supplemental vitamins and minerals), and 5) exercise (regular aerobic and weight training at least three times a week).

PHARMACOLOGIC THERAPY

- See **Table 67–5** for product and dosing information on medications for bipolar disorder.
- See **Table 67–6** for guidelines for laboratory monitoring of patients on mood stabilizers.
- **Lithium, divalproex sodium (valproate), extended-release carbamazepine, aripiprazole, asenapine, olanzapine, quetiapine, risperidone,** and **ziprasidone** are currently approved by the FDA for treatment of acute mania. **Lithium, divalproex sodium, aripiprazole, olanzapine,** and **lamotrigine** are approved for maintenance treatment.
- **Lithium** is the drug of choice for bipolar disorder with euphoric mania, whereas valproate has better efficacy for mixed states, irritable/dysphoric mania, and rapid cycling.
- Combination therapies (eg, lithium plus **valproate** or **carbamazepine**; lithium or valproate plus a second-generation antipsychotic) may provide better acute response and prevention of relapse and recurrence than monotherapy in some bipolar patients, especially those with mixed states or rapid cycling.
- Useful guidelines include the following: Canadian Network for Mood and Anxiety Treatments (CANMAT); International Society for Bipolar Disorders Guidelines; Practice Guideline for the Treatment of Patients with Bipolar Disorder (Revision) published by the American Psychiatric Association; Texas Medication Algorithm Project developed by the Texas Department of Mental Health and Mental Retardation; and Practice Parameters for the Assessment and Treatment of Children and Adolescents with Bipolar Disorder, developed by the American Academy of Child and Adolescent Psychiatry.

Lithium

- Lithium is a first-line agent for acute mania, acute bipolar depression, and maintenance treatment of bipolar I and II disorders.
- Lithium is rapidly absorbed, neither protein bound nor metabolized, and excreted unchanged in the urine and other body fluids.
- It may require 6 to 8 weeks to show antidepressant efficacy. It is more effective for elated mania and less effective for mania with psychotic features, mixed episodes, rapid cycling, and when alcohol and drug abuse is present. Maintenance therapy is more effective in patients with fewer episodes, good functioning between episodes, and a family history of good response to lithium. It produces a prophylactic response in up to two thirds of patients and reduces suicide risk by 8- to 10-fold.
- Lithium augmentation of carbamazepine, lamotrigine, and valproate can improve response in bipolar I patients, but it may increase the risk of sedation, weight gain, GI complaints, and tremor.
- Combining lithium with **first-generation antipsychotics** (**FGA**) in elderly patients has been reported to cause neurotoxicity (eg, delirium, severe tremors, cerebellar dysfunction, and extrapyramidal symptoms). Withdraw lithium and discontinue at least 2 days before electroconvulsive therapy (ECT), and resume 2 to 3 days after the last ECT treatment.
- Combining lithium with **verapamil** or **diltiazem** is reported to cause neurotoxicity and severe bradycardia.
- Initial side effects are often dose related and are worse at peak serum concentrations (1–2 hours postdose). Lowering the dose, taking smaller doses with food, using extended-release products, and once-daily dosing at bedtime may help.

TABLE 67–5 Products, Dosage and Administration, and Clinical Use of Agents Used in the Treatment of Bipolar Disorder

Drug	Initial Dosing	Usual Dosing; Special Population Dosing	Comments
"Brand name"			
Lithium salts: FDA-approved for bipolar disorder			
Lithium carbonate[a,b] "Eskalith" "Eskalith CR" "Lithobid" Lithium citrate[a,b] "Cibalith-S"	300 mg twice daily	900–2,400 mg/day in two to four divided doses, preferably with meals Renal impairment: lower doses required with frequent serum monitoring There is wide variation in the dosage needed to achieve therapeutic response and trough serum lithium concentration (i.e., 0.6–1.2 mEq/L [mmol/L] for maintenance therapy and 1–1.2 mEq/L [mmol/L] for acute mood episodes taken 8–12 hours after the last dose)	Use alone or in combination with other drugs (eg, valproate, carbamazepine, antipsychotics) for the acute treatment of mania and for maintenance treatment
Anticonvulsants: FDA-approved for bipolar disorder			
Divalproex sodium[a] "Depakote" "Depakote ER" Valproic acid[a] "Stavzor"	250–500 mg twice daily A loading dose of divalproex (20–30 mg/kg/day) can be given	750–3,000 mg/day (20–60 mg/kg/day) given once daily or in divided doses Titrate to clinical response Dose adjustment needed with hepatic impairment	Use alone or in combination with other drugs (eg, lithium, carbamazepine, antipsychotics) for the acute treatment of mania and for maintenance treatment Use caution when combining with lamotrigine because of potential drug interaction

(*continued*)

TABLE 67–5 Products, Dosage and Administration, and Clinical Use of Agents Used in the Treatment of Bipolar Disorder (*Continued*)

Drug	Initial Dosing	Usual Dosing; Special Population Dosing	Comments
Lamotrigine[b] "Lamictal"	25 mg daily	50–400 mg/day in divided doses. Dosage should be slowly increased (eg, 25 mg/day for 2 weeks, then 50 mg/day for weeks 3 and 4, and then 50-mg/day increments at weekly intervals up to 200 mg/day) Dose adjustment needed with hepatic impairment	Use alone or in combination with other drugs (eg, lithium, carbamazepine) for long-term maintenance treatment for bipolar I disorder
Carbamazepine "Equetro[a]"	200 mg twice daily	200–1,800 mg/day in two to four divided doses Titrate to clinical response Dose adjustment needed with hepatic impairment	Use alone or in combination with other medications (eg, lithium, valproate, antipsychotics) for the acute and long-term maintenance treatment of mania or mixed episodes for bipolar I disorder. APA guidelines recommend reserving it for patients unable to tolerate or who have inadequate response to lithium or valproate Extended-release tablets should be swallowed whole and not be broken or chewed
Anticonvulsants: not FDA-approved for bipolar disorder			
Carbamazepine "Tegretol" "Epitol" "Tegretol-XR" "Carbatrol"	200 mg twice daily	200–1,800 mg/day in two to four divided doses Titrate to clinical response Dose adjustment needed with hepatic impairment	Carbatrol capsules can be opened and contents sprinkled over food

Valproic acid "Depakene" Valproate sodium "Depacon"	250–500 mg twice daily A loading dose of divalproex (20–30 mg/kg/day) can be given	750–3,000 mg/day (20–60 mg/kg/day) given once daily or in divided doses Titrate to clinical response Dose adjustment needed with hepatic impairment	Use caution when combining with lamotrigine because of potential drug interaction
Oxcarbazepine "Trileptal"	300 mg twice daily	300–1,200 mg/day in two divided doses Titrate based on clinical response Dose adjustment required with severe renal impairment	Use after patients have failed treatment with carbamazepine or have intolerable side effects May have fewer adverse effects and be better tolerated than carbamazepine
Atypical antipsychotics: FDA-approved for bipolar disorder			
Aripiprazole[a,b] "Abilify"	10–15 mg daily	10–30 mg/day once daily	May be used in combination with lithium, valproate, or carbamazepine for the acute treatment of mania or mixed states (primarily with psychotic features) for bipolar I disorder
Asenapine[a] "Saphris"	5–10 mg twice daily sublingually	5–10 mg twice daily sublingually	
Olanzapine[a,b] "Zyprexa," "Zyprexa Zydis"	2.5–5 mg twice daily	5–20 mg/day once daily or in divided doses	
Olanzapine and fluoxetine[c] "Symbyax"	6 mg olanzapine and 25 mg fluoxetine daily	6–12 mg olanzapine and 25–50 mg fluoxetine daily	

(*continued*)

TABLE 67–5 Products, Dosage and Administration, and Clinical Use of Agents Used in the Treatment of Bipolar Disorder (*Continued*)

Drug	Initial Dosing	Usual Dosing; Special Population Dosing	Comments
Quetiapine[a,b] "Seroquel"	50 mg twice daily	50–800 mg/day in divided doses or once daily when stabilized	
Risperidone[a] "Risperdal" "Risperdal M-Tab"	0.5–1 mg twice daily	0.5–6 mg/day once daily or in divided doses	
Ziprasidone[a] "Geodon"	40–60 mg twice daily	40–160 mg/day in divided doses. Administer with food	
Benzodiazepines	Dosage should be slowly adjusted up and down according to response and adverse effects		Use in combination with other medications (eg, antipsychotics, lithium, valproate) for the acute treatment of mania or mixed episodes Use as a short-term adjunctive sedative–hypnotic agent

FDA-approved agents may be used as monotherapy in various phases of the illness as noted in table footnotes.[a,b,c]

[a]FDA-approved for acute mania.
[b]FDA-approved for maintenance.
[c]FDA-approved for acute bipolar depression.

TABLE 67–6 Guidelines for Baseline and Routine Laboratory Tests and Monitoring for Agents Used in Treatment of Bipolar Disorder

	Baseline: Physical Examination and General Chemistry[a]	Hematologic Tests[b]		Metabolic Tests[c]		Liver Function Tests[d]		Renal Function Tests[e]		Thyroid Function Tests[f]		Serum Electrolytes[g]		Dermatologic[h]	
	Baseline	Baseline	6–12 months	Baseline	6–12 months	Baseline	6–12 months	Baseline	6–12 months	Baseline	6–12 months	Baseline	6–12 months	Baseline	6–12 months
SGAs[i]	X			X	X										
Carbamazepine[j]	X	X	X			X	X	X				X	X	X	X
Lamotrigine[k]	X													X	X
Lithium[l]	X	X	X	X	X			X	X	X	X	X	X	X	X
Oxcarbazepine[m]	X											X	X		
Valproate[n]	X	X	X	X	X	X	X							X	X

[a]Screen for drug abuse and serum pregnancy.
[b]Complete blood cell count (CBC) with differential and platelets.
[c]Fasting glucose, serum lipids, and weight.
[d]Lactate dehydrogenase, aspartate aminotransferase, alanine aminotransferase, total bilirubin, and alkaline phosphatase.
[e]Serum creatinine, blood urea nitrogen, urinalysis, urine osmolality, and specific gravity.
[f]Triiodothyronine, total thyroxine, thyroxine uptake, and thyroid-stimulating hormone.
[g]Serum sodium.
[h]Rashes, hair thinning, and alopecia.
[i]Second-generation antipsychotics: Monitor for increased appetite with weight gain (primarily in patients with initial low or normal body mass index); monitor closely if rapid or significant weight gain occurs during early therapy; cases of hyperlipidemia and diabetes reported.

(*continued*)

TABLE 67–6 **Guidelines for Baseline and Routine Laboratory Tests and Monitoring for Agents Used in Treatment of Bipolar Disorder (*Continued*)**

[j]Carbamazepine: Manufacturer recommends CBC and platelets (and possibly reticulocyte counts and serum iron) at baseline, and that subsequent monitoring be individualized by the clinician (eg, CBC, platelet counts, and liver function tests every 2 weeks during the first 2 months of treatment, and then every 3 months if normal). Monitor more closely if patient exhibits hematologic or hepatic abnormalities or if the patient is receiving a myelotoxic drug; discontinue if platelets are <100,000/mm^3 (<100 × 10^9/L), if white blood cell (WBC) count is <3,000/mm^3 (<3 × 10^9/L), or if there is evidence of bone marrow suppression or liver dysfunction. Serum electrolyte levels should be monitored in the elderly or those at risk for hyponatremia. Carbamazepine interferes with some pregnancy tests.

[k]Lamotrigine: If renal or hepatic impairment, monitor closely and adjust dosage according to manufacturer's guidelines. Serious dermatologic reactions have occurred within 2–8 weeks of initiating treatment and are more likely to occur in patients receiving concomitant valproate, with rapid dosage escalation, or using doses exceeding the recommended titration schedule.

[l]Lithium: Obtain baseline electrocardiogram for patients older than 40 years or if preexisting cardiac disease (benign, reversible T-wave depression can occur). Renal function tests should be obtained every 2–3 months during the first 6 months, and then every 6–12 months; if impaired renal function, monitor 24-hour urine volume and creatinine every 3 months; if urine volume >3 L/day, monitor urinalysis, osmolality, and specific gravity every 3 months. Thyroid function tests should be obtained once or twice during the first 6 months, and then every 6–12 months; monitor for signs and symptoms of hypothyroidism; if supplemental thyroid therapy is required, monitor thyroid function tests and adjust thyroid dose every 1–2 months until thyroid function indices are within normal range, and then monitor every 3–6 months.

[m]Oxcarbazepine: Hyponatremia (serum sodium concentrations <125 mEq/L [mmol/L]) has been reported and occurs more frequently during the first 3 months of therapy; serum sodium concentrations should be monitored in patients receiving drugs that lower serum sodium concentrations (eg, diuretics or drugs that cause inappropriate antidiuretic hormone secretion) or in patients with symptoms of hyponatremia (eg, confusion, headache, lethargy, and malaise). Hypersensitivity reactions have occurred in approximately 25–30% of patients with a history of carbamazepine hypersensitivity and require immediate discontinuation.

[n]Valproate: Weight gain reported in patients with low or normal body mass index. Monitor platelets and liver function during first 3–6 months if evidence of increased bruising or bleeding. Monitor closely if patients exhibit hematologic or hepatic abnormalities or in patients receiving drugs that affect coagulation, such as aspirin or warfarin; discontinue if platelets are <100,000/mm^3/L (<100 × 10^9/L) or if prolonged bleeding time. Pancreatitis, hyperammonemic encephalopathy, polycystic ovary syndrome, increased testosterone, and menstrual irregularities have been reported; not recommended during first trimester of pregnancy due to risk of neural tube defects.

- GI distress may be minimized by standard approaches or by adding antacids or antidiarrheals. Diarrhea can sometimes be improved by switching to a liquid formulation.
- Muscle weakness and lethargy occur in ~30% of patients and is usually transient. Polydipsia with polyuria and nocturia occurs in up to 70% of patients and is managed by changing to once-daily dosing at bedtime.
- A fine hand tremor occurs in up to 50% of patients. It may be treated by switching to a long-acting preparation, lowering the dose, or adding **propranolol**, 20 to 120 mg/day.
- Lithium reduces the kidneys' ability to concentrate urine and may cause a nephrogenic diabetes insipidus with low urine-specific gravity and low osmolality polyuria (urine volume >3 L/day). This may be treated with **loop diuretics, thiazide diuretics,** or **triamterene**. If a thiazide diuretic is used, lithium doses should be decreased by 50% and lithium and potassium levels monitored. Amiloride has weaker natriuretic effects and seems to have little effect on lithium clearance.
- Long-term lithium therapy is associated with a 10% to 20% risk of morphologic renal changes.
- Lithium-induced nephrotoxicity is rare if patients are maintained on the lowest effective dose, once-daily dosing is used, good hydration is maintained, and toxicity is avoided.
- Up to 30% of patients on maintenance lithium therapy develop transiently elevated serum concentrations of thyroid-stimulating hormone, and 5% to 35% of patients develop a goiter and/or hypothyroidism, which is 10 times more likely to occur in women. This is managed by adding **levothyroxine**.
- Lithium may cause cardiac effects including T-wave flattening or inversion (up to 30% of patients), atrioventricular block, and bradycardia.
- Other late-appearing lithium side effects are benign reversible leukocytosis, acne, alopecia, exacerbation of psoriasis, pruritic dermatitis, maculopapular rash, folliculitis, and weight gain.
- Lithium toxicity can occur with serum levels greater than 1.5 mEq/L (mmol/L), but the elderly may have toxic symptoms at therapeutic levels. Severe toxic symptoms may occur with serum concentrations above 2 mEq/L (mmol/L), including vomiting, diarrhea, incontinence, incoordination, impaired cognition, arrhythmias, and seizures, and permanent neurologic impairment and kidney damage may occur.
- Factors predisposing to lithium toxicity include sodium restriction, dehydration, vomiting, diarrhea, age greater than 50 years, heart failure, cirrhosis, drug interactions that decrease lithium clearance, heavy exercise, sauna baths, hot weather, and fever. Tell patients to maintain adequate sodium and fluid intake and to avoid alcohol and excessive coffee, tea, cola, and other caffeine-containing beverages.
- If lithium toxicity is suspected, the patient should discontinue lithium and go immediately to the emergency room. Intermittent hemodialysis is generally required when serum lithium levels are greater than 3.5 to 4 mEq/L (mmol/L) for patients on long-term treatment and continued until the concentration is below 1 mEq/L (mmol/L).
- Thiazide diuretics, nonsteroidal anti-inflammatory drugs, angiotensin-converting enzyme inhibitors, and salt-restricted diets can elevate lithium levels. Neurotoxicity can occur when lithium is combined with carbamazepine, diltiazem, losartan, methyldopa, metronidazole, phenytoin, and verapamil.
- Lithium is usually initiated with 600 mg/day for prophylaxis and 900 to 1200 mg/day for acute mania. Give immediate-release preparations two or three times daily and extended-release products once or twice daily. After patients are stabilized, many patients can switch to once-daily dosing.
- Initially, check serum lithium concentrations once or twice weekly. After a desired serum concentration is achieved, check levels in 2 weeks, and when stable, check them every 3 to 6 months.
- Lithium clearance increases by 50% to 100% during pregnancy. Monitor serum levels monthly during pregnancy and weekly the month before delivery. At delivery, reduce dose to prepregnancy levels and maintain hydration.

- A reasonable therapeutic trial in outpatients is at least 4 to 6 weeks with lithium serum concentrations of 0.6 to 1.2 mEq/L (mmol/L). Patients with serum concentrations between 0.8 mEq/L and 1 mEq/L (mmol/L) may have fewer relapses than those with lower serum concentrations. Acutely manic patients can require serum concentrations of 1 to 1.2 mEq/L (mmol/L), and some need up to 1.5 mEq/L (mmol/L). Draw lithium levels 12 hours postdose. For bipolar prophylaxis in elderly patients, serum concentrations of 0.4 to 0.6 mEq/L (mmol/L) are recommended.

Anticonvulsants

- For more in-depth information on the side effects, pharmacokinetics, and drug interactions of anticonvulsants, refers to Chap. 53.

Valproate Sodium and Valproic Acid

- **Divalproex sodium** (**sodium valproate**), approved for acute manic or mixed episodes, is the most prescribed mood stabilizer in the United States. It is as effective as **lithium** and **olanzapine** for pure mania, and it can be more effective than lithium for rapid cycling, mixed states, and bipolar disorder with substance abuse. It reduces the frequency of (or prevents) recurrent manic, depressive, and mixed episodes.
- **Lithium, carbamazepine, antipsychotics,** or **benzodiazepines** can augment the antimanic effects of valproate. Valproate can be added to lithium to achieve synergistic effects, and the combination has demonstrated efficacy in maintenance therapy of bipolar I disorder. Combinations of valproate and carbamazepine can have synergistic effects, but the potential for drug interactions necessitate blood level monitoring of both agents. **Second-generation antipsychotics (SGA)** can be added to valproate for breakthrough mania, but they can increase the risk of sedation and weight gain. Combining valproate with lamotrigine increases the risk of rashes, ataxia, tremor, sedation, and fatigue.
- The most frequent dose-related side effects of valproate are GI complaints, fine tremor, and sedation. Reducing the dose or adding a β-blocker may alleviate tremors. Other side effects are ataxia, lethargy, alopecia, pruritus, prolonged bleeding, transient increases in liver enzymes, weight gain, and hyperammonemia. Fatal necrotizing hepatitis is rare and idiosyncratic, occurring in children on multiple anticonvulsants. Life-threatening pancreatitis has been reported.
- Initial dosing is 250 to 500 mg twice daily; a loading dose of 20 to 30 mg/kg/day of divalproex can be given over 12 hours. The daily dose is adjusted by 250 to 500 mg every 1 to 3 days based on response and tolerability. The maximum dose is 60 mg/kg/day (see **Table 67–5**).
- After establishing the optimal dose, the dose can be given twice daily or at bedtime if tolerated.
- Extended-release divalproex can be given once daily, but bioavailability can be 15% lower than that of immediate release products.
- Most clinicians seek a serum concentration range of 50 to 125 mcg/mL (347 to 866 μmol/L) measured 12 hours after the last dose. Patients with cyclothymia or bipolar II disorder respond at lower blood levels, while patients with more severe forms may require up to 150 mcg/mL (1040 μmol/L). Serum levels are most useful when assessing for compliance or toxicity.

Carbamazepine

- **Carbamazepine** is commonly used for acute and maintenance therapy. Only the extended-release formulation is FDA approved for bipolar disorder in the United States.
- It is usually reserved for lithium-refractory patients, rapid cyclers, or mixed states. It has acute antimanic effects, but its long-term effectiveness is unclear. It may be less effective than lithium for maintenance therapy and for bipolar depression.
- The combination of carbamazepine with **lithium, valproate,** and antipsychotics is often used for manic episodes in treatment-resistant patients. Carbamazepine with nimodipine can be beneficial for refractory patients.

- Carbamazepine induces the hepatic metabolism of antidepressants, anticonvulsants, antipsychotics, and many other medications; thus, dosage adjustments may be required. Women who receive carbamazepine require higher doses of **oral contraceptives** or alternative contraceptive methods.
- Certain medications that inhibit CYP3A4 (eg, **cimetidine, diltiazem, erythromycin, fluoxetine, fluvoxamine, itraconazole, ketoconazole, nefazodone,** and **verapamil**) added to carbamazepine therapy may cause carbamazepine toxicity. When carbamazepine is combined with valproate, reduce the carbamazepine dose, as its free levels can be increased. Do not combine clozapine and carbamazepine because of possible additive bone marrow suppression.
- For inpatients in an acute manic episode, doses can be started at 400 to 600 mg/day in divided doses with meals and increased by 200 mg/day every 2 to 4 days up to 10 to 15 mg/kg/day. Outpatients should be titrated upward more slowly to avoid side effects. Many patients tolerate once-daily dosing after stabilization.
- During the first month of therapy, serum concentrations may be decreased because of autoinduction of metabolizing enzymes, requiring a dose increase.
- Carbamazepine serum levels are usually obtained every 1 or 2 weeks during the first 2 months, then every 3 to 6 months during maintenance. Serum samples are drawn 10 to 12 hours after the dose and at least 4 to 7 days after dosage initiation or change. Most clinicians attempt to maintain levels between 6 and 10 mcg/mL (25–42 μmol/L), but some patients may require 12 to 14 mcg/mL (51–59 μmol/L).
- Use of carbamazepine in patients of Asian ancestry requires genetic testing for human leukocyte antigen (HLA) allele, HLA-B 1502, to help detect a higher risk of Stevens-Johnson syndrome and toxic epidermal necrolysis.

Oxcarbazepine

- **Oxcarbazepine** is not FDA approved for treatment of bipolar disorder in the United States. It has mood-stabilizing effects similar to those of carbamazepine, but with milder side effects, no autoinduction of metabolizing enzymes, and potentially fewer drug interactions.
- Dose-related side effects include dizziness, sedation, headache, ataxia, fatigue, vertigo, abnormal vision, diplopia, vomiting, and abdominal pain. It causes more hyponatremia than carbamazepine.
- It is a CYP 2C19 inhibitor and a 3A3/4 inducer. It induces the metabolism of **oral contraceptives**, necessitating alternative contraception measures.
- Initial dosing is usually 150 to 300 mg twice daily, and daily doses can be increased by 300 to 600 mg every 3 to 6 days up to 1200 mg/day in divided doses (with or without food.

Lamotrigine

- **Lamotrigine**, effective for maintenance treatment of bipolar I and II disorder in adults, has both antidepressant and mood-stabilizing effects. It may have augmenting properties when combined with lithium or valproate. It has a low rate of switching patients to mania. Although it is less effective for acute mania compared with lithium and valproate, it may be beneficial for the maintenance therapy of treatment-resistant bipolar I and II disorders, rapid cycling, and mixed states. It seems most effective for prevention of bipolar depression.
- Common adverse effects include headache, nausea, dizziness, ataxia, diplopia, drowsiness, tremor, maculopapular rash (10% of patients), and pruritus. Although most rashes resolve with continued therapy, some progress to life-threatening Stevens–Johnson syndrome. The incidence of rash is greatest with concomitant administration of **valproate**, rapid dose escalation of lamotrigine, and higher than recommended lamotrigine initial doses. In patients taking valproate, dose lamotrigine at about one half the standard doses, and titrate upward more slowly than usual.
- For maintenance treatment of bipolar disorder, the usual dosage range of lamotrigine is 50 to 300 mg/day. The target dose is generally 100 mg/day when combined with **valproate** and 400 mg/day when combined with **carbamazepine**. For patients not

taking medications that affect lamotrigine's clearance, the dose is 25 mg/day for the first 2 weeks, then 50 mg/day for weeks 3 and 4, 100 mg/day for the next week, then 200 mg/day. Patients who stop dosing for more than a few days should restart the dose escalation schedule.

Antipsychotics

- First- and second-generation antipsychotics, such as **aripiprazole, asenapine, haloperidol, olanzapine, quetiapine, risperidone,** and **ziprasidone** are effective as monotherapy or as add-on therapy to lithium or valproate for acute mania. Long-term antipsychotics can be needed for some patients, but the risks versus benefits must be weighed in view of long-term side effects (eg, obesity, type 2 diabetes, hyperlipidemia, hyperprolactinemia, cardiac disease, and tardive dyskinesia).
- Both first- and second-generation antipsychotics are effective in ~70% of patients with acute mania associated with agitation, aggression, and psychosis.
- **Haloperidol decanoate, fluphenazine decanoate,** and **risperidone, aripiprazole, and olanzapine long-acting injection** are monotherapy options for maintenance therapy of bipolar disorder with noncompliance or treatment resistance.
- Controlled studies in acute mania suggest that **lithium** or **valproate** plus an antipsychotic is more effective than any of these agents alone.
- **Quetiapine** and the combination of **fluoxetine/olanzapine** are effective for acute bipolar depression.
- **Clozapine** monotherapy has acute and long-term mood stabilizing effects in refractory bipolar disorder, including mixed mania and rapid cycling, but requires regular white blood cell monitoring for agranulocytosis.
- Higher initial doses of antipsychotics (eg, 20 mg/day of **olanzapine**) are required for acute mania. After mania is controlled (usually 7–28 days), the antipsychotic can be gradually tapered and discontinued.
- For more information on the side effects, pharmacokinetics, and drug interactions of specific antipsychotics, refer to Chap. 69 on schizophrenia.

Alternative Medication Treatment

- High-potency benzodiazepines (eg, **clonazepam** and **lorazepam**) are commonly used alternatives to (or adjuncts to) antipsychotics for acute mania, agitation, anxiety, panic, and insomnia or in those who cannot take mood stabilizers. **Intramuscular (IM) lorazepam** may be used for acute agitation. A relative contraindication for long-term benzodiazepines is a history of drug or alcohol abuse or dependency.
- Data suggest that adjunctive antidepressants may be no better than placebo for acute bipolar depression when combined with mood stabilizers. Many clinicians consider them third line for acute bipolar depression, except in those with no history of severe and/or recent mania or potentially in bipolar II patients. The rate of mood switching from depression to mania with **tricyclic antidepressants** and **venlafaxine** is higher than the rate associated with use of selective serotonin reuptake inhibitors. Before initiating an antidepressant, be sure the patients has a therapeutic dose or blood level of a primary mood stabilizer. Be cautious in using antidepressants in those with a history of mania after a depressive episode, and those with frequent cycling must be treated cautiously with antidepressants. Generally, the antidepressant should be withdrawn 2 to 6 months after remission.

Special Populations

- Prophylaxis with mood stabilizers (eg, **lithium** or **valproate**) is recommended immediately postpartum to decrease the risk of depressive relapse in bipolar women.
- The occurrence of Epstein anomaly in infants exposed to lithium during the first trimester is estimated at 1:1000 to 1:2000.
- When **lithium** is used during pregnancy, use the lowest effective dose to prevent relapse, thus lessening the risk of "floppy" infant syndrome, hypothyroidism, and nontoxic goiter in the infant.
- Breast-feeding is usually discouraged for women taking lithium.

- When **valproate** is taken during the first trimester, the risk of neural tube defects is ~5%. For **carbamazepine,** the risk is estimated to be 0.5% to 1%. Administration of folic acid can reduce the risk of neural tube defects.
- Women taking valproate may breast-feed, but mother and infant should have identical laboratory monitoring.
- A guideline for treatment of children and adolescents with bipolar disorder is *Practice Parameters for the Assessment and Treatment of Children and Adolescents with Bipolar Disorder.*
- The elimination half-life of lithium and valproate increases with age. Demented patients can have increased sensitivity to side effects of mood stabilizers and antipsychotics.

EVALUATION OF THERAPEUTIC OUTCOMES

- Monitoring parameters are shown in **Table 67–3**.
- Patients with partial response or nonresponse to therapy should be reassessed for accurate diagnosis, concomitant medical or psychiatric conditions, and medications or substances that exacerbate mood symptoms.
- Involve patients and family members in treatment to monitor target symptoms, response, and side effects and to enhance adherence and reduce stressors. Standardized rating scales may be useful in monitoring for response.

See Chapter 52, Bipolar Disorder, authored by Shannon J. Drayton and Christine M. Pelic, for a more detailed discussion of this topic.

Major Depressive Disorder

68 CHAPTER

- The essential feature of *major depressive disorder* is a clinical course characterized by one or more major depressive episodes without a history of manic or hypomanic episodes.

PATHOPHYSIOLOGY

- *Biogenic amine hypothesis:* Decreased brain levels of the neurotransmitters norepinephrine, serotonin (5-HT), and dopamine may cause depression.
- *Postsynaptic changes in receptor sensitivity:* Studies have demonstrated that desensitization or downregulation of norepinephrine or 5-HT_{1A} receptors may relate to onset of antidepressant effects.
- *Dysregulation hypothesis:* This theory emphasizes a failure of homeostatic regulation of neurotransmitter systems, rather than absolute increases or decreases in their activities. Effective antidepressants may restore efficient regulation.
- *5-HT/norepinephrine link hypothesis:* This theory suggests that 5-HT and norepinephrine activities are linked, and that both the serotonergic and noradrenergic systems are involved in the antidepressant response.
- *The role of dopamine:* Several studies suggest that increased dopamine activity in the mesolimbic pathway contributes to antidepressant activity.
- A disruption of brain derived neurotrophic factor expression in the hippocampus may be associated with depression.

CLINICAL PRESENTATION

- *Emotional symptoms*: diminished ability to experience pleasure, loss of interest in usual activities, sadness, pessimism, crying, hopelessness, anxiety (present in ~90% of depressed outpatients), guilt, and psychotic features (eg, auditory hallucinations and delusions).
- Physical symptoms: fatigue, pain (especially headache), sleep disturbance, decreased or increased appetite, loss of sexual interest, and gastrointestinal (GI) and cardiovascular complaints (especially palpitations).
- *Intellectual or cognitive symptoms*: decreased ability to concentrate or slowed thinking, poor memory for recent events, confusion, and indecisiveness.
- *Psychomotor disturbances*: psychomotor retardation (slowed physical movements, thought processes, and speech) or psychomotor agitation.

DIAGNOSIS

- Major depressive disorder is characterized by one or more major depressive episodes, as defined by the *Diagnostic and Statistical Manual of Mental Disorders,* 5th ed. Five or more of the following must have been present nearly every day during the same 2-week period and cause significant distress or impairment (NOTE: depressed mood or loss of interest or pleasure must be present in adults [or irritable mood in children and adolescents]): depressed mood; diminished interest or pleasure in almost all activities; weight loss or gain; insomnia or hypersomnia; psychomotor agitation or retardation; fatigue or loss of energy; feelings of worthlessness or excessive guilt; diminished concentration or indecisiveness; recurrent thoughts of death, suicidal ideation without a specific plan, suicide attempt, or a plan for committing suicide. The depressive episode must not be attributable to physiological effects of a substance or medical condition. Lastly, there must not be a history of manic-like or hypomanic-like episodes unless they were induced by a substance or medical condition.

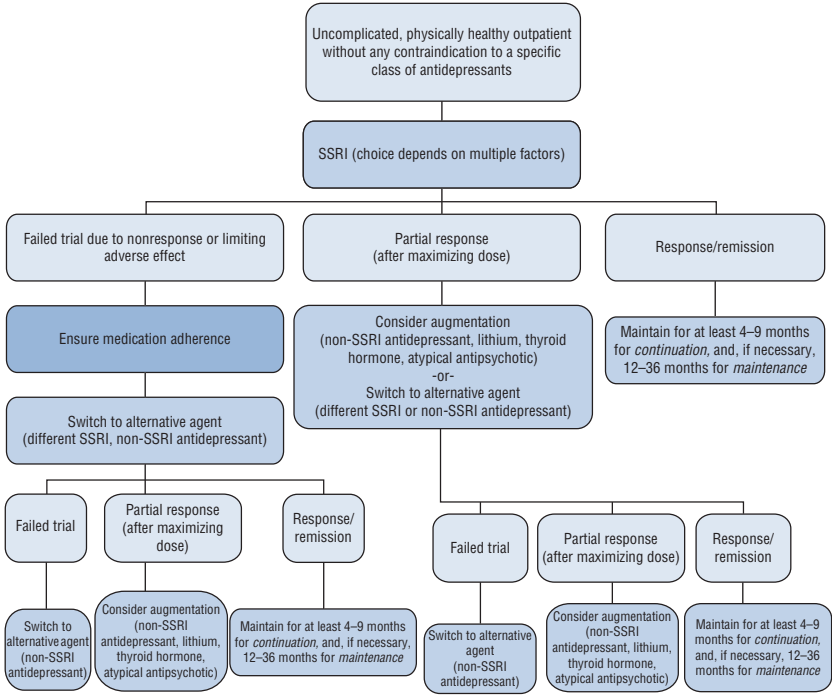


FIGURE 68–1. "(SSRI, selective serotonin reuptake inhibitor)." Algorithm for treatment of uncomplicated major depressive disorder.

- Diagnosis requires a medication review, physical examination, mental status examination, a complete blood count with differential, thyroid function tests, and electrolyte determinations.
- Many chronic illnesses and substance abuse and dependence disorders are associated with depression. Medications associated with depression include many antihypertensives, oral contraceptives, isotretinoin, interferon-β_{1a}, and many others.

TREATMENT

- Goals of Treatment: The goals are to reduce symptoms of depression, minimize adverse effects, ensure adherence to the prescribed regimen, facilitate return to premorbid functioning, and prevent further depressive episodes.

NONPHARMACOLOGIC TREATMENT

- Psychotherapy may be first-line therapy for mild to moderately severe major depressive episode. The efficacy of psychotherapy and antidepressants is considered to be additive. Psychotherapy alone is not recommended for acute treatment of severe and/or psychotic major depressive disorder. For uncomplicated, nonchronic major depressive disorder, combined treatment may provide no unique advantage. Cognitive therapy, behavioral therapy, and interpersonal psychotherapy appear to be equal in efficacy.
- Electroconvulsive therapy (ECT) is a safe and effective treatment for major depressive disorder. It is considered when a rapid response is needed, risks of other treatments outweigh potential benefits, there is history of a poor response to drugs, and the patient prefers ECT. A rapid therapeutic response (10–14 days) has been reported.
- Repetitive transcranial magnetic stimulation has demonstrated efficacy and does not require anesthesia as does ECT.

PHARMACOLOGIC THERAPY

General Approach

- **Figure 68–1** shows an algorithm for treatment of uncomplicated major depressive disorder. **Table 68–1** shows adult doses of antidepressants and a classification system for antidepressants.
- In general, antidepressants are equal in efficacy in groups of patients when administered in comparable doses.
- Choice of antidepressant is influenced by the patient's or family member's history of response, concurrent medical conditions, presenting symptoms, potential for drug–drug interactions, side effect profiles, patient preference, and drug cost.
- Between 65% and 70% of patients with major depression improve with drug therapy.
- Psychotically depressed individuals generally require either ECT or combination therapy with an antidepressant and antipsychotic.
- A 6-week trial of an antidepressant at maximum dosage is considered an adequate trial of that medication.
- The acute phase of treatment lasts 6 to 12 weeks, and the goal is remission (ie, absence of symptoms). The continuation phase (4–9 months after remission) seeks to eliminate residual symptoms or prevent relapse. The maintenance phase (12–36 months or more) has a goal to prevent recurrence of a new episode of depression.
- Give elderly patients one half of the initial dose given to younger adults, and increase the dose more slowly. The elderly may require 6 to 12 weeks of treatment to achieve the desired antidepressant response.
- Some clinicians recommend lifelong therapy for persons younger than 40 years with two or more prior episodes and for all persons with three or more prior episodes.
- Educate patients and their support systems about the delay in antidepressant response (typically 2–4 weeks) and the importance of adherence before starting therapy and throughout treatment.

TABLE 68–1 Adult Dosing Guidance for Currently Available Antidepressant Medications

Drug	Brand Name	Initial Dose (mg/day)	Usual Dosage Range (mg/day)	Comments (eg, Maximum Daily Dosage, Suggested Therapeutic Plasma Concentration)[a]
Selective Serotonin Reuptake Inhibitors (SSRIs)				
Citalopram	Celexa	20	20–40	Doses greater than 40 mg/day not recommended due to QT prolongation risk; maximum 20 mg/day for CYP2C19 poor metabolizers or coadministration with CYP2C19 inhibitors
Escitalopram	Lexapro	10	10–20	Maximum 20 mg/day; dose may be increased to maximum daily dose after at least 1 week if needed; 5 mg tablet available for unique circumstances
Fluoxetine	Prozac	20	20–60	Maximum 80 mg/day; dose may be increased in 20 mg increments; doses of 5 or 10 mg/day have been used as initial therapy; doses >20 mg/day may be given in a single daily dose or divided twice daily
Fluvoxamine	Luvox	50	50–300	Maximum 300 mg/day; daily doses >100 mg total dose should be divided twice daily, with the larger dose given at night
Paroxetine	Paxil	20	20–60	Maximum 50 mg/day (IR); titrate 10 mg/day increments weekly
				Maximum 62.5 mg/day (CR); titrate 12.5 mg/day increments weekly
Sertraline	Zoloft	50	50–200	Maximum 200 mg/day; titrate 25 mg/day increments weekly
Serotonin–Norepinephrine Reuptake Inhibitors (SNRIs)				
Newer-generation SNRIs				
Desvenlafaxine	Pristiq	50	50	Doses up to 400 mg/day have been studied; however, AEs are increased and no additional benefit has been shown at doses exceeding 50 mg/day
Duloxetine	Cymbalta	30	30–90	Maximum 120 mg/day (given once or twice daily); doses exceeding 60 mg/day not shown to provide increased efficacy for the treatment of MDD
Venlafaxine	Effexor	37.5–75	75–225	Maximum 375 mg/day (IR); maximum 225 mg/day (ER); may increase in increments up to 75 mg/day at a minimum of every 4 days. Dose reductions may be required if sustained hypertension occurs

(*continued*)

TABLE 68–1 Adult Dosing Guidance for Currently Available Antidepressant Medications (*Continued*)

Drug	Brand Name	Initial Dose (mg/day)	Usual Dosage Range (mg/day)	Comments (e.g., Maximum Daily Dosage, Suggested Therapeutic Plasma Concentration)[a]
Tricyclic antidepressants (TCAs)				
Amitriptyline	Elavil	25	100–300	Maximum 300 mg/day for MDD; may be given as a single daily dose at bedtime or in divided doses throughout the day
				Therapeutic serum level 100–250 ng/mL (370–925 nmol/L); parent drug plus metabolite (ie, nortriptyline)
Desipramine	Norpramin	25	100–300	Maximum 300 mg/day
				Suggested therapeutic concentration range for combined imipramine + desipramine: 150–300 ng/mL (550–1100 nmol/L)
Doxepin	Sinequan	25	100–300	Maximum 300 mg/day; may be given in a single daily dose at bedtime (if tolerated) or in divided doses throughout the day; a single dose should not exceed 150 mg
Imipramine	Tofranil	25	100–300	Maximum 300 mg/day; may be given in a single daily dose at bedtime (if tolerated) or in divided doses throughout the day
				Suggested therapeutic concentration range for combined imipramine + desipramine: 150–300 ng/mL (550–1100 nmol/L)
Nortriptyline	Pamelor	25	50–150	Maximum 150 mg/day; total daily may be given as a single daily dose (if tolerated) or 25 mg doses given three to four times daily
				Therapeutic serum level 50–150 ng/mL (190–570 nmol/L)
Norepinephrine and Dopamine Reuptake Inhibitor (NDRI)				
Bupropion	Wellbutrin	150	150–300	Please see text for proper dosing, which can help decrease seizure risk
				Maximum 450 mg/day (IR, ER), 400 mg/day (SR); ER dosed once daily; SR dosed once or twice daily; IR may be dosed up to three times daily

Mixed Serotonergic Effects (Mixed 5-HT)				
Nefazodone	Serzone	100	300–600	Maximum 600 mg/day; daily doses should be divided twice daily
Trazodone	Desyrel; Oleptro	50	150–300	Maximum 600 mg/day; IR daily dose should be divided three times daily and may increase by 50 mg/day increments every 3–7 days; ER dose titration initiated at 150 mg at bedtime and can be increased 75 mg/day every 3 days
Vilazodone	Viibryd	10	40	Target dose = 40 mg/day unless coadministered with CYP3A4 inhibitor (dose not to exceed 20 mg/day); doses greater than 40 mg/day have not been assessed
				Dose titration: 10 mg/day for 7 days, 20 mg/day for 7 days, and then 40 mg/day
Serotonin and α_2-Adrenergic Antagonist				
Mirtazapine	Remeron	15	15–45	Maximum 45 mg/day; may increase dose no more frequently than every 1–2 weeks; dose adjustment may be required for renal impairment
Monoamine Oxidase Inhibitors (MAOIs)				
Phenelzine	Nardil	15	30–90	Early phase recommended dosing: 15 mg three times daily; dosing may be increased to 90 mg/day based on tolerance and response
				Maintenance phase: dose should be reduced over several weeks to a daily dose as low as 15 mg/day or 15 mg every other day
Selegiline (transdermal)	Emsam	6	6–12	Not to exceed 12 mg/24 hours; dose may be increased by 3 mg/day increments every 2 weeks; transdermal delivery system designed to deliver dose continuously over a 24-hour period
Tranylcypromine	Parnate	10	20–60	Maximum 60 mg/day; divided dosing; if no response after 2 weeks, increase by 10 mg increments at 1- to 3-week intervals
				Medication cross-taper: allow at least 1 medication-free week, and then initiate tranylcypromine at 50% of usual starting dose for at least 1 week

AE, adverse effects; CR, continuous release; ER, extended release; IR, immediate release; MDD, major depressive disorder; SR, sustained release.

[a]SI conversion for cases where reference ranges are for a mixture of parent drug and active metabolite is calculated based on a 1:1 ratio..

Drug Classification

- Table 68–2 shows antidepressant potency and relative selectivity for inhibition of norepinephrine and 5-HT reuptake and side effect profiles.
- The **selective serotonin reuptake inhibitors** (SSRIs) inhibit the reuptake of 5-HT into the presynaptic neuron. They are generally chosen as first-line antidepressants because of their relative safety in overdose and improved tolerability compared with earlier agents.
- **Tricyclic antidepressant** (TCA) use has diminished because of the availability of equally effective therapies that are safer on overdose and better tolerated. In addition to inhibiting the reuptake of norepinephrine and 5-HT, they have affinity for adrenergic, cholinergic, and histaminergic receptor.
- The monoamine oxidase inhibitors (MAOIs) **phenelzine** and **tranylcypromine** increase the concentrations of norepinephrine, 5-HT, and dopamine within the neuronal synapse through inhibition of monoamine oxidase (MAO). Both drugs are nonselective inhibitors of MAO-A and MAO-B. Table 68–3 shows dietary and medication restrictions for patients taking phenelzine and tranylcypromine. **Selegiline,** available as a transdermal patch for treatment of major depression, inhibits MAO-A and MAO-B in the brain but has reduced effects on MAO-A in the gut.
- The triazolopyridines **trazodone** and **nefazodone** antagonize the 5-HT_2 receptor and inhibit the reuptake of 5-HT. They can also enhance 5-HT_{1A} neurotransmission. They have negligible affinity for cholinergic and histaminergic receptors. Nefazodone carries a black box warning for liver failure.
- The aminoketone **bupropion** blocks the reuptake of dopamine, and to a lesser extent, norepinephrine.
- The serotonin–norepinephrine reuptake inhibitors include **venlafaxine, desvenlafaxine,** and **duloxetine**.
- **Vilazodone** inhibits 5-HT reuptake and is a 5-HT_{1A} partial agonist.
- **Mirtazapine** enhances central noradrenergic and serotonergic activity by antagonizing central presynaptic α_2-adrenergic autoreceptors and heteroreceptors. It also antagonizes 5-HT_2 and 5-HT_3 receptors and blocks histamine receptors.
- **St. John's wort,** an herbal medication containing hypericum, may be effective for mild to moderate depression. It is associated with several drug–drug interactions. All antidepressant regimens should be overseen by a trained healthcare professional.

Adverse Effects

- See Table 68–2 for antidepressant adverse effect profiles and Table 68–4 for adverse effects and monitoring parameters of new-generation antidepressants.
- Early in treatment, all antidepressants can increase suicidal thinking and behavior in children, adolescents, and young adults 18 to 24 years of age.
- Any antidepressant that enhances serotonergic activity can be associated with serotonin syndrome characterized by mental status changes, autonomic instability, and neuromuscular abnormalities.

Tricyclic Antidepressants and Other Heterocyclics

- Anticholinergic side effects (eg, dry mouth, blurred vision, constipation, urinary retention, tachycardia, memory impairment, and delirium) and sedation are more likely to occur with the tertiary amine **TCAs** than with the secondary amine TCAs.
- **Desipramine** carries an increased risk of death in patients with a family history of sudden cardiac death, cardiac dysrhythmias, or cardiac conduction disturbances.
- Orthostatic hypotension and resultant syncope, a common adverse effect of the **TCAs,** result from α_1-adrenergic antagonism. Additional side effects include cardiac conduction delays and heart block, especially in patients with preexisting conduction disease. Other side effects that may lead to nonadherance are weight gain and sexual dysfunction.
- Abrupt withdrawal of **TCAs** (especially high doses) may result in cholinergic rebound (eg, dizziness, nausea, diarrhea, insomnia, and restlessness).

TABLE 68–2 Relative Potencies of Norepinephrine and Serotonin Reuptake Blockade and Selected Side Effect Profile of Antidepressants

	Reuptake Antagonism		Anticholinergic Effects	Sedation	Orthostatic Hypotension	Seizures[a]	Conduction Abnormalities[a]
	Norepinephrine	Serotonin					
Selective Serotonin Reuptake Inhibitors (SSRIs)							
Citalopram	0	++++	0	+	0	++	++
Escitalopram	0	++++	0	0	0	0	0
Fluoxetine	0	+++	0	0	0	++	0
Fluvoxamine	0	++++	0	+	0	++	0
Paroxetine	0	++++	+	+	0	++	0
Sertraline	0	++++	0	0	0	++	0
Serotonin–Norepinephrine Reuptake Inhibitors (SNRIs)							
Duloxetine[b]	++++	++++	+	0	+	0	0
Venlafaxine[c] and desvenlafaxine	++++	++++	+	+	0	++	+
Tricyclic Antidepressants (TCAs)							
Amitriptyline	++	++++	++++	++++	+++	+++	+++
Desipramine	++++	+	++	++	++	++	++
Doxepin	++	++	+++	++++	++	+++	++
Imipramine	+++	+++	+++	+++	++++	+++	+++
Nortriptyline	+++	++	++	++	+	++	++

(*continued*)

TABLE 68–2 Relative Potencies of Norepinephrine and Serotonin Reuptake Blockade and Selected Side Effect Profile of Antidepressants (*Continued*)

	Reuptake Antagonism		Anticholinergic Effects	Sedation	Orthostatic Hypotension	Seizures[a]	Conduction Abnormalities[a]
	Norepinephrine	Serotonin					
Mixed Serotonergic (Mixed 5-HT)							
Nefazodone	0	++	0	+++	+++	++	+
Trazodone	0	++	0	++++	+++	++	+
Vilazodone	0	++++	0	+	0	++	0
Norepinephrine and Dopamine Reuptake Inhibitor (NDRI)							
Bupropion[d]	+	0	+	0	0	++++	+
Serotonin and α2-Receptor Antagonist							
Mirtazapine	0	0	+	++	++	0	+

++++, high; +++, moderate; ++, low; +, very low; 0, absent.

[a] These are uncommon side effects of antidepressant drugs, particularly when used at normal therapeutic doses; they may be dose-dependent, resulting in corresponding dose restrictions (eg, citalopram 40 mg/day maximum due to QTc prolongation concerns).

[b] Duloxetine: balanced 5-HT and NE reuptake inhibition.

[c] Venlafaxine: primarily 5-HT at lower doses, NE at higher doses, and DA at very high doses.

[d] Bupropion: also blocks dopamine reuptake.

TABLE 68–3 Dietary and Medication Restrictions for Patients Taking Monoamine Oxidase Inhibitors[a]

Foods	
Aged cheeses[b]	Liver (chicken or beef, more than 2 days old)
Sour cream[c]	Raisins
Yogurt[c]	Pods of broad beans (fava beans)
Cottage cheese[c]	Yeast extract and other yeast products
American cheese[c]	Soy sauce
Mild Swiss cheese[c]	Chocolate[e]
Wine[d] (especially Chianti and sherry)	Coffee[e]
Beer	Ripe avocado
Sardines	Sauerkraut
Canned, aged, or processed meats	Licorice
Monosodium glutamate	
Medications	
Amphetamines	Levodopa
Appetite suppressants	Local anesthetics containing sympathomimetic vasoconstrictors
Asthma inhalants	Meperidine
Buspirone	Methyldopa
Carbamazepine	Methylphenidate
Cocaine	Other antidepressants[f]
Cyclobenzaprine	Other MAOIs
Decongestants (topical and systemic)	Reserpine
Dextromethorphan	Rizatriptan
Dopamine	Stimulants
Ephedrine	Sumatriptan
Epinephrine	Sympathomimetics
Guanethidine	Tryptophan

[a] According to the FDA-approved prescribing information for the transdermal selegiline patch, patients receiving the 6-mg/24-hour dose are not required to modify their diet. However, patients receiving the 9- or 12-mg/24-hour dose are still required to follow the dietary restrictions similar to the other MAOIs.
[b] Clearly warrants absolute prohibition (eg, English Stilton, blue, Camembert, cheddar).
[c] Up to 2 oz daily is acceptable.
[d] Three ounce white wine or a single cocktail is acceptable.
[e] Up to 2 oz daily is acceptable: larger amounts of decaffeinated coffee are acceptable.
[f] Tricyclic antidepressants may be used with caution by experienced clinicians in treatment-resistant populations.

- **Amoxapine** blocks postsynaptic dopamine receptors and may cause extrapyramidal side effects.
- **Maprotiline,** a tetracyclic drug, causes seizures at a higher incidence than do standard TCAs and is contraindicated in patients with a history of seizure disorder. The ceiling dose is 225 mg/day.

TABLE 68–4 Adverse Drug Reactions and Monitoring Parameters Associated with Select New-Generation Antidepressants

Drug	ADR(s)	Monitoring	Comments
Antidepressants from Each Pharmacologic Class			
Common to all antidepressants			
	Suicidality	Behavioral changes Mental status	(U.S. boxed warning) for all antidepressants; caregivers should be alerted to monitor for acute changes in behavior
Selective Serotonin Reuptake Inhibitors (SSRIs)			
Common to all SSRIs			
	Anxiety or nervousness	Assess severity and impact on patient functioning and quality of life	Most prominent on initial treatment; generally subsides over time as antidepressant causes neurochemical adaptations
	Insomnia	Sleep patterns	Among SSRI class: fluoxetine may be more activating; fluvoxamine and paroxetine may be more sedating
	Nausea	Frequency and severity	
	Serotonin syndrome	Autonomic function (eg, pulse, temperature); neuromuscular function	Criteria include mental status change, clonus, hyperthermia, diaphoresis, and tachycardia
	Sexual dysfunction	Assess severity and impact on patient functioning and quality of life	Spontaneous self-reporting may be low; clinician should assess symptoms; reversible on drug discontinuation
SSRI-Specific			
Citalopram	QT interval prolongation	Electrocardiogram; electrolytes (eg, potassium, magnesium)	Caution use in "at-risk" patients (eg, electrolyte disturbance); discontinue if QTc persistently >500 milliseconds
Fluoxetine	Anorexia	Weight (over time)	SSRIs are generally considered weight neutral

Fluvoxamine	Somnolence	Mental status	May be less tolerable than other SSRIs
Paroxetine	Anticholinergic effects	Symptoms: dry mouth, constipation, urinary retention, mental status	Paroxetine possesses relatively more anticholinergic effects than other SSRIs
Serotonin–Norepinephrine Reuptake Inhibitors (SNRIs)			
Common to all SNRIs			
	Insomnia	Sleep patterns	Possibly less likely with duloxetine
	Nausea	Frequency and severity	
	Serotonin syndrome	Autonomic function (eg, pulse temperature); neuromuscular function	Criteria include mental status changes, clonus, hyperthermia, diaphoresis, and tachycardia
	Sexual dysfunction	Assess severity and impact on patient functioning and quality of life	Spontaneous self-reporting may be low; clinician should assess symptoms; reversible on drug discontinuation
SNRI-Specific			
Desvenlafaxine	Hyperlipidemia	Lipid profile	Elevations in total cholesterol, low-density lipoproteins, and triglycerides
Duloxetine	Orthostatic *hypo*-tension	Blood pressure, pulse	Initial treatment or on dose increase
Venlafaxine	Dose-related *hyper*-tension	Blood pressure, pulse	May need to lower dose or discontinue

(*continued*)

TABLE 68–4 Adverse Drug Reactions and Monitoring Parameters Associated with Select New-Generation Antidepressants (*Continued*)

Drug	ADR(s)	Monitoring	Comments
Mixed Serotonergic Effects (Mixed 5-HT)			
Nefazodone	Liver toxicity	Liver function tests	Nefazodone use is extremely limited in the United States due to concerns about liver toxicity
Trazodone	Orthostatic hypotension	Blood pressure, pulse	May be more severe as compared with other antidepressants; rate-limiting side effect
	Priapism	Patient report of sexual side effects, especially painful erection	Patient should seek medical attention for prolonged erection (ie, >4 hours)
Vilazodone	Serotonin syndrome	Autonomic function (eg, pulse temperature); neuromuscular function	Criteria include mental status changes, clonus, hyperthermia, diaphoresis, and tachycardia
Serotonin and α_2-Adrenergic Antagonist			
Mirtazapine	Weight gain	Body weight	Frequently occurring and significant (>7%) weight gain among adults
Norepinephrine and Dopamine Reuptake Inhibitor (NDRI)			
Bupropion	Seizure activity	Electroencephalogram	See text for proper dosing, which can help decrease seizure risk; caution use in patients with eating disorders or alcohol use disorders

Serotonin-Norepinephrine Reuptake Inhibitors

- **Venlafaxine** may cause a dose-related increase in diastolic blood pressure. Dosage reduction or discontinuation may be necessary if sustained hypertension occurs. Other side effects are similar to those associated with SSRIs.
- The most common side effects of **duloxetine** are nausea, dry mouth, constipation, decreased appetite, insomnia, and increased sweating.

Selective Serotonin Reuptake Inhibitors

- The SSRIs produce fewer sedative, anticholinergic, and cardiovascular adverse effects than the TCAs and are less likely to cause weight gain. The primary adverse effects are nausea, vomiting, diarrhea, headache, insomnia, fatigue, and sexual dysfunction. A few patients have anxiety symptoms early in treatment. Citalopram has been linked to an increase in QT interval at doses above 40 mg/day (see Table 68–1).

Triazolopyridines

- **Trazodone** and **nefazodone** cause minimal anticholinergic effects. Sedation, dizziness, and orthostatic hypotension are the most frequent dose-limiting side effects.
- Priapism occurs rarely with trazodone (1 in 6000 male patients). Surgical intervention may be required, and impotence may result.
- A black box warning for life-threatening liver failure was added to the prescribing information for nefazodone. Do not initiate nefazodone in individuals with active liver disease or elevated serum transaminases.

Aminoketone

- The occurrence of seizures with **bupropion** is dose related and may be increased by predisposing factors (eg, history of head trauma or central nervous system [CNS] tumor). At the ceiling dose (450 mg/day), the incidence of seizures is 0.4%. Other side effects are nausea, vomiting, tremor, insomnia, dry mouth, and skin reactions. It is contraindicated in patients with bulimia or anorexia nervosa. It causes less sexual dysfunction than SSRIs.

Mirtazapine

- **Mirtazapine**'s most common adverse effects are somnolence, weight gain, dry mouth, and constipation.

Monoamine Oxidase Inhibitors

- The most common adverse effect of MAOIs is postural hypotension (more likely with **phenelzine** than **tranylcypromine**), which can be minimized by divided-daily dosing. Anticholinergic side effects are common but less severe than with the TCAs. Phenelzine is mildly to moderately sedating, but tranylcypromine is often stimulating, and the last dose of the day is administered in the early afternoon. Sexual dysfunction in both genders is common. Phenelzine has been associated with hepatocellular damage and weight gain.
- Hypertensive crisis is a potentially fatal reaction that can occur when MAOIs are taken concurrently with certain foods, especially those high in tyramine, and with certain drugs (see Table 68–3). Symptoms of hypertensive crisis include occipital headache, stiff neck, nausea, vomiting, sweating, and sharply elevated blood pressure. Hypertensive crisis may be treated with agents such as captopril. Education of patients taking MAOIs regarding dietary and medication restrictions is critical. Patients taking transdermal selegiline patch doses greater than 6-mg/24 hours must follow the dietary restrictions.

Pharmacokinetics

- The pharmacokinetics of the antidepressants is summarized in **Table 68–5**.
- Metabolism of the **TCAs** occurs through demethylation, hydroxylation, and glucuronide conjugation, and it appears to be linear within the usual dosage range. Dose-related kinetics cannot be ruled out in the elderly. Factors reported to influence TCA plasma concentrations include renal or hepatic dysfunction, genetics, age, cigarette smoking, and concurrent drug administration.

TABLE 68–5 Pharmacokinetic Properties of Antidepressants

Generic Name	Elimination Half-Life[a]	Time of Peak Plasma Concentration (Hours)	Plasma Protein Binding (%)	Percentage Bioavailable	Clinically Important Metabolites
Selective Serotonin Reuptake Inhibitors (SSRIs)					
Citalopram	33 hours	2–4	80	≥80	None
Escitalopram	27–32 hours	5	56	80	None
Fluoxetine	4–6 days[b]	4–8	94	95	Norfluoxetine
Fluvoxamine	15–26 hours	2–8	77	53	None
Paroxetine	24–31 hours	5–7	95		None
Sertraline	27 hours	6–8	99	36[c]	None
Serotonin–Norepinephrine Reuptake Inhibitors (SNRIs)					
Desvenlafaxine	11 hours	7.5	30	80	None
Duloxetine	12 hours	6	90	50	None
Venlafaxine	5 hours	2	27–30	45	*O*-Desmethylvenlafaxine
TCAs					
Amitriptyline	9–46 hours	1–5	90–97	30–60	Nortriptyline
Desipramine	11–46 hours	3–6	73–92	33–51	2-Hydroxydesipramine
Doxepin	8–36 hours	1–4	68–82	13–45	Desmethyldoxepin
Imipramine	6–34 hours	1.5–3	63–96	22–77	Desipramine
Nortriptyline	16–88 hours	3–12	87–95	46–70	10-Hydroxynortriptyline

Mixed Serotonergic (Mixed 5-HT)					
Nefazodone	2–4 hours	1	99	20	*meta*-Chlorophenylpiperazine
Trazodone	6–11 hours	1–2	92	[d]	*meta*-Chlorophenylpiperazine
Vilazodone	25 hours	4–5	>95	72[e]	
Norepinephrine/Dopamine Reuptake Inhibitor (NDRI)					
Bupropion	10–21 hours	3	82–88	[d]	Hydroxybupropion Threohydrobupropion Erythrohydrobupropion
Serotonin and α_2-Adrenergic Antagonists					
Mirtazapine	20–40 hours	2	85	50	None

[a] Biologic half-life in slowest phase of elimination.
[b] Four to 6 days with chronic dosing; norfluoxetine, 4–16 days.
[c] Increases 30–40% when taken with food.
[d] No data available.
[e] Take with food to increase area under the curve concentrations.

- The SSRIs, with the possible exceptions of **citalopram** and **sertraline,** may have a nonlinear pattern of drug accumulation with chronic dosing. Hepatic impairment, renal impairment, and age can influence the pharmacokinetics of **SSRIs**
- **Mirtazapine** is primarily eliminated in the urine.
- In acutely depressed patients, there is a correlation between antidepressant effect and plasma concentrations for some **TCAs**. Table 68–1 shows suggested therapeutic plasma concentration ranges. The best-established therapeutic range is for **nortriptyline**, and data suggest a therapeutic window.
- Some indications for TCA plasma level monitoring include inadequate response; relapse; serious or persistent adverse effects; use of higher than standard doses; suspected nonadherence, pharmacokinetic interactions, or toxicity; elderly, pediatric, and adolescent patients; pregnant patients; patients of African or Asian descent (because of slower metabolism); cardiac disease; and changing brands. Plasma concentrations should be obtained at steady state, usually after a minimum of 1 week at constant dosage, during the elimination phase, and usually in the morning 12 hours after the last dose. Samples collected in this manner are comparable for patients on once-daily, twice-daily, or thrice-daily regimens.

Drug–Drug Interactions

- **TCAs** may interact with other drugs that modify hepatic cytochrome P450 (CYP450) enzyme activity or hepatic blood flow. TCAs also are involved in interactions through displacement from protein-binding sites.
- Increased plasma concentrations of TCAs and symptoms of toxicity may occur when **fluoxetine** and **paroxetine** are added.
- The very slow elimination of **fluoxetine** and **norfluoxetine** makes it critical to ensure a 5-week washout after fluoxetine discontinuation before starting an **MAOI**. Potentially fatal reactions may occur when any **SSRI** or **TCA** is coadministered with an MAOI. TCAs and MAOIs can be combined in refractory patients by experienced clinicians with careful monitoring.
- Combining an SSRI with another 5-HT augmenting agent can lead to the serotonin syndrome.
- The ability of any antidepressant to inhibit or induce the CYP450 enzymes can be a significant factor in determining its capability to cause a pharmacokinetic drug–drug interaction. If an SSRI is added to a regimen which includes drugs known to interact with SSRIs, the SSRI starting dose should be low and slowly titrated.
- Table 68–6 compares second- and third-generation antidepressants for their effects on the CYP450 enzymes. CYP2D6 and 3A4 are responsible for the metabolism of more than 80% of currently marketed drugs. Mirtazapine, venlafaxine, duloxetine, and bupropion have relatively little inhibition on CYP450 enzymes; thus their drug interactions are largely pharmacodynamic, not pharmacokinetic.
- Consult the drug interaction literature for detailed information concerning any real or potential psychotherapeutic drug interactions.

SPECIAL POPULATIONS

Elderly Patients

- In the elderly, depressed mood may be less prominent than other symptoms, such as loss of appetite, cognitive impairment, sleeplessness, fatigue, physical complaints, and loss of interest and enjoyment in usual activities.
- The **SSRIs** are often considered first-choice antidepressants in elderly patients.
- **Bupropion, venlafaxine, and mirtazapine** are also effective and well tolerated.

Pediatric Patients

- Symptoms of depression in childhood include boredom, anxiety, failing adjustment, and sleep disturbance.
- Data supporting efficacy of antidepressants in children and adolescents are sparse. **Fluoxetine** is the only FDA approved antidepressant for treating depression in patients below 18 years of age.

TABLE 68–6 Second- and Third-Generation Antidepressants and Cytochrome (CYP) P450 Enzyme Inhibitory Potential

	CYP Enzyme			
Drug	**1A2**	**2C**	**2D6**	**3A4**
Bupropion	0	0	+	0
Citalopram	0	0	+	NA
Duloxetine	0	0	+++	0
Escitalopram	0	0	+	0
Fluoxetine	0	++	++++	++
Fluvoxamine	++++	++	0	+++
Mirtazapine	0	0	0	0
Nefazodone	0	0	0	++++
Paroxetine	0	0	++++	0
Sertraline	0	++	+	+
(des)Venlafaxine	0	0	0/+	0

++++, high; +++, moderate; ++, low; +, very low; 0, absent.

- The FDA has established a link between antidepressant use and suicidality (suicidal thinking and behaviors) in children, adolescents, and young adults 18 to 24 years old. All antidepressants carry a black box warning for caution when using antidepressants in this population, and the FDA recommends specific monitoring parameters. Consult the FDA-approved labeling or the FDA website for additional information. However, several retrospective longitudinal reviews of the use of antidepressants in children found no significant increase in the risk of suicide attempts or deaths.
- Several cases of sudden death have been reported in children and adolescents taking **desipramine**. A baseline electrocardiogram (ECG) is recommended before initiating a TCA in children and adolescents, and an additional ECG is advised when steady-state plasma concentrations are achieved. TCA plasma concentration monitoring is critical to ensure safety.

Pregnancy

- As a general rule, if effective, nondrug approaches are preferred when treating depressed pregnant patients. For those with history of relapse after antidepressant discontinuation, the antidepressant can be continued throughout pregnancy.
- One study showed that pregnant women who discontinued antidepressants were five times more likely to relapse during pregnancy than women who continued treatment.
- There is a possible association of **SSRIs** with low birth weight and respiratory distress. Another study reported a sixfold greater likelihood of persistent pulmonary hypertension in newborn infants exposed to an SSRIs after the twentieth week of gestation.
- Consider the risks of untreated depression in pregnancy, including low birth weight, maternal suicidality, potential for hospitalization or marital discord, poor prenatal care, and difficulty caring for other children.

Relative Resistance and Treatment-Resistant Depression

- Most "treatment-resistant" depressed patients have received inadequate therapy. In patients who have not responded to treatment, consider the following: (1) Is the diagnosis correct? (2) Does the patient have a psychotic depression? (3) Has the patient received an adequate dose and duration of treatment? (4) Do adverse effects

preclude adequate dosing? (5) Has the patient adhered to the prescribed regimen? (6) Was treatment outcome measured adequately? (7) Is there a coexisting or preexisting medical or psychiatric disorder? (8) Was a stepwise approach to treatment used? (9) Are there other factors that interfere with treatment?

- The STAR*D study showed that one in three depressed patients who did not achieve remission with an antidepressant became symptom-free when an additional medication (eg, **sustained-release bupropion**) was added, and one in four achieved remission after switching to a different antidepressant (eg, **extended-release venlafaxine**).
- The current antidepressant may be stopped and a trial initiated with different agent (eg, **mirtazapine** or **nortriptyline**).
- Alternatively, the current antidepressant may be augmented (potentiated) by addition of another agent (eg, **lithium** or **triiodothyronine [T_3]**), or another antidepressant can be added. An atypical antipsychotic can be used to augment antidepressant response.
- The practice guideline of the American Psychiatric Association recommends that after 6 to 8 weeks of antidepressant treatment, partial responders should consider changing the dose, augmenting the antidepressant, or adding psychotherapy or ECT. For those with no response, options include changing to another antidepressant or the addition of psychotherapy or ECT. Figure 68–1 is an algorithm for treatment of depression including refractory patients.

EVALUATION OF THERAPEUTIC OUTCOMES

- Several monitoring parameters, in addition to plasma concentrations, are useful. Monitor regularly for adverse effects (see Table 68–4), remission of target symptoms, and changes in social or occupational functioning. Assure regular monitoring for several months after discontinuation of antidepressants.
- Regularly monitor blood pressure of patients given venlafaxine.
- Order a pretreatment ECG before starting TCA therapy in patients over 40 years of age, and perform follow-up ECGs periodically.
- Monitor for emergence of suicidal ideation after initiation of any antidepressant, especially in the first few weeks of treatment.
- In addition to the clinical interview, use psychometric rating instruments to rapidly and reliably measure the nature and severity of depressive and associated symptoms.

See Chapter 51, Major Depressive Disorder, authored by Christian J. Teter, Judith C. Kando, and Barbara G. Wells, for a more detailed discussion of this topic.

CHAPTER 69

Schizophrenia

- *Schizophrenia* is characterized by delusions, hallucinations, disorganized thinking and speech, abnormal motor behavior, and negative symptoms.

PATHOPHYSIOLOGY

- Increased ventricular size and decreased gray matter, have been reported.
- Schizophrenia causation theories include genetic predisposition, obstetric complications, increased neuronal pruning, immune system abnormalities, neurodevelopmental disorders, neurodegenerative theories, dopamine receptor defect, and regional brain abnormalities including hyper- or hypo-activity of dopaminergic processes in specific brain regions.
- Positive symptoms may be more closely associated with dopamine receptor hyperactivity in the mesocaudate, whereas negative and cognitive symptoms may be most closely related to dopamine receptor hypofunction in the prefrontal cortex.
- *Glutamatergic dysfunction*. A deficiency of glutamatergic activity produces symptoms similar to those of dopaminergic hyperactivity and possibly schizophrenic symptoms.
- *Serotonin (*5-hydroxytriptamine *[5-HT]) abnormalities*. Schizophrenic patients with abnormal brain scans have higher whole blood 5-HT concentrations, which correlate with increased ventricular size.

CLINICAL PRESENTATION

- Symptoms of the acute episode may include: being out of touch with reality; hallucinations (especially hearing voices); delusions (fixed false beliefs); ideas of influence (actions controlled by external influences); disconnected thought processes (loose associations); ambivalence (contradictory thoughts); flat, inappropriate, or labile affect; autism (withdrawn and inwardly directed thinking); uncooperativeness, hostility, and verbal or physical aggression; impaired self-care skills; and disturbed sleep and appetite.
- After the acute psychotic episode has resolved, typically there are residual features (eg, anxiety, suspiciousness, lack of motivation, poor insight, impaired judgment, social withdrawal, difficulty in learning from experience, and poor self-care skills). Comorbid substance abuse and nonadherence with medications are common.
- Positive symptoms – delusions, disorganized speech (association disturbance), hallucinations, behavior disturbance (disorganized or catatonic), and illusions.
- Negative symptoms – alogia (poverty of speech), avolition, flat affect, anhedonia, and social isolation.
- Cognitive dysfunction– impaired attention, working memory, and executive function.

DIAGNOSIS

- The *Diagnostic and Statistical Manual of Mental Disorders*, 5th ed. (*DSM-5*), specifies the following diagnostic criteria:
  - ✓ Continuous symptoms that persist for at least 6 months with at least one month of active phase symptoms (Criterion A) and may include prodromal or residual symptoms.
    - ❖ Criterion A: For at least 1 month, there must be at least two of the following present for a significant portion of time: delusions, hallucinations, disorganized speech, grossly disorganized or catatonic behavior, and negative symptoms. At least one symptom must be delusions, hallucinations, or disorganized speech.
    - ❖ Criterion B: Significantly impaired functioning

TREATMENT

- Goals of Treatment: The goal is to alleviate target symptoms, avoid side effects, improve psychosocial functioning and productivity, achieve compliance with the prescribed regimen, and involve the patient in treatment planning.
- Before treatment, perform a mental status examination, physical and neurologic examination, complete family and social history, psychiatric diagnostic interview, and laboratory workup (complete blood count [CBC], electrolytes, hepatic function, renal function, electrocardiogram [ECG], fasting serum glucose, serum lipids, thyroid function, and urine drug screen).

GENERAL APPROACH

- Antipsychotics and dosage ranges are shown in **Table 69–1**. Second-generation antipsychotics (SGAs) (also known as *atypical antipsychotics*), except clozapine, are the

TABLE 69–1 Available Antipsychotics and Dosage Ranges

Generic Name	Trade Name	Starting Dose (mg/day)	Usual Dosage Range (mg/day)	Comments
First-Generation Antipsychotics				
Chlorpromazine	Thorazine	50–150	300–1,000	Most weight gain among FGAs
Fluphenazine	Prolixin	5	5–20	
Haloperidol	Haldol	2–5	2–20	Higher dropout rate in first episode
Loxapine	Loxitane	20	50–150	
Loxapine inhaled	Adasuve	10	10	Maximum 10 mg per 24 hours Approved REMS program only
Perphenazine	Trilafon	4–24	16–64	
Thioridazine	Mellaril	50–150	100–800	Significant QTc prolongation
Thiothixene	Navane	4–10	4–50	
Trifluoperazine	Stelazine	2–5	5–40	
Second-Generation Antipsychotics				
Aripiprazole	Abilify	5–15	15–30	
Asenapine	Saphris	5	10–20	Sublingual only
Clozapine	Clozaril	25	100–800	Check plasma level before exceeding 600 mg
Iloperidone	Fanapt	1–2	6–24	Care with dosing in CYP2D6 slow metabolizers
Lurasidone	Latuda	20–40	40–120	
Olanzapine	Zyprexa	5–10	10–20	Avoid in first episode because of weight gain
Paliperidone	Invega	3–6	3–12	Bioavailability increased when administered with food
Quetiapine	Seroquel	50	300–800	
Risperidone	Risperdal	1–2	2–8	
Ziprasidone	Geodon	40	80–160	Take with food

Note: In first-episode patients, starting dose and target dose should generally be 50% of the usual dose range. See Long-Acting Injectable Antipsychotics in text for dosing for these agents.

first choice agents for schizophrenia. SGAs (eg, **clozapine, olanzapine, risperidone, quetiapine, ziprasidone,** and **aripiprazole**) may have superior efficacy for negative symptoms and cognition, but this is controversial.

- SGAs are said to cause few or no acutely occurring extrapyramidal side effects, minimal or no propensity to cause tardive dyskinesia (TD), and less effect on serum prolactin than the first-generation antipsychotics (FGAs) (typical antipsychotics). **Clozapine** is the only SGA that fulfills all these criteria.
- SGAs increase risk for metabolic side effects, including weight gain, hyperlipidemia, and diabetes mellitus.
- The Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) study showed that olanzapine, compared with quetiapine, risperidone, ziprasidone, and perphenazine, has modest superiority in persistence of maintenance therapy but more metabolic side effects.
- Base antipsychotic selection on (1) the need to avoid certain side effects, (2) concurrent medical or psychiatric disorders, and (3) patient or family history of response. **Figure 69–1** is an algorithm for management of first episode psychosis. Clozapine has superior efficacy for suicidal behavior.
- Predictors of good antipsychotic response include prior good response to the drug selected, absence of alcohol or drug abuse, acute onset and short duration of illness, acute stressors or precipitating factors, later age of onset, affective symptoms, family history of affective illness, medication compliance, and good premorbid adjustment. Negative symptoms are generally less responsive to antipsychotic therapy.
- An initial dysphoric response, that is, a dislike of the medication or feeling worse, combined with anxiety or akathisia, portends a poor drug response, adverse effects, and nonadherence.

PHARMACOKINETICS

- Pharmacokinetic parameters and major metabolic pathways of antipsychotics are summarized in **Table 69–2**.
- Antipsychotics, highly lipophilic and highly bound to membranes and plasma proteins, have large volumes of distribution and are largely metabolized by cytochrome P450 pathways (except ziprasidone).
- **Risperidone** and its active metabolite 9-OH-resperidone are metabolized by CYP2D6. Polymorphic metabolism should be considered in those with side effects at low doses. Polymorphism in CYP1A2 can cause decreased metabolism of **clozapine**. Eating or drinking within 10 minutes of **asenapine** sublingual administration reduces bioavailability.
- Most antipsychotics have half-lives of elimination in the range of 20 to 40 hours. After dosage stabilization, most antipsychotics (except **quetiapine** and **ziprasidone**) can be dosed once daily. It may be possible to dose SGAs less often than their plasma kinetics suggest.
- A 12-hour postdose **clozapine** serum concentration of at least 350 ng/mL (1.07 µmol/L) is associated with efficacy. Monitor serum concentrations of clozapine before exceeding 600 mg daily, in patients with unusual or severe adverse effects, in those taking potentially interacting concomitant medications, in those with age or pathophysiologic changes suggesting altered kinetics, and in those suspected of medication nonadherence.

INITIAL THERAPY

- The goals during the first 7 days are decreased agitation, hostility, anxiety, and aggression and normalization of sleep and eating. Average doses are about at the middle of the ranges shown in **Table 69–1**. For first episode psychosis, the dose range is about 50% of that of chronically ill patients.
- Titrate over the first few days to an average effective dose. Titrate iloperidone and clozapine more slowly due to risk of hypotension. After 1 week at a stable dose, a modest dosage increase may be considered. If there is no improvement within 3 to

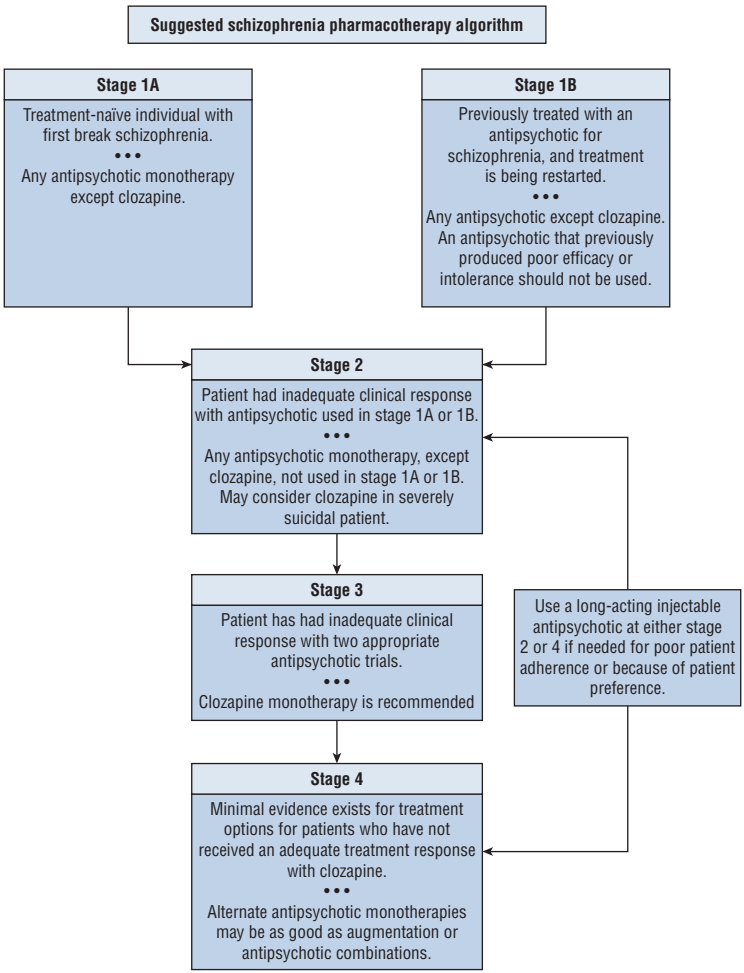


FIGURE 69–1. Suggested pharmacotherapy algorithm for treatment of schizophrenia. Schizophrenia should be treated in the context of an interprofessional model that addresses the psychosocial needs of the patient, necessary psychiatric pharmacotherapy, psychiatric comorbidities, treatment adherence, and any medical problems the patient may have.

4 weeks at therapeutic doses, then an alternative antipsychotic should be considered (ie, move to the next treatment stage in **Fig. 69–1**).

- In partial responders who are tolerating the antipsychotic well, it may be reasonable to titrate above the usual dose range with close monitoring.
- Rapid titration of antipsychotic dose is not recommended.
- Intramuscular (IM) antipsychotic administration (eg, aripiprazole 5.25–9.75 mg, ziprasidone 10–20 mg, olanzapine 2.5–10 mg, or haloperidol 2–5 mg) can be used to calm agitated patients. However, this approach does not improve the extent of response, time to remission, or length of hospitalization.

