

# HANDBOOK OF APPLIED THERAPEUTICS

NINTH EDITION

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HANDBOOK OF  
**APPLIED THERAPEUTICS**



# HANDBOOK OF APPLIED THERAPEUTICS

NINTH EDITION

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The authors, editors, and publisher have exerted every effort to ensure that drug selection and dosage set forth in this text are in accordance with the current recommendations and practice at the time of publication. However, in view of ongoing research, changes in government regulations, and the constant flow of information relating to drug therapy and drug reactions, the reader is urged to check the package insert for each drug for any change in indications and dosage and for added warnings and precautions. This is particularly important when the recommended agent is a new or infrequently employed drug.

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# Preface

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The text, *Applied Therapeutics: The Clinical Use of Drugs*,<sup>1</sup> provides a unique blend of factual information and practical application for both the beginning student and the mature practitioner. In the day-to-day management of patients, the clinician often needs quick access to “clinical pearls” to formulate rapid therapeutic decisions. It is for this purpose that the first edition of *The Handbook of Applied Therapeutics* was published. Now, several editions and many years later, this newest edition has been prepared to reflect the substantial increase in drug knowledge since the 2006 publication of the 8th edition.

In these times of national attention on medical errors, escalating costs, and shortages of nurses and pharmacists, we hope that the ready accessibility of clinically important drug information will make *The Handbook of Applied Therapeutics* a valuable tool for assisting in the safe and efficient use of drugs. The editor has abstracted hundreds of valuable tables and other information from the 10th edition of *Applied Therapeutics: The Clinical Use of Drugs*. To achieve portability of size, only the most essential data has been included. Therefore, the user is strongly encouraged to refer to the primary text for more detail and for literature documentation.

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<sup>1</sup>*Applied Therapeutics: The Clinical Use of Drugs*, 10th ed., 2012, edited by Brian K. Alldredge, Robin L. Corelli, Michael E. Ernst, B. Joseph Guglielmo, Pamala A. Jacobson, Wayne A. Kradjan, Bradley R. Williams (ISBN 9781609137137).

# Notice to the Reader

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Drug therapy information is constantly evolving. Our ever-changing knowledge and experience with drugs and the continual development of new drugs necessitates changes in treatment and drug therapy. The editor, authors, and publisher of this work have made every effort to ensure that the information provided herein was accurate at the time of publication. *It remains the responsibility of every practitioner to evaluate the appropriateness of a particular opinion or therapy in context of the actual clinical situation and with due consideration of any new developments in the field.* Although the editor has been careful to recommend dosages that are in agreement with current standards and responsible literature, the student or practitioner should consult several appropriate information sources when dealing with new and unfamiliar drugs.

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# Assessment of Therapy and Medication Therapy Management\*

## Medication Therapy Management Services

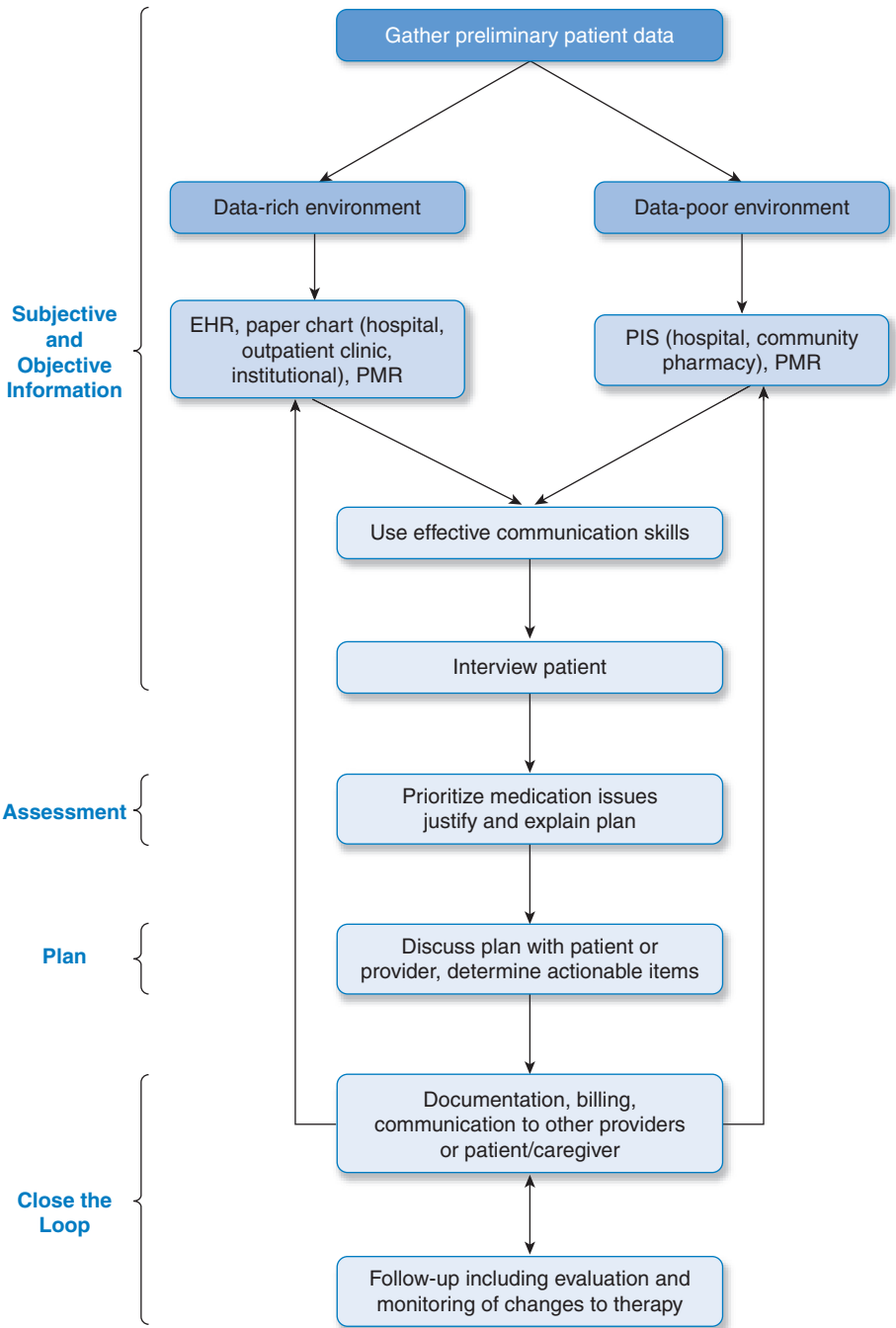
- Medication Therapy Management Services (MTMS) include comprehensive medication therapy review, developing a personalized medication record, a medication action plan, intervention or referral, and documentation of the encounter. They can be applied to any patient in a variety of settings. Data needed to perform MTMS can be obtained from many sources including the patient, paper chart, pharmacy information system, and electronic health record.
- The general approach to an MTMS patient encounter is shown in Figure 1.1.
  - Data-rich environments (e.g., hospitals, long-term care facilities, outpatient medical clinics) are those settings where there is a wealth of information available to practitioners from the medical record, pharmacy profile, and medication administration record.
  - Data-poor environments (e.g., community pharmacies) are those settings where clinicians are often required to make assessments with limited information. Pharmacy information systems are generally considered to be data poor, requiring information requests from patients or other clinicians.
- Taking an accurate and complete medication history is crucial to a successful MTMS encounter. A proactive interview of the patient or caregiver by the clinician using effective communication principles is particularly important in the data-poor environment (Table 1.1).

## Obtaining Patient History

- Use of a standardized form to complete MTMS facilitates quick retrieval of information, minimizes inadvertent omission of data, and enhances the ability of other practitioners to use shared records.
- A careful and complete patient interview should include a medical, medication, and social history and must be provided in a culturally sensitive manner.
- The goal of the medication history is to obtain and assess prescription and nonprescription medications, the intended purpose and appropriateness for each medication, how they are being taken, how long they have been used, and whether the patient believes they are providing therapeutic benefit.
- Medication reconciliation is the comprehensive evaluation of a patient's medication regimen any time there is a transition in care. The goal is to avoid medication errors such as omissions, duplications, dosing errors, or drug interactions and to assess compliance and adherence patterns.

---

\*The reader is referred to Chapter 1, Assessment of Therapy and Medication Therapy Management, written by Marilyn R. Stebbins, PharmD, Timothy W. Cutler, PharmD, CGP, and Patricia L. Parker, PharmD, BCPS, in the 10th edition of *Applied Therapeutics: The Clinical Use of Drugs* for a more in-depth discussion. All notations to reference numbers are based on the reference list at the end of that chapter. The editor of this handbook expresses her thanks to Drs. Stebbins, Cutler, and Parker and acknowledges that this chapter is based on their work.



**Figure 1.1** General approach to a patient encounter. EHR, electronic health record; PIS, pharmacy information system; PMR, personal medication record.



TABLE 1.1 Interviewing the Patient

**IMPORTANCE OF INTERVIEWING THE PATIENT**

Establishes professional relationship with the patient to:

- Obtain subjective data on medical problems
- Obtain patient-specific information on drug efficacy and toxicity
- Assess the patient's knowledge about, attitudes toward, and pattern of medication use
- Formulate a problem list
- Formulate plans for medication teaching and pharmaceutical care

**HOW TO SET THE STAGE FOR THE INTERVIEW**

- Have the patient complete a written health and medication questionnaire, if available
- Introduce yourself
- Make the setting as private as possible
- Do not allow friends or relatives without permission of the patient
- Do not appear rushed
- Be polite
- Be attentive
- Maintain eye contact
- Listen more than you talk
- Be nonjudgmental
- Encourage the patient to be descriptive
- Clarify by restatement or patient demonstration (e.g., of a technique)

**GENERAL INTERVIEW RULES**

- Read the chart or patient profile first
- Ask for the patient's permission to conduct an interview or make an appointment to do so
- Begin with open-ended questions
- Move to close-ended questions
- Document interaction clearly and succinctly

**INFORMATION TO BE OBTAINED**

- History of allergies
- History of adverse drug reactions
- Weight and height
- Drugs: dose, route, frequency, and reason for use
- Perceived efficacy of each drug
- Perceived side effects
- Adherence to prescribed drug regimen
- Nonprescription medication use (including complementary and alternative medications)
- Possibility of pregnancy in women of childbearing age
- Family or other support systems

Source: Teresa O'Sullivan, PharmD, University of Washington.

**Assessment of Patient Therapy**

- The general approach to the patient encounter should follow the problem-oriented medical record (POMR), where data are organized by medical problem (Table 1.2). Problems are listed in order of importance and are supported by subjective and objective evidence gathered during the patient encounter.
- Subjective and objective data provide the clinician with information to assess whether a problem continues to exist and that therapeutic outcomes are being achieved. Assessment of drug therapy and disease-specific problems follows data collection. Assessment is the clinician's justification of the plan. The final step is developing the medication action plan and processing any billing requirements. The SOAP (subjective/objective/assessment/plan) note is a common format used when documenting a patient encounter in the hospital setting.
- Communication of the plan with the patient/caregiver is required to ensure there is an understanding of the medical problem(s) and the goal of all treatment plans.

TABLE 1.2 Elements of the Problem-Oriented Medical Record<sup>a</sup>

*Problem name:* Each “problem” is listed separately and given an identifying number. Problems may be a patient complaint (e.g., headache), a laboratory abnormality (e.g., hypokalemia), or a specific disease name if prior diagnosis is known. When monitoring previously described drug therapy, more than one drug-related problem may be considered (e.g., nonadherence, a suspected adverse drug reaction or drug interaction, or an inappropriate dose). Under each problem name, the following information is identified:

Subjective	Information that explains or delineates the reason for the encounter. Information that the patient reports concerning symptoms, previous treatments, medications used, and adverse effects encountered. These are considered nonreproducible data because the information is based on the patient’s interpretation and recall of past events.
Objective	Information from physical examination, laboratory test results, diagnostic tests, pill counts, and pharmacy patient profile information. Objective data are measurable and reproducible.
Assessment	A brief but complete description of the problem, including a conclusion or diagnosis that is supported logically by the above subjective and objective data. The assessment should not include a problem or diagnosis that is not defined above.
Plan	A detailed description of recommended or intended further workup (e.g., laboratory tests, radiology, consultation), treatment (e.g., continued observation, physiotherapy, diet, medications, surgery), patient education (e.g., self-care, goals of therapy, medication use and monitoring), monitoring, and follow-up relative to the above assessment.

<sup>a</sup>Sometimes referred to as the SOAP (subjective, objective, assessment, plan) note.

# Interpretation of Clinical Laboratory Tests\*

## General Principles

- Laboratory findings can be helpful in assessing clinical disorders, establishing a diagnosis, assessing drug therapy, or evaluating disease progression.
- The serum, urine, and other fluids of patients are routinely analyzed; however, laboratory tests should be ordered only if the results of the tests will affect decisions about the therapeutic management of the patient.
- Laboratory values must be assessed in the context of the clinical situation. They should not be evaluated in isolation of the subjective and objective findings.
- When interpreting laboratory test results, clinicians should use the normal values listed by their own laboratory facility rather than those published in reference texts, because laboratories may use different methods of assay.
- Laboratory error should always be considered when laboratory results do not correlate with clinical expectations.
- Most countries, other than the United States, report clinical laboratory values in the metric system (SI units).

## Reference Values

- Blood chemistry reference values are shown in Table 2.1.
- Hematologic laboratory values are shown in Table 2.2.
- Equations are commonly used to estimate a patient's creatinine clearance (CrCl) in lieu of a 24-hour urine collection.
  - When serum creatinine (SCr) concentrations are <1.5 mg/dL, the Cockcroft–Gault formula is typically used:

$$\text{Estimated CrCl for males (mL/minute)} = \frac{(140 - \text{Age})(\text{Body weight in kg})}{(72)(\text{SCr in mg/dL})}$$

Ideal body weight is used unless actual body weight is less than the ideal weight. The result is multiplied by 0.85 for females.

- When SCr concentrations are >1.5 mg/dL, the Jelliffe method is typically used:

$$\text{Estimated CrCl for males (mL/minute/1.73 m}^2) = \frac{98 - [(0.8)(\text{Age} - 20)]}{(\text{SCr in mg/dL})}$$

The result is multiplied by 0.9 for females.

---

\*The reader is referred to Chapter 2, Interpretation of Clinical Laboratory Tests, written by Catrina R. Schwartz, PharmD, and Mark W. Garrison, PharmD, FCCP, in the 10th edition of *Applied Therapeutics: The Clinical Use of Drugs*, for a more in-depth discussion. All notations to reference numbers are based on the reference list at the end of that chapter. The editor of this handbook expresses her thanks to Drs. Schwartz and Garrison and acknowledges that this chapter is based on their work.

TABLE 2.1 Blood Chemistry Reference Values

Laboratory Test	Normal Reference Values		Conversion Factor	Comments
	Conventional Units	SI Units		
<b>ELECTROLYTES</b>				
Sodium	135–145 mEq/L	135–145 mmol/L	1	Low sodium is usually caused by excess water (e.g., ↑ serum antidiuretic hormone) and is treated with water restriction. ↑ in severe dehydration, diabetes insipidus, significant renal and GI losses.
Potassium	3.5–5 mEq/L	3.5–5 mmol/L	1	↑ with renal dysfunction, acidosis, K-sparing diuretics, hemolysis, burns, crush injuries. ↓ by diuretics, or with alkalosis, severe vomiting and diarrhea, heavy NG suctioning.
CO <sub>2</sub> content	22–28 mEq/L	22–28 mmol/L	1	Sum of HCO <sub>3</sub> <sup>-</sup> and dissolved CO <sub>2</sub> . Reflects acid–base balance and compensatory pulmonary (CO <sub>2</sub> ) and renal (HCO <sub>3</sub> <sup>-</sup> ) mechanisms.
Chloride	95–105 mEq/L	95–105 mmol/L	1	Primarily reflects HCO <sub>3</sub> <sup>-</sup> . Important for acid–base balance. ↓ by GI loss of chloride-rich fluid (vomiting, diarrhea, GI suction, intestinal fistulas, overdiuresis).
BUN	8–20 mg/dL	2.8–7.1 mmol/L	0.357	End product of protein metabolism, produced by liver, transported in blood, excreted renally. ↑ in renal dysfunction, high protein intake, upper GI bleeding, volume contraction.
Creatinine	0.6–1.2 mg/dL	53–106 μmol/L	88.4	Major constituent of muscle; rate of formation constant; affected by muscle mass (lower with aging); excreted renally. ↑ in renal dysfunction. Used as a primary marker for renal function (GFR).
CrCl	90–130 mL/minute	1.5–2.16 mL/second	0.01667	Reflects GFR; ↓ in renal dysfunction. Used to adjust dosage of renally eliminated drugs.
Estimated GFR	90–120 mL/minute/1.73 m <sup>2</sup>	n/a	n/a	Possibly a more accurate reflection of renal function than CrCl. Still influenced by muscle mass.
Cystatin C	<1.0 mg/dL	<0.749 μmol/L	0.749	Indicator of renal function—not influenced by patient muscle mass, age, or sex. May also help predict patients at risk for cardiovascular disease.
Glucose (fasting)	70–99 mg/dL	3.9–5.5 mmol/L	0.05551	↑ in diabetes or by adrenal corticosteroids.

TABLE 2.1 **Blood Chemistry Reference Values (Continued)**

Laboratory Test	Normal Reference Values		Conversion Factor	Comments
	Conventional Units	SI Units		
Glycosylated hemoglobin	<4%–5.6%	<4%–5.6%	1	Used to assess average blood glucose during 1–3 months. Helpful for monitoring chronic blood glucose control in patients with diabetes. Values >8% seen in patients with poor glucose control.
Calcium—total	8.5–10.5 mg/dL	2.1–2.6 mmol/L	0.250	Regulated by body skeleton redistribution, parathyroid hormone, vitamin D, calcitonin. Affected by changes in albumin concentration. ↓ in hypothyroidism, loop diuretics, vitamin D deficiency; ↑ in malignancy and hyperthyroidism.
Calcium—unbound	4.5–5.6 mg/dL	1.13–1.4 mmol/L	0.250	Physiologically active form. Unbound “free” calcium remains unchanged as albumin fluctuates. Total calcium ↓ when albumin ↓.
Magnesium	1.5–2.4 mEq/L	0.75–1.2 mmol/L	0.51	↓ in malabsorption, severe diarrhea, alcoholism, pancreatitis, diuretics, hyperaldosteronism (symptoms of weakness, depression, agitation, seizures, hypokalemia, arrhythmias). ↑ in renal failure and hypothyroidism, and with magnesium-containing antacids.
Phosphate <sup>a</sup>	2.5–4.5 mg/dL	0.8–1.45 mmol/L	0.323	↑ in renal dysfunction, hypervitaminosis D, hypocalcemia, hypoparathyroidism. ↓ with excess aluminum antacids, malabsorption, renal losses, hypercalcemia, refeeding syndrome.
Uric acid	<7 mg/dL	<0.42 mmol/L	0.06	↑ in gout, neoplastic, or myeloproliferative, disorders, and with drugs (diuretics, niacin, low-dose salicylate, cyclosporin).
<b>PROTEINS</b>				
Prealbumin	15–36 mg/dL	150–360 mg/L	10	Indicates acute changes in nutritional status, useful for monitoring TPN.
Albumin	3.3–4.8 g/dL	33–48 g/L	10	Produced in liver; important for intravascular osmotic pressure. ↓ in liver disease, malnutrition, ascites, hemorrhage, protein-wasting nephropathy. May influence highly protein-bound drugs.

*Continued on following page*



TABLE 2.1 Blood Chemistry Reference Values (Continued)

Laboratory Test	Normal Reference Values		Conversion Factor	Comments
	Conventional Units	SI Units		
Globulin	2.3–3.5 g/dL	23–35 g/L	10	Active role in immunologic mechanisms. Immunoglobulins ↑ in chronic infection, rheumatoid arthritis, multiple myeloma.
CK	<150 units/L	<2.5 $\mu$ kat/L	0.01667	In tissues that use high energy (skeletal muscle, myocardium, brain). ↑ with IM injections, MI, acute psychotic episodes. Isoenzyme CK-MM in skeletal muscle; CK-MB in myocardium; CK-BB in brain. MB fraction >5%–6% suggests acute MI.
CK-MB	0–12 units/L	0–0.2 $\mu$ kat/L	0.01667	More specific than CK-MB for myocardial damage, elevated sooner and remains elevated longer than CK-MB. cTnI >2.0 suggests acute myocardial injury.
cTnI	<1.5 ng/mL	<1.5 $\mu$ g/L	1	
Myoglobin	<90 mcg/L	<90 $\mu$ g/L	1	Early elevation (within 3 hours), but less specific for myocardial injury compared with CK-MB.
Homocysteine	4.6–11.9 $\mu$ mol/L	4.6–11.9 $\mu$ mol/L	1	Damages vessel endothelial, which may increase the risk for cardiac disease. Associated with deficiencies in folate, vitamin B <sub>6</sub> , and vitamin B <sub>12</sub> .
LDH	<200 units/L	<3.33 $\mu$ kat/L	0.01667	High in heart, kidney, liver, and skeletal muscle. Five isoenzymes: LD1 and LD2 mostly in heart, LD5 mostly in liver and skeletal muscle, LD3 and LD4 are nonspecific. ↑ in malignancy, extensive burns, PE, renal disease.
BNP	<100 pg/mL	<100 ng/L	1	BNP >500 ng/L indicates left ventricular dysfunction. Released from heart with ↑ workload placed on heart (e.g., CHF).
NT-proBNP	<60 pg/mL (males) <150 pg/mL (females)	<60 ng/L (males) <150 ng/L (females)	1	Component of a precursor to BNP. NT-proBNP has similar clinical utility to BNP as a marker for cardiovascular disease.
CRP	0–1.6 mg/dL	0–16 mg/L	1	Nonspecific indicator of acute inflammation. Similar to ESR, but more rapid onset and greater elevation. CRP >3 mg/dL increases risk of cardiovascular disease.

TABLE 2.1 Blood Chemistry Reference Values (Continued)

Laboratory Test	Normal Reference Values		Conversion Factor	Comments
	Conventional Units	SI Units		
hs-CRP	0–2.0 mg/L	0–2.0 mg/L	1	More sensitive measure of CRP; concentrations 0.5–10 mg/L; hs-CRP <1.0 mg/L low risk for cardiovascular disease; 1.0–3.0 mg/L average risk; and >3.0 mg/L high risk for cardiovascular disease.
<b>LIVER FUNCTION</b>				
AST	0–35 units/L	0–0.58 $\mu$ kat/L	0.01667	Large amounts in heart and liver; moderate amounts in muscle, kidney, and pancreas. $\uparrow$ with MI and liver injury. Less liver specific than ALT.
ALT	0–35 units/L	0–0.58 $\mu$ kat/L	0.01667	From heart, liver, muscle, kidney, pancreas. $\uparrow$ negligibly unless parenchymal liver disease. More liver specific than AST.
ALP	30–120 units/L	0.5–2.0 $\mu$ kat/L	0.01667	Large amounts in bile ducts, placenta, bone. $\uparrow$ in bile duct obstruction, obstructive liver disease, rapid bone growth (e.g., Paget disease), pregnancy.
GGT	0–70 units/L	0–1.17 $\mu$ kat/L	0.01667	Sensitive test reflecting hepatocellular injury; not helpful in differentiating liver disorders. Usually high in chronic alcoholics.
Bilirubin—total	0.1–1 mg/dL	1.7–17.1 $\mu$ mol/L	17.1	Breakdown product of hemoglobin, bound to albumin, conjugated in liver. Total bilirubin includes direct (conjugated) and indirect bilirubin. $\uparrow$ with hemolysis, cholestasis, liver injury.
Bilirubin—direct	0–0.2 mg/dL	0–3.4 $\mu$ mol/L	17.1	
<b>MISCELLANEOUS</b>				
Amylase	35–120 units/L	0.58–2.0 $\mu$ kat/L	0.01667	Pancreatic enzyme; $\uparrow$ in pancreatitis or duct obstruction.
Lipase	0–160 units/L	0–2.67 $\mu$ kat/L	0.01667	Pancreatic enzyme, $\uparrow$ in acute pancreatitis, elevated for longer period than amylase.
PSA	0–4 ng/mL	0–4 $\mu$ g/L	1	$\uparrow$ in benign prostatic hypertrophy (BPH) and also in prostate cancer. PSA levels of 4–10 ng/mL should be worked up. Risk of prostate cancer increased if free PSA/total PSA <0.25.
TSH	0.4–5 $\mu$ units/mL	0.4–5 $\mu$ units/L	1	$\uparrow$ TSH in primary hypothyroidism requires exogenous thyroid supplementation.

Continued on following page

TABLE 2.1 Blood Chemistry Reference Values (Continued)

Laboratory Test	Normal Reference Values		Conversion Factor	Comments
	Conventional Units	SI Units		
Procalcitonin	<0.5 ng/mL	<0.5 µg/L	1	↑ in bacterial infections—low risk of sepsis if <0.5 ng/mL; high risk of severe sepsis if >2.0 ng/mL. May assist in when to start/stop antibiotic therapy.
<b>TOTAL</b>				
Cholesterol	<200 mg/dL	<5.2 mmol/L	0.02586	Desirable = Total <200; LDL 70–160 (depends on risk factors); HDL >45 mg/dL; ↑ LDL or ↓ HDL are risk factors for cardiovascular disease. Consult NCEP and ATP guidelines for most current target goals and description of patient risk factors.
LDL	70–160 mg/dL	<4.13 mmol/L	0.02586	
HDL	40 mg/dL	1.03 mmol/L	0.02586	
Triglycerides (fasting)	<150 mg/dL	<1.70 mmol/L	0.0113	↑ by alcohol, saturated fats, drugs (propranolol, diuretics, oral contraceptives). Obtain fasting level.

<sup>a</sup>Phosphate as inorganic phosphorus.

ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; ATP, Adult Treatment Panel; BNP, brain natriuretic peptide; BPH, benign prostatic hypertrophy; BUN, blood urea nitrogen; CHF, congestive heart failure; CK, creatine kinase (formerly known as creatine phosphokinase); CrCl, creatinine clearance; CRP, C-reactive protein; cTnI, cardiac troponin I; ESR, erythrocyte sedimentation rate; GFR, glomerular filtration rate; GGT, γ-glutamyl transferase; GI, gastrointestinal; HDL, high-density lipoprotein; IM, intramuscular; LDH, lactate dehydrogenase; LDL, low-density lipoprotein; MI, myocardial infarction; NCEP, National Cholesterol Education Program; NG, nasogastric; PE, pulmonary embolism; PSA, prostate-specific antigen; SI, International System of Units; TPN, total parenteral nutrition; TSH, thyroid-stimulating hormone.

TABLE 2.2 Hematologic Laboratory Values

Laboratory Test	Normal Reference Values		Comments
	Conventional Units	SI Units	
RBC count			
Male	4.3–5.9 × 10 <sup>6</sup> /µL	4.3–5.9 × 10 <sup>12</sup> /L	
Female	3.5–5.0 × 10 <sup>6</sup> /µL	3.5–5.0 × 10 <sup>12</sup> /L	
Hct			↓ with anemias, bleeding, hemolysis. ↑ with polycythemia, chronic hypoxia.
Male	39%–49%	0.39–0.49	
Female	33%–43%	0.33–0.43	
Hgb			Similar to Hct.
Male	14–18 g/dL	140–180 g/L	
Female	12–16 g/dL	120–160 g/L	
MCV	76–100 µm <sup>3</sup>	76–100 fL <sup>a</sup>	Describes average RBC size; ↑ MCV = macrocytic, ↓ MCV = microcytic.
MCH	27–33 pg	27–33 pg	Measures average weight of Hgb in RBC.

TABLE 2.2 Hematologic Laboratory Values (Continued)

Laboratory Test	Normal Reference Values		Comments
	Conventional Units	SI Units	
MCHC	33–37 g/dL	330–370 g/L	More reliable index of RBC hemoglobin than MCH. Measures average concentration of Hgb in RBC. Concentration will not change with weight or size of RBC.
Reticulocyte count (adults)	0.1%–2.4%	0.001–0.024	Indicator of RBC production; increase suggests ↑ number of immature erythrocytes released in response to stimulus (e.g., iron in iron-deficiency anemia).
ESR			Nonspecific; ↑ with inflammation, infection, neoplasms, connective tissue disorders, pregnancy, nephritis. Useful monitor of temporal arteritis and polymyalgia rheumatica.
Male	0–20 mm/hour	0–20 mm/hour	
Female	0–30 mm/hour	0–30 mm/hour	
WBC count	4–11 × 10 <sup>3</sup> /μL	4–11 × 10 <sup>9</sup> /L	Consists of neutrophils, lymphocytes, monocytes, eosinophils, and basophils; ↑ in infection and stress.
ANC	2,000 cells/μL		ANC = WBC × (% neutrophils + % bands)/100; if <500 ↑ risk of infection, if >1,000 ↓ risk of infection.
Neutrophils	40%–70%	0.4–0.7	Increase in neutrophils suggests bacterial or fungal infection. Increase in bands suggests bacterial infection.
Bands	3%–5%	0.03–0.05	
Lymphocytes	20%–40%	0.20–0.40	
Monocytes	0%–11%	0–0.11	
Eosinophils	0%–8%	0–0.08	Eosinophils ↑ with allergies and parasitic infections.
Basophils	0%–3%	<0.03	
Platelets	150–450 × 10 <sup>3</sup> /μL	150–450 × 10 <sup>9</sup> /L	<100 × 10 <sup>3</sup> /μL = thrombocytopenia; <20 × 10 <sup>3</sup> /μL = ↑ risk for severe bleeding.
Iron			
Male	80–180 mcg/dL	14–32 μmol/L	Body stores two-thirds in Hgb; one-third in bone marrow, spleen, liver; only small amount present in plasma. Blood loss major cause of deficiency.
Female	60–160 mcg/dL	11–29 μmol/L	↑ needs in pregnancy and lactation.
TIBC	250–460 mcg/dL	45–82 μmol/L	↑ capacity to bind iron with iron deficiency.

<sup>a</sup>fL, femtoliter; femto, 10<sup>-15</sup>; pico, 10<sup>-12</sup>; nano, 10<sup>-9</sup>; micro, 10<sup>-6</sup>; milli, 10<sup>-3</sup>.

ANC, absolute neutrophil count; ESR, erythrocyte sedimentation rate; Hct, hematocrit; Hgb, hemoglobin; MCH, mean corpuscular hemoglobin; MCHC, mean cell hemoglobin concentration; MCV, mean cell volume; RBC, red blood cell; SI, International System of Units; TIBC, total iron-binding capacity; WBC, white blood cell.

## Medication Monitoring

- Therapeutic drug monitoring assists with appropriate dosing adjustments to optimize therapy (Table 2.3).
- Laboratory monitoring for common therapeutic agents are shown in Table 2.4.

TABLE 2.3 Therapeutic Drug Monitoring Reference Ranges

Drug	Peak Reference Range	SI Units	Trough Reference Range	SI Units	Notes
<b>ANTIBIOTICS<sup>a</sup></b>					
Amikacin	25–35 mcg/mL	43–60 $\mu$ mol/L	<10 mcg/mL	<17 $\mu$ mol/L	Traditional dosing
Gentamicin or Tobramycin	6–10 mcg/mL	13–21 $\mu$ mol/L	<2 mcg/mL	<4.2 $\mu$ mol/L	Traditional dosing
Gentamicin or Tobramycin	20 mcg/mL	42.5 $\mu$ mol/L	Undetectable	Undetectable	Extended dosing
Vancomycin	Not recommended		10 mcg/mL	3 $\mu$ mol/L	Recommended to keep >10 mcg/mL to avoid development of resistance
			15–20 mcg/mL	10–14 $\mu$ mol/L	Complicated infections (bacteremia, endocarditis, osteomyelitis, meningitis, and hospital-acquired pneumonia caused by <i>Staphylococcus aureus</i> )
<b>ANTIEPILEPTIC DRUGS<sup>b</sup></b>					
Carbamazepine	4–12 mcg/mL <sup>c</sup>	17–51 $\mu$ mol/L			
Phenobarbital	10–40 mcg/mL	43–170 $\mu$ mol/L			
Phenytoin	10–20 mcg/mL	40–79 $\mu$ mol/L			
Primidone	4–12 mcg/mL	18–55 $\mu$ mol/L			
Valproic acid	50–125 mcg/mL	350–690 $\mu$ mol/L			
<b>ANTIDEPRESSANTS AND RELATED AGENTS<sup>d</sup></b>					
Amitriptyline	120–250 ng/mL	433–903 nmol/L			
Clozapine	200–350 ng/mL	0.6–1 $\mu$ mol/L			
Desipramine	100–300 ng/mL	281–1125 nmol/L			
Doxepin	100–250 ng/mL	107–537 nmol/L			
Imipramine	125–300 ng/mL	446–893 nmol/L			
Lithium	0.6–1.2 mEq/L	0.6–1.2 nmol/L			
Nortriptyline	50–170 ng/mL	190–646 nmol/L			
<b>ANTIARRHYTHMICS<sup>e</sup></b>					
Amiodarone	0.5–2.5 mcg/mL	1.5–4 $\mu$ mol/L			
Digoxin	0.8–2 ng/mL	0.9–2.5 nmol/L			
Flecainide	0.2–1 mcg/mL	0.5–2.4 $\mu$ mol/L			
Lidocaine	1.5–6 mcg/mL	6.4–26 $\mu$ mol/L			
Procainamide	4–10 mcg/mL	17–42 $\mu$ mol/L			
Quinidine	2–5 mcg/mL	6–15 $\mu$ mol/L			

<sup>a</sup>Peak and trough targets may vary with dosing interval, type or severity of infection, and patient-specific factors.

<sup>b</sup>Therapeutic targets may vary with seizure control and patient-specific factors.

<sup>c</sup>From this point onward, the value in this column indicate therapeutic reference level.

<sup>d</sup>Therapeutic targets may vary with response and patient-specific factors.

<sup>e</sup>Clinically therapeutic targets may vary with response and patient-specific factors.

TABLE 2.4 Laboratory Monitoring for Common Therapeutic Agents<sup>a</sup>

Drug or Drug Class	SCr, CrCl	BUN	Na	K	CO <sub>2</sub>	Ca	Mg	Phos	Glu	CBC	WBC Indices	RBC Indices	LFT(s)	Lipids	TSH	Drug Level	Other	Notes
ACEI, ARB	✓			✓														
Acitretin									✓				✓	✓				
Aldosterone antagonists	✓	✓		✓														
Amiodarone				✓			✓								✓		Free T <sub>4</sub>	Chest x-ray Also see clozapine
Atypical antipsychotics									✓					✓				
Calcipotriol/ calcipotriene						✓												
Carbamazepine	✓	✓								✓			✓			✓	Calcium and vit D levels	Genotyping, drug interactions possible
Clozapine									✓		✓						Absolute neutrophil count	
DMARDs	✓									✓			✓					
Digoxin	✓		✓	✓	✓	✓	✓									✓		
Diuretics	✓	✓	✓	✓	✓	✓	✓		✓								Uric acid	
Enoxaparin	✓																Platelets	Anti-Xa (obesity, renal dysfunction, pregnancy)
Ethosuximide													✓			✓		
Felbamate										✓								
Fenofibrate													✓					CK if muscle symptoms
Fexofenadine	✓																	Dose-adjusted CrCl <80 mL/minute

Continued on following page

TABLE 2.4 Laboratory Monitoring for Common Therapeutic Agents<sup>a</sup> (Continued)

Drug or Drug Class	SCr, CrCl	BUN	Na	K	CO <sub>2</sub>	Ca	Mg	Phos	Glu	CBC	WBC Indices	RBC Indices	LFT(s)	Lipids	TSH	Drug Level	Other	Notes
Flecainide				✓												✓		
Gemfibrozil										✓			✓					CK if muscle symptoms
Glitazones													✓					
Glyburide	✓								✓								A <sub>1c</sub>	Not recommended CrCl <50 mL/minute
HMG-CoA inhibitors													✓				Lipids, baseline CK	CK, TSH if muscle symptoms
Lithium	✓	✓	✓	✓	✓	✓				✓					✓	✓		Pregnancy test
Metformin	✓											✓					Hgb, Hct, vit B <sub>12</sub> , folic acid	
Niacin				✓				✓	✓				✓				Uric acid	CK if muscle symptoms
NSAIDs	✓									✓			✓					
Oxcarbazepine			✓												✓			
Phenytoin										✓						✓	Albumin, calcium, and vit D levels	
PPIs																	Vit B <sub>12</sub>	
Ranitidine	✓																Vit B <sub>12</sub>	Dose-adjusted CrCl <50 mL/minute
Retinoids (oral)									✓				✓	✓				Monthly pregnancy test
Theophylline																✓		Drug interactions possible

Thyroid replacement				✓	Free T <sub>4</sub>
Topiramate					Bicarbonate Ammonia if symptomatic
Valproic acid	✓		✓	✓	Plt count, Ammonia if symptomatic
Warfarin					coagulation tests INR, Hct Genotyping, drug interactions possible

\*Frequency and type of monitoring may vary based on clinical situation.

A<sub>1c</sub>, hemoglobin A<sub>1c</sub>; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BUN, blood urea nitrogen; CBC, complete blood count; CK, creatine kinase; CrCl, creatinine clearance; DMARDs, disease-modifying antirheumatic drugs; Hct, hematocrit; Hgb, hemoglobin; HMG-CoA, 3-hydroxy-3-methylglutaryl-coenzyme A; INR, international normalized ratio; LFTs, liver function tests; NSAIDs, nonsteroidal anti-inflammatory drugs; Plt, platelet; PPIs, proton-pump inhibitors; RBC, red blood cell; SCr, serum creatinine; T<sub>4</sub>, thyroxine; TSH, thyroid-stimulating hormone; Vit, vitamin; WBC, white blood cell.

Adapted from Therapeutic Research Center. Recommended lab monitoring for common medications. *Pharm Lett.* 2010;26(260704).



# Anaphylaxis and Drug Allergies\*

## General Principles

- Allergic or hypersensitivity reactions are a subset of adverse drug reactions. They account for one-third of all adverse drug reactions and may affect 10% to 15% of hospitalized patients.
- The immunopathological mechanisms that lead to an allergic drug reaction have traditionally been thought to occur in two phases: initial sensitization and subsequent elicitation. Sensitization occurs as a result of binding of a drug or a metabolite to a carrier protein in a process referred to as haptization. This drug protein (or drug metabolite-protein) complex induces the production of drug-specific T or B lymphocytes and IgM, IgG, and IgE. Upon reexposure to the drug, the patient is likely to present with allergic symptoms.
- Other models for explaining allergic reactions have been proposed, including direct pharmacologic interaction (where some drugs bind directly to T-cell receptors in a reversible, noncovalent manner) and the danger hypothesis (where idiosyncratic drug reactions are the result of damaged or stressed cells that release “danger signals”).

## Classification of Allergic Drug Reactions

- Allergic drug reactions can be classified into four different immunological types (Table 3.1). The exact immunologic mechanism is unknown for many allergic reactions to drugs, and patients often present with several symptoms characteristic of more than one type.
- Drug allergies can be grouped into three categories: generalized reactions, organ-specific reactions, and pseudoallergic reactions.
- **Generalized reactions** involve multiple organ systems and have variable clinical manifestations.
  - **Anaphylaxis** is a serious allergic reaction that has a rapid onset and can cause death. The symptoms vary widely, depending on the route of exposure, rate or exposure, and dose of allergen. Treatment of anaphylaxis involves several drugs and drug classes (Table 3.2).
  - **Serum sickness** is a hypersensitivity reaction that results from production of antibodies directed against heterologous protein or drug protein with subsequent tissue deposition. Clinical presentation is shown in Table 3.3.
  - **Drug fever** is a febrile reaction to a drug without cutaneous symptoms and is estimated to occur in 3% to 5% of inpatients (Table 3.4).
  - **Hypersensitivity vasculitis** is characterized by inflammation of the small blood vessel walls (Table 3.5).
  - **Drug-induced vasculitis** is a hypersensitivity reaction that can involve multiple organ systems. Diagnosis is based on five clinical criteria (Table 3.6), three of which must be present.
  - **Autoimmune drug reactions** are the result of drugs that can induce an autoimmune process characterized by the presence of antibodies (Table 3.7).

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\*The reader is referred to Chapter 3, Anaphylaxis and Drug Allergies, written by Robert K. Middleton, PharmD, in the 10th edition of *Applied Therapeutics: The Clinical Use of Drugs* for a more in-depth discussion. All notations to reference numbers are based on the reference list at the end of that chapter. The editor of this handbook expresses her thanks to Dr. Middleton and acknowledges that this chapter is based on his work.

TABLE 3.1 Immunological Classification of Allergic Drug Reactions

Immunologic Class	Antibody	Mechanism	Common Clinical Manifestations
Type I (immediate)	IgE	Drug-hapten reacts with IgE antibody on the surface of mast cells and basophils, resulting in the release of mediators	Urticaria, bronchospasm, anaphylaxis
Type II (cytotoxic)	IgG	Hapten-cell reaction: Drug interacts with cell surfaces, resulting in the formation of an immunogenic complex and the production of antibodies	Hemolytic anemia
—	IgM	Immune complex reaction: Drug reacts with antibody in circulation, forming a complex that with complement binds to the cell, resulting in injury (hematologic reactions only)	Granulocytopenia
—	—	Autoimmune reaction: Drug induces autoantibody production against platelets	Thrombocytopenia
Type III (immune complex)	IgG	Same as type II immune complex reactions (nonhematologic reactions)	Serum sickness, vasculitis
Type IVa-d (cell mediated)	—	Interaction of sensitized T lymphocytes with drug antigen	Contact dermatitis, chronic allergic rhinitis, maculopapular exanthema

Sources: VanArsdel P. Drug hypersensitivity. In: Bierman C, ed. *Allergic Diseases from Infancy to Adulthood*. Philadelphia, PA: WB Saunders; 1988:684; Pichler WJ et al. Drug hypersensitivity reactions: pathomechanism and clinical symptoms. *Med Clin North Am*. 2010;94:645.

TABLE 3.2 Drug Therapy of Anaphylaxis

Drug	Indication	Adult Dosage	Complications
<b>FIRST-LINE THERAPY</b>			
Epinephrine	Hypotension, bronchospasm, laryngeal edema, urticaria, angioedema	0.3–0.5 mL of a 1 mg/1 mL solution IM every 5 minutes PRN; if progressing to cardiorespiratory arrest 1–3 mL of 1:10,000 (0.1–0.3 mg) IV for 3 minutes 1 mL of 1 mg/mL (1:1,000) in 250 mL of normal saline IV at a rate of 4–10 mcg/minute (preferred over intermittent injections) 3–5 mL of 1:10,000 intratracheally every 10–20 minutes PRN	Arrhythmias, hypertension, nervousness, tremor
Oxygen	Hypoxemia	40%–100%	None
Albuterol		0.5 mL of 0.5% solution in 2.5 mL of saline via nebulizer (i.e., 2.5 mg)	Arrhythmias, hypertension, nervousness, tremor
IV fluids	Hypotension	1 L of normal saline every 20–30 minutes PRN (rates as high as 1–2 mL/kg/minute may be necessary)	Pulmonary edema, CHF

**SECOND-LINE THERAPY**

Antihistamines	Hypotension, urticaria	—	—
H <sub>1</sub> receptor antagonists	—	Diphenhydramine 25–50 mg IV, IM, PO every 6–8 hours PRN Hydroxyzine 25–50 mg IM or PO every 6–8 hours PRN	Drowsiness, dry mouth, urinary retention; may obscure symptoms of continuing reaction

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TABLE 3.2 Drug Therapy of Anaphylaxis (Continued)

Drug	Indication	Adult Dosage	Complications
H <sub>2</sub> receptor antagonists		Cimetidine 300 mg IV for 3–5 minutes or PO every 6–8 hours PRN Ranitidine 50 mg IV for 3–5 minutes every 8 hours PRN or 150 mg PO BID PRN Famotidine 20 mg IV for 3–5 minutes every 12 hours PRN or 20 mg PO BID PRN	—
Corticosteroids	Bronchospasm; patients undergoing prolonged resuscitation or severe reaction	Hydrocortisone sodium succinate 100 mg IM or IV every 3–6 hours for two to four doses or Methylprednisolone sodium succinate 40–125 mg IV every 6 hours for two to four doses	Hyperglycemia, fluid retention
Dopamine	Hypotension refractory to epinephrine	400 mg in 500 mL dextrose 5% at 2–20 mcg/kg/minute	Hypertension, tachycardia, palpitations, arrhythmias
Norepinephrine	Hypotension refractory to epinephrine	4 mg in 1 L dextrose 5% IV at a rate of 2–12 mcg/minute	Arrhythmias, hypertension, nervousness, tremor
Glucagon <sup>b</sup>	Refractory hypotension	1 mg IV for 5 minutes, followed by 5–15 mcg/minute in fusion	Nausea, vomiting

<sup>a</sup>Although not effective during acute anaphylaxis, these agents may reduce or prevent recurrent or prolonged reactions.

<sup>b</sup>Glucagon may be particularly useful in patients taking  $\beta$ -adrenergic blockers because it can increase both cardiac rate and contractility regardless of  $\beta$ -adrenergic blockade. Choice of agent and starting doses should be patient specific, weighing safety and efficacy.

BID, twice a day; IM, intramuscularly; IV, intravenously; PO, orally; PRN, as needed.

TABLE 3.3 Hypersensitivity Reactions to Drugs: Serum Sickness

Clinical manifestations	Fever, cutaneous eruptions (95% of cases), lymphadenopathy, and joint systems (10%–50%). Onset 1–2 weeks after exposure, 2–4 days in sensitized individuals. Laboratory data relatively nonspecific: elevated ESR and circulating immune complexes. Complements C3 and C4 are often low, whereas activation products C3a and C3a desarginine are elevated. RF sometimes present. UA may reveal proteinuria, hematuria, or an occasional cast.
Prognosis	Usually mild and self-limiting. Most resolve within a few days to weeks after withdrawal of inciting agent.
Treatment	Aspirin and antihistamines can relieve arthralgias and pruritus. Corticosteroids may be required for severe cases and tapered for 10–14 days.

ESR, erythrocyte sedimentation rate; RF, rheumatoid factor; UA, urinalysis.

Sources: Buhner D, Grant JA. Serum sickness. *Dermatol Clin*. 1985;3:107; Lawley TJ et al. A study of human serum sickness. *J Invest Dermatol*. 1985;85(1 Suppl):129s; Erffmeyer JE. Serum sickness. *Ann Allergy*. 1986;56:105; Lin RY. Serum sickness syndrome. *Am Fam Physician*. 1986;33:157.

TABLE 3.4 Hypersensitivity Reactions to Drugs: Drug-Induced Fever

Frequency	True frequency is unknown because fever is a common manifestation and almost any drug can cause fever. Estimate is that 3%–5% of hospitalized patients experiencing adverse drug reaction suffer from drug fever alone or as part of multiple symptoms.
Clinical manifestations	Temperatures may be 38°C or higher and do not follow a consistent pattern. Although patients may have high fevers with shaking chills, patients generally have few symptoms or serious systemic illness. Skin rash (18%), eosinophilia (22%), chills (53%), headache (16%), myalgias (25%), and bradycardia (11%) can occur in patients with drug fever. Onset of fever after exposure to the offending agent is highly variable, ranging from an average of 6 days for antineoplastics to 45 days for cardiovascular agents. Occurrence of fever is independent of the dose of the offending agent.
Treatment	Although drug fever can be treated symptomatically (e.g., with antipyretics, cooling blankets), stopping the offending agent is the only therapy that will eliminate fevers. Patients generally defervesce within 48–72 hours of stopping the suspect drug.
Prognosis	Drug fever is usually benign, although one review <sup>57</sup> found a mean increased length of hospitalization of 9 days per episode of drug fever. Rechallenge with the offending drug usually results in rapid return of the fever. Although reexposure to the suspect drug was previously thought to be potentially hazardous, there is little risk of serious sequelae.

Sources: Patel RA, Gallagher JC. Drug fever. *Pharmacotherapy*. 2010;30:57; Tabor PA. Drug-induced fever. *Drug Intell Clin Pharm*. 1986;20:413; Mackowiak PA, LeMaistre CF. Drug fever: a critical appraisal of conventional concepts. An analysis of 51 episodes in two Dallas hospitals and 97 episodes reported in the English literature. *Ann Intern Med*. 1987;106:728; Cunha BA, Shea KW. Fever in the intensive care unit. *Infect Dis Clin North Am*. 1996;10:185.

TABLE 3.5 Criteria<sup>a</sup> for the Classification of Hypersensitivity Vasculitis

Development of symptoms after age 16
Medication at disease onset that may have been a precipitating factor
Slightly elevated purpuric (hemorrhagic) rash over one or more areas of the skin that does not blanch with pressure and is not related to thrombocytopenia
Maculopapular rash over one or more areas of the skin
Biopsy showing granulocytes around an arteriole or venule

<sup>a</sup>The diagnosis of hypersensitivity vasculitis can be made if a patient exhibits at least three of these criteria.

Source: Calabrese LH et al. The American College of Rheumatology 1990 criteria for the classification of hypersensitivity vasculitis. *Arthritis Rheum*. 1990;33:1108.

TABLE 3.6 Hypersensitivity Reactions to Drugs: Clinical Manifestations of Drug-Induced Vasculitis

- Palpable purpura and maculopapular rash occurring symmetrically predominantly on the lower extremities
- Multiple organ systems may be involved:
  - Renal*: microscopic hematuria to nephrotic syndrome and acute renal failure
  - Liver*: enlarged liver, elevated enzymes
  - Joints*: arthritis
  - Gastrointestinal*: abdominal pain
- Laboratory data usually show nonspecific abnormalities of inflammation: elevated erythrocyte sedimentation rate and leukocytosis. Peripheral eosinophilia may be present and serum complement concentrations can be low. Histologic findings on biopsy reveal small blood vessels with leukocytoclastic or necrotizing vasculitis
- Onset typically 7–21 days after initiation of therapy

Sources: Valeyrie-Allanore L et al. Drug-induced skin, nail and hair disorders. *Drug Saf*. 2007;30:1011; Martinez-Taboada VM et al. Clinical features and outcome of 95 patients with hypersensitivity vasculitis. *Am J Med*. 1997;102:186.

TABLE 3.7 Hypersensitivity Reactions to Drugs: Autoimmune Drug-Induced Lupus

Frequency	Less likely to affect women and black patients than idiopathic SLE. Drug-induced lupus is more common in individuals with slow acetylator phenotype.
Clinical manifestations	Milder disease than idiopathic SLE. Arthralgias, myalgias, fever, malaise, pleurisy, and slight weight loss. Mild splenomegaly and lymphadenopathy. <i>Onset</i> : Usually abrupt, occurring several months to years after continuous therapy with the offending drug. <i>Appearance</i> : Photosensitivity appears in about 25% of patients, but the classic butterfly malar rash, discoid lesions, oral mucosal ulcers, Raynaud phenomenon, and alopecia are unusual features with drug-induced lupus as opposed to idiopathic SLE. <i>Laboratory studies</i> : Positive ANA (predominantly single-stranded DNA and antihistone antibodies), anemia, and elevated erythrocyte sedimentation rate. Many patients demonstrate ANA without development of lupus disease. It is not necessary, therefore, to discontinue therapy in asymptomatic patients with positive ANA.
Treatment	Clinical features subside and disappear days to weeks after discontinuation of the offending drug. Serologic tests resolve more slowly. ANA may persist for a year or longer.
Prognosis	Drug-induced lupus does not predispose to development of idiopathic SLE. Lupus-inducing drugs do not appear to increase the risk of exacerbation of idiopathic SLE. Long-term treatment with interferon- $\lambda$ may, however, worsen preexisting SLE.

ANA, antinuclear antibody; SLE, systemic lupus erythematosus.

Sources: Valeyrie-Allanore L et al. Drug-induced skin, nail and hair disorders. *Drug Saf.* 2007;30:1011; Antonov D et al. Drug-induced lupus erythematosus. *Clin Dermatol.* 2004;22:157.

- **Organ-specific reactions** can affect many organ systems.
  - **Blood: Immune Cytopenias.** Typical symptoms include chills, fever, petechiae, and mucous membrane bleeding.
  - **Liver.** Reactions can be classified as cholestatic or cytotoxic. Jaundice is usually the first sign of cholestatic reaction, along with pruritus, pale stools, and dark urine.
  - **Lung.** Pulmonary manifestations of drug hypersensitivity include asthma and infiltrative reactions.
  - **Kidney.** Interstitial nephritis is the most common hypersensitivity reaction (see Chapter 30).
  - **Skin.** Adverse reactions of the skin are the most common clinical manifestation of drug allergy (see Chapter 39).
- **Pseudoallergic reactions** are drug reactions with clinical signs and symptoms of an allergic response, but are not immunologically mediated (see Table 3.8). Pseudoallergic reactions can manifest as relatively benign symptoms or as severe, life-threatening events indistinguishable from anaphylaxis.
- **Latex allergies** have become more prevalent, with health professionals being at greatest risk due to frequent exposure to latex products. Three types of latex allergies include irritant contact dermatitis, allergic contact dermatitis, and immediate hypersensitivity.

## Patient Assessment

- Allergic reactions can be differentiated from other types of adverse drug reactions by assessing common clinical features of the allergic drug reaction (Table 3.9) and by a detailed drug history (Table 3.10).
- The temporal relationship between drugs and reactions is often the strongest evidence implicating an allergic reaction to a given agent.
- Skin testing and drug rechallenge are the most definitive methods of diagnosing drug allergy. Only penicillin currently has skin test antigens (Table 3.11). Skin testing should not be done in patients receiving antihistamines because they block the response to the antigen and can result in misinterpretation.

TABLE 3.8 Hypersensitivity Reactions to Drugs: Pseudoallergic Reactions

Frequency	Highly variable, depending on the agent involved. For example, up to 30% of patients taking aspirin exhibit a cutaneous pseudoallergic response. On the other hand, pseudoallergic reactions to other agents, such as phytonadione and thiamine, are rare.
Clinical manifestations	Range from benign reactions (e.g., pruritus and flushing) to a life-threatening clinical syndrome indistinguishable from anaphylaxis. Commonly require a higher drug dose to elicit the response than a true IgE-mediated reaction. May arise less quickly (>15 minutes after exposure) than true allergic reaction.
Diagnostic workup	Skin tests and identification of specific antibodies are negative.
Treatment	Pseudoallergic reactions are treated the same as true allergic reactions (i.e., according to the clinical presentations of the patient). Thus, some reactions simply may require removal of the suspect agent, whereas some anaphylactoid reactions may require aggressive therapy (e.g., epinephrine, antihistamines, corticosteroids).
Prognosis	As with true allergic reactions, patients who have experienced a pseudoallergic drug reaction may have a similar reaction on reexposure. The severity of response may lessen, however, with repeated administration. Furthermore, for some drugs, the frequency and severity of the reaction also may be influenced by the dose or rate of intravenous administration. Pretreatment regimens to reduce the frequency and the severity of responses have been developed for some drugs well known to cause pseudoallergic reactions (e.g., radiocontrast media).

Sources: Pichler WJ et al. Drug hypersensitivity reactions: pathomechanism and clinical symptoms. *Med Clin North Am.* 2010;94:645; Schnyder B. Approach to the patient with drug allergy. *Immunol Allergy Clin North Am.* 2009;29:405; Sanchez-Borges M. NSAID hypersensitivity (respiratory, cutaneous, and generalized anaphylactic symptoms). *Med Clin North Am.* 2010;94:853.

## Risk Factors

- The prevalence of allergic reactions can be affected by either drug idiosyncrasies or patient-related variables.
- **Age and Gender.** Adults are more susceptible to drug allergies than are children. Females are more prone than males.
- **Genetic Factors.** Patients with allergic rhinitis, asthma, or atopic dermatitis tend to experience more severe drug reactions. Ethnic predisposition to drug allergy is increasingly recognized. Slow acetylators are more likely to develop antinuclear antibodies and symptoms of systemic lupus erythematosus when treated with procainamide or hydralazine. Anticonvulsant syndrome is more common in patients with a heritable deficiency in epoxide hydrolase. Genetic differences in CYP-metabolizing enzymes may explain the predisposition of some patients to drug allergy and hypersensitivity. Genetic screening for the major histocompatibility complex (MHC) has reduced the occurrence of reactions with abacavir.

TABLE 3.9 Clinical Features of Allergic Drug Reactions

- Are unpredictable
- Occur only in susceptible individuals
- Have no correlation with known pharmacologic properties of the drug
- Require an induction period on primary exposure but not on readministration
- Can occur with doses far below therapeutic range
- Can affect most organs, but commonly involves the skin
- Most commonly manifests as an erythematous or maculopapular rash, but includes angioedema, serum sickness syndrome, anaphylaxis, and asthma
- Occur in a small proportion of the population (10%–15%)
- Disappear on cessation of therapy and reappear after readministration of a small dose of the suspected drug(s) of similar chemical structure
- Desensitization may be possible

Sources: Assem E. Drug allergy and tests for its detection. In: Davies DM, ed. *Textbook of Adverse Drug Reactions*. New York, NY: Oxford University Press; 1991:689; Schnyder B. Approach to the patient with drug allergy. *Immunol Allergy Clin North Am.* 2009;29:405.

TABLE 3.10 Detailed Drug History

- Name of the medication
- Route of administration
- Reason medication was prescribed
- Nature and severity of reaction
- Temporal relationships between drugs and reaction (dose, date initiated, duration, when during the course of treatment did the reaction occur)
- Prior allergy history
- When did the reaction occur (days to weeks vs. months to years)
- Similar reactions in family members
- Prior exposure to the same or structurally related medications
- Concurrent medications
- Management of the reaction (effect of drug discontinuation; therapies required to treat the reaction)
- Response to treatment
- Prior diagnostic testing or rechallenge
- Other medical problems (if any)

Sources: Khan DA, Solensky R. Drug allergy. *J Allergy Clin Immunol.* 2010;125(2 Suppl 2):S126; Celik G. Drug allergy. In: Adkinson NF, ed. *Middleton's Allergy: Principles and Practice.* 7th ed. St. Louis, MO: Mosby; 2008:1205; Marquardt DL et al. Anaphylaxis. In: Middleton E Jr et al., eds. *Allergy. Principles and Practices.* 4th ed. St. Louis, MO: Mosby; 1993:1365.

TABLE 3.11 Penicillin Skin Testing Procedure

Agent	Procedure	Interpretation
Penicilloyl polylysine (Pre-Pen)	Puncture (scratch) test one drop of full-strength solution ( $6 \times 10^{-5}$ mol/L) <sup>a</sup>	<i>No wheal or erythema or wheal &lt;5 mm in diameter after 15 minutes:</i> proceed with intradermal test.
Major determinant		<i>Wheal or erythema of 5–15 mm in diameter or more within 15 minutes:</i> choose alternative agent, consider desensitization if no other alternatives exist.
PPL	Intradermal test: inject sufficient volume PPL to raise an intradermal bleb of 3 mm in diameter <sup>a</sup> Saline: negative control	Read at 20 minutes. Negative response: no increase in size of original bleb and no greater than reaction at control site. Positive response: itching and increase in size of original bleb to at least 5 mm and greater than saline control: choose alternative agent; consider desensitization if no other alternatives exist.
	Histamine: positive control (optional; useful if it is suspected that patient may be anergic)	
Penicillin G potassium (>1 week old) most important of the minor determinants	Scratch test one drop of 10,000 unit/mL solution	Same as scratch test with PPL (see above).
Penicillin G potassium	Intradermal test: 0.002 mL of 10,000 unit/mL solution	Same as intradermal test with PPL (see above).
—	Serial testing with 10, 100, or 1,000 unit/mL solutions can be performed in those with strong history or serious reactions	

<sup>a</sup>PPL is administered initially as a scratch test. If no wheal or erythema develops, then intradermal testing is performed. PPL, penicilloyl polylysine.

Source: Pre-Pen benzylpenicilloyl polylysine injection solution [package insert]. Round Rock, TX: ALK-Abelló, Inc; 2010. <http://www.prepen.com/package-insert>. Accessed November 7, 2010.

- **Associated Illnesses.** Maculopapular rashes are more common in ampicillin-treated patients with Epstein-Barr virus infections, lymphocytic leukemia, or gout. The occurrence of reactions to trimethoprim-sulfamethoxazole in patients who are HIV-positive is about 10-fold higher than in HIV-negative patients. Liver or kidney disease may alter the metabolism or elimination of reactive drug metabolites, increasing the risk of allergic response.
- **Drug-Related Factors.** Frequent intermittent drug exposure, route of administration (e.g., risk of sensitization, highest to lowest: topical > subcutaneous > intramuscular > oral > intravenous), and occasionally high dose (e.g., penicillin-induced hemolytic anemia) can influence development of drug allergy.
- **Previous Drug Administration.** Previous history of allergic reaction to a drug being considered for treatment, or one that is immunochemically similar, is the most reliable risk factor for development of a subsequent allergic reaction.

## Prevention and Management of Allergic Reactions

- The first step in managing an allergic reaction is to determine its etiology. Second, a decision as to whether or not to discontinue the suspected drug should be made on the basis of the severity of the reaction, the condition being treated, and the availability of suitable alternatives.
- If suitable alternative exist, the offending agent should be discontinued and the reaction treated symptomatically.
- If it is inappropriate or not possible to change to an alternative therapy, and the sensitivity reaction is severe or life-threatening, desensitization can be considered.
- Desensitization protocols for beta-lactams are shown in Tables 3.12 and 3.13. The desensitized state, once achieved, will persist for approximately 48 hours after the last full dose of antibiotic.

TABLE 3.12  $\beta$ -Lactam Oral Desensitization Protocol

Stock Drug Concentration (mg/mL) <sup>a</sup>	Dose No.	Amount (mL)	Drug Dose (mg)	Cumulative Drug (mg)
0.5	1 <sup>b</sup>	0.05	0.025	0.025
0.5	2	0.10	0.05	0.075
0.5	3	0.20	0.10	0.175
0.5	4	0.40	0.20	0.375
0.5	5	0.80	0.40	0.775
5.0	6	0.15	0.75	1.525
5.0	7	0.30	1.50	3.025
5.0	8	0.60	3.00	6.025
5.0	9	1.20	6.00	12.025
5.0	10	2.40	12.00	24.025
50	11	0.50	25.00	49.025
50	12	1.20	60.00	109.025
50	13	2.50	125.00	234.025
50	14	5.00	250.00	484.025

<sup>a</sup>Dilutions using 250 mg/5 mL of pediatric suspension.

<sup>b</sup>Oral dose doubled approximately every 15 to 30 minutes.

Dosing for the oral protocol is arbitrary and should be adjusted for individual patients based on the clinical sensitivity and the desired drug dose end point.

Sources: Sullivan TJ et al. Desensitization of patients allergic to penicillin using orally administered beta-lactam antibiotics. *J Allergy Clin Immunol.* 1982;69:275; Wendel GD Jr et al. Penicillin allergy and desensitization in serious infections during pregnancy. *N Engl J Med.* 1985;312:1229.



TABLE 3.13  $\beta$ -Lactam Intravenous Desensitization Protocol

Stock Drug Concentration (mg/mL) <sup>a</sup>	Dose No. <sup>b</sup>	Amount per 50 mL (mg/mL) <sup>c</sup>	Cumulative Drug (mg)
0.005	1	0.0001	0.005
0.025	2	0.0005	0.030
0.125	3	0.0025	0.155
0.625	4	0.0125	0.780
3.125	5	0.0625	3.905
15.625	6	0.3125	19.530
31.25	7	0.625	50.780
62.50	8	1.25	113.280
125.00	9	2.5	238.280
250.00	10 <sup>d</sup>	5.0	488.280

<sup>a</sup>Stock drug solutions are prepared using serial dilutions of the desired goal (e.g., 500 mg of  $\beta$ -lactam). Doses 1 through 5 represent fivefold dilutions; doses 6 through 10 represent twofold dilutions.

<sup>b</sup>Interval between doses is 1 to 30 minutes. If desensitization is interrupted for  $>2$  half-lives of the  $\beta$ -lactam, desensitization should be repeated.

<sup>c</sup>Mix 1 mL of stock drug solution in 50 mL 5% dextrose/0.225 normal saline or other compatible solution. Infuse each dose for 20 to 45 minutes. Dilution volume may vary with patient age and weight.

<sup>d</sup>If all 10 doses are administered and tolerated, the remainder of a full therapeutic dose of the  $\beta$ -lactam should be administered.

Dosing for the IV protocol is arbitrary and should be adjusted for individual patients based on the clinical sensitivity and the desired drug dose end point.

Source: Borish L, Tamir R, Rosenwasser LJ. Intravenous desensitization to beta-lactam antibiotics. *J Allergy Clin Immunol.* 1987;80(3, pt 1):314.

# Managing Drug Overdoses and Poisonings\*

## General Principles

- According to the American Association of Poison Control Centers, 48.4% of the poisonings reported in 2012 occurred in Children <6 years of age.
- In most situations, it is best to help the patient contact a poison center rather than trying to care for the patient yourself. Poison centers are better prepared to obtain the necessary information, make assessments, and recommend specific treatment.
- Effective communication is essential to the assessment of potential poisonings:
  - Calm the caller by reassuring him or her that telephoning for help was appropriate.
  - Determine the age and identity of the patient and name of the caller.
  - Determine if the patient is conscious, breathing, and has a pulse. Obtain the phone number and address if it is determined that emergency personnel should be summoned, and then call 9-1-1.
- Information resources commonly used for toxicology information include *Poisonindex* (online), *Goldfrank's Toxicologic Emergency* (textbook), and *Poisoning and Drug Overdose* (handbook). Textbooks are not effective for acute situations. Poison control centers provide the most accurate information.
- Pharmacokinetic and pharmacodynamic behavior of drugs can be substantially altered by large drug overdoses, especially with drugs associated with dose-dependent pharmacokinetics.
  - Rate of drug absorption is generally slowed by large oral overdoses.
  - Time to reach peak serum drug concentrations can be prolonged with large oral overdose.
  - Volume of distribution of a drug can be increased.
  - Usual metabolic pathways can become saturated and secondary pathways can be important.
- Substances most commonly involved in poisonings are shown in Table 4.1.

## Patient Assessment

- Gather information about the history of exposure. Try to determine why the individual believes an accidental ingestion or overdose occurred, probable intoxicants, maximum amount ingested, dosage form, and when the ingestion occurred.
- Determine the condition of the patient: state of consciousness, current symptoms, prior medical problems, likely medications to treat those problems, and allergies.
- **Qualitative urine drug screens** may be useful in patients with a coma of unknown etiology, when the history is inconsistent with clinical findings, or when more than one drug was ingested.
- **Quantitative tests** of drugs in serum can be useful to determine if the concentration in the blood correlates with toxic effects. They are helpful when turnaround time for results is rapid and when treatment can be guided by serum concentration of the drug.

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\*The reader is referred to Chapter 4, Managing Drug Overdoses and Poisonings, written by Judith A. Alsop, PharmD, in the 10th edition of *Applied Therapeutics: The Clinical Use of Drugs* for a more in-depth discussion. All notations to reference numbers are based on the reference list at the end of that chapter. The editor of this handbook expresses her thanks to Dr. Alsop and acknowledges that this chapter is based on her work.

TABLE 4.1 Substances Most Commonly Involved in Poisonings<sup>a</sup>

Children	Adults	Fatal Exposures (All Ages)
Personal care products	Analgesics	Sedatives/hypnotics/antipsychotics
Analgesics	Sedatives/hypnotics/antipsychotics	Cardiovascular agents
Cleaning substances	Antidepressants	Opioids
Topical products	Cleaning substances	Acetaminophen-containing products
Vitamins	Cardiovascular agents	Antidepressants
Antihistamines	Alcohols	Acetaminophen
Cough and cold products	Bites, envenomations	Alcohols
Pesticides	Pesticides	Stimulants and street drugs
Plants	Antiepileptic agents	Muscle relaxants
GI products	Personal care products	Cyclic antidepressants
Antimicrobials	Antihistamines	Antiepileptic agents
Arts and office supplies	Hormones and hormone antagonists	Fumes/gases/vapors
Alcohols	Antimicrobials	Aspirin
Hormones and hormone antagonists	Chemicals	Nonsteroidal anti-inflammatory drugs
Cardiovascular agents	Fumes/gases/vapors	Antihistamines
	Hydrocarbons	

<sup>a</sup>Poisoning exposures are listed in order of frequency encountered.

GI, gastrointestinal.

Source: Bronstein AC et al. 2009 Annual report of the American Association of Poison Control Centers' National Poison Data System (NPDS): 27th Annual Report. *Clin Toxicol (Phila)*. 2010;48:979.

- The assessment and treatment of the potentially poisoned patient can be separated into seven functions:
  - Gather history of exposure
  - Evaluate clinical presentation
  - Evaluate clinical laboratory patient data
  - Remove the toxic source (e.g., irrigate eyes, decontaminate exposed skin)
  - Consider antidotes and specific treatment
  - Enhance systemic clearance
  - Monitor patient outcome

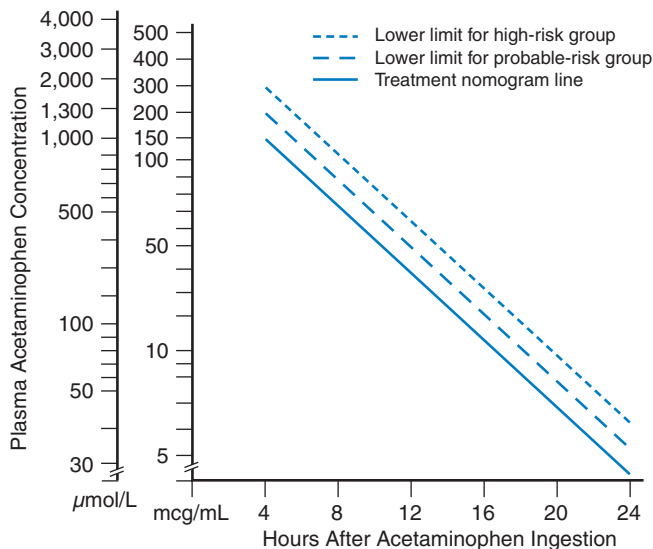
## Treatment

- Basic support of airways, breathing, and circulation (the “ABCs”) is paramount. Emergency personnel should be summoned and cardiopulmonary resuscitation (CPR) initiated while waiting for help to arrive.
- In less life-threatening situations, management often centers on symptomatic and supportive care until the substance is cleared from the body.
- Gastrointestinal (GI) decontamination should be considered after airway and cardiopulmonary systems are supported. The most appropriate method for GI tract decontamination is not defined. Efficacy varies depending on when the process is initiated relative to the time of ingestion.
  - **Lavage, emesis, and cathartics** are rarely used because there is no evidence they improve patient outcome.
  - **Activated charcoal** is generally safe but the risk:benefit should be assessed first. A dose of 1 g/kg is used when the patient has ingested a substance known to be absorbed by activated charcoal provided it is given within 1 hour of the toxin ingestion.
  - **Whole body irrigation** using polyethylene glycol-balanced electrolyte solution can successfully remove substances (iron, lithium, sustained-release dosage forms) from the entire GI tract in a period of several hours.

- Systemic clearance can be enhanced through **hemodialysis** (e.g., methanol, ethylene glycol, aspirin, theophylline, lithium) and **alkalinization of the urine** (e.g., aspirin, phenobarbital).
- **Antidotes** exist for only a small fraction of ingested substances.
  - Naloxone can displace opioids from receptor sites.
  - Flumazenil can displace benzodiazepines from receptor sites.
  - N-Acetylcysteine (NAC) can inhibit the formation of toxic acetaminophen metabolites.
  - Fomepizole can inhibit the formation of toxic methanol metabolites.

## Management of Specific Drug Overdoses

- **Acetaminophen**
  - Toxicity is associated with acute ingestions  $>150$  mg/kg or  $>7.5$  g total in adults. A nomogram for interpreting the severity of acetaminophen overdose is shown in Figure 4.1.
  - Symptoms include vomiting, anorexia, abdominal pain, malaise, and progression to characteristic centrilobular hepatic necrosis.
  - Acetaminophen-induced hepatotoxicity is universal by 36 hours after ingestion. Patients who receive NAC within 8 to 10 hours after ingestion rarely exhibit hepatotoxicity. Instituting therapy with NAC early is essential.
  - There is no consensus on the best route of NAC administration, optimal dosage regimen, or optimal duration of therapy. Regimens that have been used include:
    - **Intravenous NAC** given as 150 mg/kg loading dose, followed by a maintenance dose of 50 mg/kg for 4 hours and then 100 mg/kg for 16 hours. Oral therapy should be initiated as soon as the patient tolerates oral administration.
    - **Oral NAC** dosed as 140 mg/kg using either the 10% or 20% mucolytic solutions formulated for inhalation therapy; 17 additional maintenance doses of 70 mg/kg are administered at 4-hour intervals after the initial dose, for a total of 72 hours of therapy. Shorter oral NAC regimens (20 hours of therapy) have also been used.



**Figure 4.1** Nomogram for interpretation of severity of acetaminophen poisoning. (Adapted with permission from Smilkstein MJ et al. Efficacy of oral *N*-acetylcysteine in the treatment of acetaminophen overdose: analysis of national multicenter study (1976–1985). *N Engl J Med.* 1988;319:1557.)

- **Iron**
  - Acute elemental iron ingestions of  $<20$  mg/kg are usually nontoxic; doses of 20 to 60 mg/kg result in mild to moderate toxicity; doses  $>60$  mg/kg are potentially fatal.
  - Symptoms include nausea, vomiting, diarrhea, abdominal pain, hematemesis, bloody stools, central nervous system (CNS) depression, hypotension, and shock.
  - Activated charcoal is not indicated as it does not absorb iron. Whole bowel irrigation may be considered as a means of minimizing further absorption.
  - Chelation therapy may be needed. If serum concentrations are  $>500$  mcg/dL or  $>60$  mg/kg were ingested, start **deferoxamine** at a dose of 15 mg/kg/hour; doses up to 45 mg/kg/hour may be needed in severe poisoning. The total dose should not exceed 6 g every 24 hours.
- **Salicylates**
  - Acute ingestion of 150 to 300 mg/kg aspirin causes mild to moderate intoxication; greater than 300 mg/kg indicates severe poisoning, and  $>500$  mg/kg is potentially lethal. Chronic salicylate intoxication is usually associated with ingestion of  $>100$  mg/kg/day for  $>2$  to 3 days.
  - Symptoms of intoxication include vomiting, tinnitus, delirium, tachypnea, metabolic acidosis, respiratory alkalosis, hypokalemia, irritability, hallucinations, stupor, coma, hyperthermia, coagulopathy, and seizures.
  - Patients with chronic salicylate exposure, acidosis, or CNS symptoms and those who are elderly are high risk and should be considered for early dialysis.
  - Treatment can include use of:
    - Activated charcoal to minimize further absorption if ingestion was within an hour of treatment
    - Hypotonic saline dextrose solutions with 20 to 40 mEq/L potassium as needed for hypernatremia and hypokalemia
    - Vitamin K if prothrombin time is prolonged
    - Hemodialysis or benzodiazepines if seizures occur
- **Tricyclic Antidepressants (TCA)**
  - Severe TCA toxicity has been associated with doses of 15 to 25 mg/kg.
  - Symptoms include tachycardia with prolongation of the PR, QTc, and QRS intervals, ST and T-wave changes, acidosis, seizures, coma, hypotension, and adult respiratory distress syndrome. A QRS segment greater than 100 milliseconds is commonly seen in severe TCA overdose. CNS toxicity is common (agitation, hallucinations, coma, myoclonus, seizures).
  - Treatment can include the following:
    - Alkalinization of the serum and sodium loading by administration of IV hypertonic sodium bicarbonate, and treatments directed at reversing ventricular arrhythmias and conduction delays.
    - Benzodiazepines are the drug of choice to treat seizures.

# End-of-Life Care\*

### General Principles

- End-of-life care consists of palliative and hospice care. It is ideally introduced early in the disease progression to provide support to patients of all ages with a serious chronic or life-threatening illness. The basic principle of end-of-life care is to optimize the quality of life for the patient and family in the last months and weeks of life, as well as to provide support for the family beyond the end of life into bereavement.
- Hospice and palliative care are similar, but distinct, terms sharing the common belief that the relief of suffering is a long-standing, fully legitimate aim of medicine.
- **Palliative care**, which includes hospice care, is ideally introduced early in the disease progression. It can be provided concurrently with other treatments to cure or reduce disease, or it can be provided independently. Palliative care:
  - Affirms life and regards dying as a normal process
  - Provides relief from pain and other distressing symptoms
  - Intends neither to hasten nor to postpone death
  - Integrates the psychological and spiritual aspects of patient care
  - Offers a support system to help the patient live as actively as possible until death
  - Uses a multidisciplinary team approach to address the needs of the patient and his/her family during the patient's illness
  - Provides bereavement counseling when indicated
- **Hospice care** is both a philosophy of care and a place to deliver care. Hospice care focuses on the palliation of pain and other symptoms when active treatment to cure a terminal illness ends. Hospice care provides an interdisciplinary team approach to the individualized symptom management.
- Medicare patients who enter a hospice program agree to relinquish their regular Medicare benefits as they relate to the terminal illness and accept the palliative rather than curative approach that will be provided by hospice.

### Patient Assessment

- To qualify for hospice services under the Medicare Hospice Benefit, patients must be at a stage where death is expected within the next 6 months.
- Patients with chronic diseases (Alzheimer disease, Parkinson disease, heart failure) can be sufficiently ill and debilitated to need custodial care, but might not be sufficiently ill to meet the definition of a terminal illness.

### Goals of Therapy

- The goal of therapy in hospice care is focused on management of discomforting symptoms and improving quality of life; it does not focus on curative treatment.

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\*The reader is referred to Chapter 5, End-of-Life Care, written by Victoria F. Ferraresi, PharmD, FASHP, FCSHP, in the 10th edition of *Applied Therapeutics: The Clinical Use of Drugs* for a more in-depth discussion. All notations to reference numbers are based on the reference list at the end of that chapter. The editor of this handbook expresses her thanks to Dr. Ferraresi and acknowledges that this chapter is based on her work.

## Treatment

- Hospices are required to provide (pay for) medications related to the terminal diagnosis for the palliation of symptoms within the hospice plan of care.
- In hospice care, unnecessary medications should be discontinued and alternatives added to manage two or more symptoms concurrently.
- Patients at end of life should be regularly assessed for symptoms of pain, dyspnea, and depression, and for therapies proven to be effective for these symptoms.
- Duplicative pain medications should be replaced with one opioid. Methadone or extended-release morphine are reasonable options.
- Treatment of dyspnea at end of life is shown in Table 5.1.
- Palliative sedation has a small potential to shorten life but the need to relieve terminal agitation may justify the risk. It should only be initiated as a last resort in severe cases not responsive to other palliative measures.

## Drug Therapy

- **Anticholinergic Agents.** An anticholinergic agent (e.g., glycopyrrolate, hyoscyamine, scopolamine, atropine) can be administered in an attempt to dry pharyngeal secretions that patients have difficulty clearing as they near death. These secretions can generate sounds known as the death rattle, which caregivers/family members may find concerning.
- **Haloperidol.** Small doses (0.5–1 mg) are useful for the treatment of restlessness, delirium, or nausea and vomiting.
- **Lorazepam.** A short-acting benzodiazepine (e.g., lorazepam 0.5 mg every 4 hours as needed) is useful for the treatment of anxiety, a common symptom in patients with respiratory symptoms.
- **Pain Management**
  - **Methadone** can improve overall pain management because it has activity against neuro-pathic pain. Conversion of oral morphine to oral methadone is shown in Table 5.2.
  - **Morphine.** Every hospice cancer patient should have a short-acting opioid available for the palliation of unrelieved dyspnea and pain. Hospice patients do not usually have IV access,

TABLE 5.1 Treatment of Dyspnea at End of Life

Nonpharmacologic methods	<p>Pursed-lip breathing</p> <p>Upright position</p> <p>Relaxation</p> <p>Meditation</p> <p>Use of a fan or open window to circulate air over the face</p>
Pharmacologic therapy	<p><b>Systemic opioids (short-acting)</b> in small doses given orally, sublingually, or via injection can be given every 1–2 hours as needed.</p> <p><b>Long-acting agents</b> can be added to supplement the routine use of short-acting opioids.</p> <p><b>Inhaled opioids</b> deliver medication via nebulization directly into the airway, avoiding first-pass metabolism, allowing use of smaller doses, and theoretically minimizing side effects such as drowsiness. May cause local histamine release, leading to bronchospasm. Use nonpreservative sterile injectable products. More cumbersome and expensive owing to use of nebulizer and nonpreservative parenteral products; evidence does not show that nebulized opioids provide greater benefit than nebulized saline.</p> <p>Agents: morphine 2.5–10 mg in 2 mL of 0.9% saline; hydromorphone 0.25–1 mg in 2 mL of 0.9% saline; fentanyl 25 mcg in 2 mL of 0.9% saline</p> <p>Generally given every 2–4 hours as needed for breathlessness.</p> <p><b>Benzodiazepines</b> are useful for the anxiety associated with breathlessness.</p>

TABLE 5.2 Conversion of Oral Morphine Dose to Oral Methadone Requirement

Total Daily Baseline Oral Morphine Dose (i.e., Dose of Morphine Equivalents) (mg)	Estimated Daily Oral Methadone Requirement (as % of Total Daily Morphine Dose)
<100	20–30
100–300	10–20
300–600	8–12
600–1,000	5–10
>1,000	<5

so medications are primarily administered orally. Sublingual, buccal, transdermal, rectal, or subcutaneous routes are other alternatives. When patients lose the ability to swallow, the sublingual or buccal routes are most useful.

- **Transdermal fentanyl** should be reserved for patients who cannot take oral medication; it is generally not effective in very thin, cachectic patients.
- **Extended-release oxycodone** should only be used when the patient cannot tolerate morphine, has significant renal impairment, or has other contraindications to morphine use.
- **Prochlorperazine**. When patients cannot take oral medications to manage nausea and vomiting, rectal suppositories of prochlorperazine can be effective.



# Nausea and Vomiting\*

## General Principles

- The emetic response can be described in three phases: nausea, vomiting, and retching (rhythmic contraction of the abdominal muscles without actual emesis).
- Nausea and vomiting are caused by many disorders including, but not limited to, conditions affecting the central nervous system (increased intracranial pressure, migraine headaches, brain metastases, anxiety); infectious conditions (viral gastroenteritis, food poisoning, meningitis, urinary tract infections); metabolic conditions (hypercalcemia, uremia, hyperglycemia, hyponatremia); and gastrointestinal conditions (gastroparesis, bowel obstruction). Medications can also be a cause.
- Uncontrolled nausea and vomiting can lead to dehydration, electrolyte imbalances, malnutrition, aspiration pneumonia, and esophageal tears.

## Classification

- **Motion sickness** occurs in response to an unusual perception of real or apparent motion. Travel by boat is more likely to cause symptoms; air, car, and train travel are less likely. Acetylcholine is thought to be the primary neurotransmitter involved.
- **Chemotherapy-induced nausea and vomiting (CINV)** occurs in different phases. The acute phase occurs within hours after administration of chemotherapy. Delayed CINV symptoms peak at 2 to 3 days and can last 6 to 7 days. Breakthrough nausea and vomiting occur if the primary prophylactic antiemetics fail to work completely.
- **Radiation-induced nausea and vomiting** occurs through the same basic pathways as CINV.
- **Postoperative nausea and vomiting (PONV)** is a common complication of surgery.

## Patient Assessment

- The initial assessment should include onset of symptoms, severity and duration of symptoms, hydration status, precipitating factors, current medical conditions and medications, and food and infectious contacts.
- The etiology of nausea and vomiting should be determined so that the underlying cause can be treated.

## Risk Factors

- **Motion Sickness.** Children and adolescents
- **CINV.** Patient factors (age below 50 years, female gender, poor control of symptoms in prior cycles, history of motion sickness, nausea with pregnancy, anxiety, depression); therapy regimen factors (short infusion time, high dose, multiple chemotherapy cycles, chemotherapy drugs used)
- **Radiation-Induced Nausea and Vomiting.** Size and area to be irradiated, larger fractional doses of radiation, and whether the patient had prior chemotherapy

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\*The reader is referred to Chapter 6, Nausea and Vomiting, written by Lisa K. Lohr, PharmD, BCPS, BCOP, in the 10th edition of *Applied Therapeutics: The Clinical Use of Drugs* for a more in-depth discussion. All notations to reference numbers are based on the reference list at the end of that chapter. The editor of this handbook expresses her thanks to Dr. Lohr and acknowledges that this chapter is based on her work.

- **PONV.** Patient factors (female gender, history of motion sickness, nonsmoking status, obesity, history of PONV, young age); surgical factors (long duration of surgery, type of surgical procedure); anesthetic factors (use of volatile anesthetics or nitrous oxide, intraoperative or postoperative opioid use)

## Goals of Therapy

- Antiemetic efficacy, or complete emetic response, for CINV is defined as no emesis and no nausea or only mild nausea in the first 24 hours after chemotherapy administration.

## Treatment

- Supportive treatment should be initiated, if needed, including fluid and electrolyte replacement.
- **Motion Sickness**
  - Nonpharmacologic measures or natural remedies may be useful to reduce symptoms (e.g., riding in middle of boat, lying in semirecumbent position, etc.).
  - Medications for the prevention or treatment of motion sickness in adults are shown in Table 6.1. Anticholinergic agents and antihistamines that cross the blood–brain barrier

TABLE 6.1 Medications for Prevention or Treatment of Motion Sickness in Adults

Medication (Trade Name)	Dosage	Recommended Use	Adverse Effects
Scopolamine (Transderm-Scop)	1.5 mg TOP behind the ear every 3 days. Apply at least 3 hours (preferably 6–8 hours) before exposure.	Long-term exposure (>6 hours) to moderate to intense stimulus. Alternative treatment for shorter or milder stimulus	Dry mouth, drowsiness, blurred vision, confusion, fatigue, ataxia
Dimenhydrinate (Dramamine)	50–100 mg PO every 4–6 hours (max 400 mg/day). May be taken PRN or on scheduled basis if required.	Short- or long-term exposure to mild to moderate stimulus. Alternative for intense stimulus	Drowsiness, dry mouth, thickening of secretions, dizziness
Promethazine (Phenergan)	25 mg PO every 4–6 hours. May be taken PRN or on scheduled basis if required. 25–50 mg IM every 4–6 hours for established severe symptoms. May be taken PRN or on scheduled basis if required.	In combination with dextroamphetamine for short exposure to intense stimulus. Alternative for longer or milder stimulus	Drowsiness, orthostatic hypotension, dry mouth
Meclizine (Antivert, Bonine)	12.5–50 mg PO every 6–24 hours. May be taken PRN or on scheduled basis if required.	Alternative for mild stimulus or in combination for moderate to severe stimulus	Drowsiness, dry mouth, thickening of secretions, dizziness
Dextroamphetamine (Dexedrine)	5–10 mg PO every 4–6 hours. May be taken PRN or on scheduled basis if required.	In combination with promethazine for short exposure of intense stimulus	Restlessness, abuse potential, insomnia, overstimulation, tachycardia, palpitations, hypertension
Cyclizine (Marezine)	50 mg PO every 4–6 hours (max 200 mg/day). May be taken PRN or on scheduled basis if required.	Alternative for mild stimulus situations	Drowsiness, dry mouth

IM, intramuscular; PO, oral; PRN, as needed; TOP, topically.

Sources: Priesol AJ. Motion sickness. *UpToDate*. [http://www.uptodate.com/contents/motion-sickness?source=search\\_result&selectedTitle=1%7E51](http://www.uptodate.com/contents/motion-sickness?source=search_result&selectedTitle=1%7E51). Accessed September 27, 2010; Shupak A, Gordon CR. Motion sickness: advances in pathogenesis, prediction, prevention, and treatment. *Aviat Space Environ Med*. 2006;77:1213.

effectively prevent and treat motion sickness. Serotonin (5-HT<sub>3</sub>) and neurokinin (NK1) receptor antagonists have not been shown to be effective. Nonsedating antihistamines are not as effective as other antihistamines because they do not sufficiently cross the blood–brain barrier.

- Transdermal scopolamine is recommended for prophylaxis of motion sickness for moderate to severe stimuli.
- Dimenhydrinate or promethazine are recommended for treatment of breakthrough symptoms.
- **CINV**
  - Nonpharmacologic measures can include guided imagery, hypnosis, relaxation techniques, systematic desensitization, and music therapy.
  - Appropriate antiemetic therapy is based on the emetogenicity of the chemotherapy regimen (Table 6.2) and patient risk factors.
  - Combinations of antiemetics from different therapeutic classes will be more effective in most situations.
  - Antiemetic agents for CINV are shown in Table 6.3. The predominant classes of antiemetics used for CINV are serotonin (5-HT<sub>3</sub>) antagonists, neurokinin (NK1) antagonists, and corticosteroids. Other drug classes remain useful for breakthrough symptoms or for patients who are refractory to standard therapy.

**TABLE 6.2 Emetogenicity of Selected Antineoplastic Agents by Dose and Route of Administration**

Chemotherapy Agent	Injectable Administration	Oral Administration
Aldesleukin (Proleukin)	>12–15 million units/m <sup>2</sup> = Moderate ≤12 million units/m <sup>2</sup> = Low	
Alemtuzumab (Campath)	Minimal	
Altretamine (Hexalen)		High
Arsenic trioxide (Trisenox)	Moderate	
Asparaginase (Elspar)	Minimal	
Azacitidine (Vidaza)	Moderate	
Bendamustine (Treanda)	Moderate	
Bevacizumab (Avastin)	Minimal	
Bexarotene (Targretin)		Low
Bleomycin (Blenoxane)	Minimal	
Bortezomib (Velcade)	Low	
Busulfan (Busulfex, Myleran)	Moderate	≥4 mg = Moderate <4 mg = Minimal
Cabazitaxel (Javtana)	Moderate	
Capecitabine (Xeloda)		Low
Carboplatin (Paraplatin)	Moderate with high risk of delayed CINV	
Carmustine (BiCNU)	>250 mg/m <sup>2</sup> = High ≤250 mg/m <sup>2</sup> = Moderate	
Chlorambucil (Leukeran)		Minimal
Cetuximab (Erbix)	Minimal	
Cisplatin (Platinol)	≥50 mg/m <sup>2</sup> = High <50 mg/m <sup>2</sup> = Moderate High risk of delayed CINV	
Cladribine (Leustatin)	Minimal	
Clofarabine (Clolar)	Moderate	
Cyclophosphamide (Cytoxan)	>1,500 mg/m <sup>2</sup> = High ≤1,500 mg/m <sup>2</sup> = Moderate High risk of delayed CINV	≥100 mg/m <sup>2</sup> /day = Moderate <100 mg/m <sup>2</sup> /day = Low

**TABLE 6.2 Emetogenicity of Selected Antineoplastic Agents by Dose and Route of Administration (Continued)**

Chemotherapy Agent	Injectable Administration	Oral Administration
Cytarabine (Ara-C, Cytosar-U)	>200 mg/m <sup>2</sup> = Moderate 100–200 mg/m <sup>2</sup> = Low <100 mg/m <sup>2</sup> = Minimal	
Dacarbazine (DTIC)	High	
Dactinomycin (Cosmegen)	Moderate	
Dasatinib (Sprycel)		Minimal
Daunorubicin (Cerubidine)	Moderate	
Decitabine (Dacogen)	Minimal	
Docetaxel (Taxotere)	Low	
Doxorubicin (Adriamycin)	Moderate High risk of delayed CINV	
Doxorubicin liposomal (Doxil)	Moderate	
Epirubicin (Ellence)	Moderate High risk of delayed CINV	
Erlotinib (Tarceva)		Minimal
Etoposide (VePesid)	Low	Moderate
Everolimus (Afinitor)		Minimal
Fludarabine (Fludara)	Minimal	Low
Fluorouracil (Adrucil)	Low	
Gefitinib (Iressa)		Minimal
Gemcitabine (Gemzar)	Low	
Hydroxyurea (Hydrea)		Minimal
Idarubicin (Idamycin)	Moderate High risk of delayed CINV	
Ifosfamide (Ifex)	Moderate	
Imatinib (Gleevec)		Moderate
Interferon $\alpha$ -2b (Intron A)	$\geq 10$ million units/m <sup>2</sup> = Moderate <10 million units/m <sup>2</sup> = Low	
Irinotecan (Camptosar)	Moderate Some risk of delayed CINV	
Ixabepilone (Ixempra)	Low	
Lapatinib (Tykerb)		Low
Lenalidomide (Revlimid)		Minimal
Lomustine (CeeNU)		Moderate
Mechlorethamine (Mustargen)	High	
Melphalan (Alkeran)	Moderate	Minimal
Mercaptopurine (Purinethol)		Minimal
Methotrexate (Trexall)	$\geq 250$ mg/m <sup>2</sup> = Moderate 50–249 mg/m <sup>2</sup> = Low <50 mg/m <sup>2</sup> = Minimal Some risk of delayed CINV	Minimal
Mitomycin (Mutamycin)	Low	
Mitoxantrone (Novantrone)	Low	
Nelarabine (Arranon)	Minimal	
Nilotinib (Tasigna)		Low
Oxaliplatin (Eloxatin)	Moderate	
Paclitaxel (Taxol)	Low	
Paclitaxel Protein Bound (Abraxane)	Low	
Panitumumab (Vectibix)	Minimal	
Pazopanib (Votrient)		Low
Pegasparginase (Oncaspar)	Minimal	
Pemetrexed (Alimta)	Low	
Pentostatin (Nipent)	Low	

*Continued on following page*

**TABLE 6.2 Emetogenicity of Selected Antineoplastic Agents by Dose and Route of Administration (Continued)**

Chemotherapy Agent	Injectable Administration	Oral Administration
Pralatrexate (Foloty <sup>n</sup> )	Moderate	
Procarbazine (Matulane)		High
Rituximab (Rituxan)	Minimal	
Romidepsin (Istodax)	Low	
Sorafenib (Nexavar)		Minimal
Streptozocin (Zanosar)	High	
Sunitinib (Sutent)		Minimal
Temozolamide (Temodar)	Moderate	>75 mg/m <sup>2</sup> /day = Moderate ≤75 mg/m <sup>2</sup> /day = Low
Temsirolimus (Torisel)	Minimal	
Teniposide (Vumon)	Low	
Thalidomide (Thalomid)		Minimal
Thioguanine (Tabloid)		Minimal
Thiotepa (Thiotepa)	Low	
Topotecan (Hycamptin)	Moderate	Low
Trastuzumab (Herceptin)	Minimal	
Tretinoin (Vesano <sup>id</sup> )		Low
Vinblastine (Velban)	Minimal	
Vincristine (Oncovin)	Minimal	
Vinorelbine (Navelbine)	Minimal	
Vorinostat (Zolinza)		Low

High, >90% (of patients would experience chemotherapy-induced nausea and vomiting [CINV] without antiemetic premedication); Moderate, 30% to 90%; Low, 10% to 30%; Minimal, <10%.

Sources: Ettinger DS et al. Antiemesis: clinical practice guidelines in oncology. V2.2010. [http://www.nccn.org/professionals/physician\\_gls/pdf/antiemesis.pdf](http://www.nccn.org/professionals/physician_gls/pdf/antiemesis.pdf). Accessed September 30, 2010; Grunberg SM et al. Evaluation of new antiemetic agents and definition of antineoplastic agent emetogenicity—an update. *Support Care Cancer*. 2005;13:80; American Society of Clinical Oncology et al. American Society of Clinical Oncology guideline for antiemetics in oncology: update 2006 [published correction appears in *J Clin Oncol*. 2006;24:5341]. *J Clin Oncol*. 2006;24:2932; Roila F et al. Guideline update for MASCC and ESMO in the prevention of chemotherapy- and radiotherapy-induced nausea and vomiting: results of the Perugia consensus conference. *Ann Oncol*. 2010;21(Suppl 5):v232.

**TABLE 6.3 Antiemetic Agents for Chemotherapy-Induced Nausea and Vomiting (CINV)**

Medication (Trade Name)	Class	Indication	Dose in Adults (Doses Should Be Given 30–60 Minutes before Chemotherapy)
Aprepitant (Emend)	NK1 antagonist	Acute and delayed	PO: 125 mg on day 1, 80 mg on days 2 and 3
Dexamethasone (Decadron)	Corticosteroid	Acute (high emetogenicity) Acute (moderate emetogenicity) Acute (low emetogenicity) Delayed	PO/IV: 12 mg (with aprepitant) or 20 mg (without aprepitant) PO/IV: 8–12 mg PO/IV: 4–8 mg PO/IV: 8 mg daily days 2–4 or days 2 and 3 or PO: 4 mg BID days 2–4
Dolasetron (Anzemet)	5-HT <sub>3</sub> antagonist	Acute	PO: 100–200 mg
Dronabinol (Marinol)	Cannabinoid	Breakthrough	PO: 2.5–10 mg PO TID to QID
Droperidol (Inapsine)	Butyrophenone	Breakthrough	IV: 0.625–1.25 mg every 4–6 hours PRN
Fosaprepitant (Emend)	NK1 antagonist	Acute	IV: 150 mg × 1 dose or 115 mg initial dose (followed by aprepitant 80 mg PO on days 2 and 3)

**TABLE 6.3 Antiemetic Agents for Chemotherapy-Induced Nausea and Vomiting (CINV) (Continued)**

Medication (Trade Name)	Class	Indication	Dose in Adults (Doses Should Be Given 30–60 Minutes before Chemotherapy)
Granisetron (Kytrel)	5-HT <sub>3</sub> antagonist	Acute	IV: 1 mg or 0.01 mg/kg PO: 2 mg TOP: 3.1 mg/24-hours patch applied 24–48 hours before chemotherapy and kept on until 24 hours after chemotherapy or up to 7 days
Haloperidol (Haldol)	Butyrophenone	Breakthrough	PO/IV/IM: 0.5–1 mg every 6 hours PRN
Metoclopramide (Reglan)	Dopamine antagonist	Breakthrough	PO/IV: 10–40 mg every 6 hours PRN
Lorazepam (Ativan)	Benzodiazepine	Breakthrough	PO/IV/IM/SL: 0.5–2 mg every 6 hours PRN
Nabilone (Cesamet)	Cannabinoid	Refractory symptoms	PO: 1–2 mg BID (max 2 mg TID)
Olanzapine (Zyprexa)	Serotonin/dopamine antagonist	Acute/delayed/breakthrough	PO: 2.5–10 mg QHS or 2.5 mg BID or 2.5 mg TID plus 5 mg QHS
Ondansetron (Zofran)	5-HT <sub>3</sub> antagonist	Acute (moderate or high emetogenicity) Delayed	IV: 8–12 mg or 0.15 mg/kg PO: 16–24 mg 8 mg PO BID or 8 mg IV daily
Palonosetron (Aloxi)	5-HT <sub>3</sub> antagonist	Acute/delayed	IV: 0.25 mg PO: 0.5 mg
Prochlorperazine (Compazine)	Dopamine antagonist	Breakthrough Acute	PO/IV/IM: 5–10 mg (up to 20 mg) every 4–6 hours PRN or PR: 25 mg every 12 hours PRN PO/IV: 10 mg
Promethazine (Phenergan)	Dopamine antagonist	Breakthrough	PO/IV/IM/PR: 12.5–25 mg every 4–6 hours PRN

BID, twice daily; IM, intramuscular; IV, intravenous; NK1, neurokinin 1; PO, oral; PR rectal; PRN, as needed; QHS, at bedtime; QID, four times daily; TID, three times daily.

Sources: Ettinger DS et al. *Antiemesis: clinical practice guidelines in oncology*. V2.2010. [http://www.nccn.org/professionals/physician\\_gls/pdf/antiemesis.pdf](http://www.nccn.org/professionals/physician_gls/pdf/antiemesis.pdf). Accessed September 30, 2010; American Society of Clinical Oncology et al. American Society of Clinical Oncology guideline for antiemetics in oncology: update 2006 [published correction appears in *J Clin Oncol*. 2006;24:5341]. *J Clin Oncol*. 2006;24:2932; Roila F et al. Guideline update for MASCC and ESMO in the prevention of chemotherapy- and radiotherapy-induced nausea and vomiting: results of the Perugia consensus conference. *Ann Oncol*. 2010;21(Suppl 5):v232.

- Recommended antiemetic regimens for CINV by emetogenicity of chemotherapy regimen (Table 6.4) and algorithms for selection of treatment (Figures 6.1 and 6.2) can help guide therapy.
- **Radiation-Induced Nausea and Vomiting**
  - Symptoms can be prevented with 5-HT<sub>3</sub> antagonists, corticosteroids, or both (Table 6.5).
- **PONV**
  - Optimal prophylactic regimen matches medication choice with patient risk level. Patients with no risk factors usually will not need prophylaxis. Patients with moderate risk (two to three risk factors) should receive one or two agents. Patient with the highest risk (at least four risk factors) should receive a combination of two to three agents.
  - Medications for the prevention and treatment of PONV are shown in Table 6.6.

**TABLE 6.4 Recommended Antiemetic Regimens for Chemotherapy-Induced Nausea and Vomiting (CINV) by Emetogenicity of Chemotherapy Regimen**

Emetogenicity Potential	Acute-Phase CINV (Doses Should Be Given 30–60 Minutes before Chemotherapy)	Delayed-Phase CINV	Breakthrough CINV
High-risk IV chemotherapy regimens	Day 1: single-dose 5-HT <sub>3</sub> antagonist + dexamethasone + aprepitant/fosaprepitant	Dexamethasone days 2–4 + aprepitant days 2 and 3 (not needed if fosaprepitant 150-mg dose was used)	Two agents for PRN use
Moderate-risk IV chemotherapy regimens with high risk of delayed CINV	Day 1: single-dose 5-HT <sub>3</sub> antagonist + aprepitant/fosaprepitant	Dexamethasone days 2 and 3 + aprepitant days 2 and 3 <sup>a</sup>	Two agents for PRN use
Other moderate-risk IV chemotherapy regimens	Day 1: single-dose 5-HT <sub>3</sub> antagonist + dexamethasone	None	One agent for PRN use
Low-risk IV chemotherapy regimens	Single-dose dexamethasone or metoclopramide or prochlorperazine	None	Either none or one agent for PRN use
Minimal-risk IV chemotherapy regimens	None	None	Usually none
High-moderate-risk PO chemotherapy regimens	5-HT <sub>3</sub> antagonist	None	One agent for PRN use
Low-risk PO chemotherapy regimens	None	None	One agent for PRN use

<sup>a</sup>NCCN guidelines also include as options dexamethasone alone days 2 and 3 or ondansetron/granisetron/dolasetron days 2 and 3 of chemotherapy.

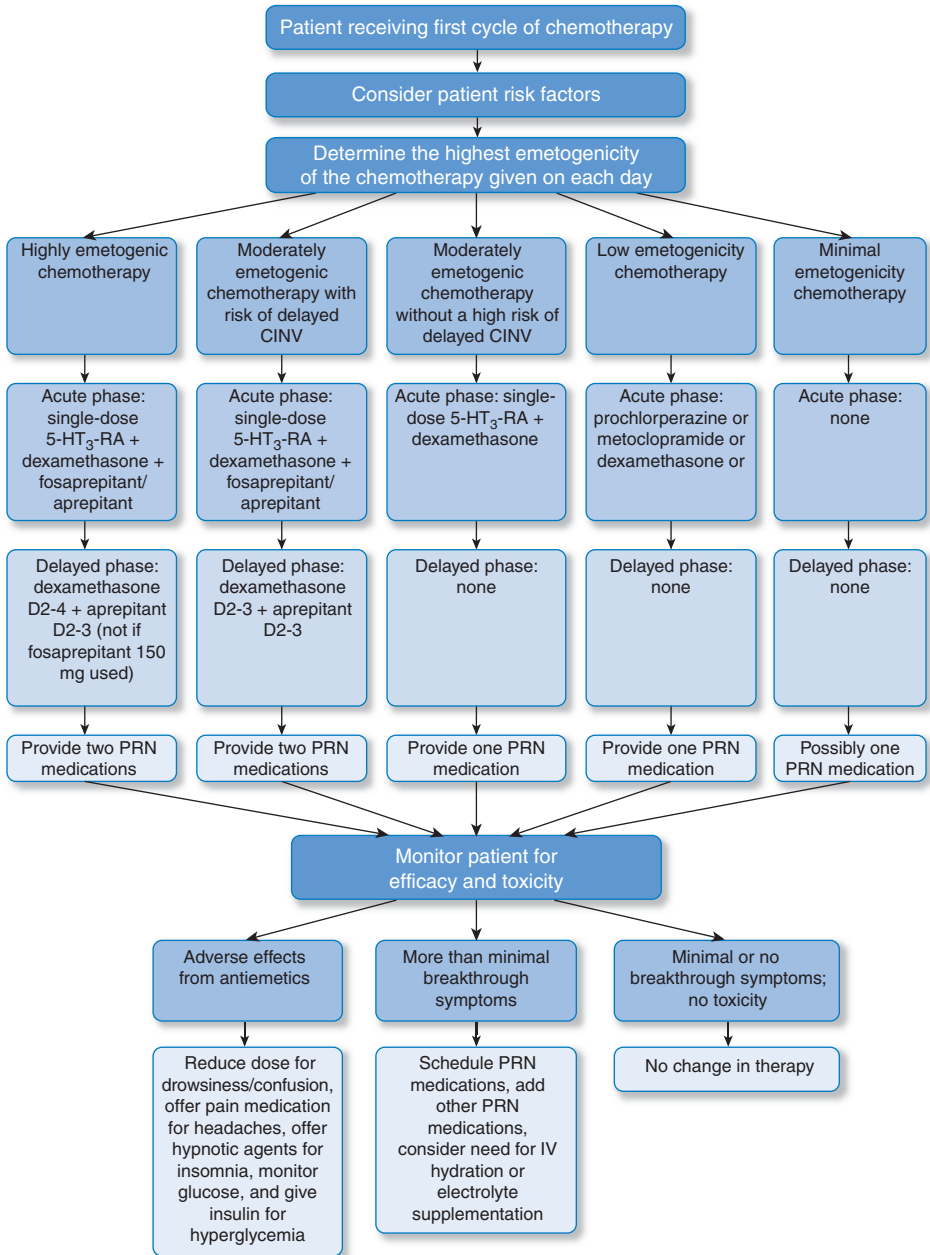
5-HT<sub>3</sub>, serotonin; CINV, chemotherapy-induced nausea and vomiting; PRN, as needed.

Sources: Ettinger DS et al. *Antiemesis: clinical practice guidelines in oncology*. V2.2010. [http://www.nccn.org/professionals/physician\\_gls/pdf/antiemesis.pdf](http://www.nccn.org/professionals/physician_gls/pdf/antiemesis.pdf). Accessed September 30, 2010; American Society of Clinical Oncology et al. American Society of Clinical Oncology guideline for antiemetics in oncology: update 2006 [published correction appears in *J Clin Oncol*. 2006;24:5341]. *J Clin Oncol*. 2006;24:2932; Roila F et al. Guideline update for MASCC and ESMO in the prevention of chemotherapy- and radiotherapy-induced nausea and vomiting: results of the Perugia consensus conference. *Ann Oncol*. 2010;21(Suppl 5):v232.

**TABLE 6.5 Prophylaxis for Radiation-Induced Nausea and Vomiting (RINV) for Adults**

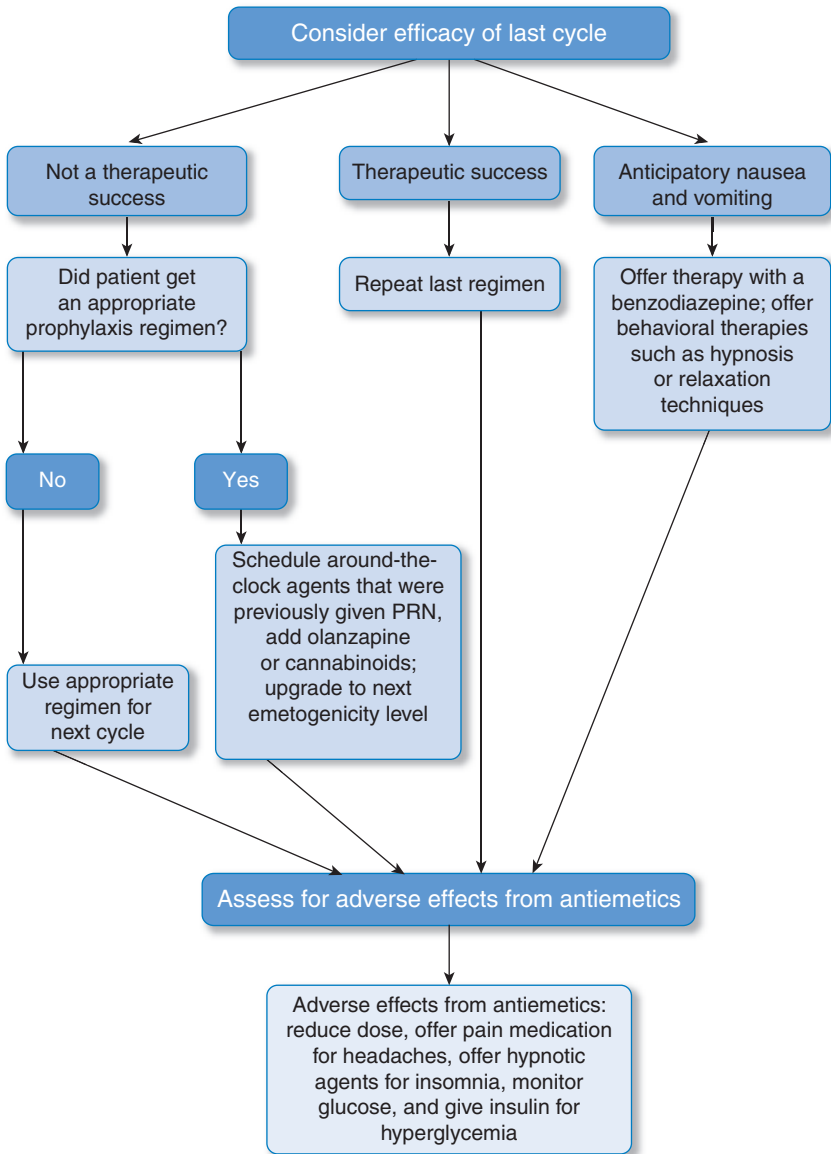
Emetic Risk	Radiation Area	Recommendation
High risk	Total body irradiation	Prophylaxis with a 5-HT <sub>3</sub> antagonist (e.g., ondansetron 8 mg PO BID–TID or granisetron 2 mg PO daily + dexamethasone 2 mg PO TID)
Moderate risk	Upper abdomen	Prophylaxis with a 5-HT <sub>3</sub> antagonist (e.g., ondansetron 8 mg PO BID or granisetron 2 mg PO daily) ± dexamethasone 4 mg PO daily
Low risk	Lower thorax, pelvis, cranium, craniospinal region, head/neck	Prophylaxis or rescue with a 5-HT <sub>3</sub> antagonist
Minimal risk	Extremities, breast	Rescue with a dopamine antagonist or a 5-HT <sub>3</sub> antagonist

Sources: Ettinger DS et al. *Antiemesis: clinical practice guidelines in oncology*. V2.2010. [http://www.nccn.org/professionals/physician\\_gls/pdf/antiemesis.pdf](http://www.nccn.org/professionals/physician_gls/pdf/antiemesis.pdf). Accessed September 30, 2010; Grunberg SM et al. Evaluation of new antiemetic agents and definition of antineoplastic agent emetogenicity—an update. *Support Care Cancer*. 2005;13:80; Roila F et al. Guideline update for MASCC and ESMO in the prevention of chemotherapy- and radiotherapy-induced nausea and vomiting: results of the Perugia consensus conference. *Ann Oncol*. 2010;21(Suppl 5):v232; Feyer P et al. Radiotherapy-induced nausea and vomiting (RINV): MASCC/ESMO guideline for antiemetics in radiotherapy: update 2009. *Support Care Cancer*. 2010 Aug 10 [Epub ahead of print]; Abdelsayed GG. Management of radiation-induced nausea and vomiting. *Exp Hematol*. 2007;35(4 Suppl 1):34; Urba S. Radiation-induced nausea and vomiting. *J Natl Compr Canc Netw*. 2007;5:60.



**Figure 6.1** Algorithm for antiemetic selection for an initial chemotherapy cycle. CINV, chemotherapy-induced nausea and vomiting; D, days; 5-HT<sub>3</sub>-RA, serotonin type 3 receptor antagonist; PRN, as needed.





**Figure 6.2** Algorithm for selection of antiemetic regimens for subsequent chemotherapy cycles. PRN, as needed.

**TABLE 6.6 Medications for Prevention and Treatment of Postoperative Nausea and Vomiting (PONV) in Adults**

Medication	Prophylactic Dose	Treatment or Rescue Dose
Aprepitant	40 mg PO within 3 hours before induction of anesthesia	None
Dexamethasone	4–10 mg at the start of induction of anesthesia	2–4 mg IV
Dolasetron	12.5 mg IV at end of surgery	12.5 mg IV
Droperidol	0.625–1.25 mg IV at end of surgery	0.625–1.25 mg IV or IM every 4–6 hours
Metoclopramide	10–20 mg IV at end of surgery	10–20 mg IV or IM every 6 hours
Granisetron	0.35–1 mg IV at end of surgery	0.1 mg
Ondansetron	4–8 mg IV at end of surgery	1 mg IV every 8 hours
Palonosetron	0.075 mg IV immediately prior to induction of anesthesia	None
Prochlorperazine	5–10 mg IV at end of surgery	5–10 mg IV or IM every 4–6 hours
Promethazine	12.5–25 mg IV at induction or end of surgery	12.5–25 mg IV or IM every 4–6 hours
Scopolamine	1.5 mg TOP evening before surgery or at least 4 hours before end of surgery	

IM, intramuscular; IV, intravenous; PO, oral; TOP, topical.

Sources: Gan TJ et al. Consensus guidelines for managing postoperative nausea and vomiting. *Anesth Analg.* 2003;97:62; Golembiewski J et al. Prevention and treatment of postoperative nausea and vomiting. *Am J Health Syst Pharm.* 2005;62:1247; Kloth D. New pharmacologic findings for the treatment of PONV and PDNV. *Am J Health Syst Pharm.* 2009;66(1 Suppl 1):S11; Ignoffo RJ. Current research on PONV/PDNV: practical implications for today's pharmacist. *Am J Health Syst Pharm.* 2009;66(1 Suppl 1):S19; Kovac AL. Prevention and treatment of postoperative nausea and vomiting. *Drugs.* 2000;59:213; Gan TJ et al. Society for Ambulatory Anesthesia guidelines for the management of postoperative nausea and vomiting. *Anesth Analg.* 2007;105:1615; Wilhelm SM et al. Prevention of postoperative nausea and vomiting. *Ann Pharmacother.* 2007;41:68; Golembiewski J, Tokumaru S. Pharmacological prophylaxis and management of adult postoperative/postdischarge nausea and vomiting. *J Perianesth Nurs.* 2006;21:385.

# Pain Management\*

### General Principles

- Pain is a reactionary response to real or potential bodily harm. It cannot be measured objectively.
- Pain affects more than 25% of Americans above 20 years of age. A person's perception of pain is affected by environmental, emotional, cultural, spiritual, and cognitive factors.
- Between 30% and 54% of patients with chronic pain present with symptoms of depression.

### Classification

- **Syndromes:** patient presents with a constellation of symptoms that cannot be attributed to any definitive diagnosis or disease process.
- **Acute Pain:** caused by an injury or illness. It alerts the patient to withdraw from the noxious stimulus.
- **Chronic Pain:** characterized by persistent pain that lasts beyond the length of the illness or healing of an injury. Chronic pain can be further classified into:
  - **Musculoskeletal or Inflammatory Pain:** constant, aching pain
  - **Neuropathic Pain:** tingling, sharp, shooting, stabbing, burning feelings. It may be constant or intermittent.
- **Visceral Pain:** can have a vague presentation as the enteric and autonomic nervous systems are involved.
- **Dysfunctional Pain:** pain in the absence of physiologic tissue damage with the perception of pain being very real (e.g., irritable bowel syndrome, fibromyalgia, interstitial cystitis).

### Patient Assessment

- Pain is very subjective and difficult to quantify. A thorough history is essential (Table 7.1).
- Pain intensity should be measured using an appropriate pain scale according to the patient's ability to communicate. The 0 to 10 Numeric Rating Scale (NRS) has been validated across age groups. The pain thermometer has both the NRS and faces pain scale (Figure 7.1). The most useful assessment is patient information about how much time they spend on hobbies and how well they perform activities of daily living.

### Risk Factors

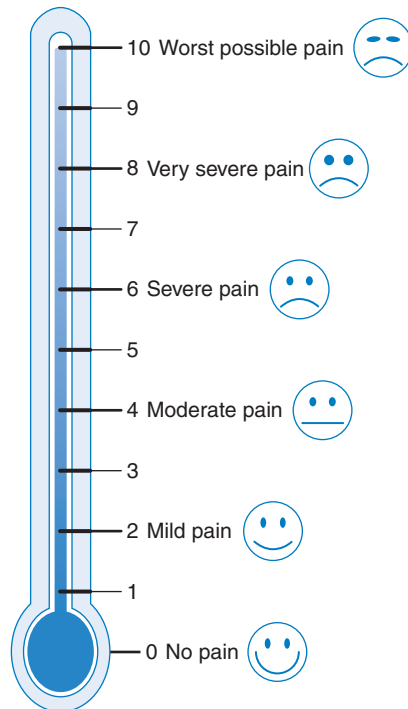
- Factors that increase pain and suffering are shown in Figure 7.2.
- Risk factors for developing chronic pain are individual predisposition (e.g., female gender, increasing age, genetic predisposition), environmental factors (e.g., previous pain experiences), and psychological factors (e.g., anxiety, depression).

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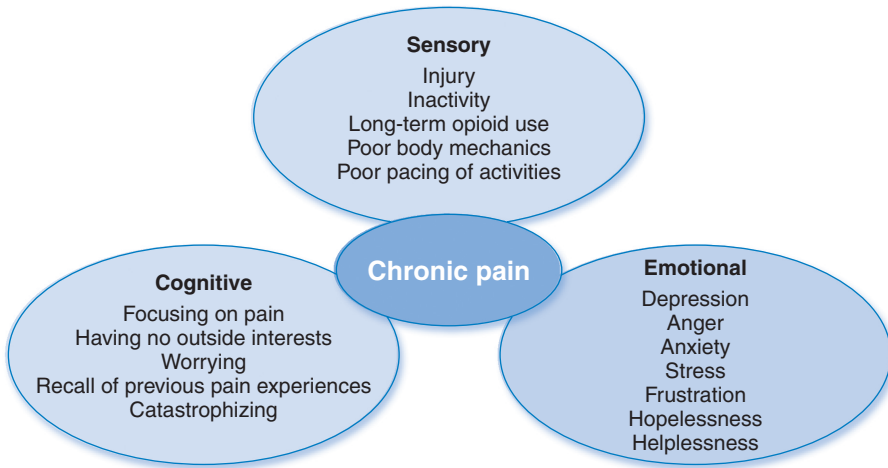
\*The reader is referred to Chapter 7, Pain and Its Management, written by Lee A. Kral, PharmD, BCPS, and Virginia L. Ghafoor, PharmD in the 10th edition of *Applied Therapeutics: The Clinical Use of Drugs* for a more in-depth discussion. All notations to reference numbers are based on the reference list at the end of that chapter. The editor of this handbook expresses her thanks to Drs. Kral and Ghafoor and acknowledges that this chapter is based on their work.