TABLE 69–2 Pharmacokinetic Parameters of Selected Antipsychotics

Drug	Bioavailability (%)	Half-Life	Major Metabolic Pathways	Active Metabolites
Selected First-Generation Antipsychotics (FGAs)				
Chlorpromazine	10–30	8–35 hours	FMO3, CYP3A4	7-Hydroxy, others
Fluphenazine	20–50	14–24 hours	CYP2D6	?
Fluphenazine decanoate		14.2 ± 2.2[a] days	CYP2D6	
Haloperidol	40–70	12–36 hours	CYP1A2, CYP2D6, CYP3A4	Reduced haloperidol
Haloperidol decanoate		21 days	CYP1A2, CYP2D6, CYP3A4	Reduced haloperidol
Perphenazine	20–25	8.1–12.3 hours	CYP2D6	7-OH-perphenazine
Second-Generation Antipsychotics (SGAs)				
Aripiprazole	87	48–68 hours	CYP2D6, CYP3A4	Dehydroaripiprazole
Asenapine	<2 orally 35 SL Nonlinear	13–39 hours	UGT1A4, CYP1A2	None known
Clozapine	12–81	11–105 hours	CYP1A2, CYP3A4, CYP2C19	Desmethylclozapine
Iloperidone	96	18–33 hours	CYP2D6, CYP3A4	P88
Lurasidone	10–20	18 hours	CYP3A4	ID-14233 and ID-14326
Olanzapine	80	20–70 hours	CYP1A2, CYP3A4, FMO3	N-Glucuronide; 2-OH-methyl; 4-N-oxide

(*continued*)

TABLE 69–2 Pharmacokinetic Parameters of Selected Antipsychotics (*Continued*)

Drug	Bioavailability (%)	Half-Life	Major Metabolic Pathways	Active Metabolites
Paliperidone ER	28	23 hours	Renal unchanged (59%) CYP3A4 and multiple pathways	None known
Paliperidone palmitate		25–49 days	Renal unchanged (59%) CYP3A4 and multiple pathways	None known
Quetiapine	9 ± 4	6.88 hours	CYP3A4	7-OH-quetiapine
Risperidone	68	3–24 hours	CYP2D6	9-OH-risperidone
Risperidone Consta		3–6 days	CYP2D6	9-OH-risperidone
Ziprasidone	59	4–10 hours	Aldehyde oxidase, CYP3A4	None

[a]Based on multiple-dose data. Single-dose data indicate a β–half-life of 6–10 days.

- IM **lorazepam,** 2 mg, as needed added to the maintenance antipsychotic may be more effective for agitation than additional doses of antipsychotic. Combining IM lorazepam with **olanzapine** or **clozapine** is not recommended because of the risk of hypotension, CNS depression, and respiratory depression.

STABILIZATION THERAPY

- During weeks 2 and 3, the goals is to improve socialization, self-care, and mood. Improvement in formal thought disorder may require an additional 6 to 8 weeks.
- Dose titration may continue every 1 to 2 weeks as long as the patient has no side effects.
- If symptom improvement is unsatisfactory after 8 to 12 weeks at adequate doses, consider the next algorithm stage. (See **Fig. 69–1.**)

MAINTENANCE THERAPY

- Continue medication for at least 12 months after remission of the first psychotic episode. Lifetime pharmacotherapy is necessary in most schizophrenic patients.
- Antipsychotics (especially FGAs and **clozapine**) should be tapered slowly before discontinuation to avoid rebound cholinergic symptoms.
- In general, when switching from one antipsychotic to another, the first should be tapered and discontinued over 1 to 2 weeks while the second antipsychotic is initiated and tapered upward.

Depot Antipsychotic Medications

- With partial or poor adherence, a long-acting injectable antipsychotic should be considered (eg, risperidone microspheres, paliperidone palmitate, extended-release olanzapine, haloperidol decanoate, or fluphenazine decanoate).
- Conversion from oral antipsychotics to depot formulations:
  - ✓ Stabilize on an oral dosage form of the same agent (or at least a short trial of 3–7 days) to ensure adequate tolerance.
- **Risperidone Consta** is started at 25 mg. Usual dosing range is 25 to 50 mg deep IM every 2 weeks. Oral medication must be administered for at least 3 weeks after beginning injections. Make dose adjustments no more often than every 4 weeks.
- **Paliperidone palmitate** is started at 234 mg and 156 mg 1 week later given in the gluteal or deltoid muscle. No overlap of oral dosing is necessary. Monthly IM doses are then titrated between 39 mg and 234 mg.
- Olanzapine pamoate monohydrate is administered every 2 or 4 weeks by deep gluteal injection. The initial dose varies from 210 mg to 405 mg. About 2% of patients have a postinjection sedation/delirium syndrome (black box warning), and it must be administered in a registered healthcare facility with patient observation by a professional for at least 3 hours postdose.
- For **fluphenazine decanoate**, the simplest conversion is the Stimmel method—1.2 times the oral daily dose for stabilized patients, rounding up to the nearest 12.5 mg interval, administered IM in weekly doses for the first 4 to 6 weeks (1.6 times the oral daily dose for more acutely ill patients). Subsequently, fluphenazine decanoate may be administered once every 2 to 3 weeks. Oral fluphenazine may be overlapped for 1 week.
- For **haloperidol decanoate**, a factor of 10 to 15 times the oral daily dose is commonly recommended, rounding up to the nearest 50-mg interval, administered IM once-monthly with oral haloperidol overlap for 1 month.
- Administer haloperidol and fluphenazine decanoate by a deep, "Z-track" IM method. Inject long-acting risperidone deep IM in the gluteus maximus; Z-tracking is not necessary.

MANAGEMENT OF TREATMENT-RESISTANT SCHIZOPHRENIA

- Only **clozapine** has shown superiority over other antipsychotics in randomized trials for treatment-resistant schizophrenia. Improvement with clozapine often occurs

slowly in resistant patients; as high as 60% of patients may improve if clozapine is used for up to 6 months.
- Because of the risk of orthostatic hypotension, clozapine is usually titrated more slowly than other antipsychotics. If a 12.5 mg test dose does not produce hypotension, then 25 mg of clozapine at bedtime is recommended, increased to 25 mg twice daily after 3 days, then increased in 25 to 50 mg/day increments every 3 days until a dose of at least 300 mg/day is reached.
- Augmentation therapy involves the addition of a nonantipsychotic drug to an antipsychotic in a poorly responsive patient, whereas combination treatment involves using two antipsychotics simultaneously.
- Responders to augmentation therapy usually improve rapidly. Discontinue the augmenting agent if there is no improvement.
- Mood stabilizers (eg, **lithium, valproic acid,** and **carbamazepine**) used as augmentation agents may improve labile affect and agitation. A placebo-controlled trial supports faster symptom improvement when **divalproex** is combined with either **olanzapine** or **risperidone**. The 2009 Schizophrenia Patient Outcomes Research Team (PORT) recommendations do not endorse mood stabilizer augmentation in resistant patients.
- **Selective serotonin reuptake inhibitors (SSRIs)** have been used for obsessive-compulsive symptoms that worsen or arise during **clozapine** treatment.
- Combining an FGA and an SGA and combining different SGAs have been suggested, but no data exist to support or refute these strategies, and the 2009 PORT recommendations do not support their use. If a series of antipsychotic monotherapies fails, a time-limited combination trial may be attempted. If there is no improvement within 6 to 12 weeks, discontinue one of the drugs.

ADVERSE EFFECTS

- Table 69–3 shows relative incidence of common categories of antipsychotic side effects.

Anticholinergic Effects

- Anticholinergic side effects, most likely to occur with low potency FGA, clozapine, and olanzapine, include impaired memory, dry mouth, constipation, tachycardia, blurred vision, inhibition of ejaculation, and urinary retention. Elderly patients are especially sensitive to these side effects.
- Dry mouth can be managed with increased intake of fluids, oral lubricants (Xerolube), ice chips, or the use of sugarless chewing gum or hard candy. Constipation can be treated with increases in exercise, fluid, and dietary fiber intake.

Central Nervous System

EXTRAPYRAMIDAL SYSTEM

Dystonia

- Dystonias are prolonged tonic muscle contractions, (occurring usually within 24–96 hours of dosage initiation or dosage increase); they may be life threatening (eg, pharyngeal-laryngeal dystonias). Other dystonias are trismus, glossospasm, tongue protrusion, blepharospasm, oculogyric crisis, torticollis, and retrocollis. They occur primarily with FGAs. Risk factors include younger patients (especially male) and use of high-potency agents and high dose.
- Treatment includes IM or IV anticholinergics (Table 69–4) or **benzodiazepines**. **Benztropine mesylate**, 2 mg, or **diphenhydramine**, 50 mg, may be given IM or IV, or **diazepam**, 5 to 10 mg slow IV push, or **lorazepam**, 1 to 2 mg IM, may be given. Relief usually occurs within 15 to 20 minutes of IM injection or 5 minutes of IV administration.
- Prophylactic anticholinergic medications (but not amantadine) are reasonable when using high-potency FGAs (eg, **haloperidol** and **fluphenazine**), in young men, and in patients with a prior dystonia.

TABLE 69–3 Relative Side Effect Incidence of Commonly Used Antipsychotics[a,b]

	Sedation	EPS	Anticholinergic	Orthostasis	Weight Gain	Prolactin
Aripiprazole	+	+	+	+	+	+
Asenapine	+	++	±	++	+	+
Chlorpromazine	++++	+++	+++	++++	++	+++
Clozapine	++++	+	++++	++++	++++	+
Fluphenazine	+	++++	+	+	+	++++
Haloperidol	+	++++	+	+	+	++++
Iloperidone	+	±	++	+++	++	+
Lurasidone	+	+	+	+	±	±
Olanzapine	++	++	++	++	++++	+
Paliperidone	+	++	+	++	++	++++
Perphenazine	++	++++	++	+	+	++++
Quetiapine	++	+	+	++	++	+
Risperidone	+	++	+	++	++	++++
Thioridazine	++++	+++	++++	++++	+	+++
Thiothixene	+	++++	+	+	+	++++
Ziprasidone	++	++	+	+	+	+

EPS, extrapyramidal side effects. Relative side effect risk: ±, negligible; +, low; ++, moderate; +++, moderately high; ++++, high.

[a]Side effects shown are relative risk based on doses within the recommended therapeutic range.
[b]Individual patient risk varies depending on patient-specific factors.

TABLE 69–4 Agents Used to Treat Extrapyramidal Side Effects

Generic Name	Equivalent Dose (mg)	Daily Dosage Range (mg)
Antimuscarinics		
Benztropine[a]	1	1–8[b]
Biperiden[a]	2	2–8
Trihexyphenidyl	2	2–15
Antihistaminic		
Diphenhydramine[a]	50	50–400
Dopamine Agonist		
Amantadine	NA	100–400
Benzodiazepines		
Lorazepam[a]	NA	1–8
Diazepam	NA	2–20
Clonazepam	NA	2–8
***β*-Blockers**		
Propranolol	NA	20–160

NA, not applicable

[a]Injectable dosage form can be given intramuscularly for relief of acute dystonia.
[b]In treatment-refractory cases, dosage can be titrated to 12 mg/day with careful monitoring; nonlinear pharmacokinetics have been reported.

- Dystonias can be minimized by using lower initial doses of FGAs and by using SGAs instead of FGAs.

Akathisia

- Symptoms include subjective complaints (feelings of inner restlessness) and/or objective symptoms (pacing, shifting, shuffling, or tapping feet).
- Treatment with anticholinergics is disappointing. Reduction in antipsychotic dose may be the best intervention. Alternatively, switch to an SGA, although akathisia occasionally occurs with the SGAs. **Quetiapine** and **clozapine** appear to have the lowest risk. **Benzodiazepines** may be used, but not in patients with a history of substance abuse. **Propranolol** (up to 160 mg/day), **nadolol** (up to 80 mg/day), and **metoprolol** (up to 100 mg/day) are reported to be effective.

Pseudoparkinsonism

- Patients with pseudoparkinsonism may have any of four cardinal symptoms:
  - ✓ Akinesia, bradykinesia, or decreased motor activity, including mask-like facial expression, micrographia, slowed speech, and decreased arm swing
  - ✓ Tremor—predominantly at rest; decreasing with movement
  - ✓ Rigidity—stiffness; cogwheel rigidity is seen as the patient's limbs yield in jerky, ratchet-like fashion when moved passively by the examiner
  - ✓ Postural abnormalities—stooped, unstable posture and slow, shuffling, or festinating gait
- Risk factors—FGAs (especially in high dose), increasing age, and possibly female gender.
- Accessory symptoms—seborrhea, sialorrhea, hyperhidrosis, fatigue, weakness, dysphagia, and dysarthria.
- The onset of symptoms is usually 1 to 2 weeks after initiation of antipsychotic therapy or dose increase. The risk of pseudoparkinsonism with SGAs is low except with **risperidone** in doses greater than 6 mg/day.
- **Benztropine** has a half-life that allows once- to twice-daily dosing. Typical dosing is 1 to 2 mg twice daily up to a maximum of 8 mg daily. **Trihexyphenidyl, diphenhydramine,** and **biperiden** usually require three-times-daily dosing (**Table 69–4**). Diphenhydramine produces more sedation. All of the anticholinergics have been abused for euphoriant effects.
- **Amantadine** is as efficacious as anticholinergics with less effect on memory.
- Attempt to taper and discontinue these agents 6 weeks to 3 months after symptoms resolve.

Tardive Dyskinesia

- ***Tardive Dyskinesia*** (TD) is characterized by abnormal involuntary movements occurring with chronic antipsychotic therapy.
- The classic presentation is buccolingual-masticatory (BLM) or orofacial movements. Symptoms may become severe enough to interfere with chewing, wearing dentures, speech, respiration, or swallowing. Facial movements include frequent blinking, brow arching, grimacing, upward deviation of the eyes, and lip smacking. Restless choreiform and athetotic movements of the limbs occur in later stages. Movements may worsen with stress, decrease with sedation, and disappear with sleep.
- Screen at baseline and at least quarterly using the Abnormal Involuntary Movement Scale (AIMS) and the Dyskinesia Identification System: Condensed User Scale (DISCUS) to detect TD.
- Dosage reduction or discontinuation may reduce symptoms, and some patients may have complete disappearance of symptoms if implemented early in the course of TD.
- Prevention of TD—(1) use SGAs as first-line agents; (2) use the DISCUS or other scales to assess for early signs of TD at least quarterly; and (3) discontinue antipsychotics or switch to SGAs at the earliest symptoms of TD, if possible.
- Risk factors for TD—duration of antipsychotic therapy, higher dose, possibly cumulative dose, increasing age, occurrence of acute extrapyramidal symptoms, poor

antipsychotic response, and diagnosis of organic mental disorder, diabetes mellitus, mood disorders, and possibly female gender.
- Switching to clozapine is a first-line strategy in patients with moderate to severe dyskinesias.

SEDATION AND COGNITION

- Administration of most or the entire daily dose at bedtime can decrease daytime sedation and may eliminate the need for hypnotics.
- Compared to FGAs, the SGAs have shown cognitive benefits. However, the CATIE trial showed no difference in cognitive improvement between SGAs and the FGA perphenazine.

SEIZURES

- All patients treated with antipsychotics have an increased risk of seizures. The highest risk for antipsychotic-induced seizures is with the use of **chlorpromazine** or **clozapine**. Seizures are more likely with initiation of treatment and with higher doses and rapid dose increases.
- When an isolated seizure occurs, a dosage decrease is recommended, and anticonvulsant therapy is usually not recommended.
- If a change in antipsychotic therapy is required, **risperidone, thioridazine, haloperidol, pimozide, trifluoperazine,** and **fluphenazine** may be considered.

THERMOREGULATION

- In temperature extremes, patients taking antipsychotics may experience their body temperature adjusting to ambient temperature (poikilothermia). Hyperpyrexia can lead to heat stroke. Hypothermia is also a risk, particularly in elderly patients. These problems are more common with the use of low-potency FGAs and can occur with the more anticholinergic SGAs.

NEUROLEPTIC MALIGNANT SYNDROME

- Neuroleptic malignant syndrome occurs in 0.5% to 1% of patients taking FGAs. It has been reported with the SGAs, including **clozapine**, but is less frequent than with the FGAs.
- Symptoms develop rapidly over 24 to 72 hours and include body temperature exceeding 38°C (100.4°F), altered level of consciousness, autonomic dysfunction (tachycardia, labile blood pressure, diaphoresis, tachypnea, and urinary or fecal incontinence), and rigidity.
- Laboratory evaluation frequently shows leukocytosis, increases in creatine kinase (CK), aspartate aminotransferase (AST), alanine aminotransferase (ALT), lactate dehydrogenase (LDH), and myoglobinuria.
- Discontinue antipsychotics, and provide supportive care. **Bromocriptine** reduces rigidity, fever, or CK levels in up to 94% of patients. **Amantadine** has been used successfully in up to 63% of patients. **Dantrolene** has been used with favorable effects on temperature, heart rate, respiratory rate, and CK in up to 81% of patients.
- Rechallenge with the lowest effective dose of SGA or low potency FGA may be considered only for patients in need of reinstitution of antipsychotics following observation for at least 2 weeks without antipsychotics. Monitor carefully and titrate the dose slowly.

Endocrine System

- Antipsychotic-induced elevations in prolactin levels with associated galactorrhea, decreased libido, and menstrual irregularities are common. These effects may be dose related and are more common (up to 87%) with the use of FGAs, risperidone, and palperidone.
- Possible management strategies for galactorrhea include switching to an SGA (eg, **asenapine, iloperidone,** or **lurasidone**).
- Weight gain is frequent with antipsychotic therapy involving SGAs, but **ziprasidone**, **aripiprazole**, **asenapine**, and **lurasidone** cause minimal weight gain.

- Schizophrenics have a higher prevalence of type 2 diabetes than nonschizophrenics. Antipsychotics may adversely affect glucose levels in diabetic patients. New-onset diabetes has been reported with use of the SGAs. Olanzapine and clozapine have the highest risk of new-onset diabetes, followed by risperidone and quetiapine. The risk with aripiprazole and ziprasidone is likely less than with other SGA. The 2009 PORT do not recommend olanzapine as first-line therapy.

Cardiovascular System

- The incidence of orthostatic hypotension (defined as >20 mm Hg drop in systolic pressure upon standing) is greatest with low-potency FGAs, **clozapine**, **iloperidone**, **quetiapine**, **risperidone**, and combination antipsychotics. Diabetics with cardiovascular disease and the elderly are predisposed. Reducing the dose or changing to an antipsychotic with less α-adrenergic blockade may help, and tolerance may develop within 2 or 3 months.
- Low-potency piperidine phenothiazines (eg, **thioridazine**), **clozapine**, **iloperodone**, and **ziprasidone** are the most likely to cause ECG changes. ECG changes include increased heart rate, flattened T waves, ST-segment depression, and prolongation of QT and PR intervals. Torsades de pointes has been reported with **thioridazine** (black box warning).
- Ziprasidone prolonged the QTc interval about one half as much as thioridazine. Ziprasidone's effect on the ECG is probably without clinical sequelae except in patients with baseline risk factors. Iloperidone prolongs the QTc in a dose related manner. High IV doses of haloperidol also can prolong the QTc.
- It has been recommended to discontinue a medication associated with QTc prolongation if the interval consistently exceeds 500 msec.
- Those taking FGAs or SGAs have twice the risk of sudden cardiac death that nonusers have.
- In patients older than 50 years, pretreatment ECG and serum potassium and magnesium levels are recommended.

Lipid Effects

- Some SGAs and phenothiazines cause elevations in serum triglycerides and cholesterol. The risk for this effect may be less with **risperidone**, **ziprasidone**, **aripiprazole**, **asenapine**, **iloperidone**, and **lurasidone**.
- Metabolic syndrome consists of raised triglycerides (≥150 mg/dL [170 mmol/L]), low high-density lipoprotein cholesterol (≤40 mg/dL [1.03 mmol/L] for males, ≤50 mg/dL [1.29 mmol/L] for females), elevated fasting glucose (≥100 mg/dL [5.6 mmol/L]), blood pressure elevation (≥130/85 mm Hg), and weight gain (abdominal circumference >102 cm [40 in] for males, >88 cm [35 in] for females.

Psychiatric Side Effects

- Akathisia, akinesia, and dysphoria can result in apathy, withdrawal, and pseudodepression (behavioral toxicity).
- Chronic confusion and disorientation can occur in the elderly.
- Delirium and psychosis may occur with high doses of FGAs or combinations of FGAs with anticholinergics.

Ophthalmologic Effects

- Exacerbation of narrow-angle glaucoma can occur with use of antipsychotics and/or anticholinergics.
- Opaque deposits in the cornea and lens may occur with chronic phenothiazine treatment, especially **chlorpromazine**. Although visual acuity is not usually affected, periodic slit-lamp examinations are recommended with long-term phenothiazine use. Baseline and periodic slit-lamp examinations are also recommended for **quetiapine**-treated patients because of cataract development in animal studies.
- **Thioridazine** doses greater than 800 mg daily (the recommended maximum dose) can cause retinitis pigmentosa with permanent visual impairment or blindness.

Genitourinary System

- Urinary hesitancy and retention are common, especially with low-potency FGAs and **clozapine**, and in men with benign prostatic hypertrophy.
- Urinary incontinence may result from α-blockade, and among the SGA, it is especially problematic with **clozapine**.
- Risperidone produces at least as much sexual dysfunction as FGAs, but other SGAs (which have a weaker effect of prolactin) are less likely to have this effect.

Hematologic System

- Antipsychotic can cause transient leukopenia, but it usually does not progress to clinical significance.
- If the white blood cell count (WBC) is less than 3000/mm^3 (3 × 10^9/L), or the absolute neutrophil count (ANC) is less than 1000/mm^3 (1 × 10^9/L), the antipsychotic should be discontinued, and the WBC monitored closely until it returns to normal, with monitoring for secondary infections.
- Agranulocytosis reportedly occurs in 0.01% of patients receiving FGAs, and it may occur more frequently with **chlorpromazine** and **thioridazine**. The onset is usually within the first 8 weeks of therapy. It may initially manifest as a local infection (eg, sore throat, leukoplakia, and erythema and ulcerations of the pharynx), which should trigger an immediate WBC.
- The risk of developing agranulocytosis with **clozapine** is approximately 0.8%. Increasing age and female gender increase risk. The greatest risk is between months 1 and 6 of treatment. WBC monitoring is required weekly for the first 6 months, every 2 weeks for months 7 through 12, then monthly if all WBCs are normal. If the WBC drops to less than 2000/mm^3 (2 × 10^9/L) or the ANC is less than 1000/mm^3 (1 × 10^9/L), clozapine should be discontinued. In cases of mild to moderate neutropenia (granulocytes between 2000 and 3000/mm^3 [2 × 10^9/L and 3 × 10^9/L]) or ANC between 1000 and 1500/mm^3 (1 × 10^9/L and 1.5 × 10^9/L), which occurs in up to 2% of patients, clozapine should be discontinued, with daily monitoring of CBC until values return to normal.

Dermatologic System

- Allergic reactions are rare and usually occur within 8 weeks of initiating therapy. They manifest as maculopapular, erythematous, or pruritic rashes. Drug discontinuation and topical steroids are recommended.
- Contact dermatitis, including on the oral mucosa, may occur. Swallowing of the oral concentrate quickly may decrease this problem.
- Both FGAs and SGAs can cause photosensitivity with severe sunburns. Educate patients to use maximal blocking sunscreens, hats, protective clothing, and sunglasses when in the sun.
- Blue-gray or purplish discoloration of skin exposed to sunlight may occur with higher doses of low-potency phenothiazines (especially **chlorpromazine**) long term. This may occur with concurrent corneal or lens pigmentation.

USE IN PREGNANCY AND LACTATION

- There is a slightly increased risk of birth defects with low-potency FGAs.
- There is no relationship between **haloperidol** use and teratogenicity.
- Schizophrenic women taking FGAs have a greater than two-fold increased risk of preterm birth compared with unaffected mothers not taking antipsychotics.
- A retrospective study found nearly twofold greater odds of gestational diabetes in women taking antipsychotics during pregnancy.
- The FDA requires the pregnancy section of antipsychotic labeling to highlight the potential risk for extrapyramidal symptoms and withdrawal symptoms in newborns whose mothers received antipsychotics during the third trimester.
- Antipsychotics appear in breast milk, with milk:plasma ratios of 0.5:1, however, 1-week postdelivery clozapine milk concentrations were found to be 279% of serum concentrations. Use of clozapine during breast-feeding is not recommended.

DRUG INTERACTIONS

- Antipsychotic drug interactions often involve additive hypotensive, anticholinergic, or sedative effects.
- Asenapine, an inhibitor of CPY2D6, is the only antipsychotic found to significantly affect the pharmacokinetics of other medications. Fluvoxamine increases clozapine serum concentrations by twofold to threefold or more. Fluoxetine and erythromycin can increase clozapine serum concentrations to a lesser extent. Reduce the iloperidone dose by 50% when used with CYP2D6 inhibitors, such as fluoxetine or paroxetine.
- Antipsychotic pharmacokinetics can be significantly affected by concomitantly administered enzyme inducers or inhibitors. Smoking is a potent inducer of hepatic enzymes and may increase antipsychotic clearance by as much as 50%. Consult the published literature for antipsychotic drug interactions.

EVALUATION OF THERAPEUTIC OUTCOMES

- The Positive Symptom Rating Scale and the Brief Negative Symptom Assessment are brief enough to be useful in the outpatient setting. Patient-rated self-assessments can also be useful, as they engage the patient in treatment and can open the door for patient education and addressing misconceptions.
- Systematically monitor for side effects (**Table 69–5**). Monitor body weight monthly for 3 months, then quarterly. Monitor body mass index, waist circumference, blood pressure, fasting plasma glucose, and fasting lipid profile at the end of 3 months, then annually.

TABLE 69–5 Antipsychotic Adverse Effects and Monitoring Parameters

Adverse Reaction	Monitoring Parameter	Frequency	Comments
Adverse Effect Monitoring Parameters for all Antipsychotic Medications			
Akathisia	Ask about restless or anxiety. Observe patient for restlessness. Barnes Akathisia Scale can also be used	Every visit	
Anticholinergic side effects	Ask patient about constipation, blurry vision, urinary retention, or unusual dry mouth	Every visit	
Glucose intolerance	FBS or HbA1c	At baseline, after 3 months, and if normal, then annually	
Hyperlipidemia	Lipid profile	At baseline, after 3 months, and if normal, then annually	
Orthostatic hypotension	Ask patient about dizziness on standing. If present, check BP and HR in sitting and standing positions	Every visit	The degree of orthostatic change in BP to produce symptoms varies. In general, a BP change of 20 mm Hg or more is significant

(*continued*)

TABLE 69–5 Antipsychotic Adverse Effects and Monitoring Parameters (*Continued*)

Adverse Reaction	Monitoring Parameter	Frequency	Comments
Hyperprolactinemia	In women, ask about expression of milk from the breast and menstrual irregularities. In men, ask about breast enlargement or expression of milk from nipples. If symptoms present, check serum prolactin level	Every visit	In the absence of symptoms, there is no need to monitor serum prolactin
Sedation	Ask patient about unusual sedation or sleepiness	Every visit	
Sexual dysfunction	Ask patient about decreased sexual desire, difficulty being aroused, or problems with orgasm	Every visit	Patients with schizophrenia have more sexual dysfunction than the normal population. Compare symptoms with medication-free state
Tardive dyskinesia	Standardized rating scale such as the AIMS or the DISCUS	At baseline, and then every 3 months for FGAs and every 6 months for SGAs	
Weight gain	Measure body weight, BMI, and waist circumference	At baseline, monthly for the first 3 months, and then quarterly	Waist circumference is the single best predictor of cardiac morbidity
Adverse Effect Monitoring Parameters for Specific Antipsychotics			
Agranulocytosis	White blood cell (WBC) and absolute neutrophil counts (ANC)	At baseline, weekly for 6 months, then every 2 weeks for 6 months, and then monthly	Clozapine only
Sialorrhea or excess drooling	Ask patient about problems with excess drooling, waking in the morning with a wet ring on his or her pillow. Visual observation of the patient for drooling	Every visit	Clozapine only

(*continued*)

TABLE 69–5 Antipsychotic Adverse Effects and Monitoring Parameters (*Continued*)

Adverse Reaction	Monitoring Parameter	Frequency	Comments
Bronchospasm, respiratory distress, respiratory depression, respiratory arrest	Before administration, patients must be screened for a history of asthma, chronic obstructive pulmonary disease, or other lung disease associated with bronchospasm. Monitor patient every 15 minutes for a minimum of 1 hour after drug administration for signs and symptoms of bronchospasm (ie, vital signs and chest auscultation). Only one 10 mg dose can be given every 24 hours	Every dose administration	Inhaled Loxitane only. Can be administered only in approved healthcare facilities registered in REMS program
Postinjection sedation/delirium syndrome	Observation of the patient for at least 3 hours after drug administration. Monitor for possible sedation, altered level of consciousness, coma, delirium, confusion, disorientation, agitation, anxiety, or other cognitive impairment	Every dose administration	Long-acting olanzapine pamoate monohydrate only. Can be administered only in approved healthcare facilities registered in REMS program

See Chapter 50, Schizophrenia, authored by M. Lynn Crismon, Tami R. Argo, and Peter F. Buckley, for a more detailed discussion of this topic.

CHAPTER 70

Sleep-Wake Disorders

- The *Diagnostic and Statistical Manual of Mental Disorders*, 5th ed., category of sleep-wake disorders encompasses insomnia, hypersomnolence, narcolepsy, breathing-related sleep disorders, circadian rhythm sleep-wake disorders, non-rapid eye movement (NREM) sleep arousal disorders, nightmare disorder, rapid eye movement (REM) sleep behavior disorder, restless legs syndrome, and substance/medication-induced sleep disorder.

SLEEP PHYSIOLOGY

- Humans typically have four to six cycles of non–rapid eye movement (NREM) and REM sleep each night, each cycle lasting 70 to 120 minutes. Usually there is progression through the four stages of NREM sleep before the first REM period.
- Stage 1 of NREM is the stage between wakefulness and sleep. Stages 3 and 4 sleep are called *delta sleep* (ie, slow-wave sleep).
- In REM sleep, there is a low-amplitude, mixed-frequency electroencephalogram, increased electric and metabolic activity, increased cerebral blood flow, muscle atonia, poikilothermia, vivid dreaming, and fluctuations in respiratory and cardiac rate.
- The elderly have lighter more fragmented sleep with more arousals and gradual reduction in slow-wave sleep.
- REM sleep is turned on by cholinergic cells. Dopamine has an alerting effect. Neurochemicals involved in wakefulness include norepinephrine and acetylcholine in the cortex and histamine and neuropeptides (eg, substance P and corticotropin-releasing factor) in the hypothalamus.
- Polysomnography (PSG) measures multiple electrophysiologic parameters simultaneously during sleep (eg, electroencephalogram, electrooculogram, and electromyogram) to characterize sleep and diagnose sleep disorders.

INSOMNIA

CLINICAL PRESENTATION AND DIAGNOSIS

- Patients with insomnia complain of difficulty falling asleep, maintaining sleep, or experiencing nonrestorative sleep.
- Transient (two or three nights) and short-term (<3 weeks) insomnia is common and is usually related to a precipitating factor. Chronic insomnia (>1 month) may be related to medical or psychiatric disorders or medication, or it may be psychophysiologic.
- Causes of insomnia include stress; jet lag or shift work; pain or other medical problems; mood or anxiety disorders; substance withdrawal; stimulants, steroids, or other medications.
- In patients with chronic disturbances, a diagnostic evaluation includes physical and mental status examinations, routine laboratory tests, and medication and substance abuse histories.

TREATMENT

- Goals of Treatment: Correct the underlying sleep complaint, improve daytime functioning, and avoid adverse drug effects.

General Approach

- Behavioral and educational interventions that may help include short-term cognitive behavioral therapy, relaxation therapy, stimulus control therapy, cognitive therapy, sleep restriction, paradoxical intention, and sleep hygiene education (**Table 70–1**).

TABLE 70–1 Nonpharmacologic Recommendations for Management of Insomnia

Stimulus control procedures
1. Establish regular times to wake up and to go to sleep (including weekends)
2. Sleep only as much as necessary to feel rested
3. Go to bed only when sleepy. Avoid long periods of wakefulness in bed. Use the bed only for sleep or intimacy; do not read or watch television in bed
4. Avoid trying to force sleep; if you do not fall asleep within 20–30 minutes, leave the bed and perform a relaxing activity (eg read, listen to music, or watch television) until drowsy. Repeat this as often as necessary
5. Avoid daytime naps
6. Schedule worry time during the day. Do not take your troubles to bed
Sleep hygiene recommendations
1. Exercise routinely (three to four times weekly) but not close to bedtime because this can increase wakefulness
2. Create a comfortable sleep environment by avoiding temperature extremes, loud noises, and illuminated clocks in the bedroom
3. Discontinue or reduce the use of alcohol, caffeine, and nicotine
4. Avoid drinking large quantities of liquids in the evening to prevent nighttime trips to the restroom
5. Do something relaxing and enjoyable before bedtime

- Management includes identifying the cause of insomnia, educating about sleep hygiene, managing stress, monitoring for mood symptoms, and eliminating unnecessary pharmacotherapy.
- Transient and short-term insomnia should be treated with good sleep hygiene and careful use of sedative-hypnotics if necessary. Chronic insomnia calls for careful assessment for a medical cause, nonpharmacologic treatment, and careful use of sedative-hypnotics if necessary.
- **Antihistamines** (eg, **diphenhydramine, doxylamine**, and **pyrilamine**) are less effective than **benzodiazepines**, but side effects are usually minimal. Their anticholinergic side effects may be problematic, especially in the elderly.
- The antidepressants are good alternatives for patients who should not receive benzodiazepines, especially those with depression or a history of substance abuse.
- **Amitriptyline, doxepin**, and **nortriptyline** are effective, but side effects include anticholinergic effects, adrenergic blockade, and cardiac conduction prolongation.
- **Trazodone**, 25 to 100 mg, is often used for insomnia induced by selective serotonin reuptake inhibitors or bupropion and in patients prone to substance abuse. Side effects include serotonin syndrome (when used with other serotonergic drugs), oversedation, α-adrenergic blockade, dizziness, and, rarely, priapism.
- **Ramelteon** is a melatonin receptor agonist selective for the MT_1 and MT_2 receptors. The dose is 8 mg at bedtime. It is well tolerated, but side effects include headache, dizziness, and somnolence. It is not a controlled substance. It is effective for patients with chronic obstructive pulmonary disease and sleep apnea.
- **Valerian**, a herbal product, is available without a prescription. The recommended dose is 300 to 600 mg. Purity and potency concerns are an issue. It may cause daytime sedation.
- The benzodiazepine receptor agonists are the most commonly used drugs for insomnia. They carry a caution regarding anaphylaxis, facial angioedema, complex sleep behaviors (eg, sleep driving, phone calls, and sleep eating). They include the newer nonbenzodiazepine γ-aminobutyric acid$_A$ ($GABA_A$) agonists and the traditional benzodiazepines, which also bind to $GABA_A$ (**Table 70–2**).

TABLE 70–2 Pharmacokinetics of Benzodiazepine Receptor Agonists

Generic Name (Brand Name)	t_{max}[a] (Hours)	Half-Life[b] (Hours)	Daily Dose Range (mg)	Metabolic Pathway	Clinically Significant Metabolites
Estazolam (ProSom)	2	12–15	1–2	Oxidation	—
Eszopiclone (Lunesta)	1–1.5	6	2–3	Oxidation Demethylation	—
Flurazepam (Dalmane)	1	8	15–30	Oxidation *N*-Dealkylation	Hydroxyethylflurazepam, flurazepam aldehyde *N*-Desalkylflurazepam[c]
Quazepam (Doral)	2	39	7.5–15	Oxidation, *N*-dealkylation	2-Oxo-quazepam, *N*-desalkylflurazepam[c]
Temazepam (Restoril)	1.5	10–15	15–30	Conjugation	—
Triazolam (Halcion)	1	2	0.125–0.25	Oxidation	—
Zaleplon (Sonata)	1	1	5–10	Oxidation	—
Zolpidem (Ambien; Intermezzo)	1.6	2–2.6	1.75–10[d]	Oxidation	—

[a]Time to peak plasma concentration.
[b]Half-life of parent drug.
[c]*N*-Desalkylflurazepam, mean half-life 47–100 hours.
[d]Oral and sublingual dosing 5–10 mg, sublingual tablets for middle-of-the night dosing 1.75–3.5 mg (1.75 for women, 3.5 mg for men).

Nonbenzodiazepine $GABA_A$ Agonists

- In general, the nonbenzodiazepine hypnotics do not have significant active metabolites, and they are associated with less withdrawal, tolerance, and rebound insomnia than the benzodiazepines.
- **Zolpidem** has minimal anxiolytic and no muscle relaxant or anticonvulsant effects. It is comparable in effectiveness to benzodiazepine hypnotics, and it has little effect on sleep stages. Its duration is approximately 6 to 8 hours. Common side effects are drowsiness, amnesia, dizziness, headache, and gastrointestinal (GI) complaints. Rebound effects when discontinued and tolerance with prolonged use are minimal, but theoretical concerns about abuse exist. It appears to have minimal effects on next-day psychomotor performance. The usual dose is 5 mg in women, the elderly, and those with liver impairment, and 5 to 10 mg in men. Sleep eating has been reported. It should be taken on an empty stomach.
- **Zaleplon** has a rapid onset, a half-life of ~1 hour, and no active metabolites. It also binds to the $GABA_A$ receptor. It does not reduce nighttime awakenings or increase the total sleep time. It does not appear to cause significant rebound insomnia or next-day psychomotor impairment. The most common side effects are dizziness, headache, and somnolence. The recommended dose is 10 mg (5 mg in the elderly).
- **Eszopiclone** has a rapid onset and duration of action of up to 6 hours. The most common adverse effects are somnolence, unpleasant taste, headache, and dry mouth. It may be taken nightly for up to 6 months.

Benzodiazepine Hypnotics

- The pharmacokinetics and dosing of benzodiazepine receptor agonists are summarized in **Table 70–2**.
- Benzodiazepines have sedative, anxiolytic, muscle relaxant, and anticonvulsant properties. They increase stage 2 sleep and decrease REM and delta sleep.
- Overdose fatalities are rare unless benzodiazepines are taken with other CNS depressants.
- **Triazolam** is distributed quickly because of its high lipophilicity and thus has a short duration of effect. **Erythromycin, nefazodone, fluvoxamine**, and **ketoconazole** reduce the clearance of triazolam and increase plasma concentrations.
- The effects of **flurazepam** and **quazepam** are long because of active metabolites.

BENZODIAZEPINE ADVERSE EFFECTS

- Side effects include drowsiness, psychomotor incoordination, decreased concentration, cognitive deficits, and anterograde amnesia which is minimized by using the lowest dose possible.
- Tolerance to daytime CNS effects (eg, drowsiness, decreased concentration) may develop in some individuals.
- Tolerance to hypnotic effects develops after 2 weeks of continuous use of **triazolam**. Efficacy of **flurazepam, quazepam**, and **temazepam** lasts for at least 1 month of nightly use. **Estazolam** reportedly maintains efficacy at maximum dosage for up to 12 weeks.
- Rebound insomnia occurs frequently with high doses of **triazolam**, even when used intermittently.
- Rebound insomnia is minimized by using the lowest effective dose and tapering the dose upon discontinuation.
- Long elimination half-life benzodiazepines are associated with falls and hip fractures; thus, **flurazepam,** and **quazepam** should be avoided in the elderly.

SLEEP APNEA

- Apnea is repetitive episodes of cessation of breathing during sleep.

OBSTRUCTIVE SLEEP APNEA

- Obstructive sleep apnea (OSA) is potentially life threatening and characterized by repeated episodes of nocturnal breathing cessation. It is caused by occlusion of the upper airway, and blood oxygen (O_2) desaturation can occur. Episodes may be caused by obesity or fixed upper airway lesions, enlarged tonsils, amyloidosis, and hypothyroidism. Complications include arrhythmias, hypertension, cor pulmonale, and sudden death.
- Heavy snoring, severe gas exchange disturbances, respiratory failure, and gasping occur in severe episodes. Patients with OSA usually complain of excessive daytime sleepiness. Other symptoms are morning headache, poor memory, and irritability.
- The apneic episode is terminated by a reflex action in response to the fall in blood O_2 saturation that causes an arousal with resumed breathing.

Treatment

- Goal of Treatment: The goal is alleviate sleep-disordered breathing (**Fig. 70–1**).
- Nonpharmacologic approaches are the treatments of choice (eg, weight loss [for all overweight patients], tonsillectomy, nasal septal repair, and nasal positive airway pressure [PAP], which may be continuous or bilevel). Other surgical therapies, such as uvulopalatopharyngoplasty and tracheostomy, may be necessary in severe cases.
- Management parameters are published by the American Academy of Sleep Medicine. Avoid of all CNS depressants and drugs that promote weight gain. **Angiotensin-converting enzyme (ACE) inhibitors** can also worsen sleep-disordered breathing.
- **Modafinil** and **armodafinil** are approved by the FDA to improve wakefulness in those with residual daytime sleepiness. They should be used only in patients without cardiovascular disease who are using optimal PAP therapy.

CENTRAL SLEEP APNEA

- Central sleep apnea (CSA), less frequent than OSA, is characterized by repeated episodes of apnea caused by temporary loss of respiratory effort during sleep. It may be caused by autonomic nervous system lesions, neurologic diseases, high altitudes, opioid use, and congestive heart failure.

Treatment

- PAP with or without supplemental O_2 improves CSA.
- **Acetazolamide** causes metabolic acidosis that stimulates respiratory drive and may be beneficial for high altitude, heart failure, and idiopathic CSA.

NARCOLEPSY

- Essential features are sleep attacks, cataplexy, hypnagogic and hypnopompic hallucinations, and sleep paralysis. Patients complain of excessive daytime sleepiness, sleep attacks that last up to 30 minutes, fatigue, impaired performance, and disturbed nighttime sleep.
- Cataplexy, which occurs in 70% to 80% of narcoleptics, is sudden bilateral loss of muscle tone with collapse. It is often precipitated by highly emotional situations.
- The hypocretin/orexin neurotransmitter system may play a central role in narcolepsy. An autoimmune process may cause destruction of hypocretin-producing cells.

TREATMENT

- Goals of Treatment: The goal is to maximize alertness during waking hours and improve quality of life (**Fig. 70–1**).
- Encourage good sleep hygiene and two or more daytime naps daily (as little as 15 min).
- Pharmacotherapy (**Table 70–3**) focuses on excessive daytime sleepiness and REM sleep abnormalities.

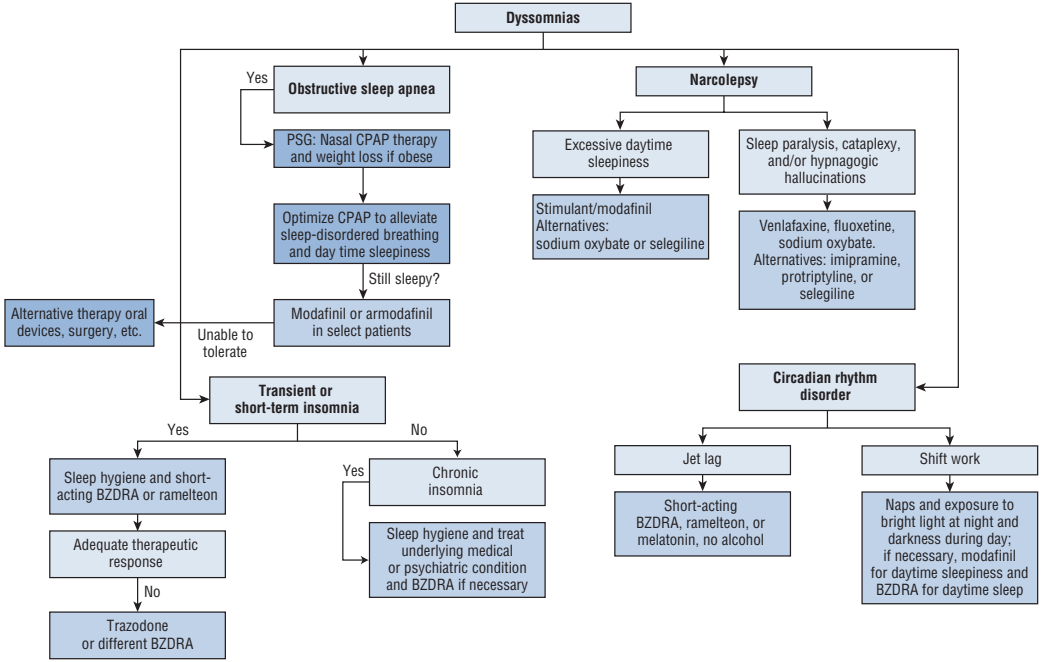


FIGURE 70–1. Algorithm for treatment of dyssomnias. (BZDRA, benzodiazepine receptor agonist; CPAP, continuous positive airway pressure.) *(Adapted with permission from Jermaine DM. Sleep Disorders. In: Carter BL, Angaran DM, Lake KD, Raebel MA, eds. Pharmacotherapy Self-Assessment Program, 2nd ed. Neurology and Psychiatry. Kansas City: American College of Clinical Pharmacy, 1995;139–154.)*

TABLE 70–3 Drugs Used to Treat Narcolepsy

Generic Name	Brand Name	Initial Dose (mg)	Usual Dose (mg)	Comments
Excessive Daytime Somnolence				
Dextroamphetamine	Dexedrine	5–10	5–60	Concurrent use of amphetamines and acidic foods may reduce amphetamine absorption
Dextroamphetamine/ amphetamine salts[a]	Adderall	5–20	5–60	See above
Methamphetamine[b]	Desoxyn	5–15	5–15	See above
Lisdexamfetamine	Vyvanse	20–30	20–70	Prodrug of dextroamphetamine
Methylphenidate	Ritalin	10–40	30–80	May increase risk of bleeding with concomitant warfarin therapy
Modafinil	Provigil	100–200	200–400	May reduce effectiveness of hormonal contraceptives
Armodafinil	Nuvigil	150	150–250	May reduce effectiveness of hormonal contraceptives
Sodium oxybate[c]	Xyrem	4.5 g/night	4.5–9 g/night	Do not use with other CNS depressants
Agents for Cataplexy				
Fluoxetine	Prozac	10–20	20–80	Will see cataplexy benefits sooner than antidepressant benefits
Imipramine	Tofranil	50–100	50–250	Anticholinergic side effects
Nortriptyline	Aventyl, Pamelor	50–100	50–200	Anticholinergic side effects
Protriptyline	Vivactil	5–10	5–30	
Venlafaxine	Effexor	37.5	37.5–225	May increase blood pressure
Selegiline	Eldepryl	5–10	20–40	Doses less than 10 mg/day do not require dietary tyramine restrictions

[a]Dextroamphetamine sulfate, dextroamphetamine saccharate, amphetamine aspartate, and amphetamine sulfate.
[b]Not available in some states.
[c]Also is effective at treating cataplexy.

- **Modafinil,** the standard for treatment of excessive daytime sleepiness, and **armodafinil** (the active R-isomer) are FDA approved. They do not treat cataplexy. Evidence suggests no risk of tolerance, withdrawal, or risk of abuse. Side effects of modafinil include headache, nausea, nervousness, and insomnia.
- **Amphetamines** and **methylphenidate** have a fast onset of effect and durations of 3 to 4 hours and 6 to 10 hours, respectively, for excessive daytime sleepiness. Amphetamines have more risk of abuse and tolerance. Side effects include insomnia, hypertension, palpitations, and irritability.
- The most effective treatments for cataplexy are the **tricyclic antidepressants, fluoxetine**, or **venlafaxine**. **Imipramine, protriptyline, clomipramine, fluoxetine**, and **nortriptyline** are effective in approximately 80% of patients. **Selegiline** improves hypersomnolence and cataplexy.
- **Sodium oxybate** (*γ*-**hydroxybutyrate**; a potent sedative-hypnotic) improves excessive daytime sleepiness and decreases episodes of sleep paralysis, cataplexy, and hypnagogic hallucinations. Give at bedtime and repeat 2.5 to 4 hours later. Side effects include nausea, somnolence, confusion, dizziness, and incontinence.

EVALUATION OF THERAPEUTIC OUTCOMES

- Assess patients with short-term or chronic insomnia after 1 week of therapy for drug effectiveness, adverse events, and adherence to nonpharmacologic recommendations. Patients should maintain a daily recording of awakenings, medications taken, naps, and an index of sleep quality.
- Assess patients with OSA after 1 to 3 months of treatment for improvement in alertness, daytime symptoms, and weight reduction. The bed partner can report on snoring and gasping.
- Pharmacotherapy monitoring parameters include reduction in daytime sleepiness, cataplexy, hypnagogic and hypnopompic hallucinations, and sleep paralysis. Assess patients regularly during medication titration, then every 6 to 12 months for side effects (eg, hypertension, sleep disturbances, and cardiovascular abnormalities).

See Chapter 55, Sleep Disorders, authored by John M. Dopp and Bradley G. Phillips, for a more detailed discussion of this topic.

CHAPTER 71

Substance-Related Disorders

- The *Diagnostic and Statistical Manual of Mental Disorders*, 5th edition (DSM-5) divides substance-related disorders (encompassing 10 separate classes of drugs) into (1) substance use disorders and (2) substance-induced disorders (eg, intoxication, withdrawal, and substance-induced mental disorders).
- The diagnosis of substance use disorder is based on a pathologic pattern of behaviors related to use of the substance. Diagnostic criteria fall into the categories of (1) impaired control, (2) social impairment, (3) risky use, and (4) pharmacological criteria, including tolerance and withdrawal.
- DSM-5 does not separate the diagnoses of substance abuse and substance dependence. Criteria are provided for substance use disorder, accompanied by criteria for intoxication, withdrawal, substance-induced disorders, and unspecified substance-related disorders in some cases.
- *Addiction:* A primary chronic neurobiologic disease, with genetic, psychosocial, and environmental factors influencing its development and manifestations; it is characterized by one or more of the following five Cs: chronicity, impaired control over drug use, compulsive use, continued use despite harm, and craving.
- *Intoxication:* Development of a substance-specific syndrome after recent ingestion and presence in the body of a substance; it is associated with maladaptive behavior during the waking state caused by effects of the substance on the central nervous system (CNS).
- *Physical dependence:* A state of adaptation manifested by a drug class–specific withdrawal syndrome that can be produced by abrupt cessation, rapid dose reduction, decreasing blood level of the drug, and/or administration of an antagonist.
- *Substance abuse:* A maladaptive pattern of substance use characterized by repeated adverse consequences related to the repeated use of the substance.
- *Substance dependence:* The characteristic feature is a continued maladaptive pattern of substance use in spite of repeated adverse consequences related to the repeated use.
- *Tolerance:* A state of adaptation in which exposure to a drug induces changes that result in a diminution of one or more of the drug's effects over time.
- *Withdrawal:* The development of a substance-specific syndrome after cessation of or reduction in intake of a substance that was used regularly.

CENTRAL NERVOUS SYSTEM DEPRESSANTS

ALCOHOL

- **Table 71–1** relates the effects of **alcohol** to the blood alcohol concentration (BAC).
- Signs and symptoms of alcohol intoxication include slurred speech, ataxia, incoordination, sedation, nystagmus, impaired judgment, unconsciousness, nausea, vomiting, respiratory depression, and coma. Signs and symptoms of alcohol withdrawal include tachycardia, diaphoresis, hyperthermia, hallucinations, delirium, and seizures.
- Alcohol withdrawal includes (1) a history of cessation or reduction in heavy and prolonged alcohol use and (2) the presence of two or more of the symptoms of alcohol withdrawal.
- There is 14 g of alcohol in 12 oz of beer, 4 oz of wine, or 1.5 oz (one shot) of 80-proof whiskey. This amount will increase the BAC by approximately 20 to 25 mg/dL (4.3–5.4 mmol/L) in a healthy 70 kg (154 lb) man. Deaths generally occur when BACs are greater than 400 to 500 mg/dL (87–109 mmol/L).
- Absorption of alcohol begins in the stomach within 5 to 10 minutes of ingestion. Peak concentrations are usually achieved 30 to 90 minutes after finishing the last drink.
- Alcohol is metabolized by alcohol dehydrogenase to acetaldehyde, which is metabolized to carbon dioxide and water by aldehyde dehydrogenase. Catalase and the microsomal alcohol oxidase system are also involved.

TABLE 71–1 Specific Effects of Alcohol Related to BAC

BAC (%)[a] (mmol/L)	Effect
0.02–0.03 (4–8)	No loss of coordination, slight euphoria, and loss of shyness
0.04–0.06 (9–14)	Feeling of well-being, relaxation, lower inhibitions, sensation of warmth. Euphoria. Some minor impairment of reasoning and memory, lowering of caution
0.07–0.09 (15–21)	Slight impairment of balance, speech, vision, reaction time, and hearing. Euphoria. Judgment and self-control are reduced, and caution, reason, and memory are impaired. It is illegal to operate a motor vehicle in some states at this level
0.10–0.125 (22–27)	Significant impairment of motor coordination and loss of good judgment. Speech can be slurred; balance, vision, reaction time, and hearing impaired. Euphoria. It is illegal to operate a motor vehicle at this level of intoxication
0.13–0.15 (28–34)	Gross motor impairment and lack of physical control. Blurred vision and major loss of balance. Euphoria is reduced, and dysphoria is beginning to appear
0.16–0.20 (35–43)	Dysphoria (anxiety, restlessness) predominates; nausea can appear. The drinker has the appearance of a "sloppy drunk"
0.25 (54)	Needs assistance in walking; total mental confusion. Dysphoria with nausea and some vomiting
0.30 (65)	Loss of consciousness
≥0.40 (>87)	Onset of coma, possible death caused by respiratory arrest

BAC, blood alcohol concentration.

[a]Grams of ethyl alcohol per 100 mL of whole blood.

- Most clinical laboratories report BAC in milligrams per deciliter. In legal cases, results are reported in percentage (grams of alcohol per 100 mL of whole blood). Thus, a BAC of 150 mg/dL = 0.15% = 34 mmol/L.

BENZODIAZEPINES AND OTHER SEDATIVE-HYPNOTICS

- Benzodiazepine ingestions most commonly seen in emergency rooms are **alprazolam** and **clonazepam** ingestions, but **lorazepam** and **diazepam** are also commonly abused.
- Benzodiazepine intoxication is manifested as slurred speech, poor coordination, swaying, drowsiness, hypotension, nystagmus, and confusion.
- Likelihood and severity of withdrawal are a function of dose and duration of exposure. Gradual tapering of dosage is necessary to minimize withdrawal and rebound anxiety.
- Signs and symptoms of benzodiazepine withdrawal are similar to those of alcohol withdrawal, including muscle pain, anxiety, restlessness, confusion, irritability, hallucinations, delirium, seizures, and cardiovascular collapse. Withdrawal from short-acting benzodiazepines (eg, **oxazepam, lorazepam**, and **alprazolam**) has an onset within 12 to 24 hours of the last dose. **Diazepam, chlordiazepoxide**, and **clorazepate** have elimination half-lives (or active metabolites with elimination half-lives) of 24 to more than 100 hours. Thus, withdrawal may be delayed for several days after their discontinuation.
- **Flunitrazepam** (Rohypnol) is most commonly ingested orally, frequently in conjunction with alcohol or other drugs. Often called a *date-rape drug*, it has been given to women (without their knowledge) to lower their inhibitions.

γ-HYDROXYBUTYRATE

- γ-**Hydroxybutyrate,** another date-rape drug, is sold as a liquid or powder, and its effects include amnesia, hypotonia, abnormal sequence of rapid eye movement and non–rapid eye movement sleep, and anesthesia.
- Toxic effects include decreased cardiac output, coma, seizures, vomiting, and respiratory depression. Treatment is nonspecific supportive care.
- Withdrawal symptoms include mental status changes, tremors, elevated blood pressure, tachycardia, tremors, and severe agitation. Benzodiazepines may be useful to control agitation.

CARISOPRODOL

- Carisoprodol is used for muscle spasms and back pain. Meprobamate is one of its metabolites.
- It can cause drowsiness, dizziness, vertigo, ataxia, tremor, irritability, headache, syncope, insomnia, tachycardia, postural hypotension, nausea, agitation, depression, weakness, and confusion.
- Overdose can cause stupor, coma, respiratory depression, and death.

OPIATES

- Signs and symptoms of opioid intoxication include euphoria, dysphoria, apathy, sedation, and attention impairment. Signs and symptoms of withdrawal include lacrimation, rhinorrhea, mydriasis, piloerection, diaphoresis, diarrhea, yawning, fever, insomnia, and muscle aches. The onset of withdrawal ranges from a few hours after stopping heroin to 3 to 5 days after stopping methadone. Duration of withdrawal ranges from 3 to 14 days. Occurrence of delirium suggests withdrawal from another drug (eg, **alcohol**).
- **Heroin** can be snorted, smoked, and given IV. Complications of heroin use include overdoses, anaphylactic reactions to impurities, nephrotic syndrome, septicemia, endocarditis, and acquired immunodeficiency.
- **Hydrocodone** is the most widely abused pharmaceutical controlled substance in the United States.
- A controlled-release dosage form of **Oxycodone** is sometimes crushed by abusers and then snorted or injected to get the full 12-hour effect almost immediately, sometimes leading to overdose and death.
- **Opiates** are commonly combined with stimulants (eg, cocaine [speedball]) or alcohol.
- Methadone has caused an increased number of deaths in recent years. Converting to methadone from other opioid agonists can be tricky, and lethal when done improperly. Peak respiratory depressant effects occur later and last longer than peak analgesic effects.
- **Dextromethorphan,** an over-the-counter drug, causes depressant and mild hallucinogenic effects in high doses and significant hallucinations and CNS depression in excessive doses. Acute overdoses are treated with naloxone**.**

CENTRAL NERVOUS SYSTEM STIMULANTS

COCAINE

- **Cocaine** may be the most behaviorally reinforcing of all drugs. Ten percent of people who begin to use the drug "recreationally" go on to heavy use.
- It blocks reuptake of catecholamine neurotransmitters and causes a depletion of brain dopamine.
- The hydrochloride salt is inhaled or injected. The high from snorting lasts 15 to 30 minutes. Smoking cocaine base (crack or rock) is almost instantly absorbed and causes intense euphoria. The high from smoking lasts 5 to 10 minutes. Tolerance to the "high" develops quickly. The elimination half-life of cocaine is 1 hour.

- In the presence of alcohol, cocaine is metabolized to cocaethylene, a longer-acting compound than cocaine with a greater risk for causing death.
- Adverse events include ulceration of nasal mucosa and nasal septal collapse, tachycardia, heart failure, hyperthermia, shock, seizures, psychosis (similar to paranoid schizophrenia), and sudden death.
- Signs and symptoms of cocaine intoxication include agitation, elation, euphoria, grandiosity, loquacity, hypervigilance, sweating or chills, nausea, vomiting, tachycardia, arrhythmias, respiratory depression, mydriasis, altered blood pressure, and seizures.
- Withdrawal symptoms begin within hours of discontinuation and last up to several days. Signs and symptoms of withdrawal include fatigue, sleep disturbances, nightmares, depression, changes in appetite, bradyarrhythmias, myocardial infarction (MI), and tremors.

METHAMPHETAMINE

- **Methamphetamine** (known as speed, meth, and crank) can be taken orally, rectally, intranasally, by IV injection, and by smoking. The hydrochloride salt is known as ice, crystal, and glass.
- Systemic effects of methamphetamine are similar to those of cocaine. Inhalation or IV injection results in an intense rush that lasts a few minutes. Methamphetamine has a longer duration of effect than cocaine. Pharmacologic effects can include increased wakefulness, increased physical activity, decreased appetite, dental caries, increased respiration, hyperthermia, euphoria, irritability, insomnia, confusion, tremors, anxiety, paranoia, aggressiveness, convulsions, increased heart rate and blood pressure, stroke, and death.
- Individuals in withdrawal may exhibit depression, cognitive impairment, drug craving, dyssomnia, and fatigue, but they are usually not in acute distress. Duration of withdrawal ranges from 2 days to several months. Occurrence of delirium suggests withdrawal from another drug (eg, **alcohol**).
- **Ephedrine** and **pseudoephedrine** can be extracted from cold and allergy tablets and converted to methamphetamine. In the United States, federal law now requires that pseudoephedrine-containing products be kept behind a counter and that identification be shown at the time of purchase.

OTHER DRUGS OF ABUSE

NICOTINE

- Cigarette smoking is the leading cause of preventable morbidity and mortality in the United States. It increases the risks of cardiovascular diseases, lung cancer, other cancers, and nonmalignant respiratory diseases.
- **Nicotine** is a ganglionic cholinergic-receptor agonist with dose-dependent pharmacologic effects. Effects include stimulation and depression in the central and peripheral nervous systems; respiratory stimulation; skeletal muscle relaxation; catecholamine release by the adrenal medulla; peripheral vasoconstriction; and increased blood pressure, heart rate, cardiac output, and oxygen consumption. Low doses produce increased alertness and improved cognitive functioning. Higher doses stimulate the "reward" center in the brain.
- Abrupt cessation results in withdrawal symptoms usually within 24 hours, including anxiety, cravings, difficulty concentrating, frustration, irritability, hostility, insomnia, and restlessness.

METHAMPHETAMINE ANALOGUES

- The analogues of current concern are 3,4-methylenedioxyamphetamine **(MDA)** and 3,4-methylenedioxymethamphetamine (**MDMA**; ecstasy).
- MDMA is usually taken by mouth as a tablet, capsule, or powder, but it can also be smoked, snorted, or injected; if taken by mouth, effects last 4 to 6 hours.

- MDMA stimulates the CNS, causes euphoria and relaxation, and produces a mild hallucinogenic effect. It can cause muscle tension, nausea, faintness, chills, sweating, panic, anxiety, depression, hallucinations, convulsions, and paranoid thinking. It increases heart rate and blood pressure and destroys serotonin (5-HT)–producing neurons in animals. It is considered to be neurotoxic in humans.

SYNTHETIC CATHINONES (BATH SALTS)

- **Bath salts** (a misnomer) are synthetic, sympathomimetic, designer drugs that can cause intoxication, dependence, and death. Cathine and cathinone are CNS stimulants that can cause MI, esophagitis, gastritis, oral keratotic lesions, and liver failure. The pharmacology of the various synthetic cathinones and related drugs is not well-studied.
- Adverse effects of bath salts include tachycardia, hypertension, diabetic ketoacidosis, delusions, paranoid psychosis, hyperthermia, agitation, headache, hyponatremia, and suicide. They are schedule I controlled substances.

MARIJUANA

- **Marijuana** (known as reefer, pot, grass, and weed) is the most commonly used illicit drug. The principal psychoactive component is **Δ^9-tetrahydrocannabinol** (**THC**). **Hashish**, the dried resin of the top of the plant, is more potent than the plant itself. Pharmacologic effects begin immediately and last 1 to 3 hours. One in 10 marijuana users become addicted.
- Initial effects of marijuana use include increased heart rate, dilated bronchial passages, and bloodshot eyes. Subsequent effects include euphoria, dry mouth, hunger, tremor, sleepiness, anxiety, fear, distrust, panic, incoordination, poor recall, amotivation, and toxic psychosis. Other physiologic effects include sedation, difficulty in performing complex tasks, and disinhibition. Endocrine effects include amenorrhea, decreased testosterone production, and inhibition of spermatogenesis. Recent findings suggest a neurotoxic effect on the adolescent brain.
- Heavy users may have a withdrawal syndrome after abrupt discontinuation.
- THC is detectable on toxicologic screening for up to 4 to 5 weeks in chronic users.

SYNTHETIC CANNABINOIDS

- Over 100 compounds are cannabinoid receptor agonists called **synthetic marijuana** (Spice, K2, dream, red X dawn, others). The product is inert dry plant material sprayed with these compounds. Toxic symptoms are similar to the effects of marijuana plus sympathomimetic effects, including agitation, anxiety, tachycardia, hypertension, nausea and vomiting, muscle spasms, seizures, tremors, diaphoresis, hallucinations, and suicidal thoughts and behaviors.

LYSERGIC ACID DIETHYLAMIDE

- Signs and symptoms of **LSD** intoxication include mydriasis, tachycardia, diaphoresis, palpitations, blurred vision, tremor, incoordination, dizziness, weakness, and drowsiness; psychiatric signs and symptoms include perceptual intensification, depersonalization, derealization, illusions, psychosis, synesthesia, and flashbacks. It produces tolerance but is not addictive. There is no withdrawal syndrome.
- LSD can cause either agonist or antagonist effects on 5-HT activity.
- LSD is sold as tablets, capsules, a liquid, and on squares of decorated paper, each square being one dose.

INHALANTS

- Organic solvents inhaled by abusers include **gasoline, glue, aerosols, amyl nitrite, butyl nitrite, typewriter correction fluid, lighter fluid, cleaning fluids, paint products, nail polish remover, waxes**, and **varnishes**. Chemicals in these products include **nitrous oxide, toluene, benzene, methanol, methylene chloride, acetone, methylethyl ketone, methylbutyl ketone, trichloroethylene**, and **trichloroethane**.

- Physiologic effects include CNS depression similar to the effects of alcohol, headache, nausea, anxiety, hallucinations, and delusions. With chronic use, the drugs are toxic to virtually all organ systems. Death may occur from arrhythmias or suffocation by plastic bags.

TREATMENT

- Goals of Treatment: The goals include cessation of use of the drug, termination of drug-seeking behaviors, and return to normal functioning. The goals of treatment of withdrawal include prevention of progression to life-threatening severity, thus enabling comfort and functionality conducive to participation in a treatment program.

INTOXICATION

- In treating acute intoxications, drug therapy should be avoided when possible, but it may be indicated if patients are agitated, combative, or psychotic (**Table 71–2**).
- When toxicology screens are desired, blood or urine should be collected immediately upon arrival for treatment.
- *Benzodiazepine overdose*: **Flumazenil** is not indicated in all cases, and it is contraindicated when cyclic antidepressant use is known or suspected because of seizure risk. Use with caution when benzodiazepine physical dependence is suspected, as it may precipitate withdrawal.
- *Opiate intoxication*: **Naloxone** may revive unconscious patients with respiratory depression, but it may precipitate physical withdrawal in dependent patients.
- **Cocaine** *intoxication*: Treat pharmacologically only if the patient is agitated or psychotic. Injectable **lorazepam** can be used for agitation. Low-dose antipsychotics can be used short term for psychosis. Treat seizures supportively, but IV lorazepam or **diazepam** can be used for status epilepticus.
- Many patients with **hallucinogen, marijuana**, or **inhalant** intoxication respond to reassurance, but short-term antianxiety and/or antipsychotic therapy can be used.

WITHDRAWAL

- Treatment of withdrawal from some common drugs of abuse is summarized in **Table 71–3**.

Alcohol

- Most clinicians agree that symptom-triggered treatment with **benzodiazepines** is the standard of care for **alcohol** detoxification.
- Lorazepam is preferred by many clinicians because it can be administered IV, intramuscularly, or orally with predictable results (**Table 71–4**). Address fluid, electrolyte, and vitamin deficiencies as in **Table 71–4**.
- With symptom-triggered therapy, medication is given only if symptoms emerge, resulting in shorter treatment duration and avoidance of oversedation compared to a fixed-dose schedule. A typical regimen would be lorazepam 2 mg administered every hour as needed when a structured assessment scale (eg, Clinical Institute Withdrawal Assessment–Alcohol, Revised) indicates that symptoms are moderate to severe.
- Alcohol withdrawal seizures do not require anticonvulsant drug treatment unless they progress to status epilepticus. Patients with seizures should be treated supportively. An increase in the dosage and slowing of the tapering schedule of the **benzodiazepine** used for detoxification or a single injection of a benzodiazepine may be necessary to prevent further seizure activity.

Benzodiazepines

- For benzodiazepine withdrawal, use the same drugs and dosages that are used for alcohol withdrawal (see **Table 71–3**).
- The onset of withdrawal from long-acting benzodiazepines may be up to 7 days after discontinuation of the drug. Initiate treatment at usual doses and maintain this dose

TABLE 71–2 Pharmacologic Treatment of Substance Intoxication

Drug Class	Nonpharmacologic Therapy	Pharmacologic Therapy	Level of Evidence[a,b]
Benzodiazepines	Support vital functions	Flumazenil 0.2 mg/min IV initially; repeat up to 3 mg maximum	A1
Alcohol, barbiturates, and sedative–hypnotics (nonbenzodiazepines)	Support vital functions	None	B3
Opiates	Support vital functions	Naloxone 0.4–2 mg IV every 3 minutes	A1
Cocaine and other CNS stimulants	Monitor cardiac function	Lorazepam 2–4 mg IM every 30 minutes to 6 hours as needed for agitation	B2
		Haloperidol 2–5 mg (or other antipsychotic agent) every 30 minutes to 6 hours as needed for psychotic behavior	B3
Hallucinogens, marijuana, and inhalants	Reassurance; "talk-down therapy"; support vital functions	Lorazepam and/or haloperidol as above	B3
Phencyclidine	Minimize sensory input	Lorazepam and/or haloperidol as above	B3

[a]Strength of recommendations, evidence to support recommendation: A, good; B, moderate; C, poor.
[b]Quality of evidence: 1, evidence from more than one properly randomized controlled trial; 2, evidence from more than one well-designed clinical trial with randomization, from cohort or case–control analytic studies or multiple time series, or dramatic results from uncontrolled experiments; 3, evidence from opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert communities.

TABLE 71–3 Treatment of Withdrawal From Some Common Drugs of Abuse

Drug or Drug Class	Pharmacologic Therapy	Level of Evidence[a,b]
Benzodiazepines		
Short- to intermediate-acting	Lorazepam 2 mg three to four times a day; taper over 5–7 days	A1
Long-acting	Lorazepam 2 mg three to four times a day; taper over additional 5–7 days	A1
Barbiturates	Pentobarbital tolerance test; initial detoxification at upper limit of tolerance test; decrease dosage by 100 mg every 2–3 days	B3
Opiates	Methadone 20–80 mg orally daily; taper by 5–10 mg daily or buprenorphine 4–32 mg orally daily, or clonidine 2 mcg/kg three times a day × 7 days; taper over additional 3 days	A1 (methadone and buprenorphine) B1 (clonidine)
Mixed-substance withdrawal		
Drugs are cross-tolerant	Detoxify according to treatment for longer-acting drug used	B3
Drugs are not cross-tolerant	Detoxify from one drug while maintaining second drug (cross-tolerant drugs), and then detoxify from second drug	B3
CNS stimulants	Supportive treatment only; pharmacotherapy often not used; bromocriptine 2.5 mg three times a day or higher may be used for severe craving associated with cocaine withdrawal	B2

[a]Strength of recommendations, evidence to support recommendation: A, good; B, moderate; C, poor.
[b]Quality of evidence: 1, evidence from more than one properly randomized controlled trial; 2, evidence from more than one well-designed clinical trial with randomization, from cohort or case–control analytic studies or multiple time series, or dramatic results from uncontrolled experiments; 3, evidence from opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert communities.

for 5 days. The dose is then tapered over 5 days. Alprazolam withdrawal may require a more gradual taper of the benzodiazepine used for detoxification.

Opiates

- Unnecessary detoxification with drugs should be avoided if possible (eg, if symptoms are tolerable). **Heroin** withdrawal reaches a peak within 36 to 72 hours and may last for 7 to 10 days, and the **methadone** withdrawal peaks at 72 hours, but can last for 2 weeks or longer.
- Conventional drug therapy for opiate withdrawal has been **methadone**, a synthetic opiate. Usual starting doses have been 20 to 40 mg/day. The dosage can be tapered in decrements of 5 to 10 mg/day until discontinued. Some clinicians use discontinuation schedules over 30 days or over 180 days.
- Other detoxification regimens (eg, adrenergic agonists) also are effective. Regardless of detoxification strategy, most heroin users relapse to heroin use.
- **Buprenorphine** in two formulations (both assigned to schedule III) is available for office-based management of opioid dependence by qualified physicians. Once-daily dosage is titrated to a target of 16 mg/day (range 4–24 mg/day).

TABLE 71–4 Dosing and Monitoring of Pharmacologic Agents Used in the Treatment of Alcohol Withdrawal

Drug	Dose Per Day (Unless Otherwise Stated)	Indication	Monitoring	Duration of Dosing	Level of Evidence for Efficacy[a]
Multivitamin	1 tablet	Malnutrition	Diet	At least until eating a balanced diet at caloric goal	B3
Thiamine	50–100 mg	Deficiency	CBC, WBC, nystagmus	Empiric × 5 days. More if evidence of deficiency	B2
Crystalloid fluids (typically D5–0.45 NS with 20 mEq of KCl per liter)	50–100 mL/h	Dehydration	Weight, electrolytes, urine output, nystagmus if dextrose	Until intake and outputs stabilize and oral intake is adequate	A3
Clonidine oral (Catapres)	0.05–0.3 mg Consider dose reduction in the elderly	Autonomic tone rebound and hyperactivity	Shaking, tremor, sweating, blood pressure	3 days or less	B2
Clonidine transdermal (Catapres-TTS)	TTS-1 to TTS-3 Consider dose reduction in the elderly	Autonomic tone rebound and hyperactivity	Shaking, tremor, sweating, blood pressure	1 week or less. One patch only	B3
Labetalol	20 mg IV every 2 hours as needed; dosage reduction (eg by about 50% for oral dosage) is advised in patients with hepatic impairment	Hypertensive urgencies and above	Blood pressure target	Individual doses as needed	B3
Antipsychotics, haloperidol (Haldol)	2.5 to 5 mg every 4 hours	Agitation unresponsive to benzodiazepines, hallucinations (tactile, visual, auditory, or otherwise), or delusions	Subjective response plus rating scale (CIWA-AR or equivalent)	Individual doses as needed	B1

(*continued*)

TABLE 71–4 Dosing and Monitoring of Pharmacologic Agents Used in the Treatment of Alcohol Withdrawal (*Continued*)

Drug	Dose Per Day (Unless Otherwise Stated)	Indication	Monitoring	Duration of Dosing	Level of Evidence for Efficacy[a]
Antipsychotics, atypical		Agitation unresponsive to benzodiazepines, hallucinations, or delusions in patients intolerant of conventional antipsychotics	Subjective response plus rating scale (CIWA-AR or equivalent)	Individual doses as needed in addition to scheduled antipsychotic	C3
Quetiapine (Seroquel)	25–200 mg; dosage adjustment is necessary in hepatic impairment				
Aripiprazole (Abilify)	5–15 mg				
Benzodiazepines		Tremor, anxiety, diaphoresis, tachypnea, dysphoria, seizures	Subjective response plus rating scale (CIWA-AR or equivalent)	Individual doses as needed. Underdosing is more common than overdosing	A2
Lorazepam (Ativan)	0.5–2 mg				
Chlordiazepoxide (Librium)	5–25 mg				
Clonazepam (Klonopin)	0.5–2 mg				
Diazepam (Valium)	2.5–10 mg				
Alcohol oral		Prevent withdrawal	Subjective signs of withdrawal	Wide variation	C3
Alcohol IV		Prevent withdrawal	Subjective signs of withdrawal	Wide variation	C3

CBC, complete blood count; CIWA-AR, Clinical Institute Withdrawal Assessment for Alcohol, Revised; D5, dextrose 5%; KCl, potassium chloride; NS, normal saline; WBC, white blood cell count.

[a]Strength of recommendations, evidence to support recommendation: A, good; B, moderate; C, poor.

Quality of evidence: 1, evidence from more than one properly randomized controlled trial; 2, evidence from more than one well-designed clinical trial with randomization, from cohort or case–control analytic studies or multiple time series, or dramatic results from uncontrolled experiments; 3, evidence from opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert communities.

- **Subutex** (**buprenorphine**) is typically used at the beginning of treatment for opiate abuse. **Suboxone** (**buprenorphine** and **naloxone**) is often used in maintenance treatment of opiate addiction.
- Medically supervised withdrawal with buprenorphine consists of an induction phase and a dose reduction phase. The Substance Abuse and Mental Health Services Administration provides evidence-based recommendations for use of buprenorphine for opioid addiction.
- Maintenance treatment with buprenorphine for opioid addiction consists of induction phase (as observed treatment), stabilization phase, and maintenance phase (may be indefinite. To minimize the risk of causing withdrawal, patients transferring from long-acting opioids (eg, methadone, sustained-release morphine, sustained-release oxycodone) to buprenorphine should be inducted using buprenorphine monotherapy, but switched to buprenorphine/naloxone soon thereafter (refer to the treatment protocols of the Substance Abuse and Mental Health Services Administration).
- **Clonidine** can attenuate the noradrenergic hyperactivity of opiate withdrawal without interfering significantly with activity at the opiate receptors. Monitor blood pressure, supine and standing, at least daily.

SUBSTANCE USE DISORDERS

- The treatment of drug dependence or addiction is primarily behavioral. The goal is complete abstinence, and treatment is a lifelong process. Most drug-dependent treatment programs embrace treatment based on the Alcoholics Anonymous approach (ie, a 12-step model).

Alcohol Dependence

- **Disulfiram** deters a patient from drinking by producing an aversive reaction if the patient drinks. It inhibits aldehyde dehydrogenase in the pathway for alcohol metabolism, allowing acetaldehyde to accumulate, resulting in flushing, vomiting, headache, palpitations, tachycardia, fever, and hypotension. Severe reactions include respiratory depression, arrhythmias, MI, seizures, and death. Inhibition of the enzyme continues for as long as 2 weeks after stopping disulfiram. Disulfiram reactions have occurred with the use of alcohol-containing mouthwashes and aftershaves. **Table 71–5** shows dosing and monitoring of drug therapy for alcohol dependence.
- Prior to starting disulfiram, obtain baseline liver function tests (LFTs), and repeat at 2 weeks, 3 months, and 6 months, then twice yearly. Wait at least 24 hours after the last drink before starting disulfiram, usually at a dose of 250 mg/day.
- **Naltrexone** reduces craving and the number of drinking days. It should not be given to patients currently dependent on opiates, as it can precipitate severe withdrawal syndrome. A depot formulation allows monthly administration in a usual dose of 380 mg intramuscularly.
- Naltrexone is hepatotoxic and contraindicated in patients with hepatitis or liver failure. LFTs should be monitored monthly for the first 3 months, then every 3 months. Side effects include nausea, headache, dizziness, nervousness, insomnia, and somnolence.
- **Acamprosate**-treated patients (999–1998 mg/day and higher) have less craving and more success in maintaining abstinence than placebo-treated patients. The most common acamprosate side effect is diarrhea.

Nicotine

- The Agency for Healthcare Research and Quality released a clinical guideline for smoking cessation in 2008. Every smoker should receive at least minimal treatment at every clinician visit.
- First-line pharmacotherapies for smoking cessation are **bupropion sustained release, nicotine gum, nicotine inhaler, nicotine lozenge, nicotine nasal spray, nicotine patch**, and **varenicline**. Combinations of these should be considered if a single agent has failed. Second-line pharmacotherapies include **clonidine** and **nortriptyline** and should be considered if first-line therapy fails.

TABLE 71–5 Dosing and Monitoring of Pharmacologic Agents Used in the Treatment of Alcohol Dependence

Drug	Dosage Range Per Day	Indication	Monitoring	Duration of Dosing	Level of Evidence for Efficacy[a]
Disulfiram (Antabuse)	250–500 mg; used with extreme caution in patients with hepatic cirrhosis or insufficiency	Deterrence	Facial flushing, liver enzymes	Indefinite	B2
Acamprosate (Campral)	999–1,998 mg and higher (333 mg tablets)	Craving	Patient-reported craving, renal function	Indefinite	A1
	Dosage adjustment necessary in renal impairment				
Naltrexone (ReVia)	50–100 mg; dosage adjustment may be needed in renal and liver impairment	Craving	Patient-reported craving	Indefinite	A1
Mood stabilizers (eg lamotrigine [Lamictal], topiramate [Topamax], carbamazepine [Tegretol], valproic acid [Depakote])	Seizure disorder doses	Craving	Patient-reported craving, plasma drug levels	Indefinite	B2
Antidepressants (eg clomipramine [Anafranil], bupropion [Wellbutrin], doxepin [Sinequan], fluoxetine [Prozac])	Depression doses	Craving, depression, anxiety	Patient-reported craving	Indefinite	B2

[a]Strength of recommendations: A, B, and C, good, moderate, and poor evidence to support recommendation, respectively.

Quality of evidence: 1, evidence from more than one properly randomized controlled trial; 2, evidence from more than one well-designed clinical trial with randomization, from cohort or case–control analytic studies or multiple time series, or dramatic results from uncontrolled experiments; 3, evidence from opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert communities.

- Interventions are more effective when they last longer than 10 minutes, involve contact with multiple types of clinicians, include at least four sessions, and provide **nicotine-replacement therapy** (**NRT**). Group and individual counseling is effective, and interventions are more successful when they include social support and training in problem solving, stress management, and relapse prevention.

NICOTINE-REPLACEMENT THERAPY

- Dosing and monitoring of pharmacotherapy for smoking cessation is shown in **Table 71–6**. Use of NRT doubles the odds of successfully quitting compared to placebo.
- NRT should be used with caution in patients within 2 weeks post-MI, those with serious arrhythmias, and those with serious or worsening angina.
- The **2-mg gum** is recommended for those smoking fewer than 25 cigarettes/day, and the 4-mg gum for those smoking 25 or more cigarettes/day. Generally, the gum should be used for up to 12 weeks at no more than 24 pieces per day. It should be chewed slowly until a peppery or minty taste emerges and then parked between the cheek and gums for about 30 minutes or until the taste dissipates. Patients should be given specific dosing instructions, not just as needed.
- The **patch** is available as a prescription and nonprescription medication. Treatment of 8 weeks or less is as effective as longer treatments. The 16- and 24-hour patches have comparable efficacy. A new patch should be placed on a relatively hairless location each morning.
- **Nicotine nasal spray** requires a prescription. Recommended duration of therapy is 3 to 6 months at no more than 40 mg/day. A dose is one 0.5 mg delivery to each nostril (1 mg total). Initial doses are gradually increased as needed for symptom relief.
- NRT products have few side effects. Nausea and light-headedness may indicate nicotine overdose. Rotate the patch site to minimize skin irritation. Nonprescription **hydrocortisone** or **triamcinolone** cream may improve skin irritation. Sleep disturbances are reported in 23% of patients using the patch. Eating or drinking anything except water should be avoided for 15 minutes before and during administration of the lozenge and gum. Long-term NRT may be needed in some patients.

OTHER

- **Bupropion sustained release** (**SR**) is contraindicated in patients with a current or past seizure disorder, a current or prior diagnosis of bulimia or anorexia nervosa, and use of a **monoamine oxidase inhibitor within the last 14 days**. Concurrent use of medications that lower the seizure threshold is a concern. It can be used in combination with NRT.
- Insomnia and dry mouth are the most frequent side effects. Others include tremor, rash, and anaphylactoid reactions. Like other antidepressants, bupropion has a black-box warning for causing agitation and suicidality in patients aged 24 years or younger.
- Bupropion SR should be dosed at 150 mg once daily for 3 days, then twice daily for 7 to 12 weeks or longer, with or without NRT. Patients should stop smoking during the second week of treatment.
- **Varenicline** is a partial agonist that binds selectively to nicotinic acetylcholine receptors with a greater affinity than nicotine, producing a lesser response than nicotine. Prescribe for 12 weeks, and a second 12-week treatment can be given if the patient is not abstinent. It may result in a higher rate of cessation than bupropion.
- Side effects of varenicline include suicidal thoughts and erratic and aggressive behavior. Screen patients for psychiatric illness or behavior change after starting varenicline. The Food and Drug Administration (FDA) required a boxed warning and updated medication guide. It may be associated with a small increased risk of cardiovascular events.

SECOND-LINE MEDICATIONS

- **Clonidine** is an effective smoking-cessation treatment. It is given for 3 to 10 weeks and should not be discontinued abruptly. Abrupt discontinuation may cause

TABLE 71–6 Dosing and Monitoring of Pharmacologic Agents Used for Smoking Cessation

Drug	Place in Therapy	Dosage Range	Duration	Comments/Monitoring Parameters	LOEE[a]
Bupropion SR[b,c] (Zyban)	First-line	Titrate up to 150 mg orally twice daily. May require reduced initial dose in elderly	3–6 months	Patients receiving both bupropion and a nicotine patch should be monitored for hypertension	A1
Clonidine[c,d] (Catapres)	Second-line	Titrate to response; 0.2–0.75 mg/day. Consider dose reduction in the elderly	6–12 months	Monitor baseline electrolyte and lipid profiles, renal function, uric acid, complete blood count, and blood pressure	B2
Nicotine polacrilex (gum)[b] (Nicorette)	First-line	Initial dose depends on smoking history: 2–4 mg every 1–8 hours	12 weeks (taper down over time)	Heart rate and blood pressure should be monitored periodically during nicotine replacement therapy	A1
Nicotine inhaler[b] (Nicotrol)	First-line	24–64 mg/day (total daily dose)	3–6 months (taper down over time)	Heart rate and blood pressure should be monitored periodically during nicotine replacement therapy	A1
Nicotine nasal spray[b] (Nicotrol NS)	First-line	8–40 mg/day (total daily dose)	14 weeks (taper down over time)	Heart rate and blood pressure should be monitored periodically during nicotine replacement therapy	A1
Nicotine patch[b] (NicoDerm, Nicotrol)	First-line	Initial dose depends on smoking history: 7–21 mg topically once daily	6 weeks (taper down over time)	Heart rate and blood pressure should be monitored periodically during nicotine replacement therapy	A1
Nortriptyline[c,d] (Aventyl)	Second-line	Titrate up to 75–100 mg orally daily	6–12 months	Dry mouth, blurred vision, and constipation are dose-dependent adverse effects	B2
Varenicline[c] (Chantix)	First-line	Titrate up to 1 mg orally twice daily. If CrCl <30 mL/min, 0.5 mg once per day	3–6 months	Monitor renal function, especially in elderly patients. Nausea, headache, insomnia are dose-dependent adverse effects	A1

LOEE, level of evidence for efficacy.

[a]Strength of recommendations, evidence to support recommendation: A, good; B, moderate; C, poor.
Quality of evidence: 1, evidence from more than one properly randomized controlled trial; 2, evidence from more than one well-designed clinical trial with randomization, from cohort or case–control analytic studies or multiple time series, or dramatic results from uncontrolled experiments; 3, evidence from opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert communities.
[b]Nicotine replacement therapies can be combined with each other and/or bupropion to increase long-term abstinence rates.
[c]Do not abruptly discontinue. Taper up initially, and taper off once therapy is complete.
[d]Clonidine and nortriptyline are not FDA-approved for smoking cessation.

nervousness, agitation, headache, tremor, and rapid rise in blood pressure. Dosing varies from 0.15 to 0.75 mg/day orally and from 0.1 to 0.2 mg/day transdermally.

- The most common clonidine side effects include dry mouth, dizziness, sedation, and constipation. Monitor blood pressure.
- **Nortriptyline** is initiated 10 to 28 days before the quit date. The dose is initiated at 25 mg/day, gradually increasing to 75 to 100 mg/day. Treatment duration is commonly 12 weeks in trials, and common side effects include sedation, dry mouth, blurred vision, urinary retention, and light-headedness.

See Chapter 48, Substance-Related Disorders I: Overview and Depressants, Stimulants, and Hallucinogens, authored by Paul L. Doering and Robin Moorman Li, and Chapter 49, Substance-Related Disorders II: Alcohol, Nicotine, and Caffeine, authored by Paul L. Doering and Robin Moorman Li, for a more detailed discussion of the topic.

This page intentionally left blank

Edited by Cecily V. DiPiro

CHAPTER 72

Acid–Base Disorders

- *Acid–base disorders* are caused by disturbances in hydrogen ion (H^+) homeostasis, which is ordinarily maintained by extracellular buffering, renal regulation of hydrogen ion and bicarbonate, and ventilatory regulation of carbon dioxide (CO_2) elimination.

GENERAL PRINCIPLES

- Buffering refers to the ability of a solution to resist change in pH after the addition of a strong acid or base. The body's principal extracellular buffer system is the carbonic acid/bicarbonate (H_2CO_3/HCO_3^-) system.
- Most of the body's acid production is in the form of CO_2 and is produced from catabolism of carbohydrates, proteins, and lipids.
- There are four primary types of acid–base disturbances, which can occur independently or together as a compensatory response.
- Metabolic acid–base disorders are caused by changes in plasma bicarbonate concentration (HCO_3^-). Metabolic acidosis is characterized by decreased HCO_3^-, and metabolic alkalosis is characterized by increased HCO_3^-.
- Respiratory acid–base disorders are caused by altered alveolar ventilation, producing changes in arterial carbon dioxide tension ($Paco_2$). Respiratory acidosis is characterized by increased $Paco_2$, whereas respiratory alkalosis is characterized by decreased $Paco_2$.

DIAGNOSIS

- Blood gases (**Table 72–1**), serum electrolytes, medical history, and clinical condition are the primary tools for determining the cause of acid–base disorders and for designing therapy.
- Arterial blood gases (ABGs) are measured to determine oxygenation and acid–base status (**Fig. 72–1**). Low pH values (<7.35) indicate acidemia, whereas high values (>7.45) indicate alkalemia. The $Paco_2$ value helps determine whether there is a primary respiratory abnormality, whereas the HCO_3^- concentration helps determine whether there is a primary metabolic abnormality. Steps in acid–base interpretation are described in **Table 72–2**.

METABOLIC ACIDOSIS

PATHOPHYSIOLOGY

- Metabolic acidosis is characterized by decreased pH and serum HCO_3^- concentrations, which can result from adding organic acid to extracellular fluid (eg, lactic acid and ketoacids), loss of HCO_3^- stores (eg, diarrhea), or accumulation of endogenous acids due to impaired renal function (eg, phosphates and sulfates).
- Serum anion gap (SAG) can be used to elucidate the cause of metabolic acidosis (**Table 72–3**). SAG is calculated as follows:

$$SAG = [Na^+] - [Cl^-] - [HCO_3^-]$$

TABLE 72–1 Normal Blood Gas Values

	Arterial Blood	Mixed Venous Blood
pH	7.40 (7.35–7.45)	7.38 (7.33–7.43)
Po_2	80–100 mm Hg (10.6–13.3 kPa)	35–40 mm Hg (4.7–5.3 kPa)
Sao_2	95% (0.95)	70%–75% (0.70–0.75)
Pco_2	35–45 mm Hg (4.7–6.0 kPa)	45–51 mm Hg (6.0–6.8 kPa)
HCO_3^-	22–26 mEq/L (22–26 mmol/L)	24–28 mEq/L (24–28 mmol/L)

HCO_3^-, bicarbonate; Pco_2, partial pressure of carbon dioxide; Po_2, partial pressure of oxygen; Sao_2, saturation of arterial oxygen.

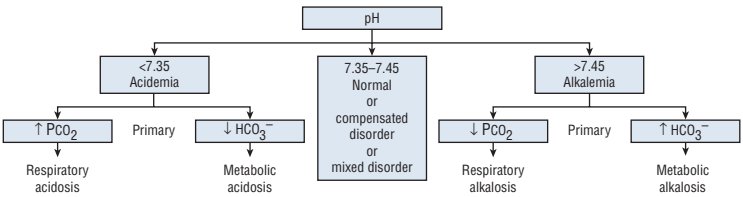


FIGURE 72–1. Analysis of arterial blood gases (ABGs). (HCO_3^-, bicarbonate; Pco_2, partial pressure of carbon dioxide.)

The normal anion gap is approximately 9 mEq/L (9 mmol/L), with a range of 3 to 11 mEq/L (3–11 mmol/L). SAG is a relative rather than an absolute indication of the cause of metabolic acidosis.

- The primary compensatory mechanism is to decrease $Paco_2$ by increasing the respiratory rate.

CLINICAL PRESENTATION

- Relatively asymptomatic; major manifestations are bone demineralization with the development of rickets in children and osteomalacia and osteopenia in adults.
- Acute severe metabolic acidemia (pH <7.2) involves the cardiovascular, respiratory, and central nervous systems. Hyperventilation is often the first sign of metabolic acidosis. Respiratory compensation may occur as Kussmaul respirations (ie, deep, rapid respirations characteristic of diabetic ketoacidosis).

TABLE 72–2 Steps in Acid–Base Diagnosis

1. Obtain ABGs and electrolytes simultaneously.
2. Compare [HCO_3^-] on ABG and electrolytes to verify accuracy.
3. Calculate SAG.
4. Is acidemia (pH <7.35) or alkalemia (pH >7.45) present?
5. Is the primary abnormality respiratory (alteration in $Paco_2$) or metabolic (alteration in HCO_3^-)?
6. Estimate compensatory response (see Table 37–7 in *Pharmacotherapy: A Pathophysiologic Approach,* ninth edition).
7. Compare change in [Cl^-] with change in [Na^+].

ABGs, arterial blood gases; [Cl^-], chloride ion; [HCO_3^-], bicarbonate; [Na^+], sodium ion; $Paco_2$, partial pressure of carbon dioxide from arterial blood; SAG, serum anion gap.

TABLE 72–3 Common Causes of Metabolic Acidosis

Increased Serum Anion Gap	Normal Serum Anion Gap/Hyperchloremic States
Lactic acidosis	**GI bicarbonate loss**
Diabetic ketoacidosis	Diarrhea
Renal failure (acute or chronic)	External pancreatic or small bowel drainage (fistula)
Methanol ingestion	Ureterosigmoidostomy, ileostomy
Ethylene glycol ingestion	**Drugs**
Salicylate overdosage	Cholestyramine (bile acid diarrhea)
Starvation	Magnesium sulfate (diarrhea)
	Calcium chloride (acidifying agent)
	Renal tubular acidosis
	Hypokalemia
	Proximal renal tubular acidosis (type II)
	Distal renal tubular acidosis (type I)
	Carbonic anhydrase inhibitors (eg, acetazolamide)
	Hyperkalemia
	Generalized distal nephron dysfunction (type IV)
	Mineralocorticoid deficiency or resistance
	Tubulointerstitial disease
	Drug-induced hyperkalemia
	Potassium-sparing diuretics (amiloride, spironolactone, triamterene)
	Trimethoprim
	Pentamidine
	Heparin
	Angiotensin-converting enzyme inhibitors and receptor blockers
	Nonsteroidal anti-inflammatory drugs
	Cyclosporin A
	Other
	Acid ingestion (ammonium chloride, hydrochloric acid, hyperalimentation)
	Expansion acidosis (rapid saline administration)

TREATMENT

- The primary treatment is to correct the underlying disorder. Additional treatment depends on the severity and onset of acidosis.
- Manage asymptomatic patients with mild to moderate acidemia (HCO_3^- 12–20 mEq/L [12–20 mmol/L]; pH 7.2–7.4) with gradual correction of the acidemia over days to weeks using oral **sodium bicarbonate** or other alkali preparations (**Table 72–4**). The dose of bicarbonate can be calculated as follows:

$$\text{Loading dose (mEq or mmol/L)} = (\text{Vd } HCO_3^- \times \text{body weight}) \times (\text{desired } [HCO_3^-] - \text{current } [HCO_3^-]),$$

where Vd HCO_3^- is the volume of distribution of HCO_3^- (0.5 L/kg).

TABLE 72–4 Therapeutic Alternatives for Oral Alkali Replacement

Generic Name	Trade Name(s)	Milliequivalents of Alkali	Dosage Form(s)	Comment
Shohl's solution, sodium citrate/citric acid	Bicitra (Willen)	1 mEq Na/mL; equivalent to 1 mEq bicarbonate	Solution (500 mg Na citrate, 334 mg citric acid/5 mL)	Citrate preparations increase absorption of aluminum
Sodium bicarbonate	Various (eg, Soda mint)	3.9 mEq bicarbonate/tablet (325 mg)	325 mg tablet	Bicarbonate preparations can cause bloating because of carbon dioxide production
		7.8 mEq bicarbonate/tablet (650 mg)	650 mg tablet	
	Baking soda (various)	60 mEq bicarbonate/tsp (5 g/tsp)	Powder	
Potassium citrate	Urocit-K (Mission)	5 mEq citrate/tablet	5 mEq tablet	See above
Potassium bicarbonate/ potassium citrate	K-Lyte (Bristol)	25 mEq bicarbonate/tablet	25 mEq tablet (effervescent)	See above
	K-Lyte DS (Bristol)	50 mEq bicarbonate/tablet (double strength)	50 mEq tablet (effervescent)	
Potassium citrate/citric acid	Polycitra-K (Willen)	2 mEq K/mL; equivalent to 2 mEq bicarbonate	Solution (1100 mg K citrate, 334 mg citric acid/5 mL)	See above
		30 mEq bicarbonate/unit dose packet	Crystals for reconstitution (3300 mg K citrate, 1002 mg citric acid/unit dose packet)	
Sodium citrate/potassium citrate/citric acid	Polycitra (Willen) Polycitra-LC (Willen)	1 mEq K, 1 mEq Na/mL; equivalent to 2 mEq bicarbonate	Syrup (Polycitra) solution (Polycitra-LC) (both contain 550 mg K citrate, 500 mg Na citrate, 334 mg citric acid/5 mL)	See above

- Alkali therapy can be used to treat patients with acute severe metabolic acidosis due to hyperchloremic acidosis, but its role is controversial in patients with lactic acidosis. Therapeutic options include **sodium bicarbonate** and **tromethamine.**
  - ✓ Sodium bicarbonate is recommended to raise arterial pH to 7.2. However, no controlled clinical studies have demonstrated reduced morbidity and mortality compared with general supportive care. If IV sodium bicarbonate is administered, the goal is to increase, not normalize, pH to 7.2 and HCO_3^- to 8 to 10 mEq/L (8–10 mmol/L).
  - ✓ Tromethamine, a highly alkaline solution, is a sodium-free organic amine that acts as a proton acceptor to prevent or correct acidosis. However, no evidence exists that tromethamine is beneficial or more efficacious than sodium bicarbonate. The usual empiric dosage for tromethamine is 1 to 5 mmol/kg administered IV over 1 hour, and an individualized dose can be calculated as follows:

$$\text{Dose of tromethamine (in mL)} = 1.1 \times \text{body weight (in kg)} \times (\text{normal } [HCO_3^-] - \text{current } [HCO_3^-])$$

METABOLIC ALKALOSIS

PATHOPHYSIOLOGY

- Metabolic alkalosis is *initiated* by increased pH and HCO_3^-, which can result from loss of H^+ via the gastrointestinal (GI) tract (eg, nasogastric suctioning, vomiting) or kidneys (eg, diuretics, Cushing syndrome) or from gain of bicarbonate (eg, administration of bicarbonate, acetate, lactate, or citrate).
- Metabolic alkalosis is *maintained* by abnormal renal function that prevents the kidneys from excreting excess bicarbonate.
- The respiratory response is to increase $Paco_2$ by hypoventilation.

CLINICAL PRESENTATION

- No unique signs or symptoms are associated with mild to moderate metabolic alkalosis. Some patients complain of symptoms related to the underlying disorder (eg, muscle weakness with hypokalemia or postural dizziness with volume depletion) or have a history of vomiting, gastric drainage, or diuretic use.
- Severe alkalemia (pH >7.60) can be associated with cardiac arrhythmias and neuromuscular irritability.

TREATMENT

- Aim treatment at correcting the factor(s) responsible for maintaining the alkalosis and depends on whether the disorder is sodium chloride responsive or resistant (**Fig. 72–2**).

RESPIRATORY ALKALOSIS

PATHOPHYSIOLOGY

- Respiratory alkalosis is characterized by a decrease in $Paco_2$ that leads to an increase in pH.
- $Paco_2$ decreases when ventilatory CO_2 excretion exceeds metabolic CO_2 production, usually because of hyperventilation.
- Causes include increases in neurochemical stimulation via central or peripheral mechanisms, or physical increases in ventilation via voluntary or artificial means (eg, mechanical ventilation).
- The earliest compensatory response is to chemically buffer excess bicarbonate by releasing hydrogen ions from intracellular proteins, phosphates, and hemoglobin. If prolonged (>6 hours), the kidneys attempt to further compensate by increasing bicarbonate elimination.

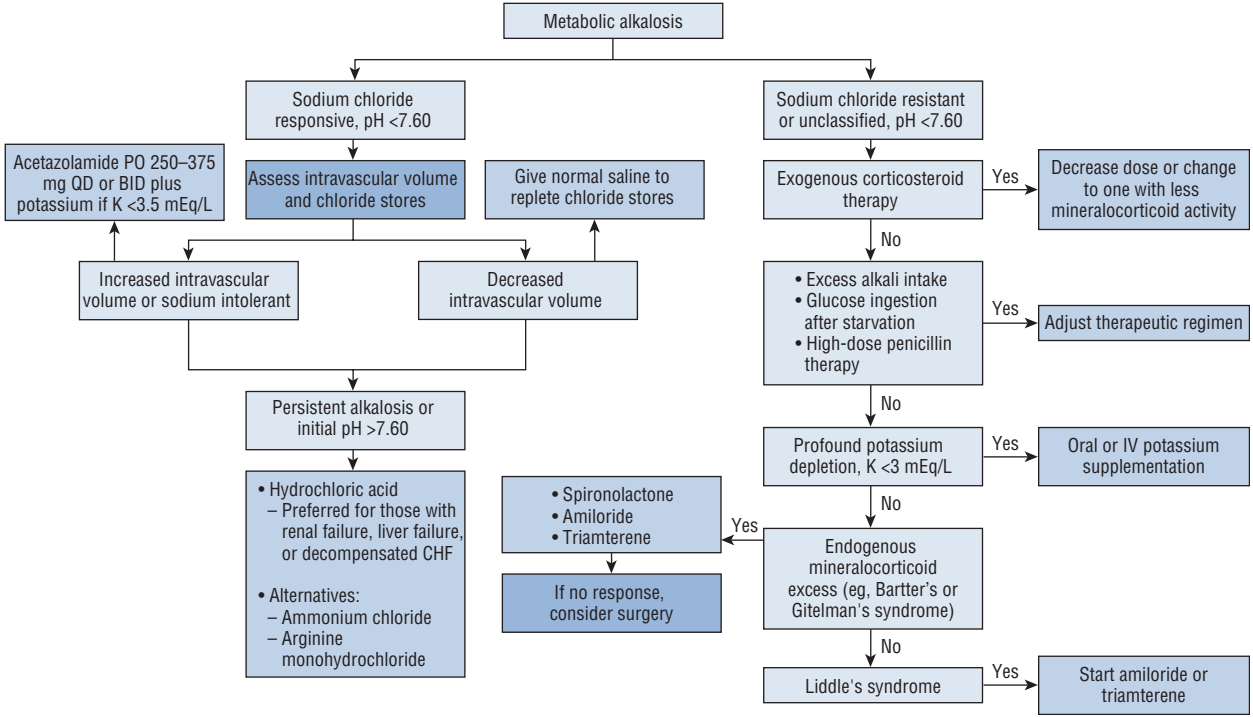


FIGURE 72–2. Treatment algorithm for patients with primary metabolic alkalosis. (BID, twice daily; CHF, chronic heart failure; IV, intravenous; K, potassium [serum potassium in mEq/L is numerically equal to mmol/L]; PO, orally; QD, every day.)

CLINICAL PRESENTATION

- Although usually asymptomatic, respiratory alkalosis can cause adverse neuromuscular, cardiovascular, and GI effects.
- Light-headedness, confusion, decreased intellectual functioning, syncope, and seizures can be caused by decreased cerebral blood flow.
- Nausea and vomiting can occur, probably due to cerebral hypoxia.
- Serum electrolytes can be altered; serum chloride is usually increased; serum potassium, phosphorus, and ionized calcium are usually decreased.

TREATMENT

- Treatment is often unnecessary because most patients have few symptoms and only mild pH alterations (ie, pH <7.50).
- Direct measures (eg, treatment of pain, hypovolemia, fever, infection, or salicylate overdose) can be effective. A rebreathing device (eg, paper bag) can help control hyperventilation in patients with anxiety/hyperventilation syndrome.
- Correct respiratory alkalosis associated with mechanical ventilation by decreasing the number of mechanical breaths per minute, using a capnograph and spirometer to adjust ventilator settings more precisely, or increasing dead space in the ventilator circuit.

RESPIRATORY ACIDOSIS

PATHOPHYSIOLOGY

- Respiratory acidosis is characterized by an increase in $Paco_2$ and a decrease in pH.
- Respiratory acidosis results from disorders that restrict ventilation or increase CO_2 production, airway and pulmonary abnormalities, neuromuscular abnormalities, or mechanical ventilator problems.
- Early compensatory response to acute respiratory acidosis is chemical buffering. If prolonged (>12–24 hours), proximal tubular HCO_3^- reabsorption, ammoniagenesis, and distal tubular H^+ secretion are enhanced, resulting in an increase in serum HCO_3^- concentration that raises pH to normal.

CLINICAL PRESENTATION

- Neuromuscular symptoms include altered mental status, abnormal behavior, seizures, stupor, and coma. Hypercapnia can mimic a stroke or CNS tumor by producing headache, papilledema, focal paresis, and abnormal reflexes. CNS symptoms are caused by increased cerebral blood flow and are variable, depending in part on the acuity of onset.

TREATMENT

- Provide adequate ventilation if CO_2 excretion is acutely and severely impaired ($Paco_2$ >80 mm Hg [>10.6 kPa]) or if life-threatening hypoxia is present (arterial oxygen tension [Pao_2] <40 mm Hg [<5.3 kPa]). Ventilation can include maintaining a patent airway (eg, emergency tracheostomy, bronchoscopy, or intubation), clearing excessive secretions, administering oxygen, and providing mechanical ventilation.
- Treat underlying cause aggressively (eg, administration of bronchodilators for bronchospasm or discontinuation of respiratory depressants such as narcotics and benzodiazepines). Bicarbonate administration is rarely necessary and is potentially harmful.
- Chronic respiratory acidosis (eg, chronic obstructive pulmonary disease [COPD]) is treated essentially the same as acute respiratory acidosis with a few important exceptions. Oxygen therapy should be initiated carefully and only if the Pao_2 is less than 50 mm Hg (<6.7 kPa) because the drive to breathe depends on hypoxemia rather than hypercarbia.
- For information on chronic respiratory acidosis, see Chap. 78.

MIXED ACID–BASE DISORDERS

PATHOPHYSIOLOGY

- Failure of compensation is responsible for mixed acid–base disorders such as respiratory acidosis and metabolic acidosis, or respiratory alkalosis and metabolic alkalosis. In contrast, excess compensation is responsible for metabolic acidosis and respiratory alkalosis, or metabolic alkalosis and respiratory acidosis.
- Respiratory and metabolic acidosis can develop in patients with cardiorespiratory arrest, with chronic lung disease and shock, and with metabolic acidosis and respiratory failure.
- The most common mixed acid–base disorder is respiratory and metabolic alkalosis, which occurs in critically ill surgical patients with respiratory alkalosis caused by mechanical ventilation, hypoxia, sepsis, hypotension, neurologic damage, pain, or drugs; and with metabolic alkalosis caused by vomiting or nasogastric suctioning and massive blood transfusions.
- Mixed metabolic acidosis and respiratory alkalosis occur in patients with advanced liver disease, salicylate intoxication, and pulmonary-renal syndromes.
- Metabolic alkalosis and respiratory acidosis can occur in patients with COPD and respiratory acidosis who are treated with salt restriction, diuretics, and possibly glucocorticoids.

TREATMENT

- Treat mixed respiratory and metabolic acidosis by initiating oxygen delivery to improve hypercarbia and hypoxia. Mechanical ventilation can be needed to reduce $Paco_2$. During initial therapy, give appropriate amounts of alkali to reverse the metabolic acidosis.
- Correct the metabolic component of mixed respiratory and metabolic alkalosis by administering **sodium** and **potassium chloride solutions.** Readjust the ventilator or treat the underlying disorder causing hyperventilation to treat the respiratory component.
- Treatment of mixed metabolic acidosis and respiratory alkalosis should be directed at the underlying cause.
- In metabolic alkalosis and respiratory acidosis, pH does not usually deviate significantly from normal, but treatment can be required to maintain Pao_2 and $Paco_2$ at acceptable levels. Aim treatment at decreasing plasma bicarbonate with sodium and potassium chloride therapy, allowing renal excretion of retained bicarbonate from diuretic-induced metabolic alkalosis.

EVALUATION OF THERAPEUTIC OUTCOMES

- Patients should be monitored closely because acid–base disorders can be serious and even life threatening.
- ABGs are the primary tools for evaluation of therapeutic outcome.

See Chapter 37, Acid–Base Disorders, authored by John W. Devlin and Gary R. Matzke, for a more detailed discussion of this topic.

CHAPTER 73

Acute Kidney Injury

- *Acute kidney injury* (AKI) is a clinical syndrome generally defined by an abrupt reduction in kidney functions as evidenced by changes in laboratory values, serum creatinine (S_{cr}), blood urea nitrogen (BUN), and urine output.
- RIFLE (Risk, Injury, Failure, Loss of Kidney Function, and End-Stage Renal Disease) and AKIN (Acute Kidney Injury Network) criteria are two criteria-based classification systems developed to predict patient outcomes. The Kidney Disease: Improving Global Outcomes (KDIGO) Clinical Practice Guidelines were developed to provide one standardized definition of AKI (**Table 73–1**).
- KDIGO defines AKI as being present if any of the following criteria is met:
  1. Increase in S_{cr} by at least 0.3 mg/dL (27 μmol/L) within 48 hours
  2. Increase in S_{cr} by at least 1.5 times baseline within the prior 7 days
  3. Decrease in urine volume to less than 0.5 mL/kg/h for 6 hours

PATHOPHYSIOLOGY

- AKI can be categorized as prerenal (resulting from decreased renal perfusion in the setting of undamaged parenchymal tissue), intrinsic (resulting from structural damage to the kidney, most commonly the tubule from an ischemic or toxic insult), and postrenal (resulting from obstruction of urine flow downstream from the kidney) (**Fig. 73–1**).

CLINICAL PRESENTATION

- Patient presentation varies widely and depends on the underlying cause. Outpatients often are not in acute distress; hospitalized patients may develop AKI after a catastrophic event.
- Symptoms in the outpatient setting include acute change in urinary habits, weight gain, and flank pain. Signs include edema, colored or foamy urine, and, in volume-depleted patients, orthostatic hypotension.

DIAGNOSIS

- Thorough medical and medication histories, physical examination, assessment of laboratory values, and, if needed, imaging studies are important in the diagnosis of AKI.
- S_{cr} cannot be used alone to diagnose AKI because it is insensitive to rapid changes in glomerular filtration rate (GFR) and therefore may not reflect current renal function. The use of BUN in AKI is very limited because urea's production and renal clearance are heavily influenced by extrarenal factors such as critical illness, volume status, protein intake, and medications.
- Urine output measured over a specified period of time allows for short-term assessment of kidney function, but its utility is limited to cases in which it is significantly decreased.
- In addition to BUN and S_{cr}, selected blood tests, urinary chemistry, and urinary sediment are used to differentiate the cause of AKI and guide patient management (**Tables 73–2** and **73–3**).
- Simultaneous measurement of urine and serum electrolytes and calculation of the fractional excretion of sodium (FE_{Na}) can help determine the etiology of AKI (Table 73–2). The FE_{Na} is calculated as

$$FE_{Na} = (U_{Na} \times S_{Cr} \times 100)/(U_{Cr} \times S_{Na})$$

where U_{Na} = urine sodium, S_{Cr} = serum creatinine, U_{Cr} = urine creatinine, and S_{Na} = serum sodium.

TABLE 73–1 RIFLE, AKIN, and KDIGO Classification Schemes for Acute Kidney Injury[a]

RIFLE Category	S_{cr} and GFR[b] Criteria	Urine Output Criteria
Risk	S_{cr} increase to 1.5-fold or GFR decrease >25% from baseline	<0.5 mL/kg/h for ≥6 hours
Injury	S_{cr} increase to twofold or GFR decrease >50% from baseline	<0.5 mL/kg/h for ≥12 hours
Failure	S_{cr} increase to threefold or GFR decrease >75% from baseline, or S_{cr} ≥4 mg/dL (≥354 µmol/L) with an acute increase of at least 0.5 mg/dL (44 µmol/L)	Anuria for ≥12 hours
Loss	Complete loss of function (RRT) for >4 weeks	
ESKD	RRT >3 months	
AKIN Criteria	**S_{cr} Criteria**	**Urine Output Criteria**
Stage 1	S_{cr} increase ≥0.3 mg/dL (≥27 µmol/L) or 1.5- to 2-fold from baseline	<0.5 mL/kg/h for ≥6 hours
Stage 2	S_{cr} increase >2- to 3-fold from baseline	<0.5 mL/kg/h for ≥12 hours
Stage 3	S_{cr} increase >3-fold from baseline, or S_{cr} ≥4 mg/dL (≥354 µmol/L) with an acute increase of at least 0.5 mg/dL (≥44 µmol/L), or need for RRT	<0.3 mL/kg/h for ≥24 hours or anuria for ≥12 hours
KDIGO Criteria	**S_{cr} Criteria**	**Urine Output Criteria**
Stage 1	S_{cr} increase ≥0.3 mg/dL (≥27 µmol/L) or 1.5–1.9 times from baseline	<0.5 mL/kg/h for 6–12 hours
Stage 2	S_{cr} increase 2–2.9 times from baseline	<0.5 mL/kg/h for ≥12 hours
Stage 3	S_{cr} increase three times from baseline, or S_{cr} ≥4 mg/dL (≥354 µmol/L), or need for RRT, or eGFR[c] <35 mL/min/1.73 m^2 (<0.34 mL/s/m^2) in patients <18 years	Anuria for ≥12 hours

AKIN, Acute Kidney Injury Network; ESKD, end-stage kidney disease; eGFR, estimated glomerular filtration rate; h, hours; KDIGO, Kidney Disease: Improving Global Outcomes; RIFLE, Risk, Injury, Failure, Loss of Kidney Function, and End-Stage Kidney Disease; RRT, renal replacement therapy; S_{cr}, serum creatinine.

[a]For all staging systems, the criterion that leads to worst possible diagnosis should be used.
[b]GFR calculated using the Modification of Diet in Renal Disease (MDRD) equation.
[c]GFR calculated using the Schwartz formula.

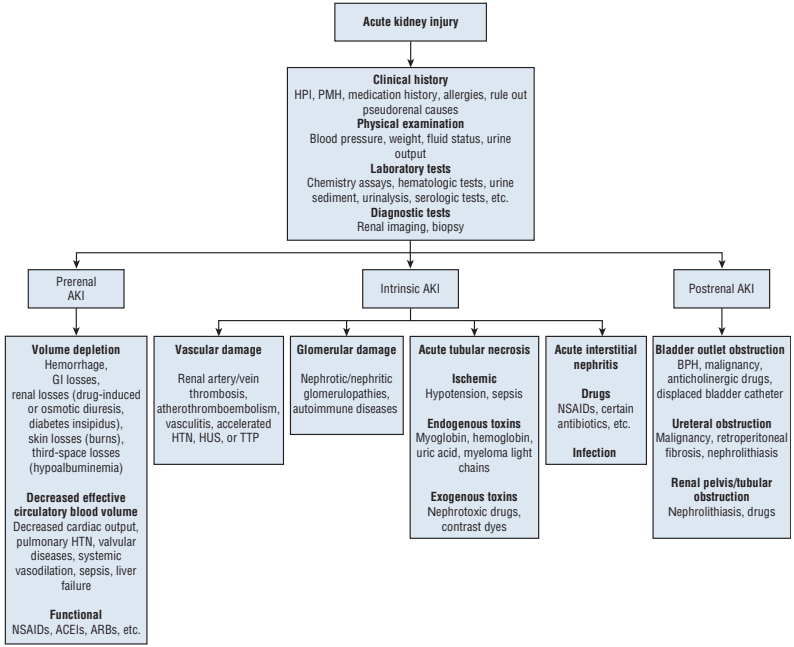


FIGURE 73–1. Classification of acute kidney injury (AKI) based on etiology. (ACEIs, angiotensin-converting enzyme inhibitors; ARBs, angiotensin receptor blockers; BPH, benign prostatic hyperplasia; GI, gastrointestinal; HPI, history of present illness; HTN, hypertension; HUS, hemolytic uremic syndrome; NSAIDs, nonsteroidal anti-inflammatory drugs; PMH, past medical history; TTP, thrombotic thrombocytopenic purpura.)

TABLE 73–2 Diagnostic Parameters for Differentiating Causes of AKI[a]

Laboratory Test	Prerenal AKI	Intrinsic AKI	Postrenal AKI
Urine sediment	Hyaline casts, may be normal	Granular casts, cellular debris	Cellular debris
Urinary RBC	None	2–4+	Variable
Urinary WBC	None	2–4+	1+
Urine Na (mEq/L or mmol/L)	<20	>40	>40
FE_{Na} (%)	<1	>2	Variable
Urine/serum osmolality	>1.5	<1.3	<1.5
Urine/S_{cr}	>40:1	<20:1	<20:1
BUN/S_{cr} (urea/S_{cr}, SI)	>20 (>80)	~15 (~60)	~15 (~60)
Urine specific gravity	>1.018	<1.012	Variable

AKI, acute kidney injury; BUN, blood urea nitrogen; FE_{Na}, fractional excretion of sodium; S_{cr}, serum creatinine; RBC, red blood cell; WBC, white blood cell.

[a]Common laboratory tests are used to classify the cause of AKI. Functional AKI, which is not included in this table, would have laboratory values similar to those seen in prerenal AKI. However, the urine osmolality-to-plasma osmolality ratios may not exceed 1.5, depending on the circulating levels of antidiuretic hormone. The laboratory results listed under intrinsic AKI are those seen in acute tubular necrosis, the most common cause of intrinsic AKI.

- A number of new serum and urinary biomarkers are under investigation for early detection and prediction of prognosis of AKI.

PREVENTION

- Goals of Prevention: The goals are to screen and identify patients at risk; monitor high-risk patients; and implement prevention strategies when appropriate.

GENERAL APPROACH TO PREVENTION

Nonpharmacologic Therapies

- Hydration is routinely used to prevent contrast-induced nephropathy (CIN), a common cause of acute tubular necrosis in the inpatient setting. Evidence supports use of isotonic crystalloids over colloids and parenteral over oral administration in high-risk individuals, including those with chronic kidney disease (CKD), diabetes, volume depletion, concurrent nephrotoxic drug therapy, or hemodynamic instability.
- KDIGO guidelines recommend either sodium bicarbonate or normal saline infusions. A common sodium bicarbonate regimen is 154 mEq/L (154 mmol/L) infused at 3 mL/kg/h for 1 hour before the procedure and at 1 mL/kg/h for 6 hours after the procedure. One frequently cited normal saline regimen is 1 mL/kg/h for 12 hours pre- and postprocedure.

Pharmacologic Therapies

- **Ascorbic acid** (3 g orally pre- and 2 g orally twice daily for two doses postprocedure) and ***N*-acetylcysteine** (600–1200 mg orally every 12 hours for 2–3 days [first two doses precontrast]) are antioxidant options for prevention of CIN. Study results with these two agents are inconsistent.

TABLE 73–3 Urinary Findings as a Guide to the Etiology of AKI

Type of Urinary Evaluation	Presence of	Suggestive of
Urinalysis	Leukocyte esterases	Pyelonephritis
	Nitrites	Pyelonephritis
	Protein	
	Mild (<0.5 g/day)	Tubular damage
	Moderate (0.5–3 g/day)	Glomerulonephritis, pyelonephritis, tubular damage
	Large (>3 g/day)	Glomerulonephritis, nephrotic syndrome
	Hemoglobin	Glomerulonephritis, pyelonephritis, renal infarction, renal tumors, kidney stones
	Myoglobin	Rhabdomyolysis-associated tubular necrosis
	Urobilinogen	Hemolysis-associated tubular necrosis
Urine sediment	Microorganisms	Pyelonephritis
Cells	Red blood cells	Glomerulonephritis, pyelonephritis, renal infarction, papillary necrosis, renal tumors, kidney stones
	White blood cells	Pyelonephritis, interstitial nephritis
	Eosinophils	Drug-induced interstitial nephritis, renal transplant rejection
	Epithelial cells	Tubular necrosis
Casts	Granular casts	Tubular necrosis
	Hyaline casts	Prerenal azotemia
	White blood cell casts	Pyelonephritis, interstitial nephritis
	Red blood cell casts	Glomerulonephritis, renal infarct, lupus nephritis, vasculitis
Crystals	Urate	Postrenal obstruction
	Calcium phosphate	Postrenal obstruction

- Current KDIGO guidelines suggest that moderate control of blood glucose to levels of 110 to 149 mg/dL (6.1–8.3 mmol/L) with **insulin** is appropriate to prevent intensive care unit–acquired AKI.
- KDIGO guidelines recommend limiting use of **loop diuretics** to management of fluid overload and avoiding use for sole purpose of preventing or treating AKI. Current evidence and KDIGO guidelines do not support use of low-dose **dopamine, erythropoietin, or fenoldopam** for prevention or treatment of AKI.

TREATMENT OF ACUTE KIDNEY INJURY

- Goals of Treatment: Short-term goals include minimizing the degree of insult to the kidney, reducing extrarenal complications, and expediting recovery of renal function. Restoration of renal function to pre-AKI baseline is the ultimate goal.

GENERAL APPROACH TO TREATMENT

- Currently, there is no definitive therapy for AKI. Supportive care is the mainstay of AKI management regardless of etiology.

Nonpharmacologic Therapies

- Supportive care goals include maintenance of adequate cardiac output and blood pressure to optimize tissue perfusion while restoring renal function to pre-AKI baseline.
- Discontinue medications associated with diminished renal blood flow. Initiate appropriate fluid and electrolyte management. Avoid use of nephrotoxins.
- In severe AKI, renal replacement therapy (RRT), such as hemodialysis and peritoneal dialysis, maintains fluid and electrolyte balance while removing waste products. See Table 73–4 for indications for RRT in AKI. Intermittent and continuous options have different advantages (and disadvantages) but, after correcting for severity of illness, have similar outcomes. Consequently, hybrid approaches (eg, sustained low-efficiency dialysis and extended daily dialysis) are being developed to provide the advantages of both.
- Intermittent hemodialysis (IHD) is the most frequently used RRT and has the advantage of widespread availability and the convenience of lasting only 3 to 4 hours. Disadvantages include difficult venous dialysis access in hypotensive patients and hypotension due to rapid removal of large amounts of fluid.
- Several continuous RRT (CRRT) variants have been developed including continuous hemofiltration, continuous hemodialysis, or a combination. CRRT gradually removes solute, resulting in better tolerability by critically ill patients. Disadvantages include limited availability of equipment, need for intensive nursing care, and the need to individualize IV replacement, dialysate fluids, and drug therapy adjustments.

Pharmacologic Therapies

- **Mannitol** 20% is typically started at a dose of 12.5 to 25 g IV over 3 to 5 minutes. Disadvantages include IV administration, hyperosmolality risk, and need for monitoring urine output and serum electrolytes and osmolality because mannitol can contribute to AKI.
- Loop diuretics effectively reduce fluid overload but can worsen AKI. Equipotent doses of loop diuretics (**furosemide, bumetanide, torsemide,** and **ethacrynic acid**) have similar efficacy. Ethacrynic acid is reserved for sulfa-allergic patients. Continuous infusions of loop diuretics appear to overcome diuretic resistance and to have fewer adverse effects than intermittent boluses. An initial IV loading dose (equivalent to furosemide 40–80 mg) should be administered before starting a continuous infusion (equivalent to furosemide 10–20 mg/h).
- Strategies are available to overcome diuretic resistance (Table 73–5). Administration of agents from different pharmacologic classes, such as diuretics that work at the

TABLE 73–4 Common Indications for Renal Replacement Therapy

Indication for Renal Replacement Therapy	Clinical Setting
A: Acid–base abnormalities	Metabolic acidosis resulting from the accumulation of organic and inorganic acids
E: Electrolyte imbalance	Hyperkalemia, hypermagnesemia
I: Intoxications	Salicylates, lithium, methanol, ethylene glycol, theophylline, phenobarbital
O: Overload of fluid	Postoperative fluid gain/overload
U: Uremia	Accumulation of uremic toxins

TABLE 73–5 Common Causes of Diuretic Resistance in Patients With Acute Kidney Injury

Causes of Diuretic Resistance	Potential Therapeutic Solutions
Excessive sodium intake (sources may be dietary, IV fluids, and drugs)	Remove sodium from nutritional sources and medications
Inadequate diuretic dose or inappropriate regimen	Increase dose, use continuous infusion or combination therapy
Reduced oral bioavailability (usually furosemide)	Use parenteral therapy; switch to oral torsemide or bumetanide
Nephrotic syndrome (loop diuretic protein binding in tubule lumen)	Increase dose, switch diuretics, use combination therapy
Reduced renal blood flow	
Drugs (NSAIDs, ACEIs, vasodilators)	Discontinue these drugs if possible
Hypotension	Intravascular volume expansion and/or vasopressors
Intravascular depletion	Intravascular volume expansion
Increased sodium resorption	
Nephron adaptation to chronic diuretic therapy	Combination diuretic therapy, sodium restriction
NSAID use	Discontinue NSAID
Heart failure	Treat the heart failure, increase diuretic dose, switch to better-absorbed loop diuretic
Cirrhosis	High-volume paracentesis
Acute tubular necrosis	Higher dose of diuretic, diuretic combination therapy; add low-dose dopamine

ACEIs, angiotensin-converting enzyme inhibitors; IV, intravenous; NSAIDs, nonsteroidal anti-inflammatory drugs.

distal convoluted tubule (thiazides) or the collecting duct (**amiloride, triamterene,** and **spironolactone**), may be synergistic when combined with loop diuretics. **Metolazone** is commonly used because, unlike other thiazides, it produces effective diuresis at GFR less than 20 mL/min (0.33 mL/s).

ELECTROLYTE MANAGEMENT AND NUTRITION INTERVENTIONS

- Serum electrolytes should be monitored daily. Hyperkalemia is the most common and serious electrolyte abnormality in AKI. Hypernatremia and fluid retention commonly occur, requiring calculation of daily sodium intake, including sodium contained in commonly administered antibiotic and antifungal agents.
- Phosphorus and magnesium should be monitored, especially in patients with significant tissue destruction due to increased amounts of released phosphorus; neither is efficiently removed by dialysis.
- Nutritional management of critically ill patients with AKI is complex due to multiple mechanisms for metabolic derangements. Nutritional requirements are altered by stress, inflammation, and injury that lead to hypermetabolic and hypercatabolic states.

DRUG-DOSING CONSIDERATIONS

- Drug therapy optimization in AKI is a challenge. Confounding variables include residual drug clearance, fluid accumulation, and use of RRTs.

TABLE 73–6 Key Monitoring Parameters for Patients With Established Acute Kidney Injury

Parameter	Frequency
Fluid ins/outs	Every shift
Patient weight	Daily
Hemodynamics (blood pressure, heart rate, mean arterial pressure, etc)	Every shift
Blood chemistries	
Sodium, potassium, chloride, bicarbonate, calcium, phosphate, magnesium	Daily
Blood urea nitrogen/serum creatinine	Daily
Drugs and their dosing regimens	Daily
Nutritional regimen	Daily
Blood glucose	Daily (minimum)
Serum concentration data for drugs	After regimen changes and after renal replacement therapy has been instituted
Times of administered doses	Daily
Doses relative to administration of renal replacement therapy	Daily
Urinalysis	
Calculate measured creatinine clearance	Every time measured urine collection performed
Calculate fractional excretion of sodium	Every time measured urine collection performed
Plans for renal replacement	Daily

- Volume of distribution for water-soluble drugs is significantly increased due to edema. Use of dosing guidelines for CKD does not reflect the clearance and volume of distribution in critically ill patients with AKI.
- Patients with AKI may have a higher residual nonrenal clearance than those with CKD with similar creatinine clearances; this complicates drug therapy individualization, especially with RRTs.
- The mode of CRRT determines rate of drug removal, further complicating individualization of drug therapy. Rates of ultrafiltration, blood flow, and dialysate flow influence drug clearance during CRRT.

EVALUATION OF THERAPEUTIC OUTCOMES

- Vigilant monitoring of patient status is essential (**Table 73–6**).
- Therapeutic drug monitoring should be monitored frequently because of changing volume status, changing renal function, and RRTs in patients with AKI.

See Chapter 28, Acute Kidney Injury, authored by William Dager and Jenana Halilovic, for a more detailed discussion of this topic.

CHAPTER 74

Chronic Kidney Disease

- *Chronic kidney disease* (CKD) is defined as abnormalities in kidney structure or function, present for 3 months or longer, with implications for health. Structural abnormalities include albuminuria of more than 30 mg/day, presence of hematuria or red cell casts in urine sediment, electrolyte and other abnormalities due to tubular disorders, abnormalities detected by histology, structural abnormalities detected by imaging, or history of kidney transplant.
- CKD is classified by cause of kidney disease, glomerular filtration rate (GFR) category, and albuminuria level based on new recommendations from the Kidney Disease: Improving Global Outcomes (KDIGO) guidelines, referred to as CGA staging (*c*ause, *G*FR, *a*lbuminuria) (**Table 74–1**).
- CKD stage 5, previously referred to as end-stage renal disease (ESRD), occurs when the GFR falls below 15 mL/min/1.73 m^2 (<0.14 mL/s/m^2) or in patients receiving renal replacement therapy (RRT). In this chapter, *ESRD* refers specifically to patients who receive chronic dialysis.
- Prognosis depends on cause of kidney disease, GFR at time of diagnosis, degree of albuminuria, and presence of other comorbid conditions.

PATHOPHYSIOLOGY

- *Susceptibility factors* increase the risk for kidney disease but do not directly cause kidney damage. They include advanced age, reduced kidney mass and low birth weight, racial or ethnic minority, family history, low income or education, systemic inflammation, and dyslipidemia.
- *Initiation factors* directly result in kidney damage and are modifiable by drug therapy. They include diabetes mellitus, hypertension, glomerulonephritis, polycystic kidney disease, Wegener granulomatosis, vascular diseases, and human immunodeficiency virus (HIV) nephropathy.
- *Progression factors* hasten the decline in kidney function after initiation of kidney damage. They include glycemia in diabetics, hypertension, proteinuria, hyperlipidemia, obesity, and smoking.
- Most progressive nephropathies share a final common pathway to irreversible renal parenchymal damage and ESRD (**Fig. 74–1**). Key pathway elements include loss of nephron mass, glomerular capillary hypertension, and proteinuria.

CLINICAL PRESENTATION

- CKD development and progression are insidious. Patients with stage 1 or 2 CKD usually do not have symptoms or metabolic derangements seen with stages 3 to 5, such as anemia, secondary hyperparathyroidism, cardiovascular disease (CVD), malnutrition, and fluid and electrolyte abnormalities that are more common as kidney function deteriorates.
- Uremic symptoms (fatigue, weakness, shortness of breath, mental confusion, nausea, vomiting, bleeding, and anorexia) are generally absent in stages 1 and 2, minimal during stages 3 and 4, and common in patients with stage 5 CKD who may also experience itching, cold intolerance, weight gain, and peripheral neuropathies.
- Signs and symptoms of uremia are foundational to the decision to implement RRT.

TREATMENT

GENERAL APPROACH

- Goal of Treatment: The goal is to delay the progression of CKD, minimizing the development or severity of complications.

TABLE 74–1 GFR Categories

KDIGO Category	GFR (mL/min/1.73 m² [mL/s/m²])	Terms	Corresponding KDOQI Category
G1	>90 (>0.87)	Normal or high	Stage 1 CKD
G2	60–89 (0.58–0.86)	Mildly decreased	Stage 2 CKD
G3a	45–59 (0.43–0.57)	Mildly to moderately decreased	Stage 3 CKD
G3b	30–44 (0.29–0.42)	Moderately to severely decreased	Stage 3 CKD
G4	15–29 (0.14–0.28)	Severely decreased	Stage 4 CKD
G5	<15 (<0.14)	Kidney failure	Stage 5 CKD (ESRD if requiring dialysis)

ESRD, end-stage renal disease; GFR, glomerular filtration rate.

- Use the most current consensus guidelines and the best clinical practices for management of CKD.

NONPHARMACOLOGIC THERAPY

- Restrict protein to 0.8 g/kg/day if GFR is less than 30 mL/min/1.73 m².
- Encourage smoking cessation to slow progression of CKD and reduce the risk of CVD.
- Encourage exercise at least 30 minutes five times per week and achievement of a body mass index (BMI) of 20 to 25 kg/m².

PHARMACOLOGIC THERAPY

Diabetes and Hypertension With CKD

- Progression of CKD can be limited by optimal control of hyperglycemia and hypertension. **Figure 74–2** provides an algorithm for management of diabetes in CKD.
- For more information on diabetes, see Chap. 19.
- Adequate blood pressure (BP) control (**Fig. 74–3**) can reduce the rate of decline in GFR and albuminuria in patients without diabetes. KDIGO guidelines recommend a target blood pressure of 140/90 mm Hg or less if urine albumin excretion or equivalent is less than 30 mg/24 h.
- If urine albumin excretion is greater than 30 mg/24 h or equivalent, the target blood pressure is 130/80 mm Hg or less and initiate first-line therapy with an angiotensin-converting enzyme inhibitor (ACEI) or an angiotensin II receptor blocker (ARB). Add a thiazide diuretic in combination with an ARB if additional reduction in proteinuria is needed. Nondihydropyridine calcium channel blockers are generally used as second-line antiproteinuric drugs when ACEIs or ARBs are contraindicated or not tolerated.
- ACEI clearance is reduced in CKD; therefore, treatment should begin with the lowest possible dose followed by gradual titration to achieve target BP and, secondarily, to minimize proteinuria. No individual ACEI is superior to another.
- For more information on hypertension, see Chap. 10.

Anemia of CKD

- *KDIGO definition of anemia*: Hemoglobin (Hb) less than 13 g/dL (130 g/L; 8.07 mmol/L) for adult males and less than 12 g/dL (120 g/L; 7.45 mmol/L) for adult females.

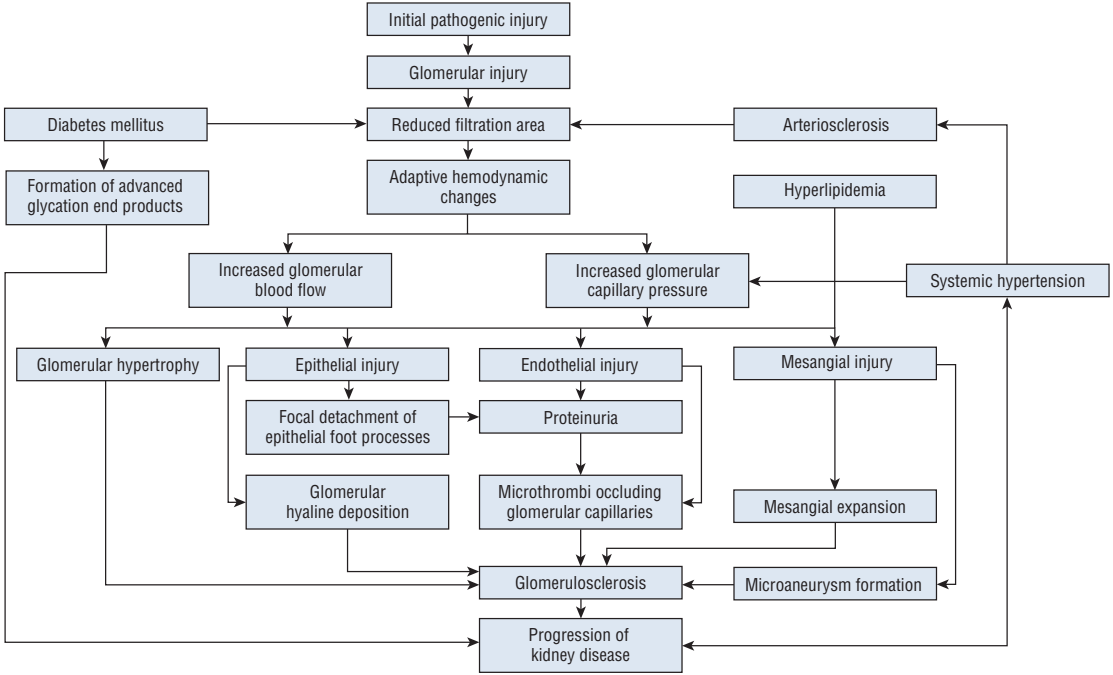


FIGURE 74–1. Proposed mechanisms for progression of renal disease.

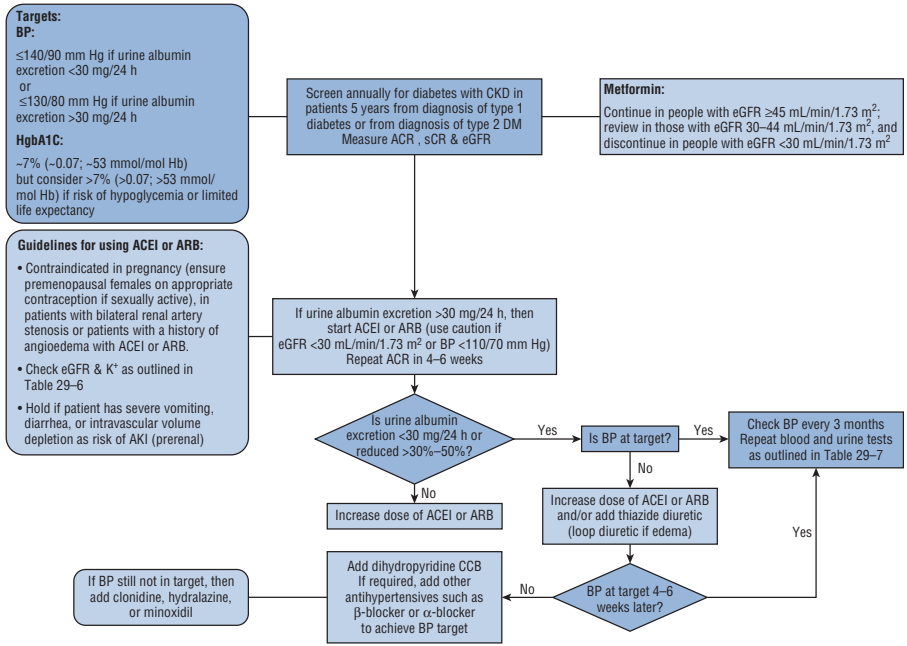


FIGURE 74–2. Diabetes with chronic kidney disease (CKD) algorithm. Strategy for screening and treatment of diabetes with CKD based on urine albumin excretion, target blood pressure, and estimated GFR (eGFR). *(Data from National Kidney Foundation, KDOQI clinical practice guidelines and clinical practice recommendations for diabetes and chronic kidney disease. Am J Kidney Dis 2007;49(Suppl 2):S1–S180; reference 1.)*

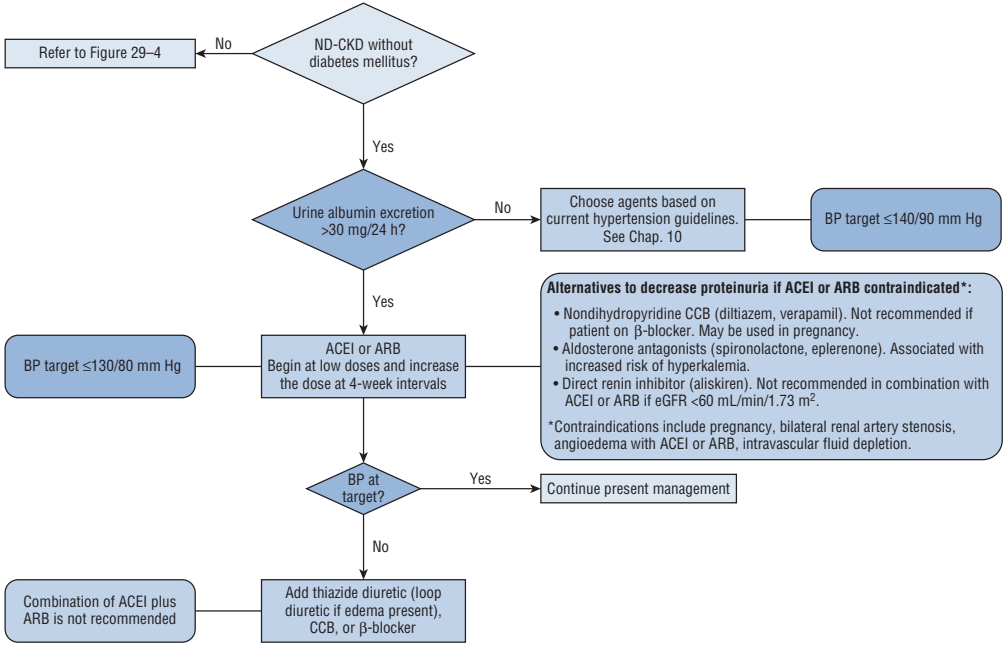


FIGURE 74–3. Treatment of hypertension in chronic kidney disease (CKD) patients, nondialysis CKD (ND-CKD) without diabetes mellitus. Strategy for treatment of hypertension based on urine albumin excretion and target blood pressure. *(Data from Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group. KDIGO 2012 clinical practice guideline for the evaluation and management of chronic kidney disease. Kidney Int Suppl 2013;3:1–150.)*

- Initiate erythropoietic-stimulating agent (ESA) therapy in all CKD patients with Hb is between 9 and 10 g/dL (90 and 100 g/L; 5.59 and 6.21 mmol/L). Target Hb is controversial.
- Iron deficiency is the primary cause of resistance to treatment of anemia with ESAs. **Iron** supplementation is required by most CKD patients to replete iron stores depleted by ongoing blood loss and increased iron demands.
- Parenteral iron therapy improves response to ESA therapy and reduces the dose required to achieve and maintain target indices. In contrast, oral therapy is limited by poor absorption and nonadherence with therapy primarily due to adverse effects (**Fig. 74–4**).
- IV iron preparations have different pharmacokinetic profiles, which do not correlate with pharmacodynamic effect.
- Adverse effects of IV iron include allergic reactions, hypotension, dizziness, dyspnea, headaches, lower back pain, arthralgia, syncope, and arthritis. Some of these reactions can be minimized by decreasing the dose or rate of infusion. Sodium ferric gluconate, iron sucrose, and ferumoxytol have a better safety record than iron dextran products.
- Subcutaneous (SC) administration of **epoetin alfa** is preferred because IV access is not required, and the SC dose that maintains target indices is 15% to 30% lower than the IV dose.
- **Darbepoetin alfa** has a longer half-life than epoetin alfa and prolonged biologic activity. Doses are administered less frequently, starting at once a week when administered IV or SC.
- ESAs are well tolerated. Hypertension is the most common adverse event.

Evaluation of Anemia Therapeutic Outcomes

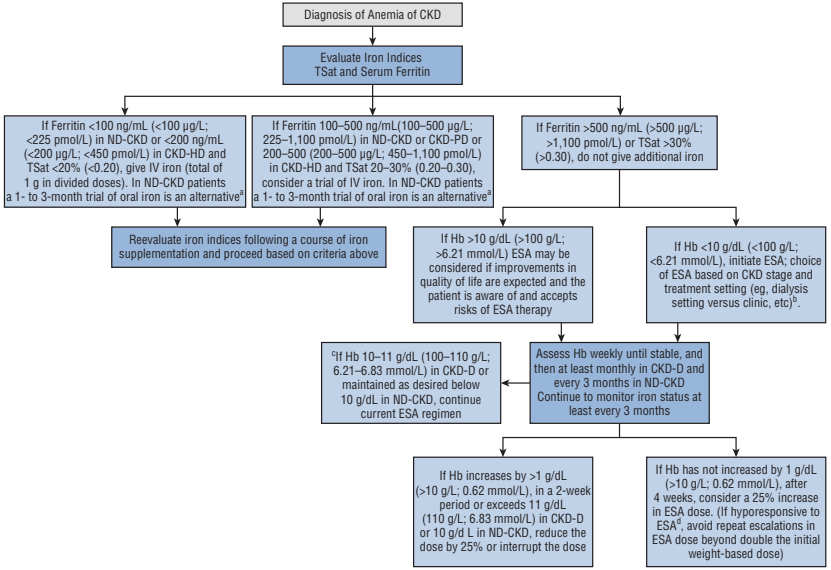
- Iron indices (transferrin saturation [TSat]; ferritin) should be evaluated before initiating an ESA. Iron status should be reassessed every month during initial ESA treatment and every 3 months for those on a stable ESA regimen.
- Hemoglobin should be monitored at least monthly, although more frequent monitoring (eg, every 1–2 weeks) is warranted after initiation of an ESA or after a dose change until hemoglobin is stable.
- Patients should be monitored for potential complications, such as hypertension, which should be treated before starting an ESA.
- For more information on anemia, see Chap. 33.

CKD-Related Mineral and Bone Disorder

- Disorders of mineral and bone metabolism (CKD-MBD) are common in the CKD population and include abnormalities in parathyroid hormone (PTH), calcium, phosphorus, the calcium-phosphorus product, vitamin D, and bone turnover, as well as soft tissue calcifications.
- Calcium-phosphorus balance is mediated through a complex interplay of hormones and their effects on bone, the gastrointestinal (GI) tract, kidneys, and the parathyroid gland. As kidney disease progresses, renal activation of vitamin D is impaired, which reduces gut absorption of calcium. Low blood calcium concentration stimulates secretion of PTH. As renal function declines, serum calcium balance can be maintained only at the expense of increased bone resorption, ultimately resulting in renal osteodystrophy (ROD).
- Secondary hyperparathyroidism is associated with increased morbidity and mortality and sudden death in hemodialysis patients.

Treatment

- Dietary phosphorus restriction, dialysis, and parathyroidectomy are nonpharmacologic approaches to management of hyperphosphatemia and CKD-MBD.
- The KDOQI guidelines provide desired ranges of calcium, phosphorus, calcium-phosphorus product, and intact PTH based on the stage of CKD (see **Table 74–2**).



[a]Route should be selected based on severity of iron deficiency, IV access, prior response to oral therapy, adverse effects with previous exposure to IV or po iron, and cost.

[b]Decision of whether to initiate ESA therapy should be individualized based on the rate of fall in Hb, risk of needing a blood transfusion, risks of ESA therapy, and presence of symptoms of anemia.

[c]Use the lowest ESA dose to reduce the need for blood transfusion.

[d]Hyporesponsiveness is defined as having no increase in Hb from baseline after the first month of ESA therapy using appropriate weight-based dosing.

FIGURE 74–4. Algorithm for management of anemia using iron and erythropoiesis-stimulating agent (ESA) therapy. *(From Kidney Disease: Improving Global Outcomes (KDIGO) Anemia Work Group. KDIGO clinical practice guideline for anemia in chronic kidney disease. Kidney Int Suppl 2012;2:279–335.)*

TABLE 74–2 Guidelines for Calcium, Phosphorus, Calcium-Phosphorus Product, and Intact Parathyroid Hormone

	Chronic Kidney Disease[a]		
Parameter	**Stage 3**	**Stage 4**	**Stage 5**
Corrected calcium	"Normal range"	"Normal range"	8.4–9.5 mg/dL[b] (2.10–2.38 mmol/L)
Phosphorus	2.7–4.6 mg/dL[c]	2.7–4.6 mg/dL[c]	3.5–5.5 mg/dL[d]
Ca × P product	<55 mg^2/dL^2[e]	<55 mg^2/dL^2[e]	<55 mg^2/dL^2[e]
Intact parathyroid hormone	35–70 pg/mL[f]	70–110 pg/mL[g]	150–300 pg/mL[h]

[a]Differences with Kidney Disease: Improving Global Outcomes (KDIGO) described in test (see Desired Outcome Under CKD-Related Mineral and Bone Disorder in test).
[b]Recommend normal range for laboratory used, but keep target at lower end of range.
[c]SI units: 0.87–1.49 mmol/L.
[d]SI units: 1.13–1.78 mmol/L.
[e]SI units: 4.4 $mmol^2/L^2$.
[f]SI units: in ng/L or 3.7–7.5 pmol/L.
[g]SI units: in ng/L or 7.5–11.8 pmol/L.
[h]SI units: in ng/L or 16–32 pmol/L.
From Kidney Disease: Improving Global Outcomes (KDIGO) CKD-MBD Work Group. KDIGO clinical practice guideline for the diagnosis, evaluation, prevention, and treatment of chronic kidney disease-mineral and bone disorder (CKD-MBD). Kidney Int 2009;113(Supp):S1–S130; and Eknoyan G, Levin A, Levin NW. Bone metabolism and disease in chronic kidney disease. Am J Kidney Dis 2003;42:1–201.

PHOSPHATE-BINDING AGENTS

- Phosphate-binding agents decrease phosphorus absorption from the gut and are first-line agents for controlling both serum phosphorus and calcium concentrations (**Table 74–3**).
- KDOQI guidelines recommend that elemental calcium from calcium-containing binders should not exceed 1500 mg/day, and the total daily intake from all sources should not exceed 2000 mg. This may necessitate a combination of calcium- and non–calcium-containing products (eg, **sevelamer HCL** and **lanthanum carbonate**).
- Adverse effects of all phosphate binders are generally limited to GI effects, including constipation, diarrhea, nausea, vomiting, and abdominal pain. Risk of hypercalcemia may necessitate restriction of calcium-containing binder use and/or reduction in dietary intake. Aluminum and magnesium binders are not recommended for regular use in CKD because aluminum binders have been associated with CNS toxicity and the worsening of anemia, whereas magnesium binders may lead to hypermagnesemia and hyperkalemia.

VITAMIN D THERAPY

- Reasonable control of calcium and phosphorus must be achieved before initiation and during continued vitamin D therapy.
- **Calcitriol,** 1,25-dihydroxyvitamin D_3, directly suppresses PTH synthesis and secretion and upregulates vitamin D receptors. The dose depends on the stage of CKD (**Table 74–4**).
- The newer vitamin D analogues **paricalcitol** and **doxercalciferol** may be associated with less hypercalcemia and, for paricalcitol, hyperphosphatemia. Vitamin D therapy, regardless of agent, is associated with decreased mortality.

TABLE 74–3 Phosphate-Binding Agents for Treatment of Hyperphosphatemia in CKD Patients

Drug	Brand Name	Compound Content	Starting Doses	Dose Titration[a]	Comments
Calcium carbonate[b]	Tums, Os-Cal, Caltrate	40% elemental calcium	0.5–1 g (elemental calcium) three times a day with meals	Increase or decrease by 500 mg per meal (200 mg elemental calcium)	First-line agent; dissolution characteristics and phosphate binding may vary from product to product Approximately 39 mg phosphorus bound per 1 g calcium carbonate
Calcium acetate (25% elemental calcium)	PhosLo	25% elemental calcium (169 mg elemental calcium per 667 mg capsule)	0.5–1 g (elemental calcium) three times a day with meals	Increase or decrease by 667 mg per meal (169 mg elemental calcium)	First-line agent; comparable efficacy to calcium carbonate with lower dose of elemental calcium Approximately 45 mg phosphorus bound per 1 g calcium acetate
	Phoslyra	667 mg calcium acetate per 5 mL			
Sevelamer carbonate	Renvela	800 mg tablet 0.8 and 2.4 g powder for oral suspension	800–1,600 mg three times a day with meals (once-daily dosing also effective)	Increase or decrease by 800 mg per meal	First-line agent; also lowers low-density lipoprotein cholesterol Consider in patients at risk for extraskeletal calcification Associated with a lower risk of acidosis and GI adverse events than Renagel (sevelamer hydrochloride) that is no longer available
Lanthanum carbonate	Fosrenol	500, 750, and 1,000 mg chewable tablets	1,500 mg daily in divided doses with meals	Increase or decrease by 750 mg/day	First-line agent; potential for accumulation of lanthanum due to GI absorption (long-term consequences unknown)
Aluminum hydroxide[b]	AlternaGel	Content varies (range 100–600 mg/unit)	300–600 mg three times a day with meals	Not for long-term use requiring titration	Not a first-line agent; risk of aluminum toxicity; do not use concurrently with citrate-containing products Reserve for short-term use (4 weeks) in patients with hyperphosphatemia not responding to other binders

[a]Based on phosphorus levels, titrate every 2–3 weeks until phosphorus goal reached.
[b]Multiple preparations available that are not listed.

TABLE 74–4 Vitamin D Agents

Generic Name	Brand Name	Form of Vitamin D	Dosage Forms	Initial Dose	Dosage Range	Frequency of Administration
Nutritional Vitamin D						
Ergocalciferol[a]	Generic	D_2	po	Varies based on 25OHD levels	400–50,000 international units	Daily (doses of 400–2,000 international units)
Cholecalciferol[a]	Generic	D_3	po			Weekly or monthly for higher doses (50,000 international units)
Active Vitamin D						
Calcitriol	Calcijex	D_3	IV	1–2 mcg	0.5–5 mcg	Three times per week
	Rocaltrol		po	0.25 mcg	0.25–5 mcg	Daily or three times per week
Vitamin D Analogs						
Paricalcitol	Zemplar	D_2	po	CKD nondialysis: 1 mcg daily or 2 mcg three times per week if PTH ≤500 pg/mL (≤500 ng/L; ≤54 pmol/L); 2 mcg daily or 4 mcg three time per week if PTH >500 pg/mL (>500 ng/L; >54 pmol/L)	1–4 mcg	Daily or three times per week
				Stage 5 CKD: mcg dose based on ratio of PTH/80 and administered three times per week		
			IV	Stage 5 CKD: 0.04–1 mcg three times per week	2.5–15 mcg	Three times per week
Doxercalciferol	Hectorol	D_2	po	CKD nondialysis: 1 mcg daily	5–20 mcg	Daily or three times per week
				Stage 5 CKD: 10 mcg three times per week		
			IV	Stage 5 CKD: 4 mcg three times per week	2–8 mcg	Three times per week

[a]Multiple preparations are available that are not listed.

CALCIMIMETICS

- **Cinacalcet** reduces PTH secretion by increasing the sensitivity of the calcium-sensing receptor. The most common adverse events include nausea and vomiting.
- The most effective way to use cinacalcet with other therapies has not been decided. The starting dose is 30 mg daily, which can be titrated to the desired PTH and calcium concentrations every 2 to 4 weeks to a maximum of 180 mg daily.

HYPERLIPIDEMIA

- The prevalence of hyperlipidemia increases as renal function declines.
- National guidelines differ on how aggressively dyslipidemia should be managed in patients with CKD. KDIGO guidelines recommend treatment with a **statin** (eg, **atorvastatin** 20 mg, **fluvastatin** 80 mg, **rosuvastatin** 10 mg, **simvastatin** 20 mg) in adults aged 50 and older with stage 1 to 5 CKD not on dialysis.
- In patients with ESRD, lipid profile should be reassessed at least annually and 2 to 3 months after changing treatment.
- For more information on dyslipidemias, see Chap. 8.

See Chapter 29, Chronic Kidney Disease, authored by Joanna Q. Hudson and Lori D. Wazny, for a more detailed discussion of this topic.

Electrolyte Homeostasis

CHAPTER 75

- *Fluid and electrolyte homeostasis* is maintained by feedback mechanisms, hormones, and many organ systems, and is necessary for the body's normal physiologic functions. Disorders of sodium and water, calcium, phosphorus, potassium, and magnesium homeostasis are addressed separately in this chapter.

DISORDERS OF SODIUM AND WATER HOMEOSTASIS

- Sixty percent of total body water (TBW) is distributed intracellularly (ICF), and 40% is contained in the extracellular space.
- Addition of an isotonic solution to the extracellular fluid (ECF) does not change intracellular volume. Adding a hypertonic solution to the ECF decreases cell volume, whereas adding a hypotonic solution increases it (**Table 75–1**).
- Hypernatremia and hyponatremia can be associated with conditions of high, low, or normal ECF sodium and volume. Both conditions are most commonly the result of abnormalities of water metabolism.

HYPONATREMIA (SERUM SODIUM <135 mEq/L [<135 mmol/L])

Pathophysiology

- Results from an excess of extracellular water relative to sodium because of impaired water excretion.
- Causes of nonosmotic release of arginine vasopressin (AVP), commonly known as *antidiuretic hormone*, include hypovolemia; decreased effective circulating volume as seen in patients with congestive heart failure (CHF); nephrosis; cirrhosis; and syndrome of inappropriate antidiuretic hormone (SIADH).
- Depending on serum osmolality, hyponatremia is classified as isotonic, hypertonic, or hypotonic (**Fig. 75–1**).
- Hypotonic hyponatremia, the most common form of hyponatremia, can be further classified as hypovolemic, euvolemic, or hypervolemic.
- Hypovolemic hypotonic hyponatremia is associated with a loss of ECF volume and sodium, with the loss of more sodium than water. It is relatively common in patients taking **thiazide diuretics**.
- Euvolemic hyponatremia is associated with a normal or slightly decreased ECF sodium content and increased TBW and ECF volume. It is most commonly the result of SIADH release.
- Hypervolemic hyponatremia is associated with an increase in ECF volume in conditions with impaired renal sodium and water excretion, such as cirrhosis, CHF, and nephrotic syndrome.

Clinical Presentation

- Most patients with hyponatremia are asymptomatic.
- Presence and severity of symptoms are related to the magnitude and rapidity of onset of hyponatremia. Symptoms progress from nausea and malaise to headache and lethargy and, eventually, to seizures, coma, and death if hyponatremia is severe or develops rapidly.
- Patients with hypovolemic hyponatremia present with decreased skin turgor, orthostatic hypotension, tachycardia, and dry mucous membranes.

Treatment

- Treatment is associated with a risk of osmotic demyelination syndrome. The rate of administration of infusate should be adjusted to avoid exceeding a rise in serum sodium greater than 12 mEq/L (12 mmol/L) per day.

TABLE 75–1 Composition of Common IV Solutions

Solution	Dextrose	[Na^+] (mEq/L or mmol/L)	[Cl^-] (mEq/L or mmol/L)	Tonicity	Distribution		Free water/L
					% ECF	% ICF	
D_5W	5 g/dL (50 g/L)	0	0	Hypotonic	40	60	1,000 mL
0.45% sodium chloride[a]	0	77	77	Hypotonic	73	37	500 mL
Ringer's lactate	0	130	105	Isotonic	97	3	0 mL
0.9% sodium chloride[b]	0	154	154	Isotonic	100	0	0 mL
3% sodium chloride[c]	0	513	513	Hypertonic	100	0	–2,331 mL

Cl^-, chloride; D_5W, 5% dextrose in water; ECF, extracellular fluid; ICF, intracellular fluid; Na^+, sodium.

[a]Also referred to as "half normal saline."
[b]Also referred to as "normal saline."
[c]This solution will result in osmotic removal of water from the intracellular space.

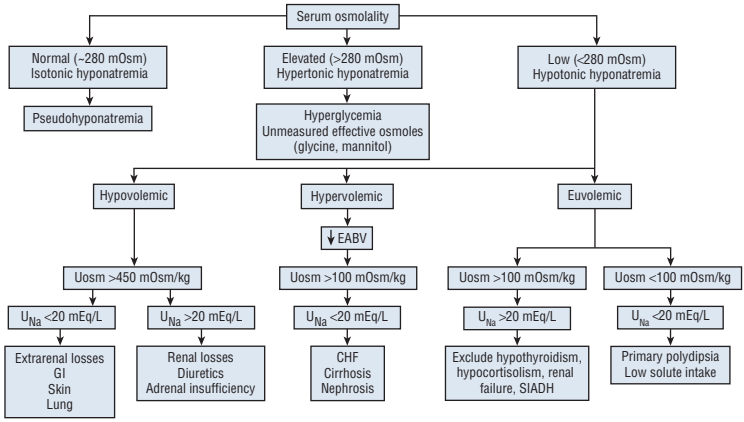


FIGURE 75–1. Diagnostic algorithm for the evaluation of hyponatremia. (CHF, congestive heart failure; EABV, effective arterial blood volume; GI, gastrointestinal; SIADH, syndrome of inappropriate antidiuretic hormone; U_{Na}, urine sodium concentration [values in mEq/L are numerically equivalent to mmol/L]; Uosm, urine osmolality [values in mOsm/kg are numerically equivalent to mmol/kg].)

ACUTE OR SEVERELY SYMPTOMATIC HYPOTONIC HYPONATREMIA

- Symptomatic patients, regardless of fluid status, should initially be treated with either a 0.9% or 3% concentrated saline solution until symptoms resolve. Resolution of severe symptoms may require only a 5% increase in serum sodium or an initial target serum sodium of 120 mEq/L (120 mmol/L).
- Treat SIADH with 3% saline plus, if the urine osmolality exceeds 300 mOsm/kg (300 mmol/kg), a loop diuretic (**furosemide**, 20–40 mg IV every 6 hours or **bumetanide**, 0.5–to 1 mg/dose every 2–3 hours for two doses).
- Treat hypovolemic hypotonic hyponatremia with 0.9% saline, initially at infusion rates of 200 to 400 mL/h until symptoms moderate.
- Treat hypervolemic hypotonic hyponatremia with 3% saline and prompt initiation of fluid restriction. Loop diuretic therapy will also likely be required to facilitate urinary excretion of free water.

NONEMERGENT HYPOTONIC HYPONATREMIA

- Treatment of SIADH involves water restriction and correction of the underlying cause. Water should be restricted to approximately 1000 to 1200 mL/day. In some cases, administration of either sodium chloride or urea tablets and a loop diuretic or of **demeclocycline** can be required.
- AVP antagonists or "vaptans" (eg, **conivaptan** and **tolvaptan**) can be used to treat SIADH as well as other causes of euvolemic and hypervolemic hypotonic hyponatremia that has been nonresponsive to other therapeutic interventions in patients with heart failure, cirrhosis, and SIADH. The vaptans have dramatic effects on water excretion and represent a breakthrough in the therapy of hyponatremia and disorders of fluid homeostasis.
- Treatment of asymptomatic hypervolemic hypotonic hyponatremia involves correction of the underlying cause and restriction of water intake to less than 1000 to 1200 mL/day. Dietary intake of sodium chloride should be restricted to 1000 to 2000 mg/day.

HYPERNATREMIA (SERUM SODIUM >145 mEq/L [>145 mmol/L])

Pathophysiology and Clinical Presentation

- Hypernatremia results from either water loss (eg, diabetes insipidus [DI]) or hypotonic fluids, or less commonly from hypertonic fluid administration or sodium ingestion.
- Symptoms are primarily caused by decreased neuronal cell volume and can include weakness, lethargy, restlessness, irritability, and confusion. Symptoms of a more rapidly developing hypernatremia include twitching, seizures, coma, and death.