TABLE 7.1 Patient Evaluation

General history	Chief complaint History of present illness (HPI) Past medical history (PMH) Family history Social history Current medications, including allergies
Pain history	Onset Duration Quality Intensity Ameliorating factors Exacerbating factors Pain rating, if possible
Analgesic history	Current analgesics Dose/route Duration of use Effectiveness Adverse effects Past analgesics Dose/route Effectiveness Duration of use Adverse effects
Clinical examination	Clinician observations of patient behavior (grimacing, withdrawing, guarding) Physical examination Functional assessment



**Figure 7.1** Pain assessment scale. (Adapted from Northeast Health Care Quality Foundation (NHCQF), the Medicare Quality Improvement Organization (QIO) for Maine, New Hampshire and Vermont, under contract with the Centers for Medicare & Medicaid Services (CMS), an agency of the U.S. Department of Health and Human Services.)



**Figure 7.2** Factors affecting chronic pain.

## Treatment Overview

- Treatment is often based on type of pain. Multimodal therapy including pharmacologic, physical rehabilitation, and cognitive behavioral therapy should be combined.
- A treatment plan should always evaluate age, comorbidities, route of administration, concurrent medications, laboratory abnormalities, and financial resources.
- **Acute pain** is usually managed with nonsteroidal anti-inflammatory drugs (NSAIDs), acetaminophen, or opioids.
- **Musculoskeletal pain** usually responds to acetaminophen, salicylates, or NSAIDs. Opioids are useful in the acute setting but less helpful in the chronic setting.
- **Neuropathic Pain:** first-line agents are antidepressants (e.g., serotonin and norepinephrine reuptake inhibitors, tricyclic antidepressants [TCA]) and anticonvulsants (e.g., sodium or calcium channel blockers, GABA agonists).
- **Localized pain** can be managed with topical agents (e.g., capsaicin, local anesthetics).
- **Visceral Pain:** antidepressants or opioids are most commonly used. No clear treatment guidelines exist.
- Addition of tramadol, tapentadol, or opioids may be considered if first-line therapies are inadequate.
- Trials of any pharmacologic therapy must be monitored for efficacy and toxicity. Even the most effective agents are expected to achieve only about 30% to 50% improvement in chronic pain. Assessment should include the “4 A’s”: analgesia, activities of daily living, adverse effects, and potential aberrant drug-related behavior.
- Several analgesic options are available for patients who are unable to tolerate or ingest solid oral dosage forms (Table 7.2).
- **Chronic Opioid Therapy**
  - Definitions of terms associated with opioid use are in Table 7.3.
  - Opioid use behaviors are stratified on the basis of risk of aberrant drug use (Table 7.4).
  - Written agreements (contracts) between the clinician and patient can be used when initiating chronic opioid therapy. The contract should include the goals of therapy, how the medications will be prescribed/taken, expectations for follow-up and monitoring, expectations regarding use of concomitant medications, and potential for weaning and discontinuing therapy.

TABLE 7.2 Analgesics for Patients Who Cannot Take Solid Oral Dosage Forms

**ORAL LIQUIDS**

Acetaminophen (elixir, liquid, solution, suspension, syrup)  
 Ibuprofen (suspension)  
 Naproxen (suspension)  
 Gabapentin (solution)  
 Carbamazepine (suspension)  
 Oxcarbazepine (suspension)  
 Nortriptyline (solution)  
 Oxycodone (solution)  
 Hydrocodone/acetaminophen (elixir, solution)  
 Morphine (solution)  
 Methadone (solution)

**OTHER ORAL PRODUCTS**

Lamotrigine (disintegrating tablet)  
 Fentanyl (mucous membrane lozenge, buccal tablet, buccal film)

**RECTAL SUPPOSITORIES**

Acetaminophen  
 Indomethacin  
 Hydromorphone  
 Morphine

**TOPICALS**

Diclofenac (gel)  
 Capsaicin (cream)  
 Local anesthetics (ointment, gel, cream)

**TRANSDERMAL PATCHES**

Diclofenac  
 Lidocaine  
 Capsaicin  
 Methyl salicylate  
 Fentanyl

TABLE 7.3 Terms Related to Opioid Use

Term	Definition
Abuse	Any use of an illegal drug, or the intentional self-administration of a medication for a nonmedical purpose such as altering one's state of consciousness (e.g., getting high).
Addiction	A primary, chronic, neurobiological disease with genetic, psychosocial, and environmental factors influencing its development and manifestations. It is characterized by behaviors that include one or more of the following: impaired control over drug use, compulsive use, continued use despite harm, and craving.
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, or administration of an antagonist.
Pseudoaddiction	Condition characterized by behaviors that outwardly mimic addiction but are in fact driven by a desire for pain relief (e.g., constantly watching the clock to dose medication "on time" so pain does not become severe). <sup>127</sup>
Tolerance	A state of adaptation in which exposure to a drug induces changes that result in a diminution of one or more opioid effects with time.

TABLE 7.4 Opioid Use Risk Stratification

More Suggestive of Addiction	Less Suggestive of Addiction
Concurrent abuse of alcohol or illicit drugs	Aggressive complaining about the need for more drugs
Evidence of a deterioration in the ability to function at work, in the family, or socially that appears to be related to drug use	Drug hoarding during periods of reduced symptoms
Injecting oral formulations	Openly acquiring similar drugs from other medical sources
Multiple dose escalations or other nonadherence with therapy despite warnings	Requesting specific drugs
Obtaining prescription drugs from nonmedical sources	Reporting psychic effects not intended by the physician
Prescription drug forgery	Resistance to a change in therapy associated with tolerable adverse effects accompanied by expression of anxiety related to the return of severe symptoms
Repeated resistance to changes in therapy despite clear evidence of physical or psychological effects	Unapproved use of the drug to treat another symptom
Repeatedly seeking prescriptions from other physicians or emergency departments	Unsanctioned dose escalation or other nonadherence with therapy on one or two occasions
Selling prescription drugs	
Stealing or borrowing drugs from others	

- Guidelines recommend that clinicians wean patients from chronic opioids if they have repeated aberrant drug-related behaviors, experience no progress in meeting therapeutic goals, or experience intolerable side effects. Duration of therapy should be considered when weaning. Approaches have ranged from a slow 10% dose reduction per week to a more rapid 25% reduction every few days.
- Equianalgesic opioid dosing is shown in Table 7.5.
- Transdermal fentanyl patches are intended for opioid-tolerant patients with chronic stable pain. Conversion from oral morphine to fentanyl patches (Duragesic) is shown in Table 7.6. The patch must be changed every 72 hours to maintain steady-state blood levels.
- Appropriate use of opioids requires minimizing side effects including sedation, nausea, vomiting, pruritus, myoclonus, and cognitive impairment (Table 7.7). Naloxone, an opioid receptor antagonist, can be used to reverse respiratory depression. It should be titrated to effect (e.g., 0.02 mg IV push every 2 minutes) to prevent profound opioid withdrawal, seizures, arrhythmias, and severe pain.
- **Breakthrough Pain** can be classified as spontaneous pain (occurring with no known stimuli), incident (secondary to a stimulus), or end-of-dose failure (pain at the end of the dosing interval).
  - **Spontaneous pain** is managed by giving a short-acting opioid as soon as pain is experienced.
  - **Incident pain** is managed by taking a dose of short-acting opioid 30 minutes before activity.
  - **End-of-dose failure** is managed by providing supplementary doses of a short-acting opioid equivalent to 5% to 10% of the total daily dose, to be taken every 2 hours, as needed.
  - **Fentanyl oral transmucosal (Actiq) or buccal (Fentora)** are options for breakthrough pain in cancer patients (see Table 7.8 for dose equivalency).
- **Methadone** is recommended when a patient has an inadequate response to other opioids or experiences intolerable side effects (delirium, myoclonus, nausea). Methadone is typically dosed every 8 hours. The most commonly used morphine-to-methadone conversions are shown in Table 7.9. Methadone doses should be rounded down to the nearest table size. Potential methadone toxicity includes respiratory depression and QTc prolongation (Table 7.10).
- **Cognitive behavioral therapy (CBT)** has been shown to be beneficial in the treatment of chronic pain (Table 7.11).

TABLE 7.5 Equianalgesic Opioid Dosing

Opioid	Equianalgesic Dose (mg)		Comments
	Oral	Parenteral	
Morphine	30	10	Standard for comparison of opioid analgesics Frequency for controlled release preparations: 8 or 12 hours for MS Contin or Oramorph 12 or 24 hours for Kadian 24 hours for Avinza Embeda (morphine sulfate and naltrexone) is a diversion-deterrent formulation. Morphine not recommended in patients with severe renal impairment
Hydromorphone (Dilaudid, Exalgo)	7.5	1.5	Exalgo (extended release) dosed every 24 hours Can be used in patients with renal or liver impairment
Fentanyl	—	0.1	Refer to Table 7.22 for transdermal fentanyl. Equianalgesic conversion ratios have not been established for transmucosal and transbuccal fentanyl formulations. Can be used in patients with renal or liver impairment
Oxycodone	20	—	OxyContin (controlled release) is dosed every 8 or 12 hours. Can be used in patients with renal impairment
Levorphanol (Levo-Dromoran)	4 acute 1 chronic	1 chronic	Long plasma half-life (12–16 hours but may be as long as 90–120 hours) Use with caution in older adults.
Buprenorphine (Buprenex, Butrans) <sup>161,162</sup>	0.3	0.4 (SL)	Available as sublingual tablets and injection Analgesic ceiling of 32 mg/day SL Butrans (transdermal buprenorphine) available Suboxone (buprenorphine and naloxone) restricted to treatment of opioid dependence Partial agonists not recommended for cancer pain management
Meperidine (Demerol) <sup>159,161</sup>	100	300	Not recommended for routine clinical use Normeperidine is a toxic metabolite that produces anxiety, tremors, myoclonus, and generalized seizures.

SL, sublingual.

TABLE 7.6 Conversion from Oral Morphine to Duragesic

Oral 24-hour Morphine (mg/day)	Duragesic Dose (mcg/hour)
60–134	25
135–224	50
225–314	75
315–404	100
405–494	125
495–584	150
585–674	175
675–764	200
765–854	225
855–944	250
945–1,034	275
1,035–1,124	300

Source: Reprinted with permission from Facts & Comparisons eAnswers. <http://online.factsandcomparisons.com/MonoDisp.aspx?monoID=fandc-hcp12689&quick=332587%7c5&search=332587%7c5&isstemmed=True#firstMatch>. Accessed March 30, 2011.



TABLE 7.7 Pharmacological Treatments for Opioid-Related Side Effects

Side Effect	Treatment
Constipation	Stool softener, laxative, methylalntrexone, oral naloxone
Sedation	Methylphenidate, modafinil
Pruritus	Diphenhydramine, hydroxyzine
Nausea	Prochlorperazine, haloperidol, metoclopramide, ondansetron, antihistamine
Dysphoria	Haloperidol, opioid rotation
Cognitive impairment	Methylphenidate, modafinil, opioid rotation
Myoclonus	Clonazepam, dose reduction, opioid rotation

TABLE 7.8 Equianalgesic Doses for Actiq (Transmucosal Fentanyl) and Fentora (Buccal Fentanyl)

Current Actiq Dose (mcg)	Initial Fentora Dose (mcg)
200	100
400	100
600	200
800	200
1,200	400
1,600	400

Source: Reprinted with permission from Facts & Comparisons eAnswers. <http://online.factsandcomparisons.com/MonoDisp.aspx?monoID=fandc-hcp12688&quick=366114%7c5&search=366114%7c5&isstemmed=True#firstMatch>. Accessed March 30, 2011.

TABLE 7.9 Morphine-to-Methadone Equianalgesic Dose Ratio

Oral Morphine Dose (mg/day)	<100	101–300	301–600	601–800	801–1,000	≥1,001
Oral morphine to oral methadone ratio	3:1	5:1	10:1	12:1	15:1	20:1

TABLE 7.10 Consensus Recommendations for Methadone QTc Prolongation

Inform patients of arrhythmia risk before prescribing methadone.  
 Obtain patient history of structural heart disease, arrhythmia, and syncope.  
 Obtain a pretreatment ECG before starting methadone and follow up 30 days after starting methadone.  
 Annual ECG is recommended. Additional ECG if the methadone dosage exceeds 100 mg/day or patient has unexplained syncope or seizures.  
 Reduce or discontinue methadone if the QTc interval exceeds 500 milliseconds.  
 Screen medication profile use of drugs that may also prolong or slow the elimination of methadone (i.e., SSRIs, antifungal agents, protease inhibitors, phenytoin, rifampin, phenobarbital, droperidol).

ECG, electrocardiogram; SSRIs, selective serotonin reuptake inhibitors.

TABLE 7.11 Cognitive Behavioral Therapy

**Meditation**—intentional self-regulation of attention using a systematic focus on particular aspects of inner and outer body experience.

**Biofeedback**—self-regulatory technique that teaches a patient how to exert control over the physiological processes exacerbating pain. Biofeedback equipment conveys physiological responses as visual or auditory signals that the patient can observe on a computer monitor. With practice, the patient learns to control and change his or her physiological responses by manipulating the auditory or visual signals.

**Guided imagery**—useful method to help patients with pain to relax and achieve a sense of control and distraction. This modality involves the generation of different mental images, evoked either by oneself or with the help from the practitioner.

**Hypnosis**—a state of heightened awareness and focused concentration that can be used to manipulate the perception of pain.

## Low Back Pain

- Low back pain is the fifth most common reason for visits to the primary care provider. The prevalence of low back pain rises with increasing age, to age 65 years.
- Low back pain affects the lumbosacral spine and associated muscles and nerves. In about 85% of cases, no pathophysiologic cause can be found.
- Patient assessment should consider other potentially serious conditions that can cause back pain (Table 7.12).
- **Treatment**
  - Most guidelines recommend a supervised exercise program, cognitive behavioral therapy, and short-term pharmacologic therapy. Bed rest is not recommended; patients should remain physically active.
  - Cold packs can reduce inflammation; heat can relax muscles.
  - Common recommendations for treatment of low back pain are shown in Table 7.13.
    - Acetaminophen is the safest choice.

TABLE 7.12 Red Flags for Potentially Serious Conditions that Cause Back Pain

Possible Fracture	Possible Tumor or Infection	Possible Cauda Equina Syndrome
Major trauma, such as vehicle accident or fall from height	Age <20 or >50 years	Saddle anesthesia
Minor trauma or strenuous lifting in older or potentially osteoporotic patients	History of cancer	Recent onset of bladder dysfunction (urinary retention, increased frequency, overflow incontinence)
	Constitutional symptoms (recent fever, chills, unexplained weight loss)	Severe or progressive neurologic deficit in the lower extremities
	Risk factors for spinal infections: Recent bacterial infection IV drug abuse Immune suppression	Unexpected laxity of the anal sphincter
	Pain that worsens when supine Severe nighttime pain	Perianal/perineal sensory loss Major motor weakness: Quadriceps (knee extension weakness) Ankle plantar flexors, evertors, and dorsiflexors (foot drop)

IV, intravenous.

TABLE 7.13 Summary of Common Recommendations for Treatment of Low Back Pain

### ACUTE OR SUBACUTE PAIN

Reassure patients that diagnosis is not serious  
 Advise to stay active  
 Prescribe medication if necessary  
 First-line: acetaminophen  
 Second-line: NSAIDs  
 Third-line: muscle relaxants, opioids, antidepressants, or anticonvulsants as coanalgesics  
 Discourage bed rest

### CHRONIC PAIN

Discourage use of alternative therapies (ultrasound, electrotherapy)  
 Short-term use of medication/manipulation  
 Supervised exercise therapy  
 Cognitive behavioral therapy  
 Multidisciplinary treatment

NSAIDs, nonsteroidal anti-inflammatory drugs.

- NSAIDs are equally effective across the drug class; some patients respond better to one agent over another. COX-2 selective inhibitors are as effective as traditional NSAIDs but may be better tolerated. See Chapter 44 for NSAID choices and doses.
- Acetaminophen may be used in combination with NSAIDs for additive analgesia.
- Muscle relaxants and weak opioids may provide short-term relief.
- Epidural steroid injections and possibly surgery may be considered in patients with persistent radicular low back pain.

## Fibromyalgia and Myofascial Pain

- A comparison between fibromyalgia and myofascial pain is shown in Table 7.14.
- **Fibromyalgia** is a debilitating condition with the primary symptoms of chronic widespread pain and fatigue. It appears to be a manifestation of CNS neurotransmitter dysfunction. Daily management of symptoms is affected by an exaggerated response to personal stressors, noxious stimuli, and non-noxious sensory stimuli.
- **Myofascial pain** has a presentation of muscular pain that arises from soft tissues and is more localized. It is typically associated with muscle knots called trigger points.
- **Treatment**
  - **Fibromyalgia.** See Table 7.15 for pharmacologic treatment of fibromyalgia.
    - Guidelines recommend a multidisciplinary approach using drug and nondrug therapies.
    - NSAIDs, acetaminophen, and opioids are not recommended for treating fibromyalgia pain, although tramadol has shown some benefit.

TABLE 7.14 Comparing Fibromyalgia and Myofascial Pain

Criteria	Fibromyalgia	Myofascial Pain
Origin of pain	CNS	Soft tissues
Epidemiology	Usually female Possible genetic link	Both genders affected
Location/spread	Widespread pain Both sides of the body Above AND below the waist	Regional pain May be only one side of the body May be either above OR below the waist
Duration	> 3 months	< or > 3 months
Localized pain	Tender points (no taut bands) Need 11/18 specified points for diagnosis	Trigger points
Range of motion	Not limited	Limited in affected muscle group
Associated syndromes/symptoms	IBS, depression, anxiety, headache, PTSD, chronic fatigue, sleep disturbance, restless legs syndrome, cognitive impairment, interstitial cystitis	Fatigue, difficulty sleeping
Pharmacologic treatment	Pregabalin Duloxetine Milnacipran Amitriptyline Gabapentin Cyclobenzaprine Pramipexole Tizanidine	Trigger point injections with local anesthetic or botulinum toxin
Nonpharmacologic treatment	Physical rehabilitation, CBT	Physical rehabilitation, improving ergonomics and postural support

IBS, irritable bowel syndrome; PTSD, posttraumatic stress disorder; CBT, cognitive behavioral therapy.

TABLE 7.15 Pharmacologic Treatment of Fibromyalgia

Drug	Fibromyalgia Dosing	Adverse Effects	Comments
Amitriptyline	25–50 mg QHS	Dry mouth, constipation, urinary retention, orthostatic hypotension, somnolence	Caution in elderly patients
Cyclobenzaprine	10–30 mg QHS	Dry mouth, constipation, urinary retention, somnolence	Caution in elderly patients
Duloxetine <sup>a</sup>	30 mg daily × 1 week, then 60 mg daily	Nausea, dry mouth, constipation, fatigue, sweating, anorexia	Monitor liver transaminases
Milnacipran <sup>a</sup>	12.5 mg × 1 day, then 12.5 mg BID × 2 days, then 25 mg BID × 4 days, then 50 mg BID, may titrate to 100 mg BID	Nausea, headache, constipation, insomnia, hot flushes	Monitor blood pressure, heart rate
Pregabalin <sup>a</sup>	75 mg BID, titrate to 150 mg TID	Somnolence, dizziness, edema, cognitive effects	Reduce dose for renal impairment
Gabapentin	300 mg QHS, titrate to 600 mg TID	Somnolence, dizziness, edema, cognitive effects	Reduce dose for renal impairment

<sup>a</sup>Food and Drug Administration–approved to treat fibromyalgia.

BID, twice daily; QHS, every night at bedtime; TID, three times a day.

- **Myofascial Pain**
  - General approaches to pain management (NSAIDs, antidepressants, anticonvulsants, opioids) may be helpful for individual patients.
  - The mainstay of treatment is trigger point injections. Dry-needling involves placing a solid filament needle into the trigger point to disrupt the muscle fibers and allow relaxation of the taut band.
- **Muscle Relaxants** are commonly used to treat chronic musculoskeletal pain. Antispasmodics are used for muscular pain and spasms associated with peripheral musculoskeletal conditions (Table 7.16). Guidelines do not recommend chronic use of muscle relaxants for musculoskeletal pain.

## Neuropathic Pain and Postherpetic Neuralgia

- Peripheral sensory neuropathy usually involves injury or insult to peripheral nerves.
- **Postherpetic neuralgia** (PHN) affects spinal nerve dermatomes. The pain tends to be fairly localized, either regionally or along an associated dermatome. About 20% of patients who have herpes zoster will experience PHN.
- PHN and diabetic peripheral neuropathy (DPN) are the most common neuropathic pain conditions.
- **Treatment**
  - Patients should be treated with the most effective therapy that has the lowest risk for adverse effects. Treatment options for neuropathic pain are shown in Table 7.17.
  - Guidelines from the American Academy of Neurology state that TCAs (amitriptyline, nortriptyline, desipramine), gabapentin, pregabalin, opioids, and topical lidocaine patches are effective. Insufficient data support one opioid over another.
  - Analgesic drug interactions are possible when treating neuropathic pain. Excess norepinephrine can cause CNS excitation and possible seizures. Excess serotonin can cause **serotonin syndrome**, a possibly life-threatening syndrome. A table of agents commonly used in pain management, the relevant cytochrome P450 enzyme involved in its metabolism, and therefore potential drug interactions are shown in Table 7.18.

TABLE 7.16 Oral Muscle Relaxants

Drug	Dose	Adverse Effects	Monitoring/Comments
<b>ANTISPASMODIC</b>			
Cyclobenzaprine	5 mg TID, titrate to 10 mg TID	Dry mouth, constipation, urinary retention, somnolence, confusion, blurred vision	Also available in extended-release formulation
Metaxalone	300 mg TID–QID	GI upset, nausea, vomiting, dizziness, headache, somnolence, hemolytic anemia, leucopenia, jaundice	Contraindicated in anemia, liver impairment, renal impairment Monitor liver function, CBC
Methocarbamol	1,500 mg TID, or 1,000 mg QID	Itching, rash, indigestion, nausea, vomiting, dizziness, headache, nystagmus, somnolence, vertigo, blurred vision, arrhythmias, hypotension, leucopenia	Monitor heart rate, blood pressure
Orphenadrine citrate	100 mg BID	Syncope, nausea, vomiting, dry mouth, dizziness, blurred vision, palpitations	Monitor CBC, liver function
Chlorzoxazone	500–750 mg TID–QID	Lightheadedness, dizziness, somnolence, malaise, liver toxicity	Monitor liver function
Carisoprodol	250–350 mg TID and at bedtime	CNS depressant, dizziness, headache, somnolence	Monitor for weakness, dizziness, confusion
<b>ANTISPASTIC</b>			
Tizanidine	4 mg TID, titrate to max of 12 mg TID	Hypotension, somnolence, muscle weakness	Monitor blood pressure, liver function
Baclofen	10 mg TID, titrate to max of 20 mg QID	Somnolence, muscle weakness, ataxia	
Benzodiazepines (diazepam)	2 mg TID, titrate to max of 10 mg TID	CNS depressant, somnolence, weakness	Monitor sedation Risk of physical dependence
Dantrolene	25 mg daily × 7 days, 25 mg TID × 7 days, titrate to max of 100 mg QID	Hepatitis, tachycardia, confusion, nausea, vomiting, depression, fatigue, dizziness, somnolence, blood dyscrasias, rash, GI obstruction	Monitor liver function

BID, twice a day; CBC, complete blood cell count; GI, gastrointestinal; QID, four times a day; TID, three times a day.

## Cancer Pain

- Pain is one of the most common symptoms of cancer; pain can be somatic, neuropathic, or visceral. Table 7.19 shows a summary of common cancer pain causes and symptoms.
- Factors influencing the degree of pain include the primary cancer, stage of disease, location of metastasis, and comorbid medical conditions.
- **Treatment**
  - Initial treatment is based on the severity of pain. Factors to consider include pain etiology, patient tolerance, setting, and previous experience.

TABLE 7.17 Pharmacologic Options for Treatment of Neuropathic Pain

Drug	Dose <sup>a</sup>	Adverse Effects	Monitoring/Comments
Carbamazepine <sup>b</sup>	200 mg TID, titrate to max 400 mg TID	Diplopia, rash, hepatitis, neutropenia, aplastic anemia, dizziness, cognitive effects, hyponatremia	Check LFTs, CBC, sodium at baseline and every 3 months during therapy
Oxcarbazepine	75 mg BID, titrate to max 1,200 mg BID	Rash, cognitive effects, hyponatremia, sedation, blurred vision	Check sodium every 2 weeks for 3 months, then with dose increases
Lamotrigine	25 mg daily, titrate to max 200 mg BID	Desquamating rash, cognitive effects	Requires very slow titration to avoid rash
Topiramate <sup>b</sup>	25 mg BID, titrate to max 200 mg BID	Nausea, anorexia, paresthesias, metabolic acidosis, cognitive effects, nephrolithiasis	Check serum bicarbonate at baseline and every 3 months or with each dose increase
Lacosamide	50 mg BID, titrate to max 200 mg BID	Nausea, vomiting, dizziness, diplopia, ataxia, fatigue, rash, atrial fibrillation/flutter	ECG at baseline and with dose adjustments, especially in patients at risk for cardiac conduction abnormality Reduce dose for renal and liver impairment
Gabapentin <sup>b</sup>	300 mg daily, titrate to max 1,200 mg TID	Somnolence, dizziness, edema, cognitive effects	Reduce dose for renal impairment or for elderly patients
Pregabalin <sup>b</sup>	75 mg BID, titrate to max 300 mg BID	Same as gabapentin	Same as gabapentin
Amitriptyline/nortriptyline	10 mg QHS, titrate to 100 mg QHS	Dry mouth, constipation, urinary retention, orthostatic hypotension, somnolence	Caution in elderly patients
Duloxetine <sup>b</sup>	30 mg daily, titrate to max 60 mg daily	Nausea, dry mouth, headache, diarrhea, fatigue, sweating, anorexia	Contraindicated with liver disease or concurrent alcohol consumption
Venlafaxine	37.5 mg daily, titrate to max 225 mg daily	Headache, nausea, sweating, sedation, hypertension, seizures, tachycardia	Serotonergic effects <150 mg and noradrenergic effects >150 mg Monitor blood pressure and heart rate
Opioids <sup>b</sup>	10–15 mg morphine every 4 hours or equianalgesic dose of other opioid	Somnolence, dry mouth, constipation, urinary retention	May cause confusion in elderly patients Use with a bowel regimen
Tramadol <sup>b</sup>	25 mg QID to max 100 mg QID	Somnolence, dry mouth, constipation	Caution with antidepressants
Capsaicin cream <sup>b</sup>	Apply QID	Rash, burning feeling on skin	Avoid contact with mucous membranes, eyes
Capsaicin patch <sup>b</sup>	Apply 1 patch for 1 hour, every 3 months	Skin irritation at application site, burning feeling on skin	Must be applied in medical office
Lidocaine patch <sup>b</sup>	Apply 1–3 patches daily for 12 hours	Skin reaction at site of application	

<sup>a</sup>All oral agents are titrated up to reduce adverse effects and titrated down when discontinuing therapy.

<sup>b</sup>Food and Drug Administration–approved for treating pain conditions.

BID, twice a day; CBC, complete blood cell count; ECG, electrocardiogram; LFTs, liver function tests; QHS, every night at bedtime; QID, four times a day; TID, three times a day.

TABLE 7.18 Drug Interactions with Analgesics

CYP1A2	CYP2C9	CYP2C19	CYP2D6	CYP3A4
<b>SUBSTRATES</b>				
Amitriptyline	Amitriptyline	Amitriptyline	Amitriptyline, mexiletine	Alprazolam, methadone
Naproxen	Celecoxib	Citalopram	Nortriptyline, morphine	Amitriptyline, prednisone
R-warfarin	Diclofenac	Diazepam	Cyclobenzaprine, codeine	Buspirone, sertraline
Duloxetine	Fluoxetine	Indomethacin	Desipramine, oxycodone	Clonazepam, temazepam
Methadone	Ibuprofen	Topiramate	Doxepin, paroxetine	Codeine, zaleplon
Theophylline	Naproxen		Fluoxetine, sertraline	Cyclobenzaprine, zolpidem
Tizanidine	Piroxicam		Hydrocodone, tramadol	Diazepam, R-warfarin
	S-warfarin		Methadone, venlafaxine	Fentanyl, carbamazepine
	Phenytoin		Fentanyl, duloxetine	Lidocaine, erythromycin
<b>INDUCERS</b>				
Carbamazepine	Carbamazepine	Carbamazepine	Carbamazepine	Carbamazepine
Phenytoin	Fluoxetine	Phenytoin	Phenytoin	Oxcarbazepine
	Cimetidine			Phenytoin
	Metronidazole			
	Fluconazole			
<b>INHIBITORS</b>				
Cimetidine	Carbamazepine	Fluoxetine	Celecoxib	Fluoxetine
Ciprofloxacin	Paroxetine	Indomethacin	Desipramine	Sertraline
	Sertraline	Paroxetine	Fluoxetine	Ketoconazole
	Valproic acid	Topiramate	Methadone	Cyclosporine
	Phenytoin		Paroxetine	
			Sertraline	
			Valproic acid	

CYP, cytochrome P-450.

TABLE 7.19 Common Cancer Pain Presentation

Syndrome	Associated Cancer or Treatment	Associated Signs and Symptoms
Bone metastasis	Breast cancer, lung cancer, multiple myeloma, prostate cancer	<ul style="list-style-type: none"> <li>Pain is usually described as dull or aching.</li> <li>Pain is usually localized to the metastatic site.</li> <li>Spine metastasis to the base of the skull may produce headache, pain associated with head movement, and pain in the face, neck, and shoulder.</li> </ul>
Epidural spinal cord compression	Breast cancer, lung cancer, melanoma, multiple myeloma, prostate cancer, renal cancer	<ul style="list-style-type: none"> <li>Pain is usually midline.</li> <li>Pain can be sharp and shooting in a radicular distribution if nerve roots are involved.</li> <li>Cervical lesions: pain can radiate down one or both arms.</li> <li>Thoracic lesions: pain is described as a “tight band” around the patient’s chest.</li> <li>Lumbosacral lesions: pain can radiate down one or both legs.</li> <li>Other signs: bowel and bladder dysfunction.</li> </ul>
Cervical plexopathy	Metastasis to the cervical lymph nodes; local extension of primary head and neck tumors	<ul style="list-style-type: none"> <li>Pain is characterized by aching discomfort that may radiate into the neck and shoulders.</li> </ul>
Brachial plexopathy	Breast cancer, lung cancer, lymphoma	<ul style="list-style-type: none"> <li>Pain usually begins in the shoulder and is associated with shooting or electrical sensations in the thumb and index finger if the upper plexus is damaged by tumor.</li> <li>Pain usually begins in the shoulder and radiates into the elbow, arm, and medial forearm and into the fourth and fifth digits if the lower plexus is damaged by tumor.</li> </ul>

Syndrome	Associated Cancer or Treatment	Associated Signs and Symptoms
Lumbar plexopathy	Colorectal cancer, endometrial cancer, renal cancer, sarcoma, lymphoma	<ul style="list-style-type: none"> <li>• Pain is usually felt in the lower abdomen, buttock, and leg.</li> <li>• Perineal and perirectal pain may occur if tumor invades the sacral plexus.</li> <li>• Associated symptoms can include weakness, sensory loss, or urinary incontinence.</li> </ul>
Peripheral neuropathies	Multiple myeloma Chemotherapy (vinca alkaloids, taxanes, platinum compounds, thalidomide) Postsurgical pain syndrome	<ul style="list-style-type: none"> <li>• Sensory motor neuropathy is characterized by distal paresthesias, sensory loss, weakness, and muscle wasting. It may occasionally ascend upward in a manner similar to Guillain-Barre syndrome.</li> <li>• Chemotherapy dose-related peripheral neuropathies are characterized by dysesthesias in the feet and hands, and hyporeflexia.</li> <li>• Post-radical neck dissection: tight, burning sensation in the area of sensory loss; dysesthesias and shock-like pain may be present.</li> <li>• Postmastectomy pain: tight, constricting pain in the posterior wall, axilla, and anterior chest wall that is exacerbated by movement</li> <li>• Postthoracotomy pain: aching sensation in the distribution of the incision with sensory loss with or without autonomic changes</li> <li>• Postnephrectomy pain: numbness, fullness, or heaviness in the flank, anterior abdomen, and groin associated with dysesthesias</li> <li>• Post-limb amputation: pain occurs at the site of the surgical pain and is characterized by a burning, dysestic sensation that is exacerbated by movement.</li> </ul>

- In general, mild pain (pain rating  $\leq 4$  on a 10-point scale) can be managed with nonopioid or a combination of nonopioid and opioid analgesics.
- Moderate to severe pain (pain ratings  $>4$ ) usually require an opiate.
- Neuropathic pain may require use of an anticonvulsant or antidepressant.
- Neuraxial opioid administration (epidural or intrathecal) can be used to treat cancer pain that is refractory to conventional measures.

## Other Pain Types

- **Complex regional pain syndrome (CRPS)** is a syndrome that usually develops after some type of injury. An inflammatory response causes peripheral sensitization and localized pain, vasodilation, release of inflammatory markers, and accumulation of immunoglobulin in the affected area.
  - **Symptoms.** Burning pain, allodynia, hyperalgesia, edema, sweating, reduced skin blood flow
  - **Treatment.** A specific treatment plan is not possible as the pathology is not known; corticosteroids and bisphosphonates reduce pain and edema and increase the range of motion of the affected limb. Dimethyl sulfoxide (DMSO), *N*-acetyl cysteine, and gabapentin have some benefit. Intravenous regional blocks with local anesthetics or other medications can improve the vasomotor effects.
- **Chronic pain in the elderly** is common but often poorly assessed and managed. Consequences include sleep loss, malnutrition, decline in social and recreational activities, depression, anxiety, and impaired cognition. Osteoarthritis (OA) is a frequent complaint in the elderly (see Chapter 43 for a summary of OA).



- **Treatment.** Analgesic and anti-inflammatory medications are important for OA pain management. They should be used concurrently with nutritional, physical, educational, and cognitive-behavior interventions. Recommended oral analgesic medications for older patients are shown in Table 7.20.
  - Acetaminophen is recommended as first-line therapy in all guidelines (Table 7.21). Dose limits of 2 to 3 g/day have been suggested to minimize the risk of renal or hepatic toxicity with prolonged use.
  - NSAIDs are another option for first-line therapy for moderate to severe pain and inflammation.
  - Opioids are second-line option in patients who have an inadequate response to other agents. Morphine and codeine should be avoided in older patients with chronic renal insufficiency. Long-acting formulations should be reserved for patients who tolerate around-the-clock dosing of short-acting agents.
  - Tramadol and tapentadol are alternative analgesics with mild opioid activity.
  - Topical agents (capsaicin, diclofenac gel) are an option that allow for reduced side effects.

TABLE 7.20 Recommended Oral Analgesic Medications for Older Adults

Drug	Recommended Starting Dose	Comments
<b>NONOPIOID ANALGESICS</b>		
Acetaminophen (Tylenol)	500–1,000 mg every 6 hours	Maximum dose usually 4 g daily. Reduce maximum dose 50%–75% in patients with hepatic insufficiency or history of alcohol abuse.
Celecoxib (Celebrex)	100 mg daily	Higher doses associated with higher incidence of gastrointestinal and cardiovascular side effects. Patients with indications for cardioprotection require aspirin supplement; therefore, older individuals will still require concurrent gastroprotection.
Naproxen sodium	220 mg twice daily	May have less cardiovascular toxicity.
Ibuprofen	200 mg three times a day	May have less cardiovascular toxicity.
Tramadol (Ultram)	25 mg every 4–6 hours	Maximum dose 300 mg/day. Risk of seizures if used in higher doses. May precipitate serotonin syndrome if used with selective serotonin reuptake inhibitors.
Tapentadol (Nucynta)	50 mg every 4–6 hours (equivalent to oxycodone 10 mg every 4–6 hours)	Clinical trials suggest lower incidence of gastrointestinal side effects compared with other opioids.
<b>OPIOID ANALGESICS</b>		
Hydromorphone (Dilaudid)	1–2 mg every 3–4 hours	For breakthrough pain or around-the-clock dosing.
Morphine (immediate-release)	2.5–10 mg every 4 hours	Most commonly used for episodic or breakthrough pain. Toxic metabolites may limit usefulness in patients with renal insufficiency.
MS Contin or Oramorph SR (long-acting morphine)	15 mg every 12 hours	Usually started after initial dose determined by the effects of immediate-release opioid.
Oxycodone (immediate-release)	2.5–5 mg every 4–6 hours	Useful for acute recurrent, episodic, or breakthrough pain.
OxyContin (long-acting oxycodone)	10 mg every 12 hours	Usually started after initial dose determined by effects of immediate-release opioid.

**TABLE 7.21 Summary of Pharmacologic Therapy Recommendations<sup>a</sup> from Osteoarthritis Guidelines**

Medication	ACR	EULAR	OARSI	AAOS	NICE
Acetaminophen	1	1	1	1	1
Tramadol	2				
Opioids	2	2	2		2
NSAIDs	1	2	1	1	2
COX-2	2	2	1	2	2
Topical NSAID	2	1	1	2	1
Capsaicin	2	1	1		2
Topical salicylate	2	1			NR
Intraarticular steroids	1	2	2	Short-term	2
Intraarticular hyaluronic acid	2	2	2	NR	NR
Glucosamine and chondroitin		2	2	NR	NR

<sup>a</sup>Strength of recommendation: 1, first-line; 2, second-line; NR, not recommended.

AAOS, American Academy of Orthopedic Surgeons (2008); ACR, American College of Rheumatology (2000); COX-2, cyclo-oxygenase-2; EULAR, European League Against Rheumatism (2003, knee; 2005, hip); NICE, National Institute of Health and Clinical Excellence (2008); NSAID(s), nonsteroidal anti-inflammatory drug(s); ORSI, Osteoarthritis Research Society International (2008).

- **Functional abdominal pain syndrome (FAPS)** is a chronic pain disorder localized to the abdomen that cannot be explained by structural or metabolic disorders. Syndrome-related behaviors of FAPS are shown in Table 7.22.
  - **Treatment.** Recommendations are empirical. Antidepressants (e.g., TCAs) in low daily doses may be useful. NSAIDs offer little benefit. Gabapentin and pregabalin have not established efficacy.

**TABLE 7.22 Symptom-Related Behaviors of Functional Abdominal Pain Syndrome**

Expressing pain of varying intensity through verbal and nonverbal methods
Urgent reporting of intense symptoms disproportionate to available clinical and laboratory data
Minimizing or denying a role for psychosocial contributors, anxiety, depression; attributing symptoms of anxiety or depression to presence of pain
Requesting diagnostic studies or surgery to validate the condition as “organic”
Focusing attention on complete relief of symptoms
Seeking health care frequently
Taking limited personal responsibility for self-management
Making requests for narcotic analgesics when other treatment options have been implemented

# Perioperative Care\*

## General Principles

- The perioperative period is defined as the preoperative, intraoperative, and postoperative periods.

## Preoperative Medications

- **Goals of Therapy:** to decrease patient anxiety and produce sedation. Other possible goals are to provide analgesia, produce amnesia, reduce anesthetic requirements, prevent autonomic responses that would otherwise result in intraoperative hemodynamic instability, decrease salivation and secretions, reduce gastric fluid volume, and increase gastric pH.
- **Treatment**
  - Factors to consider when selecting a preoperative drug include patient's physical status, medical conditions, degree of anxiety, age, surgical procedure, length of procedure, postoperative admission status, drug allergies, previous experience with medications, and concurrent drug therapy.
  - For outpatient surgeries, agents with a long duration of action should be avoided.
  - Agents used in the preoperative period are shown in Table 8.1.
  - Timing and route of administration are important: oral agents should be given 30 to 60 minutes before arriving in the OR; IM route should be avoided.
  - **Chronic Medications Prior to Surgery.** Consequences of stopping a chronic medication before, or failing to restart post-surgery, can have significant consequence. Individual patient assessment is needed.
  - **Aspiration Pneumonitis Prophylaxis:** a potentially fatal condition that results from regurgitation and aspiration of stomach contents and can cause obstruction or an inflammatory response. Risk factors include increased gastric acid, elevated intragastric pressure, gastric or intestinal hypomotility, digestive structural disorders, neuromuscular incoordination, and depressed sensorium.
    - Medications can reduce the risk of pneumonitis if aspiration occurs (e.g., antacids, gastric motility stimulants, H<sub>2</sub> receptor antagonists).

## Intra- and Postoperative Medications

### INTRAVENOUS ANESTHETIC AGENTS

- General anesthesia is a state of drug-induced unconsciousness. Drugs should produce unconsciousness rapidly and smoothly while minimizing cardiovascular challenges.
- The onset and duration of effect are the most important factors when IV anesthetic agents are used for induction of anesthesia (Table 8.2).
- IV anesthetic agents can produce a variety of adverse and beneficial effects besides loss of consciousness (Table 8.3).

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\*The reader is referred to Chapter 8, Perioperative Care, written by Andrew J. Donnelly, PharmD, MBA, FASHP, Julie A. Golembiewski, PharmD, and Andrei M. Rakic, MD, in the 10th edition of *Applied Therapeutics: The Clinical Use of Drugs* for a more in-depth discussion. All notations to reference numbers are based on the reference list at the end of that chapter. The editor of this handbook expresses her thanks to Drs. Donnelly, Golembiewski, and Rakic and acknowledges that this chapter is based on their work.

TABLE 8.1 Indications, Routes of Administration, and Doses of Preoperative Agents<sup>a</sup>

Agent	Indications	Routes of Administration	Doses <sup>b</sup>
<b>BENZODIAZEPINES</b>			
Diazepam	Anxiolysis, amnesia, sedation	PO	Adults: 5–10 mg
Lorazepam	Anxiolysis, amnesia, sedation	IV	Adults: 2–10 mg (titrate dose)
		PO	0.025–0.05 mg/kg (range, 1–4 mg for adults)
Midazolam	Anxiolysis, amnesia, sedation	IV	Adults: 0.025–0.04 mg/kg; Pediatrics: 0.01–0.05 mg/kg (titrate dose; max: 2 mg)
		PO	Adults: 20 mg; Pediatrics: 0.5–0.75 mg/kg (max: 20 mg)
		IM	Adults: 0.05–0.08 mg/kg (max: 10 mg); Pediatrics: 0.1–0.15 mg/kg (max: 10 mg)
		IV	Adults: 1–2.5 mg (titrate dose); Pediatrics: 0.05–0.1 mg/kg (6 months–5 years); 0.025–0.05 mg/kg (6–12 years)
		IN	Pediatrics: 0.2 mg/kg (max: 15 mg)
<b>OPIOIDS</b>			
Morphine	Analgesia, sedation	IM	Adults: 2–10 mg; Pediatrics: 0.05–0.1 mg/kg
		IV	Titrate dose
Fentanyl	Analgesia, sedation	IV	Adults: 25–100 mcg (titrate dose); Pediatrics: 0.5–2 mcg/kg
<b>ANTICHOLINERGICS</b>			
Atropine (A)	Antisialagogue (S > G > A), sedation (S > A > G)	IM/IV	Adults: 0.4–0.6 mg; Pediatrics: 0.02 mg/kg IM, 0.01 mg/kg IV (max: 0.4 mg)
Scopolamine (S)	Sedation, amnesia, antisialagogue	IM/IV	Adults: 0.2–0.6 mg; Pediatrics: 6 mcg/kg/dose (max: 0.3 mg/dose)
Glycopyrrolate (G)	Antisialagogue	IM/IV	Adults: 0.1–0.3 mg; Pediatrics: 0.005–0.01 mg/kg (max: 0.1 mg)
<b>GASTRIC MOTILITY STIMULANTS</b>			
Metoclopramide	Reduce gastric volume, antiemetic	PO	Adults: 10 mg; Pediatrics: 0.15 mg/kg
		IV	Adults: 0.1–0.2 mg/kg (5–10 mg); Pediatrics: 0.1–0.15 mg/kg
<b>H<sub>2</sub>-RECEPTOR ANTAGONISTS</b>			
Cimetidine	↑ Gastric pH	PO	Adults: 300 mg; Pediatrics: 7.5 mg/kg
		IV	Adults: 300 mg; Pediatrics: 7.5 mg/kg
Ranitidine	↑ Gastric pH	PO	Adults: 150 mg; Pediatrics: 2 mg/kg
Famotidine	↑ Gastric pH	IV	Adults: 50 mg; Pediatrics: 0.5–1 mg/kg
		PO	Adults: 40 mg; Pediatrics: 0.5 mg/kg
Nizatidine	↑ Gastric pH	IV	Adults: 20 mg; Pediatrics: 0.25 mg/kg
		PO	Adults: 150–300 mg
<b>NONPARTICULATE ANTACIDS</b>			
Citric acid and sodium citrate	↑ Gastric pH	PO	Adults: 30 mL

<sup>a</sup>General dosage guidelines; doses must be individualized on the basis of patient-specific parameters.

<sup>b</sup>Doses listed are for agents when used as sole premedicant; doses may need to be reduced if premedicants are administered in combination (e.g., opioids, benzodiazepines).

IM, intramuscular; IN, intranasal; IV, intravenous; PO, oral; mo, month; yo, years old.

TABLE 8.2 Pharmacokinetic Comparison of Common Intravenous Anesthetic Agents

Drug	Half-Life (hours)	Onset (seconds)	Clinical Duration (minutes) <sup>a</sup>	Hangover Effect <sup>b</sup>
Etomidate	2–5	≤30	3–12	+
Ketamine	1–3	30–60	10–20	++ to +++ <sup>c</sup>
Methohexital	4	≤30	5–10	+
Midazolam	1–4	30–90	10–20	+++ <sup>d</sup>
Propofol	0.5–7	≤45	5–10	0 to +

<sup>a</sup>Time from injection of agent to return to conscious state.

<sup>b</sup>Residual psychomotor impairment after awakening from induction dose.

<sup>c</sup>When ketamine is administered as the induction agent (e.g., 5 to 10 mg/kg IM).

<sup>d</sup>When midazolam is administered as the induction agent (e.g., 0.15 mg/kg IV).

TABLE 8.3 Effects of Intravenous Induction Agents

Adverse Effect	Etomidate	Ketamine	Methohexital	Midazolam	Propofol	Remifentanyl
Adrenocorticoid suppression	+	–	–	–	–	–
Cerebral protection	+	–	+	+	+	–
Cardiovascular depression	–	–	++	+	++	–/+ <sup>a</sup>
Emergence delirium or euphoria	–	++	–	–	+	–
Myoclonus	+++	+	++	–	+	–/+ <sup>a</sup>
Nausea/vomiting	+++	++	++	+	– <sup>b</sup>	++
Pain on injection	++	–	+	–	++	–
Respiratory depression	++	–	++	+/+++	++	+/+++ <sup>a</sup>
Anxiolysis/amnesia	–	–/+ <sup>a</sup>	–	++++	–/+ <sup>a</sup>	–
Analgesia	–	+++	–	–	–	++++

<sup>a</sup>Dose-dependent effects.

<sup>b</sup>Has antiemetic effects.

+ to +++++, likelihood of adverse effect relative to other agents; –, no effect.

- Selection of an agent should be based on patient characteristics (e.g., history of postoperative nausea and vomiting [PONV], allergy profile, psychiatric history, and cardiovascular status).

### VOLATILE INHALATIONAL AGENTS

- Volatile inhalational agents are used to maintain general anesthesia. They produce all components of the anesthetic state to varying degrees (e.g., minimal analgesia), with immobility to surgical stimuli and amnesia as the predominant effects.
- Balanced anesthesia (using a combination of drugs) is most common as it allows for advantages of smaller doses of each agent thereby avoiding the disadvantages of high doses of individual agents.
- All volatile inhalation agents depress ventilation and dilate constricted bronchial musculature in a dose-dependent manner.
- Potency of volatile inhalation agents is compared in terms of minimum alveolar concentration (MAC). The lower an agent's MAC, the greater its potency. Pharmacologic and pharmacokinetic parameters of the available agents are in Table 8.4. Sevoflurane can be used for mask induction of general anesthesia because it is not as pungent as other agents.
- Opioids, benzodiazepines,  $\alpha_2$ -adrenergic agonists, and neuromuscular blocking agents potentiate the effects of volatile inhalation agents.

TABLE 8.4 Pharmacologic and Pharmacokinetic Properties of the Volatile Inhalation Agents

Property or Effect	Desflurane	Sevoflurane	Isoflurane	Enflurane
MAC in O <sub>2</sub> (adults)	6.0	1.71	1.15	1.7
Blood–gas partition coefficient <sup>a</sup>	0.42	0.69	1.46	1.91
Brain–blood partition coefficient <sup>b</sup>	1.29	1.7	1.6	1.4
Muscle–blood partition coefficient <sup>c</sup>	2.02	3.13	2.9	1.7
Fat–blood partition coefficient <sup>d</sup>	27.2	47.5	45	36
Metabolism (%)	0.02	3	0.2	2
Molecular weight (g)	168	201	184.5	184.5
Liquid density <sup>e</sup>	1.45	1.505	1.496	1.517

<sup>a</sup>The greater the blood–gas partition coefficient, the greater the blood solubility.

<sup>b</sup>The greater the brain–blood partition coefficient, the greater the brain solubility.

<sup>c</sup>The greater the muscle–blood partition coefficient, the greater the muscle solubility.

<sup>d</sup>The greater the fat–blood partition coefficient, the greater the fat solubility.

<sup>e</sup>Density determined at 25°C for desflurane, sevoflurane, and enflurane and at 20°C for sevoflurane.

MAC, minimum alveolar concentration to prevent movement in 50% of subjects.

TABLE 8.5 Classification of Neuromuscular Blocking Agents

Agent	Type of Block	Clinical Duration of Action <sup>a</sup>	Structure
Atracurium (Tracrium)	–	Intermediate	Benzylisoquinolinium
Cisatracurium (Nimbex)	–	Intermediate	Benzylisoquinolinium
Pancuronium (Pavulon)	–	Long	Steroidal
Rocuronium (Zemuron)	–	Intermediate	Steroidal
Succinylcholine (Anectine, Quelicin)	+	Ultrashort	Acetylcholine like
Vecuronium (Norcuron)	–	Intermediate	Steroidal

<sup>a</sup>Time from injection of agent to return to twitch height to 25% of control (time at which another dose of agent will need to be administered to maintain paralysis); in general, clinical duration of a standard intubating dose of ultrashort agents ranges from 3 to 5 minutes, intermediate agents from 30 to 40 minutes, and long agents from 60 to 120 minutes.

+, depolarizing; –, nondepolarizing.

## NEUROMUSCULAR BLOCKING AGENTS

- Neuromuscular blocking agents (NMBs) are used as an adjunct to general anesthesia to facilitate endotracheal intubation and relax skeletal muscle during surgery under general anesthesia. In the intensive care unit setting, they are used to paralyze mechanically ventilated patients.
- NMBs have no known effect on consciousness or pain threshold. Adequate sedation and analgesia must be ensured.
- NMB therapy is monitored using a peripheral nerve stimulator. Adequate blockade is present when the train-of-four count is 1 or 2 of 4 (one or two visible muscle twitches of a possible four).
- NMBs are classified by type of blockade produced, structure, and duration of action (Table 8.5).
- Several drugs interact with NMBs; always check for potential interactions.
- Rapid sequence intubation is indicated for patients at risk for aspiration of gastric contents. The goal of rapid sequence intubation is to minimize the time during which the airway is unprotected by intubating the patient as quickly as possible (e.g., within 60 seconds). The time to onset, normal intubating doses, and other information related to NMBs are shown in Table 8.6.
- When selecting an NMB, the patient's renal and hepatic function must be considered (Table 8.7).

**TABLE 8.6 Pharmacokinetic and Pharmacodynamic Parameters of Action of Neuromuscular Blocking Agents**

Agent	Cl (mL/kg/ minute)	Vd <sub>ss</sub> (L/kg)	Half-Life (minutes)	ED <sub>95</sub> (mg/kg)	Intubating Dose (mg/kg) <sup>a,b</sup>	Onset (minutes) <sup>c</sup>	Clinical Duration of Action of Initial Dose (minutes)
Atracurium <sup>d</sup>	5–7	0.2	20	0.2–0.25	0.4–0.5	2–3	25–30
Cisatracurium	4.6	0.15	22	0.05	0.15–0.2	2–2.5	50–60
Pancuronium	1–2	0.3	80–120	0.07	0.04–0.1	3–5	80–100
Rocuronium <sup>d</sup>	4	0.3	60–70	0.3	0.6–1.2	1–1.5	30–60
Succinylcholine <sup>d</sup>	37	0.04	0.65	0.25	1–1.5	1	5–20
Vecuronium <sup>d</sup>	4.5	0.4	50–70	0.05–0.06	0.1	2–3	25–30

<sup>a</sup>Dose when nitrous oxide–opioid technique is used.

<sup>b</sup>Intermittent maintenance doses to maintain paralysis, as a general rule, will be approximately 20% to 25% of the initial dose.

<sup>c</sup>Time to intubation.

<sup>d</sup>Also can be administered as a continuous infusion to maintain paralysis. Suggested infusion ranges under balanced anesthesia are atracurium, 4 to 12 mcg/kg/minutes; cisatracurium, 1 to 2 mcg/kg/minutes; rocuronium, 6 to 14 mcg/kg/minutes; succinylcholine, 50 to 100 mcg/kg/minutes; vecuronium, 0.8 to 2 mcg/kg/minutes.

Cl, clearance; ED<sub>95</sub>, effective dose causing 95% muscle paralysis; Vd<sub>ss</sub>, steady-state volume of distribution.

**TABLE 8.7 Elimination of Neuromuscular Blocking Agents**

Agent	Renal (%)	Hepatic (%)	Biliary (%)	Plasma
Atracurium	10		NS	Hofmann elimination, ester hydrolysis
Cisatracurium	NS		NS	Hofmann elimination
Pancuronium	80	10	5–10	
Rocuronium	10–25	10–20	50–70	
Succinylcholine				Plasma cholinesterase
Vecuronium	15–25	20–30	40–75	

NS, not significant.

## LOCAL ANESTHETICS

- Some surgical procedures can be performed under local or regional anesthesia (anesthesia selective for a part of the body) rather than general anesthesia (total body anesthesia where the patient is rendered unconscious).
- Epidural, spinal (intrathecal), peripheral nerve block, or local infiltration anesthesia are options to consider. Disadvantages for epidural, spinal, or peripheral nerve block include time to perform the procedure, possible complications or pain from invasive catheter placement, slow onset of effect, failure of technique, and potential toxicity.
- Local anesthetics are the mainstay of therapy (Table 8.8). They are often given in combination with other agents. Systemic absorption of local anesthetics is related to vascularity of injection site (intravenous > epidural > brachial plexus > subcutaneous).
- Potency of local anesthetics is related to lipid solubility. Choice of agent is based on surgical procedure and duration of action. Properties of local anesthetics are in Table 8.9.
- Addition of sodium bicarbonate (0.1 mEq; 0.1 mL of a 1 mEq/mL solution) to a local anesthetic will increase the pH of injection, resulting in faster onset of action and reduced pain of injection.

TABLE 8.8 Clinical Uses of Local Anesthetic Agents

Agent	Primary Clinical Use
<b>ESTERS</b>	
Chloroprocaine	Epidural
Cocaine	Topical
Tetracaine	Topical
<b>AMIDES</b>	
Bupivacaine	Local infiltration, nerve block, epidural, spinal
Lidocaine	Local infiltration, nerve block, epidural, spinal, topical, intravenous regional
Mepivacaine	Local infiltration, nerve block, epidural
Ropivacaine	Local infiltration, nerve block, epidural

TABLE 8.9 Physicochemical and Pharmacokinetic Properties of Local Anesthetic Agents

Agent	pK <sub>a</sub>	Potency	Toxicity	Onset	Duration <sup>a</sup>	Maximum Recommended Dose <sup>b</sup>	
						Plain (mg)	With Epinephrine (mg)
<b>ESTERS</b>							
Cocaine <sup>c</sup>	—	—	—	—	—	1.5 mg/kg	—
Chloroprocaine	9.1	Low	Very low	Very fast	Short	800	1,000
Tetracaine	8.4	High	Moderate	Slow	Very long	100 (topical)	200
<b>AMIDES</b>							
Bupivacaine	8.1	High	High	Slow	Long	175	225
Lidocaine	7.8	Moderate	Moderate	Fast	Moderate	300	500
Mepivacaine	7.7	Moderate	Moderate	Moderate	Moderate	300	500
Ropivacaine	8.1	High	Moderate	Slow	Long	300	—

<sup>a</sup>Depends on factors such as injection site, dose, and addition of epinephrine. In general, a short duration is <1 hour, a moderate duration is 1 to 3 hours, and a long or very long duration of action is 3 to 12 hours when the local anesthetic is administered without epinephrine.

<sup>b</sup>Maximum recommended single dose for infiltration or peripheral nerve block in 70-kg adults.

<sup>c</sup>Topical use only; concentrations >4% are not recommended owing to increased risk for systemic adverse effects.

## ANTIEMETIC AGENTS

- PONV typically lasts less than 24 hours. Multiple factors place adult patients at risk for developing PONV including female gender, history of PONV or motion sickness, nonsmoking status, use of postoperative opioids, duration of anesthesia, and general anesthesia with inhalational agents. Risk factors for pediatric patients include age above 3 years, surgery more than 30 minutes, strabismus surgery, and history of PONV in the child, parents, or siblings.
- Several classes of antiemetic agents are available. The action, dosing, and select adverse effects are shown in Table 8.10. Combination therapy is most efficacious for preventing PONV in a high-risk patient.
  - Droperidol, metoclopramide, and serotonin antagonists are most effective when given near the end of surgery.
  - Dexamethasone and neurokinin-1 antagonists are most effective when given at the beginning of surgery.
  - Multiple doses of phenothiazines may be needed due to their short duration of action.
  - Scopolamine patches should be applied before surgery as the onset is 4 hours after application.
- Perioperative use of opioids is associated with PONV. The use of NSAIDs, when appropriate, can reduce the need for postoperative opioids.



TABLE 8.10 Classification, Proposed Site(s) of Action, Usual Dose, and Adverse Effects of Select Antiemetic Drugs

Antiemetic Drug	Proposed Receptor Site of Action	Usual Dose <sup>a</sup>	Duration of Action	Adverse Effects	Comments
<b>BUTYROPHENONES</b>					
Droperidol	D <sub>2</sub>	<i>Adult:</i> 0.625–1.25 mg IV <i>Pediatric:</i> 20–50 mcg/kg IV for prevention; 10–20 mcg/kg IV for treatment	≤12–24 hours	Sedation, restlessness or agitation, hallucinations, hypotension (especially in hypovolemic patients), EPS	Monitor ECG for QT prolongation, torsades de pointes
<b>PHENOTHIAZINES</b>					
Prochlorperazine	D <sub>2</sub>	<i>Adult:</i> 5–10 mg IM or IV; 25 mg PR <i>Pediatric:</i> <sup>b</sup> 0.1–0.15 mg/kg IM, 0.1 mg/kg PO, 2.5 mg PR	4–6 hours (12 hours when given PR)	Sedation, hypotension (especially in hypovolemic patients), EPS	
<b>ANTIMUSCARINICS</b>					
Promethazine	D <sub>2</sub> , H <sub>1</sub> , M <sub>1</sub>	<i>Adult:</i> 6.25–25 mg IM, IV, or PR <sup>c</sup>	4–6 hours	Sedation, hypotension (especially in hypovolemic patients), EPS, serious tissue injury from inadvertent arterial injection or IV extravasation	Limit concentration to 25 mg/mL; dilute in 10–20 mL of saline, inject through a running line, and advise patient to report IV-site discomfort
Diphenhydramine	H <sub>1</sub> , M <sub>1</sub>	<i>Adult:</i> 12.5–50 mg IM or IV <i>Pediatric:</i> 1 mg/kg IV, PO (max: 25 mg for children younger than 12 years)	4–6 hours	Sedation, dry mouth, blurred vision, urinary retention	
Scopolamine	M <sub>1</sub>	<i>Adult:</i> 1.5 mg transdermal patch	72 hours <sup>d</sup>	Sedation, dry mouth, visual disturbances, dysphoria, confusion, disorientation, hallucinations	Apply at least 4 hours before end of surgery; wash hands after handling patch; not appropriate for children, elderly, or patients with renal or hepatic impairment

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**BENZAMIDES**

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Metoclopramide	D <sub>2</sub>	<i>Adult:</i> 20 mg IV <i>Pediatric:</i> 0.25 mg/kg IV	≤6 hours	Sedation, hypotension, EPS	Consider for rescue if N/V is believed to be caused by gastric stasis; reduce dose to 5 mg in renal impairment; give slow IV push
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**SEROTONIN ANTAGONISTS**

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Ondansetron	5-HT <sub>3</sub>	<i>Adult:</i> 4 mg IV <i>Pediatric:</i> 0.05–0.1 mg/kg IV	Up to 24 hours	Headache, lightheadedness, constipation, QT prolongation
Dolasetron	5-HT <sub>3</sub>	<i>Adult:</i> 12.5 mg IV <i>Pediatric:</i> 0.35 mg/kg IV	Up to 24 hours	Headache, lightheadedness, constipation, QT prolongation
Granisetron	5-HT <sub>3</sub>	<i>Adult:</i> 1 mg IV <i>Pediatric:</i> Not known	Up to 24 hours	Headache, lightheadedness, constipation, QT prolongation
Palonosetron	5-HT <sub>3</sub>	<i>Adult:</i> 0.075 mg IV	Up to 24 hours	Headache, constipation, QT prolongation

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**NK<sub>1</sub> ANTAGONISTS**

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Aprepitant	NK <sub>1</sub>	<i>Adult:</i> 40 mg PO up to 3 hours before surgery	Up to 24 hours	Headache
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**OTHER**

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Dexamethasone	Unknown	<i>Adult:</i> 4 mg IV <i>Pediatric:</i> 0.15 mg/kg IV	Up to 24 hours	Hyperglycemia, fluid retention
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<sup>a</sup>Unless otherwise indicated, pediatric doses should not exceed adult doses.

<sup>b</sup>Children >10 kg or older than 2 years only. Change from IM to PO as soon as possible. When administering PR, the dosing interval varies from 8 to 24 hours, depending on the child's weight.

<sup>c</sup>Maximum of 12.5 mg in children younger than 12 years.

<sup>d</sup>Remove after 24 hours. Instruct patient to thoroughly wash the patch site and their hands.

D<sub>2</sub>, dopamine type 2 receptor; ECG, electrocardiogram; EPS, extrapyramidal symptoms (e.g., motor restlessness or acute dystonia); 5-HT<sub>3</sub>, serotonin type 3 receptor; H<sub>1</sub>, histamine type 1 receptor; IV, intravenous; IM, intramuscular; M<sub>1</sub>, muscarinic cholinergic type 1; NK<sub>1</sub>, neurokinin type 1 receptor; N/V, nausea or vomiting; PO, orally (by mouth); PR, per rectum.

## ANALGESICS

- Most patients will have pain at rest after surgery, with the magnitude generally correlating to the invasiveness of the procedure. Significant individual differences in pain perception exist.
- Unrelieved acute postoperative pain has detrimental physiological and psychological effects: impaired pulmonary function, thromboembolism, tachycardia, hypertension, increased cardiac work, impaired immune function, nausea, vomiting, anxiety, fatigue, and fear.
- Pain should be prevented; once established, severe pain is difficult to control.
- Goals of therapy are to provide pain relief while minimizing analgesic-related side effects, allow patients to return to daily activities, and minimize the detrimental effects from unrelieved pain.
- Treatment options include systemic administration of pain medications (e.g., acetaminophen, NSAIDs, opioids), patient-controlled analgesia (PCA; on-demand administration of IV opioids), epidural analgesia (continuous and on-demand), local nerve blockade, and non-pharmacologic measures (e.g., application of heat or cold, guided imagery, music, relaxation).
- Local anesthetics, opioids, acetaminophen, and NSAIDs can be used alone or in combination. For mild to moderate pain, consider nonopioid analgesics (acetaminophen, NSAIDs); opioids are indicated for moderate to severe pain.
- **PCA.** Small frequent opioid doses are provided on demand, allowing the patient to control his own pain. Frequent doses are intended to maintain analgesia. Therapy can be individualized. Patients must be able to understand the concept behind PCA and to operate the drug administration button. Drug of choice is based on patients' past experiences, allergies, adverse effects, and organ function. Adult analgesic doses and lock-out intervals are shown in Table 8.11. Routine use of basal (continuous) infusion of opioids is not recommended for acute pain management. Adverse effects from opioids include sedation, confusion, euphoria, nausea, vomiting, constipation, urinary retention, and pruritus.
- **Epidural Analgesia:** offers superior pain relief compared with traditional parenteral routes and allows for reduced systemic effects (GI, pulmonary, cardiovascular). Postoperative pain should be localized at an appropriate level for placement in the epidural space.
  - Most commonly an opioid and local anesthetic are administered in combination (Table 8.12). The spinal actions, efficacy, and adverse effects of opioids and local anesthetics given by the epidural route are in Table 8.13. Choice of agent is based on pharmacokinetic differences between the agents (Table 8.14).
  - Additional adjunctive analgesics may be needed for breakthrough pain.
  - Use of an anticoagulant can increase the risk of epidural or spinal hematoma formation, which can lead to prolonged or permanent paralysis. Use of antiplatelet or anticoagulant drugs also results in greater risk of hemorrhagic complications. Timing of catheter removal is important (e.g., at least 12 hours after the last dose of prophylactic doses of LMWH, with subsequent LMWH to occur a minimum of 2 hours after catheter removal). When

TABLE 8.11 **Adult Analgesic Dosing Recommendations for Intravenous Patient-Controlled Analgesia<sup>a</sup>**

Drug	Usual Concentration	Demand Dose (mg)		Lock-Out Interval (minutes)
		Usual	Range	
Fentanyl (as citrate)	10 mcg/mL	0.01–0.02	0.01–0.04	10
Hydromorphone hydrochloride	0.2 mg/mL	0.2–0.3	0.1–0.4	10
Morphine sulfate	1 mg/mL	1–2	0.5–2.5	10

<sup>a</sup>Analgesic doses are based on those required by a healthy 55- to 70-kg, opioid-naïve adult. Analgesic requirements vary widely among patients. Doses may need to be adjusted because of age, condition of the patient, and prior opioid use.

TABLE 8.12 **Adult Analgesic Dosing Recommendations for Epidural Infusion**

Drug Combination <sup>a</sup>	Infusion Concentration <sup>b</sup>	Usual Infusion Rate <sup>b</sup> (mL/hour)
Morphine + bupivacaine	12.5–25 mcg/mL (M) 0.5–1.25 mg/mL (B)	4–10
Hydromorphone + bupivacaine	3–10 mcg/mL (H) 0.5–1.25 mg/mL (B)	4–10
Fentanyl + bupivacaine	2–5 mcg/mL (F) 0.5–1.25 mg/mL (B)	4–10
Sufentanil + bupivacaine	1 mcg/mL (S) 0.5–1.25 mg/mL (B)	4–10

<sup>a</sup>Use only preservative-free products and preservative-free 0.9% sodium chloride as the admixture solution.

<sup>b</sup>Exact concentrations and rates are institution specific. Initial concentration and rate often depend on the age and general condition of the patient and the location of the catheter.

B, bupivacaine; F, fentanyl; H, hydromorphone; M, morphine; S, sufentanil.

TABLE 8.13 **A Comparison of the Spinal Actions, Efficacy, and Adverse Effects of Opioids and Local Anesthetics<sup>a</sup>**

	Opioids	Local Anesthetics
<b>ACTIONS</b>		
Site of action	Substantia gelatinosa of dorsal horn of spinal cord <sup>b</sup>	Spinal nerve roots
Modalities blocked	“Selective” block of pain conduction	Blockade of pain nerve fibers; can block sensory or motor fibers
<b>EFFICACY</b>		
Surgical pain	Partial relief	Complete relief possible
Labor pain	Partial relief	Complete relief
Postoperative pain	Fair or good relief	Complete relief
Adverse effects	Nausea, vomiting, sedation, pruritus, constipation or ileus, urinary retention, respiratory depression	Hypotension, urinary retention, loss of sensation, loss of motor function (patient may not be able to bear weight and ambulate)

<sup>a</sup>Epidurally administered morphine and local anesthetics exert their effects mainly by a spinal mechanism of action; lipophilic opioids such as fentanyl and sufentanil achieve therapeutic plasma concentrations when administered epidurally and therefore exert their effects by a systemic mechanism of action.

<sup>b</sup>Other sites where opioid receptor binding sites are present.

TABLE 8.14 **Pharmacokinetic Comparison of Common Epidural Opioid Analgesics<sup>115,116,124,125</sup>**

Agent	Partition Coefficient <sup>a</sup>	Onset of Action of Bolus (minutes)	Duration of Action of Bolus (hours)	Dermatomal Spread
Fentanyl	955	5	2–4	Narrow
Hydromorphone	525	15	6–12	Intermediate
Morphine sulfate (Duramorph)	1	30	12–24	Wide
Sufentanil	1,737	5	2–4	Narrow

<sup>a</sup>Octanol–water partition coefficient; used to assess lipophilicity; higher numbers indicate greater lipophilicity.

treatment doses of LMWH or fondaparinux are used, the catheter should be removed before the first dose is given, with the first dose of anticoagulant given at least 2 hours after catheter removal.

- Pruritus has been seen with almost all opioids, usually within 2 hours; it generally subsides as the opioid effect wears off. Use of a small dose of a  $\mu$ -antagonist (naloxone 0.04 mg or

nalbuphine 2.5 mg) can reverse opioid side effects without affecting analgesia. Although rare, respiratory depression is the most dangerous adverse effect of epidural opioids. Adverse effects of epidural anesthetics include hypotension, urinary retention, lower limb paresthesias, numbness, or lower limb motor weakness.

- Multimodal pain management is often required to provide postoperative analgesia. A comparison of select opioids for perioperative pain management is shown in Table 8.15. Commonly used analgesic drugs and nonpharmacologic techniques for postoperative pain management are summarized in Table 8.16.

TABLE 8.15 Comparison of Select Opioids for Perioperative Pain Management

Property	Intravenous Morphine	Intravenous Hydromorphone	Intravenous Fentanyl	Oral Hydrocodone	Oral Oxycodone
Onset	5 minutes	≤5 minutes	≤2 minutes	30–60 minutes	30–60 minutes
Peak effect	15–20 minutes	10–20 minutes	5–7 minutes	1–2 hours	1.5–2 hours
Duration	3–4 hours	2–3 hours	30–60 minutes	4–6 hours	3–4 hours
Approximate equianalgesic dose	2 mg	0.3 mg	20 mcg	4 mg	4 mg

TABLE 8.16 Commonly Used Analgesic Drugs and Nonpharmacologic Techniques for Postoperative Pain Management

Type of Agent	Examples	Potential Adverse Effects
Local anesthetics	Tissue infiltration, wound instillation, peripheral nerve block, epidural	Tingling, numbness, motor weakness, hypotension, CNS and cardiac effects from systemic absorption
NSAIDs	Ketorolac (IV, IM, oral), ibuprofen (oral), naproxen (oral), celecoxib (oral)	GI upset, edema, hypertension, dizziness, drowsiness, GI bleeding, operative site bleeding (not celecoxib)
Other nonopioids	Acetaminophen (oral, intravenous, rectal)	GI upset, hepatotoxicity, hypotension (IV formulation)
Nonpharmacologic	Ice or cold therapy	Excessive vasoconstriction, skin irritation
Opioid combination products (oral)	Distraction, music, deep breathing for relaxation Hydrocodone + acetaminophen, oxycodone + acetaminophen	Nausea, vomiting, pruritus, constipation, rash, sedation, respiratory depression
Opioids	Morphine (IV, epidural), hydromorphone (IV, epidural), fentanyl (IV, epidural), oxycodone (oral)	Nausea, vomiting, pruritus, constipation, rash, sedation, respiratory depression

CNS, central nervous system; GI, gastrointestinal; IM, intramuscular; IV, intravenous; NSAIDs, nonsteroidal anti-inflammatory drugs.

## Acid–Base Disorders\*

### General Principles

- To protect body proteins, acid–base balance must be tightly controlled in an attempt to maintain a normal extracellular pH of 7.35 to 7.45, and an intracellular pH of 7.0 to 7.3.
- Acid–base balance is normally maintained by the primary extracellular buffer system of  $\text{HCO}_3^-$ – $\text{CO}_2$ .
- Serum electrolytes are obtained to calculate the anion gap, an estimate of the unmeasured cations and anions in serum (helpful in determining the probable cause of a metabolic acidosis).
- Severe acid–base disorders can affect multiple organ systems, including cardiovascular (impaired contractility, arrhythmias), pulmonary (impaired oxygen delivery, respiratory muscle fatigue, dyspnea), renal (hypokalemia, nephrolithiasis), or neurologic (decreased cerebral blood flow, seizures, coma).
- The relationship between pH and the concentration of acid–base pairs is:

$$\text{pH} = 6.1 + \log [\text{HCO}_3^- / (0.03)(\text{PaCO}_2)]$$

- Anion gap is calculated as follows:

$$\text{Anion gap} = \text{Na}^+ - (\text{Cl}^- + \text{HCO}_3^-)$$

- Laboratory values in simple acid–base disorders are shown in Table 9.1. Normal compensation mechanisms are shown in Table 9.2.

TABLE 9.1 Laboratory Values in Simple Acid–Base Disorders

Disorder	Arterial pH	Primary Change	Compensatory Change
Metabolic acidosis	↓	↓ $\text{HCO}_3^-$	↓ $\text{PaCO}_2$
Respiratory acidosis	↓	↑ $\text{PaCO}_2$	↑ $\text{HCO}_3^-$
Metabolic alkalosis	↑	↑ $\text{HCO}_3^-$	↑ $\text{PaCO}_2$
Respiratory alkalosis	↑	↓ $\text{PaCO}_2$	↓ $\text{HCO}_3^-$

TABLE 9.2 Normal Compensation in Simple Acid–Base Disorders

Disorder	Compensation <sup>a</sup>
Metabolic acidosis	↓ $\text{PaCO}_2$ (mm Hg) = $1.0 - 1.2 \times \text{HCO}_3^-$ (mEq/L)
Metabolic alkalosis	↑ $\text{PaCO}_2$ (mm Hg) = $0.5 - 0.7 \times \uparrow\text{HCO}_3^-$ (mEq/L)
Respiratory acidosis	
Acute	↑ $\text{HCO}_3^-$ (mEq/L) = $0.1 \times \uparrow\text{PaCO}_2$ (mm Hg)
Chronic	↑ $\text{HCO}_3^-$ (mEq/L) = $0.4 \times \uparrow\text{PaCO}_2$ (mm Hg)
Respiratory alkalosis	
Acute	↓ $\text{HCO}_3^-$ (mEq/L) = $0.2 \times \downarrow\text{PaCO}_2$ (mm Hg)
Chronic	↓ $\text{HCO}_3^-$ (mEq/L) = $0.4 - 0.5 \times \downarrow\text{PaCO}_2$ (mm Hg)

<sup>a</sup>Based on change from normal  $\text{HCO}_3^- = 24$  mEq/L and  $\text{PaCO}_2 = 40$  mm Hg.

\*The reader is referred to Chapter 9, Acid–Base Disorders, written by Luis S. Gonzalez, III, PharmD, BCPS, and Raymond W. Hammond, PharmD, in the 10th edition of *Applied Therapeutics: The Clinical Use of Drugs* for a more in-depth discussion. All notations to reference numbers are based on the reference list at the end of that chapter. The editor of this handbook expresses her thanks to Drs. Gonzalez and Hammond and acknowledges that this chapter is based upon their work.

## Patient Assessment

- Laboratory data used to evaluate acid–base status are arterial pH, arterial carbon dioxide tension ( $\text{PaCO}_2$ ), and serum bicarbonate ( $\text{HCO}_3^-$ ). Normal arterial blood gas values are shown in Table 9.3.
- When arterial pH is  $< 7.35$ , that patient is acidemic; when arterial pH is  $> 7.45$ , the patient is alkalemic.
- Evaluation of acid–base disorders should be done using a stepwise approach to avoid missing complicated disorders that may not be readily apparent.
  - Obtain a detailed patient history and clinical assessment.
  - Check the arterial blood gas, sodium, chloride, and  $\text{HCO}_3^-$ . Identify all abnormalities in pH,  $\text{PaCO}_2$ , and  $\text{HCO}_3^-$ .
  - Determine which abnormalities are primary and which are compensatory on the basis of pH.
    - If the pH is  $< 7.40$ , then a respiratory or metabolic acidosis is primary.
    - If the pH is  $> 7.40$ , then a respiratory or metabolic alkalosis is primary.
    - If the pH is normal (7.40) and there are abnormalities in  $\text{PaCO}_2$  and  $\text{HCO}_3^-$ , a mixed disorder is probably present because metabolic and respiratory compensations rarely return the pH to normal.
  - Always calculate the anion gap. If it is  $\geq 20$ , a clinically important metabolic acidosis is usually present even if the pH is within a normal range.
  - If the anion gap is increased, calculate the excess anion gap (anion gap  $- 10$ ). Add this value to the  $\text{HCO}_3^-$  to obtain corrected value.
    - If the corrected value is  $> 26$ , a metabolic alkalosis is also present.
    - If the corrected value is  $< 22$ , a nonunion gap metabolic acidosis is also present.
  - Consider other laboratory tests to further differentiate the cause of the disorder.
    - If the anion gap is normal, consider calculating the urine anion gap.
    - If the anion gap is high and a toxic ingestion is expected, calculate an osmolal gap.
    - If the anion gap is high, measure serum ketones and lactate.
  - Compare the identified disorders to the patient history and begin patient-specific therapy.

## Treatment

- Treatment is directed at the underlying cause of the disturbance rather than merely the change in pH.

## Metabolic Acidosis

- Metabolic acidosis is characterized by loss of bicarbonate (e.g., diarrhea), decreased acid excretion by the kidney (e.g., renal tubular acidosis), or increased endogenous acid production (e.g., diabetic ketoacidosis). Table 9.4 lists the common causes of metabolic acidosis.
- **Normal Anion Gap (Hyperchloremic) Metabolic Acidosis**
  - Normally caused by loss of bicarbonate
  - Can be further classified as hypokalemic or hyperkalemic

TABLE 9.3 Normal Arterial Blood Gas Values

ABGs	Normal Range
pH	7.36–7.44
$\text{PaO}_2$	90–100 mm Hg
$\text{PaCO}_2$	35–45 mm Hg
$\text{HCO}_3^-$	22–26 mEq/L

ABG, arterial blood gas.

TABLE 9.4 Common Causes of Metabolic Acidosis

Normal AG	Elevated AG
<b>Hypokalemic</b>	<b>Renal Failure</b>
Diarrhea	<b>Lactic Acidosis</b> (see Table 9.5)
Fistulous disease	<b>Ketoacidosis</b>
Ureteral diversions	Starvation
Type 1 RTA	Ethanol
Type 2 RTA	Diabetes mellitus
Carbonic anhydrase inhibitors	<b>Drug Intoxications</b>
<b>Hyperkalemic</b>	Ethylene glycol
Hypoaldosteronism	Methanol
Hydrochloric acid or precursor	Salicylates
Type 4 RTA	
Potassium-sparing diuretics	
Amiloride	
Spirolactone	
Triamterene	

AG, anion gap; RTA, renal tubular acidosis.

TABLE 9.5 Common Causes of Lactic Acidosis

Type A	Type B
Anemia	Diabetes mellitus
Carbon monoxide poisoning	Liver failure
Congestive heart failure	Renal failure
Shock	Seizure disorder
Sepsis	Leukemia
	Drugs
	Didanosine
	Ethanol
	Isoniazid
	Metformin
	Methanol
	Salicylates
	Zidovudine

- **Metabolic Acidosis with Elevated Anion Gap**

- An elevated anion gap often indicates lactic acidosis resulting from intoxications or ketoacidosis induced by diabetes mellitus, starvation, or alcohol.
- Lactic acidosis has been divided into Type A (associated with inadequate delivery of oxygen to the tissue) and Type B (associated with defective oxygen utilization at the mitochondrial level) (Table 9.5).
- If IV bicarbonate is given, the amount required to correct serum  $\text{HCO}_3^-$  and arterial pH can be estimated using the equation below. Bicarbonate administration can result in over alkalinization and a paradoxical transient intracellular acidosis.

$$\text{Bicarbonate dose (mEq)} = 0.5 \text{ (L/kg)} \times \text{body weight (kg)} \\ \times \text{desired increase in serum } \text{HCO}_3^- \text{ (mEq/L)}$$

- Tromethamine acetate (THAM) is an alternative to  $\text{HCO}_3^-$  for use as an alkalinizing agent. Its use is contraindicated in anuric or uremic patients.



## Metabolic Alkalosis

- Metabolic alkalosis is associated with an increase in serum  $\text{HCO}_3^-$  concentration and a compensatory increase in  $\text{PaCO}_2$  (caused by hypoventilation). Metabolic alkalosis can be classified according to saline responsiveness (Table 9.6).
- Treatment should be directed at removing the underlying cause.
- The initial goal is to correct fluid deficits and replace chloride and potassium.
- The severity of alkalosis dictates how rapidly fluid and electrolytes should be administered.
- Patients unresponsive to sodium and potassium therapy or those at risk for complications can be treated with acetazolamide or dilute hydrochloric acid.

$$\text{Dose of HCl (mEq)} = 0.5 \times \text{body weight (kg)} \times (\text{plasma bicarbonate} - 24)$$

## Respiratory Acidosis

- Respiratory acidosis occurs as a result of inadequate ventilation by the lungs. Causes are shown in Table 9.7.
- Common symptoms are dyspnea, headache, drowsiness, disorientation, confusion, delirium, hallucinations, and flushing.
- Treatment involves correcting the underlying disorder. Treatment with IV sodium bicarbonate is not typically recommended because an absolute deficiency of  $\text{HCO}_3^-$  is not present.

TABLE 9.6 Classification of Metabolic Alkalosis

Saline-Responsive	Saline-Resistant
Diuretic therapy	Normotensive
Extracellular volume contraction	Potassium depletion
Gastric acid loss	Hypercalcemia
Vomiting	Hypertensive
Nasogastric suction	Mineralocorticoids
Exogenous alkali administration	Hyperaldosteronism
Blood transfusions	Hyperreninism
	Licorice

TABLE 9.7 Common Causes of Respiratory Acidosis

<b>Airway Obstruction</b>	<b>Cardiopulmonary</b>
Foreign body aspiration	Cardiac arrest
Asthma	Pulmonary edema or infiltration
COPD	Pulmonary embolism
$\beta$ -adrenergic blockers	Pulmonary fibrosis
<b>CNS Disturbances</b>	<b>Neuromuscular</b>
Cerebral vascular accident	Amyotrophic lateral sclerosis
Sleep apnea	Guillain-Barré syndrome
Tumor	Myasthenia gravis
CNS depressant drugs	Hypokalemia
Barbiturates	Hypophosphatemia
Benzodiazepines	Drugs
Opioids	Aminoglycosides
	Antiarrhythmics
	Lithium
	Phenytoin

CNS, central nervous system; COPD, chronic obstructive pulmonary disease.

## Respiratory Alkalosis

- Respiratory alkalosis usually is not a severe disorder. Excessive rate or depth of respiration results in increased excretion of  $\text{CO}_2$ , fall in  $\text{PaCO}_2$ , and rise in arterial pH.
- Common causes of respiratory alkalosis are shown in Table 9.8.
- Symptoms include deep, rapid breathing, paresthesias of the extremities, lightheadedness, and tachycardia.
- Treatment involves correcting the underlying disorder. In cases of hyperventilation associated with anxiety, the patient should rebreathe expired air from a paper bag.

**TABLE 9.8 Common Causes of Respiratory Alkalosis**

<b>CNS Disturbances</b>	<b>Pulmonary</b>
Bacterial septicemia	Pneumonia
Cerebrovascular accident	Pulmonary edema
Fever	Pulmonary embolus
Hepatic cirrhosis	<b>Tissue Hypoxia</b>
Hyperventilation	High altitude
Anxiety-induced	Hypotension
Voluntary	HF
Meningitis	<b>Other</b>
Pregnancy	Excessive mechanical ventilation
Trauma	Rapid correction of metabolic acidosis
Drugs	
Progesterone derivatives	
Respiratory stimulants	
Salicylate overdose	

HF, heart failure; CNS, central nervous system.

# Fluid and Electrolyte Disorders\*

## General Principles

- Body water distributes into intracellular fluid and extracellular fluid compartments.

$$\text{Total body water} = 0.6 \text{ L/kg} \times \text{lean body weight (for men)}$$

$$\text{Total body water} = 0.5 \text{ L/kg} \times \text{lean body weight (for women)}$$

- The kidneys play an important role in maintaining a constant extracellular environment by regulating the excretion of water and various electrolytes.
- Potassium, magnesium, and phosphate are the major ions in the intracellular compartment. Sodium, chloride, and bicarbonate are the predominant ions in the extracellular space.
- Osmolality is defined as the number of particles per kilogram of water (mOsm/kg). It is determined by the number of particles, not by particle size or valence. Normal plasma osmolality is 280 to 295 mOsm/kg.
- Plasma osmolality is maintained within normal limits through a delicate balance between water intake and excretion. The primary osmoles that affect water distribution between the interstitium and the plasma are plasma proteins. Water moves from an area of low osmolality to one of high osmolality.

$$P(\text{osm}) = (\text{Na in mmol/L}) + \frac{\text{glucose(mg/dL)}}{18}$$

- An osmolal gap exists when the difference between the measured and calculated osmolality is  $>10$  mOsm/kg; it signifies the presence of unidentified particles.
- Antidiuretic hormone (ADH) plays an important role in maintaining fluid balance in the body.
- Aldosterone is the main regulatory hormone for sodium homeostasis.

## Disorders in Volume Regulation

- Because water and sodium are inherently linked, the assessment of volume status and selection of a replacement fluid require examination of sodium concentration.
- Signs of volume depletion include orthostatic hypotension, dry mucous membranes, poor skin turgor, and the absence of edema.
- When renal perfusion is decreased, the renin–angiotensin–aldosterone system is activated; proximal reabsorption of sodium and chloride is increased.
- The choice of replacement fluid to replenish the extracellular volume depends on the sodium status. The treatment goal is to achieve a positive fluid balance.
  - In patients who are neither hypo- nor hypernatremic, normal saline should be used.
  - In patients who are hypernatremic, half-isotonic saline or dextrose solutions should be used.

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\*The reader is referred to Chapter 10, Fluid and Electrolyte Disorders, written by Alan H. Lau, PharmD, and Priscilla P. How, PharmD, BCPS, in the 10th edition of *Applied Therapeutics: The Clinical Use of Drugs* for a more in-depth discussion. All notations to reference numbers are based on the reference list at the end of that chapter. The editor of this handbook expresses her thanks to Drs. Lau and How and acknowledges that this chapter is based on their work.

- **Nephrotic syndrome** is characterized by hypoalbuminemia, urine protein excretion  $> 3.5$  g/day, hyperlipidemia, lipiduria, and edema. Hyponatremia is present.
  - Salt restriction is important to control generalized edema. Modest restriction to approximately 50 mEq/day may be sufficient to maintain neutral sodium balance.
  - For patients who are very sodium avid (urine sodium concentration  $< 10$  mEq/mL), it is difficult to sufficiently restrict sodium intake. Slowing the rate of edema formation rather than hastening its resolution should be the treatment goal.
  - Loop diuretics are the mainstay of therapy for nephrotic edema.
  - Infusions of albumin provide only temporary relief and should be used only for resistant edema.

## Disorders in Osmoregulation (Sodium)

### HYPONATREMIA

- A patient may have hypotonic, isotonic, or hypertonic hyponatremia depending on plasma osmolality.
- Clinical presentation and treatment of hyponatremia is shown in Table 10.1.
  - For each 100 mg/dL increment in serum glucose, serum sodium decreases by 1.3 to 1.6 mEq/L.
  - Calculation of the sodium deficit will determine how much sodium replacement is required.

$$\text{Na Deficit} = \text{TBW} \times (\text{desired} - \text{current Na concentration})$$

- **Hypotonic hypovolemic hyponatremia** can occur with volume depletion and extracellular fluid depletion. Treatment involves sodium replacement to correct the deficit. Approximately one-third of the deficit can be replaced in the first 12 hours at a rate of  $< 0.5$  mEq/L/hour. The balance can be replaced over the next several days.
- **Hypervolemic hypotonic hyponatremia** is caused by excess water intake relative to sodium. It is also seen in patients with heart failure, liver or renal failure, and nephrotic syndrome. Water restriction is the mainstay of therapy.
- **Normovolemic hypotonic hyponatremia** can be caused by syndrome of inappropriate antidiuretic hormone (SIADH). Persistent ADH secretion together with water ingestion results in hyponatremia. All fluids should be reduced. Diuretics (furosemide 20–40 mg/day) or demeclocycline (300–600 mg twice daily) are treatment options.
- Neurological symptoms can be seen with acute or severe hyponatremia. Low plasma osmolality causes water to move into the brain causing cerebral edema, increased intracranial pressure, and central nervous system symptoms.
- Rapid or overly aggressive correction of hyponatremia can result in osmotic demyelination, a constellation of neurologic findings (seizures, akinetic mutism, features of pontine disorder). While severe hyponatremia is associated with high rates of morbidity and mortality, treatment can also result in morbidity.
- Vasopressin receptor antagonists (“vaptans”) are a class of drugs for the treatment of hyponatremia.
  - **Conivaptan** is a parenteral product given by IV administration indicated for euvolemic and hypervolemic hyponatremia. It is for short-term (4 days) inpatient use only.
  - **Tolvaptan** is an oral agent indicated for hypervolemic and euvolemic hyponatremia in patients with heart failure, cirrhosis, and SIADH.

### HYPERNATREMIA

- Hyponatremia can occur with normal total body sodium and pure water loss, low total body sodium with hypotonic fluid loss, and high total body sodium as a result of salt gain.

TABLE 10.1 Clinical Presentation and Treatment of Hyponatremia

Na <sup>+</sup> and H <sub>2</sub> O Status	Clinical Presentation/Cause	Treatment
<b>EDEMATOUS, FLUID OVERLOAD (HYPERVOLEMIC, HYPOTONIC)</b>		
↑ Total body Na <sup>+</sup> ↑↑ Total body H <sub>2</sub> O	<i>Cirrhosis/ HF/ nephrotic syndrome:</i> A ↓ in renal blood flow activates renin-angiotensin system. ↑ Aldosterone leads to ↑ Na <sup>+</sup> , and ↑ ADH leads to free H <sub>2</sub> O retention. Urine Na <sup>+</sup> is low (0–20 mEq/L) and urine osmolality ↓. Diuretics can induce paradoxical effects on urine Na <sup>+</sup> and osmolality. This form also can occur in patients with renal failure who drink excessive amounts of water. Patients have symptoms of fluid overload (ascites, distended neck veins, edema).	Fluid and Na <sup>+</sup> restriction. Correct underlying disorder (e.g., paracentesis for ascites). Diurese cautiously <sup>4</sup> ; avoid ↓ ECF and accompanying ↓ tissue perfusion. ↑ BUN may indicate overly rapid diuresis. <i>Conivaptan:</i> Loading dose of 20 mg IV for 30 minutes, followed by 20 mg IV as continuous infusion for 24 hours for an additional 1–3 days; may titrate up to maximal dose of 40 mg/day; maximal duration is 4 days after the loading dose. Dedicated IV line recommended and site of peripheral IV lines should be changed every 24 hours. Caution if used together with fluid restriction. <i>Tolvaptan:</i> Start 15 mg PO once daily. Dose may be increased at intervals of at least 24 hours to 30 mg PO once daily and then to a maximum of 60 mg PO once daily as needed. Caution if used together with fluid restriction.
<b>NONEDEMATOUS HYPOVOLEMIC (HYPOTONIC WITH ECF DEPLETION)</b>		
↓↓ Total body Na <sup>+</sup> ↓ Total body H <sub>2</sub> O	Occurs in GI fluid loss (e.g., diarrhea) with hypotonic electrolyte-poor fluid replacement, overdiuresis, “third spacing,” Addison disease, renal tubular acidosis, and osmotic diuresis. Replacement of fluid losses with solute-free fluid predisposes these patients to hyponatremia. Kidneys concentrate urine to conserve fluid (urine Na <sup>+</sup> <10 mEq/L). <i>Symptoms:</i> nonedematous; ECF depletion (collapsed neck veins, dehydration, orthostasis). <i>Neurologic symptoms:</i> see “Hyponatremia: Neurologic Manifestations” in text.	Discontinue diuretics. Replace fluid and electrolyte (especially K <sup>+</sup> ) losses. Saline of 0.9% preferred. If Na <sup>+</sup> deficit <sup>b</sup> is severe, then use 3%–5% saline.
<b>NONEDEMATOUS, NORMOVOLEMIC (NORMOVOLEMIC, HYPOTONIC)</b>		
↓ Total body Na <sup>+</sup> ↑ Total body H <sub>2</sub> O	<i>SIADH<sup>a</sup>:</i> Hyponatremia, hypo-osmolality, renal Na <sup>+</sup> wasting (>40 mEq/L), absence of fluid depletion, U <sub>osm</sub> > P <sub>osm</sub> , normal renal and adrenal function. Free H <sub>2</sub> O retained while Na <sup>+</sup> lost. <i>Causes:</i> (a) ADH production (infectious disease, vascular disease, cerebral neoplasm, cancer of lung, pancreas, duodenum); (b) exogenous ADH administration; (c) drugs; (d) psychogenic polydipsia.	See earlier for dosing of VRA (conivaptan and tolvaptan) <i>Chronic treatment:</i> Restrict fluids to less than urine loss. Demeclocycline (300–600 mg BID) induces reversible diabetes insipidus. Emergency treatment for unresponsive patients includes furosemide diuresis to achieve negative H <sub>2</sub> O balance with careful replacement of Na <sup>+</sup> and K <sup>+</sup> using hypertonic saline solutions. <sup>c</sup>

<sup>4</sup>Remove estimated excess free water with IV furosemide (1 mg/kg). Repeat as necessary. Because furosemide generates a urine that resembles 0.5% NaCl, urine losses of sodium and potassium must be carefully measured and replaced hourly with hypertonic salt solutions. Correction rate: 1 to 2 mEq Na/hour in symptomatic patients; 0.5 mEq/hour in asymptomatic patients.

<sup>b</sup>Estimate sodium deficit: (mEq) = TBW (sodium desired – sodium observed). Rate of sodium and fluid repletion used depends on severity. Mild: replace with NS. First one-third for 6 to 12 hours at a rate of <0.5 mEq/L/hour, remaining two-thirds for 24 to 48 hours. Severe (e.g., seizures): Use 3% to 5% saline, rate gauged by patient’s ability to tolerate sodium and volume load. Monitor central nervous system function, skin turgor, blood pressure, urine sodium, signs of sodium or water overload, especially in patients with cardiovascular, renal, and pulmonary disease.

<sup>c</sup>Total body water (TBW) = 0.6 L/kg × weight in kg (for men) and 0.5 L/kg × weight in kg (for women).

TBW excess = TBW – [TBW (observed serum NA) / (desired serum NA)].

ADH, antidiuretic hormone; BID, twice daily; BUN, blood urea nitrogen; HF, heart failure; ECF, extracellular fluid; GI, gastrointestinal; IV, intravenous; NS, normal saline (0.9% Na); PO, orally; SIADH, syndrome of inappropriate ADH; TBW, total body weight.

- Management includes correcting the underlying cause of the hypertonic state, replacing water deficits, and administering adequate water to match ongoing losses.

$$\text{Water deficit} = \text{TBW} \times \frac{\text{observed serum Na}}{\text{desired serum Na}}$$

- The rate at which hyponatremia should be corrected depends on the severity of symptoms and degree of hypertonicity. Too rapid correction can precipitate cerebral edema, seizures, and irreversible neurologic damage.
- For asymptomatic patients, the rate of correction should not exceed changes of 0.5 mEq/L/hour in plasma sodium. A rule of thumb is to replace half of the corrected deficit with hypotonic solutions over the course of 12 to 24 hours.

### CLINICAL USE OF DIURETICS

- Diuretics reduce sodium and chloride reabsorption in the renal tubules, thereby increasing urine volume. Individual diuretics can be categorized according to their site of action in the renal tubules.
- **Loop diuretics** (e.g., furosemide, bumetanide, torsemide, ethacrynic acid) are the most potent diuretics.
- **Thiazide diuretics** and other sulfonamide diuretics (e.g., chlorthalidone) are less potent than loop diuretics. They can enhance reabsorption of calcium, so are useful in patients with kidney stones. Magnesium excretion is increased by thiazides.
- **Potassium-sparing diuretics** (e.g., spironolactone, triamterene, amiloride) are less potent but offer the advantage of sparing potassium loss.
- **Acetazolamide** inhibits carbonic anhydrase. It has limited diuretic and natriuretic effects.
- **Osmotic diuretics** (e.g., mannitol, urea) are nonresorbable solutes.

### Potassium

- Potassium is distributed unevenly between the intracellular and extracellular compartments, with 98% of total body potassium found in the intracellular compartment.
- Total body stores are 45 to 55 mEq/kg; normal plasma concentrations are 3.5 to 5.0 mEq/L.
- Normal potassium dietary intake is 50 to 100 mEq/day; most is excreted renally.

### HYPOKALEMIA

- The three main causes of hypokalemia include low dietary intake, increased cellular uptake, and excessive loss via the kidneys, GI tract, or skin.
- Drugs that can induce hypokalemia are shown in Table 10.2.
- Clinical presentation:
  - Patients are usually asymptomatic when the plasma potassium is between 3.0 and 3.5 mEq/L.
  - Muscle weakness, cramps, general malaise, fatigue, restless leg syndrome, and paresthesias can occur with levels < 2.5 to 3.0 mEq/L.
  - Severe depletion (<2.5 mEq/L) can result in elevation of serum creatine phosphokinase, aldolase, and aspartate aminotransferase.
- **Treatment**
  - The amount of potassium deficit and rate of continued potassium loss should be determined to guide replacement therapy. It is estimated that a 1-mEq/L decrease in serum potassium from 4 to 3 mEq/L represents a total body deficit of approximately 200 mEq.
  - Serum potassium concentrations should be closely monitored.
  - Route of potassium administration depends on acuity and severity of hypokalemia.
    - Oral supplementation is usually preferred.

TABLE 10.2 Drugs that Most Commonly Induce Hypokalemia

Drug	Mechanism	Predisposing Factors
Acetazolamide	Marked ↑ in renal K <sup>+</sup> loss	Most profound with short-term therapy
Amphotericin	Renal K <sup>+</sup> loss (renal tubular acidosis)	Concurrent piperacillin, ticarcillin
β <sub>2</sub> -Agonists	Intracellular shift of K <sup>+</sup>	
Cisplatin	Renal K <sup>+</sup> loss secondary to renal tubular damage	May be dose related but can occur after a single 50-mg/m <sup>2</sup> dose
Corticosteroids	Renal K <sup>+</sup> loss. Enhanced Na <sup>+</sup> reabsorption at distal tubule and collecting ducts in exchange for K <sup>+</sup> and H <sup>+</sup>	Supraphysiologic doses of agents with moderate to strong mineralocorticoid activity (e.g., prednisone, hydrocortisone)
Insulin with glucose	Intracellular shift of K <sup>+</sup>	Predictable effect when insulin administered to patients with diabetic ketoacidosis' combination used to treat hyperkalemia
Penicillins (piperacillin, ticarcillin)	High Na <sup>+</sup> load and nonresorbable anions can ↑ K <sup>+</sup> loss	Was more common with carbenicillin when it was available; newer penicillins are used in lower doses; less likely to produce hypokalemia
Thiazide and loop diuretics	Renal K <sup>+</sup> loss. ↑ Na <sup>+</sup> delivery to the late distal tubule, resulting in Na <sup>+</sup> resorption in exchange for K <sup>+</sup>	Patients with hyperaldosteronism (e.g., cirrhosis, HF) predisposed; may be dose related

HF, heart failure.

- The parenteral route should be used in patients who cannot tolerate oral therapy or in those with severe or symptomatic hypokalemia. Potassium chloride 40 mEq/L can be infused at a rate not to exceed 10 mEq/hour. For patients with life-threatening hypokalemia or a serum potassium < 2 mEq/L, a more concentrated solution (60 mEq/L) can be infused at a rate not to exceed 40 mEq/hour. ECG monitoring is mandatory to identify life-threatening hyperkalemia that can result from overcorrection.

## HYPERKALEMIA

- The etiology of hyperkalemia should be identified. Various causes exist (decreased renal excretion, increased dietary intake, redistribution from the intracellular to extracellular space); medications can also be a cause. Spurious hyperkalemia can result from leukocytosis, thrombocytosis, or hemolysis within the blood-collection tube.
- Cardiac toxicity of hyperkalemia is a major cause of morbidity and mortality. ECG changes begin to occur with concentrations > 5.5 mEq/L.
- **Treatment**
  - Three therapeutic modalities are available: agents that antagonize the cardiac effects of hyperkalemia (e.g., calcium), agents that shift potassium from the extracellular into the intracellular space (e.g., insulin and glucose, β-agonists), and agents that enhance potassium elimination (e.g., sodium polystyrene sulfonate, dialysis). Treatment options are summarized in Table 10.3.

## Calcium

- Healthy adults have about 1,400 g of calcium in the body, of which over 99% is stored in bone.

TABLE 10.3 Treatment of Hyperkalemia

Drug	Mechanism	Dose	Comment
Calcium gluconate	Reverse cardiotoxicity caused by $K^+$	10–20 mL 10% calcium gluconate IV over 1–3 minutes; may repeat once	Onset: 1–3 minutes Duration: 30–60 minutes. $[K^+]$ remains unchanged
Insulin and glucose	Redistribution of $K^+$ intracellularly	5–10 units regular insulin with 50 mL 50% dextrose, then $D_{10}W$ infused at 50 mL/hour <sup>a</sup>	Onset: 15–30 minutes Duration: several hours Watch for hypoglycemia and hypokalemia. Does not ↓ total body $K^+$
$\beta_2$ -agonists (e.g., albuterol)	Redistribution of $K^+$ intracellularly	Oral: 2 or 4 mg TID–QID Inhalation: 20 mg in 4 mL saline via nebulizer	Onset: 30–60 minutes Duration: 2 hours
SPS	Cationic binding resin. 1 g of resin binds 0.5 to 1 mEq $K^+$ in exchange for $Na^+$	Oral: 15–20 g with 20–100 mL 70% sorbitol every 4–6 hours; PRN preferred Retention enema: 50 g in 50 mL (70% sorbitol and 150 mL $H_2O$ ). Retain 30 minutes and follow with nonsaline irrigation	Onset: Slow; 50 g will lower $[K^+]$ by 0.5–1 mEq/L over 4–6 hours; watch for $Na^+$ overload (100 mg $Na^+$ /1 g SPS)
$NaHCO_3$	Redistribution of $K^+$ intracellularly	50 mEq IV for 5 minutes. Repeat PRN	Onset: variable, ≈30 minutes May work best in acidosis Watch for $Na^+$ overload and hyperosmolar state No change in total body $K^+$
Dialysis	Removal of $K^+$		Use as last resort

<sup>a</sup>Glucose unnecessary in patients with high glucose concentrations.

BID, twice daily; IV, intravenous; PRN, as needed; QID, four times daily; SPS, sodium polystyrene sulfonate; TID, three times daily.

- Normal plasma concentrations are between 8.5 and 10.5 mg/dL; about 40% of plasma is protein bound, primarily to albumin. Each 1 g/dL increase in serum albumin concentration is expected to increase the protein-bound calcium by 0.8 mg/dL.

$$\text{Correct Ca} = \text{Observed Ca} + 0.8 (\text{normal albumin} - \text{observed albumin})$$

$$\text{where normal albumin} = 4 \text{ g/dL}$$

## HYPERCALCEMIA

- There are many possible causes of hypercalcemia including malignancy (hematologic malignancies more so than solid tumors), hyperparathyroidism, and post-kidney transplant. Drugs can also be a cause.
- The clinical presentation is variable with the severity of symptoms correlating well with serum concentrations. There can be abnormalities in neurologic, cardiovascular, pulmonary, renal, gastrointestinal, and musculoskeletal systems. Symptoms can include fatigue, muscle weakness, anorexia, thirst, polyuria, dehydration, and a shortened QT interval.
- **Treatment**
  - Several therapeutic approaches are used including increasing urinary calcium excretion (e.g., hydration and diuresis), inhibiting release of calcium from bone (e.g., calcitonin, bisphosphonates), reducing intestinal calcium absorption (e.g., phosphate), and enhancing calcium complex formation (Table 10.4).



TABLE 10.4 Treatment of Hypercalcemia

Intervention	Dose	Comment
Saline and furosemide	1–2 L NS; then furosemide 80–100 mg every 2–4 hours Establish and maintain normovolemia Other electrolytes as needed	Saline diuresis and volume expansion depresses $\text{Ca}^{2+}$ reabsorption in tubules. Lowers $[\text{Ca}^{2+}]$ within 24 hours. Treatment of choice in patients without HF or renal failure.
Calcitonin	4 international units/kg SC or IM every 12 hours. ↑ Dose or use another therapy if unresponsive after 24 hours (Max: 8 international units/kg every 6 hours).	Inhibits osteoclast resorption and renal reabsorption of calcium. Preferred second-line agent because it has a rapid onset (6 hours) and is nontoxic. It can be used safely in HF and renal failure. Nausea is the major adverse effect. Tolerance occurs in 24–72 hours. Concomitant plicamycin can lead to hypocalcemia. Only the salmon-derived product is available.
Biphosphonates (etidronate, pamidronate)	Etidronate: 7.5 mg/kg IV daily × 3 days over at least 2 hours Maintenance: 20 mg/kg/day PO Pamidronate: 60–90 mg IV for 4 hours × 1. Repeat in 7 days PRN.	Inhibits osteoclast reabsorption in malignancy state. Efficacy 75%–100%. Onset 48 hours. Duration, days. Concomitant hydration is imperative. Do not use in renal failure. Adverse effects: ↑ phosphorus, ↑ $\text{SCr}$ , N/V (oral).
Zoledronic acid	Doses: 4 mg IV administration for 15 minutes	Potent effect on bone resorption. Preferred bisphosphonate for hypercalcemia of malignancy. May have promising effects on skeletal complications secondary to bone metastasis.
Gallium nitratephosphate	100–200 mg/m <sup>2</sup> /day infused IV over 24 hours for 5 days (depending on severity of hypercalcemia)  If calcium levels return to normal before 5 days, therapy may be discontinued. IV $\text{PO}_4^-$ not recommended PO $\text{PO}_4^-$ gradually titrate to 30–60 mmol/day (1–3 g/day in divided doses)	Inhibits bone resorption. Patients should be well hydrated during therapy. A urine output of ~2 L/day should be maintained owing to risk for nephrotoxicity (10%).  Inhibits bone resorption; soft tissue calcification. IV onset 24 hours, but not drug of choice. Oral agents used for chronic therapy. Contraindicated in renal failure.
Corticosteroids	Prednisone: 60–80 mg/day Hydrocortisone: 5 mg/kg/day IV × 2–3 days	Impair GI absorption and bone resorption. Onset several days. Best in patients with multiple myeloma, vitamin D intoxication, or granulomatous conditions. Can be used in HF, renal failure.
Indomethacin	75–150 mg/day	Reports of efficacy are mixed.

GI, gastrointestinal; HF, heart failure; IM, intramuscularly; IV, intravenously; NS, normal saline; N/V, nausea and vomiting; PO, orally; PRN, as needed; SC, subcutaneously;  $\text{SCr}$ , serum creatinine.

## Phosphorus

- Phosphorus is found primarily in bone (85%) and soft tissue (14%); < 1% is in extracellular fluid.
- Phosphate concentrations are reported as mg/dL or mmol/dL, rather than mEq/volume.
- The normal phosphorus range is 2.5 to 4.5 mg/dL. A balanced diet contains 800 to 1,500 mg/day.

### HYPOPHOSPHATEMIA

- Hypophosphatemia can be caused by conditions that impair absorption (e.g., malabsorption, prolonged NG suction, vomiting), increase renal elimination (e.g., diuresis), or shift phosphorus from the extracellular to intracellular compartments (e.g., glucose and insulin).

- Hypophosphatemia is commonly associated with diabetic ketoacidosis, chronic alcoholism, chronic obstructive airway disease, and extensive thermal burns.
- A rapid decline in phosphorus concentrations results in sudden and serious organ dysfunction. Symptoms can include generalized muscle weakness, confusion, paresthesias, seizure, and coma.
- **Treatment**
  - Prophylactic supplementation should be used in situations that predictably increase the risk for developing hypophosphatemia.
  - In patients with asymptomatic, mild hypophosphatemia (1.5–2.5 mg/dL) phosphorus supplementation is not generally needed. In moderate hypophosphatemia oral supplementation is the preferred mode. Several oral phosphorus products are available. Oral doses of 30 to 60 mmol/day, usually given in two to four divided doses to minimize GI effects, are used. Milk can also be used as a phosphate supplement.
  - In severe hypophosphatemia or when the patient is unable to take oral medication, IV administration of 0.08 to 0.5 mmol/kg body weight over the course of 4 to 12 hours is safe and effective in restoring serum phosphorus concentration. More aggressive regimens (i.e., infusions over 2 hours) have been suggested for critically ill patients.
  - Parenteral replacement therapy should stop when the serum phosphorus concentration reaches 2 mg/dL and when oral supplementation has started.
  - Serum phosphorus, calcium, and magnesium concentrations should be closely monitored because IV phosphorus administration can induce hyperphosphatemia, hypocalcemia, or hypomagnesemia quite rapidly.

## Magnesium

- Magnesium is found primarily intracellularly in bone (65%) and muscle (20%); only 2% is in the extracellular compartment.
- Normal serum concentrations are 1.5 to 2.4 mEq/L, with approximately 20% bound to proteins.
- Dietary intake in the United States is about 20 to 30 mEq daily; 30% to 40% of elemental magnesium is absorbed.
- Magnesium is important for many metabolic processes, particularly in energy transfer, storage, and utilization.
- Measuring body stores of magnesium is difficult; serum concentrations do not provide an accurate indication of total body load.

### HYPOMAGNESEMIA

- Hypomagnesemia can be caused by decreased intake or absorption (e.g., malnutrition, alcoholism, malabsorption, prolonged parenteral nutrition), increased magnesium requirements (e.g., pregnancy, infants), or increased losses (e.g., diarrhea, bowel resection, prolonged NG suction, diuretics).
- Symptoms reflect abnormal function of the neurologic, neuromuscular, and cardiovascular systems. Findings include Chvostek and Trousseau signs, muscle fasciculation, tremors, spasticity, generalized convulsions, weakness, anorexia, vomiting, and ECG changes.
- **Treatment**
  - The specific regimen for magnesium replacement depends on the clinical presentation of the patient, with symptomatic patients requiring more aggressive therapy.
  - Because 50% of the dose administered is lost through renal excretion, magnesium should be replenished over several days.
  - Oral replacement is indicated for mild depletion. Magnesium-containing antacids, milk of magnesia, and magnesium oxide are options. Sustained-release preparations are preferred.

- Parenteral therapy is needed for symptomatic patients. Magnesium can be given IM as a 50% solution but the injections are painful and potentially sclerosing, and multiple injections are needed. For this reason, IV therapy is the preferred parenteral route. Patients should remain in the supine position after IV magnesium administration to avoid hypotension.

### **HYPERMAGNESEMIA**

- A common cause of hypermagnesemia is use of magnesium-containing medications in patients with impaired renal function. Other causes include adrenal insufficiency, hypothyroidism, and medication use.
- Elevated serum magnesium concentrations alter the normal function of the neurologic, neuromuscular, and cardiovascular systems. When serum magnesium concentrations are  $>4$  mEq/L, deep tendon reflexes are depressed; flaccid quadriplegia can develop at concentrations of 8 to 10 mEq/L. Respiratory paralysis, hypotension, and difficulty talking and swallowing can also be present.
- **Treatment**
  - Magnesium-containing medications should be discontinued.
  - If potentially life-threatening complications are present, 5 to 10 mEq of IV calcium should be given to antagonize the respiratory and cardiac effects of magnesium.
  - In patients with good renal function without life-threatening complications, IV furosemide plus 0.45% sodium chloride will enhance urinary magnesium excretion while preventing volume depletion.
  - Hemodialysis or peritoneal dialysis is indicated in patients with significant renal impairment or, possibly, in those with severe hypermagnesemia.

# Vaccinations\*

### General Principles

- The principle of vaccination is that the introduction of a small amount of the pathogen to the body produces protective immunologic memory (active immunity) so that if the pathogen is reintroduced at a later time, a greater immunologic response occurs.
- Recommended immunization schedules are designed to optimize immune response, standardize regimens, and enhance immunization rates.
- Infant, child, adolescent, and adult immunization schedules are reviewed and updated annually.

### Classification

- Vaccines can be either live attenuated, killed (inactivated) whole organism, or subcellular/subunit.
- Live attenuated vaccines contain a weakened or inactivated form of the pathogen that replicates within the host and elicits antibody and cell-mediated response.
- Killed whole organism (inactive) do not replicate within the host; their effectiveness may be impaired by circulating antibodies, maternal antibodies (in infants), or concomitant infections.
- Subcellular/subunit vaccines contain either a protein or polysaccharide antigen within the vaccine and elicit less reaction than whole pathogen vaccines.

### Goals of Therapy

- The goal of immunization is to prevent specific infectious diseases and their sequelae.

### Treatment

- The current recommended schedules for childhood, adolescent, and adult immunizations can be found at the Center for Disease Control (CDC) website: [www.cdc.gov](http://www.cdc.gov). An overview of the vaccines available and their recommended regimens are shown in Table 11.1. Some combination vaccines are also available (Table 11.2).
- Immunization schedules can be adjusted to meet individual needs and may begin at any time of year.
- Vaccines should not be administered at time intervals shorter than those recommended to allow for maximal immune responses before administration of subsequent doses.
- Alternative immunization schedules are available for patients with altered immunity to ensure protection from vaccine-associated disease.
- To catch up within an immunization series, it is not necessary to restart from the first dose of the schedule. A delay in receiving subsequent doses does not interfere with final immunity gained from the vaccination.

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\*The reader is referred to Chapter 11, Vaccinations, written by Sherry Luedtke, PharmD, FPPAG, and Molly G. Minze, PharmD in the 10th edition of *Applied Therapeutics: The Clinical Use of Drugs* for a more in-depth discussion. All notations to reference numbers are based on the reference list at the end of that chapter. The editor of this handbook expresses her thanks to Drs. Luedtke and Minze and acknowledges that this chapter is based on their work.

TABLE 11.1 Vaccine Overview

	Vaccines	Recommended Regimens	Comment
Diphtheria, tetanus, pertussis (inactivated; intramuscular)	DTaP, DT	2, 4, 6, 15–18 months; booster at 4–6 years	Minimum age 6 weeks; fourth dose can be administered at 12 months of age if at least 6 months since third dose
	Tdap Td	11–12 years Every 10 years	Minimum age 10 years (Boostrix) and 11 years (Adacel)
<i>Haemophilus influenzae</i> type b (inactivated; intramuscular)	Hib	2, 4, 6, 12–15 months	Minimum age is 6 weeks If PRP-OMP at 2 and 4 months, no 6-month dose indicated Hiberix should only be used for final dose (12 months–4 years)
Hepatitis B (inactivated; intramuscular)	HepB	Birth, 1–2 months, 6–15 months	Monovalent vaccine to be administered for any doses before 6 weeks Administer birth dose within 12 hours if HBsAG + mother Final dose should not be given before 6 months of age
Hepatitis A (inactivated; intramuscular)	HepA	Two doses 6 months apart First dose at 23 months	Minimum age 12 months
Human papillomavirus vaccine (inactivated; intramuscular)	HPV2	Three doses 9–26 years	Administer to females before sexual activity
	HPV4	Second dose 1–2 months after first Third dose 6 months after first Annually	Administer to males to reduce likelihood of genital warts
Influenza (TIV = inactivated; intramuscular) (LAIV = live attenuated; intranasal)	IIV3, IIV4, RIV3 LAIV4	Annually	Minimum age TIV 6 months
		Two doses 4 weeks apart at first annual vaccination	Minimum age LAIV 2 years Two doses required for patients aged 2–8 years at first annual vaccination
Measles, mumps, rubella (live attenuated; subcutaneous)	MMR	12–15 months; repeat dose 4–6 years	Minimum age 12 months; second dose may be administered at 4 years as long as 4 weeks from previous dose
Meningococcal (MCV = inactivated; intramuscular) (MPSV = subcutaneous)	MCV4	Two doses 8 weeks apart; age 2–10 years	Minimum age 2 years
	MPSV4	one dose age 11–55 years  Ages 56 and older	Two doses for patients with immunodeficiency One dose for patients at high risk
Pneumococcal (Inactivated polysaccharide; usually intramuscular, but subcutaneous ok)	PCV 7, PCV 13 PPSV	2, 4, 6, 12–15 months	PCV minimum age 6 weeks
		One dose ≥ 65 years  Two doses if <65 at time of first dose	PPSV minimum age 2 years Administer second dose of PPSV 5 years after first
Polio (Inactivated; usually intramuscular, but subcutaneous ok)	IPV	2, 4, 6–18 months	IPV minimum age 6 weeks If four or more doses given before 4 years of age, repeat booster at 4–6 years Final dose should be after 4th birthday and at least 6 months after previous dose

TABLE 11.1 Vaccine Overview (Continued)

	Vaccines	Recommended Regimens	Comment
Rotavirus (live attenuated; oral)	RV1	2, 4 months	Initial dose: minimum age 6 weeks, maximum age 14 weeks 6 days Final dose: maximum age 8 months Rotarix (RV1): 6-month dose not indicated
Varicella (live attenuated; subcutaneous)	RV5 VZV	2, 4, 6 months 12–15 months; repeat dose at 4–6 years	Minimum age 12 months; second dose may be administered at 4 years as long as 3 months from previous dose one dose
Zoster (live attenuated; subcutaneous)	ZV	50 years of age (usually >60)	one dose

HBsAG+, hepatitis-B surface antigen positive; PRP-OMP, PedvaxHIB or Comvax (Hep B-Hib).

Sources: National Center for Immunization and Respiratory Diseases. General recommendations on immunizations—recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR Recomm Rep.* 2011;60:1; Centers for Disease Control. Recommended immunization schedules for persons aged 0 through 18 years—United States, 2011 [published correction appears in *MMWR.* 2011;60:315]. *MMWR Morb Mortal Wkly Rep.* 2011;60:1; Committee on Infectious Diseases, American Academy of Pediatrics. Policy statement: recommended childhood and adolescent immunization schedules—United States 2011. *Pediatrics.* 2011;127:387; Centers for Disease Control. Recommended adult immunization schedule—United States, 2011. *MMWR Morb Mortal Wkly Rep.* 2011;60:1; Advisory Committee on Immunization Practices. Recommended adult immunization schedule: United States, 2011. *Ann Intern Med.* 2011;154:168.

TABLE 11.2 Combination Vaccines

Combination Vaccine <sup>a</sup>	Antigens <sup>b</sup>	Age Indicated	Regimen
Comvax <sup>d</sup>	HepB-Hib	6 weeks–71 months	2, 4, 12–15 months
Kinrix	DTaP-IPV	4–6 years	Only for fourth dose IPV and fifth dose DTaP
Pediarix <sup>c</sup>	DTaP-HepB-IPV	6 weeks–6 years	2, 4, 6 months
Pentacel	DTaP-IPV-Hib	6 weeks–4 years	2, 4, 6, 15–18 months An extra monovalent IPV recommended for IPV at 4–6 years (total, five doses)
ProQuad <sup>e</sup>	MMR-V	12 months–12 years	12–15 months, 4–6 years
TriHIBit	DTaP-Hib	15–18 months	15–18 months
Twinrix	HepA-HepB	18+ years	0, 1, 6 months

<sup>a</sup>Vaccine interchangeability: If combination and single antigen vaccines are used to complete an immunization series, it is preferred to use products from the same manufacturer. Immunogenicity of vaccine antigens between different manufacturers is unknown.