Treatment

- Begin treatment of hypovolemic hypernatremia with 0.9% saline. After hemodynamic stability is restored and intravascular volume is replaced, replace free-water deficit with 5% dextrose or 0.45% saline solution.
- The correction rate should be approximately 1 mEq/L (1 mmol/L) per hour for hypernatremia that developed over a few hours and 0.5 mEq/L (0.5 mmol/L) per hour for hypernatremia that developed more slowly.
- Treat central DI with intranasal **desmopressin**, beginning with 10 mcg/day and titrating as needed, usually to 10 mcg twice daily.
- Treat nephrogenic DI by decreasing ECF volume with a thiazide diuretic and dietary sodium restriction (2000 mg/day), which often decreases urine volume by as much as 50%. Other treatment options include drugs with antidiuretic properties (**Table 75–2**).
- Treat sodium overload with loop diuretics (**furosemide**, 20–40 mg IV every 6 hour) and 5% dextrose at a rate that decreases serum sodium by approximately 0.5 mEq/L (0.5 mmol/L) per hour or, if hypernatremia developed rapidly, 1 mEq/L (1 mmol/L) per hour.

EDEMA

Pathophysiology and Clinical Presentation

- Edema, defined as a clinically detectable increase in interstitial fluid volume, develops when excess sodium is retained either as a primary defect in renal sodium excretion or as a response to a decrease in the effective circulating volume despite an already expanded or normal ECF volume.
- Edema occurs in patients with decreased myocardial contractility, nephrotic syndrome, or cirrhosis.
- Edema is initially detected in the feet or pretibial area in ambulatory patients and in the presacral area in bed-bound individuals, and is defined as "pitting" when the depression caused by briefly exerting pressure over a bony prominence does not rapidly refill.

TABLE 75–2 Drugs Used to Manage Central and Nephrogenic Diabetes Insipidus

Drug	Indication	Dose
Desmopressin acetate	Central and nephrogenic	5–20 mcg intranasally every 12–24 h
Chlorpropamide	Central	125–250 mg orally daily
Carbamazepine	Central	100–300 mg orally twice daily
Clofibrate	Central	500 mg orally 4 times daily
Hydrochlorothiazide	Central and nephrogenic	25 mg orally every 12–24 h
Amiloride	Lithium-related nephrogenic	5–10 mg orally daily
Indomethacin	Central and nephrogenic	50 mg orally every 8–12 h

Treatment

- Diuretics are the primary pharmacologic therapy for edema. Loop diuretics are the most potent, followed by thiazide diuretics and then potassium-sparing diuretics.
- Pulmonary edema requires immediate pharmacologic treatment. Other forms of edema can be treated gradually with, in addition to diuretic therapy, sodium restriction and correction of underlying disease state.

DISORDERS OF CALCIUM HOMEOSTASIS

- ECF calcium is moderately bound to plasma proteins (46%), primarily albumin. Ionized or free calcium is the physiologically active form.
- Each 1 g/dL (10 g/L) drop in serum albumin concentration less than 4 g/dL (40 g/L) decreases total serum calcium concentration by 0.8 mg/dL (0.20 mmol/L).

HYPERCALCEMIA (TOTAL SERUM CALCIUM >10.5 mg/dL [>2.62 mmol/L])

Pathophysiology and Clinical Presentation

- Cancer and hyperparathyroidism are the most common causes of hypercalcemia. Primary mechanisms include increased bone resorption, increased GI absorption, and increased tubular reabsorption by the kidneys.
- Clinical presentation depends on the degree of hypercalcemia and rate of onset. Mild to moderate hypercalcemia (serum calcium concentration <13 mg/dL [<3.25 mmol/L] or ionized calcium concentration <6 mg/dL [<1.50 mmol/L)) can be asymptomatic.
- Hypercalcemia of malignancy develops quickly and is associated with anorexia, nausea and vomiting, constipation, polyuria, polydipsia, and nocturia. Hypercalcemic crisis is characterized by acute elevation of serum calcium to greater than 15 mg/dL (>3.75 mmol/L), acute renal insufficiency, and obtundation. Untreated hypercalcemic crisis can progress to oliguric renal failure, coma, and life-threatening ventricular arrhythmias.
- Chronic hypercalcemia (ie, hyperparathyroidism) is associated with metastatic calcification, nephrolithiasis, and chronic renal insufficiency.
- Electrocardiographic (ECG) changes include shortening of the QT interval and coving of the ST-T wave.

Treatment

- Treatment approach depends on the degree of hypercalcemia, acuity of onset, and presence of symptoms requiring emergent treatment (**Fig. 75–2**).
- Management of asymptomatic, mild to moderate hypercalcemia begins with attention to the underlying condition and correction of fluid and electrolyte abnormalities.
- Hypercalcemic crisis and acute symptomatic hypercalcemia are medical emergencies requiring immediate treatment. Rehydration with normal saline followed by loop diuretics can be used in patients with normal to moderately impaired renal function. Initiate treatment with **calcitonin** in patients in whom saline hydration is contraindicated (**Table 75–3**).
- Rehydration with saline and **furosemide** administration can decrease total serum calcium by 2 to 3 mg/dL (0.50–0.75 mmol/L) within 24 to 48 hours.
- **Bisphosphonates** are indicated for hypercalcemia of malignancy. Total serum calcium decline begins within 2 days and nadirs in 7 days. Duration of normocalcemia varies but usually does not exceed 2 to 3 weeks, depending on treatment response of underlying malignancy.
- **Denosumab** is a monoclonal antibody approved for treatment of osteoporosis. It has been shown to be useful in hypercalcemia of malignancy, particularly in patients with a suboptimal response to bisphosphonates.

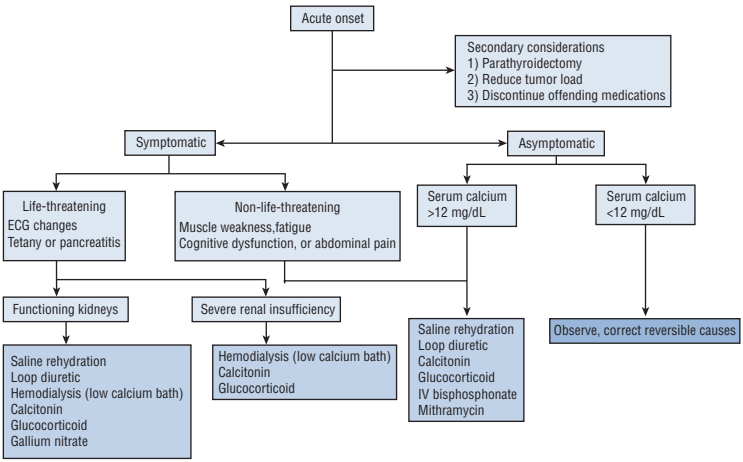


FIGURE 75–2. Pharmacotherapeutic options for the acutely hypercalcemic patient. Serum calcium of 12 mg/dL is equivalent to 3 mmol/L.

HYPOCALCEMIA (TOTAL SERUM CALCIUM <8.5 mg/dL [<2.13 mmol/L])

Pathophysiology

- Hypocalcemia results from altered effects of parathyroid hormone and vitamin D on the bone, gut, and kidney. Primary causes are postoperative hypoparathyroidism and vitamin D deficiency.
- Symptomatic hypocalcemia commonly occurs because of parathyroid gland dysfunction secondary to surgical procedures involving the thyroid, parathyroid, and neck.
- Hypomagnesemia can be associated with severe symptomatic hypocalcemia that is unresponsive to calcium replacement therapy. Calcium normalization is dependent on magnesium replacement.

Clinical Presentation

- Clinical manifestations are variable and depend on the onset of hypocalcemia. Tetany is the hallmark sign of acute hypocalcemia, which manifests as paresthesias around the mouth and in the extremities; muscle spasms and cramps; carpopedal spasms; and, rarely, laryngospasm and bronchospasm.
- Cardiovascular manifestations result in ECG changes characterized by a prolonged QT interval and symptoms of decreased myocardial contractility often associated with CHF.

Treatment

- Acute, symptomatic hypocalcemia requires IV administration of soluble calcium salts (Fig. 75–3). Initially, 100 to 300 mg of elemental calcium (eg, 1 g **calcium chloride**, 2–3 g **calcium gluconate**) should be given IV over 5 to 10 minutes (≤60 mg of elemental calcium per minute).
- The initial bolus dose is effective for only 1 to 2 hours and should be followed by a continuous infusion of elemental calcium (0.5–2 mg/kg/h) for 2 to 4 hours and then by a maintenance dose (0.3–0.5 mg/kg/h).

TABLE 75–3 Drug Dosing Table for Hypercalcemia

Drug/Brand Name	Starting Dosage	Time Frame to Initial Response	Special Population Considerations
0.9% saline ± electrolytes/NA	200–300 mL/h	24–48 hours	CI in renal insufficiency; congestive heart failure
Loop diuretics Furosemide/Lasix® Bumetandide/Bumex® Torsemide/Demadex®	40–80 mg IV q 1–4 h	N/A	CI in patients with allergy to sulfas (use ethacrynic acid)
Calcitonin/Miacalcin®	4 units/kg q 12 h SC/IM 10–12 units/h IV	1–2 hours	CI in patients with allergy to calcitonin
Pamidronate/Aredia®	30–90 mg IV over 2–24 hours	2 days	CI in renal insufficiency
Etidronate/Didronel®	7.5 mg/kg/day IV over 2 hours	2 days	CI in renal insufficiency
Zoledronate/Zometa®	4–8 mg IV over 15 minutes	1–2 days	CI in renal insufficiency
Ibandronate/Boniva®	2–6 mg IV bolus	2 days	CI in renal insufficiency
Gallium nitrate/Ganite®	200 mg/m^2/day	?	CI in severe renal insufficiency
Mithramycin/Mithracin®	25 mcg/kg IV over 4–6 hours	12 hours	CI in decreased liver function; renal insufficiency; thrombocytopenia
Glucocorticoids	40–60 mg oral prednisone equivalents daily	3–5 days	CI in patients with serious infections; hypersensitivity

CI, contraindicated; SC, subcutaneous.

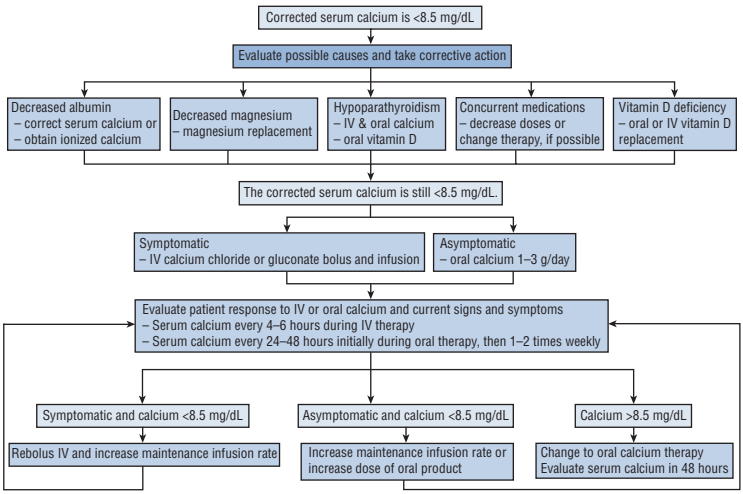


FIGURE 75–3. Hypocalcemia diagnostic and treatment algorithm. Serum calcium of 8.5 mg/dL is equivalent to 2.13 mmol/L.

- **Calcium gluconate** is preferred over **calcium chloride** for peripheral administration because the latter is more irritating to veins.
- After acute hypocalcemia is corrected, the underlying cause and other electrolyte problems should be corrected. Magnesium supplementation is indicated for hypomagnesemia.
- Oral calcium supplementation (eg, 1–3 g/day of elemental calcium initially, then 2–8 g/day in divided doses) is indicated for chronic hypocalcemia due to hypoparathyroidism and vitamin D deficiency. If serum calcium does not normalize, add a vitamin D preparation.

DISORDERS OF PHOSPHORUS HOMEOSTASIS

HYPERPHOSPHATEMIA (SERUM PHOSPHORUS >4.5 mg/dL [>1.45 mmol/L])

Pathophysiology

- Most commonly caused by decreased phosphorus excretion, secondary to decreased glomerular filtration rate (GFR).
- Intracellular phosphate release can occur with rhabdomyolysis, hemolysis, and tumor lysis syndrome, a complication of chemotherapy administered to treat acute leukemia and lymphoma.

Clinical Presentation

- Acute symptoms include gastrointestinal (GI) disturbances, lethargy, obstruction of the urinary tract, and, rarely, seizures. Calcium phosphate crystals are likely to form when the product of the serum calcium and phosphate concentrations exceeds 50 to 60 mg^2/dL^2 (4–4.8 $mmol^2/L^2$).
- The major effect is related to the development of hypocalcemia and damage resulting from calcium phosphate precipitation into soft tissues, intrarenal calcification, nephrolithiasis, or obstructive uropathy.
- For more information on hyperphosphatemia and renal failure, see Chap. 74.

Treatment

- The most effective way to treat nonemergent hyperphosphatemia is to decrease phosphate absorption from the GI tract with phosphate binders (see Chap. 74, Table 74–2).
- Severe symptomatic hyperphosphatemia manifesting as hypocalcemia and tetany is treated by the IV administration of calcium salts.

HYPOPHOSPHATEMIA (SERUM PHOSPHORUS <2 mg/dL [<0.65 mmol/L])

Pathophysiology

- Hyperphosphatemia results from decreased GI absorption, reduced tubular reabsorption, or extracellular to intracellular redistribution.
- Hypophosphatemia is associated with chronic alcoholism, parenteral nutrition with inadequate phosphate supplementation, chronic ingestion of antacids, diabetic ketoacidosis, and prolonged hyperventilation.

Clinical Presentation

- Severe hypophosphatemia (serum phosphorus <1 mg/dL [<0.32 mmol/L]) has diverse clinical manifestations that affect many organ systems, including the following:
  - ✓ Neurologic manifestations: Progressive syndrome of irritability, apprehension, weakness, numbness, paresthesias, dysarthria, confusion, obtundation, seizures, and coma.
  - ✓ Skeletal muscle dysfunction: Myalgia, bone pain, weakness, and potentially fatal rhabdomyolysis.
  - ✓ Respiratory muscle weakness and diaphragmatic contractile dysfunction resulting in acute respiratory failure.
  - ✓ Congestive cardiomyopathy, arrhythmias, hemolysis, and increased risk of infection can also occur.
- Chronic hypophosphatemia can cause osteopenia and osteomalacia because of enhanced osteoclastic resorption of bone.

Treatment

- Severe (<1 mg/dL; <0.32 mmol/L) or symptomatic hypophosphatemia should be treated with IV phosphorus replacement. The infusion of 15 mmol of phosphorus in 250 mL of IV fluid over 3 hours is a safe and effective treatment, but the recommended dosage of IV phosphorus (0.08–0.64 mmol/kg) and infusion recommendations (over 4–12 hours) are highly variable.
- Asymptomatic patients or those who exhibit mild to moderate hypophosphatemia can be treated with oral phosphorus supplementation in doses of 1.5 to 2 g (50–60 mmol) daily in divided doses, with the goal of correcting serum phosphorus concentration in 7 to 10 days (**Table 75–4**).
- Monitor patients with frequent serum phosphorus and calcium determinations, especially if phosphorus is given IV or if renal dysfunction is present.
- Add phosphorus (12–15 mmol/L) routinely to hyperalimentation solutions to prevent hypophosphatemia.

DISORDERS OF POTASSIUM HOMEOSTASIS

HYPOKALEMIA (SERUM POTASSIUM <3.5 mEq/L [<3.5 mmol/L])

Pathophysiology

- Results from a total body potassium deficit or shifting of serum potassium into the intracellular compartment.
- Many drugs can cause hypokalemia (**Table 75–5**), and it is most commonly seen with use of loop and thiazide diuretics. Other causes of hypokalemia include diarrhea, vomiting, and hypomagnesemia.

TABLE 75–4 Phosphorus Replacement Therapy

Product (Salt)	Phosphate Content	Initial Dosing Based on Serum K
Oral Therapy (Potassium Phosphate + Sodium Phosphate)		
Neutra-Phos® (7 mEq/packet each of Na and K)	250 mg (8 mmol)/packet	One packet three times daily[a]
Neutra-Phos-K® (14.25 mEq/packet of K)	250 mg (8 mmol)/packet	Serum K >5.5 mEq/L (>5.5 mmol/L); not recommended
K-Phos Neutral® (13 mEq/tablet Na and 1.1 mEq/tablet K)	250 mg (8 mmol)/tablet	Serum K >5.5 mEq/L (>5.5 mmol/L) one tablet three times daily
Uro-KP-Neutral® (10.9 mEq/tablet Na and 1.27 mEq/tablet K)	250 mg (8 mmol)/tablet	Serum K >5.5 mEq/L (>5.5 mmol/L) one tablet three times daily
Fleets Phospho-soda® (sodium phosphate solution)	4 mmol/mL	Serum K >5.5 mEq/L (>5.5 mmol/L) 2 mL three times daily
IV Therapy		
Sodium PO_4 (4 mEq/mL Na)	3 mmol/mL	Serum K >3.5 mEq/L (>3.5 mmol/L) 15–30 mmol IVPB
Potassium PO_4 (4.4 mEq/mL K)	3 mmol/mL	Serum K <3.5 mEq/L (<3.5 mmol/L) 15–30 mmol IVPB

IVPB, IV piggyback; K, potassium; Na, sodium; PO_4, phosphate.
[a]Monitor serum K closely.

TABLE 75–5 Mechanism of Drug-Induced Hypokalemia

Transcellular Shift	Enhanced Renal Excretion	Enhanced Fecal Elimination
β_2-Receptor agonists	**Diuretics**	**Laxatives**
Epinephrine	Acetazolamide	Sodium polystyrene sulfonate
Albuterol	Thiazides	Phenolphthalein
Terbutaline	Indapamide	Sorbitol
Fomoterol	Metolazone	
Salmeterol	Furosemide	
Isoproterenol	Torsemide	
Ephedrine	Bumetanide	
Pseudoephedrine	Ethacrynic acid	
Tocolytic agents	**High-dose penicillins**	
Ritodrine	Nafcillin	
Nylidrin	Ampicillin	
Theophylline	Penicillin	
Caffeine	**Mineralocorticoids**	
Insulin overdose	**Miscellaneous**	
	Aminoglycosides	
	Amphotericin B	
	Cisplatin	

Clinical Presentation

- Signs and symptoms are nonspecific and variable and depend on the degree of hypokalemia and rapidity of onset. Mild hypokalemia is often asymptomatic.
- Cardiovascular manifestations cardiac arrhythmias (eg, heart block, atrial flutter, paroxysmal atrial tachycardia, ventricular fibrillation, and digitalis-induced arrhythmias). In severe hypokalemia (serum concentration <2.5 mEq/L; <2.5 mmol/L), ECG changes include ST-segment depression or flattening, T-wave inversion, and U-wave elevation.
- Moderate hypokalemia is associated with muscle weakness, cramping, malaise, and myalgias.

Treatment

- In general, every 1 mEq/L (1 mmol/L) decrease in potassium below 3.5 mEq/L (3.5 mmol/L) corresponds with a total body deficit of 100 to 400 mEq (100–400 mmol). To correct mild deficits, patients receiving chronic loop or thiazide diuretics generally need 40 to 100 mEq (40–100 mmol) of potassium.
- Whenever possible, potassium supplementation should be administered by mouth. Of the available salts, potassium chloride is most commonly used because it is the most effective for common causes of potassium depletion.
- Limit IV administration to severe hypokalemia, signs and symptoms of hypokalemia, or inability to tolerate oral therapy. IV supplementation is more dangerous than oral therapy due to the potential for hyperkalemia, phlebitis, and pain at the infusion site. Potassium should be administered in saline because dextrose can stimulate insulin secretion and worsen intracellular shifting of potassium. Generally, 10 to 20 mEq (10–20 mmol) of potassium is diluted in 100 mL of 0.9% saline and administered through a peripheral vein over 1 hour. If infusion rates exceed 10 mEq/h (10 mmol/h), ECG should be monitored.
- Evaluate serum potassium following infusion of each 30 to 40 mEq (30–40 mmol) to direct further potassium supplementation.

HYPERKALEMIA (SERUM POTASSIUM >5 mEq/L [>5 mmol/L])

Pathophysiology

- Hyperkalemia develops when potassium intake exceeds excretion or when the transcellular distribution of potassium is disturbed.
- Primary causes of true hyperkalemia include increased potassium intake, decreased potassium excretion, tubular unresponsiveness to aldosterone, and redistribution of potassium to the extracellular space.

Clinical Presentation

- Hyperkalemia is frequently asymptomatic; patients might complain of heart palpitations or skipped heartbeats.
- The earliest ECG change (serum potassium 5.5–6 mEq/L; 5.5–6 mmol/L) is peaked T waves. The sequence of changes with further increases in serum potassium concentration is widening of the PR interval, loss of the P wave, widening of the QRS complex, and merging of the QRS complex with the T wave resulting in a sine-wave pattern.

Treatment

- Treatment depends on the desired rapidity and degree of lowering (**Fig. 75–4**, **Table 75–6**). Dialysis is the most rapid way to lower serum potassium concentration.
- Calcium administration rapidly reverses ECG manifestations and arrhythmias, but it does not lower serum potassium concentrations. Calcium is short acting and therefore must be repeated if signs or symptoms recur.
- Rapid correction of hyperkalemia requires administration of drugs that shift potassium intracellularly (eg, insulin and dextrose, sodium bicarbonate, or albuterol).
- **Sodium polystyrene sulfonate** is a cation-exchange resin suitable for asymptomatic patients with mild to moderate hyperkalemia. Each gram of resin exchanges 1 mEq

TABLE 75–6 Therapeutic Alternatives for the Management of Hyperkalemia

Medication	Dose	Route of Administration	Onset/Duration of Action	Acuity	Mechanism of Action	Expected Result
Calcium	1 g	IV over 5–10 minutes	1–2 min/10–30 min	Acute	Raises cardiac threshold potential	Reverses electrocardiographic effects
Furosemide	20–40 mg	IV	5–15 min/4–6 h	Acute	Inhibits renal Na^+ reabsorption	Increased urinary K^+ loss
Regular insulin	5–10 units	IV or SC	30 min/2–6 h	Acute	Stimulates intracellular K^+ uptake	Intracellular K^+ redistribution
Dextrose 10%	1,000 mL (100 g)	IV over 1–2 hours	30 min/2–6 h	Acute	Stimulates insulin release	Intracellular K^+ redistribution
Dextrose 50%	50 mL (25 g)	IV over 5 minutes	30 min/2–6 h	Acute	Stimulates insulin release	Intracellular K^+ redistribution
Sodium bicarbonate	50–100 mEq (50–100 mmol)	IV over 2–5 minutes	30 min/2–6 h	Acute	Raises serum pH	Intracellular K^+ redistribution
Albuterol	10–20 mg	Nebulized over 10 minutes	30 min/1–2 h	Acute	Stimulates intracellular K^+ uptake	Intracellular K^+ redistribution
Hemodialysis	4 hours	N/A	Immediate/variable	Acute	Removal from serum	Increased K^+ elimination
Sodium polystyrene sulfonate	15–60 g	Oral or rectal	1 h/variable	Nonacute	Resin exchanges Na^+ for K^+	Increased K^+ elimination

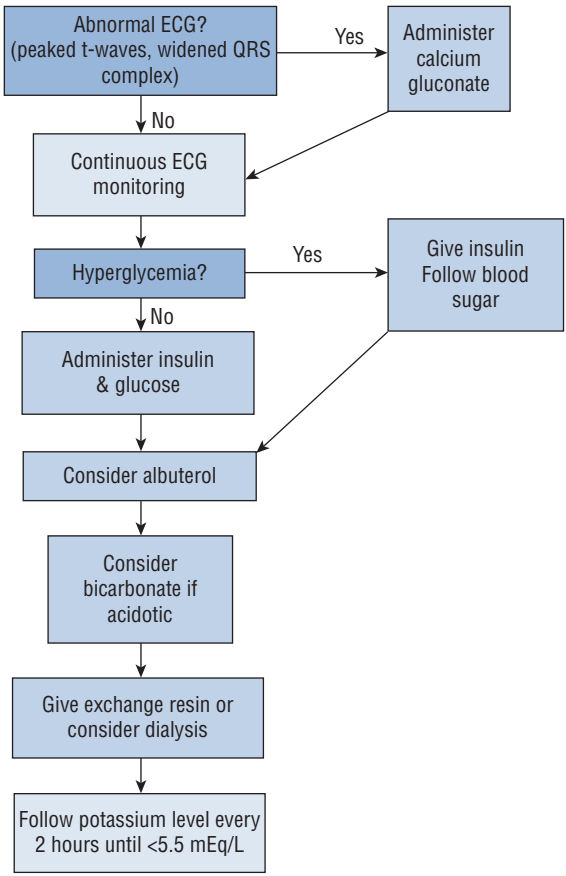


FIGURE 75–4. Treatment approach for hyperkalemia. Serum potassium of 5.5 mEq/L is equivalent to 5.5 mmol/L.

(1 mmol) of sodium for 1 mEq (1 mmol) of potassium. The sorbitol component promotes excretion of exchanged potassium by inducing diarrhea. The oral route is better tolerated and more effective than the rectal route.

DISORDERS OF MAGNESIUM HOMEOSTASIS

HYPOMAGNESEMIA (SERUM MAGNESIUM <1.4 mEq/L [<0.70 mmol/L])

Pathophysiology

- Hypomagnesemia is usually associated with disorders of the intestinal tract or kidneys. Drugs (eg, **aminoglycosides**, **amphotericin B**, **cyclosporine**, diuretics, **digitalis**, and **cisplatin**) or conditions that interfere with intestinal absorption or increase renal excretion of magnesium can cause hypomagnesemia.
- Commonly associated with alcoholism.

Clinical Presentation

- Although typically asymptomatic, the dominant organ systems involved are the neuromuscular and cardiovascular systems. Symptoms include heart palpitations, tetany, twitching, and generalized convulsions.
- Ventricular arrhythmias are the most important and potentially life-threatening cardiovascular effect.
- ECG changes include widened QRS complexes and peaked T waves in mild deficiency. Prolonged PR intervals, progressive widening of the QRS complexes, and flattening of T waves occur in moderate to severe deficiency.
- Many electrolyte disturbances occur with hypomagnesemia, including hypokalemia and hypocalcemia.

Treatment

- The severity of magnesium depletion and the presence of symptoms dictate the route of magnesium supplementation. Intramuscular magnesium is painful and should be reserved for patients with severe hypomagnesemia and limited venous access. IV bolus injection is associated with flushing, sweating, and a sensation of warmth.
- Oral magnesium supplementation is appropriate when the serum magnesium concentration is greater than 1 mEq/L (0.5 mmol/L). Sustained release products are preferred due to improved patient compliance and less GI side effects (eg, diarrhea).
- Administer IV magnesium if serum concentrations are less than 1 mEq/L (<0.5 mmol/L) or if signs and symptoms are present regardless of serum concentration. Infuse 4 to 6 g of magnesium over 12 to 24 hours and repeat as needed to maintain serum concentrations above 1 mEq/L (0.5 mmol/L). Continue until signs and symptoms resolve. Reduce magnesium dose by 25% to 50% with renal insufficiency.

HYPERMAGNESEMIA (SERUM MAGNESIUM >2 mEq/L [>1 mmol/L])

Pathophysiology

- Magnesium concentrations steadily increase as the GFR decreases below 30 mL/min/1.73 m^2 (0.29 mL/s/m^2) and is generally associated with advanced CKD.
- Other causes include magnesium-containing antacids in patients with renal insufficiency, enteral or parenteral nutrition in patients with multiorgan system failure, magnesium for treatment of eclampsia, lithium therapy, hypothyroidism, and Addison disease.

Clinical Presentation

- Symptoms are rare when the serum magnesium concentration is less than 4 mEq/L (<2 mmol/L).
- The sequence of neuromuscular signs as serum magnesium increases from 5 to 12 mEq/L (2.5–6 mmol/L) is sedation, hypotonia, hyporeflexia, somnolence, coma, muscular paralysis, and, ultimately, respiratory depression.
- The sequence of cardiovascular signs as serum magnesium increases from 3 to 15 mEq/L (1.5–7.5 mmol/L) is hypotension, cutaneous vasodilation, QT-interval prolongation, bradycardia, primary heart block, nodal rhythms, bundle branch block, QRS- and then PR-interval prolongation, complete heart block, and asystole.

Treatment

- IV calcium (100–200 mg of elemental calcium; eg, calcium gluconate 2 g IV) is indicated to antagonize the neuromuscular and cardiovascular effects of magnesium. Doses should be repeated as often as hourly in life-threatening situations.
- Forced diuresis with 0.45% NaCl and loop diuretics (eg, **furosemide**, 40 mg IV) can promote magnesium elimination in patients with normal renal function or stage 1, 2, or 3 CKD. In dialysis patients, change to a magnesium-free dialysate.

EVALUATION OF THERAPEUTIC OUTCOMES

- The primary end point for monitoring treatment of fluid and electrolyte disorders is the correction of the abnormal serum electrolyte. In general, monitoring is

initially performed at frequent intervals and, as homeostasis is restored, subsequently performed at less frequent intervals.
- Monitor all electrolytes as individual electrolyte abnormalities typically coexist with another abnormality (eg, hypomagnesemia with hypokalemia and hypocalcemia, or hyperphosphatemia with hypocalcemia).
- Monitor patients for resolution of clinical manifestations of electrolyte disturbances and for treatment-related complications.

See Chapter 34, Disorders of Sodium and Water Homeostasis, authored by Katherine Hammond Chessman and Gary R. Matzke; Chapter 35, Disorders of Calcium and Phosphorus Homeostasis, authored by Amy Barton Pai; and Chapter 36, Disorders of Potassium and Magnesium Homeostasis, authored by Donald F. Brophy, for a more detailed discussion of this topic.

CHAPTER 76

Allergic Rhinitis

- *Allergic rhinitis* involves inflammation of nasal mucous membranes in sensitized individuals when inhaled allergenic particles contact mucous membranes and elicit a response mediated by immunoglobulin E (IgE). There are two types: seasonal and persistent (formerly called "perennial") allergic rhinitis.

PATHOPHYSIOLOGY

- Airborne allergens enter the nose during inhalation and are processed by lymphocytes, which produce antigen-specific IgE, sensitizing genetically predisposed hosts to those agents. On nasal reexposure, IgE bound to mast cells interacts with airborne allergens, triggering release of inflammatory mediators.
- An immediate reaction occurs within seconds to minutes, resulting in rapid release of preformed and newly generated mediators from the arachidonic acid cascade. Mediators of immediate hypersensitivity include histamine, leukotrienes, prostaglandin, tryptase, and kinins. These mediators cause vasodilation, increased vascular permeability, and production of nasal secretions. Histamine produces rhinorrhea, itching, sneezing, and nasal obstruction.
- A late-phase reaction may occur 4 to 8 hours after initial allergen exposure due to cytokine release from mast cells and thymus-derived helper lymphocytes. This inflammatory response causes persistent chronic symptoms, including nasal congestion.

CLINICAL PRESENTATION

- Seasonal (hay fever) allergic rhinitis occurs in response to specific allergens (pollen from trees, grasses, and weeds) present at predictable times of the year (spring and/or fall) and typically causes more acute symptoms.
- Persistent allergic rhinitis occurs year-round in response to nonseasonal allergens (eg, dust mites, animal dander, and molds) and usually causes more subtle, chronic symptoms.
- Many patients have a combination of both types, with symptoms year-round and seasonal exacerbations.
- Symptoms include clear rhinorrhea, sneezing, nasal congestion, postnasal drip, allergic conjunctivitis, and pruritic eyes, ears, or nose.
- In children, physical examination may reveal dark circles under the eyes (allergic shiners), a transverse nasal crease caused by repeated rubbing of the nose, adenoidal breathing, edematous nasal turbinates coated with clear secretions, tearing, and periorbital swelling.
- Patients may complain of loss of smell or taste, with sinusitis or polyps the underlying cause in many cases. Postnasal drip with cough or hoarseness can be bothersome.
- Untreated rhinitis symptoms may lead to insomnia, malaise, fatigue, and poor work or school performance.
- Allergic rhinitis is associated with asthma; 10% to 40% of allergic rhinitis patients have asthma.
- Complications include recurrent and chronic sinusitis and epistaxis.

DIAGNOSIS

- Medical history includes careful description of symptoms, environmental factors and exposures, results of previous therapy, use of medications, previous nasal injury or surgery, and family history.
- Microscopic examination of nasal scrapings typically reveals numerous eosinophils. Peripheral blood eosinophil count may be elevated, but it is nonspecific and has limited usefulness.
- Allergy testing can help determine whether rhinitis is caused by immune response to allergens. Immediate-type hypersensitivity skin tests are commonly used. Percutaneous testing is safer and more generally accepted than intradermal testing, which is usually reserved for patients requiring confirmation. The radioallergosorbent test (RAST) can detect IgE antibodies in the blood that are specific for a given antigen, but it is less sensitive than percutaneous tests.

TREATMENT

- Goals of Treatment: Minimize or prevent symptoms, minimize or avoid medication side effects, provide economical therapy, and maintain normal lifestyle.
- See **Fig. 76–1** for a treatment algorithm for allergic rhinitis.

NONPHARMACOLOGIC THERAPY

- Avoiding offending allergens is important but difficult to accomplish, especially for perennial allergens. Mold growth can be reduced by keeping household humidity less than 50% and removing obvious growth with bleach or disinfectant.
- Patients sensitive to animals benefit most by removing pets from the home, if feasible. Reducing exposure to dust mites by encasing bedding with impermeable covers and washing bed linens in hot water has little benefit, except perhaps in children.
- Patients with seasonal allergic rhinitis should keep windows closed and minimize time spent outdoors during pollen seasons. Filter masks can be worn while gardening or mowing the lawn.

PHARMACOLOGIC THERAPY

Antihistamines

- Histamine H_1-receptor antagonists bind to H_1 receptors without activating them, preventing histamine binding and action. They are effective in preventing the histamine response but not in reversing its effects after they have occurred.
- Oral antihistamines are divided into two categories: nonselective (first-generation or sedating antihistamines) and peripherally selective (second-generation or nonsedating antihistamines). However, individual agents should be judged on their specific sedating effects because variation exists among agents within these categories (**Table 76–1**). The sedating effect may depend on ability to cross the blood–brain barrier. Most older antihistamines are lipid soluble and cross this barrier easily. Peripherally selective agents have little or no central or autonomic nervous system effects.
- Symptom relief is caused in part by an anticholinergic drying effect that reduces nasal, salivary, and lacrimal gland hypersecretion. Antihistamines antagonize increased capillary permeability, wheal-and-flare formation, and itching.
- Drowsiness is the most frequent side effect, and it can interfere with driving ability or adequate functioning. Sedative effects can be beneficial in patients who have difficulty sleeping because of rhinitis symptoms.
- Adverse anticholinergic such as dry mouth, difficulty in voiding urine, constipation, and cardiovascular effects may occur (see **Table 76–1**). Antihistamines should be used with caution in patients predisposed to urinary retention and in those with increased intraocular pressure, hyperthyroidism, and cardiovascular disease.
- Other side effects include loss of appetite, nausea, vomiting, and epigastric distress. Taking medication with meals or a full glass of water may prevent gastrointestinal (GI) side effects.

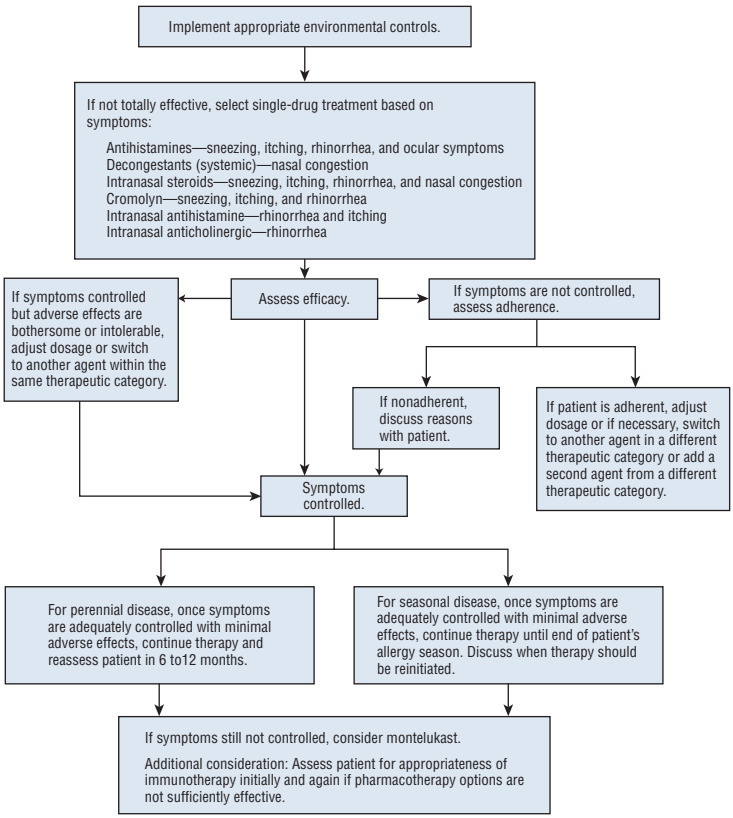


FIGURE 76–1. Treatment algorithm for allergic rhinitis.

- Table 76–2 lists recommended doses of oral agents. Antihistamines are more effective when taken 1 to 2 hours before anticipated exposure to the offending allergen.
- **Azelastine** (Astelin) is an intranasal antihistamine that rapidly relieves symptoms of seasonal allergic rhinitis. However, caution patients about potential for drowsiness because systemic availability is approximately 40%. Patients may also experience drying effects, headache, and diminished effectiveness over time. **Olopatadine** (Patanase) is another intranasal antihistamine that may cause less drowsiness because it is a selective H_1-receptor antagonist.
- **Levocabastine** (Livostin), **olopatadine** (Patanol), and **bepotastine** (Bepreve) are ophthalmic antihistamines that can be used for conjunctivitis associated with allergic rhinitis. Systemic antihistamines are usually also effective for allergic conjunctivitis. Ophthalmic agents are a useful addition to nasal corticosteroids for ocular symptoms. They are also useful for patients whose only symptoms involve the eyes or for patients whose ocular symptoms persist on oral antihistamines.

Decongestants

- Topical and systemic decongestants are sympathomimetic agents that act on adrenergic receptors in nasal mucosa to produce vasoconstriction, shrink swollen mucosa, and improve ventilation. Decongestants work well in combination with antihistamines when nasal congestion is part of the clinical picture.

TABLE 76–1 Relative Adverse Effect Profiles of Antihistamines

Medication	Relative Sedative Effect	Relative Anticholinergic Effect
Alkylamine class, nonselective		
Brompheniramine maleate	Low	Moderate
Chlorpheniramine maleate	Low	Moderate
Dexchlorpheniramine maleate	Low	Moderate
Ethanolamine class, nonselective		
Carbinoxamine maleate	High	High
Clemastine fumarate	Moderate	High
Diphenhydramine hydrochloride	High	High
Ethylenediamine class, nonselective		
Pyrilamine maleate	Low	Low to none
Tripelennamine hydrochloride	Moderate	Low to none
Phenothiazine class, nonselective		
Promethazine hydrochloride	High	High
Piperidine class, nonselective		
Cyproheptadine hydrochloride	Low	Moderate
Phenindamine tartrate	Low to none	Moderate
Phthalazinone class, peripherally selective		
Azelastine (nasal only)	Low to none	Low to none
Bepotastine (ophthalmic only)	Low to none	Low to none
Piperazine class, peripherally selective		
Cetirizine	Low to moderate	Low to none
Levocetirizine	Low to moderate	Low to none
Piperidine class, peripherally selective		
Desloratadine	Low to none	Low to none
Fexofenadine	Low to none	Low to none
Loratadine	Low to none	Low to none
Olopatadine (nasal and ophthalmic only)	Low to none	Low to none

- Topical decongestants are applied directly to swollen nasal mucosa via drops or sprays (**Table 76–3**). They result in little or no systemic absorption.
- Rhinitis medicamentosa (rebound vasodilation with congestion) may occur with prolonged use of topical agents (>3–5 days). Patients with this condition use more spray more often with less response. Abrupt cessation is an effective treatment, but rebound congestion may last for several days or weeks. Nasal steroids have been used successfully but take several days to work. Weaning off the topical decongestant can be accomplished by decreasing dosing frequency or concentration over several weeks. Combining the weaning process with nasal steroids may be helpful.
- Other adverse effects of topical decongestants are burning, stinging, sneezing, and dryness of the nasal mucosa.
- These products should be used only when absolutely necessary (eg, at bedtime) and in doses that are as small and infrequent as possible. Duration of therapy should be limited to 3 to 5 days.

TABLE 76–2 Oral Dosages of Commonly Used Antihistamines and Decongestants

	Dosage and Interval[a]	
Medication	**Adults**	**Children**
Nonselective (first-generation) antihistamines		
Chlorpheniramine maleate, plain[b]	4 mg daily every 6 h	6–12 years: 2 mg daily every 6 h 2–5 years: 1 mg every 6 h
Chlorpheniramine maleate, sustained-release	8–12 mg daily at bedtime, 8 mg every 8–12 h, or 12 mg every 12 h	6–12 years: 8 mg at bedtime <6 years: Not recommended
Clemastine fumarate[b]	1.34 mg every 8 h	6–12 years: 0.67 mg every 12 h
Diphenhydramine hydrochloride[b]	25–50 mg every 8 h	5 mg/kg/day divided every 8 h (up to 25 mg per dose)
Peripherally selective (second-generation) antihistamines		
Loratadine[b]	10 mg once daily	6–12 years: 10 mg once daily 2–5 years: 5 mg once daily
Fexofenadine	60 mg twice daily or 180 mg once daily	6–11 years: 30 mg twice daily
Cetirizine[b]	5–10 mg once daily	1–5 years: 2.5 mg once daily >6 years: 5 mg once daily
Levocetirizine	5 mg in evening	6–11 years: 2.5 mg in evening
Oral decongestants		
Pseudoephedrine, plain	60 mg every 4–6 h	6–12 years: 30 mg every 4–6 h 2–5 years: 15 mg every 4–6 h
Pseudoephedrine, sustained-release[c]	120 mg every 12 h	Not recommended
Phenylephrine	10–20 mg every 4 h	6–12 years: 5 mg every 4 h 4–6 years: 2.5 mg every 4 h

Note: Fexofenadine and levocetirizine are available by prescription only.

[a]Dosage adjustment may be needed in renal/hepatic dysfunction. Refer to manufacturers' prescribing information.
[b]Available in liquid form.
[c]Controlled-release product also available: 240 mg once daily (60 mg immediate-release with 180 mg controlled-release).

- **Pseudoephedrine** (see **Table 76–2**) is an oral decongestant that has a slower onset of action than topical agents but may last longer and cause less local irritation. Rhinitis medicamentosa does not occur with oral decongestants. Doses up to 180 mg produce no measurable change in blood pressure or heart rate. However, higher doses (210–240 mg) may raise both blood pressure and heart rate. Systemic decongestants should be avoided in hypertensive patients unless absolutely necessary. Severe hypertensive reactions can occur when pseudoephedrine is given with monoamine oxidase inhibitors. Pseudoephedrine can cause mild CNS stimulation, even at therapeutic doses. Because of misuse as a component in the illegal manufacture of methamphetamine,

TABLE 76–3 Duration of Action of Topical Decongestants

Medication	Duration (Hours)
Short-acting	
Phenylephrine hydrochloride	Up to 4
Intermediate-acting	
Naphazoline hydrochloride	4–6
Tetrahydrozoline hydrochloride	4–6
Long-acting	
Oxymetazoline hydrochloride	Up to 12
Xylometazoline hydrochloride	Up to 12

pseudoephedrine is restricted to behind-the-counter sale with a limit on monthly purchases.

- **Phenylephrine** has replaced pseudoephedrine in many nonprescription antihistamine–decongestant combination products because of legal restrictions on pseudoephedrine sales.
- Combination oral products containing a decongestant and antihistamine are rational because of different mechanisms of action. Consumers should read product labels carefully to avoid therapeutic duplication and use combination products only for short courses.

Nasal Corticosteroids

- Intranasal corticosteroids relieve sneezing, rhinorrhea, pruritus, and nasal congestion with minimal side effects (Table 76–4). They reduce inflammation by blocking mediator release, suppressing neutrophil chemotaxis, causing mild vasoconstriction, and inhibiting mast cell–mediated, late-phase reactions.
- These agents are an excellent choice for persistent rhinitis and can be useful in seasonal rhinitis, especially if begun in advance of symptoms. Some authorities recommend nasal steroids as initial therapy over antihistamines because of their high degree of efficacy when used properly along with allergen avoidance.

TABLE 76–4 Dosage of Nasal Corticosteroids

Medication	Dosage and Interval
Beclomethasone dipropionate, monohydrate	>12 years: 1–2 inhalations per nostril (42–84 mcg) twice daily 6–11 years: One inhalation per nostril twice daily to start
Budesonide	>6 years: Two sprays (64 mcg) per nostril in AM and PM or four sprays per nostril in AM (maximum 256 mcg)
Flunisolide	Adults: Two sprays (50 mcg) per nostril twice daily (maximum, 400 mcg) Children: One spray per nostril three times daily
Fluticasone	Adults: Two sprays (100 mcg) per nostril once daily; after a few days decrease to 1 spray per nostril Children >4 years and adolescents: One spray per nostril once daily (maximum 200 mcg/day)
Mometasone furoate	>12 years: Two sprays (100 mcg) per nostril once daily
Triamcinolone acetonide	>12 years: Two sprays (110 mcg) per nostril once daily (maximum 440 mcg/day)

- Side effects include sneezing, stinging, headache, epistaxis, and rare infections with *Candida albicans*.
- Some patients improve within a few days, but peak response may require 2 to 3 weeks. The dosage may be reduced once a response is achieved.
- Blocked nasal passages should be cleared with a decongestant or saline irrigation before administration to ensure adequate penetration of the spray.

Cromolyn Sodium

- **Cromolyn sodium** (Nasalcrom), a mast cell stabilizer, is available as a nonprescription nasal spray for symptomatic prevention and treatment of allergic rhinitis. It prevents antigen-triggered mast cell degranulation and release of mediators, including histamine. The most common side effect is local irritation (sneezing and nasal stinging).
- Dosage for persons at least 2 years of age is one spray in each nostril three or four times daily at regular intervals. Nasal passages should be cleared before administration, and inhaling through the nose during administration enhances distribution to the entire nasal lining.
- For seasonal rhinitis, treatment should be initiated just before the start of the offending allergen's season and continue throughout the season.
- In persistent rhinitis, effects may not be seen for 2 to 4 weeks; antihistamines or decongestants may be needed during this initial phase of therapy.

Ipratropium Bromide

- **Ipratropium bromide** (Atrovent) nasal spray is an anticholinergic agent useful in persistent allergic rhinitis. It exhibits antisecretory properties when applied locally and provides symptomatic relief of rhinorrhea.
- The 0.03% solution is given as two sprays (42 mcg) two or three times daily. Adverse effects are mild and include headache, epistaxis, and nasal dryness.

Montelukast

- **Montelukast** (Singulair) is a leukotriene receptor antagonist approved for treatment of persistent allergic rhinitis in children as young as 6 months and for seasonal allergic rhinitis in children as young as 2 years. It is effective alone or in combination with an antihistamine.
- Dosage for adults and adolescents older than 14 years is one 10-mg tablet daily. Children ages 6 to 14 years may receive one 5-mg chewable tablet daily. Children ages 6 months to 5 years may be given one 4-mg chewable tablet or oral granule packet daily.
- Montelukast is no more effective than antihistamines and less effective than intranasal corticosteroids; therefore, it is considered third-line therapy after those agents.

IMMUNOTHERAPY

- Immunotherapy is the slow, gradual process of injecting increasing doses of antigens responsible for eliciting allergic symptoms into a patient with the intent of inducing tolerance to the allergen when natural exposure occurs.
- Beneficial effects of immunotherapy may result from induction of IgG-blocking antibodies, reduction in specific IgE (long-term), reduced recruitment of effector cells, altered T-cell cytokine balance, T-cell anergy, and alteration of regulatory T cells.
- Good candidates for immunotherapy include patients with a strong history of severe symptoms unsuccessfully controlled by avoidance and pharmacotherapy and patients unable to tolerate adverse effects of drug therapy. Poor candidates include patients with medical conditions that would compromise the ability to tolerate an anaphylactic-type reaction, patients with impaired immune systems, and patients with a history of nonadherence.
- In general, very dilute solutions are given initially once or twice weekly. The concentration is increased until the maximum tolerated dose or highest planned dose is achieved. This maintenance dose is continued in slowly increasing intervals over

several years, depending on clinical response. Better results are obtained with year-round rather than seasonal injections.
- Common mild local adverse reactions include induration and swelling at the injection site. More severe reactions (generalized urticaria, bronchospasm, laryngospasm, vascular collapse, and death from anaphylaxis) occur rarely. Severe reactions are treated with epinephrine, antihistamines, and systemic corticosteroids.

EVALUATION OF THERAPEUTIC OUTCOMES

- Monitor patients regularly for reduction in severity of identified target symptoms and presence of side effects.
- Ask patients about their satisfaction with the management of their allergic rhinitis. Management should result in minimal disruption to their normal lifestyle.
- The Medical Outcomes Study 36-Item Short Form Health Survey and the Rhinoconjunctivitis Quality of Life Questionnaire measure symptom improvement and parameters such as sleep quality, nonallergic symptoms (eg, fatigue and poor concentration), emotions, and participation in a variety of activities.

See Chapter 76, Allergic Rhinitis, authored by J. Russell May and Philip H. Smith, for a more detailed discussion of this topic.

CHAPTER 77

Asthma

- *Asthma* is a chronic inflammatory disorder of the airways causing airflow obstruction and recurrent episodes of wheezing, breathlessness, chest tightness, and coughing.

PATHOPHYSIOLOGY

- There is a variable degree of airflow obstruction (related to bronchospasm, edema, and hypersecretion), bronchial hyperresponsiveness (BHR), and airway inflammation.
- In acute inflammation, inhaled allergens in allergic patients causes early-phase allergic reaction with activation of cells bearing allergen-specific immunoglobulin E (IgE) antibodies. After rapid activation, airway mast cells and macrophages release proinflammatory mediators such as histamine and eicosanoids that induce contraction of airway smooth muscle, mucus secretion, vasodilation, and exudation of plasma in the airways. Plasma protein leakage induces a thickened, engorged, edematous airway wall and narrowing of lumen with reduced mucus clearance.
- Late-phase inflammatory reaction occurs 6 to 9 hours after allergen provocation and involves recruitment and activation of eosinophils, T lymphocytes, basophils, neutrophils, and macrophages. Eosinophils migrate to airways and release inflammatory mediators.
- T-lymphocyte activation leads to release of cytokines from type 2 T-helper (TH_2) cells that mediate allergic inflammation (interleukin [IL]-4, IL-5, and IL-13). Conversely, type 1 T-helper (TH_1) cells produce IL-2 and interferon-γ that are essential for cellular defense mechanisms. Allergic asthmatic inflammation may result from imbalance between TH_1 and TH_2 cells.
- Mast cell degranulation results in release of mediators such as histamine; eosinophil and neutrophil chemotactic factors; leukotrienes C_4, D_4, and E_4; prostaglandins; and platelet-activating factor (PAF). Histamine can induce smooth muscle constriction and bronchospasm and may contribute to mucosal edema and mucus secretion.
- Alveolar macrophages release inflammatory mediators, including PAF and leukotrienes B_4, C_4, and D_4. Production of neutrophil chemotactic factor and eosinophil chemotactic factor furthers the inflammatory process. Neutrophils also release mediators (PAFs, prostaglandins, thromboxanes, and leukotrienes) that contribute to BHR and airway inflammation. Leukotrienes C_4, D_4, and E_4 are released during inflammatory processes in the lung and produce bronchospasm, mucus secretion, microvascular permeability, and airway edema.
- Bronchial epithelial cells participate in inflammation by releasing eicosanoids, peptidases, matrix proteins, cytokines, and nitric oxide. Epithelial shedding results in heightened airway responsiveness, altered permeability of airway mucosa, depletion of epithelial-derived relaxant factors, and loss of enzymes responsible for degrading inflammatory neuropeptides. The exudative inflammatory process and sloughing of epithelial cells into the airway lumen impair mucociliary transport. Bronchial glands increase in size, and goblet cells increase in size and number.
- The airway is innervated by parasympathetic, sympathetic, and nonadrenergic inhibitory nerves. Normal resting tone of airway smooth muscle is maintained by vagal efferent activity, and bronchoconstriction can be mediated by vagal stimulation in small bronchi. Airway smooth muscle contains noninnervated β_2-adrenergic receptors that produce bronchodilation. The nonadrenergic, noncholinergic nervous system in the trachea and bronchi may amplify inflammation by releasing nitric oxide.

CLINICAL PRESENTATION

CHRONIC ASTHMA

- Symptoms include episodes of dyspnea, chest tightness, coughing (particularly at night), wheezing, or a whistling sound when breathing. These often occur with exercise but may occur spontaneously or in association with known allergens.
- Signs include expiratory wheezing on auscultation; dry, hacking cough; and atopy (eg, allergic rhinitis or eczema).
- Asthma can vary from chronic daily symptoms to only intermittent symptoms. Intervals between symptoms may be days, weeks, months, or years.
- Severity is determined by lung function, symptoms, nighttime awakenings, and interference with normal activity prior to therapy. Patients can present with mild intermittent symptoms that require no medications or only occasional short-acting inhaled β_2-agonists to severe chronic symptoms despite multiple medications.

ACUTE SEVERE ASTHMA

- Uncontrolled asthma can progress to an acute state in which inflammation, airway edema, mucus accumulation, and severe bronchospasm result in profound airway narrowing that is poorly responsive to bronchodilator therapy.
- Patients may be anxious in acute distress and complain of severe dyspnea, shortness of breath, chest tightness, or burning. They may be able to say only a few words with each breath. Symptoms are unresponsive to usual measures (short-acting inhaled β-agonists).
- Signs include expiratory and inspiratory wheezing on auscultation; dry, hacking cough; tachypnea; tachycardia; pallor or cyanosis; and hyperinflated chest with intercostal and supraclavicular retractions. Breath sounds may be diminished with severe obstruction.

DIAGNOSIS

CHRONIC ASTHMA

- Diagnosis is made primarily by history of recurrent episodes of coughing, wheezing, chest tightness, or shortness of breath and confirmatory spirometry.
- Patients may have family history of allergy or asthma or symptoms of allergic rhinitis. History of exercise or cold air precipitating dyspnea or increased symptoms during specific allergen seasons suggests asthma.
- Spirometry demonstrates obstruction (forced expiratory volume in 1 second [FEV_1]/forced vital capacity [FVC] <80%) with reversibility after inhaled β_2-agonist administration (at least 12% improvement in FEV_1). If baseline spirometry is normal, challenge testing with exercise, histamine, or methacholine can be used to elicit BHR.

ACUTE SEVERE ASTHMA

- Peak expiratory flow (PEF) and FEV_1 are less than 40% of normal predicted values. Pulse oximetry reveals decreased arterial oxygen and O_2 saturations. The best predictor of outcome is early response to treatment as measured by improvement in FEV_1 at 30 minutes after inhaled β_2-agonists.
- Arterial blood gases may reveal metabolic acidosis and low partial pressure of oxygen (PaO_2).
- History and physical examination should be obtained while initial therapy is provided. History of previous asthma exacerbations (eg, hospitalizations, intubations) and complicating illnesses (eg, cardiac disease, diabetes) should be documented. Patient should be examined to assess hydration status; use of accessory muscles of respiration; and the presence of cyanosis, pneumonia, pneumothorax, pneumomediastinum, and upper airway obstruction. Complete blood count may be appropriate for patients with fever or purulent sputum.

TREATMENT

- Goals of Treatment: Goals for chronic asthma management include:
  - ✓ *Reducing impairment*: (1) prevent chronic and troublesome symptoms (eg, coughing or breathlessness in the daytime, at night, or after exertion), (2) require infrequent use (≤2 days/wk) of inhaled short-acting β_2-agonist for quick relief of symptoms (not including prevention of exercise-induced bronchospasm [EIB]), (3) maintain (near-) normal pulmonary function, (4) maintain normal activity levels (including exercise and attendance at work or school), and (5) meet patients' and families' expectations and satisfaction with care.
  - ✓ *Reducing risk*: (1) prevent recurrent exacerbations and minimize need for emergency department visits or hospitalizations; (2) prevent loss of lung function; for children, prevent reduced lung growth; and (3) minimal or no adverse effects of therapy.
- For acute severe asthma, treatment goals are to (1) correct significant hypoxemia, (2) rapidly reverse airway obstruction (within minutes), (3) reduce likelihood of recurrence of severe airflow obstruction, and (4) develop a written action plan in case of future exacerbation.
- **Figure 77–1** depicts the National Asthma Education and Prevention Program (NAEPP) stepwise approach for managing chronic asthma. **Figure 77–2** illustrates the recommended therapies for home treatment of acute asthma exacerbations.

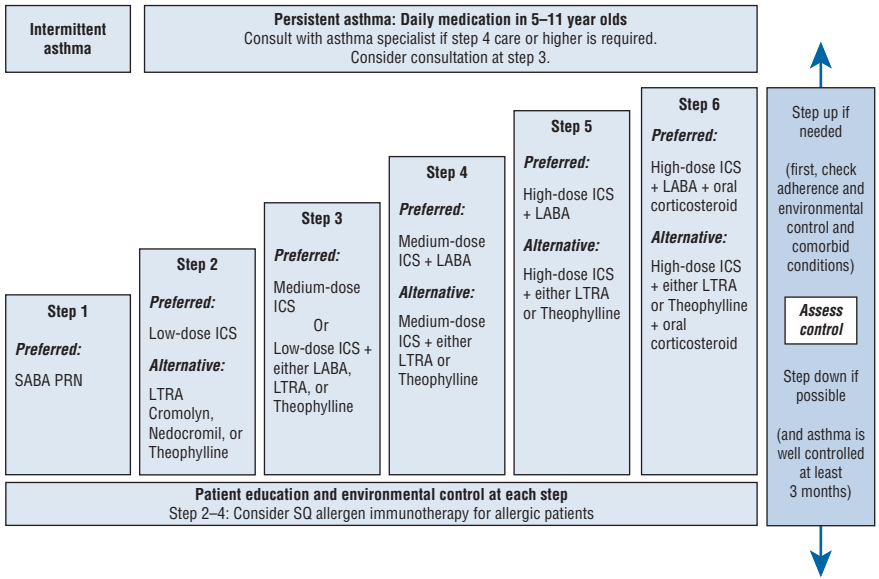
NONPHARMACOLOGIC THERAPY

- Patient education is mandatory to improve medication adherence, self-management skills, and use of healthcare services.
- Objective measurements of airflow obstruction with a home peak flow meter may not improve patient outcomes. NAEPP advocates PEF monitoring only for patients with severe persistent asthma who have difficulty perceiving airway obstruction.
- Avoidance of known allergenic triggers can improve symptoms, reduce medication use, and decrease BHR. Environmental triggers (eg, animals) should be avoided in sensitive patients, and smokers should be encouraged to quit.
- Patients with acute severe asthma should receive oxygen to maintain PaO_2 greater than 90% (>95% in pregnancy and heart disease). Dehydration should be corrected; urine specific gravity may help guide therapy in children when assessment of hydration status is difficult.

PHARMACOTHERAPY

β_2-Agonists

- Short-acting β_2-agonists (**Table 77–1**) are the most effective bronchodilators. Aerosol administration enhances bronchoselectivity and provides more rapid response and greater protection against provocations (eg, exercise, allergen challenges) than systemic administration.
- **Albuterol** and other inhaled short-acting selective β_2-agonists are indicated for intermittent episodes of bronchospasm and are the treatment of choice for acute severe asthma and EIB. Regular treatment (four times daily) does not improve symptom control over as-needed use.
- **Formoterol** and **salmeterol** are inhaled long-acting β_2-agonists for adjunctive long-term control for patients with symptoms who are already on low to medium doses of inhaled corticosteroids prior to advancing to medium- or high-dose inhaled corticosteroids. Short-acting β_2-agonists should be continued for acute exacerbations. Long-acting agents are ineffective for acute severe asthma because it can take up to 20 minutes for onset and 1 to 4 hours for maximum bronchodilation.
- In acute severe asthma, continuous nebulization of short-acting β_2-agonists (eg, albuterol) is recommended for patients having unsatisfactory response after three doses (every 20 min) of aerosolized β_2-agonists and potentially for patients presenting initially with PEF or FEV1 values less than 30% of predicted normal. Dosing guidelines are presented in **Table 77–2**.


Intermittent asthma
Persistent asthma: Daily medication in 5–11 year olds
Consult with asthma specialist if step 4 care or higher is required.
Consider consultation at step 3.
Step 1
Preferred:
SABA PRN
Step 2
Preferred:
Low-dose ICS
Alternative:
LTRA
Cromolyn, Nedocromil, or Theophylline
Step 3
Preferred:
Medium-dose ICS
Or
Low-dose ICS + either LABA, LTRA, or Theophylline
Step 4
Preferred:
Medium-dose ICS + LABA
Alternative:
Medium-dose ICS + either LTRA or Theophylline
Step 5
Preferred:
High-dose ICS + LABA
Alternative:
High-dose ICS + either LTRA or Theophylline
Step 6
Preferred:
High-dose ICS + LABA + oral corticosteroid
Alternative:
High-dose ICS + either LTRA or Theophylline + oral corticosteroid
Step up if needed
(first, check adherence and environmental control and comorbid conditions)
Assess control
Step down if possible
(and asthma is well controlled at least 3 months)
Patient education and environmental control at each step
Step 2–4: Consider SQ allergen immunotherapy for allergic patients

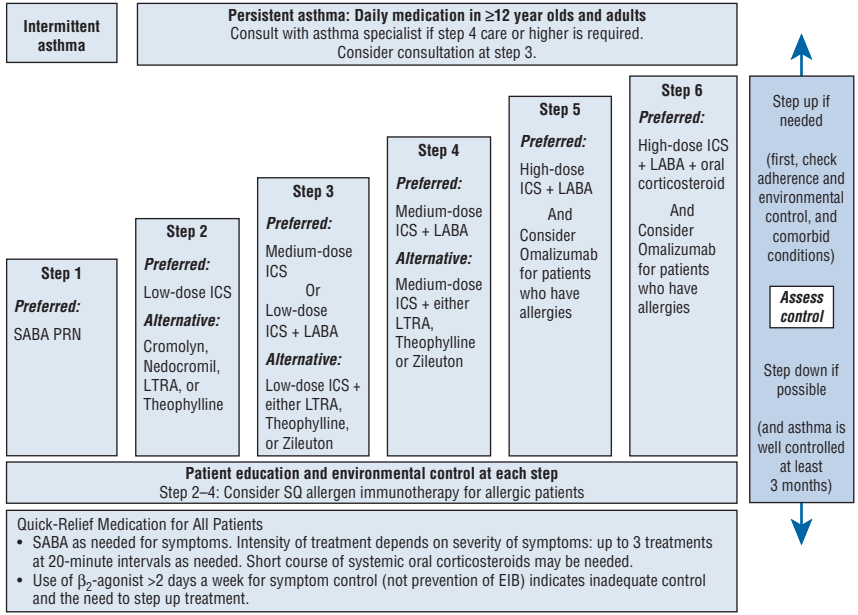


FIGURE 77–1. Stepwise approach for managing asthma in adults and children age 5 years and older. (EIB, exercise-induced bronchospasm; ICS, inhaled corticosteroid; LABA, long-acting β-agonist; LTRA, leukotriene receptor antagonist; SABA, short-acting β-agonist.) *(From NHLBI, National Asthma Education and Prevention Program. Full Report of the Expert Panel: Guidelines for the Diagnosis and Management of Asthma (EPR-3); July 2007. http://www.nhlbi.nih.gov/guidelines/asthma.)*

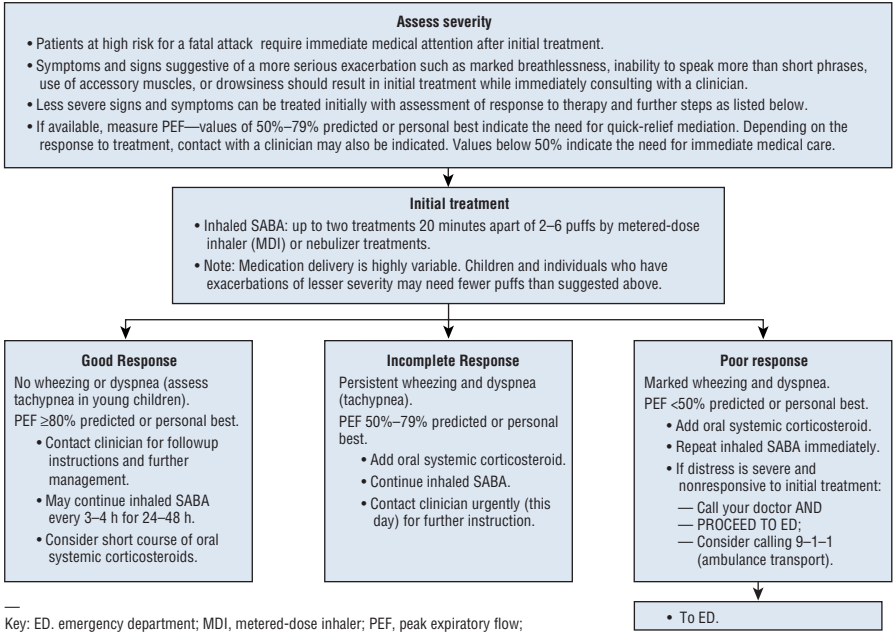


FIGURE 77–2. Home management of acute asthma exacerbation. Patients at risk of asthma-related death should receive immediate clinical attention after initial treatment. Additional therapy may be required. *(From NHLBI, National Asthma Education and Prevention Program. Full Report of the Expert Panel: Guidelines for the Diagnosis and Management of Asthma (EPR-3); July 2007. http://www.nhlbi.nih.gov/guidelines/asthma.)*

TABLE 77–1 Relative Selectivity, Potency, and Duration of Action of β-Adrenergic Agonists

	Selectivity			Duration of Action[b]		
Agent	**β_1**	**β_2**	**Potency, β_2[a]**	**Bronchodilation (Hours)**	**Protection (Hours)[c]**	**Oral Activity**
Isoproterenol	++++	++++	1	0.5–2	0.5–1	No
Albuterol	+	++++	2	4–8	2–4	Yes
Pirbuterol	+	++++	5	4–8	2–4	Yes
Terbutaline	+	++++	4	4–8	2–4	Yes
Formoterol	+	++++	0.12	≥12	6–12	Yes
Salmeterol	+	++++	0.5	≥12	6–12	No

[a]Relative molar potency to isoproterenol: 15, lowest potency.
[b]Median durations with the highest value after a single dose and lowest after chronic administration.
[c]*Protection* refers to the prevention of bronchoconstriction induced by exercise or nonspecific bronchial challenges.

TABLE 77–2 Dosages of Drugs for Acute Severe Exacerbations of Asthma in the Emergency Department or Hospital

	Dosages		
Medications	**≥12 Years Old**	**<12 Years Old**	**Comments**
Inhaled β-agonists			
Albuterol nebulizer solution (5 mg/mL, 0.63 mg/3 mL, 1.25 mg/3 mL, 2.5 mg/3 mL)	2.5–5 mg every 20 min for three doses, then 2.5–10 mg every 1–4 hours as needed, or 10–15 mg/h continuously	0.15 mg/kg (minimum dose 2.5 mg) every 20 min for three doses, then 0.15–0.3 mg/kg up to 10 mg every 1–4 h as needed, or 0.5 mg/kg/h by continuous nebulization	Only selective β_2-agonists are recommended; for optimal delivery, dilute aerosols to minimum of 4 mL at gas flow of 6–8 L/min
Albuterol MDI (90 mcg/puff)	4–8 puffs every 30 minutes up to 4 h, then every 1–4 h as needed	4–8 puffs every 20 min for three doses, then every 1–4 h as needed	In patients in severe distress, nebulization is preferred
Levalbuterol nebulizer solution (0.31 mg/3 mL, 0.63 mg/3 mL, 2.5 mg/1 mL, 1.25 mg/3 mL	Give at one-half the mg dose of albuterol above	Give at one-half the mg dose of albuterol above	The single isomer of albuterol is twice as potent on a mg basis
Levalbuterol MDI (45 mcg/puff)	See albuterol MDI dose	See albuterol MDI dose	
Pirbuterol MDI (200 mcg/puff)	See albuterol dose	See albuterol dose; one-half as potent as albuterol on a mcg basis	Has not been studied in acute severe asthma
Systemic β-agonists			
Epinephrine 1:1000 (1 mg/mL)	0.3–0.5 mg every 20 min for three doses subcutaneously	0.01 mg/kg up to 0.5 mg every 20 min for three doses subcutaneously	No proven advantage of systemic therapy over aerosol
Terbutaline (1 mg/mL)	0.25 mg every 20 min for three doses subcutaneously	0.01 mg/kg every 20 min for three doses, then every 2–6 h as needed subcutaneously	Not recommended

Anticholinergics			
Ipratropium bromide nebulizer solution (0.25 mg/mL)	500 mcg every 30 min for three doses, then every 2–4 h as needed	250 mcg every 20 min for 3 doses, then 250 mcg every 2–4 h	May mix in same nebulizer with albuterol; do not use as first-line therapy; only add to β_2-agonist therapy
Ipratropium bromide MDI (18 mcg/puff)	8 puffs every 20 min as needed for up to 3 h	4–8 puffs every 20 min as needed for up to 3 h	
Corticosteroids			
Prednisone, methylprednisolone, prednisolone	40–80 mg/day in one or two divided doses until PEF reaches 70% of predicted or personal best	1–2 mg/kg/day in two divided doses (max 60 mg/day) until PEF is 70% of normal predicted	For outpatient "burst," use 1–2 mg/kg/day, (max 60 mg) for 3–10 days in children and 40–60 mg/day in one or two divided doses for 5–10 days in adults

FEV_1, forced expiratory volume in the first second of expiration; MDI, metered-dose inhaler; PEF, peak expiratory flow.

Note: No advantage has been found for very-high-dose corticosteroids in acute severe asthma, nor is there any advantage for IV administration over oral therapy. The usual regimen is to continue the oral corticosteroid for the duration of hospitalization. The final duration of therapy following a hospitalization or emergency department visit may be from 3 to 10 days. If the patient is then started on inhaled corticosteroids, there is no need to taper the systemic corticosteroid dose. The inhaled corticosteroids can be started at any time during the exacerbation.

- Inhaled β_2-agonists agents are the treatment of choice for EIB. Short-acting agents provide complete protection for at least 2 hours; long-acting agents provide significant protection for 8 to 12 hours initially, but duration decreases with chronic regular use.
- In nocturnal asthma, long-acting inhaled β_2-agonists are preferred over oral sustained-release β_2-agonists or sustained-release theophylline. However, nocturnal asthma may be an indicator of inadequate antiinflammatory treatment.

Corticosteroids

- Inhaled corticosteroids are the preferred long-term control therapy for persistent asthma because of potency and consistent effectiveness; they are the only therapy shown to reduce risk of dying from asthma. Comparative doses are included in **Table 77–3**. Most patients with moderate disease can be controlled with twice-daily dosing; some products have once-daily dosing indications. Patients with more severe disease require multiple daily dosing. Because inflammation inhibits steroid receptor binding, patients should be started on higher and more frequent doses and then tapered down once control has been achieved. Response to inhaled corticosteroids is delayed; symptoms improve in most patients within the first 1 to 2 weeks and reach maximum improvement in 4 to 8 weeks. Maximum improvement in FEV_1 and PEF rates may require 3 to 6 weeks.
- Systemic toxicity of inhaled corticosteroids is minimal with low to moderate doses, but risk of systemic effects increases with high doses. Local adverse effects include dose-dependent oropharyngeal candidiasis and dysphonia, which can be reduced by using a spacer device.
- Systemic corticosteroids (**Table 77–4**) are indicated in all patients with acute severe asthma not responding completely to initial inhaled β_2-agonist administration (every 20 min for 3 or 4 doses). Prednisone, 1 to 2 mg/kg/day (up to 40–60 mg/day), is administered orally in two divided doses for 3 to 10 days. Because short-term (1–2 week), high-dose systemic steroids do not produce serious toxicities, the ideal method is to use a short burst and then maintain appropriate long-term control therapy with inhaled corticosteroids.
- In patients who require chronic systemic corticosteroids for asthma control, the lowest possible dose should be used. Toxicities may be decreased by alternate-day therapy or high-dose inhaled corticosteroids.

Methylxanthines

- **Theophylline** appears to produce bronchodilation through nonselective phosphodiesterase inhibition. Methylxanthines are ineffective by aerosol and must be taken systemically (orally or IV). Sustained-release theophylline is the preferred oral preparation, whereas its complex with ethylenediamine (**aminophylline**) is the preferred parenteral product due to increased solubility. IV theophylline is also available.
- Theophylline is eliminated primarily by metabolism via hepatic CYP P450 enzymes (primarily CYP1A2 and CYP3A4) with less than or equal to10% excreted unchanged in urine. CYP P450 enzymes are susceptible to induction and inhibition by environmental factors and drugs. Significant reductions in clearance can result from cotherapy with cimetidine, erythromycin, clarithromycin, allopurinol, propranolol, ciprofloxacin, interferon, ticlopidine, zileuton, and other drugs. Some substances that enhance clearance are rifampin, carbamazepine, phenobarbital, phenytoin, charcoal-broiled meat, and cigarette smoking.
- Because of large interpatient variability in theophylline clearance, routine monitoring of serum theophylline concentrations is essential for safe and effective use. A steady-state range of 5 to 15 mcg/mL (27.75–83.25 µmol/L) is effective and safe for most patients.
- **Figure 77–3** gives recommended dosages, monitoring schedules, and dosage adjustments for theophylline.

TABLE 77–3 Available Inhaled Corticosteroid Products, Lung Delivery, and Comparative Daily Dosages

Inhaled Corticosteroids	Product	Lung Deliverya
Beclomethasone dipropionate (BDP)	40 and 80 mcg/actuation HFA MDI, 120 actuations	55%–60%
Budesonide (BUD)	90 or 180 mcg/dose DPI, Flexhaler, 200 doses	32% (15%–30%)
	200 and 500 mcg ampules, 2 mL each	5%–8%
Ciclesonide (CIC)	80 or 160 mcg/actuation HFA MDI	50%
Flunisolide (FLU)	250 mcg/actuation CFC MDI, 100 actuations	20%
	80 mcg/actuation HFA MDI, 120 actuations	68%
Fluticasone propionate (FP)	44, 110, and 220 mcg/actuation HFA MDI, 120 actuations	20%
	50, 100, and 250 mcg/dose DPI, Diskus, 60 doses	15%
Mometasone furoate (MF)	110 and 220 mcg/dose DPI, Twisthaler, 14, 30, 60, and 120 doses	11%

	Comparative Daily Dosages (mcg) of Inhaled Corticosteroids		
	Low Daily Dose Child[a]/Adult	**Medium Daily Dose Child[a]/Adult**	**High Daily Dose Child[a]/Adult**
BDP HFA MDI	80–160/80–240	>160–320/>240–480	>320/>480
BUD			
DPI	180–360/180–540	>360–720/>540–1,080	>720/>1080
Nebules	500/UK	1000/UK	2000/UK
CIC HFA MDI	80–160/160–320	>160–320/>320/640	>320/>640
FLU HFA MDI	160/320	320/320–640	≥640/>640
FP			
HFA MDI	88–176/88–264	176–352/264–440	>352/>440
DPIs	100–200/100–300	200–400/300–500	>400/>500
MF, DPI	110/220	220–440/440	>440/>400

DPI, dry-powder inhaler; HFA, hydrofluoroalkane; MDI, metered-dose inhaler; UK, unknown.

[a]Five to 11 years of age, except for BUD Nebules, which is 2 to 11 years of age.

TABLE 77–4 Comparison of Systemic Corticosteroids

Systemic	Anti-inflammatory Potency	Mineralocorticoid Potency	Duration of Biologic Activity (Hours)	Elimination Half-Life (Hours)
Hydrocortisone	1	1	8–12	1.5–2
Prednisone	4	0.8	12–36	2.5–3.5
Methylprednisolone	5	0.5	12–36	3.3
Dexamethasone	25	0	36–54	3.4–4

- Sustained-release oral preparations are preferred for outpatients, but each product has different release characteristics. Preparations unaffected by food that can be administered every 12 or 24 hours are preferable.
- Adverse effects include nausea, vomiting, tachycardia, jitteriness, and difficulty sleeping; more severe toxicities include cardiac tachyarrhythmias and seizures.
- Sustained-release theophylline is less effective than inhaled corticosteroids and no more effective than oral sustained-release β_2-agonists, cromolyn, or leukotriene antagonists.
- Addition of theophylline to optimal inhaled corticosteroids is similar to doubling the dose of the inhaled corticosteroid and is less effective overall than long-acting β_2-agonists as adjunctive therapy.

Anticholinergics

- **Ipratropium bromide** and **tiotropium bromide** produce bronchodilation only in cholinergic-mediated bronchoconstriction. Anticholinergics are effective bronchodilators but are not as effective as β_2-agonists. They attenuate but do not block allergen- or exercise-induced asthma in a dose-dependent fashion.

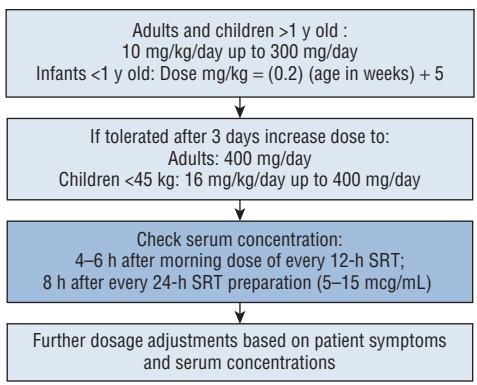


FIGURE 77–3. Algorithm for slow titration of theophylline dosage and guide for final dosage adjustment based on serum theophylline concentration measurement. For infants younger than 1 year of age, the initial daily dosage can be calculated by the following regression equation:

$$\text{Dose (mg/kg)} = (0.2)\,(\text{age in weeks}) + 5.$$

Whenever side effects occur, dosage should be reduced to a previously tolerated lower dose. (SRT, sustained-release theophylline.)

- Time to reach maximum bronchodilation from aerosolized ipratropium is longer than from aerosolized short-acting β_2-agonists (30–60 min vs 5–10 min). However, some bronchodilation is seen within 30 seconds, and 50% of maximum response occurs within 3 minutes. Ipratropium bromide has a duration of action of 4 to 8 hours; tiotropium bromide has a duration of 24 hours.
- Inhaled ipratropium bromide is only indicated as adjunctive therapy in severe acute asthma not completely responsive to β_2-agonists alone because it does not improve outcomes in chronic asthma. Studies of tiotropium bromide in asthma are ongoing.

Mast Cell Stabilizers

- **Cromolyn sodium** has beneficial effects that are believed to result from stabilization of mast cell membranes. It inhibits the response to allergen challenge as well as EIB but does not cause bronchodilation.
- Cromolyn is effective only by inhalation and is available as a nebulizer solution. Cough and wheezing have been reported after inhalation.
- Cromolyn is indicated for prophylaxis of mild persistent asthma in children and adults. Effectiveness is comparable to theophylline or leukotriene antagonists. It is not as effective as inhaled β_2-agonists for preventing EIB, but it can be used in conjunction for patients not responding completely to inhaled β_2-agonists.
- Most patients experience improvement in 1 to 2 weeks, but it may take longer to achieve maximum benefit. Patients should initially receive cromolyn four times daily; after stabilization of symptoms, the frequency may be reduced to three times daily.

Leukotriene Modifiers

- **Zafirlukast** (Accolate) and **montelukast** (Singulair) are oral leukotriene receptor antagonists that reduce the proinflammatory (increased microvascular permeability and airway edema) and bronchoconstriction effects of leukotriene D_4. In persistent asthma, they improve pulmonary function tests, decrease nocturnal awakenings and β_2-agonist use, and improve symptoms. However, they are less effective than low-dose inhaled corticosteroids. They are not used to treat acute exacerbations and must be taken on a regular basis, even during symptom-free periods. Adult zafirlukast dose is 20 mg twice daily, taken at least 1 hour before or 2 hours after meals; dose for children ages 5 through 11 years is 10 mg twice daily. Montelukast adult dose is 10 mg once daily, taken in the evening without regard to food; dose for children ages 6 to 14 years is one 5-mg chewable tablet daily in the evening.
- Rare elevations in serum aminotransferase concentrations and clinical hepatitis have been reported. An idiosyncratic syndrome similar to the Churg–Strauss syndrome, with marked circulating eosinophilia, heart failure, and associated eosinophilic vasculitis, has been reported rarely; a direct causal association has not been established.
- **Zileuton** (Zyflo) is a 5-lipoxygenase inhibitor; use is limited due to potential for elevated hepatic enzymes, especially in first 3 months of therapy, and inhibition of metabolism of some drugs metabolized by CYP3A4 (eg, theophylline and warfarin). Dose of zileuton tablets is 600 mg four times daily with meals and at bedtime. Dose of zileuton extended-release tablets is two 600-mg tablets twice daily, within 1 hour after morning and evening meals (total daily dose 2400 mg).

Combination Controller Therapy

- Addition of a second long-term control medication to inhaled corticosteroid therapy is one recommended treatment option in moderate to severe persistent asthma.
- Single-inhaler combination products containing fluticasone propionate and salmeterol (Advair) or budesonide and formoterol (Symbicort) are currently available. The inhalers contain varied doses of the inhaled corticosteroid with a fixed dose of the long-acting β_2-agonist. Addition of a long-acting β_2-agonist allows 50% reduction in inhaled corticosteroid dosage in most patients with persistent asthma. Combination therapy is more effective than higher-dose inhaled corticosteroids alone in reducing asthma exacerbations in patients with persistent asthma.

Omalizumab

- **Omalizumab** (Xolair) is an anti-IgE antibody approved for treatment of allergic asthma not well controlled by oral or inhaled corticosteroids. Dosage is determined by baseline total serum IgE (international units/mL) and body weight (kg). Doses range from 150 to 375 mg subcutaneously at either 2- or 4-week intervals.
- Because of high cost, omalizumab is only indicated as step 5 or 6 care for patients with allergies and severe persistent asthma inadequately controlled with combination of high-dose inhaled corticosteroids and long-acting β_2-agonists and at risk for severe exacerbations.
- Because of 0.2% incidence of anaphylaxis, observe patients for a reasonable period after injection because 70% of reactions occur within 2 hours. Some reactions have occurred up to 24 hours after injection.

EVALUATION OF THERAPEUTIC OUTCOMES

CHRONIC ASTHMA

- Asthma control involves reducing both impairment and risk domains. Regular follow-up is essential at 1- to 6-month intervals, depending on control.
- Components of assessment include symptoms, nighttime awakenings, interference with normal activities, pulmonary function, quality of life, exacerbations, adherence, treatment-related adverse effects, and satisfaction with care. Ask patients about exercise tolerance.
- Categories of well controlled, not well controlled, and very poorly controlled are recommended. Validated questionnaires can be administered regularly, such as Asthma Therapy Assessment Questionnaire, Asthma Control Questionnaire, and Asthma Control Test.
- Spirometric tests are recommended at initial assessment, after treatment is initiated, and then every 1 to 2 years. Peak flow monitoring is recommended in moderate to severe persistent asthma.
- All patients on inhaled drugs should have their inhalation technique evaluated monthly initially and then every 3 to 6 months.
- After initiation of antiinflammatory therapy or increase in dosage, most patients should experience decreased symptoms within 1 to 2 weeks and achieve maximum improvement within 4 to 8 weeks. Improvement in baseline FEV_1 or PEF should follow a similar time course, but decrease in BHR as measured by morning PEF, PEF variability, and exercise tolerance may take longer and improve over 1 to 3 months.

ACUTE SEVERE ASTHMA

- Patients at risk for acute severe exacerbations should monitor morning peak flows at home.
- Monitor lung function, either spirometry or peak flows, 5 to 10 minutes after each treatment. Monitoring of pulse oximetry, lung auscultation, and observation for supraclavicular retractions are useful.
- Most patients respond within the first hour of initial inhaled β-agonists. Monitor patients not achieving initial response every 0.5 to 1 hour.

See Chapter 15, Asthma, authored by H. William Kelly and Christine A. Sorkness, for a more detailed discussion of this topic.

CHAPTER 78

Chronic Obstructive Pulmonary Disease

- *Chronic obstructive pulmonary disease* (COPD) is characterized by progressive airflow limitation that is not fully reversible. Two principal conditions include:
  - ✓ *Chronic bronchitis*: chronic or recurrent excess mucus secretion with cough that occurs on most days for at least 3 months of the year for at least 2 consecutive years.
  - ✓ *Emphysema*: abnormal, permanent enlargement of the airspaces distal to the terminal bronchioles, accompanied by destruction of their walls, without fibrosis.

PATHOPHYSIOLOGY

- Chronic inflammatory changes lead to destructive changes and chronic airflow limitation. The most common cause is exposure to tobacco smoke.
- Inhalation of noxious particles and gases activates neutrophils, macrophages, and $CD8^+$ lymphocytes, which release chemical mediators, including tumor necrosis factor-α, interleukin-8, and leukotriene B_4. Inflammatory cells and mediators lead to widespread destructive changes in airways, pulmonary vasculature, and lung parenchyma.
- Oxidative stress and imbalance between aggressive and protective defense systems in the lungs (proteases and antiproteases) may also occur. Oxidants generated by cigarette smoke react with and damage proteins and lipids, contributing to tissue damage. Oxidants also promote inflammation and exacerbate protease–antiprotease imbalance by inhibiting antiprotease activity.
- The protective antiprotease α_1-antitrypsin (AAT) inhibits protease enzymes, including neutrophil elastase. In presence of unopposed AAT activity, elastase attacks elastin, a major component of alveolar walls. Hereditary AAT deficiency increases risk for premature emphysema. In emphysema from cigarette smoking, imbalance is associated with increased protease activity or reduced antiprotease activity.
- Inflammatory exudate in airways leads to increased number and size of goblet cells and mucus glands. Mucus secretion increases and ciliary motility is impaired. There is thickening of the smooth muscle and connective tissue in airways. Chronic inflammation leads to scarring and fibrosis. Diffuse airway narrowing occurs and is more prominent in small peripheral airways.
- Smoking-related COPD usually results in centrilobular emphysema that primarily affects respiratory bronchioles. Panlobular emphysema is seen in AAT deficiency and extends to the alveolar ducts and sacs.
- Vascular changes include thickening of pulmonary vessels that may lead to endothelial dysfunction of pulmonary arteries. Later, structural changes increase pulmonary pressures, especially during exercise. In severe COPD, secondary pulmonary hypertension leads to right-sided heart failure (cor pulmonale).

CLINICAL PRESENTATION

- Initial symptoms include chronic cough and sputum production; patients may have symptoms for several years before dyspnea develops.
- Physical examination is normal in most patients in milder stages. When airflow limitation becomes severe, patients may have cyanosis of mucosal membranes, development of a "barrel chest" due to hyperinflation of the lungs, increased resting respiratory rate, shallow breathing, pursing of lips during expiration, and use of accessory respiratory muscles.
- Patients experiencing COPD exacerbation may have worsening dyspnea, increased sputum volume, or increased sputum purulence. Other features of exacerbation include chest tightness, increased need for bronchodilators, malaise, fatigue, and decreased exercise tolerance.

DIAGNOSIS

- Diagnosis is based in part on patient symptoms and history of exposure to risk factors such as tobacco smoke and occupational substances.
- Classification of disease severity is based on assessment of airflow limitation by spirometry, measurement of symptom severity, and assessment of exacerbation frequency. Symptom severity is assessed by the COPD Assessment Test (CAT) or the modified Medical Research Council (mMRC) scale. Patients are first classified according to severity of airflow obstruction (Grades 1–4) and then placed into a Group (A, B, C, or D) based on the impact of symptoms and risk for future exacerbations.

SPIROMETRY

- Spirometry is the standard for assessing airflow limitation. The forced expiratory volume after 1 second (FEV_1) is reduced except in very mild disease. The forced vital capacity (FVC) may also be decreased. The hallmark of COPD is reduced FEV_1:FVC ratio to less than 70%. A postbronchodilator FEV_1 less than 80% of predicted confirms the presence of airflow limitation that is not fully reversible. Improvement in FEV_1 of less than 12% after inhalation of a rapid-acting bronchodilator is evidence of irreversible airflow obstruction.

ARTERIAL BLOOD GASES

- Significant changes in arterial blood gases (ABG) are not usually present until FEV_1 is less than 1 L. At this stage, hypoxemia and hypercapnia may become chronic. Hypoxemia usually occurs initially with exercise but develops at rest as the disease progresses.
- Patients with severe COPD can have low arterial oxygen tension (partial pressure of O_2 [Pao_2] 45–60 mm Hg) and elevated arterial carbon dioxide tension (partial pressure of CO_2 [$Paco_2$] 50–60 mm Hg). Hypoxemia results from hypoventilation (V) of lung tissue relative to perfusion (Q). The low V:Q ratio progresses over several years, resulting in a decline in Pao_2.
- Some patients lose ability to increase rate or depth of respiration in response to persistent hypoxemia. This decreased ventilatory drive may be due to abnormal peripheral or central respiratory receptor responses. Relative hypoventilation leads to hypercapnia; in this situation, the central respiratory response to chronically increased $Paco_2$ can be blunted. Because changes in Pao_2 and $Paco_2$ are subtle and progress over many years, the pH is usually near normal because the kidneys compensate by retaining bicarbonate.
- If acute respiratory distress develops (eg, due to pneumonia or COPD exacerbation), $Paco_2$ may rise sharply, resulting in uncompensated respiratory acidosis.

DIAGNOSIS OF ACUTE RESPIRATORY FAILURE IN CHRONIC OBSTRUCTIVE PULMONARY DISEASE

- Diagnosis of acute respiratory failure is based on acute drop in Pao_2 of 10–15 mm Hg or any acute increase in $Paco_2$ that decreases serum pH to less than or equal to 7.3.
- Acute manifestations include restlessness, confusion, tachycardia, diaphoresis, cyanosis, hypotension, irregular breathing, miosis, and unconsciousness.
- The most common cause of acute respiratory failure is acute exacerbation of bronchitis with increased sputum volume and viscosity. This worsens obstruction and further impairs alveolar ventilation, thereby worsening hypoxemia and hypercapnia.

TREATMENT

- Goals of Treatment: Prevent or minimize disease progression, relieve symptoms, improve exercise tolerance, improve health status, prevent and treat exacerbations, prevent and treat complications, and reduce morbidity and mortality.

NONPHARMACOLOGIC THERAPY

- Smoking cessation is the only intervention proven to affect long-term decline in FEV_1 and slow COPD progression.
- Pulmonary rehabilitation programs include exercise training, breathing exercises, optimal medical treatment, psychosocial support, and health education.
- Administer vaccinations as appropriate (eg, pneumococcal vaccine, annual influenza vaccine).
- Once patients are stabilized as outpatients and pharmacotherapy is optimized, institute long-term oxygen therapy if either (1) resting Pao_2 less than 55 mm Hg or SaO_2 less than 88% with or without hypercapnia, or (2) resting Pao_2 55 to 60 mm Hg or SaO_2 less than 88% with evidence of right-sided heart failure, polycythemia, or pulmonary hypertension. The goal is to raise PaO_2 above 60 mm Hg.

PHARMACOLOGIC THERAPY

- An approach to initial pharmacotherapy of stable COPD based on combined assessment of airflow limitation, symptom severity, and risk of exacerbations is shown in **Table 78–1**. Treat patients with intermittent symptoms and low risk for exacerbations (Group A) with short-acting inhaled bronchodilators as needed. When symptoms become more persistent (Group B), initiate long-acting inhaled bronchodilators. For patients at high risk for exacerbations (Groups C and D), consider inhaled corticosteroids.
- Short-acting inhaled bronchodilators (β_2-agonists or anticholinergics) are initial therapy for patients with intermittent symptoms; they relieve symptoms and increase exercise tolerance.
- Long-acting inhaled bronchodilators (β_2-agonists [LABA] or anticholinergics) are recommended for moderate to severe COPD when symptoms occur on a regular basis or when short-acting agents provide inadequate relief. They relieve symptoms, reduce exacerbation frequency, and improve quality of life and health status.

Sympathomimetics

- β_2-Selective sympathomimetics cause relaxation of bronchial smooth muscle and bronchodilation and may also improve mucociliary clearance. Administration via metered-dose inhaler (MDI) or dry-powder inhaler (DPI) is at least as effective as nebulization therapy and is usually favored because of cost and convenience.
- **Albuterol, levalbuterol, bitolterol, pirbuterol**, and **terbutaline** are preferred short-acting agents because they have greater β_2 selectivity and longer durations of action than other short-acting agents (isoproterenol, metaproterenol, isoetharine). Inhalation is preferred over oral and parenteral administration in terms of efficacy and adverse effects.
- Short-acting agents can be used for acute relief of symptoms or on a scheduled basis to prevent or reduce symptoms. Duration of action is 4 to 6 hours.
- **Salmeterol**, **formoterol**, and **arformoterol** are LABAs that are dosed every 12 hours on a scheduled basis and provide bronchodilation throughout the dosing interval. **Indacaterol** is an ultra-long-acting agent that requires only once-daily dosing. In addition to providing greater convenience for patients with persistent symptoms, LABAs produce superior outcomes in terms of lung function, symptom relief, reductions in exacerbation frequency, and quality of life when compared with short-acting β_2-agonists. These agents are not recommended for acute relief of symptoms.

Anticholinergics

- When given by inhalation, anticholinergics produce bronchodilation by competitively inhibiting cholinergic receptors in bronchial smooth muscle.
- **Ipratropium bromide** is the primary short-acting anticholinergic agent used for COPD. It has a slower onset of action than short-acting β_2-agonists (15–20 min vs 5 min for albuterol). It may be less suitable for as-needed use, but it is often

TABLE 78–1 Initial Pharmacologic Management of COPD[a]

Patient Group	Recommended First Choice	Alternative Choice	Other Possible Treatments[b]
A	Short-acting anticholinergic prn *or* Short-acting beta$_2$-agonist prn	Long-acting anticholinergic *or* Long-acting beta$_2$-agonist *or* Short-acting beta$_2$-agonist and short-acting anticholinergic	Theophylline
B	Long-acting anticholinergic *or* Long-acting beta$_2$-agonist	Long-acting anticholinergic and long-acting beta$_2$-agonist	Short-acting beta$_2$-agonist *and/or* Short-acting anticholinergic Theophylline
C	Inhaled corticosteroid + long-acting beta$_2$-agonist *or* Long-acting anticholinergic	Long-acting anticholinergic and long-acting beta$_2$-agonist *or* Long-acting anticholinergic and phosphodiesterase-4 inhibitor *or* Long-acting beta$_2$-agonist and phosphodiesterase-4 inhibitor	Short-acting beta$_2$-agonist *and/or* Short-acting anticholinergic Theophylline

D	Inhaled corticosteroid + long-acting $beta_2$-agonist *and/or* Long-acting anticholinergic	Inhaled corticosteroid + long-acting $beta_2$-agonist and long-acting anticholinergic *or* Inhaled corticosteroid + long-acting $beta_2$-agonist and phosphodiesterase-4 inhibitor *or* Long-acting anticholinergic and long-acting $beta_2$-agonist *or* Long-acting anticholinergic and phosphodiesterase-4 inhibitor	Carbocysteine Short-acting $beta_2$-agonist *and/or* Short-acting anticholinergic Theophylline

[a]Medications in each box are mentioned In alphabetical order, and therefore not necessarily in order of preference
[b]Medications in this column can be used alone or in combination with other options in the Recommended First Choice and Alternative Choice columns

(Reprinted with permission from the Global Strategy for the Diagnosis, Management and Prevention of COPD, Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2013. Available from http://www.goldcopd.com.

prescribed in this manner. Ipratropium has a more prolonged effect than short-acting β_2-agonists. Its peak effect occurs in 1.5 to 2 hours, and its duration is 4 to 6 hours. The recommended dose via MDI is two puffs four times daily with upward titration often to 24 puffs/day. It is also available as a solution for nebulization. The most frequent patient complaints are dry mouth, nausea, and, occasionally, metallic taste. Because it is poorly absorbed systemically, anticholinergic side effects are uncommon (eg, blurred vision, urinary retention, nausea, and tachycardia).

- **Tiotropium bromide** is a long-acting agent that protects against cholinergic bronchoconstriction for more than 24 hours. Its onset of effect is within 30 minutes, with a peak effect in 3 hours. The recommended dose is inhalation of the contents of one capsule (18 mcg) once daily using the HandiHaler, a single-load, dry-powder, breath-actuated device. Because it acts locally, tiotropium is well tolerated; the most common complaint is dry mouth. Other anticholinergic effects have also been reported.
- **Aclidinium bromide** is a long-acting agent administered twice daily using the PressAir DPI multi-dose device.

Combination Anticholinergics and Sympathomimetics

- Combination of an inhaled anticholinergic and β_2-agonist is often used, especially as the disease progresses and symptoms worsen. Combinations allow the lowest effective doses to be used and reduce adverse effects from individual agents. Combination of both short- and long-acting β_2-agonists with ipratropium provides added symptomatic relief and improvements in pulmonary function.
- **Combivent** contains **albuterol** and **ipratropium** in an MDI for maintenance therapy of COPD.

Methylxanthines

- **Theophylline** and **aminophylline** produce bronchodilation by inhibiting phosphodiesterase and other mechanisms.
- Chronic theophylline use in COPD improves lung function, including vital capacity and FEV_1. Subjectively, theophylline reduces dyspnea, increases exercise tolerance, and improves respiratory drive.
- Methylxanthines have a very limited role in COPD therapy because of drug interactions and interpatient variability in dosage requirements. Theophylline may be considered in patients intolerant of or unable to use inhaled bronchodilators. It may also be added to the regimen of patients not achieving optimal response to inhaled bronchodilators.
- Subjective parameters, such as perceived improvements in dyspnea and exercise tolerance, are important in assessing acceptability of methylxanthines for COPD patients.
- Sustained-release theophylline preparations improve adherence and achieve more consistent serum concentrations than rapid-release products. Caution should be used in switching from one sustained-release preparation to another because of variations in sustained-release characteristics.
- Initiate therapy with 200 mg twice daily and titrated upward every 3 to 5 days to the target dose; most patients require 400 to 900 mg daily.
- Make dose adjustments based on trough serum concentrations. A therapeutic range of 8 to 15 mcg/mL (44.4–83.3 μmol/L) is often targeted to minimize risk of toxicity. Once a dose is established, monitor concentrations once or twice a year unless the disease worsens, medications that interfere with theophylline metabolism are added, or toxicity is suspected.
- Common theophylline side effects include dyspepsia, nausea, vomiting, diarrhea, headache, dizziness, and tachycardia. Arrhythmias and seizures may occur, especially at toxic concentrations.
- Factors that may decrease theophylline clearance and lead to reduced dosage requirements include advanced age, bacterial or viral pneumonia, heart failure, liver dysfunction, hypoxemia from acute decompensation, and drugs such as cimetidine, macrolides, and fluoroquinolone antibiotics.

- Factors that may enhance theophylline clearance and result in need for higher doses include tobacco and marijuana smoking, hyperthyroidism, and drugs such as phenytoin, phenobarbital, and rifampin.

Corticosteroids

- Corticosteroids reduce capillary permeability to decrease mucus, inhibit release of proteolytic enzymes from leukocytes, and inhibit prostaglandins.
- Appropriate situations for corticosteroids in COPD include (1) short-term systemic use for acute exacerbations and (2) inhalation therapy for chronic stable COPD. Chronic systemic corticosteroids should be avoided in COPD management because of questionable benefits and high risk of toxicity.
- Inhaled corticosteroid therapy may be beneficial in patients with severe COPD at high risk of exacerbation (Groups C and D) who are not controlled with inhaled bronchodilators.
- Side effects of inhaled corticosteroids are mild and include hoarseness, sore throat, oral candidiasis, and skin bruising. Severe side effects such as adrenal suppression, osteoporosis, and cataract formation occur less frequently than with systemic corticosteroids, but clinicians should monitor patients receiving high-dose chronic inhaled therapy.
- Combination of inhaled corticosteroids and long-acting bronchodilators (fluticasone plus salmeterol or budesonide plus formoterol) is associated with greater improvements in FEV_1, health status, and exacerbation frequency than either agent alone. Availability of combination inhalers makes administration of both drugs convenient and decreases the total number of inhalations needed daily.

Phosphodiesterase Inhibitors

- **Roflumilast** is a phosphodiesterase 4 (PDE4) indicated to reduce risk of exacerbations in patients with severe COPD associated with chronic bronchitis and a history of exacerbations.
- The dose is 500 mcg orally once daily, with or without food. Major adverse effects include weight loss and neuropsychiatric effects such as suicidal thoughts, insomnia, anxiety and new or worsened depression.
- Roflumilast is metabolized by CYP3A4 and 1A2; co-administration with strong CYP P450 inducers is not recommended due to potential for subtherapeutic plasma concentrations. Use caution when administering roflumilast with strong CYP P450 inhibitors due to potential for adverse effects.
- Roflumilast may be beneficial in patients with severe or very severe COPD who are at high risk of exacerbation (Group C and D) and are not controlled by inhaled bronchodilators. It may also be considered for patients who are intolerant or unable to use inhaled bronchodilators or corticosteroids. Roflumilast is not recommended for use with theophylline because the drugs share similar mechanisms.

TREATMENT OF COPD EXACERBATIONS

- Goals of Treatment: The goals are to 1) prevent hospitalization or reduce length of hospital stay, 2) prevent acute respiratory failure and death, 3) resolve symptoms, and 4) return to baseline clinical status and quality of life.

NONPHARMACOLOGIC THERAPY

- Consider oxygen therapy for patients with hypoxemia. Use caution because many COPD patients rely on mild hypoxemia to trigger their drive to breathe. Overly aggressive oxygen administration to patients with chronic hypercapnia may result in respiratory depression and respiratory failure. Adjust oxygen to achieve PaO_2 greater than 60 mm Hg or oxygen saturation (SaO_2) greater than 90%. Obtain ABG after oxygen initiation to monitor CO_2 retention resulting from hypoventilation.

- Noninvasive positive-pressure ventilation (NPPV) provides ventilatory support with oxygen and pressurized airflow using a face or nasal mask without endotracheal intubation. NPPV is not appropriate for patients with altered mental status, severe acidosis, respiratory arrest, or cardiovascular instability. Intubation and mechanical ventilation may be needed in patients failing NPPV or who are poor candidates for NPPV.

PHARMACOLOGIC THERAPY

Bronchodilators

- Dose and frequency of bronchodilators are increased during acute exacerbations to provide symptomatic relief. Short-acting β_2-agonists are preferred because of rapid onset of action. Anticholinergic agents may be added if symptoms persist despite increased doses of β_2-agonists.
- Bronchodilators may be administered via MDIs or nebulization with equal efficacy. Nebulization may be considered for patients with severe dyspnea who are unable to hold their breath after actuation of an MDI.
- Theophylline should generally be avoided due to lack of evidence documenting benefit. It may be considered for patients not responding to other therapies.

Corticosteroids

- Patients with acute COPD exacerbations may receive a short course of IV or oral corticosteroids. Although optimal dose and duration are unknown, prednisone 40 mg orally daily (or equivalent) for 10 to 14 days can be effective for most patients.
- If treatment is continued for longer than 2 weeks, employ a tapering oral schedule because of hypothalamic-pituitary-adrenal axis suppression.

Antimicrobial Therapy

- Antibiotics are of most benefit and should be initiated if at least two of the following three symptoms are present: 1) increased dyspnea, 2) increased sputum volume, and 3) increased sputum purulence. Utility of sputum Gram stain and culture is questionable because some patients have chronic bacterial colonization of the bronchial tree between exacerbations.
- Selection of empiric antimicrobial therapy should be based on the most likely organisms: *Haemophilus influenzae, Moraxella catarrhalis, Streptococcus pneumoniae*, and *Haemophilus. parainfluenzae*.
- Initiate therapy within 24 hours of symptoms to prevent unnecessary hospitalization and generally continue for at least 7 to 10 days. Five-day courses with some agents may produce comparable efficacy.
- In uncomplicated exacerbations, recommended therapy includes a **macrolide** (**azithromycin** or **clarithromycin**), **second- or third-generation cephalosporin**, or **doxycycline**. Avoid trimethoprim–sulfamethoxazole because of increasing pneumococcal resistance. Amoxicillin and first-generation cephalosporins are not recommended because of β-lactamase susceptibility. Erythromycin is not recommended because of insufficient activity against *H. influenzae*.
- In complicated exacerbations where drug-resistant pneumococci, β-lactamase-producing *H. influenzae* and *M. catarrhalis*, and some enteric gram-negative organisms may be present, recommended therapy includes **amoxicillin/clavulanate** or a fluoroquinolone with enhanced pneumococcal activity (**levofloxacin, gemifloxacin**, or **moxifloxacin**).
- In complicated exacerbations with risk of *Pseudomonas aeruginosa*, recommended therapy includes a fluoroquinolone with enhanced pneumococcal and *P. aeruginosa* activity (**levofloxacin**). If IV therapy is required, a β-lactamase-resistant penicillin with antipseudomonal activity or a third- or fourth-generation cephalosporin with antipseudomonal activity should be used.

EVALUATION OF THERAPEUTIC OUTCOMES

- In chronic stable COPD, assess pulmonary function tests with any therapy addition, change in dose, or deletion of therapy. Other outcome measures are dyspnea score, quality-of-life assessments, and exacerbation rates (including emergency department visits and hospitalizations).
- In acute exacerbations of COPD, assess white blood cell count, vital signs, chest radiograph, and changes in frequency of dyspnea, sputum volume, and sputum purulence at the onset and throughout the exacerbation. In more severe exacerbations, ABG and SaO_2 should also be monitored.
- Evaluate patient adherence, side effects, potential drug interactions, and subjective measures of quality of life.

See Chapter 16, Chronic Obstructive Pulmonary Disease, authored by Sharya V. Bourdet and Dennis M. Williams, for a more detailed discussion of this topic.

This page intentionally left blank

Edited by Cecily V. DiPiro

CHAPTER 79

Benign Prostatic Hyperplasia

- *Benign prostatic hyperplasia* (BPH), a nearly ubiquitous condition, is the most common benign neoplasm of American men.

PATHOPHYSIOLOGY

- Three types of prostate gland tissue: epithelial or glandular, stromal or smooth muscle, and capsule. Both stromal tissue and capsule are embedded with α_1-adrenergic receptors.
- The precise pathophysiologic mechanisms that cause BPH are not clear. Both intraprostatic dihydrotestosterone (DHT) and type II 5α-reductase are thought to be involved.
- BPH commonly results from both static (gradual enlargement of the prostate) and dynamic (agents or situations that increase α-adrenergic tone and constrict the gland's smooth muscle) factors. Examples of drugs that can exacerbate symptoms include testosterone, α-adrenergic agonists (eg, decongestants), and those with significant anticholinergic effects (eg, antihistamines, phenothiazines, tricyclic antidepressants, antispasmodics, and antiparkinsonian agents).

CLINICAL PRESENTATION

- Patients present with a variety of signs and symptoms categorized as obstructive or irritative. Symptoms vary over time.
- Obstructive signs and symptoms result when dynamic and/or static factors reduce bladder emptying. Patients experience urinary hesitancy, urine dribbles out of the penis, and the bladder feels full even after voiding.
- Irritative signs and symptoms are common and result from long-standing obstruction at the bladder neck. Patients experience urinary frequency, urgency, and nocturia.
- BPH progression may produce complications including chronic kidney disease, gross hematuria, urinary incontinence, recurrent urinary tract infection, bladder diverticula, and bladder stones.

DIAGNOSIS

- Includes careful medical history, physical examination, objective measures of bladder emptying (eg, peak and average urinary flow rate and postvoid residual [PVR] urine volume), and laboratory tests (eg, urinalysis and prostate-specific antigen [PSA]).
- On digital rectal examination, the prostate is usually but not always enlarged (>20 g), soft, smooth, and symmetric.

TREATMENT

- Goals of Treatment: The goals are to control symptoms, prevent progression of complications, and delay need for surgical intervention.
- Management options include watchful waiting, drug therapy, and surgical intervention. The choice depends on severity of signs and symptoms (**Table 79–1**).

TABLE 79–1 Categories of BPH Disease Severity Based on Symptoms and Signs

Disease Severity	AUA Symptom Score	Typical Symptoms and Signs
Mild	≤7	Asymptomatic Peak urinary flow rate <10 mL/s PVR urine volume >25–50 mL
Moderate	8–19	All of the above signs plus obstructive voiding symptoms and irritative voiding symptoms (signs of detrusor instability)
Severe	≥20	All of the above plus one or more complications of BPH

AUA, American Urological Association; BPH, benign prostatic hyperplasia; PVR, postvoid residual.

- Watchful waiting is appropriate for patients with mild disease (**Fig. 79–1**). Patients are reassessed at 6 to 12 month intervals and educated about behavior modification, such as fluid restriction before bedtime, avoiding caffeine and alcohol, frequent emptying of the bladder, and avoiding drugs that exacerbate symptoms.

PHARMACOLOGIC THERAPY

- Pharmacologic therapy is appropriate for patients with moderate BPH symptoms and as an interim measure for patients with severe BPH.
- Pharmacologic therapy interferes with the stimulatory effect of testosterone on prostate gland enlargement (reduces the static factor), relaxes prostatic smooth muscle (reduces the dynamic factor), or relaxes bladder detrusor muscle (**Table 79–2**).
- Initiate therapy with an α_1-adrenergic antagonist for faster onset of symptom relief. Select a 5α-reductase inhibitor in patients with a prostate gland more than 40 g. Consider combination therapy for symptomatic patients with a prostate gland more than 40 g and PSA of 1.4 ng/mL or more (1.4 mcg/L).
- Consider monotherapy with a phosphodiesterase inhibitor or use in combination with an α-adrenergic antagonist when erectile dysfunction and BPH are present.
- Agents that interfere with androgen stimulation of the prostate are not popular in the United States because of adverse effects. Luteinizing hormone–releasing hormone agonists **leuprolide** and **goserelin** decrease libido and can cause erectile dysfunction, gynecomastia, and hot flashes. Antiandrogens **bicalutamide** and **flutamide** cause nausea, diarrhea, and hepatotoxicity.

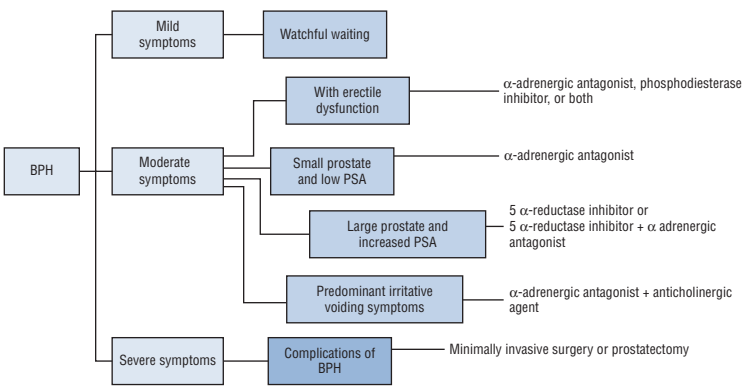


FIGURE 79–1. Management algorithm for benign prostatic hyperplasia (BPH).

TABLE 79–2 Medical Treatment Options for Benign Prostatic Hyperplasia

Category	Mechanism	Drug (Brand Name)
Reduces dynamic factor	Blocks α_1-adrenergic receptors in prostatic stromal tissue	Prazosin (Minipress)
		Alfuzosin (Uroxatral)
		Terazosin (Hytrin)
		Doxazosin (Cardura)
	Blocks α_{1A}-receptors in the prostate	Tamsulosin (Flomax)
		Silodosin (Rapaflo)
	Causes smooth muscle relaxation of prostate, bladder neck, and prostatic urethra	Tadalafil (Cialis)
Reduce static factor	Blocks 5α-reductase enzyme	Finasteride (Proscar)
	Blocks dihydrotestosterone at its intracellular receptor	Dutasteride (Avodart)
		Bicalutamide (Casodex)[a]
	Blocks pituitary release of luteinizing hormone	Flutamide (Eulexin)[a]
		Leuprolide (Lupron)[a]
	Blocks pituitary release of luteinizing hormone and blocks androgen receptor	Goserelin (Zoladex)[a]
		Megestrol acetate (Megace)[a]
Other	Relaxes detrusor muscle of bladder	Tolterodine (Detrol)
		Oxybutynin (Ditropan)
		Trospium (Sanctura)
		Solifenacin (Vesicare)
		Darifenacin (Enablex)
		Fesoterodine (Toviaz)

[a]Not FDA approved for treatment of BPH.

α-Adrenergic Antagonists

- α-Adrenergic antagonists relax smooth muscle in the prostate and bladder neck, increasing urinary flow rates by 2 to 3 mL/sec in 60% to 70% of patients and reducing PVR urine volumes.
- α_1-Adrenergic antagonists do not decrease prostate volume or PSA levels.
- **Prazosin, terazosin, doxazosin**, and **alfuzosin** are second-generation α_1-adrenergic antagonists. They antagonize peripheral vascular α_1-adrenergic receptors in addition to those in the prostate. Adverse effects include first-dose syncope, orthostatic hypotension, and dizziness. Alfuzosin is less likely to cause cardiovascular adverse effects than other second-generation agents.
- Slowly titrate to a maintenance dose at bedtime to minimize orthostatic hypotension and first-dose syncope with immediate-release formulations of terazosin and doxazosin. Sample titration schedules for terazosin include:

Titration Schedules	
Terazosin Slow	**Terazosin Quicker**
Days 1–3: 1 mg at bedtime	Days 1–3: 1 mg at bedtime
Days 4–14: 2 mg at bedtime	Days 4–14: 2 mg at bedtime
Weeks 2–6: 5 mg at bedtime	Weeks 2–3: 5 mg at bedtime
Weeks 7 and on: 10 mg at bedtime	Weeks 4 and on: 10 mg at bedtime

- **Tamsulosin** and **silodosin**, third-generation α_1-adrenergic antagonists, are selective for prostatic α_{1A}-receptors. Therefore, they do not cause peripheral vascular smooth muscle relaxation and associated hypotension.
- Tamsulosin is a good choice for patients who cannot tolerate hypotension; has severe coronary artery disease, volume depletion, cardiac arrhythmias, severe orthostasis, or liver failure; or are taking multiple antihypertensives. Tamsulosin is also suitable for patients who want to avoid the delay of dose titration.
- Potential drug interactions include decreased metabolism of α_1-adrenergic antagonists with CYP 3A4 inhibitors **(**eg, **cimetidine** and **diltiazem)** and increased catabolism of α_1-adrenergic antagonists with concurrent use of CYP 3A4 stimulators (eg, **carbamazepine** and **phenytoin).**
- Reduce the dose of silodosin in patients with moderate renal impairment or hepatic dysfunction.

5α-Reductase Inhibitors

- 5α-Reductase inhibitors interfere with the stimulatory effect of testosterone. These agents slow disease progression and decrease the risk of complications.
- Compared with α_1-adrenergic antagonists, disadvantages of 5α-reductase inhibitors include 6 months of use to maximally shrink prostate, less likely to induce objective improvement and more sexual dysfunction.
- Whether the pharmacodynamic advantages of **dutasteride** confer clinical advantages over **finasteride** is unknown. Dutasteride inhibits types I and II 5α-reductase, whereas finasteride inhibits only type II. Dutasteride more quickly and completely suppresses intraprostatic DHT (vs 80%–90% for finasteride) and decreases serum DHT by 90% (vs 70%).
- 5α-Reductase inhibitors may be preferred in patients with uncontrolled arrhythmias, poorly controlled angina, use multiple antihypertensives, or cannot tolerate hypotensive effects of α_1-adrenergic antagonists.
- Measure PSA at baseline and again after 6 months of therapy. If PSA does not decrease by 50% after 6 months of therapy in a compliant patient, evaluate the patient for prostate cancer.
- 5α-Reductase inhibitors are in FDA pregnancy category X and are therefore contraindicated in pregnant women. Pregnant and potentially pregnant women should not handle the tablets or have contact with semen from men taking 5α-reductase inhibitors.

Phosphodiesterase Inhibitors

- Increase in cyclic GMP by phosphodiesterase inhibitors (PI) may relax smooth muscle in prostate and bladder neck. Effectiveness may be result of direct relaxation of detrusor muscle of bladder.
- **Tadalafil** 5 mg daily improves voiding symptoms but does not increase urinary flow rate or reduce PVR urine volume. Combination therapy with α-adrenergic antagonist results in significant improvement in lower urinary tract symptoms, increased urinary flow rates, and decreased PVR volume.

Anticholinergic Agents

- Addition of **oxybutynin** and **tolterodine** to α-adrenergic antagonists relieves irritative voiding symptoms including urinary frequency, urgency, and nocturia. Start with lowest effective dose to determine tolerance of CNS adverse effects and dry mouth. Measure PVR urine volume before initiating treatment (should be less than 250 mL).
- If systemic anticholinergic adverse effects are poorly tolerated, consider transdermal or extended-release formulations or uroselective agents (eg, **darifenacin** or **solifenacin**).

SURGICAL INTERVENTION

- Prostatectomy, performed transurethrally or suprapubically, is the gold standard for treatment of patients with moderate or severe symptoms of BPH and for all patients with complications.
- Retrograde ejaculation complicates up to 75% of transurethral prostatectomy procedures. Other complications seen in 2% to 15% of patients are bleeding, urinary incontinence, and erectile dysfunction.

PHYTOTHERAPY

- Although widely used in Europe for BPH, phytotherapy with products such as saw palmetto berry (*Serenoa repens*), stinging nettle (*Urtica dioica*), and African plum (*Pygeum africanum*) should be avoided. Studies are inconclusive, and the purity of available products is questionable.

EVALUATION OF THERAPEUTIC OUTCOMES

- The primary therapeutic outcome of BPH therapy is restoring adequate urinary flow without causing adverse effects.
- Outcome depends on the patient's perception of effectiveness and acceptability of therapy. The American Urological Association Symptom Score is a validated standardized instrument that can be used to assess patient quality of life.
- Objective measures of bladder emptying (eg, urinary flow rate and PVR urine volume) are useful measures in patients considering surgery.
- Monitor laboratory tests (eg, blood urea nitrogen, creatinine, and PSA) and urinalysis regularly. An annual digital rectal examination is recommended if life expectancy is at least 10 years.

See Chapter 67, Benign Prostatic Hyperplasia, authored by Mary Lee, for a more detailed discussion of this topic.

Erectile Dysfunction

CHAPTER 80

- *Erectile dysfunction* (ED) is the persistent failure (minimum of 3 months) to achieve a penile erection suitable for sexual intercourse. Patients often refer to it as impotence.

PATHOPHYSIOLOGY

- ED can result from an abnormality in one of the four systems necessary for a normal penile erection or from a combination of abnormalities. Vascular, nervous, or hormonal etiologies of ED are referred to as organic ED. Abnormality of the fourth system (ie, patient's psychological receptivity to sexual stimuli) is referred to as psychogenic ED.
- The penis has two corpora cavernosa and one corpus spongiosum which contain interconnected sinuses that fill with blood to produce an erection.
- Acetylcholine works with other neurotransmitters (ie, cyclic guanylate monophosphate, cyclic adenosine monophosphate, and vasoactive intestinal polypeptide) to produce penile arterial vasodilation and ultimately an erection.
- Organic ED is associated with diseases that compromise vascular flow to the corpora cavernosum (eg, peripheral vascular disease, arteriosclerosis, and essential hypertension), impair nerve conduction to the brain (eg, spinal cord injury and stroke), or impair peripheral nerve conduction (eg, diabetes mellitus). Secondary ED is associated with hypogonadism.
- Psychogenic ED is associated with malaise, reactive depression or performance anxiety, sedation, Alzheimer disease, hypothyroidism, and mental disorders. Patients with psychogenic ED generally have a higher response rate to interventions than those with organic ED.
- Social habits (eg, cigarette smoking and excessive ethanol intake) and medications (**Table 80–1**) can also cause ED.

CLINICAL PRESENTATION

- Signs and symptoms of ED can be difficult to detect. The patient's partner is often the first to report ED to the healthcare provider.
- Nonadherence to drugs thought to cause ED can be a sign of ED.

DIAGNOSIS

- Key diagnostic assessments include ED severity, medical and surgical history, concurrent medications, physical examination, and laboratory tests (ie, serum blood glucose, lipid profile, and testosterone level).
- Assess the severity of ED with a standardized questionnaire.
- Complete a cardiovascular risk assessment before initiating ED therapy in men older than 50 years and in those at intermediate and high risk for cardiovascular disease.

TREATMENT

- Goal of Treatment: The goal is to improve the quantity and quality of penile erections suitable for intercourse.
- The first step in management of ED is to identify and, if possible, reverse underlying causes. Psychotherapy can be used as monotherapy for psychogenic ED or as an adjunct to specific treatments.
- Treatment options include vacuum erection devices (VEDs), drugs (**Table 80–2**), and surgery. Although no option is ideal, the least invasive options are chosen first (**Fig. 80–1**).

TABLE 80–1 Medication Classes That Can Cause Erectile Dysfunction

Drug Class	Proposed Mechanism by Which Drug Causes Erectile Dysfunction	Special Notes
Anticholinergic agents (antihistamines, antiparkinsonian agents, tricyclic antidepressants, phenothiazines)	Anticholinergic activity	• Second-generation nonsedating antihistamines (eg, loratadine, fexofenadine, or cetirizine) are associated with less erectile dysfunction (ED) than first-generation agents. • Selective serotonin reuptake inhibitor (SSRI) antidepressants cause less ED than tricyclic antidepressants. Of the SSRIs, paroxetine, sertraline, and fluoxetine cause ED more commonly than venlafaxine, nefazodone, trazodone, or mirtazapine. • Phenothiazines with less anticholinergic effect (eg, chlorpromazine) can be substituted in some patients if ED is a problem.
Dopamine antagonists (eg, metoclopramide, phenothiazines)	Inhibit prolactin inhibitory factor, thereby increasing prolactin levels	• Increased prolactin levels inhibit testicular testosterone production; depressed libido results.
Estrogens, antiandrogens (eg, luteinizing hormone–releasing hormone superagonists, digoxin, spironolactone, ketoconazole, cimetidine)	Suppress testosterone-mediated stimulation of libido	• In the face of a decreased libido, a secondary ED develops because of diminished sexual drive.
Central nervous system depressants (eg, barbiturates, narcotics, benzodiazepines, short-term use of large doses of alcohol, anticonvulsants)	Suppress perception of psychogenic stimuli	
Agents that decrease penile blood flow (eg, diuretics, peripheral β-adrenergic antagonists, or central sympatholytics [methyldopa, clonidine, guanethidine])	Reduce arteriolar flow to corpora	• Any diuretic that produces a significant decrease in intravascular volume can decrease penile arteriolar flow. • Safer antihypertensives include angiotensin-converting enzyme inhibitors, postsynaptic α_1-adrenergic antagonists (terazosin, doxazosin), calcium channel blockers, and angiotensin II receptor antagonists.

(*continued*)

TABLE 80–1 Medication Classes That Can Cause Erectile Dysfunction (*Continued*)

Drug Class	Proposed Mechanism by Which Drug Causes Erectile Dysfunction	Special Notes
Miscellaneous	Unknown mechanism	
• Finasteride, dutasteride		
• Lithium carbonate		
• Gemfibrozil		
• Interferon		
• Clofibrate		
• Monoamine oxidase inhibitors		

TABLE 80–2 Dosing Regimens for Selected Drug Treatments for Erectile Dysfunction

Drug	Brand Name	Initial Dose	Usual Range	Special Population Dose	Other
Phosphodiesterase Inhibitor					
Sildenafil	Viagra	50 mg orally 1 hour before intercourse	25–100 mg 1 hour before intercourse. Limit to one dose per day	In patients age 65 years and older, start with 25 mg dose. In patients with creatinine clearance less than 30 mL/minute or severe hepatic impairment, limit starting dose to 25 mg. In patients taking potent P450 CYP3A4 inhibitors, limit starting dose to 25 mg	Titrate dose so that erection lasts no more than 1 hour. Food decreases absorption by 1 hour. Contraindicated with nitrates by any route of administration
Vardenafil	Levitra	5–10 mg orally 1 hour before intercourse	5–20 mg 1 hour before intercourse. Limit to one dose per day	In patients age 65 years and older, start with 5 mg Levitra. In patients with moderate hepatic impairment, start with 5 mg Levitra. In patients taking potent P450 CYP3A4 inhibitors, limit starting dose to 2.5–5 mg every 24–72 hours	Titrate dose so that erection lasts no more than 1 hour. Food decreases absorption by 1 hour. Contraindicated with nitrates by any route of administration
	Staxyn	10 mg tablet to dissolve on the tongue 1 hour before intercourse	10 mg tablet to dissolve on the tongue 1 hour before intercourse. Limit to one dose per day.	Dose of Staxyn requires no adjustment in patients 65 years or older or in patients with creatinine clearance less than 30 mL/minute. Do not use in patients with severe hepatic impairment or those taking potent P450 CYP3A4 inhibitors. Do not initiate Staxyn in patients taking *α*-adrenergic antagonists	Staxyn should be taken without any liquid or food. The tablet should be placed on the tongue where it will dissolve. No uptitration of dose is recommended

(*continued*)

TABLE 80–2 Dosing Regimens for Selected Drug Treatments for Erectile Dysfunction (*Continued*)

Drug	Brand Name	Initial Dose	Usual Range	Special Population Dose	Other
Tadalafil	Cialis	5–10 mg orally before intercourse *or* 2.5–5 mg orally once daily	10–20 mg before intercourse. Limit to one dose per day; the drug improves erectile function for up to 36 hours 2.5–5 mg once daily. Limit to one dose per day	Dose of tadalafil requires no dosage adjustment in patients 65 years or older. In patients with creatinine clearance of 30–50 mL/min, limit starting dose to 10 mg every 48 hours; if less than 30 mL/min, limit starting dose to 5 mg every 72 hours. In patients with mild-moderate hepatic impairment, limit starting dose to 10 mg every 24 hours. Do not use in patients with severe hepatic impairment. In patients taking potent P450 CYP3A4 inhibitors, limit starting dose to 10 mg every 72 hours	Titrate dose so that erection lasts not more than 1 hour. Food does not affect rate or extent of drug absorption. Contraindicated with nitrates by any route of administration. When taken with large amounts of ethanol, tadalafil may cause orthostatic hypotension
Avanafil	Stendra	100 mg orally 30 minutes before intercourse	50–200 mg orally 30 minutes before intercourse	In patients with creatinine clearance of 30–89 mL/min, no dosage adjustment is needed. Do not use if creatinine clearance is less than 30 mL/min, if the patient has severe hepatic disease, or if the patient is taking P450 CYP3A4 inhibitors	May be taken with food. When taken with large amounts of ethanol, avanafil may cause orthostatic hypotension

Prostaglandin E1					
Alprostadil intracavernosal injection	Caverject, Edex	2.5 mcg intracavernosally 5–10 minutes before intercourse	10–20 mcg 5–10 minutes before intercourse. Maximum recommended dose is 60 mcg. Limit to not more than one injection per day and not more than three injections per week	Titrate dose to achieve an erection that lasts 1 hour	Patient will require training on an aseptic intracavernosal injection technique. Avoid intracavernosal injections in patients with sickle cell anemia, multiple myeloma, leukemia, severe coagulopathy, schizophrenia, poor manual dexterity, severe venous incompetence, or severe cardiovascular disease
Alprostadil intraurethral pellet	Muse	125–250 mcg intraurethrally 5–10 minutes before intercourse	250–1,000 mcg just before intercourse. Limit to not more than two doses per day		Patient will require training on proper intraurethral administration techniques Use applicator provided to administer medications to avoid urethral injury
Testosterone Supplements					
Methyltestosterone	Android, Testred, Methitest	10 mg once daily	10–50 mg once daily		Not recommended for use due to extensive first-pass hepatic catabolism and because it is associated with hepatotoxicity
Fluoxymesterone	Androxy	5 mg once daily	5–20 mg once daily	Contraindicated in patients with severe renal or hepatic impairment	Not recommended because it is associated with hepatotoxicity. This is a 17*α*-alkylated androgen

(*continued*)

TABLE 80–2 Dosing Regimens for Selected Drug Treatments for Erectile Dysfunction (*Continued*)

Drug	Brand Name	Initial Dose	Usual Range	Special Population Dose	Other
Testosterone buccal system	Striant	30 mg every 12 hours, morning and evening	30 mg every 12 hours, morning and evening		Place buccal system just above incisor tooth on both sides of the mouth. To remove, slide buccal system down toward the tooth. Buccal tablet may become detached during eating. If this occurs, discard and replace with new buccal system. Do not chew or swallow buccal system
Testosterone cypionate intramuscular injection	Depo-Testosterone	200–400 mg every 2–4 weeks	200–400 mg every 2–4 weeks	Contraindicated in patients with severe hepatic or renal impairment	During the dosing interval, supraphysiologic serum concentrations of testosterone are produced during a portion of the dosing interval. This has been linked to mood swings
Testosterone enanthate	Delatestryl	200–400 mg every 2–4 weeks	200–400 mg every 2–4 weeks	Although not so labeled, it should probably not be used in patients with severe hepatic or renal impairment	During the dosing interval, supraphysiologic serum concentrations of testosterone are produced during a portion of the dosing interval. This has been linked to mood swings

Testosterone transdermal patch	Androderm	4 mg as a single dose at bedtime	2–6 mg as a single dose at bedtime	Safety in patients with hepatic or renal dysfunction has not been evaluated	When administered at bedtime, serum concentrations of testosterone in the usual circadian pattern are produced. Apply to those sites recommended in the package labeling: upper arm, back, abdomen, and thigh. Rotate application sites. Avoid swimming, showering, or washing administration site for 3 hours after patch application
Testosterone gel	Androgel 1%, Testim 1%	5–10 g (equivalent to 50–100 mg testosterone, respectively) gel as a single dose in the morning	5–10 g (equivalent to 50–100 mg testosterone, respectively) gel as a single dose in the morning. Titrate dose up at 14-day intervals		Cover application site to avoid inadvertent transfer to others. Avoid swimming, showering, or washing administration site for 2 hours after gel application. Apply to those sites recommended in the product labeling: shoulders, upper arms, abdomen. Children and women should avoid contact with unclothed or unwashed application sites. Patients should wash hands with soap and water after administration of transdermal testosterone product

(*continued*)

TABLE 80–2 Dosing Regimens for Selected Drug Treatments for Erectile Dysfunction (*Continued*)

Drug	Brand Name	Initial Dose	Usual Range	Special Population Dose	Other
Testosterone transdermal spray	Fortesta	Four sprays (equivalent to 40 mg testosterone) once daily	Four to seven sprays (equivalent to 40–70 mg testosterone) once daily. Titrate dose up at 14- to 35-day intervals.		Cover application site to avoid inadvertent transfer to others. Avoid swimming, showering, or washing administration site for 2 hours after spray application. Apply to those sites recommended in the product labeling: front and inner thighs. Children and women should avoid contact with unclothed or unwashed application sites. Patients should wash hands with soap and water after administration of transdermal testosterone product
Testosterone transdermal solution	Axiron	One to four (30–90 mg, respectively) pump sprays to left or right axilla daily	One to four (30–120 mg, respectively) pump sprays to left or right axilla daily. Titrate dose up at 14- to 35-day intervals		Limit application to axilla. Apply antiperspirant or deodorant before Axiron

Testosterone subcutaneous implant pellet	Testopel	150–450 mg as a single dose every 3–6 months. Administration of the dose requires a forearm incision and subcutaneous dose implant under local anesthesia	150–450 mg as a single dose every 3–6 months		Trained health professional is required to administer the dose. Should use sterile implanter kit. Clinical onset is delayed for 3–4 months after initial dose

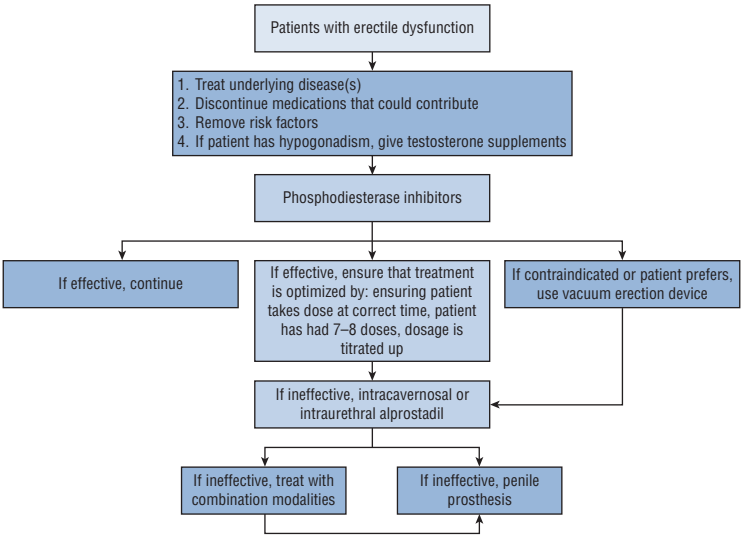


FIGURE 80–1. Algorithm for selecting treatment for erectile dysfunction (ED).

NONPHARMACOLOGIC TREATMENT

Vacuum Erection Device

- First-line therapy for older patients in stable relationships. Onset of action is slow (ie, 3–20 minutes).
- An erection can be prolonged through use of constriction bands or tension rings.
- Consider VEDs as second-line therapy after failure of oral or injectable drugs. Response rate improves with addition of **alprostadil** or a phosphodiesterase inhibitor (PI).
- VEDs are contraindicated in patients with sickle cell disease. Use cautiously in patients on warfarin because, through a poorly understood and idiosyncratic mechanism, it can cause priapism.

Surgery

- Surgical insertion of a penile prosthesis, the most invasive treatment for ED, is used after failure of less invasive treatments and for patients who are not candidates for other treatments.
- Adverse effects of prosthesis insertion include early- and late-onset infection, mechanical failure, and erosion of the rods through the penis.

PHARMACOLOGIC TREATMENTS

Phosphodiesterase Inhibitors

- Phosphodiesterase mediates catabolism of cyclic guanylate monophosphate, a vasodilatory neurotransmitter in the corporal tissue.
- PIs are selective for isoenzyme type 5 in genital tissue. Inhibition of this isoenzyme in nongenital tissues (eg, peripheral vascular tissue, tracheal smooth muscle, and platelets) can produce adverse effects.
- Available agents (**avanafil, sildenafil, tadalafil,** and **vardenafil)** have different pharmacokinetic profiles (Table 80–3), drug–food interactions, and adverse effects. They are considered equally effective despite no comparative clinical trial data.

TABLE 80–3 Pharmacodynamics and Pharmacokinetics of Phosphodiesterase Inhibitors

	Sildenafil (Viagra)	Vardenafil (Levitra/Staxyn)	Tadalafil (Cialis)	Avanafil (Stendra)
Inhibits PDE-5	Yes	Yes	Yes	Yes
Inhibits PDE-6	Yes	Minimally	No	Minimally
Inhibits PDE-11	No	No	Yes	Minimally
Time to peak plasma level (hours)	0.5–1	0.7–0.9/1.5	2	0.5–0.8
Oral bioavailability (%)	40	15/21–44	Not determined	15
Fatty meal decreases rate of oral absorption?	Yes	Yes/No[a]	No	No
Mean plasma half-life (hours)	3.7	4.4–4.8/4–6	18	4–5
Active metabolite	Yes	Yes/Yes	No	Yes
Percentage of dose excreted in feces	80	91–95/91–95	61	62
Percentage of dose excreted in urine	13	2–6/2–6	36	21
Onset (minutes)	30	30/60	45	30–45
Duration (hours)	4	4–5/4–6	24–36	4–5

PDE, phosphodiesterase.
[a]When Staxyn is taken with water, the area under the curve decreases by 29%.

- PIs are first-line therapy for younger patients. Effectiveness appears to be dose related; nonresponse rate is 30% to 40%. Patient education is critical for clinical success.
- Hepatic metabolism of all four PIs can be inhibited by enzyme inhibitors of CYP 3A4. Use a lower starting dose to minimize dose-related adverse effects.
- Avoid exceeding prescribed doses due to increased frequency of adverse effects and inconsistent erectile responses.
- In usual doses, the most common adverse effects include headache, facial flushing, dyspepsia, nasal congestion, and dizziness that are all dose related.
- Sildenafil and vardenafil decrease systolic/diastolic blood pressure by 8 to 10/5 to 6 mm Hg for 1 to 4 hours after a dose. Although most patients are asymptomatic, multiple antihypertensives, **nitrates**, and baseline hypotension increase the risk of developing adverse effects. Avanafil is associated with similar decreases in blood pressure. Tadalafil is not associated with blood pressure decreases, but use with caution in patients with cardiovascular disease because of the inherent risk associated with sexual activity.
- Guidelines are available for stratifying patients on the basis of their cardiovascular risk (**Table 80–4**).
- Use PIs cautiously in patients at risk for retinitis pigmentosa and by pilots who rely on blue and green lights to land airplanes. Evaluate patients with sudden vision loss before continuing treatment.
- Tadalafil inhibits type 11 phosphodiesterase, which is thought to account for the dose-related back and muscle pain seen in 7% to 30% of patients.
- PIs are contraindicated in patients taking nitrates. Use cautiously in patients taking α-adrenergic antagonists.

TABLE 80–4 Recommendations of the Third Princeton Consensus Conference for Cardiovascular Risk Stratification of Patients Being Considered for Phosphodiesterase Inhibitor Therapy

Risk Category	Description of Patient's Condition	Management Approach
Low risk	Has asymptomatic cardiovascular disease with <3 risk factors for cardiovascular disease Has well-controlled hypertension Has mild congestive heart failure (NYHA class I or II) Has mild valvular heart disease Had a myocardial infarction >8 weeks ago	Patient can be started on phosphodiesterase inhibitor
Intermediate risk	Has ≥3 risk factors for cardiovascular disease Has mild or moderate, stable angina Had a recent myocardial infarction or stroke within the past 2–8 weeks Has moderate congestive heart failure (NYHA class III) History of stroke, transient ischemic attack, or peripheral artery disease	Patient should undergo complete cardiovascular workup and treadmill stress test to determine tolerance to increased myocardial energy consumption associated with increased sexual activity. Reclassify in low or high risk category
High risk	Has unstable or refractory angina, despite treatment Has uncontrolled hypertension Has severe congestive heart failure (NYHA class IV) Had a recent myocardial infarction or stroke within past 2 weeks Has moderate or severe valvular heart disease Has high-risk cardiac arrhythmias Has obstructive hypertrophic cardiomyopathy	Phosphodiesterase inhibitor is contraindicated; sexual intercourse should be deferred

NYHA, New York Heart Association..

Testosterone-Replacement Regimens

- **Testosterone**-replacement regimens restore serum testosterone levels to the normal range (300–1100 ng/dL; 10.4–38.2 nmol/L). These regimens are indicated for symptomatic patients with hypogonadism as confirmed by both a decreased libido and low serum testosterone concentrations.
- Testosterone-replacement regimens correct secondary ED by improving libido. Improved muscle strength, sexual drive, and mood are observed within days or weeks of initiating treatment.
- Oral, buccal, parenteral, and transdermal products are available (Table 80–2). Injectable regimens are preferred because they are effective, inexpensive, and do not have the bioavailability problems or adverse hepatotoxic effects of oral regimens. Testosterone patches, gels, and sprays are more expensive than other forms and should be reserved for patients who refuse injections.
- Screen patients 40 years and older for benign prostatic hyperplasia (BPH) and prostate cancer before starting therapy. Continue treatment for 2 to 3 months before an increase in dosage is considered.
- Testosterone replacement can cause sodium retention, which can result in weight gain or exacerbate hypertension, congestive heart failure, and edema; gynecomastia; serum lipoprotein changes; and polycythemia.
- Oral testosterone-replacement regimens can cause hepatotoxicity, ranging from mildly elevated hepatic transaminases to serious liver diseases (eg, peliosis hepatitis, hepatocellular and intrahepatic cholestasis, and benign or malignant tumors).
- Topical testosterone patches may cause contact dermatitis that responds to topical corticosteroids.

Alprostadil

- **Alprostadil**, or prostaglandin E_1, stimulates adenyl cyclase to increase production of cyclic adenosine monophosphate, a neurotransmitter that ultimately enhances blood flow to and blood filling of the corpora.
- Alprostadil is approved as monotherapy for the management of ED. It is generally prescribed after failure of VEDs and PIs and for patients who cannot use these therapies. The intracavernosal route is more effective than the intraurethral route.

INTRACAVERNOSAL INJECTION

- Intracavernosal alprostadil is effective in 70% to 90% of patients, but 30% to 50% discontinue therapy during first 6 to 12 months. Perceived ineffectiveness, inconvenience of administration, unnatural, nonspontaneous erection, needle phobia, loss of interest, and cost of therapy are reasons given for discontinuation.
- Intracavernosal alprostadil is used successfully in combination with VEDs or vasoactive agents (eg, papaverine and phentolamine) that act by different mechanisms.
- Intracavernosal alprostadil acts rapidly, with an onset of 5 to 15 minutes. Duration of action is dose related and, within the usual dosage range, lasts less than 1 hour. The maximum number of injections is one daily and three weekly.
- Usual dose is 10 to 20 mcg up to a maximum of 60 mcg. The manufacturer recommends slow dose titration, but in clinical practice most patients start with 10 mcg and titrate quickly.
- Local adverse effects occur during the first year of therapy, including cavernosal plaques or fibrosis at the injection site (2%–12% of patients), penile pain (10%–44%), and priapism (1%–15%). Penile pain is usually mild and self-limiting, but priapism (ie, painful, drug-induced erection lasting >1 hours) necessitates immediate medical attention.
- Use cautiously in patients at risk of priapism (eg, sickle cell disease or lymphoproliferative disorders) and bleeding complications secondary to injections.

INTRAURETHRAL ADMINISTRATION

- Instill intraurethral alprostadil, 125 to 1000 mcg 5 to 10 minutes before intercourse after emptying the bladder. No more than two doses daily are recommended.

- Intraurethral administration is associated with mild pain in 24% to 32% of patients. Prolonged painful erections are rare.
- Female partners may experience vaginal burning, itching, or pain, which is probably related to transfer of alprostadil during intercourse.

Unapproved Agents

- A variety of commercially available and investigational agents have been used for management of ED. Examples include **trazodone** (50–200 mg/day), **yohimbine** (5.4 mg three times daily), **papaverine** (7.5–60 mg [single-agent therapy] or 0.5–20 mg [combination therapy] intracavernosal injection), and **phentolamine** (1 mg [combination therapy] intracavernosal injection).

EVALUATION OF THERAPEUTIC OUTCOMES

- The primary therapeutic outcomes for ED are improving the quantity and quality of penile erections suitable for intercourse and avoiding adverse drug reactions and interactions.
- Assess the patient at baseline and after a treatment trial period of 1 to 3 weeks.
- Identify patients with unrealistic expectations and counsel accordingly to avoid adverse effects due to excessive use of erectogenic agents.

See Chapter 66, Erectile Dysfunction, authored by Mary Lee, for a more detailed discussion of this topic.

CHAPTER 81

Urinary Incontinence

- *Urinary incontinence* (UI) is the complaint of involuntary leakage of urine.

PATHOPHYSIOLOGY

- The urethral sphincter, a combination of smooth and striated muscles within and external to the urethra, maintains adequate resistance to the flow of urine from the bladder until voluntary voiding is initiated.
- Volitional and involuntary bladder contractions are mediated by acetylcholine. Bladder smooth muscle cholinergic receptors are mainly of the M_2 variety; however, M_3 receptors are responsible for both emptying contraction of normal micturition and involuntary bladder contractions, which can result in UI. Therefore, most pharmacologic antimuscarinic therapy is anti-M_3 based.
- UI occurs as a result of overfunctioning or underfunctioning of the urethra, bladder, or both.
- Urethral underactivity is known as *stress UI* (SUI) and occurs during activities such as exercise, lifting, coughing, and sneezing. The urethral sphincter no longer resists the flow of urine from the bladder during periods of physical activity.
- Bladder overactivity is known as *urge UI* (UUI) and is associated with increased urinary frequency and urgency, with or without urge incontinence. The detrusor muscle is overactive and contracts inappropriately during the filling phase.
- Urethral overactivity and/or bladder underactivity is known as overflow incontinence. The bladder is filled to capacity but is unable to empty, causing urine to leak from a distended bladder past a normal outlet and sphincter. Common causes of urethral overactivity include benign prostatic hyperplasia (see Chap. 79); prostate cancer (see Chap. 64); and, in women, cystocele formation or surgical overcorrection after SUI surgery.
- Mixed incontinence includes the combination of bladder overactivity and urethral underactivity.
- Functional incontinence is not caused by bladder- or urethra-specific factors but rather occurs in patients with conditions such as cognitive or mobility deficits.
- Many medications can aggravate voiding dysfunction and UI (**Table 81–1**).

CLINICAL PRESENTATION

- Signs and symptoms of UI depend on the underlying pathophysiology (**Table 81–2**). Patients with SUI generally complain of urine leakage with physical activity, whereas those with UUI complain of frequency, urgency, high-volume incontinence, and nocturia and nocturnal incontinence.
- Urethral overactivity and/or bladder underactivity is a rare but important cause of UI. Patients complain of lower abdominal fullness, hesitancy, straining to void, decreased force of stream, interrupted stream, and sense of incomplete bladder emptying. Patients can also have urinary frequency, urgency, and abdominal pain.

DIAGNOSIS

- A complete medical history, physical examination (ie, abdominal examination to exclude distended bladder, pelvic examination in women looking for evidence of prolapse or hormonal deficiency, and genital and prostate examination in men), and brief neurologic assessment of the perineum and lower extremities are recommended.

TABLE 81–1 Medications that Influence Lower Urinary Tract Function

Medication	Effect
Diuretics, acetylcholinesterase inhibitors	Polyuria, frequency, urgency
α-Receptor antagonists	Urethral relaxation and stress urinary incontinence in women
α-Receptor agonists	Urethral constriction and urinary retention in men
Calcium channel blockers	Urinary retention
Narcotic analgesics	Urinary retention from impaired contractility
Sedative hypnotics	Functional incontinence caused by delirium, immobility
Antipsychotic agents	Anticholinergic effects and urinary retention
Anticholinergics	Urinary retention
Antidepressants, tricyclic	Anticholinergic effects, α-antagonist effects
Alcohol	Polyuria, frequency, urgency, sedation, delirium
ACEIs	Cough as a result of ACEIs may aggravate stress urinary incontinence by increasing intraabdominal pressure

ACEIs, angiotensin-converting enzyme inhibitors.

- For SUI, the preferred diagnostic test is observation of urethral meatus while the patient coughs or strains.
- For UUI, the preferred diagnostic tests are urodynamic studies. Perform urinalysis and urine culture to rule out urinary tract infection.
- For urethral overactivity and/or bladder underactivity, perform digital rectal examination or transrectal ultrasound to rule out prostate enlargement. Perform renal function tests to rule out renal failure.

TREATMENT

- Goals of Treatment: Restoration of continence, reduction in the number of UI episodes, and prevention of complications.

TABLE 81–2 Differentiating Bladder Overactivity from Urethral Underactivity-Related UI

Symptoms	Bladder Overactivity (UUI)	Urethral Underactivity (SUI)
Urgency (strong, sudden desire to void)	Yes	Sometimes
Frequency with urgency	Yes	Rarely
Leaking during physical activity (eg, coughing, sneezing, lifting)	No	Yes
Amount of urinary leakage with each episode of incontinence	Large if present	Usually small
Ability to reach the toilet in time following an urge to void	No or just barely	Yes
Nocturnal incontinence (presence of wet pads or undergarments in bed)	Yes	Rare
Nocturia (waking to pass urine at night)	Usually	Seldom

NONPHARMACOLOGIC TREATMENT

- Nonpharmacologic, nonsurgical treatment (eg, lifestyle modifications, toilet scheduling regimens, and pelvic floor muscle rehabilitation) is first-line treatment for UI.
- Surgery rarely plays a role in initial management of UI but can be required for secondary complications (eg, skin breakdown or infection). The decision to surgically treat symptomatic UI requires that lifestyle compromise warrant an elective operation and that nonoperative therapy be proven undesirable or ineffective.

PHARMACOLOGIC TREATMENT

Bladder Overactivity: Urge Urinary Incontinence

- The pharmacotherapy of first choice for UUI is anticholinergic/antispasmodic drugs, which antagonize muscarinic cholinergic receptors (**Table 81–3**).

OXYBUTYNIN

- **Oxybutynin immediate-release** (IR) is the drug of first choice for UUI and the "gold standard" against which other drugs are compared. Financial considerations favor generic oxybutynin IR.
- Many patients discontinue oxybutynin IR because of adverse effects due to antimuscarinic effects (eg, dry mouth, constipation, vision impairment, confusion, cognitive dysfunction, and tachycardia), α-adrenergic inhibition (eg, orthostatic hypotension), and histamine H_1 inhibition (eg, sedation and weight gain).
- Optimize tolerability of oxybutynin IR by initiating therapy with no more than 2.5 mg twice daily and increasing 2.5 mg three times daily after 1 month. Titrate in 2.5 mg/day increments every 1 to 2 months until the desired response, maximum recommended dose, or maximum tolerated dose is attained.
- **Oxybutynin extended-release** (XL) is better tolerated than oxybutynin IR and as effective in clinical outcomes. Maximum benefits seen up to 4 weeks after starting therapy or dose escalation.
- **Oxybutynin transdermal system** (TDS) has similar efficacy but is better tolerated than oxybutynin IR presumably because this route avoids first-pass metabolism in the liver, which generates the metabolite thought to cause adverse events, especially dry mouth.
- **Oxybutynin gel** is also available for daily use. No data are available comparing it with an active control.

TOLTERODINE

- **Tolterodine**, a competitive muscarinic receptor antagonist, is considered first-line therapy in patients with urinary frequency, urgency, or urge incontinence.
- Controlled studies demonstrate that tolterodine is more effective than placebo and as effective as oxybutynin IR in efficacy outcomes with lower drug discontinuation rates.
- Tolterodine undergoes hepatic metabolism involving cytochrome (CYP) 2D6 and 3A4 isoenzymes. Therefore, elimination may be impaired by CYP 3A4 inhibitors, including **fluoxetine, sertraline, fluvoxamine**, macrolide antibiotics, azole antifungals, and grapefruit juice.
- Tolterodine's most common adverse effects include dry mouth, dyspepsia, headache, constipation, and dry eyes. The maximum benefit of tolterodine is not realized for up to 8 weeks after starting therapy or dose escalation.
- **Tolterodine long acting** (LA) offers once-daily dosing and may also take up to 8 weeks after starting therapy or dose escalation to see maximum benefit.
- Fesoterodine fumarate is a prodrug for tolterodine and is considered an alternative first-line therapy for UI in patients with urinary frequency, urgency, or urge incontinence.

TABLE 81–3 Dosing of Medications Approved for OAB or UUI

Drug	Brand Name	Initial Dose	Usual Range	Special Population Dose	Comments
Anticholinergics/Antimuscarinics					
Oxybutynin IR	Ditropan	2.5 mg twice daily	2.5–5 mg two to four times daily		Titrate in increments of 2.5 mg/day every 1–2 months; available in oral solution
Oxybutynin XL	Ditropan XL	5–10 mg once daily	5–30 mg once daily		Adjust dose in 5-mg increments at weekly interval; swallow whole
Oxybutynin TDS	Oxytrol		3.9 mg/day apply one patch twice weekly		Apply every 3 to 4 days; rotate application site
Oxybutynin gel 10%	Gelnique		One sachet (100 mg) topically daily		Apply to clean and dry, intact skin on abdomen, thighs or upper arms/ shoulders; contains alcohol
Oxybutynin gel 3%	Gelnique 3%		Three pumps (84 mg) topically daily		Same as above
Tolterodine IR	Detrol		1–2 mg twice daily	1 mg twice daily if patient is taking CYP3A4 inhibitors, or with renal/hepatic impairment	
Tolterodine LA	Detrol LA		2–4 mg once daily	2 mg once daily in those who are taking CYP3A4 inhibitors or with renal/hepatic impairment	Swallow whole; avoid in patients with creatinine clearance ≤10 mL/min (0.17 mL/s)
Trospium chloride IR	Sanctura		20 mg twice daily	20 mg once daily in patient age ≥75 years or creatinine clearance ≤30 mL/min (0.5 mL/s)	Take 1 hour before meals or on empty stomach; patient age ≥75 years should take at bedtime
Trospium chloride ER	Sanctura XR		60 mg once daily	Avoid in patient age ≥75 years or creatinine clearance ≤30 mL/min (0.5 mL/s)	Take 1 hour before meals or on empty stomach; swallow whole

Solifenacin	VESIcare	5 mg daily	5–10 mg once daily	5 mg daily if patient is taking CYP3A4 inhibitors or with creatinine clearance ≤30 mL/min (0.5 mL/s) or moderate hepatic impairment; avoid in severe hepatic impairment	Swallow whole
Darifenacin ER	Enablex	7.5 mg once daily	7.5–15 mg once daily	7.5 mg daily if patient is taking potent CYP3A4 inhibitors or with moderate hepatic impairment; avoid in severe hepatic impairment	Titrate dose after at least 2 weeks; swallow whole
Fesoterodine ER	Toviaz	4 mg once daily	4–8 mg once daily	4 mg daily if patient is taking potent CYP3A4 inhibitors or with creatinine clearance ≤30 mL/min (0.5 mL/s); avoid in severe hepatic impairment	Prodrug (metabolized to 5-hydroxymethyl tolterodine); swallow whole
β_3-Adrenergic Agonist					
Mirabegron ER	Myrbetriq	25 mg once daily	25–50 mg once daily	25 mg once daily if creatinine clearance 15–29 mL/min (0.25–0.49 mL/s); avoid in patients with ESRD or severe hepatic impairment	Swallow whole

CYP, cytochrome P450 enzyme; ER, extended release; ESRD, end-stage renal disease; IR, immediate-release; LA, long-acting; OAB, overactive bladder; TDS, transdermal system; UUI, urge urinary incontinence; XL, extended-release.

OTHER PHARMACOLOGIC THERAPIES FOR URGE URINARY INCONTINENCE

- **Trospium chloride IR**, a quaternary ammonium anticholinergic, is superior to placebo and is equivalent to oxybutynin IR and tolterodine IR. It causes the expected anticholinergic adverse effects with increased frequency in patients 75 years or older. An extended-release product is also available. Take on an empty stomach.
- **Solifenacin succinate** and **darifenacin** are second-generation antimuscarinic agents. Both have been shown to improve quality-of-life domains. Drug interactions are possible if CYP 3A4 inhibitors are given with solifenacin succinate or CYP 2D6 or 3A4 inhibitors with darifenacin.
- **Mirabegron** is a β_3-adrenergic agonist alternative to anticholinergic/antimuscarinic drugs for managing UUI. It has modest efficacy as compared with placebo. Hypertension, nasopharyngitis, urinary tract infection, and headache were the most common adverse effects reported. It is a moderate inhibitor of CYP2D6.
- Use of other agents, including tricyclic antidepressants, **propantheline, flavoxate**, **hyoscyamine**, and **dicyclomine hydrochloride**, is not recommended. They are less effective, not safer, or have not been adequately studied.
- Selection of initial drug therapy depends on side-effect profile, comorbidities, concurrent drug therapy, and patient preference in drug delivery methods (**Table 81–4**).
- **Botulinum toxin A** temporarily paralyzes smooth or striated muscle. It is approved for the treatment of refractory UUI associated with neurogenic detrusor overactivity. It is recommended by the American Urological Association as third-line in patients with idiopathic overactive bladder as an off-label use.
- Adverse effects of botulinum toxin A include dysuria, hematuria, urinary tract infection, and urinary retention (up to 20%). Therapeutic and adverse effects are seen 3 to 7 days after injection and subside after 6 to 8 months.
- Patients with UUI and elevated postvoid residual urine volume should be treated by intermittent self-catheterization along with frequent voiding between catheterizations.

TABLE 81–4 Adverse Event Incidence Rates with Approved Drugs for Bladder Overactivity[a]

Drug	Dry Mouth	Constipation	Dizziness	Vision Disturbance
Oxybutynin IR	71	15	17	10
Oxybutynin XL	61	13	6	14
Oxybutynin TDS	7	3	NR	3
Oxybutynin gel	10	1	3	3
Tolterodine	35	7	5	3
Tolterodine LA	23	6	2	4
Trospium chloride IR	20	10	NR	1
Trospium chloride XR	11	9	NR	2
Solifenacin	20	9	2	5
Darifenacin ER	24	18	2	2
Fesoterodine ER	27	5	NR	3
Mirabegron ER	3	3	3	NR

IR, immediate-release; LA, long-acting; NR, not reported; TDS, transdermal system; XL, extended-release; XR/ER, extended-release.

[a]All values constitute mean data, predominantly using product information from the manufacturers.

Urethral Underactivity: Stress Urinary Incontinence

- Treatment of SUI is aimed at improving urethral closure by stimulating α-adrenergic receptors in smooth muscle of the bladder neck and proximal urethra, enhancing supportive structures underlying the urethral epithelium, or enhancing serotonin and norepinephrine effects in the micturition reflex pathways.

ESTROGENS

- Historically, local and systemic **estrogens** have been the mainstays of pharmacologic management of SUI.
- In open trials, estrogens were administered orally, intramuscularly, vaginally, or transdermally. Regardless of the route, estrogens exerted variable effects on urodynamic parameters, such as maximum urethral closure pressure, functional urethral length, and pressure transmission ratio.
- Results of four placebo-controlled comparative trials have not been as favorable, finding no significant clinical or urodynamic effect for oral estrogen compared with placebo.

α-ADRENERGIC RECEPTOR AGONISTS

- Many open trials support the use of a variety of α-adrenergic receptor agonists in SUI. Combining an α-adrenergic receptor agonist with an estrogen yields somewhat superior clinical and urodynamic responses compared with monotherapy.
- Contraindications to these agents include hypertension, tachyarrhythmias, coronary artery disease, myocardial infarction, cor pulmonale, hyperthyroidism, renal failure, and narrow-angle glaucoma.

DULOXETINE

- **Duloxetine**, a dual inhibitor of serotonin and norepinephrine reuptake indicated for depression and painful diabetic neuropathy, is approved in many countries for the treatment of SUI, but not in the United States. Duloxetine is thought to facilitate the bladder-to-sympathetic reflex pathway, increasing urethral and external urethral sphincter muscle tone during the storage phase.
- Six placebo-controlled studies showed that duloxetine reduces incontinent episode frequency and the number of daily micturitions, increases micturition interval, and improves quality-of-life scores. These benefits were statistically significant but clinically modest.
- Monitor patients taking concurrent CYP 2D6 and 1A2 substrates or inhibitors closely.
- The adverse event profile might make adherence problematic. Adverse events include nausea, headache, insomnia, constipation, dry mouth, dizziness, fatigue, somnolence, vomiting, and diarrhea.

OVERFLOW INCONTINENCE

- Overflow incontinence secondary to benign or malignant prostatic hyperplasia may be amenable to pharmacotherapy (see Chaps. 64 and 79).

EVALUATION OF THERAPEUTIC OUTCOMES

- Total elimination of UI signs and symptoms may not be possible. Therefore, realistic goals should be established for therapy.
- In the long-term management of UI, the clinical symptoms of most distress to the individual patient need to be monitored.

- Survey instruments used in UI research along with quantitating the use of ancillary supplies (eg, pads) can be used in clinical monitoring.
- Therapies for UI frequently have nuisance adverse effects, which need to be carefully elicited. Adverse effects can necessitate drug dosage adjustments, use of alternative strategies (eg, chewing sugarless gum, sucking on hard sugarless candy, or use of saliva substitutes for xerostomia), or even drug discontinuation.

See Chapter 68, Urinary Incontinence, authored by Eric S. Rovner, Jean Wyman, and Sum Lam, for a more detailed discussion of this topic.