<sup>b</sup>Extra antigens: Administration of extra antigens by using combination vaccines should be avoided. Availability of monovalent vaccines should be provided to avoid giving extra antigens and increase risk of adverse effects, particularly for inactivated vaccines which are reactogenic (e.g., DTaP vaccine).

<sup>c</sup>Hepatitis B: Combination vaccines not recommended for hepatitis B birth doses (<6 weeks).

<sup>d</sup>ProQuad: MMRV may be associated with an increased risk of febrile seizures when used at age 12 to 47 months. The use of MMR is preferred during this time.

DTaP, diphtheria, tetanus, and acellular pertussis; HepA, hepatitis A; HepB, hepatitis B; Hib, *Haemophilus influenzae* type b; IPV, inactivated poliovirus vaccine; MMR, measles, mumps, and rubella vaccine; V, varicella vaccine.

Sources: National Center for Immunization and Respiratory Diseases. General recommendations on immunizations—recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR Recomm Rep.* 2011;60:1; Combination vaccines for childhood immunization: recommendations of the Advisory Committee on Immunization Practices (ACIP), the American Academy of Pediatrics (AAP), and the American Academy of Family Practice (AAFP). *Pediatrics.* 1999;103:1064; Marin M et al. Use of combination measles, mumps, rubella and varicella vaccine: recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR Recomm Rep.* 2010;59(RR-3):1.

TABLE 11.3 Subcutaneous and Intramuscular Vaccine Administration Techniques

Patient Age	Site	Injection Area	Typical Needle Length (inch)	Needle Gauge
Birth to 12 months	Subcutaneous	Fatty tissue over the anterolateral thigh muscle	5/8	23–25
12 months and older	Subcutaneous	Fatty tissue over anterolateral thigh or fatty tissue over triceps	5/8	23–25
Newborn (0–28 days)	Intramuscular	Anterolateral thigh muscle	5/8	22–25
Infant (1–12 months)	Intramuscular	Anterolateral thigh muscle	1	22–25
Toddler (1–3 years)	Intramuscular	Anterolateral thigh muscle OR Deltoid muscle of arm if muscle mass is adequate	1–1¼ 5/8–1	22–25
Children (3–18 years)	Intramuscular	Deltoid muscle OR Anterolateral thigh muscle	5/8–1 1–1¼	22–25
Adults ≥ 9 years	Intramuscular	Deltoid muscle OR Anterolateral thigh muscle	1–1½	22–25

- Adverse reactions are dependent, in part, on the type of vaccine preparation used. Effects from live attenuated vaccines mimic the disease but are less severe; they occur 7 to 10 days after vaccination. Adverse effects from inactivated and live vaccines can include soreness at the site of injection within 24 hours after vaccination.
- Contraindications to vaccine administration include acute, severe febrile illness, history of anaphylaxis to the vaccine or its components, and history of a severe reaction to an immunization. A minor illness, even with a mild fever, is not a contraindication.
- Family history of seizures, allergies, and sudden infant death syndrome are not contraindications for immunizations.
- **Vaccine Administration** (Table 11.3):
  - Intramuscular vaccinations are administered at a 90-degree angle into the muscle.
  - Subcutaneous vaccinations are administered at a 45-degree angle into the subcutaneous tissue by pinching the tissue to prevent insertion into the muscle.
  - When multiple vaccinations are given at the same site, each injection should be separated by 1 inch.

## Inactivated Vaccines

- **Hepatitis B**
  - Hepatitis B is transmitted via exposure to contaminated blood, exposure to body fluids, and transplacentally from an HBsAg-positive mother.
  - The highest risk of hepatitis B is in young adults. Vaccination is recommended in adults who participate in high-risk behavior and in those who are in close contact with infected persons.
  - Vaccination is effective for both preexposure and postexposure prophylaxis.
  - To prevent vertical transmission to an infant from the mother it is important to provide vaccination within 12 hours of birth. If the mother was HBsAg-positive, hepatitis B immunoglobulin should also be given to the infant.

- Two formulations are available in the United States: Recombivax-HB and Engerix-B, which are both given as a three-dose series. Either formulation can be used as the immune response from a series using different vaccines is comparable to that of a full series using the same product.
- **Hepatitis A**
  - Hepatitis A is commonly contracted through household or sexual contact, day-care attendance, employment, international travel, or food/waterborne outbreaks.
  - Vaccination is targeted to toddlers with the aim of preventing transmission to adolescents and adults.
  - Two formulations are available in the US market: Havrix and Vaqta, each with adult and pediatric formulations. Vaccination involves a two-dose regimen.
  - The pediatric formulations are for infants older than 12 months of age and contain half the antigen of the adult formulations.
- **Diphtheria/Tetanus/Pertussis**
  - Pertussis is characterized by a paroxysmal cough with a whooplike, high-pitched inspiratory noise, vomiting, and lymphocytosis. It is a highly communicable infection that can affect 90% of infants and young children in nonimmunized households and is associated with serious morbidity and mortality.
  - Waning immunity against pertussis has resulted in outbreaks in the United States.
  - The pertussis vaccine is commonly administered in combination with diphtheria and tetanus vaccines (DTaP). Products currently available contain the acellular pertussis antigen.
  - Three DTaP vaccines are available in the US market for primary vaccination: Infanrix, Tripedia, and Daptacel. If possible, the same DTaP product should be used for all five doses in the series because safety and effectiveness of interchangeability are not known.
  - Adolescents and adults, particularly those in close contact with young infants, should receive a single dose of pertussis booster vaccine (Tdap). The pertussis booster may be given regardless of the time since receipt of a tetanus booster (Td).
  - The Tdap vaccine is recommended with each subsequent pregnancy during the third trimester.
  - Two Tdap vaccines are available in the US market for booster vaccination: BOOSTRIX and ADACEL.
  - Diphtheria ad tetanus toxoid preparations (products without pertussis) are available for individuals with a previous reaction to pertussis-containing vaccines. DT products should be used for primary prevention in children younger than 7 years of age. Td products should be used for children above 7 years and adults. Booster doses of Td should be administered every 10 years.
- **Haemophilus Influenzae B**
  - *Haemophilus influenzae* type B (Hib) was a common cause of bacterial meningitis and leading cause of serious bacterial diseases in young children.
  - Immunization recommendations for *Haemophilus influenzae* type B are age dependent. The older an infant is at presentation, the fewer doses needed to elicit a response.
  - Several Hib vaccines are available in the US market: ProHIBiT, PedvaxHIB, ActHIB, OmniHIB, and HibTITER. Vaccination requires a priming series and a booster dose. If possible, the primary series should be completed with the same product. Data support the interchangeability of products for priming and booster doses.
- **Polio**
  - Polio is a highly contagious enterovirus that is transmitted by direct fecal–oral contact or indirect exposure to infectious saliva, feces, or contaminated water.
  - Oral polio vaccine (OPV) provides lifelong immunity, gastrointestinal polio virus immunity, and prevents the carrier state. However, it is associated with the risk of vaccine-associated paralytic polio, so its use is limited to unique situations (e.g., outbreaks, unvaccinated infants traveling in < 4 weeks to an endemic area).



- Inactivated polio vaccine (IPV) is recommended over OPV because it is associated with a lower incidence of vaccine-associated paralytic polio and provides the same immunity.
- Routine vaccination of adults against polio with IPV is not recommended unless travel to endemic areas is planned.
- One IPV product is available in the US market. It is given as a four-dose series.
- **Meningococcus**
  - *Neisseria meningitidis* is a prominent cause of bacterial meningitis.
  - Vaccination is recommended for populations at risk for contracting *Neisseria meningitidis*, including travelers to endemic areas, patients with specific immunodeficiencies, functional/anatomical asplenia, lab personnel dealing with meningococcus, and college students residing in the dormitory.
  - Three formulations are available in the United States: Menomune (a polysaccharide product for patients 2–10 years of age) and Menactra or Menveo (conjugate products for patients 11–55 years of age and for unvaccinated college students). Vaccination is given as a one-dose primary series with a booster for adolescents.
- **Human Papillomavirus (HPV)**
  - HPV commonly infects the genital track and is primarily transmitted by sexual contact.
  - The three-dose vaccination series is recommended for adolescent females for the prevention of cervical and anogenital cancers, anogenital warts, and recurrent respiratory papillomatosis. It is also recommended for males for the prevention of genital warts.
  - Two products are available in the United States: Gardasil (a quadravalent product that is active against HPV strains 6, 11, 16, and 18) and Cervarix (a bivalent product active against HPV strains 16 and 18). Gardasil is indicated for males and females 9 to 26 years of age. Cervarix is indicated for females 10 to 25 years of age.
- **Pneumococcus**
  - *Streptococcus pneumoniae* (pneumococcus) infection can cause meningitis, pneumonia, sinusitis, and otitis media. It mostly affects young children and the elderly.
  - Three products are available in the US market: Pneumovax (a polysaccharide vaccine) and two conjugated vaccines (Pneumnar 7 and Pneumnar 13).
  - The conjugate vaccine (Pneumnar) protects against 80% (PCV-7) and 90% (PCV-13) of infectious strains that cause disease in children younger than 6 years of age. Routine vaccination with Pneumnar 13 is recommended for all children aged 2 to 59 months and children aged 60 to 71 months who have underlying medical conditions placing them at risk for pneumococcal disease.
  - The polysaccharide vaccine (Pneumovax) does not elicit an immune response in children younger than 2 years. It protects against 23 strains of *S. pneumoniae* that typically cause adult disease.
- **Influenza**
  - Vaccination is recommended for anyone older than 6 months of age who does not have a current contraindication.
  - Each year the influenza vaccine is formulated to contain three or four inactivated influenza virus strains that are predicted to be in circulation in the United States.
  - The inactivated vaccine injection is given intramuscularly and is recommended for children at least 6 months of age to adults.
  - The live attenuated intranasal vaccine is indicated for use in healthy nonpregnant patients 2 to 49 years of age.
  - A high-dose injectable vaccine (Fluzone High-Dose) is for patients aged 65 and older. The higher concentration of antigens in this product is intended to elicit a better immune response from the elderly who typically respond with lower antibody titers.
  - Recombinant influenza vaccine (RIV3) is recommended for individuals 18 to 49 years old and is the only egg-free vaccine in the US market.

## Live Attenuated Vaccines

- **Rotavirus**

- Rotavirus is a major cause of gastroenteritis and subsequent dehydration in the United States.
- Routine immunization is recommended for infants. Virus will be shed in the feces after immunization. Risk of transmission to an immunocompromised individual is relatively low if precautions are taken.
- Two products are available in the US market: Rotateq (a pentavalent vaccine given as a three-dose series) and Rotarix (a monovalent vaccine given as a two-dose series). They are believed to be equally effective. It is preferred to use the same product for the series. If Rotateq is used as part of the series, three doses should be given.

- **Measles/Mumps/Rubella**

- Measles is a highly contagious disease of childhood associated with high fever, rash, cough, rhinitis, and conjunctivitis. Mumps rarely causes complications in children. The most significant consequence of rubella infection is in pregnant women (spontaneous abortion, miscarriages, stillbirths, fetal anomalies).
- In the United States, mumps and rubella antigens are combined with measles in the MMR vaccine.
- The risk of autism has been falsely associated with the MMR vaccine. Counseling should be provided to parents to ensure protection against measles.
- MMR vaccination is given as a two-dose series: the first dose at 12 to 15 months of age and a second dose upon entrance to grade school.
- Women of childbearing age should use contraception and avoid pregnancy for 28 days following vaccination with a rubella-containing product.

- **Varicella**

- Varivax is a live attenuated vaccine against varicella zoster (chickenpox). It is given as a two-dose series (12–15 months followed by 4–6 years of age). Its use is generally not recommended in children who have cellular immunodeficiencies.
- Postexposure prophylaxis with the varicella vaccine is recommended within 5 days of exposure for those unvaccinated or who have not received a second dose of vaccine.
- After primary infection with varicella, 15% to 30% of the population will experience a latent infection in the sensory nerve ganglia that reactivated, causing herpes zoster (shingles).
- Zostavax is a herpes zoster vaccination that is recommended in adults older than 60 years of age to prevent reactivation of previously acquired wild-type varicella zoster infections. Zostavax is not interchangeable with Varivax.

# Anemias\*

## General Principles

- Anemia is a reduction in red blood cell (RBC) mass, described as either a decrease in the number of RBCs per microliter or as a decrease in the hemoglobin (Hgb) concentration in blood to a level below the normal physiologic requirement.
- Anemia is an objective sign of a disease, not a diagnosis. It can be associated with multiple etiologies including nutritional deficiencies and acute and chronic diseases; it can also be drug induced.

## Classification

- Anemias are classified according to pathophysiologic and morphologic characteristics (Table 12.1).
- Routine laboratory information can help distinguish among the most common forms of anemia (Figure 12.1).

## Patient Assessment

- Signs and symptoms vary with the degree of RBC reduction.
- Slowly developing anemias can be asymptomatic or include symptoms such as slight exertional dyspnea, increased angina, fatigue, or malaise.
- In severe anemia, there are changes in heart rate and stroke volume in an attempt to improve oxygen delivery to tissues. This can result in systolic murmurs, angina pectoris, high-output heart failure, pulmonary congestion, and edema.
- On physical examination, there may be pallor, postural hypotension, and tachycardia.
- A full laboratory evaluation is needed to confirm the diagnosis (Tables 12.2 and 12.3).

## Goals of Therapy

- Treatment should be directed at control of the underlying cause of anemia.

## Iron-Deficiency Anemia

- Iron-deficiency anemia is a state of negative iron balance in which the daily iron intake and stores are unable to meet the RBC and other body tissue needs. It is the most common nutritional deficiency worldwide.
- Table 12.4 shows the causes of iron-deficiency anemia.
- Symptoms include pallor, cardiovascular, respiratory and cognitive complications, and decreased quality of life.
- Oral absorption of iron is roughly 10% of ingested iron in individuals with normal iron stores. Absorption increases threefold to fivefold in individuals with iron deficiency. Animal sources of iron are better absorbed than plant sources. Dietary reference intake for iron is shown in Table 12.5.

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\* The reader is referred to Chapter 12, Anemias, written by Cindy L. O'Bryant, PharmD, BCOP, and Lisa A. Thompson, PharmD, in the 10th edition of *Applied Therapeutics: The Clinical Use of Drugs* for a more in-depth discussion. All notations to reference numbers are based on the reference list at the end of that chapter. The editor of this handbook expresses her thanks to Drs. O'Bryant and Thompson and acknowledges that this chapter is based on their work.

TABLE 12.1 Classifications of Anemia

**Pathophysiologic (Classifies Anemias on the Basis of Pathophysiologic Presentation)****BLOOD LOSS**

Acute: trauma, ulcer, hemorrhoids

Chronic: ulcer, vaginal bleeding, aspirin ingestion

**INADEQUATE RED BLOOD CELL PRODUCTION**

Nutritional deficiency: vitamin B<sub>12</sub>, folic acid, iron

Erythroblast deficiency: bone marrow failure (aplastic anemia, irradiation, chemotherapy, folic acid antagonists) or bone marrow infiltration (leukemia, lymphoma, myeloma, metastatic solid tumors, myelofibrosis)

Endocrine deficiency: pituitary, adrenal, thyroid, testicular

Chronic disease: renal, liver, infection, granulomatous, collagen vascular

**EXCESSIVE RED BLOOD CELL DESTRUCTION**

Intrinsic factors: hereditary (G6PD), abnormal hemoglobin synthesis

Extrinsic factors: autoimmune reactions, drug reactions, infection (endotoxin)

**Morphologic (Classifies Anemias by Red Blood Cell Size [Microcytic, Normocytic, Macrocytic] and Hemoglobin Content [Hypochromic, Normochromic, Hyperchromic])****MACROCYTIC**

Defective maturation with decreased production

Megaloblastic: pernicious (vitamin B<sub>12</sub> deficiency), folic acid deficiency

**NORMOCHROMIC, NORMOCYTIC**

Recent blood loss

Hemolysis

Chronic disease

Renal failure

Autoimmune

Endocrine

**MICROCYTIC, HYPERCHROMIC**

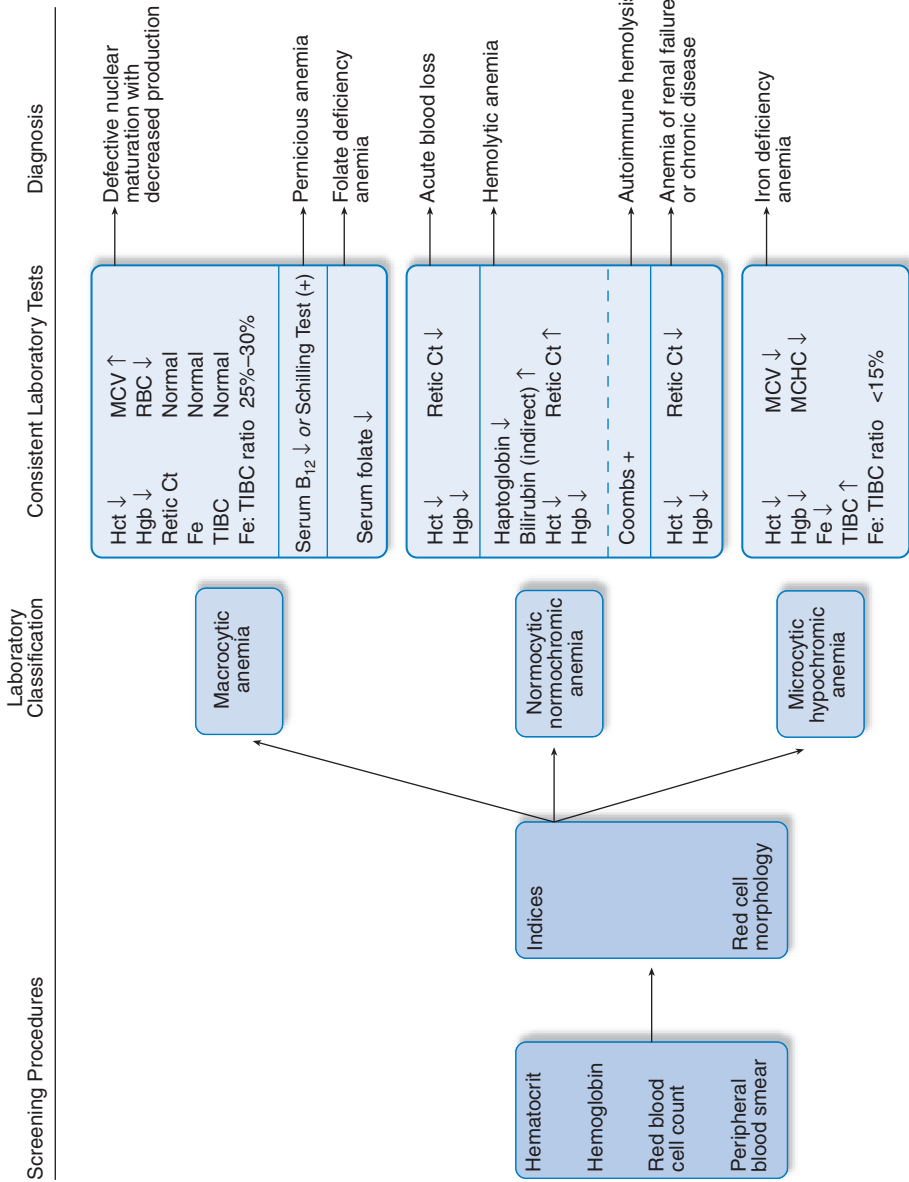
Iron deficiency

Genetic abnormalities: sickle cell, thalassemia

G6PD, glucose-6-phosphate dehydrogenase.

- **Treatment**

- The goals of treatment are to normalize the Hgb and Hct concentrations and replenish iron stores.
- Iron replacement with oral or parenteral therapy is needed. Table 12.6 compares the iron content of various oral iron preparations. The ferrous form of iron is absorbed three times more readily than the ferric form.
- Parenteral iron may be needed in patients who do not respond to oral therapy (nonadherence, inflammatory conditions, malabsorption, continuing blood loss, need for rapid iron replacement). Parenteral forms of iron available in the United States are iron dextran, iron sucrose, sodium ferric gluconate, and ferumoxytol.
  - **Iron dextran** can be given by slow IV injection at a rate not to exceed 50 mg/minute. Although not included in the product label, infusions have been given over 2 to 6 hours. Some forms of iron dextran given by intramuscular (IM) injection in the gluteus muscle using the Z-track method to avoid skin staining is another option. A test dose should be given due to the risk for allergic reactions.
  - **Ferric gluconate** can be given undiluted as a slow IV injection (not to exceed 12.5 mg/minute) or as an IV infusion (125 mg over 1 hour).



**Figure 12.1** Laboratory diagnosis of anemia.

TABLE 12.2 Routine Laboratory Evaluation for Anemia Workup

Complete blood count (CBC): Hgb, Hct, RBC count, RBC indices (MCV, MCH, MCHC), WBC count (and differential)
Platelet count
RBC morphology
Reticulocyte count
Bilirubin and LDH
Serum iron, TIBC, serum ferritin, transferrin saturation
Peripheral blood smear examination
Stool examination for occult blood
Bone marrow aspiration and biopsy <sup>a</sup>

<sup>a</sup>Performed in patients with abnormal peripheral blood smears.

Hct, hematocrit; Hgb, hemoglobin; LDH, lactate dehydrogenase; MCV, mean corpuscular volume; MCH, mean corpuscular hemoglobin; MCHC, mean corpuscular hemoglobin concentration; RBC, red blood cell; TIBC, total iron-binding capacity; WBC, white blood cell.

TABLE 12.3 Supplemental Hematology Values

Laboratory Test	Pediatric	Adult	
	1–15 years	Male	Female
Erythropoietin (milliunits/mL)	4–26	4–26	4–26
Reticulocyte count (%)	0.5–1.5	0.5–1.5	0.5–1.5
TIBC (mg/dL)	250–400	250–400	250–400
Fe (mg/dL)	50–120	50–160	40–150
Fe/TIBC (%)	20–30	20–40	16–38
Ferritin (ng/mL)	7–140	15–200	12–150
Folate (ng/mL)	7–25	7–25	7–25
RBC folate (ng/mL)	—	140–960	140–960
Vitamin B <sub>12</sub> (pg/mL)	>200	>200	>200

Fe, iron; RBC, red blood cell; TIBC, total iron-binding capacity.

TABLE 12.4 Iron-Deficiency Anemia Causes

#### BLOOD LOSS

Menstruation, gastrointestinal (e.g., peptic ulcer), trauma

#### DECREASED ABSORPTION

Medications, gastrectomy, regional enteritis

#### INCREASED REQUIREMENT

Infancy, pregnant/lactating women

#### IMPAIRED UTILIZATION

Hereditary, iron use

TABLE 12.5 Dietary Reference Intake for Iron

	mg/day
Healthy, nonmenstruating adults	8
Menstruating women	18
Pregnant women	27
Lactating women	9
Vegetarians	16 <sup>a</sup>

<sup>a</sup>Twofold higher than those not consuming a vegetarian diet.

TABLE 12.6 Comparisons of Iron Preparations

Preparation	Dose (mg)	Fe <sup>2+</sup> Content (mg)	Fe (%)
Ferrous sulfate	325	65	20
Ferrous fumarate	324	106	33
Ferrous gluconate	300	34	11
Carbonyl iron	—	45	—
Slow Fe (time-released)	160	50	31

- **Iron sucrose** can be given as a slow IV injection (not to exceed 20 mg/minute) or as an infusion (100 mg over 15 minutes).
- **Ferumoxylol** can be given as an IV injection (undiluted at 1 mL/second) at an initial dose of 510 mg, with a second dose given 3 to 8 days later.

## Megaloblastic Anemia

- Megaloblastic anemia is a common disorder that can have several causes including vitamin B<sub>12</sub> or folic acid deficiency, or metabolic or inherited defects associated with decreased ability to use these vitamins.
- Distinguishing between vitamin B<sub>12</sub>-deficient and folic acid-deficient megaloblastic anemia is important to minimize potentially permanent effects of these deficiencies.
- Symptoms include fatigue; exaggeration of preexisting cardiovascular or pulmonary problems; sore, pale, smooth tongue; diarrhea or constipation; anorexia; edema; and urticaria.
- Folate deficiency must be differentiated from vitamin B<sub>12</sub> deficiency before folate therapy is initiated because folate can reverse the hematological, but not the neurological, damage caused by vitamin B<sub>12</sub> deficiency.
- **Vitamin B<sub>12</sub> deficiency** results from deficiency or poor utilization of vitamin B<sub>12</sub>. Humans must get vitamin B<sub>12</sub> from the diet. Intrinsic factor is essential for the absorption of vitamin B<sub>12</sub>. Partial or total gastrectomy can result in loss of intrinsic factor requiring ongoing vitamin B<sub>12</sub> supplementation post-surgery.
  - **Pernicious anemia**, a condition where there is a lack of intrinsic factor production, can result in vitamin B<sub>12</sub> anemia due to poor vitamin B<sub>12</sub> absorption.
  - Treatment of vitamin B<sub>12</sub> deficiency involves replenishing vitamin B<sub>12</sub> stores (Table 12.7). IM or deep subcutaneous administration provides sustained release of vitamin B<sub>12</sub>. An oral table or intranasal formulation can be used for maintenance therapy.
  - With long-standing vitamin B<sub>12</sub> deficiency, it may take several months before some symptoms are resolved.
- **Folic acid deficiency** is commonly associated with alcoholism, rapid cell turnover, and dietary deficiency. It can also occur with chronic hemodialysis, diseases that impair absorption in the small intestine, and extensive jejunal resections, and by drugs that alter folate metabolism.
  - Human requirements for folate vary with age but are generally 3 mcg/kg/day. Because absorption from food is incomplete, a daily intake of 200 mcg is recommended for adults.
  - The body's folate stores are low, so deficiency and anemia can occur within a few months of decreased folate intake.

## Sickle Cell Anemia

- Sickle cell anemia is an inherited, autosomal recessive Hgb disorder. Sickled RBCs are more rigid and may become lodged when passing through the microvasculature, resulting in vascular occlusions.
- There are several inheritance patterns. Patients with sickle cell anemia are homozygous whereas patients with sickle cell trait are heterozygous.

**TABLE 12.7 Cyanocobalamin (Vitamin B<sub>12</sub>) Supplementation Regimens for Macrocytic Anemia**

Patient Population	Initial Supplementation			Chronic Supplementation (Lifelong)		
	Dose	Frequency	Route	Dose	Frequency	Route
US regimens	100 mcg	Daily for 7 days, then on alternate days for 14 days, then q 3–4 days for 2–3 weeks	IM or SQ	100–200 mcg	Monthly	IM or SQ
UK regimen, without neurological involvement	1,000 mcg	Weekly for 4–6 weeks	IM or SQ	Up to 1,000 mcg <sup>d</sup> 500 mcg	Daily Weekly	Oral Intranasal
	1,000–2,000 mcg	Daily for 1 month	Oral	1,000 mcg	Monthly	IM or SQ
	250–1,000 mcg	On alternating days for 1–2 weeks, then 250 mcg weekly until counts normalize	IM or SQ	125–500 mcg 1,000 mcg	Daily Monthly	Oral IM or SQ
UK regimen, with neurological involvement	1,000 mcg	On alternating days as long as symptoms occur	IM or SQ			

<sup>d</sup>In patients with normal gastrointestinal absorption, doses of 1 to 25 mcg daily are considered sufficient as a dietary supplement. IM, intramuscular; SQ, subcutaneous.



- The clinical course is variable. Patients carrying the sickle cell trait have milder symptoms than those with sickle cell disease. Organs such as the kidneys, retina, spleen, and bones are frequent sites of vaso-occlusive events. Pain, anemia, infections, and other complications can occur.
- **Treatment**
  - Treatment is organ specific and aimed at supportive measures.
  - Patients with sickle cell disease should receive appropriate preventive care, including infection prophylaxis with penicillin and routine immunizations.
  - Acute sickle cell crises (vaso-occlusion episodes) are an urgent situation that can cause severe pain and organ damage. Patients should be managed with pain control, transfusions, oxygen, or antibiotic therapy, as appropriate. The goal of treatment is to prevent progression to acute respiratory failure.
  - **Hydroxyurea** (15–35 mg/kg/day) has been used in patients with recurrent moderate/severe vaso-occlusive crisis. It increases hemoglobin F synthesis, which may reduce the frequency of crises. Risk versus benefit must be carefully assessed as there are many toxicities, including bone marrow suppression.
  - Patients requiring chronic transfusions of PRBCs are at increased risk for iron toxicity. Iron chelation therapy (Table 12.8) may be needed for iron overload.

## Anemia of Chronic Disease

- Anemia of chronic disease is a mild to moderate anemia that results from decreased RBC production associated with a number of disorders. Inflammatory cytokines are thought to play a major role in its development. This anemia is not usually progressive or life threatening but it does affect a person's quality of life.
- Anemia can occur secondary to chronic renal failure, malignancy or chemotherapy, chronic inflammatory conditions, or chronic infections. Anemia is a common finding in patients with AIDS, and it correlates with the severity of the clinical syndrome. Anemia is a risk factor for early death in AIDS patients.
- **Treatment**
  - Treatment focuses on the underlying disease and the use of EPO.
  - Response to EPO depends on the dose and the underlying cause of anemia. Lack of response to erythropoiesis-stimulating agents is commonly associated with iron deficiency. Lower response is also seen in patient who received intensive chemotherapy.
  - Therapeutic uses and regimens for EPO are shown in Table 12.9.

**TABLE 12.8 FDA-Approved Iron Chelation Therapies**

Medication	Dose	Frequency	Route	Common/Serious Adverse Effects	Notes
Deferoxamine (DFO, Desferal)	25–50 mg/kg/day, titrate to effect (maximal dose 40 mg/kg for children)	Daily, Monday–Friday	Subcutaneously for 8–12 hours	<i>Common:</i> headache, upper respiratory tract infection, abdominal pain, nausea, vomiting, pyrexia, pain, arthralgia, cough, nasopharyngitis, constipation, chest pain, injection site reactions, muscle spasms, viral infection <i>Serious:</i> audiotoxicity, hepatotoxicity, nephrotoxicity, ocular toxicity, hypotension, anaphylaxis, respiratory distress syndrome, growth retardation	Requires a syringe pump or balloon infuser Rotate sites to prevent scarring
Deferasirox (Exjade)	20 mg/kg/day, titrate to effect	Once daily	Oral drink	<i>Common:</i> headache, abdominal pain, nausea, pyrexia, vomiting, diarrhea, back pain, upper respiratory tract infection, arthralgia, pain, cough, nasopharyngitis, rash, constipation, chest pain <i>Serious:</i> nephrotoxicity, cytopenias, hepatic failure, GI hemorrhage, anaphylaxis, ocular disturbances	Should be dissolved in juice for administration

FDA, Food and Drug Administration; GI, gastrointestinal.

**TABLE 12.9 Therapeutic Uses and Regimens for Recombinant Human Erythropoietin (rhEPO)<sup>a</sup>**

Anemia Pathogenesis	Epoetin Alfa		Darbepoetin Alfa		Time to Respond (weeks)	Overall Response Rate (%)
	Dose (units/kg)	Frequency	Dose (mcg/kg)	Frequency		
HIV zidovudine therapy <sup>b</sup>	100	3×/week			8–12	17–35
Chemotherapy-induced malignancy	150 or 40,000 units (total dose)	3×/week or once a week, respectively	2.25 or 500 mcg (total dose)	Once a week or once every 3 weeks, respectively	2–8	32–61 <sup>c</sup> 48–83 <sup>d</sup>
Renal insufficiency	50–100	3×/week	0.45	Once a week	2–8	90–97

<sup>a</sup>Adult dosing.

<sup>b</sup>Patients with AIDS with endogenous erythropoietin levels ≤500 units/L; zidovudine dose ≤4,200 mg/wk.

<sup>c</sup>Epoetin alfa.

<sup>d</sup>Darbepoetin alfa.

# SECTION II • CARDIAC AND VASCULAR DISORDERS

## CHAPTER 13

### Dyslipidemias, Atherosclerosis, and Coronary Heart Disease\*

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#### General Principles

- Cholesterol is a naturally occurring sterol that is essential for life (involved with formation of bile acids, cell membranes, and steroid hormones); triglycerides are an important source of stored energy in adipose tissue.
- Risk for atherosclerosis is directly related to increasing levels of serum cholesterol.
- Three major lipoproteins (cholesterol) are found in the blood of fasting patients (Table 13.1).
  - VLDL-C accounts for 15% to 20% of Total Cholesterol (TC).
  - LDL-C accounts for 60% to 70% of TC; it is the greatest contributor to atherosclerosis.
  - HDL-C transports cholesterol from peripheral cells to the liver; higher levels are desired.

TABLE 13.1 Classification and Properties of Plasma Lipoproteins

	Chylomicron	VLDL	IDL	LDL	HDL
Density (g/mL)	<0.94	0.94–1.006	1.006–1.019	1.006–1.063	1.063–1.210
Composition (%)					
Protein	1–2	6–10	12–18	18–22	45–55
Triglyceride	85–95	50–65	20–50	4–8	2–7
Cholesterol	3–7	20–30	20–40	51–58	18–25
Phospholipid	3–6	15–20	15–25	18–24	26–32
Physiologic origin	Intestine	Intestine and liver	Produced from VLDL	Product of IDL catabolism	Liver and intestine
Physiologic function	Transport dietary CH and TG to liver	Transport endogenous TG and CH	Transport endogenous TG and CH	Transport endogenous CH to cells	Transport CH from cells to liver
Plasma appearance	Cream layer	Turbid	Clear	Clear	Clear
Electrophoretic mobility	Origin	Pre- $\beta$	Slow pre- $\beta$	$\beta$	$\alpha$
Apolipoproteins	A-IV, B-48, C-I, C-II, C-III	B-100, C-I, C-III, C-III, E	B-100, C-I, C-II, C-III, E	B-100, (a)	A-I, A-II, A-IV

CH, cholesterol; HDL, high-density lipoprotein; IDL, intermediate-density lipoprotein; LDL, low-density lipoprotein; TG, triglyceride; VLDL, very-low-density lipoprotein.

\*The reader is referred to Chapter 13, Cardiac and Vascular Disorders, written by Joseph J. Saseen, PharmD, FCCP, FASHP, BCPS, and Jean M. Nappi, PharmD, FCCP, BCPS, in the 10th edition of *Applied Therapeutics: The Clinical Use of Drugs* for a more in-depth discussion. All notations to reference numbers are based on the reference list at the end of that chapter. Chapter author William L. Baker, PharmD, FCCP, BCPS, as well as the editor of this handbook express their thanks to Drs. Saseen and Nappi and acknowledge that this chapter is based on their work.

- LDL-C is no longer the primary target according to the 2013 American College of Cardiology (ACC)/American Heart Association (AHA) guidelines update (decreasing LDL-C is associated with decreased risk for coronary heart disease).
  - Treatment is based on patient characteristics/comorbidities and 10-year atherosclerotic cardiovascular disease (ASCVD) risk.

## Patient Assessment

- Every new patient with dyslipidemia should be evaluated for four things:
  - Secondary causes of the high cholesterol level (e.g., diabetes, hypothyroidism, nephrotic syndrome, obstructive liver disease, drug induced [see Table 13.2])
  - Familial disorders
  - Presence of coronary heart disease (CHD) and CHD equivalents
  - CHD risk factors
- The 2013 ACC/AHA guidelines do not provide targets for either LDL-C or non-HDL-C.
- How to manage low HDL-C or high TG is still unclear.
- $TC = LDL-C + HDL-C + VLDL$

TABLE 13.2 Drug-Induced Hyperlipidemia

	Effect on Plasma Lipids			Comments
	Cholesterol (%)	Triglycerides (%)	HDL-C (%)	
<b>Diuretics</b>				
Thiazides	↑5–7 initially ↑0–3 later	↑30–50	↑1	Effects transient; monitor for long-term effects
Loop	No change	No change	↓ to 15	
Indapamide	No change	No change	No change	
Metolazone	No change	No change	No change	
Potassium-sparing	No change	No change	No change	
<b>β-Blockers</b>				
Nonselective	No change	↑20–50	↓10–15	Selective β-blockers have greater effects than nonselective; β-blockers with ISA or α-blocking effects are lipid neutral.
Selective	No change	↑15–30	↓5–10	
<b>α-Blocking</b>	No change or ↓	No change	No change	In general, drugs that affect α-receptors ↓cholesterol and ↑HDL-C
<b>α-Agonists and Antagonists (e.g., prazosin and clonidine)</b>	↓0–10	↓0–20	↑0–15	
<b>ACE Inhibitors</b>	No change	No change	No change	
<b>Calcium-Channel Blockers</b>	No change	No change	No change	
<b>Oral Contraceptives</b>				
α-Monophasics	↑5–20	↑10–45	↑15–↓15	Effects caused by reduced lipolytic activity or ↑VLDL synthesis; mainly caused by progestin component; estrogen alone protective
α-Triphasics	↑10–15	↑10–15	↑5–10	
<b>Glucocorticoids</b>	↑5–10	↑15–20		Marked elevations can occur in patients who are hypertriglyceridemic.
<b>Ethanol</b>	No change	↑up to 50	↑	
<b>Isotretinoin</b>	↑5–20	↑50–60	↓10–15	Changes may reverse 8 weeks after stopping drug.
<b>Cyclosporine</b>	↑15–20	No change	No change	

ACE, angiotensin-converting enzyme; HDL-C, high-density lipoprotein cholesterol; ISA, intrinsic sympathomimetic activity; VLDL, very-low-density lipoprotein.

- VLDL = TG/5
- Non-HDL-C = TC – HDL-C (formula to use when TG >400 mg/dL or patient has not fasted).

### Characterization of Lipid Disorders

- Diagnosis of type of lipid disorder requires assessing lipoprotein profile, physical examination, presence of tendon or palmar xanthomas, family history of CHD, and age of coronary symptoms (if present).
- Characteristics of common lipid disorders are shown in Table 13.3.
- Patients with high TG typically also have low HDL-C.
- Very high TG levels (>500 mg/dL) are not commonly associated with increased CHD risk, but are associated with increased risk of pancreatitis.

**TABLE 13.3 Characteristics of Common Lipid Disorders**

Disorder	Metabolic Defect	Lipid Effect	Main Lipid Parameter	Diagnostic Features
Polygenic hypercholesterolemia	↓LDL clearance	↑LDL-C	LDL-C: 130–250 mg/dL	None distinctive
Atherogenic dyslipidemia	↑VLDL secretion ↑ApoC-III synthesis ↓LPL activity ↓VLDL removal	↑TG ↑Remnant VLDL ↓HDL ↑Small, dense LDL	TG: 150–500 mg/dL HDL-C: <40 mg/dL	Frequently accompanied by central obesity or diabetes
Familial hypercholesterolemia—heterozygous	Reduction in functional LDL receptor	↑LDL-C	LDL-C: 250–450 mg/dL	Family history of premature CHD, tendon xanthomas, corneal arcus
Familial hypercholesterolemia—homozygous	Absent LDL receptors	↑LDL-C	LDL-C: >450 mg/dL	Family history of premature CHD, tendon xanthomas, corneal arcus; affected individuals exhibit CHD by second decade of life
Familial defective apoB-100	Defective apoB on LDL and VLDL	↑LDL-C	LDL-C: 250–450 mg/dL	Family history of CHD, tendon xanthomas
Dysbetalipoproteinemia (type III hyperlipidemia)	ApoE2:E2 phenotype, ↓VLDL remnant clearance	↑Remnant VLDL, ↑IDL	LDL-C: 300–600 mg/dL TGs: 400–800 mg/dL	Palmar xanthomas, tuberoeruptive xanthomas
Familial combined hyperlipidemia	↑ApoB and VLDL production	↑CH, TG, or both	LDL-C: 250–350 mg/dL TGs: 200–800 mg/dL	Family history, CHD Family history, hyperlipidemia
Familial hyperapobetalipoproteinemia	↑ApoB production	↑ApoB	ApoB: >125 mg/dL	None distinctive
Hypoalphalipoproteinemia	↑HDL catabolism	↓HDL-C	HDL-C: <40 mg/dL	None distinctive

ApoB, apolipoprotein B; ApoC-III, apolipoprotein C-III; ApoE, apolipoprotein E; CH, cholesterol; CHD, coronary heart disease; HDL, high-density lipoprotein; HDL-C, high-density lipoprotein cholesterol; IDL, intermediate-density lipoprotein; LDL, low-density lipoprotein; LDL-C, low-density lipoprotein cholesterol; TGs, triglycerides; VLDL, very-low-density lipoprotein.

## Goals of Therapy and Treatment Essentials

- The 2013 ACC/AHA guidelines did not find any evidence to support lowering LDL-C or non-HDL-C to specific levels.
- Therefore, no recommendations are made for or against specific LDL-C or non-HDL-C goals for preventing ASCVD, either as primary or as secondary treatment.
- Four distinct statin benefit groups were identified:
  - Patients with clinical ASCVD (high-intensity statin)
  - Patients without ASCVD but primary elevations of LDL-C  $\geq 190$  mg/dL (high-intensity statin)
  - Patients without ASCVD, but with diabetes, aged 40 to 75 years, and with an LDL-C between 70 and 189 mg/dL (moderate-intensity statin)
  - Patients without ASCVD or diabetes, aged 40 to 75 years with an LDL-C between 70 and 189 mg/dL and an estimated 10-year ASCVD risk  $\geq 7.5\%$  (moderate-to-high-intensity statin)
- Patients' 10-year risk for developing ASCVD should be assessed using the tool described in the 2013 ACC/AHA guidelines.
- Choice of statin is based on intensity (Table 13.4).
- Metabolic syndrome occurs when any three factors in Table 13.5 are present; the syndrome is associated with substantial increased risk for CHD.

**TABLE 13.4 The 2013 ACC/AHA Guideline Definition of High-, Moderate-, and Low-Intensity Statin Therapy**

High-Intensity Statin Therapy	Moderate-Intensity Statin Therapy	Low-Intensity Statin Therapy
Agents that lower LDL-C on average, by $\sim \geq 50\%$	Agents that lower LDL-C on average, by $\sim 30\%$ – $50\%$	Agents that lower LDL-C on average, by $\sim < 30\%$
Atorvastatin (40 <sup>a</sup> )–80 mg	Atorvastatin 10 (20) mg	Simvastatin 10 mg
Rosuvastatin 20 (40) mg	Rosuvastatin (5) 10 mg	Pravastatin 10–20 mg
	Simvastatin 20–40 mg <sup>b</sup>	Lovastatin 20 mg
	Pravastatin 40 (80) mg	Fluvastatin 20–40 mg
	Lovastatin 40 mg	Pitavastatin 1 mg
	Fluvastatin XL 80 mg	
	Fluvastatin 40 mg BID	
	Pitavastatin 2–4 mg	

Statin and doses are approved by the United States Food and Drug Administration (FDA) but were not tested in clinical trials are listed in *italics*.

<sup>a</sup>Evidence from 1 RCT only: down-titration if unable to tolerate atorvastatin 80 mg.

<sup>b</sup>Although simvastatin 80 mg was evaluated in RCTs, initiation of or titration to that dose is not recommended by the FDA due to increased risk of myopathy, including rhabdomyolysis.

**TABLE 13.5 Clinical Identification of the Metabolic Syndrome**

Presence of any three of the following:

- Waist circumference
  - Men  $\geq 40$  inches ( $> 35$  inches for Asian Americans)
  - Women  $\geq 35$  inches ( $> 31$  inches for Asian Americans)
- Triglycerides  $\geq 150$  mg/dL (or on drug treatment for elevated triglycerides)
- High-density lipoprotein cholesterol (HDL-C)
  - Men  $< 40$  mg/dL (or on drug treatment for reduced HDL-C)
  - Women  $< 50$  mg/dL (or on drug treatment for reduced HDL-C)
- Blood pressure (systolic/diastolic)  $\geq 130/\geq 85$  mm Hg (or on drug treatment for hypertension)
- Fasting glucose  $> 100$  mg/dL (or on drug treatment for elevated glucose)

## Drug Therapy

- Therapeutic lifestyle changes (TLC; Table 13.6) and exercise should be considered in all patients; additional therapeutic interventions should not be delayed in high-risk patients.
- Lipid-lowering potential is dependent on therapeutic class and agent. Average effects of select agents are shown in Table 13.7. Dose-related LDL-C lowering by drug is shown in Table 13.8.

TABLE 13.6 2013 ACC/AHA Guideline Recommended Therapeutic Lifestyle Change Diet

Nutrient	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
Carbohydrate	50%–60% of total calories
Fiber	20–30 g/day
Cholesterol	<200 mg/day
Protein	Approximately 15% of total calories

TABLE 13.7 Average Effects of Selected Drugs on Lipoprotein Cholesterol and Triglycerides

Drug	LDL (%)	HDL (%)	TG (%)
Bile acid resin	–15 to –30	±3	+3 to –10
Ezetimibe	–18 to –22	0 to 2	0 to –5
Niacin	–15 to –30	20 to 35	–30 to –60
Statin	–25 to –60	5 to 15	–10 to –45
Fibrates	±10 to –25	10 to 30	–30 to –60

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

TABLE 13.8 Dose-Related LDL-C Lowering of Nonstatin Drugs

Daily	Dosage	LDL-C Lowering (%)
Bile acid resins (cholestyramine, colestipol)	5 g	–15
	10 g	–23
	15 g	–27
Bile acid resin (colesevelam)	3.8 g	–15
	4.5 g	–18
Ezetimibe <sup>160</sup>	10 mg	–18 to –22
	10 mg/10 mg	–45
	10 mg/20 mg	–52
	10 mg/40 mg	–55
Extended-release niacin/simvastatin	10 mg/80 mg	–60
	500 mg/20 mg	–12.9 <sup>a</sup>
	1,000 mg/20 mg	–17.5 <sup>a</sup>
	1,500 mg/20 mg	–18.9 <sup>a</sup>
Niacin (crystalline) <sup>161</sup>	2,000 mg/20 mg	–19.5 <sup>a</sup>
	1,000 mg	–6
	1,500 mg	–13
	2,000 mg	–16
Extended-release niacin	3,000 mg	–22
	1,000 mg	–9
	1,500 mg	–14
	2,000 mg	–17

<sup>a</sup>Values are change in non-HDL-C compared with simvastatin 20 mg.

LDL-C, low-density lipoprotein cholesterol; non-HDL-C, non-high-density lipoprotein cholesterol.

- Drug of choice is guided by type of lipid disorders (Table 13.9), dosing considerations, and cost. Dosing guidelines for several lipid-modulating agents are shown in Table 13.10.
  - Statins produce the most effective LDL-C-lowering effect and are the drugs of first choice recommended by 2013 ACC/AHA guidelines to lower cholesterol and reduce CHD risk. They work by inhibiting the enzyme (HMG-CoA reductase) responsible for cholesterol synthesis.
  - Niacin is a low-cost agent that has a long history of use and evidence that it reduces CHD events. It inhibits mobilization of free fatty acids from peripheral adipose tissue to the liver. Because it can increase glucose by 10% to 20%, it should be used with caution in patients with diabetes.
  - Ezetimibe reduces LDL-C but has little effect on TG or HDL-C. It interferes with cholesterol absorption from the intestinal lumen.
  - Bile acid resins are well tolerated as they are not absorbed. Older forms are limited by taste and inconvenient preparations. Colesevelam is better tolerated. These agents bind bile acids in the intestines with subsequent elimination in the stool.
  - Fibrates (gemfibrozil, fenofibric acid, fenofibrate) lower TG and raise HDL-C. They are not recommended for LDL-C lowering only.
  - Fish oil lowers TG and has no effect on LDL-C. Prescription-grade omega-3 fatty acid has EPA and DHA. Dietary fish oil supplements have variable concentrations of EPA and DHA; products should be carefully selected.
- Four drugs effectively reduce LDL-C: statin, resin, ezetimibe, and niacin. When two or more agents are combined, an additive LDL-C-lowering effect is achieved. Side effects are the major limiting factor in combining drugs.
- Four drugs are appropriate for patients with metabolic syndrome who are not at their non-HDL-C goal: statins and statins combined with ezetimibe, niacin, or a fibrate.
- No effective drugs substantially and specifically increase HDL-C. The 2013 ACC/AHA guidelines recommend aggressive LDL-C lowering with a statin in patients with a low HDL-C.
- Monitoring parameters, adverse effects, and drug interactions with major cholesterol-lowering agents are shown in Table 13.11.

TABLE 13.9 Drugs of Choice for Dyslipidemia

Lipid Disorder	Drug of Choice	Alternative Agents	Combination Therapy
Polygenic hypercholesterolemia	Statin	Resin, ezetimibe, niacin combination	Statin–ezetimibe, statin–resin, resin–niacin, statin–niacin
Familial hypercholesterolemia (FH) or severe polygenic hypercholesterolemia	Statin (high potency, moderate to high dose)	Ezetimibe LDL apheresis for homozygous FH	Statin–ezetimibe, statin–resin, resin–niacin, statin–niacin, statin–ezetimibe–niacin, statin–resin–niacin
Atherogenic dyslipidemia	Statin, niacin, fibrate <sup>a</sup>	Statin, niacin, fibrate <sup>a</sup>	Statin–niacin, niacin–resin, niacin–fibrate
Isolated low HDL	Statin	Niacin	Statin–niacin

<sup>a</sup>Use cautiously because there is an increased risk of myopathy. HDL, high-density lipoprotein; LDL, low-density lipoprotein.



TABLE 13.10 Dosages of Selected Lipid-Modulating Drugs

Drug	Initial Dosage	Usual Dosage	Maximal Dosage	Comment
Cholestyramine	4 g before main meal	4 g BID before heaviest meals	8 g BID before heaviest meals	May prescribe 24 g/day, but few patients can tolerate
Colestipol	5 g of powder or 2 g of tablets every day before main meal	5 g of powder or 4 g of tablets BID before heaviest meals	10 g of powder or 8 g of tablets BID before heaviest meals	May prescribe 30 g of powder per day, but few patients can tolerate
Colesevelam	6 × 0.63-g tablets/day	Same	7 × 0.63-g tablets/day	Less bulk is associated with less gastrointestinal intolerance.
Niaspan	500 mg QHS	1,000–2,000 mg QHS	2,000 mg QHS	Increase dose by 500 mg daily every 4 weeks.
Atorvastatin	10–40 mg every day	10–40 mg every day	80 mg every day	Administer any time of day.
Fluvastatin	20–40 mg QHS	20–40 mg QHS	40 mg BID 80 mg XL every day	Modified-release form (XL) has similar efficacy but has less bioavailability (and less risk of adverse effects).
Lovastatin	20 mg with dinner	20–40 mg with dinner	40 mg BID	Administration with food increases bioavailability. BID dosing provides greater LDL-C–lowering efficacy than every day.
Pitavastatin	1–2 mg every day	1–2 mg every day	4 mg every day	Administer any time of the day with or without food.
Pravastatin	10–40 mg every day	10–40 mg every day	80 mg every day	Administer with food to reduce dyspepsia.
Rosuvastatin	10–20 mg every day	10–20 mg every day	40 mg every day	Administer any time of the day.
Simvastatin	20–40 mg every evening	20–40 mg every evening	80 mg every evening <sup>b</sup>	Administer with food to reduce dyspepsia.
Gemfibrozil	600 mg BID	Same	Same	
Fenofibrate <sup>a</sup>	67–201 mg every day	Same	201 mg every day	

<sup>a</sup>Multiple formulations are available and doses do vary.

<sup>b</sup>Restricted to patients who have been taking simvastatin 80 mg chronically (e.g., for 12 months or more) without evidence of muscle toxicity. For more information regarding simvastatin, please see <http://www.fda.gov/Drugs/DrugSafety/ucm256581.htm>BID, twice daily; LDL-C, low-density lipoprotein cholesterol; QHS, every evening at bedtime.

TABLE 13.11 Monitoring Parameters, Adverse Effects, and Drug Interactions with Major Cholesterol-Lowering Drugs

Drug	Adverse Effects	Drug Interactions	Monitoring Parameters
Resin	Indigestion, bloating, nausea, constipation, abdominal pain, flatulence	GI binding and reduced absorption of anionic drugs (warfarin, $\beta$ -blockers, digitoxin, thyroxine, thiazide diuretics); administer drugs 12 hours before or 4 hours after resin	Lipid profile every 4–8 weeks until stable dose; then every 6–12 months long term. Check TG level after stable dose achieved, then as needed.

Drug	Adverse Effects	Drug Interactions	Monitoring Parameters
Niacin	Flushing, itching, tingling, headache, nausea, gas, heartburn, fatigue, rash, worsening of peptic ulcer, elevation in serum glucose and uric acid, hepatitis, and elevation in hepatic transaminase levels	Hypotension with BP-lowering drugs such as $\alpha$ -blockers possible; diabetics taking insulin or oral agents may require dosage adjustment because of increase in serum glucose levels	Lipid profile after 1,000–1,500 mg/day and then after stable dosage achieved; then every 6–12 months long term. LFT at baseline and every 6–8 weeks during dose titration; then as needed for symptoms. Uric acid and glucose at baseline and again after stable dose reached (or symptoms produced), more frequently in diabetic patients.
Statins	Headache, dyspepsia, myositis (myalgia, CPK >10 times normal), elevation in hepatic transaminase levels	Increased myositis risk with concurrent use of drugs that inhibit or compete for CYP3A4 system (e.g., cyclosporine, erythromycin, calcium-channel blockers, fibrates, nefazodone, niacin, ketoconazole); risk greater with lovastatin and simvastatin; caution with concurrent fibrate or niacin use; lovastatin increases the INR with concurrent warfarin <sup>a</sup>	Lipid profile 4–8 weeks after dose change, then every 6–12 months long term. LFT at baseline, in 3 months, and periodically thereafter. CPK at baseline and if the patient has symptoms of myalgia.

<sup>a</sup>For more information regarding simvastatin, please see <http://www.fda.gov/Drugs/DrugSafety/ucm256581.htm>  
 BP, blood pressure; CPK, creatinine phosphokinase; CYP, cytochrome P-450; GI, gastrointestinal; INR, international normalized ratio; LFT, liver function tests; TG, triglyceride.

# Essential Hypertension\*

## General Principles

- Hypertension is the most frequently encountered chronic medical condition, affecting 30% of adult Americans. Across all age groups, blacks have a higher prevalence than do whites or Hispanics.
- Elevated blood pressure (BP) is almost always asymptomatic but can cause serious long-term complications.
- Elevated systolic blood pressure (SBP) is more predictive of cardiovascular (CV) disease than elevations in diastolic blood pressure (DBP). SBP is the target of evaluation and intervention for most patients with hypertension.
- Most patients have essential (primary) hypertension where there is no identifiable cause. In some cases, there is a secondary cause (Table 14.1) which should be treated or removed, if possible.

TABLE 14.1 Secondary Causes of Hypertension

Alcoholism
Chronic kidney disease
Chronic steroid therapy and Cushing syndrome
Coarctation of the aorta
Drug-induced or drug-related
<ul style="list-style-type: none"> <li>• Amphetamines (amphetamine, dexamethylphenidate, dextroamphetamine, lisdexamfetamine, methylphenidate, phendimetrazine, and phentermine)</li> <li>• Antidepressants (bupropion, desvenlafaxine, and venlafaxine)</li> <li>• Antihypertensive agents that are abruptly stopped (only <math>\beta</math>-blockers and central <math>\alpha_2</math>-agonists)</li> <li>• Anabolic steroids (e.g., testosterone)</li> <li>• Calcineurin inhibitors (cyclosporine and tacrolimus)</li> <li>• Cocaine and other illicit drugs</li> <li>• Corticosteroids (cortisone, dexamethasone, fludrocortisone, hydrocortisone, methylprednisolone, prednisolone, prednisone, and triamcinolone)</li> <li>• Ephedra alkaloids</li> <li>• Erythropoiesis-stimulating agents (darbepoetin-alfa and erythropoietin)</li> <li>• Ergot alkaloids (ergonovine and methysergide)</li> <li>• Estrogen-containing oral contraceptives (ethinyl estradiol)</li> <li>• Licorice (including some chewing tobacco)</li> <li>• Monoamine oxidase inhibitors (isocarboxazid, phenelzine, tranylcypromine sulfate) when given with tyramine-containing foods or with an interacting drug</li> <li>• Nonsteroidal anti-inflammatory drugs (all types)</li> <li>• Oral decongestants (e.g., pseudoephedrine)</li> <li>• Phenylephrine (ocular administration)</li> <li>• Vascular endothelial growth factor inhibitor (bevacizumab)</li> <li>• Vascular endothelial growth factor receptor tyrosine kinase inhibitor (sorafenib and sunitinib)</li> </ul>
Pheochromocytoma
Primary aldosteronism
Renovascular disease
Sleep apnea
Thyroid or parathyroid disease

\*The reader is referred to Chapter 14, Essential Hypertension, written by Joseph J. Saseen, PharmD, FCCP, FASHP, BCPS, in the 10th edition of *Applied Therapeutics: The Clinical Use of Drugs* for a more in-depth discussion. All notations to reference numbers are based on the reference list at the end of that chapter. The editor of this handbook expresses her thanks to Dr. Saseen and acknowledges that this chapter is based on his work.

- Resistant hypertension is defined as a failure to attain BP goal despite treatment with a three-drug regimen at full doses, or treatment in any patient requiring four or more drugs.

## Patient Assessment

- Diagnosis is based on the mean of two or more seated BP measurements.
- Classification of blood pressure in adults is shown in Table 14.2.
- $MAP = (SBP \times 1/3) + (DBP \times 2/3)$
- Table 14.3 and Figure 14.1 detail the proper technique for measuring blood pressure and the types of sounds heard when deflating the BP cuff.
- Wrist or finger devices that measure BP and automated devices found in stores are generally not accurate.
- Hypertension-associated complications and major CV risk factors are shown in Table 14.4.

TABLE 14.2 Classification of Blood Pressure in Adults

Classification <sup>a</sup>	SBP (mm Hg)	DBP (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

<sup>a</sup>If SBP and DBP are in different categories, the overall classification is determined on the basis of the higher of the two blood pressure categories.

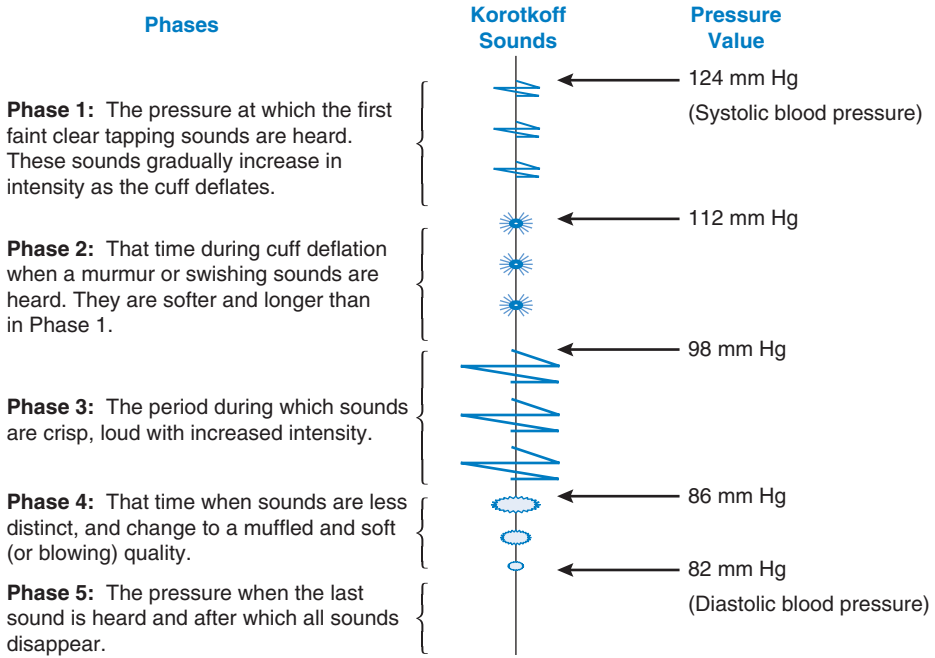
DBP, diastolic blood pressure; SBP, systolic blood pressure.

TABLE 14.3 Auscultatory Method for Blood Pressure Measurement in Adults as Recommended by the American Heart Association

- PATIENT:** Patient should be seated for 5 minutes with arm bared, unrestricted by clothing, and supported at heart level. Smoking or food ingestion should not have occurred within 30 minutes before the measurement.
- CUFF:** An appropriately sized cuff should be used. The internal inflatable bladder width should be at least 40% and the bladder length and cover at least 80% of the upper arm circumference. The cuff should be wrapped snugly around the arm with the center of the bladder over the brachial artery.
- MONITOR:** Measurements should be taken with a correctly calibrated mercury sphygmomanometer, an aneroid manometer, or a validated electronic device.
- PALPATORY METHOD:** SBP should be estimated using the palpatory method. The cuff is rapidly inflated in 10-mm Hg increments, while simultaneously palpating the radial pulse on the patient's wrist on the cuffed arm while observing the manometer. The pressure when the radial pulse is no longer palpable is the estimated SBP. The cuff is then deflated rapidly.
- KOROTKOFF SOUNDS:** The head of the stethoscope, ideally using the bell, should be placed over the brachial artery, with each earpiece in the clinician's ear. The cuff should then be rapidly inflated to 20–30 mm Hg above the estimated SBP from the palpatory method. The cuff is slowly deflated at a rate of 2 mm Hg per second while the clinician simultaneously listens for phase 1 (the first appearance of sounds) and phase 5 (the disappearance of sounds) Korotkoff sounds while also observing the manometer. When the pressure is 10–20 mm Hg below phase 5, the cuff can be rapidly deflated.
- DOCUMENTATION:** BP values should always be recorded. The BP values (SBP/DBP) should be recorded using even numbers (rounded up from an odd number)<sup>a</sup> along with the patient's position (seated, standing, or supine), arm used, cuff size, time, and date.
- REPEAT:** A second measurement should be taken after at least 1 minute in the same arm. If the readings differ by > 5 mm Hg, additional measurements should be obtained. The mean of these values should be used to make clinical decisions. BP should be taken in both arms at the initial visit with the BP measured in the arm with the higher reading at subsequent visits.

<sup>a</sup>Terminal digit preference (i.e., tendency to report readings that end in 0 or 5) should be avoided.

BP, blood pressure; DBP, diastolic blood pressure; SBP, systolic blood pressure.



**Figure 14.1** Phases of the Korotkoff sounds heard when indirectly measuring blood pressure.

**TABLE 14.4 Hypertension-Associated Complications and Major Cardiovascular Risk Factors**

**HYPERTENSION-ASSOCIATED COMPLICATIONS**

- Atherosclerotic vascular disease
  - Coronary artery disease (sometimes called coronary heart disease)
    - Myocardial infarction
    - Acute coronary syndromes
    - Chronic stable angina
  - Carotid artery disease
    - Ischemic stroke
    - Transient ischemic attack
  - Peripheral arterial disease
  - Abdominal aortic aneurysm
  - Other forms of CV disease
    - Left ventricular dysfunction (systolic heart failure)
    - Chronic kidney disease
    - Retinopathy

**MAJOR CV RISK FACTORS**

- Advanced age (>55 years for men, >65 years for women)
- Cigarette smoking
- Diabetes mellitus
- Dyslipidemia
- Family history of premature atherosclerotic vascular disease (men <55 years or women <65 years) in primary relatives
- Hypertension
- Kidney disease (microalbuminuria or estimated GFR <60 mL/minute/1.73 m<sup>2</sup>)
- Obesity (BMI ≥ 30 kg/m<sup>2</sup>)
- Physical inactivity

BMI, body mass index; CV, cardiovascular; GFR, glomerular filtration rate.

## Goals of Therapy

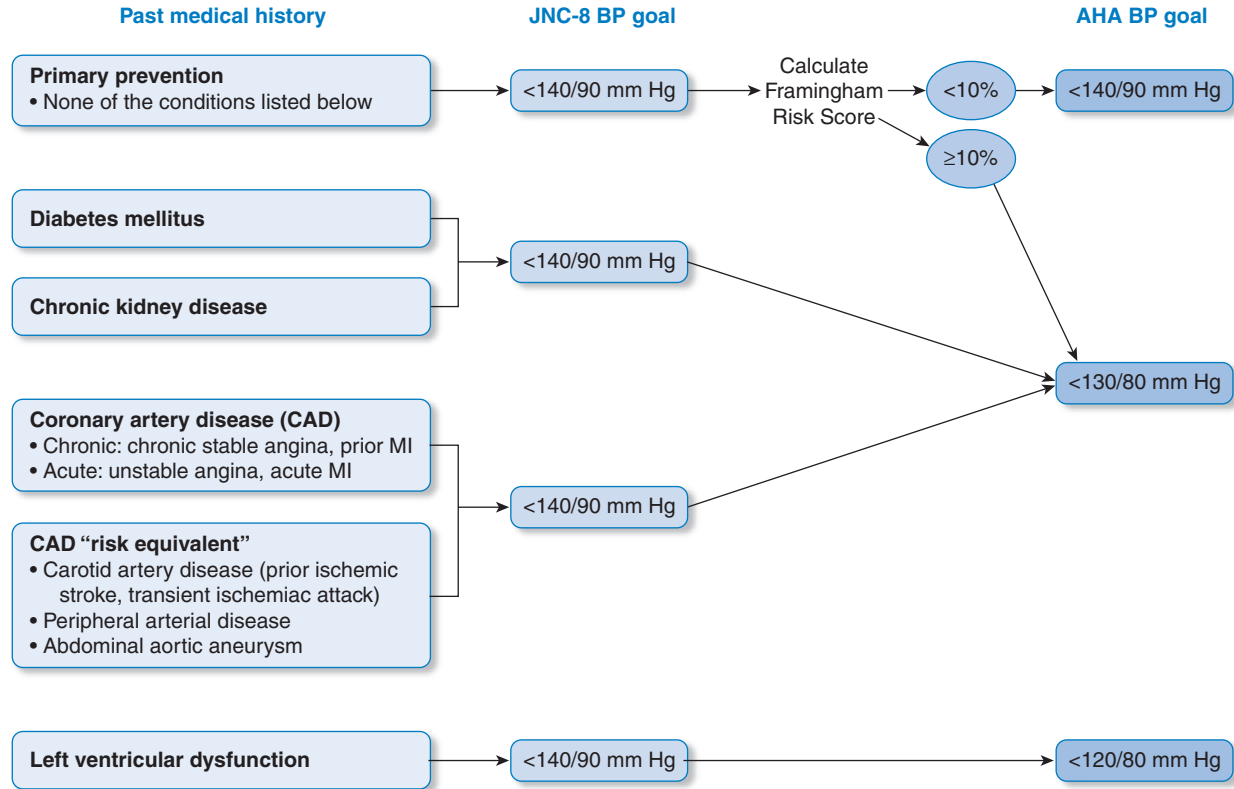
- The overarching goal of treating hypertension is to reduce associated morbidity and mortality. Control of BP is the most feasible clinical end point to guide therapy.
- Most patients with hypertension have a recommended BP goal of <140/90 mm Hg. Patients above a certain age have a goal of <150/90 mm Hg. A guide to goal BP is shown in Figure 14.2.

## Treatment

- Patient education is essential to ensure an understanding of the disease and its complications. A guide to patient–provider interactions is shown in Table 14.5.
- Lifestyle modifications (Table 14.6) are an important part of treatment for all patients with hypertension; pharmacotherapy is often also needed.
- Available evidence shows that antihypertensive pharmacotherapy reduces the risk of hypertension-associated complications. Specific evidence-based pharmacotherapy recommendations, including preferred treatments for patients with compelling indications, are shown in Figure 14.3.
- For **primary prevention** patients, angiotensin-converting enzyme inhibitors (ACEI), angiotensin receptor blockers (ARB), calcium-channel blockers (CCB), thiazide diuretic, or two-drug combination are appropriate options for first-line therapy (all are comparable options, with one not preferred over the other).  $\beta$ -blocker therapy is not as effective in reducing CV risks; it should only be used as add-on therapy for primary prevention.
- For patients with **stage 2 hypertension**, two-drug therapy is recommended from the start for initial treatment. Two drugs with different mechanisms of action should be chosen.
- **Race.** Black patients are best treated with thiazide diuretics or CCBs, alone or in combination. ACEI is not appropriate monotherapy unless the patient has a compelling indication due to reduced efficacy and increased risk of angioedema and cough.
- **Age.** Elderly patients have the lowest rate of BP control. Use of thiazides or CCBs is preferred as first-line therapy. To minimize side effects, only one antihypertensive agent should be started in patients above 80 years of age.
- **Concomitant Diseases.** Choice of therapy may be affected by concomitant diseases. Whenever possible an agent that benefits more than one condition (compelling indications) should be used.
- Considerations for the antihypertensive agent of choice are shown in Table 14.7. Most patients with hypertension need two or more drugs to attain BP goals.
- Lack of response to therapy can occur for several reasons (Table 14.8).

## Drug Therapy

- **Diuretics.** Thiazides or thiazide-likes are the diuretics of choice for most patients. At commonly used doses, chlorthalidone is more effective at lowering BP than hydrochlorothiazide. The initial diuresis lasts 4 to 6 weeks and is then replaced by a decrease in peripheral vascular resistance (PVR). Loop diuretics produce a more potent diuresis but a smaller decrease in PVR. Potassium-sparing diuretics have minimal effect on lowering BP but are used in combination with thiazides to minimize potassium loss. Table 14.9 shows the diuretic agents.
- **ACEIs.** Most ACEI are considered interchangeable if used in equivalent doses (Table 14.10). It may take 2 to 4 weeks to see the full antihypertensive effects of ACEI. For all compelling indications (Figure 14.3), ACEI has been shown to reduce CV risk.
- **ARBs.** Comparative dosing of ARBs is shown in Table 14.11. Unlike ACEIs, ARBs do not cause cough. A history of ACEI-induced angioedema does not preclude use of an ARB. ARBs should not be used in combination with ACEIs.
- **CCBs.** Two primary subtypes of CCBs exist (Table 14.12). Dihydropyridines are potent vasodilators of peripheral and coronary arteries. Nondihydropyridines are only moderately potent



**Figure 14.2** Goal blood pressure (BP) determination based on patient-specific history and cardiovascular risk assessment. AHA, American Heart Association; JNC-7, The Seventh Report of the Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure.

TABLE 14.5 Patient–Provider Interactions for Hypertension

## PATIENT EDUCATION

- Assess patient’s understanding and acceptance of the diagnosis of hypertension.
- Discuss patient’s concerns and clarify misunderstandings.
- When measuring BP, inform the patient of the reading both verbally and in writing.
- Assure patient understands his or her goal BP value.
- Ask patient to rate (1–10) his or her chance of staying on treatment.
- Inform patient about recommended treatment, including lifestyle modification. Provide specific written information using standard brochures when available.
- Elicit concerns and questions and provide opportunities for patient to state specific behaviors to carry out treatment recommendations.
- Emphasize:
  - the need to continue treatment
  - that control does not mean cure
  - that elevated BP is usually not accompanied by symptoms

## INDIVIDUALIZE TREATMENT REGIMENS

- Include the patient in decision making.
- Simplify the regimen to once-daily dosing, whenever possible.
- Incorporate treatment into patient’s daily lifestyle.
- Set realistic short-term objectives for specific components of the medication and lifestyle modification plan.
- Encourage discussion of diet and physical activity, adverse drug effects, and concerns.
- Encourage self-monitoring with validated BP devices.
- Minimize the cost of therapy, when possible.
- Discuss adherence at each clinical encounter.
- Encourage gradual sustained weight loss.

BP, blood pressure.

TABLE 14.6 Lifestyle Modifications to Prevent and Treat Hypertension

Modification	Recommendation
Weight management	Lose weight if overweight or obese, ideally attaining a BMI <25 kg/m <sup>2</sup> . Maintain a desirable BMI (18.5–24.9 kg/m <sup>2</sup> ) if not overweight or obese.
Adopt DASH-type dietary patterns	Consume a diet that is rich in fruits and vegetables (8–10 servings/day), rich in low-fat dairy products (2–3 servings/day), but has reduced amounts of saturated fat and cholesterol.
Reduced sodium intake	Reduce daily dietary sodium intake as much as possible—ideally to <65 mmol/day (equal to 1.5 g/day sodium, or 3.8 g/day sodium chloride).
Moderation of alcohol consumption	For patients who drink alcohol, limit consumption to no more than two drinks/day in men and no more than one drink/day in women and lighter-weight people. <sup>a</sup> Do not recommend alcohol consumption in patients who do not drink alcohol.
Regular physical activity	Regular moderate-intensity aerobic physical activity; at least 40 minutes of continuous or intermittent 3–4 day/week, but preferably daily.

<sup>a</sup>One drink is defined as 12 ounces of regular beer, 5 ounces of wine (12% alcohol), and 1.5 ounces of 80-proof distilled spirits. BMI, body mass index; DASH, Dietary Approaches to Stop Hypertension.

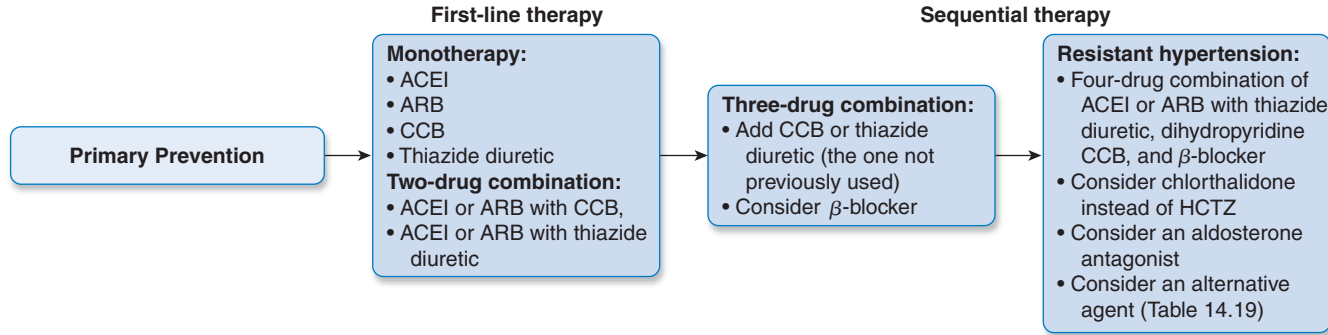
vasodilators and directly decrease AV nodal conduction thereby reducing cardiac contractility. Sustained-release formulations are preferred for the treatment of hypertension due to the short half-life of CCBs.

- **$\beta$ -blockers.**  $\beta$ -blockers should not be the primary agent for primary prevention but are effective as add-on therapy (Table 14.13). Evidence supports the use of  $\beta$ -blockers in patients with concomitant coronary artery disease. When discontinuing therapy,  $\beta$ -blockers should be gradually stopped to avoid rebound hypertension (decrease dose by 50% for 3 days and then by another 50% for 3 days).

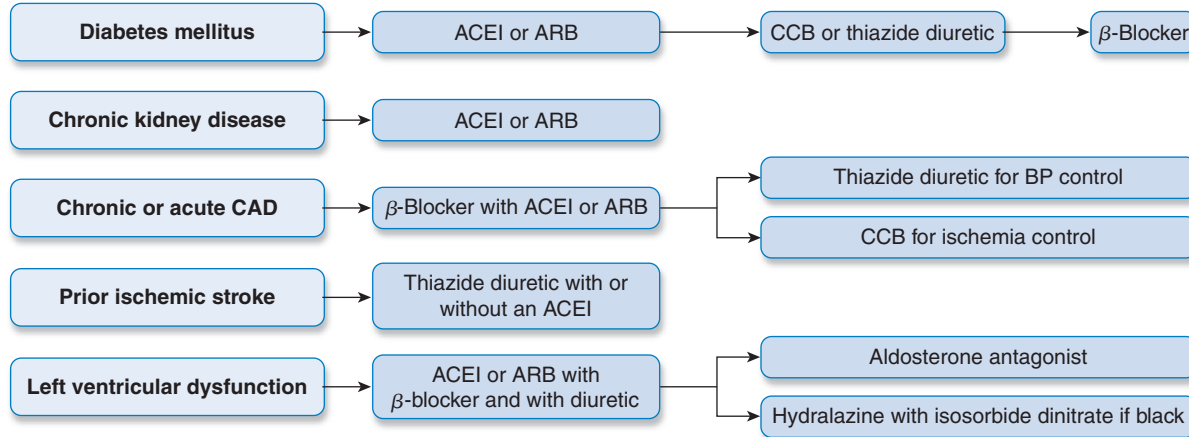


Past medical history  
(see Figure 14.2)

Specific evidence-based  
pharmacotherapy recommendations



Compelling indication for specific pharmacotherapy



**Figure 14.3** Recommended pharmacotherapy based on clinical trials evidence demonstrating long-term reductions in morbidity and mortality in patients with hypertension and specific comorbid conditions and cardiovascular risk. Combination therapy with two antihypertensive drugs is an option for patients with stage 1 hypertension (see Table 14.1) and is strongly recommended in patients with stage 2 hypertension. ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; CAD, coronary artery disease; CCB, calcium-channel blocker.

TABLE 14.7 Additional Considerations in Antihypertensive Drug Choice<sup>a</sup>

Antihypertensive Agent	Situations with Potentially Favorable Effects	Situations with Potentially Unfavorable Effects <sup>b</sup>	Avoid Use
ACEI	Low-normal potassium, elevated fasting glucose, microalbuminuria (with or without diabetes)	High-normal potassium or hyperkalemia	Pregnancy, bilateral renal artery stenosis, history of angioedema
ARB	Low-normal potassium, elevated fasting glucose, microalbuminuria (with or without diabetes)	High-normal potassium or hyperkalemia	Pregnancy, bilateral renal artery stenosis
CCB: dihydropyridine	Raynaud's phenomenon, elderly patients with isolated systolic hypertension, cyclosporine-induced hypertension	Peripheral edema, left ventricular dysfunction (all except amlodipine and felodipine), high-normal heart rate or tachycardia	Left ventricular dysfunction (not with amlodipine or felodipine)
CCB: nondihydropyridine	Raynaud's phenomenon, migraine headache, supraventricular arrhythmias, high-normal heart rate or tachycardia	Peripheral edema, low-normal heart rate	Second- or third-degree heart block, left ventricular dysfunction
Thiazide diuretic and thiazide-like diuretics	Osteoporosis or at increased risk for osteoporosis, high-normal potassium	Gout, hyponatremia, elevated fasting glucose (as monotherapy), low-normal potassium or sodium	Anuria, kidney failure

<sup>a</sup>These considerations should never replace drug recommendations for a compelling indication.

<sup>b</sup>May use but requires diligent monitoring.

High-normal refers to patients in the high end of the normal range, but not above the range.

Low-normal refers to patients in the low end of the normal range, but not below the range.

ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; CCB, calcium-channel blocker.

TABLE 14.8 Reasons for Not Attaining Goal Blood Pressure despite Antihypertensive Pharmacotherapy

Drug Related	Health Condition or Lifestyle Related	Other
Nonadherence	Volume overload	Improper blood pressure measurement
Inadequate antihypertensive dose	Excess sodium intake	Resistant hypertension
Inappropriate antihypertensive combination therapy	Volume retention from chronic kidney disease	White-coat hypertension
Inadequate diuretic therapy	Secondary disease causes (Table 14.1)	Pseudohypertension
Secondary drug-induced causes (Table 14.1)	Obesity	
Clinician failure to intensify or augment therapy (i.e., clinical inertia)	Excessive alcohol intake	

- **Alternative Agents.** Several alternative antihypertensive agents are available (Table 14.14). Use of these agents should be used to provide additional BP lowering only after first- and second-line agents have been tried.
- See Table 14.15 for side effects and contraindications of antihypertensive agents.

TABLE 14.9 Diuretics in Hypertension

Category	Selected Products	Usual Dosage Range (mg/day)	Dosing Frequency
Thiazide and thiazide-like	Chlorthalidone	12.5–25	Daily
	Hydrochlorothiazide	12.5–50	Daily
	Indapamide	1.25–5	Daily
	Metolazone	2.5–10	Daily
	Metolazone	0.5–1.0	Daily
Loop	Bumetanide	0.5–4	BID
	Furosemide	20–80	BID
	Torsemide	2.5–10	Daily
Potassium-sparing	Amiloride	5–10	Daily to BID
	Triamterene	50–100	Daily to BID
Potassium-sparing combination	Triamterene/HCTZ	37.5/25–75/50	Daily
	Spironolactone/HCTZ	25/25–50/50	Daily
	Amiloride/HCTZ	5–10/50–100	Daily
Aldosterone antagonist	Eplerenone	50–100	Daily to BID
	Spironolactone	12.5–50	Daily to BID

BID, twice daily; HCTZ, hydrochlorothiazide.

TABLE 14.10 Angiotensin-Converting Enzyme Inhibitors in Hypertension

Drug	Usual Starting Dose (mg/day) <sup>a</sup>	Usual Dosage Range (mg/day)	Dosing Frequency
Benazepril	10	20–40	Daily to BID
Captopril	25	50–100	BID to TID
Enalapril	5	10–40	Daily to BID
Fosinopril	10	20–40	Daily
Lisinopril	10	20–40	Daily
Moexipril	7.5	7.5–30	Daily to BID
Perindopril	4	4–16	Daily
Quinapril	10	20–80	Daily to BID
Ramipril	2.5	2.5–20	Daily to BID
Trandolapril	1	2–4	Daily

<sup>a</sup>Starting dose may be decreased 50% if patient is volume depleted, in acute heart failure exacerbation, or very elderly ( $\geq 75$  year). BID, twice daily; TID, three times daily.

TABLE 14.11 Angiotensin Receptor Blockers in Hypertension

Drug	Starting Dose (mg/day) <sup>a</sup>	Usual Dosage Range (mg/day)	Dosing Frequency
Azilsartan medoxomil	80	80	Daily
Candesartan cilexetil	16	8–32	Daily to BID
Eprosartan mesylate	600	600–800	Daily to BID
Irbesartan	150	75–300	Daily
Losartan potassium	50	25–100	Daily to BID
Olmesartan medoxomil	20	20–40	Daily
Telmisartan	40	20–80	Daily
Valsartan	80–160	80–320	Daily

<sup>a</sup>Starting dose may be decreased 50% if patient is volume depleted, very elderly, or taking a diuretic. BID, twice daily.

TABLE 14.12 Calcium-Channel Blockers in Hypertension<sup>a</sup>

Drug	Usual Dosage Range (mg/day)	Dosing Frequency
<b>NONDIHYDROPYRIDINES<sup>b</sup></b>		
Diltiazem, sustained-release	120–480	Daily
Diltiazem, extended-release <sup>c</sup>	120–540	Daily
Verapamil, sustained-release	180–480	Daily to BID
Verapamil, controlled-onset extended-release <sup>c</sup>	180–480	QHS
Verapamil, chronotherapeutic oral drug-absorption system <sup>c</sup>	100–400	QHS

Drug	Usual Dosage Range (mg/day)	Dosing Frequency
<b>DIHYDROPYRIDINES</b>		
Amlodipine	2.5–10	Daily
Felodipine, extended-release tablet	2.5–10	Daily
Isradipine, controlled-release tablet	5–20	Daily
Nicardipine, sustained-release capsule	60–120	BID
Nifedipine, sustained-release tablet <sup>d</sup>	30–90	Daily
Nisoldipine, extended-release tablet	17–34	Daily

<sup>a</sup>Immediate-release (IR) diltiazem, nifedipine, and verapamil should be avoided in hypertension.

<sup>b</sup>Many different long-acting products exist. Because their individual release characteristics vary, they are not exactly interchangeable using a milligram-per-milligram conversion.

<sup>c</sup>Chronotherapeutic agents are dosed primarily at bedtime and have a delayed drug release for a period of hours, followed by slow delivery of drug that starts just before morning, with no delivery during the early evening; because they use different delivery systems, they are not interchangeable products.

<sup>d</sup>Only sustained-release nifedipine is approved for hypertension. Immediate-release nifedipine should be avoided for the management of hypertension.

BID, twice daily; QHS, every night.

TABLE 14.13 Common  $\beta$ -Blockers in Hypertension

Drug	Usual Dosage Range (mg/day)	Dosing Frequency	Half-Life (hours)	$\beta_1$ Selectivity	Lipid Solubility
Atenolol	25–100	Daily to BID	6–7	++	Low
Bisoprolol	5–20	Daily	9–12	+++	High
Carvedilol	12.5–50	BID	6–10	0	High
Carvedilol, controlled release	10–80	Daily	6–10	0	High
Labetalol	200–800	BID	6–8	0	Moderate
Metoprolol tartrate	100–400	BID	3–7	+	Moderate to high
Metoprolol succinate	25–400	Daily	3–7	+	Moderate to high
Nebivolol	5–10	Daily	12–19	+++	High
Propranolol	40–180	Daily (LA and XL) or BID	3–5	0	High

BID, twice daily.

TABLE 14.14 Alternative Antihypertensive Agents

Drugs/Mechanism of Action	Usual Dosage Range (mg/day)	Dosing Frequency
<b>ALDOSTERONE ANTAGONISTS (see Table 14.9)</b>		
<b><math>\alpha_1</math>-BLOCKERS</b>		
Doxazosin	1–8	Daily
Prazosin	2–20	BID to TID
Terazosin	1–20	Daily to BID
<b>DIRECT RENIN INHIBITOR</b>		
Aliskiren	150–300	Daily
<b><math>\alpha_2</math>-AGONISTS (CENTRAL)</b>		
Clonidine	0.1–0.8	BID
Clonidine transdermal	0.1–0.3	Once weekly
Methyldopa	250–1,000	BID
<b>ARTERIAL VASODILATORS</b>		
Hydralazine	25–100	BID to TID
Minoxidil	2.5–80	Daily to BID
<b>ADRENERGIC NEURON BLOCKERS</b>		
Reserpine	0.05–0.25	Daily

BID, twice daily; TID, three times daily.

TABLE 14.15 Side Effects and Contraindications of Antihypertensive Agents

	Side Effects			
	Innocuous but Sometimes Annoying	Potentially Harmful	Usually Requires Cessation of Therapy, at Least Temporarily	Precautions
Thiazide Diuretics	Increased urination (at onset of therapy), muscle cramps, hyperuricemia (without gout)	Hypokalemia, <sup>a</sup> hyponatremia, hyperglycemia, hypovolemia, pancreatitis, photosensitivity, hypercholesterolemia, hypertriglyceridemia, hyperuricemia with gout, orthostatic hypotension (more frequent in elderly)	Hypercalcemia, azotemia, skin rash (cross-reacts with only certain sulfonamide allergies), purpura, bone marrow depression, lithium toxicity in patients on lithium therapy, hyponatremia	Anuria, kidney failure
Loop Diuretics	Increased urination, muscle cramps, hyperuricemia (less than with thiazides)	Hypokalemia, <sup>a</sup> hyperglycemia, hypovolemia, pancreatitis, hypercholesterolemia, hypertriglyceridemia, hearing loss with large IV doses, orthostatic hypotension (more pronounced in elderly)	Hyponatremia, hypocalcemia, azotemia, skin rash (cross-reacts with only certain sulfonamide allergies), photosensitivity, lithium toxicity in patients on lithium therapy	Anuria
ACEI	Dizziness, dry cough	Orthostatic hypotension (more pronounced in elderly treated with a diuretic), increased serum creatinine, increased potassium	Angioedema, severe hyperkalemia, increase in serum creatinine >35%	Bilateral renal artery stenosis, volume depletion, hyponatremia, pregnancy, history of angioedema
ARB	Dizziness	Orthostatic hypotension (more pronounced in elderly treated with a diuretic), increased serum creatinine, increased potassium	Severe hyperkalemia, increase in serum creatinine >35%	Bilateral renal artery stenosis, volume depletion, hyponatremia, pregnancy

CCB: Dihydropyridines	Dizziness, headache, flushing	Peripheral edema, tachycardia	Significant peripheral edema	Left ventricular dysfunction (not with amlodipine or felodipine)
CCB: Nondihydropyridines	Dizziness, headache, constipation	Bradycardia	Heart block, left ventricular dysfunction, interactions with certain drugs	Left ventricular dysfunction, second- or third-degree heart block, sick sinus syndrome
$\beta$ -Blocker	Bradycardia, weakness, exercise intolerance	Masking the symptoms of hypoglycemia in diabetes, hyperglycemia, aggravation of peripheral arterial disease, erectile dysfunction, increased triglycerides, decreased HDL-C	Left ventricular dysfunction (not with carvedilol, metoprolol, bisoprolol), bronchospasm in patients with asthma or COPD (more pronounced with nonselective agents)	Severe asthma, second- or third-degree heart block, acute left ventricular dysfunction exacerbation, coronary artery disease for agents with intrinsic sympathomimetic activity
Aldosterone Antagonist	Menstrual irregularities (spironolactone only) or gynecomastia (spironolactone only)	Increased potassium	Hyperkalemia, hyponatremia	Kidney failure. kidney impairment (for eplerenone: CrCl <50 mL/minute, or type 2 diabetes with proteinuria, and creatinine >1.8 in women, >2.0 in men), hyperkalemia, hyponatremia

<sup>a</sup>Routine addition of potassium supplementation or empiric concurrent potassium-sparing diuretics should be discouraged unless hypokalemia is demonstrated, the patient is taking digoxin, or potassium is in the low-normal range.

ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; CCB, calcium-channel blocker; COPD, chronic obstructive pulmonary disease; CrCl, creatinine clearance; HDL-C, high-density lipoprotein cholesterol; IV, intravenous.

# Peripheral Vascular Disorders\*

## PERIPHERAL ARTERIAL DISEASE

### General Principles

- Peripheral arterial disease (PAD) is a common complication that comes from stenosis or occlusion in the peripheral arteries of the legs.
- Although sometimes painful, most patients with PAD are largely asymptomatic.
- Intermittent claudication (IC) is the predominant complication of occlusive PAD. IC causes aching, cramping, tightness, or weakness of the legs, usually during exertion. Pain is often relieved when the exertion stops.
- IC can severely limit mobility and lead to tissue necrosis or amputation of the affected limb.

### Patient Assessment

- Risk factors for developing occlusive PAD are similar to those for coronary artery disease (diabetes, cigarette smoking, hypertension, dyslipidemias).
- Symptoms of IC indicate an inadequate supply of arterial blood to peripheral muscles. Exercise may induce IC if lesions are >50% stenosis; pain at rest occurs with >80% stenosis.

### Goals of Therapy

- The goal of treatment is preventing further claudication pain, lessening current pain, arresting progression of the underlying disease, and decreasing risk of cardiovascular events.

### Treatment

- Medical treatment of PAD and the expected outcomes are shown in Table 15.1.
- Smoking cessation, if relevant, is the most important modifiable factor in preventing the development of rest pain, prolonged limb ischemia, and need for amputation. Smoking confers a sevenfold increase in risk for PAD. Patient outcomes based on smoking status are in Table 15.2.
- Exercise is the most effective means of preserving and increasing mobility; exercise is more effective than the most effective pharmacologic therapy.
- Aggressive glucose control is appropriate in patients with type 2 diabetes.
- **Lipid-Lowering Therapy.** All patients with evidence of atherosclerotic disease and an LDL cholesterol of >100 mg/dL are candidates for lipid-lowering therapy, although few prospective data show clinical benefit in regression or stabilization of peripheral lesions or reduced clinical events.
- **Antiplatelet Therapy.** *Aspirin* (75–162 mg/day) is recommended in patients with vascular disease of any origin. Despite evidence of efficacy, *ticlopidine* is not commonly used due to poor tolerability (diarrhea, hematologic toxicity). Although the effects of *clopidogrel* on specific PAD outcomes are not known, it is an appropriate alternative in patients unable to take aspirin.

\*The reader is referred to Chapter 15, Peripheral Vascular Disorders, written by Patricia M. Schuler, PharmD, and C. Wayne Weart, PharmD, BCPS, FASHP, FAPhA, in the 10th edition of *Applied Therapeutics: The Clinical Use of Drugs* for a more in-depth discussion. All notations to reference numbers are based on the reference list at the end of that chapter. The editor of this handbook expresses her thanks to Drs. Schuler and Weart and acknowledges that this chapter is based on their work.

TABLE 15.1 Medical Treatment of Peripheral Arterial Disease and Expected Outcomes

Intervention	Improve Leg Symptoms?	Prevent Systemic Complications?
Smoking cessation	Yes	Yes
Exercise	Yes	No
Cilostazol	Yes	No
Statin drugs	Yes	Yes
Angiotensin-converting enzyme inhibitors	Yes	Yes
Blood pressure control	No	Yes
Antiplatelet therapy <sup>a</sup>	No	Yes

<sup>a</sup>Aspirin or clopidogrel.

TABLE 15.2 Patient Outcomes Based on Smoking Status after Intermittent Claudication Diagnosis

Outcome	Length of Follow-Up (years)	Patient Population	
		Current Smokers (%)	Past Smokers <sup>a</sup>
Rest pain	7	16	0
Myocardial infarction	10	53	11
Amputation	5	11	0
Mortality	10	54	18

<sup>a</sup>Quit after intermittent claudication diagnosis.

- **Cilostazol.** One of the few agents that have FDA-labeling for treatment of IC, fixed doses of 100 mg twice daily have been shown to increase walking distance by 50%. Several drawbacks to its use exist, including bothersome side effects (headache, diarrhea) and a contraindication in patients with heart failure.
- **Rheologic Agents.** While pentoxifylline has FDA-labeling for treatment of IC, its use is limited because data demonstrating its usefulness are controversial, cost is high, and potential for side effects exist.
- **Vasodilators.** Numerous vasodilators have been used to treat IC but none has convincingly or consistently improved exercise performance. Verapamil is one agent with vasodilating properties that may be useful in patients with IC.
- **Ginkgo Biloba.** Ginkgo has antiplatelet properties and few side effects. It is one of the few herbal therapies with evidence to support its use for IC.

## RAYNAUD'S PHENOMENON

### General Principles

- Raynaud's phenomenon is an exaggerated vasospastic response to cold or emotion. It is usually limited to the skin of the hands and fingers, but can also occur in the feet.

### Patient Assessment

- Primary Raynaud's phenomenon has an idiopathic origin (criteria in Table 15.3). Secondary Raynaud's has a similar clinical presentation in the presence of an associated disease or condition, most commonly a connective tissue disorder.
- Raynaud's can also be associated with medications (e.g.,  $\beta$ -blockers, ergots, cytotoxic drugs, interferon).
- Prevalence is 3% to 4% across ethnic groups. It is more common in women than in men.



TABLE 15.3 Criteria for Diagnosis of Primary Raynaud's Phenomenon

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Vasospastic attacks caused by cold or emotional stress  
 Symmetric attacks involving both hands  
 No evidence of digital ulcerations, pitting, or gangrene  
 Normal nailfold capillaries  
 No suggestion of a secondary cause  
 A negative antinuclear antibody test  
 A normal erythrocyte sedimentation rate

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## Treatment

- Most patients respond to conservative management. Avoiding cold stimuli is the primary treatment.
- Medications can be used to treat Raynaud's if it interferes with the patient's ability to work or perform daily activities. Other than calcium-channel blockers (CCB) no proven therapy for Raynaud's exists.
- Controlled release nifedipine is the main CCB used for treatment. It has been shown to decrease the number of attacks by 50% and decrease the severity of attacks by a third.
- Patients who do not benefit from nifedipine are not likely to benefit from other CCBs.
- Application of nitroglycerin ointment to the hands has been tried for decades. Data supporting this use are sparse. Treatment should be discontinued if no benefit is observed after 2 to 3 weeks.

## NOCTURNAL LEG CRAMPS

### General Principles

- Nocturnal leg cramps are idiopathic, involuntary contractions occurring at rest that cause a visible and palpable knot in the affected muscle.
- Prevalence of nocturnal leg cramps is 37% in people >50 years of age and 54% in people >80 years of age.

### Patient Assessment

- Nocturnal leg cramps typically occur in the early hours of sleeping. They are asymmetrical and primarily affect the muscles of the calf and small muscles of the foot.
- Other causes of leg cramps should be assessed (Table 15.4).

TABLE 15.4 Other Causes of Muscle Cramps

Drug-Induced Cramps	Biochemical Causes	Other
Alcohol	Dehydration	Contractures
Antipsychotics (dystonia)	Hemodialysis	Diabetes
$\beta$ -Agonists (e.g., albuterol, terbutaline, salbutamol)	Hypocalcemia	Lower motor neuron disease
Cimetidine	Hypokalemia	
Clofibrate	Hypomagnesemia	Peripheral vascular disease
Diuretics	Hyponatremia	Tetany
Lithium	Uremia	Thyroid disease
Narcotic analgesics		
Nicotinic acid		
Nifedipine		
Penicillamine		
Statins		
Steroids		

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## Goals of Therapy

- The goal of treatment is to prevent episodes of nocturnal leg cramps.

## Treatment

- Prophylactic stretching and alterations of sleeping position should be tried first.
- Acute therapy consists of dorsiflexion (grasping the toes and pulling them upward in the opposite direction of the cramp).
- Quinine is the most frequently prescribed medication for nocturnal leg cramps (324 mg at bedtime). Controversy exists about its benefit; efficacy has been shown but the magnitude of benefit is rather small. If a response is not seen within 2 weeks, therapy should be discontinued.

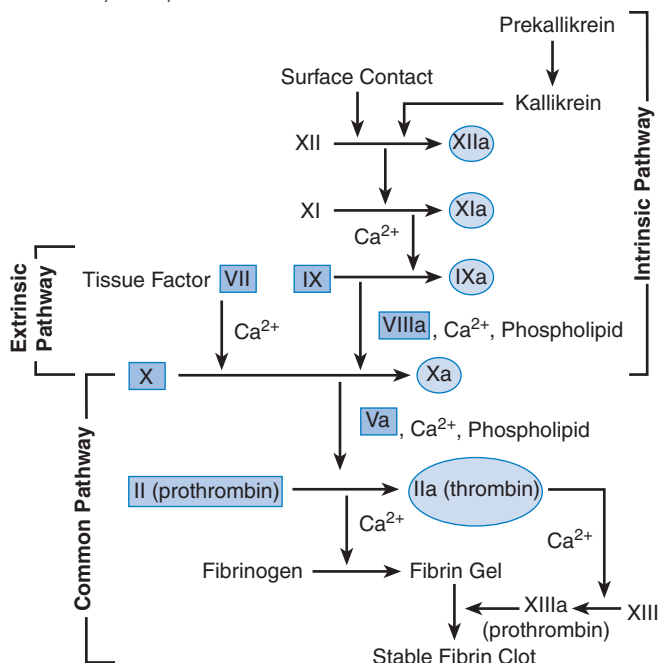
# Thrombosis\*

## General Principles

- Thrombosis is the process involved in the formation of a fibrin blood clot. An embolus is a small part of a clot that breaks off and is carried via the blood to another part of the vascular system.
- Abnormal thrombotic events include venous thromboembolism (VTE), deep venous thrombosis (DVT), pulmonary embolism (PE), stroke, and other systemic manifestations of embolized clots.
- Endothelial damage results in activation of the clotting cascade (Figure 16.1).

## Characterization of Thrombi

- Pathological thrombi are classified according to location and composition.
- Arterial thrombi occur in areas of rapid blood flow and are typically initiated by spontaneous or mechanical rupture of atherosclerotic plaques.
- Venous thrombi are found primarily in the venous circulation and are composed almost entirely of fibrin and erythrocytes.



**Figure 16.1** Simplified clotting cascade. Components in ovals are influenced by heparin; components in boxes are influenced by warfarin.

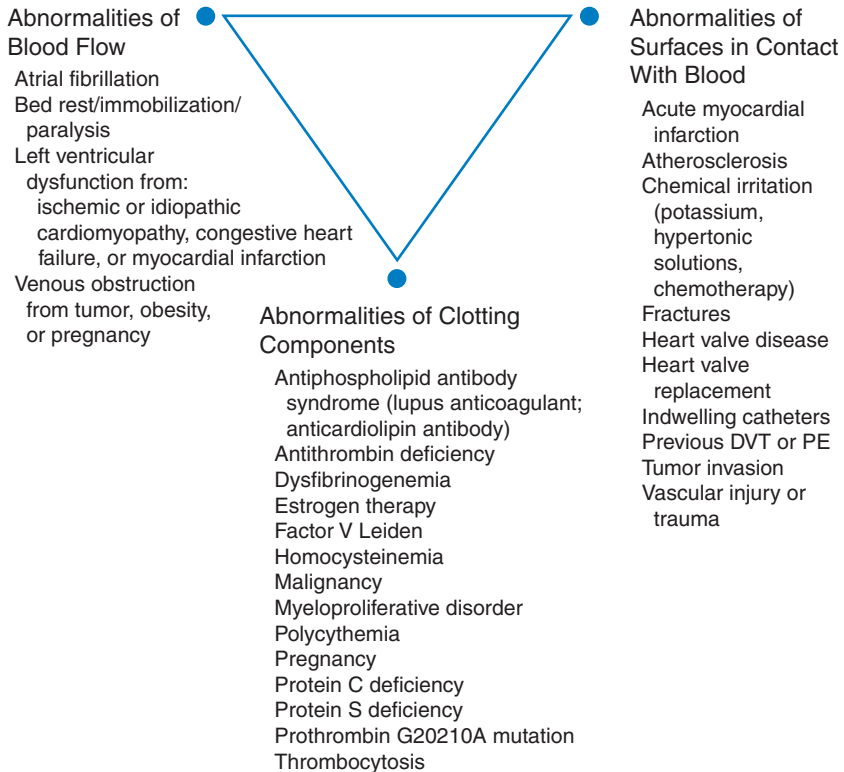
\*The reader is referred to Chapter 16, Thrombosis, written by Ann K. Wittkowsky, PharmD, CACR, FASHP, FCCP, and Edith A. Nutescu, PharmD, FCCP, in the 10th edition of *Applied Therapeutics: The Clinical Use of Drugs* for a more in-depth discussion. All notations or reference numbers are based on the reference list at the end of that chapter. The editor of this handbook expresses her thanks to Drs. Wittkowsky and Nutescu and acknowledges that this chapter is based on their work.

## Patient Assessment and Risk Factors

- Three primary risk factors influence the formation of pathological clots (Figure 16.2).
- **DVT** typically presents as unilateral leg swelling that is often accompanied by warmth and local tenderness or pain. Many patients (>50%) can present with asymptomatic disease.
- **PE** is often associated with nonspecific symptoms (dyspnea, pleuritic chest pain, apprehension, cough, and sometimes hemoptysis). DVT precedes PE in 80% or more patients. The probability of developing a PE can be assessed using clinical characteristics (Table 16.1).
- **Pregnant patients** should receive unfractionated heparin (UFH) or low-molecular-weight heparin (LMWH). Warfarin should not be used during pregnancy. See Table 16.2 for recommendations for anticoagulation during pregnancy.
- **Prevention** of cardiogenic thromboembolism is needed in patients with atrial fibrillation, after cardioversion, for paroxysmal, permanent or persistent atrial fibrillation, or cardiac valve replacements (Table 16.3).

## Goals of Therapy

- Anticoagulant therapy is aimed at preventing pathological clot formation in patients at risk and at preventing clot extension and/or embolization in patients who have had thrombosis. Optimal anticoagulation dosing and duration of therapy are shown in Tables 16.3 and 16.4.
- Prompt and optimal anticoagulant therapy for DVT is indicated to minimize thrombus extension and its vascular complications, and to prevent PE.



**Figure 16.2** Risk factors for thromboembolism. DVT, deep venous thrombosis; PE, pulmonary embolism.

TABLE 16.1 Clinical Model for Evaluating the Pretest Probability of Pulmonary Embolism<sup>a</sup>

Clinical Characteristic	Score
Cancer	+1
Hemoptysis	+1
Previous PE or DVT	+1.5
Heart rate >100 beats/minute	+1.5
Recent surgery or immobilization	+1.5
Clinical signs of DVT	+3
Alternative diagnosis less likely than PE	+3

<sup>a</sup>Clinical probability of PE: low, 0 to 1; moderate, 2 to 6; high, ≥7.

DVT, deep vein thrombosis; PE, pulmonary embolism.

Source: Wells PS. Advances in the diagnosis of venous thromboembolism. *J Thromb Thrombolysis*. 2006;21:31.

TABLE 16.2 Recommendations for Anticoagulation During Pregnancy

Clinical Situation	Peripartum Options	Postpartum
<b>1. PROPHYLAXIS</b>		
Known hypercoagulable state with no prior history of VTE	<ul style="list-style-type: none"> <li>• Surveillance</li> <li>• Prophylactic UFH/LMWH</li> </ul>	Warfarin to INR 2–3 for 4–6 weeks with UFH/LMWH overlap until INR >2.0
Single prior episode of VTE associated with transient risk factors, not receiving long-term anticoagulants	<ul style="list-style-type: none"> <li>• Surveillance</li> </ul>	Warfarin to INR 2–3 for 4–6 weeks with UFH/LMWH overlap until INR >2.0
Single prior episode of idiopathic or thrombophilia-related VTE, not receiving long-term anticoagulants	<ul style="list-style-type: none"> <li>• Surveillance</li> <li>• Prophylactic UFH/LMWH</li> <li>• Intermediate-dose UFH/LMWH</li> </ul>	Warfarin to INR 2–3 for 4–6 weeks with UFH/LMWH overlap until INR >2.0
Multiple prior episodes of VTE and/or receiving long-term oral anticoagulants for VTE	<ul style="list-style-type: none"> <li>• Adjusted-dose UFH/LMWH</li> <li>• Intermediate-dose LMWH (or 75% of adjusted-dose LMWH)</li> </ul>	Long-term warfarin to INR 2–3 with UFH/LMWH overlap until INR >2.0
Long-term oral anticoagulants for mechanical valve replacement	<ul style="list-style-type: none"> <li>• Adjusted-dose SC UFH</li> <li>• Adjusted-dose BID LMWH (adjusted to achieve manufacturer recommended 4-hour postdose peak anti-factor Xa concentration)</li> </ul>	Long-term warfarin to prior INR goal with UFH/LMWH overlap until INR above lower limit of therapeutic range
<b>2. TREATMENT OF VTE THAT OCCURS DURING PREGNANCY</b>		
	<ul style="list-style-type: none"> <li>• IV UFH for ≥5 days, followed by adjusted-dose SC UFH</li> <li>• Adjusted-dose LMWH</li> </ul>	Warfarin to INR 2–3 for a minimum of 6 weeks with UFH/LMWH overlap until INR >2.0

BID, twice daily; INR, international normalized ratio; LMWH, low-molecular-weight heparin; SC, subcutaneous; UFH, unfractionated heparin; VTE, venous thromboembolic disease.

Prophylactic dose UFH: 5,000 international units SC every 12 hours.

Intermediate-dose UFH: adjusted to 0.1 to 0.3 international units/mL anti-Xa activity.

Adjusted-dose UFH: adjusted to maintain therapeutic aPTT at mid-dosing interval.

Prophylactic LMWH: enoxaparin 40 mg SC daily or dalteparin 5,000 units SC daily.

Intermediate-dose LMWH: enoxaparin 40 mg SC every 12 hours or dalteparin 5,000 units SC every 12 hours.

Adjusted-dose LMWH (weight-adjusted full-treatment doses): enoxaparin 1 mg/kg SC every 12 hours or dalteparin 200 units/kg, or dalteparin 100 units/kg SC every 12 hours and adjusted throughout pregnancy to maintain 4-hour postinjection peak anti-Xa activity level of 0.5 to 1.2 units/mL (VTE) or >1.0 units/mL (mechanical valves).

Source: Bates SM et al. VTE, thrombophilia, antithrombotic therapy and pregnancy: American College of Chest Physicians Evidence-Based Practice Guidelines (9th ed.). *Chest*. 2012;141(Suppl):e691S.

TABLE 16.3 Optimal Therapeutic Range and Duration of Anticoagulation

Indication	Target INR (Range)	Duration	Comment
<b>NONVALVULAR ATRIAL FIBRILLATION/ATRIAL FLUTTER</b>			
CHA <sub>2</sub> DS <sub>2</sub> -VASc score <sup>a</sup> = 0	None	None	Omit antithrombotic therapy
CHA <sub>2</sub> DS <sub>2</sub> -VASc score = 1	2.5 (2.0–3.0)	Chronic	No therapy, aspirin 81–325 mg daily, or oral anticoagulation may be considered
CHA <sub>2</sub> DS <sub>2</sub> -VASc score = 2 or greater	2.5 (2.0–3.0)	Chronic	Options include warfarin, apixaban, dabigatran, or rivaroxaban
After open heart surgery (in NSR)	2.5 (2.0–3.0)	4 weeks	
Precardioversion (AF or flutter >48 hours)	2.5 (2.0–3.0)	3 weeks	
Postcardioversion (in NSR)	2.5 (2.0–3.0)	4 weeks	
<b>ISCHEMIC STROKE</b>			
Noncardioembolic stroke or TIA	None	Chronic	Use antiplatelet therapy
Cardioembolic stroke or TIA	2.5 (2.0–3.0)	Chronic	
• With contraindications to warfarin	None	Chronic	Use ASA 81–235 mg daily
• Associated with aortic atherosclerotic lesions	None	Chronic	Use antiplatelet therapy
• Associated with mobile aortic arch thrombi	2.5 (2.0–3.0)	Chronic	Or antiplatelet therapy
• Associated with patent foramen ovale	None	Chronic	Use antiplatelet therapy
<b>MYOCARDIAL INFARCTION</b>			
After MI	2.5 (2.0–3.0)	Up to 4 years	And aspirin 81 mg daily; or INR 3–4 alone
After MI in high-risk <sup>b</sup> patients	2.5 (2.0–3.0)	At least 3 months	And aspirin 81 mg daily
Thromboembolism (DVT, PE)	<b>(With concurrent UFH/LMWH/fondaparinux for at least 5 days and until INR &gt;2 for 24 hours)</b> (for DVT, add elastic compression stockings with 30–40 mm Hg at ankle for 2 years)		
Treatment/prevention of recurrence <b>(including calf vein DVT, UE DVT, UE DVT associated with catheter use, and asymptomatic DVT/PE)</b>			
• Transient risk factors	2.5 (2.0–3.0)	3 months	
• Unprovoked/first event			
~Proximal DVT or PE	2.5 (2.0–3.0)	Chronic	
~Distal DVT	2.5 (2.0–3.0)	3 months	Consider chronic therapy
• Unprovoked/second event	2.5 (2.0–3.0)	Chronic	
• With malignancy	2.5 (2.0–3.0)	Chronic	Preceded by LMWH × 3–6 months
Chronic thromboembolic pulmonary hypertension	2.5 (2.0–3.0)	Chronic	
Cerebral venous sinus thrombosis	2.5 (2.0–3.0)	Up to 12 months	
Spontaneous superficial vein thrombosis	2.5 (2.0–3.0)	4 weeks	Or prophylactic LMWH

Continued on following page

TABLE 16.3 Optimal Therapeutic Range and Duration of Anticoagulation (Continued)

Indication	Target INR (Range)	Duration	Comment
<b>VALVULAR DISEASE</b>			
Mitral valve prolapse			
• With TIAs or ischemic stroke	None	Chronic	Use aspirin 81 mg daily
• With recurrent TIA despite ASA therapy	2.5 (2.0–3.0)	Chronic	
Mitral annular calcification with AF	2.5 (2.0–3.0)	Chronic	
Rheumatic mitral valve disease			
• With AF, hx systemic embolism, LA thrombus, or LA >55 mm	2.5 (2.0–3.0)	Chronic	
• s/p thromboembolic event despite anticoagulation	2.5 (2.0–3.0)	Chronic	Add aspirin 81 mg daily or INR 2.5–3.5
<b>VALVE REPLACEMENT, BIOPROSTHETIC</b>			
Aortic	2.5 (2.0–3.0)	3 months	Followed by aspirin 81 mg daily
Mitral	2.5 (2.0–3.0)	3 months	Followed by aspirin 81 mg daily
With LA thrombus	2.5 (2.0–3.0)	Until resolution	
With prior history of systemic embolism	2.5 (2.0–3.0)	At least 3 months	
With additional risk factors <sup>c</sup> for thromboembolism	2.5 (2.0–3.0)	Chronic	Add aspirin 81 mg daily if low bleed risk
<b>VALVE REPLACEMENT, MECHANICAL</b>			
Aortic			
• Bileaflet in NSR w/nl LA size	2.5 (2.0–3.0)	Chronic	
• Medtronic Hall tilting disk in NSR w/nl LA size	2.5 (2.0–3.0)	Chronic	
• After prosthetic valve thrombosis	3.5 (3.0–4.0)	Chronic	Plus aspirin 81 mg daily
Mitral			
• Bileaflet or tilting disk	3.0 (2.5–3.5)	Chronic	
• After prosthetic valve thrombosis	4.0 (3.5–4.5)	Chronic	Plus aspirin 81 mg daily
Caged ball or caged disk (aortic or mitral)	3.0 (2.5–3.5)	Chronic	
With additional risk factors <sup>d</sup> for thromboembolism	3.0 (2.5–3.5)	Chronic	Add aspirin 81 mg daily if low bleed risk
With systemic embolism despite adequate anticoagulation	Increase INR goal	Chronic	Or add aspirin 81 mg daily

<sup>a</sup>Risk factors: age >75 years; history of hypertension; diabetes; congestive heart failure or moderate/severe left ventricular dysfunction.

<sup>b</sup>Risk factors: anterior MI, significant heart failure, intracardiac thrombus, history of thromboembolism.

<sup>c</sup>Risk factors: AF, hypercoagulable condition, low ejection fraction.

<sup>d</sup>Risk factors: AF, MI, LA enlargement, hypercoagulable condition, low ejection fraction.

AF, atrial fibrillation; ASA, aspirin; CHF, congestive heart failure; DVT, deep vein thrombosis; hx, history; INR, international normalized ratio; LA, left atrium; LMWH, low-molecular-weight heparin; MI, myocardial infarction; nl, normal; NSR, normal sinus rhythm; PE, pulmonary embolism; s/p, status post; TIA, transient ischemic attack; UE, upper extremity; UFH, unfractionated heparin.

**TABLE 16.4 Duration of Anticoagulation Therapy in Patients with Venous Thrombosis (Deep Vein Thrombosis and/or Pulmonary Embolism)**

**FIRST EVENT**

Provoked	3 months
Unprovoked	At least 3 months; reevaluate risk–benefit at 3 months
Unprovoked with proximal presentation and low risk of bleeding	indefinite therapy
Cancer-associated	LMWH for 3–6 months, then indefinite therapy or until cancer is resolved

**RECURRENT EVENTS**

Provoked	Indefinite therapy
Unprovoked	Indefinite therapy

Source: Kearon C et al. Antithrombotic therapy for VTE disease: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (9th ed.). *Chest*. 2012;141(Suppl):e419S–e494S.

- Prevention of VTE is important in patients undergoing surgery. Guidelines for prevention are shown in Table 16.5.
- When PE is suspected, treatment should be initiated immediately. Mortality associated with PE is as high as 17.5% over 3 months.

**Treatment**

- Selection of an antithrombotic agent is influenced by the type of thrombus to be treated.
  - UFH, LMWH, factor Xa inhibitors, direct thrombin inhibitors, and warfarin are used for treatment and prevention of both arterial and venous thrombi.
  - Drugs that alter platelet function (e.g., aspirin, clopidogrel) are used in the prevention of arterial clots (see Chapter 15).
  - Fibrinolytic agents are used for rapid dissolution of thromboemboli (see Chapter 18).
- A comparison of UFH, LMWH, and fondaparinux is shown in Table 16.6.
- **Bridge therapy** is often necessary to reverse the effects of warfarin when an invasive procedure is planned in order to minimize the risk of bleeding associated with the procedure. Risk stratification for determining the need for bridge therapy (Table 16.7) and guidelines for bridge therapy (Table 16.8) are available.
- Guidelines for management of warfarin in patients having **dental procedures** are based on the bleeding risk of the procedure (Table 16.9).

**Drug Therapy**

- UFH
  - A rapid acting anticoagulant that attaches to and irreversibly inactivates factor IIa (thrombin) and factor Xa.
  - In addition to anticoagulant effects, it also inhibits platelet function and increases vascular permeability, properties that contribute to its hemorrhagic effects.
  - UFH can be administered intravenously (IV) or subcutaneously (SQ), although bioavailability is greatly reduced with SQ administration. Intramuscular administration should be avoided due to risk for hematoma formation.
  - A loading dose required to achieve therapeutic levels more quickly.
  - Weight-based IV dosing (80 units/kg loading dose; 18 units/kg/hour initial infusion rate) increases the frequency of therapeutic activated partial thromboplastin time (aPTT) at 6 and 24 hours.



**TABLE 16.5 Prevention of Venous Thromboembolism**

**GENERAL SURGERY, GI SURGERY, GYNECOLOGIC SURGERY, UROLOGIC SURGERY, BARIATRIC SURGERY, VASCULAR SURGERY, AND PLASTIC AND RECONSTRUCTIVE SURGERY**

Very low risk	No specific pharmacologic or mechanical prophylaxis other than early ambulation Mechanical prophylaxis (preferably IPC)
Low-risk patients undergoing minor procedures, with no additional risk factors	
Moderate-risk patients undergoing major procedures, no high risk of major bleeding	LMWH, LDUFH every 8–12 hours, or fondaparinux, or IPC
Moderate-risk patients undergoing major procedures at high risk of major bleeding	Mechanical prophylaxis (preferably IPC)
Higher-risk patients undergoing major procedures for cancer	LMWH, LDUFH every 8 hours, or fondaparinux
High-risk patients with multiple risk factors, no high risk of major bleeding	LMWH, LDUFH every 8 hours, or fondaparinux + GCS and/or IPC

**ORTHOPEDIC SURGERY**

Hip replacement	LMWH daily OR BID, fondaparinux, warfarin (INR 2–3), apixaban, or rivaroxaban
Knee replacement	LMWH BID, fondaparinux, warfarin (INR 2–3), apixaban, or rivaroxaban
Hip fracture surgery	Fondaparinux, LMWH BID, or warfarin (INR 2–3)
Trauma	LMWH BID + IPC and/or GCS
Acute spinal cord injury	LMWH BID or LMWH/LDUFH + IPC/GCS
Neurosurgery	IPC/GCS ± LDUFH every 12 hours, or LMWH daily
Acutely medically ill	LDUFH every 8–12 hours or LMWH

BID, twice daily; GCS, graduated compression stockings; INR, international normalized ratio; IPC, intermittent pneumatic compression; LDUFH, low-dose unfractionated heparin (5,000 international units subcutaneously every 8–12 hours); LMWH, low-molecular-weight heparin (enoxaparin 40 mg subcutaneously daily or 30 mg SC every 12 hours; dalteparin 2,500–5,000 international units subcutaneously daily); fondaparinux (2.5 mg subcutaneously daily); VTE, venous thromboembolism.

**TABLE 16.6 Comparison of Unfractionated Heparin, Low-Molecular-Weight Heparins, and Fondaparinux**

Property	UFH	LMWH	Fondaparinux
Molecular weight range <sup>a</sup>	3,000–30,000	1,000–10,000	1,728
Average molecular weight <sup>a</sup>	12,000–15,000	4,000–5,000	1,728
Anti-Xa:anti-IIa activity	1:1	2:1–4:1	>100:1
aPTT monitoring required	Yes	No	No
Inactivation by platelet factor 4	Yes	No	No
Capable of inactivation of platelet-bound factor Xa	No	Yes	Yes
Inhibition of platelet function	+++	++	No
Increases vascular permeability	Yes	No	No
Protein binding	++++	+	No
Endothelial cell binding	+++	+	No
Dose-dependent clearance	Yes	No	No
Primary route of elimination	1. Saturable binding processes 2. Renal	Renal	Renal
Elimination half-life	30–150 minutes	2–6 hours	17 hours

<sup>a</sup>Measured in daltons.