APPENDIX 1

Allergic and Pseudoallergic Drug Reactions

TABLE A1–1 Classification of Allergic Drug Reactions

Type	Descriptor	Characteristics	Typical Onset	Drug Causes
I	Anaphylactic (IgE mediated)	Allergen binds to IgE on basophils or mast cells, resulting in release of inflammatory mediators.	Within 30 min to <2 hours	Penicillin immediate reaction Blood products Polypeptide hormones Vaccines Dextran
II	Cytotoxic	Cell destruction occurs because of cell-associated antigen that initiates cytolysis by antigen-specific antibody (IgG or IgM). Most often involves blood elements.	Typically >72 h to weeks	Penicillin, quinidine, heparin, phenylbutazone, thiouracils, sulfonamides, methyldopa
III	Immune complex	Antigen–antibody complexes form and deposit on blood vessel walls and activate complement. Result is a serum sickness-like syndrome.	>72 h to weeks	May be caused by penicillins, sulfonamides, minocycline, hydantoins
IV	Cell-mediated (delayed)	Antigens cause activation of T lymphocytes, which release cytokines and recruit effector cells (e.g., macrophages, eosinophils).	>72 h	Tuberculin reaction Maculopapular rashes to a variety of drugs; Contact dermatitis Bullous exanthems Pustular exanthems

TABLE A1–2 Top 10 Drugs and Agents Reported to Cause Skin Reactions

	Reactions per 1,000 Recipients
Amoxicillin	51.4
Trimethoprim–sulfamethoxazole	33.8
Ampicillin	33.2
Iopodate	27.8
Blood	21.6
Cephalosporins	21.1
Erythromycin	20.4
Dihydralazine hydrochloride	19.1
Penicillin G	18.5
Cyanocobalamin	17.9

TABLE A1–3 Treatment of Anaphylaxis

1. Place patient in recumbent position and elevate lower extremities.
2. Monitor vital signs frequently (every 2–5 minutes) and stay with the patient.
3. Administer epinephrine 1:1,000 into nonoccluded site (adults: 0.01 [mg] mL/kg up to a maximum of 0.2–0.5 [mg] mL every 5 to 10 minutes as needed, children: 0.01 [mg] mL/kg up to a maximum dose of 0.3 [mg] mL) IM in the lateral aspect of the thigh or subcutaneously. If deemed necessary, the 5-minute interval between injections can be liberalized.
4. Administer oxygen, usually 8–10 L/min; however, lower concentrations may be appropriate for patients with chronic obstructive pulmonary disease. Maintain airway with oropharyngeal airway device.
5. Consider the antihistamine diphenhydramine (adults 25–50 mg; children 1 mg/kg, up to 50 mg) IM or by slow IV infusion.
6. Consider ranitidine 50 mg in adults and 12.5 to 50 mg (1 mg/kg) in children. The dose may be diluted in 5% dextrose in water to a volume of 20 mL and injected over 5 minutes.
7. Treat hypotension with IV fluids or colloid replacement and consider use of a vasopressor such as dopamine. In adults, 1–2 L of 0.9% saline solution given at a rate of 5–10 mL/kg may be needed in the first 5–10 minutes. Children should receive up to 30 mL/kg in the first hour.
8. Consider inhaled β-agonists (albuterol) metered-dose inhaler two to six puffs or nebulized 2.5–5 mg in 3 mL saline; repeat as necessary for bronchospasm resistant to epinephrine.
9. Consider hydrocortisone, 5 mg/kg, or approximately 250 mg IV (prednisone 20 mg orally can be given in mild cases) to reduce the risk of recurring or protracted anaphylaxis. These doses can be repeated every 6 hours as required.
10. In cases of refractory bronchospasm or hypotension not responding to epinephrine because a β-adrenergic blocker is complicating management, glucagon 1–5 mg IV (20–30 mcg/kg; maximum, 1 mg in children) given IV over 5 minutes may be useful. A continuous infusion of glucagon, 5–15 mcg/min may be given if required.
11. Consider intraosseous access for either adults or children if attempts at IV access are unsuccessful.

IM, intramuscular.

TABLE A1–4 Procedure for Performing Penicillin Skin Testing

A. Percutaneous (Prick) Skin Testing (Using a 22- to 28-Gauge Needle)

Materials	Volume
Pre-Pen 6×10^6 M	1 drop
Penicillin G 10,000 units/mL	1 drop
β-Lactam drug (amoxicillin) 2 mg/mL	1 drop
Saline control	1 drop
Histamine control (1 mg/mL)	1 drop

1. Place a drop of each test material on the volar surface of the forearm.
2. Prick the skin with the needle to make a single shallow puncture of the epidermis through the drop.
3. Interpret skin responses during the next 15 minutes. Observe for a wheal or erythema and the occurrence of itching.
4. A wheal in diameter of 5 mm or greater surrounding the puncture site is considered a positive test result.
5. Wipe off the solution near the puncture site.
6. If the prick test result is negative or equivocal (wheal <5 mm in diameter with no itching or erythema), proceed to the intradermal test.
7. If the histamine control is nonreactive, the test is considered uninterpretable. Ensure no interference by antihistamines.

B. Intradermal Skin Testing[a]

Materials	Volume
Pre-Pen 6×10^6 M	0.02 mL
Penicillin G 10,000 units/mL	0.02 mL
β-Lactam drug (amoxicillin) 2 mg/mL	0.02 mL
Saline control	0.02 mL
Histamine control (0.1 mg/mL)	0.02 mL

1. Inject 0.02–0.03 mL of Pre-Pen intradermally (amount sufficient to produce a small bleb of approximately 3 mm in diameter) in duplicate at least 2 cm apart.
2. Inject 0.02–0.03 mL of the other materials at least 5 cm from the Pre-Pen sites.
3. Interpret skin responses after 20 minutes.
4. Itching or a significant increase in the size of the original bleb to at least 5 cm is considered a positive result. An ambiguous response is a wheal only slightly larger than the original bleb or discordance between the duplicates. The control site should show no increase in the original bleb.
5. If the histamine control is nonreactive, the test is considered uninterpretable. Antihistamines may blunt the response and cause false-negative results.

[a]Using a 0.5- to 1-cc syringe with a 3/8- to 5/8-inch long, 26- to 30-gauge short-bevel needle

Pre-Pen (benzylpenicilloyl polylysine injection, solution) Product Information, AllerQuest LLC and ALK-Abello, Inc., Round Rock TX, 2009.

TABLE A1–5 Protocol for Oral Desensitization

	Phenoxymethyl Penicillin			
Step[a]	Concentration (units/mL)	Volume (mL)	Dose (units)	Cumulative Dose (units)
1	1,000	0.1	100	100
2	1,000	0.2	200	300
3	1,000	0.4	400	700
4	1,000	0.8	800	1,500
5	1,000	1.6	1,600	3,100
6	1,000	3.2	3,200	6,300
7	1,000	6.4	6,400	12,700
8	10,000	1.2	12,000	24,700
9	10,000	2.4	24,000	48,700
10	10,000	4.8	48,000	96,700
11	80,000	1.0	80,000	176,700
12	80,000	2.0	160,000	336,700
13	80,000	4.0	320,000	656,700
14	80,000	8.0	640,000	1,296,700
		Observe for 30 min		
15	500,000	0.25	125,000	
16	500,000	0.5	250,000	
17	500,000	1.0	500,000	
18	500,000	2.25	1,125,000	

[a]The interval between steps is 15 min.

Reprinted from Immunol Allerg Clin North, Vol. 18, Weiss ME, Adkinson NF, Diagnostic Testing for Drug Hypersensivity, Immunol Allerg Clin North, 731–734, Copyright © 1998, with permission from Elsevier.

See e/CHAPTER 22, Allergic and Pseudoallergic Drug Reactions, authored by Lynne M. Sylvia, for a more detailed discussion of this topic.

APPENDIX 2

Geriatrics

TABLE A2–1 Physiologic Changes with Aging

Organ System	Manifestation
Balance and gait	↓ Stride length and slower gait
	↓ Arm swing
	↑ Body sway when standing
Body composition	↓ Total body water
	↓ Lean body mass
	↑ Body fat
	↔ or ↓ Serum albumin
	↑ a_1-Acid glycoprotein (↔ or ↑ by several disease states)
Cardiovascular	↓ Cardiovascular response to stress
	↓ Baroreceptor activity leading to ↑ orthostatic hypotension
	↓ Cardiac output
	↑ Systemic vascular resistance with loss of arterial elasticity and dysfunction of systems maintaining vascular tone
	↓ Resting and maximal heart rate
Central nervous system	↓ Size of the hippocampus and frontal and temporal lobes
	↓ Number of receptors of all types and ↑ sensitivity of remaining receptors
	↓ Short-term memory, coding and retrieval, and executive function
	Altered sleep patterns
Endocrine	↓ Estrogen, testosterone, TSH, and DHEA-S levels
	Altered insulin signaling
Gastrointestinal	↓ Motility of the large intestine
	↓ Vitamin absorption by active transport mechanisms
	↓ Splanchnic blood flow
	↓ Bowel surface area
Genitourinary	Atrophy of the vagina with decreased estrogen
	Prostatic hypertrophy with androgenic hormonal changes
	Detrusor hyperactivity may predispose to incontinence
Hepatic	↓ Hepatic size
	↓ Hepatic blood flow
	↓ Phase I (oxidation, reduction, hydrolysis) metabolism
Immune	↓ Antibody production in response to antigen
	↑ Autoimmunity
Oral	Altered dentition
	↓ Ability to taste salt, bitter, sweet, and sour

(*continued*)

TABLE A2–1	Physiologic Changes with Aging (*Continued*)
Organ System	**Manifestation**
Pulmonary	↓ Respiratory muscle strength
	↓ Chest wall compliance
	↓ Arterial oxygenation and impaired carbon dioxide elimination
	↓ Vital capacity
	↓ Maximal breathing capacity
	↑ Residual volume
Renal	↓ GFR
	↓ Renal blood flow
	↓ Filtration fraction
	↓ Tubular secretory function
	↓ Renal mass
Sensory	Presbyopia (diminished ability to focus on near objects)
	↓ Night vision
	Presbycusis (high-pitch, high-frequency hearing loss)
	↓ Sensation of smell and taste
Skeletal	↓ Skeletal bone mass (osteopenia)
	Joint stiffening caused by reduced water content in tendons, ligaments, and cartilage
Skin/hair	Thinning of stratum corneum
	↓ Langerhans cells, melanocytes, and mast cells
	↓ Depth and extent of the subcutaneous fat layer
	Thinning and graying of hair caused by more hairs in the resting phase and shortening of the growth phase as well as changes in follicular melanocytes

DHEA-S, dehydroepiandrosterone-S; GFR, glomerular filtration rate; TSH, thyroid-stimulating hormone.

TABLE A2–2 Age-Related Changes in Drug Pharmacokinetics

Pharmacokinetic Phase	Pharmacokinetic Parameters
Gastrointestinal absorption	Unchanged passive diffusion and no change in bioavailability for most drugs
	↓ Active transport and ↓ bioavailability for some drugs
	↓ First-pass metabolism, ↑ bioavailability for some drugs, and ↓ bioavailability for some prodrugs
Distribution	↓ Volume of distribution and ↑ plasma concentration of water-soluble drugs
	↑ Volume of distribution and ↑ terminal disposition half-life ($t_{1/2}$) for lipid-soluble drugs
Hepatic metabolism	↓ Clearance and ↑ $t_{1/2}$ for some drugs with poor hepatic extraction (capacity-limited metabolism); phase I metabolism may be affected more than phase II
	↓ Clearance and ↑ $t_{1/2}$ for drugs with high hepatic extraction ratios (flow-limited metabolism)
Renal excretion	↓ Clearance and ↑ $t_{1/2}$ for renally eliminated drugs and active metabolites

TABLE A2–3 Atypical Disease Presentation in Older Adults

Disease	Presentation
Acute myocardial infarction	Only ~50% present with chest pain. In general, older adults present with weakness, confusion, syncope, and abdominal pain; however, electrocardiographic findings are similar to those in younger patients.
Congestive heart failure	Instead of dyspnea, older patients may present with hypoxic symptoms, lethargy, restlessness, and confusion.
Gastrointestinal bleed	Although the mortality rate is ~10%, presenting symptoms are nonspecific, ranging from altered mental status to syncope with hemodynamic collapse. Abdominal pain often is absent.
Upper respiratory infection	Older patients typically present with lethargy, confusion, anorexia, and decompensation of a preexisting medical condition. Fever, chills, and a productive cough may or may not be present.
Urinary tract infection	Dysuria, fever, and flank pain may be absent. More commonly, older adults present with incontinence, confusion, abdominal pain, nausea or vomiting, and azotemia.

TABLE A2-4 Guidelines for Monitoring Medication Use in Long Term Care Facility Patients

Drug	Monitoring	Monitoring Interval (in mo)
Acetaminophen (>4 g/d)	Hepatic function tests	[a]
Amiodarone	Hepatic function tests, TSH level	6
Antiepileptic agents (carbamazepine, phenobarbital, phenytoin, primidone, valproate)	Drug levels	3–6
Angiotensin-converting enzyme inhibitors or angiotensin I receptor blockers	Potassium levels	6
Antipsychotic agents	Extrapyramidal side effects, fasting serum glucose, serum lipid panel	6
Appetite stimulants	Weight, appetite	[a]
Digoxin	Serum blood urea nitrogen, creatinine, trough drug level	6
Diuretic	Serum sodium and potassium levels	3
Erythropoiesis stimulants	Blood pressure, iron and ferritin levels, CBC	1
Fibrates	Hepatic function test, CBC	6
Hypoglycemic agents	Fasting serum glucose level or glycated hemoglobin level	6
Iron	Iron and ferritin levels, CBC	a
Lithium	Trough serum drug levels	3
Metformin	Serum blood urea nitrogen, creatinine levels	
Niacin	Blood sugar levels, hepatic function tests	6
Statins	Hepatic function tests	6
Theophylline	Trough serum drug levels	3
Thyroid replacement	TSH level on tests	6
Warfarin	Prothrombin time or international normalized ratio	1

CBC, complete blood count; TSH, thyroid-stimulating hormone.
[a]Consensus agreement about interval could not be reached.

TABLE A2–5 Medication Appropriateness Index

Questions to Ask About Each Individual Medication
1. Is there an indication for the medication?
2. Is the medication effective for the condition?
3. Is the dosage correct?
4. Are the directions correct?
5. Are the directions practical?
6. Are there clinically significant drug–drug interactions?
7. Are there clinically significant drug–disease or drug–condition interactions?
8. Is there unnecessary duplication with other medication(s)?
9. Is the duration of therapy acceptable?
10. Is this medication the least expensive alternative compared with others of equal utility?

Reprinted and adapted from J Clin Epidemiol, Vol. 45, Hanlon JT, Schmader KE, Samsa GP, et al. A method for assessing drug therapy appropriateness, Pages 1045–1051, Copyright © 1992, with permission from Elsevier.

See e/CHAPTER 8, Geriatrics, authored by Emily R. Hajjar, Shelly L. Gray, Patricia W. Slattum, Catherine I. Starner, Robert L. Maher Jr., Lauren R. Hersh, and Joseph T. Hanlon, for a more detailed discussion of this topic.

Drug-Induced Hematologic Disorders

APPENDIX 3

TABLE A3–1 Drugs Associated with Aplastic Anemias
Observational study evidence
Carbamazepine
Furosemide
Gold salts
Mebendazole
Methimazole
NSAIDs
Oxyphenbutazone
Penicillamine
Phenobarbital
Phenothiazines
Phenytoin
Propylthiouracil
Sulfonamides
Thiazides
Tocainide
Case report evidence (*probable* or *definite* causality rating)
Acetazolamide
Aspirin
Captopril
Chloramphenicol
Chloroquine
Chlorothiazide
Chlorpromazine
Dapsone
Felbamate
Interferon alfa
Lisinopril
Lithium
Nizatidine
Pentoxifylline
Quinidine
Sulindac
Ticlopidine

NSAID, nonsteroidal antiinflammatory drug.

TABLE A3–2 Drugs Associated with Agranulocytosis

Observational Study Evidence	Case Report Evidence (*probable* or *definite* causality rating)	
β-Lactam antibiotics	Acetaminophen	Levodopa
Carbamazepine	Acetazolamide	Meprobamate
Carbimazole	Ampicillin	Methazolamide
Clomipramine	Captopril	Methyldopa
Digoxin	Carbenicillin	Metronidazole
Dipyridamole	Cefotaxime	Nafcillin
Ganciclovir	Cefuroxime	NSAIDs
Glyburide	Chloramphenicol	Olanzapine
Gold salts	Chlorpromazine	Oxacillin
Imipenem–cilastatin	Chlorpropamide	Penicillamine
Indomethacin	Chlorpheniramine	Penicillin G
Macrolide antibiotics	Clindamycin	Pentazocine
Methimazole	Clozapine	Phenytoin
Mirtazapine	Colchicine	Primidone
Phenobarbital	Doxepin	Procainamide
Phenothiazines	Dapsone	Propylthiouracil
Prednisone	Desipramine	Pyrimethamine
Propranolol	Ethacrynic acid	Quinidine
Spironolactone	Ethosuximide	Quinine
Sulfonamides	Flucytosine	Rifampin
Sulfonylureas	Gentamicin	Streptomycin
Ticlopidine	Griseofulvin	Terbinafine
Valproic acid	Hydralazine	Ticarcillin
Zidovudine	Hydroxychloroquine	Tocainide
	Imipenem–cilastatin	Tolbutamide
	Imipramine	Vancomycin
	Lamotrigine	

NSAID, nonsteroidal antiinflammatory drug.

TABLE A3–3 Drugs Associated with Hemolytic Anemia
Observational Study Evidence
Phenobarbital
Phenytoin
Ribavirin
Case Report Evidence (*probable* or *definite* causality rating)
Acetaminophen
Angiotensin-converting enzyme inhibitors
β-Lactam antibiotics
Cephalosporins
Ciprofloxacin
Clavulanate
Erythromycin
Hydrochlorothiazide
Indinavir
Interferon alfa
Ketoconazole
Lansoprazole
Levodopa
Levofloxacin
Methyldopa
Minocycline
NSAIDs
Omeprazole
p-Aminosalicylic acid
Phenazopyridine
Probenecid
Procainamide
Quinidine
Rifabutin
Rifampin
Streptomycin
Sulbactam
Sulfonamides
Sulfonylureas
Tacrolimus
Tazobactam
Teicoplanin
Tolbutamide
Tolmetin
Triamterene

NSAID, nonsteroidal antiinflammatory drug.

TABLE A3–4 Drugs Associated with Oxidative Hemolytic Anemia

Observational Study Evidence
Dapsone
Rasburicase
Case Report Evidence (*probable* or *definite* causality rating)
Ascorbic acid
Metformin
Methylene blue
Nalidixic acid
Nitrofurantoin
Phenazopyridine
Primaquine
Sulfacetamide
Sulfamethoxazole
Sulfanilamide

TABLE A3–5 Drugs Associated with Megaloblastic Anemia

Case Report Evidence (*probable* or *definite* causality rating)
Azathioprine
Chloramphenicol
Colchicine
Cotrimoxazole
Cyclophosphamide
Cytarabine
5-Fluorodeoxyuridine
5-Fluorouracil
Hydroxyurea
6-Mercaptopurine
Methotrexate
Oral contraceptives
p-Aminosalicylate
Phenobarbital
Phenytoin
Primidone
Pyrimethamine
Sulfasalazine
Tetracycline
Vinblastine

TABLE A3–6 Drugs Associated with Thrombocytopenia

Observational Study Evidence

Carbamazepine
Phenobarbital
Phenytoin
Valproic acid

Case Report Evidence (*probable* or *definite* causality rating)

Abciximab
Acetaminophen
Acyclovir
Albendazole
Aminoglutethimide
Aminosalicylic acid
Amiodarone
Amphotericin B
Ampicillin
Aspirin
Atorvastatin
Captopril
Chlorothiazide
Chlorpromazine
Chlorpropamide
Cimetidine
Ciprofloxacin
Clarithromycin
Clopidogrel
Danazol
Deferoxamine
Diazepam
Diazoxide
Diclofenac
Diethylstilbestrol
Digoxin
Ethambutol
Felbamate
Fluconazole
Gold salts
Haloperidol
Heparin
Hydrochlorothiazide
Ibuprofen
Inamrinone
Indinavir
Indomethacin
Interferon-*α*
Isoniazid
Isotretinoin
Itraconazole
Levamisole
Linezolid
Lithium
Low-molecular-weight heparins
Measles, mumps, and rubella vaccine
Meclofenamate
Mesalamine
Methyldopa
Minoxidil
Morphine
Nalidixic acid
Naphazoline
Naproxen
Nitroglycerin
Octreotide
Oxacillin
p-Aminosalicylic acid
Penicillamine
Pentamidine
Pentoxifylline
Piperacillin
Primidone
Procainamide
Pyrazinamide
Quinidine
Quinine
Ranitidine
Recombinant hepatitis B vaccine
Rifampin
Simvastatin
Sirolimus
Sulfasalazine
Sulfonamides
Sulindac
Tamoxifen
Tolmetin
Trimethoprim
Vancomycin

See e/CHAPTER 24, Drug-Induced Hematologic Disorders, authored by Kamakshi V. Rao, for a more detailed discussion of this topic.

APPENDIX 4

Drug-Induced Liver Disease

TABLE A4–1 An Approach to Evaluating a Suspected Hepatotoxic Reaction

Points	−3	−1	0	+1	+2	+3
What is the temporal relationship? (days)						
From the start of therapy	—	—	??	<5	>90	5–90
From the end of therapy	>30	—	??	—	—	<30
Is there evidence of the concurrent use of a hepatotoxin[a]?	Yes	Maybe	??	—	—	No
Is there an alternate cause, such as, viral hepatitis?	Yes	Most likely—Yes	??	Most likely—No		No
Are there extrahepatic signs or symptoms?						
Dermatologic: rash, palmar erythema, cutaneous vasculitis	—	—	No	Yes (+1 for each)	—	—
Dermatologic: spider nevi, white nails (aka Terry's nails)	—	—	No	Yes (+1 for each)	—	—
Hematologic: coagulation disorders	—	—	No	Yes (+1 for each)	—	—
Endocrine disorders: insulin resistance, thyroid dysfunction	—	—	No	Yes (+1 for each)	—	—
Endocrine disorders: adrenal insufficiency, hypogonadism	—	—	No	Yes (+1 for each)	—	—
Skeletal muscular: arthralgias, arthritis	—	—	No	Yes (+1 for each)	—	—
Neurological: encephalopathy	—	—	No	Yes (+1 for each)	—	—
Portopulmonary hypertension	—	—	No	Yes (+1 for each)	—	—
Does the literature support a connection with this drug?						
Listed in the product labeling	—	—	—	—	—	Yes
Published reports in the literature	—	—	—	—	Yes	—
No information available, reaction is undocumented	—	—	Yes	—	—	—
Results from a rechallenge with the drug	Negative	—	—	Inconclusive	—	Positive

??, Uncertain.
A total score <7 makes it unlikely that this is a hepatotoxic reaction.
As the score approaches 14; the possibility that this is a hepatotoxic reaction increases toward certainty.
[a]*Drug, herbal remedy or other occupational exposure known to be potentially hepatotoxic.*

TABLE A4–2 Environmental Hepatotoxins and Associated Occupations at Risk for Exposure

Hepatotoxin	Associated Occupations at Risk for Exposure
Arsenic	Chemical plant, agricultural workers
Carbon tetrachloride	Chemical plant workers, laboratory technicians
Copper	Plumbers, sculpture artists, foundry workers
Dimethylformamide	Chemical plant workers, laboratory technicians
2,4-Dichlorophenoxyacetic acid	Horticulturists
Fluorine	Chemical plant workers, laboratory technicians
Toluene	Chemical plant, agricultural workers, laboratory tech
Trichloroethylene	Printers, dye workers, cleaners, laboratory technicians
Vinyl chloride	Plastics plant workers; also found as a river pollutant

TABLE A4–3 Relative Patterns of Hepatic Enzyme Elevation versus Type of Hepatic Lesion

Enzyme	Abbreviations	Necrotic	Cholestatic	Chronic
Alkaline phosphatase	AlkPhos, AP	↑	↑↑↑	↑
5′-Nucleotidase	5-NC, 5NC	↑	↑↑↑	↑
γ-Glutamyltransferase	GGT, GGTP	↑	↑↑↑	↑↑
Aspartate aminotransferase	AST, SGOT	↑↑↑	↑	↑↑
Alanine aminotransferase	ALT, SGPT	↑↑↑	↑	↑↑
Lactate dehydrogenase	LDH	↑↑↑	↑	↑

↑, <100% of normal; ↑↑, >100% of normal, ↑↑↑, >200% of normal.

See e/CHAPTER 17, Drug-Induced Liver Disease, authored by William R. Kirchain and Rondall E. Allen, for a more detailed discussion of this topic.

APPENDIX 5

Drug-Induced Pulmonary Disease

TABLE A5–1 Drugs That Induce Apnea

	Relative Frequency of Reactions
Central nervous system depression	
Narcotic analgesics	F
Barbiturates	F
Benzodiazepines	F
Other sedatives and hypnotics	I
Tricyclic antidepressants	R
Phenothiazines	R
Ketamine	R
Promazine	R
Anesthetics	R
Antihistamines	R
Alcohol	R
Fenfluramine	I
L-dopa	R
Oxygen	R
Respiratory muscle dysfunction	
Aminoglycoside antibiotics	I
Polymyxin antibiotics	I
Neuromuscular blockers	I
Quinine	R
Digitalis	R
Myopathy	
Corticosteroids	F
Diuretics	I
Aminocaproic acid	R
Clofibrate	R

F, frequent; I, infrequent; R, rare.

TABLE A5–2 Drugs That Induce Bronchospasm

	Relative Frequency of Reactions
Anaphylaxis (IgE-mediated)	
Penicillins	F
Sulfonamides	F
Serum	F
Cephalosporins	F
Bromelin	R
Cimetidine	R
Papain	F
Pancreatic extract	I
Psyllium	I
Subtilase	I
Tetracyclines	I
Allergen extracts	I
L-Asparaginase	F
Pyrazolone analgesics	
Direct airway irritation	
Acetate	R
Bisulfite	F
Cromolyn	R
Smoke	F
N-acetylcysteine	F
Inhaled steroids	I
Precipitating IgG antibodies	
β-Methyldopa	R
Carbamazepine	R
Spiramycin	R
Cyclooxygenase inhibition	
Aspirin/nonsteroidal antiinflammatory drugs	F
Phenylbutazone	I
Acetaminophen	R

(*continued*)

TABLE A5–2 Drugs That Induce Bronchospasm (*Continued*)

	Relative Frequency of Reactions
Anaphylactoid mast-cell degranulation	
Narcotic analgesics	I
Ethylenediamine	R
Iodinated-radiocontrast media	F
Platinum	R
Local anesthetics	I
Steroidal anesthetics	I
Iron–dextran complex	I
Pancuronium bromide	R
Benzalkonium chloride	I
Pharmacologic effects	
α-Adrenergic receptor blockers	I-F
Cholinergic stimulants	I
Anticholinesterases	R
β-Adrenergic agonists	R
Ethylenediamine tetraacetic acid	R
Unknown mechanisms	
Angiotensin-converting enzyme inhibitors	I
Anticholinergics	R
Hydrocortisone	R
Isoproterenol	R
Monosodium glutamate	I
Piperazine	R
Tartrazine	R
Sulfinpyrazone	R
Zinostatin	R
Losartan	R

F, frequent; I, infrequent; IgE, immunoglobulin E; R, rare.

TABLE A5–3 Tolerance of Antiinflammatory and Analgesic Drugs in Aspirin-Induced Asthma

Cross-Reactive Drugs	Drugs with No Cross-Reactivity
Diclofenac	Acetaminophen[a]
Diflunisal	Benzydamine
Fenoprofen	Chloroquine
Flufenamic acid	Choline salicylate
Flurbiprofen	Corticosteroids
Hydrocortisone hemisuccinate	Dextropropoxyphene
Ibuprofen	Phenacetin[a]
Indomethacin	Salicylamide
Ketoprofen	Sodium salicylate
Mefenamic acid	
Naproxen	
Noramidopyrine	
Oxyphenbutazone	
Phenylbutazone	
Piroxicam	
Sulindac	
Sulfinpyrazone	
Tartrazine	
Tolmetin	

[a]A very small percentage (5%) of aspirin-sensitive patients react to acetaminophen and phenacetin.

TABLE A5–4 Drugs That Induce Pulmonary Edema

	Relative Frequency of Reactions
Cardiogenic pulmonary edema	
Excessive IV fluids	F
Blood and plasma transfusions	F
Corticosteroids	F
Phenylbutazone	R
Sodium diatrizoate	R
Hypertonic intrathecal saline	R
β_2-Adrenergic agonists	I
Noncardiogenic pulmonary edema	
Heroin	F
Methadone	I
Morphine	I
Oxygen	I
Propoxyphene	R
Ethchlorvynol	R
Chlordiazepoxide	R
Salicylate	R
Hydrochlorothiazide	R
Triamterene + hydrochlorothiazide	R
Leukoagglutinin reactions	R
Iron–dextran complex	R
Methotrexate	R
Cytosine arabinoside	R
Nitrofurantoin	R
Dextran 40	R
Fluorescein	R
Amitriptyline	R
Colchicine	R
Nitrogen mustard	R
Epinephrine	R
Metaraminol	R
Bleomycin	R
Iodide	R
Cyclophosphamide	R
VM-26	R

F, frequent; I, infrequent; R, rare; VM-26, teniposide (Vumon).

TABLE A5–5 Drugs That Induce Pulmonary Infiltrates with Eosinophilia (Loeffler's Syndrome)

Drug	Relative Frequency of Reactions
Nitrofurantoin	F
para-Aminosalicylic acid	F
Amiodarone	F
Iodine	F
Captopril	F
Bleomycin	F
L-tryptophan	F
Methotrexate	F
Phenytoin	F
Gold salts	F
Sulfonamides	I
Penicillins	I
Carbamazepine	I
Granulocyte-macrophage colony stimulating factor	I
Imipramine	I
Minocycline	I
Nilutamide	I
Propylthiouracil	I
Sulfasalazine	I
Tetracycline	R
Procarbazine	R
Cromolyn	R
Niridazole	R
Chlorpromazine	R
Naproxen	R
Sulindac	R
Ibuprofen	R
Chlorpropamide	R
Mephenesin	R

F, frequent; I, infrequent; R, rare.

TABLE A5–6 Drugs That Induce Pneumonitis and/or Fibrosis

Drug	Relative Frequency of Reactions
Oxygen	F
Radiation	F
Bleomycin	F
Busulfan	F
Carmustine	F
Hexamethonium	F
Paraquat	F
Amiodarone	F
Mecamylamine	I
Pentolinium	I
Cyclophosphamide	I
Practolol	I
Methotrexate	I
Mitomycin	I
Nitrofurantoin	I
Methysergide	I
Sirolimus	I
Azathioprine, 6-mercaptopurine	R
Chlorambucil	R
Melphalan	R
Lomustine and semustine	R
Zinostatin	R
Procarbazine	R
Teniposide	R
Sulfasalazine	R
Phenytoin	R
Gold salts	R
Pindolol	R
Imipramine	R
Penicillamine	R
Phenylbutazone	R
Chlorphentermine	R
Fenfluramine	R
Leflunomide	R
Mefloquine	R
Pergolide	R

F, frequent; I, infrequent; R, rare.

TABLE A5-7	Possible Causes of Pulmonary Fibrosis
Idiopathic pulmonary fibrosis (fibrosing alveolitis)	
Pneumoconiosis (asbestosis, silicosis, coal dust, talc berylliosis)	
Hypersensitivity pneumonitis (molds, bacteria, animal proteins, toluene diisocyanate, epoxy resins)	
Smoking	
Sarcoidosis	
Tuberculosis	
Lipoid pneumonia	
Systemic lupus erythematosus	
Rheumatoid arthritis	
Systemic sclerosis	
Polymyositis/dermatomyositis	
Sjögren's syndrome	
Polyarteritis nodosa	
Wegener granuloma	
Byssinosis (cotton workers)	
Siderosis (arc welders' lung)	
Radiation	
Oxygen	
Chemicals (thioureas, trialkylphosphorothioates, furans)	
Drugs, various	

TABLE A5-8 Drugs That May Induce Pleural Effusions and Fibrosis

	Relative Frequency of Reactions
Idiopathic	
Methysergide	F
Practolol	F
Pindolol	R
Methotrexate	R
Nitrofurantoin	R
Drug-Induced lupus syndrome	
Procainamide	F
Hydralazine	F
Isoniazid	R
Phenytoin	R
Mephenytoin	R
Griseofulvin	R
Trimethadione	R
Sulfonamides	R
Phenylbutazone	R
Streptomycin	R
Ethosuximide	R
Tetracycline	R
Pseudolymphoma syndrome	
Cyclosporine	R
Phenytoin	R

F, frequent; I, infrequent; R, rare.

See e/CHAPTER 15, Drug-Induced Pulmonary Diseases, authored by Hengameh H. Raissy and Michelle Harkins, for a more detailed discussion of this topic.

Drug-Induced Kidney Disease

APPENDIX 6

TABLE A6–1 Drug-Induced Kidney Structural-Functional Alterations

Tubular epithelial cell damage

Acute tubular necrosis
- Aminoglycoside antibiotics
- Radiographic contrast media
- Cisplatin, carboplatin
- Amphotericin B
- Cyclosporine, tacrolimus
- Adefovir, cidofovir, tenofovir
- Pentamidine
- Foscarnet
- Zoledronate

Osmotic nephrosis
- Mannitol
- Dextran
- IV immunoglobulin

Hemodynamically mediated kidney injury
- Angiotensin-converting enzyme inhibitors
- Angiotensin II receptor blockers
- Nonsteroidal antiinflammatory drugs (NSAIDs)
- Cyclosporine, tacrolimus
- OKT3

Obstructive nephropathy

Intratubular obstruction
- Acyclovir
- Sulfonamides
- Indinavir
- Foscarnet
- Methotrexate

Nephrolithiasis
- Sulfonamides
- Triamterene
- Indinavir

Nephrocalcinosis
- Oral sodium phosphate solution

Glomerular disease
- Gold
- Lithium
- NSAIDs, cyclooxygenase-2 inhibitors
- Pamidronate

Tubulointerstitial disease

Acute allergic interstitial nephritis
- Penicillins
- Ciprofloxacin
- NSAIDs, cyclooxygenase-2 inhibitors
- Proton pump inhibitors
- Loop diuretics

Chronic interstitial nephritis
- Cyclosporine
- Lithium
- Aristolochic acid

Papillary necrosis
- NSAIDs, combined phenacetin, aspirin, and caffeine analgesics

Renal vasculitis, thrombosis, and cholesterol emboli

Vasculitis and thrombosis
- Hydralazine
- Propylthiouracil
- Allopurinol
- Penicillamine
- Gemcitabine
- Mitomycin C
- Methamphetamines
- Cyclosporine, tacrolimus
- Adalimumab
- Bevacizumab

Cholesterol emboli
- Warfarin
- Thrombolytic agents

TABLE A6–2 Potential Risk Factors for Aminoglycoside Nephrotoxicity

(A) Related to aminoglycoside dosing:
Large total cumulative dose
Prolonged therapy
Trough concentration exceeding 2 mg/L[a]
Recent previous aminoglycoside therapy
(B) Related to synergistic nephrotoxicity. Aminoglycosides in combination with
Cyclosporine
Amphotericin B
Vancomycin
Diuretics
Iodinated radiographic contrast agents
Cisplatin
NSAIDs
(C) Related to predisposing conditions in the patient
Preexisting kidney disease
Diabetes
Increased age
Poor nutrition
Shock
Gram-negative bacteremia
Liver disease
Hypoalbuminemia
Obstructive jaundice
Dehydration
Hypotension
Potassium or magnesium deficiencies

[a]The equivalent concentration in SI molar units are 4.3 µmol/L for tobramycin, 4.2 µmol/L for gentamicin.

TABLE A6–3 Recommended Interventions for Prevention of Contrast Nephrotoxicity

Intervention	Recommendation	Recommendation Grade[a]
Contrast	• Minimize contrast volume/dose	A-1
	• Use noniodinated contrast studies	A-2
	• Use low- or iso-osmolar contrast agents	A-2
Medications	• Avoid concurrent use of potentially nephrotoxic drugs, for example, NSAIDs, aminoglycosides	A-2
Isotonic sodium chloride (0.9%)	• Initiate infusion 3–12 hours prior to contrast exposure and continue 6–24 hours postexposure	A-1
	• Infuse at 1–1.5 mL/kg/h adjusting postexposure as needed to maintain a urine flow rate of ≥150 mL/h	
	• Alternatively, in urgent cases, initiate infusion at 3 mL/kg/h, beginning 1 hour prior to contrast exposure, then continue at 1 mL/kg/h for 6 hours postexposure	
Isotonic sodium bicarbonate (154 mEq/L [154 mmol/L])	• Initiate and maintain infusion as per isotonic sodium chloride above	B-2
	• Alternatively, initiate infusion at 3 mL/kg/h, beginning 1 hour prior to contrast exposure, then continue at 1 mL/kg/h for 6 hours postexposure	
N-acetylcysteine	• Administer 600–1,200 mg by mouth (PO) every 12 hours, 4 doses beginning prior to contrast exposure (i.e., 1 dose prior to exposure and 3 doses postexposure)	B-1

[a]*Strength of recommendations*: A, B, and C are good, moderate, and poor evidence to support recommendation, respectively. *Quality of evidence*: 1, evidence from more than 1 properly randomized, controlled trial; 2, evidence from more than 1 well-designed clinical trial with randomization, from cohort or case-controlled analytic studies or multiple time series, or dramatic results from uncontrolled experiments; 3, evidence from opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert communities.

TABLE A6–4 Drugs Associated with Allergic Interstitial Nephritis	
Antimicrobials	
Acyclovir	Indinavir
Aminoglycosides	Rifampin
Amphotericin B	Sulfonamides
β-Lactams	Tetracyclines
Erythromycin	Trimethoprim–sulfamethoxazole
Ethambutol	Vancomycin
Diuretics	
Acetazolamide	Loop diuretics
Amiloride	Triamterene
Chlorthalidone	Thiazide diuretics
Neuropsychiatric	
Carbamazepine	Phenytoin
Lithium	Valproic acid
Phenobarbital	
Nonsteroidal antiinflammatory drugs	
Aspirin	Ketoprofen
Indomethacin	Phenylbutazone
Naproxen	Diclofenac
Ibuprofen	Zomepirac
Diflunisal	Cyclooxygenase-2 inhibitors
Piroxicam	
Miscellaneous	
Acetaminophen	Lansoprazole
Allopurinol	Methyldopa
Interferon-*a*	Omeprazole
Aspirin	*P*-aminosalicylic acid
Azathioprine	Phenylpropanolamine
Captopril	Propylthiouracil
Cimetidine	Radiographic contrast media
Clofibrate	Ranitidine
Cyclosporine	Sulfinpyrazone
Glyburide	Warfarin sodium
Gold	

See CHAPTER 31, Drug-Induced Kidney Disease, authored by Thomas D. Nolin, for a more detailed discussion of this topic.

This page intentionally left blank

Index

Page numbers followed by *f* or *t* indicate figures or tables, respectively.

A

Abacavir in HIV infection, 373*t*–374*t*, 376*t*, 379
Abatacept in rheumatoid arthritis, 27, 28*f*, 30*t*, 35
Abciximab in acute coronary syndromes, 42, 45
Abdominal laparotomy, 398
Abdominal pain, 14, 31*t*, 126, 189, 213, 223*t*, 248
  pancreatic, 247
  symptom of peptic ulcer disease (PUD), 251
Abiraterone, in prostate cancer, 659, 662*t*
Abscess, 400*t*
  chronic renal, 490
  crypt, 221, 222*t*
  intraabdominal infection, 394, 395, 404
  perirectal, 223*t*
  peritonsillar, 420
Absorption of drugs, 210
Acamprosate in alcohol dependence, 765
Acarbose in diabetes mellitus, 167*t*, 169
ACE inhibitors. *See* Angiotensin-converting enzyme inhibitors
Acebutolol in hypertension, 90*t*, 95
Acetaminophen, 252
  in acute otitis media, 418
  in bronchitis, acute, 405
  in chronic pancreatitis, 248
  dosing guidelines, 567*t*
  for follicular lymphoma, 651
  in migraine headache, 546*t*
  in osteoarthritis, 10, 11*t*, 14
  in pain management, 560*t*, 563, 573*t*, 575*t*
  in respiratory tract infections, 420
  for sickle cell crisis, 311
  in tension-type headache, 293, 555
  in thyroid disorders, 181
Acetazolamide
  in glaucoma, 671*t*
  for specific seizure disorders, 525
Acetohexamide in diabetes mellitus, 166*t*
Acetylsalicylic acid. *See* Aspirin
Acid-base diagnosis, 772*t*
Acid-base disorders, 771–778
  general principles, 771
  metabolic acidosis, 771–775
    treatment, 773–775
  metabolic alkalosis, 775
  mixed, 778
  respiratory acidosis, 777
  respiratory alkalosis, 775, 777
Acid secretion, 251
  gastric, 96, 210
Acidemia
  in acid-base diagnosis, 772*t*
  in arterial blood gases, 772*f*
  lactic, 397*t*
  metabolic, 772
Acidosis
  metabolic, 62, 63, 111, 535*t*, 536*t*, 593, 751, 771–775, 778
  respiratory, 777, 836
    pathophysiology of, 777
Acinetobacter infections, 316*t*, 413*t*
Acitretin in psoriasis, 151
Aclidinium bromide, in chronic obstructive pulmonary disease, 840
ACLS (advanced cardiac life support), 60
Acne, noninflammatory, 135
Acne vulgaris, 135–140
  drug mechanisms, 136*f*
  exfoliants, 137
  general approach to treatment of, 135
  nonpharmacologic therapy, 136
  pathogenesis, 136*f*
Acneiform drug reactions, 143
ACS (acute coronary syndromes), 37–47
ACTH. *See* Adrenocorticotropic hormone
Activated partial thromboplastin time (aPTT), 128

Acute coronary syndrome (ACS), 37–47
  classification of, 37
  early pharmacotherapy
    for non-ST-segment-elevation ACS, 44–46, 45*f*
    for ST-segment-elevation MI, 38–44
  fibrinolytic therapy, 39, 41
  nonpharmacologic therapy in, 38
Acute generalized exanthematous pustulosis (AGEP), 143
Acute gouty arthritis, 2–5
  colchicine, 4–5
  corticosteroids, 2, 4
  nonsteroidal antiinflammatory drugs, 4*t*
  nonpharmacologic therapy, 2
  prophylactic therapy of intercritical gout, 8
  treatment algorithm, 2, 3*f*
Acute kidney injury. *See* Kidney injury, acute
Acute migraine therapies. *See* Migraine Headaches
Acute pancreatitis. *See* Pancreatitis, acute
Acute Physiology and Chronic Health Evaluation II (APACHE II) score in sepsis and septic shock, 430*t*
Acyclovir, 294, 331*t*
  for genital herpes, 441, 444*t*
  for HIV, 383*t*
  penetration into cerebrospinal fluid (CSF), 326*t*
Adalimumab, 29*t*
  in dermatologic disorders, 151
  in inflammatory bowel disease, 224, 225*t,* 227, 229*t*
  in psoriasis, 151
  in rheumatoid arthritis, 27, 31*t,* 35
Adapalene in acne vulgaris, 138
Addison's disease, 155, 158, 159, 232*t,* 695*t,* 811
Adefovir in hepatitis B, 216
Adenocarcinoma of prostate, 654
Adenoma
  adrenal, 156, 157*t*
  familial adenomatous polyposis, 631
  pituitary, 155
  thyroid-stimulating hormone (TSH)-secreting pituitary, 177
  toxic, 178
Adenosine, 57
  in paroxysmal supraventricular tachycardia (PSVT), 57
Adrenal gland disorders. *See* Adrenal insufficiency
Adrenal insufficiency, 158–160
  nonpharmacologic therapy in, 159
  pharmacotherapy of, 159–160
Adrenergic agonists
  α-benign prostatic hyperplasia, 845
    vasovagal syncope, 58
  α_2-bipolar disorder
    in glaucoma, 665, 669*t*
    secondary causes of mania, 695*t*
  β_3-urinary incontinence, 869*t*
Adrenergic antagonists
  α-erectile dysfunction, 861
    urologic disorders, 847–848
  β-erectile dysfunction, 851*t*
  α_1-in anxiety disorders, 693
  α_2-in depression, 717*t*, 724*t*
  β-in neurologic disorders, 554
  α_2-in psychiatric disorders, 695*t*
β-adrenergic antagonists, 50
Adrenergic blockers, β-acute coronary syndromes, 43
  asthma, 827*t*
  glaucoma, 665
  ischemic heart disease, 104
Adrenocorticotropic hormone (ACTH), 116*f,* 155, 224, 655*f*
  in gout, 4
Adriamycin. *See* Doxorubicin
Advanced cardiac life support (ACLS), 60
AED (automated external defibrillator), 60
Aerosolized β-adrenergic therapy, 410
AGEP (acute generalized exanthematous pustulosis), 143
Agoraphobia, 674, 686
Akathisia, 733, 740, 742, 744*t*
  in psychiatric disorders, 740, 742, 744*t*
Albumin, 16, 29*t,* 113
  in infectious diseases, 431
  markers of hepatic synthetic activity, 187

Albuterol
in allergic rhinitis and asthma, 294
in anxiety disorders, 676*t*
in asthma, 823, 827*t,* 828*t*
in bronchitis, chronic, 407
in chronic obstructive pulmonary disease, 837
for hyperkalemia, 808, 810*f*
in pneumonia, 415
in renal disorders, 807*t*
Alclometasone dipropionate in psoriasis, 149*t*
Alcohol
causing cirrhosis, 186*t*
as central nervous system depressants, 685, 755–756
intoxication, 695*t,* 761*t*
substance-related disorders, 765
withdrawal from pharmacologic agents used in, 763*t*–764*t*
Aldosterone antagonists
in heart failure, 80
in hypertension, 94
Aldosterone receptor antagonist in chronic heart failure, 76
Aldosteronism, hypertension in, 87, 88
Alefacept in psoriasis, 152
Alendronate in osteoporosis, 19, 21*t*
Alfuzosin
in prostate hyperplasia, benign, 847*t*
in urologic disorders, 847
Alginic acid and antacids in gastroesophageal reflux disease, 210
Aliskiren in hypertension, 93*t,* 95
Alkaline phosphatase levels, in liver disorders, 187
Alkalosis, 397*t,* 775
metabolic, 775, 776*f,* 777
respiratory, 775, 777, 778
Allergic contact dermatitis (ACD), 141
Allergic rhinitis, 813–820
topical decongestants, duration of action, 818*t*
treatment of
algorithm for, 815*f*
immunotherapy, 819–820
nonpharmacologic therapy, 814
pharmacologic therapy
antihistamines, 814–815
cromolyn sodium, 819
decongestants, 815–818
ipratropium bromide, 819
montelukast, 819
nasal corticosteroids, 818–819, 818*t*
Allopurinol, in hyperuricemia, 7
Almotriptan in migraine headache, 548*t,* 550*t*
Alogliptin in diabetes mellitus, 167*t,* 170
Alprazolam
in antiemetic preparations, 236*t*
for anxiety disorders, 677*t,* 683*t*
pharmacokinetics of benzodiazepine antianxiety agents, 684*t*
as sedative-hypnotic, 756
treatment of panic disorder, 687*t,* 689
withdrawal from, 762
Alprostadil, 863–864
in erectile dysfunction, 855*t,* 863
intracavernosal injection, 863
intraurethral administration, 863–864
Alteplase
in acute coronary syndromes, 41
in stroke, 121, 123*t*
in venous thromboembolism (VTE), 133
Aluminum acetate in contact dermatitis, 144
Aluminum hydroxide in chronic kidney disease, 795*t*
Alvimopan, 198
Alzheimer's disease (AD), 511–517
antidepressants, 517
antipsychotics, 516
cholinesterase inhibitors, 516
cognitive symptoms, treatment options for, 513–516, 514*t*–515*t*
dementia, noncognitive symptoms, 516*t*
diagnosis of, 511–512
memantine in, 516
noncognitive symptoms, pharmacotherapy of, 516–517

Alzheimer's disease (AD) (*Cont.*)
treatment of
cholinesterase inhibitors, 513
memantine, 513–516
nonpharmacologic therapy, 512–513
Amantadine
in anxiety disorders, 676*t*
drugs associated with anxiety symptoms, 676*t*
in influenza, 388, 392*t*
in Parkinson's disease, 579, 580*t,* 581*t*, 583, 585*t*
Amcinonide in psoriasis, 149*t*
Amenorrhea, 155, 176, 275, 276, 759
American Association of Clinical Endocrinologists on diabetes mellitus therapy goals, 162*t*
American Society of Anesthesiologists Physical Status Classification, 468*t*
Amikacin
in antimicrobial regimen, 316*t*–317*t*
in tuberculosis drugs for adults and children, 484*t,* 487*t*
for urinary tract infections, 494*t*
Amiloride
in acute kidney injury, 785
in central and nephrogenic diabetes insipidus, 801*t*
in hypertension, 90*t,* 773*t*
Aminoglutethimide
in Cushing's syndrome, 156
in prostate cancer, 659
treatment plans in Cushing's syndrome based on etiology, 157*t*
Aminoglycoside antibiotics, 318
in bacterial meningitis, 325*t,* 332
in bacterial pneumonia, 417*t*
for cellulitis caused by various pathogens, 460*t*
interaction with other drugs, 319*t*
penetration into the cerebrospinal fluid (CSF), 326*t*
in sepsis, 431*t*
for urinary tract infections, 494*t*
Aminophylline
in asthma, 830
in chronic obstructive pulmonary disease, 840
in respiratory disorders, 840
5-Aminosalicylic acid. *See* Mesalamine
Amiodarone, 50–52, 51*t*, 52*t*, 57
in atrial flutter, 54*t*
in cardiac arrest, 62
Amitriptyline, 691, 716*t*, 719*t*, 726*t*
in major depression, 726*t*
in neurologic disorders, 554
for pain management, 559*f*
in posttraumatic stress disorder, 692*t*
as prophylactic migraine therapies, 551*t*
in sleep disorders, 748
Amlodipine
in acute coronary syndromes, 44
in ischemic heart disease, 106
Amoxapine in depression, 721
Amoxicillin, 419*t*
in acute bacterial sinusitis, 424
in bronchitis, chronic, 409*t*
dosing guidelines
for acute bacterial sinusitis, 425*t*
for pharyngitis, 422*t*
to eradicate *Helicobacter pylori,* 254*t*
in gastrointestinal disorders, 253
in infectious diseases, 315*t*–138*t,* 419
for pharyngitis, 420
in pneumonia, 416*t*
regimens for dental procedure, 345*t*
for surgical prophylaxis, 469*t*
to treat sexually transmitted diseases, 295*t*
for treatment of acute respiratory exacerbations, 409*t*
in urinary tract infections, 498
Amoxicillin-clavulanate, 419*t*, 453*t*, 454*t*
for acute bacterial sinusitis, 425*t,* 426*t*
in bronchitis, chronic, 409*t*
for cellulitis, 461*t*
in chronic obstructive pulmonary disease, 842
for diabetic foot infections, 463*t*
for dog bites, 464
for pneumonia in pediatric patients, 416*t*
for skin and soft-tissue infections, 464, 465
in urinary tract infections, 493*t,* 496*t,* 498

Amphetamines
anxiety disorders, 676*t*
associated with anxiety symptoms, 676*t*
hypertension, 87
induce mania, 695*t*
bipolar disorder, 697*t*
in obesity, 604
in narcolepsy, 754
Amphotericin B, 331*t*
for blastomycosis, 352*t,* 353
for cryptococcosis, 354*t,* 358
drug interactions, 319*t*
in infectious diseases, 350
for invasive candidiasis, 356*t*
penetration into cerebrospinal fluid (CSF), 326*t*
for histoplasmosis, 348*t,* 349*t*
Ampicillin, 330*t*
in bronchitis, chronic, 409*t*
dosing of, 455*t*
in enterococcal endocarditis, 342
in gynecologic and obstetric disorders, 299
in infectious diseases, 315*t*–317*t*
for intraabdominal infections, 399*t*
in meningitis, 327*t*–328*t*
in pneumonia, 413*t,* 416*t*
Ampicillin-sulbactam
for dog bites, 464
for human bites, 465
in pneumonia, 416*t*
in urinary tract infections, 494*t*
Anakinra in rheumatoid arthritis, 28, 30*t*, 35
Analgesics, 10
causing constipation, 195*t*
for management of acute pain, 558*f*
for migraine headaches, 549*f*
in neurologic disorders, 545, 563
pain management in oncology patients, 559*f*
Anaphylaxis
in allergic drug reactions, 820
shock in, 111
Anastrozole in breast cancer, 624, 625*t*
Anemia, 301, 301–307. *See also specific types*
classification systems for, 302*f*
megaloblastic, 307
in pediatric populations, 305
treatment of, 304, 306*t,* 788, 792
folate-deficiency, 305
of inflammation, 305
iron-deficiency, 304
vitamin B_{12}-deficiency, 304–305
Anesthetics, local, 576*t*
Angioedema, 141
Angiotensin-converting enzyme (ACE) inhibitors, 81
cause of metabolic acidosis, 773*t*
causing diarrhea, 201*t*
in chronic heart failure, 76
in chronic kidney disease, 761*f*
in heart failure, 88
in hypertension, 90–93
in managing renal disease in diabetic individuals, 790*f*
routinely used for treatment of heart failure, 78*t*
in secondary prevention after myocardial infarction, 46
for ST-segment-elevation myocardial infarction, 38
in systolic heart failure, 78–79
Angiotensin II receptor blockers, 79–80, 88
in hypertension, 93
Angiotensin receptor blockers in secondary prevention after myocardial infarction, 46
Antacids
causing diarrhea, 201*t*
in gastroesophageal reflux disease, 207, 208*f,* 208*t*
in nausea and vomiting, 232, 235*t*
in renal disorders, 806
vitamin interactions, 608*t*
Anthonisen criteria, for antibiotic therapy, 408
Anthracyclines in breast cancer, 627
Anthralin in psoriasis, 150
Antiarrhythmic drugs
in cardiac arrest, 62
classification of, 50–51
side effects, 54*t*
Antibiotics
in bronchiolitis, 410
in bronchitis
acute, 406
chronic, 408, 408*f,* 409*t*
for diarrhea, 366

Antibiotics (*Cont.*)
for enterotoxigenic (cholera-like) diarrhea, 363*t*
in intraabdominal infections, 395, 401*t*–403*t,* 404
intraperitoneal administration of, 404
in pneumonia, 415, 416*t,* 417*t*
for *Vibrio cholerae* infection, 363*t*
vitamin interactions, 608*t*
Anticholinergic effects, 96, 424, 678, 719*t*–720*t,* 738, 739*t,* 744*t*, 837, 840, 845, 866*t,* 870
Anticholinergic medications, 579, 583, 666*t*, 740, 848
Anticholinergics in anxiety disorders, 676*t*
Anticoagulants in acute coronary syndromes, 42–43, 44
Anticonvulsant drugs, 20*t,* 141, 143, 174, 512, 554–555, 559*f,* 699*t,* 708
adverse effects, 591*t*–592*t*
associated with anxiety symptoms, 676*t*
in bipolar I disorder, 698*t,* 701*t*–703*t*
dosing of, 590*t*
in generalized convulsive status epilepticus (GCSE), algorithm for, 589*f*
for pain in oncology patients, 559*f*
in posttraumatic stress disorder, 692*f*
in refractory generalized convulsive status epilepticus, 595*t*–596*t*
Antidepressant drugs
adult dosages for, 715*t*
cytochrome (CYP) P450 enzyme and second- and third-generation, 729*t*
in dementia, 516*t*
newer-generation, drug interactions of, 722*t*–724*t*
norepinephrine and serotonin reuptake blockade and side effect profile, 719*t*–720*t*
ophthalmic disorders, 666*t*
pharmacokinetic properties of, 726*t*–727*t*
Antiepileptic drugs
dosing, target serum concentration ranges, 528*t*–529*t*
pharmacokinetic data, 526*t*–527*t*
side effects, 531*t*–536*t*
Antiestrogens in breast cancer, 625*t*
Antifungal agents, 145
Antihistamines
adverse effects, 816*t*
in anxiety disorders, 676*t*
drug-induced skin reactions, 144
ophthalmic disorders, 666*t*
dosages of, 817*t*
Antihypertensive agents, 93*t*
Antimicrobial prophylaxis. *See also* Antimicrobial regimen
use of, 468*t*
Antimicrobial regimen, 313–322, 468*t*
in bacterial cellulitis, 459
combinations, 321
disadvantages of, 321
confirming presence of infection, 313
fever, 313
signs and symptoms, 313
drug factors, 318, 321
drugs of choice, first, and alternative(s), 315*t*–138*t*
evidence-based empiric, 415*t*–416*t*
failure of, 322
goals of, 398
host factors, 314, 318
identification of pathogen, 314
major drug interactions with, 319*t*–320*t*
monitoring therapeutic response, 321
in respiratory disorders, 842
selection of presumptive, 314
in sepsis and septic shock, 429
synergistic activity, 321
systematic approach, for selection of, 314*t*
for otitis media, 419
Antimotility drugs, 361
Antipsychotics
in dementia, 516*t*
depot, 737
dosage range, 732*t*
monitoring parameters, 744*t*–746*t*
pharmacokinetic parameters of, 735*t*–736*t*
side effect of, 739*t,* 744*t*–746*t*
Antiresorptive therapy in osteoporosis, 17–24
Antituberculosis drugs adults/children, doses, 482*t*–485*t*

Anxiety disorders, 673–693
drug choices for, 677*t*
drugs used in, 690*t*
nonbenzodiazepine antianxiety agents for, 678*t*
panic disorder
alprazolam/clonazepam, 686
antidepressants, 686
benzodiazepines, 686–687
dosing and administration, 687, 689
general approach, 686
therapeutic outcomes, evaluation of, 689
pharmacotherapy algorithm, 689*f*
posttraumatic stress disorder, 691–693
social anxiety disorder, 689–693
treatment
abuse, dependence, withdrawal, and tolerance, 685
adverse events, 685
antidepressants, 678
benzodiazepine discontinuation, 685
benzodiazepine therapy, 678, 683
buspirone therapy, 685
dosing and administration, 685, 686
drug interactions, 685
generalized, 677–683
pharmacokinetics, 683
Anxiety symptoms
common medical illnesses, 676*t*
drugs associated with, 676*t*
Apixaban
in atrial flutter, 54
in venous thromboembolism (VTE), 130
Apomorphine
in neurologic disorders, 581*t*, 586
in Parkinson's disease, 580*t*, 584*t*
Appendicitis, 400*t*
Apraclonidine, 667
Arformoterol in chronic obstructive pulmonary disease, 837
Aripiprazole, 703*t*, 710
in bipolar disorder, 710
in dementia, 516*t*
in schizophrenia, 735*t*, 739*t*
side effects, 739*t*
Aromatase inhibitors in breast cancer, 624, 625*t*
Arrhythmia, 48–50
Arterial blood gases, analysis of, 772*f*
Arteriovenous malformation (AVM), 120
Ascites, 185, 189, 191
Asenapine, 703*t*
in bipolar disorder, 710
in schizophrenia, 739*t*
Aspiration pneumonia, 415*t*
Aspirin
in acute bronchitis, 405
in acute coronary syndromes, 41, 44
in Alzheimer's disease, 513
in migraine headache, 546*t*
in pain management, 560*t*
Reye's syndrome in children, 406
in rheumatoid arthritis, 33*t*
in secondary prevention after myocardial infarction, 46
in stroke, 121
in tension-type headache, 555
vitamin interactions, 608*t*
Asthma
acute exacerbation, home management of, 826*f*
β-adrenergic agonists, relative selectivity, 827*t*
in adults/children, management of, 824*f*–825*f*
inhaled corticosteroids lung delivery, 831*t*
systemic corticosteroids comparison of, 832*t*
theophylline dosage, titration of algorithm, 832*f*
treatment
drugs, dosages of, 828*t*–829*t*
nonpharmacologic therapy, 823
pharmacotherapy
β_2-agonists, 823, 830
anticholinergics, 832–833
combination controller therapy, 833
corticosteroids, 830
leukotriene modifiers, 833
mast cell stabilizers, 833
methylxanthines, 830–832
omalizumab, 834
zafirlukast, 833

Atazanavir in HIV infection, 372, 377*t*
Atenolol
  in acute coronary syndromes, 43
  in hypertension, 95
  in posttraumatic stress disorder, 691
Atopic dermatitis, 141, 143
Atorvastatin in hyperlipidemia, 69*t*, 70*t*, 71, 797
Atrial fibrillation, treatment algorithm for, 55*f*
Atrioventricular block, atropine in, 58
Atropine
  in atrioventricular block, 58
  in diarrhea, 203
Attapulgite, antidiarrheal preparations, 204*t*
Auranofin in rheumatoid arthritis, 28, 30*t*
Automated external defibrillator (AED), 60
Avanafil for erectile dysfunction, 854*t*, 860, 861*t*
Azalide in bacterial pneumonia, 416*t*
Azathioprine, 227, 228, 229*t*
  in inflammatory bowel disease, 224, 225*t*
  in rheumatoid arthritis, 28, 31*t*
Azelaic acid in acne vulgaris, 138
Azelastine in allergic rhinitis, 815, 816*t*
Azithromycin
  in acute exacerbation of COPD, 842
  in acute otitis media, 419*t*
  in bronchitis
    acute, 406
    chronic, 409*t*
  in chlamydial infections, 440, 442*t*
  in gastrointestinal infections, 366
  in pneumonia, 413*t*, 416*t*
  to treat sexually transmitted diseases, 295*t*
Azithromycin/amoxicillin in gonorrhea, 437*t*
Aztreonam
  dosing by age group, 330*t*
  dosing of, 455*t*
  in infectious diseases, 317*t*
  in intraabdominal infections, 399*t*–400*t*
  for urinary tract infections, 495*t*, 495*t*

B

B cells in rheumatoid arthritis, 26, 27
Back pain in osteoporosis-related spinal fractures, 16
Bacteremia, 315*t*, 322, 333, 335, 346, 382*t*–383*t*, 428*t*, 459
Bacterial infections, 153, 308, 361, 364
  associated with elevated granulocyte counts, 313
  bronchiolitis, 409, 410
  bronchitis, 406
  peritonitis, 394–404
  pneumonia, 410–417
Bacterial sinusitis
  acute
    antibiotic recommendations, 425*t*–426*t*
    dosing guidelines for, 425*t*–426*t*
Bacteriuria
  asymptomatic, 293
  in catheterization, 499
  in pregnancy, 498
  significant, diagnostic criteria for, 491*t*
Bacteroides infections, peritonitis, 394, 395, 396*t*
Balance disorders, nausea and vomiting, 243
Balloon pump, intraaortic, in heart failure, 85
Balsalazide in inflammatory bowel disease, 225*t*
Barbiturates
  causing erectile dysfunction, 851*t*
  in dermatologic disorders, 141, 143
  dosing and target serum concentration ranges, 528*t*
  medications used to prevent and treat osteoporosis, 20*t*
  in neurologic disorders, 525
  nonbenzodiazepine $GABA_A$ agonists, 750
  secondary causes of mania, 695*t*
  substance intoxication, 761*t*
  treatment of withdrawal, 762*t*
Barrett esophagus, 206, 212
Barrier technique, for contraception, 257, 261
Basal metabolic rate, 599
Beclomethasone dipropionate, as nasal corticosteroids, 818*t*, 831*t*
Bed sore, 462

Bendamustine, 651
Benign prostatic hyperplasia (BPH), 845–849
  cardiovascular risk stratification of, 862*t*
  categories of, 846*t*
  management algorithm for, 846*f*
  medical treatment options for, 847*t*
  treatment of, 845–849
    α-adrenergic antagonists, 847–848
    pharmacologic therapy, 846–848
    phosphodiesterase inhibitors, 848
    phytotherapy, 849
    5α-reductase inhibitors, 848
    surgical intervention, 849
Benserazide, 583
Benzodiazepines
  adverse effects, 681*t*, 750
  antianxiety agents, 673, 677*t*, 683*t*
    pharmacokinetics of, 684*t*
  antiemetic preparations and adult dosage regimens, 236*t*
  dosing and target serum concentration ranges, 528*t*
  in bipolar disorder, 698*t*, 704*t*
  hypnotics, 750
  in nausea and vomiting, 232*t*
  in neurologic disorders, 525, 593
  ophthalmic disorders, 666*t*
  in posttraumatic stress disorder, 691
  receptor agonists, pharmacokinetics of, 749*t*
  as sedative-hypnotics, 756
  in status epilepticus, 593
  treatment of generalized social anxiety disorder, 690*t*
Benzodiazepines in alcohol withdrawal, 764*t*
Benzodiazepine receptor agonists, pharmacokinetics of, 749*t*
Benzoyl peroxide in acne vulgaris, 138
Benztropine
  in causing constipation, 195*t*
  extrapyramidal side effects, treatment of, 739*t*
  in Parkinson's disease, 580*t*, 581*t*
Bepotastine in allergic rhinitis, 815, 816*t*
Betamethasone
  in adrenal gland disorders, 159*t*
  to prevent preterm labor, 299
Betamethasone dipropionate
  in atopic dermatitis, 145
  in psoriasis, 149*t*
Betaxolol, 669*t*
  in hypertension, 95
Bethanechol, 211
Bevacizumab, 233*t*
  in breast cancer, 629*t*
  emetogenicity, 233*t*
  lung cancer, treatment of, 644*t*, 645
  for metastatic colorectal cancer, 635, 636*t*, 637*t*, 640*t*
Bicalutamide
  for advanced prostate cancer, 659, 660*t*
  in prostate hyperplasia, benign, 846, 847*t*
Bichloracetic acid in genital papillomavirus warts, 446*t*, 447*t*
Biguanides in diabetes mellitus, 165, 167*t*, 169
Bile acid resins in hyperlipidemia, 68, 71
  in combination therapy, 69*t*
Bimatoprost in glaucoma, 667, 671*t*
Biperiden for antipsychotic drug side effects, 739*t*
Bipolar disorder
  baseline and routine laboratory tests, 705*t*–706*t*
  course of, 694–695
  general principles for management of, 697*t*
  hypomanic episode, 694
  major depressive episode, 694
  manic episode, 694
  products, dosage and administration, 701*t*–704*t*
  treatment
    alternative, 710
    antipsychotics, 710
    carbamazepine, 708–709
    general approach, 695–697
    lamotrigine, 709–710
    lithium, 700, 707–708
    nonpharmacologic therapy, 697, 700
    oxcarbazepine, 709
    pharmacologic therapy, 700–711
    in special populations, 710–711
    valproate sodium, 708

Bisacodyl in constipation, 196
Bismuth subsalicylate (Pepto-Bismol), 202
  antidiarrheal preparations, 205*t*
Bisoprolol
  in heart failure, 79
  in hypertension, 95
Bisphosphonates in osteoporosis, 19, 23, 25
Bitolterol in chronic obstructive pulmonary disease, 837
Bivalirudin in acute coronary syndromes, 42–43, 44, 45
Blackhead (open comedo), 135
Bleomycin, 233*t*
  in Hodgkin lymphoma, 649*t*
β-Blockers
  in acute coronary syndromes, 46
  as antiarrhythmic drugs, 50, 51*t*
  in chronic heart failure, 76
  in hypertension, 88, 94–95
  in ischemic heart disease, 104, 109
  for patients with paroxysmal supraventricular tachycardia (PSVT), 57
  in secondary prevention after myocardial infarction, 46
  in systolic heart failure, 79
Blood alcohol concentration, effects of, 756*t*
Blood gases, 771, 772*t*
Blood pressure, 50, 62, 78, 262, 362*t*, 757
  arterial, 87
  diastolic, 87
  episcleral venous, 665
  systolic, 87, 114*f*, 115*f*
Body mass index, 16, 599, 605, 744
Bone and joint disorders, 1–36
Bone mineral density
  depot medroxyprogesterone acetate (DMPA) reducing, 274
  in osteoporosis, 16, 18*f*, 289, 530, 658
Bordetella pertussis infections, acute bronchitis, 405
Borrelia burgdorferi infections, 318*t*
Bortezomib, chemotherapeutic agents, 233*t*
BPH. *See* Benign prostatic hyperplasia
Bradyarrhythmias, 49, 58, 758
Breast cancer, 622*t*–623*t*
  locally advanced breast cancer (stage III), 624
  metastatic breast cancer (stage IV)
    biologic/targeted therapy, 627, 630
    chemotherapy, 627
    endocrine therapy, 624, 627
    radiation therapy, 630
  oral contraceptive use in, 272
  pathologic evaluation, 620
  prevention of, 630
  prognostic factors, 620
  staging, 619–620
  treatment of, early
    adjuvant biologic therapy, 621
    adjuvant chemotherapy, 621
    adjuvant endocrine therapy, 624
    local-regional therapy, 620–621
    systemic adjuvant therapy, 621
Breast-feeding, 274, 368, 393, 710
Brimonidine in glaucoma, 667, 670*t*
Brinzolamide, 670*t*
Bromocriptine, 158
  in Parkinson's disease, 581*t*, 586
  in schizophrenia, 741
  used in Parkinson's disease, 580*t*
Brompheniramine maleate in allergic rhinitis, 816*t*
Bronchiolitis, 408–410
Bronchitis, 405–410
  acute
  chronic, 407–408
    acute exacerbation of, 407*t*, 409*t*
    bacterial isolates in, 407*t*
    classification of, 408*f*
    clinical algorithm for, 408*f*
    pharmacologic therapy, 407–408
    physical examination, 407*t*
    treatment, 407–408
Bronchospasm, 95, 104, 189, 746*t*, 777, 823
Brudzinski's sign, 323
Budesonide/formoterol
  in asthma, 831*t*
  in pregnancy, 294
  for inflammatory bowel disease, 225*t*
Bumetanide in heart failure, 78, 81
Bupivacaine in regional analgesia, 299, 563, 576*t*
Buprenorphine in pain management, 565*t*, 571*t*

Bupropion, 718
as antidepressant, 716*t*, 720*t*, 724*t*, 726*t*, 727*t*, 729*t*
in anxiety symptoms, 676*t*
Buspirone, 681*t*
in anxiety disorders, 673, 677*t*, 685, 689*f*
for generalized anxiety disorder, 678*t*
Busulfan as chemotherapeutic agent, 233*t*
Butalbital
in migraine headache, 545
in tension-type headache, 555
Butorphanol
adult dosing guidelines, 565*t*
for migraine headaches, 549*f*, 550
in pain management, 571*t*
Butyrophenones in nausea and vomiting, 236*t*

C

C-reactive protein in pancreatitis, 245
Cabazitaxel, in prostate cancer, 659
CAD. *See* Coronary artery disease
Caffeine, 17, 207*t*, 252, 545, 676*t*, 697*t*, 807*t*
Calamine lotion in contact dermatitis, 144
Calcimimetics, 797
Calcipotriene in psoriasis, 150
Calcitonin in osteoporosis, 22*t*, 23–24
Calcitriol, 20*t*, 794
in chronic kidney disease, 796*t*
Calcium
in osteoporosis, 17, 19
recommended dietary allowances, 19*t*
Calcium acetate in chronic kidney disease, 795*t*
Calcium carbonate
in chronic kidney disease, 795*t*
in osteoporosis, 17
Calcium channel blockers, 88
in acute coronary syndromes, 44, 46
causing erectile dysfunction, 851*t*
in hypertension, 93–94
in ischemic heart disease, 106, 109
primary antihypertensive agents, 89*t*
in secondary prevention after myocardial infarction, 46
Calcium chloride in hypocalcemia, 805*f*
Calcium citrate in osteoporosis, 17
Calcium gluconate, 805, 811
Campylobacter infections, 364*t*, 365*t*, 366, 383*t*, 434*t*
Candesartan
in hypertension, 46, 80, 89*t*
in heart failure, 80
Candida infections, intraabdominal, 404
Cannabinoids in nausea and vomiting, 237*t*, 240
Capecitabine
in breast cancer, 627, 627, 628*t*, 629*t*
for metastatic colorectal cancer, 634*t*, 636*t*, 639*t*
Capreomycin as antituberculosis drugs for, 484*t*
Capsaicin
in endocrinologic disorders, 174
in osteoarthritis, 11*t*, 14
Captopril
in hypertensive urgencies, 99
primary antihypertensive agents, 89*t*
in secondary prevention after myocardial infarction, 46
for treatment of heart failure, 78*t*
Carbachol in glaucoma, 667, 670*t*
Carbamazepine, 525, 538
as antiepileptic drugs, 531*t*
in anxiety disorders, 676*t*, 685
associated with acute pancreatitis, 245*t*
in bipolar disorder, 698*t*, 702*t*, 711
in dementia, 516*t*
in dermatologic disorders, 141, 143
dosing and target serum concentration ranges, 528*t*
elimination pathways and major effects on hepatic enzymes, 537*t*
endocrinologic disorders, 174
in neurologic disorders, 517
pharmacokinetic data, 526*t*
during pregnancy, 297
to prevent and treat osteoporosis, 20*t*
in prostate hyperplasia, benign, 846
in psychiatric disorders, 708–709
side effects, 531*t*
for specific seizure disorders, 521*t*

Carbapenems
in bacterial peritonitis, 400*t*
in bacterial pneumonia, 417*t*
Carbidopa in Parkinson's disease, 580*t*
Carbocysleine in chronic obstructive pulmonary disease, 839*t*
Carbon dioxide, 755, 771
in arterial blood gas, 771, 772*f,* 836
Carboplatin, 233*t*
in lung cancer, 643, 644*t,* 646
in non-Hodgkin lymphoma, 653
Carcinoembryonic antigen (CEA), 631
Cardiac arrest, 59
acid-base management, 63
advanced cardiac life support (ACLS) algorithm, 61*f*
treatment of, 59–60
asystole, 62–63
pulseless electrical activity, 62–63
ventricular fibrillation, 60, 62
ventricular tachycardia, 60, 62
Cardiac index
in heart failure, 81
normal values for, 86
in shock, 116*f*
Cardiac output
in heart failure, 63, 75
normal values for, 112*t*
in shock, 114*f*
Cardiopulmonary resuscitation, 58, 59, 60, 61*f*
Cardiovascular disorders, 37–133
Cardioversion, 56*f,* 57
Carisoprodol in substance-related disorders, 757
Carmustine, 233*t*
Carnitine levels, 607
Carotid sinus hypersensitivity, 50, 58
Carteolol, 669*t*
in hypertension, 95
Carvedilol in heart failure, 79
Caspofungin in aspergillosis, 360
Castor oil, 196
Cataplexy, 752*f,* 753*t,* 754
Catechol-*O*-methyltransferase inhibitors, 581*t*, 584–585, 585*t*
in Parkinson's disease, 579, 580*t*
Cathartics, vitamin interactions with, 608*t*
Cefaclor
for cellulitis, 460*t*
dosing of, 454*t*
Cefadroxil
dosing of, 454*t*
for soft-tissue infections, 453*t*
Cefazolin
dosing of, 455*t*
for endocarditis, 339*t*
for gynecologic and obstetric disorders, 299
in intraabdominal infections, 398*t*
in peritonitis, dialysis-associated, 404
recommendations for surgical prophylaxis, 469*t,* 470*t,* 471*t,* 472*t,* 473, 474
Cefdinir in acute otitis media, 419*t*
Cefepime
for diabetic foot infections, 463*t*
dosing of, 456*t*
in intraabdominal infections, 398*t,* 399*t*
in peritonitis, dialysis-associated, 404
in pneumonia, 414*t,* 417*t*
Cefixime, to treat sexually transmitted diseases, 295*t*
Cefixime/Ceftriaxone
for acute bacterial sinusitis, 425*t,* 426*t*
in gonorrhea, 433, 437*t*
in syphilis, 439*t*
in urinary tract infections, 494*t*
Cefotaxime, 192, 311, 315*t*–138*t*
for acute bacterial sinusitis, 426*t*
in bacterial meningitis, 325*t,* 327*t*–328*t,* 332
dosing of, 456*t*
in intraabdominal infections, 398*t,* 399*t,* 400*t*
Cefotetan, 316*t*
for surgical prophylaxis, 469*t,* 470*t,* 474
Cefoxitin, 316*t*
dosing of, 456*t*
in intraabdominal infections, 398*t*
for skin and soft-tissue infections, 465
for surgical prophylaxis, 469*t,* 474
Cefpodoxime, 316*t,* 419*t*
for acute bacterial sinusitis, 425*t*
for urinary tract infections, 494*t*

Ceftazidime, 317*t*
dosing, 330*t,* 456*t*
in intraabdominal infections, 398*t,* 399*t*
penetration of antimicrobial agents, 326*t*
in peritonitis, dialysis-associated, 404
in pneumonia, 417*t*
in sepsis, 431*t*
for urinary tract infections, 494*t*
Ceftizoxime in gonorrhea, 437*t*
Ceftriaxone, 311, 315*t*–138*t,* 329, 399*t,* 400*t*
in acute otitis media, 419*t*
for central nervous system infections, 329
for a dental procedure, 345*t*
dosing of, 456*t*
in intraabdominal infections, 398*t*
in pneumonia, 414*t,* 417*t*
streptococcal endocarditis, 335
for surgical prophylaxis, 469*t*
therapy of native valve endocarditis, 338*t*
therapy of prosthetic valve endocarditis, 340*t*
to treat sexually transmitted diseases, 295*t*
Ceftriaxone/cefixime in gonorrhea, 433, 437*t*
in syphilis, 439*t*
Cefuroxime, 316*t,* 318*t*
in acute otitis media, 419*t*
for cellulitis, 460*t*
dosing of, 456*t*
in intraabdominal infections, 398*t*
penetration of, 326*t*
for surgical prophylaxis, 471*t*
for urinary tract infections, 494*t*
Cefuroxime axetil dosing, 454*t*
Celecoxib
in acute pancreatitis, 245*t*
in colorectal cancer, 631
in gouty arthritis, 2, 4*t*
as nonopioid analgesics for pain, 562*t*
in rheumatoid arthritis, 33*t*
Cellulitis, 449, 449*t,* 459
initial treatment regimens for, 460*t*–461*t*
Central α_2-agonists in hypertension, 96
Central nervous system infections. *See* CNS infections
Cephalexin, 453*t*, 459
in bronchitis, chronic, 409*t*
for diabetic foot infections, 463*t*
dosing of, 454*t*
in urinary tract infection, 293, 498
Cephalosporins, 141, 192, 319*t,* 342, 399*t,* 400*t,* 414*t,* 417*t,* 460*t*–461*t,* 468, 842
in bacterial pneumonia, 417*t*
in intraabdominal infections, 399*t*–400*t*
in pneumonia, 417*t*
Certolizumab, 225*t*, 227, 229*t*
in rheumatoid arthritis, 27, 29*t*, 35
Cervical cap, 260*t*, 261
Cetirizine in allergic rhinitis, 294, 816*t*, 817*t*
Cetuximab, 233*t*
in colorectal cancer, 635, 637*t,* 640*t*
in lung cancer, 643, 644*t*
Chancroid, 295*t*, 368, 434*t,* 446*t*
Chemoreceptor trigger zone in nausea and vomiting, 231
Chest compressions, 60, 63
in cardiopulmonary resuscitation, 61*f*
Chest pain, 39*f,* 43, 49, 58, 59, 101, 103, 126, 212, 642
Child-Pugh classification of liver disease, 187, 187*f,* 188*t*, 190*f*
Chlamydia infections, 103, 295*t*, 339–441
pneumoniae, acute bronchitis in, 405
sexually transmitted, 294, 434*t*
treatment of, 317*t,* 434*t,* 437*t,* 440, 442*t*
Chlorambucil in lymphoma, 651
Chloramphenicol, 540
drug interactions, 319*t*
penetration of, 326*t*
Chlordiazepoxide, 683, 683*t,* 684*t*, 756, 764*t*
alcohol withdrawal, 764*t*
Chloroprocaine as local anesthetic, 576*t*
Chlorpheniramine maleate in allergic rhinitis, 816*t,* 817*t*
Chlorpromazine, 238*t,* 545, 735*t,* 739*t,* 742, 743, 851*t*
in schizophrenia, 739*t*
Chlorpropamide, 165, 166*t,* 801*t*
Chlorthalidone in hypertension, 89*t,* 94

Cholangiopancreatography, 246, 246*f,* 248
Cholangitis, 400*t*
Cholecalciferol
  in chronic kidney disease, 796*t*
  in osteoporosis, 19, 20*t*
Cholecystitis, acute, 400*t,* 469*t*
Cholera, 364
Cholesterol levels, 66*t*
Cholestyramine
  in hyperlipidemia, 68, 69*t,* 70*t*, 71
  vitamin interactions, 608*t*
Cholinergic agonists in glaucoma, 670*t*
Cholinesterase inhibitors
  in Alzheimer's disease, 514*t*–515*t*
  in neurologic disorders, 513
Chondrocytes in osteoarthritis, 9
Chondroitin in osteoarthritis, 15
Chondroitin sulfate in osteoarthritis, 13
Chronic obstructive pulmonary disease (COPD), 407, 408*f,* 835–843
  classification of, 408*f*
  exacerbation, treatment of, 841–843, 842
  initial pharmacologic management of, 838*t*–839*t*
  treatment of
    nonpharmacologic therapy, 837
    pharmacologic therapy, 837–841
      anticholinergic agents, 840
      anticholinergics and sympathomimetics, 840
      corticosteroids, 841
      methylxanthines, 840–841
      sympathomimetics, 837
Chronic pancreatitis (CP). *See* Pancreatitis, chronic
Ciclesonide in asthma, 831*t*
Cilostazol, 174
Cimetidine, 234, 237*t*
  in gastroesophageal reflux disease, 208*f,* 208*t,* 209*t*
  ophthalmic disorders, 666*t*
  in respiratory disorders, 840
  in urologic disorders, 848
Cinacalcet, 797
Ciprofloxacin, 453*t*
  in acne vulgaris, 139
  in acute pancreatitis, 247
  bacterial resistance, 139
  in bronchitis, chronic, 409*t*
  for dog bites, 464
  dosing of, 454*t*, 456*t*
  in inflammatory bowel disease, 224
  interaction with other drugs, 319*t*
  in intraabdominal infections, 398*t,* 400*t*
  in pneumonia, 417*t*
  for surgical prophylaxis, 470*t,* 473
  in urinary tract infections, 493*t*, 495*t*, 496*t*
Cirrhosis, 185, 399*t*
  laboratory abnormalities of, 187–188
  outcome assessment in, 193
  portal hypertension and varices, 185
  treatment of, general approaches to, 188
Cisplatin, 233*t*
  in lung cancer, 643, 644*t*, 645*t*, 646
  in non-Hodgkin lymphoma, 653
Citalopram, 516*t*, 517, 677*t*, 687*t*, 690*t,* 715*t*, 719*t*, 722*t*, 726*t*, 729*t*
Citric acid in metabolic acidosis, 319*t,* 744*t*
CKD. *See* Kidney disease, chronic
Cladribine, 651
Clarithromycin
  in acute exacerbation of COPD, 842
  in acute gouty arthritis, 5
  in acute otitis media, 419*t*
  in acute pancreatitis, 245*t*
  in bacterial pneumonia, 416*t*
  in bronchitis, chronic, 409*t*
  for dental procedure, in antibiotic regimens, 345*t*
  in epilepsy, 538
  in pneumonia, 416*t*
  in sepsis, 431*t*
Clemastine fumarate, 816*t,* 817*t*
Clindamycin, 453*t*
  in acne vulgaris, 138
  for acute bacterial sinusitis, 425*t*
  for cellulitis, 461*t*
  for diabetic foot infections, 463*t*
  dosing of, 454*t*, 456*t*
  gynecologic and obstetric disorders, 299
  for human bites, 465
  for surgical prophylaxis, 471*t*
  to treat sexually transmitted diseases, 295*t*

Clobazam, 528*t*, 537*t*, 538
side effects of, 531*t*
pharmacokinetic data of, 526*t*
Clobetasone propionate
for atopic dermatitis, 145
in psoriasis, 149*t*
Clofibrate in hyperlipidemia, 69*t*, 72
Clomipramine, 677*t*
Clonazepam, 522*t*–524*t*, 528*t*, 677*t*, 683*t*, 684*t*, 687, 687*t*, 689*f*, 691, 739*t*, 764*t*
in alcohol withdrawal, 764*t*
Clonidine, 180
in alcohol withdrawal, 763*t*
in anxiety disorders, 676*t*
for hot flushes, 287*t*
in hypertension, 96
in hypertensive urgencies, 99
Clopidogrel
in acute coronary syndromes, 41, 44, 45, 45*f*
myocardial infarction, secondary prevention after, 46
in stroke, 121
Clorazepate, 525, 683, 683*t*, 684*t*, 756
Clostridium difficile infections, 367, 396*t*
perfringens infections, 316*t*
treatment, 316*t*, 364*t*
Clozapine, 585*t*, 699*t*, 733, 735*t*, 738
in schizophrenia, 739*t*
CNS (central nervous system infections) infections, 323–332
cancer metastasis, 645
cerebrospinal fluid, mean values, 324*t*
laboratory tests, 324
pharmacologic treatment in, 325–332
dexamethasone as an adjunctive treatment, 325–326
empirical therapy by age group, 325*t*
penetration of antimicrobial agents into the CSF, 326*t*
signs and symptoms, 324
Coagulation defects, 186
Coal tar
adverse effects of, 150
in psoriasis, 150
Cobalamin, 304
Cocaine and anxiety disorders, 676*t*
Codeine
in acute bronchitis, 406
in chronic pancreatitis, 248
in pain management, 564*t*, 568*t*
in tension-type headache, 555
Cognition, sedation and, 741
Colchicine, 4–5
Colesevelam, 170
in hyperlipidemia, 68, 69*t*, 70*t*, 71
Colestipol
in hyperlipidemia, 68, 69*t*, 70*t*, 71
vitamin interactions with, 608*t*
Colorectal cancer, 631–641
metastasis, 632
chemotherapy regimens for, 634*t*
clinical manifestations of, 631
diagnosis of, 631–632
metastatic disease
chemotherapy, 633–635
initial therapy, 633–635
personalized pharmacotherapy, 640–641
second-line therapy, 635, 640, 640*t*
operable disease, 632–633
adjuvant chemotherapy, 633, 634*t*
adjuvant radiation therapy, 632
surgery, 473
prevention and screening, 631
prognosis of, 632
treatment, 632–641
Colorectal surgery, 473, 632
Comedones, 135, 136, 137
closed (whitehead), 135
noninflammatory acne, 135–136
open (blackhead), 135
Condoms, 259*t*, 261
Conivaptan in acute decompensated heart failure, 85
Conjunctivitis, 180, 221, 294, 442*t*
Constipation
definition of, 194
dietary modification and bulk-forming agents, 195
drugs causing, 195*t*
pharmacologic therapy, 196–199
during pregnancy, 292
treatment of, general approach to, 195
Contact dermatitis, 141

Contraception, 257–275
choice of, 273
considerations with use, 262, 272
contraceptive rings, 261*t*, 274
drug interactions, 273
emergency contraception, 273–274
hormonal (*See* Hormonal contraception)
injectable progestins, 274
intrauterine devices, 275
long-acting injectable and implantable contraceptives, 274–275
managing side effects, 273
nonpharmacologic therapy in, 257, 261
oral contraceptive
discontinuation of, 273
general considerations for, 272–273
transdermal contraceptives, 261*t*
pharmacologic therapy in, 261–262, 261*t*
subdermal progestin implants, 275
transdermal contraceptives, 274
COPD. *See* Chronic obstructive pulmonary disease
Copper IUD, for contraception, 261*t*, 269*t*
Coronary artery disease (CAD), 37, 49, 59, 65, 75, 92*f*, 96, 97, 99, 103, 107, 108*f*, 109, 118
evaluation of, 39*f*
Coronary artery spasm, treatment of, 109
Coronary heart disease, 174–175
Corticosteroids, 2, 4, 29*t*, 31*t*
in acne vulgaris, 140
in acute exacerbation of COPD, 842
in adrenal insufficiency, 159–160
drug-induced skin reactions, 144
in gout, 2, 4
in inflammatory bowel disease, 224, 227, 229*t*
in nausea and vomiting, 234, 237*t*, 240
ophthalmic disorders, 666*t*
in osteoarthritis, 10, 14
to prevent preterm labor, 299
in psoriasis, 148
in rheumatoid arthritis, 35–36
in shock, 119
in thyroid disorders, 181
vitamin interactions with, 608*t*
Cortisone
Cortisol levels, 155, 158
in acute adrenal insufficiency, 159
in adrenal gland disorders, 159*t*
Cosyntropin-stimulation test, 159
Coumadin. *See* Warfarin
Creatinine, 15, 16, 84, 88, 103, 310*f*
Crizotinib, in lung cancer, 643
Crohn's disease, 222
active treatments for, 227
Activity Index, 229–230
maintenance of remission, 228
treatment approaches for, 228*f*
Cromolyn sodium, 294, 819, 833
Crystalloid fluids for alcohol withdrawal, 763*t*
Cushing's syndrome, 155
adrenolytic agents, 156–158
glucocorticoid-receptor blocking agents, 158
neuromodulators of adrenocorticotropic hormone (ACTH) release, 158
nonpharmacologic therapy, 156
pharmacotherapy, 156–158
steroidogenic inhibitors, 156
treatment based on etiology, 157*t*
Cutaneous drug eruptions, 142*f*
Cyanocobalamin, 304. *See also* Vitamin B_{12}
Cyclooxygenase-2 inhibitors, 2
in gout, 2
in osteoarthritis, 10
Cyclophosphamide, 28, 30*t*, 32*t*, 233*t*, 622*t*–623*t*, 650*t*
in non-Hodgkin's lymphoma (CHOP), 652*t*
for follicular lymphoma, 651
in Hodgkin's lymphoma, 650*t*
in lung cancer, 646
in rheumatoid arthritis, 28, 32*t*
Cycloserine in tuberculosis, 483*t*
Cyclosporine, 1, 30*t*, 32*t*, 151, 224, 225*t*, 227, 320*t*
in gout, 1
in psoriasis, 151
in rheumatoid arthritis, 28
Cyclothymic disorder, 694

Cyproheptadine, 157*t,* 158, 816*t*
Cyproterone acetate in acne vulgaris, 139–140
Cystitis, 490, 497*t,* 658
Cytarabine, 233*t*
  in acute pancreatitis, 245*t*
  in non-Hodgkin lymphoma, 653
Cytochrome P450, 85, 379, 530, 586
Cytomegalovirus infections in HIV infection, 369*t,* 383*t*
Cytotoxic drugs, 1

D

D-dimer test in venous thromboembolism, 127
Dabigatran, 122
  in atrial flutter, 54
Dacarbazine, 233*t*
  in Hodgkin's lymphoma, 649*t*
Dactinomycin as chemotherapeutic agent, 233*t*
Dalteparin, 130
  in venous thromboembolism (VTE), 130
Dantrolene in neuroleptic malignant syndrome, 741
Dapsone, 138–139
Daptomycin, 456*t*
  drug monitoring, 344*t*
  for staphylococcal endocarditis, 342
Darbepoetin alfa, for anemia, 305
  of chronic kidney disease, 792
Darifenacin
  in prostate hyperplasia, benign, 847*t*
  in urinary incontinence, 869*t,* 870, 870*t*
Darunavir in HIV infection and AIDS, 372, 374*t*–375*t,* 377*t*
Date-rape drugs, 756
Daunorubicin, 233*t*
de Quervain's thyroiditis, 176
Decitabine in sickle cell disease, 311
Decongestants, 294, 419, 816, 818, 819
Decubitus ulcers, 462
Deep vein thrombosis (DVT), 125
Defibrillation, 60, 62
Degarelix, in prostate cancer, 663*t*
Dehydration in diarrhea, 362*t,* 707
Delavirdine in HIV infection, 375*t,* 376*t*
Denosumab in osteoporosis, 22*t*, 23
Deoxycorticosterone trimethylacetate in adrenal insufficiency, 159
Depot medroxyprogesterone acetate (DMPA), 261*t*, 268*t*, 274
Depressive disorder. *See also* Major depressive disorder
  treatment algorithm, 713*f*
Depresssive disorder, major
  treatment
    adverse effects, 718
    aminoketone, 725
    children and adolescents, 728–729
    drug classification, 718
    drug–drug interactions, 728
    elderly patients, 728
    nonpharmacologic treatment, 714
    pharmacokinetics, 725–728
    pharmacologic therapy, 714–728
    pregnancy, 729
    relative resistance, 729–730
Dermatitis, 7, 141, 144–145, 150
Dermatologic disorders, 135–153
Dermatologic drug reactions, 141–146
  treatments, 144
    for atopic dermatitis, 145
    for contact dermatitis, 144
    for diaper dermatitis, 144–145
    for drug-induced skin reactions, 144
Desipramine, 716*t,* 718, 719*t,* 726*t*
Desloratadine in allergic rhinitis, 816*t*
Desmopressin in diabetes insipidus, 801*t*
Desogestrel in oral contraceptives, 263*t,* 264*t*
Desonide in psoriasis, 149*t*
Desoximetasone in psoriasis, 149*t*
Desvenlafaxine
  in depression, 715*t,* 718, 719*t*, 723*t*, 726*t*
  in hot flushes, 286*t*
Dexamethasone, 155, 158, 159*t,* 181*t,* 234, 237*t*, 240, 241*t*–242*t,* 325, 653, 832*t*
  to prevent preterm labor, 299
Dexchlorpheniramine maleate in allergic rhinitis, 816*t*
Dexlansoprazole, 209*t*, 210
Dextran solutions in hypovolemic shock, 113

Dextroamphetamine in narcolepsy, 753*t*
Dextromethorphan in acute bronchitis, 406
Diabetes insipidus, 707, 781*f,* 801*t*
Diabetes mellitus (DM), 97, 161–175
  α-glucosidase inhibitors, 169
  amylinomimetic, 164–165
  biguanides, 165, 169
  bile acid sequestrants, 170
  dipeptidyl peptidase-4 (DPP-4) inhibitors, 169–170
  glucagon-like peptide 1 (GLP-1) agonists in, 164
  glycemic goals of therapy, 162*t*
  insulins and other injectable preparations, 163*t*
  nonpharmacologic therapy, 162
  oral contraceptive use in, 267
  pharmacologic therapy, 162–170
  relationship between insulin and glucose, 171*f*
  short-acting insulin secretagogues (meglitinides), 165
  sulfonylureas in, 165
  thiazolidinediones, 169
  treatment of
    complications, 173–175
    general approach to, 162
  type 1, pharmacotherapy of, 170–172
  type 2
    oral agents for treatment of, 166*t*–168*t*
    pharmacotherapy of, 172–173
      insulin algorithm, 173*f*
Diabetic dyslipidemia, treatment of, 74
Diabetic foot infections, 459, 462, 463*t*
Dialysis, 301
  peritonitis in, 399*t,* 404
Diaper dermatitis, 141, 143
Diarrhea, 200–205
  dysenteric, 363*t,* 365*t*
  laboratory tests, 201*t*
  pharmacologic therapy in, 202–203
  recommendations for antibiotic therapy, 363*t*–364*t*
  signs and symptoms, 201*t*
  traveler's, 364*t,* 366–367
  treatments of, general principles to, 200–202, 202*f*, 203*f*
  watery, 363*t*, 365*t*
Diazepam, 293, 528*t*, 589*f,* 590*t*, 591*t*, 593, 683, 683*t*, 687*t*, 739*t,* 764*t*
  alcohol withdrawal, 764*t*
Dichloralphenazone in migraine headache, 545
Diclofenac
  in migraine headache, 546*t*
  in pain management, 560*t*
  in rheumatoid arthritis, 33*t*
  in tension-type headache, 555
  in osteoarthritis, 11*t*, 14
Dicloxacillin, 453*t*, 454*t*, 459, 463*t*
Didanosine in HIV infection and AIDS, 374*t,* 376*t*
Dienogest in oral contraceptives, 265*t*
Diethylpropion in obesity, 601, 603*t*
Difenoxin in diarrhea, 204*t*
Diflorasone diacetate in psoriasis, 149*t*
Diflunisal in rheumatoid arthritis, 33*t*
Digoxin, 51, 319*t*
  and anxiety, 676*t*
  in chronic heart failure, 76
  in heart failure, 80
  for patients with paroxysmal supraventricular tachycardia (PSVT), 57
Dihydroergotamine in migraine headache, 545, 547*t*
Dihydropyridines, 94
Dihydrotestosterone (DHT), 654
Diltiazem, 51, 180
  in acute coronary syndromes, 44
  as antiarrhythmic drug, 51*t*
  in benign prostatic hyperplasia, 848
  in hypertension, 94
  in ischemic heart disease, 106
  variant angina pectoris, 109
Dimenhydrinate in nausea and vomiting, 235*t,* 242*t*
Dipeptidyl peptidase-IV inhibitors, in diabetes mellitus, 169–170
Diphenhydramine, 235*t,* 651, 739*t,* 816*t*
Diphenoxylate in diarrhea, 204*t,* 361, 367
Diphtheria antitoxin, 500–502
Diphtheria toxoid, 465, 500–502
Dipivefrin in glaucoma, 667
Dipyridamole, 58, 103, 121
  bradyarrhythmias, 58
Direct arterial vasodilators in hypertension, 96
Direct-current cardioversion (DCC), 51

Direct renin inhibitor in hypertension, 95
Disease-modifying antirheumatic drug (DMARD), 27, 34–36
Disopyramide, 54*t*
  in antiarrhythmic drugs, 51*t,* 52*t*
  bradyarrhythmias, 58
  for patients with paroxysmal supraventricular tachycardia (PSVT), 57
Disulfiram, 446, 765
Diuretics
  in acute decompensated heart failure, 81–83
  in gout, 1
  vitamin interactions, 608*t*
Divalproex, 554, 701*t,* 708, 738
  side effects of, 554
Divalproex sodium, 541–542
Dobutamine, 82*f,* 83, 114*f,* 117, 118
  in acute decompensated heart failure, 83
  in sepsis, 432
Docetaxel, 233*t*, 621, 622*t,* 628*t,* 629*t*
  in lung cancer, 643, 644*t*
  in prostate cancer, 659
Docosahexaenoic acid in hyperlipidemia, 72
Docusate in constipation, 196, 197–198, 197*t*
Dofetilide in arrhythmias, 51, 51*t,* 52*t,* 54*t*
Dolasetron in nausea and vomiting, 240, 241*t*
Donepezil in Alzheimer's disease, 513, 514*t*
Dopamine, 58, 82*f,* 83–84, 115*f,* 117*t,* 118, 207*t,* 695*t*
  in acute decompensated heart failure, 83–84
  atrioventricular block, 58
  in sepsis, 432
Dopamine agonists in Parkinson's disease, 580*t,* 581*t*–582*t*, 583
Doripenem, 398*t*, 400*t,* 456*t*
Dorzolamide in glaucoma, 670*t*
Doxazosin, 93*t,* 95, 847, 847*t*
  in hypertension, 95
  in prostate hyperplasia, benign, 847*t*
  in urologic disorders, 847
Doxepin, 551*t,* 716*t,* 719*t,* 726*t*
Doxercalciferol in chronic kidney disease, 794, 796*t*
Doxorubicin, 233*t,* 622*t,* 628*t*, 649*t*
  for non-Hodgkin's lymphoma (CHOP), 652*t*
  in Hodgkin's lymphoma, 649*t*
  in lung cancer, 646
Doxycycline, 139, 174, 315*t*–138*t,* 364, 415*t,* 474, 842
  in acne vulgaris, 139
  for acute bacterial sinusitis, 425*t*
  in bronchitis, chronic, 409*t*
  in chlamydia infections, 440
  for dog bites, 464
  dosing of, 454*t*
  in syphilis, 439*t*, 440*t*
Doxycycline/azithromycin in gonorrhea, 433
Doxylamine in insomnia, 243, 292
Dronabinol in nausea and vomiting, 237*t,* 240
Dronedarone in antiarrhythmic drugs, 51, 51*t,* 52*t*, 54*t*
Droperidol in nausea and vomiting, 236*t,* 242*t*
Drospirenone in oral contraceptives, 264*t*
Drug reactions, dermatologic. *See* Dermatologic drug reactions
Duloxetine, 174, 678*t*, 715*t*, 718, 719*t*, 723*t*, 725, 726*t*, 729*t*, 871
  for anxiety disorders, 677*t*
  endocrinologic disorders, 174
  in osteoarthritis, 13, 15
Duodenum, peptic ulcer disease of, 583
Dust mites, allergic rhinitis from, 813
Dutasteride
  in benign prostatic hyperplasia, 847*t,* 848, 852*t*
  in prostate cancer, 654
Dyslipidemia, 65. *See also* Hyperlipidemia
  drugs used in treatment, comparison of, 70*t*
  nonpharmacologic therapy, 68, 68*t*
  oral contraceptive use in, 267
  pharmacologic therapy, 69*t*–70*t*
  treatment recommendations, 73
  general approach for, 66–68, 66*t,* 67*t*
Dyssomnias, algorithm for treatment of, 752*f*
Dystonia from antipsychotic drugs, 584, 738, 740

E

Ear infections, otitis media in, 419
Echocardiography, 103, 110, 128*f,* 334*t*
Echothiophate in glaucoma, 670*t*
Eclampsia, 98, 292, 811
Ecstasy (3,4-methylenedioxy-methamphetamine), 676*t,* 758
Efavirenz
  in HIV infection, 297, 372, 374*t,* 377*t*
  vitamin interactions, 608*t*
Eicosapentaenoic acid, in hyperlipidemia, 72
Electrocardiography, 59
Electroconvulsive therapy, 700, 714
Electroencephalogram (EEG), 518
Electrolyte balance, 144, 200, 612*t,* 784
Electrolyte homeostasis
  calcium, disorders of, 802
    hypercalcemia, 802
    hypocalcemia, 803
  magnesium, disorders of
    hypermagnesemia, 811
    hypomagnesemia, 810–811
  phosphorus, disorders of
    hyperphosphatemia, 805–806
    hypophosphatemia, 806
  potassium homeostasis, disorders of
    hyperkalemia, 808–810
    hypokalemia, 806, 808
  sodium/water, disorders of, 798–805
    acute/severely symptomatic hypotonic hyponatremia, 800
    edema, 801–802
    hypernatremia, 801
    hyponatremia, 798
    nonemergent hypotonic hyponatremia, 800
Eletriptan in migraine headache, 548*t,* 550*t*
Emergency cardiovascular care (ECC), 60
Emesis. *See* Nausea and vomiting
Emphysema, 347, 835
Emtricitabine in HIV infection, 372, 376*t*
Enalapril and myocardial infarction, secondary prevention after, 46
Encephalitis, in toxoplasmosis and HIV infection, 382*t*
Endocarditis, 333, 333–346
  antibiotic regimens for a dental procedure, 345*t*
  infective endocarditis, 334*t*
  enterococcal endocarditis, 342, 345
  etiologic organisms, in infective endocarditis, 334*t*
  histoplasma, 349*t*
  native valve endocarditis, 338*t*–339*t*
  nonpharmacologic therapy, 335
  prevention of, 346
  prosthetic valve, 340*t*–341*t*
  risk factors for, 333
  staphylococcal, 335, 338*t*–339*t,* 342
  streptococcal, 335
  treatment of, 333, 335, 336*t*–337*t,* 342, 345
    staphylococcal prosthetic valve endocarditis, 342
    Staphylococcus endocarditis in IV drug abusers, 342
Endocrinologic disorders, 155–184
Enfuvirtide in HIV infection, 375*t,* 378*t*
Enoxaparin, 40*f,* 42–43, 45*f,* 128*f,* 130
  in acute coronary syndromes, 42–43, 44
  in venous thromboembolism (VTE), 130
Entacapone in Parkinson's disease, 580*t,* 581*t*, 583, 584–585
Entecavir in hepatitis B, 216, 218*f*
Enteral nutrition (EN), 609–614
  administration methods, 609–611
  drug delivery via feeding tube, 611, 614
  enteral access, 609
  enteral feeding formulations, classification of, 611
  formulations, 611
  initiation and advancement protocol, 609
  monitoring for patients, 614*t*
  nasoduodenal, 610*t*
  nasogastric, 210, 362*t*
  nasogastric intubation, 610*t*
  nasojejunal intubation, 610*t*
  treatment complications, 611
Enterobacter infections, 396*t,* 407*t*
Enterococcal infections, peritonitis in, 395, 396*t,* 399*t*

Enterotoxigenic (cholera-like) diarrhea, 361, 364, 366
cholera *(Vibrio cholerae)* treatment, 364
Clostridium difficile, 367
Escherichia coli, 363*t,* 365*t,* 366
recommendations for antibiotic therapy, 363*t*
Enzalutamide in prostate cancer, 661*t*
Enzymes (lactase) as antidiarrheal preparations, 205*t*
Ephedrine-induced hypokalemia, 807*t*
in renal disorders, 807*t*
Epididymitis, 435*t,* 435*t*, 441*t,* 445*t*
Epilepsy, 518–542
algorithm for treatment of, 524*f*
carbamazepine, 538
clobazam, 538
ethosuximide, 538
ezogabine, 538–539
felbamate, 539
gabapentin, 539
lacosamide, 539
lamotrigine, 539
levetiracetam, 539
oxcarbazepine, 540
phenobarbital, 540
phenytoin, 540–541
pregabalin, 541
rufinamide, 541
tiagabine, 541
topiramate, 541
treatment of
adverse effects, 530
drug–drug interactions, 530, 537*t*, 538
efficacy, 530
in female patient, special considerations, 520, 525
general approach, 520
mechanism of action, 520
pharmacokinetics, 525
serum concentration monitoring, role of, 525, 528*t*–529*t*
valproic acid and divalproex sodium, 541–542
vigabatrin, 542
zonisamide, 542
Epileptic seizures, international classification of, 519*t*
Epinephrine
in asthma, 828*t*
atrioventricular block, 58
in cardiac arrest, 62, 63
in renal disorders, 807*t*
in sepsis, 432
in shock, 116, 118
in sickle cell disease, 311
in torsades de pointes (TdP), 58
Epirubicin, 233*t*
in breast cancer, 621, 622*t*
Eplerenone, 40*f,* 46, 80, 94
in hypertension, 94
in myocardial infarction, secondary prevention after, 46
Epoetin alfa, for anemia, 305, 792
Eprosartan in hypertension, 89*t*
Eptifibatide in acute coronary syndromes, 42, 44, 45
Erectile dysfunction (ED), 850–864
dosing regimens for, 853*t*–859*t*
medication classes, 851*t*–852*t*
surgery for, 860
treatment of, 850–864
algorithm for, 860*f*
pharmacodynamics and pharmacokinetics of, 861*t*
pharmacologic treatments
alprostadil, 863
phosphodiesterase inhibitors, 860–861, 862*t*
testosterone-replacement regimens, 863
unapproved agents, 864
vacuum erection device, 860
Ergocalciferol
in chronic kidney disease, 796*t*
in osteoporosis, 19, 20*t*
Ergotamine tartrate in migraine headache, 293, 545, 546*t*, 549*f*
Eribulin in breast cancer, 627, 628*t*
Erlotinib as chemotherapeutic agents, 233*t,* 643
Ertapenem, 400*t,* 413*t,* 461*t,* 463*t*, 465, 495*t*
dosing of, 456*t*
in intraabdominal infections, 398*t*
Erysipelas, 448, 449*t,* 453*t*
Erythritol tetranitrate in angina pectoris, 105*t*
Erythrocytes. *See* Red blood cells

Erythromycin, 453*t*
in acne vulgaris, 139
in bronchitis, chronic, 409*t*
in chlamydial infections, 442t
in colorectal surgery, 473
dosing of, 454*t*
in endocrinologic disorders, 174
in gastrointestinal infections, 366
in gonorrhea, 437t
gynecologic and obstetric disorders, 299
in pneumonia, 416*t*
for surgical prophylaxis, 469*t*
in syphilis, 439t, 440t
to treat sexually transmitted diseases, 295*t*
Erythropoiesis-stimulating agents (ESAs) for anemia, 305, 307
Erythropoietin, 87
Escherichia coli infections, 316*t*
bronchitis in, 407*t*
peritonitis in, 394, 396*t*
Escitalopram, 516*t,* 677, 677*t,* 678*t*, 687*t*, 690*t,* 715*t*, 719*t,* 726*t*
as antidepressant, 516*t*, 729*t*
Esmolol
in atrial flutter, 51
in thyroid disorders, 181
Esomeprazole, 208*f,* 209*t,* 210, 211
Estazolam in insomnia, 749*t,* 750
Estradiol, 257, 280, 281*t*–283*t*
Estrogen agonists/antagonists in osteoporosis, 23
Estrogen-receptor modulators, 288
Estrogen therapy in osteoporosis, 24
Eszopiclone in insomnia, 749*t,* 750
Etanercept, 29*t*
dermatologic disorders, 151–152
in psoriasis, 152
in rheumatoid arthritis, 27, 34
Ethacrynic acid in acute renal failure, 245*t,* 784
Ethambutol, 1
antimicrobial agents, 331*t*
antituberculosis drugs for, 483*t*
during pregnancy, 486
Ethinyl estradiol, 139, 262, 263*t*–266*t,* 626*t*
Ethionamide in tuberculosis, 483*t,* 486
Ethosuximide, 538
antiepileptic drug side effects, 531*t*
dosing and target serum concentration ranges, 528*t*
elimination pathways and major effects on hepatic enzymes, 537*t*
pharmacokinetic data, 526*t*
in seizures, 522*t,* 525
Ethynodiol diacetate in oral contraceptives, 263*t*
Etidronate in hypercalcemia, 804*t*
Etodolac, 4*t,* 33*t,* 560*t*
acute gouty arthritis, 4*t*
Etomidate in Cushing's syndrome, 156
Etonogestrel, 274, 275
Etoposide, 233*t,* 643, 645*t,* 646, 649*t*
as chemotherapeutic agent, 233*t*
in Hodgkin's lymphoma, 649*t*
in non-Hodgkin lymphoma, 653
Etravirine in HIV infection, 375*t*, 377*t*
Exanthematous drug reactions, 141
Exemestane in breast cancer, 624, 625*t*
Exenatide in diabetes mellitus, 163*t,* 164
Eye movements in sleep, 691
Ezetimibe in hyperlipidemia, 69*t*–70*t,* 72
Ezogabine, 537*t*, 538–539
antiepileptic drug side effects of, 532*t*
pharmacokinetic data of, 526*t*

F

Factor VIII therapy in hypovolemic shock, 125
Famciclovir, 245*t,* 441, 444*t*
Famciclovir/valacyclovir, 294, 383*t,* 444*t*
Famotidine, 208*f,* 208*t,* 209*t,* 211, 234, 237*t*
Fasciitis, necrotizing, 420, 449*t*
Febuxostat
in gout, 7
uric acid, 7
Feeding tubes, 609
Felbamate, 540
antiepileptic drug side effects, 532*t*
dosing and target serum concentration ranges, 529*t*
elimination pathways and major effects on hepatic enzymes, 537*t*
in seizures, 526*t,* 532*t,* 538

Felodipine
in acute coronary syndromes, 44
in anxiety disorders, 676*t*
in hypertension, 44, 77*f,* 89*t*
Femring (estradiol acetate vaginal ring), 283*t*
Fenofibrate in hyperlipidemia, 69*t,* 70*t,* 72
Fenoldopam mesylate
in hypertensive emergencies, 100*t*
ophthalmic disorders, 666*t*
Fenoprofen, 4*t,* 33*t,* 561*t*
in acute gouty arthritis, 4*t*
Fentanyl, 299, 311, 565*t,* 574, 574*t*
in pain management, 569*t*–570*t*
Ferrous fumarate in iron deficiency, 304*t*
Ferrous gluconate in iron deficiency, 304*t*
Ferrous sulfate in iron deficiency, 229, 304*t*
Ferumoxytol in anemia, 306*t*
Fesoterodine
in benign prostate hyperplasia, 847*t*
in urinary incontinence, 869*t*, 870*t*
Fexofenadine in allergic rhinitis, 816*t,* 817*t*
Fibrate monotherapy in hyperlipidemia, 72
Fibrillation, 9, 48, 49, 51–56, 56*f,* 60, 62, 122
Fibrinolytic therapy, 42
in acute coronary syndromes, 39, 41, 44
Fibrosing mediastinitis, 348*t*
Fibrosis, 27, 31*t,* 54*t,* 185, 322, 586, 835
Finasteride in benign prostatic hyperplasia, 654, 847*t,* 848
Fish oils in hyperlipidemia, 69*t,* 72
Fixed drug eruptions, 143
Flecainide, 50, 52*t*
in arrhythmias, 51*t*
for paroxysmal supraventricular tachycardia (PSVT), 57
side effects of, 54*t*
Fluconazole, 326*t,* 331*t,* 352*t,* 353, 354*t,* 355*t,* 357*t,* 358–359
Flucytosine, 326*t,* 331*t,* 354*t,* 358, 381*t*
Fludarabine
as chemotherapeutic agents, 233*t*
in lymphoma, 651
Fludrocortisone, 58, 159, 160
Fluid balance, 398, 617*f*
Fluid intake, 71, 76, 86, 195, 292, 393, 410, 707
Fluid therapy, 113, 311, 430*t*
Flumazenil, 192, 192*t*
Flunisolide, 818*t*
Flunitrazepam, 756
Fluocinolone acetonide in psoriasis, 149*t*
Fluoroquinolones, 247, 315*t*–317*t*
in bacterial pneumonia, 417*t*
enteral nutrition, 615*t*
in urinary tract infections, 493*t*
Fluorouracil, 233*t,* 621, 622*t*–623*t*, 633, 634*t,* 635, 636*t,* 638*t*–639*t*, 667
Fluoxetine, 287*t,* 687*t*, 691, 715*t*, 719*t,* 722*t*, 726*t*, 867
antidepressants, 692*t*, 729*t*
for dementia, 516*t*
hot flushes, treatment of, 287*t*
Fluoxymesterone, 626*t,* 855*t*
in breast cancer, 626*t*
in erectile dysfunction,
Fluphenazine, 710, 732*t,* 735*t,* 738
in schizophrenia, 737, 739*t*
Fluphenazine decanoate, 737
Flurandrenolide in psoriasis, 149*t*
Flurazepam in insomnia, 749*t,* 750
Flurbiprofen, 33*t*
Flutamide, 659, 660*t*
in prostate hyperplasia, benign, 846, 847*t*
Fluticasone, 149*t,* 818*t,* 831*t,* 833, 841
Fluticasone propionate, 831*t*
Fluvastatin in hyperlipidemia, 69*t,* 71, 797
Fluvoxamine, 677*t*, 686, 687*t*, 689, 690*t*, 715*t*, 719*t,* 723*t*, 726*t*, 729*t,* 867
as antidepressant, 729*t*
Folic acid, 32, 151, 228, 229, 301, 305, 309, 608*t,* 711
Follicle-stimulating hormone, 257, 258*f,* 276, 654, 655*f*
Folliculitis, 148, 150, 453*t,* 707
Fondaparinux, 40*f,* 44, 130
in acute coronary syndromes, 42–43, 44
Fondaparinux sodium in venous thromboembolism (VTE), 130
Foot Ulcers, 174

Formoterol, 823, 827*t*
in asthma, 827*t*
in chronic obstructive pulmonary disease, 837
Fosamprenavir in HIV infection, 377*t*
Foscarnet, 319*t,* 326*t,* 331*t*
Fosfomycin in urinary tract infections, 315*t,* 493*t,* 496*t*
Fosinopril, 78*t,* 89*t*
Fosphenytoin, 540
adverse effects, 591*t*
Fosphenytoin in status epilepticus, 589*f,* 590*t,* 593–594
Frovatriptan in migraine headache, 548*t,* 550*t,* 552*t,* 555
Fulvestrant in breast cancer, 625*t,* 627
Fungal infections, 347–360, 396*t*
allergic bronchopulmonary aspergillosis, 359
aspergilloma, 359
Aspergillus infection, 359–360
therapy of invasive candidiasis, 356*t*–358*t*
blastomycosis, 351
therapy, 351, 352*t*
Candida infections, 359
coccidioidomycosis, 351, 353
therapy, 353
cryptococcosis, 353
treatment of, 354*t*–355*t,* 358–359
hematogenous candidiasis, 359
histoplasmosis, 347–351
treatment of, 347, 350–351
invasive aspergillosis, 360
Furosemide, 78, 78*t,* 81, 191, 784, 801, 809*t*
used in heart failure, 78, 78*t*
Furuncles, 453*t*

G

Gabapentin, 174, 277*f,* 287*t,* 521*t,* 526*t,* 529*t*, 532*t,* 537*t*, 538, 540, 556, 677*t*, 689*f,* 690*t,* 691
antiepileptic drug side effects, 532*t*
hot flushes, treatment of, 287*t*
neurologic disorders, 517
in tension-type headache, 556
Galantamine in Alzheimer's disease, 513, 514*t*
Gallium nitrate in hypercalcemia, 803*f,* 804*t*
Gallstone pancreatitis, 245
Gamma-glutamyl transpeptidase levels in liver disorders, 186*t,* 187
Ganciclovir, in cytomegalovirus infections and HIV infection, 326*t,* 383*t*
Gardnerella vaginalis infections, 316*t,* 434*t,* 435*t*
Gastroenteritis, 243, 365*t,* 366*t*. *See also* Acute viral gastroenteritis
Gastroenteritis, acute viral
agents responsible for, 366*t*
astroviruses, 366*t*
coronavirus-like particles, 366*t*
enteric adenoviruses, 366*t*
enteroviruses, 366*t*
noroviruses, 366*t*
pestiviruses, 366*t*
rotaviruses, 366*t*
Gastroesophageal reflux disease (GERD), 206–212
antacids and antacid-alginic acid products, 210
clinical presentation of, 206
combination therapy, 211
general approach to treatment of, 207–209
H_2-receptor antagonists in, 211
maintenance therapy, 212
mucosal protectants in, 211
nonpharmacologic treatment, 209–210
promotility agents in, 211
proton pump inhibitors in, 210–211
therapeutic approach to, in adults, 208*t*–209*t*
Gastrointestinal infections, 361–367
bacterial, 361, 364
clinical assessment of degree of dehydration in children, 362*t*
oral rehydration and maintenance, 361, 363*t*
recommendations for antibiotic therapy, 363*t*–364*t*
rehydration, antimotility and probiotic therapy, 361
Gastroparesis in diabetes mellitus, 174, 232*t,* 240, 545
Gastrostomy for enteral nutrition, 469*t,* 610*t*

Gemcitabine, 233*t,* 627, 628*t*, 629*t,* 643, 644*t,* 645*t*
in breast cancer, 627, 627
Gemfibrozil in hyperlipidemia, 69*t*, 70*t,* 72, 73
Gemifloxacin
in acute exacerbation of COPD, 417*t,* 842
in infectious diseases, 315*t*
in pneumonia, 417*t*
Generalized anxiety disorder, 674*t*
Generalized convulsive status epilepticus (GCSE)
adverse effects, 591*t*–592*t*
algorithm for management of, 589*f*
initial treatment, 590*t*
treat refractory, 595*t*–596*t*
Genital herpes infections, 441, 443*t*
treatment of, 441–442, 444*t*
Gentamicin, 315*t,* 330*t,* 335, 338*t,* 340*t*–341*t,* 343*t,* 345, 471*t*
dosing of, 457*t*
drug monitoring, 344*t*
in enterococcal endocarditis, 342
in peritonitis, dialysis-associated, 404
in pneumonia, 417*t*
in urinary tract infections, 494*t*
Ghon complex, 476
Ginkgo biloba in Alzheimer's disease, 513
Glaucoma
open-angle, 667–672
treatment of
closed-angle glaucoma, 667
ocular hypertension, 667
Glimepiride in diabetes mellitus, 166*t*
Glipizide in diabetes mellitus, 166*t,* 168*t*
Glitazones in diabetes mellitus, 169
Glomerular filtration rate categories, 788*t*
Glucocorticoids
in adrenal insufficiency, 159*t*
in inflammatory bowel disease, 224
in osteoporosis, 24–25
in rheumatoid arthritis, 36
Glucosamine, in osteoarthritis, 15
Glucosamine sulfate in osteoarthritis, 13
α-Glucosidase inhibitors in diabetes mellitus, 169
Glyburide
in diabetes mellitus, 166*t,* 168*t*
in gestational diabetes mellitus, 292
Glycerin, 196, 198
Glycoprotein IIb/IIIa receptor inhibitors, 45
in acute coronary syndromes, 42
Goiter, multinodular, 178
Gold salts in rheumatoid arthritis, 28, 30*t*, 31*t*
Golimumab in rheumatoid arthritis, 27, 35
Gonorrhea, 316*t*, 433–434, 437*t*
treatment of, 295*t*, 433–434
Goserelin, 624, 625*t,* 627, 663*t,* 847*t*
in breast cancer, 625*t*
in prostate cancer, 658
in prostate hyperplasia, benign, 846, 847*t*
Gout, 1–8
colchicine in, 4–5
corticosteroid therapy in, 2, 4
nonpharmacologic therapy in, 2
prophylactic therapy in, 8
treatment algorithm, 3*f,* 6*f*
GP IIb/IIIa inhibitor in acute coronary syndromes, 44
Granisetron in nausea and vomiting, 240, 241*t,* 242*t*
Granuloma inguinale, 434*t*
Graves' disease, 177–178, 179, 180
Guanabenz in hypertension, 96
Guanadrel, 201*t*
Guanethidine, 201*t,* 851*t*
Guanfacine in hypertension, 96
Guillain–Barré syndrome, 412

H

Haemophilus influenzae infections, 316*t*
bronchitis in, chronic, 407*t*
otitis media in, 418
pneumonia in, 413*t,* 416*t*
type B conjugate vaccine products, 503–504, 504*t,* 506*t*
Halcinonide in psoriasis, 149*t*
Hallucinations in schizophrenia, 731
Hallucinogens, 695*t,* 697*t,* 761*t*
Hallucinosis, drug-induced, in Parkinson's disease, 585*t*
Halobetasol propionate in psoriasis, 149*t*
Haloperidol, 242*t*
in alcohol withdrawal, 763*t*
in bipolar disorder, 710
in schizophrenia, 737, 739*t*

Haloperidol decanoate in schizophrenia, 735*t,* 737
Hashimoto's thyroiditis, 181
Hay fever, 813
Heart block, 44, 100*t,* 104, 808, 811
Heart Failure, acute decompensated
  general approach to treatment of, 81, 82*f*
  pharmacotherapy of, 81–85
    diuretics, 81–83
    dobutamine, 83
    dopamine, 82–83
    milrinone, 83
    nesiritide, 84–85
    nitroglycerin, 84
    nitroprusside, 84
    vasodilators, 84
    vasopressin receptor antagonists, 85
Heart failure (HF), 4, 34, 37, 46, 49, 75–86, 102, 169, 301, 751, 785*t*
  acute decompensated heart failure, 81
    general treatment algorithm, 82*f*
    pharmacotherapy, 81–85
  chronic heart failure, 77–81
    general approach for treatments, 76–77
    pharmacologic therapy, 77–81
  mechanical circulatory support, 85
  surgical therapy, 85
    acute decompensated heart failure, 86
    chronic heart failure, 85–86
Heartburn in gastroesophageal reflux disease, 206, 208*t,* 212
Heberden's nodes, 9
Helicobacter pylori infections, peptic ulcer disease in, 251, 253*f*
Hematocrit, reference range for, 245, 305*t,* 398
Hematologic disorders, 301–312, 477*t*
Hemodialysis, 219*t,* 487*t,* 784, 803*f,* 809*t*
Hemolytic anemia, 165, 308
β-Hemolytic streptococcal pharyngitis, clinical prediction of, 421*t*
Hemorrhage, 111, 120, 121, 185, 191, 469*t*
Hemorrhoids, 194, 221, 223*t*
  in pregnancy, 292
Hemostasis, 125
Heparin-associated thrombocytopenia (HAT), 129
Heparin-induced thrombocytopenia (HIT), 129
Hepatic encephalopathy, 185, 192
Hepatitis A, 213–214
  goal of therapy, 213
  prevention, 213–214
  vaccination recommendations, 214*t,* 215*t*
Hepatitis B, 214–216
  causing cirrhosis, 186*t*
  interpretation of serologic tests in, 216*t*
  prevention of, 215
  treatment of, 215–216
    algorithm, 218*f*
  vaccination recommendations, 217*t*
Hepatitis C, 216–220
  causing cirrhosis, 186*t*
  screening, recommendations for, 219*t*
  treatment, 219–220
    algorithm, 219*t*
    side effects, 220*t*
Hepatitis vaccines, 505, 505*t,* 506*t*
Hepatopulmonary syndrome, 193*t*
Hepatorenal syndrome, 188, 189
Heroin, 574
Herpes. *See* Genital herpes infections
Herpes simplex virus infections, 434*t,* 435*t*
Herpes zoster vaccination, 384*t,* 504*t*
High-density lipoprotein (HDL), 65
Histamine$_2$-receptor antagonists, 207, 211, 234, 249*f,* 292, 608*t*
Histoplasmosis, 347–351
  Chronic cavitary pulmonary histoplasmosis, 349*t*
Histoplasmosis, disseminated, 349*t*
HMG-CoA reductase inhibitor therapy. *See* Statin therapy
Hodgkin lymphoma, 648*t,* 650*t*
  combination chemotherapy regimens, 649*t*–650*t*
  general treatment recommendations for, 648*t*
Homan's sign in venous thromboembolism, 126
Hormonal contraception, 261–262
  components of, 262
  composition, 261–262, 263*t*–266*t*

drug monitoring for, 268*t*–269*t*
serious symptoms associated with, 267*t*
U.S. medical eligibility criteria for, 270*t*–271*t*
Human immunodeficiency virus (HIV) infection, 368–386
primary HIV infection in adults, 371*t*
etiology, 368
general approach to treatment of, 372
infectious complications of, 380–386
for common opportunistic pathogens in, 381*t*–383*t*
Pneumocystis carinii, 380
for prophylaxis of first-episode opportunistic diseases, 384*t*–385*t*
transmission of human immunodeficiency virus, 368
pharmacologic therapy, 372–379
antiretroviral agents, 372–379, 373*t*–375*t*
selected pharmacologic characteristics, 376*t*–378*t*
treatment during pregnancy, 379
postexposure prophylaxis, 379
prophylaxis, 386
revised classification system, 371*t*
surveillance case definition for HIV infection, 369*t*–370*t*
therapeutic failure, 379–380
treatment of, 372–379
Human papillomavirus vaccine, 504*t,* 505, 506*t*
Humidification of inspired air in chronic bronchitis, 407
Huperzine A in Alzheimer's disease, 513
Hyaluronic acid injections, in osteoarthritis, 13, 15
Hydralazine, 76, 77*f,* 81, 96, 98, 311
in chronic heart failure, 76
in heart failure, 81
in hypertension, 96
Hydrochlorothiazide, 71, 82*f,* 83, 89*t,* 801*t*
in hypertension, 94
in systolic heart failure, 77
Hydrocodone, 248, 311, 564*t*, 569*t*
Hydrocortisone, 71, 149*t,* 832*t*
in acute adrenal insufficiency, 159, 159*t*, 160
in diaper dermatitis, 145
in myxedema coma, 184
Hydromorphone, 248, 248, 311, 559*f,* 568*t*, 564*t*, 574*t*
γ-Hydroxybutyrate, 28*f*
Hydroxychloroquine in rheumatoid arthritis, 27, 29*t*, 33
Hydroxyethyl starch in hypovolemic shock, 113
5-Hydroxytryptamine-3 receptor antagonists, 237*t*
Hydroxyurea, 153, 309, 310*f,* 312
in psoriasis, 153
Hydroxyzine, 235*t,* 294, 677, 677*t*, 678*t*
Hyperalimentation, 773*t,* 806
Hypercalcemia, 20*t,* 24, 194, 802, 804*t*
Hypercortisolism, 155, 156, 158
Hyperemesis gravidarum, 292
Hyperfunction of the adrenal glands, 155
Hyperglycemia, 33, 62, 71, 161, 162, 810*f*
Hyperkalemia, 62, 80, 94, 160, 808–810
Hyperlipidemia. *See also* Dyslipidemia
in chronic kidney disease, 797
Hyperlipoproteinemia, 71, 72
Hypermagnesemia, 784*t,* 811
Hypernatremia, 71, 785, 801
Hyperparathyroidism, 87, 802
Hyperphosphatemia, 795*t,* 805–806
Hyperpigmentation, 136, 151, 153, 159, 186*t*
drug-induced, 141
Hypertension, 87–101
definition, 87
in elderly, 88*t,* 98
nonpharmacologic therapy in, 88
oral contraceptive use in, 262
pharmacologic therapy in, 88–96, 89*t*–90*t,* 91*f,* 92*f,* 93*t*
treatment algorithm, 91*f*
Hyperthyroidism, 76, 176–181, 815, 841
Hypertriglyceridemia, 71, 72, 100*t,* 151
treatment of, 73
Hyperuricemia, 1–8, 71, 94
Hypervolemic hyponatremia, 798
Hypocalcemia, 23, 94, 113, 245, 803, 805*f*

Hypoglycemia, 62, 97, 164, 165, 169, 172, 175, 790*f*
Hypokalemia, 48, 58, 94, 222, 773*t,* 777, 806, 808
Hypomagnesemia, 48, 58, 62, 94, 639*t,* 803, 805, 810–811
Hyponatremia, 85, 531*t,* 533*t*, 798, 800
Hypophosphatemia, 17, 806
Hypotension, 24, 43, 49, 58, 80, 82*f,* 85, 100*t,* 103, 174, 428*t,* 563, 593, 719*t*–720*t,* 757, 798
Hypothalamic-pituitary-ovarian axis, 276
Hypothermia, 62, 182, 429*t*
Hypothyroidism, 176, 180, 181–184, 303*f*
  treatment of, 182–183
    thyroid preparations used in, 183*t*
Hypovolemia, 62, 85, 114*f,* 777
Hypoxanthine-guanine phosphoribosyl transferase (HGPRT), 1
Hypoxemia in COPD, 777
Hysterectomy, 277*f*
  hormone therapy and, 278, 284
Hysterectomy, surgical site infections in, 470*t,* 474

I

I-tositumomab in lymphoma radioimmunotherapy, 651
Ibandronate
  in hypercalcemia, 804*t*
  in osteoporosis, 19, 21*t*
Ibritumomab tiuxetan in lymphoma radioimmunotherapy, 651
Ibuprofen, 4*t*, 561*t*
  in acute gouty arthritis, 4*t*
  with anxiety symptoms, 676*t*
  in bronchitis, acute, 405–406
  in migraine headache, 545, 546*t,* 549*f,* 555
  in pancreatitis, 245*t*
  in respiratory tract infections
    lower, 405–406
    upper, 418–419
  in rheumatoid arthritis, 33*t*
  in tension-type headache, 293
Ibutilide, 51*t*
  as antiarrhythmic drug, 51, 51*t*
  intravenous dosage of, 52*t*
  side effects of, 54*t*
Idarubicin as chemotherapeutic agent, 233*t*
Ifosfamide
  as chemotherapeutic agent, 233*t*
  in non-Hodgkin lymphoma, 653
Iloperidone in schizophrenia, 739*t*
Imidazoles in diaper dermatitis, 145
Imipenem
  in bacterial pneumonia, 417*t*
  in sepsis, 431*t*
  in urinary tract infections, 495*t*
Imipenem-cilastatin
  dosing of, 457*t*
  in intraabdominal infections, 398*t,* 400*t*
  in pancreatitis, acute, 247
  in urinary tract infections, 495*t*
Imipramine, 716*t*
  for anxiety disorders, 677*t*
  closed-angle glaucoma, 666*t*
  in depression, 719*t,* 726*t*
  in dyssomnias, 752*f*
  in generalized anxiety disorder, 677*t,* 678*t,* 678*t*
  in narcolepsy, 753*t,* 754
  in panic disorder, 687, 687*t*
  in posttraumatic stress disorder, 691, 692*t*
Immune globulin. *See* Immunoglobulins
Immune response
  in inflammatory bowel disease (IBD), 221
  in influenza, 388
  nutrition affecting, 606
  in respiratory disorders, 814
  in rheumatoid arthritis, 26
Immunization. *See also* Vaccinations
Immunocompromised hosts
  blastomycosis in, 352*t*
  candidiasis in, 356*t*
  cryptococcosis in, 354*t*
  vaccinations in influenza, 390
Immunoglobulins, 500, 502–503, 509–510
  in atopic dermatitis, 141
  in hepatitis A, 213, 214*t,* 509*t*
  in hepatitis B, 509*t*
  IgE
    in allergic rhinitis, 813
    in asthma, 821
  in infectious diseases, 509*t*

in prophylaxis therapies, 384*t*
in rheumatoid arthritis (RA), 26
Rho(D), 510
in tetanus, 465
Impetigo, 448–449, 449*t*, 453*t*
Impotence, 658, 850
Incontinence, urinary, 865–872
treatment
α-adrenergic receptor agonists, 871
bladder overactivity, 867, 868*t*–869*t*, 870*t*
duloxetine, 871
estrogens, 871
nonpharmacologic, 867
overflow incontinence, 871
oxybutynin immediate-release (IR), 867
pharmacologic, 867–871, 868*t*–869*t*
tolterodine, 867
urethral underactivity, 871
urge urinary incontinence, 870–871
Indacaterol in chronic obstructive pulmonary disease, 837
Indapamide
in hypertension, 89*t*
in hypokalemia, 807*t*
Indinavir
in acute pancreatitis, 245*t*
in HIV infection, 375*t*, 377*t*
in infectious diseases, 377*t*
Indolent lymphomas, 651
Indomethacin
in acute pancreatitis, 245*t*
in anxiety, 676*t*
in diabetes insipidus, 801*t*
in acute gout, 2, 4*t*
in rheumatoid arthritis, 33*t*
Infarction
cerebral, 120
myocardial (*See* Myocardial ischemia and infarction)
Infections
antibiotic selection in, 313–322
of central nervous system, 323–332
diagnosis, 313
drug-resistant, 322
endocarditis, 333–346
fungal, 347–360
gastrointestinal, 361–367
hepatitis, 213–220
HIV infection and AIDS, 368–386
influenza, 387–393
intraabdominal, 394–404
Community-acquired intraabdominal infections, 400*t*
opportunistic, in HIV infection and AIDS, 368, 380, 381*t*–383*t*, 384*t*–385*t*
pathogen identification in, 314
respiratory, 405–417, 405–426
sepsis and septic shock in, 427–432
sexually transmitted, 433–447
in pregnancy, 294
in sickle cell disease, prevention of, 308–312
of skin and soft tissues, 448–465
surgical site, 466–475
tuberculosis, 476–489
of urinary tract, 490–499
vaccines and toxoids in prevention of, 500–510
Inflammation
in acne vulgaris, 135, 137, 139
in acute pancreatitis, 244
in allergic rhinitis, 813
in asthma, 821
in chronic pancreatitis, 247
in dermatologic disorders, 145, 152
in endocarditis, 333
in gouty arthritis, 1
in infections, 313
intrauterine, 275
in osteoarthritis, 9, 10
in otitis media, 418
in rheumatoid arthritis, 26, 32
in sinusitis, 422
in thyroid disorders, 178
Inflammatory bowel disease, 221–230
drug monitoring guidelines, 229*t*
nonpharmacologic treatment for, 224
pharmacologic therapy for, 224–228, 225*t*
selected complications, 228
systemic manifestations, 228
toxic megacolon, 228
treatment of, 224–229

Inflammatory response syndrome, systemic, 244, 427, 428*t*
Infliximab
  dermatologic disorders, 152
  in inflammatory bowel disease, 224, 225*t,* 226, 226*f,* 227, 229*t*
  in pancreatitis, 245*t*
  in psoriasis, 152
  in rheumatoid arthritis, 27, 29*t,* 31*t,* 34–35
Influenza, 387–393
  acute bronchitis in, 405, 406
  antiviral drugs in, 390
    recommended daily dosage, 390, 391*t*–392*t*
  goals of therapy, 390
  laboratory tests, 387
  pharmacologic therapy in, 393
  postexposure prophylaxis in, 388, 390, 391*t*–392*t*
  in pregnancy, 393
  prevention of, 387–393
  signs and symptoms of, 387
  treatment for, 390–393
  vaccination, 387–390, 389*t*–390*t,* 506*t*
    in adults, 504*t*
    in children, 387–390, 389*t*–390*t*
    chronic obstructive pulmonary disease, 837
    in HIV infection, 385*t*
    live-attenuated, 388, 389*t*–390*t,* 390
    in pregnancy, 390, 393
    trivalent, 385*t,* 388, 389*t*–390*t*
Influenza virus vaccine, 506*t*
Inotropic agents, 83
  in heart failure, 80
  in shock, 117
Insomnia, 747–750
  treatment, 747–750
Insulin, 87
  diabetes mellitus, therapy in, 162–164, 163*t,* 164*t,* 170–173
    adverse effects of, 164
    glucose levels in, 164, 171*f*
    infusion pump delivery of, 171*f,* 172
    monitoring of, 175
    pharmacokinetics of, 164*t*
    in pregnancy, 292
    preparations available, 163*t*
    in type 2 disease, 164, 166*t*–168*t*
  in hypertension, 87
Insulin secretagogues, short-acting, in diabetes mellitus, 165
Interferon therapy
  in hepatitis B, 216, 218*f,* 219*t,* 220*t*
  in hepatitis C, 220*t*
Interleukin-1 (IL-1)
  in osteoarthritis, 9
  in rheumatoid arthritis, 26
Interleukin-6 (IL-6), in rheumatoid arthritis, 26
Intoxication in substance abuse, 755, 760, 761*t*
  of alcohol, 755, 761*t*
  of benzodiazepines, 756, 761*t*
  of cocaine, 758, 760, 761*t*
  of marijuana, 695*t,* 758, 761*t*
  of methamphetamine, 758
  of opiates, 757, 761*t*
  of phencyclidine, 761*t*
Intraabdominal infections, 394–404
  anaerobic coverage for, 401*t*
  anti-MRSA therapy for, 401*t*
  antienterococcal therapy for, 401*t*
  antifungal therapy for, 401*t*
  antimicrobial agents and, 401*t*
  community acquired, 401*t*
    complicated treatment, agents recommended for, 398*t*
  duration of therapy for, 401*t*
  evidence-based recommendations for, 401*t*–403*t*
  health care-associated, 401*t*
  initial antimicrobial agents, guidelines for, 399*t*–400*t*
  microbiology in, 394–395
  nonpharmacologic treatment, 398
  oral completion therapy for, 401*t*
  pathogens isolated from patients, 396*t*
  pharmacologic therapy, 398–404
  treatment for, 396, 398–404
Intraaortic balloon pump (IABP) in acute decompensated heart failure, 85
Intracerebral hemorrhage, 120
Intracranial aneurysm, 120
Intracranial hemorrhage (ICH), 41
Intramuscular immunoglobulin, indications and dosage of, 509*t*
Intranasal oxygen in acute coronary syndromes, 44

Intrauterine devices for contraception, 275
Iodide in thyroid disorders, 179–180
Iodine, radioactive
  as therapy in hyperthyroidism, 180
  uptake in hyperthyroidism, 177
Ipratropium bromide
  in allergic rhinitis, 819
  in asthma, 829*t,* 832
  in bronchitis, chronic, 407
  in chronic obstructive pulmonary disease, 837, 840
  ophthalmic disorders, 666*t*
Irbesartan in hypertension, 89*t*
Irinotecan
  chemotherapeutic agents, 233*t*
  in colorectal cancer, 635, 640*t*
    metastatic, 637*t*–638*t*
    side effects of, 640
  in lung cancer, 645*t,* 646
Iron
  constipation, as cause of, 195*t*
  deficiency of, 222, 301
    in children, 301, 305*t*
    treatment of, 304
  GERD symptoms, 207*t*
  total binding capacity, 303*f*
Iron dextran in anemia, 306*t*
Iron sucrose in anemia, 306*t*
Irritant contact dermatitis (ICD), 141
Ischemia, cerebral, 122, 323
Ischemic heart disease (IHD), 102
  nonpharmacologic treatment, 104
  pharmacologic therapy of, 104–109, 105*t,* 107*t*–108*t,* 108*f*
Isoetharine in chronic obstructive pulmonary disease, 837
Isometheptene in migraine headache, 545
Isoniazid
  as antimicrobial agents, 331*t*
  in anxiety disorders, 676*t*
  interaction with other drugs, 319*t,* 608*t,* 676*t*
  in pregnancy, 486
  therapeutic levels in cerebrospinal fluid (CSF), 326*t*
  therapies for prophylaxis, 384*t*
  in tuberculosis, 479*t*
    active, 479
    culture-positive, 480*t*–481*t*
    dose adjustment in renal failure, 482*t,* 486
    latent, 478
  vitamin interactions, 608*t*
Isoproterenol
  in arrhythmias, 58
  in asthma, 827*t*
  in chronic obstructive pulmonary disease, 837
  in hypokalemia, 807*t*
  in renal disorders, 807*t*
  in torsades de pointes (Td^P), 58
Isosorbide dinitrate in systolic heart failure, 76
Isosorbide mononitrate for ischemic heart disease, 105
Isotretinoin
  in acne vulgaris, 139
  vitamin interactions, 608*t*
Itraconazole, 210, 686
  for blastomycosis, 352*t*
  for cryptococcocosis, 354*t*
  for histoplasmosis, 350
Ixabepilone in breast cancer, 627, 628*t*, 629*t*

J

Jarisch-Herxheimer reaction, 438
Jejunostomy for enteral nutrition, 610*t*

K

Kanamycin antituberculosis drugs for, 484*t*
Kaolin-pectin, 202, 204*t*
Kernig sign, 323
Ketoacidosis, diabetic, 161, 232*t,* 772
Ketoconazole, 156, 158, 210, 349*t,* 709, 750
  adverse effects of, 659
  for blastomycosis, 353
  for coccidioidomycosis, 353
  Cushing's syndrome, 156, 157*t*
  erectile dysfunction, 851*t*
Ketoprofen, 552*t*
  acute gouty arthritis, 4*t*
  neurologic disorders, 555
  nonopioid analgesics for pain, 561*t*
  pancreatitis, acute, 245*t*

Ketorolac, 545
acute pancreatitis, 245*t*
as nonopioid analgesics for pain, 561*t*–562*t*
in tension-type headache, 555
Kidney disease, chronic, 98, 787–797
anemia in erythropoiesis-stimulating agent (ESA) therapy, algorithm for, 793*f*
clinical presentation, 787
guidelines for calcium, phosphorus, calcium-phosphorus product, and intact parathyroid hormone, 794*t*
hyperlipidemia, 797
hyperphosphatemia, phosphate-binding agents for, 795*t*
hypertension management algorithm, 761*f*
pathophysiology of, 787
phosphate-binding agents, 794
related mineral and bone disorder, 792
treatment of
anemia with, 788, 792
diabetes with, 788, 790*f*
hypertension with, 788, 791*f*
nonpharmacologic therapy, 788
pharmacologic therapy, 788–794
vitamin D therapy, 794, 796*t*
Kidney injury, acute
classification of, 781*f*
definitions of, 779
diagnostic parameters for, 782*t*
diuretic resistance, common causes of, 785*t*
general approach
nonpharmacologic therapies, 782
pharmacologic therapies, 782–783
key monitoring parameters for, 786*t*
prevention of, 782
RIFLE/AKIN/KDIGO classification, 780*t*
treatment of, 783–785
drug-dosing considerations, 785–786
electrolyte management and nutrition interventions, 785
general approach, 784–785
nonpharmacologic therapies, 784
pharmacologic therapies, 784–785
urinary findings, 783*t*
Klebsiella infections, 191, 293, 317*t*, 394, 396*t*, 407*t*
Kyphosis in osteoporosis, 16

L

Labetalol
alcohol withdrawal, 763*t*
antihypertensive agents, 90*t*
in hypertension
in pregnancy, 297
urgencies, 99
in ischemic heart disease, 104
Labor and delivery
analgesia, 299–300
antenatal glucocorticoids, 298
cervical ripening, 299
induction, 299
preterm, 298–299
Streptococcus infection in, 299
tocolytic therapy, 298–299
Lacosamide, 537*t*, 540
antiepileptic drug side effects, 532*t*–533*t*
dosing and target serum concentration ranges, 529*t*
pharmacokinetic data of, 526*t*
in refractory generalized convulsive status epilepticus, 595*t*
Lactase in diarrhea, 205*t*
Lactate dehydrogenase, 247, 650, 741
Lactated Ringer solution, 113, 114*f*, 115*f*, 361, 398, 431
Lactation. *See* Pregnancy
Lactic acidosis, 111, 165, 429*t*
metabolic acidosis, 773*t*
sepsis, 428*t*
Lactobacillus in diarrhea, 202, 202, 205*t*
Lactulose, 192, 193*t*
for constipation, 192*t*, 196–197, 198, 292
Lamivudine, 216
acute pancreatitis, 245*t*
in HIV infection, 297, 379
Lamotrigine, 141, 143, 529*t*, 540, 692*f*, 702*t*
as antiepileptic drug, 521*t*–524*t*, 533*t*
pharmacokinetic data, 526*t*
side effects, 533*t*

bipolar disorder, 709–710
elimination pathways and major effects on hepatic enzymes, 537*t*
pharmacokinetic data, 526*t*
during pregnancy, 297
Lansoprazole
enteral nutrition, 615*t*
gastric acid, 208*f*
gastroesophageal reflux disease (GERD) in adults, 208*t*
proton pump inhibitors, 210, 211
ulcer healing, 255*t*
Lanthanum carbonate in chronic kidney disease, 795*t*
Lapatinib, 233*t*
in breast cancer, 627
Latanoprost in glaucoma, 667, 671*t*
Laxatives, 20*t,* 196–198
causing diarrhea, 201*t*
Lean body mass assessment, visceral proteins used for, 606*t*
Leflunomide in rheumatoid arthritis, 27, 29*t*, 31*t*, 32
Legionella infections, pneumonia in, 410
Letrozole in breast cancer, 624, 625*t*
Leucovorin
chemotherapy, 635
colorectal cancer, 634*t,* 636*t,* 638*t*–639*t*
HIV-infection, 382*t*
Leukocytes. *See* White blood cells
Leuprolide
in breast cancer, 625*t,* 627
in prostate cancer, 658, 662*t*
in prostate hyperplasia, benign, 846, 847*t*
Levalbuterol
respiratory disorders, 828*t*
sympathomimetics, 837
Levetiracetam, 525, 529*t*, 538, 540
antiepileptic drug pharmacokinetic data, 526*t*
antiepileptic drug side effects, 533*t*
elimination pathways and major effects on hepatic enzymes, 537*t*
seizure disorders, 521*t*–524*t,* 589*f*, 595*t*, 597
Levobunolol, 669*t*
Levocabastine in allergic rhinitis, 815
Levocetirizine in allergic rhinitis, 816*t*, 817*t*
Levodopa, 579, 583–584
in anxiety disorders, 676*t*
in gout, 1
in Parkinson's disease, 580*t,* 581*t*
Levofloxacin, 453*t*
for acute bacterial sinusitis, 425*t*, 426*t*
in acute exacerbation of COPD, 842
in acute pancreatitis, 247
antimicrobial agents, 330*t*
in bronchitis
acute, 406
chronic, 409*t*
for diabetic foot infections, 463*t*
for dog bites, 464
dosing of, 455*t*, 457*t*
in intraabdominal infections, 398*t,* 400*t*
in pneumonia, 417*t*
for surgical prophylaxis, 473
in urinary tract infections, 493*t*, 495*t*, 496*t*
Levonorgestrel
IUD, for contraception, 261*t*, 268*t*–269*t*
in oral contraceptives, 263*t*–266*t*
Levothyroxine
in anxiety disorders, 676*t*
in bipolar disorder, 707
in hypothyroidism, 183
in myxedema coma, 184
Lidocaine, 50
in antiarrhythmic drugs, 51*t*
in cardiac arrest, 62
local anesthetics, 576*t*
side effects of, 54*t*
in status epilepticus, 591*t*, 595*t*, 597
Linaclotide, gastrointestinal disorders, 198
Linagliptin in diabetes mellitus, 167*t,* 170
Linezolid, 463*t*
as antimicrobial agents, 330*t*
dosing of, 457*t*
drug monitoring, 344*t*
Lingual spray in secondary prevention after myocardial infarction, 47

Liothyronine
in hypothyroidism, 183
in myxedema coma, 184
Liotrix in hypothyroidism, 183
Lipid amphotericin B as antimicrobial agents, 331*t,* 348*t*
Lipid levels, 162
Lipoprotein
high-density, 165, 288
primary/genetic, 65
recommended drug, 69*t*
serum, 863
Liraglutide in diabetes mellitus, 163*t*, 164
Lisinopril
in heart failure, 78*t*
in hypertension, 89*t*
in myocardial infarction, secondary prevention after, 46
Listeria monocytogenes, 323, 325*t,* 327*t,* 332
Lithium, 700, 707–708
in bipolar disorder, 698*t,* 699*t,* 701*t*
nephrotoxicity, 707
renal replacement therapy, 784*t*
serum, 708
toxicity, 707
Liver disorders, 683, 841
abscess, 400*t*
Lomitapide, 69*t*, 70*t*
Loop diuretics, 94
in heart failure, 78, 78*t*
Loperamide as antidiarrheal preparations, 204*t,* 361, 366
Lopinavir in HIV infection, 377*t*
Loratadine in allergic rhinitis, 816*t*, 817*t*
Lorazepam, 687*t*
adverse effects, 591*t*
alcohol withdrawal, 764*t*
benzodiazepine antianxiety agents, 683, 683*t,* 684*t*
dosage regimens, 236*t*
dosing and target serum concentration ranges, 528*t*
in status epilepticus, 589*f*, 590*t*, 593
substance-related disorders, 756
Lorcaserin in obesity, 601, 602*t*
Lovastatin, 69*t*, 70*t*, 71
Low-density lipoprotein (LDL) cholesterol, 65
treatment of, 73
Low-molecular-weight heparins (LMWHs)
in pregnancy, 293
in stroke, 122
in venous thromboembolism (VTE), 129–130
Lubiprostone, gastrointestinal disorders, 198
Lugol solution, thyroid storm, 179, 181*t*
Lung cancer
cancer metastasis, 645
chemotherapy regimens, 644*t*–645*t*
staging, 642–643
treatment
chemotherapy, radiation therapy, and surgery, 643–645
non–small cell lung cancer, 643–645
small cell lung cancer, 645–646
surgery and radiation therapy, 645–646
Lupus erythematosus, 272, 676*t,* 695*t*
Lurasidone in schizophrenia, 739*t*
Luteinizing hormone (LH), 257
menstrual cycle events, 258*f*
Luteinizing hormone-releasing hormone (LHRH), 624, 658
in metastatic breast cancer, 625*t*
in prostate cancer, 654
Lymph node involvement, 619, 632, 643
Lymphangitis, 449*t,* 453*t*
Lymphocyte count, nutritional disorders, 606
Hodgkin's lymphoma
diagnosis and staging, 647
initial chemotherapy, 648
salvage chemotherapy, 648
treatment of, 647–648
non-Hodgkin's lymphoma
diagnosis and staging, 650
in immunodeficiency syndrome, 653
treatment
advanced disease, 652
advanced follicular lymphoma, 651–652
aggressive lymphomas, 652
general principles, 650–651
indolent, 651

localized disease, 652
localized follicular, 651
refractory/relapsed disease, 652–653
Lymphoproliferative disorders, 1, 31*t*, 153, 347
Lysergic acid diethylamide (LSD), 759

M

Macrolide, antimicrobials
in acute exacerbation of COPD, 842
for sickle cell disease, 311
in bacterial pneumonia, 416*t*
Macules, 141, 143
Maculopapular skin reaction, 141
Magnesium, 38
in cardiac arrest, 62
gastrointestinal disorders, 197*t*
homeostasis, disorders of, 810–811
hypermagnesemia, 811
hypomagnesemia, 810–811
oral rehydration solutions, 204*t*
postresuscitative care, 63
Magnesium sulfate in torsades de pointes (TdP), 58
Malabsorption
in pancreatitis, 248
of protein, 247
Malnutrition, 248, 525, 605
Mania
antipsychotics, 710
bipolar disorder, 699*t*
secondary causes of, 695*t*
Mannitol, acute kidney injury, 784
Maprotiline in depression, 721
Maraviroc in HIV infection, 378*t*
Marijuana, 676*t*
Measles, mumps, rubella (MMR), 504*t*, 506*t*
Measles vaccine, 507
Mechanical ventilation, 413, 775, 777, 778, 842
Mechlorethamine
chemotherapeutic agents, 233*t*
in Hodgkin's, lymphoma, 649*t*
Meclizine in nausea and vomiting, 235*t*
Meclofenamate
bone and joint disorders, 33*t*
in osteoarthritis, 12*t*
pain management, 560*t*
Medroxyprogesterone
contraception, 274
hormone therapy in menopause, 284, 284*t*
low-dose hormone therapy, 285*t*
in metastatic breast cancer, 626*t*
Mefenamic acid
acute pancreatitis, 245*t*
in osteoarthritis, 12
in pain management, 560*t*
Megaloblastic anemia, 307
Megestrol acetate
hot flushes, treatment of, 287*t*
in metastatic breast cancer, 626*t*
in prostate hyperplasia, benign, 847*t*
Meglitinides, 165
Meloxicam, 33*t*
Memantine in Alzheimer's disease, 513, 514*t*, 515*t*
Meningitis, 325–326, 327*t*–328*t*, 329, 332
dexamethasone as an adjunctive treatment for, 325–326
Gram-negative bacillary meningitis, 316*t*, 332
Haemophilus influenzae common cause of, 329
Listeria monocytogenes cause of, 332
Neisseria meningitidis, 326, 329
Streptococcus pneumoniae leading cause of, 329
dosing of antimicrobial agents, 330*t*–331*t*
treatments, 329
treatment and prevention, 329
Meningococcal infections, 324, 326, 329
Meningococcal polysaccharide vaccine, 507
Menopause, 276
alternative drug treatments for, 284–289
alternatives to estrogen for treatment of hot flashes, 286*t*–287*t*
androgen regimens used for women, 284, 285, 288*t*
combinational hormone therapy, 284, 285*t*, 289
estrogen products for treatment of, 281*t*–283*t*
estrogens for replacement therapy, 280

Menopause (*Cont.*)
follicle-stimulating hormone (FSH) concentrations, 276
hormone therapy in, 277*f,* 278–284
guidelines, in symptom management, 279*t*
risks of, 289
pathophysiologic changes associated with, 276
progestogens therapy, 284
selective estrogen-receptor modulators, 288
therapeutic
outcomes, evaluation of, 289–290
use of testosterone in women, 284
tibolone in, 286*t,* 288–289
treatment of, 276–289
Menstrual cycle, 257, 258*f*
Meperidine/congeners, 311, 564*t*
MAO-B inhibitor, 584
for migraine headaches, 550
in pain management, 569*t*, 574
parenteral, 247
Mepivacaine in local anesthetics, 576*t*
Mercaptopurine
immunosuppressive agents, 227
in inflammatory bowel disease, 224, 225*t*
vitamin interactions, 608*t*
Meropenem, 330*t*
dosing of, 457*t*
in intraabdominal infections, 398*t,* 400*t*
in pneumonia, 417*t*
in urinary tract infections, 495*t*
Mesalamine, 224, 225, 225*t,* 226*f,* 227, 228, 229*t*
in inflammatory bowel disease, 225*t*
Mesna, 653
Mestranol in oral contraceptives, 262, 263*t*
Metabolic acidosis, common causes of, 773*t*
Metabolic alkalosis, primary, treatment algorithm for patients, 776*f*
Metaproterenol in respiratory disorders, 837
Metastatic breast cancer
chemotherapy regimens for, 628*t*–629*t*
endocrine therapies used for, 625*t*–626*t*
Metastatic colorectal cancer, chemotherapeutic regimens for, 636*t*–639*t*
Metformin in diabetes mellitus, 165, 167*t*, 169
Methadone, 311
analgesic duration of, 574
dosing guidelines, 565*t*
in pain management, 570*t*
substance-related disorders, 757
Methamphetamine
drugs of abuse, 758–759
substance-related disorders, central nervous system stimulants, 758
Methazolamide in glaucoma, 671*t*
Methicillin
in infectious diseases, 315*t*
for *S. aureus,* 468
Methimazole, 179
Methotrexate, 29*t*, 31*t*, 32, 224, 227, 229*t*
in anemia, 301
in breast cancer, 621
chemotherapeutic agents, 233*t,* 622*t*–623*t*
in inflammatory bowel disease, 224, 225*t*
in psoriasis, 151
in rheumatoid arthritis, 27
vitamin interactions, 608*t*
Methyldopa
in hypertension, 96
for hypertension in pregnancy, 298
Methylnaltrexone, 198
Methylphenidate
in anxiety disorders, 676*t*
in narcolepsy, 753*t*
Methylprednisolone
in adrenal gland disorders, 159*t*
in asthma, 829*t*, 832*t*
bone and joint disorders, 35
in gout, 4
in non-Hodgkin lymphoma, 653
in osteoarthritis, 11*t*
in rheumatoid arthritis, 35
in thyroid storm, 181*t*
Methylprednisolone acetate
in osteoarthritis, 11*t*
in rheumatoid arthritis, 35
Methyltestosterone for erectile dysfunction, 856*t*

Methylxanthines
in asthma, 830–832
in chronic obstructive pulmonary disease, 840–841
Metipranolol, 669*t*
Metoclopramide, 300
in endocrinologic disorders, 174
in gastrointestinal disorders, 211
in migraine and tension-type, 548*t*
in migraine headache, 545
in nausea and vomiting, 238*t*, 240
Metolazone
in acute kidney injury, 785
in cardiovascular disorders, 77, 83
in heart failure, 82*f*
in renal disorders, 807*t*
in systolic heart failure, 77
Metoprolol, 51, 95
in acute coronary syndromes, 43
bradyarrhythmias, 58
in migraine prophylaxis, 554
Metoprolol CR/XL in heart failure, 79
Metronidazole, 193, 367
in acute pancreatitis, 247
for cellulitis, 461*t*
in cirrhosis, 193*t*
dosing of, 455*t*, 457*t*
for human bites, 465
in inflammatory bowel disease, 224, 227
interactions with other drugs, 319*t*
in intraabdominal infections, 398*t,* 400*t*
in pancreatitis, acute, 245*t*
sexually transmitted diseases, 442
for surgical prophylaxis, 470*t,* 474
to treat sexually transmitted diseases, 295*t*, 296*t*
trichomoniasis, treatment of, 445*t*
Metyrapone in Cushing's syndrome, 156, 157*t*
Mexiletine in antiarrhythmic drugs, 50, 51*t,* 52*t*, 54*t*
Microcomedone, 135
Midazolam, 589*f*
in status epilepticus, 590*t,* 593, 595*t*
Midodrine in bradyarrhythmias, 58
Mifepristone in Cushing's syndrome, 157*t*, 158
Miglitol in diabetes mellitus, 167*t,* 169
Migraine headaches, 543
clinical presentation in, 543–544
symptoms, 543–544
commonly reported triggers of, 544*t*
nausea and vomiting, 232*t*
oral contraceptive use in, 272
prophylactic management, treatment algorithm for, 553*f*
treatment, 545
acute, pharmacologic, 545
analgesics and nonsteroidal antiinflammatory drugs, 545
β-antagonists, 554
anticonvulsants, 554–555
antidepressants, 554
ergot alkaloids and derivatives, 545
nonpharmacologic, 544
nonsteroidal antiinflammatory drugs, 555
opioids, 550
pharmacologic prophylaxis of, 550–555
serotonin receptor agonists (triptans), 549–550
treatment algorithm for, 549*f*
Milk of magnesia, 196
Milrinone
in acute decompensated heart failure, 83
in heart failure, 83
Mineral oil in constipation, 198
Mini-Mental State Examination, in Alzheimer's disease, 512, 5112*t*
Minimum inhibitory concentration (MIC), 415
Minocycline, 28, 29*t*, 33, 317*t,* 409*t*
in acne vulgaris, 139
in chronic bronchitis, 409*t*
in rheumatoid arthritis, 28
Minoxidil in hypertension, 96
Mipomersen, 69*t*, 70*t*
Mirabegron in urinary incontinence, 869*t*, 870, 870*t*
Mirtazapine, 158, 556, 691, 692*f,* 692*t*, 718, 718*t,* 720*t,* 727*t,* 728, 729*t*
antidepressants, 516*t*, 724*t*, 729*t*
Mithramycin in hypercalcemia, 803*f*
Mitomycin C in ophthalmic disorders, 667