LMWH, low-molecular-weight heparin; UFH, unfractionated heparin.

Sources: Garcia DA et al. Parenteral anticoagulants. American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (9th ed.). *Chest*. 2012;141(Suppl):e24S–e43S; Petitou M et al. The synthetic pentasaccharide fondaparinux: first in a class of antithrombotic agents that selectively inhibit coagulation factor Xa. *Semin Thromb Hemost*. 2002;28:393.

**TABLE 16.7 Risk Stratification for Determining the Need for Bridge Therapy**

Risk Stratum	Indication for VKA Therapy		
	Mechanical Heart Valve	Atrial Fibrillation	Venous Thromboembolism
High	<ul style="list-style-type: none"> <li>Any mitral valve prosthesis</li> <li>Older (caged-ball or tilting disk) aortic valve prosthesis</li> <li>Recent (within 6 months) stroke or transient ischemic attack</li> </ul>	<ul style="list-style-type: none"> <li>CHADS<sub>2</sub> score of 5 or 6</li> <li>Recent (within 3 months) stroke or transient ischemic attack</li> <li>Rheumatic valvular heart disease</li> </ul>	<ul style="list-style-type: none"> <li>Recent (within 3 months) VTE</li> <li>Severe thrombophilia (e.g., deficiency of protein C, protein S or antithrombin, antiphospholipid antibodies, or multiple abnormalities)</li> </ul>
Moderate	<ul style="list-style-type: none"> <li>Bileaflet aortic valve prosthesis and one of the following: atrial fibrillation, prior stroke or transient ischemic attack, hypertension, diabetes, congestive heart failure, age &gt;75 years</li> </ul>	<ul style="list-style-type: none"> <li>CHADS<sub>2</sub> score of 3 or 4</li> </ul>	<ul style="list-style-type: none"> <li>VTE within the past 3–12 months (consider VTE prophylaxis rather than full-intensity bridge therapy)</li> <li>Nonsevere thrombophilic conditions (e.g., heterozygous factor V Leiden mutation, heterozygous factor II mutation)</li> <li>Recurrent VTE</li> <li>Active cancer (treated within 6 months or palliative)</li> </ul>
Low	<ul style="list-style-type: none"> <li>Bileaflet aortic valve prosthesis without atrial fibrillation and no other risk factors for stroke</li> </ul>	<ul style="list-style-type: none"> <li>CHADS<sub>2</sub> score of 0–2 (no prior stroke or transient ischemic attack)</li> </ul>	<ul style="list-style-type: none"> <li>Single VTE occurred more than 12 months ago and no other risk factors</li> </ul>

VTE, venous thromboembolism.

Source: Douketis JD et al. Perioperative management of antithrombotic therapy: American College of Chest Physicians Evidence-Based Practice Guidelines (9th ed.). *Chest*. 2012;141(Suppl):e326S–e350S.

**TABLE 16.8 Bridge Therapy Guidelines for Invasive Procedures<sup>a</sup>**

Thromboembolic Risk	Renal Function	Bridge Therapy
Low	All patients	<ul style="list-style-type: none"> <li>Last dose of warfarin on day –6 preprocedure</li> <li>Hold warfarin day –5 through day –1</li> <li>Consider vitamin K 2.5 mg PO on day –2 or –1 if INR &gt;1.5</li> <li>Resume warfarin 12–48 hours postprocedure at usual maintenance dose (decision based on postprocedure assessment of bleeding risk)</li> </ul>
High or moderate	CrCl >30 mL/minute	<ul style="list-style-type: none"> <li>Last dose of warfarin on day –6 preprocedure</li> <li>Hold warfarin day –5 through day –1</li> <li>Start LMWH on day –3 (or when INR &lt;lower limit of range)</li> <li>Consider vitamin K 2.5 mg PO on day –2 or –1 if INR &gt;1.5</li> <li>Last dose LMWH 24 hours preprocedure (on day –1, give half dose LMWH if patient is receiving once-daily LMWH)</li> <li>Resume warfarin 12–24 hours postprocedure at usual maintenance dose (decision predicated on postprocedure assessment of bleeding risk)</li> <li>Resume LMWH 24 hours postprocedure (or 48–72 hours for major surgery or high bleeding risk procedure) and continue until INR &gt;lower limit of therapeutic range</li> </ul>

*Continued on following page*

TABLE 16.8 Bridge Therapy Guidelines for Invasive Procedures<sup>a</sup> (Continued)

Thromboembolic Risk	Renal Function	Bridge Therapy
	CrCl < 30 mL/minute	<ul style="list-style-type: none"> <li>• Last dose of warfarin on day -6 preprocedure</li> <li>• Hold warfarin day -5 through day -1</li> <li>• Consider vitamin K 2.5 mg PO or 1 mg IV on day -2 or -1 preprocedure if INR &gt;1.5</li> <li>• Admit on day -1 preprocedure and begin IV UFH (70 international units/kg bolus, 15 international units/kg/hour infusion and adjust per inpatient protocol)</li> <li>• Stop IV UFH 6 hours preprocedure</li> <li>• Resume warfarin 12–24 hours postprocedure at usual maintenance dose (decision based on postprocedure assessment of bleeding risk)</li> <li>• Resume IV UFH 24 hours postprocedure (or 48–72 hours for major surgery or high bleeding risk procedure) and continue until INR &gt; lower limit of therapeutic range</li> </ul>

<sup>a</sup>University of Washington Medical Center.

CrCl, creatinine clearance; INR, international normalized ratio; IV, intravenous; LMWH, low-molecular-weight heparin; PO, orally; UFH, unfractionated heparin.

TABLE 16.9 Suggestions for Anticoagulation Management Before and After Dental Procedures<sup>a</sup>

	Low Bleeding Risk	Moderate Bleeding Risk	High Bleeding Risk
Procedure	<ul style="list-style-type: none"> <li>• Supragingival scaling</li> <li>• Simple restorations</li> <li>• Local anesthetic injections</li> </ul>	<ul style="list-style-type: none"> <li>• Subgingival scaling</li> <li>• Restorations with subgingival preparations</li> <li>• Standard root canal therapy</li> <li>• Simple extractions</li> <li>• Regional injection of local anesthetics</li> </ul>	<ul style="list-style-type: none"> <li>• Extensive surgery</li> <li>• Apicoectomy (root removal)</li> <li>• Alveolar surgery (bone removal)</li> <li>• Multiple extractions</li> </ul>
Suggestions	<ul style="list-style-type: none"> <li>• Do not interrupt warfarin treatment</li> <li>• Use local measures to prevent/control bleeding</li> </ul>	<ul style="list-style-type: none"> <li>• Interruption of warfarin treatment is not necessary</li> <li>• Use local measures to prevent or control bleeding; consult with dentist to determine comfort with use of local measures to prevent bleeding when anticoagulation is not interrupted</li> </ul>	<ul style="list-style-type: none"> <li>• May need to reduce international normalized ratio or return to normal hemostasis</li> <li>• Follow bridge therapy guidelines for invasive procedures based on risk of thromboembolism</li> </ul>

<sup>a</sup>University of Washington Medical Center.

- Dosing can be based on body weight (use actual body weight [ABW] for patients <100 kg and adjusted-dose weight for patients >100 kg).
  - Ideal body weight [IBW] + 0.3 (ABW - IBW) or
  - IBW + 0.4 (ABW - IBW)
- Therapy is monitored and doses adjusted using aPTT (Table 16.10).
- Side effects include thrombocytopenia, bleeding (typically in soft tissue, GI, and urinary tracts), and osteoporosis (with long-term use of doses >20,000 units/day).
  - Reductions in platelet counts of >50% from baseline suggest possibility of heparin-induced thrombocytopenia (HIT).
  - HIT occurs in 3% of patients after 5 days of UFH and in up to 6% of patients after 14 days of continuous UFH therapy.

TABLE 16.10 Heparin Dosing Nomogram<sup>a</sup>

- Suggested loading dose
  - Treatment of DVT/PE: 80 units/kg (rounded to nearest 500 units)
  - Prevention, including cardiovascular indications: 70 units/kg (rounded to nearest 500 units)
- Suggested initial infusion
  - Treatment of DVT/PE: 18 units/kg/hour (rounded to nearest 100 units)
  - Prevention, including cardiovascular indications: 15 units/kg/hour (rounded to nearest 100 units)
- First aPTT check: 6 hours after initiating therapy
- Dosing adjustments: per this chart (rounded to nearest 100 units)

aPTT <sup>b</sup> (seconds)	Heparin Bolus	Infusion Hold Time	Infusion Rate Adjustment	Next aPTT
<50	4,000 units	0	Increase by 200 units/hour	In 6 hours
50–59	2,000 units	0	Increase by 100 units/hour	In 6 hours
60–100	0	0	None	Every morning
101–110	0	0	Decrease by 100 units/hour	In 6 hours
111–120	0	0	Decrease by 200 units/hour	In 6 hours
121–150	0	30 minutes	Decrease by 200 units/hour	In 6 hours
151–199	0	60 minutes	Decrease by 200 units/hour	In 6 hours
>200	0	PRN	Hold until aPTT <100	Every hour until <100

<sup>a</sup>University of Washington Medical Center.

<sup>b</sup>Based on aPTT reagent-specific therapeutic range of 60 to 100 seconds corresponding to a plasma heparin concentration of 0.3 to 0.7 units/mL determined by anti-factor Xa activity.

aPTT, activated partial thromboplastin time; DVT, deep vein thrombosis; PE, pulmonary embolism; PRN, as necessary.

- 4-T score is a pretest probability test to estimate the likelihood of HIT (Table 16.11).
- Heparin therapy should be discontinued in patients who develop HIT. Treatment alternatives include direct thrombin inhibitors. LMWH use is contraindicated in patients with HIT.
- **LMWH**
  - LMWH differ from heparin with respect to molecular weight, pharmacokinetic properties, adverse effects, and monitoring requirements (Table 16.6).
  - The anti-Xa properties of LMWH are more significant than their anti-IIa properties, so aPTT is not prolonged. Monitoring of therapy is not routinely required.
  - LMWH has better SQ bioavailability over UFH, resulting in a predictable dose response and a longer pharmacodynamic effect, making it a good choice when the goal is to treat patients at home.
  - Dosing of LMWH for treatment of VTE is shown in Table 16.12. Dosing in patients with renal dysfunction is in Table 16.13.
- **Fondaparinux**
  - Fondaparinux acts as a selective indirect factor Xa inhibitor.
  - It has a long elimination half-life allowing for once-daily SQ dosing (Table 16.6).
  - Like LMWH, there is no need for routine monitoring.
- **Oral Direct Thrombin Inhibitors**
  - Injectable agents include argatroban, lepirudin, and bivalirudin (Table 16.14).
  - Oral agents include dabigatran.
- **Oral Factor Xa Inhibitors**
  - Apixaban
  - Rivaroxaban
- **Warfarin**
  - Warfarin acts as a vitamin K antagonist.
  - Concentrations of clotting factors II, VII, IX, and X are gradually diminished in accordance with their elimination half-lives (Table 16.15).

**TABLE 16.11 The 4T Score: Pretest Probability of Heparin-Induced Thrombocytopenia**

Category	2 Points	1 Point	0 Points
1. Thrombocytopenia	Platelet count fall >50% and platelet nadir $\geq 20 \times 10^9 L^{-1}$	Platelet count fall 30%–50% or platelet nadir $10\text{--}19 \times 10^9 L^{-1}$	Platelet count fall <30% or platelet nadir $<10 \times 10^9 L^{-1}$
2. Timing of platelet count fall	Clear onset between days 5 and 10 or platelet fall $\leq 1$ day (prior heparin exposure within 30 days)	Consistent with days 5–10 fall, but not clear (e.g., missing platelet counts) or onset after day 10 or fall $\leq 1$ day (prior heparin exposure 30–100 days ago)	Platelet count fall <4 days without recent heparin exposure
3. Thrombosis or other sequelae	New thrombosis (confirmed) or skin necrosis at heparin injection sites or acute systemic reaction after intravenous heparin bolus	Progressive or recurrent thrombosis or non-necrotizing (erythematous) skin lesions or suspected thrombosis (not proven)	None
4. Other causes for thrombocytopenia	None apparent	Possible	Definite

TOTAL SCORE <3 = low probability of HIT 4–5 = intermediate probability of HIT >6 = high probability of HIT.

Source: Lo GK et al. Evaluation of pretest clinical score (4 T's) for the diagnosis of heparin-induced thrombocytopenia in two clinical settings. *J Thromb Haemost.* 2006;4:759.

**TABLE 16.12 Dosing of Low-Molecular-Weight Heparin and Fondaparinux for the Treatment of Venous Thromboembolism**

Dalteparin	Enoxaparin	Tinzaparin	Fondaparinux
100 international units/kg SC every 12 hours OR 200 international units/kg SC every 24 hours	1 mg/kg SC every 12 hours OR 1.5 mg/kg SC every 24 hours	175 international units/kg SC every 24 hours	5 mg SC every 24 hours if weight <50 kg 7.5 mg SC every 24 hours if weight 50–100 kg 10 mg SC every 24 hours if weight >100 kg

SC, subcutaneously.

**TABLE 16.13 Dosing of Low-Molecular-Weight Heparins in Patients with Renal Impairment (CrCl <30 mL/minute)<sup>a</sup>**

LMWH	Dalteparin	Enoxaparin	Tinzaparin
Product information recommendations	Use with caution	Prophylaxis—30 mg SC daily Treatment—1 mg/kg SC daily	Use with caution
Dosing suggestions based on agent-specific pharmacokinetic observations	CrCL <30 <sup>a</sup> mL/minute: no dose adjustment needed up to 1 week with prophylactic doses  For use longer than 1 week, consider monitoring of anti-Xa activity and adjust dose if accumulation is noted  CrCL 30–50 mL/minute: no dose adjustment needed	CrCL <30 <sup>a</sup> mL/minute: Consider a 40%–50% dose decrease and subsequent monitoring of anti-Xa activity  CrCL 30–50 mL/minute: Consider a 15%–20% dose decrease with prolonged use (longer than 10–14 days) and subsequent monitoring of anti-Xa activity	CrCL <30 <sup>a</sup> mL/minute: consider a dose decrease of 20% and subsequent monitoring of anti-Xa activity  CrCL 30–50 mL/minute: no dose adjustment needed

<sup>a</sup>In patients with a CrCl <20 mL/minute, data are very limited and use of unfractionated heparin is suggested.

**TABLE 16.14 Pharmacologic and Clinical Properties of Injectable Direct Thrombin Inhibitors**

	<b>Lepirudin</b>	<b>Bivalirudin</b>	<b>Argatroban</b>
Route of administration	IV or SC (BID)	IV	IV
FDA-approved indication	Treatment of thrombosis in patients with HIT	Patients with UA undergoing PTCA; PCI with provisional use of GPI; patients with or at risk of HIT/HITTS undergoing PCI	Treatment of thrombosis in patients with HIT; patients at risk for HIT undergoing PCI
Binding to thrombin	Irreversible at catalytic site and exosite-1	Partially reversible at catalytic site and exosite-1	Reversible at catalytic site
Half-life in healthy subjects	1.3–2 hours	25 minutes	40–50 minutes
Monitoring	aPTT (IV) SC <sub>r</sub> /CrCl	aPTT/ACT SC <sub>r</sub> /CrCl	aPTT/ACT Liver function
Clearance	Renal	Enzymatic (80%) Renal (20%)	Hepatic
Antibody development	Antihirudin antibodies in up to 40%–60% of patients	May cross-react with antihirudin antibodies	No
Effect on INR	Slight increase	Slight increase	Increase
Initial dose for HIT	HITTS: Bolus <sup>a</sup> : 0.4 mg/kg, up to a maximum of 110 kg, given over 15–20 seconds Infusion: 0.15 mg/kg/hour HIT: no bolus; 0.1 mg/kg/hour infusion	No bolus Infusion: 0.15 mg/kg/hour	Infusion: 2 mcg/kg/minute <sup>b</sup> In critically ill patients: consider lower infusion rate of 0.5–1 mcg/kg/minute
Initial dose for PCI	NA	Bolus: 0.75 mg/kg Infusion: 1.75 mg/kg/hour PCI: Bolus: no dose adjustment	NA
Dosing in renal impairment	Bolus <sup>a</sup> : 0.2 mg/kg (bolus dose is best avoided in patients with renal impairment) Infusion:  CrCl 45–60: 0.075 mg/kg/hour CrCl 30–44: 0.045 mg/kg/hour CrCl 15–29: 0.0225 mg/kg/hour CrCl <15 mg/kg/hour: no bolus; avoid or stop infusion HD: stop infusion and additional IV bolus doses of 0.1 mg/kg every other day should be considered if the aPTT ratio falls below 1.5	Infusion:  CrCl <30: 1 mg/kg/hour HD: 0.25 mg/kg/hour HIT:  No bolus  Infusion: CrCl <30: 0.08 mg/kg/hour HD: 0.02 mg/kg/hour	CrCl <30 mg/kg/hour: mean doses of 0.8 mcg/kg/minute have been reported  Note: Dose adjustment not required per product information, but recent literature support dose adjustment as above

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**TABLE 16.14 Pharmacologic and Clinical Properties of Injectable Direct Thrombin Inhibitors (Continued)**

	Lepirudin	Bivalirudin	Argatroban
Dosing in hepatic impairment	Dose adjustment not required	Dose adjustment not required	Initiate at 0.5 mcg/kg/minute then titrate to aPTT 1.5–3.0 × baseline

<sup>a</sup>Initial IV bolus ONLY recommended when life-threatening thrombosis is present.

<sup>b</sup>Recent reports indicate that lower initial infusion rates of ~1.5 mcg/kg/minute may be more appropriate.

ACT, activated clotting time; aPTT, activated partial thromboplastin time; BID, twice daily; CrCl, creatinine clearance;

GPI, glycoprotein IIb-IIIa inhibitor; HD, hemodialysis; HIT, heparin-induced thrombocytopenia; HITTS, heparin-

induced thrombocytopenia and thrombosis syndrome; IV, intravenous; PCI, percutaneous coronary intervention;

PTCA, percutaneous transluminal coronary angioplasty; SC, subcutaneous; SCr, serum creatinine; UA, unstable angina.

**TABLE 16.15 Elimination Half-lives of Vitamin K–Dependent Clotting Factors**

Clotting Factor	Half-Life (hours)
II	42–72
VII	4–6
IX	21–30
X	27–48
Protein C	9
Protein S	60

- The onset of effect of warfarin is delayed, typically taking 5 to 7 days to reach a steady state of anticoagulation. Heparin therapy should be continued for at least 5 days after initiating warfarin, even if the international normalized ratio (INR) is therapeutic before then because of the time required for adequate elimination of factors II and X by warfarin.
- A flexible dosing protocol for initiating warfarin therapy is shown in Table 16.16. An example of a dose-adjustment nomogram is shown in Table 16.17. Patients who are more sensitive to warfarin are expected to require lower doses (Table 16.18).
- Successful warfarin therapy depends on active participation by the patient. Key elements of patient education are shown in Table 16.19.
- Therapy is monitored using prothrombin time or, more commonly, the INR. Frequency of monitoring is shown in Table 16.20.
- Side effects include bleeding (commonly in the nose, oral pharynx, soft tissue, and GI and urinary tracts), skin necrosis (rare, but serious side effect), and purple toe syndrome (rare).
- Vitamin K is used for reversal of an elevated INR caused by warfarin (Table 16.21).
- Warfarin can have interactions with disease states (Table 16.22) and drugs (Table 16.23). Use of a drug known to interact with warfarin is not an absolute contraindication to its use; frequent monitoring is required if used.

## Monitoring

- Assessment of baseline hemostatic status is needed before initiating therapy (i.e., Hgb, Hct, PT, aPTT).
- **Prothrombin time (PT)** is prolonged by deficiencies in clotting factors II, VII, IX, and X and by low levels of fibrinogen. PT reflects alterations in the extrinsic and common pathway of the clotting cascade but not the intrinsic system (Figure 16.1). PT is used to monitor warfarin therapy.
  - To convert PT to INR

$$\text{INR} = (\text{PT patient} / \text{PT mean normal})^{\text{ISI}}$$

**TABLE 16.16 Flexible Initiation Dosing Protocol for Warfarin Dosing, Including 10-mg and 5-mg Starting Dose Options**

Day	INR	10-mg Initiation Dose (mg)	5-mg Initiation Dose (mg)
1		10	5
2	<1.5	7.5–10	5
	1.5–1.9	2.5	2.5
	2.0–2.5	1.0–2.5	1–2.5
	>2.5	0	0
3	<1.5	5–10	5–10
	1.5–1.9	2.5–5	2.5–5
	2.0–2.5	0–2.5	0–2.5
	2.5–3.0	0–2.5	0–2.5
	>3.0	0	0
4	<1.5	10	10
	1.5–1.9	5–7.5	5–7.5
	2.0–3.0	0–5	0–5
	>3.0	0	0
5	<1.5	10	10
	1.5–1.9	7.5–10	7.5–10
	2.0–3.0	0–5	0–5
	>3.0	0	0
6	<1.5	7.5–12.5	7.5–12.5
	1.5–1.9	5–10	5–10
	2.0–3.0	0–7.5	0–7.5
	>3.0	0	0

INR, international normalized ratio.

Source: Crowther MA et al. Warfarin: less may be better. *Ann Intern Med.* 1997;127:332.

**TABLE 16.17 Warfarin Dose-Adjustment Nomogram for Maintenance Therapy<sup>a</sup>**

For Goal INR 2–3	Adjustment	For Goal INR 2.5–3.5
INR <1.5	<ul style="list-style-type: none"> <li>• Increase maintenance dose by 10%–20%</li> <li>• Consider a booster dose of 1.5–2 times daily maintenance dose</li> <li>• Consider resumption of prior maintenance dose if factor causing decreased INR is considered transient (e.g., missed warfarin dose[s])</li> </ul>	INR <2.0
INR 1.5–1.8	<ul style="list-style-type: none"> <li>• Increase maintenance dose by 5%–15%</li> <li>• Consider a booster dose of 1.5–2 times daily maintenance dose</li> <li>• Consider resumption of prior maintenance dose if factor causing decreased INR is considered transient (e.g., missed warfarin dose[s])</li> </ul>	INR 2.0–2.3
INR 1.8–1.9	<ul style="list-style-type: none"> <li>• No dosage adjustment may be necessary if the last two INRs were in range, if there is no clear explanation for the INR to be out of range, and if in the judgment of the clinician the INR does not represent an increased risk of thromboembolism for the patient</li> <li>• If dosage adjustment is needed, increase by 5%–10%</li> <li>• Consider a booster dose of 1.5–2 times daily maintenance dose</li> <li>• Consider resumption of prior maintenance dose if factor causing decreased INR is considered transient (e.g., missed warfarin dose[s])</li> </ul>	INR 2.3–2.4
INR 2.0–3.0	Desired range	INR 2.5–3.5

Continued on following page



TABLE 16.17 Warfarin Dose-Adjustment Nomogram for Maintenance Therapy<sup>a</sup> (Continued)

For Goal INR 2–3	Adjustment	For Goal INR 2.5–3.5
INR 3.1–3.2	<ul style="list-style-type: none"> <li>No dosage adjustment may necessary if the last two INRs were in range, if there is no clear explanation for the INR to be out of range, and if in the judgment of the clinician the INR does not represent an increased risk of hemorrhage for the patient</li> <li>If dosage adjustment needed, decrease by 5%–10%</li> <li>Consider resumption of prior maintenance dose if factor causing elevated INR is considered transient (e.g., acute alcohol ingestion)</li> </ul>	INR 3.6–3.7
INR 3.3–3.4	<ul style="list-style-type: none"> <li>Decrease maintenance dose by 5%–10%</li> <li>Consider resumption of prior maintenance dose if factor causing elevated INR is considered transient (e.g., acute alcohol ingestion)</li> </ul>	INR 3.8–3.9
INR 3.5–3.9	<ul style="list-style-type: none"> <li>Consider holding one dose</li> <li>Decrease maintenance dose by 5%–15%</li> <li>Consider resumption of prior maintenance dose if factor causing elevated INR is considered transient (e.g., acute alcohol ingestion)</li> </ul>	INR 4.0–4.4
INR >4.0	<ul style="list-style-type: none"> <li>Hold until INR &lt; upper limit of therapeutic range</li> <li>Consider use of minidose oral vitamin K</li> <li>Decrease maintenance dose by 5%–20%</li> <li>Consider resumption of prior maintenance dose if factor causing elevated INR is considered transient (e.g., acute alcohol ingestion)</li> </ul>	INR >4.5

<sup>a</sup>University of Washington Medical Center.  
INR, international normalized ratio.

- Regular intensity therapy has a target INR of 2.5 (range, 2.0–3.0), and high-intensity therapy has a target INR of 3.0 (range, 2.5–3.5).
- **Activated partial thromboplastin time (aPTT)** reflects alterations in the intrinsic pathway (Figure 16.1). aPTT is used to monitor heparin therapy.
- **Anti-factor Xa** activity is used with LMWH therapy. Routine monitoring with LMWH use is not needed but certain clinical situations (renal failure, patients weighing >150 kg, pregnancy, unexpected bleeding) may require assessment of anti-factor Xa activity.

TABLE 16.18 Factors that Increase Sensitivity to Warfarin

- Age older than 75 years
- Clinical congestive heart failure
- Clinical hyperthyroidism
- Decreased oral intake
- Diarrhea
- Drug–drug interactions
- Elevated baseline INR
- End-stage renal disease
- Fever
- Hepatic disease
- Hypoalbuminemia
- Known CYP2C9 variant
- Malignancy
- Malnutrition
- Postoperative status

INR, international normalized ratio.

**TABLE 16.19 Key Elements of Patient Education Regarding Warfarin**

Identification of generic and brand names
Purpose of therapy
Expected duration of therapy
Dosing and administration
Visual recognition of drug and tablet strength
What to do if a dose is missed
Importance of prothrombin time/INR monitoring
Recognition of signs and symptoms of bleeding
Recognition of signs and symptoms of thromboembolism
What to do if bleeding or thromboembolism occurs
Recognition of signs and symptoms of disease states that influence warfarin dosing requirements
Potential for interactions with prescription and over-the-counter medications and natural/herbal products
Dietary considerations and use of alcohol
Avoidance of pregnancy
Significance of informing other health care providers that warfarin has been prescribed
When, where, and with whom follow-up will be provided

INR, international normalized ratio.

**TABLE 16.20 Frequency of International Normalized Ratio Monitoring and Patient Assessment During Warfarin Therapy****INITIATION THERAPY**

Inpatient initiation	Daily
Outpatient flexible initiation method	Daily through day 4, then within 3–5 days
Outpatient average daily dosing method	Within 3–5 days, then within 1 week
After hospital discharge	If stable, within 3–5 days If unstable, within 1–3 days
First month of therapy	Every 1–4 days until therapeutic, then weekly

**MAINTENANCE THERAPY**

Medically stable inpatients	Every 1–3 days
Medically unstable inpatients	Daily
After hospital discharge	If stable, within 3–5 days If unstable, within 1–3 days In 1–2 days
Routine follow-up in medically stable and reliable patients	Every 4–6 weeks
Routine follow-up in medically unstable or unreliable patients	Every 1–2 weeks
Dose held today for significant overanticoagulation	In 1–2 days
Dosage change today	Within 1–2 weeks
Dosage change <2 weeks ago	Within 2–4 weeks

TABLE 16.21 Guidelines for Reversal of an Elevated International Normalized Ratio

INR	Recommendation
<4.5	Lower or hold dose.
4.5–10	Hold one or two doses. Recommend against using oral vitamin K.
≥10	Hold warfarin and give vitamin K (2.5–5 mg orally). Use additional vitamin K, if necessary.
Serious bleeding with high INR	Hold warfarin and give vitamin K (10 mg slow IV infusion) supplemented with fresh-frozen plasma, prothrombin complex concentrates, or recombinant factor VIIa. May repeat vitamin K every 12 hours, if necessary.
Life-threatening bleeding	Hold warfarin and give fresh-frozen plasma, prothrombin complex concentrates, or recombinant factor VIIa supplemented with vitamin K (10 mg slow IV infusion). Repeat as necessary.

INR, international normalized ratio; IV, intravenously.

Source: Holbrook A et al. Evidence-based therapy and prevention of thrombosis. American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (9th ed.) *Chest*. 2012;141(Suppl):152S–e181S.

TABLE 16.22 Warfarin Interactions with Disease States and Clinical Conditions

Clinical Condition	Effect on Warfarin Therapy
Advanced age	Increased sensitivity to warfarin due to reduced vitamin K stores and/or lower plasma concentrations of vitamin K–dependent clotting factors
Pregnancy	Teratogenic; avoid exposure during pregnancy
Lactation	Not excreted in breast milk; can be used postpartum by nursing mothers
Alcoholism	<ul style="list-style-type: none"> <li>• Acute ingestion: inhibits warfarin metabolism, with acute elevation in INR</li> <li>• Chronic ingestion: induces warfarin metabolism, with higher dose requirements</li> </ul>
Liver disease	<ul style="list-style-type: none"> <li>• May induce coagulopathy by decreased production of clotting factors, with baseline elevation in INR</li> <li>• May reduce clearance of warfarin</li> </ul>
Renal disease	Reduced activity of CYP2C9, with lower warfarin dose requirements
Heart failure	Reduced warfarin metabolism due to hepatic congestion
Cardiac valve replacement	Enhanced sensitivity to warfarin postoperatively due to hypoalbuminemia, lower oral intake, decreased physical activity, and reduced clotting factor concentrations after cardiopulmonary bypass
Nutritional status	Changes in dietary vitamin K intake (intentional or as the result of disease, surgery, etc.) alter response to warfarin
Use of tube feedings	Decreased sensitivity to warfarin, possibly caused by changes in absorption or vitamin K content of nutritional supplements
Thyroid disease	<ul style="list-style-type: none"> <li>• Hypothyroidism: decreased catabolism of clotting factors requiring increased dosing requirements</li> <li>• Hyperthyroidism: increased catabolism of clotting factors causing increased sensitivity to warfarin</li> </ul>
Smoking and tobacco use	<ul style="list-style-type: none"> <li>• Smoking: may induce CYP1A2, increasing warfarin dosing requirements</li> <li>• Chewing tobacco: may contain vitamin K, increasing warfarin dosing requirements</li> </ul>
Fever	Increased catabolism of clotting factors, causing acute increase in INR
Diarrhea	Reduction in secretion of vitamin K by gut flora, causing acute increase in INR
Acute infection/inflammation	Increased sensitivity to warfarin
Malignancy	Increased sensitivity to warfarin by multiple factors

INR, international normalized ratio.

Source: Wittkowsky AK. Warfarin. In: Murphy J (ed.) *Clinical Pharmacokinetics* (5th ed). Bethesda, MD: American Society of Health System Pharmacists; 2011:345.

**TABLE 16.23 Warfarin Drug Interactions**

Target	Effect	Response	Examples (Not Inclusive)			
Clotting factors	Increased synthesis	Decreased INR	Vitamin K			
	Decreased synthesis	Increased INR	Broad-spectrum antibiotics			
Warfarin metabolism	Increased catabolism	Increased INR	Thyroid hormones			
	Decreased catabolism	Decreased INR	Methimazole		Propylthiouracil	
	Inhibition	Increased INR	Acetaminophen	Allopurinol	Amiodarone	Azole antifungals
Hemostasis	Induction	Decreased INR	Cimetidine	Fluoroquinolones	Macrolides	Metronidazole
			Propafenone	SSRIs	Statins	Sulfa antibiotics
	Additive antithrombotic effects	Increased bleeding risk	Barbiturates	Carbamazepine	Doxycycline	Griseofulvin
			Nafcillin	Phenytoine	Primidone	Rifampin
Additive anticoagulant response	Increased bleeding risk	Aspirin	NSAIDs	Salicylates	GPIIb/IIIa inhibitors	
		Heparin	LMWH	Direct thrombin inhibitors	Thrombolytics	
Absorption	Reduced	Decreased INR	Cholestyramine	Colestipol	Sucralfate	
Unknown		Decreased INR	Ascorbic acid	Azathioprine	Corticosteroids	Cyclosporine
		Increased INR	Androgens	Fenofibrate	Cyclophosphamide	Gemfibrozil

GP, glycoprotein; INR, international normalized ratio; LMWH, low-molecular-weight heparin; NSAIDs, nonsteroidal anti-inflammatory drugs.

# Chronic Stable Angina\*

## General Principles

- Angina pectoris typically occurs when myocardial oxygen demand exceeds myocardial oxygen supply.
- Angina pectoris is a common manifestation of coronary heart disease (CHD). Because it is a marker for underlying heart disease, its management is very important.
- Angina often reflects an underlying atherosclerotic narrowing of the coronary arteries. If the atherosclerotic plaque obscures <50% of the diameter of the vessel, coronary blood flow can be augmented sufficiently during exertion and the patient is pain free. In patients with chronic stable angina, most coronary artery stenoses are >70%.

## Patient Assessment

- Angina is a clinical syndrome characterized by discomfort in the chest, jaw, shoulder, back, or arm. The presentation can be variable. Patients may not consider the sensations as pain and may instead describe them as a sense of pressure or heaviness.
- Characterizing the nature of chest pain (location, duration, and quality) is important for determining the type of angina, which, in turn, guides therapy (Table 17.1).
- **Chronic stable angina**, or exertional angina, presents as a reproducible pattern of angina that is associated with a certain level of physical activity. Physical findings are nonspecific and include shortness of breath, tachycardia, diaphoresis, and nausea. Chronic stable angina is the first clinical sign of CHD in approximately 50% of patients.
- **Unstable angina** presents as new-onset angina or a change in angina intensity, frequency, or duration.
- **Variant (Prinzmetal) angina** involves coronary artery spasm. No hemodynamic factors appear to contribute to this form of angina. Clinical manifestations include chest pain at rest, often occurring in the morning hours. Patients tend to be younger and do not carry a risk profile.
- **Syndrome X (microvascular ischemia)** is a syndrome of angina or angina-like chest pain in the setting of a normal coronary arteriogram.
- Induction of stress via exercise or pharmacologic means is a common and highly useful procedure for diagnosis. Pharmacologic stress can be achieved through the use of dipyridamole, adenosine, or dobutamine.

## Goals of Therapy

- Primary goals for treatment include acute symptom relief, prevention of further chest pain episodes, improvement in quality of life, minimization of treatment adverse events, and prevention of serious morbidity and mortality.

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\*The reader is referred to Chapter 17, Chronic Stable Angina, written by Toby C. Trujillo, PharmD, BCPS, and Paul E. Nolan, Jr., PharmD, in the 10th edition of *Applied Therapeutics: The Clinical Use of Drugs* for a more in-depth discussion. All notations to reference numbers are based on the reference list at the end of that chapter. The editor of this handbook expresses her thanks to Drs. Trujillo and Nolan and acknowledges that this chapter is based on their work.

TABLE 17.1 Characteristics of Angina Pectoris

**SYMPTOMS**

Sensation of pressure or heavy weight on chest alone or with pain  
 Pain described variably as feeling of tightness, burning, crushing, squeezing, vicelike, aching, or “deep”  
 Gradual increase in intensity followed by gradual fading away (distinguished from esophageal spasm)<sup>a</sup>  
 Shortness of breath with feeling of constriction about the larynx of upper trachea

**DURATION OF SYMPTOMS**

0.5–30 minutes

**LOCATION OF PAIN OR DISCOMFORT**

Over the sternum or very near to it  
 Anywhere between epigastrium and pharynx  
 Occasionally limited to left shoulder and left arm  
 Rarely limited to right arm  
 Lower cervical or upper thoracic spine  
 Left interscapular or suprascapular area

**RADIATION OF PAIN**

Medial aspect of left arm  
 Left shoulder  
 Jaw  
 Occasionally, right arm

**ELECTROCARDIOGRAM**

ST-segment depression >2 mm  
 T-wave inversion

**PRECIPITATING FACTORS**

Mild, moderate, or heavy exercise, depending on patient  
 Effort that involves use of arms above the head  
 Cold environment  
 Walking against the wind  
 Walking after a large meal  
 Emotions: fright, anger, or anxiety  
 Coitus

**NITROGLYCERIN RELIEF<sup>a</sup>**

Relief of pain occurring within 45 seconds to 5 minutes of taking nitroglycerin

<sup>a</sup>Esophageal spasm and other gastrointestinal disorders occasionally mimic anginal pain and also can be relieved by nitroglycerin.

**Treatment**

- Modification of cardiovascular risk factors and adoption of a healthy lifestyle are key strategies for primary prevention and for slowing progression of established disease (Table 17.2).
- Pharmacologic control of angina is, in part, directed toward improving oxygen supply (through vasodilation of the epicardial coronary arteries) and decreasing myocardial oxygen demand (by decreasing heart rate, myocardial contractility, or ventricular volume and pressure).
- Myocardial revascularization can be done with either percutaneous coronary intervention (PCI) or coronary artery bypass surgery (CABG). Both procedures are equally effective at relieving symptoms. A mortality advantage may exist for patients at high risk for morbidity and mortality from coronary artery disease (CAD). In patients not at high risk, optimal medical management is as good as PCI in the long-term management of chronic stable angina.

**TABLE 17.2 AHA/ACC Guidelines for the Secondary Prevention for Patients with Coronary and Other Atherosclerotic Vascular Disease**

Risk Factor	Intervention and Goal
Smoking	Complete cessation No exposure to environmental tobacco smoke
Blood pressure	<130/80 mm Hg <130/80 mm Hg if patient has diabetes or chronic kidney disease
Lipid management	LDL-C <100 mg/dL If triglycerides >200 mg/dL, non-HDL-C should be <130 mg/dL
Diabetes	Hemoglobin A <sub>1c</sub> <7%
Physical activity	At least 30 minutes of moderate intensity aerobic activity (e.g., brisk walking) for minimum of 5 days/week
Weight management	BMI between 18.5 and 24.9 kg/m <sup>2</sup> Waist circumference, men <40 inches Waist circumference, women <35 inches
Influenza vaccination	Patients with CAD should have an annual influenza vaccination

BMI, body mass index; CAD, coronary artery disease; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol.

Sources: Smith SC Jr et al. AHA/ACC guidelines for secondary prevention for patients with coronary and other atherosclerotic vascular disease: 2006 update: endorsed by the National Heart, Lung, and Blood Institute [published correction appears in *Circulation*. 2006;113:e847]. *Circulation*. 2006;113:2363; Rosendorff C et al. Treatment of hypertension in the prevention and management of ischemic heart disease: a scientific statement from the American Heart Association Council for High Blood Pressure Research and the Councils on Clinical Cardiology and Epidemiology and Prevention. *Circulation*. 2007;115:2761.

## Drug Therapy

### • Antiplatelet Therapy

- All patients with chronic stable angina should receive antiplatelet therapy to prevent MI and death. In most patients, aspirin monotherapy is the agent of choice; clopidogrel is an alternative for patients who cannot tolerate aspirin.
- **Aspirin** has been shown to reduce the incidence of MI and sudden cardiac death in patients with chronic stable angina. Guidelines from the American College of Cardiology (ACC)/American Heart Association (AHA) recommend doses of 75 to 162 mg daily.
- **Clopidogrel** inhibits platelet function as a noncompetitive antagonist of the P2Y<sub>12</sub> platelet adenosine diphosphate receptor. It is considered a second-line choice behind aspirin in patients with CAD. A dose of 75 mg daily is recommended for patients with chronic stable angina. Higher doses (loading dose of 600 mg) are recommended for patients undergoing PCI. Clopidogrel nonresponsiveness (high on-treatment platelet reactivity) can occur in up to 44% of patients.
- **Prasugrel or ticagrelor** are alternatives to clopidogrel for patients undergoing PCI.
- Dual antiplatelet therapy in patients with CAD is currently limited to those who have had recent acute coronary syndrome (ACS) or PCI plus stent placement.

### • Anti-ischemic Therapy

- Options for chronic prevention of angina episodes include  $\beta$ -blockers, calcium-channel blockers, long-acting nitrates, and ranolazine. Although each are considered relatively equivalent in prevention of ischemia, current guidelines recommend use of  $\beta$ -blockers before a nitrate or calcium-channel blocker.
- **$\beta$ -Blockers** are the preferred initial agent for prevention of ischemic symptoms, especially in patients who have a history of MI or heart failure. They lower myocardial oxygen demand by lowering heart rate, myocardial contractility, and intramyocardial wall tension. Choice of agent depends on cost, number of daily doses, and presence of comorbidities.

Dose should be titrated to a goal resting heart rate of 55 to 60 beats/minute.  $\beta$ -Blockers should be avoided in patients with primary vasospastic angina and may worsen symptoms in patients with reactive airway disease or peripheral arterial disease.  $\beta$ -Blocker withdrawal is a rebound phenomenon that increases myocardial oxygen demand and platelet aggregation; patients should not abruptly discontinue  $\beta$ -blocker therapy. Instead the dose should be gradually tapered over 1 to 2 weeks.

- **Calcium-channel blockers (CCB)** produce an increase in myocardial oxygen supply through vasodilation of the coronary arteries. They reduce myocardial oxygen demand through lowering of intramyocardial wall tension. Long-acting CCB are typically added to  $\beta$ -blocker therapy if additional control of ischemic symptoms is needed. Both diltiazem and verapamil are moderate peripheral vasodilators and potent coronary artery vasodilators. Dihydropyridines (e.g., nifedipine, nicardipine, amlodipine) are potent peripheral vasodilators and may be associated with a reflex increase in heart rate; they do not slow cardiac conduction and have no antiarrhythmic action. The dosing, physiological effects and side effects of the CCBs are shown in Tables 17.3 and 17.4. CCBs are effective for vasospastic and classic exertional angina, and for Prinzmetal variant angina.

TABLE 17.3 Calcium-Channel Blockers in Anginal Syndromes

Drug Name	FDA Approved <sup>a</sup>	Usual Dose for Chronic Stable Angina <sup>b</sup>	Product Availability
<b>DIHYDROPYRIDINES</b>			
Amlodipine	Angina, hypertension	2.5–10 mg every day	2.5, 5, 10 mg tab
Felodipine	Hypertension	5–20 mg every day	5, 10 mg ER tab
Isradipine	Hypertension	2.5–10 mg BID	2.5, 5 mg IR cap
		5–10 mg every day	5, 10 mg CR tab
Nicardipine	Angina (IR only), hypertension	20–40 mg TID	20, 30 mg IR cap
		30–60 mg BID	30, 45, 60 mg SR cap
Nifedipine	Angina, hypertension	10–30 mg TID	10, 20 mg IR cap
		30–180 mg every day	30, 60, 90 mg ER tab
Nisoldipine	Hypertension	20–60 mg every day	10, 20, 30, 40 mg ER tab
<b>DIPHENYLALKYLAMINES</b>			
Verapamil	Angina, hypertension, SVT	30–120 mg TID/QID	40, 80, 120 mg IR tab
		120–240 mg BID	120, 180, 240 mg SR tab
		120–480 mg every HS	180, 240 mg DR, ER tab
			120, 180, 240, 360 mg ER cap
			100, 200, 300 mg DR, ER tab
<b>BENZOTHIAZEPINES</b>			
Diltiazem	Angina, hypertension, SVT	30–120 mg TID/QID	30, 60, 90, 120 mg IR tab
		60–180 mg BID	60, 90, 120, 180 mg SR cap
		120–480 mg every day	120, 180, 240, 300, 360 mg cap
			120, 180, 240 mg ER cap
			120, 180, 240, 300, 360, 420 mg ER cap

<sup>a</sup>FDA-approved indications vary among IR and ER products. However, most have been used clinically for both angina and hypertension. Avoid IR-release products in hypertension.

<sup>b</sup>Because of short half-lives, most of these drugs are given TID if using IR tabs or caps. Amlodipine has a long half-life and is given once daily.

BID, twice a day; cap, capsules; CD, controlled diffusion; CR, controlled release; DR, delayed release; ER, extended release; FDA, US Food and Drug Administration; HS, bedtime; IR, immediate release; QID, four times a day; SR, sustained release; SVT, supraventricular including atrial fibrillation, atrial flutter, and reentry; tab, tablets; TID, three times a day.



TABLE 17.4 Calcium-Channel Blocker Hemodynamic and Electrophysiologic Profile

Effect	Dihydropyridine Derivatives <sup>a</sup>	Diltiazem	Verapamil
Peripheral vasodilation <sup>b</sup>	+++	++	++
Coronary vasodilation <sup>b</sup>	+++	+++	++
Negative inotropes <sup>c</sup>	±	++	+++
AV node suppression <sup>c</sup>	±	+	++
Heart rate	Increase (reflex)	Decrease or unchanged	Decrease or unchanged
Pharmacokinetics <sup>d</sup>			
Dosing <sup>e</sup>			
<b>SIDE EFFECTS</b>			
Nausea, vomiting	+ (most)	+/1	±
Constipation	Not observed	±	+
Hypotension, dizziness <sup>f</sup>	++	+	+
Flushing, headache	++	+	+
Bradycardia, HF symptoms	±	+	++
Reflex tachycardia, angina	+	Not observed	Not observed
Peripheral edema	+	±	±

<sup>a</sup>Dihydropyridine derivatives that are US Food and Drug Administration approved for angina: amlodipine (Norvasc), nifedipine (Cardene), and nifedipine (Adalat, Procardia). See Table 13.6 for others that are approved for hypertension but have been used clinically for angina. Investigational: nitrendipine (Baypress).

<sup>b</sup>Peripheral and coronary vasodilation helpful for angina, hypertension, and possibly HF, but peripheral dilation is the basis for side effects of flushing, headache, and hypotension.

<sup>c</sup>AV node suppression is helpful for controlling supraventricular arrhythmias, but this property plus the negative inotropic effect may worsen HF. Nifedipine has less negative inotropic effect than verapamil and diltiazem, but still may worsen HF. Amlodipine may have the least negative inotropic effect.

<sup>d</sup>All have poor bioavailability owing to high first-pass metabolism and all are eliminated primarily by hepatic metabolism; intradivisional and interindividual variability in bioavailability and metabolism is extensive. Diltiazem, nifedipine, nifedipine, and verapamil have a short half-life (<5 hours) requiring frequent dosing or use of sustained-release products. Amlodipine, isradipine (8 hours), and felodipine (10–20 hours) have longer half-lives.

<sup>e</sup>See Table 17.3.

<sup>f</sup>Hypotension and reflex tachycardia most with immediate-release nifedipine, occasional with immediate-release diltiazem and verapamil, minimal with sustained-release products or intrinsically long-acting agents.

- **Nitrates** are available in many formulations (Table 17.5), all of which are effective at preventing or relieving ischemic symptoms. Nitrates increase myocardial oxygen supply through vasodilation of the coronary arteries. They reduce myocardial oxygen demand through reduction of preload. Long-acting nitrates should never be used as monotherapy but only as add-on therapy to other anti-ischemic options. Tolerance can be limited by maintaining a nitrate-free interval of 10 to 12 hours daily. Nitrate dosing should be based on when angina symptoms occur (day vs. night). All patients with chronic stable angina should receive a prescription for sublingual nitroglycerin for relief of acute angina attack (0.4 mg, with dose up to three doses in 15 minutes, if needed). Concomitant use of phosphodiesterase type 5 inhibitors (within 24 hours for sildenafil and vardenafil, 48 hours for tadalafil) is contraindicated due to the risk of life-threatening hypotension.
- **Ranolazine** is typically reserved for second-line therapy. It inhibits sodium influx thereby reducing intracellular sodium. This effectively prevents ischemic-induced contractile dysfunction and delays onset of angina. Ranolazine has no effect on heart rate or blood pressure, making it an option in patients with a low heart rate or blood pressure. Dosing is initiated at 500 mg twice daily, titrating up to 1,000 mg twice daily. Because it is extensively metabolized through CYP3A4 and CYP2D6, there is the potential for significant drug interactions. Considerations for use of ranolazine are shown in Table 17.6.

TABLE 17.5 Commonly Prescribed Organic Nitrates

Drug	Dosage Form	Duration	Onset (minutes)	Usual Dosage
<b>SHORT-ACTING</b>				
NTG	SL	10–30 minutes	1–3	0.4–0.6 mg <sup>a,b</sup>
NTG	Translingual spray	10–30 minutes	2–4	0.4 mg/metered spray <sup>a,b</sup>
NTG	IV	3–5 minutes <sup>c</sup>	1–2	Initially 5 mcg/minute. Increase every 3–5 minutes until pain is relieved or hypotension occurs
<b>LONG-ACTING<sup>d</sup></b>				
NTG	SR capsule	4–8 hours	30	6.5–9 mg every 8 hours
NTG	Topical ointment <sup>e</sup>	4–8 hours	30	1–2 inches every 4–6 hours <sup>f</sup>
NTG	Transdermal patch	4–8 hours	30–60	0.1–0.2 mg/hour to start; titrate up to 0.8 mg/hour <sup>f</sup>
NTG	Transmucosal	3–6 hours	2–5	1–3 mg every 3–5 hours <sup>f</sup>
ISDN	SL	2–4 hours	2–5	2.5–10 mg every 2–4 hours <sup>f</sup>
	Chewable	2–4 hours	2–5	5–10 mg every 2–4 hours <sup>f</sup>
	Oral	2–6 hours	15–40	10–60 mg every 4–6 hours <sup>f</sup>
	SR capsule	4–8 hours	15–40	40–80 mg every 6–8 hours <sup>f</sup>
ISMN <sup>g</sup>	Tablet (ISMO, Monoket)	7–8 hours	30–60	10–20 mg BID (morning and midday) to start; titrate to 20–40 mg BID <sup>f</sup>
	Extended-release tablet (Imdur)	8–12 hours	30–60	60 mg every day to start; titrate to 30–120 mg every day

<sup>a</sup>When using sublingual or translingual spray forms of NTG, patients should administer the dose while sitting to minimize tachycardia, hypotension, dizziness, headache, and flushing. The optimal dose relieves symptoms with <10- to 15-mm Hg drop in systolic blood pressure or <10-beats/minute rise in pulse. Pain relief is rapid (onset 1–2 minutes; relief in 3–5 minutes), but up to three doses at 5-minute intervals may be given. After this, medical assistance should be summoned.

<sup>b</sup>Sublingual NTG tablets are degraded rapidly by heat, moisture, and light. They should be stored in a cool, dry place; do not leave the lid open or refrigerate. Tablets should be stored in the original manufacturer's container or a glass vial because the tablets volatilize and bind to many plastic vials and cotton. Previously, stinging of the tongue was an indicator of fresh tablets, but newer formulations only cause stinging in approximately 75% of patients.

<sup>c</sup>Duration after infusion discontinued.

<sup>d</sup>Longer-acting forms of nitrates are effective drugs, but it is important to understand their limitations to optimize effectiveness. Sublingual ISDN tablets display an onset and duration intermediate between that of sublingual NTG and oral ISDN. Because of high presystemic (first-pass) metabolism of the oral forms of both NTG and ISDN, very large doses may be required compared with SL or chewable dosage forms. Small oral doses (2.5 mg NTG, 5 mg ISDN) are probably not effective; doses as large as 9 mg NTG and 60 mg ISDN are not uncommon. Despite claims for longer activity, ointments and oral forms are often only effective for 4 to 8 hours, even when given as SR preparations. Also, continued daily use leads to rapid development of tolerance (see note *f*).

<sup>e</sup>Squeeze 1 to 2 inches of ointment onto the calibrated paper enclosed in the package with tube. Carefully spread the ointment on chest in a thin layer approximately 2 by 2 inches in size. Keep area covered with applicator paper. Wipe off previous dose before adding new dose or if hypotensive. If another person applies the ointment, avoid contact with fingers or eyes to prevent headache or hypotension.

<sup>f</sup>Dosage regimens should maintain a nitrate-free interval (e.g., bedtime) to decrease tolerance development. Give last oral dose or remove ointment or transdermal patch at 7 PM. Give last dose of SR ISDN in early afternoon.

<sup>g</sup>Major active metabolite of ISDN; 100% bioavailable; no first-pass metabolism, but tolerance may still occur. Rapid-release form (ISMO, Monoket) as 10- and 20-mg tablets. Extended-release form (Imdur) as 60-mg tablets. Okay to cut Imdur in half; do not crush or chew.

BID, twice daily; ISDN, isosorbide dinitrate; ISMN, isosorbide monohydrate; IV, intravenous; NTG, nitroglycerin; SL, sublingual; SR, sustained release.

### • Myocardial Revascularization

- Patients who undergo myocardial revascularization should still receive optimal pharmacotherapy for chronic stable angina.
- **Percutaneous coronary intervention**, also known as angioplasty, involves the percutaneous insertion of a balloon catheter into the femoral artery so that the coronary artery obstruction is mechanically dilated. Intracoronary stents (bare metal or drug-eluting) are

**TABLE 17.6 Considerations for the Use of Ranolazine in Patients with Chronic Stable Angina**

Clinical Issue	Recommended Management Strategy
Renal insufficiency	Ranolazine plasma levels may increase up to 50%. Caution with dose titration to maximal recommended dose
Hepatic insufficiency	Ranolazine is contraindicated in patients with clinically significant hepatic impairment.
<b>DRUG INTERACTIONS: EFFECTS ON RANOLAZINE</b>	
Strong CYP3A4 inhibitors	Plasma concentrations of ranolazine are significantly elevated when combined with potent inhibitors of CYP3A4. Ranolazine is contraindicated in patients receiving strong CYP3A4 inhibitors (ketoconazole, clarithromycin, nelfinavir, etc.).
Moderate CYP3A4 inhibitors	Limit the dose of ranolazine to 500 mg twice daily in patients receiving moderate inhibitors of CYP3A4 (diltiazem, verapamil, erythromycin, fluconazole, etc.).
CYP3A4 inducers	Coadministration of ranolazine with CYP3A4 inducers is contraindicated and should be avoided.
P-glycoprotein inhibitors	Caution should be exercised when coadministering ranolazine with P-glycoprotein inhibitors, and the dose of ranolazine may need to be lowered on the basis of clinical response.
<b>DRUG INTERACTIONS: EFFECTS ON OTHER MEDICATIONS</b>	
Simvastatin	Plasma levels of simvastatin are increased twofold with coadministration with ranolazine through CYP3A4 inhibition by ranolazine; closely monitor for adverse effects (e.g., myositis) from simvastatin.
Digoxin	Ranolazine coadministration increases plasma concentrations of digoxin by 1.5 times. Adjust dose of digoxin accordingly to maintain desired therapeutic level and response.
CYP2D6 substrates	Ranolazine can inhibit the activity of CYP2D6, and plasma concentrations of 2D6 substrates ( $\beta$ -blockers, tricyclic antidepressants, antipsychotics) may be increased and lower doses of these agents may be required.
QT prolongation	Caution is recommended if the patient is on other QT prolonging drugs or has QT prolongation as baseline

now commonly used as a means to maintain vessel patency. Current evidence suggests that PCI offers no long-term improvement in the incidence of MI or cardiovascular death over medical therapy, but it has been shown to decrease the incidence of recurrent symptoms in the short term. Potent antiplatelet and antithrombotic strategies are needed to prevent acute thrombotic events. Current strategies include use of aspirin, clopidogrel, an anti-thrombin agent, and glycoprotein IIb/IIIa receptor antagonists (tirofiban, eptifibatide, or abciximab). Dual antiplatelet therapy (clopidogrel, prasugrel, or ticagrelor plus aspirin) is recommended after stent placement due to the effectiveness at reducing in-stent thrombosis. Dual therapy should continue ideally for up to 1 year.

- **Coronary artery bypass graft (CABG)** is a complicated surgical procedure where the atherosclerotic vessel is bypassed using either the patient's saphenous vein or internal mammary artery. The graft allows blood to flow past the obstruction in the native vessel. It remains the preferred strategy for patients with three-vessel disease.

# Acute Coronary Syndrome\*

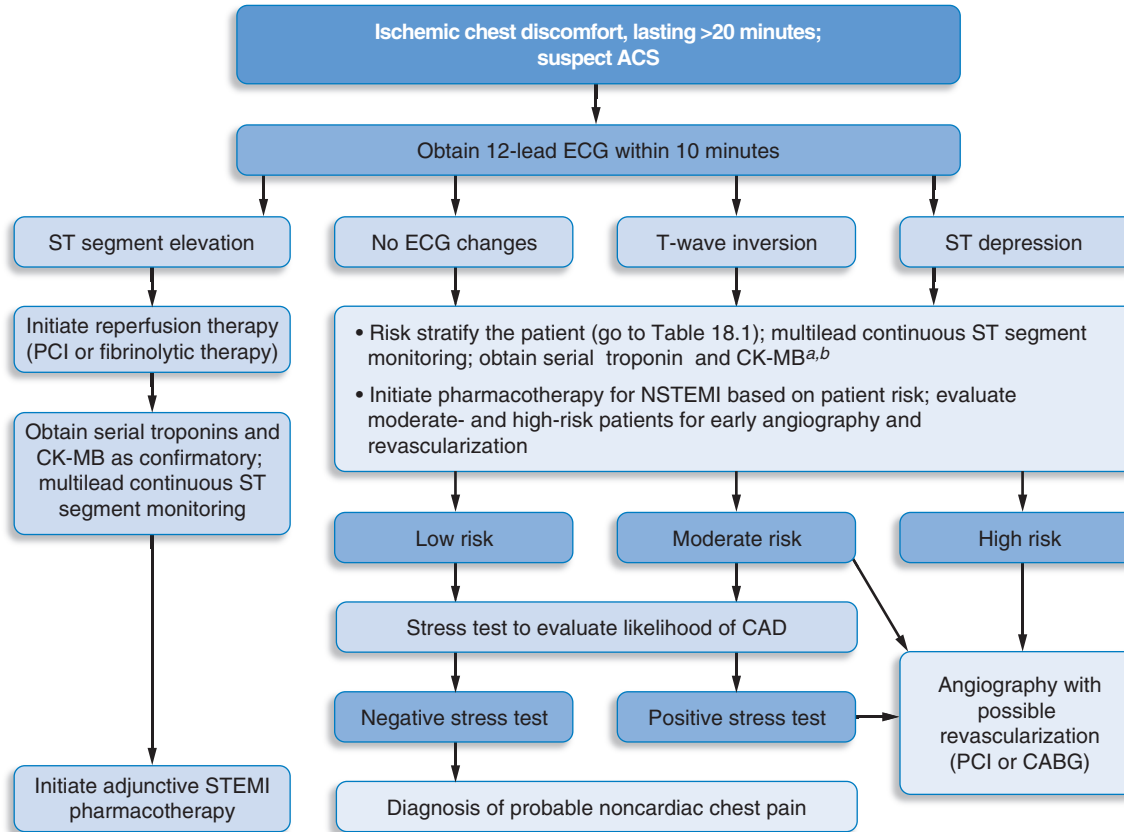
## General Principles

- Acute coronary syndrome (ACS) is an umbrella term that includes patients who present with either unstable angina (UA) or acute myocardial infarction (AMI) consisting of ST segment elevation myocardial infarction (STEMI) or non-ST segment myocardial infarction (NSTEMI).
- ACS originates from the erosion or rupture of unstable plaques within the coronary artery leading to the formation of an occlusive or nonocclusive thrombus.
- The majority of ACS results from occlusion of a coronary artery secondary to thrombus formation; 80% of patients presenting with ACS have two or more active plaques.
- The primary complications of AMI include pump failure, arrhythmias, and recurrent ischemia and reinfarction. Nearly 20% of patients with ACS are rehospitalized within 1 year.

## Patient Assessment

- Hallmark symptoms for ACS include increasing frequency of exertional angina or chest pain at rest, new-onset severe chest discomfort, or increasing angina with a duration exceeding 20 minutes. Chest discomfort can be described as pressure or tightness around the chest rather than pain. At least 20% of patients have no pain or discomfort (i.e., “silent” MIs).
- Most infarctions are located in a specific region of the heart and are described as such (e.g., anterior, lateral, inferior). An anterior wall infarct carries a worse prognosis than an inferior or lateral wall infarct because it is more commonly associated with development of left ventricular failure, cardiogenic shock, and mortality.
  - The ECG is a critical tool in the diagnosis of ACS and the decision pathway for management of the patient (Figure 18.1). The 12-lead ECG is helpful in determining the location of an infarct.
  - Measurement of sensitive and specific enzymes is routine in establishing the diagnosis of AMI (i.e., troponins T or I; creatine kinase isoenzymes, CK-MB being most specific for the myocardium). Troponin has become the preferred biomarker for assessment of myocardial damage due to its high cardiac specificity and sensitivity.
- Patients presenting with STEMI usually complain of unrelenting chest pain whereas patients with UA or NSTEMI will present with either angina at rest, new-onset (2 months or less) angina, or angina that increases in frequency, duration, or intensity. STEMI patients are considered medical emergencies.
- Examination of the patient begins with stratification for risk of death and reinfarction. Patients are stratified into low, medium, and high risk for mortality and need for urgent coronary angiography and percutaneous coronary intervention (PCI) (Figure 18.1). The Thrombolysis in Myocardial Infarction (TIMI) risk score can be used with either STEMI or UA/NSTEMI (Table 18.1).

\*The reader is referred to Chapter 18, Acute Coronary Syndrome, written by Robert Lee Page, II, PharmD, MSPH, FCCP, FASHP, FAHA, FASCP, BCPS, CGP, and Jean M. Nappi, PharmD, FCCP, BCPS, in the 10th edition of *Applied Therapeutics: The Clinical Use of Drugs* for a more in-depth discussion. All notations to reference numbers are based on the reference list at the end of that chapter. The editor of this handbook expresses her thanks to Drs. Page and Nappi and acknowledges that this chapter is based on their work.



**Figure 18.1** Evaluation algorithm for the patient presenting with acute coronary syndrome. ACS, acute coronary syndrome; CAD, coronary artery disease; CABG, coronary artery bypass graft; CK, creatinine; ECG, electrocardiogram; PCI, percutaneous coronary intervention; NSTEMI, non-ST segment myocardial infarction; STEMI, ST segment myocardial infarction. <sup>a</sup>Positive, above the myocardial infarction limit; <sup>b</sup>Negative, below the myocardial infarction limit. (Adapted with permission from Spinler SA. Evolution of antithrombotic therapy used in acute coronary syndromes. In: Richardson M, Chessman K, Chant C, Cheng J, Hemstreet B, Hume AI, eds. *Pharmacotherapy Self-Assessment Program*. 7th ed. Cardiology. Lenexa, KS: American College of Clinical Pharmacy; 2010:62.)

TABLE 18.1 Risk Stratifications Tools for Acute Coronary Syndrome

TIMI Risk Score <sup>a</sup>			
STEMI		NSTEMI	
Risk Factor	No. of Points	Risk Factor	No. of Points
Age 65–75 years	2	Age $\geq$ 65 years	1
Age $\geq$ 75 years	3	$\geq$ 3 risk factors for CAD <sup>b</sup>	1
SBP < 100 mm Hg	3	Prior history of CAD <sup>c</sup>	1
Heart rate > 100 beats/minute	2	Aspirin use in past 7 days	1
Killip class II–IV	2	$\geq$ 2 anginal events in past 24 hours	1
Weight < 67 kg	1	ST segment deviation $\geq$ 0.5 mm	1
History of HTN, diabetes, or angina	1	Elevation of cardiac markers <sup>d</sup>	1
Time to reperfusion therapy > 4 hours	1		
Anterior ST segment elevation or left bundle branch block	1		

Killip Class <sup>e</sup>		
Class	Symptoms	In-Hospital and 1-Year Mortality (%)
I	No heart failure	5
II	Mild heart failure, rales, S <sub>3</sub> , congestion on chest radiograph	21
III	Pulmonary edema	35
IV	Cardiogenic shock	67

<sup>a</sup>TIMI risk score data from Antman EM et al. The TIMI risk score for unstable angina/non-ST-elevation MI: A method for prognostication and therapeutic decision making. *JAMA*. 2000;284:835; Morrow DA et al. Application of the TIMI risk score for ST-elevation MI in the National Registry of Myocardial Infarction 3. *JAMA*. 2001;286:1356. A risk score is calculated by adding the total number of risk factors. Total points for STEMI are 0 to 14, in which risk scores of 0, 2, 4, 6, 7, and  $>$ 8 correspond to a 30-day mortality rate of 0.8%, 2.2%, 7.3%, 16%, 23%, and 36%, respectively. Total points for NSTEMI are 0 to 7, in which scores of 0 or 1, 3, 5, and 7 correspond to a 3%, 5%, 12%, or 19% risk of death or repeat MI at 14 days, respectively.

<sup>b</sup>Risk factors include smoking, diabetes, hypertension, family history of coronary artery disease, and hypercholesterolemia.

<sup>c</sup>Defined as a prior coronary stenosis  $\geq$ 50%; history of previous myocardial infarction, percutaneous coronary intervention, or coronary artery bypass graft; or chronic stable angina pectoris associated with a positive exercise tolerance test or pharmacologically induced nuclear imaging or echocardiographic changes (positive nuclear imaging or echocardiographic changes required if female).

<sup>d</sup>Either troponin I or T or creatine kinase-MB.

<sup>e</sup>Killip class data from Killip T, III, Kimball JT. Treatment of myocardial infarction in a coronary care unit. A 2 year experience with 250 patients. *Am J Cardiol*. 1967;20:457.

CAD, coronary artery disease; HTN, hypertension; NSTEMI, non-ST segment elevation myocardial infarction; SBP, systolic blood pressure; STEMI, ST segment elevation myocardial infarction; TIMI, Thrombolysis in Myocardial Infarction.

## Goals of Therapy

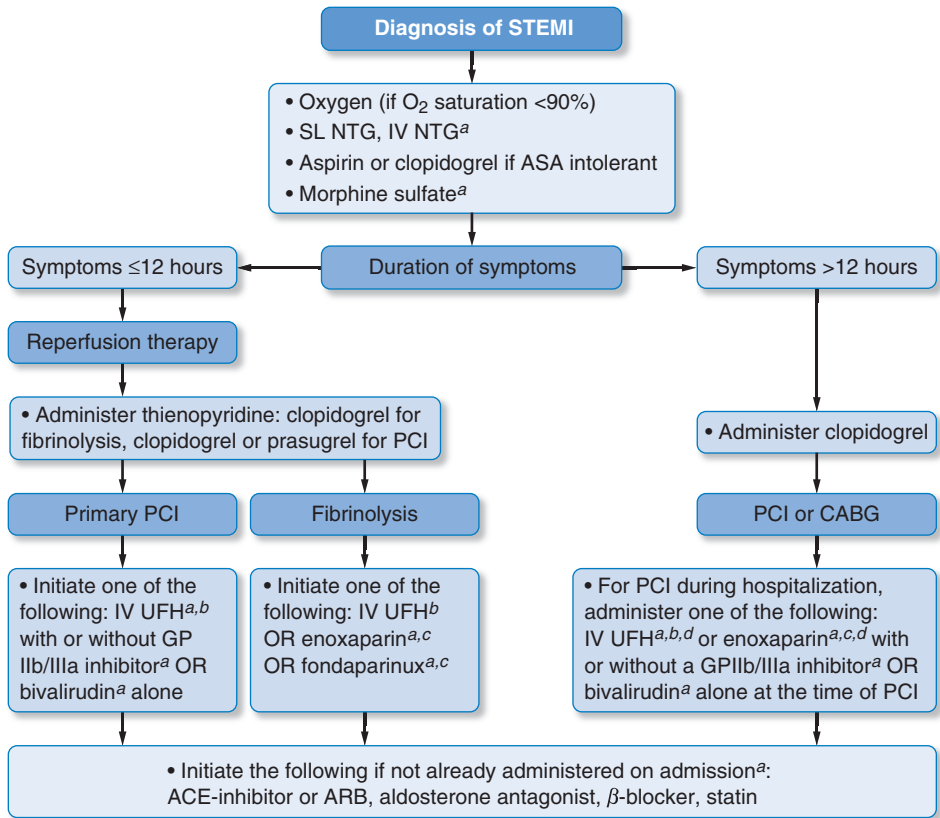
- With both STEMI and NSTEMI, the immediate therapeutic objective is to restore blood flow to the infarct-related artery, arrest infarct expansion, alleviate symptoms, and prevent death.
- Therapy goals are achieved primarily by restoring coronary blood flow and lowering myocardial oxygen demand.
- Target time to initiate reperfusion for STEMI is within 30 minutes of hospital presentation for thrombolytic therapy and within 90 minutes from presentation for PCI.
- Long-term treatment goals are to prevent or minimize recurrent ischemic symptoms, reinfarction, heart failure, and sudden cardiac death.

## Treatment

- Management of ACS is based on reperfusion and revascularization using a variety of strategies including thrombolytic, antiplatelet, and anticoagulant therapies, and nonpharmacological interventions such as PCI and coronary artery bypass grafting (CABG).
- Guidelines developed by the American College of Cardiology (ACC) and American Heart Association (AHA) serve as the foundation of care for patients with ACS.
- ACC/AHA guidelines state that early therapy should include oxygen (if oxygen saturation is <90%), sublingual nitroglycerin, aspirin or clopidogrel, stool softener,  $\beta$ -blocker, statin, and anticoagulant.
- The initial treatment algorithm for STEMI is shown in Figure 18.2. STEMI is a medical emergency, and rapid administration of drug therapy is crucial to save myocardial tissue.
- The initial treatment algorithm for UA/NSTEMI is shown in Figure 18.3. There are two pathways of treatment: early invasive strategy and early conservative strategy.
- Nondrug measures include a low-cholesterol, low-saturated-fat diet, weight loss, smoking cessation, hemoglobin A1C < 7%, low-density lipoprotein (LDL) < 70 mg/dL, and blood pressure goal of <130/80 mm Hg.
- PCI is an alternative to thrombolytic therapy for STEMI.

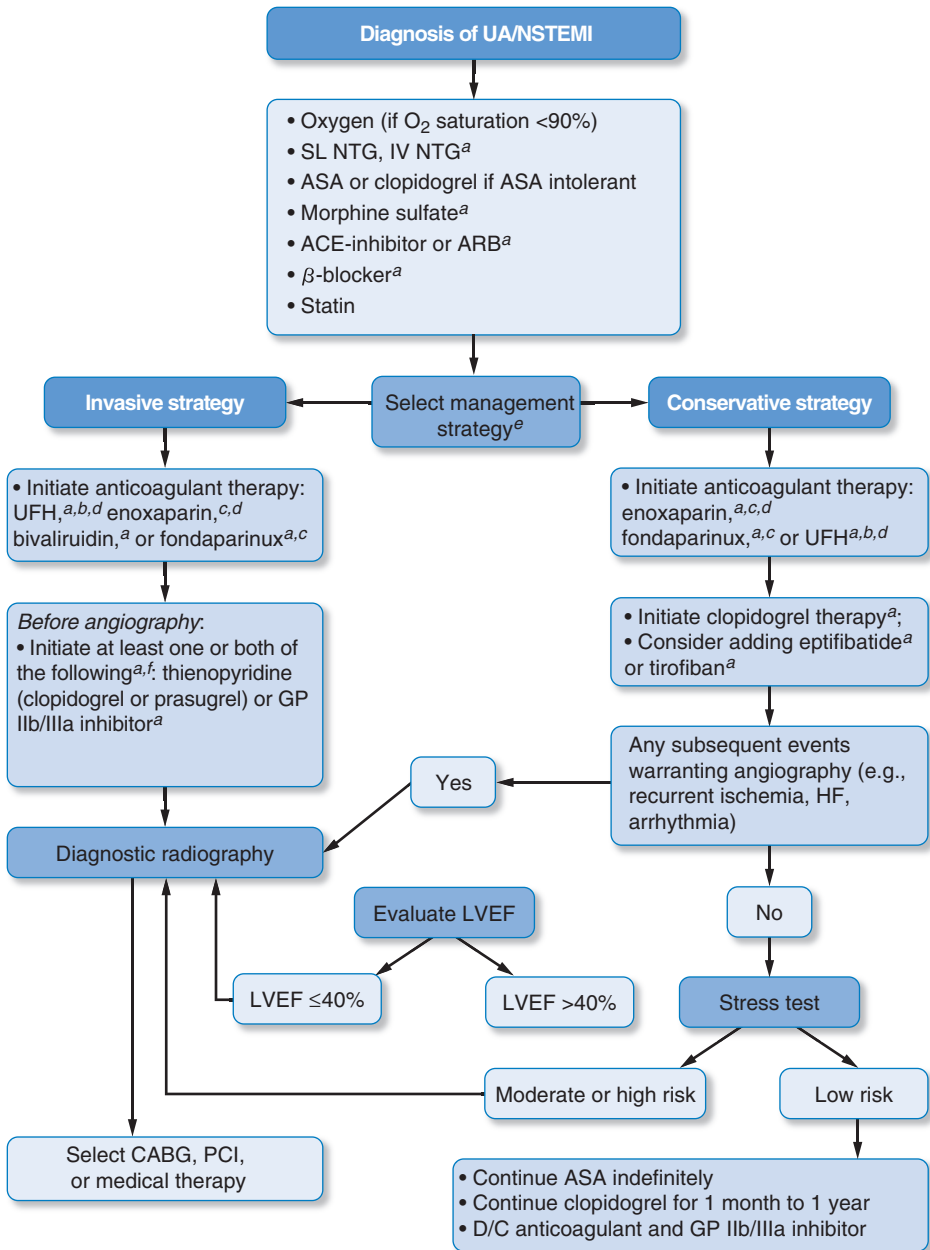
## Drug Therapy

- Key points related to the evidence-based pharmacotherapies for ACS are shown in Table 18.2.
- **Thrombolytic Therapy**
  - Thrombolytic agents enhance the body's own fibrinolytic system. Agents include streptokinase, alteplase (t-PA), reteplase (r-PA), and tenecteplase (TNK).
  - The pharmacological properties and dosing considerations are shown in Table 18.3. To minimize the risk of bleeding complications, contraindications to the use of thrombolytic agents must be evaluated before administration (Table 18.4).
  - Mortality benefit in patients with STEMI is greatest when thrombolytic therapy is administered within 2 hours of symptom onset; significant benefit is associated with administration up to 12 hours from onset of chest pain with a trend toward benefit when given between 13 and 24 hours.
  - Thrombolytic agents are not recommended in patients with UA or NSTEMI as thrombi in these patients are not typically fibrin rich, so they are less responsive to therapy.
- **Antiplatelet Therapy**
  - Antiplatelet agents include aspirin, thienopyridines (clopidogrel, prasugrel), ticagrelor, and glycoprotein IIb/IIIa inhibitors (e.g., tirofiban, eptifibatide, abciximab; dosing shown in Table 18.5).
  - Immediate administration of aspirin 162 to 325 mg is indicated for all patients with ACS. In the acute setting, aspirin should be chewed because it is absorbed more quickly.
  - Clopidogrel (300–600 mg loading dose followed by 75 mg daily) should be added to aspirin regardless of whether the patient undergoes reperfusion with fibrinolytic therapy.
  - Current guidelines recommend initiating dual antiplatelet therapy with aspirin and a thienopyridine.
  - Antiplatelet therapy with aspirin should be lifelong for secondary prevention of reinfarction.
- **Anticoagulant Therapy**
  - Anticoagulant agents include unfractionated heparin (UFH), low-molecular-weight heparin (LMWH), and direct thrombin inhibitors (DTI; bivalirudin).
  - Current guidelines recommend beginning anticoagulant therapy for all patients with NSTEMI (without contraindications) as soon as possible. Enoxaparin or fondaparinux can be substituted for UFH; however, UFH is the agent of choice in patients receiving CABG or PCI because of its rapid clearance.



**Figure 18.2** Initial treatment algorithm for STEMI. <sup>a</sup>Refer to Table 18.2 for indications, dosing, and contraindications. <sup>b</sup>For at least 48 hours. <sup>c</sup>For the duration of the hospitalization, up to 8 days. <sup>d</sup>Preferred therapy. ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; CABG, coronary artery bypass graft; GP IIB/IIIa, glycoprotein IIB/IIIa; NTG, nitroglycerin; O<sub>2</sub>, oxygen; PCI, percutaneous coronary intervention; SL, sublingual; STEMI, ST segment elevation myocardial infarction; UFH, unfractionated heparin. (Source: Kushner FG et al. 2009 Focused Updates: ACC/AHA Guidelines for the Management of Patients With ST Elevation Myocardial Infarction [Updating the 2004 Guideline and 2007 Focused Update] and ACC/AHA/SCAI Guidelines on Percutaneous Coronary Intervention [Updating the 2005 Guideline and 2007 Focused Update]: A Report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines [published corrections appear in *J Am Coll Cardiol.* 2010;55:612 (dosage error in article text); *J Am Coll Cardiol.* 2009;54:2464]. *J Am Coll Cardiol.* 2009;54:2205; Anderson JL et al. ACC/AHA 2007 guidelines for the management of patients with unstable angina/non-ST elevation myocardial infarction: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines [Writing Committee to Revise the 2002 Guidelines for the Management of Patients With Unstable Angina/Non-ST Elevation Myocardial Infarction]: developed in collaboration with the American College of Emergency Physicians, the Society for Cardiovascular Angiography and Interventions, and the Society of Thoracic Surgeons endorsed by the American Association of Cardiovascular and Pulmonary Rehabilitation and the Society for Academic Emergency Medicine [published correction appears in *J Am Coll Cardiol.* 2008;51:974]. *J Am Coll Cardiol.* 2007;50:e1.)





**Figure 18.3** Initial treatment algorithm for NSTEMI. <sup>a</sup>Refer to Table 18.2 for indications, dosing, and contraindications. <sup>b</sup>For at least 48 hours. <sup>c</sup>For the duration of the hospitalization, up to 8 days. <sup>d</sup>Preferred therapy. <sup>e</sup>An invasive strategy would be considered if one or more of the following occurs: recurrent angina or ischemia at rest; presence of elevated cardiac biomarkers; new or presumably new ST segment depression; signs or symptoms of heart failure (HF) or new worsening mitral regurgitation; hemodynamic instability; sustained ventricular tachycardia; percutaneous coronary intervention (PCI) within 6 months; prior coronary artery bypass graft (CABG); considered high risk per Thrombolysis in Myocardial Infarction (TIMI) risk score, left ventricular ejection fraction (LVEF) <40%. A conservative approach would be considered if the patient is classified as low-moderate risk per the TIMI risk score or if the patient or physician prefers a conservative approach in the absence of high-risk features. <sup>f</sup>Factors favoring administration of both include delay to angiography, high-risk features, and early recurrent ischemia. ACE, angiotensin-converting enzyme; ARB,

- ***β-Blocker Therapy***

- *β*-Blockers should be administered independently of the planned reperfusion strategy as they reduce recurrent ischemia and reinfarction rates.
- They should be initiated within 24 hours after the onset of symptoms for all patients without contraindications and should be continued indefinitely. *β*-Blockers with intrinsic sympathomimetic activity should be avoided as they have not been well studied and lack efficacy data.
- Metoprolol is typically used in the acute setting because of its *β*-1 selectivity, ease of use, and weight of evidence. Intravenous *β*-blocker therapy should not be administered to patients with transient cardiac decompensation.
- Metoprolol succinate and carvedilol are first-line choices in patients with heart failure. Atenolol, metoprolol tartrate, or metoprolol succinate should be considered in patients with stable asthma or bronchospastic pulmonary disorder.

- ***Statin Therapy***

- High-intensity statin therapy should be administered on the basis of evidence that shows reduced long-term morbidity and mortality in patients with cardiovascular disease.

- ***Vasodilator Therapy***

- Vasodilators reduce oxygen demand and myocardial wall stress by reducing preload and afterload.
- Oral ACE inhibitors have been shown to reduce mortality; intravenous ACE inhibitor therapy should be avoided. Current guidelines recommend initiating oral ACE inhibitor therapy within 24 hours of presentation for patients with an ejection fraction <40%.
- Nitroglycerin lowers left ventricular filling pressure and systemic vascular resistance, which reduces myocardial oxygen consumption and myocardial ischemia.
- Calcium-channel blockers (CCB) dilate the coronary and peripheral vascular beds.
- ACC/AHA guidelines recommend CCBs for patients with persistent or recurrent symptoms after treatment with full-dose nitrates and *β*-blockers, for patients with contraindications to *β*-blockers, or for patients with Prinzmetal or variant angina.

- ***Analgesic Therapy***

- Prompt management of pain is an important measure to minimize myocardial oxygen demand associated with pain and anxiety. Morphine is the analgesic of choice.
- Nonselective and cyclo-oxygenase-2-selective nonsteroidal anti-inflammatory agents should be avoided as they have been associated with an increased risk of mortality, reinfarction, hypertension, heart failure, and myocardial rupture.

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**Figure 18.3** (continued)

angiotensin receptor blocker; ASA, aspirin; CABG, coronary artery bypass graft; D/C, discontinue; LVEF, left ventricular ejection fraction; GP IIB/IIIa, glycoprotein IIB/IIIa; HF, heart failure; NSTEMI, non-ST segment elevation myocardial infarction; O<sub>2</sub>, oxygen; PCI, percutaneous coronary intervention; TIMI, Thrombolysis in Myocardial Infarction; SL, sublingual; UFH, unfractionated heparin. (Adapted with permission from Anderson JL et al. ACC/AHA 2007 guidelines for the management of patients with unstable angina/non-ST-Elevation myocardial infarction: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines [Writing Committee to Revise the 2002 Guidelines for the Management of Patients With Unstable Angina/Non-ST-Elevation Myocardial Infarction]: developed in collaboration with the American College of Emergency Physicians, the Society for Cardiovascular Angiography and Interventions, and the Society of Thoracic Surgeons endorsed by the American Association of Cardiovascular and Pulmonary Rehabilitation and the Society for Academic Emergency Medicine [published correction appears in *J Am Coll Cardiol*. 2008;51:974]. *J Am Coll Cardiol*. 2007;50:e1; and Wright SR, Anderson JL, Adams CD, et al. 2011 ACCF/AHA focused update for the management of patients with unstable angina/non-ST-elevation myocardial infarction, [updating the 2007 guideline]: a report of the American College of Cardiology Foundation/American Heart Association Task Force on practice guidelines. *J Am Coll Cardiol*. 2011;57:e1–e40.)

TABLE 18.2 Evidenced-Based Pharmacotherapies for Acute Coronary Syndromes

Drug	Indication	Dose and Duration	Therapeutic End Points	Precautions	Comments
ACE inhibitors <sup>d</sup>	STEMI and NSTEMI within the first 24 hours of presentation for those with EF $\leq$ 40% or s/s of HF STEMI and NSTEMI for late hospital care for patients with hypertension, EF $\leq$ 40%, DM, or CKD STEMI and NSTEMI for indefinite use for all patients with EF $\leq$ 40%	Usual captopril dose 12–50 mg TID; then start longer-acting ACE inhibitor. Duration indefinite	Titrate to usual doses and maintain systolic BP >90–110 mm Hg	Avoid IV therapy within 48 hours of infarct Avoid with SBP <100 mm Hg, pregnancy, acute renal failure, angioedema, bilateral renal stenosis, serum potassium $\geq$ 5.5 mEq/L	
Angiotensin receptor blockers <sup>d</sup>	STEMI and NSTEMI with ACE inhibitor intolerance	Usual doses of ARBs (see Chapter 19). Continue indefinitely.	Same as for ACE inhibitors	Same as for ACE inhibitors	
Aldosterone antagonists <sup>d</sup>	STEMI and NSTEMI with EF $\leq$ 40% and either DM or HF symptoms already receiving therapeutic doses of an ACE inhibitor and $\beta$ -blocker	Spirolactone 12.5–50 mg daily or eplerenone 25–50 mg daily. Duration indefinite.	Titrate to heart failure symptom control without evidence of hyperkalemia	Hyperkalemia, hypotension Avoid if potassium $\geq$ 5 mEq/L or SCr $\geq$ 2.5 mg/dL for men and 2.0 mg/dL for women or CrCl $\leq$ 30 mL/minute	Dose can be increased every 4–8 weeks.
Aspirin <sup>d</sup>	STEMI and NSTEMI for all patients	162–325 mg during AMI, then 75–325 mg/day for an indefinite period.	No firm end point	Active bleeding, thrombocytopenia	Unless clear contraindication exists, aspirin should be given to all AMI patients. For contraindications, see Chapter 17.

$\beta$ -Blockers <sup>a</sup>	STEMI and NSTEMI in all patients without contraindications	Variable; titrate to HR and BP. It is reasonable to administer an IV $\beta$ -blocker at the time of presentation to STEMI patients who are hypertensive and who do not have any of the following: (a) signs of heart failure, (b) evidence of a low output state, (c) increased risk <sup>c</sup> for cardiogenic shock, or (d) other relative contraindications to $\beta$ -blockade (PR interval >0.24 seconds, 2nd- or 3rd-degree heart block, active asthma, or reactive airway disease). Duration indefinite	Titrate to resting HR approximately 60 beats/minute, maintain systolic BP >100 mm Hg	Observe HR and BP closely when given IV Contraindicated in patients with HR <50 beats/minute; PR ECG segment >0.24 seconds, 2nd- or 3rd-degree heart block, persistent hypotension, pulmonary edema, bronchospasm, risk of cardiogenic shock, severe reactive airway disease	Unless clear contraindication exists, $\beta_1$ -selective agents such as metoprolol and atenolol should be given to all AMI patients. In patients with systolic dysfunction, metoprolol or carvedilol can be considered.
Bivalirudin <sup>a</sup>	STEMI and NSTEMI patients undergoing PCI who are at high risk of bleeding	<p>PCI: 0.75 mg/kg IV bolus followed by 1.75 mg/kg/hour infusion. If UFH given, discontinue UFH and wait 30 minutes before starting bivalirudin.</p> <p>Discontinue at the end of PCI or continue at 0.2 mg/kg/hour if prolonged anticoagulation necessary.</p> <p><i>Medical management before PCI:</i> 0.1 mg/kg IV bolus followed by 0.25 mg/kg/hour infusion.</p>		Avoid in patients with active bleeding	Reduce dose with renal dysfunction

Continued on following page

TABLE 18.2 Evidenced-Based Pharmacotherapies for Acute Coronary Syndromes (Continued)

Drug	Indication	Dose and Duration	Therapeutic End Points	Precautions	Comments
Calcium-channel blockers	STEMI and NSTEMI for patients with ongoing ischemia who are receiving adequate doses of nitrates and $\beta$ -blockers. Consider diltiazem or verapamil for patients with contraindication to $\beta$ -blocker if EF is normal	Usual doses of calcium-channel blockers are used. Duration dictated by clinical scenario	Titrate to usual doses and maintain SBP > 90 mm Hg	Usual calcium-channel blocker contraindications. Avoid nondihydropyridines in patients with pulmonary congestion or EF <40%	In patients with good EF, most calcium-channel blockers will exert beneficial effects. Some data support use of verapamil or diltiazem for non-Q-wave AMI, but not dihydropyridine types.
Clopidogrel <sup>a</sup>	STEMI and NSTEMI for patients allergic to aspirin	75 mg/day	No firm end point	Active bleeding, thrombotic thrombocytopenia purpura (rare)	
Clopidogrel + aspirin <sup>a</sup>	STEMI, before fibrinolytic therapy or before PCI after fibrinolytic therapy	<i>STEMI with fibrinolytic therapy without PCI:</i> 300–600 mg load followed by 75 mg daily and continue for 14 days to 1 year; aspirin 162–325 mg on first day, then 75–162 mg daily indefinitely.	No firm end point	Active bleeding, thrombotic thrombocytopenia purpura (rare)	Whether administered before thrombolytic or PCI, clopidogrel + aspirin reduced CV death, MI, or ischemia at 30 days. The 600-mg load should be considered if a GP IIb/IIIa is not used.
	NSTEMI or STEMI before PCI	<i>STEMI with fibrinolytic therapy with PCI:</i> 300–600 mg load, <sup>b</sup> then no additional treatment; aspirin 162–325 mg on first day, then 75–162 mg daily indefinitely.		Avoid loading dose in patients $\geq 75$ years of age	Clopidogrel + aspirin reduced death, reinfarction, or stroke through index hospitalization
	For NSTEMI and unstable angina patients	<i>STEMI or NSTEMI with PCI:</i>		Discontinue at least 5 days for CABG	

		300–600 mg load, followed by 75 mg daily or 150 mg daily for 6 days followed by 75 mg daily. If a coronary stent is deployed, continue clopidogrel for 12–15 months. For a BMS, administer aspirin 162–325 mg daily for at least 1 month after PCI, then decrease to 75–162 mg indefinitely. For a DES, administer aspirin 162–325 mg daily for 3 months for a sirolimus-eluting stent and 6 months for a paclitaxel-eluting stent after PCI, then decrease to 75–162 mg daily indefinitely.			
		300–600 mg load, followed by 75 mg daily for 1–12 months; aspirin 75–325 mg daily.			
Enoxaparin <sup>d</sup>	STEMI as an alternative for UFH or LMWH for patients receiving fibrinolytic therapy or for those not undergoing reperfusion therapy NSTEMI for patients undergoing a conservative or invasive approach For PCI, as an alternative for UFH or LMWH	STEMI or NSTEMI:  1 mg/kg SQ every 12 hours (CrCl > 30 mL/minute)  1 mg/kg SQ daily (CrCl 15–29 mL/minute) NSTEMI undergoing PCI:	No firm end point	Avoid in patients with active bleeding, history of HIT, planned CABG, SCr ≥2.5 mg/dL in men and ≥2.0 mg/dL in women, or CrCl < 15 mL/minute	Reduce dose with renal dysfunction

Continued on following page

TABLE 18.2 Evidenced-Based Pharmacotherapies for Acute Coronary Syndromes (Continued)

Drug	Indication	Dose and Duration	Therapeutic End Points	Precautions	Comments
Fibrinolytic therapy <sup>d</sup>	STEMI presenting within 12 hours after onset of symptoms, can be considered in patients presenting within 12–24 hours after onset of symptoms with continuing s/s of ischemia	<p>A supplemental 0.3 mg/kg IV dose should be administered at the time of PCI if the last dose of SC enoxaparin was given 8–12 hours before PCI</p> <p><i>STEMI with fibrinolytic therapy:</i></p> <p>Age &lt;75 years, administer 30 mg IV bolus followed by 1 mg/kg SQ every 12 hours (max dose of 100 mg for patients weighing <math>\geq</math>100 kg)</p> <p>Age <math>\geq</math>75, administer 0.75 mg/kg SQ every 12 hours (first two doses administer max dose of 75 mg for patients weighing <math>\geq</math>75 kg)</p> <p>For STEMI and NSTEMI continue throughout hospitalization or up to 8 days</p> <p>See Table 18.3</p>	Improved TIMI grade flow	See Table 18.4	

Fondaparinux <sup>a</sup>	STEMI as an alternative for UFH or LMWH for patients receiving fibrinolytic therapy or for those not undergoing reperfusion therapy NSTEMI as an alternative for UFH or LMWH for patients undergoing a conservative or invasive approach	STEMI and NSTEMI: 2.5 mg SQ daily starting on day 2 of hospitalization, continue for 8 days or discharge	No firm end point	Avoid with active bleeding, SCr ≥ 3.0 mg/dL, or CrCl < 30 mL/minute	In STEMI, fondaparinux reduced mortality and reinfarction without increased bleeds or strokes compared with UFH, but only in patients not undergoing PCI. In NSTEMI, fondaparinux was at least as effective as enoxaparin but exhibited less bleeding. Can possibly be used in HIT.
GP IIb/IIIa inhibitors <sup>a</sup>	NSTEMI for patients undergoing PCI or those without high-risk features not undergoing PCI STEMI for patients undergoing PCI	NSTEMI: 2.5 mg SQ daily for 6 days See Table 18.5	No firm end point No firm end point	Avoid with active bleeding, thrombocytopenia, prior stroke	
Heparin <sup>a</sup>	STEMI for patients undergoing PCI or for patients treated with fibrinolytic therapy NSTEMI in combination with antiplatelet therapy for conservative or invasive approach	STEMI with fibrinolytic therapy or NSTEMI: 60 units/kg IV bolus (max 4,000 units) followed by 12 units/kg/hour (max 1,000 units/hour) STEMI with PCI: 50–70 units/kg IV bolus if a GP IIb/IIIa inhibitor planned; or 70–100 units/kg IV bolus if no GP IIb/IIIa inhibitor Continue for 48 hours or until end of PCI	aPTT ratio 1.5–2.5 patient's control value, first aPTT should be obtained 4–6 hours if not treated with fibrinolytic therapy or PCI and within 3 hours if treated with fibrinolytic therapy	Avoid with active bleeding, thrombocytopenia, recent stroke	Unless clear contraindication exists, UFH should be given to all AMI patients who do not receive thrombolytic therapy

Continued on following page



TABLE 18.2 Evidenced-Based Pharmacotherapies for Acute Coronary Syndromes (Continued)

Drug	Indication	Dose and Duration	Therapeutic End Points	Precautions	Comments
Lidocaine	Treatment of VT, VF	Variable, 1.5 mg/kg loading dose, then 1–4 mg/minute. Use for <48 hours.	Cessation of arrhythmia	Bradycardia. Observe for CNS toxicity.	Some data indicate increased mortality with routine use.
Morphine and other analgesics	STEMI and NSTEMI for patients whose symptoms not relieved by NTG or adequate anti-ischemic therapy	2–5 mg IV every 5–30 minutes PRN	Decreased chest pain and HR	Avoid morphine with bradycardia, right ventricular infarct, hypotension, confusion.	Has been associated with higher risk of death; discontinue nonselective NSAIDs and COX-2 selective agents.
Prasugrel <sup>a</sup>	STEMI and NSTEMI added to aspirin for PCI	60 mg loading dose followed by 10 mg (if $\geq 60$ kg) or 5 mg (if <60 kg). If a coronary stent is deployed, continue prasugrel for 12–15 months. For a BMS, administer aspirin 162–325 mg daily for at least 1 month after PCI, then drop to 75–162 mg indefinitely; For a DES, administer aspirin 162–325 mg daily for 3–6 months after PCI, then drop to 75–162 mg daily indefinitely.	No firm end point	Avoid with active bleeding, prior stroke or TIA, age $\geq 75$ years. Do not start if urgent CABG is needed; discontinue 7 days before elective CABG.	
Nitrates <sup>a</sup>	STEMI and NSTEMI with persistent ischemia, hypertension, or control of pulmonary congestion	Variable; titrate to pain relief or SBP: 5–10 mcg/minute titrated to 200 mcg/minute typical regimen. Usually maintain IV therapy for 24–48 hours after infarct.	Titrate to pain relief or SBP >90 mm Hg	Avoid with SBP <90 mm Hg, right ventricular infarction, sildenafil or vardenafil within 24 hours or tadalafil within 48 hours.	Use acetaminophen or narcotics for headache. NTG should be tapered gradually in ischemic heart disease patients. Topical patches or oral nitrates are acceptable alternatives for patients with refractory symptoms

Ticagrelor + Aspirin	STEMI, NSTEMI, Unstable Angina with or without PCI	STEMI, NSTEMI, or Unstable Angina: 180 mg load followed by 90 mg twice daily for at least 1 year; administer 325 mg load of aspirin followed by a maintenance dose of 75–100 mg daily indefinitely.	No firm endpoints	Avoid in patients with severe hepatic impairment or active bleeding. Maintenance doses of aspirin above 100 mg daily can decrease ticagrelor's effectiveness. Discontinue at least 5 days for CABG.	Monitor closely for dyspnea.
Warfarin	STEMI and NSTEMI for left ventricular thrombus or for patients with AF with CHAD2 score $\geq 2$	Variable; titrate to INR 3. Duration usually for several months to indefinitely	INR 2–3 times patient's control value	Usual warfarin problems such as noncompliance, bleeding, diatheses	May be useful in the presence of a left ventricular thrombus to prevent embolism

<sup>a</sup>Indicates specific drug therapies that are known to reduce morbidity or mortality.

<sup>b</sup>For patients given fibrin- and non-fibrin-specific fibrinolytic drugs who are undergoing PCI within 24 hours, 300 mg should be used; for patients given a fibrin-specific fibrinolytic undergoing PCI after >24 hours, 300 to 600 mg should be used; for patients given a non-fibrin-specific fibrinolytic undergoing PCI between 24 and 48 hours, 300 mg should be used; for patients given a non-fibrin-specific fibrinolytic undergoing PCI after 48 hours, 300 to 600 mg should be considered.

<sup>c</sup>Risk factors for cardiogenic shock (the greater the number of risk factors present, the higher the risk of developing cardiogenic shock) are age >70 years, SBP <120 mm Hg, sinus tachycardia >110 beats/minute or HR <60 beats/minute.

ACE, angiotensin-converting enzyme; AF, atrial fibrillation; AMI, acute myocardial infarction; aPTT, activated partial thromboplastin time; ARBs, angiotensin receptor blockers; BMS, bare-metal stent; CABG, coronary artery bypass graft; CHADS2, risk score for atrial fibrillation comprising congestive heart failure, hypertension, age, diabetes, and prior stroke; CKD, chronic kidney disease; CNS, central nervous system; COX-2, cyclo-oxygenase-2; CrCl, creatinine clearance; CV, cardiovascular; DES, drug-eluting stent; DM, diabetes mellitus; ECG, electrocardiogram; EF, ejection fraction; GP IIb/IIIa, glycoprotein IIb/IIIa inhibitor; HF, heart failure; HIT, heparin-induced thrombocytopenia; HR, heart rate; INR, international normalized ratio; IV, intravenously; LMWH, low-molecular-weight heparin; MI, myocardial infarction; NSAIDs, nonsteroidal anti-inflammatory drugs; NSTEMI, non-ST segment elevation myocardial infarction; NTG, nitroglycerin; PCI, percutaneous coronary intervention; PRN, as needed; SBP, systolic blood pressure; SCr, serum creatinine; SQ, subcutaneously; s/s, signs and symptoms; STEMI, ST segment elevation myocardial infarction; TIA, transient ischemic attack; TID, three times a day; TIMI, Thrombolysis in Myocardial Infarction; UHF, unfractionated heparin; VF, ventricular fibrillation; VT, ventricular tachycardia.

TABLE 18.3 Pharmacologic Properties of Approved Thrombolytic Agents

Drug	Enzymatic Efficiency for Clot Lysis	Fibrin Specificity	Potential Antigenicity	TIMI Grade Flow at 90 Minutes (% of Patients)	Average Dose	Dosing Administration	Cost
Streptokinase (Streptase)	High	Minimal	Yes	32	1.5 million units	1-hour IV infusion	Low
Alteplase (Activase)	High	Moderate	No	54	100 mg	15-mg IV bolus, 50 mg for 30 minutes, then 35 mg for 60 minutes <sup>a</sup>	High
Retepase (Retavase)	High	Moderate	No	60	10 + 10 units	10-U IV bolus, 2nd bolus 30 minutes later	High
Tenecteplase (TNK)	High	High	No	63	30–50 mg (based on weight) <sup>b</sup>	Bolus for 5–10 seconds	High

<sup>a</sup>For patients = 65 kg; reduced doses for patients weighing <65 kg.

<sup>b</sup>For patients <60 kg, 30 mg; 60 to 69 kg, 35 mg; 70 to 79 kg, 40 mg; 80 to 89 kg, 45 mg; 90 kg, 50 mg.

IV, intravenous; TIMI, Thrombolysis in Myocardial Infarction.

Source: Kumar A, Cannon CP. Acute coronary syndromes: diagnosis and management, part II. *Mayo Clin Proc.* 2009;84:1021.

TABLE 18.4 Risk Factors Associated with Bleeding Complications Secondary to Thrombolytic Use

<b>Major</b> (thrombolytic agents contraindicated)	<ul style="list-style-type: none"> <li>Intracranial tumor (primary or metastatic)</li> <li>Prior intracranial hemorrhage</li> <li>Recent head or facial trauma within 3 months</li> <li>Suspected aortic dissection</li> <li>Ischemic stroke within 3 months, EXCEPT acute ischemic stroke within 3 hours</li> <li>Active internal bleeding or bleeding diathesis (excluding menses)</li> </ul>
<b>Important</b> (relative contraindication)	<ul style="list-style-type: none"> <li>Uncontrolled hypertension on presentation (SBP &gt;180 mm Hg, DBP &gt;110 mm Hg)</li> <li>Chronic, severe, poorly controlled hypertension</li> <li>Prior ischemic stroke &gt;3 months, dementia, or known intracranial pathology</li> <li>Puncture of a noncompressible vessel</li> <li>Cardiopulmonary resuscitation for &gt;10 minutes</li> <li>Major surgery (&lt;3 weeks)</li> <li>Recent internal bleeding within 24 weeks</li> <li>Active peptic ulcer</li> <li>Current use of anticoagulants (the higher the INR, the greater the risk for bleeding)</li> <li>Pregnancy</li> <li>For streptokinase or anistreplase: prior exposure (&gt;5 days) or prior allergic reaction</li> </ul>

DBP, diastolic blood pressure; INR, international normalized ratio; SBP, systolic blood pressure.

Source: Antman EM et al. ACC/AHA guidelines for the management of patients with ST-elevation myocardial infarction—executive summary. A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to revise the 1999 guidelines for the management of patients with acute myocardial infarction) [published correction appears in *J Am Coll Cardiol.* 2005;45:1376]. *J Am Coll Cardiol.* 2004;44:671.

TABLE 18.5 Dosing of Glycoprotein IIb/IIIa in Acute Coronary Syndromes

Medication	Dosing for STEMI PCI	Dose for NSTEMI with or without PCI	Comments
Abciximab	0.25-mg/kg IV bolus followed by 0.125-mcg/kg/minute infusion (max of 10 mcg/minute), continue for 12 hours at the discretion of the physician	Not recommended	
Eptifibatid	180-mcg/kg IV bolus, then begin 2-mcg/kg/minute infusion followed by second IV bolus of 180 mcg/kg 10 minutes after first bolus, continue infusion for 12–18 hours after PCI at the discretion of the physician	180-mcg/kg IV bolus, then begin 2-mcg/kg/minute infusion, continue infusion for 12–18 hours Repeat bolus dose after 10 minutes for PCI.	Reduce infusion by 50% in patients with CrCl < 50 mL/minute; not studied in patients with SCr > 4.0 mg/dL. Avoid in patients on hemodialysis.
Tirofiban	25-mcg/kg IV bolus followed by an infusion of 0.15 mcg/kg/minute, continue up to 18 hours at the discretion of the physician	0.4-mg/kg IV bolus administered for 30 minutes followed by an infusion of 0.1 mcg/kg/minute for 12–24 hours	Reduce infusion by 50% in patients with CrCl <30 mL/minute

CrCl, creatinine clearance; IV, intravenous; NSTEMI, non-ST segment elevation myocardial infarction; PCI, percutaneous coronary intervention; SCr, serum creatinine; STEMI, ST segment elevation myocardial infarction.

- **Stool Softener Therapy**

- Docusate should be administered to minimize the undesirable effects that straining has on the cardiovascular system.

- **Antiarrhythmic Therapy**

- Lidocaine and amiodarone are the drugs of choice for the treatment of ventricular arrhythmias in the peri-infarction period.

# Heart Failure\*

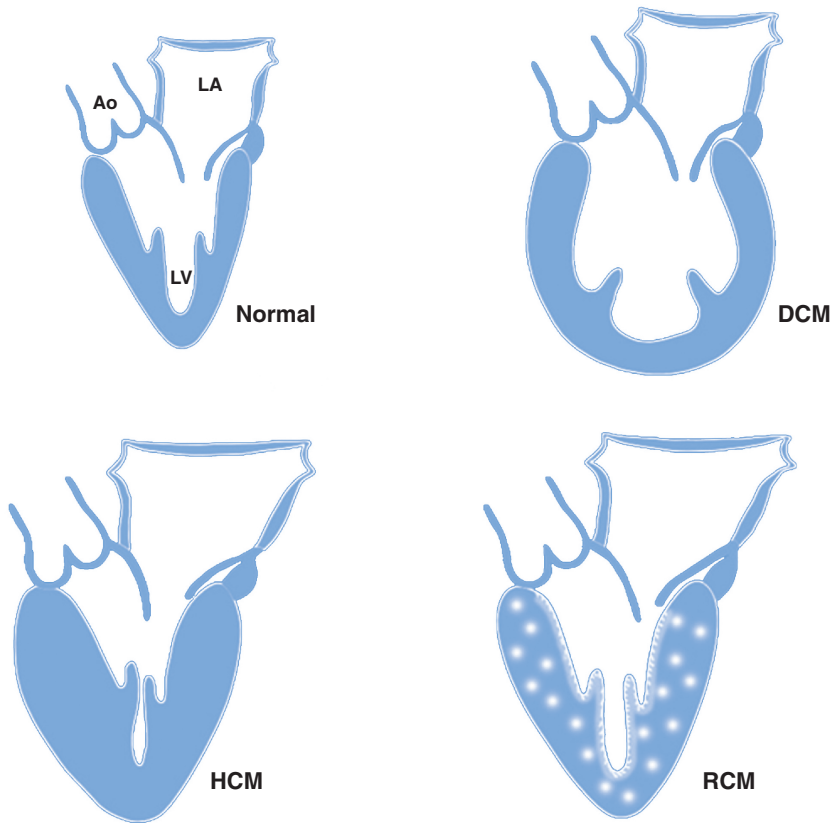
## General Principles

- Heart failure (HF) “is a complex clinical syndrome that can result from any structural or functional cardiac disorder that impairs the ability of the ventricle to fill with or eject blood.” It occurs when the heart fails to pump enough blood to meet the body’s metabolic needs.
- A common factor to all forms of HF is increased cardiac workload. Four major determinants contribute to left ventricular (LV) workload:
  - Preload—forces acting on the venous side of circulation that affect myocardial wall tension
  - Afterload—tension in the ventricular wall as contraction (systole) occurs
  - Contractility—the myocardium’s inherent ability to develop force and shorten its fibers independent of preload and afterload
  - Heart rate (HR)
- **Stroke volume (SV)** is the volume of blood ejected by the heart with each systolic contraction (normal, 4–7 L/minute).
- **Cardiac output (CO)** is the amount of blood pumped in 1 minute ( $CO = SV \times HR$ ).
- **Left ventricular ejection fraction (LVEF)** is the percentage of LV end-diastolic volume expelled during each systolic contraction (normal, 60%–70%).
- **Systolic dysfunction**, also known as low ejection fraction HF, is when the LVEF is <40%.
- Progression of HF results in a process referred to as **cardiac remodeling** (Figure 19.1).

## Classification

- HF can be classified as either low- or high-output failure or diastolic dysfunction (Table 19.1).
  - Low-output HF is further classified into left and right ventricle dysfunction, or a combination of the two.
  - Isolated right-sided ventricular dysfunction is usually caused by pulmonary arterial hypertension (either primary or secondary).
  - LV dysfunction refers to impaired relaxation and increased stiffness of the left ventricle. It is subdivided into systolic and diastolic dysfunction.
  - Ischemic HF is caused by damage to the heart muscle or valves because of chronic coronary ischemia or after myocardial infarction (MI).
  - In HF, there can be reduced LVEF, termed HF<sub>r</sub>EF, or preserved LVEF (HF<sub>p</sub>EF; previously called diastolic dysfunction).
- Congestive heart failure (CHF) is a specific subset of HF characterized by LV systolic dysfunction and volume excess presenting as an enlarged, blood-congested heart (normal, 60–130 mL).
- The American College of Cardiology (ACC) and the American Heart Association (AHA) have a staging algorithm for HF. The New York Heart Association (NYHA) has four categories of functional disability. Classification of HF involves both systems (Figure 19.2).

\*The reader is referred to Chapter 19, Heart Failure, written by Harleen Singh, PharmD, and Joel C. Marrs, PharmD, BCPS (AQ Cardiology), CLS, in the 10th edition of *Applied Therapeutics: The Clinical Use of Drugs* for a more in-depth discussion. All notations to reference numbers are based on the reference list at the end of that chapter. The editor of this handbook expresses her thanks to Drs. Singh and Marrs and acknowledges that this chapter is based on their work.



**Figure 19.1** Cardiac remodeling. Dilated cardiomyopathy (DCM) results in thinning of the left ventricular walls and a decrease in systolic function; in hypertrophic cardiomyopathy (HCM), there is a marked thickening of the left ventricular walls leading to diastolic or systolic failure; and in restrictive cardiomyopathy (RCM), the left ventricular walls may be normal, hypertrophic, or slightly dilated, resulting in a decrease in diastolic compliance. (Adapted with permission from Topol EJ et al, eds. *Textbook of Cardiovascular Medicine*. 3rd ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2006.)

## Patient Assessment

- The symptoms of HF can be divided into those that primarily reflect LV failure and those that denote right ventricular (RV) failure (Table 19.2).
- Coexisting medical conditions that lead to HF include ischemic heart disease, hypertension, atrial fibrillation, diabetes mellitus, and sleep apnea.
- Medical conditions that result from HF include atrial fibrillation, cachexia, and depression.

## Risk Factors

- Risk factors include advanced age, coronary artery disease, diabetes, chronic kidney disease, hypertension, MI, cardiomyopathy, obesity, smoking, excessive alcohol intake, dyslipidemia, and anemia. African Americans may present with HF at a younger age than do Caucasians.
- Several categories of medications may precipitate HF symptoms in patients with previously compensated HF (Table 19.3). Drug-induced HF is mediated by three mechanisms: inhibition of myocardial contractility, proarrhythmic effects, or expansion of plasma volume. Nonsteroidal anti-inflammatory drugs (NSAIDs) should be avoided in patients with HF.

TABLE 19.1 Classification and Etiology of Left Ventricular Dysfunction

Type of Failure	Characteristics	Contributing Factors	Etiology
Low output, systolic dysfunction (dilated cardiomyopathy) <sup>a</sup>	Hypofunctioning left ventricle; enlarged heart (dilated left ventricle); ↑left ventricular end-diastolic volume; EF < 40%; ↓stroke volume; ↓CO; S <sub>3</sub> heart sound present	<ol style="list-style-type: none"> <li>1. ↓Contractility (cardiomyopathy)</li> <li>2. ↑Afterload (elevated SVR)</li> </ol>	<ol style="list-style-type: none"> <li>1. Coronary ischemia,<sup>b</sup> MI, mitral valve stenosis or regurgitation, alcoholism, viral syndromes, nutritional deficiency, calcium and potassium depletion, drug induced, idiopathic</li> <li>2. Hypertension, aortic stenosis, volume overload</li> </ol>
Diastolic dysfunction	Normal left ventricular contractility; normal-sized heart; stiff left ventricle; impaired left ventricular relaxation; impaired left ventricular filling; normal EF; S <sub>4</sub> heart sound	<ol style="list-style-type: none"> <li>1. Thickened left ventricle (hypertrophic cardiomyopathy)</li> <li>2. Stiff left ventricle (restrictive cardiomyopathy)</li> <li>3. ↑Preload</li> </ol>	<ol style="list-style-type: none"> <li>1. Coronary ischemia,<sup>b</sup> MI hypertension, aortic stenosis and regurgitation, pericarditis, enlarged left ventricular septum (hypertrophic cardiomyopathy)</li> <li>2. Amyloidosis, sarcoidosis</li> <li>3. Sodium and water retention</li> </ol>
High-output failure (uncommon)	Normal or ↑contractility; normal-sized heart; normal left ventricular end-diastolic volume; normal or ↑EF; normal or increased stroke volume; ↑CO	↑Metabolic and oxygen demands	Anemia and hyperthyroidism

<sup>a</sup>Same as congestive heart failure if symptoms also present.

<sup>b</sup>Heart failure caused by coronary artery ischemia or myocardial infarction classified as ischemic etiology. All other types combined classified as nonischemic.

CO, cardiac output; EF, ejection fraction; MI, myocardial infarction; SVR, systemic vascular resistance.

TABLE 19.2 Signs and Symptoms of Heart Failure

	Left Ventricular Failure	Right Ventricular Failure <sup>a</sup>
<i>Subjective</i>	DOE SOB Orthopnea (two to three pillows) PND, cough Weakness, fatigue, confusion Weakness, fatigue	Peripheral edema
<i>Objective</i>	LVH ↓BP EF < 40% <sup>b</sup> Rales, S <sub>3</sub> gallop rhythm Reflex tachycardia ↑BUN (poor renal perfusion)	Weight gain (fluid retention) Neck vein distension Hepatomegaly Hepatojugular reflux

<sup>a</sup>Isolated right-sided failure occurs with long-standing pulmonary disease (cor pulmonale) or after pulmonary hypertension.

<sup>b</sup>Ejection fraction normal in patients with diastolic dysfunction.

BP, blood pressure; BUN, blood urea nitrogen; DOE, dyspnea on exertion; EF, ejection fraction; LVH, left ventricular hypertrophy; PND, paroxysmal nocturnal dyspnea; SOB, shortness of breath.

## Goals of Therapy

- Treatment goals are to improve/abolish symptoms, decrease hospitalizations, avoid complications (e.g., arrhythmias), improve quality of life, and prolong survival. There is no cure for HF.
- In acute decompensated HF prompt recognition of symptoms and appropriate treatment are critical.

TABLE 19.3 Drugs That May Induce Heart Failure

NEGATIVE INOTROPIC AGENTS	
$\beta$ -Blockers <sup>a</sup>	Most evident with propranolol or other nonselective agents Less with agents with intrinsic sympathomimetic activity (acebutolol, carteolol, pindolol); can also be caused by use of timolol eye drops
Calcium-channel blockers <sup>a</sup>	Verapamil has the most negative inotropic and AV-blocking effects; amlodipine has the least
Antiarrhythmics	Most with disopyramide; also quinidine Least with amiodarone
DIRECT CARDIOTOXINS	
Cocaine, amphetamines	Overdoses and long-term myopathy
Anthracycline cancer chemotherapeutic drugs	Daunorubicin and doxorubicin (Adriamycin); dose related; keep total cumulative dose <600 mg/m <sup>2</sup>
PROARRHYTHMIC EFFECTS	
Class IA, Class III antiarrhythmic drugs	QT interval widening Probable torsades de pointes HF develops if disturbed rhythm compromises cardiac functioning
Nonantiarrhythmic drugs (see Crouch et al. <sup>93</sup> for a complete list)	Same mechanism as above Often associated with drug interactions that inhibit metabolism of the offending drug, leading to higher-than-desired plasma levels
EXPANSION OF PLASMA VOLUME	
Antidiabetics	Metformin high dose may increase risk of lactic acidosis Na retention with pioglitazone (Actos) and rosiglitazone (Avandia)
NSAID	Prostaglandin inhibition; Na retention
Glucocorticoids, androgens, estrogens	Mineralocorticoid effect; Na retention
Licorice	Aldosteronelike effect; Na retention
Antihypertensive vasodilators (hydralazine, methyldopa, prazosin, minoxidil)	↓Renal blood flow, activation of renin–angiotensin system
Drugs high in Na <sup>+</sup>	Selected IV cephalosporins and penicillins Effervescent or bicarbonate-containing antacids or analgesics Also liquid nutrition supplements
UNKNOWN MECHANISM	
Tumor necrosis factor antagonists	Multiple case reports of new-onset HF or exacerbation of prior HF with etanercept and infliximab in patients with Crohn's disease or rheumatoid arthritis

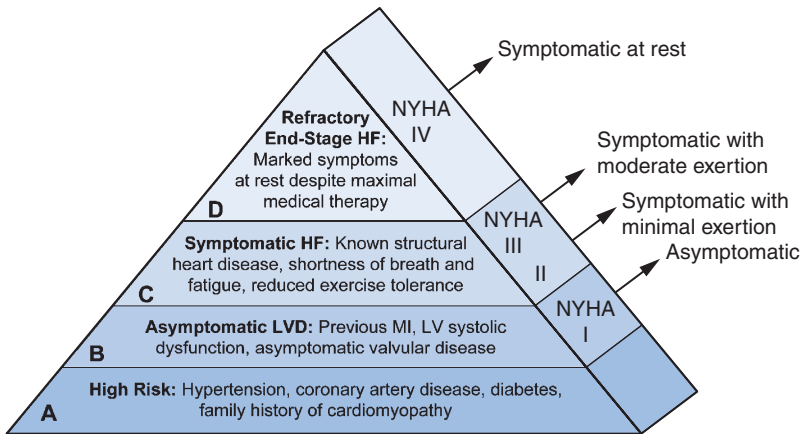
<sup>a</sup> $\beta$ -Blockers and verapamil may be beneficial in diastolic HF. Carvedilol and metoprolol counteract autonomic hyperactivity in systolic dysfunction.

AV, atrioventricular; HF, heart failure; IV, intravenous; Na, sodium; NSAID, nonsteroidal anti-inflammatory drugs.

## Treatment

- Appropriate therapeutic interventions in the early stages (stages A and B) can prevent progression to overt HF symptoms.
- Nonspecific medical management includes addressing CV risk factors, correcting underlying disease states, performing moderate physical activity, maintaining a low sodium diet (limited to 2.5–5 g NaCl/day), undergoing immunization with influenza and pneumococcal vaccines, and discontinuing any possible drug-induced causes (Table 19.3).
- National guidelines from the ACC/AHA serve as the primary basis for therapy. A clinical algorithm is shown in Figure 19.3.
- Guidelines state that most patients with HF should routinely be managed with a combination of the four classes of drugs: an angiotensin-converting enzyme (ACE) inhibitor





**Figure 19.2** Staging and New York Heart Association (NYHA) classification of heart failure. (Hunt SA et al. ACC/AHA Guidelines for the evaluation and management of chronic heart failure in the adult: executive summary. A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines [Committee to Revise the 1995 Guidelines for the Evaluation and Management of Heart Failure]: developed in collaboration with the International Society for Heart and Lung Transplantation; endorsed by the Heart Failure Society of America. *Circulation*. 2001;104:2996.)

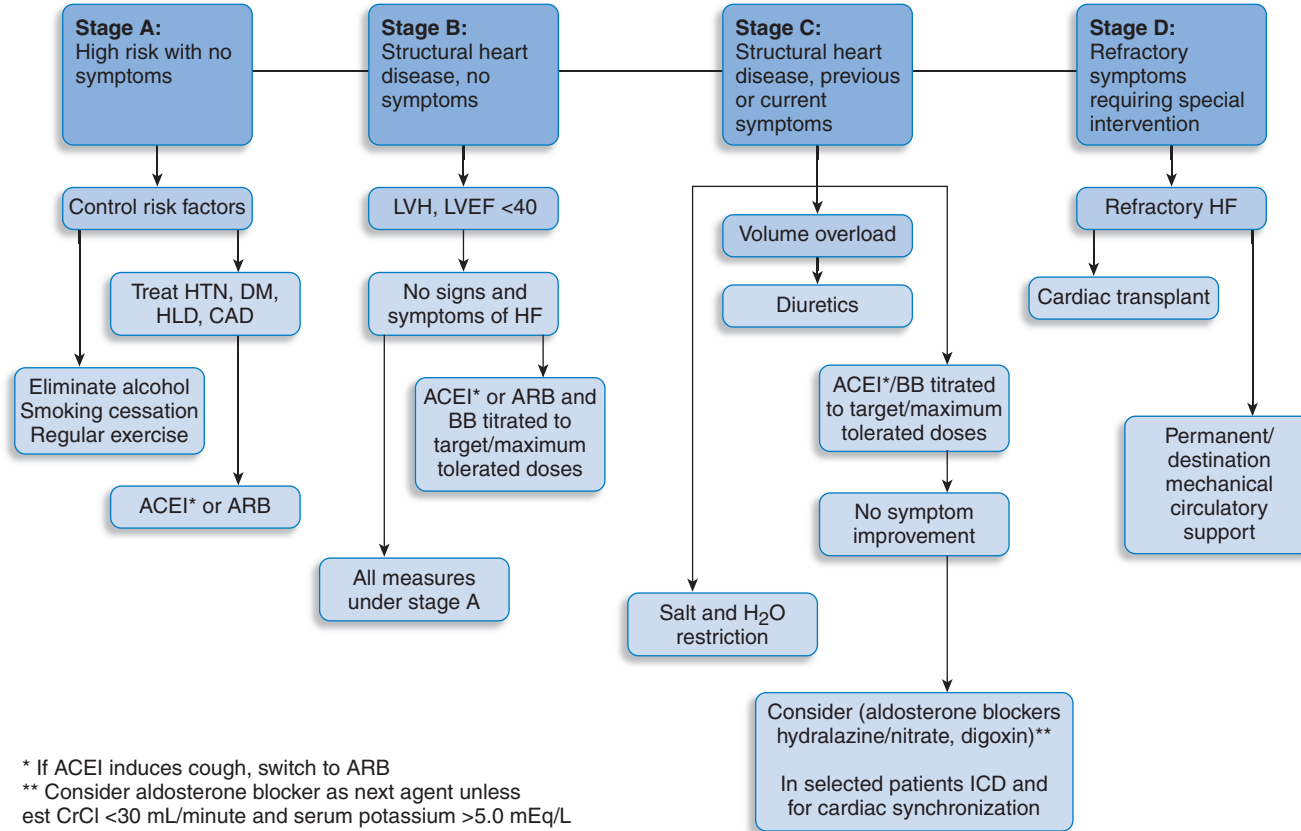
(or angiotensin receptor blockers [ARBs]), a  $\beta$ -blocker, diuretics, and aldosterone antagonists. A combination of hydralazine/isosorbide dinitrate can be used in the treatment of African Americans while digoxin can be added to patients who remain symptomatic, despite use of the agents above.