Mitomycin chemotherapeutic agent, 233*t*
Mitotane in Cushing's syndrome, 156, 157*t,* 158
Mitoxantrone, 233*t*
  in non-Hodgkin's lymphoma, 653
Modafinil, 751, 752*f,* 753*t,* 754
Model for end-stage liver disease (MELD), 188
Moexipril in hypertension, 89*t*
Molds, allergic rhinitis from, 813
Mometasone furoate, 149*t,* 818*t,* 831*t*
Monoamine oxidase inhibitors, 180, 550, 574, 579, 582*t*, 584, 666*t,* 690*t,* 695*t,* 717*t*, 718, 721*t,* 817
  dietary restrictions for, 721*t*
Monoclonal antibodies, 152, 442, 630, 643, 651
Montelukast, 815*f,* 819, 833
Mood disorders by episodes
  algorithm and guidelines for, 698*t*–699*t*
Moraxella catarrhalis infections, 315*t*, 408, 418
  chronic bronchitis, bacterial isolates in, 407*t*
Morphine, 38, 40*f,* 45*f,* 204*t,* 247, 311, 563, 564*t,* 574
  in acute coronary syndromes, 44
  in chronic pancreatitis, 248
  dosing guidelines, 567*t*
  in pain management, 574*t*
Moxifloxacin, 315*t,* 326*t*, 330*t*
  for acute bacterial sinusitis, 425*t*, 426*t*
  in acute exacerbation of COPD, 842
  in bacterial pneumonia, 417*t*
  in bronchitis, chronic, 409*t*
  in complicated intraabdominal infections, 398*t*
  for diabetic foot infections, 463*t*
  for dog bites, 464
  dosing of, 455*t*, 457*t*
  in intraabdominal infections, 400*t*
  in meningitis, 327*t*–328*t*
  in respiratory tract infections, 409*t*
  in sepsis, 431*t*
  in soft-tissue infections, 453*t*
  in tuberculosis, 485*t*
Mucolytic agents in chronic bronchitis, 407, 424
Multiple-organ dysfunction syndrome, 428*t*
Multivitamin and alcohol withdrawal, 763*t*
Mumps vaccination, 507
Mupirocin ointment
  dosing of, 455*t*
  in impetigo, 449
Myalgias, 26
Mycophenolate mofetil in psoriasis, 153
Mycoplasma pneumoniae infections, 317*t*, 405, 412, 416*t*
  acute bronchitis in, 405
  antibiotics in, 406
  pneumonia in, 412, 414*t*
Myeloproliferative disorders, hyperuricemia and gout in, 1
Myocardial infarction (MI), 62.
Myocardial ischemia and infarction, 75, 189
Myoclonic jerks, 519
Myxedema coma treatment of, 184

N

Nabilone in nausea and vomiting, 237*t,* 240
Nabumetone in rheumatoid arthritis, 33*t*
Nadolol
  in cirrhosis and portal hypertension, 188, 189
  in hypertension, 90*t,* 95
  in hyperthyroidism, 180
  in migraine prophylaxis, 551*t,* 554
  in schizophrenia, treatment-resistant, 740
Nafcillin, 326*t*–327*t,* 330*t*
  in cellulitis, 460*t*
  dosing of, 457*t*
  in endocarditis, 340*t,* 342
  in infectious diseases, 315*t*
Nalbuphine in pain management, 565*t,* 571*t*
Naloxone, 589*f*
  in opioid reversal, 563, 571*t,* 575, 761*t*
Naltrexone in alcohol dependence, 765
Naphazoline hydrochloride in allergic rhinitis, 818*t*
Naproxen
  in acute gouty arthritis, 4*t*
  in gout, 2, 4*t*

in osteoarthritis, 12*t*
in pain management, 561*t*
in rheumatoid arthritis, 33*t*
in tension-type headache, 545, 546*t,* 552*t,* 555
Naratriptan in migraine headache, 547*t,* 550*t,* 552*t,* 555
Narcolepsy, 751, 754
drugs used to treat, 753*t*
Nasal corticosteroids, 818*t*
Nasal decongestants in sinusitis, 424
Natalizumab, 224, 225*t*, 229*t*
Nateglinide in diabetes mellitus, 165, 166*t*
National Asthma Education and Prevention Program, 823, 824*f*–825*f,* 826*f*
National Cholesterol Education Program, Adult Treatment Panel III, 66, 174
Nausea and vomiting
antiemetic use
in children, 243
during pregnancy, 243
chemotherapy-induced, 240
disorders of balance, 243
dosage recommendations for chemotherapy-induced nausea and vomiting (CINV) for adult patients, 241*t*
drug class information for, 232, 234–240
emetogenicity of chemotherapeutic agents, 233*t*
etiologies associated with, 231, 232*t*
pharmacologic management, 231–232, 234–240
postoperative, 240, 242*t,* 243
presentation of, 234*t*
treatment of, general approach to, 231
Necrolysis, toxic epidermal, 143
Necrotizing fasciitis, 420, 449*t*
Nefazodone
in depression, 710, 717*t,* 719*t*, 723*t*, 725, 729*t*
and cytochrome P450 activity, 729*t*
pharmacokinetics of, 727*t*
side effects of, 851*t*
drug classification, 718
Neisseria gonorrhoeae infections. *See* Gonorrhea
Neisseria meningitidis, 316*t*, 324, 326, 329
Nelfinavir
in HIV infection, 375*t,* 377*t*
pharmacologic characteristics of, 377*t*
Neomycin, 193
in cirrhosis, 193*t*
in colorectal surgery, 473
as poliovirus vaccine, 508
as rubella vaccine, 509
in surgical site infections, 469*t*
Nephropathy
in acute kidney injury, 782
in diabetes mellitus, 161, 174
uric acid, 1
Nephrotoxin
in acute kidney injury, 784
interactions with other drugs, 319*t*
Nesiritide in heart failure, 84–85
Neurofibrillary tangles in Alzheimer's disease, 511
Neurokinin$_1$ receptor antagonists in nausea and vomiting, 240
Neuroleptic malignant syndrome, 741–743
Neurologic disorders, 511–597
Alzheimer's disease (AD), 511–517
anxiety symptoms, 516*t*
in central nervous system infections, 323
coccidioidomycosis, 351, 353
cryptococcal, 353
epilepsy, 518–542
and status epilepticus, 587–597
headache in, 543–556
Parkinson's disease, 578–586
Neuropathy
diabetic, 174, 557
optic, in glaucoma, 665
Neurosurgery, surgical site infections in, 472*t,* 475
Neurosyphilis, 296*t*, 318*t,* 436, 438*t,* 439*t,* 695*t*
Neutral protamine Hagedorn (NPH), 163
Neutropenia, side effect of colchicine, 5
Neutrophil count in infections, 313
Nevirapine in HIV infection, 374*t,* 377*t*

Nexplanon as implantable contraceptive, 275
Niacin in dyslipidemia, 69*t*, 70*t*, 71, 72, 74
  in combination therapy, 74
  and coronary artery disease, 174
Niaspan, 71
Nicardipine in hypertension, 89*t,* 100*t*
Nicotine, 758
  in anxiety disorders, 676*t*
  dependence on, 765, 767
    replacement therapy in, 292, 767, 768*t*
  transdermal, in smoking cessation, 767, 768*t*
Nicotinic acid, in gout, 1
Nifedipine
  in acute coronary syndromes, 44
  in ischemic heart disease, 106
  to prevent preterm labor, 299
  in variant angina pectoris, 109
Nilutamide in prostate cancer, 659, 661*t*
Nimodipine
  in bipolar disorder, 708
  in hemorrhagic stroke, 122, 124*t*
Nisoldipine in hypertension, 89*t*
Nitrates
  in acute coronary syndromes, 43–44, 46
  in heart failure, 81
  products for ischemic heart disease, 105*t*
  therapy in ischemic heart disease, 104–106, 109
  in variant angina pectoris, 109
Nitric oxide in osteoarthritis, 9
Nitrofurantoin in urinary tract infections, 293, 493*t,* 496*t*
Nitroglycerin
  in acute coronary syndromes, 43
    in non–ST-segment elevation, 45*f*
    in ST-segment elevation MI, 38, 40*f*
  in acute decompensated heart failure, 84
  in angina pectoris, 105, 107*t,* 108*f,* 109
  in heart failure, 84, 85
  in hypertensive emergencies, 100*t*
  in variant angina pectoris, 109
  sublingual (SL) for ongoing ischemia, 46
Nitroprusside
  in heart failure, 84
  in hypertensive emergencies, 99, 100*t*
Nizatidine
  in gastroesophageal reflux disease, 208*f,* 208*t,* 209*t*
  in nausea and vomiting, 234, 237*t*
  in peptic ulcer disease, 255*t*
Nociceptors in pain sensation, 557
Nodules
  rheumatoid, 27
  thyroid, 178
Non-Hodgkin's lymphoma, combination chemotherapy for, 652*t*
Nondihydropyridine calcium channel blockers in PSVT, 57
Noninvasive positive-pressure ventilation (NPPV), 842
Nonopioids, adult dosing guidelines for, 560*t*–562*t*
Nonsteroidal anti-inflammatory drugs (NSAIDs), 2, 29*t*, 87, 311
  in chronic pancreatitis, 248
  dosing guidelines, 567*t*
  in migraine headache, 546*t*
  in osteoarthritis, 10, 14
  for pain management, 559, 573*t*, 575*t*
  in respiratory tract infections, 420
  in rheumatoid arthritis, 28, 31*t,* 32
Norepinephrine, function
  in anxiety disorders, 673, 687*t,* 689
  in depression, 712, 719*t,* 725
Norepinephrine therapy
  in cardiopulmonary resuscitation, 75, 79
  in sepsis, 430*t,* 432, 432*t*
  in shock, 116, 117–118, 117*t*
Norethindrone in oral contraceptives, 263*t*–266*t*
Norethisterone, 284
  in menopause therapy, 284*t*
Norfloxacin, 192, 364*t*
  in gastrointestinal infections, 189, 192
  interaction with other drugs, 319*t*
Norfluoxetine in depression, 726*t,* 728

Norgestimate in oral contraceptives, 139, 264*t*, 265*t*
Norgestrel
  in menopause therapy, 284*t*
  in oral contraceptives, 263*t*
Nortriptyline
  in cataplexy, 754
  in depression, 719*t*, 728
    dosage of, 716*t*
    pharmacokinetics of, 726*t*
    therapeutic plasma concentration of, 716*t*
  in migraine prophylaxis, 551*t*
  in narcolepsy, 753*t*
  in smoking cessation, 768*t*
  in substance-related disorders, 765
Nosocomial infections
  with intraabdominal infection, 396*t*
  pneumonia in, 413
  of urinary tract, 490
Nutrient deficiencies, 606–607
Nutrient requirements, assessment of, 607
  drug-nutrient interactions, 608
  energy requirements
    fluid, 607
    micronutrients, 607–608
    protein, 607
Nutrition
  in acute kidney injury, 786*t*
  assessment of, 605–618
    anthropometric measurements, 605
    biochemical and immune function studies, 606
    clinical evaluation, 605
  in cirrhosis, 193*t*
  in Crohn's disease, 223*t*
  deficiencies, 606–607
  in diabetes mellitus, 162, 292
  enteral, 609–614
    access routes, 609, 610*t*
    administration methods, 609–611
    adult, feeding formulation classification system, 612*t*–613*t*
    bolus, 609
    complications in, 611
    continuous, 609, 611
    cyclic, 609
    drug administration in, 615*t*
    formulations in, 611
    intermittent, 609
    medications, 615*t*
    monitoring of, 617*f*
  evaluation and support, 599–618
    energy requirements, 607–608
  in inflammatory bowel disease, 224
  interventions of, 785
  parenteral, 614–617
    components of, 616–617
    peripheral, 616–617
  pharmacotherapy treatment algorithm, 601*f*
  requirements, 607
    drug-nutrient interactions, 608
    energy, 607–608
      fluid, 607
      micronutrients, 607–608
      protein, 607
  screening of, 605
  support, 224, 246
NuvaRing (contraceptive vaginal ring), 274
Nylidrin in renal disorders, 807*t*
Nystatin in candidiasis and HIV infection, 381*t*

O

Obesity
  by body mass index (BMI), 600*t*
  oral contraceptive use in, 272
  treatment
    general approach to, 600
    pharmacologic therapy, 600–604
Octreotide, 158, 174, 189, 190*f*, 192*t*, 193*t*, 203, 205*t*, 247
Ofloxacin, 192, 326*t*, 442*t*
Olanzapine, 238*t*, 516*t*, 698*t*, 703*t*, 710, 733, 738, 739*t*, 742
Oliguria, 126, 428*t*, 429, 429*t*
Olmesartan in hypertension, 89*t*
Olopatadine in allergic rhinitis, 815, 816*t*
Olsalazine in inflammatory bowel disease, 225*t*
Omalizumab in asthma, 825*f*, 834
Omega-3-acid ethyl esters in hyperlipidemia, 72
Omeprazole, 208*t*, 209*t*, 210, 211, 255*t*, 615*t*
  enteral nutrition, 615*t*

Oncologic disorders, 619–664
Oncology patients, pain management, algorithm for, 559*f*
Ondansetron in nausea and vomiting, 240, 241*t,* 242*t,* 243
Oophorectomy in breast cancer, 624
Open-angle glaucoma
  pharmacotherapy, 669*t*–671*t*
    algorithm for, 668*f*
Ophthalmia neonatorum, 437*t*
Ophthalmic disorders, 665–672
  intraocular pressure, drugs, 666*t*
Opiates, 194, 195*t,* 232*t,* 757, 762*t*
Opioids
  adult dosing guidelines for, 560*t*–562*t*
  as analgesics, 13, 15, 558*f,* 559*f,* 573*t,* 574
    in osteoarthritis, 13
  endogenous, 557
  intraspinal, 574*t*
  in pain management, 575*t*
Opium tincture as antidiarrheal preparations, 204*t*
Opportunistic infections in HIV infection and AIDS, 368, 380, 381*t*–383*t,* 384*t*–385*t*
Optic neuropathy in glaucoma, 665
Oral alkali replacement, therapeutic alternatives for, 744*t*
Oral contraceptives
  containing estrogen, in acne vulgaris, 139–140
  continuation rates of, 261*t*
  discontinuation of, 273
  general considerations for, 272–273
Oral rehydration solutions, 204*t,* 361, 363*t*
Orchiectomy in prostate cancer, 658
Orlistat
  in obesity, 601, 602*t*
  vitamin interactions with, 608*t*
Ortho Evra, 274
Orthopedic surgery, surgical site infections in, 471*t,* 475
Orthotopic cardiac transplantation in acute decompensated heart failure, 85
Oseltamivir in influenza, 388, 391*t,* 393
Osmolality, 204*t,* 363*t*
Ospemifene, 288
Osteoarthritis (OA), 9–15
  hand, 14
  hip, 10, 13
  knee, 10, 13
  nonpharmacologic therapy, 10
  pharmacologic therapy, 10–15, 11*t*–13*t*
  topical therapies, 14
  treatment in, 10–15, 11*t*–13*t,* 20*t*–22*t*
Osteodystrophy, renal, 20*t*
Osteomyelitis in diabetic foot infections, 459
Osteonecrosis of the jaw (ONJ), 23
Osteopenia, 17, 18*f,* 658, 772, 806
Osteophytes in osteoarthritis, 10
Osteoporosis, 16
  anabolic therapies, 24
  glucocorticoids-induced, 24–25
  nonpharmacologic therapy, 17
  pharmacologic therapy, 17–25, 18*f*
Otitis media, 418–420
  acute, 418
    antibiotic recommendations, 419*t*
  antibiotic prophylaxis of recurrent infections, 420
  middle ear, inflammation of, 418
  treatment of, 418–420, 419*t*
Overweight, classification of, 600*t*
Ovulation, 257, 258*f*
Oxacillin, 330*t*
  for cellulitis, 460*t*
  for infectious diseases, 315*t*
  in treatment of staphylococcal endocarditis, 342
Oxaliplatin, 233*t,* 634*t*
  in colorectal cancer, 633, 635, 636*t,* 640*t*
Oxaprozin, 33*t*
Oxazepam, 683, 683*t,* 684*t,* 756
Oxcarbazepine, 540
  antiepileptic drug side effects, 533*t*
  in bipolar disorder, 709
  dosing and target serum concentration ranges, 529*t*
  elimination pathways and major effects on hepatic enzymes, 537*t*
  pharmacokinetic data, 526*t*
  for specific seizure disorders, 521*t*–523*t*

Oxybutynin
in prostate hyperplasia, benign, 847*t*
in urinary incontinence, 867, 868*t*, 870*t*
Oxycodone
in gastrointestinal disorders, 248
in migraine, 550
in osteoarthritis, 11*t*
for pain management, 559*f*, 564*t*, 569*t*
Oxygen
administration in cardiovascular disorders, 38, 40*f*
arterial oxygen saturation, 86
arterial oxygen tension, 777
blood oxygen desaturation, 751
free radicals, 26
intranasal, 44
low oxygen saturation in pneumonia, 412*t*
myocardial oxygen demand, 60, 84, 563
oxygen-carrying capacity, 102
oxygen therapy, 410, 823
partial pressure of oxygen, 822
venous oxygen saturation, 430*t*
Oxymetazoline, 294, 424, 818*t*
Oxymorphone in pain management, 564*t*, 568*t*
Oxytocin in labor induction, 299

P

Paclitaxel, 233*t*, 245*t*, 621, 622*t*, 628*t*, 629*t*, 643, 644*t*, 645*t*, 646
Pain management, 557
adjuvant analgesics, 575
in adults, FDA-approved nonopioid analgesics for, 560*t*–562*t*
algorithm for, 558*f*
cancer pain, special considerations in, 576
signs, 557–558
symptoms, 557
in noncancer pain, chronic, special considerations in, 575*t*, 576
regional analgesia, 576
treatment, 558–576
central analgesic, 575
meperidine/congeners, 574
methadone/congeners, 574
morphine/congeners, 563, 574
nonopioid agents, 559–563
opioid agents, 563–575
opioid agonist-antagonist derivatives, 574
opioid antagonists, 575
Paliperidone in schizophrenia, 732*t*, 736*t*, 737, 739*t*
Palonosetron in nausea and vomiting, 240, 241*t*
Pamidronate, 804*t*
P-Amino-Salicylic acid (PAS) antituberculosis drugs for, 484*t*
Pancreatic enzyme supplements in pancreatitis, 206, 244, 248, 250, 250*t*
Pancreatitis
acute
medications, 245*t*
nonpharmacologic treatment, 246, 246*f*
pharmacologic treatment, 246–247
chronic
nonpharmacologic treatment of, 248
pharmacologic treatment of, 248–249
Panic attack, 674*t*
Panic disorder
drugs used in, 687*t*
pharmacotherapy, algorithm for, 688*f*
Panitumumab, 233*t*
in colorectal cancer, 635, 637*t*, 640, 640*t*
Pannus formation in rheumatoid arthritis, 26
Pantoprazole, 208*f*, 209*t*, 210, 211
Papaverine in erectile dysfunction, 864
Papillomavirus infections, 446*t*
Papules, 137, 141, 143
Paracentesis, 188, 191, 192*t*, 785*t*
Paraneoplastic syndromes in lung cancer, 642
Paregoric in diarrhea, 204*t*
Parenteral nutrition (PN), 224, 246, 359, 398, 614–617
components of, 616–617
monitoring strategy for, 617*f*
peripheral, 616–617
Paricalcitol in chronic kidney disease, 794, 796*t*

Parkinson's disease (PD), 578–586
drug-induced hallucinosis and psychosis management of, 585*t*
drugs for, 580*t*
management, general approach, 579*f*
motor complications, initial treatments, 584*t*
treatment
amantadine, 583
anticholinergic medications, 579, 583
catechol-*O*-methyltransferase inhibitors, 584–585
dopamine agonists, 585–586
levodopa and carbidopa/levodopa, 583–584
monoamine oxidase B inhibitors, 584
pharmacologic therapy, 579–586
potential adverse reactions, 581*t*–582*t*
Paroxetine, 726*t*
antidepressants, 516*t*, 692*t*, 715*t*, 719*t*, 723*t*, 729*t*
for anxiety disorders, 677*t*
bradyarrhythmias, 58
for generalized anxiety disorder, 677, 678*t*
hot flushes, treatment of, 286*t*
in panic disorder, 687*t*
in posttraumatic stress disorder, 691
treatment of generalized social anxiety disorder, 690*t*
Paroxysmal supraventricular tachycardia (PSTV), 56–57
algorithm for treatment, 56*f*
Pasireotide, 158
Pasteurella multocida infections, 317*t,* 449*t,* 462
Pedialyte oral rehydration solution, 204*t,* 363*t*
Pegylated interferon (PEG-IFN), 220*t*
Pelvic inflammatory disease, 262, 274, 275, 433, 436*t,* 441*t,* 445*t*
Pemetrexed
as chemotherapeutic agents, 233*t*
in lung cancer, 643, 644*t,* 646
Penbutolol in hypertension, 90*t,* 95
Penicillamine in rheumatoid arthritis, 28, 30*t,* 32*t,* 32*t*
Penicillin
antimicrobial agents, 330*t*
in bacterial pneumonia, 416*t*
for cellulitis, 461*t*
dosing of, 455*t*, 457*t*
in enterococcal endocarditis, 342
gynecologic and obstetric disorders, 299
for pharyngitis, 420
in sickle cell disease, prevention of, 309
in syphilis, 438, 439*t*–440*t*
to treat sexually transmitted diseases, 296*t*
Pentaerythritol in angina pectoris, 105*t*, 109
Pentamidine, 161, 245*t,* 319*t,* 380, 381*t,* 608*t,* 773*t*
vitamin interactions, 608*t*
Pentazocine in pain management, 563, 565*t*, 570*t,* 574
Pentobarbital, 590*t,* 591*t*, 592*t*, 594, 595*t*
Peptic ulcer disease (PUD), 251–255
drug regimens to eradicate *Helicobacter pylori,* 254*t*
nausea and vomiting, 232*t*
nonpharmacologic treatment, 252
oral drug regimens used to, 255*t*
perforated, peritonitis in, 400*t*
Peptide-based enteral nutrition formulations, 248, 612*t*
Pepto-Bismol (bismuth subsalicylate), antidiarrheal preparations, 205*t*
Peramivir, in influenza, 393
Pericarditis, 27, 37, 75, 326, 348*t,* 387
Perimenopause, 276
Perindopril, 78*t,* 89*t*
Peripheral arterial disease, 65, 99
Peripheral vascular disease, 174
Peritoneal dialysis, 394, 395*t,* 397*t,* 404
peritonitis in, 399*t,* 404
Peritonitis, bacterial, 394–396, 397*t*
causes of, 395*t*
microbiology in, 394–395, 396*t*
primary, 394–396, 395*t,* 397*t,* 399*t*
treatment of, 396, 399*t*
secondary, 394–396, 395*t,* 396*t,* 397*t,* 400*t*
treatment of, 396, 400*t*

Perphenazine in schizophrenia, 739*t*
Pertussis vaccination, 504*t,* 505*t,* 507–508
Pertuzumab in breast cancer, 627
P-glycoprotein, 5
Pharyngitis, 420–422
  antibiotics and dosing for, 422*t*
  dosing guidelines for, 422*t*
  oropharynx/nasopharynx, 420
  treatment, 420–422
Phencyclidine, 761*t*
Phendimetrazine in obesity, 603*t*
Phenelzine, 554, 677*t*, 681*t*, 687*t*, 689*f,* 690*t,* 691, 692*t*, 717*t*, 718
Phenindamine tartrate in allergic rhinitis, 816*t*
Phenobarbital, 540–541
  antiepileptic drug side effects, 533*t*
  dosing and target serum concentration ranges, 528*t*
  elimination pathways and major effects on hepatic enzymes, 537*t*
  pharmacokinetic data, 526*t*
  during pregnancy, 294
  in seizures, 521*t,* 530
  vitamin interactions with, 608*t*
Phenothiazines, 195*t,* 234, 238*t,* 666*t*, 742, 851*t*
Phentermine in obesity, 601, 602*t*–603*t*
Phentolamine for erectile dysfunction, 863, 864
Phenylephrine, 116, 117*t,* 118, 311, 424, 432*t,* 676*t,* 817*t,* 818, 818*t*
  in allergic rhinitis, 818*t*
Phenytoin, 319*t*, 541
  adverse effects, 591*t*
  in anemia, 301
  antiepileptic drug side effects, 534*t*
  in anxiety disorders, 676*t*
  in dermatologic disorders, 141
  dosing and target serum concentration ranges, 528*t*
  elimination pathways and major effects on hepatic enzymes, 537*t*
  enteral nutrition, 615*t*
  in hypertension, 292
  in neurologic disorders, 525
  pharmacokinetic data, 526*t*
  during pregnancy, 297
  in prostate hyperplasia, benign, 846
  seizure disorders, 521*t*
  in seizures, 590*t*
  in status epilepticus, 589*f*, 593
  vitamin interactions with, 608*t*
Pheochromocytoma, hypertension in, 87, 88
Phosphate-binding agents in chronic kidney disease, 794
Phosphodiesterase inhibitors in erectile dysfunction, 860–863
Phosphoribosyl pyrophosphate (PRPP) synthetase, 1
Phosphorus, 16, 777, 785, 794*t*
  hyperphosphatemia, 805–806
  hypophosphatemia, 806
Phytonadione, 131
  in reversal of warfarin therapy, 131
  in venous thromboembolism (VTE), 131
Phytotherapy in benign prostatic hyperplasia, 849
Pilocarpine in glaucoma, 667, 670*t*
Pimecrolimus in atopic dermatitis, 145
Pimozide in seizures, 741
Pindolol in hypertension, 95
Pioglitazone in diabetes mellitus, 167*t,* 169
Piperacillin, 326*t,* 328*t,* 399*t*
Piperacillin-tazobactam, 316*t,* 317*t,* 398*t,* 399*t,* 400*t,* 464, 494*t*
  for diabetic foot infections, 463*t*
  dosing of, 458*t*
  for human bites, 465
  in pneumonia, 413*t,* 417*t*
Pirbuterol, 827*t,* 828*t*
  in asthma, 827*t*
  in chronic obstructive pulmonary disease, 837
Piroxicam, 4*t,* 33*t*
  acute gouty arthritis, 4*t*
Pitavastatin in hyperlipidemia, 70*t*, 71
Pituitary gland disorders, 155
Platelet P2Y12 Inhibitors, 41–42, 44
Pleural effusions and fibrosis, drug-induced, 27
Pneumococcal infections, 324
Pneumococcal vaccines, 506*t*, 508
Pneumocystis jiroveci pneumonia in HIV infection, 369*t*

Pneumonia, 410–417
anaerobic, 412
antibiotics in, 415, 416*t,* 417*t*
doses for, 416*t*–417*t*
aspiration, 415*t*
bacterial, antibiotic doses for, 416*t*–417*t*
community-acquired, 411*t,* 415*t*–416*t*
empirical antimicrobial therapy for, 416*t*
pediatric patients, 416*t*
evidence-based empiric antimicrobial therapy for, 415*t*–416*t*
gram-positive and -negative bacterial, 411–412
hospital-acquired pneumonia (HAP), 413
Mycoplasma pneumoniae, 412
nosocomial, 413
treatment, 414–415
viral, 410, 412–413
in children, 416*t*
Podofilox in genital papillomavirus warts, 447*t*
Podophyllin in genital papillomavirus warts, 447*t*
Poikilothermia from antipsychotic drugs, 594, 741, 747
Poliovirus vaccination, 508–509
Polycarbophil, 197*t,* 204*t*
antidiarrheal preparations, 204*t*
Polyethylene glycol-electrolyte lavage solution in constipation, 196, 198
Polymerase chain reaction technique
in HIV infection, 368
in meningitis, 324, 387
Polyposis, familial adenomatous, 631
Polysomnography, 747
Portal hypertension, 185, 187, 188–189, 190*f*
Portosystemic shunts, transjugular intrahepatic, surgical site infections in, 192, 192*t*
Positive pressure ventilation, noninvasive, in chronic obstructive pulmonary disease, 86, 842
Postmyocardial infarction, 97
Postthrombotic syndrome, 126, 127, 133
Posttraumatic stress disorder, 675, 675*t*
antidepressants used, 692*t*
pharmacotherapy algorithm, 692*f*
Potassium, 38, 48, 80, 94, 204*t*, 776*f*
hyperkalemia, 808–810
hypokalemia, 806, 808
Potassium chloride in hypokalemia, 207*t*
Potassium citrate in metabolic acidosis, 744*t*
Potassium iodide in hyperthyroidism, 179, 181
Potassium phosphate in hypophosphatemia, 807*t*
Potassium-sparing diuretics in hypertension, 94
Pramipexole in Parkinson's disease, 580*t,* 582*t*, 583, 586
Pramlintide in diabetes mellitus, 163*t,* 164–165, 171*f*
Prasugrel, 45, 45*f*
in acute coronary syndromes, 41–42
myocardial infarction, secondary prevention after, 46
Pravastatin, 69*t,* 70*t,* 71, 245*t*
in hyperlipidemia, 71
Prazosin, 93*t,* 95, 692*f,* 693, 847*t*
in hypertension, 95
in prostate hyperplasia, benign, 847*t*
in urologic disorders, 847
Prednisolone, 159*t*, 292, 829*t,* 829*t*
Prednisone
and anxiety, 676*t*
in asthma, 832*t*
chemotherapy for non-Hodgkin's lymphoma (CHOP), 652*t*
drug-induced skin reactions, 144
for follicular lymphoma, 651
in gout, 4
in Hodgkin's lymphoma, 649*t,* 650*t*
in inflammatory bowel disease, 226, 226*f*
in rheumatoid arthritis, 35
Preeclampsia, 98, 292–293
Pregabalin, 174, 249, 522*t,* 526*t,* 529*t*, 534*t,* 541, 677, 677*t*, 678*t*, 682*t*, 689*f*, 691
antiepileptic drug side effects, 534*t*
elimination pathways and major effects on hepatic enzymes, 537*t*

Pregnancy, 291–300
acute care issues in, 292–293
headache, 293
sexually transmitted diseases, 294
urinary tract infection, 293–294
cervical ripening and labor induction, 299
chronic illnesses in, 294–296
allergic rhinitis, 294
asthma, 294
depression during, 298
diabetes during, 294
drug selection during, 291
drug use during lactation, 300
epilepsy during, 294, 297
group B *Streptococcus* infection, 299
human immunodeficiency virus infections during, 297
hypertension during, 297–298
labor analgesia, 299–300
in nausea and vomiting, 232*t*
physiologic and pharmacokinetic factors, 291
preconception planning, 292
preterm labor
antenatal glucocorticoids, 299
tocolytic therapy, 298–299
relactation, 300
therapeutic considerations associated with, 291–300
thyroid abnormalities, 293
Pregnancy-influenced issues, 292–293
gastrointestinal tract, 292
gestational diabetes mellitus, 292
hypertension during pregnancy, 292–293
venous thromboembolism in pregnancy, 293
Premature ventricular complexes, 57
Pressure sores, 449*t,* 462, 612*t*
classification, 464*t*
Preterm labor, 293
Priapism in sickle cell disease, 309*t*
Prilocaine
local anesthetics, 576*t*
in regional analgesia, 576*t*
Primidone
antiepileptic drug side effects, 535*t*
dosing and target serum concentration ranges, 528*t*
in seizures, 526*t,* 530, 535*t,* 608*t*
vitamin interactions, 608*t*
Prinzmetal's variant angina, 102, 103
Proarrhythmias, 57
ventricular, 49
Probenecid, 7, 319*t,* 439*t*
Probiotics, 361
Procainamide, 57, 51*t*
for patients with paroxysmal supraventricular tachycardia, 57
side effects of, 54*t*
Procaine as local anesthetics, 576*t*
Procaine penicillin G, 458*t*
Procarbazine, 650*t*, 233*t*
in Hodgkin's lymphoma, 649*t*
Progestins, 104, 261*t*, 262, 263*t*–266*t,* 267, 269*t*, 272, 274, 289, 627
Progestogen, 24, 278, 284, 284*t,* 289
Prolactin serum levels in seizures, 519, 741
Promethazine, 239*t,* 242*t,* 816*t*
Promotility agents in gastroesophageal reflux disease, 211
Propafenone in antiarrhythmic drugs, 51*t,* 52*t*, 54*t*
Prophylactic migraine therapies, 551*t*
Prophylaxis, surgical recommendations for, 468, 469*t*–472*t*
Propionibacterium acnes, 135
Propofol, 245*t,* 592*t*, 596*t,* 597, 612*t*
Propoxyphene, 245*t*
Propranolol, 43, 51, 90*t,* 104, 179, 180, 188, 189, 211, 551*t,* 554, 691, 691, 707, 740
in acute coronary syndromes, 43
in ischemic heart disease, 104
in thyroid disorders, 180
Propylthiouracil (PTU), 179
in hyperthyroidism, 181*t*
Prostaglandin analogues in glaucoma, 665
Prostate cancer, 654–664
chemoprevention, 654
management of, 656*t*–657*t*
pharmacologic therapy
alternative drug treatments, 659
antiandrogens, 659
chemotherapy, 659
combined androgen blockade (CAB), 659

Prostate cancer (*Cont.*)
gonadotropin-releasing hormone (GnRH), 658–659
immunotherapy, 664
luteinizing hormone-releasing hormone agonists, 658
screening for, 654
treatment for
general approach to, 655, 658
nonpharmacologic therapy, 658
pharmacologic therapy, 658–664
Prostate gland, hormonal regulation of, 655*f*
Prostate-specific antigen (PSA), 654, 846
Prostatectomy, 656*t*–657*t*
Prostatitis, 436*t,* 445*t,* 490, 497*t,* 654
empirical treatment of, 497*t*
Prosthesis, 466
Protamine sulfate
in bleeding complications of heparin therapy, 129, 130
in venous thromboembolism, 130
Protease inhibitors
in HIV infection, 372, 377*t*
and vitamin interactions, 608*t*
Proteus mirabilis infections, 317*t,* 396*t*
Prothrombin time in shock, 132*f,* 187, 193*t,* 320*t*
Proton pump inhibitors
in gastroesophageal reflux disease, 207
vitamin interactions with, 608*t*
Protozoal infections, 203*f,* 434*t*
Protriptyline, 551*t,* 752*f*
Providencia stuartii infections, 317*t*
Pseudoephedrine, 676*t,* 695*t,* 807*t,* 817–818, 817*t*
in renal disorders, 807*t*
Pseudomonas aeruginosa infections, 317*t,* 321, 328*t,* 332, 399*t,* 427, 449*t,* 466
bronchitis in, 407*t*
peritonitis in, 394, 399*t*
pneumonia in, 413*t*
Pseudoparkinsonism from antipsychotic drugs, 740
Psoriasis, 147–153
alternative drug treatments, 153
combination therapies, 152–153
nonpharmacologic therapy, 147–148
pharmacologic therapy, 148–153, 148*f,* 149*t*
photochemotherapy, 150–151
phototherapy, 150–151
systemic therapies, 151
with biologic response modifiers, 151–152
topical therapy, 148–150
treatment algorithm, 148*f*
Psyllium in constipation, 197*t*
Pulmonary artery catheterization in shock, 114*f,* 119
Pulmonary embolism (PE), 62, 125
Purines, dietary, 1
Pyelonephritis
in nausea and vomiting, 232*t*
in urinary tract infection, 293, 490, 492, 497*t*
Pyrazinamide, 1, 480*t*
antimicrobial agents, 331*t*
antituberculosis drugs for, 483*t*
in tuberculosis, 479*t*
Pyridoxine
in nausea and vomiting, 243, 292
in status epilepticus, 589*f*
in tuberculosis, 478
Pyrilamine in insomnia, 748
Pyrilamine maleate in allergic rhinitis, 816*t*
Pyrimethamine in toxoplasmic encephalitis and HIV infection, 382*t*
Pyuria, 491*t*

Q

Q waves in acute coronary syndromes, 38
QRS complex in paroxysmal supraventricular tachycardia, 48, 56–57
Quazepam in psychiatric disorders, 749*t,* 750
Quetiapine
adverse effects, 682*t*
alcohol withdrawal, 764*t*
in algorithm for pharmacotherapy of posttraumatic stress, 692*f*
antipsychotics, dosage range, 732*t*
for anxiety disorders, 677, 677*t*, 693
for bipolar disorder, 698*t,* 704*t*
for generalized anxiety disorder, 678*t*

for noncognitive symptoms of dementia, 516*t*
in Parkinson's disease, 585*t*
in schizophrenia, 739*t*
in substance-related disorders, 764*t*
treatment of generalized social anxiety disorder, 690*t*
Quinapril
as antihypertensive agents, 89*t*
in heart failure, 78*t*
Quinidine, 50, 52*t*
in antiarrhythmic drugs, 51*t*
causing diarrhea, 201*t*
for patients with paroxysmal supraventricular tachycardia,(PSVT), 57
side effects of, 54*t*
Quinolone antibiotics
in anxiety disorders, 676*t*
drug interactions, 319*t*
for intraabdominal infections, 399*t*
to prevent and treat osteoporosis, 20*t*
for sickle cell disease, 311
in urinary tract infection, 294, 497*t*
Quinupristin-dalfopristin, 315*t*
drug monitoring, 344*t*
in peritonitis, 399*t*

R

Rabeprazole, 208*f,* 209*t,* 210
Rabies, 465
Radiation therapy, 232*t,* 632, 643, 651, 656*t*–657*t,* 658
Radiofrequency ablation procedures in supraventricular tachycardia, 56*f*
Radiography, 206, 252, 642, 647
Radioimmunotherapy in lymphoma, 651, 652
Raloxifene, 18*f,* 22*t,* 23, 288, 289, 630
in breast cancer, 288
in osteoporosis, 23
Ramelteon, 748
Ramipril in myocardial infarction, secondary prevention after, 46
Ranitidine, 208*f,* 208*t,* 209*t,* 234, 237*t,* 255*t,* 292
Ranolazine in ischemic heart disease, 106
Rasagiline in Parkinson's disease, 579*f,* 580*t,* 582*t*, 584
Receptor activator of nuclear factor kappa B (RANK), 23
Receptor blockers α_1, in hypertension, 95
Rectal cancer, adjuvant therapy, 633
Rectal examination, digital, 845, 849
Recurrent stroke, 98
Red blood cells, 37, 113, 202*f,* 203*f,* 301, 308, 398, 783*t*
5α-Reductase inhibitors, 848
Reed–Sternberg cells in Hodgkin's lymphoma, 647
Reentry supraventricular tachycardia, paroxysmal, 48
Regorafenib in colorectal cancer, 640, 640*t*
Rehydralyte oral rehydration solution, 204*t*
Relactation, 300
Renal disease
glomerular filtration rate categories, 788*t*
proposed mechanisms for progression of, 789*f*
therapeutic strategies to prevent progression in diabetic individuals, 790*f*
Renal disorders, 771–812
acute hypercalcemia
drug dosing, 804*t*
pharmacotherapeutic options for, 803*f*
drug-induced hypokalemia, mechanism of, 807*t*
hyperkalemia
management of, therapeutic alternatives for, 809*t*
treatment approach, 810*f*
hypocalcemia, diagnostic, treatment algorithm, 805*f*
hyponatremia, evaluation of diagnostic algorithm for, 800*f*
intravenous solutions, composition of, 799*t*
nephrogenic diabetes insipidus drugs, 801*t*
phosphorus replacement therapy, 807*t*
Renal function, dosing recommendations, 487*t*

Renal insufficiency, 80
Renal replacement therapy, 784*t,* 786*t,* 787
Renin inhibitors in hypertension, 90, 98, 298
Repaglinide in diabetes mellitus, 165, 166*t*
Reserpine in hypertension, 96
Resistance to drugs, 479, 486
Resorcinol in acne vulgaris, 137
Respiratory disorders, 813–843. *See also* Respiratory tract infections
  bronchiolitis, 408–410
  in infections, 405–417
    bronchitis, 405–410
    otitis media, 418–420
    pneumonia, 410–417
Respiratory failure in chronic obstructive pulmonary disease, 836
Respiratory tract infections, 405
  bronchitis
    acute, 405–406
      treatment, 405–406
    chronic, 407–408
      bacterial isolates, 407*t*
      diagnosis/treatment, clinical algorithm, 408*f*
      oral antibiotics, 407*t*
Resting energy expenditure, 599
Retapamulin ointment, 455*t*
Reteplase in acute coronary syndromes, 41
Retinoids, topical, 136*f,* 137–138
Retinopathy, diabetic, 161, 173–174
Reverse transcriptase inhibitors in HIV infection, 372, 376*t*–377*t*
Reye's syndrome in children, aspirin effect of, 406
Rheumatoid arthritis (RA), 26–36
  clinical monitoring of drug therapy, 31*t*–32*t*
  doses and monitoring parameters, 29*t*–30*t*
  nonpharmacologic therapy, 27
  pharmacologic therapy, 27–36, 28*f*
  treatment, 27, 28*f*
Rheumatoid factors, 26
Rhinitis, 180, 294, 813, 814, 816, 817
Rhinosinusitis, 422–426
Rho(D) IG (RDIg), 510
Ribavirin, 219–220, 219*t,* 410
  in bronchiolitis, 410
Rifabutin, 382*t,* 478, 482*t*
Rifampin, 20*t,* 158, 183, 245*t,* 273, 320*t,* 344*t*, 379, 478, 480*t,* 481*t,* 486, 686
  antimicrobial agents, 331*t*
Rifapentine in tuberculosis, 480*t,* 482*t*
Rifaximin
  in cirrhosis, 193*t*
  in gastrointestinal infections, 193, 363*t,* 364*t*
Rimantadine in influenza, 388, 391*t*
Ringer's solution, lactated, in hypovolemic shock, 113, 114*f*
Risedronate in osteoporosis, 19, 21*t*
Risperidone, 516*t,* 692*f,* 693, 704*t*, 710
  in schizophrenia, 737, 739*t*
Ritodrine in renal disorders, 807*t*
Ritonavir in HIV infection, 375*t*, 378*t,* 379
Rituximab, 28*f,* 29*t,* 31*t,* 35, 653
  chemotherapeutic agents, 233*t*
  for follicular lymphoma, 651
  in rheumatoid arthritis, 27, 35
Rivaroxaban
  in atrial flutter, 54
  in venous thromboembolism (VTE), 130
Rivastigmine in Alzheimer's disease, 513, 514*t*
Rizatriptan in migraine headache, 548*t,* 550*t*
Ropinirole in Parkinson's disease, 580*t,* 582*t*, 583, 586
Ropivacaine
  local anesthetics, 576*t*
  in regional analgesia, 576*t*
Rosiglitazone in diabetes mellitus, 167*t,* 168*t,* 169
Rosuvastatin in hyperlipidemia, 69*t,* 70*t,* 71, 73, 797
Rotavirus vaccines, 505*t*
Rotigotine in Parkinson's disease, 582*t*, 586
RU-486 in Cushing's syndrome, 158
Rubella vaccine, 509
Rufinamide, 541
  antiepileptic drug side effects, 535*t*
  dosing and target serum concentration ranges, 529*t*

elimination pathways and major effects on hepatic enzymes, 537*t*
pharmacokinetic data, 526*t*

S
Salicylates, 1
Salicylic acid
in acne vulgaris, 137
in psoriasis, 150
Saline cathartics in constipation, 196, 198
Salmeterol, 807*t,* 827*t*
in asthma, 823, 827*t*
in chronic obstructive pulmonary disease, 837
in renal disorders, 807*t*
Salmonella infections, 317*t,* 363*t,* 365*t,* 366, 370*t*
Salpingitis, 395*t,* 434*t,* 435*t*
Salsalate in osteoarthritis, 252
Saquinavir in HIV infection, 319*t,* 375*t,* 378*t*
Saxagliptin in diabetes mellitus, 167*t,* 170
Scalp psoriasis, 150
Schizophrenia
adverse effects, 738–743
drug interactions, 744
treatment
algorithm for, 734*f*
asenapine, 739*t*
general approach, 732–733
initial therapy, 733, 734, 737
maintenance therapy, 737
pharmacokinetics, 733
stabilization therapy, 737
treatment-resistant, management of, 737–738
use, in pregnancy and lactation, 743
Sclerotherapy in variceal hemorrhage, 189
Scopolamine, 58, 236*t,* 242*t,* 243
patches, bradyarrhythmias, 58
Sebum production in acne vulgaris, 135
Secondary prevention after myocardial infarction, 46–47
pharmacotherapy in, 46–47
Sedation, cognition and, 741
Seizures, 217*t,* 292, 412, 518, 519, 520, 525, 593, 594, 758, 840. *See also* Epilepsy
epileptic, 519*t*
Selective serotonin reuptake inhibitors (SSRIs), 58, 249, 284, 298, 517, 666*t,* 679*t*, 690*t,* 691, 692*f,* 715*t*, 719*t*, 722*t*, 725, 738, 851*t*
Selegiline, 580*t,* 584, 717*t*, 718
in Parkinson's disease, 582*t*
Senna in constipation, 196
Sepsis, 428, 428*t*
antimicrobial therapy, 429–431
cardiovascular agents receptor activity in, 432*t*
empiric antimicrobial regimens, 431*t*
etiology, 427
evidence-based treatment recommendations, 430*t*
hemodynamic support, 431
inotrope/vasoactive drug support, 431–432
protocol for, 432
signs and symptoms, 429*t*
treatment of, 429–432
adjunctive therapy, 432
early goal-directed, 432
Septic shock. *See* Sepsis
Serotonin, 158, 557
Serotonin-norepinephrine reuptake inhibitors, 550, 680*t*, 690*t,* 715*t*, 718, 719*t*, 723*t*, 725
Serotonin receptor agonists in migraine headache, 552*t*
Serotonin syndrome, 550, 584
Serratia marcescens infections, 317*t*
Sertraline, 58, 245*t,* 678*t,* 678*t*, 687*t*, 690*t,* 691, 715*t*, 719*t*, 726*t*, 867
antidepressants, 516*t*, 692*t*, 729*t*
bradyarrhythmias, 58
Serum ferric gluconate in anemia, 306*t*
Serum sickness-like reactions, 143
Sevelamer carbonate in chronic kidney disease, 795*t*
Sevelamer hydrochloride in chronic kidney disease, 795*t*

Sexually transmitted diseases (STDs), 434*t,* 446, 446*t*–447*t*
chlamydial, 339–441
gonorrhea, 433–434, 434*t*
herpes simplex virus, 434*t,* 435*t,* 441–442
HIV infection, 329, 368–386, 369*t*–370*t*
pathogens associated with, 434*t*
spectrum of, 433
syphilis, 434–438
treatment regimens for, 446*t*–447*t*
trichomoniasis, 442
Sexually transmitted pathogens syndromes, 435*t*
Shigella infections, 363*t,* 365*t,* 366
Shock, 111–119
fluid resuscitation for hypovolemic shock, 113
blood products, 113
colloids, 113
crystalloids, 113
general approaches for treatments, 113
hypovolemia protocol for adults, 114*f*
hypovolemic, pharmacologic therapy for, 113
monitoring of, 111–112
pathophysiology of, 111
pharmacologic therapy, 113–119
septic
algorithmic approach to management, 116*f*
pharmacologic therapy for, 116–117
tissue perfusion, management of, 115*f*
Shunt procedures, 472*t*
Sibutramine, 87
Sick sinus syndrome, 49
Sickle cell disease, 308–312
fetal hemoglobin inducers, 309, 311
general principles of treatment, 309
hydroxyurea use in, 310*f*
treatment of
complications, 311
sickle cell crisis, 311–312
Sickle cell trait, 308, 309*t*
Sildenafil, 44, 174, 853*t,* 860
endocrinologic disorders, 174
erectile dysfunction, 861*t*
treatments for, 853*t*
urologic disorders, 861
Silodosin in prostate hyperplasia, benign, 847*t,* 848
Silver sulfadiazine in pressure ulcers, 462
Simvastatin in hyperlipidemia, 69*t,* 70*t,* 71, 73, 797
Sinus bradyarrhythmias, 58
Sinusitis, 422, 425*t*–426*t*
acute bacterial
antibiotic recommendations, 425*t*–426*t*
dosing guidelines for, 425*t*–426*t*
treatment of, 425*t*–426*t*
Sipuleucel-T, in prostate cancer, 664
Sitagliptin in diabetes mellitus, 167*t,* 170
Skin and soft-tissue infections (SSTIs), 448–465
cellulitis, 459
treatment of, 459
development of, 448
diabetic foot infections, 459, 462, 463*t*
erysipelas, 448
evidence-based recommendations for treatment of, 450*t*–452*t*
impetigo, 448–449, 449*t*, 453*t*
treatment of, 449
infected bite wounds
cat, 465
dog, 462, 464–465
human, 465
infected pressure ulcers, 462
prevention and treatment, 462
treatment of, evidence-based recommendations for, 450*t*–452*t*
Skin reactions, drug-induced, 141
Sleep apnea
central (CSA), 751
obstructive (OSA), 751
Sleep disorders
insomnia
nonpharmacologic therapy, 748*t*
treatment, 747–750
narcolepsy, 751, 754
treatment of, 751, 754
sleep physiology, 747
Smoking
cessation, pharmacologic agents used for, 768*t*
in chronic bronchitis, 406

chronic obstructive pulmonary disease in, 835, 837, 841
lung cancer, 642
oral contraceptive use in, 262
osteoporosis in, 16, 17
peptic ulcer disease in, 251, 252
in pregnancy, 292
Social anxiety disorder, 674
treatment of
algorithm on, 688*f*
drug choices in, 677*t*
Sodium channel blockers, 50, 50
Sodium citrate in metabolic acidosis, 744*t*
Sodium hyaluronate in osteoarthritis, 15
Sodium iodide, 180
Sodium nitroprusside in acute decompensated heart failure, 84
Sodium oxybate, 752*f,* 754
Sodium phosphates, 197*t*
Sodium polystyrene sulfonate in hyperkalemia, 807*t,* 808
Soft-tissue infections. *See also* Skin and soft-tissue infections
bacterial classification of, 449*t*
evidence-based recommendations, 450*t*–452*t*
recommended oral drugs, 453*t*
Solifenacin
in prostate hyperplasia, benign, 847*t*
in urinary incontinence, 868*t,* 870, 870*t*
Somatostatin in variceal hemorrhage, 247
Sorafenib as chemotherapeutic agents, 233*t*
Sorbitol in constipation, 196–197, 198
Sotalol, 57
in antiarrhythmic drugs, 51*t*
in arrhythmias, 50, 51*t,* 52*t*
side effects of, 54*t*
Specific seizure disorders drugs of choice for, 521*t*–524*t*
Spermicide-implanted barrier techniques, 261
Spermicides, 259*t*, 260*t*, 261
Spinal surgery, surgical site infections in, 472*t*
Spirometry in asthma, 822
Spironolactone
in acne vulgaris, 139
in cirrhosis, 193*t*
in heart failure, 80
in hypertension, 94
in myocardial infarction, secondary prevention after, 46
Spleen, abscess of, 400*t*
Sponge, contraceptive, 260*t*, 261
Spontaneous bacterial peritonitis, 191–192
St. Anthony's fire, 448
St. John's wort, 379
ST segment elevation
in acute coronary syndromes, 38, 40*f*
in ischemic heart disease, 102, 103
Staphylococcal endocarditis, 335, 342
Staphylococcal infections, 335, 342
peritonitis in, 394, 396*t,* 399*t*
Statin therapy
in acute coronary syndromes, 43
in dyslipidemia, 74
in myocardial infarction, secondary prevention after, 46–47
in stroke, 122
Status epilepticus (SE), 587–597
signs, 587
symptoms, 587
international classification of, 588*t*
morbidity and mortality, 587
therapeutic, outcomes, 597
treatment, 588–597, 591*t*–592*t*
benzodiazepine, 593, 594
fosphenytoin, 593–594
phenobarbital, 594, 594
phenytoin, 593
propofol, 597
topiramate, 597
valproate, 594, 597
valproic acid, 594, 597
Stavudine in HIV infection, 374*t,* 376*t*
Steatorrhea in pancreatitis, 248, 249, 249*f*
Stem cell transplantation, 311, 648
Stenotrophomonas maltophilia infections, 317*t*
Stevens–Johnson's syndrome (SJS), 141, 143, 169–170, 380, 709
Streptococcal endocarditis, 335

Streptococcal infections
bronchitis in, chronic, 407*t*
otitis media in, 418
peritonitis in, 394, 396*t,* 399*t*
pneumonia in, 410, 416*t,* 417*t*
Streptococcal pharyngitis group A, 421*t*
Streptococcus, group A
evidence-based principles for diagnosis, 422*t*
S. pneumoniae, 329, 418
Streptokinase
in acute coronary syndromes, 41
in venous thromboembolism, 133
Streptomycin, antituberculosis drugs for, 484*t*
Streptozotocin as chemotherapeutic agents, 233*t*
Stress urinary incontinence, 866*t,* 871
Stroke, 120
hemorrhagic stroke, 120, 124*t*
ischemic stroke, 120, 124*t*
nonpharmacologic therapy, 121
pharmacologic therapy
of hemorrhagic stroke, 122
of ischemic stroke, 121–122, 122*t*–123*t,* 124*t*
recurrent, 98
for treatment, general approach, 121
Sublingual nitroglycerine (SL NTG), 105
in acute coronary syndromes, 44
for ongoing ischemia, 46
Substance intoxication, pharmacologic treatment of, 761*t*
Substance-related disorders, 755–769
central nervous system depressants, 755–757
alcohol, 755–756
benzodiazepines and other sedative-hypnotics, 756
carisoprodol, 757
γ-hydroxybutyrate, 757
opiates, 757
central nervous system stimulants, 757–758
cocaine, 757–758
methamphetamine, 758
drugs of abuse
inhalants, 759–760
lysergic acid diethylamide, 759
marijuana, 759
methamphetamine analogues, 758–759
nicotine, 758
treatment
intoxication, 760
substance use disorders, 765, 767
alcohol dependence, 765
bupropion sustained release (SR), 767
nicotine, 765, 767
nicotine-replacement therapy, 767
second-line medications, 767, 768
smoking cessation, 768*t*
withdrawal
alcohol, 760
benzodiazepine, 760, 761
opiates, 762, 765
Sucralfate, 182, 208*f,* 211, 292
Sulfamethoxazole in acne vulgaris, 139
Sulfasalazine, 28*f,* 29*t,* 33, 224, 225, 226*f,* 228, 229*t*, 608*t*
Crohn's disease, 227
inflammatory bowel disease, treatment of, 225*t*
in rheumatoid arthritis, 27, 33
vitamin interactions, 608*t*
Sulfonamides, 141, 143, 201*t,* 320*t,* 542
Sulfonylureas in diabetes mellitus, 165, 166*t*
Sulfur in acne vulgaris, 137
Sulindac, 2, 4*t,* 33*t,* 245*t*
acute gouty arthritis, 4*t*
Sumatriptan in migraine headache, 547*t,* 549, 550*t*
Sun-induced skin reactions, 143
Sunitinib, chemotherapeutic agent, 233*t*
Supraventricular arrhythmias
atrial fibrillation and atrial flutter, 48, 51–56
paroxysmal supraventricular tachycardia, 48
Surgical prophylaxis, 466–475
antibiotic issues
antimicrobial selection, 467–468
scheduling antibiotic administration, 466–467
bacteriology, 466
specific recommendations
appendectomy, 469*t,* 473
biliary tract surgery, 473

cardiac surgery, 471*t,* 474
cesarean section, 470*t,* 473–474
colorectal surgery, 469*t,* 473
gastroduodenal surgery, 468, 469*t,* 473
gynecological surgery, 470*t*
head and neck surgery, 470*t*–471*t,* 474
hysterectomy, 470*t,* 474
minimally invasive and laparoscopic surgery, 475
neurosurgery, 475
noncardiac vascular surgery, 471*t,* 474
orthopedic surgery, 471*t,* 475
urologic procedures, 470*t,* 473
surgical wound infection, risk factors for, 466
Surgical-site infection (SSI) risk of, 467*t*
Sympathetic inhibitors, postganglionic, in hypertension, 96
Syncope, vasovagal, 50, 58
Synovial fluid analysis, 2
Synovitis, 26
Synthetic cannabinoids, 759
Synthetic cathinones, 759
Synthetic marijuana, 759
Syphilis, 296*t*, 434*t*, 435
drug therapy and follow-up of, 439*t*–440*t*
latent, 436
and neurosyphilis, 436
presentation of, 438*t*
primary, 435
secondary stage of, 435
treatment of, 438
Systemic vascular resistance (SVR), 81
Systolic heart failure, 97

T

T cells
cluster of differentiation 2 (CD2), 152
in psoriasis, 147
in rheumatoid arthritis, 26
T-score in osteoporosis, 17, 18*f*
T-wave
acute coronary syndrome (ACS), 39*f*
in cardiovascular disorders, 38
electrocardiography (ECG), 38
Tachy-brady syndrome, 49
Tachycardia, 56–57
β-blockers, 51
hypertensive emergency, 100*t*
panic attack, 674*t*
paroxysmal supraventricular (PSVT), 48, 56–57
QRS, 48
reflex, 104
with sepsis, 429*t*
sinus, 48
social anxiety disorder, 675*t*
supraventricular arrhythmias, 48
sustained ventricular, 57
ventricular, 48, 57–58
treatment of, 60–62
Tacrolimus in atopic dermatitis, 145
Tadalafil
endocrinologic disorders, 174
erectile dysfunction, 861*t*
treatments for, 854*t,* 860, 861
in prostate hyperplasia, benign, 847*t,* 848
Tafluprost, 671*t*
Tamoxifen
in breast cancer, 288, 625*t,* 627, 630
oncologic disorders, 624
Tamsulosin in benign prostatic hyperplasia, 847*t,* 848
Tap water enema, 196–197, 199
Tapentadol in pain management, 566*t*, 572*t*, 575
Tardive dyskinesia (TD)
psychiatric disorders, 710
schizophrenia, 733, 740–741, 745*t*
Taxanes in breast cancer, 627
Tazarotene
in acne vulgaris, 138
dermatologic disorders, 138
in psoriasis, 150
Tazobactam and piperacillin
for diabetic foot infections, 463*t*
in pneumonia, 414*t,* 417*t*
Telbivudine, 216
Telmisartan as antihypertensive agents, 89*t*
Temazepam in psychiatric disorders, 749*t*
Tenecteplase in cardiovascular disorders, 41

Tenofovir
in hepatitis B, 216
in HIV infection, 372, 376*t*
Tension-type headache, 555–556
treatment of, 555–556
Terazosin
in hypertension, 95
in prostate hyperplasia, benign, 847*t*
in urologic disorders, 847
Terbutaline
in asthma, 827*t,* 828*t*
in chronic obstructive pulmonary disease, 837
hematologic disorders, 311
to prevent preterm labor, 299
in renal disorders, 807*t*
Teriparatide in osteoporosis, 22*t*, 24, 25
Testosterone
erectile dysfunction, treatments for, 856*t*–859*t*
hormone therapy, 284, 288*t,* 655*f*
in osteoporosis, 24
production of, 654
replacement therapy, 863
in osteoporosis, 24
Tetanus immunoglobulin, 502–503
Tetanus prophylaxis, 504*t,* 506*t*
Tetanus toxoid, 502–503, 505*t*
adsorbed, 502–503
Tetany in hypocalcemia, 803, 806
Tetracaine as local anesthetics, 576*t*
Tetracycline
in acne vulgaris, 139
in bacterial pneumonia, 416*t*
in bronchitis, chronic, 409*t*
enteral nutrition, 615*t*
gastroesophageal reflux disease (GERD) symptoms, 207*t*
ophthalmic disorders, 666*t*
in pancreatitis, acute, 245*t*
in pneumonia, 414*t,* 416*t*
Tetracycline
in chlamydial infections, 442*t*
in gonorrhea, 437*t*
in syphilis, 439*t*, 440*t*
Tetrahydrozoline hydrochloride in allergic rhinitis, 818*t*
Thalassemia, 309*t*
Theophylline
and anxiety disorders, 676*t*
arrhythmias, 58
in asthma, 824*f*–825*f*, 830
bradyarrhythmias, 58
bronchodilator, 840
gastroesophageal reflux disease, 207*t*
illnesses in pregnancy, 294
infectious diseases, 319*t*
in nausea and vomiting, 232*t*
in obstructive pulmonary disease, chronic, 838*t*–839*t*
ophthalmic disorders, 666*t*
in renal disorders, 807*t*
in respiratory disorders, 832*f*
Thiamine
and alcohol withdrawal, 763*t*
antacids, 608*t*
Thiazide diuretics, 94
cardiovascular disorders, 77–78
in hypertension, 88, 91*f,* 99
hypokalemia, 807*t*
osteoporosis, 20*t*
in renal disorders, 807*t*
in systolic heart failure, 77–78
Thiazolidinediones in diabetes mellitus, 167*t,* 169
Thionamides in thyroid disorders, 179
Thiopurine *S*-methyltransferase (TPMT), 227
Thioridazine, 743
in schizophrenia, 739*t*
Thiothixene in schizophrenia, 739*t*
Thioureas, 179
in thyroid disorders, 179
Thoracic surgery, surgical site infections in, 471*t*
Thrombectomy in venous thromboembolism, 127
Thrombin inhibitors, direct, in venous thromboembolism, 130–131
Thrombocytopenia
in gastrointestinal disorders, 245
heparin-induced (HIT), 129
with low-molecular-weight heparins (LMWHs), 129–130
in neurologic disorders, 536*t*
Thromboembolism
fondaparinux sodium (Arixtra), 130
and oral contraceptive use, 267, 272
risk of, 51
venous, 125
alteplase, 133
coagulation cascade, 126*f*

dalteparin, 130
definition of, 125
direct thrombin inhibitors for, 130–131
dosing for unfractionated heparin, 129*t*
enoxaparin, 130
fondaparinux sodium (Arixtra), 130
initiation of warfarin therapy, 132*f*
prevention of, 133
therapeutic outcomes in, evaluation of, 133
thrombolytic agents, 132–133
treatment of, 128*f*
Thrombolytic agents in venous thromboembolism (VTE), 132–133
Thrombolytic therapy, 103, 132–133
Thrombolytics in cardiac arrest, 62
Thrombotic thrombocytopenia purpura (TTP), 42
Thyroid disorders, 176–184
Thyroid hormone physiology, 176
Thyroid USP, 183
Thyroidectomy, 179
Thyrotoxicosis, 176–181
nonpharmacologic therapy in, 178–179
pharmacologic therapy in, 179–181
Tiagabine, 541
antiepileptic drug side effects, 535*t*
dosing and target serum concentration ranges, 529*t*
elimination pathways and major effects on hepatic enzymes, 537*t*
pharmacokinetic data, 526*t*
Tibolone, hot flushes, treatment of, 286*t*
Ticagrelor, 45*f*
in acute coronary syndromes, 41–42
Ticarcillin-clavulanate, in intraabdominal infections, 398*t*, 400*t*
Tigecycline, 458*t*
Timolol, 554
in glaucoma, 667, 669*t*, 671*t*
Tinzaparin, in venous thromboembolism (VTE), 130
Tiotropium bromide
in asthma, 832
in chronic bronchitis, 407
in chronic obstructive pulmonary disease, 840
Tipranavir, in HIV infection, 375*t*, 378*t*
Tirofiban in acute coronary syndromes, 42, 44–45
Tobramycin
antimicrobial agents, 330*t*
dosing of, 458*t*
for intraabdominal infections, 399*t*
in peritonitis, dialysis-associated, 404
in pneumonia, 417*t*
in urinary tract infections, 494*t*
Tocilizumab, in rheumatoid arthritis, 27, 30*t*, 35
Tofacitinib, 30*t*, 34
Tolazamide in diabetes mellitus, 166*t*
Tolbutamide in diabetes mellitus, 166*t*
Tolcapone in Parkinson's disease, 581*t*, 584–585
Tolterodine
in benign prostate hyperplasia, 847*t*
in urinary incontinence, 868*t*, 870*t*
Tolvaptan, in acute decompensated heart failure, 85
Tophi (urate deposits), 1
Topical erythromycin, in acne vulgaris, 138
Topical retinoids, in acne vulgaris, 137–138
Topiramate, 541, 592*t*, 597
and antiepileptic drug side effects, 535*t*–536*t*
dosing and target serum concentration ranges, 529*t*
elimination pathways and major effects on hepatic enzymes, 537*t*
ophthalmic disorders, 666*t*
pharmacokinetic data, 527*t*
seizure disorders, 521*t*
side effects of, 554
in tension-type headache, 556
treat refractory generalized convulsive status epilepticus, 596*t*
Topotecan as chemotherapeutic agents, 233*t*

Toremifene
in breast cancer, 625*t*, 627
oncologic disorders, 624
Torsades de pointes, 57–58
Torsemide, 81
use in heart failure, 78
Toxic epidermal necrolysis (TEN), 143
Toxoids
diphtheria, 465, 500–502
recommendations, 500
tetanus, 465, 502–503
Toxoplasmosis in HIV infection, 370*t*
Tramadol
in chronic pancreatitis, 248
in endocrinologic disorders, 174
in osteoarthritis, 13, 14–15
in pain management, 565*t*, 571*t*, 575
Trandolapril in myocardial infarction, secondary prevention after, 46
Transcutaneous catheter ablation, 57
Transdermal contraceptives, 261*t*, 274
Transferrin, lean body mass, visceral proteins, 606*t*
Transferrin saturation (TSat) in iron-deficiency anemia, 303
Transfusions
blood, 311, 368, 778
red blood cell, 311
Transplantation
cardiac orthotopic, 85
heart, 85
hematopoietic stem cell, 311, 648
liver, 191, 356*t*
Tranylcypromine, 717*t*, 718
Trastuzumab as chemotherapeutic agents, 233*t*, 621, 627
Trauma, abdominal, acute contamination in, 400*t*
Travoprost in glaucoma, 667, 671*t*
Trazodone, 718
in Alzheimer's disease, 516*t*
as antidepressant drug, 720*t*, 724*t*, 726*t*, 727*t*
in erectile dysfunction, 864
in sleep disorders, 748
in urologic disorders, 864
Treponema pallidum infections, 318*t*, 434*t*, 435*t*. *See also* Syphilis
Tretinoin
in acne vulgaris, 138
dermatologic disorders, 138
Triamcinolone, 159*t*
Triamcinolone acetonide
in allergic rhinitis, 818*t*
in gout, 4
in psoriasis, 149*t*
in rheumatoid arthritis, 36
Triamcinolone hexacetonide
in osteoarthritis, 11*t*
in rheumatoid arthritis, 36
Triazolam, 749*t*
Tricalcium phosphate in osteoporosis, 17
Trichomonas infections, 445*t*
Trichomoniasis, 296*t*, 442, 446
treatment of, 442, 445*t*, 446
by *Trichomonas vaginalis*, 442
Tricyclic antidepressants, 680*t*
Triglycerides, 65
Trimethoprim
in acne vulgaris, 139
bacterial resistance, 139
in urinary tract infection, 293
vitamin interactions, 608*t*
Trimethoprim-sulfamethoxazole, 386, 453*t*, 470*t*
antimicrobial agents, 330*t*
bacterial resistance, 139
in bronchitis, chronic, 409*t*
for dog bites, 464
dosing of, 455*t*
for human bites, 465
infectious diseases, 315*t*, 316*t*, 317*t*
respiratory tract infections, lower, 409*t*
in urinary tract infections, 493*t*, 496*t*, 497*t*, 498
Tripelennamine hydrochloride in allergic rhinitis, 816*t*
Triptans, pharmacokinetic characteristics of, 550*t*
Triptorelin
in breast cancer, 625*t*, 627
in prostate cancer, 658, 663*t*
Trolamine salicylate, in osteoarthritis, 14
Trospium chloride in urinary incontinence, 868*t*, 870, 870*t*

Trospium in benign prostate hyperplasia, 847*t*
Tuberculin skin test, criteria for, 477*t*
Tuberculosis (TB), 476–489
  culture positive, drug regimens for, 480*t*–481*t*
  drug monitoring recommendations, 488*t*–489*t*
  infection, recommended drug regimens for treatment, 479*t*
  pharmacologic treatment, 478–486
    drug resistance, 479, 486
    latent infection, 478
    patient monitoring, evaluation of, 486–487
    special populations, 486
    treating active disease, 478–479
  progressive primary, 476
  treatment of, 478–486
Tumor necrosis factor-α (TNF- α), 9, 26, 147, 427, 557, 835
  inhibitors, in rheumatoid arthritis, 34–35
  in rheumatoid arthritis, 26

U

Ulcerative colitis, 186*t,* 203*f,* 221–227
  clinical presentation of, 222–223, 223*t*
  drug therapy, 225–227
  maintenance of remission, 227
  treatment approaches for, 225–227, 226*f*
Ulcers, 14, 222*t*
  foot, 174
  formation of pressure, 462
  gastric, 251
  healing, 255
  NSAID-induced, 253
  pain, 254
  peptic ulcer disease, 251
  symptoms, 253*f*
  therapy, 462
Ultrasonography, 127, 245, 248, 631
Ultraviolet light therapies, 145
Undernutrition, 605, 606
Unfractionated heparin (UFH)
  in acute coronary syndromes, 42, 44
  in pregnancy, 293
  in stroke, 122
  in venous thromboembolism, 127–129
Urate crystals, 1
Urea breath test (UBT), 252
Ureaplasma urealyticum infections, 434*t,* 435*t*
Uremia. *See also* Renal disease
  nausea and vomiting, 232*t*
  renal replacement therapy, 784*t*
Urethra
  chlamydia infections, 441*t*
  common sexually transmitted pathogens, 435*t*
  gonorrhea infections, 436*t,* 437*t*
  lower tract infections, 490, 496*t*
Urethral syndrome, acute, 496*t*
Urethral underactivity, bladder overactivity, differentiating, 866*t*
Urethritis
  common sexually transmitted pathogens, 435*t*
  lower tract infections, 490
  nongonococcal, 434*t*
  postgonococcal, 434*t*
  Trichomonas infections, 445*t*
Uric acid, 1, 7
  allopurinol, 7
  liver function, 74
  nephrolithiasis, 1
  production of, 1
  renal clearance of, 1, 7
  serum level, 8
  stone formation, 7
  uricosurics, 7
  xanthine oxidase inhibitors, 7
Uricosuric drugs in gout, 7
Urinalysis, 786*t*
  kidney injury, acute, 783*t*
  uncomplicated cystitis, acute, 492
Urinary tract infections, lower, outpatient antimicrobial therapy, 496*t*
Urinary incontinence (UI), 865–872
  treatment of
    nonpharmacologic treatment, 867
    pharmacologic treatment, 867–871, 868*t*–869*t*
      bladder overactivity, 867, 868*t*–869*t*, 870*t*
      duloxetine, 871
      estrogens, 871
      overflow incontinence, 871

Urinary incontinence (UI) (*Cont.*)
oxybutynin immediate-release, 867
α-receptor agonists, 871
tolterodine, 867
urethral underactivity, 871
urge urinary incontinence, 870–871
Urinary tract function, lower, medications, 866*t*
Urinary tract infections (UTIs), 316*t*, 490–499
antimicrobial agents, uses, 493*t*–495*t*
catheterized patients, 499
empirical treatment of, 497*t*
in men, management of, 499*f*
in pregnancy, 497*t*, 498
treatment of
acute uncomplicated cystitis, 492
complication, 492
in men, 492, 496
pharmacologic treatment, 491–498
pyelonephritis, acute, 492
recurrent infections, 496–498
women, management of, 498*f*
Urine output
cardiovascular disorders, 112
in kidney injury, acute, 780*t*, 781*f*
weight loss, 361, 362*t*
Urokinase in venous thromboembolism, 133
Urologic disorders, 845–872
Urticaria, 141
Ustekinumab
dermatologic disorders, 152
in psoriasis, 152

V

Vaccinations
hepatitis A, 214*t*, 504*t*, 506*t*
hepatitis B virus, 216*t*, 217*t*, 504*t*, 505*t*
herpes zoster, 504*t*
with Hib, 329, 503–504, 504*t*, 506*t*
human papillomavirus, 504*t*, 506*t*
influenza virus, 388, 504*t*, 506*t*
trivalent influenza vaccine, 390
measles, mumps, rubella, 504*t*, 506*t*
meningococcal, 504*t*, 506*t*
meningococcal polysaccharide, 507
mumps, 507
pertussis, 507–508
pneumococcal, 506*t*, 508
pneumococcal polysaccharide, 504*t*
poliovirus, 508–509
of pregnant women, 500
recommendations, 500
dosing of, 215*t*
tetanus prophylaxis, 506*t*
varicella, 384*t*, 504*t*
Vacuum erection devices (VEDs), 860, 860*f*
Vaginal atrophy in menopause, 288
Vaginal ring, contraceptive, 261*t*, 274
Vaginosis, bacterial, 294, 295*t*, 434*t*
Valganciclovir, 383*t*
Valproate elimination pathways and major effects on hepatic enzymes, 537*t*
Valproate sodium in bipolar disorder, 708
Valproic acid, 529*t*, 538, 541–542
in Alzheimer's disease, 516*t*
antiepileptic drug
pharmacokinetic data, 527*t*
side effects, 536*t*
bipolar disorder, 698*t*, 701*t*, 703*t*, 708
drug–drug interactions, 538
in epilepsy, 538
fetal malformations, 525
neurologic disorders, 517, 521*t*–524*t*
in pancreatitis, 245*t*
during pregnancy, 297
side effects of, 554
treat refractory generalized convulsive status epilepticus, 596*t*
Valsartan, 46
in heart failure, 80
in hypertension, 89*t*
in myocardial infarction, secondary prevention after, 46
Vancomycin
antimicrobial agents, 330*t*
central nervous system infections, 327*t*, 329, 330*t*
in dermatologic disorders, 144
for diabetic foot infections, 463*t*
dosing of, 458*t*
drug monitoring, 344*t*
endocarditis, 337*t*
enterococcal endocarditis, 342

Enterococcus faecium, 345
gastrointestinal infections, 367
gynecologic and obstetric disorders, 299
in intraabdominal infections, 399*t,* 400*t*
methicillin-resistant *S. aureus* (MRSA), 468
oxacillin-resistant strains, 339*t*
in peritonitis, dialysis-associated, 404
in pneumonia, 417*t*
with rifampin, 342
sepsis and septic shock, 431*t*
Staphylococcus aureus strains, 342
streptococcal endocarditis, 335, 338*t*–339*t*
surgical prophylaxis, 471*t,* 474
Vardenafil
cardiovascular disorders, 44
endocrinologic disorders, 174
erectile dysfunction, treatments for, 853*t,* 860, 861*t*
urologic disorders, 853*t,* 861
Varenicline, 767, 768*t*
Variant angina pectoris, treatment of, 109
Variceal bleeding, 188–189, 191*t*
acute variceal hemorrhage, 189
management of, 188–189
prevention of rebleeding, 189
primary prophylaxis, 188–189
Varicella virus vaccine, 506*t*, 509
Varicella zoster vaccine, 509
Vasodilators
in acute decompensated heart failure, 84
direct arterial, 96
in heart failure, 81, 82*f,* 84
in hypertension, 93*t,* 185
ophthalmic disorders, 666*t*
Vasopressin, 60, 117, 193*t*
arginine vasopressin, 798
in cardiac arrest, 62, 63
in cardiovascular disorders, 118
gastrointestinal disorders, 189
receptor antagonists, 85
Vasopressin receptor antagonists in acute decompensated heart failure, 85
Vasopressors
cardiovascular disorders, 118
in shock, 118, 430*t*
Vasovagal syncope, 58
Venlafaxine
in algorithm for pharmacotherapy of posttraumatic stress, 692*f*
as antidepressant drug, 686, 715*t*, 719*t,* 723*t*, 726*t*, 729*t*
anxiety disorders, 677, 677*t*, 678*t*, 691, 692*t*
depressive disorder, 725
drug classification, 718
endocrinologic disorders, 174
headache, 554
hot flushes, treatment of, 286*t*
neurologic disorders, 556
ophthalmic disorders, 666*t*
in panic disorder, 687*t*
prophylactic migraine therapies, 551*t*
psychiatric disorders, 689*f*
to treat narcolepsy, 753*t*
treatment of generalized social anxiety disorder, 690*t*
Venous stasis, 125
Venous thromboembolism (VTE), 125–133
coagulation cascade, 126*f*
direct thrombin inhibitors for, 130–131
dosing for unfractionated heparin, 129*t*
fondaparinux sodium (Arixtra), 130
initiation of warfarin therapy, 132*f*
low-molecular-weight heparins for, 129–130
prevention of, 133
thrombolytic agents, 132–133
treatment of, 128*f*
Ventilatory support
chronic obstructive pulmonary disease, 842
with O_2 and pressurized airflow, 842
Ventricular arrhythmias
cardiovascular effect, 811
intravenous antiarrhythmic dosing, 52*t*
premature ventricular complexes (PVCs), 48

Ventricular assist devices in acute decompensated heart failure, 85
Ventricular fibrillation, 49, 58, 60–62
  nonpharmacologic therapy, 60
  pharmacologic therapy, 62
  postresuscitative care, 63
Ventricular proarrhythmia, 49, 57
Ventricular remodeling in MI, 37
Ventricular tachycardia (VT), 48, 57–58, 60–62
  acute, 57
  nonpharmacologic therapy, 60
  pharmacologic therapy, 62
    antiarrhythmics, 62
    magnesium, 62
    thrombolytics, 62
    vasopressin, 62
  postresuscitative care, 63
  sustained, 57
Verapamil, 51
  in acute coronary syndromes, 44
  in antiarrhythmic drugs, 51*t*
  in hypertension, 93
  in ischemic heart disease, 106
  in migraine prophylaxis, 555
  variant angina pectoris, 109
Vibrio cholerae infection, 361, 363*t*, 364
Vigabatrin, 542
  antiepileptic drug side effects, 536*t*
  dosing and target serum concentration ranges, 529*t*
  elimination pathways and major effects on hepatic enzymes, 537*t*
  pharmacokinetic data, 527*t*
Vilazodone, 717*t*, 720*t*, 724*t*, 726*t*, 727*t*
Vinblastine, 233*t*
  in Hodgkin's lymphoma, 649*t*
Vincristine, 233*t*
  chemotherapy for non-Hodgkin's lymphoma (CHOP), 652*t*
  in Hodgkin's lymphoma, 649*t*, 650*t*
  in lung cancer, 646
Vinorelbine
  in breast cancer, 627, 627, 628*t*
  as chemotherapeutic agent, 233*t*
  in lung cancer, 643, 645*t*
  in oncologic disorders, 644*t*
Viral hepatitis, 213–220
Viral infections
  bronchiolitis in, 408–409
  bronchitis in, 405, 406
  diarrhea in, 367
  pneumonia in, 410, 412–413
    in children, 416*t*
Virchow triad, 125
Vitamin A
  in dermatologic disorders, 138
  fat-soluble, absorption of, 71
  nutrition, 608*t*
Vitamin B_{12}
  anemias, 301, 304–305
  Crohn's disease, 222
  gastroesophageal reflux disease, 210
Vitamin B_2 as prophylactic migraine therapies, 551*t*
Vitamin D
  bone and joint disorders, 17, 19*t*
  fat-soluble, absorption of, 71
  nonpharmacologic therapy, 17
  in osteoporosis, 16, 17, 19, 20*t*
  recommended dietary allowances, 19*t*
  supplementation in osteoporosis, 19
Vitamin E
  in Alzheimer's disease, 513
  fat-soluble, absorption of, 71
Vitamin interactions, 608*t*
Vitamin K
  fat-soluble, absorption of, 71
  neurologic disorders, 525
Voriconazole as antimicrobial agent, 331*t*

W

Waist circumference measurements, 605
Warfarin, 14
  enteral nutrition, 615*t*
  in stroke, 122
  in venous thromboembolism (VTE), 131–132, 132*f*
  vitamin interactions, 608*t*
Warts, genital/anal, 435*t*, 446*t*–447*t*
Weight loss, pharmacotherapeutic agents for, 602*t*–603*t*
White blood cells, 202*f*, 203*f*
  Crohn's disease, 223*t*
  general algorithm for, 303*f*

leukocytosis, 313
and platelets, 125
Whitehead (closed comedone), 135
Withdrawal symptoms, 574, 683, 758
mental status, 757
World Health Organization (WHO), 16
anemia, 301
oral rehydration solutions, 204*t*
tumor node metastases (TNM) staging, 642–643
Wound infection
from bite, 449*t*, 462, 464–465
from burn, 449*t*
pressure sores, 612*t*
risk factors for, 466

X

Xanthine oxidase inhibitor in hyperuricemia, 7
Xanthomas
cardiovascular disorders, 74
genetic lipid disorder, 74
Xylometazoline hydrochloride in allergic rhinitis, 818*t*

Y

Yersinia enterocolitica, 364*t*, 365*t*
Yohimbine in erectile dysfunction, 864

Z

Zafirlukast in asthma, 833
Zalcitabine, in acute pancreatitis, 245*t*
Zaleplon, sleep disorders, 749*t*, 750
Zanamivir, in influenza, 388, 391*t*, 393
Zegerid, 210
Zidovudine
in human immunodeficiency virus infections, 297, 376*t*, 379
vitamin interactions, 608*t*
Zileuton, in asthma, 833
Zinc oxide in diaper dermatitis, 145
Ziprasidone
in bipolar disorder, 704*t*, 710
effect, 742
in schizophrenia, 731, 739*t*
cytochrome P450 pathways, 733
dosage range, 732*t*
pharmacokinetic parameters of, 736*t*
side effect, 739*t*
Zoledronic acid
in acute hypercalcemia, 804*t*
in osteoporosis, 19, 21*t*, 25
Zolmitriptan as migraine therapies, acute, 547*t*, 550*t*, 552*t*, 555
Zolpidem, 749*t*, 750
Zonisamide
pharmacokinetic data, 527*t*
side effects, 536*t*
dosing and target serum concentration ranges, 529*t*
drugs of choice, 522*t*–524*t*
elimination pathways and major effects on hepatic enzymes, 537*t*
in epilepsy, 542