- Mechanical therapies include:
  - **Implantable cardioverter-defibrillator (ICD)** for primary prevention of sudden cardiac death in patients with nonischemic dilated cardiomyopathy, ischemic heart disease at least 40 days after MI, or after MI in patients with reduced LVEF.
  - **Cardiac resynchronization therapy (CRT)** in patients with advanced HF with LVEF <35%, presence of electric asynchrony as shown by QRS interval of  $\geq 120$  milliseconds, and receiving optimal HF medical treatment.
  - **Left ventricular assist device (LVAD)**, a mechanical pump that is surgically implanted to maintain the pumping ability of the heart, for use as a bridge to transplant or in those who do not qualify for transplant.
- Guidelines do not recommend routine use of natural supplements for HF. Hawthorn and coenzyme Q both appear to be safe and offer some symptomatic improvement, especially in patients with mild HF. Only coenzyme Q has been shown to be of benefit as an adjunct to conventional therapies.

## Drug Therapy

- **Diuretics** are indicated in HF patients with congestion (pulmonary and peripheral edema) or cardiac distension (enlarged heart). They produce symptom relief more rapidly than do other HF drugs. Diuretics should be combined with an ACE inhibitor, a  $\beta$ -blocker, and an aldosterone antagonist unless contraindications exist; they should not be used as monotherapy. The goal of diuretic therapy is to provide symptom relief by decreasing excess volume without causing intravascular depletion. Guidelines recommend diuretics, both acutely and chronically, if clinical volume overload is evident.

### Management of Heart Failure



**Figure 19.3** Stages in the development of heart failure and recommended therapy by stage. ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BB,  $\beta$ -blocker; CAD, coronary artery disease; CrCl, creatinine clearance; DM, diabetes mellitus; EF, ejection fraction; HLD, hyperlipidemia; HTN, hypertension; ICD, implantable cardioverter-defibrillator; LVH, left ventricular hypertrophy.

- Loop diuretics are preferred in most patients (see dosing in Table 19.4). Increasing single doses beyond the ceiling dose produces no additional benefit. Furosemide is the most commonly used loop diuretic because of data supporting its use (20–40 mg/dose, IV or oral). Bumetanide and torsemide have more predictable absorption. Ethacrynic acid is not preferred due to ototoxicity.
- Combinations of loop diuretics with metolazone (5–10 mg) or a thiazide is useful in patients who are refractory to high-dose loop diuretic therapy. The combination allows for drugs that work on different parts of the tubule, so there is an additive diuretic effect.
- Monitoring parameters for patients receiving diuretics are shown in Table 19.5.
- Potassium supplementation or potassium-sparing diuretics are not needed unless serum potassium is <3.5 mEq/L. The average potassium replacement dose is 20 to 60 mEq/day.
- **ACE inhibitors and ARBs** have both preload- and afterload-reducing properties and volume-reducing potential.
  - ACE inhibitors are the drugs of choice for initial therapy, even in patients with relatively mild LV dysfunction. Guidelines recommend ACE inhibitors as first-line therapy in all patients with HF caused by LV systolic dysfunction (LVSD) unless they have a contraindication to their use or are unable to tolerate them.
  - ACE inhibitors are typically used in combination with  $\beta$ -blockers.
  - Dosing of ACE inhibitors is shown in Table 19.6; therapy should be initiated at low doses. There is not a compelling reason to favor one agent over another.

TABLE 19.4 Loop Diuretic Dosing

	Furosemide	Bumetanide	Torsemide
IV loading doses	40 mg	1 mg	20 mg
Maximum total daily dose	600 mg	10 mg	200 mg
Ceiling dose			
Normal renal function	80–160 mg (PO/IV)	1–2 mg (PO/IV)	20–40 mg (PO/IV)
Cl <sub>cr</sub> : 20–50 mL/minute	160 mg (PO/IV)	2 mg (PO/IV)	40 mg (PO/IV)
Cl <sub>cr</sub> : <20 mL/minute	200 mg (IV), 400 mg (PO)	8–10 mg (PO/IV)	100 mg (PO/IV)
Bioavailability	10%–100%	80%–90%	80%–100%
Duration of action	6–8 hours	4–6 hours	12–16 hours

Cl<sub>cr</sub>, creatinine clearance; IV, intravenous; PO, oral.

TABLE 19.5 Monitoring Parameters with Diuretics

↓CHF Symptoms (see Table 19.2)

Weight loss or gain; goal is 1- to 2-pound weight loss/day until “ideal weight” achieved<sup>d</sup>

Signs of volume depletion

Weakness

Hypotension, dizziness

Orthostatic changes in BP<sup>b</sup>

↓Urine output

↑BUN<sup>c</sup>

Serum potassium and magnesium (avoid hypokalemia and hypomagnesemia)

↑Uric acid

↑Glucose

<sup>a</sup>Weight loss may be greater during first few days when significant edema is present.

<sup>b</sup>A ↓ in systolic BP of 10 to 15 mm Hg or a ↓ in diastolic BP of 5 to 10 mm Hg.

<sup>c</sup>A rising BUN can be caused by either volume depletion from diuretics or poor renal blood flow from poorly controlled HF.

Small boluses of 0.9% saline can be given cautiously to differentiate a rising BUN from volume depletion versus poor cardiac output. If volume depletion is present, saline will cause an ↑ in urine output and a ↓ in BUN. However, if the patient has severe HF, the saline could cause pulmonary edema.

BP, blood pressure; BUN, blood urea nitrogen; HF, heart failure.

TABLE 19.6 ACE Inhibitor Dosing in Systolic Dysfunction<sup>a</sup>

Drug	Available Dosage Form	Initial Dose <sup>b</sup>	Maximal Dose
Captopril <sup>c</sup>	12.5, 25, 50, 100 mg tablets	6.25–12.5 mg TID	100 mg TID
Enalapril <sup>d</sup>	2.5, 5, 10, 20 mg tablets	2.5–5 mg every day	20 mg BID
Fosinopril	10, 20, 40 mg tablets	5–10 mg every day	40 mg every day
Lisinopril	2.5, 5, 10, 20, 40 mg tablets	2.5–5 mg every day	40 mg every day
Quinapril <sup>d</sup>	5, 10, 20, 40 mg tablets	5–10 mg every day	20 mg BID
Perindopril	2, 4, 8 mg tablets	2 mg every day	16 mg every day
Ramipril <sup>d</sup>	1.25, 2.5, 5, 10 mg capsules	1.25–2.5 mg every day	10 mg BID
Trandolapril	1, 2, 4 mg tablets	1 mg every day	8 mg every day

<sup>a</sup>Benazepril, cilazapril, moexipril, perindopril, ramipril, trandolapril not labeled for use in heart failure.

<sup>b</sup>Start with the lowest dose to avoid bradycardia, hypotension, or renal dysfunction. All but captopril given every day in the morning at starting doses. Increase dose slowly at 2- to 4-week intervals to assess full effect and tolerance.

<sup>c</sup>Captopril is short acting. Start with a 6.25- or 12.5-mg test dose, then 6.25 to 12.5 mg TID.

<sup>d</sup>Enalapril, quinapril, ramipril could possibly be given every day instead of BID on the basis of half-life.

ACE, angiotensin-converting enzyme; BID, twice a day; TID, three times a day.

- Adverse effects include hypotension, hyperkalemia, cough, and angioedema. Guidelines recommend continuing ACE therapy if the cough is not severe. Angioedema is a potentially life-threatening complication of ACE inhibitor treatment. ACE inhibitors are contraindicated in pregnancy.
- ARBs should be used in ACE-intolerant patients or as add-on therapy to ACE inhibitors and  $\beta$ -blockers. Patients should not use the combination of an ACE inhibitor and aldosterone antagonist. ARBs should be used cautiously in patients who have angioedema from ACE inhibitors.
- **$\beta$ -Adrenergic blocking agents** are considered first-line agents, in combination with ACE inhibitors, in patients with HF and LVSD. Guidelines recommend bisoprolol, metoprolol succinate, or carvedilol for all patients with stable HF caused by LVSD. Therapy should be initiated at low doses, with gradual tapering over 1 to 2 weeks, as tolerated. Abrupt withdrawal of  $\beta$ -blocker therapy can lead to clinical deterioration and should be avoided. There is no consensus regarding the relative superiority of one agent over another.
  - Two dosage forms of metoprolol are marketed: metoprolol succinate (extended release) and metoprolol tartrate (immediate release). Both formulations have been used although only the succinate salt is Food and Drug Administration (FDA) labeled for HF. It may take 2 to 3 months of therapy to see a beneficial response with metoprolol.
  - Carvedilol is a mixed  $\alpha$ - and  $\beta$ -blocking agent. It is metabolized by the CYP2D6 system, so potential drug interactions should be considered.
- **Aldosterone antagonists** (eplerenone and spironolactone) have a mild diuretic effect. Guidelines recommend addition of an aldosterone antagonist in patients with HF and LVEF <35%, unless contraindicated. Spironolactone (25–50 mg daily) is most commonly used. Hyperkalemia is more prevalent when aldosterone antagonists are used in the elderly, those with renal dysfunction, or in combination with ACE inhibitor therapy.
- **Hydralazine and isosorbide dinitrate** should be used in African American patients added to ACE inhibitors and  $\beta$ -blockers. They have complimentary effects when used in combination and are particularly effective in reducing pulmonary edema.
  - Hydralazine is a potent arterial dilating agent that provides symptomatic relief of HF by decreasing afterload. The average maintenance dose is 200 to 400 mg daily (50–100 mg every 6 hours).
  - Nitrates (nitroglycerin, isosorbide dinitrate, isosorbide mononitrate) have venous dilating properties that decrease preload. Nitrate monotherapy is used in patients with valvular

TABLE 19.7 Digoxin Drug Interactions<sup>a</sup>

Drug	Effect
<b>DRUGS LOWERING SERUM DIGOXIN CONCENTRATION</b>	
Rifampin <sup>257</sup>	Probable induction of intestinal P-glycoprotein causing ↓bioavailability. ↓Serum concentration after oral, but not IV digoxin. No change in digoxin renal clearance or half-life.
St. John's wort <sup>258</sup>	Possible induction of P-glycoprotein (33% reduction in digoxin trough concentrations). <sup>259</sup>
Sulfasalazine doses > 2 g/day	Malabsorption of digoxin (decrease AUC of digoxin by 24%). <sup>259</sup>
<b>DRUGS RAISING SERUM DIGOXIN CONCENTRATION</b>	
Amiodarone <sup>243,253</sup>	↑Serum digoxin levels by inhibit intestinal P-glycoprotein (70% in 1 day). <sup>259</sup>
Atorvastatin <sup>260</sup>	20% increase in serum digoxin concentration with 80-mg dose, minimal effect with 20-mg dose. Speculated to inhibit intestinal P-glycoprotein, but not proven.
Calcium-channel blockers <sup>243,253,261</sup>	Inhibition of P-glycoprotein. Best documented with verapamil (70%–80%). <sup>262</sup> Diltiazem increases digoxin concentrations by 50% in some patients. <sup>259</sup>
Clarithromycin <sup>263</sup>	Inhibition of P-glycoprotein, decreased digoxin renal clearance. Digoxin clearance may be reduced by 60%, and plasma concentrations may increase by twofold. <sup>259</sup>
Cyclosporine <sup>243,253</sup>	Inhibition of P-glycoprotein, decreased digoxin renal clearance.
Erythromycin	↑Bioavailability in persons who normally metabolize digoxin in intestinal tract. May also inhibit P-glycoprotein in gut. Digoxin concentrations may increase by 100% in some cases. <sup>259</sup>
Itraconazole <sup>265</sup>	↑Serum digoxin levels by unknown mechanism. In one study, the AUC for digoxin was increased by 50% and renal elimination was decreased by 20%. <sup>259</sup>
Propafenone <sup>243,266</sup>	Inhibition of P-glycoprotein. Increases digoxin concentrations by 30%–60%. <sup>259</sup>
Quinidine <sup>243,253,254,256,267–271</sup> (usually doses above 500 mg/day may increase digoxin serum concentrations)	Inhibition of P-glycoprotein; decreased digoxin renal clearance and increased bioavailability. Increases 25%–100% digoxin concentrations. <sup>259</sup>

<sup>a</sup>References<sup>243,253,255</sup> include a discussion of many of these interactions that do not include a specific reference citation. AUC, area under curve; IV, intravenous.

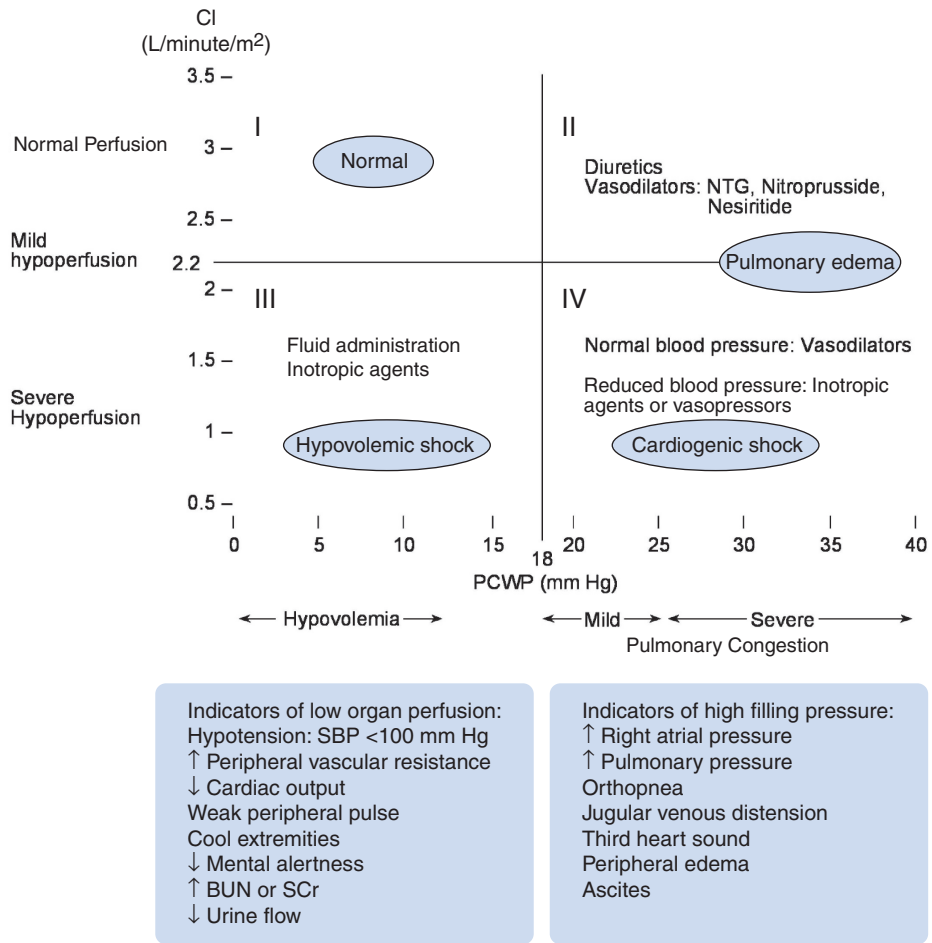
defects and in patients with signs and symptoms of isolated pulmonary and venous congestion. IV nitrates are used for patients with acute decompensated HF.

- **Digoxin** decreases conduction velocity, prolongs the refractory period of the atrioventricular (AV) node, and has effects on contractility. Guidelines recommend its use in symptomatic patients with Stage C or D HF to reduce HF-related hospitalizations. Published data do not demonstrate a beneficial effect on survival, so its use is not recommended in patients with Stage A or B disease. Digoxin is typically dosed at 0.125 mg daily with target therapeutic levels of 1 ng/mL. Older recommendations for higher target levels are no longer valid and should be abandoned. Common signs of digoxin toxicity include hyperkalemia, vague gastrointestinal symptoms, central nervous system (CNS) symptoms, and ventricular arrhythmias. Frequently noncardiac symptoms are the only manifestation of toxicity. Drug interactions with digoxin are shown in Table 19.7.
- **Other inotropic agents**, such as dopamine and dobutamine, are commonly used in decompensated HF. Their use is limited by the need for IV administration.

- **Calcium-channel blockers (CCBs)**—Only amlodipine and felodipine have been documented to be safe in HF. Until more data are available, use of other CCBs is contraindicated in patients with HF due to their negative inotropic effects.
- **Tolvaptan**—Use should be restricted to patients who present with hypervolemic hyponatremia associated with severe HF despite fluid restriction and diuretic use.
- **Antiarrhythmic agents**—Supraventricular arrhythmias are frequently encountered in HF. Drug therapy for arrhythmias should be aimed at controlling ventricular rate and preventing thromboembolic events. Guidelines do not recommend routine ambulatory monitoring for asymptomatic arrhythmias in HF, and they recommend against treatment if arrhythmias are inadvertently detected.
  - Digoxin,  $\beta$ -blockers, and amiodarone are reasonable choices. Amiodarone has both antiarrhythmic properties and coronary vasodilating effects, which make it a good choice.
  - Use of most antiarrhythmic agents (quinidine, procainamide, propafenone, and other class III antiarrhythmics), except amiodarone and dofetilide, are associated with worse prognosis and should be avoided in patients with HF.
- **Anticoagulant agents**—Guidelines do not support routine use of anticoagulants in HF unless the patient has concomitant A-fib or evidence of an active thrombus.

## Management of Acute HF

- The most common reasons for HF hospitalization include noncompliance, MI, uncontrolled comorbidities, and inappropriate prescribing. In-hospital mortality for acute HF is as high as 20%. Postdischarge mortality is 11% at 30 days and 37% at 1 year.
- Most patients with acute HF can be classified into one of four hemodynamic profiles (Figure 19.4).
  - The primary goal of therapy in subset II (wet and warm) is to relieve congestion.
  - Diuretics should be used cautiously in subset IV.
- **Intravenous vasodilators**—Guidelines recommend use of vasodilators in conjunction with diuretics to reduce congestion in patients with fluid overload. In the presence of asymptomatic hypotension IV nitroglycerin, nitroprusside, or nesiritide may be considered cautiously.
  - Nitroprusside dilates both arterial and venous vessels. It is potentially of value in severely congested patients with hypertension or severe mitral valve regurgitation. Its major disadvantage is hypotension.
  - Nitroglycerin IV primarily dilates the venous system. Patients with acute MI and pulmonary edema are often the best candidates for therapy.
  - Nesiritide is a B-type natriuretic peptide that is generally reserved for patients with acute HF exacerbations who have fluid overload and a high pulmonary-capillary wedge pressure despite high doses of diuretics and IV nitroglycerin. It should be avoided in patients with a systolic blood pressure < 90 to 100 mm Hg.
- **Inotropic agents**—IV inotropic agents (dobutamine, dopamine, milrinone) are indicated in symptomatic patients with reduced LVEF, low CO, or end-organ dysfunction. Dobutamine may be the drug of choice in patients with low-output HF. Concomitant use of  $\beta$ -blockers may antagonize the action of dobutamine. Milrinone is used for short-term parenteral treatment of severe congestive failure.



**Figure 19.4** Hemodynamic profile of acute heart failure. BUN, blood area nitrogen; CI, cardiac index; NTG, nitroglycerin; PCWP, pulmonary-capillary wedge pressure; SBP, systolic blood pressure; SCr, serum creatinine. (Adapted with permission from Forrester JS et al. Correlative classification of clinical and hemodynamic function after acute myocardial infarction. *Am J Cardiol.* 1977;39:137.)

# Cardiac Arrhythmias\*

## General Principles

- Adequate blood pumping depends on continuous, well-coordinated electrical activity within the heart.
- Normal cardiac electrical activity begins with automatic impulse generation (automaticity) at the sinoatrial (SA) node and then normal impulse conduction through the heart. The cardiac conduction system is shown in Figure 20.1. Pacemaker cells are located in the SA and atrioventricular (AV) nodes and the His–Purkinje system.
- The action potential has five phases: phases 0 to 4. The P wave represents depolarization of the atria. The QRS complex reflects ventricular depolarization. The T wave reflects repolarization of the ventricles. The action potential duration is the length of time from phase 0 to the end of phase 3. The effective refractory period is the length of time that the cell is refractory and will not propagate another impulse.
- The most common abnormal conduction leading to arrhythmias is reentry. Another form of abnormal impulse occurs when the normal conducting pathway is blocked and the impulse is forced to travel through nonpathway tissues to cause depolarization.

## Classification of Arrhythmias

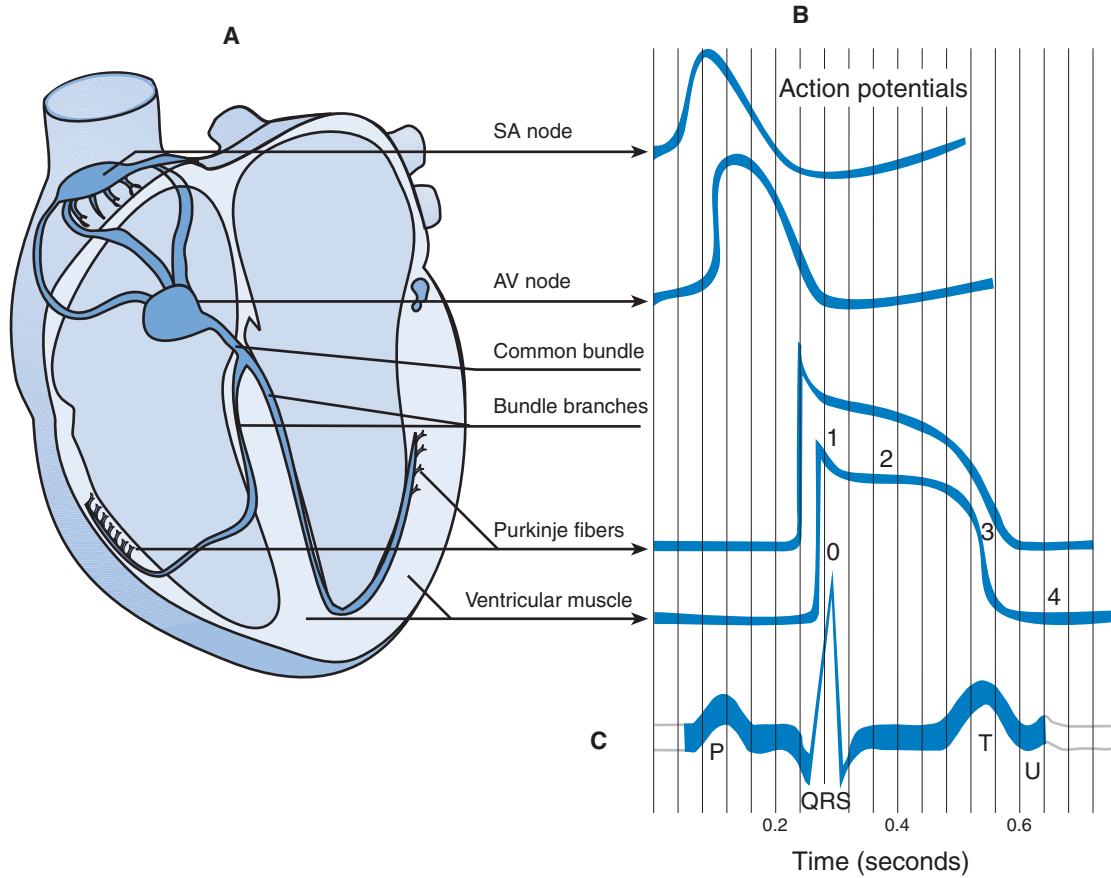
- **Supraventricular Arrhythmias:** all arrhythmias above the bundle of His and are all characterized by a normal QRS complex. They include sinus bradycardia, sinus tachycardia, paroxysmal supraventricular tachycardia (PSVT), atrial flutter, atrial fibrillation (AF), Wolff–Parkinson–White (WPW) syndrome, and premature atrial contractions (PAC).
  - **AF** is usually initiated when an impulse occurs from an ectopic focus or reentrant circuit. AF is commonly associated with, or a manifestation of, other conditions (Table 20.1).
  - **PSVT** is caused by reentry within the AV node.
- **Ventricular Arrhythmias:** all arrhythmias originating below the bundle of His. They include premature ventricular contractions (PVC), ventricular tachycardia (VT), and ventricular fibrillation (VF). Conduction blocks can be categorized by:
  - Level or location (e.g., first-, second-, third-degree block) or in the ventricle (right or left bundle branch block)
  - Rate—either bradyarrhythmia (<60 beats/minute) or tachyarrhythmia (>100 beats/minute).

## Patient Assessment

- **AF.** Chest palpitations, lightheadedness, dizziness, and reduced exercise tolerance are the most common symptoms. Stroke is one of the most severe complications.
- **PSVT:** tachycardia (180–200 beats/minute), nervousness, anxiety. May progress to angina, heart failure (HF), or shock, depending on underlying conditions.

\*The reader is referred to Chapter 20, Cardiac Arrhythmias, written by C. Michael White, PharmD, FCP, FCCP, Jessica C. Song, MA, PharmD, and James S. Kalus, PharmD, BCPS, in the 10th edition of *Applied Therapeutics: The Clinical Use of Drugs* for a more in-depth discussion. All notations to reference numbers are based on the reference list at the end of that chapter. The editor of this handbook expresses her thanks to Drs. White, Song, and Kalus and acknowledges that this chapter is based on their work.





**Figure 20.1** The cardiac conduction system. **A:** Cardiac conduction system anatomy. **B:** Action potentials of specific cardiac cells.

**C:** Relationship of surface electrocardiogram to the action potential. SA, sinoatrial; AV, atrioventricular.

TABLE 20.1 Causes of Atrial Fibrillation and Flutter

Alcohol	Nonrheumatic heart disease
Atrial septal defect	Pericarditis
Cardiac surgery	Pneumonia
Cardiomyopathy	Pulmonary embolism
Cerebrovascular accident	Sick sinus syndrome
Chronic obstructive pulmonary disease	Stimulants
Fever	Thyrotoxicosis
Hypothermia	Trauma
Ischemic heart disease	Tumors
Mitral valve disease	Wolff–Parkinson–White syndrome

- **Conduction Blocks:** First-degree AV block is usually asymptomatic. The electrocardiogram (ECG) in second-degree block shows progressive lengthening of the P–R interval with each beat until an impulse is not conducted. In third-degree block, none of the impulses from the SA node reaches the ventricles.
- **Torsades de Pointes** (TdP) is a rapid polymorphic VT preceded by QTc interval prolongation that can degenerate into VF, making it potentially life threatening.

## Risk Factors

- Causes of abnormal automaticity include hypoxia, ischemia, or excess catecholamine activity.
- Bundle branch blocks, particularly in the left fascicle, are associated with coronary artery disease, systemic hypertension, aortic valve stenosis, and cardiomyopathy.
- Common factors that cause ventricular arrhythmias are ischemia, organic heart disease, exercise, metabolic or electrolyte imbalance, or medications.
- Hypokalemia, hypomagnesemia, hypocalcemia, concurrent use of >1 QT-prolonging drug, advanced age, female gender, heart disease, treatment with diuretics, impaired hepatic drug metabolism, and bradycardia are risk factors for TdP in hospitalized patients. Class Ia and III agents have been shown to induce TdP. Amiodarone and Class Ic agents are least likely to induce TdP. Nonantiarrhythmic agents can also prolong the QT interval and cause TdP (Table 20.2).

## Goals of Therapy

- **Atrial Fibrillation/Flutter:** control ventricular rate (resting heart rate between 60 and 80 beats/minute) and reduce the risk of stroke

## Treatment

- There are four Vaughn–Williams antiarrhythmic drug classes (Table 20.3).
  - Class I: sodium-channel blockers (further broken down into Ia, Ib, Ic on the basis of duration of channel blockade)
  - Class II:  $\beta$ -adrenergic blockers
  - Class III: potassium-channel blockers
  - Class IV: calcium-channel blockers (CCBs)
- Class Ia and III agents increase repolarization time, the QTc interval, and have the risk of TdP.
- Class II and IV agents can decrease heart rate, decrease the force of ventricular contractility, and prolong the PR interval.
- Class Ib agents work only in ventricular tissue.
- Class Ic agents should never be used after myocardial infarction (MI) or with HF or severe left ventricle hypertrophy.
- Class III agents prolong refractoriness in the atria, ventricles, and AV node.

**TABLE 20.2 Nonantiarrhythmic Agents Implicated in QTc Interval Prolongation or Torsades de Pointes<sup>a</sup>**

Drug Class	Agent	Drugs That Increase Blood Concentrations of These QTc Interval–Prolonging Drugs
Antianginal	Ranolazine	CYP3A4 inhibitors
Antibiotics: macrolides	Erythromycin (lactobionate and base)	CYP3A4 inhibitors
Antibiotics: fluoroquinolones	Gatifloxacin, grepafloxacin, lomefloxacin, moxifloxacin, sparfloxacin	
Antibiotics: other	Trimethoprim-sulfamethoxazole, pentamidine isethionate	
Antidepressants	Tricyclics, maprotiline	CYP1A2, 2D6, or 2C9 inhibitors
Antiemetics	Dolasetron	
Antimalarials	Mefloquine, quinine	Sodium bicarbonate, acetazolamide, cimetidine
Antipsychotics	Atypicals, butyrophenones, typicals	CYP1A2, 2D6, 2C9, 3A4 inhibitors
Calcium-channel blockers	Bepridil	
Dopaminergics	Amantadine	Hydrochlorothiazide, quinidine, quinine, trimethoprim-sulfamethoxazole
Narcotics	Methadone	CYP3A4 and 1A2 inhibitors
Sympathomimetics	Albuterol, ephedra, epinephrine, metaproterenol, terbutaline, salmeterol	Monoamine oxidase inhibitors
Other	Arsenic, organophosphates	

<sup>a</sup>An up-to-date list can be found at <http://www.azcert.org>

- Agents used to control ventricular rate in supraventricular tachycardias are shown in Table 20.4.
- **AF**
  - Digoxin,  $\beta$ -blockers, and nondihydropyridine CCBs are appropriate rate-controlling medications. Digoxin is usually adjunctive therapy.
  - Antiarrhythmic drugs are recommended in patients with symptoms but are not needed in asymptomatic patients.
  - When the duration of AF is >48 hours (or the duration is unknown), anticoagulation (e.g., warfarin, apixaban, dabigatran, rivaroxaban) should be given for 3 weeks (target international normalized ratio [INR] 2–3) before cardioversion due to the risk of emboli.
  - Class Ia, Ic, and III agents are used to prevent recurrence of AF. Flecainide and propafenone are effective at suppressing AF.
- **PSVT**
  - Vagal techniques (pressure over the bifurcation of the carotid arteries or the Valsalva maneuver) are often tried first. Drug therapy involves use of agents that slow conduction and increase refractoriness in the AV node (adenosine, verapamil, diltiazem,  $\beta$ -blockers, digoxin).
- **Conduction Blocks:**
  - Treatment is different from other arrhythmias
  - Atropine is a short-term fix to increase heart rate (0.5 mg intravenous [IV] bolus, max 2 mg)
- **PVCs:**
  - Guidelines recommend routine use of oral  $\beta$ -blocker therapy during the first 24 hours (if no contraindication exists) to prevent occurrence of VF.

TABLE 20.3 Vaughn–Williams Classification of Antiarrhythmic Agents

Drug and Classification	Pharmacokinetics	Indications	Side Effects
<b>CLASS IA (CAN CAUSE TORSADES DE POINTES SIMILAR TO CLASS III AGENTS)</b>			
Quinidine sulfate (83% quinidine; SR: Quinidex) Quinidine gluconate (62% quinidine; SR: Quinaglute)	$t_{1/2} = 6.2 \pm 1.8$ hours (affected by age, cirrhosis); Vd = 2.7 L/kg ( $\downarrow$ in HF); liver metabolism, 80%; renal clearance, 20%; Cp = 2–6 mcg/mL, CYP3A4 substrate, CYP2D6 inhibitor, P-glycoprotein inhibitor	AF (conversion or prophylaxis), WPW, PVCs, VT	Diarrhea, hypotension, N/V, cinchonism, fever, thrombocytopenia, proarrhythmia
Procainamide (Pronestyl)	$t_{1/2} = 3 \pm 0.6$ hours; Vd = 1.9 $\pm$ 0.3 L/kg; liver metabolism 40%; renal clearance (GFR + possible CTS) 60%; active metabolite (NAPA) <sup>a</sup> Cp = 4–10 mcg/mL, possible CTS substrate	AF (conversion or prophylaxis), WPW, PVCs, VT	Hypotension, fever, agranulocytosis, SLE (joint/muscle pain, rash, pericarditis), headache, proarrhythmia
Disopyramide (Norpace; SR: Norpace CR)	$t_{1/2} = 6 \pm 1$ hours; Vd = 0.59 $\pm$ 0.15 L/kg; liver metabolism, 30%; renal clearance, 70%; Cp = 3–6 mcg/mL	AF, WPW, PSVT, PVCs, VT	Anticholinergic (dry mouth, blurred vision, urinary retention), HF, proarrhythmia
<b>CLASS IB<sup>b</sup> (CANNOT USE TO TREAT ATRIAL ARRHYTHMIAS)</b>			
Lidocaine (Xylocaine)	$t_{1/2} = 1.8 \pm 0.4$ hours; Vd = 1.1 $\pm$ 0.4 L/kg; liver metabolism, 100%; Cp = 1.5–6 mcg/mL	PVCs, VT, VF	Drowsiness, agitation, muscle twitching, seizures, paresthesias, proarrhythmia
Mexiletine (Mexilitil)	$t_{1/2} = 10.4 \pm 2.8$ hours; Vd = 9.5 $\pm$ 3.4 L/kg; liver metabolism, 35%–80%; Cp = 0.5–2 mcg/mL	PVCs, VT, VF	Drowsiness, agitation, muscle twitching, seizures, paresthesias, proarrhythmia, N/V, diarrhea
<b>CLASS IC (CANNOT BE USED IN PATIENTS WITH STRUCTURAL HEART DISEASE)</b>			
Flecainide (Tambacor)	$t_{1/2} = 12$ –27 hours; CYP2D6 substrate, 75%; renal clearance, 25%; Cp = 0.4–1 mcg/mL	AF, PSVT, severe ventricular arrhythmias	Dizziness, tremor, lightheadedness, flushing, blurred vision, metallic taste, proarrhythmia
Propafenone (Rythmol)	$t_{1/2} = 2$ hours (extensive metabolizer); 10 hours (poor metabolizer); Vd = 2.5–4 L/kg, CYP2D6 substrate/inhibitor, P-glycoprotein inhibitor	PAF, WPW, severe ventricular arrhythmias	Dizziness, blurred vision, taste disturbances, nausea, worsening of asthma, proarrhythmia
Moricizine (Ethmozine)	$t_{1/2} = 1.3$ –3.5 hours; Vd >300 L	Severe ventricular arrhythmias	Nausea, dizziness, perioral numbness, euphoria
<b>CLASS III (CAN CAUSE TORSADE DE POINTES SIMILARLY TO CLASS IA AGENTS, AMIODARONE AND DRONEDARONE HAVE LOWER RISK)</b>			
Amiodarone (Cordarone)	$t_{1/2} = 40$ –60 days; Vd = 60–100 L/kg; erratic absorption; liver metabolism, 100%; oral F = 50%, Cp = 0.5–2.5 mcg/mL, CYP1A2, 2D6, 2C9, 3A4 inhibitor, P-glycoprotein inhibitor	AF, PAF, PSVT, severe ventricular arrhythmias, VF	Blurred vision, corneal microdeposits, photophobia, skin discoloration, constipation, pulmonary fibrosis, ataxia, hypothyroid or hyperthyroid, hypotension, N/V
Sotalolol <sup>c</sup> (Betapace)	$t_{1/2} = 10$ –20 hours; Vd = 1.2–2.4 L/kg; renal clearance, 100%	AF (prophylaxis), PSVT, severe ventricular arrhythmias	Fatigue, dizziness, dyspnea, bradycardia, proarrhythmia

Continued on following page

TABLE 20.3 Vaughn–Williams Classification of Antiarrhythmic Agents (Continued)

Drug and Classification	Pharmacokinetics	Indications	Side Effects
Dofetilide (Tikosyn)	$t_{1/2}$ = 7.5–10 hours; Vd = 3 L/kg; renal elimination, 60% (GFR + CTS), CYP3A4 substrate	AF or atrial flutter conversion and prophylaxis	Chest pain, dizziness, headache, proarrhythmia
Ibutilide (Corvert)	$t_{1/2}$ = 6 (2–12) hours; Vd = 11 L/kg, $C_p$ = undefined	AF or atrial flutter conversion	Headache, nausea, proarrhythmia
Dronedaronone (Multaq)	$t_{1/2}$ = 13–19 hours; Vd = 20 L/kg, $T_{max}$ = 3–6 hours, CYP3A4 substrate, CYP 2D6, 3A4 inhibitor, P-glycoprotein inhibitor, take with food for maximal absorption	AF or atrial flutter prophylaxis	Diarrhea, nausea, dermatitis or rash, bradycardia, hepatotoxicity, pregnancy category X

<sup>a</sup>NAPA is 100% renally eliminated and possesses class III antiarrhythmic activity.

<sup>b</sup>Phenytoin is classified as a class Ib antiarrhythmic.

<sup>c</sup>Possesses both class II and III antiarrhythmic activity.

AF, atrial fibrillation;  $C_p$ , steady-state plasma concentration; CR, controlled release; CTS, cation tubular secretion; CYP, cytochrome P-450; F, bioavailability; GFR, glomerular filtration rate; HF, heart failure; NAPA, N-acetylprocainamide; N/V, nausea and vomiting; PAF, paroxysmal atrial fibrillation; PSVT, paroxysmal supraventricular tachycardia; PVC, premature ventricular contraction; SLE, systemic lupus erythematosus; SR, sustained release;  $t_{1/2}$ , half-life; Vd, volume of distribution; VF, ventricular fibrillation; VT, ventricular tachycardia; WPW, Wolff–Parkinson–White syndrome.

TABLE 20.4 Agents Used for Controlling Ventricular Rate in Supraventricular Tachycardias<sup>a</sup>

Drug	Loading Dose	Usual Maintenance Dose	Comments
Digoxin (Lanoxin)	10–15 mcg/kg LBW up to 1–1.5 mg IV or PO for 24 hours (e.g., 0.5 mg initially, then 0.25 mg every 6 hours)	PO: 0.125–0.5 mg/day; adjust for renal failure (see Chapter 19)	Maximal response may take several hours; use with caution in patients with renal impairment
Esmolol (Brevibloc)	0.5 mg/kg IV for 1 minute	50–300 mcg/kg/minute continuous infusion with bolus between increases	Hypotension common; effects additive with digoxin and calcium-channel blockers
Propranolol (Inderal)	0.5–1.0 mg IV repeated every 2 minutes (up to 0.1–0.15 mg/kg)	IV infusion: 0.04 mg/kg/minute PO: 10–120 mg TID	Use with caution in patients with HF or asthma; additive effects seen with digoxin and calcium-channel blockers
Metoprolol (Lopressor)	5 mg IV at 1 mg/minute	PO: 25–100 mg BID	Use with caution in patients with HF or asthma; additive effects seen with digoxin and calcium-channel blockers
Verapamil (Isoptin, Calan)	5–10 mg (0.075–0.15 mg/kg) IV for 2 minutes; if response inadequate after 15–30 minutes, repeat 10 mg (up to 0.15 mg/kg)	IV infusion: 5–10 mg/hour PO: 40–120 mg TID or 120–480 mg in sustained-release form daily	Hypotension with IV route; AV blocking effects are additive with digoxin and $\beta$ -blockers; may increase digoxin levels
Diltiazem (Cardizem)	0.25 mg/kg IV for 2 minutes; if response inadequate after 15 minutes, repeat 0.35 mg/kg for 2 minutes	IV infusion: 5–15 mg/hour PO: 60–90 mg TID or QID or 180–360 mg in extended release form daily	Response to IV therapy occurs in 4–5 minutes; hypotension; effects additive with digoxin and $\beta$ -blockers

<sup>a</sup>AV nodal ablation is a nonpharmacologic alternative to control the ventricular response, but the effect is permanent and requires chronic ventricular pacing afterward.

AV, atrioventricular; BID, twice a day; HF, heart failure; LBW, lean body weight; PO, orally; IV, intravenously; QID, four times a day; TID, three times a day.

- Long-term oral  $\beta$ -blockers are indicated for secondary prevention in patients with low ejection fraction, HF, or postshock.
- In high-risk patients with MI who are not candidates for  $\beta$ -blockers, amiodarone can be considered.
- **Nonsustained VT:**
  - $\beta$ -Blockers have been shown to decrease mortality. If contraindications to their use exist, use amiodarone or sotalol.
- **Sustained VT:**
  - Acute treatment depends on hemodynamic stability. If unstable, use synchronous cardioversion.
- **TdP:**
  - Magnesium is the drug of choice in a hemodynamically stable patient. Before giving magnesium, potassium should be at the high normal range (4.5–5 mmol/L).
  - Class 1b agents (mexiletine, lidocaine) are a second class of agents to use.

## Drug Therapy

- **Digoxin** prolongs the effective refractory period of the AV node and reduces the number of impulses conducted through the AV node. Its value as a rate-controlling agent in AF is limited (not effective when there is high sympathetic tone). Guidelines note that digoxin should be used for control of ventricular response rate in AF in patients with impaired left ventricular function or HF or for use as an add-on therapy when treatment with a  $\beta$ -blocker or CCB provides inadequate rate control. Dosing is shown in Table 20.5. The loading and maintenance doses need to be adjusted in patients with renal dysfunction. Target serum levels are generally 0.5 to 1.0 ng/mL.
- **$\beta$ -Adrenergic blocking agents** control ventricular rate at rest and during exercise. Because of their negative inotropic effects, they should not be used acutely to control ventricular response in patients with systolic HF. They should also be avoided in patients with asthma, and blood glucose should be closely monitored if used in diabetic patients.

TABLE 20.5 Commonly Used Drugs in Cardiac Arrest

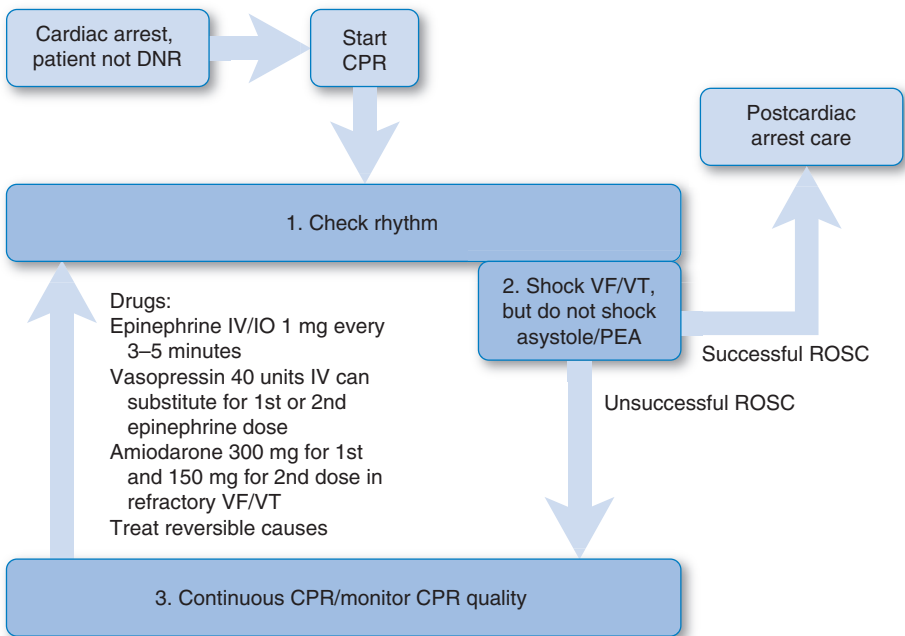
Drug	Formulation	Dosage/Administration	Rationale/Indications	Comments
Amiodarone	50 mg/mL Vials: 3, 9, 18 mL	300 mg diluted in 20–30 mL D5W or NS; additional 150 mg (diluted solution) can be given for recurrent or refractory VT or VF.	Exhibits antiadrenergic properties and blocks sodium, potassium, and calcium channels. First- line antiarrhythmic for pulseless VT and VF	Excipients (polysorbate 80 and benzyl alcohol) can induce hypotension. Failing to dilute can induce phlebitis.
Epinephrine	0.1 mg/mL (1:10,000) or 1 mg/mL (1:1,000)	10 mL of a 1:10,000 solution of epinephrine (1 mg; dilute 1:1,000 solution in 0.9% sodium chloride) every 3–5 minutes	Increases coronary sinus perfusion pressure through $\alpha_1$ stimulation Indicated in pulseless VT, VF, asystole, and PEA	If administered through peripheral catheter, need to flush the line to get drug into the central compartment.
Vasopressin	20 units/mL Vials: 0.5, 1 mL, 10 mL	40-unit dose can be used to replace first or second dose of epinephrine	Increases coronary sinus perfusion pressure through vasopressin receptor stimulation Indicated in pulseless VT, VF, asystole, and PEA	Vasopressin is an acceptable alternative to epinephrine, may work better if time from cardiac arrest to ACLS is delayed.

ACLS, Advanced cardiac life support; D5W, 5% dextrose in water; NS, normal saline; PEA, pulseless electrical activity; VF, ventricular fibrillation; VT, ventricular tachycardia.

- **CCBs** (nondihydropyridine) slow ventricular rate at rest and during exercise. Verapamil and diltiazem can be used for PSVT. Verapamil is given as 2.5 to 5 mg IV for 2 minutes; the dose can be repeated in 10- to 15-minute intervals to a maximum dose of 20 mg. Diltiazem is given as a 0.25 mg/kg bolus over 2 minutes, with a second bolus of 0.35 mg/kg given 15 minutes later, if needed.
- **Ibutilide (IV)** is a class III agent that is used to terminate recent-onset AF and atrial flutter. It is administered as a 1-mg infusion for 10 minutes, followed by another 1-mg infusion over 10 minutes.
- **Propafenone** is a class Ic agent with  $\beta$ -blocking properties. The AF conversion rate ranges from 41% to 57%. It is given in doses of 450 to 750 mg orally.
- **Flecainide** is a class Ic agent which, when given in a 300 mg oral dose, converted 68% of AF patients within 3 hours and 91% by 8 hours.
- Class III agents (sotalol, amiodarone, dofetilide, dronedarone)
  - Amiodarone is more effective at maintaining normal sinus rhythm than is sotalol. It is primarily indicated for patients presenting with hemodynamically stable VT, polymorphic VT with normal QT interval, and wide-complex tachycardia of uncertain origin. Patients should be monitored for pulmonary fibrosis, liver toxicity, hypo/hyperthyroidism, and blue-gray skin discoloration.
  - Dofetilide can be used for conversion to and maintenance of normal sinus rhythm. The dose is based on CrCl (500, 250, or 125 mg twice daily for CrCl > 60, 40–60, and 20–39 mL/minute, respectively). The incidence of TdP is directly related to serum levels. Dofetilide is a first-line agent in patients with HF or coronary artery disease. Because of the risk of TdP therapy must be initiated in the hospital.
  - Dronedarone has modest efficacy in maintaining sinus rhythm. While it is less effective than amiodarone, Dronedarone is also less likely to cause thyroid, neurological, skin, or ocular adverse effects. Gastrointestinal (GI) effects are common. It is appropriate first- or second-line therapy for patient with AF and concomitant coronary artery disease. Dronedarone should be avoided in patients with HF or permanent AF.
  - Sotalol is contraindicated in patients with renal dysfunction (CrCl < 40 mL/minute). Side effects include bradycardia, dizziness, and GI disturbance. It should not be used in patients with systolic HF. Sotalol may be arrhythmogenic in high doses. Three days of ECG monitoring is required when initiating therapy due to the risk of TdP.
- **Adenosine** blocks the AV node and is the drug of choice for PSVT. It is administered as a 6-mg IV bolus followed by one or two 12-mg IV boluses if the first dose was unsuccessful. A common side effect is chest heaviness, flushing, or the feeling of anxiety.
- **Electrical conversion** (direct current cardioversion) quickly and effectively restores 85% to 90% of patients with AF to normal sinus rhythm. It is indicated in patients who are hemodynamically unstable. **Implantable cardiac defibrillators (ICDs)** are devices implanted under the skin with wires attached to the ventricular myocardium. They are used in patients with left ventricular dysfunction (primary prevention) and prior VTs (secondary prevention).
- **Antithrombotic therapy** may be appropriate in patients with AF due to the increased risk of stroke. Selection of the most appropriate regimen should be based on assessment of risk for stroke and bleeding. CHADS<sub>2</sub> or CHA<sub>2</sub>DS<sub>2</sub>-VASc scoring systems can be used to guide therapy: warfarin (INR target 2–3) for a score of 2 or greater; aspirin monotherapy for CHADS<sub>2</sub> score of 0 to 1. Aspirin with clopidogrel may be an option for patients who cannot take warfarin. Newer agents such as apixaban 5 mg twice daily, dabigatran 150 mg twice daily, or rivaroxaban 20 mg daily are alternatives to warfarin.
- **Food supplements/minerals** are not generally recommended. Omega-3 polyunsaturated fatty acids, coenzyme Q10, and L-carnitine are the best studied alternative therapies for arrhythmias.

## Cardiopulmonary Arrest

- Cardiac arrest from VF, pulseless FT, pulseless electrical activity, and asystole are life-threatening emergencies.
- Commonly used drugs for cardiac arrest are shown in Table 20.5.
  - The recommended dose of epinephrine is 1 mg given by IV push. The dose can be repeated in 3- to 5-minute intervals during resuscitation.
  - A single dose of vasopressin 40 units is an alternative to either the first or second dose of epinephrine in the treatment of VF (or pulseless VT).
  - Advanced cardiac life support (ACLS) guidelines call for amiodarone in VF or pulseless VT that does not respond to cardiopulmonary resuscitation (CPR), shock, and a vasopressor.
- Figure 20.2 outlines the key features of management of pulseless arrest.



**Figure 20.2** Cardiac arrest treatment algorithm. CPR, cardiopulmonary resuscitation; DNR, do not resuscitate; IO, intraosseous; IV, intravenous; PEA, pulseless electrical activity; ROSC, restoration of spontaneous circulation; VF, ventricular fibrillation; VT, ventricular tachycardia.



# Hypertensive Crises\*

## General Principles

- Hypertensive crisis is defined as a diastolic blood pressure (BP) >120 mm Hg. It is further classified as hypertensive urgency or hypertensive emergency. Characteristics of these conditions are shown in Table 21.1.
- **Hypertensive urgency** is not immediately life threatening, and BP reduction can occur more slowly over 24 to 48 hours.
- **Hypertensive emergency** is a clinical situation in which the BP is immediately life threatening and needs to be lowered to a safe level within a matter of minutes to hours in order to prevent/minimize end-organ damage.

## Patient Assessment

- **Hypertensive urgency** symptoms include headache, dizziness, visual changes, chest discomfort, nausea, epistaxis, fatigue, and psychomotor agitation.
- **Hypertensive emergency** symptoms are highly variable and reflect the degree of damage to specific organ systems. Recent-onset severe headache, nausea, vomiting, acute onset angina, and acute heart failure (HF) are possible presentations. Organs primarily affected by a hypertensive emergency are the central nervous system, eyes, heart, and kidneys.

TABLE 21.1 Hypertensive Emergencies versus Urgencies

Emergencies	Urgencies
Severely elevated blood pressure (diastolic >120 mm Hg) <sup>a</sup>	Severely elevated blood pressure (diastolic >120 mm Hg) <sup>a</sup>
Potentially life threatening	Not acutely life threatening
End-organ damage acute or progressing	Chronic end-organ damage that is not progressing
CNS (dizziness, N/V, encephalopathy, confusion, weakness, intracranial or subarachnoid hemorrhage, stroke)	Optic disc edema
Eyes (ocular hemorrhage or fundoscopic changes, blurred vision, loss of sight)	
Heart (left ventricular failure, pulmonary edema, MI, angina, aortic dissection)	
Renal failure or insufficiency	
Requires immediate pressure reduction	Treated for several hours to days
Requires IV therapy (Table 21.2)	Oral therapy (Table 21.3)

<sup>a</sup>Degree of blood pressure elevation less diagnostic than rate of pressure rise and presence of concurrent diseases or end-organ damage (see Chapter 14, for staging of hypertension).

CNS, central nervous system; IV, intravenous; MI, myocardial infarction; N/V, nausea and vomiting.

\*The reader is referred to Chapter 21, Hypertensive Crises, written by Kristin Watson, PharmD, BCPS, Brian Watson, PharmD, BCPS, Kelly Summers, PharmD, and Robert Michocki, PharmD, in the 10th edition of *Applied Therapeutics: The Clinical Use of Drugs* for a more in-depth discussion. All notations to reference numbers are based on the reference list at the end of that chapter. The editor of this handbook expresses her thanks to Drs. Watson, Watson, Summers, and Michocki and acknowledges that this chapter is based on their work.

## Risk Factors

- Risk factors for development of a hypertensive crisis include, but are not limited to, medication nonadherence, cocaine use, and drug–drug or drug–food interactions.

## Goals of Therapy

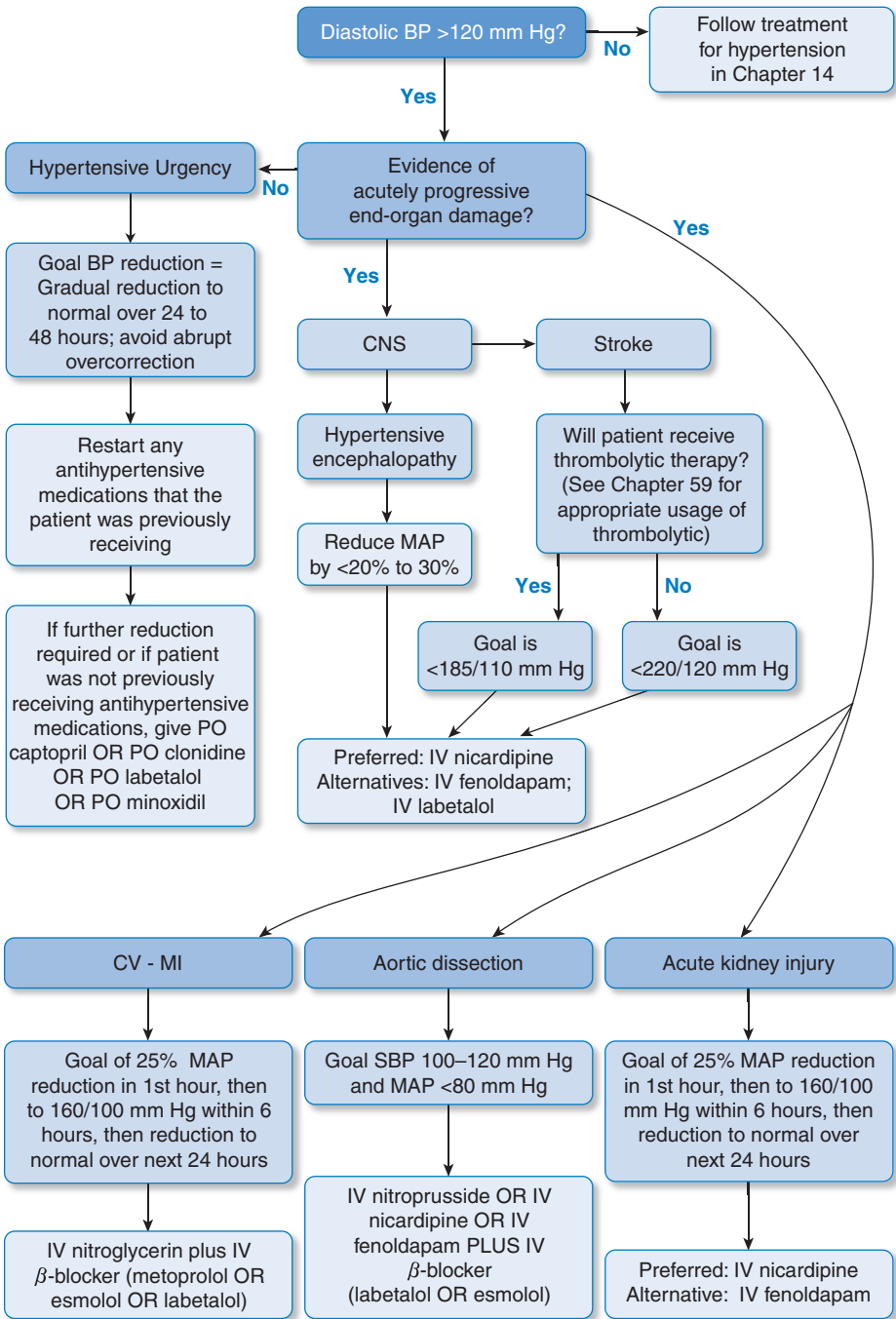
- The rate of BP lowering must be individualized. Patients who have chronically elevated BP are less likely to tolerate abrupt reductions in their BP.
- **Hypertensive Urgency:** Lower BP gradually over 24 to 48 hours.
- **Hypertensive Emergency.** Immediate reduction in BP is needed to prevent end-organ damage.
- General guidelines suggest mean arterial pressure (MAP) should be reduced initially by no more than 25% (within minutes to 1 hour); then, if stable, further reduction to a goal of 160/100 mm Hg within 2 to 6 hours is appropriate. Gradual reduction to normal BP should occur over the next 8 to 24 hours.

## Treatment

- An overview of the management for a hypertensive crisis is shown in Figure 21.1.
- **Hypertensive Urgency.** Oral antihypertensive regimens are appropriate because aggressive lowering of BP in the absence of signs of end-organ damage is not without risk and can lead to morbidity. Timely follow-up within 1 week after treatment is important.
- **Hypertensive Emergency.** Immediate hospitalization, usually in an intensive care unit (ICU) setting, and administration of parenteral antihypertensive medications to reduce arterial pressure is needed. Treatment recommendations are shown in Table 21.2. Two fundamental concepts apply when managing these patients:
  - Immediate and intensive therapy takes precedence over time-consuming diagnostic procedures.
  - Choice of drugs will depend on their time course of action and hemodynamic and metabolic effects.
- **Aortic dissection** typically requires a reduction in pulsatile load or aortic stress by lowering BP. Nitroprusside, fenoldopam, or nicardipine in combination with a  $\beta$ -blocker to keep heart rate at 55 to 65 beats/minute is appropriate. Labetalol monotherapy is an alternative. Hydralazine should be avoided.
- **Cocaine-induced hypertensive crisis** should be controlled with nicardipine, verapamil, or nitroglycerin. Fenoldopam and nitroprusside are alternatives.  $\beta$ -blockers should be avoided.

## Drug Therapy

- **Hypertensive urgencies** are treated with oral drugs (Table 21.3).
  - Clonidine, labetalol, minoxidil, and captopril are useful options. All of them take several hours to adequately lower BP. Minoxidil should be used only in patients who are not responding to other therapies or who were previously taking this agent. Labetalol can cause profound orthostatic hypotension, so patients should remain in the supine position after dosing.
  - Oral angiotensin-converting enzyme (ACE) inhibitors, other than captopril, are not useful as their onset of action is too slow.
  - Administration of immediate-release nifedipine capsules or other rapid-acting calcium-channel blockers (CCBs) sublingually, by the “bite and chew” method, is not recommended.
- **Hypertensive emergencies** are treated with parenteral drugs (Table 21.4).
  - Nitroprusside, fenoldopam, and IV nitroglycerin are useful options. Either nitroprusside or fenoldopam are preferred in patients with concomitant decompensated HF. Parenteral nitroglycerin is most useful in patients with coronary insufficiency, ischemic heart disease, myocardial infarction (MI), or hypertension after coronary bypass surgery.



**Figure 21.1** Overview of management for a hypertensive crisis. BP, blood pressure; CNS, central nervous system; IV, intravenous; MAP, mean arterial pressure; MI, myocardial infarction; SBP, systolic blood pressure.

**TABLE 21.2 Treatment Recommendations for Hypertensive Emergency**

Clinical Presentation	Recommendation	Rationale
Aortic dissection	Nitroprusside, nicardipine, or fenoldopam plus esmolol or IV metoprolol; labetalol; trimethaphan. Avoid inotropic therapy.	Vasodilator will decrease pulsatile stress in aortic vessel to prevent further dissection expansion. $\beta$ -blockers will prevent vasodilator-induced reflex tachycardia.
Angina, myocardial infarction	Nitroglycerin plus esmolol or metoprolol; labetalol. Avoid nitroprusside.	Coronary vasodilation, decreased cardiac output, myocardial workload, and oxygen demand. Nitroprusside may cause coronary steal.
Acute pulmonary edema, left ventricular failure	Nitroprusside, nicardipine, or fenoldopam plus nitroglycerin and a loop diuretic. Alternative: enalaprilat. Avoid nondihydropyridines, $\beta$ -blockers.	Promotion of diuresis with venous dilatation to decrease preload. Nitroprusside, enalaprilat decrease afterload. Nicardipine may increase stroke volume.
Acute kidney injury	Nicardipine or fenoldopam. Avoid nitroprusside, enalaprilat.	Peripheral vasodilation without renal clearance. Fenoldopam shown to increase renal blood flow.
Cocaine overdose	Nicardipine, fenoldopam, verapamil, or nitroglycerin. Alternative: labetalol. Avoid $\beta$ -selective blockers.	Vasodilation effects without potential unopposed $\alpha$ -adrenergic receptor stimulation. CCBs control overdose-induced vasospasm.
Pheochromocytoma	Nicardipine, fenoldopam, or verapamil. Alternatives: phentolamine, labetalol. Avoid $\beta$ -selective blockers.	Vasodilation effects without potential unopposed $\beta$ -adrenergic receptor stimulation.
Hypertensive encephalopathy, intracranial hemorrhage, subarachnoid hemorrhage, thrombotic stroke	Nicardipine, fenoldopam, or labetalol. Avoid nitroprusside, nitroglycerin, enalaprilat, hydralazine.	Vasodilation effects without compromised CBF induced by nitroprusside and nitroglycerin. Enalaprilat and hydralazine may lead to unpredictable BP changes when carefully controlled BP management is required.

BP, blood pressure; CBF, cerebral blood flow; CCB, calcium-channel blocker; IV, intravenous.

**TABLE 21.3 Oral Drugs Commonly Used in the Treatment of Hypertensive Urgencies**

Drug <sup>a</sup> (Brand Name)	Dose/Route	Onset of Action	Duration of Action	Major Side Effects <sup>a</sup>	Mechanism of Action	Avoid or Use Cautiously in Patients with These Conditions
Captopril <sup>b</sup> (Capoten) 12.5-, 25-, 50-, 100-mg tablets	6.5–50 mg PO	15 minutes	4–6 hours	Hyperkalemia, angioedema, increased BUN if dehydrated, rash, pruritus, proteinuria, loss of taste	ACE inhibitor	Renal artery stenosis, hyperkalemia, dehydration, renal failure, pregnancy
Clonidine (Catapres) 0.1-, 0.2-, 0.3-mg tablets	0.1–0.2 mg PO initially, then 0.1 mg/hour up to 0.8 mg total	0.5–2 hours	6–8 hours	Sedation, dry mouth, constipation	Central $\alpha_2$ -agonist	Altered mental status, severe carotid artery stenosis
Labetalol (Normodyne, Trandate) 100-, 200-, 300-mg tablets	200–400 mg PO repeated every 2–3 hours	30 minutes–2 hours	4 hours	Orthostatic hypotension, nausea, vomiting	$\alpha$ - and $\beta$ -adrenergic blocker	Heart failure, asthma, bradycardia

*Continued on following page*

**TABLE 21.3 Oral Drugs Commonly Used in the Treatment of Hypertensive Urgencies (Continued)**

Drug <sup>a</sup> (Brand Name)	Dose/Route	Onset of Action	Duration of Action	Major Side Effects <sup>a</sup>	Mechanism of Action	Avoid or Use Cautiously in Patients with These Conditions
Minoxidil (Loniten) 2.5-, 10-mg tablets	5–20 mg PO	30–60 minutes; maximum response in 2–4 hours	12–16 hours	Tachycardia, fluid retention	Arterial and venous vasodilator	Angina, heart failure

<sup>a</sup>All may cause hypotension, dizziness, and flushing.

<sup>b</sup>Other oral ACE inhibitors too slow in onset to be useful but should be used for maintenance therapy to improve adherence as captopril requires multiple daily doses

ACE, angiotensin-converting enzyme; BUN, blood urea nitrogen; PO, orally.

**TABLE 21.4 Parenteral Drugs Commonly Used in the Treatment of Hypertensive Emergencies**

Drug (Brand Name)	Class of Drug	Dose/Route	Onset of Action	Duration of Action
Clevidipine (Cleviprex) 0.5 mg/mL	Arterial vasodilator (calcium-channel blocker)	Initial: 1–2 mg/hour; titrate dose to desired BP or to a max of 16 mg/hour	2–4 minutes	10–15 minutes after D/C
Enalaprilat <sup>a</sup> (Vasotec IV) 1.25 mg/mL, 2.5 mg/2 mL	ACE inhibitor	0.625–1.25 mg IV every 6 hours	15 minutes (max, 1–4 hours)	6–12 hours
Esmolol <sup>b</sup> (Brevibloc) 100 mg/10 mL, 2,500 mg/10 mL concentrate	$\beta$ -adrenergic blocker	250–500 mcg/kg for 1 minute, then 50–300 mcg/kg/minute	1–2 minutes	10–20 minutes
Fenoldopam (Corlopam) 10 mg/mL, 20 mg/2 mL, 50 mg/5 mL	Dopamine-1 agonist	0.1–0.3 mcg/kg/minute	<5 minutes	30 minutes
Hydralazine <sup>c</sup> (generic) 20 mg/mL	Arterial vasodilator	10–20 mg IV	5–20 minutes	2–6 hours
Labetalol <sup>d</sup> (Normodyne) 20 mg/4 mL, 40 mg/8 mL, 100 mg/20 mL, 200 mg/20 mL	$\alpha$ - and $\beta$ -adrenergic blocker	2 mg/minute IV or 20–80 mg every 10 minutes up to 300 mg total dose	2–5 minutes	3–6 hours
Nicardipine <sup>e</sup> (Cardene IV) 25 mg/10 mL	Arterial vasodilator (calcium-channel blocker)	IV loading dose 5 mg/hour increased by 2.5 mg/hour every 5 minutes to desired BP or a max of 15 mg/hour every 15 minutes, followed by maintenance infusion of 3 mg/hour	2–10 minutes (max, 8–12 hours)	40–60 minutes after D/C infusion
Nitroglycerin <sup>f</sup> (Tridil, Nitro-Bid IV, Nitro-Stat IV) 5 mg/mL, 5 mg/10 mL, 25 mg/5 mL, 50 mg/10 mL, 100 mg/20 mL	Arterial and venous vasodilator	IV infusion pump 5–100 mcg/minute	2–5 minutes	5–10 minutes after D/C infusion

Drug (Brand Name)	Class of Drug	Dose/Route	Onset of Action	Duration of Action
Nitroprusside <sup>e</sup> (Nitropress), 50 mg/2 mL (most commonly used)	Arterial and venous vasodilator	IV infusion. <sup>a</sup> Start: 0.5 mcg/kg/minute; Usual: 2–5 mcg/kg/ minute; Max: 8 mcg/kg/minute	Seconds	3–5 minutes after D/C infusion
Phentolamine (Regitine)	$\alpha$ -adrenergic blocker	1–5 mg IV initially, repeat as needed	Immediate	10–15 minutes

Major Side Effects (All Can Cause Hypotension)	Avoid or Use Cautiously in Patients With These Conditions
Atrial fibrillation, nausea, vomiting, headache, acute renal failure, reflex tachycardia, MI	Allergy to soybeans, soy products, eggs or egg products, severe aortic stenosis, defective lipid metabolism, heart failure
Hyperkalemia	Hyperkalemia, renal failure in patients with dehydration or bilateral renal artery stenosis, pregnancy (teratogenic)
Nausea, thrombophlebitis, painful extravasation	Asthma, bradycardia, decompensated HF, advanced heart block
Tachycardia, headache, nausea, flushing	Glaucoma
Tachycardia, headache, angina	Angina pectoris, MI, aortic dissection
Abdominal pain, nausea, vomiting, diarrhea	Asthma, bradycardia, decompensated HF
Headache, flushing, nausea, vomiting, dizziness, tachycardia; local thrombophlebitis change infusion site after 12 hours	Angina pectoris, decompensated HF, increased intracranial pressure
Methemoglobinemia, headache, tachycardia, nausea, vomiting, flushing, tolerance with prolonged use	Pericardial tamponade, constrictive pericarditis, or increased intracranial pressure
Nausea, vomiting, diaphoresis, weakness, thiocyanate toxicity, <sup>h</sup> cyanide toxicity (rare), <sup>i</sup> chest pain, nausea, vomiting, dizziness, headache, nasal congestion, arrhythmia	Renal failure (thiocyanate accumulation), pregnancy, increased intracranial pressure, angina pectoris, coronary insufficiency, MI or history of MI, hypersensitivity to mannitol

<sup>a</sup>Not approved by the U.S. Food and Drug Administration for treatment of acute hypertension.

<sup>b</sup>Approved for intraoperative and postoperative treatment of hypertension.

<sup>c</sup>Parenteral hydralazine is an intermediate treatment between oral agents and more aggressive therapies such as nitroprusside. It can be given IV or intramuscularly, but there is no appreciable difference in onset of action (20–40 minutes) between the two routes. This slow onset minimizes hypotension.

<sup>d</sup>Labetalol is contraindicated in acute decompensated heart failure because of its  $\beta$ -blocking properties. A solution for continuous infusion is prepared by adding two 100-mg ampules to 160 mL of IV fluid to give a final concentration of 1 mg/mL. Infusions start at 2 mg/minute and are titrated until a satisfactory response or a cumulative dose of 300 mg is achieved.

<sup>e</sup>Indicated for short-term treatment of hypertension when the oral route is not feasible or desirable.

<sup>f</sup>Requires special delivery system owing to drug binding to polyvinyl chloride tubing. Also see Chapters 17 and 18 for further information regarding nitroglycerin.

<sup>g</sup>Nitroprusside is the drug of choice for acute hypertensive emergencies. It is supplied as 50 mg of lyophilized powder that is reconstituted with 2 to 3 mL of 5% dextrose in water (D<sub>5</sub>W), yielding a red-brown solution. The contents of the vial are added to 250, 500, or 1,000 mL of D<sub>5</sub>W to produce a solution for IV administration at a concentration of 200, 100, or 50 mcg/mL, respectively. The container should be wrapped with metal foil to prevent light-induced decompensation. Under these conditions, the solution is stable for 4 to 24 hours. A rising BP may indicate loss of potency. A change in color to yellow does not indicate effectiveness. The appearance of a dark brown, green, or blue color indicates loss in activity. The drug is more effective if the head of the bed is slightly raised. When changing to a new bag, the administration rate may require adjustment.

<sup>h</sup>Thiocyanate levels rise gradually in proportion to the dose and duration of administration. The half-life of thiocyanate is 2.7 days with normal renal function and 9 days in patients with renal failure. Toxicity occurs after 7 to 14 days in patients with normal renal function and 3 to 6 days in renal failure patients. Thiocyanate serum levels should be measured after 3 to 4 days of therapy, and the drug should be discontinued if levels exceed 10 to 12 mg/dL. Thiocyanate toxicity causes a neurotoxic syndrome of toxic psychosis, hyperreflexia, confusion, weakness, tinnitus, seizures, and coma.

<sup>i</sup>Signs of cyanide toxicity include lactic acidosis, hypoxemia, tachycardia, altered consciousness, seizures, and the smell of almonds on the breath. Concurrent administration of sodium thiosulfate or hydroxocobalamin may reduce the risk of cyanide toxicity in high-risk patients.

ACE, angiotensin-converting enzyme; BP, blood pressure; D/C, discontinued; HF, heart failure; IV, intravenous; MI, myocardial infarction.

- IV labetalol may be useful in patients with cerebrovascular disease as it does not significantly reduce cerebral blood flow. Older patients require lower doses.
- Hydralazine is rarely used because response is less predictable and it has a long half-life.
- Other parenteral therapies that have been used include enalaprilat and IV calcium-channel blockers.
- Phentolamine is primarily used when the hypertensive emergency is caused by catecholamine excess (e.g., pheochromocytoma).
- Use of potent IV diuretics is not generally useful except in patients with concomitant volume overload or HF.

## Shock\*

## General Principles

- Shock is a syndrome of impaired tissue perfusion usually, but not always, accompanied by hypotension. If left untreated, impairment of tissue perfusion eventually leads to cellular dysfunction, organ damage, and death.
- **Systemic inflammatory response syndrome (SIRS)** is the umbrella term to describe any acute, overwhelming inflammatory response, independent of cause. It is usually a late manifestation of hypovolemic shock, is uncommon in cardiogenic shock, and is the hallmark of septic shock.
- Normal hemodynamic values and derived indices are described in Table 22.1.

TABLE 22.1 Normal Hemodynamic Values and Derived Indices

	Definition/Equation	Normal Value	Units
<b>DIRECTLY MEASURED</b>			
Blood pressure (BP) (systolic [SBP]/diastolic [DBP])	Pressure in the central arterial bed, determined by cardiac output and systemic vascular resistance	120–140/80–90	mm Hg
Cardiac output (CO)	Amount of blood ejected from the left ventricle per minute; determined by stroke volume and heart rate $CO = SV \times HR$	4–7	L/minute
Central venous pressure (CVP) <sup>a</sup>	Measures mean pressure in right atrium and reflects right ventricular filling pressure and volume status. Primarily determined by venous return to the heart. The goal in most critically ill patients is 8–12 mm Hg.	2–6	mm Hg <sup>a</sup>
Heart rate (HR) (pulse)	Number of myocardial contractions per minute	60–80	beats/minute
Pulmonary artery pressure (PAP) systolic (SPAP)/diastolic (DPAP)/mean (MPAP)	<i>Systolic (SPAP)</i> : measures pulmonary artery pressure during systole; reflects pressure generated by the contraction of the right ventricle. <i>Diastolic (DPAP)</i> : measures pulmonary artery pressure during diastole; reflects diastolic filling pressure in the left ventricle. May approximate pulmonary capillary wedge pressure (PCWP); normal gradient <5 mm Hg between DPAP and PCWP	20–30/8–12	mm Hg
Pulmonary capillary wedge pressure (PCWP)	Measures pressure distal to the pulmonary artery; reflects left ventricular filling pressures ( <i>preload</i> ). Usually lower than or within 5 mm Hg of pulmonary artery diastolic pressure (DPAP)	5–12 <sup>b</sup>	mm Hg

Continued on following page

\*The reader is referred to Chapter 22, Shock, written by Andrew D. Barnes, PharmD, and Susan H. Lee, PharmD, in the 10th edition of *Applied Therapeutics: The Clinical Use of Drugs* for a more in-depth discussion. All notations to reference numbers are based on the reference list at the end of that chapter. The editor of this handbook expresses her thanks to Drs. Barnes and Lee and acknowledges that this chapter is based on their work.



TABLE 22.1 Normal Hemodynamic Values and Derived Indices (Continued)

	Definition/Equation	Normal Value	Units
Central venous oxygen saturation (Scvo <sub>2</sub> )	The oxygen saturation of blood returning to the heart	>70	%
Mixed venous oxygen saturation (Svo <sub>2</sub> )	The oxygen saturation of blood in the pulmonary artery	>65	%
<b>DERIVED INDICES</b>			
Cardiac index (CI)	Cardiac output per square meter of body surface area (BSA <sup>c</sup> ). CI = CO/BSA	2.5–4.2	L/minute/m <sup>2</sup>
Left ventricular stroke work index (LVSWI)	Amount of work the left ventricle exerts during systole; adjusted for body surface area (BSA). A measure of <i>contractility</i> , the inotropic state of the myocardium LVSWI = (MAP – PCWP) × SVI × 0.0136	35–85	g/m <sup>2</sup> /beat
Mean arterial pressure (MAP)	MAP = [(2 × DBP) + SBP]/3	80–100	mm Hg
Oxygen delivery (o <sub>2</sub> )	The amount of oxygen delivered by the body per unit time o <sub>2</sub> = CO × Cao <sub>2</sub> where Cao <sub>2</sub> = Hgb × Sao <sub>2</sub> × 13.9	700–1,200	mL/minute
Oxygen consumption (V̇O <sub>2</sub> )	The amount of oxygen consumed by the body per unit time. The product of cardiac output and the difference between the arterial and venous oxygen concentration V̇O <sub>2</sub> = CO × (Cao <sub>2</sub> – Cvo <sub>2</sub> ), where Cvo <sub>2</sub> = Hgb × Svo <sub>2</sub> × 13.9	200–400	mL/minute
Perfusion pressure (PP)	The pressure gradient between the coronary arteries and the pressure in either the right atrium or left ventricle during diastole. A major determinant of coronary blood flow and oxygen supply to the heart PP = MAP – PCWP	50	mm Hg
Pulmonary vascular resistance (PVR)	Primary determinant of right ventricular <i>afterload</i> PVR = [(MPAP – PCWP)/CO] × 74	20–120	dynes·s·cm <sup>-5</sup>
Stroke volume (SV)	Amount of blood ejected from the ventricle with each systolic contraction SV = CO/HR	60–130	mL/beat
Stroke volume index (SVI)	Stroke volume adjusted for body surface area SVI = SV/BSA	30–75	mL/beat/m <sup>2</sup>
Systemic vascular resistance (SVR)	Measure of impedance applied by systemic vascular system to systolic effort of left ventricle; determined by autonomic nervous system and condition of vessels. Determinant of left ventricular <i>afterload</i> SVR = [(MAP – CVP)/CO] × 74	800–1,440	dynes·s·cm <sup>-5</sup>
Systemic vascular resistance index (SVRI)	SVR adjusted for body surface area SVRI = SVR × BSA	1,680–2,580	dyne·s·cm <sup>-5</sup> ·m <sup>2</sup>

<sup>c</sup>CVP is essentially synonymous with RAP.

<sup>b</sup>May optimally ↑ PCWP to 16 to 18 mm Hg in critically ill patients.

<sup>c</sup>BSA, body surface area = 1.7 m<sup>2</sup> (average male).

## Classification

- Classification of shock and precipitating events are shown in Table 22.2. Different types of shock can appear at the same time.
  - **Hypovolemic Shock.** Shock secondary to a reduction in intravascular volume. Severity depends on a person's capacity for compensation. Losses of >80% generally overwhelm compensatory mechanisms.
  - **Cardiogenic Shock.** Shock arising primarily from an abnormality of cardiac function (either mechanical or nonmechanical in nature) where there is an inability to maintain cardiac output (CO) unrelated to hypovolemia.
  - **Distributive Shock.** Shock characterized by overt loss of vascular tone causing acute tissue hypoperfusion. Numerous events (e.g., anaphylaxis, neurogenic causes, sepsis) can initiate distributive shock. **Septic shock** is characterized by a profound vasodilatory response and resultant decrease in blood pressure.
- Hemodynamic findings in various shock states are shown in Table 22.3.

## Patient Assessment

- Diagnosis is based on the finding of impaired tissue perfusion. Hypotension is often described as a hallmark symptom, but it is not necessarily present in all patients. Hemodynamic monitoring is vital for the determination of the type of shock and assessment of response to therapy.

TABLE 22.2 Classification of Shock and Precipitating Events

### HYPOVOLEMIC SHOCK

Hemorrhagic  
 Gastrointestinal bleeding  
 Trauma  
 Internal bleeding: ruptured aortic aneurysm, retroperitoneal bleeding  
 Nonhemorrhagic  
 Dehydration: vomiting, diarrhea, diabetes mellitus, diabetes insipidus, overuse of diuretics  
 Sequestration: ascites, third-space accumulation  
 Cutaneous: burns, nonreplaced perspiration, and insensible water losses

### CARDIOGENIC SHOCK

Nonmechanical causes  
 Acute myocardial infarction  
 Low cardiac output syndrome  
 Right ventricular infarction  
 End-stage cardiomyopathy  
 Mechanical causes  
 Rupture of septum or free wall  
 Mitral or aortic insufficiency  
 Papillary muscle rupture or dysfunction  
 Critical aortic stenosis  
 Pericardial tamponade

### DISTRIBUTIVE SHOCK

Septic shock  
 Anaphylaxis  
 Neurogenic  
 Spinal injury, cerebral damage, severe dysautonomia  
 Drug-induced  
 Anesthesia, ganglionic and adrenergic blockers, overdoses of barbiturates and narcotics  
 Acute adrenal insufficiency

TABLE 22.3 Hemodynamic Findings in Various Shock States

	Hypovolemic	Cardiogenic	Distributive (Septic)
Heart rate	↑	↑	↑
Blood pressure <sup>a</sup>	↓	↑/↓	↓
Cardiac output	↓	↓	↓ <sup>b</sup>
Preload (PCWP)	↓	↑	↑/↓
Afterload (SVR)	↑	↑	↓

<sup>a</sup>Patients may be in a state of compensated shock in which blood pressure is normal but clinical signs of hypoperfusion are evident.

<sup>b</sup>Cardiac output is increased early in sepsis but can be decreased in late or severe sepsis. PCWP, pulmonary capillary wedge pressure; SVR, systemic vascular resistance.

- Clinical findings in shock may include:
  - Systolic blood pressure (SBP) < 90 mm Hg, or a > 40 mm Hg decrease from baseline in a hypertension patient, or a mean arterial pressure
  - Tachycardia (heart rate [HR] > 90 beats/minute)
  - Tachypnea (respiratory rate > 20 breaths/minute)
  - Cutaneous vasoconstriction: cold, clammy, mottled skin
  - Mental confusion: agitation, stupor, coma
  - Oliguria (urine output < 20 mL/hour)
  - Elevated blood lactate levels leading to metabolic acidosis
  - Decreased venous oxygen saturation
- The actual degree of blood loss in acute hemorrhage is not accurately reflected by the hemoglobin and hematocrit values.
- Clinical features of septic shock are fever, chills, nausea, vomiting, and diarrhea. Lab findings include leukocytosis or leucopenia, thrombocytopenia, and hyperbilirubinemia. Hemodynamic signs include hypotension, tachycardia, elevated CO, low systemic vascular resistance, and low pulmonary capillary wedge pressure (PCWP).

## Causes

- The most common causes of shock are situations that result in a reduction of intravascular volume, myocardial pump failure, or increased vascular resistance.
- Common causes of hypovolemia in surgical patients are postoperative bleeding, third spacing, and temperature-related vasodilation.
- The most common cause of cardiogenic shock is left ventricular dysfunction and necrosis as a result of acute myocardial infarction (AMI).
- Persons most at risk for septic shock are those who are immunocompromised, have underlying conditions that render them susceptible to blood-stream invasion, neonates, elderly, patients with acquired immune deficiency syndrome, alcoholics, childbearing women, and those undergoing surgery or who have experienced trauma.

## Goals of Therapy

- Most critically ill patients require a cardiac index (CI) > 2.5 L/minute/m<sup>2</sup>, PCWP of 10 to 18 mm Hg, or a central venous pressure (CVP) of 8 to 14 mm Hg to maintain an acceptable MAP of 65 to 75 mm Hg.
- **Hypovolemic Shock:** correction of inadequate tissue perfusion and oxygenation, and limiting secondary insults.
- **Cardiogenic Shock.** In addition to maintaining the CI and MAP as noted above, HR should be <125 beats/minute and urine output should be at least 0.5 mL/kg/hour. The goal is to optimize preload increase contractility and reduce afterload if the blood pressure permits.

- **Septic Shock.** In addition to eradicating the precipitating infection, the goal is to optimize delivery of oxygen to tissues and control abnormal use of oxygen and anaerobic metabolism by reducing the tissue oxygen demand.

## Treatment

- Treatment requires addressing the underlying cause of shock and early, aggressive measures to maintain adequate perfusion to vital organs. The type of treatment for shock required depends on the etiology.
- **Hypovolemic Shock.** Infusion of IV fluids (crystalloids or colloids) is critical. For resuscitation of hemorrhagic shock, crystalloids should be the initial fluid choice (either normal saline or lactated Ringer's).
- **Cardiogenic Shock.** Hypovolemia should always be evaluated first. Inotropic support is directed at establishing or maintaining a reasonable arterial pressure and ensuring adequate tissue perfusion by improving CO. Optimizing preload to improve CO is crucial. Inotropic agents or vasopressors should be used to increase systemic blood pressure (BP) and reestablish coronary perfusion.
- **Septic Shock.** Management is directed at eradication of the source of infection, hemodynamic support and control of tissue hypoxia, and inhibition/attenuation of the initiators and mediators of sepsis. The mainstay of therapy is volume expansion to increase intravascular volume, enhance CO, and delay associated development of refractory tissue hypoxia. Inotropic and vasopressor agents are often required for additional cardiovascular support.

## Drug Therapy

- Fluids for Rehydration:
  - **Crystalloids:** isotonic solutions that contain either saline (0.9% NaCl) or a saline equivalent (lactated Ringer's solution). For each 1 mL of blood loss, 3 mL of crystalloid is infused.
  - **Colloids:** solutions that contain large oncologically active molecules that come from natural products (e.g., albumin, dextrans, starches). Albumin solutions contain citrate, which can lower serum calcium concentrations. Hetastarch or hydroxyethyl starch (HES) is a synthetic colloid that closely resembles human serum albumin but is less costly.
  - For a given infusion volume, colloidal solutions will expand the intravascular space two to four times more than crystalloids.
  - **Blood** replacement may be needed in patients who have considerable blood loss.
- **Inotropic Agents** (dosing a pharmacological effects shown in Table 22.4)
  - **Dopamine** has inotropic, chronotropic, and vasoactive properties. Hemodynamic response to dopamine is highly variable. Adverse effects include increased HR, angina pain, arrhythmias, headache, hypertension, vasoconstriction, nausea, and vomiting. Dopamine is preferred in patients with depressed CO, normal or moderately elevated PCWP, and moderate/severe hypotension.
  - **Dobutamine** is a potent inotropic agent (equal to or greater than dopamine). Adverse effects include arrhythmias, nausea, anxiety, and tremors.
  - **Epinephrine** has dose-dependent hemodynamic effects. It is frequently used in cardiac surgery. Use should be reserved for patients with markedly depressed CO in conjunction with severe hypotension.
- **Vasopressors** (dosing a pharmacological effects shown in Table 22.4)
  - **Norepinephrine** vasoconstricts arterioles at all infusion rates which increases systemic vascular resistance. HR and CO usually remain constant. It is commonly used as adjunctive therapy when inotropic agents alone are unsuccessful. Adverse effects are primarily related to vasoconstriction.
  - **Phenylephrine** is a pure  $\alpha$ -agonist that may be used as a second-line agent.
  - **Vasopressin** has direct vasoconstricting effects. It is an option in patients with septic

TABLE 22.4 Inotropic Agents and Vasopressors

Drug	Usual Dose	Receptor Sensitivity			Pharmacologic Effect			
		$\alpha$	$\beta_1$	$\beta_2$	VD	VC	INT	CHT
Dobutamine	2.5–15 mcg/kg/minute	+	+++	++	++	--	+++ <sup>a</sup>	+
Dopamine	0.5–2 mcg/kg/minute <sup>b</sup> (renal)	--	--	--	-- <sup>b</sup>	+	+	+
	2–5 mcg/kg/minute	--	+	--	-- <sup>b</sup>	+	+	+
	5–10 mcg/kg/minute	+	++	--	++	++	++	++
	15–20 mcg/kg/minute	+++	++	--	-- <sup>b</sup>	+++	++	++
Epinephrine <sup>c</sup>	0.01–0.1 mcg/kg/ minute	+	+++	++	+	--	+++	++
	0.1 mcg/kg/minute	+++	++	++	--	+++	++	++
Isoproterenol	0.01–0.1 mcg/kg/ minute	--	++++	+++	+++	--	+++	+++
Milrinone	50 mcg/kg bolus, then 0.375–0.75 mcg/kg/ minute	--	--	--	+++	--	++	--
Norepinephrine	0.05–0.5 mcg/kg/ minute	++++	++	--	--	+++	+ <sup>d</sup>	+
	Highly variable, titrate to desired MAP							
Phenylephrine	0.5–5 mcg/kg/minute	+++	--	--	--	+++	--	--
	Highly variable, titrate to desired MAP							
Vasopressin <sup>e</sup>	0.04 units/minute <sup>f</sup>	--	--	--	--	+++	--	--

<sup>a</sup>Dobutamine and milrinone have more inotropic effect than dopamine.

<sup>b</sup>Dopamine at 0.5 to 2 mcg/kg/minute stimulates dopaminergic receptors, causing vasodilation in the splanchnic and renal vasculature.

<sup>c</sup>Epinephrine has predominant inotropic effects; norepinephrine has predominant vasoconstrictive effect. Epinephrine may vasodilate at low dosages, vasoconstrict at high dosages.

<sup>d</sup>Cardiac output unchanged or may decline because of vagal reflex responses that slow the heart.

<sup>e</sup>Vasopressin stimulates V<sub>1</sub> receptors to cause vasoconstriction in the periphery.

<sup>f</sup>Dosing for sepsis; in other vasodilatory conditions, may be titrated from 0.01 to 0.1 units/minute.

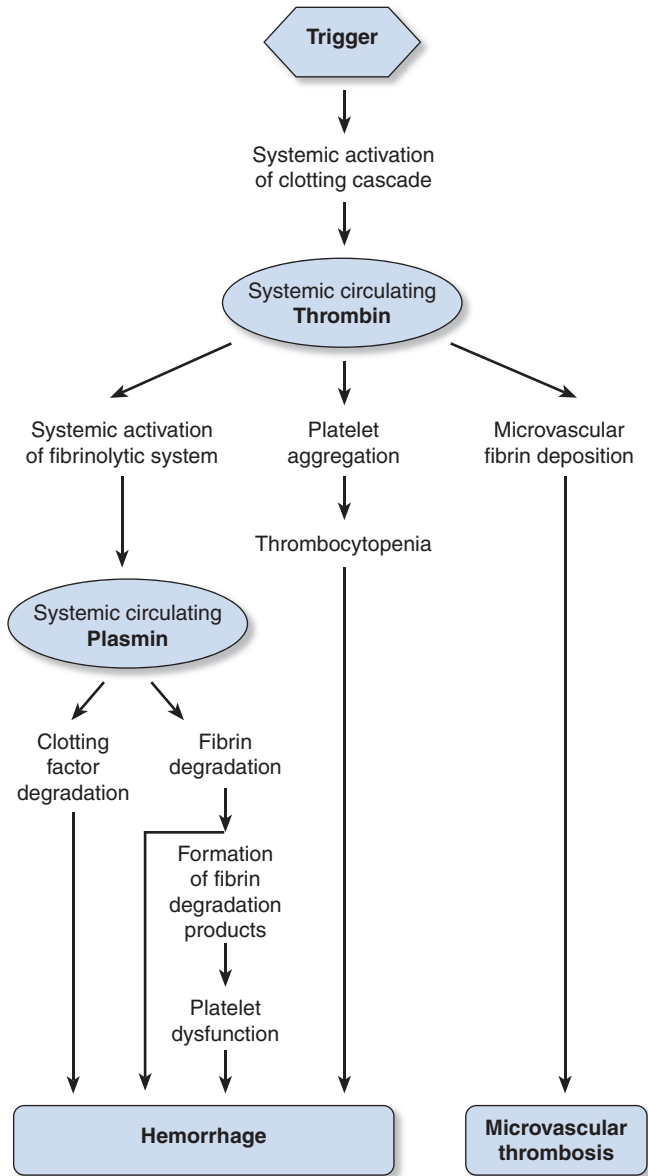
CHT, chronotropic; INT, inotropic; MAP, mean arterial pressure; VC, peripheral vascular vasoconstriction; VD, peripheral vascular vasodilation.

shock as these patients have increased sensitivity to and decreased endogenous levels of vasopressin.

- Corticosteroid therapy, while not typically appropriate for the general population of patients in septic shock, may be appropriate as early treatment for patients unresponsive to vasopressors.

### Disseminated Intravascular Coagulation

- Disseminated intravascular coagulation (DIC) is a diffuse response to systemic activation of the coagulation system (Figure 22.1). Clinical conditions associated with DIC are shown in Table 22.5.
- A scoring system is used in the diagnosis of DIC (Table 22.6).
- Patients have paradoxical bleeding secondary to overactivation and eventual consumption of available clotting factors and platelets.
- Thrombotic manifestations result in the obstruction of blood flow to multiple organs.
- The most important element of treatment is alleviation of the underlying cause to eliminate the stimulus for continued thrombosis and hemorrhage.



**Figure 22.1** Pathophysiology of disseminated intravascular coagulation.

**TABLE 22.5 Clinical Conditions Associated with Disseminated Intravascular Coagulation**

<b>INFECTIOUS DISEASES</b>	<b>TISSUE INJURY</b>
Aspergillosis	Burns
Bacterial infections	Crush injuries
Candidiasis	Extensive surgery
Cytomegalovirus	Multiple trauma
Fungal infections	
Gram-negative sepsis	<b>VASCULAR DISORDERS</b>
Gram-positive sepsis	Aortic aneurysm
Hepatitis	Giant hemangioma
Histoplasmosis	
Miscellaneous infections	<b>MISCELLANEOUS</b>
Mycobacterial malaria	Acidosis
Mycoplasma	Anaphylaxis
Psittacosis	Acute respiratory distress syndrome
Rocky Mountain spotted fever	Cardiopulmonary bypass
Varicella	Hematologic disorders
Viral infections	Heat stroke
	Hepatic disease
<b>INTRAVASCULAR HEMOLYSIS</b>	Hypoperfusion
Hemolytic transfusion reactions	Hypovolemia
Massive transfusions	Severe allergic reaction
Minor hemolysis	Snake bites
	Transplant rejection
<b>MALIGNANCY</b>	
Myeloproliferative diseases	
Solid tumor	
<b>OBSTETRIC STATES</b>	
Amniotic fluid embolism	
Eclampsia	
Retained dead fetus	
Septic or saline abortion	

**TABLE 22.6 International Society on Thrombosis and Haemostasis Disseminated Intravascular Coagulation Scoring System**

**Does the patient have an underlying disorder known to be associated with DIC? (If YES, continue with scoring.)**

Laboratory Test	Result	Point Score
Platelet count	>100,000	0
	<100,000	1
	<50,000	2
Fibrin-related markers	No increase	0
	Moderate increase	2
	Strong increase	3
PT (vs. baseline)	<3 seconds	0
	3–6 seconds	1
	>6 seconds	2
Fibrinogen	>1 g/L	0
	<1 g/L	1
TOTAL SCORE	≥5	Compatible with overt DIC (repeat daily)
	<5	Suggestive but not affirmative for nonovert DIC (repeat in 1–2 days)

DIC, disseminated intravascular coagulation; PT, prothrombin time.

Source: Taylor FB Jr et al. Towards definition, clinical and laboratory criteria, and a scoring system for disseminated intravascular coagulation. *Thromb Haemost.* 2001;86:1327.

## Asthma\*

### General Principles

- Asthma is a chronic inflammatory disorder of the airways in which many cells and cellular elements play a role. It is an obstructive airway disease that narrows air passages, creates air turbulence, and increases resistance to airflow primarily during expiration.
- Airway inflammation causes an increase in the existing bronchial hyperresponsiveness to a variety of stimuli.
- Applying the principles from the national guidelines results in improved clinical outcomes.
- All patients with asthma must get an annual flu shot and be up to date with their pneumococcal vaccine.

### Classification

- **Childhood-Onset Asthma:** usually associated with atopy, a genetic predisposition for the development of immunoglobulin E (IgE)-mediated response to common aeroallergens. A common presentation in children is a positive family history of asthma and allergy to tree and grass pollen, house dust mites, household pets, and mold.
- **Adult-Onset Asthma:** often a negative family history and negative skin tests to common aeroallergens.
- Classification of asthma severity is important in defining initial long-term treatment. Frequency of symptoms is a key component in asthma classification (intermittent, mild persistent, moderate persistent, or severe persistent). Classification by age group is shown in Tables 23.1 to 23.3.

### Patient Assessment

- Diagnosis of asthma is based on detailed history of intermittent symptoms (Table 23.4) and demonstration of reversible airway obstruction. Chest radiographs are not routinely recommended but should be obtained in patients suspected of having complications (e.g., pneumonia).
- The clinical presentation of asthma includes recurrent episodes of wheezing, breathlessness, chest tightness, and cough, particularly at night and in the early morning. Morning cough with or without bronchospasm may indicate nocturnal asthma.
- Episodes are usually associated with widespread but variable airflow obstruction that is often reversible, either spontaneously or with treatment.
- Signs of impending respiratory failure include increased heart rate, decreased breath sounds, agitation from worsening hypoxia, or lethargy. Arterial blood gases should be monitored.
- Patients with asthma who are aspirin sensitive often react to other nonsteroidal anti-inflammatory drugs (NSAIDs; e.g., ibuprofen) by developing asthma symptoms with the first dose. Although drug-induced asthma may present as relatively mild, fatal asthma has occurred.

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\*The reader is referred to Chapter 23, Asthma, written by Timothy H. Self, PharmD, Cary R. Chrisman, PharmD, and Christopher K. Finch, PharmD, BCPS, in the 10th edition of *Applied Therapeutics: The Clinical Use of Drugs* for a more in-depth discussion. All notations to reference numbers are based on the reference list at the end of that chapter. The editor of this handbook expresses her thanks to Drs. Self, Chrisman, and Finch and acknowledges that this chapter is based on their work.



**TABLE 23.1 Classifying Asthma Severity in Children 0 to 4 Years of Age**

**Classifying Severity in Children Who Are Not Currently Taking Long-Term Control Medication**

Components of Severity		Classification of Asthma Severity			
		Intermittent	Persistent		
		Mild	Moderate	Severe	
<b>Impairment</b>	Symptoms	≤2 days/week	>2 days/week but not daily	Daily	Throughout the day
	Nighttime awakenings	0	1–2 × /month	3–4 × /month	>1 × /week
	SABA use for symptom control (not prevention of EIB)	≤2 days/week	>2 days/week but not daily	Daily	Several times per day
	Interference with normal activity	None	Minor limitation	Some limitation	Extremely limited
<b>Risk</b>	Exacerbations requiring oral systemic corticosteroids	0–1/year	≥2 exacerbation in 6 months requiring oral corticosteroids or ≥4 wheezing episodes in 1 year lasting >1 day AND risk factors for persistent asthma		

← Consider severity and interval since last exacerbation. Frequency and severity may fluctuate with time. Exacerbations of any severity may occur in patients in any severity category. →

Level of severity is determined by both impairment and risk. Assess impairment domain by caregiver's recall of previous 2–4 weeks. Assign severity to the most severe category in which any feature occurs. At present, there are inadequate data to correspond frequencies of exacerbations with different levels of asthma severity. For treatment purposes, patients who had ≥2 exacerbations requiring oral corticosteroids in the past 6 months, or ≥4 wheezing episodes in the past year, and who have risk factors for persistent asthma may be considered the same as patients who have persistent asthma, even in the absence of impairment levels consistent with persistent asthma.

**Classifying Severity in Patients After Asthma Becomes Well Controlled, by Lowest Level of Treatment Required to Maintain Control**

Lowest level of treatment required to maintain control	Classification of Asthma Severity			
	Intermittent	Mild	Moderate	Severe
	Step 1	Step 2	Step 3 or 4	Step 5 or 6

EIB, exercise-induced bronchospasm; SABA, short-acting inhaled β<sub>2</sub>-agonist.  
 Source: Reprinted from National Institutes of Health. *Expert Panel Report 3: Guidelines for the Diagnosis and Management of Asthma*. Bethesda, MD: National Heart, Lung, and Blood Institute; 2007. NIH publication 07-4051.

- Monitoring parameters include spirometric measures such as forced expiratory volume in 1 second (FEV<sub>1</sub>), the gold standard test for determining reversibility of airway disease and bronchodilator efficacy. Patient self-monitoring includes peak expiratory flow (PEF) and symptom assessment. Acute care monitoring includes FEV<sub>1</sub>, PEF, arterial O<sub>2</sub> saturation, and arterial blood gases (the best indicators of overall lung function).
  - Significant clinical reversibility is defined as a 12% improvement in FEV<sub>1</sub> after administration of a short-acting bronchodilator.
  - Improvement of 20% in FEV<sub>1</sub> provides noticeable subjective relief of symptoms.

**TABLE 23.2 Classifying Asthma Severity in Children 5 to 11 Years of Age**

**Classifying Severity in Children Who Are Not Currently Taking Long-Term Control Medication**

Components of Severity		Classification of Asthma Severity			
		Intermittent	Persistent		
	Mild		Moderate	Severe	
<b>Impairment</b>	Symptoms	≤2 days/week	>2 days/week but not daily	Daily	Throughout the day
	Nighttime awakenings	≤2×/month	3–4 × /month	>1 × /week but not nightly	Often 7 × /week
	SABA use for symptom control (not prevention of EIB)	≤2 days/week	>2 days/week but not daily	Daily	Several times per day
	Interference with normal activity	None	Minor limitation	Some limitation	Extremely limited
<b>Risk</b>	Lung function	<ul style="list-style-type: none"> <li>• Normal FEV<sub>1</sub> between exacerbations</li> <li>• FEV<sub>1</sub> &gt;80% predicted</li> <li>• FEV<sub>1</sub>/FVC &gt;85%</li> </ul>	<ul style="list-style-type: none"> <li>• FEV<sub>1</sub> &gt;80% predicted</li> <li>• FEV<sub>1</sub>/FVC &gt;80%</li> </ul>	<ul style="list-style-type: none"> <li>• FEV<sub>1</sub> = 60%–80% predicted</li> <li>• FEV<sub>1</sub>/FVC 75%–80%</li> </ul>	<ul style="list-style-type: none"> <li>• FEV<sub>1</sub> &lt;60% predicted</li> <li>• FEV<sub>1</sub>/FVC &lt;75%</li> </ul>
	Exacerbations requiring oral systemic corticosteroids	0–1 in 1 year (see note)	≥2 in 1 year (see note)	→	

← Consider severity and interval since last exacerbation. Frequency and severity may fluctuate with time for patients in any severity category. →

Relative annual risk of exacerbations may be related to FEV<sub>1</sub>.

Level of severity is determined by both impairment and risk. Assess impairment domain by patient's or caregiver's recall of the previous 2–4 weeks and spirometry. Assign severity to the most severe category in which any feature occurs.

At present, there are inadequate data to correspond frequencies of exacerbations with different levels of asthma severity. In general, more frequent and intense exacerbations (e.g., requiring urgent, unscheduled care, hospitalization, or ICU admission) indicate greater underlying disease severity. For treatment purposes, patients who had ≥2 exacerbations requiring oral systemic corticosteroids in the past year may be considered the same as patients who have persistent asthma, even in the absence of impairment levels consistent with persistent asthma.

**Classifying Severity in Patients After Asthma Becomes Well Controlled, by Lowest Level of Treatment Required to Maintain Control**

Lowest level of treatment required to maintain control	Classification of Asthma Severity			
	Intermittent	Persistent		
	Mild	Moderate	Severe	
	Step 1	Step 2	Step 3 or 4	Step 5 or 6

EIB, exercise-induced bronchospasm; FEV<sub>1</sub>, forced expiratory volume in 1 second; FVC, forced vital capacity; ICU, intensive care unit; SABA, short-acting β<sub>2</sub>-agonist.

Source: Reprinted from National Institutes of Health. *Expert Panel Report 3: Guidelines for the Diagnosis and Management of Asthma*. Bethesda, MD: National Heart, Lung, and Blood Institute; 2007. NIH publication 07-4051.

**TABLE 23.3 Classifying Asthma Severity in Youths ≥12 Years of Age and Adults**

**Classifying Severity in Patients Who Are Not Currently Taking Long-Term Control Medication**

Components of Severity		Classification of Asthma Severity			
		Intermittent	Mild	Persistent	
				Moderate	Severe
<b>Impairment</b>	Symptoms	≤2 days/week	>2 days/week but not daily	Daily	Throughout the day
	Nighttime awakenings	≤2×/month	3–4× /month	>1 × /week but not nightly	Often 7 × /week
	SABA use for symptom control (not prevention of EIB)	≤2 days/week	>2 days/week but not >1 × /day	Daily	Several times per day
Normal FEV <sub>1</sub> /FVC: 8–19 years, 85% 20–39 years, 80% 40–59 years, 75% 60–80 years, 70%	Interference with normal activity	None	Minor limitation	Some limitation	Extremely limited
	Lung function	<ul style="list-style-type: none"> <li>• Normal FEV<sub>1</sub> between exacerbations</li> <li>• FEV<sub>1</sub> &gt;80% predicted</li> <li>• FEV<sub>1</sub>/FVC normal</li> </ul>	<ul style="list-style-type: none"> <li>• FEV<sub>1</sub> ≥80% predicted</li> <li>• FEV<sub>1</sub>/FVC normal</li> </ul>	<ul style="list-style-type: none"> <li>• FEV<sub>1</sub> &gt;60% but &lt;80% predicted</li> <li>• FEV<sub>1</sub>/FVC reduced 5%</li> </ul>	<ul style="list-style-type: none"> <li>• FEV<sub>1</sub> &lt;60% predicted</li> <li>• FEV<sub>1</sub>/FVC reduced &gt;5%</li> </ul>
<b>Risk</b>	Exacerbations requiring oral systemic corticosteroids	0–1 in 1 year (see note)	≥2 in 1 year (see note) →		

← Consider severity and interval since last exacerbation. Frequency and severity may fluctuate with time for patients in any severity category. →  
Relative annual risk of exacerbations may be related to FEV<sub>1</sub>.

Level of severity is determined by assessment of both impairment and risk. Assess impairment domain by patient's or caregiver's recall of previous 2–4 weeks and spirometry. Assign severity to the most severe category in which any feature occurs.

At present, there are inadequate data to correspond frequencies of exacerbations with different levels of asthma severity. In general, more frequent and intense exacerbations (e.g., requiring urgent, unscheduled care, hospitalization, or ICU admission) indicate greater underlying disease severity. For treatment purposes, patients who had ≥2 exacerbations requiring oral systemic corticosteroids in the past year may be considered the same as patients who have persistent asthma, even in the absence of impairment levels consistent with persistent asthma.

**Classifying Severity in Patients After Asthma Becomes Well Controlled, by Lowest Level of Treatment Required to Maintain Control**

	Classification of Asthma Severity			
	Intermittent	Mild	Persistent	
			Moderate	Severe
<b>Lowest level of treatment required to maintain control</b>	Step 1	Step 2	Step 3 or 4	Step 5 or 6

“EIB, exercise-induced bronchospasm; FEV<sub>1</sub>, forced expiratory volume in 1 second; FVC, forced vital capacity; ICU, intensive care unit; SABA, short-acting β<sub>2</sub>-agonist.  
Source: Reprinted from National Institutes of Health. *Expert Panel Report 3: Guidelines for the Diagnosis and Management of Asthma*. Bethesda, MD: National Heart, Lung, and Blood Institute; 2007. NIH publication 07-4051.

TABLE 23.4 Sample Questions for the Diagnosis and Initial Assessment of Asthma<sup>a</sup>

A “yes” answer to any question suggests that an asthma diagnosis is likely.

#### IN THE PAST 12 MONTHS . . .

- Have you had a sudden severe episode or recurrent episodes of coughing, wheezing (high-pitched whistling sounds when breathing out), chest tightness, or shortness of breath?
- Have you had colds that “go to the chest” or take more than 10 days to get over?
- Have you had coughing, wheezing, or shortness of breath during a particular season or time of the year?
- Have you had coughing, wheezing, or shortness of breath in certain places or when exposed to certain things (e.g., animals, tobacco smoke, perfumes)?
- Have you used any medications that help you breathe better? How often?
- Are your symptoms relieved when the medications are used?

#### IN THE PAST 4 WEEKS, HAVE YOU HAD COUGHING, WHEEZING, OR SHORTNESS OF BREATH . . .

- At night that has awakened you?
- On awakening?
- After running, moderate exercise, or other physical activity?

<sup>a</sup>These questions are examples and do not represent a standardized assessment or diagnostic instrument. The validity and reliability of these questions have not been assessed.

Source: Reprinted from National Institutes of Health. *Expert Panel Report 3: Guidelines for the Diagnosis and Management of Asthma*. Bethesda, MD: National Heart, Lung, and Blood Institute; 2007. NIH publication 07-4051.

- Objective monitoring of lung function at home using peak flow meters is helpful in managing asthma. Patients should be instructed about the green zone (PEF that is 80%–100% of personal best, indicating good control), yellow zone (PEF 50%–79% of personal best), and red zone (<50% of personal best). Clinicians can also perform the asthma control test (ACT) on patients to determine whether their asthma is well controlled or not.

## Risk Factors

- Major risk factors and contributing factors include viral infections, small size at birth, diet, exposure to tobacco smoke, and environmental pollutants.

## Goals of Therapy

- Goals of therapy as defined by the National Institute of Health (NIH) Expert Panel Report 3 (EPR-3) are to
  - reduce impairment (prevent symptoms, maintain “normal” pulmonary function, maintain normal activity levels, require infrequent use of short-acting inhaled  $\beta_2$ -agonists, and meet patient expectations for care)
  - reduce risk (prevent recurrent exacerbations, minimize the need for ED visits, prevent progressive loss of function, provide optimal therapy with minimal/no adverse effects)

## Treatment

- Early-phase asthmatic response occurs immediately after allergen exposure and is blocked by preadministration of  $\beta_2$ -agonists, such as albuterol.
- Late-phase asthmatic response occurs 4 to 12 hours later, is often more severe and prolonged, and is more difficult to reverse with bronchodilators.
- General treatment principles recommended by EPR-3 include four components:
  - Measures of asthma assessment and management
  - Education for a partnership in asthma care (Table 23.5)
  - Control of environmental factors and comorbid conditions that affect asthma
  - Medications

TABLE 23.5 Key Educational Messages: Teach and Reinforce at Every Opportunity

## BASIC FACTS ABOUT ASTHMA

- The contrast between airways of a person who has and a person who does not have asthma; the role of inflammation
- What happens to the airways in an asthma attack

## ROLES OF MEDICATIONS—UNDERSTANDING THE DIFFERENCE BETWEEN THE FOLLOWING:

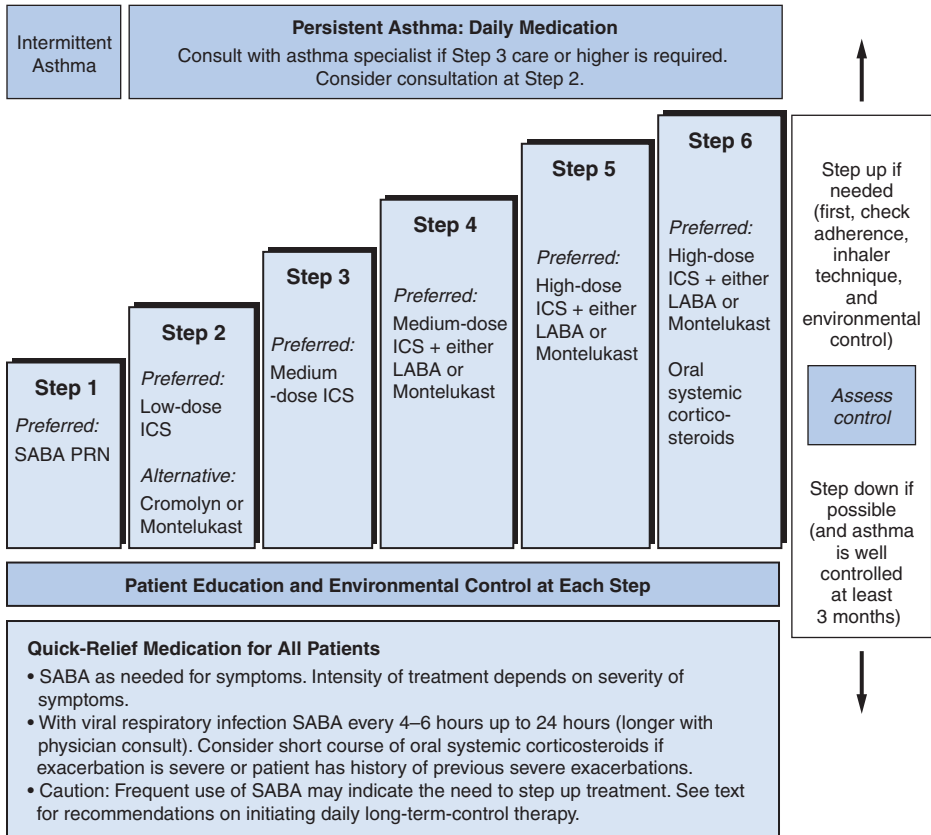
- Long-term-control medications: prevent symptoms, often by reducing inflammation. Must be taken daily. Do not expect them to give quick relief.
- Quick-relief medications: short-acting  $\beta_2$ -agonists relax muscles around the airway and provide prompt relief of symptoms. Do not expect them to provide long-term asthma control. Using quick-relief medication on a daily basis indicates the need for starting or increasing long-term control medications.

## PATIENT SKILLS

- Taking medications correctly
  - Inhaler technique (demonstrate to patient and have the patient return the demonstration)
  - Use of devices, such as prescribed valved holding chamber, spacer, nebulizer
- Identifying and avoiding environmental exposures that worsen the patient's asthma (e.g., allergens, irritants, tobacco smoke)
- Self-monitoring to:
  - Assess level of asthma control
  - Monitor symptoms and, if prescribed, peak flow
  - Recognize early signs and symptoms of worsening asthma
- Using written asthma action plan to know when and how to:
  - Take daily actions to control asthma
  - Adjust medication in response to signs of worsening asthma
  - Seek medical care as appropriate

Source: Reprinted from National Institutes of Health. *Expert Panel Report 3: Guidelines for the Diagnosis and Management of Asthma*. Bethesda, MD: National Heart, Lung, and Blood Institute; 2007. NIH publication 07-4051.

- Most patients with asthma can be well controlled using a step-care approach recommended by EPR-3 (Figures 23.1–23.3).
- When equivalent doses are given, there is no advantage of nebulized therapy over aerosolized therapy; however, some patients perceive nebulized therapy as being more potent.
- Treatment guidelines for the management of acute asthma exacerbations are shown in Figure 23.4 and Table 23.6.
- Home treatment for the management of acute exacerbations is shown in Figure 23.5.
- Agents used for long-term control of asthma are shown in Table 23.7.
- Overuse of quick reliever medication suggests inadequate asthma control, which can lead to fatal asthma. Patients should be instructed on when to seek medical assistance.
- **Inhalers**
  - There is more than one correct way to use an inhaler. Table 23.8 summarizes two commonly accepted approaches.
  - Most children <3 years of age cannot use dry powder inhalers because of inability to generate sufficient peak inspiratory flow.
  - Children <5 years of age generally have a difficult time coordinating the use of a standard metered-dose inhaler (MDI).
  - Inhalation aids (spacers) significantly improve the efficacy of medications given by MDI to young children or others who have difficulty coordinating the MDI. They should be used in virtually all patients receiving inhaled corticosteroids via an MDI because they enhance efficacy and reduce the risk of thrush.
  - A nebulized corticosteroid preparation (budesonide) is available for young children.



Key: **Alphabetical order is used when more than one treatment option is listed within either preferred or alternative therapy.** ICS, inhaled corticosteroid; LABA, inhaled long-acting  $\beta_2$ -agonist; SABA, inhaled short-acting  $\beta_2$ -agonist.

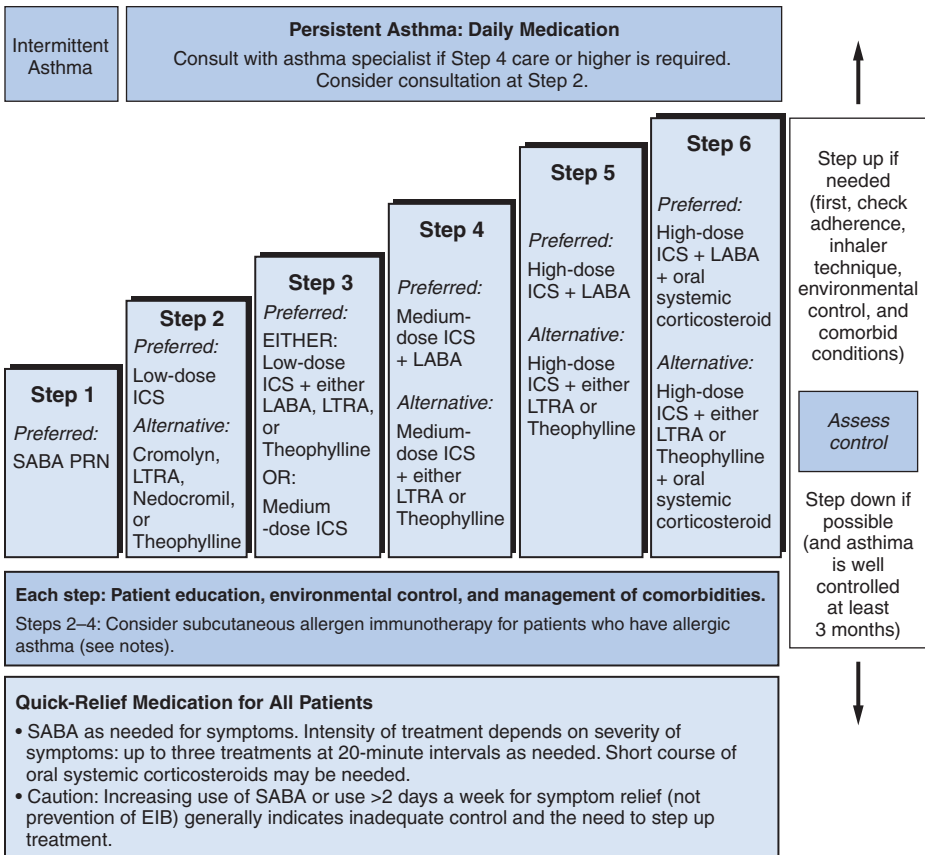
#### Notes:

- The stepwise approach is meant to assist, not replace, the clinical decision-making required to meet individual patient needs.
- If alternative treatment is used and response is inadequate, discontinue it and use the preferred treatment before stepping up.
- If clear benefit is not observed within 4–6 weeks and patient/family medication technique and adherence are satisfactory, consider adjusting therapy or alternative diagnosis.
- Studies on children 0–4 years of age are limited. Step 2 preferred therapy is based on Evidence A. All other recommendations are based on expert opinion and extrapolation from studies in older children.

**Figure 23.1** Stepwise approach for managing asthma in children 0 to 4 years of age. (Reprinted from National Institutes of Health. *Expert Panel Report 3: Guidelines for the Diagnosis and Management of Asthma*. Bethesda, MD: National Heart, Lung, and Blood Institute; 2007. NIH publication 07-4051.)

## Drug Therapy

- **$\beta_2$ -Agonists**
  - Short-acting inhaled  $\beta_2$ -agonists (SABAs) are considered the first choice for the treatment of acute asthma because of their potency and rapid onset of action. They are most effective in reversing early-phase asthma. Clinically relevant tolerance to the airway response of  $\beta_2$ -agonists does not occur.



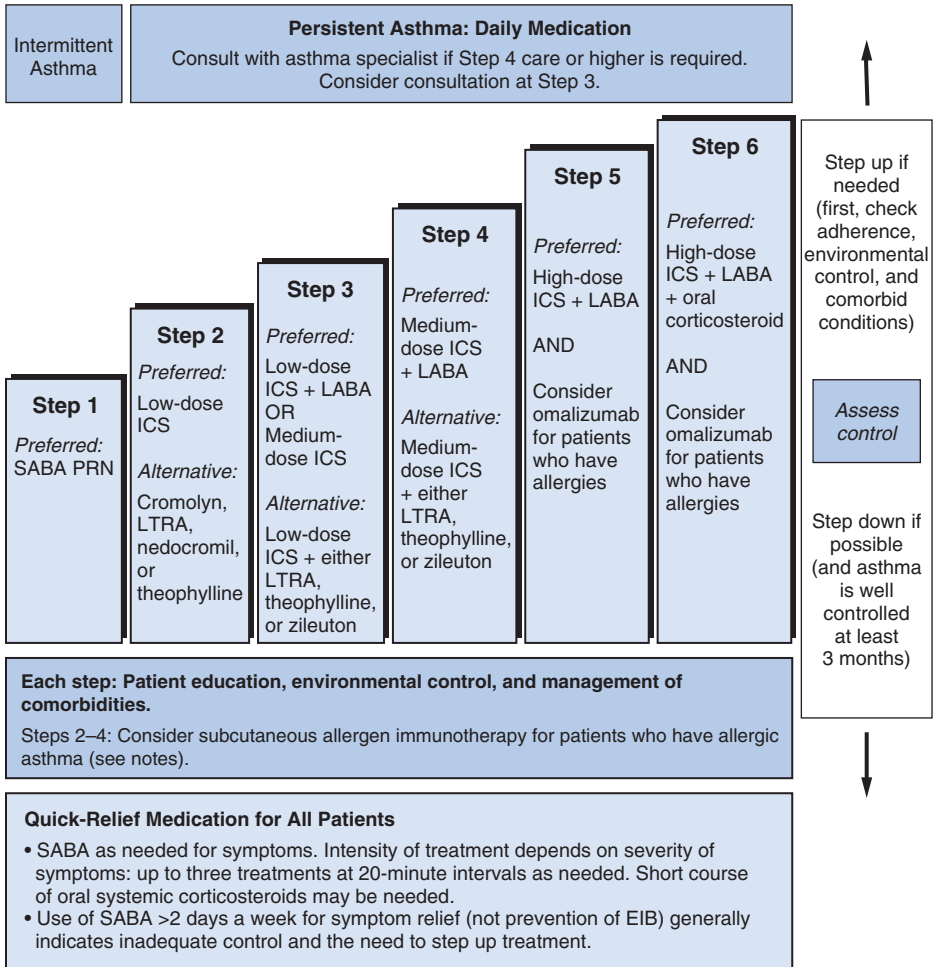
**Key:** Alphabetical order is used when more than one treatment option is listed within either preferred or alternative therapy. ICS, inhaled corticosteroid; LABA, inhaled long-acting  $\beta_2$ -agonist; LTRA, leukotriene receptor antagonist; SABA, inhaled short-acting  $\beta_2$ -agonist.

**Notes:**

- The stepwise approach is meant to assist, not replace, the clinical decision-making required to meet individual patient needs.
- If alternative treatment is used and response is inadequate, discontinue it and use the preferred treatment before stepping up.
- Theophylline is a less desirable alternative because of the need to monitor serum concentration levels.

**Figure 23.2** Stepwise approach for managing asthma in children 5 to 11 years of age. (Reprinted from National Institutes of Health. *Expert Panel Report 3: Guidelines for the Diagnosis and Management of Asthma*. Bethesda, MD: National Heart, Lung, and Blood Institute; 2007. NIH publication 07-4051.)

- Bronchodilation via the inhaled route is at least as good as that with parenteral or oral routes, with fewer side effects. Oral administration should not be used to treat acute episodes of severe asthma due to the slow onset of action, lower efficacy, and erratic absorption. Current standards discourage the use of IV  $\beta_2$ -agonists for asthma management.
- Aerosolized SABAs are considered the drug of choice for ED or hospital management of asthma.
- Albuterol inhalers are no longer interchangeable at this time. Also, important to note that Xopenox is the racemic mixture whereas albuterol is a combination of the r and s enantiomer.



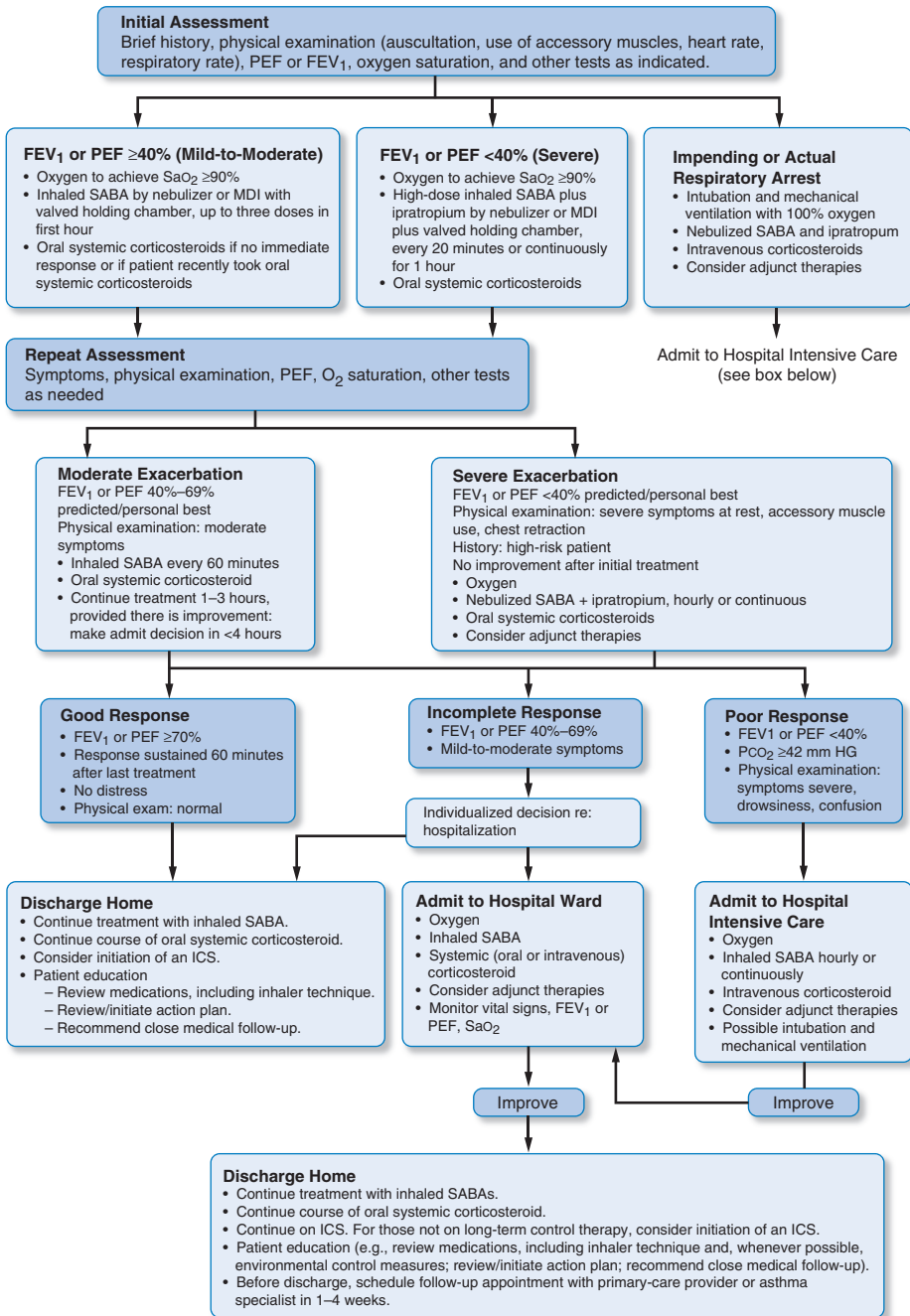
Key: **Alphabetical order is used when more than one treatment option is listed within either preferred or alternative therapy.** EIB, exercise-induced bronchospasm; ICS, inhaled corticosteroid; LABA, long-acting inhaled  $\beta_2$ -agonist; LTRA, leukotriene receptor antagonist; SABA, inhaled short-acting  $\beta_2$ -agonist.

**Notes:**

- The stepwise approach is meant to assist, not replace, the clinical decision-making required to meet individual patient needs.
- If alternative treatment is used and response is inadequate, discontinue it and use the preferred treatment before stepping up.
- Zileuton is a less desirable alternative because of limited studies as adjunctive therapy and the need to monitor liver function. Theophylline requires monitoring of serum concentration levels.
- In step 6, before oral systemic corticosteroids are introduced, a trial of high-dose ICS + LABA + either LTRA, theophylline, or zileuton may be considered, although this approach has not been studied in clinical trials.

**Figure 23.3** Stepwise approach for managing asthma in youth 12 years of age or older and adults. (Reprinted from National Institutes of Health. *Expert Panel Report 3: Guidelines for the Diagnosis and Management of Asthma.* Bethesda, MD: National Heart, Lung, and Blood Institute; 2007. NIH publication 07-4051.)





**Figure 23.4** Management of asthma exacerbations: emergency department and hospital-based care. FEV<sub>1</sub>, forced expiratory volume in 1 second; ICS, inhaled corticosteroid; MDI, metered-dose inhaler; PCO<sub>2</sub>, partial pressure of carbon dioxide; PEF, peak expiratory flow; SABA, short-acting β<sub>2</sub>-agonist; SaO<sub>2</sub>, arterial oxygen saturation. (Adapted from National Institutes of Health. *Expert Panel Report 3: Guidelines for the Diagnosis and Management of Asthma*. Bethesda, MD: National Heart, Lung, and Blood Institute; 2007. NIH publication 07-4051.)

TABLE 23.6 Dosages of Drugs for Asthma Exacerbations

Medication	Dosages		Comments
	Child Dose <sup>a</sup>	Adult Dose	
<b>INHALED SHORT-ACTING <math>\beta_2</math>-AGONISTS</b>			
<b>Albuterol</b>			
Nebulizer solution (0.63 mg/3 mL, 1.25 mg/ 3 mL, 2.5 mg/3 mL, 5.0 mg/mL)	0.15 mg/kg (minimum dose 2.5 mg) every 20 minutes for three doses, then 0.15–0.3 mg/ kg up to 10 mg every 1–4 hours as needed or 0.5 mg/kg/hour by continuous nebulization	2.5–5 mg every 20 minutes for three doses, then 2.5–10 mg every 1–4 hours as needed or 10–15 mg/ hour continuously	Only selective $\beta_2$ -agonists are recommended. For optimal delivery, dilute aerosols to minimum of 3 mL at gas flow of 6–8 L/ minute. Use large-volume nebulizers for continuous administration. May mix with ipratropium nebulizer solution
MDI (90 mcg/puff)	4–8 puffs every 20 minutes for three doses, then every 1–4 hours inhalation maneuver as needed. Use VHC; add mask in children <4 years	4–8 puffs every 20 minutes up to 4 hours, then every 1–4 hours as needed	In mild to moderate exacerbations, MDI plus VHC is as effective as nebulized therapy, with appropriate administration technique and coaching by trained personnel.
<b>Levalbuterol (R-albuterol)</b>			
Nebulizer solution (0.63 mg/3 mL, 1.25 mg/0.5 mL, 1.25 mg/3 mL)	0.075 mg/kg (minimum dose 1.25 mg) every 20 minutes for three doses, then 0.075– 0.15 mg/kg up to 5 mg every 1–4 hours as needed	1.25–2.5 mg every 20 minutes for three doses, then 1.25–5 mg every 1–4 hours as needed	Levalbuterol administered in one-half the mg dose of albuterol provides comparable efficacy and safety. Has not been evaluated by continuous nebulization
MDI (45 mcg/puff)	See albuterol MDI dose.	See albuterol MDI dose.	
<b>Pirbuterol</b>			
MDI (200 mcg/puff)	See albuterol MDI dose; thought to be half as potent as albuterol on a milligram basis	See albuterol MDI dose.	Has not been studied in severe asthma exacerbations
<b>SYSTEMIC (INJECTED) <math>\beta_2</math>-AGONISTS</b>			
<b>Epinephrine</b> 1:1,000 (1 mg/mL)	0.01 mg/kg up to 0.3–0.5 mg every 20 minutes for three doses subcutaneously	0.3–0.5 mg every 20 minutes for three doses subcutaneously	No proven advantage of systemic therapy versus aerosol
<b>Terbutaline</b> (1 mg/mL)	0.01 mg/kg every 20 minutes for three doses, then every 2–6 hours as needed subcutaneously	0.25 mg every 20 minutes for three doses subcutaneously	No proven advantage of systemic therapy versus aerosol

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TABLE 23.6 Dosages of Drugs for Asthma Exacerbations (Continued)

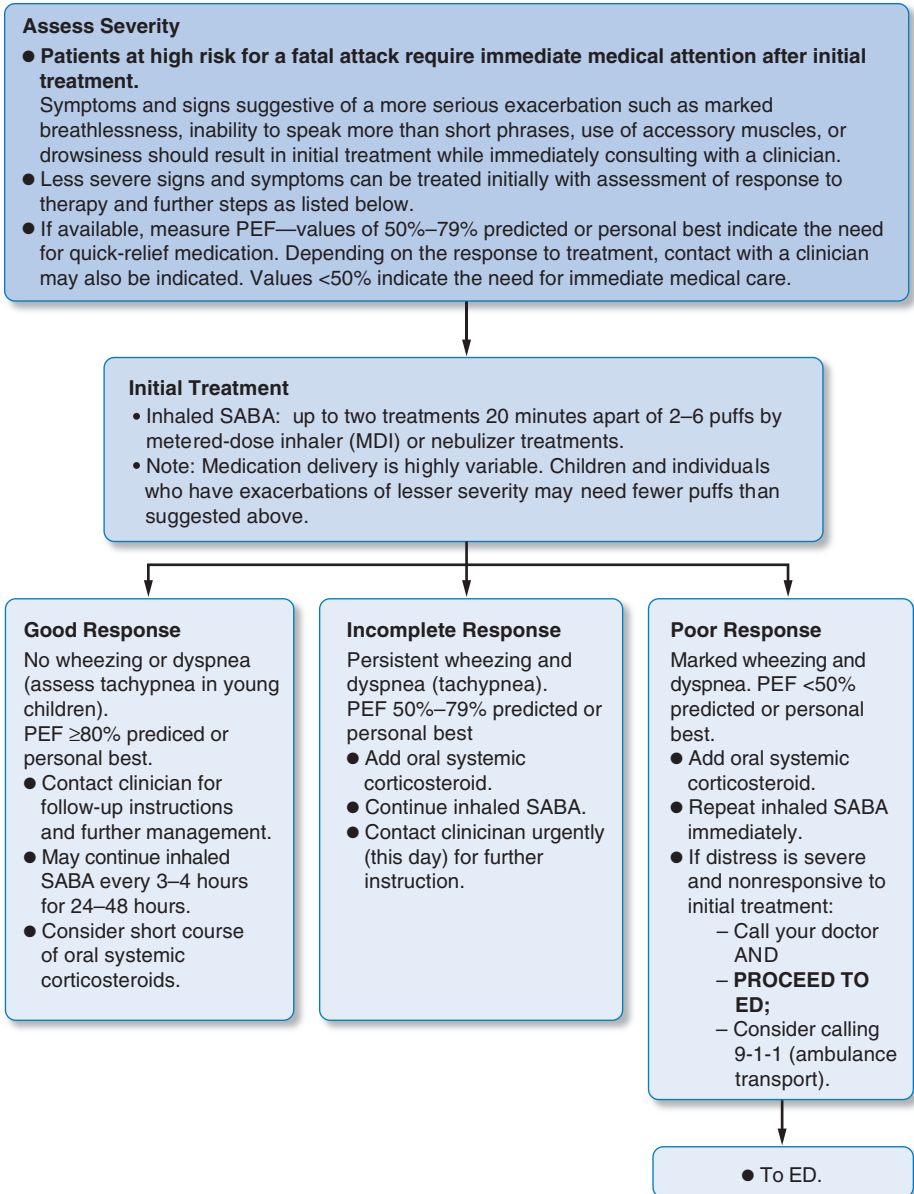
Medication	Dosages		Comments
	Child Dose <sup>a</sup>	Adult Dose	
<b>ANTICHOLINERGICS</b>			
<b>Ipratropium bromide</b>			
Nebulizer solution (0.25 mg/mL)	0.25–0.5 mg every 20 minutes for three doses, then as needed	0.5 mg every 20 minutes for three doses, then as needed	May mix in same nebulizer with albuterol. Should not be used as first-line therapy; should be added to SABA therapy for severe exacerbations. The addition of ipratropium has not been shown to provide further benefit once the patient is hospitalized.
MDI (18 mcg/puff)	4–8 puffs every 20 minutes as needed up to 3 hours	8 puffs every 20 minutes as needed up to 3 hours	Should use with VHC and face mask for children <4 years Studies have examined ipratropium bromide MDI for up to 3 hours
<b>Ipratropium with albuterol</b>			
Nebulizer solution (Each 3-mL vial contains 0.5 mg ipratropium bromide and 2.5 mg albuterol.)	1.5 mL every 20 minutes for three doses, then as needed	3 mL every 20 minutes for three doses, then as needed	May be used for up to 3 hours in the initial management of severe exacerbations. The addition of ipratropium to albuterol has not been shown to provide further benefit once the patient is hospitalized.
MDI (Each puff contains 18 mcg ipratropium bromide and 90 mcg albuterol.)	4–8 puffs every 20 minutes as needed up to 3 hours	8 puffs every 20 minutes as needed up to 3 hours	Should use with VHC and face mask for children <4 years
<b>SYSTEMIC CORTICOSTEROIDS</b>			
<b>(Applies to all three corticosteroids)</b>			
<b>Prednisone</b> <b>Methyl prednisolone</b> <b>Prednisolone</b>	1 mg/kg in two divided doses (maximum = 60 mg/day) until PEF is 70% of predicted or personal best	40–80 mg/day in one or two divided doses until PEF reaches 70% of predicted or personal best	For outpatient “burst,” use 40–60 mg in single or two divided doses for total of 5–10 days in adults (children: 1–2 mg/kg/day maximum 60 mg/day for 3–10 days).

<sup>a</sup>Children, 12 years of age or younger.

MDI, metered-dose inhaler; PEF, peak expiratory flow; SABA, short-acting  $\beta_2$ -agonist; VHC, valved holding chamber.

Source: Reprinted from National Institutes of Health. *Expert Panel Report 3: Guidelines for the Diagnosis and Management of Asthma*. Bethesda, MD: National Heart, Lung, and Blood Institute; 2007.

NIH publication 07-4051.



**Figure 23.5** Management of asthma exacerbations: home treatment. ED, emergency department; MDI, metered-dose inhaler; PEF, peak expiratory flow; SABA, short-acting  $\beta_2$ -agonist. (Adapted from National Institutes of Health. *Expert Panel Report 3: Guidelines for the Diagnosis and Management of Asthma*. Bethesda, MD: National Heart, Lung, and Blood Institute; 2007. NIH publication 07-4051.)

TABLE 23.7 Long-Term Control Medications

Name/Products (Listed Alphabetically)	Indications/Mechanisms	Potential Adverse Effects	Therapeutic Issues (Not All Inclusive)
<b>CORTICOSTEROIDS (GLUCOCORTICOIDS)</b>			
<b>Inhaled (ICS):</b>	<i>Indications</i>	<ul style="list-style-type: none"> <li>• Cough, dysphonia, oral thrush (candidiasis)</li> <li>• In high doses (Tables 23.6, 23.7), systemic effects may occur, although studies are not conclusive, and clinical significance of these effects has not been established (e.g., adrenal suppression, osteoporosis, skin thinning, and easy bruising). In low to medium doses, suppression of growth velocity has been observed in children, but this effect may be transient, and the clinical significance has not been established.</li> </ul>	<ul style="list-style-type: none"> <li>• Spacer/holding chamber devices with nonbreath-activated MDIs and mouth washing after inhalation decrease local side effects.</li> <li>• Preparations are not absolutely interchangeable on a microgram or per-puff basis (Tables 23.6, 23.7 for estimated clinical comparability). New delivery devices may provide greater delivery to airways; this change may affect dose.</li> <li>• The risks of uncontrolled asthma should be weighed against the limited risks of ICS therapy. The potential but small risk of adverse events is well balanced by their efficacy.</li> <li>• “Adjustable dose” approach to treatment may enable reduction in cumulative dose of ICS treatment with time without sacrificing maintenance of asthma control.</li> <li>• Dexamethasone is not included as an ICS for long-term control because it is highly absorbed and has long-term suppressive side effects.</li> </ul>
Beclomethasone Budesonide Ciclesonide Flunisolide Fluticasone Mometasone	<ul style="list-style-type: none"> <li>• Long-term prevention of symptoms: suppression, control, and reversal of inflammation</li> <li>• Reduce need for oral corticosteroid</li> </ul> <i>Mechanisms</i> <ul style="list-style-type: none"> <li>• Anti-inflammatory. Block late reaction to allergen and reduce airway hyperresponsiveness. Inhibit cytokine production, adhesion protein activation, and inflammatory cell migration and activation</li> <li>• Reverse <math>\beta_2</math>-receptor downregulation. Inhibit microvascular leakage</li> </ul>	<ul style="list-style-type: none"> <li>• Short-term use: reversible abnormalities in glucose metabolism, increased appetite, fluid retention, weight gain, mood alteration, hypertension, peptic ulcer, and rarely aseptic necrosis</li> <li>• Long-term use: adrenal axis suppression, growth suppression, dermal thinning, hypertension, diabetes, Cushing syndrome, cataracts, muscle weakness; in rare instances, impaired immune function</li> <li>• Consideration should be given to coexisting conditions that could be worsened by systemic corticosteroids, such as herpes virus infections, varicella, tuberculosis, hypertension, peptic ulcer, diabetes mellitus, osteoporosis, and <i>Strongyloides</i></li> </ul>	<ul style="list-style-type: none"> <li>• Use at lowest effective dose. For long-term use, alternate-day AM dosing produces the least toxicity. If daily doses are required, one study shows improved efficacy with no increase in adrenal suppression when administered at 3 PM rather than in the morning.</li> </ul>
<b>Systemic:</b> Methylprednisolone Prednisolone Prednisone	<i>Indications</i> <ul style="list-style-type: none"> <li>• For short-term (3–10 days) “burst”: to gain prompt control of inadequately controlled persistent asthma</li> <li>• For long-term prevention of symptoms in severe persistent asthma, suppression, control, and reversal of inflammation</li> </ul> <i>Mechanisms</i> <ul style="list-style-type: none"> <li>• Same as inhaled</li> </ul>		

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## IMMUNOMODULATORS

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Omalizumab (anti-IgE)

For subcutaneous use

### Indications

- Long-term control and prevention of symptoms in adults ( $\geq 12$  years old) who have moderate or severe persistent allergic asthma inadequately controlled with ICS.

### Mechanisms

- Binds to circulating IgE, preventing it from binding to the high-affinity ( $F_{c\epsilon}RI$ ) receptors on basophils and mast cells
- Decreases mast cell mediator release from allergen exposure
- Decreases the number of  $F_{c\epsilon}R1s$  in basophils and submucosal cells

- Pain and bruising of injection sites has been reported in 5%–20% of patients.
- Anaphylaxis has been reported in 0.2% of treated patients.
- Malignant neoplasms were reported in 0.5% of patients compared with 0.2% receiving placebo; relationship to drug is unclear.

- Monitor patients after injection. Be prepared and equipped to identify and treat anaphylaxis that may occur.
  - The dose is administered either every 2 or 4 weeks and is dependent on the patient's body weight and IgE level before therapy.
  - A maximum of 150 mg can be administered in one injection.
  - Needs to be stored under refrigeration at 2°–8°C.
  - Whether patients will develop significant antibody titers to the drug with long-term administration is unknown.
- 

## LEUKOTRIENE RECEPTOR ANTAGONISTS

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Montelukast tablets and granules

### Mechanisms

- Leukotriene receptor antagonist; selective competitive inhibitor of  $CysLT_1$  receptor

### Indications

- Long-term control and prevention of symptoms in mild persistent asthma for patients  $\geq 1$  year of age. May also be used with ICS as combination therapy in moderate persistent asthma

- No specific adverse effects have been identified.
- Rare cases of Churg-Strauss have occurred, but the association is unclear.

- May attenuate EIB in some patients, but less effective than ICS therapy
  - Do not use LTRA + LABA as a substitute for ICS + LABA.
  - A flat dose–response curve, without further benefit if dose is increased above those recommended
- 

*Continued on following page*

**TABLE 23.7 Long-Term Control Medications (Continued)**

Zafirlukast tablets	<ul style="list-style-type: none"> <li>• Long-term control and prevention of symptoms in mild persistent asthma for patients <math>\geq 7</math> years of age. May also be used with ICS as combination therapy in moderate persistent asthma</li> </ul>	<ul style="list-style-type: none"> <li>• Postmarketing surveillance has reported cases of reversible hepatitis and, rarely, irreversible hepatic failure resulting in death and liver transplantation.</li> </ul>	<ul style="list-style-type: none"> <li>• Administration with meals decreases bioavailability; take at least 1 hour before or 2 hours after meals.</li> <li>• Zafirlukast is a microsomal P-450 enzyme inhibitor that can inhibit the metabolism of warfarin. INRs should be monitored during coadministration.</li> <li>• Patients should be warned to discontinue use if they experience signs and symptoms of liver dysfunction (right upper quadrant pain, pruritus, lethargy, jaundice, nausea), and serum ALTs should be monitored.</li> </ul>
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**5-LIPOXYGENASE INHIBITOR**

Zileuton tablets	<p><i>Mechanisms</i></p> <ul style="list-style-type: none"> <li>• Inhibits the production of leukotrienes from arachidonic acid, both LTB<sub>4</sub> and the cysteinyl leukotrienes</li> </ul> <p><i>Indications</i></p> <ul style="list-style-type: none"> <li>• Long-term control and prevention of symptoms in mild persistent asthma for patients <math>\geq 12</math> years of age</li> <li>• May be used with ICS as combination therapy in moderate persistent asthma in patients <math>\geq 12</math> years of age</li> </ul>	<ul style="list-style-type: none"> <li>• Elevation of liver enzymes has been reported. Limited case reports of reversible hepatitis and hyperbilirubinemia</li> </ul>	<ul style="list-style-type: none"> <li>• Zileuton is microsomal P-450 enzyme inhibitor that can inhibit the metabolism of warfarin and theophylline. Doses of these drugs should be monitored accordingly.</li> <li>• Monitor hepatic enzymes (ALT).</li> </ul>
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**LONG-ACTING  $\beta_2$ -AGONISTS (LABA)**

<b>Inhaled LABA:</b> Formoterol Salmeterol	<p><i>Indications</i></p> <ul style="list-style-type: none"> <li>• Long-term prevention of symptoms added to ICS</li> <li>• Prevention of EIB</li> <li>• <i>Not to be used to treat acute symptoms or exacerbations</i></li> </ul>	<ul style="list-style-type: none"> <li>• Tachycardia, skeletal muscle tremor, hypokalemia, prolongation of QTc interval in overdose</li> <li>• A diminished bronchoprotective effect may occur within 1 week of chronic therapy. Clinical significance has not been established.</li> <li>• Potential risk of uncommon, severe, life-threatening or fatal exacerbation: see text for additional discussion regarding safety of LABAs.</li> </ul>	<ul style="list-style-type: none"> <li>• Not to be used to treat acute symptoms or exacerbations</li> <li>• Should not be used as monotherapy for long-term control of asthma or as anti-inflammatory therapy</li> <li>• May provide more effective symptom control when added to standard doses of ICS compared with increasing the ICS dosage.</li> </ul>
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*Mechanisms*

- Bronchodilation. Smooth muscle relaxation after adenylate cyclase activation and increase in cyclic AMP, producing functional antagonism of bronchoconstriction
- Compared with SABA, salmeterol (but not formoterol) has slower onset of action (15–30 minutes). Both salmeterol and formoterol have longer duration (>12 hours) compared with SABA.

**Oral:**

Albuterol, sustained-release

- Clinical significance of potentially developing tolerance is uncertain because studies show that symptom control and bronchodilation are maintained.
- Decreased duration of protection against EIB may occur with regular use.
  
- Inhaled route is preferred because LABAs are longer acting and have fewer side effects than oral sustained-release agents. Oral agents have not been adequately studied as adjunctive therapy with ICS.

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**METHYLXANTHINES**

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Theophylline, sustained-release tablets and capsules

*Indications*

- Long-term control and prevention of symptoms in mild persistent asthma or as adjunctive with ICS in moderate or persistent asthma.

*Mechanisms*

- Bronchodilation. Smooth muscle relaxation from phosphodiesterase inhibition and possibly adenosine antagonism
- May affect eosinophilic infiltration into bronchial mucosa as well as decreases T-lymphocyte numbers in epithelium
- Increases diaphragm contractility and mucociliary clearance

- Dose-related acute toxicities include tachycardia, nausea and vomiting, tachyarrhythmias (SVT), central nervous system stimulation, headache, seizures, hematemesis, hyperglycemia, and hypokalemia.
- Adverse effects at usual therapeutic doses include insomnia, gastric upset, aggravation of ulcer or reflux, increase in hyperactivity in some children, and difficulty in urination in elderly men who have prostatism.

- Maintain steady-state serum concentrations between 5 and 15 mcg/mL. Routine serum concentration monitoring is essential owing to significant toxicities, narrow therapeutic range, and individual differences in metabolic clearance. Absorption and metabolism may be affected by numerous factors that can produce significant changes in steady-state serum theophylline concentrations.
- Patients should be told to discontinue if they experience toxicity.
- Not generally recommended for exacerbations. There is minimal evidence for added benefit to optimal doses of SABA. Serum concentration monitoring is mandatory.

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ALT, alanine aminotransferase; AMP, adenosine monophosphate; Anti-IgE, anti-immunoglobulin E; EIB, exercise-induced bronchospasm; F<sub>CE</sub>RI, high-affinity IgE receptor; ICS, inhaled corticosteroids; IGS, inhaled glucocorticoids; INR, international normalized ratio; LABA, long-acting inhaled  $\beta_2$ -agonist; LTB<sub>4</sub>, leukotriene B<sub>4</sub>; LTRA, leukotriene receptor agonist; MDI, metered-dose inhaler; SABA, short-acting inhaled  $\beta_2$ -agonist; SVT, supraventricular tachycardia.

Source: Reprinted from National Institutes of Health. *Expert Panel Report 3: Guidelines for the Diagnosis and Management of Asthma*. Bethesda, MD: National Heart, Lung, and Blood Institute; 2007. NIH publication 07-4051.



TABLE 23.8 Steps to Correct Use of Metered-Dose Inhalers<sup>a</sup>

1. Shake the inhaler well and remove the dust cap.
2. Exhale *slowly* through pursed lips.<sup>b</sup>
3. If using the “closed-mouth” technique, hold the inhaler upright and place the mouthpiece between your lips. Be careful not to block the opening with your tongue or teeth.
4. If using the “open-mouth” technique, open your mouth wide and hold the inhaler upright 1–2 inches from your mouth, making sure the inhaler is properly aimed.
5. Press down on the inhaler *once* as you *start a slow, deep* inhalation.
6. Continue to inhale slowly and deeply through your mouth. Try to inhale for at least 5 seconds.
7. Hold your breath for 10 seconds (use your fingers to count to 10 slowly). If 10 seconds makes you feel uncomfortable, try to hold your breath for at least 4 seconds.
8. Exhale *slowly*.<sup>c</sup>
9. Wait at least 30–60 seconds before inhaling the next puff of medicine.

<sup>a</sup>If using a spacer, see manufacturer’s instructions. Same basic principles of slow, deep inhalation with adequate breath-hold apply. With spacers, put mouthpiece on top of your tongue to ensure that tongue does not block aerosol.

<sup>b</sup>As long as exhalation is slow, exhalation can take place for several seconds. Some experts insist on exhaling only a tidal volume, but the key is to exhale slowly.

<sup>c</sup>If patient has concomitant rhinitis, exhaling through the nose may be of benefit when using corticosteroids or ipratropium (i.e., some medication may deposit in nose).

- Long-acting  $\beta_2$ -agonists (LABAs) are not indicated for the treatment of asthma in the ED and should not be used as monotherapy for long-term control of persistent asthma. **LABA therapy should only be used in combination with inhaled corticosteroids in patients with asthma.**
- SABAs are generally the agent of choice for prophylaxis of exercise-induced asthma (given 5–10 minutes before exercise). For prolonged periods of exercise (>3 hours) LABAs may be used as they provide longer protection.
- $\beta$ -Agonists are cardiac stimulants that can cause tachycardia and (rarely) arrhythmias. There may be a small increased risk of asthma-related death and asthma exacerbation in patients receiving LABAs.
- **Theophylline**
  - EPR-3 guidelines state that theophylline is not recommended for routine management of hospitalized patients with asthma.
  - Aminophylline is not as efficacious as  $\beta_2$ -agonists and has more risks for serious side effects. Adding theophylline to optimal SABA therapy does not provide any benefit; NIH guidelines do not recommend this practice.
  - Theophylline dosing guidelines are shown in Table 23.9 (chronic use), Table 23.10 (infants), and Table 23.11 (dose adjusting based on serum levels). Factors affecting serum levels are shown in Table 23.12.
  - Side effects can include headache, nausea, vomiting, irritability or hyperactivity, insomnia, and diarrhea. With higher serum levels cardiac arrhythmias, seizures, and death can occur.
- **Anticholinergic Agents**
  - Bronchodilation from ipratropium is smaller than that seen with  $\beta_2$ -agonists.
  - Anticholinergic agents (tiotropium, ipratropium) have had limited use in asthma except in the ED and a few other rare situations. Long-term studies are needed before they are included in everyday clinical practice.
- **Corticosteroids**
  - Corticosteroids decrease airway inflammation and increase the response to  $\beta_2$ -agonists. They hasten the recovery of acute exacerbations and decrease the need for hospitalizations if given early in the management of acute asthma. Tables 23.13 and 23.14 compare the dosages of inhaled corticosteroid (ICS) products.

TABLE 23.9 Theophylline Dosing Guide for Chronic Use<sup>a,b</sup>

Starting dose for children 1–15 years <45 kg: 12–14 mg/kg/day to maximum of 300 mg/day  
 Starting dose for adults and children 1–15 years >45 kg: 300 mg/day  
 Titrate dose upward after 3 days if necessary and if tolerated to:

- 16 mg/kg/day to maximum of 400 mg/day in children 1–15 years <45 kg
- 400 mg/day in adults and children >45 kg

Titrate dose upward after 3 more days if necessary and if tolerated to:

- 20 mg/kg/day to a maximum of 600 mg/day in children 1–15 years <45 kg
- 600 mg/day in adults and in children >45 kg

<sup>a</sup>Dose using ideal body weight or actual body weight, whichever is less. These dosages do not apply if liver disease, heart failure, or other factors documented to affect theophylline clearance are present. Doses must be guided by monitoring serum concentrations to ensure optimal safety and efficacy.

<sup>b</sup>Dosing schedule dependent on product selected; sustained-release products are much preferred, if at all possible.

Source: Hendeles L et al. Revised FDA labeling guideline for theophylline oral dosage forms. *Pharmacotherapy*. 1995;15:409.

TABLE 23.10 Food and Drug Administration Guidelines for Theophylline Dosing in Infants<sup>a</sup>

#### PREMATURE NEONATES

<24 days postnatal age: 1.0 mg/kg every 12 hours  
 ≥24 days postnatal age: 1.5 mg/kg every 12 hours

#### TERM INFANTS AND INFANTS UP TO 52 WEEKS OF AGE

Total daily dose (mg) =  $([0.2 \times \text{age in weeks}] + 5.0) \times (\text{kg body weight})$

- Up to age 26 weeks; divide dose into three equal amounts administered at 8-hour intervals
- >26 weeks of age; divide dose into four equal amounts administered at 6-hour intervals

<sup>a</sup>Final doses adjusted to a peak steady-state serum theophylline concentration of 5 to 10 mcg/mL in neonates and 10 to 15 mcg/mL in older infants.

Source: Hendeles L et al. Revised FDA labeling guideline for theophylline oral dosage forms. *Pharmacotherapy*. 1995;15:409.

TABLE 23.11 Adjusting Doses of Theophylline Based on Serum Concentrations

Peak Theophylline Concentration (mcg/mL) <sup>a</sup>	Approximate Adjustment in Daily Dose	Comment
<5.0	↑ by 25%	Recheck serum theophylline concentration.
5–10	↑ by 25% if clinically indicated	Recheck serum concentration; ↑ dose only if poor response to therapy.
10–12	Cautious 10% ↑ if clinically indicated	If asymptomatic, no ↑ needed. Recheck serum theophylline concentration before further dose changes.
12–15	Occasional intolerance requires a 10% ↓	If asymptomatic, no dose change needed unless side effects present.
16–20	↓ by 10%–25%	Even if asymptomatic and side effects absent, a dose ↓ is prudent.
20–24.9	↓ by 50%	Omit one dose even if asymptomatic and side effects absent; a dose ↓ is indicated.
25–29.9	↓ by >50%	Omit next doses even if asymptomatic and side effects absent; a dose ↓ is indicated; repeat serum theophylline concentration after dose adjustment.
>30	Omit next doses; ↓ by 60%–75%	Seek medical attention and consult regional poison center even if not symptomatic; if >60 years of age, anticipate need for treatment of seizures.

<sup>a</sup>It is important that levels are obtained at steady state. If laboratory results appear questionable, suggest repeat measurements.

TABLE 23.12 Factors Affecting Serum Theophylline Concentrations<sup>a</sup>

Factor	Decreases Theophylline Concentrations	Increases Theophylline Concentrations	Recommended Action
Food	↓ or delays absorption of some sustained-release theophylline (SR) products	↑ rate of absorption (fatty foods)	Select theophylline preparation that is not affected by food.
Diet	↑ metabolism (high protein)	↓ metabolism (high carbohydrate)	Inform patients that major changes in diet are not recommended while taking theophylline.
Systemic, febrile viral illness (e.g., influenza)		↓ metabolism	Decrease theophylline dose according to serum concentration level. Decrease dose by 50% if serum concentration measurement is not available.
Hypoxia, cor pulmonale, and decompensated congestive heart failure, cirrhosis		↓ metabolism	Decrease dose according to serum concentration level.
Age	↑ metabolism (1–9 years)	↓ metabolism (<6 months, elderly)	Adjust dose according to serum concentration level.
Phenobarbital, phenytoin, carbamazepine	↑ metabolism		Increase dose according to serum concentration level.
Cimetidine		↓ metabolism	Use alternative histamine H <sub>2</sub> -antagonist (e.g., famotidine or ranitidine).
Macrolides: TAO, erythromycin, clarithromycin		↓ metabolism	Use alternative antibiotic or adjust theophylline dose.
Quinolones: ciprofloxacin, enoxacin, pefloxacin		↓ metabolism	Use alternative antibiotic or adjust theophylline dose.
Rifampin	↑ metabolism		Increase dose according to serum concentration level.
Ticlopidine		↓ metabolism	Decrease dose according to serum concentration level.
Smoking	↑ metabolism		Advise patient to stop smoking; increase dose according to serum concentration level.

<sup>a</sup>This list is not all-inclusive; for discussion of other factors, see package inserts.

TAO, troleandomycin.

Source: Modified from National Institutes of Health. *Expert Panel Report 3: Guidelines for the Diagnosis and Management of Asthma*. Bethesda, MD: National Heart, Lung, and Blood Institute; 2007. NIH publication 07-4051.

- Oral corticosteroids should be used to manage an acute attack if there is no response to SABA therapy. Their anti-inflammatory activity is delayed for about 4 to 6 hours after dose administration. Oral therapy is as effective as the intravenous route. Higher doses may be considered in patients with impending respiratory failure.
- ICS are often used for nocturnal asthma.
- When discontinuing ICS therapy, EPR-3 recommends stepping down the dose at a rate of 25% to 50% every 3 months to the lowest dose to maintain control.
- Short courses of daily corticosteroids usually have minor side effects. The minor risks are far outweighed by the marked benefits. The most common local side effect of

TABLE 23.13 Estimated Comparative Daily Dosages for Inhaled Corticosteroids in Children

Drug	Low Daily Dose		Medium Daily Dose		High Daily Dose	
	Child 0–4 Years	Child 5–11 Years	Child 0–4 Years	Child 5–11 Years	Child 0–4 Years	Child 5–11 Years
<b>Beclomethasone HFA</b> 40 or 80 mcg/puff	NA	80–160 mcg	NA	>160–320 mcg	NA	>320 mcg
<b>Budesonide DPI</b> 90, 180, or 200 mcg/ inhalation	NA	180–400 mcg	NA	>400–800 mcg	NA	>800 mcg
<b>Budesonide inhaled</b> Inhalation suspension for nebulization	0.25–0.5 mg	0.5 mg	>0.5–1 mg	1 mg	>1 mg	2 mg
<b>Fluticasone</b> <b>HFA/MDI:</b> 44, 110, or 230 mcg/puff	176 mcg	88–176 mcg	>176–352 mcg	>176–352 mcg	>352 mcg	>352 mcg
<b>DPI:</b> 50, 100, or 250 mcg/inhalation	NA	100–200 mcg	NA	>200–400 mcg	NA	>400 mcg
<b>Mometasone DPI</b> (Dosing of mometasone for 4- to 11-year-olds is 110 mcg QD) 200 mcg/inhalation	NA	NA	NA	NA	NA	NA

DPI, dry powder inhaler; HFA, hydrofluoroalkane; MDI, metered-dose inhaler; NA, not approved and no data available for this age group.

Source: Reprinted from National Institutes of Health. *Expert Panel Report 3: Guidelines for the Diagnosis and Management of Asthma*. Bethesda, MD: National Heart, Lung, and Blood Institute; 2007. NIH publication 07-4051.

TABLE 23.14 Estimated Comparative Daily Dosages for Inhaled Corticosteroids for Youths ≥ 12 Years of Age and Adults

Drug	Low Daily Dose Adult	Medium Daily Dose Adult	High Daily Dose Adult
<b>Beclomethasone HFA</b> 40 or 80 mcg/puff	80–240 mcg	>240–480 mcg	>480 mcg
<b>Budesonide DPI</b> 90, 180, or 200 mcg/ inhalation	180–600 mcg	>600–1,200 mcg	>1,200 mcg
<b>Fluticasone</b> <b>HFA/MDI:</b> 44, 110, or 220 mcg/puff	88–264 mcg	>264–440 mcg	>440 mcg
<b>DPI:</b> 50, 100, or 250 mcg/inhalation	100–300 mcg	>300–500 mcg	>500 mcg
<b>MOMETASONE DPI</b> 200 mcg/inhalation	200 mcg	400 mcg	>400 mcg

DPI, dry powder inhaler; HFA, hydrofluoroalkane; MDI, metered-dose inhaler.

Source: Reprinted from National Institutes of Health. *Expert Panel Report 3: Guidelines for the Diagnosis and Management of Asthma*. Bethesda, MD: National Heart, Lung, and Blood Institute; 2007. NIH publication 07-4051.

ICS is oropharyngeal candidiasis; rinsing the mouth with water after use of an ICS is recommended. ICS can cause a mild and temporary reduction in growth velocity in children, although final height attained in adulthood appears to be within normal limits. In very high doses, all ICS have some degree of HPA-axis suppression; the clinical significance of this has not yet been established.

- **Magnesium Sulfate**
  - IV magnesium sulfate may benefit severely ill patients with acute asthma.
- **Leukotriene Modifiers**
  - An oral agent such as montelukast with once-daily dosing at bedtime may be preferred by some patients with mild persistent asthma. Bedtime dosing is recommended so that peak activity occurs late at night and early in the morning when asthma symptoms tend to be more frequent.
- **Anti-immunoglobulin E**
  - Omalizumab (Xolair) is a humanized monoclonal anti-IgE antibody that, when bound to mast cells, blocks initiation of the allergic inflammatory cascade. It is effective at reducing oral and ICS dose requirements in patients with severe asthma and in reducing exacerbations. It is given as a 150-to-375-mg dose subcutaneously every 2 or 4 weeks.

# Chronic Obstructive Pulmonary Disease\*

## General Principles

- Chronic obstructive pulmonary disease (COPD) is characterized by chronic airflow limitation and a range of pathological changes in the lung, some significant extrapulmonary effects, and important comorbidities that may contribute to the severity of the disease in individual patients.
- Asthma can coexist with COPD; however, the pattern of airway inflammation is different and it is not considered a part of the COPD spectrum (see Chapter 23).
- The airflow obstruction caused by COPD is usually progressive and is attributed to pathologic changes in the lung. The large airways (trachea and first generation of bronchi) are a major site of inflammation and mucus hypersecretion. Overproduction of mucus results in a chronic productive cough. Recurrent infections occur due to the inability to clear pathogens.
- The natural course of COPD is highly variable, generally spanning 20 to 40 years. As COPD progresses, additional systemic consequences can arise, including cachexia, cardiac and skeletal muscle dysfunction, osteoporosis, depression, and anemia.
- COPD exacerbation is defined as an acute worsening of a patient's chronic symptoms requiring treatment. Exacerbations can be caused by respiratory tract infections (viral or bacterial), air pollution, or other environmental exposures.
- All patients with COPD must get an annual flu shot and be up to date with their pneumococcal vaccine.

## Classification

- COPD generally refers to either
  - **Emphysema:** characterized by alveolar wall destruction and airspace enlargement resulting in loss of gas-exchange surface area
  - **Chronic Bronchitis:** characterized by chronic cough for at least 3 months for 2 consecutive years with inflammation and fibrosis of the small airways
- The most recent GOLD guideline (Global Initiative for Chronic Obstructive Lung Disease) classifies disease into four stages on the basis of spirometric measurements, symptoms, and complications (Table 24.1).

## Patient Assessment

- Diagnosis of COPD is based on the presence of risk factors (generally smoking), clinical symptoms, and airflow obstruction based on spirometric testing.
- COPD usually manifests in the sixth decade of life with symptoms of cough, wheezing, or dyspnea on exertion. The severity of disease is based on staging criteria. Later objective findings include the presence of a barrel chest, rales, rhonchi, prolonged expiratory phase, and cyanosis. Symptomatic patients may present with decreased breath sounds, wheezes, or slight rales on auscultation.

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\*The reader is referred to Chapter 24, Chronic Obstructive Pulmonary Disease, written by Philip T. Diaz, MD, and Daren L. Knoell, PharmD, FCCP, in the 10th edition of *Applied Therapeutics: The Clinical Use of Drugs* for a more in-depth discussion. All notations to reference numbers are based on the reference list at the end of that chapter. The editor of this handbook expresses her thanks to Drs. Diaz and Knoell and acknowledges that this chapter is based on their work.

**TABLE 24.1 Spirometric Classification of Chronic Obstructive Pulmonary Disease (COPD) Severity Based on Postbronchodilator FEV<sub>1</sub>**

Stage	Classification	Spirometry Results
I	Mild	FEV <sub>1</sub> /FVC <0.70 FEV <sub>1</sub> ≥80% predicted
II	Moderate	FEV <sub>1</sub> /FVC <0.70 50% ≤ FEV <sub>1</sub> <80% predicted
III	Severe	FEV <sub>1</sub> /FVC < 0.70 30% ≤ FEV <sub>1</sub> <50% predicted
IV	Very severe	FEV <sub>1</sub> /FVC <0.70 FEV <sub>1</sub> <30% predicted or FEV <sub>1</sub> <50% predicted plus chronic respiratory failure <sup>a</sup>

<sup>a</sup>Respiratory failure is defined as arterial partial pressure of oxygen (PaO<sub>2</sub>) < 8.0 kPa (60 mm Hg) with or without arterial partial pressure of CO<sub>2</sub> (Paco<sub>2</sub>) > 6.7 kPa (50 mm Hg) while breathing air at sea level.

FEV<sub>1</sub>, forced expiratory volume in 1 second; FVC, forced vital capacity.

Source: Global Initiative for Chronic Obstructive Lung Disease (GOLD). *Global Strategy for the Diagnosis, Management and Prevention of COPD (Updated 2010)*. <http://www.goldcopd.org>.

- Spirometry is the gold standard measurement in assessing and monitoring COPD. Although the range of normal FEV<sub>1</sub>/FVC depends on age, sex and height of the patient, a value of <0.70 indicates airflow obstruction that is compatible with COPD.
- Chest x-ray is used to rule out other disease processes that may be contributing to the patient's symptoms.
- Pulse oximetry is used to assess the oxygen status; it should be considered in patients with dyspnea and advanced disease. Values of 88% or less are consistent with chronic respiratory failure and qualify for supplemental oxygen.
- Arterial blood gases are generally reserved for patients with severe disease (i.e., FEV<sub>1</sub> < 50% of predicted).
- Estimates of survival can be made using body mass index, lung function, and dyspnea (Table 24.2).

## Risk Factors

- Cigarette smoking is the major risk factor. Other risk factors include occupational dusts and chemicals, indoor and outdoor pollution, and certain infections (including respiratory viruses). Genetic factors may also be important.

## Goals of Therapy

- Goals of therapy are to prevent or control symptoms, reduce the frequency and severity of exacerbations, improve health status and exercise tolerance, and maximize quality of life. The major goal of COPD is smoking cessation.

## Treatment

- The only intervention that has been shown to reduce mortality in COPD are smoking cessation (see Chapter 88), oxygen therapy for patients with severe hypoxemia at rest, and lung volume reduction surgery for very select patients with advanced emphysema (Table 24.3).
- Immunizations provide protection against serious illness and death. Vaccination against influenza and pneumococcal pneumonia (Pneumovax 23) is recommended.
- Pulmonary rehabilitation, an exercise-based program aimed at maximizing the patient's functional status and quality of life, is recommended to address the systemic manifestations of COPD. The most important component is lower extremity endurance training.
- Supplemental oxygen should be considered in patients with severe resting hypoxemia (oxygen saturation < 88% or PaO<sub>2</sub> ≤ 55 mm Hg).

**TABLE 24.2 Variables and Point Values Used for the Computation of the Body Mass Index, Degree of Airflow Obstruction and Dyspnea, and Exercise Capacity (BODE) Index**

Variable	Points			
	0	1	2	3
Body mass index (kg/m <sup>2</sup> )	≥21	<21		
Obstruction of airflow (FEV <sub>1</sub> % predicted)	≥65	50–64	36–49	≤35
Dyspnea?	None or only with strenuous exertion	Walking up a slight hill	Walking on the level	Getting dressed
Exercise capacity (6-minute walk distance, feet)	>1,148	820–1,149	492–819	<492

Approximate 4-year survival based on total BODE score:

0–2 points: 80%

3–4 points: 70%

5–6 points: 60%

7–10 points: 20%

Source: Celli BR et al. The body mass index, airflow obstruction, dyspnea, and exercise capacity index in chronic obstructive pulmonary disease. *N Engl J Med.* 2004;350:1005.

**TABLE 24.3 Major Selection Criteria for Lung Volume Reduction Surgery**

Moderate to severe airflow obstruction  
 Hyperinflation  
 Upper lobe predominant emphysema  
 Nonsmoker  
 Rehabilitation potential

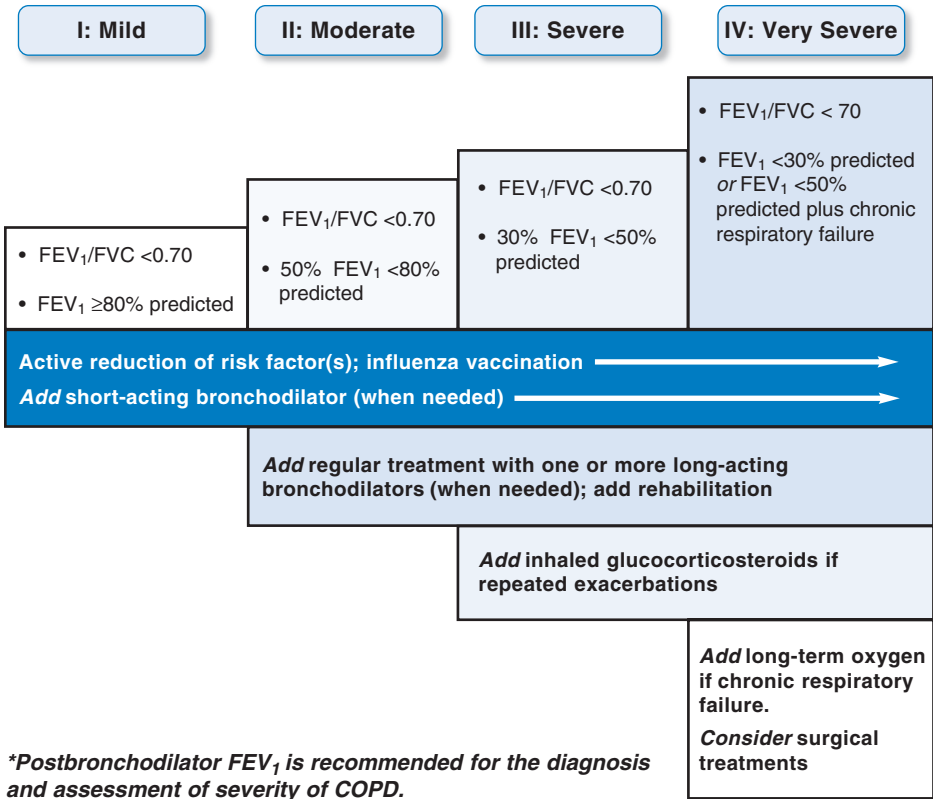
- Although currently available medications do not alter the course of disease, they are an important component of therapy. When medications are initiated or modified, a minimum trial of several weeks to a few months is recommended before determining their effect. Assessing quality of life, dyspnea, and exercise tolerance are important.
- It is expected that patients with COPD will require an increase in the dose and number of medications over time. Figure 24.1 provides a summary of the recommended strategy for pharmacologic therapy.
- Mild exacerbations can be managed with outpatient therapy. Severe exacerbations can result in respiratory failure and death and require a hospital admission. Therapeutic interventions for acute exacerbations include regular bronchodilator therapy, a short course of systemic corticosteroids, and antibiotics.

## Drug Therapy

The purpose of drug therapy for patients with COPD is mainly to delay the time to disease progression and help with symptoms. The following medications will not cure COPD:

- **Bronchodilators** are important for symptom management in COPD. They improve airflow primarily by reducing bronchial airway smooth muscle tone. No clear evidence exists for the use of one agent over another in the chronic management of COPD. Inhaled therapy is generally preferred to oral therapy due to the more rapid onset and reduced systemic effects.
  - A short-acting  $\beta_2$  agonist (e.g., albuterol) or short-acting anticholinergic (e.g., ipratropium) is considered first-line therapy in patients with mild disease. Their initial use should be as-needed. Short-acting agents should continue to be available for acute symptomatic relief. A minimum trial of 1 to 2 weeks is needed before evaluating response to therapy.
  - As disease and symptoms progress, substitution with a long-acting agent in the same class should be considered: long-acting  $\beta_2$  agonists (salmeterol or formoterol) or anticholinergics (tiotropium).





**Figure 24.1** Therapy at each stage of COPD. (Adapted with permission from Global Initiative for Chronic Obstructive Lung Disease (GOLD). *Global Strategy for the Diagnosis, Management and Prevention of COPD [Updated 2010]*. <http://www.goldcopd.org>.)

- Theophylline is reserved for patients who do not tolerate or fail to adequately respond to a combination of first-line bronchodilators.
- In general, nebulization of bronchodilators is reserved for the acute-care setting for quick symptom relief; it is not advocated for routine use at home.
- **Corticosteroids.** Data support the use of inhaled corticosteroids as a treatment option in symptomatic patients with advanced COPD and in patients with frequent exacerbations. The safety of chronic (beyond 3 years) inhaled corticosteroids is not known. Short-term use (7–10 days) of systemic corticosteroids can be used in patients experiencing an acute exacerbation. Chronic oral corticosteroids are not recommended. IV corticosteroids (e.g., methylprednisolone 125 mg every 6 hours) is effective in hospitalized patients.
- **Antibiotics** are beneficial if two of the following three symptoms are present during an acute exacerbation: increased dyspnea, sputum volume, and sputum purulence. Guidelines recommend that hospitalized patients in respiratory failure should receive broad-spectrum antimicrobials that include activity against *Pseudomonas aeruginosa*.
  - In outpatients with low risk factors, a low-cost antibiotic regimen (amoxicillin, trimethoprim-sulfamethoxazole, or doxycycline) is reasonable.
  - Patients with risk factors for poor outcomes (severe COPD, comorbid conditions, or history of frequent exacerbations) should receive a broader-spectrum antibiotic ( $\beta$ -lactam- $\beta$ -lactamase inhibitor combinations, quinolones, or second- or third-generation cephalosporins).

# Acute and Chronic Rhinitis\*

## General Principles

- Rhinitis is defined as an inflammatory condition affecting the mucous membranes of the nose and upper respiratory systems.
- The most common form of rhinitis occurs in response to an allergen; other subtypes that are not inflammatory also exist.

## Classification

- Rhinitis can be classified as acute or chronic. It can be caused by allergic, nonallergic, or mixed allergic and nonallergic triggers (Figure 25.1). Classification is based on severity of symptoms (mild, moderate, severe) and frequency (intermittent or persistent) (Figure 25.2).
- Idiopathic rhinitis is a diagnosis of exclusion. Symptoms are variable; sneezing and nasal itching are not common.

## Patient Assessment

- Symptoms include periods of rhinorrhea (nasal discharge), pruritus, sneezing, congestion, and postnasal discharge. Ocular symptoms (redness, itching, and discharge) can also occur.
- Within minutes of exposure to an allergen, the early-phase allergic response occurs, causing itching, sneezing, and congestion. Up to one-third of patients have a late-phase response about 8 hours after allergen exposure; it lasts about 4 hours and nasal congestion is the predominant feature.
- A complete patient history should be obtained to guide therapy (Figure 25.3).

## Risk Factors

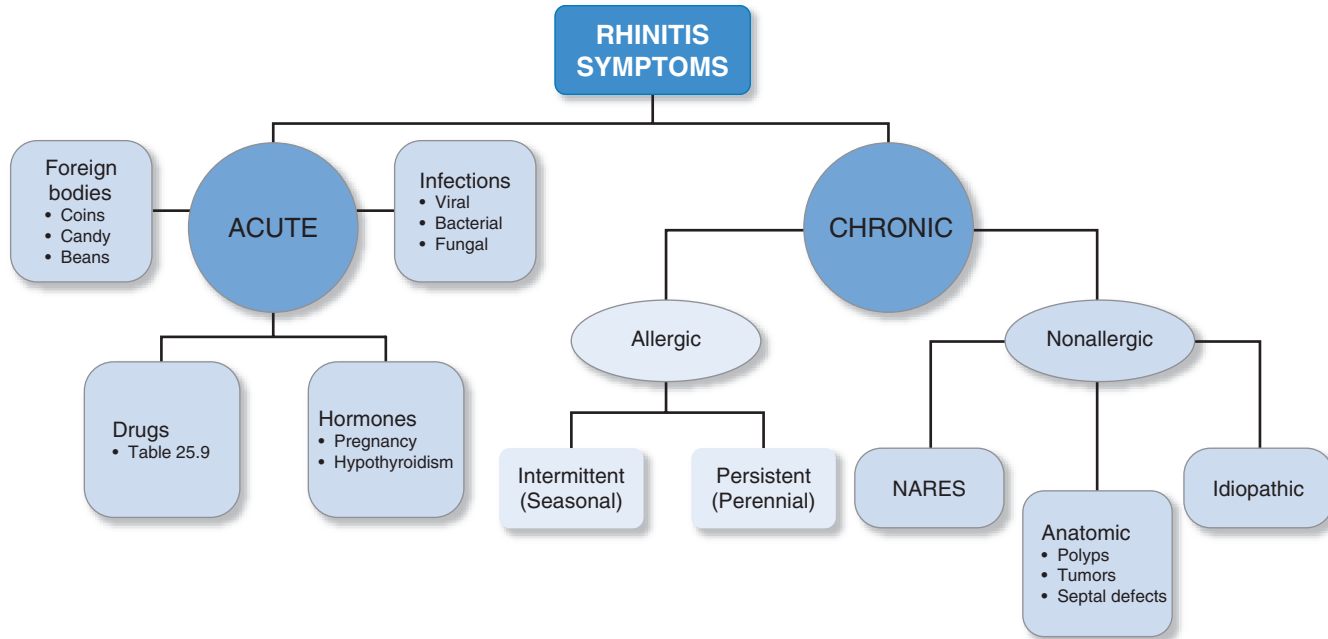
- Genetic, environmental, and lifestyle changes are associated with developing allergic rhinitis.
- In patients with seasonal or intermittent allergic rhinitis, pollens and airborne mold spores are the most common allergens.
- In patients with persistent allergic rhinitis, major allergens are house dust mites, indoor molds, animal dander, and cockroach antigen. Another common cause is occupational exposure to triggers (e.g., wood, flour, detergents).
- Several drugs can cause nasal congestion resulting in a form of drug-induced rhinitis known as rhinitis medicamentosa (Table 25.1).

## Goals of Therapy


- Treatment goals are to prevent or relieve symptoms and improve quality of life without causing excessive side effects.

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\*The reader is referred to Chapter 25, Acute and Chronic Rhinitis, written by Tina Penick Brock, MSPHarm, EdD, and Dennis M. Williams, PharmD, in the 10th edition of *Applied Therapeutics: The Clinical Use of Drugs for a more in-depth discussion*. All notations to reference numbers are based on the reference list at the end of that chapter. The editor of this handbook expresses her thanks to Drs. Brock and Williams and acknowledges that this chapter is based on their work.



**Figure 25.1** Possible causes of rhinitis symptoms. NARES, nonallergic rhinitis with eosinophilia syndrome.

Intermittent <sup>a</sup> Disease	Persistent <sup>b</sup> Disease
<b>Symptoms occur:</b> Fewer than 4 days/week <i>or</i> for fewer than 4 weeks	<b>Symptoms occur:</b> At least 4 days/week <i>and</i> for at least 4 weeks
	
Mild	Moderate–Severe
All of the following:	At least <i>one</i> of the following:
• Normal sleep	• Impaired sleep
• No impairment of usual daily activities, sports, and leisure	• Impairment of daily activities, sports, and leisure
• No interference with work or school	• Interference at work or school
• No troublesome symptoms	• Troublesome symptoms

<sup>a</sup>Formerly “seasonal” symptoms.

<sup>b</sup>Formerly “perennial” symptoms.

**Figure 25.2** ARIA classification of allergic rhinitis. ARIA, Allergic Rhinitis and its Impact on Asthma. (Bousquet J et al. Allergic rhinitis and its impact on asthma [ARIA] 2008 update [in collaboration with the World Health Organization, GA(2)LEN and AllerGen]. *Allergy*. 2008;63[Suppl 86]:8.)

## Treatment

- Common management strategies include patient education, allergen and irritant avoidance, and pharmacotherapy. Figure 25.4 shows an algorithm for general management.
- Supportive care should include application of compresses to the sinuses and humidification of mucous membranes with artificial tears or nasal saline solutions.
- Several classes of medications are used in the management of rhinitis disorders. They are administered either orally or topically, and used on a regular schedule or as-needed basis. Table 25.2 summarizes the effectiveness of agents for specific symptoms.
- The best strategy for managing rhinitis medicamentosa is prevention. Limiting the duration of topical decongestant use to fewer than 3 days is recommended to avoid rebound congestion, especially if using an over-the-counter (OTC) nasal decongestant; if longer therapy is needed, a 1-to-2-day drug holiday is advised. Abrupt discontinuation of the offending topical decongestant can result in considerable patient discomfort for up to 7 days. Use of an intranasal corticosteroid or short course of an oral decongestant may be needed.
- Pharmacotherapy for idiopathic rhinitis should be directed at the predominant symptoms (i.e., congestion, rhinorrhea, nasal obstruction). First-generation antihistamines are less effective than they are for allergic rhinitis; second-generation agents have no efficacy. Ipratropium reduces rhinorrhea but has no effect on sneezing or nasal obstruction.

## Drug Therapy

- **Antihistamines**
  - Antihistamines are the most common treatment used. They are effective for relieving rhinorrhea, sneezing, and itching. They also diminish eye symptoms. When taken orally, they have minimal effects on nasal congestion.
  - They are available in oral, ophthalmic, and intranasal formulations and are most effective when given before antigen exposure.

1. Which of the common symptoms of rhinitis is the patient experiencing?
  - Sneezing, nasal itching, runny nose, nasal congestion, postnasal drip, altered sense of smell, watery eyes, itching eyes, ear “popping”
2. What color are the nasal secretions?
  - Clear, white, yellow, green, blood-streaked, rusty brown
3. When did the symptoms first appear?
  - Infancy, childhood, adulthood
4. Were the symptoms associated with a change in state/environment?
  - After a viral upper respiratory infection, after a traumatic blow to the head or face, upon moving into/visiting a new dwelling, after obtaining a new pet
5. How often do the symptoms occur?
  - Daily, episodically, seasonally, constantly
6. For how long has this symptom pattern persisted?
  - Days, weeks, months, years
7. Which factors or conditions precipitate symptoms?
  - Specific allergens, inhaled irritants, climatic conditions, food, drinks
8. Which specific activities precipitate symptoms?
  - Dusting, vacuuming, mowing grass, raking leaves
9. Are other members of the family experiencing similar symptoms?
10. Which of the following are prevalent in the household?
  - Carpeting, heavy drapes, foam or feather pillows, stuffed toys, areas of high moisture (basements, bathrooms), tobacco use (by patient or others), pets
11. Does the patient have other medical conditions that can cause similar symptoms?
12. Is the patient taking any medications that might cause or aggravate these symptoms?
13. What prescription and nonprescription medications have been used for these symptoms in the past? Were they effective? Did they cause any unwanted effects?
14. What is the patient's occupation?
15. What are the patient's typical leisure activities?
16. To what extent have the symptoms interfered with the patient's lifestyle (i.e., are they disabling or merely annoying)?
  - Greatly, somewhat, not much

**Figure 25.3** Patient history interview.

TABLE 25.1 Drugs Capable of Causing Nasal Symptoms

**LOCAL INFLAMMATORY MECHANISMS**

Aspirin  
 Nonsteroidal anti-inflammatory drugs

**NEUROGENIC MECHANISMS****Centrally Acting Sympatholytics**

Clonidine  
 Methyldopa  
 Reserpine

**Peripherally Acting Sympatholytics**

Prazosin  
 Guanethidine  
 Doxazosin  
 Phentolamine

**Vasodilators**

Sildenafil  
 Tadalafil  
 Vardenafil

**IDIOPATHIC MECHANISMS****Antihypertensives**

Amiloride  
 Angiotensin-converting enzyme inhibitor class  
 $\beta$ -Blocker class  
 Calcium-channel blockers  
 Chlorothiazide  
 Hydralazine  
 Hydrochlorothiazide

**Hormonal Products**

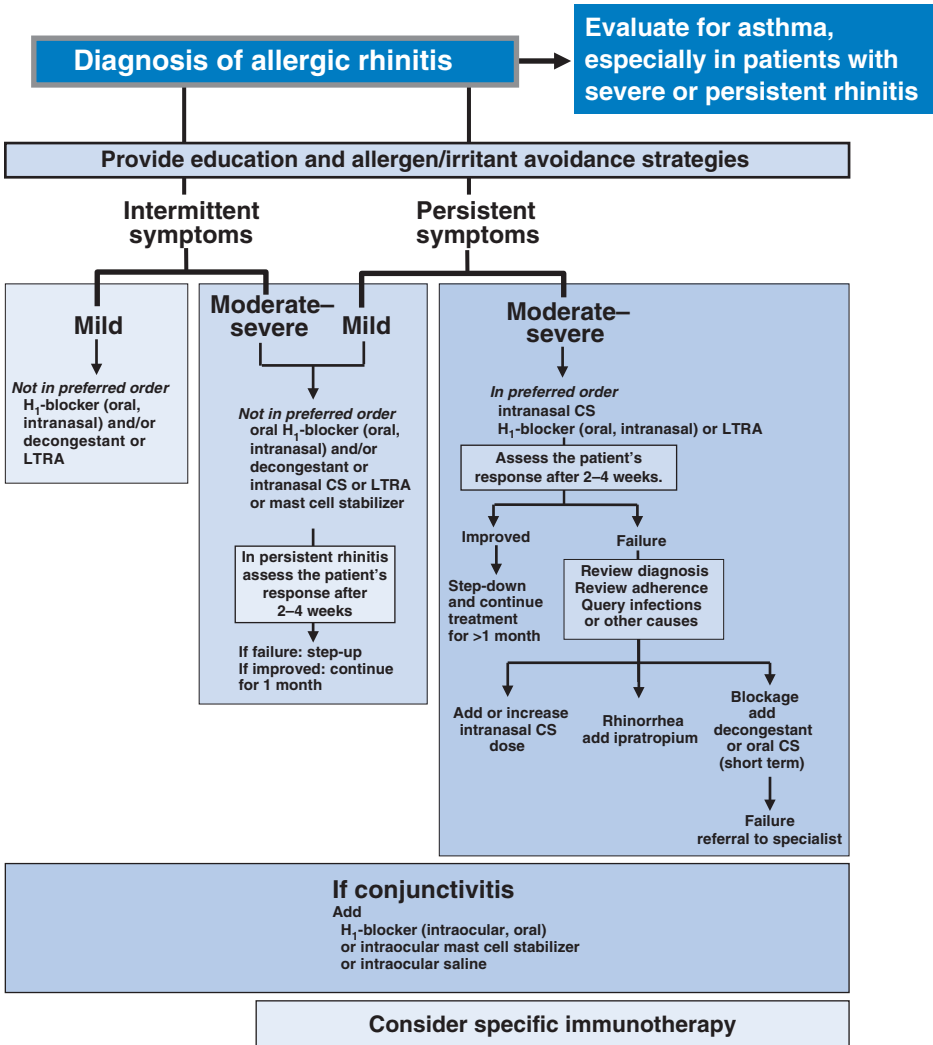
Exogenous estrogens  
 Oral contraceptives

**Neuropsychotropic Agents**

Alprazolam  
 Amitriptyline  
 Chlordiazepoxide  
 Chlorpromazine  
 Gabapentin  
 Risperidone  
 Perphenazine  
 Thioridazine

Sources: Dykewicz MS et al. Diagnosis and management of rhinitis: complete guidelines of the Joint Task Force on Practice Parameters in Allergy, Asthma and Immunology. *American Academy of Allergy, Asthma, and Immunology. Ann Allergy Asthma Immunol.* 1998;81(5, Pt 2):478; Ramey JT et al. Rhinitis medicamentosa. *J Invest Allergol Clin Immunol.* 2006;16:148; Varghese M et al. Drug-induced rhinitis. *Clin Exper Allergy.* 2010;40:381.

- First-generation agents can cause significant sedation. Second-generation agents are generally preferred to first-generation agents on the basis of their superior side-effect profile and convenience of dosing. Table 25.3 shows the agents, dosing, and comparative side effects. All agents are essentially equally effective; choice of agent is based on duration of action, side-effect profile, risk of drug interactions, and cost.
- Second-generation agents prevent symptoms better than they reverse symptoms that are already present. Their maximal effect occurs several hours after the serum concentration peaks. They should be administered before allergen exposure when possible, with chronic dosing preferred to intermittent dosing.



**Figure 25.4** Treatment algorithm for allergic rhinitis. Treatment should be directed at predominant symptoms (i.e., for eye symptoms in absence of other symptoms, use ophthalmic preparation). Prevention strategies are more effective than treatment strategies. For intermittent symptoms, begin treatment several weeks before antigen exposure and discontinue when no longer needed. CS, corticosteroid; LTRA, leukotriene receptor antagonist (leukotriene modifier). (Bousquet J et al. Allergic rhinitis and its impact on asthma [ARIA] 2008 update [in collaboration with the World Health Organization, GA(2)LEN and AllerGen]. *Allergy*. 2008;63[Suppl 86]:8.)

- Unlike oral agents, intranasal antihistamines (e.g., azelastine) are effective for patients with nonallergic or mixed rhinitis, relieving a variety of symptoms including nasal congestion.
- **Intranasal Corticosteroids**
  - Intranasal steroids are the most effective agents for treatment of allergic rhinitis, being particularly useful for more severe or persistent symptoms (itching, sneezing, rhinorrhea, and congestion). They are most beneficial when dosed on a regular schedule.
  - Topical use is very effective in controlling nasal symptoms with minimal systemic side effects. Several agents are available (Table 25.4). All are aqueous solutions delivered via a manual spray pump.

**TABLE 25.2 Effectiveness of Agents<sup>a</sup> Used in Management of Allergic Rhinitis**

	Rhinorrhea	Nasal Pruritus	Sneezing	Nasal Congestion	Eye Symptoms	Onset
<b>Antihistamines</b>						
Nasal	Moderate	High	High	Moderate	0	Rapid
Ophthalmic	0	0	0	0	Moderate	Rapid
Oral	Moderate	High	High	0/Low	Low	Rapid
<b>Decongestants</b>						
Nasal	0	0	0	High	0	Rapid
Ophthalmic	0	0	0	0	Moderate	Rapid
Oral	0	0	0	High	0	Rapid
<b>Corticosteroids</b>						
Nasal	High	High	High	High	High	Slow (days)
Ophthalmic	0	0	0	0	High	Slow (days)
<b>Mast-cell stabilizers</b>						
Nasal	Low	Low	Low	0/Low	Low	Slow (weeks)
Ophthalmic	Low	Low	Low	Low	Moderate	Slow (weeks)
<b>Anticholinergics</b>						
Nasal	High	0	0	0	0	Rapid
<b>Leukotriene modifiers</b>						
Oral	Low	0/Low	Low	Moderate	Low	Rapid

<sup>a</sup>Immunotherapy can lead to significant responses in all symptom categories; however, onset of action is delayed (months). High, significant effect; moderate, moderate effect; low, low effect; 0, no effect.

Sources: van Cauwenberge P et al. Consensus statement on the treatment of allergic rhinitis. *European Academy of Allergology and Clinical Immunology. Allergy.* 2000;55:116; Bousquet J et al. Allergic rhinitis and its impact on asthma (ARIA) 2008 update (in collaboration with the World Health Organization, GA[2]LEN and AllerGen). *Allergy.* 2008;63(Suppl 86):8; Adapted with permission from Facts & Comparisons eAnswers. <http://online.factsandcomparisons.com/index.aspx?> Accessed December 15, 2010.

**TABLE 25.3 Oral Antihistamines<sup>a,b</sup> Commonly Used in Allergic Rhinitis**

Generic Name (Example Brand Product)	Adult Dose	Pediatric Dose <sup>c</sup>	Other Effects		
			Sedative	Antiemetic	Anticholinergic
<b>FIRST GENERATION</b>					
Chlorpheniramine (Chlor-Trimeton)	4 mg every 4–6 hours	Children 6–12 years: 2 mg every 4–6 hours	+	0	++
Clemastine (Tavist)	1.34 mg every 12 hours	Children 6–12 years: 0.67 mg every 12 hours	++	++	+++
Diphenhydramine (Benadryl)	25–50 mg every 4–6 hours	Children 6–12 years: 12.5–25 mg every 4–6 hours	+++	++	+++
<b>SECOND GENERATION</b>					
Cetirizine (Zyrtec Allergy)	5–10 mg once daily	Children 6–12 years: 5–10 mg once daily Children 2–5 years: 2.5–5 mg once daily or 2.5 mg every 12 hours	+	0	±
Desloratadine <sup>d</sup> (Clarinet)	5 mg once daily	Children 6–11 years: 2.5 mg once daily Children 1–5 years: 1.25 mg once daily Children 6–11 months: 1 mg once daily	±	0	±

Continued on following page



TABLE 25.3 Oral Antihistamines<sup>a,b</sup> Commonly Used in Allergic Rhinitis (Continued)

Generic Name (Example Brand Product)	Adult Dose	Pediatric Dose <sup>c</sup>	Other Effects		
			Sedative	Antiemetic	Anticholinergic
<b>SECOND GENERATION</b>					
Fexofenadine (Allegra)	60 mg every 12 hours or 180 mg once daily	Children 2–11 years: 30 mg every 12 hours	±	0	±
Levocetirizine <sup>d</sup> (Xyzal)	5 mg once daily in the evening	Children 6–11 years: 2.5 mg once daily in the evening Children 2–5 years: 1.25 mg once daily in the evening	±	0	±
Loratadine (Claritin)	10 mg once daily	Children 6–12 years: 10 mg once daily Children 2–5 years: 5 mg once daily	±	0	±

<sup>a</sup>Many oral antihistamines are sold as combination products with the oral decongestants pseudoephedrine and phenylephrine. The addition of the decongestant may alter the dosing scheme for the product. As of 2005, pseudoephedrine products have been placed behind the pharmacy counter in the United States. Federal law limits the quantity available for purchase to 9 g/month, 3.6 g/day with signature and photo identification. Individual states may have additional restrictions regarding the sale of pseudoephedrine, consult local boards of pharmacy for details.

<sup>b</sup>Some oral antihistamines are available in both short-acting and extended- or sustained-release formulations. Refer to package insert for specific dosing instructions for long-acting products.

<sup>c</sup>In 2008, the Food and Drug Administration (FDA) issued an advisory alert recommending that OTC cough and cold agents (e.g., products containing antitussives, expectorants, decongestants, and antihistamines) not be used in infants and children younger than 2 years of age because of the potential for serious and possibly life-threatening adverse events. More recently, in October 2008, leading pharmaceutical manufacturers voluntarily modified product labels on OTC cough and cold preparations to state “do not use” in children younger than 4 years of age. Further safety reviews by the FDA regarding the use of these agents in children between the ages of 2 and 11 are ongoing.

<sup>d</sup>Currently available by prescription only.

Sources: Adapted with permission from Facts & Comparisons eAnswers. <http://online.factsandcomparisons.com/index.aspx?> Accessed December 15, 2010.

TABLE 25.4 Intranasal Corticosteroids<sup>a</sup> Commonly Used for Rhinitis

Generic Name (Example Brand Product)	Available Dosage Forms/ Strengths (mcg/spray)	Adult Dose <sup>a</sup>	Pediatric Dose <sup>a</sup>
Budesonide (Rhinocort Aqua)	32	1 spray/nostril once daily (max 4 sprays/nostril daily)	Children 6–12 years: 1 spray/nostril once daily (max 2 sprays/nostril daily)
Ciclesonide (Omnaris)	50	2 sprays/nostril once daily	Children 6–12 years: 2 sprays/nostril once daily (approved for seasonal symptoms in ages >6, and for perennial symptoms for ages >12)
Fluticasone propionate (Flonase)	50	2 sprays/nostril once daily or 1 spray/nostril twice daily	Children 4–17 years: 1–2 sprays/ nostril once daily (max 2 sprays/ nostril daily)

Fluticasone furoate (Veramyst)	27.5	2 sprays/nostril once daily	Children 2–11 years: 1–2 sprays/nostril once daily (max 2 sprays/nostril daily)
Flunisolide (no brand product available)	29	2 sprays/nostril two or three times daily (max 8 sprays/nostril daily)	Children 6–14 years: 1 spray/nostril three times daily or 2 sprays/nostril twice daily (max 4 sprays/nostril daily)
Mometasone furoate (Nasonex)	50	2 sprays/nostril once daily	Children 2–11 years: 1 spray/nostril once daily
Triamcinolone acetonide (Nasacort AQ)	55	2 sprays/nostril once daily	Children 2–5 years: 1 spray/nostril once daily (max 1 spray/nostril daily) Children 6–11 years: 1–2 sprays/nostril once daily (max 2 sprays/nostril daily)

<sup>a</sup>It is always desirable to titrate an individual patient to the minimum effective steroid dose to reduce the risk of side effects. When the maximum benefit has been achieved and symptoms have been controlled, reducing the steroid dose might be effective in maintaining control of rhinitis symptoms.

Sources: Adapted with permission from Facts & Comparisons eAnswers. <http://online.factsandcomparisons.com/index.aspx?> Accessed December 15, 2010.

- Mometasone, fluticasone, and ciclesonide have the lowest systemic effects; beclomethasone has higher systemic effects.
- The most common side effect is epistaxis, with excessive nasal dryness and crusting also reported.
- **Systemic Corticosteroids**
  - Because of the risk for numerous and potentially serious side effects, systemic corticosteroid use should be reserved for short-term, adjunctive therapy in patients with severe debilitating rhinitis.
- **Leukotriene Modifiers**
  - The benefit of leukotriene modifiers is modest; they are typically used as adjunctive therapy with first-line agents for allergic rhinitis (Table 25.5). There is no evidence they are effective for nonallergic causes of rhinitis.
- **Cromolyn**
  - Intranasal cromolyn is a nonsteroidal agent that is generally less effective than other therapies. It is only useful for symptoms associated with allergic causes.
  - It must be administered multiple times daily and requires several weeks to be effective (Table 25.5).
- **Decongestants**
  - Oral and nasal decongestants can effectively reduce nasal congestion. Agents commonly used for allergic rhinitis are shown in Table 25.6.
  - Use of an antihistamine/decongestant combination is more effective than either agent given alone.
  - Unlike topical decongestants, oral therapy is not associated with rebound congestion.
- **Anticholinergic Agents**
  - Intranasal ipratropium is an anticholinergic agent effective in reducing watery nasal secretions in allergic rhinitis, nonallergic rhinitis, and viral upper respiratory infections (Table 25.5).
- **Ophthalmic Therapies**
  - Several agents used to treat symptoms of allergic conjunctivitis (Table 25.7). They may be used in combination with oral and intranasal agents.
  - Overuse of ocular vasoconstrictors can lead to rebound conjunctivitis.

TABLE 25.5 Additional Oral and Topical Agents for Rhinitis

Generic (Brand Product)	Available Dosage Forms/Strength	Adult Dose	Pediatric Dose
<b>ORAL</b>			
Leukotriene modifiers Montelukast (Singulair)	Tablets: 10 mg Tablets, chewable: 4 mg, 5 mg Oral granules: 4 mg	10 mg once daily	Children 6–14 years: 5 mg once daily Children 2–5 years: 4 mg once daily Children 6–23 months: 4 mg once daily
<b>INTRANASAL</b>			
Antihistamine Azelastine (Astelin)	Nasal spray: 137 mcg/spray	1–2 sprays/nostril every 12 hours (for seasonal symptoms) 2 sprays/nostril every 12 hours (for perennial symptoms)	Children 5–11 years: 1 spray/nostril every 12 hours
(Astelin)	Nasal spray: 205.5 mcg/spray	2 sprays per nostril once daily or 1–2 sprays per nostril every 12 hours (for seasonal symptoms)	Not indicated for children <12 years
(Astepro)		2 sprays per nostril every 12 hours (for perennial symptoms)	
Mast-cell stabilizer Cromolyn sodium (Nasal crom) <sup>a</sup>	Nasal spray: 5.2 mg/spray	1 spray/nostril every 4–6 hours (max six times daily)	Children ≥2 years: 1 spray/nostril every 4–6 hours (max six times daily)
Anticholinergic Ipratropium bromide (Atrovent) <sup>b</sup>	Nasal spray: 21 mcg/spray (for perennial symptoms), 42 mcg/spray (for seasonal symptoms)	2 sprays/nostril up to four times daily (max = 672 mcg/day)	Children ≥5 years: 2 sprays/nostril up to four times daily (max = 672 mcg/day)

<sup>a</sup>Available without a prescription.

<sup>b</sup>Optimum dosage varies with the response of the individual patient, however. It is always desirable to titrate an individual to the minimum effective dose to reduce the risk of side effects. In addition, the safety and efficacy of the use of ipratropium 42 mcg nasal spray beyond 3 weeks in patients with seasonal allergic rhinitis has not been established.

Sources: Adapted with permission from Facts & Comparisons eAnswers. <http://online.factsandcomparisons.com/index.aspx?> Accessed December 15, 2010.

### • Immunotherapy

- Specific allergen immunotherapy should be considered for patients who have severe symptoms despite optimal pharmacotherapy, require systemic steroids, or have coexisting conditions such as sinusitis or asthma. Immunotherapy by subcutaneous injections is referred to as allergy shots.
- Allergen-specific immunotherapy has long-term efficacy and may prevent progression of allergic disease.
- Antihistamines blunt the wheal-and-flare reaction and should be discontinued before skin testing. See Tables 25.8 and 25.9 for guidelines. Other allergy medications (cromolyn, nasal corticosteroids) have no effect on skin tests.

### • Anti-IgE Therapy

- Omalizumab is a monoclonal anti-IgE antibody that reduces IgE-mediated allergic reactions. It must be administered by subcutaneous injection once or twice monthly.

TABLE 25.6 Decongestants<sup>a,b</sup> Commonly Used in Allergic Rhinitis

Generic Name (Example Brand Product)	Adult Dose	Pediatric Dose <sup>c</sup>
<b>ORAL<sup>a</sup></b>		
Pseudoephedrine (Sudafed)	60 mg every 4–6 hours (max 240 mg/day)	Children 6–12 years: 30 mg every 4–6 hours (max 120 mg/day) Children 2–5 years: 15 mg every 4–6 hours (max 60 mg/day)
Phenylephrine (Sudafed PE)	10–20 mg every 4 hours (max 120 mg/day)	Children 6–11 years: 10 mg every 4 hours (max 60 mg/day)
<b>TOPICAL<sup>d</sup></b>		
Naphazoline (Privine)	0.05% solution: 1–2 drops or sprays/nostril every 6 hours	Children <12 years: Avoid, unless under physician direction
Phenylephrine (Neo- Synephrine)	0.25%–1.0% solution: 2–3 sprays or drops/nostril every 3–4 hours	Children 6–11 years: 2–3 sprays or drops (0.25% solution)/nostril every 4 hours Children 2–5 years: 2–3 drops (0.125% solution) into each nostril not more than every 4 hours
Oxymetazoline (Afrin)	0.05% solution: 2–3 sprays/ nostril every 10–12 hours	Children 6–12 years: 2–3 sprays/nostril every 12 hours
Xylometazoline (Triaminic)	0.1% solution: 2–3 sprays into each nostril every 8–10 hours	Children 2–12 years: 1–2 sprays (0.05% solution) into each nostril every 8–10 hours

<sup>a</sup>Many oral decongestants are sold as combination products with the oral antihistamines. The addition of the antihistamine may alter the dosing scheme for the product. As of 2005, pseudoephedrine products have been placed behind the pharmacy counter in the United States. Federal law limits the quantity available for purchase to 9 g/month, 3.6 g/day with signature and photo identification. Individual states may have additional restrictions regarding the sale of pseudoephedrine, consult local boards of pharmacy for details.

<sup>b</sup>Some oral decongestants are available in both short-acting and extended- or sustained-release formulations. Refer to package insert for specific dosing instructions for long-acting products. Note that some extended-release formulations are not recommended for children younger than 12 years of age.

<sup>c</sup>In 2008, the FDA issued an advisory alert recommending that OTC cough and cold agents (e.g., products containing antitussives, expectorants, decongestants, and antihistamines) not be used in infants and children younger than 2 years of age because of the potential for serious and possibly life-threatening adverse events. More recently, in October 2008, leading pharmaceutical manufacturers voluntarily modified product labels on OTC cough and cold preparations to state “do not use” in children younger than 4 years of age. Further safety reviews by the FDA regarding the use of these agents in children between the ages of 2 and 11 are ongoing.

<sup>d</sup>Limit duration of treatment to <5 days to minimize risk of rebound congestion. Topical decongestants should never be used in infants younger than 6 months of age because they are obligate nose breathers and the resulting rebound congestion could cause obstructive apnea.

Sources: Adapted with permission from Facts & Comparisons eAnswers. [http://online.factsandcomparisons.com/index.aspx?](http://online.factsandcomparisons.com/index.aspx) Accessed December 15, 2010.

TABLE 25.7 Topical Ophthalmic Medications Commonly Used for Allergic Conjunctivitis

Generic Name (Example Brand Product)	Available Dosage Forms/ Strength	Dose
<b>ANTIHISTAMINES</b>		
Azelastine (Optivar)	Ophthalmic solution: 0.05%	Adults and children $\geq 3$ years: 1 drop in the affected eye(s) every 12 hours
Emedastine (Emadine)	Ophthalmic solution: 0.05%	Adults and children $\geq 3$ years: 1 drop in the affected eye(s) up to four times daily
<b>ANTIHISTAMINE/DECONGESTANT COMBINATIONS</b>		
Pheniramine + Naphazoline (Naphcon-A) <sup>a</sup>	Ophthalmic solution: naphazoline HCl 0.025% + pheniramine maleate 0.3%	Adults and children $\geq 6$ years: 1–2 drops in the affected eye(s) every 6 hours for up to 3 days

Continued on following page

TABLE 25.7 Topical Ophthalmic Medications Commonly Used for Allergic Conjunctivitis (Continued)

Generic Name (Example Brand Product)	Available Dosage Forms/ Strength	Dose
<b>ANTIHISTAMINE/MAST-CELL STABILIZERS</b>		
Ketotifen (Zaditor) <sup>a</sup>	Ophthalmic solution: 0.025%	Adults and children ≥3 years: 1 drop in the affected eye(s) every 8–12 hours
Olopatadine (Pataday)	Ophthalmic solution: 0.2%	Adults and children ≥3 years: 1 drop in the affected eye(s) daily
<b>MAST-CELL STABILIZERS</b>		
Cromolyn Sodium (Crolom)	Ophthalmic solution: 4%	Adults and children ≥4 years: 1–2 drops in the affected eye(s) four to six times daily
Lodoxamide (Alomide)	Ophthalmic solution: 0.1%	Adults and children ≥2 years: 1–2 drops in affected eye(s) four times daily for up to 3 months
Nedocromil (Alocril)	Ophthalmic solution: 2%	Adults and children ≥3 years: 1–2 drops in the affected eye(s) every 12 hours
Pemrolast (Alamast)	Ophthalmic solution: 0.1%	Adults and children ≥3 years: 1–2 drops in the affected eye(s) four times daily
<b>NONSTEROIDAL ANTI-INFLAMMATORY DRUGS<sup>b</sup></b>		
Ketorolac (Acular)	Ophthalmic solution: 0.5%	Adults and children ≥3 years: 1 drop in the affected eye(s) four times daily
<b>CORTICOSTEROIDS</b>		
Loteprednol (Alrex)	Ophthalmic suspension 0.2%	Adults: 1 drop in the affected eye(s) four times daily

<sup>a</sup>Available without a prescription.

<sup>b</sup>Other ophthalmic nonsteroidal anti-inflammatory drugs (diclofenac, flurbiprofen, suprofen) indicated for intraoperative miosis and for postcataract surgery, but not approved for allergic conjunctivitis.

Sources: Adapted with permission from Facts & Comparisons eAnswers. <http://online.factsandcomparisons.com/index.aspx?> Accessed December 15, 2010.

TABLE 25.8 Effects of Antihistamines on Allergen Skin Tests

Drug	Extent of Suppression <sup>a</sup>	Half-Life (hours) <sup>b</sup>	Duration of Suppression (days)
Azelastine (intranasal)	+/-	22	0
Brompheniramine	+	24.9	1–4
Cetirizine	+++	7.4–11 (7)	3–10
Chlorpheniramine	+	24.4 (11)	1–4
Clemastine	++	21.3	1–10
Cyproheptadine	+/-	16	1–4
Desloratadine	+/++	27 (27)	3–10
Diphenhydramine	+/-	4–9	1–4
Fexofenadine	++	14 (18)	3–10
Hydroxyzine	++	20 (7.1)	1–10
Loratadine	+/++	11–24 (3.1)	3–10
Promethazine	+	12	1–4

<sup>a</sup>+++ , extensive; ++ moderate; +, mild; +/-, minimal to none.

<sup>b</sup>Parenthetical numbers indicate half-life in children.

Sources: Adapted with permission from Facts & Comparisons eAnswers. <http://online.factsandcomparisons.com/index.aspx?> Accessed December 15, 2010.

**TABLE 25.9 General Recommendations for Discontinuation of Antihistamines before Allergen Skin Testing**

1. Remind patient that allergic symptoms may return during the antihistamine-free period, but that reliable skin tests cannot be performed in a patient taking antihistamines.
2. Discontinue any short-acting antihistamine (i.e., those in Table 25.7 with a duration of suppression  $\leq 4$  days) 4 days before skin testing.
3. Discontinue longer-acting antihistamines (i.e., those in Table 25.7 with a duration of suppression  $>4$  days) at an interval appropriate to their duration of effect (e.g., hydroxyzine should be discontinued 10 days before skin testing).
4. Before applying the full battery of skin tests, apply histamine (positive) control and glycerinated diluent (negative) control tests. Application of a 1-mg/mL histamine base equivalent should yield wheal-and-flare diameters of 2–7 mm and 4.5–32.5 mm, respectively, to be considered a normal histamine reaction. A normal cutaneous reaction to histamine control suggests that accurate skin testing can be performed.

Source: Bousquet J et al. Allergic rhinitis and its impact on asthma (ARIA) 2008 update (in collaboration with the World Health Organization, GA[2]LEN and AllerGen). *Allergy*. 2008;63(Suppl 86):8.

# Cystic Fibrosis\*

## General Principles

- Cystic fibrosis (CF) is a severe, complex, hereditary disease that affects 1 in every 3,200 live births. The course and severity of CF are variable and unpredictable. The mean life expectancy for a child born in 1990 is 40 years.
- CF is characterized by malabsorption and a state of chronic lung obstruction, inflammation, and infection. Respiratory disease is the principal cause of repeated hospitalizations, decline in pulmonary function, and death.
- CF is caused by a defect in the cystic fibrosis transmembrane conductance regulator (CFTR) protein, a chloride channel that regulates fluid and electrolyte transport within secretory epithelial cells throughout the body (e.g., lungs, sweat glands, salivary glands, male genital ducts, pancreas, kidney tubules, digestive tract).

## Patient Assessment

- The principle manifestations of CF include malnutrition secondary to pancreatic insufficiency and pulmonary dysfunction resulting from chronic airway obstruction, infection, and inflammation.
- A summary of clinical manifestations by organ system is shown in Table 26.1. In addition to these, sweat has a high salt content, bone mineral density is lower, patients often have intermittent symptoms of arthritis, and nasal passages can be blocked by polyps.
- The chronic cycle of airway obstruction, infection, and inflammation lead to bronchiectasis, progressive loss of lung function with eventual respiratory failure, and death.
- Diagnosis is based on newborn screening, now done in all 50 states. Confirmatory testing is done using the sweat chloride test (pilocarpine iontophoresis test) and DNA analysis to identify CFTR mutations. Patients who were not tested as newborns may show features suggestive of CF (Table 26.2).
- Acute pulmonary exacerbations are inevitable (change in respiratory signs and symptoms from the patient's baseline that requires treatment).

## Goals of Therapy

- The goal for growth in the first year of life is to have a weight-for-length status of the 50th percentile. From 2 to 20 years of age, the goal for growth is to achieve at least the 50th percentile of body mass index.
- The goals of pancreatic enzyme supplementation are to improve weight gain, minimize steatorrhea, and eliminate abdominal cramping and bloating.
- Eradication of *Pseudomonas aeruginosa* is desired; early antibiotic treatment is needed.

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\*The reader is referred to Chapter 26, Cystic Fibrosis, written by Paul M. Beringer, PharmD, FASHP, FCCP, and Michelle Condren, PharmD, AE-C, CDE, in the 10th edition of *Applied Therapeutics: The Clinical Use of Drugs* for a more in-depth discussion. All notations to reference numbers are based on the reference list at the end of that chapter. The editor of this handbook expresses her thanks to Drs. Beringer and Condren and acknowledges that this chapter is based on their work.

TABLE 26.1 Clinical Manifestations of Cystic Fibrosis

Manifestation	Approximate Incidence (%)	
	Children (Infants)	Adults
<b>PANCREATIC</b>		
Insufficiency	85 (80–85)	90
Pancreatitis	1–2	2–4
Abnormal glucose tolerance	38	75
Diabetes mellitus	14	40–50
<b>HEPATOBIILIARY</b>		
Biliary cirrhosis	10–20	>20
Cholelithiasis	5	5–10
Biliary obstruction	1–2	5
<b>INTESTINAL</b>		
Meconium ileus	20	
Meconium ileus equivalent	1–5	10–20
Rectal prolapse	10–15	1–2
Intussusception	1–5	1–2
Gastroesophageal reflux	1–5	>10
Appendiceal abscess	0–1	1–2
<b>RESPIRATORY</b>		
Nasal polyps	4–10 (<1)	15–20
Pansinusitis		90–100
Bronchiectasis	30–50	>90
Pneumothorax	1–2	10–15
Hemoptysis	5–15	50–60
<b>REPRODUCTIVE</b>		
Delayed puberty		85
Infertility		
Males		98
Females		70–80

TABLE 26.2 Phenotypic Features Consistent with Diagnosis of Cystic Fibrosis (CF)

Persistent colonization or infection with typical CF pathogens (e.g., <i>Staphylococcus aureus</i> , nontypeable <i>Haemophilus influenzae</i> , <i>Pseudomonas aeruginosa</i> , <i>Burkholderia cepacia</i> )
Chronic cough and sputum production
Persistent chest radiograph abnormalities
Airway obstruction manifested by wheezing and air trapping
Nasal polyps; radiographic or computed tomographic abnormalities of paranasal sinuses
Digital clubbing
Meconium ileus, distal intestinal obstruction syndrome, rectal prolapse
Pancreatic insufficiency, recurrent pancreatitis
Chronic hepatic disease
Failure to thrive, hypoproteinemia and edema, complications secondary to fat-soluble vitamin deficiency
Salt loss syndromes: acute salt depletion, chronic metabolic alkalosis
Male urogenital abnormalities resulting in obstructive azoospermia (CBAVD)

CBAVD, congenital bilateral absence of the vas deferens.

Source: Reprinted with permission from Farrell PM et al. Guidelines for diagnosis of cystic fibrosis in newborns through older adults: Cystic Fibrosis Foundation consensus report. *J Pediatr*. 2008;153:S4.



## Treatment

- Nutrition therapy is essential to ensure appropriate growth and improve pulmonary outcomes. CF patients are hypermetabolic and do not absorb fats and proteins normally. A diet high in calories, fat, and protein is recommended. Impaired absorption of fat-soluble vitamins (A, D, E, and K) occurs; supplementation is recommended (Table 26.3).
- The mainstay for pancreatic insufficiency is exogenous replacement of pancreatic digestive enzymes.
- Treatment of CF involves the use of medications and techniques to mobilize pulmonary secretions, antibiotics to manage infection, and anti-inflammatory agents to reduce airway inflammation. A summary of the current evidence for specific therapies is shown in Table 26.4.
- CF patients have markedly thickened mucus and impaired mucociliary clearance. Sputum in patients with CF is difficult to mobilize. Mechanical clearance methods, inhaled mucolytics, and airway hydration therapies can be helpful. A variety of mechanical approaches are available to mobilize mucus; all are about equal in efficacy and choice depends on ability, motivation, preferences, and resources of the patient.
- Coughing is an important defense mechanism; cough suppressants should not be used.
- Chronic use of  $\beta_2$ -agonists improves lung function in patients with bronchial hyperresponsiveness or a positive bronchodilator response.
- The inflammatory response in CF airways contributes to destruction of the airway. Pharmacologic intervention is a key strategy to reduce pulmonary disease progression. Corticosteroids, nonsteroidal anti-inflammatory drugs (NSAIDs) and macrolides have all been used.
- Antibiotic therapy is indicated in patients for early eradication of *P. aeruginosa* at the time of first detection to prevent or delay chronic infection; treatment of acute pulmonary exacerbations; and chronic maintenance therapy with inhaled agents to control bacterial burden within the airways to slow progression of pulmonary decline.

**TABLE 26.3 Daily Recommended Doses of Fat-Soluble Vitamins for Patients with Cystic Fibrosis and Vitamin Content in Specialty Vitamin Formulations**

Age	Vitamin A (international units)	Vitamin E (international units)	Vitamin D (international units)	Vitamin K (mg)
0–12 months	1,500	40–50	400	0.3–0.5
1–3 years	5,000	80–150	400–800	0.3–0.5
4–8 years	5,000–10,000	100–200	400–800	0.3–0.5
>8 years	10,000	200–400	400–800	0.3–0.5
<b>VITAMIN CONTENT</b>				
AquADEK chewable tablet	9,083 (87% as $\beta$ carotene)	50	400	0.35
Vitamax chewable tablet	5,000 (50% as $\beta$ carotene)	200	400	0.2
SourceCF chewable tablet	16,000 (88% as $\beta$ carotene)	200	1,000	0.8
Vitamax liquid (per 1 mL)	3,170	50	400	0.3
SourceCF liquid (per 1 mL)	4,627 (75% as $\beta$ carotene)	50	500	0.4
AquADEK liquid (per 1 mL)	5,751 (87% as $\beta$ carotene)	50	400	0.4
AquADEK softgel capsules	18,167 (92% as $\beta$ carotene)	150	800	0.7
SourceCF softgel capsules	16,000 (88% as $\beta$ carotene)	200	1,000	0.8

TABLE 26.4 Evidence-Based Review of Pulmonary Medications for Cystic Fibrosis

Treatment Question	Type of Review	Studies	Total (n)	Strength of Evidence	Estimate of Net Benefit	Recommendation
Inhaled tobramycin Moderate-severe lung disease	S C	3 RCT; 1 RCO; 2 one-arm trials	679	Good	Substantial	A
Asymptomatic-mild disease	S	2 RCT	202	Fair	Moderate	B
Other inhaled antibiotics (colistin, gentamicin, ceftazidime)	S	2 RCT, 2 RCO	206	Poor	Small	I
Dornase alfa Moderate to severe lung disease	S C	10 RCT; 3 crossover; 6 trials without comparison groups	3,140	Good	Substantial	A
Asymptomatic-mild lung disease	S	3 RCT; 1 crossover	520	Fair	Moderate	B
Hypertonic saline	S C	2 RCT; 2 RCO (compared with dornase alfa)	284	Fair	Moderate	B
Inhaled corticosteroids	S C	5 RCT; 2 RCO	388	Fair	None	D
Oral corticosteroids	S C	3 RCT	354	Good	Negative	D I
Age, >18 years	S	1 crossover	20	Poor	None	I
Oral nonsteroidal anti-inflammatory drugs	S C	3 RCT	145	Fair	Moderate	B
Leukotriene modifiers	M	2 RCO; 1 controlled trial	64	Poor	None	I
Cromolyn	M	2 RCT; 1 clinical trial	44	Poor	None	I
Macrolide antibiotics	S C	2 RCT; 1 crossover; 1 clinical trial	296	Fair	Substantial	B
Antistaphylococcal antibiotics	M C	3 RCT; 1 crossover	306	Fair	Negative	D
Inhaled $\beta_2$ -adrenergic receptor agonists	C	14 RCO: nebulized and metered dose	257	Good	Moderate	B
Inhaled anticholinergics	C	5 RCO	79	Poor	None/small	I
Oral N-acetylcysteine	M	1 phase 1 trial; 1 RCO; 1 controlled trial; 2 crossover	145	Poor	None	I

C, Cochrane; M, modified systematic; RCO, randomized crossover; RCT, randomized, controlled trial; S, systematic. Source: Reprinted with permission from Flume PA et al. Cystic fibrosis pulmonary guidelines: chronic medications for maintenance of lung health. *Am J Respir Crit Care Med.* 2007;176:957.

- Management for acute CF exacerbations includes nutritional repletion, antibiotics, and chest physiotherapy. Mild exacerbations can often be managed at home with oral antibiotics, intensification of airway clearance, and nutritional therapies. Moderate to severe exacerbations typically require hospitalization to receive a 14-day course of IV antibiotics, airway clearance, and nutrition therapy.
- Chronic maintenance therapy with oral or inhaled antibiotics is used to suppress bacterial infection to reduce the frequency and severity of pulmonary exacerbations and slow deterioration of lung function. Inhaled antibiotics are preferred as they provide relatively high sputum concentrations and low systemic bioavailability.
- Insulin therapy may be needed for managing CF-related diabetes mellitus.
- Calcium (500 mg twice daily) and vitamin D may be needed to manage CF-related osteopenia.
- Lung transplant is a potential therapeutic option for CF patients with end-stage lung disease.

## Drug Therapy

Please note that pancreatic medications are not interchangeable.

- **Pancreatic Enzyme Supplementation:** Digestive enzymes (lipase, amylase, and protease) are available in combinations with approximately one part amylase to three parts lipase and protease (Table 26.5). Dosing is based on lipase content.
  - Infants: 2,000 to 5,000 units lipase/breast-feeding (or 120 mL of bottle feeding).
  - Infants eating solid foods: 1,000 units/kg/meal.
  - Children > 4 years: 500 units/kg/meal; subsequent dosing adjustments titrated to response.
  - Daily dose of lipase should not exceed 10,000 units/kg or 2,500 units/kg/meal due to risk of stricture formation.
- **Palivizumab:** respiratory syncytial virus, a common infection in infants, may more adversely affect CF infants. Palivizumab (15 mg/kg intramuscularly once monthly) is recommended in those <2 years of age.
- **Dornase Alfa:** is an inhaled form of human deoxyribonuclease I that breaks up the extracellular DNA formed by apoptotic neutrophils and improves sputum viscosity. A trial is recommended in all patients 6 years of age and older to assess whether there is improvement in pulmonary function. Treatment is given as 2.5-mg vials administered by a vented jet nebulizer.
- **Hypertonic Saline:** inhalation of hypertonic saline (IHS; 7% NaCl) improves mucociliary clearance by rehydrating the airways through osmotic flow of water. IHS should be considered

TABLE 26.5 Pancreatic Enzyme Formulations

Product <sup>a</sup>	Microencapsulated Enzymes		
	Lipase	Protease	Amylase
Creon 3	3,000	9,500	15,000
Creon 6	6,000	19,000	30,000
Creon 12	12,000	38,000	60,000
Creon 24	24,000	76,000	120,000
Pancreaze	4,200	10,000	17,500
Pancreaze	10,500	25,000	43,750
Pancreaze	16,800	40,000	70,000
Pancreaze	21,000	37,000	61,000
Zenpep 3	3,000	10,000	16,000
Zenpep 5	5,000	17,000	27,000
Zenpep 10	10,000	34,000	55,000
Zenpep 15	15,000	51,000	82,000
Zenpep 20	20,000	68,000	109,000
Zenpep 25	25,000	85,000	136,000

<sup>a</sup>Dosing and comparison of products based on lipase content.

add-on therapy in patient with airway congestion despite optimal standard therapy. A short-acting  $\beta$ -agonist should be given before IHS to prevent bronchospasm.

- **$\beta_2$ -Agonists:** albuterol inhaler can provide bronchodilation and is used with other therapies (e.g., hypertonic saline, inhaled aztreonam) to prevent bronchospasm.
- **Anti-inflammatory Agents**
  - **Corticosteroids.** Oral agents are not recommended as long-term use is associated with unacceptable adverse effects. Inhaled agents are widely prescribed but lack data showing benefit; routine use in CF is not recommended.
  - **NSAIDs.** High-dose ibuprofen (20–30 mg/kg twice daily, with dose titrated to peak concentrations of 50–100 mg/mL) has been shown to slow the annual rate of FEV<sub>1</sub> decline in children between 5 and 13 years of age. Ibuprofen serum concentrations must be closely monitored.
  - **Azithromycin:** an antibiotic that has anti-inflammatory properties that has shown a reduction in exacerbation frequency and weight gain.
- **Antibiotic Therapy**
  - Choice of agent is based on throat culture and susceptibility data. Combination therapy using two agents with different mechanism of action is often used for infections involving *P. aeruginosa* (antipseudomonal  $\beta$ -lactam and an aminoglycoside or fluoroquinolone).
  - Multidrug-resistant strains occur in 15% to 20% of patients; treatment may require IV colistimethate. Monitor therapy closely due to risk for neuro- and nephrotoxicity.
  - Antibiotics most commonly used to treat acute pulmonary exacerbations and their dosage ranges are shown in Table 26.6.
  - $\beta$ -Lactam antibiotics can be given as intermittent, prolonged, or continuous infusions. Prolonged and continuous infusions are intended to maximize the time concentrations exceed the minimum inhibitory concentration.

TABLE 26.6 Antibiotic Doses for Cystic Fibrosis

SYSTEMIC ANTIBIOTICS

Drug	Daily Dosage (mg/kg)	Frequency	Maximal Individual Dose (mg)
Amikacin	30	Every 24 hours	TDM
Ceftazidime	150–225	Divided every 6–8 hours	2,000
Cefuroxime	150–225	Divided every 8 hours	1,500
Ciprofloxacin IV	30	Divided every 8 hours	400
Ciprofloxacin PO	40	Divided every 12 hours	1,000
Colistimethate	5	Divided every 8 hours	150
Gentamicin	10	Every 24 hours	TDM
Imipenem	40–80	Divided every 6 hours	1,000
Meropenem	50–100	Divided every 6–8 hours	2,000
Oxacillin	200	Divided every 4–6 hours	2,000
Piperacillin	200–400	Divided every 4–6 hours	4,000
Ticarcillin/Clavulanate	200–400	Divided every 4–6 hours	3,100
Tobramycin	10	Every 24 hours	TDM
TMP/SMZ	10–15	Divided every 8–12 hours	800

INHALED ANTIBIOTICS

Drug	Dosage (mg)	Interval	Comments
Aztreonam	75	TID	
TOBI	300	BID	28 days on, 28 days off
Colistin	37.5–75	BID	

BID, twice daily; TDM, therapeutic drug monitoring (gentamicin/tobramycin desired maximal concentration is 20 to 30 mg/L once-daily dosing); TID, three times daily; TMP/SMZ, trimethoprim/sulfamethoxazole; TOBI, tobramycin for inhalation.

- Extended-interval dosing of aminoglycosides (every 24 hours) is preferable to every-8-hour dosing to treat acute exacerbations. Serum concentrations are obtained between 1 and 2 hours and then between 6 and 8 hours after the end of the infusion. The extrapolated peak (target 20–30 mcg/mL) and area under the serum concentration–time curve (target 72–100 mg/L × hour) should be calculated.
- Imipenem and colistin are reserved for treatment of resistant *P. aeruginosa* infection.
- **Tobramycin for Inhalation:** used for chronic maintenance therapy in patients >6 years of age who have positive sputum cultures with *P. aeruginosa* and FEV<sub>1</sub> between 25% and 75% of predicted. The recommended dose is 300 mg twice daily in a cycle of 28 days on and 28 days off.
- **Aztreonam Lysine for Inhalation:** used for chronic maintenance therapy in patients >6 years of age to improve respiratory symptoms. Dosing is 75 mg three times daily for 28 days using a special nebulizer device. Bronchodilator use is recommended to reduce adverse effects of wheezing and cough.
- **Colistimethate for Inhalation:** may be useful in patients infected with multidrug-resistant *P. aeruginosa* or those intolerant to other inhaled agents. Routine use is not recommended due to lack of data.
- **Azithromycin Oral** (500 mg three times weekly for patients >40 kg; 250 mg three times weekly for patients <40 kg) is indicated in patients >6 years of age who are colonized with *P. aeruginosa*. Use is contraindicated in patients colonized with mycobacteria.
- **Quinolones:** the only family of antibiotics currently indicated for oral therapy of *P. aeruginosa*. Use in CF is restricted to acute exacerbations due to emergence of resistance.

# SECTION IV • GASTROINTESTINAL DISORDERS

## CHAPTER 27

### Upper Gastrointestinal Disorders\*

#### General Principles

- Upper gastrointestinal (GI) disorders include a wide spectrum of maladies that range from simple discomfort to life-threatening illness. They include illnesses such as dyspepsia, peptic ulcer disease (PUD), gastroesophageal reflux disease (GERD), and upper GI bleeding.

#### Patient Assessment

- Indications for testing and treating *Helicobacter pylori* infection are shown in Table 27.1. Prevalence of *H. pylori* varies by geographic location, socioeconomic status, ethnicity, and age. It is more common in developing countries than in industrialized nations.

#### Dyspepsia

- Dyspepsia refers to a subjective feeling of pain or discomfort located primarily in the upper abdomen. Most patients complain of acute dyspeptic symptoms (indigestion) that are often related to food consumption. Medications (nonsteroidal anti-inflammatory drugs [NSAIDs],

TABLE 27.1 Indications for Testing and Treating *Helicobacter pylori* Infection

#### RECOMMENDED (EVIDENCE ESTABLISHED)

- Uninvestigated dyspepsia (depending on *H. pylori* prevalence)
- PUD (active gastric or duodenal ulcer)
- History of PUD (confirmed ulcer not previously treated for *H. pylori*)
- Gastric MALT lymphoma
- After resection of early gastric cancer
- Reduce the risk of recurrent bleeding from gastroduodenal ulcer

#### CONTROVERSIAL (EVIDENCE NOT WELL ESTABLISHED)

- NUD
- Individuals using NSAIDs (no signs/symptoms of peptic ulcer)
- GERD
- Individuals at risk for gastric cancer
- Individuals with unexplained iron-deficiency anemia

GERD, gastroesophageal reflux disease; MALT, mucosa-associated lymphoid tissue; NUD, nonulcer dyspepsia; NSAID, nonsteroidal anti-inflammatory drug; PUD, peptic ulcer disease.

Sources: Talley NJ, Holtmann G. Approach to the patient with dyspepsia and related functional gastrointestinal complaints. In: Yamada T et al, eds. *Principles of Clinical Gastroenterology*. 5th ed. Hoboken, NJ: Wiley-Blackwell; 2008:38; Chey WD et al. American College of Gastroenterology guideline on the management of *Helicobacter pylori* infection. *Am J Gastroenterol*. 2007;102:1808; De Vries AC, Kuipers EF. *Helicobacter pylori* infection and nonmalignant diseases. *Helicobacter*. 2010;15(Suppl 1):29; Figura N et al. Extragastric manifestations of *Helicobacter pylori* infection. *Helicobacter*. 2010;15(Suppl 1):60.

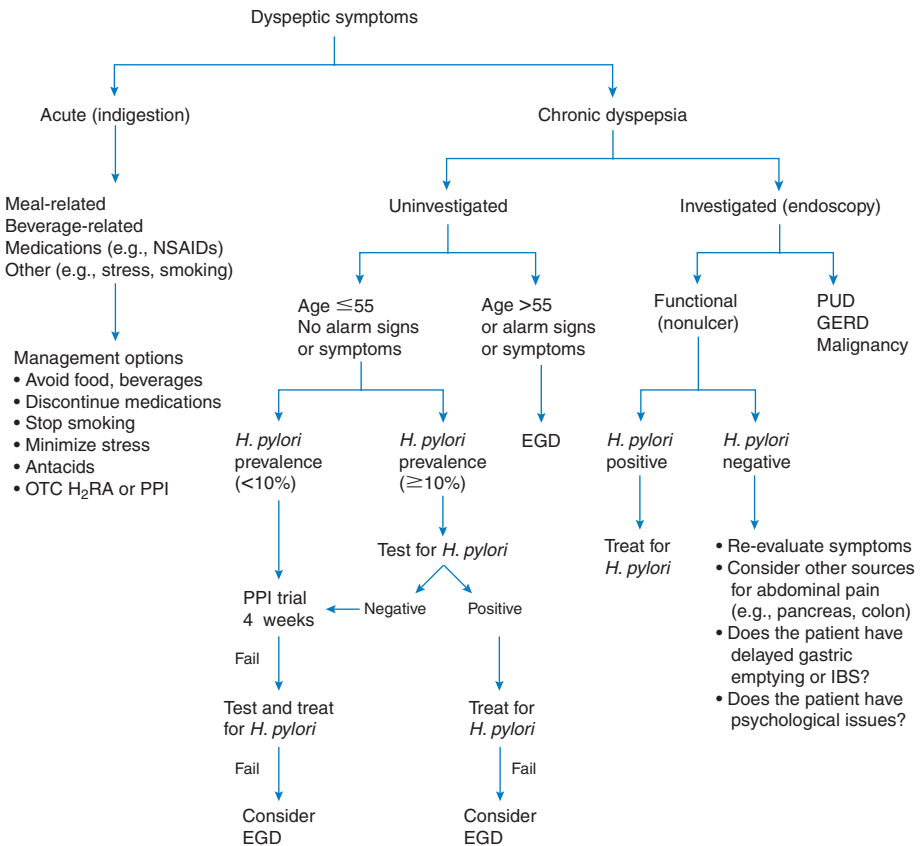
\*The reader is referred to Chapter 27, Upper Gastrointestinal Disorders, written by Randolph V. Fugit, PharmD, BCPS, and Rosemary R. Berardi, Pharm D, FCCP, FASHP, FAPhA, in the 10th edition of *Applied Therapeutics: The Clinical Use of Drugs* for a more in-depth discussion. All notations to reference numbers are based on the reference list at the end of that chapter. The editor of this handbook expresses her thanks to Drs. Fugit and Berardi and acknowledges that this chapter is based on their work.

antibiotics, iron, potassium, digoxin, theophylline, and bisphosphonates), smoking, and a stressful lifestyle can also cause acute dyspepsia. Acute dyspepsia is usually self-limiting.

- Chronic dyspepsia is defined as recurrent symptoms that include at least one of the following: epigastric pain, burning, abdominal bloating, belching, nausea, vomiting, and early satiety. It may be related to an underlying cause.
- Uninvestigated dyspepsia refers to patients who have not undergone diagnostic testing.
- **Treatment**
  - Recommended strategies for managing dyspepsia in adults are shown in Figure 27.1.
  - Proton-pump inhibitors (PPIs) should be discontinued after 1 month if the patient’s symptoms respond to treatment. If symptoms recur, longer-term PPI therapy may be considered. The need for ongoing PPI therapy should be evaluated every 6 to 12 months.
  - Use of prokinetic agents (metoclopramide, erythromycin) should be reserved for difficult-to-treat patients due to their side effects and limited efficacy.

### Peptic Ulcer Disease

- The natural history of PUD is characterized by periods of exacerbations and remissions. Chronic peptic ulcers are defects in the gastric or duodenal mucosa. Stress ulcer is a form of peptic ulcer that occurs in the critically ill (see below).



**Figure 27.1** Management of dyspeptic symptoms. EGD, esophagogastroduodenoscopy; GERD, gastroesophageal reflux disease; *H. pylori*, *Helicobacter pylori*; H<sub>2</sub>RA, H<sub>2</sub> receptor antagonist; IBS, irritable bowel syndrome; NSAID, nonsteroidal anti-inflammatory drug; OTC, over the counter; PPI, proton-pump inhibitor; PUD, peptic ulcer disease.

**TABLE 27.2 Risk Factors for Nonsteroidal Anti-inflammatory Drug–Induced Ulcer and Ulcer-Related Upper Gastrointestinal Complications**

**ESTABLISHED**

- Confirmed prior ulcer or ulcer-related complication
- Age >65 years
- Multiple or high-dose NSAID use
- Concomitant use of aspirin (including low cardioprotective dosages, e.g., 81 mg)
- Concomitant use of an anticoagulant, corticosteroid, bisphosphonate, clopidogrel, or SSRI
- Selection of NSAID (selectivity of COX-1 vs. COX-2)

**CONTROVERSIAL**

- *H. pylori*
- Alcohol consumption
- Cigarette smoking

COX-1, cyclo-oxygenase-1; COX-2, cyclo-oxygenase-2; NSAID, nonsteroidal anti-inflammatory drug; SSRI, selective serotonin reuptake inhibitor.

Sources: Soll AH, Graham DY. Peptic ulcer disease. In: Yamada T et al, eds. *Textbook of Gastroenterology*. 5th ed. Hoboken, NJ: Wiley-Blackwell; 2009:936; Chey WD et al. American College of Gastroenterology guideline on the management of *Helicobacter pylori* infection. *Am J Gastroenterol*. 2007;102:1808; Scarpignato C, Hunt RH. Nonsteroidal anti-inflammatory drug-related injury to the gastrointestinal tract: clinical picture, pathogenesis and prevention. *Gastroenterol Clin North Am*. 2010;39:433; Lanza FL et al. Guidelines for prevention of NSAID-related ulcer complications. *Am J Gastroenterol*. 2009;104:728; Malfertheiner P et al. Peptic ulcer disease. *Lancet*. 2009;374:1449; Vonkeman H et al. Risk management of risk management: combining proton-pump inhibitors with low-dose aspirin. *Drug Healthc Patient Saf*. 2010;2:191; Targownik LE et al. Selective serotonin reuptake inhibitors are associated with a modest increase in the risk of upper gastrointestinal bleeding. *Am J Gastroenterol*. 2009;104:1475; Dall M et al. There is an association between selective serotonin reuptake inhibitor use and uncomplicated peptic ulcers: a population-based case-control study. *Aliment Pharmacol Ther*. 2010;32:1383; Andrade C et al. Serotonin reuptake inhibitor antidepressants and abnormal bleeding: a review of clinicians and a reconsideration of mechanisms. *J Clin Psychiatry*. 2010;71:1565.

- *H. pylori* and NSAIDs are the two most common causes of chronic PUD. Risk factors for NSAID-induced ulcers and upper GI complications are shown in Table 27.2. The relative cyclo-oxygenase (COX) selectivity among NSAIDs varies and is thought to be an important factor in propensity for ulcer formation. COX-1–sparing agents may be associated with less GI toxicity (Table 27.3). All patients with NSAID-induced GI events should be tested for *H. pylori*.
- Risk factors for PUD include alcohol ingestion, smoking, psychological stress, corticosteroid use, and chronic diseases (renal failure, cirrhosis, pancreatitis, obstructive pulmonary disease, Crohn's disease, organ transplantation).

**TABLE 27.3 Selected Nonsteroidal Anti-inflammatory Drugs**

**SALICYLATES**

Acetylated: aspirin  
Nonacetylated: trisalicylate, salsalate

**NONSALICYLATES<sup>a</sup>**

Nonselective (traditional) NSAIDs: ibuprofen, naproxen, tolmetin, fenoprofen, sulindac, indomethacin, ketoprofen, ketorolac, flurbiprofen, piroxicam  
Partially selective NSAIDs: etodolac, diclofenac, meloxicam, nabumetone  
Selective COX-2 inhibitors: celecoxib<sup>b</sup>, rofecoxib<sup>c</sup>, valdecoxib<sup>c</sup>

<sup>a</sup>Based on COX-1/COX-2 selectivity ratio in vitro.

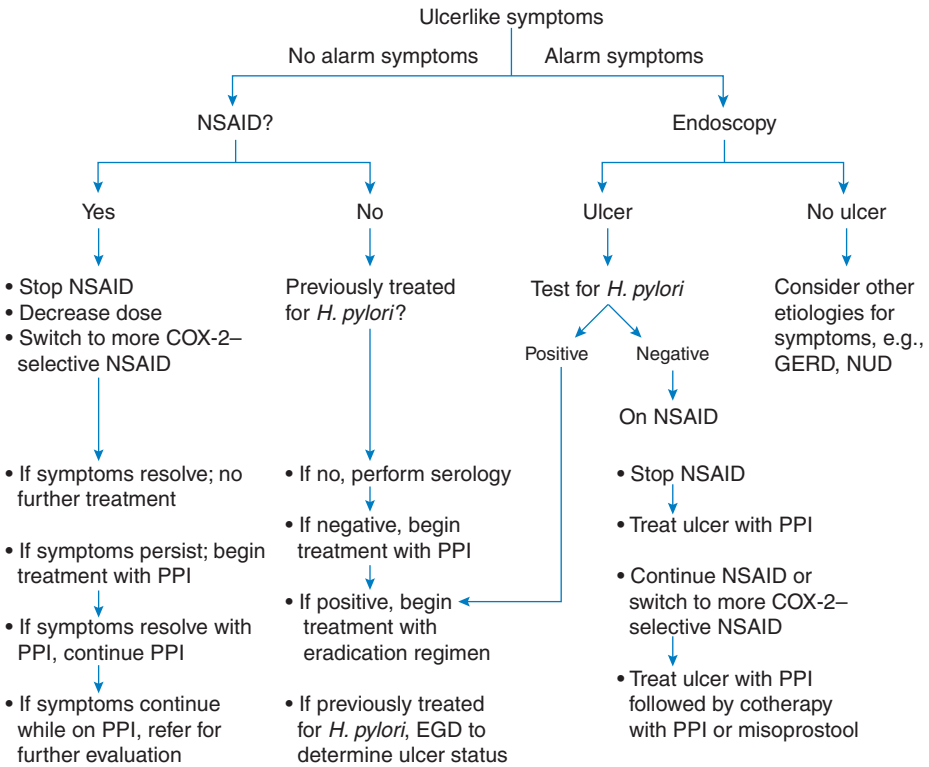
<sup>b</sup>Initially marketed as a COX-2 inhibitor, but current FDA labeling is consistent with nonselective and partially selective NSAIDs.

<sup>c</sup>Withdrawn from the US market.

COX-2, cyclo-oxygenase-2; NSAID, nonsteroidal anti-inflammatory drug.



- Symptoms range from mild epigastric pain to life-threatening GI complications. No one sign or symptom differentiates *H. pylori*- versus NSAID-induced ulcer. Ulcer-related bleeding is the most frequent complication.
- **Treatment**
  - Goals of therapy depend on the underlying cause (*H. pylori*- vs. NSAID-induced ulcer) and whether the ulcer is initial or recurrent. Treatment is aimed at relieving ulcer symptoms, healing the ulcer, preventing ulcer recurrence, eradicating the infection (if *H. pylori* is present), and reducing complications.
  - Nondrug therapy includes discontinuing NSAIDs, if possible, reducing stress, stopping (or reducing) smoking, and dietary modifications.
  - Management of PUD is shown in Figure 27.2.
  - Drug regimens used to eradicate *H. pylori* are shown in Table 27.4. PPI-based three-drug regimens are standard first-line therapy in the United States. If initial eradication fails, a second course should be based on selection of antibiotics that have not been previously used. Amoxicillin is preferred initially, leaving metronidazole for second-line therapy. Antacids and antisecretory agents provide relief of ulcer pain in most patients.
  - Drug regimens used to treat NSAID-induced ulcers are shown in Table 27.5. Strategies to reduce the risk of NSAID-induced ulcers include cotherapy with a PPI, misoprostol, or the use of a COX-2 selective agent. All PPIs are effective at standard doses for this purpose. H<sub>2</sub>RAs at standard doses are not effective for this purpose; higher doses can reduce the risk but are less effective than PPIs.



**Figure 27.2** Management of peptic ulcer disease. COX-2, cyclo-oxygenase-2; EGD, esophagogastroduodenoscopy; GERD, gastroesophageal reflux disease; *H. pylori*, *Helicobacter pylori*; NSAID, nonsteroidal anti-inflammatory drug; NUD, nonulcer dyspepsia; PPI, proton-pump inhibitor.

TABLE 27.4 Oral Drug Regimens Used to Eradicate *Helicobacter pylori* Infection

Drug Regimen	Dose	Frequency	Duration
<b>PROTON-PUMP INHIBITOR–BASED THREE-DRUG REGIMENS</b>			
PPI	Standard dose <sup>a</sup>	BID <sup>a</sup>	14 days <sup>b</sup>
Clarithromycin	500 mg	BID	14 days <sup>b</sup>
Amoxicillin <sup>c</sup>	1 g	BID	14 days <sup>b</sup>
Or			
PPI	Standard dose <sup>a</sup>	BID <sup>a</sup>	14 days <sup>b</sup>
Clarithromycin	500 mg	BID	14 days <sup>b</sup>
Metronidazole <sup>c</sup>	500 mg	BID	14 days <sup>b</sup>
<b>BISMUTH-BASED FOUR-DRUG REGIMENS</b>			
Bismuth subsalicylate <sup>d</sup>	525 mg	QID	10–14 days
Metronidazole	250–500 mg	QID	10–14 days
Tetracycline plus	500 mg	QID	10–14 days
PPI	Standard dose <sup>a</sup>	Daily or BID <sup>a</sup>	10–14 days
Or			
H <sub>2</sub> RA <sup>e</sup>	Standard dose <sup>e</sup>	BID <sup>e</sup>	4–6 weeks
<b>SEQUENTIAL THERAPY<sup>f</sup></b>			
PPI	Standard dose <sup>a</sup>	BID <sup>a</sup>	Days 1–10
Amoxicillin	1 g	BID	Days 1–5
Clarithromycin	250–500 mg	BID	Days 6–10
Metronidazole	250–500 mg	BID	Days 6–10
<b>SECONDARY OR RESCUE THERAPY</b>			
Bismuth subsalicylate <sup>d</sup>	525 mg	QID	10–14 days
Metronidazole	500 mg	QID	10–14 days
Tetracycline	500 mg	QID	10–14 days
PPI	Standard dose <sup>a</sup>	Daily or BID <sup>a</sup>	10–14 days
Or			
PPI	Standard dose <sup>a</sup>	BID <sup>a</sup>	10–14 days
Amoxicillin	1 g	BID	10–14 days
Levofloxacin	500 mg	Daily	10–14 days

<sup>a</sup>Omeprazole 20 mg BID; lansoprazole 30 mg BID; pantoprazole 40 mg BID; rabeprazole 20 mg daily or BID; esomeprazole 20 mg BID or 40 mg daily.

<sup>b</sup>Although 7-to-10-day regimens may provide acceptable eradication rates, the preferred treatment duration in the United States is 14 days.

<sup>c</sup>Use amoxicillin in non-penicillin-allergic individuals; substitute metronidazole for amoxicillin in penicillin-allergic patients.

<sup>d</sup>Pylera, a prepackaged *H. pylori* regimen, contains bismuth subcitrate potassium (bismuth salt) 140 mg as the bismuth salt in place of bismuth subsalicylate, metronidazole 125 mg, and tetracycline 125 mg per capsule. The patient is directed to take three capsules/dose with each meal and at bedtime. A standard dose of a PPI is added to the regimen and taken twice daily. All medications are taken for a 10-day period.

<sup>e</sup>See Table 27.5 for standard peptic ulcer–healing dosage regimens.

<sup>f</sup>Requires validation in the United States.

BID, twice a day; H<sub>2</sub>RA, H<sub>2</sub> receptor antagonist; PPI, proton-pump inhibitor; QID, four times a day.

Sources: Soll AH, Graham DY. Peptic ulcer disease. In: Yamada T et al, eds. *Textbook of Gastroenterology*. 5th ed. Hoboken, NJ: Wiley-Blackwell; 2009:936; Washington MK, Peek RM. Gastritis and gastropathy. In: Yamada T et al, eds. *Textbook of Gastroenterology*. 5th ed. Hoboken, NJ: Wiley-Blackwell; 2009:1005; Malfertheiner P et al. Peptic ulcer disease. *Lancet*. 2009;374:1449; Gisbert JP et al. Sequential therapy for *Helicobacter pylori* eradication: a critical review. *J Clin Gastroenterol*. 2010;44:313; Gisbert JP et al. *Helicobacter pylori* first-line treatment and rescue options in patients allergic to penicillin. *Aliment Pharmacol Ther*. 2005;22:1041; Gisbert JP et al. *Helicobacter pylori* first-line treatment and rescue option containing levofloxacin in patients allergic to penicillin. *Dig Liver Dis*. 2010;42:287; Vergara M et al. Meta-analysis: comparative efficacy of different proton-pump inhibitors in triple therapy for *Helicobacter pylori* eradication. *Aliment Pharmacol Ther*. 2003;18:647; Gisbert JP et al. Meta-analysis: proton-pump inhibitors vs. H<sub>2</sub>-receptor antagonists—their efficacy with antibiotics in *Helicobacter pylori* eradication. *Aliment Pharmacol Ther*. 2003;18:757; Gisbert JP. Review: Second-line rescue therapy of *Helicobacter pylori* infection. *Therap Adv Gastroenterol*. 2009;2:331.

TABLE 27.5 Oral Medications Used to Treat Upper Gastrointestinal Disorders

	Gastric and Duodenal Ulcer Healing	Maintenance of Gastric and Duodenal Ulcer Healing	Reduction of Gastric Ulcer Risk Associated with NSAIDs	Relief of Heartburn and Indigestion (OTC Use)	Relief of GERD Symptoms (Rx Use)	Esophageal Healing <sup>a</sup>	Maintenance of Esophageal Healing <sup>a</sup>	Hypersecretory Diseases <sup>a,b</sup>
<b>H<sub>2</sub> RECEPTOR ANTAGONISTS</b>								
Cimetidine	300 mg QID 400 mg BID 800 mg daily	400–800 mg HS	Not indicated	200 mg BID PRN	300 mg QID	400 mg QID 800 mg BID	400–800 mg HS	<sup>a</sup>
Famotidine	20 mg BID 40 mg HS	20–40 mg HS	Not indicated	10 mg BID PRN 20 mg BID PRN	20 mg BID	40 mg BID	20–40 mg BID	<sup>a</sup>
Nizatidine	150 mg BID 300 mg HS	150–300 mg HS	Not indicated	75 mg BID PRN	150 mg BID	300 mg BID	150–300 mg BID	<sup>a</sup>
Ranitidine	150 mg BID 300 mg HS	150–300 mg HS	Not indicated	75 mg BID PRN 150 mg BID PRN	150 mg BID	300 mg BID	150–300 mg BID	<sup>a</sup>
<b>PROTON-PUMP INHIBITORS</b>								
Esomeprazole	20–40 mg daily	20 mg daily	20 mg daily	Not indicated	20 mg daily	20–40 mg daily	20 mg daily	60 mg daily
Dexlansoprazole	Not indicated	Not indicated	Not indicated	Not indicated	30 mg daily	60 mg daily	30 mg daily	Not indicated
Lansoprazole	15–30 mg daily	15–30 mg daily	15–30 mg daily	15 mg daily <sup>c</sup>	15–30 mg daily	30 mg daily	15–30 mg daily	60 mg daily
Omeprazole	20 mg daily	20 mg daily	20 mg daily	20 mg daily <sup>c</sup>	20 mg daily	20–40 mg daily	20 mg daily	60 mg daily
Pantoprazole	40 mg daily	40 mg daily	40 mg daily	Not indicated	20 mg daily	40 mg daily	40 mg daily	80 mg daily
Rabeprazole	20 mg daily	20 mg daily	20 mg daily	Not indicated	20 mg daily	20 mg daily	20 mg daily	60 mg daily
Rabeprazole ER <sup>d</sup>	Not indicated	Not indicated	Not indicated	Not indicated	Unknown	50 mg daily	Unknown	Not indicated
<b>OTHER AGENTS</b>								
Sucralfate	1 g QID 2 g BID	Not indicated	Not indicated	Not indicated	Not indicated	Not indicated	Not indicated	Not indicated
Misoprostol	Not indicated	Not indicated	200 mcg TID–QID	Not indicated	Not indicated	Not indicated	Not indicated	Not indicated

<sup>a</sup>Although FDA labeled for this indication, H<sub>2</sub>RAs are not recommended even in higher dosages because they are not as effective as the PPIs.

<sup>b</sup>Initial starting dose; daily dosage must be titrated to gastric acid secretory response.

<sup>c</sup>Duration of treatment should not exceed 14 consecutive days; if needed, repeat 14-day treatment every 4 months.

<sup>d</sup>Not FDA approved at time of publication.

BID twice a day; GERD, gastroesophageal reflux disease; HS, at bedtime; NSAID, nonsteroidal anti-inflammatory drug; OTC, over the counter; PRN, as needed; QD, every day; QID, four times a day; Rx, prescription; TID, three times a day.

- Maintenance therapy with a PPI or H<sub>2</sub>RA should only be needed in high-risk patients with a history of ulcer complications, those with *H. pylori* negative ulcers, and those with concomitant acid-related disorders.

## Zollinger–Ellison Syndrome

- Zollinger–Ellison syndrome (ZES) is an uncommon gastric acid hypersecretory disease characterized by severe recurrent peptic ulcers that result from a gastrin-producing tumor.
- Abdominal pain, the primary symptom, is usually related to persistent peptic ulcers that are less responsive to antisecretory therapy. Duodenal ulcers occur most often. Other symptoms include nausea, vomiting, upper GI bleeding, and weight loss.
- **Treatment**
  - The goal of therapy is to pharmacologically control gastric acid secretion and to surgically resect the tumor, if possible.
  - Oral PPIs are the drug of choice (Table 27.5). IV PPIs should be reserved for patients not able to take oral medications. H<sub>2</sub>RAs are no longer used to treat ZES. Somatostatin analogs (e.g., octreotide) are rarely used as first-line therapy.

## Gastroesophageal Reflux Disease

- GERD is associated with a wide array of symptoms, the most frequent of which are heartburn and acid regurgitation that may be episodic or meal-related. Other symptoms include a water brash, early satiety, belching, hiccups, nausea, and vomiting. Worrisome symptoms include dysphagia, odynophagia, vomiting of blood, bloody or tarry stools, unexplained weight loss, or anemia. Atypical manifestations of GERD are shown in Table 27.6.
- Gastroesophageal reflux is defined as the retrograde passage of gastric contents from the stomach into the esophagus. Esophageal injury occurs with continued exposure of the mucosa to gastric acid, resulting in inflammation that can progress to ulceration (erosive esophagitis).
- Complications of GERD include esophageal erosions or strictures, Barrett metaplasia, and adenocarcinoma of the esophagus.
- Risk factors associated with GERD include dietary and lifestyle factors, drugs, and certain medical or surgical conditions (Table 27.7).
- **Treatment**
  - Goals of therapy are to alleviate symptoms, promote esophageal healing, prevent recurrence, and avoid long-term complications.
  - Lifestyle and dietary modifications are the initial and continued management steps (Table 27.8).
  - Management of GERD is shown in Figure 27.3. Many patients with mild, infrequent symptoms can be managed with over-the-counter (OTC) medications. Antacids and H<sub>2</sub>RAs are the drugs of choice for infrequent disease; PPIs should be reserved for patients with frequent moderate or severe GERD symptoms. Self-treatment should not exceed

TABLE 27.6 Atypical Manifestations of Gastroesophageal Reflux Disease

Noncardiac Chest Pain	Pulmonary
Ear, Nose, and Throat	Chronic cough
Laryngitis/pharyngitis	Nonallergic, nonseasonal asthma
Hoarseness	Aspiration
Globus sensation	Bronchiectasis/bronchitis
Laryngeal cancer	Sleep apnea
Sinusitis	Idiopathic pulmonary fibrosis
Otitis	Pneumonia
Other	
Hypersalivation	
Dental erosions	

TABLE 27.7 Risk Factors Associated with Gastroesophageal Reflux Disease

Drugs	Dietary
$\alpha$ -Adrenergic agonists	Foods high in fat
Anticholinergics	Spicy foods
Aspirin	Carminatives (peppermint, spearmint)
Barbiturates	Chocolate
Benzodiazepines	Caffeine (coffee, tea, colas)
$\beta_2$ -Adrenergic agonists	Garlic or onions
Bisphosphonates	Citrus fruits and juices
Calcium-channel blockers	Tomatoes and juice
Dopamine	Carbonated beverages
Estrogen	
Isoproterenol	<b>Lifestyle</b>
Iron	Cigarette/cigar smoke
Narcotics	Obesity
Nitrates	Supine body position
NSAIDs	Tight-fitting clothing
Progesterone	Heavy exercise
Potassium	
Prostaglandins	<b>Medical/Surgical Conditions</b>
Quinidine	Pregnancy
Tetracycline	Scleroderma
Theophylline	ZES
Tricyclic antidepressants	Gastroparesis
Zidovudine	Nasogastric tube intubation

NSAID, nonsteroidal anti-inflammatory drug; ZES, Zollinger-Ellison syndrome.

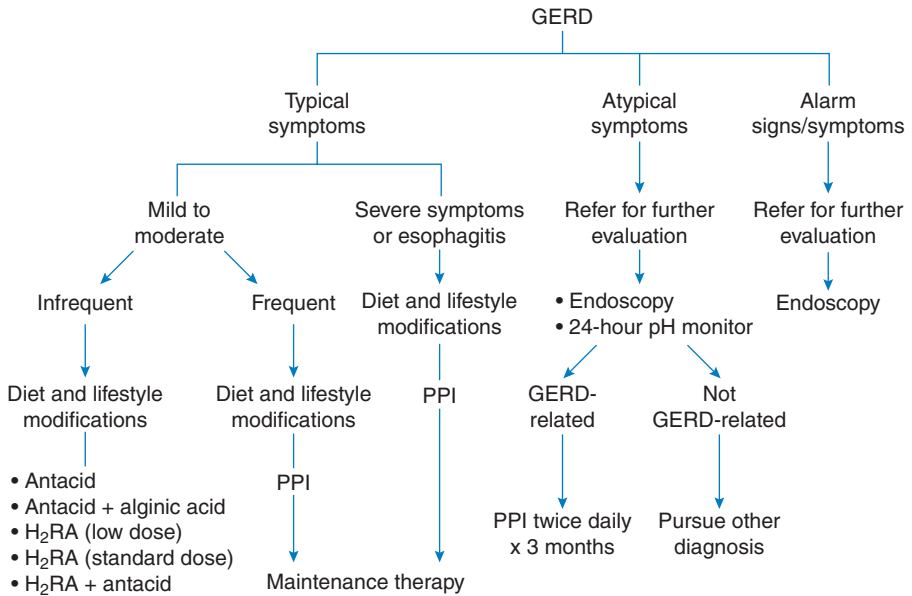
twice-daily dosing of H<sub>2</sub>RAs and treatment duration should not exceed 2 weeks. Use beyond 2 weeks should be under the care of a health care provider.

- Prokinetic agents (metoclopramide or bethanechol) are not widely used for GERD because of their numerous side effects.
- Sucralfate can work for mild cases but is not widely used because of side effects.
- Maintenance therapy is used to keep the patient symptom-free and prevent potentially life-threatening complications. Ongoing therapy with a PPI is more effective than an H<sub>2</sub>RA. The recommended maintenance dose is the dose that is required to render the patient asymptomatic.

TABLE 27.8 Dietary and Lifestyle Modifications Used to Manage Gastroesophageal Reflux Symptoms

Dietary	Medication	Lifestyle
	Avoid medications with a potential to relax the lower esophageal sphincter or that have a direct irritant effect on the esophageal mucosa	Stop or decrease smoking/tobacco
Avoid eating large meals	Medications with the potential to irritate the esophagus should be taken with a full glass of water	Avoid alcohol
Avoid eating within 3 hours of bedtime		Lose weight <sup>a</sup>
		Elevate the head of bed 6–8 inches or use a foam wedge <sup>a</sup>
		Sleep in the left lateral decubitus position <sup>a</sup>

<sup>a</sup>Sufficient evidence exists to support lifestyle modification.



**Figure 27.3** Management of gastroesophageal reflux disease. H<sub>2</sub>RA, H<sub>2</sub> receptor antagonist; PPI, proton-pump inhibitor.

- Extraesophageal manifestations of GERD should be treated with high-dose (twice daily) PPI for at least 3 months before considering therapy to be ineffective.

## Upper GI Bleeding

- Upper GI bleeding is a medical emergency. It is categorized as either variceal (see Chapter 29) or nonvariceal bleeding. Nonvariceal bleeding describes bleeding associated with PUD or stress-related mucosal bleeding (SRMB). The most common causes of upper GI bleeding in patients with PUD are NSAIDs and *H. pylori* infection. SRMB occurs in critically ill patients with severe physiological stress. Risk factors for SRMB are shown in Table 27.9.
- Symptoms of GI bleeding include the presence of melana (dark, tarry stool), hematemesis, or hematochezia (bloody diarrhea).
- **Treatment**
  - Rapid risk stratification based on presenting signs and symptoms is needed to define treatment. Patients with hemodynamic instability require immediate resuscitative measures (administration of fluids and blood products). Intravascular volume should be replenished with normal saline to prevent hypovolemic shock. Guidelines recommend transfusion of packed red blood cells for hemoglobin levels <7 mg/dL; consideration is warranted in patients with tachycardia or hypotension and a hemoglobin <10 mg/dL.
  - PPIs are the drug of choice to reduce the incidence of PUD-related rebleeding. Guidelines suggest an initial IV bolus equivalent to 80 mg of omeprazole followed by a continuous infusion of 8 mg/hour for 72 hours. H<sub>2</sub>RAs are no longer recommended because of inferior efficacy.
  - After stabilization, the patient should receive once-daily PPI therapy for continued lesion healing and prevention of rebleeding. The dose and duration of therapy should be based on the severity of the disease and identified complications. More severe disease may require twice-daily therapy.

TABLE 27.9 Risk Factors for Stress-Related Mucosal Bleeding

- Respiratory failure
- Coagulopathy
- Hypotension
- Sepsis
- Hepatic failure
- Acute renal failure
- Enteral feeding
- High-dose corticosteroids<sup>d</sup>
- Organ transplant
- Anticoagulants
- Severe burns (>35% of body surface area)
- Head injury
- Intensive care unit stay >7 days
- History of previous GI hemorrhage

<sup>d</sup>> 250 mg/day hydrocortisone or equivalent.

- Guidelines recommend prophylaxis therapy for SRMB only when the patient is mechanically ventilated, has a coagulopathy, or when two or more risk factors are present (Table 27.9). An intragastric pH > 4 is recommended. Therapeutic options are shown in Table 27.10. While antacids are effective, their use is limited by the need for frequent administration and monitoring of intragastric pH. H<sub>2</sub>RAs are effective and widely used to prevent SRMB but tolerance may develop within 72 hours. PPIs are the preferred agents; alternative administration options for patients who cannot take medications by mouth are shown in Table 27.11.

## Drug Therapy

- Oral medications used to treat upper GI disorders are shown in Table 27.5.
- **Antacids** are widely used to relieve mild and infrequent symptoms associated with acid-related diseases. They act by neutralizing gastric acid and increasing intragastric pH in a

TABLE 27.10 Stress-Related Mucosal Bleeding Prevention: Regimens and Doses

Agent	Dose and Frequency of Administration	FDA Approval <sup>a</sup>
Antacid	30 mL PO/NG every 1–2 hours	No
Cimetidine	300 mg IV every 6–8 hours or 300 mg IV loading dose, then 50 mg/hour continuous IV infusion	No Yes
Famotidine	20 mg IV every 12 hours or 1.7 mg/hour continuous infusion	No No
Ranitidine	50 mg IV every 6–8 hours or 6.25 mg/hour continuous infusion	No No
Sucralfate	1 g PO/NG every 6 hours	No
Omeprazole	20–40 mg PO/NG <sup>b</sup> every 12–24 hours	No
Omeprazole/sodium bicarbonate powder for oral suspension	40 mg PO/NG initially, followed by 40 mg in 6–8 hours as a loading dose, then 40 mg PO/ NG every 24 hours	Yes
Lansoprazole	30 mg PO/NG <sup>b,c</sup> every 12–24 hours	No
Pantoprazole	40 mg IV/PO/NG <sup>b</sup> every 12–24 hours	No
Esomeprazole	40 mg IV every 12–24 hours	No

<sup>a</sup>For prevention of stress-related mucosal bleeding.

<sup>b</sup>Extemporaneously compounded in sodium bicarbonate.

<sup>c</sup>Oral disintegrating tablet.

IV, intravenous; NG, by nasogastric tube; PO, by mouth.

TABLE 27.11 Alternative Proton-Pump Inhibitor Administration Options

	Omeprazole	Lansoprazole	Pantoprazole	Esomeprazole	Rabeprazole	Dexlansoprazole
Capsule granules sprinkled on selected soft foods (i.e., applesauce)		✓ <sup>a</sup>		✓ <sup>a</sup>		✓ <sup>a</sup>
Capsule granules mixed in water and flushed down NG tube				✓		
Capsule granules mixed in juice (can be administered via NG tube if required)	✓ <sup>a</sup>	✓ <sup>a</sup>		✓ <sup>a</sup>		
Extemporaneous compound of PPI in bicarbonate for NG tube	✓	✓	✓			
Package for oral suspension	✓ <sup>a,b</sup>	✓ <sup>a,c</sup>				
Oral disintegrating tablet		✓ <sup>a</sup>				
IV formulation	Not available in the United States	Removed from US market	✓ <sup>a</sup>	✓ <sup>a</sup>		

<sup>a</sup>Labeled by the FDA for this administration option.

<sup>b</sup>Omeprazole suspensions available in 20- and 40-mg packets with bicarbonate (1,680 mg); both contain same amount of bicarbonate, and two 20-mg packets cannot be substituted for one 40-mg packet.

<sup>c</sup>Not to be administered via NG tube, as occlusion of tube is possible.

IV, intravenous; NG, nasogastric; PPI, proton-pump inhibitor.

dose-dependent manner that usually requires a substantial dose. Antacids are quick acting (within minutes) and have a short duration of action (30 minutes on an empty stomach). The duration can be extended if given with or within 1 hour of a meal.

- Antacids are generally well tolerated. Magnesium-containing agents can cause diarrhea. Use of magnesium- and aluminum-containing antacids should be avoided in patients with renal insufficiency.
- Antacids interfere with the absorption of many orally administered drugs that require an acidic environment for dissolution and absorption (e.g., digoxin, phenytoin, isoniazid, ketoconazole, itraconazole, and iron preparations), leading to potential therapeutic failure. The majority of the drug interactions can be avoided by separating the antacid from the interacting drug by a minimum of 2 hours.
- Aluminum-containing antacids bind to dietary phosphate and can cause constipation.
- **Alginate acid** is an inactive ingredient that acts by forming a viscous solution that floats on top of the gastric contents, which then protects the esophageal mucosa from potent acid refluxate.



- **Histamine-2 receptor antagonists ( $H_2RA$ )** competitively and selectively inhibits the action of histamine on the  $H_2$  receptors of parietal cells, reducing both basal and stimulated gastric acid secretion. At typical doses the available agents (cimetidine, ranitidine, famotidine, and nizatidine) have equipotent antisecretory effects (Table 27.5).
  - $H_2RA$ s can potentially alter the absorption and reduce the bioavailability of drugs that require an acidic environment for absorption. Cimetidine has the greatest potential for drug interactions because of its ability to inhibit several hepatic cytochrome P450 (CYP450) isoenzymes. Famotidine and nizatidine do not bind to CYP450 and do not interact with drugs metabolized through this hepatic system.
  - Side effects include GI discomfort (diarrhea, constipation), CNS effects (headache, dizziness, drowsiness, and lethargy), dermatologic (rash), and hematologic (thrombocytopenia). Cimetidine, in high doses, has caused gynecomastia and impotence in men.
- **PPIs** are highly specific and potent inhibitors of gastric acid secretion that act by irreversibly binding to the  $H^+/K^+-ATP$ -ase (proton pump). They inhibit both basal and stimulated gastric acid secretion in a dose-dependent manner.
  - PPIs are prodrugs that require an acidic environment for conversion. They are most effective when taken 30 to 60 minutes before a meal on an empty stomach.
  - PPIs have a long antisecretory effect (48–72 hours) because they irreversibly bind to the proton pump.
  - Available PPIs (omeprazole, lansoprazole, rabeprazole, pantoprazole, esomeprazole, and dexlansoprazole) have similar acid-inhibitory effects and healing rates when used in equivalent doses (Table 27.5).
  - Potential CYP2C19 interactions occur with PPIs and clopidogrel, reducing the efficacy of clopidogrel. Concomitant use of omeprazole and esomeprazole should be avoided. Benefit versus risk should be assessed on a per-patient basis.
  - Side effects include GI discomfort (nausea, diarrhea, abdominal pain), CNS effects (headache, dizziness), and rare isolated reactions (skin rash, increased liver enzymes). Long-term use in older patients at high doses has been associated with an increased risk of hip fractures. PPIs have been associated with an increased risk of infections (e.g., pneumonia, enteric infections) possibly because of the ability of microorganisms to survive in the less acidic environment.
- **Sucralfate** promotes gastric mucosal protection by forming a physical barrier and shielding ulcerated tissue from aggressive factors (acid, pepsin, bile salts). There is minimal absorption and no acid suppression activity.
  - Long-term use should be avoided due to the possibility of aluminum toxicity. Constipation is the most common side effect.
  - The bioavailability of some drugs may be reduced; give sucralfate at least 2 hours after these medications.
- **Misoprostol** is a synthetic prostaglandin  $E_1$  analog that acts by enhancing mucosal defense mechanisms. It stimulates production of mucus and bicarbonate, improving mucosal blood flow, and reducing mucosal cell turnover. Its use is limited due to dose-dependent diarrhea and abdominal cramping. Use in women of childbearing age requires a negative serum pregnancy test as it is an abortifacient.
- **Bismuth** is thought to work by binding to and protecting mucosal lesions and enhancing cellular protective mechanisms. Long-term use is not recommended. Patients with salicylate allergies or sensitivities should be warned of its salicylate component. Harmless black coloring of the stools and tongue occurs with use.

## Lower Gastrointestinal Disorders\*

### General Principles

- **Inflammatory bowel disease (IBD)** is a generic classification for a group of chronic, idiopathic, relapsing inflammatory disorders of the gastrointestinal (GI) tract. Symptoms of IBD are thought to result from dysregulation of the mucosal immune system.
- **Irritable bowel syndrome (IBS)** is a common and often debilitating condition that involves abdominal pain and bloating associated with a change in bowel habits. It does not significantly affect patient morality but is associated with considerable morbidity. Its pathogenesis is poorly understood.

### Classification

- IBD is divided into two major categories: ulcerative colitis (UC) and Crohn's disease (CD). Differences between UC and CD are shown in Table 28.1.
  - UC is an inflammatory condition of the large intestine. Mild disease is defined as fewer than 4 stools a day, no systemic signs of toxicity, and a normal erythrocyte sedimentation rate (ESR). Moderate disease is characterized by more than 4 stools daily and minimal systemic toxicity. Severe disease is defined as more than 6 bloody stools a day, fever, tachycardia, anemia, or an ESR > 30.
  - CD is a chronic, transmural, patchy, granulomatous, inflammatory disease that can affect any part of the GI tract. Small and large bowel involvement is most common.

TABLE 28.1 Pathophysiological Differences between Ulcerative Colitis and Crohn's Disease

Characteristic	Ulcerative Colitis	Crohn's Disease
Incidence (per year)	6–12/100,000	5–7/100,000
Anatomical location	Colon and rectum	Mouth to anus
Distribution	Continuous, diffuse, mucosal	Segmental, focal, transmural
Bowel wall	Shortened, loss of haustral markings, generally not thickened	Rigid, thick, edematous, and fibrotic
Gross rectal bleeding	Common	Infrequent
Crypt abscesses	Common	Infrequent
Fissuring with sinus formation	Absent	Common
Noncaseating granulomas	Absent	Common
Strictures	Absent	Common
Abdominal mass	Absent	Common
Abdominal pain	Infrequent	Common
Toxic megacolon	Occasional	Rare
Bowel carcinoma	Greatly increased	Slightly increased

\*The reader is referred to Chapter 28, Lower Gastrointestinal Disorders, written by Geoffrey C. Wall, PharmD, FCCP, BCPS, CGP, in the 10th edition of *Applied Therapeutics: The Clinical Use of Drugs* for a more in-depth discussion. All notations to reference numbers are based on the reference list at the end of that chapter. The editor of this handbook expresses her thanks to Dr. Wall and acknowledges that this chapter is based upon his work.

TABLE 28.2 Extraintestinal Complications of Ulcerative Colitis and Crohn's Disease

Manifestation	Ulcerative Colitis (%)	Crohn's Disease (%)
<b>ACUTE ARTHROPATHY</b>		
Type 1: Associated with flare of gastrointestinal symptoms	35	29
Type 2: Independent of gastrointestinal symptoms	24	20
Erythema nodosum	20	20
Pyoderma gangrenosum	1	2–3
Iritis/uveitis	4–12	4–12
Ankylosing spondylitis	1–3	3–5
Sacroiliitis	9–11	9–11
Primary sclerosing cholangitis	5–10	1
Metabolic bone disease	20–40	30–50

Source: Ardizzone S et al. Extraintestinal manifestations of inflammatory bowel disease. *Dig Liver Dis.* 2008;40(Suppl 2):S253.

Mild-to-moderate CD is defined as ambulatory patients who are able to tolerate oral feeding without signs of systemic toxicity. Moderate-to-severe disease is defined as patients with symptoms of fever, weight loss, abdominal pain, nausea and vomiting, or significant anaemia.

## Patient Assessment

### INFLAMMATORY BOWEL DISEASE

- UC presents as a shallow, continuous inflammation of the colon ranging from limited forms of proctitis (rectal involvement only) to disease involving the entire colon. Symptoms associated with UC include abdominal pain, chronic loose bloody stools, and fatigue. Fistulas, fissures, abscesses, and small bowel involvement are not present. Inflammation is limited to the mucosa. Most patients experience a chronic, intermittent course of disease with relapses and remissions.
- CD usually causes significant diarrhea (often nocturnal and without frank blood), abdominal pain, and weight loss. Patients usually present with one of three patterns of disease: predominantly inflammatory, structuring, or fistulizing.
- Extraintestinal manifestations of IBD can cause significant morbidity (Table 28.2).

### IRRITABLE BOWEL SYNDROME

- The diagnosis of IBS is usually symptom based: abdominal pain or discomfort that is accompanied by a change in bowel habits for at least 3 months. Extensive testing is not generally needed provided that patients are younger than 50 years and do not present with any alarm symptoms (Table 28.3).

TABLE 28.3 Alarm Symptoms Requiring Gastroenterology Consultation

Weight loss
Gastrointestinal bleeding
Anemia
Fever
Frequent nocturnal symptoms

Source: Theis VS, Rhodes JM. Review article: minimizing tuberculosis during anti-tumour necrosis factor-alpha treatment of inflammatory bowel disease. *Aliment Pharmacol Ther.* 2008;27:19.

**TABLE 28.4 Population Characteristics of Patients at High Risk for Inflammatory Bowel Disease Development<sup>25</sup>**

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Peaks between ages of 15 and 30 years  
 European ancestry  
 Urban greater than rural dwellers  
 Caucasian race greater than non-Caucasians  
 Jewish patients living in Europe and North America greater than non-Jewish patients  
 Occurs in familial clusters  
 NOD-2 gene

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## Risk Factors

- Population characteristics of patients at high risk for IBD are shown in Table 28.4.
- Smoking has been the most consistent environmental risk factor associated with IBD; smokers have a decreased risk for developing UC but an increased risk for CD.
- Use of nonsteroidal anti-inflammatory drugs (NSAIDs) has been associated with exacerbations of IBD.

## Goals of Therapy

- Goals of therapy for IBD include complete relief of symptoms; improving quality of life; maintaining adequate nutritional status; relieving intestinal inflammation, dysfunction, and the development of cancer; and reducing the need for surgery or chronic steroid use.

## Treatment

### INFLAMMATORY BOWEL DISEASE

- Treatment of both UC and CD is divided into two areas: induction (to control the symptoms) and maintenance (to prevent recurrences). Specific therapy depends on the anatomical location of the disease. Most drug therapies for IBD have been used for both UC and CD (Table 28.5).
- The treatment algorithm for UC is shown in Figure 28.1 and for CD in Figure 28.2.
- Patients with CD respond to bowel rest, total parenteral nutrition, or total enteral nutrition.
- Symptomatic management, including pain relief and diarrhea control, is important for quality of life. Treatment of diarrhea is often difficult.
- **Induction Therapy.** Specific agents used for induction depends on the extent of disease; corticosteroids are commonly used for this purpose for both UC and CD. Topically applied agents (suppositories, foams, enemas) such as mesalamine are effective for induction in UC that is confined to the rectum (proctitis) or distal colon.
- **Maintenance Therapy.** Agents such as azathioprine or infliximab are used to maintain remission in CD. Long-term use of corticosteroids for the treatment of IBD is not effective and can result in serious adverse effects.
- Patients with IBD often require surgery to control symptoms. Surgery can be curative for UC, but not for CD.

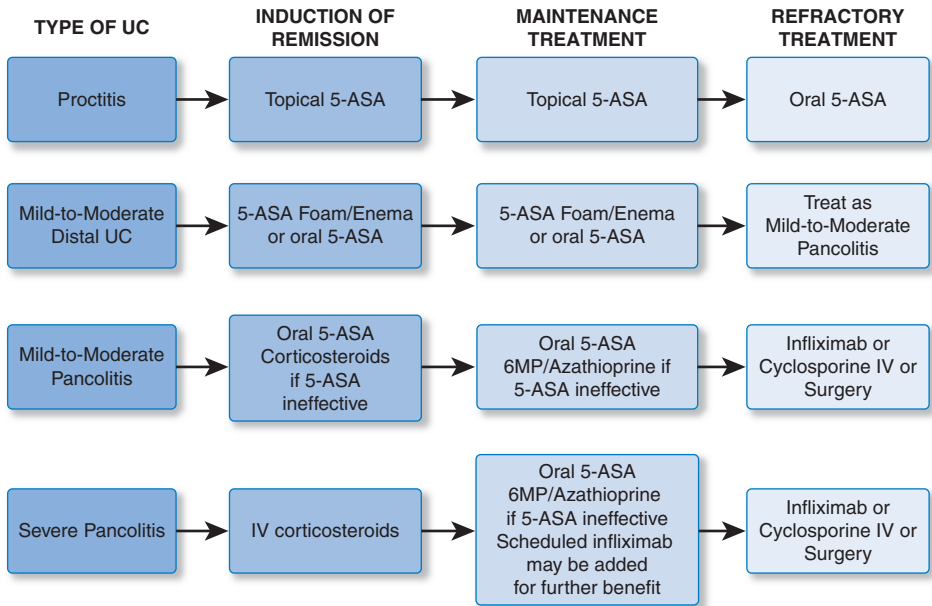
### IRRITABLE BOWEL SYNDROME

- Treatment is based on the predominant symptoms of the patient (Figure 28.3).
- For constipation-predominant symptoms (IBS-C), increased dietary fiber is considered first-line therapy. Other standard laxatives (milk of magnesia, lactulose, polyethylene glycol without electrolytes) can be used in patients who fail fiber therapy. Lubiprostone (8 mcg twice daily) is another option in nonpregnant patients.

TABLE 28.5 Pharmacotherapy for Inflammatory Bowel Disease

Drug	Indication	Dose	Adverse Reactions	Comment
Sulfasalazine	UC: mild-to-moderate maintenance CD: limited role	See Table 28.5	N/V, diarrhea, HA, rash, myelosuppression	High ADR rate has caused use to decline
Mesalamine	UC: mild-to-moderate induction/maintenance CD: limited role	See Table 28.5	N/V, diarrhea, HA, abdominal pain	Topical forms effective for proctitis and distal UC
Olsalazine	As above	See Table 28.5	As above, diarrhea common	
Balsalazide	As above	See Table 28.5	As above	
Corticosteroids	UC: mild-to-severe induction CD: mild-to-severe induction	Various	Hyperglycemia, CNS excitation, immunosuppression, osteoporosis, cataracts	Goal should be avoiding chronic use in UC and CD
Budesonide	UC: limited role CD: mild-to-moderate induction/maintenance	9 mg daily	As above for corticosteroids, probably less short-term effects	Long-term use may still cause chronic corticosteroid ADRs
6-MP/ azathioprine	UC: mild-to-severe maintenance CD: mild-to-severe maintenance	6-MP: 0.75–1.5 mg/kg/day Azathioprine: 1.5–2.5 mg/kg/day	N/V, diarrhea, HA, rash, myelosuppression (esp. neutropenia), pancreatitis	Pharmacogenomic-guided testing now commonly performed prior to initiating drug
Methotrexate	UC: limited role CD: mild-to-moderate induction/maintenance	25 mg IM/SQ weekly induction dose, then 15 mg weekly for maintenance	N/V, stomatitis, hepatotoxicity, pulmonary fibrosis	Usually reserved for patients who have failed 6-MP/azathioprine
Infliximab	UC: moderate-to-severe induction/maintenance CD: moderate-to-severe induction/maintenance (fistulizing disease)	5 mg/kg IV at weeks 0, 2, and 6, then every 8 weeks thereafter	Infusion reactions (acute and delayed), immunosuppression, reactivation of latent infection (TB, hepatitis B, histoplasmosis), may worsen neuromuscular disease and congestive heart failure	Probable small increase in lymphoma Scheduled treatment preferred to episodic treatment to maintain response and decrease delayed infusion reactions
Adalimumab	CD: moderate-to-severe induction/maintenance Loss of response to infliximab	160 mg SQ day 1, 80 mg SQ day 14, then 40 mg SQ every other week	As with infliximab, injection site reactions	Can be self-administered by patients, often used if infliximab is not effective or well tolerated
Certolizumab	CD: moderate-to-severe induction/maintenance	400 mg at weeks 0, 2, and 4. If response occurs, follow with 400 mg every 4 weeks	As with infliximab, injection site reactions	Not approved for patient self-administration

ADR, adverse drug reaction; CD, Crohn's disease; CNS, central nervous system; HA, headache; IM, intramuscularly; IV, intravenously; N/V, nausea/vomiting; 6-MP, 6-mercaptopurine; SQ, subcutaneously; TB, tuberculosis; UC, ulcerative colitis.

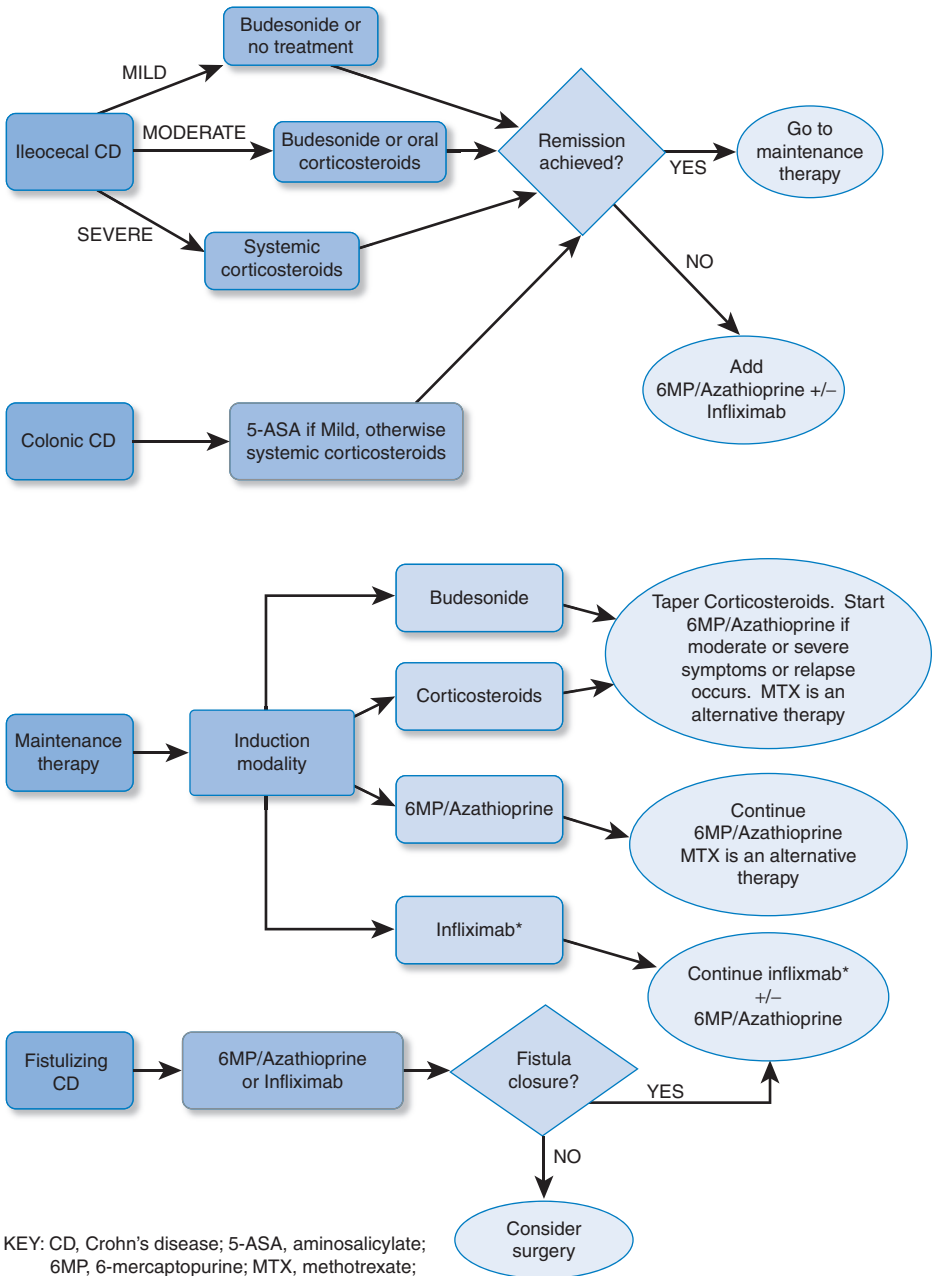


**Figure 28.1** Treatment algorithm for ulcerative colitis. Pancolitis refers to extensive ulcerative colitis. 5-ASA, mesalamine products, including mesalamine (e.g., Asacol, Pentasa, Rowasa), olsalazine, and balsalazide (see text for selection guidelines); IV, intravenous; 6-MP, 6-mercaptopurine; UC, ulcerative colitis. (Bernstein CN et al. World Gastroenterology Organization Practice Guidelines for the diagnosis and management of IBD in 2010. *Inflamm Bowel Dis.* 2010;16:112; Carter MJ et al. Guidelines for the management of inflammatory bowel disease in adults. *Gut.* 2004;53(Suppl 5):V1; Kornbluth A et al. Ulcerative colitis practice guidelines in adults: American College of Gastroenterology, Practice Parameters Committee. *Am J Gastroenterol.* 2010;105:501.)

- For diarrhea-predominant symptoms (IBS-D) antimotility agents (loperamide), antispasmodic agents (hyoscyamine, dicyclomine), and antidepressants (amitriptyline, selective serotonin reuptake inhibitors) are used.

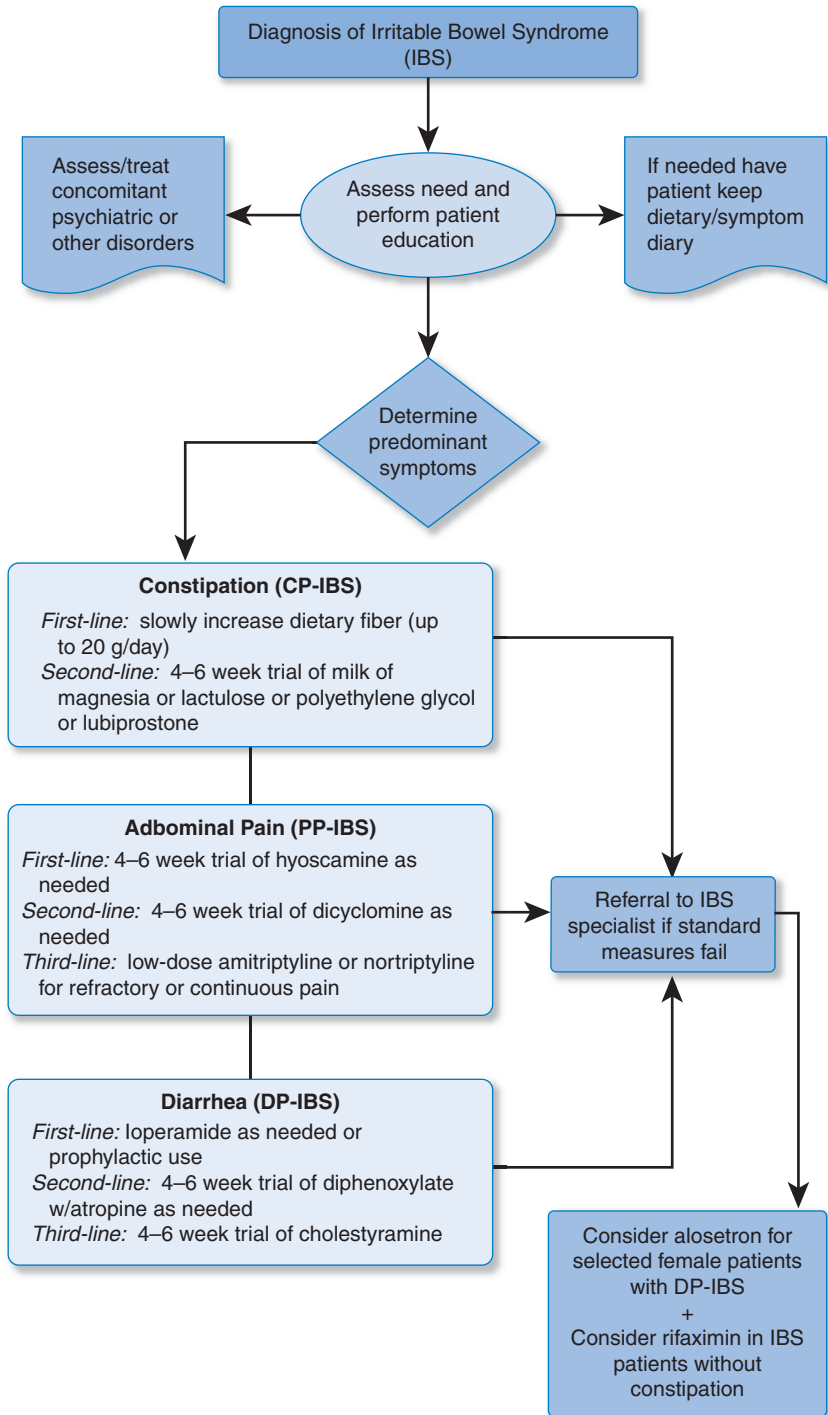
## Drug Therapy

- Indications, dosing, and adverse reactions for agents used for the treatment of IBD are shown in Table 28.5.
- **Aminosalicylates** release 5-ASA for localized action in the colon (Table 28.6). They are available for oral or rectal administration, with rectal formulations preferred for proctitis or disease confined to the distal colon. There are no efficacy advantages of one product over another. Dose-dependent adverse effects can limit patient tolerability.
- **Corticosteroids** have potent anti-inflammatory actions and are the most commonly used agents in the treatment of acute flares in patients with moderate-to-severe IBD. Oral doses should be equivalent to 40 to 60 mg of prednisone; IV doses should be equivalent to hydrocortisone 300 mg/day or methylprednisolone 40 to 60 mg/day. Once remission is induced, attempts should be made to taper steroids (typically with a dose reduction of 5%–10% a week). Topical steroids (enemas, foams, suppositories) are effective for distal colitis. Corticosteroids are not beneficial for maintaining remission. Guidelines recommend budesonide for active mild-to-moderate ileocolonic CD.
- **Immunomodulators**
  - Azathioprine (2–2.5 mg/kg/day) and 6-mercaptopurine (1–1.5 mg/kg/day) are commonly used for the management of corticosteroid-dependent IBD. They may also be used as steroid-sparing agents for maintenance disease.



KEY: CD, Crohn's disease; 5-ASA, aminosalicilate; 6MP, 6-mercaptopurine; MTX, methotrexate; \*For nonfistulizing Crohn's disease adalimumab or certolizumab are alternative options to Infliximab

**Figure 28.2** Treatment algorithm for Crohn's disease.



**Figure 28.3** Treatment algorithm for irritable bowel syndrome. (American College of Gastroenterology Task Force on Irritable Bowel Syndrome et al. An evidence-based position statement on the management of irritable bowel syndrome. *Am J Gastroenterol.* 2009;104(Suppl 1):S1; Pimentel M et al. Rifaximin therapy for patients with irritable bowel syndrome without constipation. *N Engl J Med.* 2011;364:22.)



TABLE 28.6 Comparison of Aminosalicylate Compounds

Generic (Trade)	Delivery System	Intestinal Site of Release	Usual Dose and Frequency
Balsalazide (Colazal)	Bacterial cleavage of azo bond	Colon	750 mg PO TID
Mesalamine (Apriso)	Polymer matrix/enteric coating that dissolves at pH 6	Ileum (distal), colon	1,500 mg PO every day
Mesalamine (Asacol, Asacol HD)	pH-dependent coating (Eudragit S) dissolves at pH $\geq 7$	Ileum (distal), colon	800 mg PO TID
Mesalamine (Lialda)	Multi-matrix (pH-sensitive coating and delayed-release)	Ileum (distal), colon	2.4–4.8 g PO every day
Mesalamine (Pentasa)	Controlled-release microspheres	Duodenum, jejunum, ileum, colon	1 g PO QID
Mesalamine (Rowasa)	Direct topical therapy	Rectum (supp) Descending colon/rectum (enema)	500 mg PR every day–BID 4 g/60 mL enema PR at bedtime
Olsalazine (Dipentum)	Bacterial cleavage of azo bond	Colon	500 mg PO BID
Sulfasalazine (Azulfidine)	Bacterial cleavage of azo bond	Colon	Initially 500 mg PO BID; increase to 1 g PO TID–QID

BID, twice daily; PO, orally; PR, per rectum; QID, four times daily; TID, three times daily; supp, suppository.

Sources: Reprinted with permission from Fernandez-Becker NQ, Moss AC. Improving delivery of aminosalicylates in ulcerative colitis: effect on patient outcomes. *Drugs*. 2008;68:1089; Drug Facts and Comparisons. Drug Facts and Comparisons 4.0 [online] 2010. Available from Wolters Kluwer Health Inc. Accessed January 27, 2011.

- Methotrexate (15–25 mg IM weekly) may be useful for initial and chronic treatment of CD in patients who are intolerant of, or refractory to, azathioprine or 6-mercaptopurine. It is not effective for induction or maintenance therapy of UC.
- Cyclosporine has been used to treat severe, acute UC that is refractory to corticosteroids. Serious adverse effects limit its use.
- Infectious complications are a risk with immunomodulator therapy; standard immunization schedules should be followed; live vaccinations should be avoided (see Chapter 11).
- **Biological therapies** are reserved for patients with moderate-to-severe disease.
  - Infliximab is indicated for inducing and maintaining remission in a broad spectrum of IBD patients. Response to therapy is usually rapid. Acute and delayed hypersensitivity reactions can occur. Use should be avoided in patients who have a serious active infection.
  - Natalizumab is approved for inducing and maintaining remission in patients who are unable to tolerate conventional therapies. Patients must be enrolled in a registry due to safety concerns.
  - Adalimumab may be particularly useful in patients with an attenuated response to infliximab. It offers the advantage of subcutaneous administration.
- **Antibiotics** are of limited benefit for IBD. Metronidazole has shown some benefit for GI infections.
- **Antidiarrheals** (loperamide or diphenoxylate with atropine) may help minimize chronic diarrhea. They must be used with extreme caution in patients with severe disease due to the risk of developing toxic megacolon, a life-threatening emergency.

# Complications of End-Stage Liver Disease\*

## General Principles

- Cirrhosis is defined as fibrosis of the hepatic parenchyma resulting in nodule formation, altered hepatic function, restricted venous outflow, and portal hypertension. It results from a sustained wound-healing response to chronic or acute liver injury from a variety of causes, the most common being chronic viral hepatitis chronic alcohol consumption.
- Complications of cirrhosis and the associated portal hypertension include esophageal varices, gastric varices, ascites, spontaneous bacterial peritonitis, hepatic encephalopathy, and hepatorenal syndrome.

## Patient Assessment

- Advanced alcoholic cirrhosis is associated with elevated liver function tests (aspartate aminotransferase test [AST], alkaline phosphatase, bilirubin); an enlarged, palpable liver edge; jaundice; spider angiomas on the face and upper chest; palmer erythema; and cachexia.
- Physical findings of ascites can include the presence of an enlarged fluid-filled abdomen, increased abdominal girth, a positive fluid wave, increased body weight, and peripheral edema.
- The Child–Turcotte–Pugh classification of liver disease uses a scoring system to grade disease severity, predict long-term risk of mortality, and quality of life (Table 29.1). In general, class A patients are considered to be compensated and class B and C are said to be decompensated.
- Model for End-Stage Liver Disease (MELD) score is a scoring tool used to predict short-term (3-month) mortality associated with liver disease. MELD score is used for prioritization of organ allocation of cadaveric livers for transplantation (patients with higher MELD scores are given higher priority).

$$\text{MELD score} = (0.957 \times \ln [\text{creatinine mg/dL}] + 0.378 \times \ln [\text{total bilirubin mg/dL}] + 1.12 \times \ln [\text{INR}] + 0.643) \times 10$$

TABLE 29.1 Child–Turcotte–Pugh Classification of Severity of Liver Disease

	Score <sup>a</sup>		
	1 Point	2 Points	3 Points
Bilirubin (mg/dL)	<2	2–3	>3
Albumin (mg/dL)	>3.5	2.8–3.5	<2.8
INR	<1.7	1.7–2.3	>2.3
Ascites	None	Mild to moderate	Severe
Encephalopathy (grade)	None	Mild to moderate (1 and 2)	Severe (3 and 4)

<sup>a</sup>Class A, 5 to 6 points; class B, 7 to 9 points; class C, 10 to 15 points.

INR, international normalized ratio.

\*The reader is referred to Chapter 29, Complications of End-Stage Liver Disease, written by Yasar O. Tasnif, PharmD, and Mary F. Hebert, PharmD, FCCP, in the 10th edition of *Applied Therapeutics: The Clinical Use of Drugs* for a more in-depth discussion. All notations to reference numbers are based on the reference list at the end of that chapter. The editor of this handbook expresses her thanks to Drs. Tasnif and Hebert and acknowledges that this chapter is based upon their work.

## Treatment

- Patients with compensated cirrhosis are managed by treatment of the underlying cause of the cirrhosis, and primary prevention and early diagnosis of complications.
- Treatment in patients with uncompensated cirrhosis is aimed at the complications and prevention of sequelae (secondary prevention).
- Guidelines for treatment are available from the American Association for the Study of Liver Diseases (AASLD).

### ASCITES

- Ascites, a common symptom of cirrhosis, is accumulation of fluid in the peritoneal cavity.
- Goals of treatment are to mobilize ascitic fluid; diminish abdominal discomfort, back pain, and difficulty in ambulation; and prevent complications (bacterial peritonitis, respiratory distress).
- The weight loss goal is 0.5 to 1 kg/day (corresponding to about 0.5–1 L/day of fluid volume loss). Treatment should be done gradually to permit ascitic fluid to equilibrate with intravascular fluid thereby preventing acid–base imbalances or intravascular volume depletion. **Prerenal azotemia** usually results from overdiuresis with subsequent compromise of intravascular volume and decreased renal perfusion.
- **Treatment** (AASLD recommendations):
  - Restriction of dietary sodium to 2,000 mg/day.
  - Water restriction in patients with severe dilutional hyponatremia (serum Na <120–125 mEq/L).
  - **Diuretics.** Spironolactone (100 mg) as the initial diuretic of choice. The diuretic effect is enhanced when combined with Na restriction (0.5–2 g/day). Furosemide (40 mg) can be added to minimize the risk of hyperkalemia and enhance diuresis. The dose of both oral diuretics can be increased simultaneously every 3 to 5 days, maintaining the 100:40 mg ratio (maximum daily doses are spironolactone 400 mg and furosemide 160 mg). Triamterine and amiloride are alternatives if intolerable side effects occur with spironolactone. Fluid, electrolyte, and acid–base disturbances are side effects of diuretic therapy.
  - Vasopressin 2 receptor antagonists (vaptans) are not recommended due to the lack of data in patients with cirrhosis.
  - Second-line treatment may be needed in patients experiencing respiratory distress despite diuretic therapy and sodium restriction.
    - Large-volume (>4 L) paracentesis (removal of ascitic fluid from the abdominal cavity) is used for patients with tense ascites resulting in pulmonary distress or impaired ambulation. Concomitant infusion of albumin 25% solution can help prevent paracentesis-induced circulatory dysfunction. For large-volume paracentesis  $\geq$ 6 L, 6 to 8 g albumin is typically administered for each liter of ascites removed. Hydroxyethyl starch should not be used in place of albumin as it can accumulate in hepatocytes and cause severe portal hypertension and acute liver failure.
    - Transjugular intrahepatic portosystemic shunt (TIPS) is recommended for treatment of refractory ascites when paracentesis is contraindicated or ineffective.
    - Peritoneovenous shunt is reserved for patients with ascites who are not liver transplant candidates, have failed standard therapies, and have fairly well-preserved renal and hepatic function.

### SPONTANEOUS BACTERIAL PERITONITIS

- Spontaneous bacterial peritonitis (SBP) is defined as the spontaneous infection of the ascitic fluid in the absence of an identified intra-abdominal source of infection or inflammation.
- Gram-negative enteric bacilli (most commonly *Escherichia coli* and *Klebsiella*) and pneumococci account for the majority of infections.

- Patients with a history of SBP and those with low-protein ascites with advanced liver failure or renal impairment benefit from SBP prophylaxis. Norfloxacin (400 mg/day) or trimethoprim-sulfamethoxazole (160/800 mg/day given 5 days a week) is a reasonable option.

## ESOPHAGEAL VARICES

- Varices are dilated veins in the upper gastrointestinal (GI) tract that protrude into the esophageal or gastric lumen. They do not cause significant complications unless they bleed. The progression and severity of varices is directly related to the severity of portal hypertension.
- When the portal venous pressure exceeds 12 mm Hg, patients are at increased risk of variceal hemorrhage. Prevention of bleeding is critical due to the high mortality rate associated with a bleed.
- Treatment goals for an acute bleed include volume resuscitation, acute treatment of bleeding, and prevention of recurrence of variceal bleeding.
- Risk factors for early rebleeding include age >60 years, acute renal failure, and severe initial bleeding (defined as hemoglobin <8 mg/dL). Risk factors for late rebleeding are severe liver failure, continued alcohol abuse, large variceal size, renal failure, and hepatocellular carcinoma.
- **Treatment**
  - Lavage and suctioning of stomach contents via a nasogastric (NG) tube is used to prevent airway complications (e.g., aspiration pneumonia).
  - Hypovolemia should be managed to maintain mean arterial pressure at 80 mm Hg and hemoglobin at approximately 8 mg/dL.
  - Treatment options for acute bleeding are shown in Table 29.2. Guidelines from AASLD and the American College of Gastroenterology (ACG) recommend the combination of vasoconstrictive pharmacologic therapy and variceal ligation to manage bleeding.
    - Octreotide 50 to 100 mcg bolus followed by an infusion of 25 to 50 mcg/hour for 18 hours to 5 days.
    - Vasopressin 0.2 to 0.4 units/minute as a continuous infusion, increased every hour by 0.2 units/minute until bleeding is controlled (maximum of 0.8 units/minute with therapy not to exceed 24 hours).
    - Balloon tamponade is used as a temporary measure (maximum of 24 hours) to stop massive bleeding.
  - Guidelines recommend 7 days of antibiotic prophylaxis for prevention of SBP in patients with variceal hemorrhage (norfloxacin 400 mg twice daily, ciprofloxacin IV 400 mg twice daily, or ceftriaxone IV 1 g/day).
  - **Primary prophylaxis** (preventing the initial occurrence of variceal bleeding).
    - Nonselective  $\beta$ -blockers in patients with small varices that have not bled but are at increased risk of hemorrhage, or in patients with medium/large varices that have not bled and are not at increased risk of bleeding.
    - Nonselective  $\beta$ -blockers or endoscopic variceal ligation (EVL) for patients with medium/large varices that have not bled but are at high risk of hemorrhage.
    - Nitrates (alone or in combination with  $\beta$ -blockers), shunt therapy, or sclerotherapy should not be used for primary prophylaxis.
  - **Secondary prophylaxis** (preventing rebleeding once it has occurred) should be given to all patients who survive a variceal bleeding episode to prevent recurrence.  $\beta$ -Blockers should be delayed until after recovery from the variceal hemorrhage. Eradication of varices by endoscopic procedures is effective at preventing rebleeding. TIPS may be an option for patients who fail both EVL and  $\beta$ -blocker therapy. Guidelines suggest use of a combination of nonselective  $\beta$ -blockers plus EVL.

TABLE 29.2 Treatment of Acute Bleeding

Therapy	Mechanism	Side Effects and Risks
Octreotide	Selective and potent vasoconstrictor that reduces portal and collateral blood flow by constricting splanchnic vessels	Diarrhea, hyperglycemia, hypoglycemia, constipation, rectal spasms, abnormal stools, headache, dizziness, fat malabsorption
Vasopressin	Nonspecific vasoconstrictor of all parts of the vascular bed	Abdominal cramping, nausea, tremor, skin blanching, phlebitis, hematoma at the site of the infusion, worsening of hypertension, angina, arrhythmias, myocardial infarction, bowel necrosis, gangrene, dilutional hyponatremia
Endoscopic band ligation (EBL) or endoscopic variceal ligation (EVL)	An elastic band is placed around the mucosa and submucosa of the esophageal area containing the varix, leading to strangulation, fibrosis, and ideally obliteration of the varix.	Moderate bleeding, hypotension, gastrointestinal discomfort, esophageal ulceration, perforation
Sclerotherapy	Injection of 0.5–5 mL of a sclerosing agent (e.g., concentrated saline: 11.5% NaCl or ethanolamine oleate) into each varix at points about 2 cm apart to induce immediate hemostasis (cessation of bleeding within 2–5 minutes)	Esophageal ulceration, stricture formation, esophageal perforation, retrosternal chest pain, temporary dysphagia
Balloon tamponade	Bleeding is controlled by direct compression of the varices at the gastroesophageal junction or at the bleeding site by a Sengstaken-Blakemore tube or Lintern tube (gastric varices only). The tube is passed through the mouth and into the stomach. A balloon is then inflated, which applies direct compression to the varices.	Aspiration (>10% incidence), pressure necrosis, pneumonitis, esophageal ulceration and rupture, bleeding on balloon deflation, chest pain, asphyxia (aspiration may be minimized by endotracheal intubation and continued aspiration of oropharyngeal secretions)
Transjugular intrahepatic portal systemic shunt (TIPS)	A conduit between the hepatic vein and intrahepatic segment of the portal vein with an expandable metal stent is placed during an angiographic procedure. This channel allows blood to return to the systemic circulation and reduces portal pressure.	Bleeding, thrombosis, stenosis, severe encephalopathy, hepatic failure, shunt occlusion, shunt migration

## HEPATIC ENCEPHALOPATHY

- Hepatic coma or encephalopathy is a metabolic disorder of the central nervous system that occurs with advanced cirrhosis or fulminate hepatic failure. Factors that may precipitate hepatic encephalopathy are shown in Table 29.3. Certain drugs (opioids, sedatives, and tranquilizers) have also been associated with hepatic encephalopathy.
- A staging scheme for grading severity of hepatic encephalopathy is shown in Table 29.4.
- **Treatment**
  - Identify and remove the underlying cause of hepatic coma. Treatment is then aimed at reducing the amount of ammonia or nitrogenous products in the circulatory system.
  - Daily intake of 35 to 40 kcal/kg of body weight and a protein intake of 1.2 to 1.5 g/kg body weight has been recommended for patients awaiting transplantation.
  - Lactulose (10 g/15 mL) is effective for acute and chronic hepatic encephalopathy. For acute encephalopathy, 30 to 45 mL every hour until evacuation, with the dose then titrated to 2 to 4 loose stools daily and clear mentation. Administration through an NG tube or via rectal retention enema (300 mL lactulose with 700 mL water; 125 mL of the mixture retained for 30–60 minutes) are options in patients who cannot take oral therapy.

TABLE 29.3 Factors That May Precipitate Hepatic Encephalopathy

Excess Nitrogen Load	Fluid and Electrolyte Abnormalities	Drug-Induced Central Nervous System Depression
Bleeding from gastric and esophageal varices	Hypokalemia	Sedatives
Peptic ulcer	Alkalosis	Tranquilizers
Excess dietary protein	Hypovolemia	Narcotic analgesics
Azotemia or kidney failure	Excessive diarrhea	
Deteriorating hepatic function	Over diuresis	
Infection: tissue catabolism		
Constipation	Excessive vomiting	

- Rifaxamin (550 mg twice daily) or neomycin (500–1,000 mg orally four times daily) are antibiotic options that reduce plasma ammonia concentrations.
- Guidelines state lactulose should be tried first. If satisfactory results do not occur, neomycin should be tried. If both agents fail as monotherapy, the combination of lactulose and neomycin may be reasonable.

### HEPATORENAL SYNDROME

- Hepatorenal syndrome (HRS), a complication of advanced cirrhosis, is characterized by intense renal vasoconstriction leading to very low renal perfusion and glomerular filtration rate, and a severe reduction in the ability to excrete sodium and free water. It is classified as either type 1 (acute and progressive kidney failure) or type 2 (progressive deterioration of kidney function).
- The primary goal of therapy is to reverse HRS sufficiently so that appropriate candidates for liver transplantation can survive until a suitable donor is produced.
- **Treatment:** Diuretic therapy must be stopped as it can worsen kidney disease. AASLD recommends the use of albumin plus octreotide and midodrine for type 1 HRS. No particular treatment exists for type 2 HRS. Definitive treatment for HRS is liver transplantation, an option that is generally considered in patients with refractory ascites, severe hepatic encephalopathy, esophageal or gastric varices, and hepatorenal syndrome.

TABLE 29.4 Stages of Encephalopathy

Physical Sign	Stage I Prodrome	Stage II Impending Coma	Stage III Stupor	Stage IV Coma	Stage V Coma
Mental status	Alert; slow mentation; euphoria, occasional depression, confusion; sleep pattern reversal	Stage I signs amplified; lethargic, sleepy	Arousable, but generally asleep; significant confusion	Unarousable or responds only to pain	Unarousable
Behavior	Restless, irritable, disordered speech	Combative, sullen, loss of sphincter control	Sleeping, confusion, incoherent speech	None	None
Spontaneous motor activity	Uncoordinated with tremor	Yawning, grimacing, blinking	Decreased, severe tremor	Absent	None
Asterixis	Absent	Present	Present	Absent	Absent
Reflexes	Normal	Hyperactive	Hyperactive + Babinski	Hyperactive + Babinski	Absent

## Acute Kidney Injury\*

### General Principles

- Acute kidney injury (AKI), previously known as acute renal failure, is characterized clinically by an abrupt decrease in renal function over a period of hours to days, resulting in the accumulation of nitrogenous waste products (azotemia) and the inability to maintain and regulate fluid, electrolyte, and acid–base balance.
- The clinical course of AKI has three distinct phases:
  - **Oliguric Phase:** a progressive decrease in urine production after kidney injury
  - **Diuretic Phase:** initial repair of the kidney insult with resultant diuresis of accumulated uremic toxins, waste products, and fluid
  - **Recovery Phase:** return of kidney function depending on the severity of injury

### Classification

- Classification is according to the physiologic event leading to AKI (Table 30.1): prerenal azotemia, functional, intrinsic, and postrenal.

### Risk Factors

- Risk factors for the development of AKI include older age, higher baseline serum creatinine (SCr), chronic kidney disease (CKD), diabetes, chronic respiratory illness, underlying cardiovascular disease, prior heart surgery, dehydration resulting in oliguria, acute infection, renal outflow obstruction, and exposure to nephrotoxins.

### Patient Assessment

- Assessment of blood urea nitrogen (BUN) and creatinine guides diagnosis, treatment, and monitoring of AKI.
- Urinalysis is an important diagnostic tool for differentiating prerenal azotemia, intrinsic, and obstructive AKI (Table 30.2). Urinary chemistries are used to differentiate between prerenal azotemia and intrinsic AKI. Microscopic examination of urine helps determine the cause of AKI (Table 30.3).
- Many equations exist for calculating creatinine clearance (ClCr) or estimated glomerular filtration rate (GFR).
  - Modification of diet in renal disease (MDRD) is used to quantify GFR, to detect or state the stage of CKD, and to follow progression.

$$\text{Estimated GFR (mL/minute/1.73 m}^2\text{)} = 170 \times (\text{SCr})^{-0.999}$$

$$\times (\text{age in years})^{-0.176} \times (\text{BUN})^{-0.170} \times (\text{Alb})^{-0.318}$$

$$\times (0.762 \text{ if female}) \times (1.18 \text{ if black})$$

\*The reader is referred to Chapter 30, Acute Kidney Injury, written by Myrna Y. Munar, PharmD, and Donald F. Brophy, PharmD, MSc, FCCP, FASN, BCPS, in the 10th edition of *Applied Therapeutics: The Clinical Use of Drugs* for a more in-depth discussion. All notations to reference numbers are based on the reference list at the end of that chapter. The editor of this handbook expresses her thanks to Drs. Munar and Brophy and acknowledges that this chapter is based upon their work.

TABLE 30.1 Causes of Acute Kidney Injury

Classification	Common Clinical Disorders
<i>Prerenal Azotemia</i>	<b>INTRAVASCULAR VOLUME DEPLETION</b>
	Hemorrhage (surgery, trauma) Dehydration (gastrointestinal losses, aggressive diuretic administration) Severe burns Hypovolemic shock Sequestration (peritonitis, pancreatitis)
	<b>DECREASED EFFECTIVE CIRCULATING VOLUME</b>
	Cirrhosis with ascites Heart failure
	<b>HYPOTENSION, SHOCK SYNDROMES</b>
	Antihypertensive vasodilating medications Septic shock Cardiomyopathy
<i>Functional Acute Kidney Injury</i>	<b>INCREASED RENAL VASCULAR OCCLUSION OR CONSTRICTION</b>
	Bilateral renal artery stenosis Unilateral renal stenosis in solitary kidney Renal artery or vein thrombosis (embolism, atherosclerosis) Vasopressor medications (phenylephrine, norepinephrine)
	<b>AFFERENT ARTERIOLE VASOCONSTRICTORS</b>
	Cyclosporine and tacrolimus Nonsteroidal anti-inflammatory drugs
	<b>EFFERENT ARTERIOLE VASODILATORS</b>
	Angiotensin-converting enzyme inhibitors Angiotensin II receptor antagonists
<i>Intrinsic Acute Kidney Injury</i>	<b>GLOMERULAR DISORDERS</b>
	Glomerulonephritis Systemic lupus erythematosus Malignant hypertension Vasculitic disorders (Wegener granulomatosis)
	<b>ACUTE TUBULAR NECROSIS</b>
	Prolonged prerenal states Drug induced (contrast media, aminoglycosides, amphotericin B)
	<b>ACUTE INTERSTITIAL NEPHRITIS</b>
	Drug induced (quinolones, penicillins, sulfa drugs)
<i>Postrenal Acute Kidney Injury</i>	<b>URETER OBSTRUCTION (BILATERAL OR UNILATERAL IN SOLITARY KIDNEY)</b>
	Malignancy (prostate or cervical cancer) Prostate hypertrophy Anticholinergic drugs (affect bladder outlet muscles) Renal calculi

- Cockcroft and Gault (CG) equation is used to adjust the doses of medications that are eliminated by the kidney. The formula is below. For women, the result is multiplied by 0.85 to account for decreased muscle mass

$$\text{estimated CrCl} = \frac{(140 - \text{age in years}) (\text{ideal body weight in kg})}{(72) (\text{SCr in mg/dL})}$$



TABLE 30.2 Urinary Indices in Acute Kidney Injury

Component	Prerenal Azotemia	Acute Tubular Necrosis	Postrenal Obstruction
Urine Na <sup>+</sup> (mEq/L)	<20	>40	>40
FE <sub>Na</sub>	<1%	>2%	Variable
Urine/plasma creatinine	>40	<20	<20
Specific gravity	>1.010	<1.010	Variable
Urine osmolality (mOsm/kg)	Up to 1,200	<300	<300

TABLE 30.3 Clinical Significance of Urinary Sediment in Acute Kidney Injury

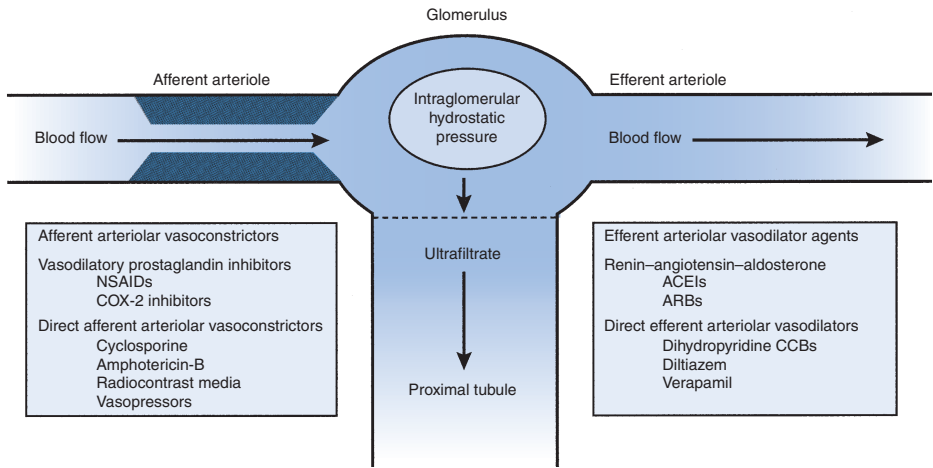
Cellular Debris	Clinical Significance
Red blood cells	Glomerulonephritis IgA nephropathy Lupus nephritis
White blood cells	Infection (pyelonephritis) Glomerulonephritis Acute tubular necrosis
Eosinophils	Drug-induced acute interstitial nephritis Pyelonephritis
Hyaline casts	Renal transplant rejection Dehydration Generally nonspecific and may be nonpathogenic
Red blood cell casts	Acute tubular necrosis Glomerulonephritis Interstitial nephritis
White blood cell casts	Pyelonephritis Interstitial nephritis
Granular casts	Dehydration Interstitial nephritis Glomerulonephritis Acute tubular necrosis
Tubular cell casts	Acute tubular necrosis
Fatty casts	Nephrotic syndrome
Myoglobin	Rhabdomyolysis
Crystals	Nonspecific

- **Prerenal and Functional AKI**

- Prerenal AKI results from reduced renal blood flow, with extracellular volume fluid loss and heart failure being the common causes. Functional AKI results from impairment of glomerular ultrafiltrate production or intraglomerular hydrostatic pressure, often caused by medications (Figure 30.1).

- **Intrinsic AKI** is seen as damage at the parenchymal level of the kidney.

- Intrinsic AKI can be divided into vascular, glomerular, or tubular disorders.
- Any disorder that produces tubular ischemia (e.g., prolonged hypotension, shock) can result in acute tubular necrosis (ATN).
- Nephrotoxic drugs are a common cause of ATN, especially when given in septic or volume-contracted patients.
- Post-streptococcal glomerulonephritis (PSGN) is the most common acute-onset, immune-mediated, diffuse glomerulopathy. It primarily affects children.
- Rapidly progressive glomerulonephritis (crescentic glomerulonephritis) is a medical emergency.



**Figure 30.1** Drugs that alter renal hemodynamics by causing afferent arteriole vasoconstriction or efferent arteriole vasodilation. ACEIs, angiotensin-converting enzyme inhibitors; ARBs, angiotensin II receptor blockers; CCBs, calcium-channel blockers; COX-2, cyclo-oxygenase-2; NSAIDs, nonsteroidal anti-inflammatory drugs.

### • Tubulointerstitial Diseases

- ATN arises most often from ischemia or drug-induced causes.
- Patients with nonoliguric renal failure have better outcomes than those with oliguria.
- Radiocontrast media use is one of the most common causes of drug-induced ATN, usually presenting as nonoliguric disease. Risk factors for contrast-induced nephropathy (CIN) are shown in Table 30.4. Any condition that decreases renal blood flow increases the risk of CIN.
- Aminoglycoside-induced nephrotoxicity usually presents as a hypo-osmolar, nonoliguric renal failure with a slow rise in SCr. Risk factors are shown in Table 30.5. Extended-interval dosing allows for comparable efficacy and similar or reduced nephrotoxicity.
- **Postrenal AKI** results from outflow obstruction in the urinary tract.
  - Common causes are stone formation, underlying malignancies of the cervix or prostate, prostatic hypertrophy, or bilateral ureter strictures.
  - Onset of symptoms (decreased force of urine stream, dribbling, polyuria) is gradual.
  - Nephrolithiasis (kidney stones) typically present as severe flank pain that radiates to the groin. Risk factors are shown in Table 30.6, and commonly used drugs that can cause crystal-induced AKI are shown in Table 30.7.

## Goals of Therapy

- Treatment goals are to minimize further kidney damage and provide symptomatic relief.

## Prevention and Treatment

- Treatment of the underlying cause of AKI should begin immediately to prevent further kidney damage; currently, there are no drugs that accelerate recovery. Supportive measures are directed at preventing morbidity and mortality.
- Strict fluid, electrolyte, and nutritional management is important. Sodium and water restriction help to reduce edema. Restriction of protein to 0.8 g/kg/day may be beneficial in patients with marked proteinuria.
- Antihypertensive drugs can be used short term to control blood pressure.

**TABLE 30.4 Proven Risk Factors for Developing Radiocontrast Media–Induced Acute Tubular Necrosis**

Diabetic nephropathy  
 Chronic kidney disease  
 Severe heart failure  
 Volume depletion and hypotension  
 Dosage and frequency of contrast administration

**TABLE 30.5 Risk Factors for Developing Aminoglycoside Nephrotoxicity****PATIENT FACTORS**

Elderly  
 Underlying renal disease  
 Dehydration  
 Hypotension and shock syndromes  
 Hepatorenal syndrome

**AMINOGLYCOSIDE FACTORS**

Aminoglycoside choice: gentamicin > tobramycin > amikacin  
 Therapy >3 days  
 Multiple daily dosing  
 Serum trough >2 mg/L  
 Recent aminoglycoside therapy

**CONCOMITANT DRUG THERAPY**

Amphotericin B  
 Angiotensin-converting enzyme inhibitors  
 Cisplatin  
 Cyclosporine  
 Foscarnet  
 Furosemide  
 Nonsteroidal anti-inflammatory drugs (NSAIDs)  
 Radiocontrast media  
 Vancomycin

**TABLE 30.6 Risk Factors for Nephrolithiasis**

Low urine volume  
 Hypercalciuria  
 Hyperoxaluria  
 Hyperuricosuria  
 Hypercitruria  
 Chronically low or high urinary pH

**TABLE 30.7 Commonly Used Drugs That Cause Crystal-Induced Acute Kidney Injury**

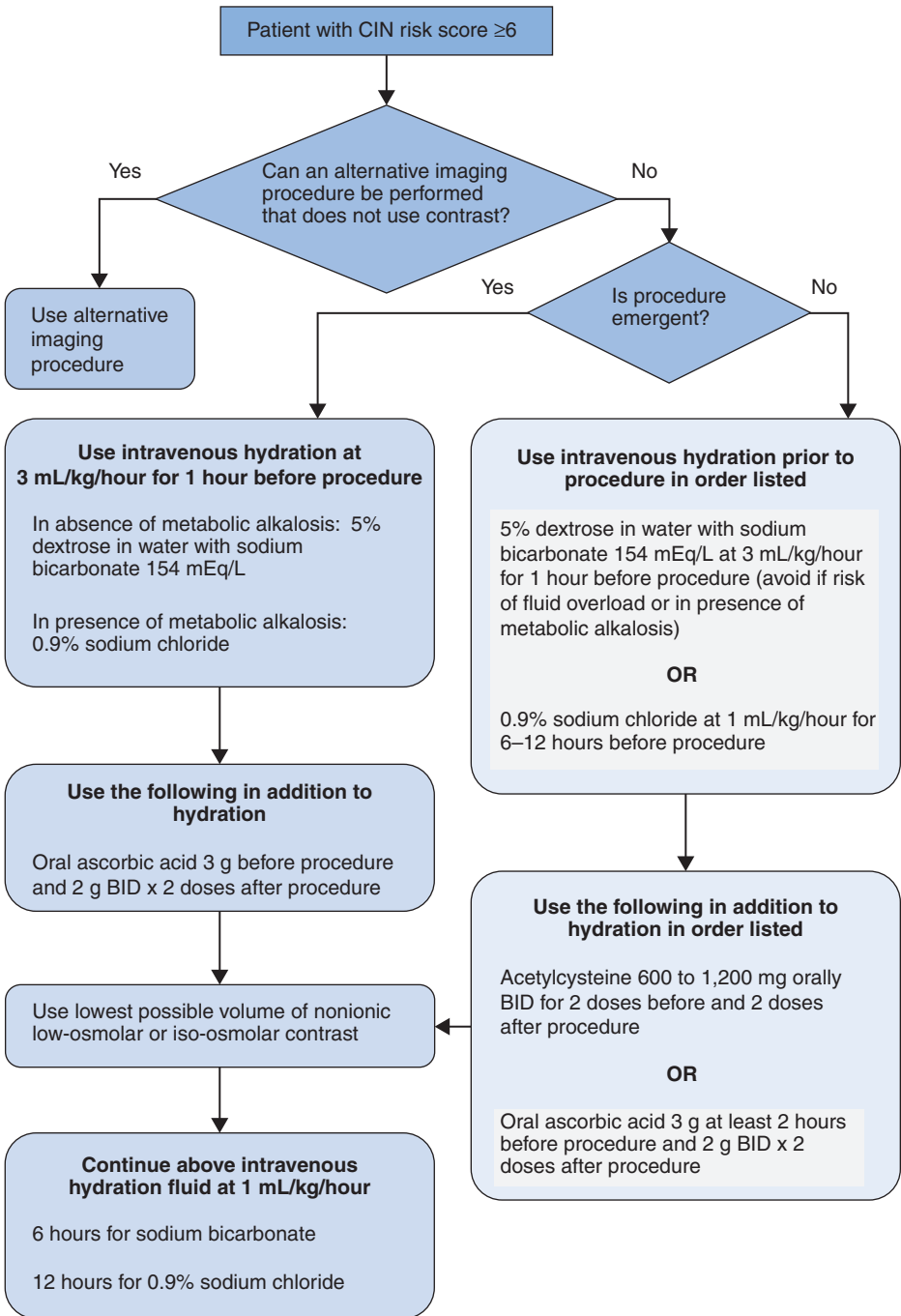
Acyclovir  
 Atazanavir  
 Indinavir  
 Methotrexate  
 Sulfonamides  
 Triamterene

- **Diuretics** have no role in preventing AKI progression or reducing mortality. Loop diuretics can be used for symptomatic pulmonary or peripheral edema. Intravenous furosemide is preferred (80–120 mg) due to its potency and pulmonary vasodilation properties. Oral furosemide should be avoided. Combinations of loop and thiazide diuretics may be needed in diuretic-resistant disease.
- Dopamine has no role in preventing or treating AKI.
- Figure 30.2 summarizes a means to prevent CIN in high-risk populations. When possible, use of another imaging study that does not require radiocontrast or use of the lowest dose of a nonionic, iso-osmolar, or low-osmolar agent should be done. Concomitant drug therapy that can impair renal perfusion (e.g., diuretics, nonsteroidal anti-inflammatory drugs [NSAIDs], angiotensin-converting enzyme [ACE] inhibitors, angiotensin II receptor blockers [ARBs]) should be discontinued 1 day before and 1 day after radiocontrast administration.
- Opiates and NSAIDs, alone or in combination, can be used short term to control pain associated with kidney stones. Increased fluid intake (2 L daily) is a preventive measure to reduce the likelihood of stone recurrence.
- Extracorporeal continuous renal replacement therapy (CRRT) is reserved for patients with severe acid–base disorders, fluid overload, hyperkalemia, symptomatic uremia, or drug intoxications. Differences among the various modalities are shown in Table 30.8.

TABLE 30.8 Comparison of Extracorporeal Continuous Renal Replacement Therapies

Parameter	Continuous Venovenous Hemofiltration (CVVH)	Continuous Arteriovenous Hemofiltration (CAVH)	Continuous Venovenous Hemodialysis (CVVHD)	Continuous Venovenous Hemodiafiltration (CVVHDF)
Volume control in hypotensive patients	Good	Variable	Good	Good
Solute control in highly catabolic patients	Adequate	Inadequate	Adequate	Adequate
Blood flow rates in hypotensive patients	Adequate	Poor	Adequate	Adequate
Ease of drug dosing	Published recommendations	Difficult	Difficult	Difficult
Dialytic solute clearance	None	None	Moderate	Moderate
Convective solute clearance	Good	Good	Minimal	Moderate
Corresponding GFR (mL/minute)	15–17	10–15	17–21	25–26
Blood pump required	Yes	No	Yes	Yes
Replacement fluid required	Yes	Yes	Yes	Yes
Pharmacy expense	High	High	High	High

GFR, glomerular filtration rate.



**Figure 30.2** Preventing contrast-induced nephropathy (CIN) in high-risk populations. (Reprinted with permission from Bolesta SB et al. Contrast-induced nephropathy. In: Dunsworth TS et al, eds. *Pharmacotherapy Self-Assessment Program*. Lenexa, KS: American College of Clinical Pharmacy; 2007:73.)

# Chronic Kidney Disease\*

## General Principles

- Chronic kidney disease (CKD) is progressive, irreversible kidney damage characterized by decreased estimated glomerular filtration rate (eGFR) or evidence of kidney damage for at least 3 months. Progression of kidney disease to end-stage renal disease (ESRD) generally occurs over months to years.
- **Diabetic nephropathy**, a microvascular complication of diabetes, is the leading cause of CKD in the United States. Optimal control of blood glucose levels is essential to slow the progression of CKD and reduce morbidity and mortality. Hypertension is the second leading cause of CKD in the United States.
- Complications of CKD develop as kidney disease progresses, most often when the patient reaches stage 3 of the disease. Complications include fluid and electrolyte abnormalities, anemia, cardiovascular disease (CVD), mineral and bone disorders, and malnutrition.
- **Azotemia** is the accumulation of nitrogenous wastes (e.g., urea) in the plasma.
- **Nephrotic syndrome** is a glomerular disease characterized by proteinuria  $>3.5$  g/day.
- **Lupus nephritis** (an autoimmune condition), **Wegener's granulomatosis** (a systemic inflammatory disease) and **focal segmental glomerulosclerosis** (sclerotic lesions of the glomeruli) are glomerular diseases that require treatment with immunosuppressive therapy.

## Classification

- CKD is classified into five stages on the basis of eGFR as defined by the National Kidney Foundation Kidney Disease Outcome Quality Initiative (NKF/DOQI) guidelines (Table 31.1).

## Patient Assessment

- Lab parameters used to evaluate kidney function/monitor disease progression include SCr, CrCl, and eGFR. The Modification of Diet in Renal Disease (MDRD) equation is used to calculate eGFR to stage CKD (see Chapter 31).

TABLE 31.1 Staging of Chronic Kidney Disease Based on eGFR

Stage	Description	eGFR (mL/minute/1.73 m <sup>2</sup> )
–	At increased risk	$\geq 90$ (with CKD risk factors)
1	Kidney damage with normal or $\uparrow$ eGFR	$\geq 90$
2	Kidney damage with mild $\downarrow$ eGFR	60–89
3	Moderate $\downarrow$ eGFR	30–59
4	Severe $\downarrow$ eGFR	15–29
5	Kidney failure	$<15$ (or need for renal replacement therapy)

CKD, chronic kidney disease; eGFR, effective glomerular filtration rate.

Source: Adapted with permission from the National Kidney Foundation. K/DOQI clinical practice guidelines for chronic kidney disease: evaluation, classification, and stratification. *Am J Kidney Dis.* 2002;39:S1.

\*The reader is referred to Chapter 31, Chronic Kidney Disease, written by Darius L. Mason, PharmD, BCPS, and Magdalene M. Assimon, PharmD, in the 10th edition of *Applied Therapeutics: The Clinical Use of Drugs* for a more in-depth discussion. All notations to reference numbers are based on the reference list at the end of that chapter. The editor of this handbook expresses her thanks to Drs. Mason and Assimon and acknowledges that this chapter is based on their work.

- Proteinuria is one of the initial diagnostic signs of kidney disease. The presence of persistent albuminuria indicates irreversible kidney damage (see Table 31.2).
- Dyslipidemias are common and are often seen concurrently with proteinuria.
- Volume overload can lead to weight gain, hypertension, edema, heart failure, and pulmonary edema.
- Metabolic acidosis results from impaired synthesis of ammonia.
- Anemia is caused by decreased erythropoietin (EPO) production by the kidneys, shortened half-life of red blood cells from uremia, and iron deficiency.
- Mineral and bone disorders (hyperphosphatemia, hypocalcemia, hyperparathyroidism, decreased production of active vitamin D, and resistance to vitamin D therapy) can all cause secondary complications of CKD. Secondary hyperparathyroidism can lead to bone pain, fractures, and myopathy.
- Signs and symptoms of uremia (uremic syndrome) are not usually seen until stages 4 and 5 of CKD. Manifestations and metabolic consequences of advance kidney disease are shown in Table 31.3.

**Risk Factors**

- Risk factors associated with the development, initiation, and progression of CKD have been identified (Table 31.4).
- Drug-induced causes of CKD:
  - Analgesic nephropathy: a slowly progressive disease that results from habitual ingestion of analgesics for many years, most often from long-term use of compound analgesics containing acetaminophen and aspirin along with caffeine or codeine. Nonsteroidal analgesics have also been implicated.
  - Lithium-induced CKD has a slow progression (average latency of 20 years) with the rate of progression related to the duration of lithium therapy.

**Goals of Therapy**

- Appropriate management includes measures to slow progression of CKD and regular evaluation of kidney function to assess changes in disease severity.
- Reversal of CKD is not possible. Goals of therapy are to delay the need for dialysis or kidney transplant as long as possible and to manage complications.

**Treatment**

- Pharmacotherapy requires interventions to manage comorbid conditions and secondary complications of CKD. Aggressive strategies to manage the disorders that cause kidney disease are important. Strict glycemic control is indicated in patients with diabetes.

TABLE 31.2 Diagnostic Criteria for Proteinuria and Albuminuria

	Total Protein			Albumin		
	24-Hour Collection (mg/day)	Spot Urine Dipstick (mg/dL)	Spot Urine Protein-SCr Ratio (mg/g)	24-Hour Collection (mg/day)	Spot Urine Dipstick (mg/dL)	Spot Urine Albumin-SCr Ratio (mg/g)
Normal	<300	<30	<200	<30	<3	<17 (men) <25 (women)
Microalbuminuria	NA	NA	NA	30–300	>3	17–250 (men) 25–355 (women)
Albuminuria or clinical proteinuria	>300	>30	>200	>300	NA	>250 (men) >355 (women)

SCr, serum creatinine.

Source: Adapted with permission from National Kidney Foundation. K/DOQI clinical practice guidelines for chronic kidney disease: evaluation, classification, and stratification. *Am J Kidney Dis.* 2002;39:S1.

TABLE 31.3 **Metabolic Effects of Progressive Kidney Disease****Cardiovascular**

Hypertension  
 Heart failure  
 Pericarditis  
 Atherosclerosis  
 Arrhythmias  
 Metastatic calcifications

**Dermatologic**

Altered pigmentation  
 Pruritus

**Endocrine**

Calcium–phosphorous imbalances  
 Hyperparathyroidism  
 Metabolic bone disease  
 Growth retardation in children  
 Altered thyroid function  
 Altered carbohydrate metabolism  
 Hypophyseal-gonadal dysfunction  
 Decreased insulin metabolism  
 Erythropoietin deficiency

**Fluid, Electrolyte, and Acid–Base Effects**

Fluid retention  
 Hyperkalemia  
 Hypermagnesemia  
 Hyperphosphatemia  
 Hypocalcemia  
 Metabolic acidosis

**Gastrointestinal**

Anorexia  
 Nausea, vomiting  
 Delayed gastric emptying  
 GI bleeding  
 Ulcers

**Hematologic**

Anemia  
 Bleeding complications  
 Immune suppression

**Musculoskeletal**

Renal bone disease  
 Amyloidosis

**Neurologic**

Lethargy  
 Depressed sensorium  
 Tremor  
 Asterixis  
 Muscular irritability and cramps (i.e., restless legs syndrome)  
 Seizures  
 Motor weakness  
 Peripheral neuropathy  
 Coma

**Psychological**

Depression  
 Anxiety  
 Psychosis  
 Miscellaneous  
 Reduced exercise tolerance



TABLE 31.4 Risk Factors for Chronic Kidney Disease

Susceptibility	Initiation	Progression
Advanced age	Diabetes mellitus	Glycemia
Reduced kidney mass	Hypertension	Hypertension
Low birth weight	Glomerulonephritis	Proteinuria
Racial/ethnic minority	Drug induced or toxicity	Smoking
Family history	Smoking	Obesity
Low income or education	Obesity	
Systemic inflammation		
Dyslipidemia		

Source: Reprinted from US Department of Health and Human Services. *Healthy People 2010*. Washington, DC: US Government Printing Office; 2000.

- **Dietary Protein Restriction (0.6–0.8 g/kg/day):** Benefits must be balanced against the potential adverse effect on overall nutritional status.
- **Fluid Balance:** sodium (<2.4 g/day) and fluid restriction (1–2 L/day). Diuretic therapy (e.g., loop diuretics) is often required. Combination therapy (e.g., loop and thiazide) may be successful in patients resistant to single-agent therapy. Thiazide monotherapy may not be effective when eGFR is <30 mL/minute/1.73 m<sup>2</sup>.
- **Hyperkalemia:** Treatment depends on serum concentration, presence/absence of symptoms, and electrocardiographic (ECG) changes. Serum potassium concentrations are generally well maintained within normal limits at eGFR > 10 to 15 mL/minute/1.73 m<sup>2</sup>. Chronic management involves prevention by limiting potassium intake. Acute management involves reversal of cardiac effects and reduction in serum potassium (see Chapter 10).
- **Metabolic Acidosis:** use of preparations containing sodium bicarbonate or sodium citrate to normalize plasma bicarbonate concentration or achieve bicarbonate levels of at least 22 mEq/L. Oral therapy can be used for patients not receiving dialysis.
- **Hypertension:** Blood pressure (BP) control is important to delay the progression of CKD. The goal BP is <130/80 mm Hg with diabetes or proteinuria, <140/90 mm Hg without proteinuria, and 150/90 mm Hg age 70 or older.
  - Angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs) are recommended as first-line treatment in patients with, or at risk of, CKD.
  - Nondihydropyridine calcium-channel blockers (e.g., diltiazem, verapamil) may be beneficial alone or in combination with an ACE inhibitor. Dihydropyridine calcium-channel blockers (e.g., amlodipine) should not be used alone but can be used in combination with ACE inhibitor or ARB therapy.
  - Diuretics may be considered for patients with diabetic nephropathy and edema, depending on their degree of kidney function. Loop diuretics are generally preferred because they retain their effect at reduced eGFR levels.
  - Use of  $\beta$ -blockers after myocardial infarction (MI) or with heart failure patients may be appropriate.
- **Dyslipidemias:** Choice of agent is based on individual lipid profile. NCEP ATIII guidelines should be followed (see Chapter 13) with a target LDL-cholesterol <100 mg/dL.
- **Anemia:** Treatment is essential to reducing cardiovascular complications and improving quality of life. Management includes use of erythropoiesis-stimulating agents (ESA) and iron supplementation. NKF/DOQI guidelines recommend a target hemoglobin of 10 to 12 g/dL in patients with CKD receiving ESA therapy. Routine maintenance of hemoglobin levels of 13 mg/dL or more is not recommended.
  - Recombinant human EPO (epoetin alfa) stimulates erythrocyte production. Doses can be given by SQ or IV injection; SQ is preferred because lower doses can be given less fre-

**TABLE 31.5 Estimated Darbepoetin Alfa Starting Doses for Patients on Dialysis Based on Previous Epoetin Alfa Dose**

Previous Weekly Epoetin Alfa Dose (units/week)	Weekly Starting Darbepoetin Alfa Dosage (mcg/week)	
	Adults	Children
<1,500	6.25	<sup>a</sup>
1,500–2,499	6.25	6.25
2,500–4,999	12.5	10
5,000–10,999	25	20
11,000–17,999	40	40
18,000–33,999	60	60
34,000–89,999	100	100
≥90,000	20	200

<sup>a</sup>For children receiving a weekly epoetin alfa dosage of <1,500 units/week, the available data are insufficient to determine a darbepoetin alfa conversion dosage <http://online.factsandcomparisons.com/MonoDisp.aspx?monoid=fandc-hcp12341&book=DFC&search=193833&pipe;5&isStemmed=True&asbooks=#fandc-hcp12341.ad-section.5>. Accessed November 13, 2010.

Source: Reprinted with permission from Facts & Comparisons eAnswers.

quently. Starting doses for epoetin alfa are 50 to 100 units/kg three times weekly; extended dosing has also been used. Darbepoetin alfa has a longer half-life allowing for SQ doses of 0.45 mcg/kg once weekly or 0.75 mcg/kg once every other week. Conversion from epoetin alfa to darbepoetin alfa for patients on dialysis is shown in Table 31.5.

- Iron deficiency is the leading cause of ESA hyporesponsiveness. Iron status should be evaluated and iron supplementation instituted for patients with a deficiency. Oral agents should be given on an empty stomach, if tolerated, to maximize absorption (Table 31.6). Intravenous (IV) therapy is indicated in patients who do not respond to oral therapy.
- Transfusions may be required in certain patients with substantially low oxygen-carrying capacity or substantial blood loss.
- **Mineral/Bone Disorders:** Dietary phosphorus restriction (800–1,000 mg/day), phosphate-binding agents, vitamin D therapy, calcimimetics, and dialysis are used to manage calcium and phosphorus concentrations and prevent/manage secondary hyperparathyroidism.
  - Calcium carbonate and calcium acetate bind phosphate (Table 31.7) and can correct hypocalcemia. Use non-calcium-containing phosphate binders (e.g., sevelamer, lanthanum) if hypercalcemia develops. Aluminum preparations should only be considered for short-term use (up to 4 weeks) in patients with severely elevated phosphorus due to the risk for aluminum toxicity.

**TABLE 31.6 Oral Iron Preparations**

Preparation	Common Brand Names	Commonly Prescribed Unit Size (Amount Elemental Iron in mg) <sup>a</sup>	Number of Units/Da to Yield 200 mg Elemental Iron
Ferrous sulfate	Slow FE, Fer-In-Sol	325 (65)	3 tablets
Ferrous gluconate	Feratab	325 (36)	5 tablets
Ferrous fumarate	Femiron, Feostat	200 (66)	3 capsules
Iron polysaccharide	Niferex, Nu-Iron	150 (150)	2 capsules
Heme iron polypeptide	Proferrin-ES	12 (12)	17 tablets
	Proferrin-Forte		

<sup>a</sup>Unit size reflects common tablet or capsule sizes prescribed and not necessarily that of the brand names listed.

TABLE 31.7 Phosphate-Binding Agents

Product	Select Available Agents <sup>a</sup>	Content of Compound	Starting Dose
Calcium carbonate (40% calcium)	Tums	200, 300, 400 mg	0.8–2 g elemental Ca with meals
	Os-Cal-500	500 mg	
	Nephro-Calci	600 mg	
	Caltrate 600	600 mg	
	Calcarb HD (powder)	2,400 mg/packet	
Calcium acetate (25% calcium)	CaCO <sub>3</sub> (multiple preparations)	200–600 mg	2–3 tablets with meals
	Phos-Lo 667 mg	169 mg	
Sevelamer hydrochloride	Renagel (tablet, capsule)	400, 800 mg (tablet)	800–1,600 mg with meals
Sevelamer carbonate (polymer-based)	Renvela (tablet, powder)	800 mg (tablet), 0.8 g (powder)	250–500 mg with meals
Lanthanum carbonate aluminum hydroxide <sup>b</sup>	Fosrenol	250, 500, 750, 1,000 mg	
	AlternaGel (suspension)	600 mg/5 mL	300–600 mg with meals
	Amphojel (tablet and suspension)	300, 600 mg (tablet)	
		320 mg/5 mL (suspension)	
	Alu-Cap (capsule)	400 mg	
	Alu-Tab	500 mg	
	Basaljel (tablet, capsule, and suspension)	500 mg (tablet, capsule), 400 mg/mL (suspension)	
70 mg		70 mg with meals	
Magnesium carbonate <sup>b</sup>	Mag-Carb (capsule)	300, 600 mg (tablet), 400, 800 mg/5 mL (suspension)	300–400 mg with meals
Magnesium hydroxide <sup>b</sup>	Milk of Magnesia (tablet and suspension)		

<sup>a</sup>Tablet unless noted otherwise.

<sup>b</sup>Not first-line choice as a phosphate binder for chronic use.

- Vitamin D therapy (calcitriol, paricalcitol, doxercalciferol) and calcimimetics (cinacalcet) help achieve proper calcium and bone metabolism.
- **Dialysis** becomes necessary when ESRD develops. The appropriate dialysis modality must be selected on the basis of patient preference and options for vascular access (see Chapter 32).
- **Transplantation** is an option for patients with ESRD provided a suitable organ match is available and there are no specified contraindications (see Chapter 33).

# Renal Dialysis\*

## General Principles

- Dialysis was developed as a means for the removal of excess water and metabolic waste products (toxins) from the body that accumulate when there is inadequate renal function. It is commonly used for patients with end-stage renal disease (ESRD). Without dialysis or transplantation, patients with ESRD will die of the metabolic complications of their renal failure.
- **Hemodialysis** (HD) is an extracorporeal process—the dialysis membrane is outside of the body.
- **Peritoneal dialysis** (PD) uses the patient's peritoneal membrane for the clearance of water and solutes.
- **Dialysate** is an electrolyte solution that simulates plasma. Electrolyte composition of HD and PD dialysate solutions are shown in Table 32.1.
- **Dialyzer** functions as an artificial kidney. It is characterized by factors such as membrane composition, size, and ability to clear solutes. Efficiency is also a function of surface area.
- **Vascular Access.** Permanent vascular access provides easy access to high blood flow for HD. Different types of access exist: arteriovenous (AV) fistula, AV graft, double-lumen or tunneled catheters, and catheters with subcutaneous implanted access ports.
- Dialyzability of drugs is dependent on molecular weight (high for drugs with a molecular weight <500 Da, less well dialyzed when the molecular weight is between 500 and 1,000 Da) and physicochemical property of the solute being removed.

## Patient Assessment

- Factors considered in the selection of the type of dialysis for a given patient include patient lifestyle, availability of a vascular access site, and patient ability to perform self-care for dialysate exchanges with PD.

TABLE 32.1 Electrolyte Composition of Hemodialysis and CAPD Dialysate Solutions

Solute	Hemodialysis (mEq/L)	CAPD (mEq/L)
Sodium	135–145	132
Potassium	0–4	0
Calcium	2.5–3.5	3.5
Magnesium	0.5–1.0	1.5
Chloride	100–124	102
Bicarbonate	30–38	
Lactate		35
pH	7.1–7.3	5.5

CAPD, continuous ambulatory peritoneal dialysis.

\*The reader is referred to Chapter 32, Renal Dialysis, written by Myrna Y. Munar, PharmD, in the 10th edition of *Applied Therapeutics: The Clinical Use of Drugs* for a more in-depth discussion. All notations to reference numbers are based on the reference list at the end of that chapter. The editor of this handbook expresses her thanks to Dr. Munar and acknowledges that this chapter is based on her work.

## Treatment

### HEMODIALYSIS

- The patient's anticoagulated blood and a dialysate solution flow in opposite directions through a dialyzer, providing constant perfusion of fresh dialysate thereby maintaining a large concentration gradient across the dialysis membrane throughout the dialysis process. Solutes (metabolic waste products, electrolytes) are removed from the blood by diffusing across concentration gradients into the dialysate.
- The rate of removal is a function of blood and dialysate flow rates through the dialyzer, relative concentration of each solute, physical characteristics of the dialysis membrane, and properties of the solute being removed (e.g., size, protein binding, volume of distribution).
- Chronic HD typically occurs for 3 to 4 hours, three times a week.
- Most patients are anticoagulated with IV heparin during dialysis to prevent blood from clotting in the extracorporeal circuit. Heparin should be discontinued 1 hour before the end of dialysis to prevent excessive bleeding.
- **Complications of HD**
  - Intradialytic hypotension caused by excessive fluid removal or excessive heating of the dialysate. Treatment options include midodrine (10–20 mg 30 minutes before dialysis), sertraline (50–100 mg daily), and IV L-carnitine (20 mg/kg at dialysis).
  - **Muscle cramps:** Treatment can include reduced ultrafiltration and infusion of hypertonic saline or glucose to improve circulation, exercise/stretching of affected limb, or vitamin E 400 IU at bedtime with vitamin C 250 mg daily for prevention.
  - Hypersensitivity, most commonly to the dialyzer membrane.
  - Dialysis disequilibrium caused by shifting of free water into the brain, causing cerebral edema. Treatment is aimed at prevention by initiating dialysis gradually. Direct treatment involves IV hypertonic saline or mannitol.
  - Thrombosis (usually a consequence of venous stenosis): alteplase or reteplase are effective for thrombolytic lysis of the vascular access site.
  - Access infection (typically caused by *S. aureus* or *S. epidermidis*): prophylactic antibiotics offer no value. If infection is suspected, prompt treatment is needed. Vancomycin 1 g repeated as needed depending on type of dialysis, or cefazolin 20 mg/kg three times weekly with gentamicin 2 mg/kg with appropriate serum concentration monitoring.
  - Aluminum toxicity (dementia, bone disease, anemia): deferoxamine can be used to chelate serum aluminum.
  - Amyloidosis caused by deposition of  $\beta_2$ -microglobulin in joints and soft tissue.
  - Malnutrition caused by inadequate dietary intake, loss of amino acids through dialysis, and the catabolic state caused by ESRD.

### PERITONEAL DIALYSIS

- Uremic toxins are removed by diffusion across a concentration gradient between the peritoneal membrane into the dialysate solution. Continuous ambulatory peritoneal dialysis (CAPD), which include continuous cycling peritoneal dialysis (CCPD) and nocturnal intermittent peritoneal dialysis (NIPD), is most common.
- CAPD involves instilling 2 to 3 L of dialysate solution into the peritoneal cavity through a surgically placed resident catheter. The solution dwells for 4 to 8 hours and is then drained and replaced with a fresh solution. The fill–dwell–drain cycle is done three to four times during a day. CAPD must be done daily throughout the week to achieve adequate urea removal.
- **Complications of PD**
  - Peritonitis (commonly caused by coagulase-negative staphylococci): symptoms include abdominal pain, nausea, vomiting, fever with/without cloudy effluent. Empiric antibiotics must cover gram-positive and gram-negative organisms. First-generation cephalosporins

(cefazolin, cephalothin) are used most commonly. Vancomycin should be reserved for methicillin-resistant *S. aureus* or *S. epidermidis* infections. Third-generation cephalosporin with or without an aminoglycoside may be used depending on the patient history and sensitivity pattern.

- **Exit-site infection:** daily gentamicin cream at the exit site is the prophylaxis of choice to prevent catheter exit-site infection, but monitoring for resistance is needed. Local erythema can be treated with topical agents. Purulent drainage indicates more significant infection that requires hypertonic saline dressings and systemic antibiotics. First-generation oral cephalosporins, a penicillinase-resistant penicillin, or trimethoprim-sulfamethoxazole are options. Oral rifampin 600 mg daily may be added for nonresponding infections with positive cultures. Rifampin monotherapy should be avoided. Oral quinolones are first-line agents for *P. aeruginosa* exit-site infections; gram-negative organisms can be treated with ciprofloxacin 500 mg orally twice daily.
- Weight gain occurs because approximately 500 to 1,000 kcal/day are absorbed as glucose from PD solutions. Modification of oral dietary intake may be needed and insulin requirements increased in diabetic patients.

# Dosing of Drugs in Renal Failure\*

## General Principles

- Many factors associated with kidney disease predispose patients to potential drug toxicity by altering pharmacokinetic disposition and pharmacodynamic effects of drugs.
  - Bioavailability can be affected by changes in gastrointestinal (GI) motility, increased gastric pH, and potential drug interactions with binding agents.
  - Changes in protein binding can result in an increase in the amount of unbound drug, which is important for highly protein-bound drugs (Tables 33.1 and 33.2).
  - Volume of distribution of drugs can change due to changes in protein binding.
  - Renal elimination can be reduced depending on the amount of drug normally excreted unchanged in the urine. Drugs most affected are those with low protein binding (or those displaced from proteins in the setting of renal disease) and those with a low molecular weight.
- Renal disease can also affect elimination of drugs that are primarily metabolized by the liver, particularly when there are pharmacologically active or toxic metabolites that can accumulate in renal disease (Table 33.3).
- The potential for toxicity from excipients used to formulate medications should also be considered.

TABLE 33.1 Protein-Bound Drugs

Drug Class	Protein Binding (%)
Angiotensin-converting enzyme inhibitors	0–97
Antiotensin receptor blockers	>90
Calcium blockers	
Diltiazem	82
Verapamil	90
Dihydropyridine type	>95
Diuretics	
Hydrochlorothiazide	40
Bumetanide	95
Furosemide	95
$\beta$ -Blockers	0–98
Statins	43–98
Nonsteroidal anti-inflammatory drugs	>90
Acetylsalicylic acid	85–95
Oral anticoagulants	98–100
Benzodiazepines	>85
Immunosuppressive agents	
Mycophenolic acid	>95

\*The reader is referred to Chapter 33, Dosing of Drugs in Renal Failure, written by David J. Quan, PharmD, and Francesca T. Aweeka, PharmD, in the 10th edition of *Applied Therapeutics: The Clinical Use of Drugs* for a more in-depth discussion. All notations to reference numbers are based on the reference list at the end of that chapter. The editor of this handbook expresses her thanks to Drs. Quan and Aweeka and acknowledges that this chapter is based on their work.

TABLE 33.2 Plasma Protein Binding (%) of Acidic Drugs in Renal Failure

Drug	Normal	Renal Failure
Cefazolin	85	69
Cefoxitin	73	25
Clofibrate	97	91
Diazoxide	94	84
Furosemide	96	94
Pentobarbital	66	59
Phenytoin	88–93	74–84
Salicylate	87–97	74–84
Sulfamethoxazole	66	42
Valproic acid	92	77
Warfarin	99	98

## Drug Removal by Dialysis

- Whether dialysis removes a specific drug from the blood must be considered. A supplemental dose of a medication may be needed after a dialysis session, or an alteration in the dosing regimen needed to maintain therapeutic drug concentrations.
- Dialysis can be initiated to hasten removal of drug from the body if needed (e.g., overdose).
- The primary literature and product-specific information should be used to determine whether information is available on the ability of dialysis to remove the drug.
- Physical and chemical characteristics of a drug can be used to predict the effectiveness of dialysis on drug removal. Drugs that are more readily dialyzed have the following properties:
  - Low molecular weight
  - Water soluble
  - Small volume of distribution
  - Low protein binding

TABLE 33.3 Drugs with Active or Toxic Metabolites Excreted by the Kidney

Drug	Metabolite
Acetohexamide	Hydroxyhexamide
Allopurinol	Oxypurinol
Bupropion	Threo/erythro-hydrobupropion
Cefotaxime	Desacetylcefotaxime
Chlorpropamide	Hydroxy metabolites
Clofibrate	Chlorphenoxyisobutyrate
Cyclophosphamide	4-Ketocyclophosphamide
Daunorubicin	Daunorubicinol
Meperidine	Normeperidine
Methyl dopa	Methyl-O-sulfate- $\alpha$ -methyl dopamine
Midazolam	$\alpha$ -Hydroxymidazolam
Morphine	Morphine-3-glucuronide Morphine-6-glucuronide
Phenylbutazone	Oxyphenbutazone
Primidone	Phenobarbital
Procainamide	N-acetylprocainamide (NAPA)
Propoxyphene	Norpropoxyphene
Rifampicin	Desacetylated metabolites
Sodium nitroprusside	Thiocyanate
Sulfonamides	Acetylated metabolites
Tramadol	O-Demethyl-N-demethyltramadol



- High-flux hemodialysis (HD) may allow for partial removal of small- to mid-sized compounds.
- Peritoneal dialysis (PD) is usually inefficient at removing drugs from the plasma.
- Continuous venovenous hemofiltration (CVVH) in the form of continuous renal replacement therapy (CRRT) removes fluid, electrolytes, and low- to mid-sized molecules from the blood.
- Data on removal of drugs by hemodialysis cannot be extrapolated to CVVH due to differences in membranes used, blood flow rates, ultrafiltration rate, dialysis flow rate, and continuous (CVVH) versus intermittent (HD) nature of the procedures.
- Hemoperfusion can be useful for removing large-size compounds or highly protein-bound drugs that are not removed efficiently by HD.

## Dose Adjustment

- The degree to which renal impairment affects elimination depends on the percentage of unchanged drug that is excreted in the kidney. Route of elimination should be determined before making dosage adjustments.
- Clearance of drugs primarily eliminated by nonrenal means is not altered significantly in patients with renal disease. However, elimination of their metabolites may be affected.
- The therapeutic window of the drug should be considered. Aggressive dose reduction may not be needed for drugs with a wide therapeutic margin and low toxicity profile.
- Cockcroft and Gault equation for calculating creatinine clearance can be used for adjusting the doses of drugs in renal dysfunction (see Chapter 30 for equation) provided SCr reflects a steady state. The Modification of Diet in Renal Disease (MDRD) equation has not been validated for dosing of most drugs in the setting of renal dysfunction.
- Product-specific information, commonly used drug dosing books, and the medical literature should be consulted for dosing guidelines for drugs used in patients with renal failure. Strategies can include extending the dosing interval and/or adjusting the dose (Table 33.4).

TABLE 33.4 Advantages and Disadvantages of General Approaches to Dosing Adjustments in Renal Disease

Method	Advantages	Disadvantages
<b>VARIABLE FREQUENCY</b>		
Use the same dose but ↑ the dosing interval	Same $C_{p_{ave}}$ , $C_{p_{max}}$ , $C_{p_{min}}$ Normal dose	Levels may remain subtherapeutic for prolonged periods in patients requiring dosing intervals >24 hours
<b>VARIABLE DOSE WITH FIXED <math>C_{p_{ave}}</math></b>		
↓ Dose to maintain a target $C_{p_{ave}}$ ; keep the dosing interval the same	Same $C_{p_{ave}}$ Normal dosing interval	↓ Peak levels, which may ↑ be subtherapeutic; ↑ trough levels, which may ↑ be potential for toxicity

$C_{p_{ave}}$ , average plasma concentration;  $C_{p_{max}}$ , maximum plasma concentration;  $C_{p_{min}}$ , minimum plasma concentration.

# SECTION VI • SOLID ORGAN TRANSPLANTATION

## CHAPTER 34

### Kidney and Liver Transplantation\*

#### General Principles

- Solid organ transplantation is an established therapeutic option for patients with end-stage kidney, liver, heart, and lung disease. One-year graft survival rates vary among the various organ types; 1-year survival post–deceased donor kidney transplant in 2012 was 97.3%.
- Risk–benefit ratio must be considered when evaluating a patient for any organ transplantation.
- Rejection can occur any time after transplant and can be classified as cellular (T-cell mediated) and/or antibody (B-cell mediated).
- Suppression of the host’s immune system and prevention of rejection are vital for prolonged graft survival.
- In kidney transplant, the 1-year conditional half-life was 15 years for living donor and 12.5 years for deceased donors.

#### Donor and Recipient Matching

- Histocompatibility antigens play an important role in organ transplantation. Compatibility between donor and recipient can impact acute and chronic rejection, graft survival, and patient survival. Testing for antibodies to human lymphocyte antigen (HLA) is done pretransplant.
- ABO blood typing is also an important factor. Transplantation of an organ with ABO incompatibility can result in hyperacute rejection and graft loss.

#### Kidney Transplantation

- Patients with end-stage renal disease (ESRD) are potential candidates for kidney transplantation unless contraindicated. Transplant can be considered preemptively, prior to the start of dialysis.
- Contraindications include active malignancy; active infection; irreversible liver, cardiac, or pulmonary disease; morbid obesity; positive donor cross-match; substance abuse; and abnormal psychosocial and noncompliant behavior.
- Immunologically high-risk patients are associated with decreased graft survival. Risk factors include advanced donor age, African American race, recipient age, retransplantation, a high PRA (>20%–50%).
- Initial renal function after transplantation can be immediate, or slow graft or delayed graft function (often defined as the need for dialysis in the immediate posttransplant period). Delayed graft function is associated with prolonged length of stay, increased costs, and poorer graft survival.

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\*The reader is referred to Chapter 34, Kidney and Liver Transplantation, written by David J. Taber, PharmD, BCPS, and Robert E. Dupuis, PharmD, in the 10th edition of *Applied Therapeutics: The Clinical Use of Drugs* for a more in-depth discussion. All notations to reference numbers are based on the reference list at the end of that chapter. The editor of this handbook expresses her thanks to Drs. Taber and Dupuis and acknowledges that this chapter is based on their work.

- **Rejection** can be classified as hyperacute (within minutes to hours), acute (days to months), and chronic (months to years). Acute rejections can be cellular or antibody mediated. Kidney biopsy is the gold standard for making the diagnosis of rejection. For cellular rejection, high-dose corticosteroids (IV methylprednisolone) or T-cell depleting therapies (e.g., antithymocyte globulin) are considered first-line therapy on the basis of rejection severity.

## Liver Transplantation

- The most common indication for liver transplant in adults in the United States is cirrhosis due to chronic hepatitis C, followed by cirrhosis due to alcoholism.
- Contraindications to liver transplantation can include nonhepatic malignancy associated with poor prognosis, cholangiocarcinoma, active systemic infection, patients with alcoholic liver disease who continue to abuse alcohol, psychosocial instability, noncompliance, severe neurologic disease, and advanced cardiopulmonary disease.
- **Rejection** can be categorized as acute (weeks to months) or chronic (months to years). Hyperacute rejection rarely occurs with liver transplantation. Treatment of acute rejection is with corticosteroids (IV methylprednisolone). Chronic rejection is irreversible, and treatment is limited and includes augmentation of immunosuppressive therapy and/or retransplantation. Maintenance double or triple immunosuppressive therapy is commonly used.

## Posttransplant Complications

- After transplantation, recipients require management and monitoring for fluid and electrolyte imbalance, blood pressure, blood glucose, surgical complications, GI complications, infection, rejection, immunosuppressive dosing and toxicity, and graft organ function.
- **BK Polyomavirus Infection:** a latent virus that is reactivated due to immunosuppression post-transplant. In kidney transplant, regular screening should be performed.
- **New Onset Diabetes after Transplant (NODAT):** Highest incidence is within the first year after transplantation. Cyclosporine, tacrolimus, and prednisone are all associated with development NODAT. An intensive approach to controlling blood glucose is needed.
- **Posttransplant Hypertension:** Blood pressure goals are similar to those for the general population (<140/90 mm Hg). Pharmacologic agents used are the same as those in the general population; drug interactions and comorbidities must be considered.
- **Posttransplant Hyperlipidemia:** Immunosuppressive agents can cause elevations in total cholesterol, low-density lipoprotein (LDL), and triglycerides and a reduction in high-density lipoprotein (HDL). Statins are considered first-line treatment; the target LDL is <100 mg/dL.
- **Posttransplant Osteoporosis:** Drugs used to prevent organ rejection predispose patients to osteoporosis. Prevention of bone loss with calcium and vitamin D is recommended for patients receiving corticosteroid therapy.
- **Infection:** major source of morbidity and mortality posttransplant, with the highest risk in the first 6 months. Prophylactic antimicrobial therapy decreases the risk of surgical infections and is individualized according to organ type. Common opportunistic infections after transplantation are shown in Table 34.1.
- **Hepatitis** recurrence is a risk post liver transplantation. Antiviral therapy may be needed.
- **Cytomegalovirus (CMV)** is a cause of morbidity and mortality after solid organ transplantation. Without prophylaxis, it often occurs in the first 3 months after transplantation. It occurs when latent viruses from a seropositive donor organ are reactivated in the presence of immunosuppression; highest at-risk are seronegative recipients who receive a seropositive organ.
- **Posttransplantation lymphoproliferative disorder (PTLD)** is a malignancy reported after solid organ transplantation. Factors strongly associated with early PTLD are primary Epstein-Barr virus infection, polyclonal antilymphocyte antibodies, and patient age (higher in children). Late PTLD occurs more in older patients. Treatment of PTLD is a challenge, with no current consensus.

TABLE 34.1 Common Opportunistic Infections after Transplantation

Organisms	Time of Onset after Transplantation
Cytomegalovirus	1–6 months
Herpes simplex virus	2 weeks–2 months
Epstein-Barr virus	2–6 months
Varicella zoster virus	2–6 months
Fungal	1–6 months
Mycobacterium	1–6 months
<i>Pneumocystis carinii</i> pneumonia	1–6 months
<i>Listeria</i>	1 month–indefinitely
<i>Aspergillus</i>	1–4 months
<i>Nocardia</i>	1–4 months
<i>Toxoplasma</i>	1–4 months
<i>Cryptococcus</i>	4 months–indefinitely

## Goals of Therapy

- The goal of immunosuppressive therapy is to prevent organ rejection, prolong graft and patient survival, and improve quality of life.

## Treatment

- Current immunosuppressive drugs provide a nonpermanent form of tolerance and lifelong immunosuppression that is required for organ survival. There is no consensus on the best induction and maintenance immunosuppressive regimen; selection depends on the program and the specific organ to be transplanted.
- Most immunosuppressive drug regimens utilize several drugs. Common combinations include a calcineurin inhibitor (cyclosporine, tacrolimus), mycophenolate or sirolimus, and prednisone. Steroid-free regimens are also used.
- Immunosuppressive agents are associated with significant long-term complications (nephrotoxicity, hypertension, hyperlipidemia, osteoporosis, diabetes).

## Drug Therapy

- The usual dose, therapeutic use, and adverse effects of the currently used immunosuppressive agents are shown in Table 34.2.
- Drug interactions (pharmacokinetic and pharmacodynamic) must be considered with immunosuppressive therapy due to their complex and highly variable pharmacokinetic profiles and relatively narrow therapeutic index (Table 34.3 shows a partial list).
- **Azathioprine**, a prodrug of 6-mercaptopurine, is a nonspecific immunosuppressive agent that interferes with DNA synthesis, and affects T-cell more than B-cell immune responses. It inhibits the early stages of cell differentiation and proliferation. It is used to prevent rejection.
- **Mycophenolate** is used as adjunctive therapy in combination with other immunosuppressive agents to prevent acute rejection. Monitoring of plasma concentrations is not generally recommended due to the lack of data showing improved outcomes with monitoring.
- **Corticosteroids** have potent immunosuppressive properties and are used to prevent and treat rejection. They are associated with significant side effects, and protocols have been developed to minimize, eliminate, or avoid their use.
- **Calcineurin inhibitors (CNI; cyclosporine, tacrolimus)** are the primary agents used in most transplant programs; tacrolimus is the preferred CNI in most transplant centers. Plasma concentrations of these drugs are monitored to prevent toxicity, optimize efficacy, and assess compliance. Target trough concentrations differ on the basis of the institution, type of transplant, time after transplantation, and other immunosuppressive agents.

TABLE 34.2 Currently Used Immunosuppressive Agents

Drug (Brand Name)	Usual Dose (How Supplied)	Therapeutic Use(s)	Adverse Effects
Alemtuzumab (Campath-H1)	30 mg × 1 dose (30-mg vial for injection)	Prevention of acute rejection; steroid-free protocols	Leukopenia, thrombocytopenia, increased infection risk
Azathioprine (Imuran)	1–2 mg/kg/day, usually 50–150 mg daily (50-mg tablet; 100-mg vial for injection)	As maintenance agent to prevent acute rejection	Leukopenia, thrombocytopenia, hepatotoxicity, nausea
Antithymocyte globulin, rabbit (Thymoglobulin)	1.5 mg/kg/day given daily for 3–5 days (25-mg/5-mL vial for injection)	Induction for high-risk individuals, delayed graft function in kidney transplant, rejection	Fever, chills, hypotension, neutropenia, flushing, rash, itching, joint pain, myalgias, thrombocytopenia, increased infection risk
Basiliximab (Simulect)	20 mg on post-op day 0 and day 4	Induction	Very rare, hypersensitivity reaction (rare)
Cyclosporine (Neoral, Gengraf)	4–8 mg/kg/day divided BID. More important to monitor trough levels, goal trough initially of 200–300 ng/ml	As maintenance agent to prevent acute rejection	Nephrotoxicity, hypertension, neurotoxicity, hair growth, gingival hyperplasia, hyperglycemia, hyperkalemia, dyslipidemia, hypomagnesemia, increased infection risk
Everolimus (Zortress)	0.5–1.5 mg PO BID (0.25-mg, 0.5-mg, 0.75-mg tablets; trough level monitoring)	As maintenance agent to prevent acute rejection; conversion agent from CNI	Dyslipidemia, thrombocytopenia, neutropenia, impaired healing, mouth ulcers, proteinuria, pneumonitis (rare)
Methylprednisolone sodium succinate (Solu-Medrol, various others)	10–1,000 mg/dose (40-mg, 125-mg, 250-mg, 500-mg, 1,000-mg, and 2,000-mg vial for injection)	Induction to prevent acute rejection; to treat acute rejection	Hyperglycemia, psychosis, impaired wound healing, osteoporosis, acne, gastritis, edema electrolyte disturbances, hypertension, dyslipidemia, leukocytosis, cataracts, cushingoid state, infection, insomnia, irritability
Mycophenolate mofetil (CellCept)	1.5–3.0 g/day divided BID IV/PO (250-mg capsule; 500-mg tablet; 200 mg/mL oral suspension; 500-mg vial for injection)	As maintenance agent to prevent acute rejection	Diarrhea, nausea and vomiting, neutropenia, dyspepsia, increased infection risk, thrombocytopenia, leukopenia
Mycophenolate sodium (Myfortic)	360–720 mg BID PO	As maintenance agent to prevent acute rejection. Alternative to MMF	Neutropenia, increased infection risk, thrombocytopenia, leukopenia
Prednisone (Deltasone, others)	5–40 mg/day (1mg, 2.5-mg, 5-mg, 10-mg, 20-mg, 50-mg, and 100-mg tablet)	As maintenance agent to prevent acute rejection	See methylprednisolone
Sirolimus (Rapamune)	2–10 mg/day (1mg and 2-mg tablet; 1 mg/mL oral solution); trough level monitoring	As maintenance agent to prevent acute rejection; conversion agent from CNI	Dyslipidemia, thrombocytopenia, neutropenia, anemia, diarrhea, impaired healing, mouth ulcers, proteinuria, pneumonitis (rare)
Tacrolimus (Prograf)	Oral As maintenance agent to prevent acute 0.15–0.3 mg/kg/day divided BID IV 0.025–0.05 mg/kg/day as continuous infusion (0.5-mg, 1-mg, and 5-mg capsule; 5 mg/mL ampule for injection)	As maintenance agent to prevent acute rejection	Nephrotoxicity, hypertension, neurotoxicity, alopecia, hyperglycemia, hyperkalemia, dyslipidemia, hypomagnesemia, increased infection risk

BID, twice daily; CNI, calcineurin inhibitor; IV, intravenous; MMF, mycophenolate mofetil; PO, orally.

TABLE 34.3 Immunosuppressant Drug Interactions

Immunosuppressant	Interacting <sup>a</sup> Drugs	Mechanism	Consequence	Clinical Management
Calcineurin inhibitors (cyclosporine and tacrolimus) mTOR inhibitors (sirolimus and everolimus)	Clarithromycin, <sup>a</sup> erythromycin, <sup>a</sup> telithromycin, <sup>a</sup> ketoconazole, <sup>a</sup> itraconazole, <sup>a</sup> fluconazole, voriconazole, <sup>a</sup> fluoxetine, fluvoxamine, nefazodone, <sup>a</sup> diltiazem, <sup>a</sup> verapamil, <sup>a</sup> delaviridine, <sup>a</sup> ritonavir, <sup>a</sup> cimetidine, <sup>a</sup> grapefruit juice, <sup>a</sup> amiodarone, saquinavir, nelfinavir, indinavir, amprenavir, chloramphenicol <sup>a</sup>	Inhibit CYP 3A4 isoenzyme in the liver and intestines	Increase the blood concentration of the IS	Will depend on severity of interaction. Use of some agents together may be contraindicated and other interactions warrant reduction of IS dose with close monitoring and follow-up.
Calcineurin inhibitors (cyclosporine and tacrolimus) and mTOR inhibitors (sirolimus and everolimus)	Carbamazepine, <sup>a</sup> phenobarbital, <sup>a</sup> phenytoin, <sup>a</sup> St. John's wort, <sup>a</sup> rifampin, <sup>a</sup> rifabutin, <sup>a</sup> efavirenz, <sup>a</sup> nevirapine <sup>a</sup>	Induce CYP 3A4 isoenzyme in the liver and intestines	Decrease the blood concentration of the IS	Will depend on severity of interaction. Use of some agents together may be contraindicated and other interactions warrant adjustment of IS dose with close monitoring and follow-up.
Mycophenolate mofetil, and mycophenolate sodium	Cholestyramine, colestipol, probucol, sevelamer, antacids (magnesium and aluminum containing), iron-containing products	Bind to IS and prevent absorption	Decrease the blood concentration of the IS	Separate administration of IS and these agents by several hours
Azathioprine	Allopurinol	Inhibits metabolism by inhibiting xanthine oxidase	Increases the blood concentration of azathioprine	Avoid use together or prospectively reduce azathioprine dose to one-third or one-fourth normal dose and monitor for increased toxicity

<sup>a</sup>These are considered either potent inhibitors or inducers.

AUC, area under the curve; CYP, cytochrome P-450; IS, immunosuppressant.

- **mTOR inhibitors (sirolimus, everolimus)** inhibits T-cell activation and proliferation via inhibition of the mammalian target of rapamycin (mTOR). The mTOR inhibitors are used for CNI-withdrawal or CNI-minimization, or can be used in various combinations with CNIs, mycophenolate, or steroids. The target trough is 6 to 10 ng/mL, with lower troughs of 4 to 8 ng/mL when used in combination with CNIs.
- **Antithymocyte globulins (ATG)** produces a rapid and profound decrease in circulating T cells and is used to prevent and treat acute rejection.
- **Monoclonal antibodies (basiliximab, alemtuzumab)** are used as induction immunosuppression to prevent acute rejection.
- **Antivirals:** Intravenous ganciclovir (5 mg/kg/dose every 12 hours; dose adjusted for renal function) is the first-line agent for the treatment of severe or life-threatening CMV disease in

solid organ transplant recipients. Oral valganciclovir (900 mg every 12 hours; dose adjusted for renal function) can be used for mild to moderate cases. Secondary prophylaxis with oral valganciclovir for 1 to 3 months may be considered following treatment completion. Prevention of CMV infection with oral valganciclovir for an average of 3 to 6 months should be initiated posttransplant. Alternative prophylactic agents are IV ganciclovir or oral valacyclovir (in kidney transplant only). Acyclovir should not be used in the treatment or prevention of CMV infection.

## Basics of Nutrition and Patient Assessment\*

### General Principles

- Adequate intake of energy sources and essential nutrients is critical to the maintenance of optimal health. A nutritional disorder can occur when there is an imbalance between supply and demand of nutrients and energy by the body.
- Energy in the diet is provided by macronutrients such as carbohydrates, proteins, and lipids. Essential nutrients are provided in the form of water, electrolytes, vitamins, and minerals.
- Energy from food is expressed in terms of the calorie. Carbohydrates provide 3.4 kcal, proteins provide 4 kcal, and lipids provide 9 kcal of energy per gram.
- Carbohydrates exist as monosaccharides, disaccharides, oligosaccharides, and polysaccharides. A typical diet contains 45% to 65% of the total energy intake from carbohydrates.
- Protein is the second largest energy store in the body, second to adipose tissue. Amino acid residues from proteins can be converted to glucose to supply a continuous source of glucose for the body after depletion of glycogen.
- Biological lipids are a form of energy storage. Approximately 35% to 40% of total daily calories consumed by the average human are in the form of lipids.
- Water plays a critical role in nearly every biologic function and is needed for life.
- Electrolyte gradients are important for hydration status, pH, and nerve and muscle function. Sodium, chloride, and bicarbonate are the main solutes in the extracellular fluid. Potassium, magnesium, phosphate, and proteins are the main solutes inside cells.
- Vitamins are organic compounds that cannot be biologically synthesized in sufficient quantities yet are vital to sustain life. Vitamins are either fat soluble (A, D, E, and K) or water soluble (eight B vitamins and C).
- Trace elements include iron, zinc, copper, manganese, and fluoride. Ultratrace elements include arsenic, boron, chromium, iodine, selenium, silicon, nickel, and vanadium.

### Malnutrition

- Malnutrition occurs when there is a change in dietary intake that results in subcellular, cellular, or organ function changes that expose someone to increased risk of morbidity or mortality. Malnutrition can be reversed by adequate nutritional intervention.
- The most common nutrition deficiency in hospitalized patients is protein–calorie malnutrition.

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\* The reader is referred to Chapter 35, Basics of Nutrition and Patient Assessment, written by Jeff F. Binkley, PharmD, BCNSP, FASHP, in the 10th edition of *Applied Therapeutics: The Clinical Use of Drugs* for a more in-depth discussion. All notations to reference numbers are based on the reference list at the end of that chapter. The editor of this handbook expresses her thanks to Dr. Binkley and acknowledges that this chapter is based on his work.



## Patient Assessment

- A complete nutritional assessment is essential before specialized nutrition is initiated. Parameters to consider are nutrition and weight history, physical examination, anthropometric and biochemical measurements, and malnutrition risk (Table 35.1). Visceral proteins commonly used for nutrition assessment are summarized in Table 35.2.
- The nutrition status of a patient can be assessed using the Subjective Global Assessment (SGA) technique, which correlates strongly with other subjective and objective measures of nutrition.
  - **Class A.** Well-nourished patient with <5% weight loss or >5% with recent gains or improvement in appetite
  - **Class B.** Moderately malnourished patient with 5% to 10% weight loss without recent stabilization or gain, poor dietary intake, and mild loss of subcutaneous tissue
  - **Class C.** Severely malnourished patient with ongoing weight loss of >10% with severe subcutaneous tissue loss and muscle wasting.
- Energy (Table 35.3) and protein (Table 35.4) requirements are assessed on the basis of disease status and patient body weight.

## Goals of Therapy

- The goal of nutritional support therapy is to meet energy requirements of metabolic processes, support the hypermetabolism associated with critical illness, and minimize protein catabolism.

## Treatment

- Patients who cannot meet their nutritional needs by consuming food orally should be considered for specialized nutrition support (i.e., parenteral or enteral nutrients). The first intervention considered should be enteral feeding through an appropriate access device (see Chapter 37). Parenteral nutrition is reserved for patients whose GI tracts are not

TABLE 35.1 Components of a Nutrition History

Medical history
Chronic illnesses
Surgical history
Psychosocial history
Socioeconomic status
History of gastrointestinal problems (nausea, vomiting, or diarrhea)
Diet history, including diets for weight gain or loss
Food preferences and intolerances
Medications
Weight history
Increase or decrease
Intentional or unintentional
Time period for weight change
Functional capacity

TABLE 35.2 Visceral Proteins for Nutrition Assessment

Visceral Protein	Half-Life (Days)	Normal Serum Concentration
Albumin	18–21	3.5–5 g/dL
Transferrin	8–10	250–300 mg/dL
Transthyretin (prealbumin)	2–3	15–40 mg/dL
Retinol-binding protein	0.5	2.5–7.5 mg/dL

TABLE 35.3 Estimation of Energy Expenditure

**BASAL ENERGY EXPENDITURE (BEE) (THIS FORMULA OVERESTIMATES FOR OBESE PATIENTS.)**

Harris–Benedict Equations

$$\text{BEE}_{\text{men}} (\text{kcal/day}) = 66.47 + 13.75 W + 5.0 H - 6.76 A$$

$$\text{BEE}_{\text{women}} (\text{kcal/day}) = 655.10 + 9.56 W + 1.85 H - 4.68 A$$

or

$$20\text{--}25 \text{ kcal/kg/day (IBW) or } 11\text{--}14 \text{ kcal/kg/day ABW for BMI } >30$$

**ENERGY REQUIREMENTS**

Hospitalized patient, mild stress	20–25 kcal/kg/day
Moderate stress, malnourished	25–30 kcal/kg/day
Severe stress, critically ill	30–35 kcal/kg/day

A, age in years; BEE, basal energy expenditure; H, height in cm; kcal, kilocalories; W, weight in kg.

TABLE 35.4 Estimation of Protein Requirements

US-recommended dietary allowance	0.8 g/kg/day
Hospitalized patient, minor stress	1–1.2 g/kg/day
Moderate stress	1.2–1.5 g/kg/day
Severe stress	1.5–2 g/kg/day
BMI 30–40	2 g/kg/day (IBW)
BMI >40	2.5 g/kg/day (IBW)

functional or cannot be accessed, hemodynamically unstable, or do not absorb sufficient nutrients to maintain adequate nutrition (see Chapter 38).

- Nutritional support regimens should be tailored on the basis of requirements, response, and patient tolerance.
- Fluid needs should consider the need to correct fluid imbalances, maintain fluid requirements, and replace ongoing fluid loss (see Chapter 10).
- Overfeeding should be avoided to prevent potential metabolic abnormalities.

# Obesity\*

## General Principles

- Obesity is a chronic medical disorder that is determined by multiple biological and environmental factors, a sedentary lifestyle, and a genetic predisposition. It is associated with an increased risk of morbidity and mortality.
- Obesity results from an imbalance of energy intake and energy expenditure. The addition of 20 to 30 kcal/day over a number of years can lead to significant weight gain.

## Classification

- Weight classes are based on body mass index (BMI) as shown in Table 36.1.

## Patient Assessment

- Patient assessment should include calculation of BMI (a measure of weight in relation to height) and waist circumference. The formula for BMI is shown in Table 36.1.
- Fat distribution in the abdominal region has been linked to many of the metabolic consequences of obesity (e.g., hypertension, hypercholesterolemia, insulin sensitivity, and coronary heart disease). Waist-to-hip ratio indicates regional fat distribution. Increased health risk is seen in patients with high intra-abdominal fat (waist-to-hip ratio  $>1$  in men, or  $>0.8$  in women).

## Risk Factors

- Medications and medical conditions that can result in weight gain are shown in Table 36.2.
- Conditions that increase the risk status in overweight or obese patients are shown in Table 36.3.

## Goals of Therapy

- The goals of therapy include weight loss or weight maintenance to improve or eliminate obesity-related medical complications.
- Obese patients should strive to lose 10% of baseline weight at a rate of 2.2 to 4.4 kg/week with an energy deficit of 500 kcal/day for 6 months.
- Overweight patients should strive to lose 1.1 kg/week with an energy deficit of 300 to 500 kcal/day for 6 months.

## Treatment

- Successful weight loss involves a change in energy balance through reduced calorie intake or increased energy expenditure. Maintaining weight loss is important for long-term management of obesity and to help control diseases associated with obesity.

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\*The reader is referred to Chapter 36, Obesity, written by Maria Ballod, PharmD, in the 10th edition of *Applied Therapeutics: The Clinical Use of Drugs* for a more in-depth discussion. All notations to reference numbers are based on the reference list at the end of that chapter. The editor of this handbook expresses her thanks to Dr. Ballod and acknowledges that this chapter is based on her work.

TABLE 36.1 Body Mass Index and Guidelines for Weight Classes

Weight Status	BMI <sup>a</sup>	Obesity Class
Underweight	<18.5	
Normal	18.5–24.9	
Overweight	25.0–29.9	
Obesity	30.0–34.9	I
	35.0–39.9	II
Extreme, morbid, or severe obesity	≥40	III

<sup>a</sup>Metric conversion formula using kilograms and meters:

$$\text{BMI} = \frac{\text{Weight in kilograms}}{\text{Height in meters}^2}$$

Nonmetric conversion formula using pounds and inches:

$$\text{BMI} = \frac{\text{Weight in pounds}}{\text{Height in inches}^2} \times 703$$

BMI, body mass index.

Source: Clinical guidelines on the identification, evaluation, and treatment of overweight and obesity in adults: executive summary. Expert Panel on the Identification, Evaluation, and Treatment of Overweight in Adults. *Am J Clin Nutr*. 1998;68:899.

- Guidelines recommend a thorough assessment of the degree of obesity and risk factors, management of weight via decrease in energy intake or increase in energy expenditure, and treatment of risk factors.
- Weight-loss treatment should be initiated for patients who are overweight, who have an increased weight circumference plus two or more risk factors, or who are obese (BMI ≥ 30).

TABLE 36.2 Medications and Medical Conditions that May Cause Weight Gain

#### MEDICATIONS

$\alpha$ -Blockers and  $\beta$ -blockers (e.g., terazosin, atenolol, propranolol)  
 Antidepressants (e.g., mirtazapine, paroxetine, phenelzine, trazodone, tricyclic antidepressants)  
 Antidiabetics (e.g., insulin, sulfonylureas, thiazolidinediones)  
 Antiepileptic drugs (e.g., carbamazepine, gabapentin, pregabalin, valproic acid)  
 Antihistamines (e.g., diphenhydramine, cyproheptadine, histamine-2 blockers)  
 Antipsychotics (e.g., most typicals, clozapine, olanzapine, risperidone, quetiapine)  
 Glucocorticoids (e.g., prednisone)  
 Mood stabilizers (e.g., lithium)  
 Progestin-containing hormones (e.g., medroxyprogesterone)  
 Protease inhibitors (e.g., ritonavir, indinavir)

#### MEDICAL CONDITIONS

Chronic heart failure  
 Cushing syndrome  
 Depression (e.g., seasonal affective disorder, premenstrual dysphoric disorder)  
 Diabetes mellitus type 2  
 Hypothyroidism  
 Polycystic ovarian syndrome  
 Schizophrenia

Source: Yager J, Powers PS, eds. *Clinical Manual of Eating Disorders*. Washington, DC: American Psychiatric Publishing; 2007.

TABLE 36.3 Conditions with Increased Risk in Overweight or Obese Patients

Disease Conditions	Risk for Disease Complications, Mortality
Coronary heart disease Atherosclerotic disease Type 2 diabetes mellitus Sleep apnea Other obesity-related diseases	Very high
Gynecologic abnormalities Osteoarthritis Gallstones and complications Stress incontinence Cardiovascular risk factors	High
Cigarette smoking Hypertension Increased LDL cholesterol Low HDL cholesterol Impaired fasting blood glucose Family history of premature CHD Age (men >45, women >55 or postmenopausal) Physical inactivity High serum triglycerides	Very high if $\geq 2$ risk factors

CHD, coronary heart disease; HDL, high-density lipoprotein; LDL, low-density lipoprotein.

Source: Clinical guidelines on the identification, evaluation, and treatment of overweight and obesity in adults: executive summary. Expert Panel on the Identification, Evaluation, and Treatment of Overweight in Adults. *Am J Clin Nutr.* 1998;68:899.

- A comprehensive treatment approach includes caloric restriction, medications, physical activity, and behavior therapy. Behavior modification programs using support groups, a balanced diet, and exercise are most effective for mild obesity (20%–40% overweight).
- Medications should only be considered for patients with a BMI  $>30$  kg/m<sup>2</sup> without risk factors, or  $>27$  kg/m<sup>2</sup> with an obesity-related risk factor.
- Severe caloric restriction and rapid weight loss can be harmful.
- Surgery should only be used for morbidly obese patients (BMI  $\geq 40$  kg/m<sup>2</sup> with comorbid conditions) in whom behavioral or pharmacologic treatments have failed. For severely obese patients, reducing the size of the stomach is most effective. Delayed- or extended-release medications may not be absorbed in patients who have this surgery. Liquid formulations or other dosage forms may be needed due to changes in gastric size.

## Drug Therapy

- Medications used for the treatment of obesity are shown in Table 36.4.
- Amphetamines and sympathomimetics can be quite effective for weight loss, but they are associated with considerable risks.
- Serotonin- or norepinephrine-augmenting agents (e.g., selective-serotonin reuptake inhibitors [SSRIs]) are effective agents for suppressing appetite drive. SSRIs have been useful to reduce binge-eating; weight loss is not always seen.
- Orlistat works by reducing dietary fat absorption by inhibiting gastrointestinal (GI) lipase activity. It does not have appetite-suppressant effects, CNS effects, or systemic absorption. The most common adverse effects are GI problems (loose stools, flatus, fatty or oily stools, etc.). Absorption of fat-soluble vitamins may be impaired; supplementation may be needed.

TABLE 36.4 Medications Marketed or Used for the Treatment of Obesity<sup>a</sup>

Generic Name	Trade Name	Dosage	DEA Schedule or Class
Amphetamine and dextroamphetamine	Adderall	5–30 mg/day	II <sup>b</sup>
Benzphetamine hydrochloride	Didrex	25–50 mg one to three times daily	III
Dextroamphetamine			
Immediate release	Dexedrine	5–10 mg before meals	II <sup>b</sup>
Extended release	Dexedrine	10–30 mg	II <sup>b</sup>
Diethylpropion hydrochloride			
Immediate release	Tenuate	25 mg TID; 75 mg AM	IV
Controlled release	Tenuate Dospan	75 mg AM	IV
Methamphetamine hydrochloride			
Immediate release	Desoxyn	2.5–5 mg before meals	II <sup>b</sup>
Orlistat	Xenical, Alli	120 mg TID, 60 mg TID	Prescription, OTC
Phendimetrazine tartrate	Bontril, Prelu-2	35 mg TID; 105 mg AM	III
Phentermine Hydrochloride	Adipex-P	8 mg TID; 30–37.5 mg AM	IV

<sup>a</sup>Amphetamines are Food and Drug Administration (FDA) indicated but not recommended for the treatment of obesity.

<sup>b</sup>High abuse potential, not recommended for routine or long-term use.

BID, twice a day; DEA, Drug Enforcement Administration; OTC, over the counter; TID, three times a day.

Sources: Campfield LA et al. Strategies and potential molecular targets for obesity treatment. *Science*. 1998;280:1383;

DeWald T et al. Pharmacological and surgical treatments for obesity. *Am Heart J*. 2006;151:604.

# Adult Enteral Nutrition\*

## General Principles

- Enteral nutrition (EN) refers to the delivery of nutrition provided into the gastrointestinal (GI) tract by a tube.
- Tube feeding allows for continued use of the GI tract when one or more steps in the normal process of obtaining nutrients from oral intake are disrupted. Some digestive and absorptive function must remain for tube feeding to be a viable option.
- Table 37.1 lists the functional anatomical units of the GI tract.
- Routes of EN intervention may include modified oral diet, including oral supplements or altered consistency diets (e.g., thickened liquids, pureed foods) and EN by tube.

## Patient Assessment

- Tube feeding is the route of choice in patients with a functional GI tract in whom oral nutrient intake is contraindicated or is insufficient to meet estimated needs.
- EN may be appropriate for patients with conditions listed in Table 37.1, depending on the extent to which normal intake, transport, digestion, and absorption of nutrients is impaired. Clinical circumstances, not diagnosis, should be the determining factor for tube feeding.
- Nutrient requirements must be assessed before selecting an enteral formula (see Chapter 35).
- Medical, medication, and dietary histories should be evaluated to determine nutritional risks associated with specific conditions.

## Risk Factors

- Patients are at risk for nutrient depletion when intake is inadequate to meet nutritional requirements for 5 to 7 days or when weight loss exceeds 10% of preillness weight within a 6-month period.

## Treatment

- The type of tube placement and site of formula delivery are determined by the anticipated duration of tube feeding, disrupted region or process in the GI tract, and the risk of aspiration. Figure 37.1 illustrates the nasogastric and enterostomy feeding sites. Feeding ostomies are generally reserved for long-term EN (i.e., 4 weeks to several months).
- Formula delivery into the stomach is preferred when feasible because it is the most physiologically normal feeding site. Transpyloric feeding into the duodenum or jejunum may be appropriate when gastric dysfunction or disease is present, when gastric emptying is impaired, when pancreatic stimulation should be avoided, or when risk of aspiration is high.
- The feeding route, formula selected, and anticipated duration of feeding influence the administration regimen.

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\*The reader is referred to Chapter 37, Adult Enteral Nutrition, written by Carol J. Rollins, PharmD, MS, RD, BCNSP, and Jennifer H. Baggs, PharmD, BCPS, in the 10th edition of *Applied Therapeutics: The Clinical Use of Drugs* for a more in-depth discussion. All notations to reference numbers are based on the reference list at the end of that chapter. The editor of this handbook expresses her thanks to Drs. Rollins and Baggs and acknowledges that this chapter is based on their work.

TABLE 37.1 Functional Units of the Gastrointestinal Tract

Functional Unit	Major Steps	Conditions/Diseases Disrupting Function
Mouth and oropharynx	Chew and lubricate food; swallow; taste	Amyotrophic lateral sclerosis, muscular dystrophy, severe RA, CVA, end-stage Parkinson disease, paralysis, coma. Anorexia due to other disease: cardiac or cancer cachexia, renal failure and uremia, liver failure, neurologic disease
Esophagus	Transport food to the stomach	Esophageal ulcer, cancer, obstruction, or fistula; esophagectomy; CVA
Stomach	Hold food for mixing and grinding; add acid and enzymes; release chyme to small bowel; osmoregulation	Severe gastritis or ulceration, gastroparesis, gastric outlet obstruction, gastric cancer, severe gastroesophageal reflux
Duodenum	Osmoregulation; neutralize stomach acid	Severe duodenal ulcer or fistula; cancer: gastric or pancreatic; surgical resection or bypass of the duodenum: Whipple-type procedures
Small bowel: jejunum and ileum	Digestion; absorption	Enterocutaneous fistula, severe enteric infection, malnutrition, malabsorption, Crohn's disease, celiac disease, ileus and dysmotility syndrome
Pancreas	Secretion of digestive enzymes	Pancreatitis, pancreatic cancer, pancreatic injury, pancreatic fistula
Colon	Absorb fluid; ferment soluble fiber and unabsorbed carbohydrate; absorb water	Ulcerative colitis, Crohn's disease, colon cancer, colocolic fistula, colovaginal fistula, diverticulitis, colitis of any etiology, colon surgery

CVA, cerebrovascular accident; RA, rheumatoid arthritis.

- Four basic schedules for formula delivery are available. Patients are typically started on continuous feedings and then transition to intermittent feedings.
  - **Continuous Infusion:** provides formula at a continuous rate for 18 to 24 hours/day and can be used with any route of feeding. The slower infusion rate may be better tolerated by patients.

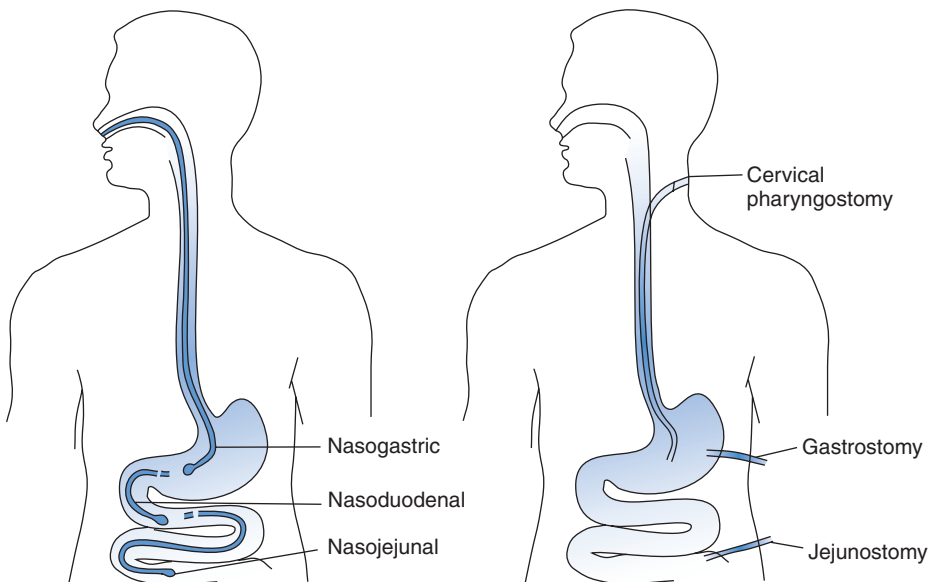


Figure 37.1 Nasoenteric and enterostomy feeding sites.



- **Cyclic Infusion:** provides formula at a continuous rate for <24 hours daily. This method is most commonly used for patients who require supplemental nutrition rather than total EN. Infusions are typically given at night for 8 to 12 hours.
- **Intermittent Infusion:** provides 3 to 8 feedings daily given over 30 to 60 minutes
- **Bolus Delivery:** provides 3 to 8 feedings daily given over 15 minutes
- **Monitoring.** Appropriate monitoring of patients receiving EN is essential to recognize and prevent complications. Table 37.2 shows the types of complications (mechanical, GI, metabolic).

TABLE 37.2 Complications of Tube Feeding

Complication	Cause/Contributing Factor	Treatment/Prevention
<b>MECHANICAL COMPLICATIONS</b>		
Aspiration	Deflated tracheostomy cuff	Inflate tracheostomy cuff before feeding; keep inflated 1 hour after feeding; consider small-bore feeding tube placed past the ligament of Treitz.
	Displaced feeding tube	Reinsert tube, check placement; consider hand restraints or feeding tube bridle.
	Reduced gastric emptying	Check residuals every 4–6 hours for gastric tube; raise head of bed 30–45 degrees; use lower-fat formula; use prokinetic medication; use small bowel feeding tube.
	Lack of gag reflex; coma	Place feeding tube into jejunum; keep head of bed elevated to 45 degrees; provide continuous feeding.
Nasal or pharyngeal irritation or necrosis; esophageal erosion; otitis media	Large-bore, polyvinyl chloride tube for long periods of time	Reposition tube daily, change tape; use smaller-bore tube; position tube to avoid pressure on tissues; moisten mouth and nose several times daily.
Tube obstruction	Poorly crushed medications	Crush medications thoroughly, dissolve in water; use liquid medications whenever possible; check compatibility of medication with tube and formula.
	Inadequate flushing after medications or thick formula	Flush tube with 50–150 mL water after medications or thick formula and every 4–6 hours with 20 mL minimum.
	Poorly dissolved or mixed formula	Use blender to mix powdered formula (check manufacturer's mixing guidelines); use ready-to-use formula.
	Formula mixed with low pH substance	Avoid checking gastric residuals when safe to do so; use larger-diameter tubes when checking residuals; avoid administering acidic medications through small-diameter tubes; consider a nonacidic therapeutic alternative; flush with a minimum of 30 mL water before and immediately after medication administration.
<b>GASTROINTESTINAL COMPLICATIONS</b>		
Nausea, vomiting, distension, cramping	Too rapid administration	Slow administration rate; change bolus to intermittent infusion.
	Osmolarity too high; intolerance to volume of formula	Change hypertonic formula to isotonic formula; increase the number of bolus or intermittent feedings so the volume per feeding is reduced or change to continuous infusion; change to a more calorically dense formula if volume is the major problem. (Osmolarity will likely increase with higher caloric density.)

Continued on following page

TABLE 37.2 Complications of Tube Feeding (Continued)

Complication	Cause/Contributing Factor	Treatment/Prevention
<b>GASTROINTESTINAL COMPLICATIONS</b>		
	Gastric retention; poor GI motility	Place feeding tube distal to the pylorus; consider a promotility agent, such as metoclopramide; evaluate medications and change those possibly contributing to gastric dysmotility, if possible.
Dumping syndrome (weakness, diaphoresis, palpitations)	Hyperosmolar load bolused or infused rapidly into the small bowel	Do not bolus into the small bowel; temporarily decrease continuous infusion rate and gradually increase rate after symptoms subside; use an isotonic formula.
Diarrhea	Rate or volume of feeding increased too fast	Temporarily decrease continuous infusion rate or volume of intermittent or bolus feeding and gradually increase rate after symptoms subside.
	Atrophy of microvilli; malabsorption related to a disease process (e.g., pancreatitis, short bowel syndrome, Crohn's disease)	Use a oligomeric formula until absorption improves; use a relatively isotonic and advance slowly; use a formula low in long-chain fatty acids when fat is malabsorbed and/or consider pancreatic enzymes.
	Hypertonic formula	Change to a lower osmolarity formula.
	Dumping syndrome	See Dumping syndrome entry in this table.
	Rapid advancement of formula volume	Temporarily reduce rate or volume, then advance slowly; consider enteral pump for better control of administration rate.
	Lactose intolerance	Change to lactose-free formula if previously using lactose-containing formula; evaluate lactose content of medications and supplemental foods, if patient is not strict NPO.
	Contaminated formula	Hang fresh formula every 4–6 hours when using an open administration system; do not add fresh formula to volume remaining in the feeding container; change the formula container and tubing daily; follow clean/aseptic technique when working with the formula or feeding tube; minimize manipulation of the feeding tube; consider changing to a closed enteral system; avoid powdered formulas requiring reconstitution.
	Medications; antibiotics; magnesium-containing antacid; high-osmolarity liquid dosage forms	Check stool for <i>C. difficile</i> and treat if present; consider probiotic agent; administer antidiarrheal if not contraindicated; consider alternate therapy such as histamine-2 blocking agent or proton pump inhibitor; use calcium-based antacid; reduce dose or divide dose into 3–4/day, when feasible to do so; dilute medication with water before administrations; consider alternate dosage form (transdermal, IV); change to crushed tablet and use appropriate precautions to avoid tube occlusion.
Constipation	Inadequate fluid or free-water intake	Increase volume and/or frequency of tube flushes to increase fluid intake; change to a formula with lower caloric density, if possible.
	Inadequate fiber intake	Change to a formula with fiber or with a higher fiber content; administer fruit juice or bulk-forming laxative (e.g., psyllium) using caution to prevent tube occlusion.

TABLE 37.2 Complications of Tube Feeding (Continued)

## GASTROINTESTINAL COMPLICATIONS

	Fecal impaction	Administer stool softener daily using caution to prevent tube occlusion if administered via the tube.
	Poor gastric/GI motility	Encourage ambulation; consider promotility agent.
	Medications, especially narcotics and anticholinergics	Use lowest effective dose of medication and transition to an alternate medication with fewer constipating effects, if possible.

## METABOLIC COMPLICATIONS

Hyperglycemia, glycosuria (can lead to dehydration, coma, or death)	Stress response; diabetes mellitus	Monitor fingerstick glucose every 6 hours, use sliding scale insulin plus appropriate routine insulin (e.g., insulin drip in critically ill).
	High-carbohydrate formula	Change formula.
	Drug therapy (steroids)	Monitor intake and output accurately.
Excess CO <sub>2</sub> production (high RQ)	High percentage of carbohydrate calories or excess calories from any source	Reduce total calories to avoid overfeeding; consider formula with higher fat calories.
	Dilutional (fluid excess, SIADH); inadequate sodium intake; excess GI losses	Use full-strength formula or change to 1.5–2 kcal/mL formula; add salt to tube feeding (1 tsp = 2 g Na = 34 mEq); use diuretics if appropriate; replace GI losses.
Hyponatremia	Inadequate free-water intake	Use 1 kcal/mL formula; monitor intake and output accurately; temperature and weight daily; increase flush volume.
	Excess water losses (diabetes insipidus, osmotic diuresis from hyperglycemia, fever)	Correct hyperglycemia and the cause of fever or diabetes insipidus.
Hypokalemia	Medications (diuretics, anti-pseudomonas penicillins, amphotericin B)	Monitor serum potassium; give PO or IV potassium replacement PRN.
	Intracellular or extracellular shifts (insulin therapy, acidosis)	Correct underlying problem.
	Excess GI losses (NG suction, small bowel fistula, diarrhea)	Routinely provide potassium in replacement fluid.
Hyperkalemia	Potassium-sparing medications (triamterene, amiloride, spironolactone, ACE inhibitors); potassium-containing medications (penicillin G potassium)	Monitor serum potassium; change to medications without potassium-sparing effect or without potassium salts.
	Renal failure	Monitor renal function; change to formula with lower potassium content.
Hypercoagulability	Warfarin antagonism due to formula	Hold formula 1–2 hours before and after warfarin dose; monitor coagulation status; check vitamin K content and change to lower vitamin K, if appropriate (most EN formulas are not high in vitamin K)

ACE, angiotensin-converting enzyme; EN, enteral nutrition; GI, gastrointestinal; IV, intravenous; NG, nasogastric; NPO, nothing by mouth; PO, oral; PRN, as needed; RQ, respiratory quotient; SIADH, syndrome of inappropriate antidiuretic hormone secretion.

- **Medication administration** should generally be done using the oral route, if possible, unless a strict NPO status is required. Whenever possible, use of the feeding tube for medication administration should be avoided due to the potential for drug interactions and potential occlusion.

## Formula Selection

- Enteral formula selection is based on nutrient requirements, fluid restrictions, and the extent of impaired digestion and absorption.
- There are three major categories of formulas: polymeric, oligomeric, and specialized (Table 37.3).
  - **Polymeric formulas** are designed for patients with full digestive capability. They are sometimes referred to as complete formulas. Polymeric formulas can be subgrouped on the basis of lactose content; lactose-free formulas are the standard for tube-fed adults.

TABLE 37.3 Generic Groups and Subgroups of Enteral Formulas with Relative Costs<sup>a</sup>

Type of Formula	Relative Cost <sup>b</sup>	Examples
<b>POLYMERIC FORMULAS<sup>c</sup></b>		
<b>STANDARD CALORIC DENSITY, STANDARD (OR HIGH NITROGEN<sup>d</sup>) CONTENT WITH VARIED FIBER CONTENT</b>		
Fiber-free for oral supplement or tube feeding	\$	Ensure; Nutren 1.0
Low fiber (from 1 up to 9 g/1,000 kcal)	\$	Nutren Probalance <sup>d</sup>
Moderate fiber (>9 to <14 g/1,000 kcal)	\$	Ensure with fiber; Fibersource HN <sup>d</sup>
High fiber (≥14 g/1,000 kcal)	\$	Glucerna; Jevity 1.2 kcal <sup>d</sup> ; Nutren 1.0 with fiber
<b>STANDARD NITROGEN CONTENT, FIBER-FREE (OR LOW FIBER<sup>e</sup>) WITH VARIED CALORIC DENSITY</b>		
Standard caloric density (1–1.2 kcal/mL)	\$	Ensure; Nutren 1.0
Moderate density (1.5 kcal/mL)	\$	Boost Plus; Ensure Plus; Isosource 1.5 kcal <sup>e</sup> ; Nutren 1.5
Calorically dense (1.8–2 kcal/mL)	\$	Nutren 2.0
<b>STANDARD CALORIC DENSITY, FIBER-FREE WITH VARIED NITROGEN (PROTEIN) CONTENT</b>		
Low nitrogen (6%–10% of kcal as protein)	\$	Resource Breeze
Standard nitrogen (11%–16% of kcal as protein)	\$	Ensure; Nutren 1.0
High nitrogen (17%–20% of kcal as protein)	\$	Isosource HN; Osmolite 1.2 kcal
Very high nitrogen (>20% of kcal as protein)	\$\$	Boost High Protein; Promote; Replete
<b>OLIGOMERIC FORMULAS</b>		
Elemental (free amino acids) <sup>f</sup>	&&	f.a.a.; Tolerex; Vivonex T.E.N.
<b>PEPTIDE-BASED</b>		
Standard protein	&	Peptamen; Peptamen with Prebio
High protein	&	Peptamen 1.5
Very high protein (NPC:N <100:1; >20% calories as protein)	&&	Crucial; Peptamen AF; Peptamen VHP
<b>SPECIALIZED FORMULAS</b>		
<b>RENAL FAILURE</b>		
Essential amino acid enriched <sup>f</sup>	&&&&	Renalcal
Polymeric, low electrolyte (less than standard potassium, phosphorus, and magnesium)	\$\$\$\$	
• Low nitrogen		Suplena
• Standard nitrogen		Novasource Renal
• High nitrogen (for dialysis)		Nepro

Continued on following page

**TABLE 37.3 Generic Groups and Subgroups of Enteral Formulas with Relative Costs<sup>a</sup> (Continued)**

Type of Formula	Relative Cost <sup>b</sup>	Examples
Hepatic failure (high BCAA, low AAA <sup>c</sup> )	&&&&	Nutrihep
<b>STRESS OR CRITICALLY ILL</b>		
Branched-chain enriched	&&&	Nutrihep
High nitrogen plus conditionally essential nutrients	\$\$	Pivot
Immune modulating	&&	Oxepa
Pulmonary disease (standard; not IMP)	\$\$	Nutren Pulmonary; Pulmocare
Glucose control	\$\$\$\$	Diabetisource AC; Glucerna; Nutren Glytrol

<sup>a</sup>Based on average cost per 1,000 calories for equivalent formulas on University of Arizona Medical Center contract from 2008 to 2010.

<sup>b</sup>Index product is a standard caloric density, standard nitrogen content, fiber-free formula. Cost is indicated relative to an index product given a value of 1:

- \$ = same cost as index product, up to 1.5 times that cost per 1,000 calories
- \$\$ = cost is 1.6 to 2.5 times the cost of the index product per 1,000 calories
- \$\$\$ = cost is 2.6 to 3.5 times the cost of the index product per 1,000 calories
- \$\$\$\$ = cost is 3.6 to 4.5 times the cost of the index product per 1,000 calories
- & = cost is 11 to 15 times the cost of the index product per 1,000 calories
- && = cost is 16 to 20 times the cost of the index product per 1,000 calories
- &&& = cost is 20 to 24 times the cost of the index product per 1,000 calories
- &&&& = cost is 25 to 30 times the cost of the index product per 1,000 calories

<sup>c</sup>All products listed in the table are lactose-free.

<sup>d</sup>High nitrogen.

<sup>e</sup>Low fiber.

<sup>f</sup>Special order, not on formulary used for price calculations.

AAA, aromatic amino acids; BCAA, branched-chain amino acids; IMP, immune-modulating pulmonary; NPC:N, nonprotein calorie to nitrogen ratio.

- **Oligomeric formulas** are also called predigested, monomeric, or chemically defined formulas. Two subgroups exist based on their protein source (elemental or peptide-based). They are designed for patients with reduced digestive function. Those most likely to benefit from their use are patients with severe pancreatic insufficiency or short bowel syndrome.
- **Specialized formulas** are designed for specific disease states or conditions. Clinical benefits of these formulas are a subject of controversy.
- General descriptions of EN content are shown in Table 37.4. Formulas with altered protein and/or fat sources are shown in Table 37.5.

**TABLE 37.4 General Descriptions of Macronutrient Quantity in Enteral Formulas**

	Caloric Density (kcal/mL)	Free Water (%)	Nitrogen (Protein) Content		Fiber Content (g/1,000 kcal)
			(% kcal as protein)	NPC:N	
Low	<1	>85	6–10	>220:1	1–9
Standard	1–1.2	80–85	11–16	200:1–130:1	None
Moderate	1.5	75–80			>9 to <14
High	1.8–2	65–75	17–20	125:1–100:1	≥14
Very high			>20	<100:1	

NPC:N, nonprotein calorie to nitrogen ratio.

TABLE 37.5 Selected High-Protein Enteral Formulas with Altered Protein or Fat Sources<sup>a</sup>

Formula <sup>b,c</sup>	kcal/mL (mOsm/kg)	Free Water (%)	Protein g/L (% kcal)	NPC:N	Protein Source	ARG g/L <sup>d</sup>	GLN g/L <sup>d</sup>	Fat g/L (% kcal)	Fat Sources	Fat kcal as MCT (%)	Ratio of ω-6FA to ω-3FA <sup>d</sup>	Fiber g/L <sup>d</sup>
Crucial <sup>c</sup>	1.5 (490)	77	94 (25)	67:1	Hydrolyzed casein; L-arginine	15	–	67.6 (39)	MCT oil; fish oil (<2%); soybean oil; lecithin	50	1.5:1	–
f.a.a <sup>c</sup>	1.0 (850)	85	50 (20)	100:1	Crystalline amino acids	–	–	11.2 (10)	Soybean oil; MCT	25	–	–
Impact <sup>c</sup>	1.0 (375)	85	56 (22)	71:1	Sodium and calcium caseinates; L-arginine	12.5	–	28 (25)	Palm kernel oil; menhaden oil	–	1.4:1	–
Impact with Fiber <sup>c</sup>	1.0 (375)	87	56 (22)	71:1	Sodium and calcium caseinates; L-arginine	12.5	–	28 (25)	Palm kernel oil; menhaden oil	–	1.4:1	10
Impact 1.5 <sup>c</sup>	1.5 (550)	78	84 (22)	71:1	Sodium and calcium caseinates; L-arginine	18.7	–	69 (40)	MCT; palm kernel oil; menhaden oil	33	1.4:1	–
Impact Glutamine <sup>c</sup>	1.3 (630)	81	78 (24)	62:1	Whey protein hydrolysate; free amino acids; sodium caseinates; L-arginine	16.3	15	43 (30)	Palm kernel oil; menhaden oil	–	1.4:1	10
Optimental <sup>b</sup>	1.0 (540)	83.2	51 (20.5)	97:1	Soy protein hydrolysate; partially hydrolyzed sodium caseinate; L-arginine	5.5	–	28.4 (25)	Structured lipid (interesterified sardine oil [EPA, DHA] and MCT); canola oil; soy oil	NA	–	5 FOS

Continued on following page

TABLE 37.5 Selected High-Protein Enteral Formulas with Altered Protein or Fat Sources<sup>a</sup> (Continued)

Formula <sup>b,c</sup>	kcal/mL (mOsm/kg)	Free Water (%)	Protein g/L (% kcal)	NPC:N	Protein Source	ARG g/L <sup>d</sup>	GLN g/L <sup>d</sup>	Fat g/L (% kcal)	Fat Sources	Fat kcal as MCT (%)	Ratio of ω-6FA to ω-3FA <sup>d</sup>	Fiber g/L <sup>d</sup>
Osmolite 1.2 Cal <sup>b</sup>	1.2 (360)	82	55.5 (18.5)	110:1	Sodium and calcium caseinate	–	–	39 (29)	High-oleic safflower oil; canola oil; MCT oil; lecithin	20	–	–
Osmolite 1.5 <sup>b</sup>	1.5 (525)	76	62.7 (16.7)	125:1	Sodium and calcium caseinates; soy protein isolates	–	–	49 (29)	High-oleic safflower oil; canola oil; MCT oil; lecithin	20	–	–
Oxepa <sup>b</sup>	1.5 (535)	78.5	62.5 (16.7)	125:1	Sodium and calcium caseinates	–	–	93.8 (55)	Canola oil; MCT oil; sardine oil; borage oil	25	–	–
Peptamen VHP <sup>c</sup>	1.0  (270–380)	84	62.4 (25)	75:1	Hydrolyzed whey protein	–	–	39 (33)	MCT oil; soybean oil (<2%); lecithin	70	7.4:1	–
Peptamen AF <sup>c</sup>	1.2 (390)	81	75.6 (21)	76:1	Hydrolyzed whey protein	–	–	54.8 (39)	MCT oil; soybean oil (<2%); fish oil (<2%); lecithin	50	1.8:1	5.2 (FOS and other fibers)
Perative <sup>b</sup>	1.3 (460)	79	66.6 (20.5)	97:1	Partially hydrolyzed sodium caseinate; whey protein hydrolysate; L-arginine	6.5	–	37.4 (25)	Canola oil; MCT oil; corn oil	40	–	6.5 FOS

Formula <sup>b,c</sup>	kcal/mL (mOsm/kg)	Free Water (%)	Protein g/L (% kcal)	NPC:N	Protein Source	ARG g/L <sup>d</sup>	GLN g/L <sup>d</sup>	Fat g/L (% kcal)	Fat Sources	Fat kcal as MCT (%)	Ratio of ω-6FA to ω-3FA <sup>d</sup>	Fiber g/L <sup>d</sup>
Pivot 1.5 Cal <sup>b</sup>	1.5 (595)	75.9	93.8 (25)	75:1	Partially hydrolyzed sodium caseinate; whey protein hydrolysate	13	6.5	50.8 (30)	Structured lipid (interesterified sardine oil [EPA, DHA] and MCT); soy oil; canola oil	20	–	7.5 FOS

<sup>a</sup>Changes periodically occur in nutrient sources and content; use this table as a general reference only and not for specific patient care issues.

<sup>b</sup>Abbott (Ross) product.

<sup>c</sup>Nestle product.

<sup>d</sup>None or unknown indicated by “–.”

AE, advanced formula; ARG, arginine; DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid; FOS, fructo-oligosaccharides; GLN, glutamine; MCT, medium-chain triglycerides; NPC:N, non-protein calorie to nitrogen; ω-3FA, ω-3 fatty acids; ω-6FA, ω-6 fatty acids; VHP, very high protein.



- **Caloric density** influences the volume of formula needed to meet nutrient requirements. Standard caloric density is 1 to 1.2 kcal/mL. Increasing caloric density increases osmolality, which can reduce gastric emptying. Risk of dehydration increases with increasing caloric density.
- **Protein Content.** Protein needs increase disproportionately to caloric needs during injury and critical illness. High-nitrogen enteral formulas are designed for patients with an increased protein requirement without a proportional increase in caloric needs. Very high-nitrogen formulas (e.g., NPN:N under 100:1) are intended for critically ill patients or those with large wounds to heal.
- **Fiber Content.** Enteral formula may contain insoluble or soluble fiber, or both. Insoluble fiber is associated with changes in fecal bulk and transit time. Soluble fiber is responsible for effects on cholesterol and glycemic control. Fiber-containing formulas often require a pump for administration due to increased viscosity. Formulas marketed for critical illness are typically fiber-free.

# Adult Parenteral Nutrition\*

## General Principles

- Parenteral nutrition is the provision of complex mixtures of nutrients by IV administration to patients who cannot eat or ingest nutrients by the gastrointestinal (GI) tract.

## Patient Assessment

- Assessment of nutritional status requires evaluation of multiple factors (see Chapter 35).
- Assessment of weight loss should include evaluation of hydration status.

## Risk Factors

- Parenteral nutrition should be considered when the patient's nutrient intake has been inadequate for 7 days or longer and the GI tract is not functioning.

## Treatment

- Peripheral or central veins can be used for parenteral nutrition depending on the anticipated duration of therapy, nutrient requirements, and availability of venous access.
  - **Peripheral administration** is considered when parenteral nutrition is expected to be needed for <10 days and when the patient has fairly low energy and protein needs. Candidates must have good peripheral venous access and must be able to tolerate large volumes of fluids.
  - **Central administration** is preferred for patients whose GI tracts are nonfunctional or should be at rest for >7 days, who have limited peripheral venous access or who have energy and protein needs that cannot be met with peripheral nutrient formulations.
- Cycling refers to infusing parenteral nutrition for <24 hours daily, providing some time free from therapy. It is usually done gradually and depends on the patient's ability to tolerate changes in fluid and dextrose intake.
- Protein goals are estimated based on weight, degree of stress, and disease state. Typically dextrose should account for 60% to 70% of nonprotein calories, and lipids account for the remaining 30% to 40% of nonprotein calories.
- **Monitoring** for adequacy of nutrition and potential complications is needed. Metabolic complications include hypokalemia, hypomagnesemia, hypophosphatemia, and hyperglycemia. Routine monitoring parameters are shown in Table 38.1.
- **Refeeding syndrome** refers to the severe hypophosphatemia and associated metabolic complications that can occur when malnourished patients without nutrition for >5 days receive a concentrated source of calories via parenteral or enteral nutrition. To minimize the risk of refeeding syndrome, all electrolyte abnormalities must be corrected before any nutrition is initiated. Nutrition should then be administered slowly.

\*The reader is referred to Chapter 38, Adult Parenteral Nutrition, written by Jane M. Gervasio, PharmD, BCNSP, FCCP, and Jennifer L. Ash, PharmD, BCNSP, in the 10th edition of *Applied Therapeutics: The Clinical Use of Drugs* for a more in-depth discussion. All notations to reference numbers are based on the reference list at the end of that chapter. The editor of this handbook expresses her thanks to Drs. Gervasio and Ash and acknowledges that this chapter is based on their work.

TABLE 38.1 Routine Monitoring Parameters for Parenteral Nutrition

## BEFORE INITIATING THERAPY

Body weight  
 Serum electrolytes (Na, K, Cl,  $\text{HCO}_3^-$ , BUN, creatinine)  
 Glucose  
 Ca, Mg, P  
 Albumin, transthyretin  
 Triglycerides  
 CBC  
 Liver-Associated tests (AST, ALT, alkaline phosphatase, bilirubin)  
 INR, prothrombin time

## DAILY

Body weight  
 Vital signs (pulse, respirations, temperature)  
 Fluid intake  
 Nutritional intake  
 Output (urine, other losses)  
 Serum electrolytes (Na, K, Cl,  $\text{HCO}_3^-$ , BUN, creatinine)  
 Glucose

## TWO OR THREE TIMES A WEEK

CBC  
 Ca, Mg, P

## WEEKLY

Albumin, transthyretin  
 Liver-associated tests (AST, ALT, alkaline phosphatase, bilirubin)  
 INR, prothrombin time  
 Nitrogen balance

ALT, alanine aminotransferase; AST, aspartate aminotransferase; BUN, blood urea nitrogen; Ca, calcium; CBC, complete blood count; Cl, chloride;  $\text{HCO}_3^-$ , bicarbonate; INR, international normalized ratio; K, potassium; Mg, magnesium; Na, sodium; P, phosphorus.

## Parenteral Nutrient Formulations

- Parenteral nutrient formulations are complex mixtures containing carbohydrate, protein, lipid, water, electrolytes, vitamins, and trace minerals.
- Three macronutrients are used in parenteral nutrient formulations: carbohydrates, lipids (fats), and protein. Their caloric density is shown in Table 38.2.
  - **Carbohydrates:** Dextrose in water is the most common carbohydrate for IV use. Glycerol is a sugar alcohol that is an option for peripheral parenteral nutrition.
  - **Lipids** for IV use are supplied as emulsions of either soybean oil or a 50:50 mixture of soybean and safflower oils. The 30% lipid emulsion is used solely for compounding formulations; it should not be used for IV piggyback administration. Lipids are needed to prevent deficiency of essential fatty acids (linoleic and  $\alpha$ -linoleic acids) that cannot be synthesized by humans.
  - **Proteins** for parenteral use are available as synthetic amino acids. They serve as the source of nitrogen, with 1 g of protein equivalent to 1 g of amino acids.
- Micronutrients are electrolytes (Table 38.3), vitamins (Table 38.4), and trace minerals (Table 38.5) needed for metabolism.
- Specially designed amino acid products that contain increased amounts of branched-chain amino acids and reduced amounts of aromatic amino acids are available for patients with hepatic failure (Table 38.6).

TABLE 38.2 Caloric Density of Intravenous Nutrients

Nutrient	kcal/g	kcal/mL
<b>AMINO ACIDS</b>	4	
Amino acids 5%		0.2
Amino acids 10%		0.4
<b>DEXTROSE</b>	3.4	
Dextrose 10%		0.34
Dextrose 50%		1.7
Dextrose 70%		2.38
<b>FAT</b>	9	
Fat emulsion 10%		1.1
Fat emulsion 20%		2
Fat emulsion 30%		3
<b>GLYCEROL</b>	4.3	
Glycerol 3%		0.129
MEDIUM-CHAIN TRIGLYCERIDES	8.3	

TABLE 38.3 Guidelines for Daily Electrolyte Requirements

Electrolyte	Amount
Sodium	80–100 mEq
Potassium	60–80 mEq
Chloride	50–100 mEq <sup>a</sup>
Acetate	50–100 mEq <sup>a</sup>
Magnesium	8–20 mEq
Calcium	10–15 mEq
Phosphorus (phosphate)	20–40 mmol

<sup>a</sup>As needed to maintain acid–base balance.

TABLE 38.4 Recommended Adult Daily Doses of Parenteral Vitamins

Vitamins	Dose
<b>FAT-SOLUBLE VITAMINS</b>	
A	3,300 international units (990 retinol equivalents)
D	200 international units (5 mg cholecalciferol)
E	10 international units (6.7 mg/dL- $\alpha$ -tocopherol)
K	150 mcg
<b>WATER-SOLUBLE VITAMINS</b>	
Thiamine (B <sub>1</sub> )	6 mg
Riboflavin (B <sub>2</sub> )	3.6 mg
Niacin (B <sub>3</sub> )	40 mg
Pyridoxine (B <sub>6</sub> )	6 mg
Cyanocobalamin (B <sub>12</sub> )	5 mcg
Folic acid	600 mcg
Pantothenic acid	15 mg
Biotin	60 mcg
Ascorbic acid (C)	200 mg

TABLE 38.5 Recommended Daily Adult Doses of Parenteral Trace Elements

Trace Element	Dose (July 2012 ASPEN Recommendations)
Chromium	1 mcg
Copper	0.3–0.5 mg
Manganese	55 mcg
Selenium	60–100 mcg
Zinc	2.5–5 mg

TABLE 38.6 Amino Acid Product Comparison

Description	Product Name	Available Concentrations (%)
<b>STANDARD FORMULATIONS</b>		
Contain essential <sup>a</sup> and nonessential <sup>b</sup> amino acids, some available with electrolytes <sup>c</sup>	Aminosyn	3.5, <sup>c</sup> 5, 7, <sup>c</sup> 8.5, <sup>c</sup> 10, <sup>c</sup> 15
	Aminosyn II	3, 8.5, 10
	FreAmine III	15
	Novamine	20
	ProSol	3.5, <sup>c</sup> 5.5, <sup>c</sup> 8.5, <sup>c</sup> 10
	Travasol	
<b>HEPATIC FAILURE FORMULATIONS</b>		
Contain essential and nonessential amino acids with a proportion of branched-chain amino acids (leucine, isoleucine, valine)	HepatAmine	8
	HepAtasol	8
<b>RENAL FAILURE FORMULATIONS</b>		
Contain primarily essential amino acids; RenAmin also contains a complement of nonessential amino acids	Aminess	5.2
	Aminosyn-RF	5.2
	NephrAmine	5.4
	RenAmin	6.5
<b>STRESS FORMULATIONS</b>		
Contain percentages of leucine, isoleucine, and valine, as well as all essential and nonessential amino acids	Aminosyn HBC	7
	FreAmine HBC	6.9
<b>SUPPLEMENTS</b>		
Contain only branched-chain amino acids (isoleucine, leucine, valine); must be used with a general formulation	BranchAmin	4

<sup>a</sup>Essential amino acids: isoleucine, leucine, lysine, methionine, phenylalanine, thionine, tryptophan, valine, histidine.

<sup>b</sup>Nonessential amino acids: cysteine, arginine, alanine, proline, glycine, glutamine, aspartate serine, tyrosine.

<sup>c</sup>These concentrations are available with or without electrolytes.

Sources: Zerr KJ et al. Glucose control lowers the risk of wound infection in diabetics after open heart operations.

*Ann Thorac Surg.* 1997;63:356; Rose BD. *Clinical Physiology of Acid-Base and Electrolyte Disorders.* 4th ed. New York, NY: McGraw-Hill; 1994:891.

# Dermatotherapy and Drug-Induced Skin Disorders\*

## General Principles

- Skin is the largest organ of the body, accounting for 17% of a person's body weight. Its major function is to protect underlying structures from trauma, temperature variations, harmful penetrations, moisture, humidity, radiation, and invasion of microorganisms.
- The three layers of skin are epidermis (outermost layer that serves as a physical barrier), dermis (protects the body from mechanical injury and supports dermal appendages), and subcutaneous layer (supports other skin layers and serves as fat storage area).

## Dermatologic Drug Delivery Systems

- Drugs can be applied topically through various delivery systems (Table 39.1). Solutions used for wet dressings or drying weeping lesions are shown in Table 39.2 and commercially available emulsion bases are shown in Table 39.3.
- Drug absorption through the epidermis is enhanced by epidermal or stratum corneum injury, increased temperature, skin hydration, dermal circulation, and drug concentration.
- The amount of topical medication needed for various dosage regimens is shown in Table 39.4.
- Appropriate dermatologic vehicle selection is based on lesion type (Table 39.5):
  - **Acute lesions** are characterized by vesiculation (blisters), erythema, swelling, warmth, pruritus, oozing, or weeping. Aqueous vehicles (solutions) should be used until the lesion becomes dry, and then solutions, lotions, powders, sprays, or aerosols should be considered.
  - **Subacute lesions** are characterized by decreased vesiculation and oozing and are often covered with crusts. They may benefit from short-course aqueous vehicles before switching to creams or gels.
  - **Chronic lesions** are characterized by erythema, scaling, lichenification, dryness, and pruritus. Ointments are preferred.

## Patient Assessment and General Treatment Guidelines

- The diagnosis of dermatologic conditions is based on six primary factors.
  - **Morphology:** the pattern and look of lesions (Tables 39.6 and 39.7.)
  - **Location:** anatomical site and distribution of lesions on the body (Table 39.8).
  - **Symptoms:** both local and systemic
  - **History:** present and related conditions (Table 39.9)
  - **Patient Age:** Lesions in patients <2 or >65 years of age may indicate systemic disease and should be evaluated by a physician.
  - **Patient Gender:** Varying frequencies and severity can be gender based (e.g., rosacea is more frequent in females but more severe in males).

\*The reader is referred to Chapter 39, Dermatotherapy and Drug-Induced Skin Disorders, written by Richard N. Herrier, PharmD, in the 10th edition of *Applied Therapeutics: The Clinical Use of Drugs* for a more in-depth discussion. All notations to reference numbers are based on the reference list at the end of that chapter. The editor of this handbook expresses her thanks to Dr. Herrier and acknowledges that this chapter is based on his work.

TABLE 39.1 Dermatological Drug Delivery Systems

Delivery System	Function	Comment
Aerosols	Do not require mechanical contact with skin and useful when mechanical application would cause pain	Most expensive and inefficient method for application of dermatological agents. Shake well before application; avoid eyes and inhalation. Cause skin drying; short-term use recommended
Baths	Typical therapies can be applied to large areas of the body through bathing. Useful in therapy of widespread eruptions	Bath oils (Alpha Keri, Lubriderm, Nutraderm) most useful for mild cases. Colloids (Aveeno oatmeal, <sup>a</sup> corn starch, <sup>b</sup> Linit, <sup>c</sup> Epsom salts <sup>d</sup> ) good for urticarial, pityriasis rosea, weeping eczemas
Creams	Best suited for subacute nonirritable dermatoses. Most are O/W and are intended to be rubbed in well until they vanish (vanishing cream)	Do not provide much occlusion. Most common mistake is failure to rub in fully or to use excessive amounts.
Emulsions	W/O emulsions most useful when dry skin conditions predominate; O/W emulsions similar to that for lotions	Water-soluble drugs should be dispersed in O/W emulsions and lipid-soluble drugs in W/O emulsions. Avoid hairy or intertriginous areas.
Gels	Nongreasy, nonstaining, nonocclusive, and quick drying. Useful for application to areas (face, hairy areas) where residue of a vehicle is cosmetically unacceptable	Thixotropic, becomes thinner with rubbing and usually contains propylene glycol and carboxypolyethylene. Tend to be drying
Lotions	Can lubricate, cool, or dry, depending on formulation. Useful for superficial dermatoses and conditions with inflammation and tenderness	Suspensions of powder or liquid in an aqueous vehicle. Helpful for sunburn, acute contact dermatitis, poison oak/ivy. Apply 3–4 × daily.
Ointments	Provide occlusive covering. Most useful in relieving dryness and brittleness and in treating fissures. Spread more easily than creams but greasier	Consist of drugs or water droplets suspended in a continuous phase of oleaginous material. Should not be applied to intertriginous or hairy areas because occlusiveness traps heat and moisture
Powders	Absorb moisture on the surface area. Useful in intertriginous areas to prevent friction	Useful in preventing bedsores; not to be applied to oozing lesions because of tendency to cake into granules that become difficult to remove
Solutions	Provide evaporative cooling, which causes vasoconstriction and mild antipruritic effects. Soothe and cool inflamed skin. Help dry oozing lesions, soften crusts, aid in cleaning and draining purulent wounds	Should be freshly prepared; store in closed containers and do not reuse. Soak the affected area by immersion for 15–30 minutes 3–6 × per day or apply soaked cloth for 5–10 minutes, then resoak and reapply; continue for 30 minutes and repeat several times per day.

<sup>a</sup>Aveeno colloidal oatmeal. Mix one cup with two cups cold water, then pour into 6 inches lukewarm bath water.<sup>b</sup>Linit hydrolyzed salt. Also corn starch. Mix two cups with four cups cold water, then pour into bath as above.<sup>c</sup>Epsom salts. Mix three cups magnesium sulfate in 6 inches lukewarm bath water.<sup>d</sup>To avoid concentration of solution = secondary to evaporation.

O/W, oil-in-water; W/O, water-in-oil.

- **Pruritus** is the most common cutaneous symptom. It has many causes and is associated with a variety of systemic diseases (Table 39.10). Topical antihistamines provide only mild relief and can cause allergic dermatitis. Systemic antihistamines are often used.
- **Atopic Dermatitis:** General goals of therapy are to decrease pruritus, suppress inflammation, lubricate the skin, and reduce anxiety. Nondrug recommendations and useful adjuncts are shown in Table 39.11.

TABLE 39.2 Solutions for Wet Dressings or Drying Weeping Lesions

Agent <sup>a</sup>	Strength	Preparation (H <sub>2</sub> O)	Germicidal Activity	Astringent Activity	Comments
Normal saline	0.9% NaCl	1 tsp NaCl per pint H <sub>2</sub> O	None	None	Inexpensive; easy to prepare
Aluminum acetate (Burow solution) (Domeboro packets/tablets)	5%	Dilute to 1:10–1:40 (0.5%–0.125%) One packet or tablet to a pint of water yields a 1:40 solution; two packets or tablets yields a 1:20 solution	Mild	+	
Potassium permanganate	65- and 330-mg tablets	Dilute to 1:4,000–1:16,000; 65-mg tablet to 250–1,000 mL; 330-mg tablet to 1,500–5,000 mL	Moderate	None	Stains skin, clothing
Silver nitrate	0.1%–0.5%	1 tsp of 50% stock solution to 1,000 mL will yield a 0.25% solution	Good	+	Stains; can cause pain
Acetic acid <sup>b</sup>	1%	Dilute 1 pint of standard 5% household vinegar with 5 parts H <sub>2</sub> O	Good	+	Unpleasant odor; can be irritating

<sup>a</sup>Although many substances are added to wet dressings, the cleansing and drying effect of the water is the major benefit.

<sup>b</sup>Used primarily for *Pseudomonas aeruginosa* infections.

Source: Arndt KA, Hsu JHS, eds. *Manual of Dermatologic Therapies: With Essentials of Diagnosis*. 7th ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2006.

TABLE 39.3 Commercially Available Emulsion Bases

Oil-in-Water	Water-in-Oil
Acid mantle cream	Aquaphor
Aquaphilic	Eucerin
Cetaphil	Lubriderm
Dermabase	Nivea Cream
Dermovan	Nutraderm
Hydrophilic ointment USP	Polysorb
Keri Lotion	Vanicream
Lanaphilic	Velvachol
Unibase	

Source: Adapted with permission from Arndt KA, Hsu JHS, eds. *Manual of Dermatologic Therapies: With Essentials of Diagnosis*. 7th ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2006.

TABLE 39.4 Amount of Topical Medication Needed for Various Dosage Regimens

Area Treated	Single Application (g)	BID for 1 Week (g)	BID for 1 Month (g)
Hands, head, face, anogenital area	2	28	120
On arm, anterior or posterior trunk	3	42	180
One leg	4	56	240
Entire body	30–60	420–840 g (14–28 oz)	1.8–3.6 kg (60–120 oz)

BID, twice a day.

Source: Arndt KA, Hsu JHS, eds. *Manual of Dermatologic Therapies: With Essentials of Diagnosis*. 7th ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2006.



**TABLE 39.5 Appropriate Dermatologic Vehicle Selection Across the Range of Dermatologic Lesions**

Range of Lesions	Range of Vehicles
<i>Acute inflammation:</i> Oozing, weeping, vesication, edema, pruritus	Aqueous vehicles and water, and then powder solutions, lotions, sprays, and aerosols
↓	↓
<i>Subacute inflammation:</i> Crusting, less oozing, pruritus	Creams, gels
↓	↓
<i>Chronic inflammation:</i> Lichenification, dryness, erythema, pruritus, scaling	Ointments

**TABLE 39.6 Dermatologic Lesions, Definitions, and Clinical Examples**

Name	Definition	Examples
<b>PRIMARY LESIONS</b>		
Macule	Nonpalpable, flat, change in color, <1 cm	Freckles, flat moles
Patch	Nonpalpable, flat, change in color, >1 cm	Vitiligo, café au lait spots, chloasma
Papule	Palpable, solid mass, may have change in color, <1 cm	Verrucae, noninflammatory acne (comedone), raised nevus
Nodule	Palpable, solid mass, most often below the plane of the skin, 1–2 cm	Erythema nodosum, severe acne
Tumor	Palpable, solid mass, >2 cm, most often above and below the plane of the skin	Neoplasms
Plaque	Flat, elevated, superficial papule with surface area greater than height, >1 cm	Psoriasis, seborrheic keratosis
Wheal	Superficial area of cutaneous edema, fluid not confined to cavity	Urticaria (hives), insect bite
Vesicle	Palpable, fluid-filled cavity, <1 cm, filled with serous fluid (blister)	Herpes simplex, herpes zoster, contact dermatitis
Bulla	Palpable, fluid-filled cavity, >1 cm, filled with serous fluid (blister)	Pemphigus vulgaris, second-degree burn
Pustule	Similar to vesicle, but filled with purulent fluid	Acne, impetigo, folliculitis
<b>SPECIAL PRIMARY LESIONS</b>		
Comedone	Plugged opening of sebaceous gland	Acne, blackhead, whitehead
Cyst	Palpable lesion filled with semiliquid material or fluid	Sebaceous cyst
Abscess	Accumulation of purulent material in dermis or subcutaneous layers of skin; purulent material not visible on surface of skin	
Furuncle	Inflammatory nodule involving a hair follicle, following an episode of folliculitis	Small boil
Carbuncle	A coalescence of several furuncles	Large boil
<b>SECONDARY LESIONS</b>		
Erosion	Loss of part of or all the epidermis	Ecthyma
Ulcer	Loss of epidermis and dermis	Stasis ulcer
Fissure	Linear crack from epidermis into dermis	Tinea pedis
Excoriation	Self-induced linear, traumatized area caused by intense scratching	Atopic dermatitis, extreme pruritus
Atrophy	Thinning of skin with loss of dermal tissue	Striae
Crusts	Dried residue of pus, serum, or blood from a wound, pustule, or vesicle	Impetigo, scabs
Lichenification	Thickening of epidermis, accentuated skin markings, usually induced by scratching or chronic inflammation	Atopic dermatitis, allergic contact dermatitis

TABLE 39.7 Descriptive Dermatologic Terms

Term	Characteristics	Examples
Annular	Ring shaped	Tinea
Acneiform	Acnelike	Acne vulgaris
Arcuate	Shaped like an arc	Syphilis
Circinate	Circular	Tinea
Confluent	Lesions run together	Psoriasis, tinea
Discrete	Lesions remain separate	Psoriasis, tinea
Eczematous	General term for dry, red flaky or lichenified skin without clear border	Chronic allergic contact dermatitis, atopic dermatitis
Geographic	Shaped like islands or continents; maplike	Generalized psoriasis
Grouped	Lesions clustered together	Herpes
Herpetiform	Appears like herpes simplex	Herpes simplex
Intertrigo	Irritant dermatitis in skin folds	Diaper dermatitis
Iris	Looks like a bull's eye, lesion within a lesion, target lesion	Erythema multiforme
Keratotic	Horny thickening	Psoriasis, corn, callus
Linear	Shaped in lines	Poison ivy
Multiform	More than one type or shape of lesion	Erythema multiforme
Papulosquamous	Papules with desquamation	Psoriasis
Serpiginous	Snakelike lesions	Cutaneous larva migrans
Zosteriform	Appears like herpes zoster	Herpes zoster

TABLE 39.8 Common Skin Diseases by Body Location

Location	Skin Diseases
Scalp	Seborrheic dermatitis, dandruff
Face	Acne, rosacea, seborrheic dermatitis, perioral dermatitis, impetigo, herpes simplex, atopic dermatitis
Ears	Seborrheic dermatitis
Chest or abdomen	Tinea versicolor, tinea corporis, pityriasis rosea, acne, herpes zoster
Back	Tinea versicolor, tinea corporis, pityriasis rosea
Genital area	Tinea cruris, scabies, pediculosis, condyloma acuminata (venereal warts)
Extremities	Atopic dermatitis (cubital and popliteal fossa)
Hands	Tinea manuum, scabies, primary irritant contact dermatitis, warts
Feet	Tinea pedis, contact dermatitis, onychomycosis
Generalized or localized	Primary irritant or contact dermatitis, photodermatitis

TABLE 39.9 Medical History Questions

1. When and how did the problem start?
2. How has it progressed or changed since its onset? How have the lesions changed in size, color, appearance, or severity?
3. What makes the condition worse or better?
4. What is the patient's past and present medical history? What other symptoms might indicate this is a dermatological manifestation of a systemic disease?
5. What are the patient's symptoms?
6. What kind of allergies does the patient have?
7. What makes the condition worse or better?
8. What events or happenings have occurred with the onset or worsening of the condition (e.g., increased stress, exposure to new products, recent travel, changes in climate)?
9. What have you used to treat the condition, and how have the treatments worked?
10. How did the patient use any previous therapy, and for how long did they use it?

TABLE 39.10 Systemic Diseases Associated with Pruritus

Brain abscesses
Carcinoid syndrome
Carcinoma of the breast, lung, or stomach
Central nervous system infarct
Diabetes mellitus
Gout
Hodgkin disease and other lymphomas
Hypertension
Iron-deficiency anemia
Multiple myeloma
Multiple sclerosis
Mycosis fungoides
Obstructive biliary disease
Polycythemia vera
Pregnancy (first trimester)
Thyroid disease (both hyperthyroidism and hypothyroidism)
Uremia

- **Xerosis (dry skin)** is primarily caused by dehydration of the stratum corneum. Table 39.12 gives general treatment recommendations.
- **Contact dermatitis** is most commonly caused by poison ivy (*Rhus*). It is an allergic reaction caused by sensitization to an allergic substance (urushiol oil) in the plant. Erythematous and vesicular lesions appear 12 to 48 hours after exposure and last 1 to 3 weeks. Calamine lotion 2 to 4 times daily and topical hydrocortisone are helpful. Oral steroids are indicated if lesions are severe or if eyes, genitals, mouth, or respiratory tract are involved. Other common contact sensitizers are shown in Table 39.13.
- **Drug eruptions** are not associated with age, diagnosis, or severity of illness. Descriptions of morphology of drug eruptions are shown in Table 39.14.

## Drug Therapy

- **Corticosteroids**
  - General principles of topical corticosteroid therapy are shown in Table 39.15.
  - Topical steroids are the drug of choice for inflammatory and pruritic eruptions. They are classified by potency (Table 39.15). Relative potency is determined by the ability to penetrate the skin, intrinsic activity at the receptor, and rate of clearance from the receptor.
  - Risk factors for systemic side effects must be considered (Table 39.16). Adverse reactions are influenced by potency, frequency and duration of use, anatomical site of application, and individual patient factors. Allergic reactions are rare as cortisol is an endogenous substance essential for life.

TABLE 39.11 Nondrug Recommendations for Patients with Atopic Dermatitis or Other Irritant Dermatoses

- Clothing should be soft and light. Cotton or corduroy is preferred. Wools and coarse, heavy synthetics should be avoided.
- Heat should be avoided because it often makes eczema worse. The environment should be well ventilated, cool, and low in humidity (30%–50%). Rapid changes in ambient temperature should be avoided.
- Bathing should be kept to a minimum (no longer than 5 minutes), and the patient should use a nonirritating soap (e.g., Basis soap). A colloid bath or the use of appropriate amounts of bath oil may be useful.
- The skin should be kept moist with frequent applications of emollients (e.g., Lubriderm, Nivea, Aquaphor, Eucerin, or petrolatum).
- Primary irritants such as paints, cleansers, solvents, and chemical sprays should be avoided.

TABLE 39.12 General Recommendations for Treatment of Dry Skin

1. Use room humidifiers.
2. Keep room temperature as low as comfortable to prevent sweating and water loss from the skin.
3. Keep bathing to a minimum (every 1–2 days) with warm, but not hot, water. After bathing, the patient should immediately apply an emollient (Table 39.2). When the skin is soaked for 5–10 minutes, the stratum corneum can absorb as much as six times its weight in water. Application of an emollient immediately after bathing will trap the water in the skin and reduce dryness.
4. Eliminate exposure to solvents, drying chemicals, harsh soaps, and cleaners. These substances remove oils from the skin and reduce its barrier function. As the barrier function is lost, water loss from the skin is increased up to 75 times higher than normal. Exposure to cold, dry winds will also enhance water loss.
5. Apply emollients (Table 39.2) three to six times a day, especially after bathing to help retain moisture in the skin from bathing.
6. The selection of emollients depends on the atmospheric moisture content of the region. In dry parts of the western United States where humidity is very low, water-in-oil emollients such as Lubriderm, Eucerin, or Nivea are preferred because the high oil content prevents the loss of moisture from the skin. In those areas, a general rule is to avoid products in which glycerin is one of the top four ingredients on the label because glycerin is hygroscopic and in low humidity will pull moisture out of the dermis, leading to drier, cracked skin. In areas with higher humidity such as the eastern United States, glycerin in both types of emollients pulls moisture from the atmosphere into the skin. Regardless of region, if application of an emollient appears to be ineffective, switching to a product with less glycerin and more oil may resolve the dryness.
7. If scaling is a problem, a keratolytic (Lac-Hydrin, AmLactin) or a higher-strength, urea-containing preparation (20%) may be useful.

TABLE 39.13 Morphology of Drug Eruptions

- **Acneiform eruptions.** Similar to common acne, but can be on any part of the body. Usually sudden onset, absence of comedones, uniform appearance
- **Allergic contact dermatitis.** Lesions are limited to areas that come in contact with the topical product.
- **Angioneurotic edema.** A more severe form of urticaria with giant hives penetrating more deeply into surrounding tissues
- **Atopic dermatitis.** Form of eczema that is most commonly a chronic pruritic inflammation of the epidermis and dermis
- **Drug hypersensitivity syndrome.** Severe systemic reaction associated with eosinophilia and systemic symptoms (high fever and widespread maculopapular-pustular rash)
- **Epidermal necrolysis.** Severe, life-threatening mucocutaneous and systemic reaction
- **Erythema multiforme.** Often a target lesion on extremities. May be multiple manifestations
- **Erythema nodosum.** Red, indurated, tender inflammatory nodules in pretibial region
- **Fixed drug eruptions.** Similar lesions appear at same site of body on repeat exposure
- **Maculopapular eruptions.** Scarletiform or morbilliform reactions
- **Photosensitivity eruptions.** Exaggerated sunburn-like reaction. Require presence of both drug/chemical and a light source of appropriate wavelength
  - **Photoallergic.** Alterations in drug from UV light causing formation of antigen or hapten. Requires prior exposure to the drug for sensitization
  - **Phototoxic.** Light source alters drug to a toxic form. Does not require prior exposure. May be dose related
- **Purpura.** Purplish hemorrhagic lesions on the skin
- **Stevens–Johnson syndrome.** Severe drug eruption with skin sloughing. Usually a moderate mucocutaneous and systemic reaction
- **Urticaria.** Immediate (abrupt onset) hypersensitivity reaction with itching and sharply raised, edematous, and erythematous lesions

TABLE 39.14 General Principles of Topical Corticosteroid Therapy

- Apply twice daily.
  - No greater benefit and higher cost with more frequent application
- Rub in thoroughly, preferably on moist skin (e.g., after bathing) to enhance absorption.
- Most chronic conditions (e.g., eczema) only need medium- to low-strength preparations.
  - High potency preparations >2 week risk systemic absorption and side effects.
  - Discontinue treatment gradually to reduce risk for rebound flair of topical lesions.
- Hydrocortisone or nonfluoridated products recommended for thin-skinned areas (face, groin) and flexures.
- Greater risk of side effects:
  - Children
  - Elderly
- Patients with liver failure
- Application with occlusion (use of plastic wrap)

TABLE 39.15 Topical Corticosteroid Preparations by Stoughton–Cornell Classification of Potency

Corticosteroid	Brand Name(s)	Vehicle
<b>1 (MOST POTENT) NO MORE THAN 2 WEEKS' USE</b>		
Betamethasone dipropionate	Diprolene 0.05%	Ointment, optimized vehicle
Clobetasol propionate	Temovate 0.05%	Cream, ointment, optimized vehicle
Diflorasone diacetate	Psorcon 0.05%	Ointment
Halobetasol propionate	Ultravate 0.05%	Cream, ointment
<b>2</b>		
Amcinonide	Cyclocort 0.1%	Cream, lotion, ointment
Betamethasone dipropionate	Diprolene AF 0.05%	Cream
Betamethasone dipropionate	Diprosone 0.05%	Ointment
Desoximetasone	Topicort 0.25%	Cream, ointment
Desoximetasone	Topicort 0.05%	Gel
Diflorasone diacetate	Florone, Maxiflor 0.05%	Ointment
Fluocinonide	Lidex 0.05%	Cream, ointment, gel
Halcinonide	Halog 0.1%	Cream
Mometasone furoate	Elocon 0.1%	Ointment
Triamcinolone acetonide	Kenalog 0.5%	Cream, ointment
<b>3</b>		
Amcinonide	Cyclocort 0.1%	Cream, lotion
Betamethasone	Benisone, Uticort 0.025%	Gel
Betamethasone benzoate	Topicort LP 0.05%	Cream (emollient)
Betamethasone dipropionate	Diprosone 0.05%	Cream
Betamethasone valerate	Valisone 0.1%	Ointment
Diflorasone diacetate	Florone, Maxiflor 0.05%	Cream
Fluocinonide	Cutivate 0.005%	Ointment
Fluticasone propionate	Lidex E 0.05%	Cream
Halcinonide	Halog 0.1%	Ointment
Triamcinolone acetate	Aristocort A 0.1%	Ointment
Triamcinolone acetate	Aristocort HP 0.5%	Cream
<b>4</b>		
Betamethasone benzoate	Benisone, Uticort 0.025%	Ointment
Betamethasone valerate	Valisone 0.1%	Lotion
Desoximetasone	Topicort LP 0.05%	Cream
Fluocinolone acetonide	Synalar HP 0.2%	Cream

**TABLE 39.15 Topical Corticosteroid Preparations by Stoughton–Cornell Classification of Potency (Continued)**

Corticosteroid	Brand Name(s)	Vehicle
Fluocinolone acetonide	Synalar 0.025%	Ointment
Flurandrenolide	Cordran 0.05%	Ointment
Halcinonide	Halog 0.25%	Cream
Hydrocortisone valerate <sup>a</sup>	Westcort 0.2%	Ointment
Mometasone furoate <sup>a</sup>	Elocon 0.1%	Cream
Triamcinolone acetonide	Aristocort, Kenalog 0.1%	Ointment
<b>5</b>		
Betamethasone benzoate	Benisone, Uticort 0.025%	Cream
Betamethasone dipropionate	Diprosone 0.02%	Lotion
Betamethasone valerate	Valisone 0.1%	Cream
Clocortolone	Cloderm 0.1%	Cream
Fluocinolone acetonide	Synalar 0.025%	Cream
Flurandrenolide	Cordran 0.05%	Cream
Fluticasone propionate	Cutivate 0.05%	Cream
Hydrocortisone buriyrate <sup>a</sup>	Locoid 0.1%	Cream
Hydrocortisone valerate <sup>a</sup>	Westcort 0.2%	Cream
Prednicarbate	Dermatop 0.1%	Cream
Triamcinolone acetonide	Aristocort 0.25%	Cream
<b>6</b>		
Alclometasone dipropionate	Aclovate 0.05%	Ointment
Betamethasone valerate	Valisone 0.1%	Lotion
Desonide <sup>a</sup>	Tridesilon 0.05%	Cream
Fluocinolone acetonide	Synalar 0.01%	Solution
Triamcinolone acetonide	Kenalog 0.1%	Cream, lotion
<b>7 (LEAST POTENT)</b>		
Hydrocortisone <sup>a</sup>	Generic 0.5%, 1.0%, 2.5%	Cream, ointment
Dexamethasone	Decadron 0.1%	Cream

<sup>a</sup>Nonfluorinated corticosteroid.

**TABLE 39.16 Risk Factors for Systemic Side Effects from Topical Corticosteroids**

Duration of application
Prolonged application (>3–4 weeks)
Potency of corticosteroid
Weak or moderately strong, 100 g/week without occlusion
Very potent, >45 g/week without occlusion
Application location
Thin stratum corneum results in easier penetration (eyelids, forehead, cheeks, armpits, groin, and genitals)
Age of patient
Very young children and elderly people have very thin epidermis
Manner of application
Occlusion
Presence of penetration-enhancing substances
Propylene glycol
Salicylic acid
Urea
Condition of the skin
General factors
Compromised liver function

- Activity of corticosteroids can be enhanced by use of occlusive dressings (generally increases potency by a factor of 10), addition of penetration-enhancing substances to the formulation (e.g., petrolatum, propylene glycol), and modifications of the steroid molecule. Consult the manufacturer prescribing information for Stoughton classification to determine potency.
- **Antibiotics**
  - See Table 39.17 for the spectrum of activity of topical antibiotics.
  - Currently available over-the-counter topical antibiotics (bacitracin, neomycin, and polymyxin) are ineffective for most dermatologic infections; they are indicated only for prophylaxis of skin infections.

TABLE 39.17 Spectrum of Activity of Antibiotics Available for Topical Use

**BACITRACIN**

Effective against all anaerobic cocci, most strains of streptococci, staphylococci, and pneumococci. Not effective against most gram-negative organisms

**GENTAMICIN**

Effective against most gram-negative organisms (similar to neomycin), including *Pseudomonas* and many strains of *Staphylococcus aureus*

**MUPIROCIN**

Very effective against *S. aureus* and does not interfere with wound healing. Currently, the only topical antibiotic that has been proved to be more effective than the vehicle based on US Food and Drug Administration guidelines

**GRAMICIDIN**

Effective against most gram-positive organisms. Not effective against most gram-negative organisms

**NEOMYCIN**

Effective against most gram-negative organisms (except *Pseudomonas*) and some gram-positive organisms. Group A streptococci are resistant.

**POLYMYXIN B**

Effective against most gram-negative organisms (including *Pseudomonas*). Most strains of *Proteus*, *Serratia*, and gram-positive organisms are resistant.

**RETAPAMULIN**

Effective against *Streptococcus pyogenes* and methicillin-sensitive strains of *S. aureus*

## CHAPTER 40

# Acne\*

### General Principles

- Acne is primarily an inherited disorder that involves the pilosebaceous follicles. It is caused by increased sebum production, abnormal keratinization within the pilosebaceous canal, *Propionibacterium acnes* colonization, and an immune-mediated inflammatory reaction.
- Inflammatory lesions are typically erythematous and can include
  - **Papules:** raised, solid lesions up to several millimeters in diameter
  - **Pustules:** raised, superficial, pus-filled lesions
  - **Nodules:** like papules, but larger and deeper in the skin
- Comedones (plugged follicle openings) can be closed (whiteheads) or open (blackheads).

### Classification

- Acne severity relates to the number and severity of lesions (Table 40.1). Acne conglobata is a severe form of acne that results in multiple lesions that coalesce into abscesses.

### Patient Assessment

- Acne primarily affects teenagers and young adults; females often develop acne at a younger age and have milder cases than males.
- Acne lesions generally appear on the face, but the chest, back, or upper arms may also be affected.
- A complete patient history should be taken (Table 40.2).

### Risk Factors

- Potential contributing factors to acne vulgaris are shown in Table 40.3.

### Goals of Therapy

- The goals of therapy are to relieve discomfort, improve skin appearance, prevent scarring, and minimize the psychosocial impact of the condition.

TABLE 40.1 Acne Severity

Mild	Comedones with or without a few or several pustules or papules
Moderate	Comedones, several pustules or papules, with or without a few or several nodules
Severe	Numerous or extensive pustules or papules and many nodules; can include cases with persistent nodules, extensive scarring, drainage, or formation of sinus tracts
Very severe	Acne variants such as acne conglobata or acne fulminans

Source: Rigopoulos D et al. The role of isotretinoin in acne therapy: why not as first-line therapy? Facts and controversies. *Clin Dermatol.* 2010;28:24.

\*The reader is referred to Chapter 40, Acne, written by Ellen R. DeGrasse, PharmD, BCPS, and Jamie J. Cavanaugh, PharmD, in the 10th edition of *Applied Therapeutics: The Clinical Use of Drugs* for a more in-depth discussion. All notations to reference numbers are based on the reference list at the end of that chapter. The editor of this handbook expresses her thanks to Drs. DeGrasse and Cavanaugh and acknowledges that this chapter is based on their work.



TABLE 40.2 Pertinent Historical Components to Be Obtained from a Patient with Acne

- Duration, including onset and peak severity
- Location and distribution
- Seasonal variation
- For female patients, relation to menstrual periods, pregnancy status, scalp hair thinning, contraceptive method (if used)
- Present and past treatments, topical and systemic, prescription and over-the-counter
- Family history, including severity
- Other skin disorders or medical problems
- Medications and drug allergies
- Occupational exposure to chemicals or oils
- Skin care routine; use of cosmetics, moisturizers, hairstyling products (pomades)
- Areas of skin friction or irritation

TABLE 40.3 Potential Contributing Factors to Acne Vulgaris

- Stress (in predisposed patients)<sup>20</sup>
- Late luteal phase of menstrual cycle (premenstrual exacerbations)<sup>8</sup>
- Hyperandrogenic states (e.g., polycystic ovary syndrome)<sup>1</sup>
- Oil-based cosmetics, pomades, and moisturizers (acne cosmetica)<sup>13</sup>
- Hot or humid conditions<sup>11</sup>
- Ultraviolet light<sup>19</sup>
- Environmental exposure to halogenated compounds, animal fats, dioxin, or petroleum derivatives<sup>21</sup>
- Mechanical irritation from hats, chin straps, backpacks, or shoulder pads (acne mechanica)<sup>13,22</sup>

## Treatment

- No known cure exists. Treatment is preventative and can reduce severity. After a drug regimen achieves control, treatment must continue with a maintenance regimen for months to years. Early, aggressive therapy prevents scarring and psychosocial sequelae.
- Drug therapies work by reducing sebum production (e.g., isotretinoin, hormonal therapy), normalizing follicular keratinization (e.g., retinoids, benzoyl peroxide, azelaic acid), reducing *P. acnes* (e.g., antibiotics, benzoyl peroxide, azelaic acid, isotretinoin), and reducing inflammation (e.g., antibiotics, retinoids).
- Topical therapy is preferred for mild to moderate acne. Guidelines recommend using a retinoid as monotherapy for mild acne. Moderate acne often requires combination therapy using agents with different mechanisms (e.g., topical retinoid augmented with topical or oral antibiotics). The most effective option for severe acne is oral isotretinoin.
- Pharmacotherapy works best to prevent new lesions, not to resolve current ones. Topical therapies should be applied regularly to the entire acne-prone area(s), not just to lesions. It may take weeks to months to see the full treatment effect.
- Nondrug therapy plays a minimal role in the management of acne. Twice-daily face washing with warm water and a mild facial cleanser removes excess sebum. Aggressive scrubbing and squeezing of lesions should be avoided.
- Current guidelines recommend drug therapy over light or laser therapies.
- Acne scarring is treated with microsurgical techniques, dermabrasion, laser therapy, chemical peels, and tissue augmentation.

## Drug Therapy

- **Antibiotics**
  - Antibiotics do not resolve existing lesions, but can prevent future lesions by decreasing *P. acnes* colonization and decreasing inflammation.

- **Topical Agents**
  - Advantages include avoiding systemic exposure and achieving high follicular concentrations.
  - Clindamycin and erythromycin are commonly used. Sodium sulfacetamide and dapsone gel offer other options. Topical tetracycline is no longer used.
  - Typically applied once or twice daily for 3 months
- **Oral Agents**
  - Should be paired with topical retinoids and potentially benzoyl peroxide in patients with moderate to severe acne. Should not be used as monotherapy
  - Oral therapy is preferred when lesions are widespread or in difficult-to-reach areas.
  - Frequently used agents and their doses are shown in Table 40.4. Most agents are given twice daily for a 3-month course.
- **Azelaic Acid**
  - Normalizes keratinization and reduces inflammation by suppressing *P. acnes*
  - Causes less skin irritation than other topical therapies (except antibiotics) but may be less effective; usually reserved for patient who cannot tolerate benzoyl peroxide or topical retinoids
  - Typically applied twice daily
- **Benzoyl Peroxide**
  - Works as an antibacterial and by exfoliating and opening pores through keratolytic activity
  - Often paired with antibiotics to prevent development of antibiotic resistance
  - Typically applied to affected area once or twice daily
  - Adverse effects include transient warmth or stinging, significant drying, or skin irritation. Begin therapy with products that are less drying (creams) and at a lower strength (2.5%).
- **Corticosteroids**
  - Used to pretreat patients if severe acne flaring is a concern: 1 to 2 weeks of prednisone 40 to 60 mg/day before isotretinoin therapy
  - Topical corticosteroids are ineffective for acne.
- **Hormonal Agents**
  - Work by reducing sebum production
  - Used for the treatment of moderate acne in female patients. Response can take 3 to 6 months of therapy.
- **Isotretinoin, Oral**
  - Works by all four mechanisms of action currently used to treat acne
  - Oral isotretinoin monotherapy should be used to treat severe acne unless its use is contraindicated. It is the only effective agent for severe nodular acne.
  - One or two 5-month courses will induce remission that lasts for several months or even years after therapy is stopped.
  - Initiate treatment with 20 mg twice daily (targeting 0.5 mg/kg/day); increase to 40 mg twice daily (1 mg/kg/day) after 1 month. Continue therapy until a cumulative dose of about 120 mg/kg is reached, usually about 5 months.

TABLE 40.4 Frequently Used Oral Antibiotics

Drug	Dose
Doxycycline	100 mg orally twice daily
Tetracycline	500 mg orally twice daily
Minocycline	50–100 mg orally twice daily (or 1 mg/kg/day)
Erythromycin	250–500 mg orally twice daily
Trimethoprim/sulfamethoxazole	160/800 mg orally twice daily

Source: Tan HH. Antibacterial therapy for acne: a guide to selection and use of systemic agents. *Am J Clin Dermatol.* 2003;4:307.

TABLE 40.5 Adverse Effects of Systemic Retinoids

Body System	Adverse Effect	Management
<b>COMMON, PHARMACOLOGIC</b>		
Reproductive	Teratogenicity (birth defects, premature birth, neonatal death)	Avoid pregnancy; patients should not donate blood during therapy.
Skin	Dryness, erythema, peeling, pruritus, photosensitivity	Use moisturizers, sunscreens, protective clothing; avoid skin waxing, dermabrasion, and other dermatologic procedures during and 6 months after therapy.
Hair, nails	Hair dryness, hair thinning, nail fragility	None; discontinue drug if severe.
Mucous membranes	Cheilitis, dry mouth, dry nose, nose bleeds, dry eyes, blepharconjunctivitis	Use lip balms, sugarless gum or candy, saline nasal spray, artificial tears or ophthalmic ointment; avoid contact lenses; lower dosage if severe or bothersome.
Metabolic	Elevated triglycerides, LDL; lowered HDL (rare reports of pancreatitis)	Reduce/eliminate alcohol; consume low-fat diet; consider drug discontinuation if changes are extreme.
Liver	Elevated transaminases	Monitor if elevation is mild; usually transient despite continued therapy; avoid drug in patients with previous liver dysfunction.
<b>UNCOMMON, TOXIC</b>		
CNS	Pseudo tumor cerebri, hearing loss, tinnitus	Discontinue drug if patient develops severe headache, nausea, vomiting, papilledema, visual changes (suggest pseudo tumor cerebri), or hearing changes.
Bones	Pain Bone mineral density loss (osteopenia), premature epiphyseal closure, hyperostosis	Monitor at each visit. Routine monitoring is not recommended for usual durations of therapy.
Muscle, ligaments	Pain, calcifications	Monitor; more likely in physically active patients; discontinue if severe.
Eyes	Impaired night vision, corneal opacities	Patients should use caution when driving.
Liver	Hepatitis	Discontinue drug.
Hematologic	Anemia, neutropenia, thrombocytopenia	Monitor CBC for changes necessitating drug discontinuation.
Psychiatric	Depression, suicide	Monitor for depressed mood and suicidal thoughts.

CBC, complete blood count; CNS, central nervous system; HDL, high-density lipoprotein; LDL, low-density lipoprotein.

Sources: Goldsmith LA et al. American Academy of Dermatology Consensus Conference on the safe and optimal use of isotretinoin: summary and recommendations. *J Am Acad Dermatol.* 2004;50:900; Marqueling AL, Zane LT. Depression and suicidal behavior in acne patients treated with isotretinoin: a systematic review. *Semin Cutan Med Surg.* 2007;26:210.

- All female patients of childbearing age must have two negative pregnancy tests before initiating therapy, and a negative test before each monthly refill. Patients taking isotretinoin should not donate blood.
- Baseline laboratory tests should include fractionated lipid panel, liver function panel, and complete blood count.
- Adverse effects to systemic retinoids are shown in Table 40.5.
- **Retinoids, Topical (e.g., Tretinoin, Adapalene, Tazrotene)**
  - Work by normalizing keratinization, unplugging follicles, preventing microcomedo formation, and reducing inflammation. They have no antibacterial properties.
  - Preferred therapy for mild acne with mostly noninflammatory lesions
  - Core component of combination therapies for moderate to severe acne
  - First-line therapy to maintain remission once acne is controlled
  - Typically applied twice daily
  - Adverse effects include skin irritation, peeling, erythema, and dryness. Avoid use during pregnancy.

# Psoriasis\*

## General Principles

- Psoriasis is a chronic, proliferative skin disease characterized by well-delineated, thickened, erythematous epidermis or dermal plaques covered with a distinctive silvery scale. Most patients (75%) present with symptoms before 46 years of age.
- Lesions commonly develop on the elbows, knees, scalp, gluteal cleft, fingernails, and toenails. Most patients have chronic localized disease.
- Psoriatic arthritis can occur in up to 40% of patients with psoriasis.

## Classification

- The National Psoriasis Foundation consensus statement classifies psoriasis on the basis of severity of the disease:
  - Up to 5% of body surface area (BSA) affected (candidates for topical therapy)
  - >5% BSA affected (candidates for systemic or phototherapy)

## Patient Assessment

- A thorough medical history to identify triggers for exacerbation should be done. A number of medications can exacerbate preexisting psoriasis (Table 41.1).

TABLE 41.1 Drugs Reported to Induce Psoriasis

Anesthetics	Procaine
Antimicrobial agents	Amoxicillin, ampicillin, imiquimod, penicillins, sulfonamides, terbinafine, tetracyclines, vancomycin
Anti-inflammatory drugs	Corticosteroids (after withdrawal), NSAIDs (indomethacin, salicylates)
Antimalarial agents	Chloroquine, hydroxychloroquine
Cardiovascular drugs	Acetazolamide, amiodarone, angiotensin-converting enzyme inhibitors (captopril, enalapril), $\beta$ -blockers (atenolol, metoprolol, propranolol, timolol), calcium-channel blockers (dihydropyridines, diltiazem, verapamil), clonidine, digoxin, gemfibrozil, quinidine
H <sub>2</sub> -antagonists	Cimetidine, ranitidine
Hormones	Oxandrolone, progesterone
Opioid analgesics	Morphine
Psychotropics	Lithium carbonate, valproic acid, fluoxetine, carbamazepine, olanzapine
Miscellaneous	Potassium iodide, mercury, $\alpha$ -interferon, $\beta$ -interferons, granulocyte-macrophage colony-stimulating factor (GM-CSF)

NSAIDs, nonsteroidal anti-inflammatory drugs.

Sources: Dika E et al. Drug-induced psoriasis: an evidence-based overview and the introduction of psoriatic drug eruption probability score. *Cutan Ocul Toxicol.* 2006;25:1; Basavaraj KH et al. The role of drugs in the induction and/or exacerbation of psoriasis. *Int J Dermatol.* 2010;49:1351; Facts & Comparisons eAnswers, accessed January 12, 2011, with permission.

\*The reader is referred to Chapter 41, Psoriasis, written by Katie L. Kiser, PharmD, BCPS, and Timothy J. Ives, PharmD, MPH, FCCP, BCPS, in the 10th edition of *Applied Therapeutics: The Clinical Use of Drugs* for a more in-depth discussion. All notations to reference numbers are based on the reference list at the end of that chapter. The editor of this handbook expresses her thanks to Drs. Kiser and Ives and acknowledges that this chapter is based on their work.

- Patients with psoriasis experience a reduced quality of life related to an impairment of social, psychological, and physical functioning.
- Psoriatic lesions are often asymptomatic. Pruritus, which is noted in 50% of patients, can be severe.

## Risk Factors

- Precipitating factors include cold weather, anxiety, stress, viral or bacterial infections, epidermal trauma, or medications. Environmental triggers play a major role in disease expression.

## Goals of Therapy

- The goal of therapy is to achieve complete clearing of psoriatic lesions, particularly during emotionally critical times. Treatment goals for severe psoriasis include safe and effective resolution of the disease and long-term maintenance using agents to induce immunosuppressive or remittive cellular changes.

## Treatment

- Psoriasis is a treatable disease but there is no cure. Treatment modalities are chosen on the basis of disease severity, cost, convenience, and patient response. Nonpharmacologic treatment is important (e.g., spa therapy, support groups).
- Patients with mild disease (up to 5% of BSA affected) can generally be treated with topical agents (Table 41.2). Topical corticosteroids are first-line treatment for mild psoriasis because of their prompt relief, convenience, and anti-inflammatory, immunosuppressant, and antipruritic properties. Alternative topical treatments for mild psoriasis (coal tar, anthralin, calcipotriene, and tazarotene) and phototherapy are not as convenient but do have well established efficacy for initial management.
- Patients with psoriasis covering more than 5% of BSA require more specialized systemic therapy or phototherapy (Table 41.3). Photochemotherapy, which combines psoralens with UVA light, is used to control severe, recalcitrant, disabling plaque psoriasis.
- Rotational therapy involves the use of alternating monotherapies to limit adverse effects associated with long-term use of one specific agent or the additive or synergistic interactions when multiple therapies are used.
- **Psoriatic Arthritis.** Nonsteroidal anti-inflammatory agents (NSAIDs) are used to suppress the musculoskeletal symptoms, but they do not induce remission. Methotrexate (10–25 mg weekly or 2.5–7.5 mg  $\times$  three doses every 12 hours over 24 hours [e.g., 8 AM, 8 PM, 8 AM]) may produce symptomatic benefits. TNF- $\alpha$  inhibitors have been shown to slow down or halt radiographic progression.

## Drug Therapy

### TOPICAL AGENTS (TABLE 41.2)

- **Anthralin**
  - Effective for widespread, discrete psoriatic plaques. Use has declined due to availability of more cosmetically appealing preparations.
  - Typically applied once daily
- **Calcipotriene**
  - Good for topical maintenance therapy in patients with generalized mild to moderate psoriasis; has a slower onset of action
  - Easy to apply, odorless, and nonstaining
  - Applied twice daily as a cream, ointment, or solution. A 100 g/week limit should be enforced; exceeding this limit results in negative effects on calcium and bone metabolism.
- **Coal Tar**
  - Generally considered second-line therapy due to difficulty with application, smell, staining properties, and low potency compared with other treatment options.

**TABLE 41.2 Topical Agents for the Treatment of Psoriasis (Mild to Moderate; <5% Body Surface Area Involvement)**

Treatment Modality	Advantages	Disadvantages
Emollients	Basic adjunct for all treatments; safe, inexpensive, reduces scaling, itching, and related discomfort	Provide minimal relief alone
Keratolytics (salicylic acid, urea, $\alpha$ -hydroxy acids [i.e., glycolic and lactic acids])	Reduce hyperkeratosis; enable other topical modalities to better penetrate; inexpensive	Provide minimal relief individually; nonspecific; salicylism (tinnitus, nausea, vomiting) with salicylic acid if applied extensively
Topical corticosteroids	Rapid response; control inflammation and itching; best for intertriginous areas and face; convenient, not messy; mainstay topical treatment modality for psoriasis	Temporary relief; less effective with continued use (tachyphylaxis occurs); withdrawal can produce flare-ups; atrophy, telangiectasia, and striae with continued use after skin returns to normalized state; expensive; adrenal suppression possible
Coal tar	Particularly effective for “flaky” scalp lesions; newer preparations are more cosmetically appealing; efficacy enhanced in combination with UVB (i.e., Goeckerman regimen)	Effective only for mild psoriasis or scalp psoriasis; inconvenient with difficult application; stains clothing and bedding, not skin; strong smelling; folliculitis and contact allergy (bronchospasm in atopic patient with asthma after inhalation of vapor); carcinogenicity in animals
Anthralin	Effective for widespread, refractory plaques; produces long remissions; short, concentrated programs preferred; enhanced efficacy in combination with UVB (i.e., Ingram regimen)	Purple-brown staining (skin, clothing, and bath fixtures); irritating to normal skin and flexures; careful application is required; can precipitate generalized psoriasis
Calcipotriene	As effective as topical corticosteroids, although slower onset, without long-term corticosteroid adverse effects; convenient, well tolerated	Slow onset; expensive; potential effects on bone metabolism (hypercalcemia); irritant dermatitis on face and intertriginous areas; contraindicated during pregnancy
Tazarotene	Extended response; convenient (applied once daily, in gel formulation); maintenance therapy; effective on scalp and face; used in combination with topical corticosteroids	Slow onset; local irritation and pruritus; teratogenic (adequate contraception is required)
Ultraviolet B (UVB)	Effective as maintenance therapy; eliminates problems of topical corticosteroids	Expensive; office-based therapy; sunburn (exacerbates psoriasis); photoaging; skin cancers

- Typically applied once or twice daily; avoid use on face, flexures, and genitalia.
- Tar shampoos are useful for psoriasis of the scalp.
- **Corticosteroids**
  - More potent corticosteroids are frequently needed, often with occlusion.
  - Intermittent or pulse therapy with several weeks between successive courses may provide the best long-term results and minimize tachyphylaxis and adverse effects. Continuous use for more than 3 to 4 weeks is discouraged.
  - Systemic corticosteroids should not be used for the treatment of psoriasis.
  - Flare-ups of pustular psoriasis can be precipitated by withdrawal from systemic corticosteroids or high-potency topical corticosteroids applied with occlusion.
- **Tazarotene**
  - A topical, synthetic retinoid that works slowly but has sustained effects after treatment is discontinued.
  - Applied once daily
  - Contraindicated in pregnancy as it is Category X; use of adequate contraception is essential.

**SYSTEMIC AGENTS (TABLE 41.3)**

- **Acitretin**
  - Second-generation systemic retinoid used for recalcitrant psoriatic disease
  - Teratogenic and accumulates in fatty tissues; strict contraception during treatment and for 2 to 3 years afterward is recommended. Patients should be advised not to donate blood during and for 1 year after therapy.
- **Cyclosporine**
  - Used in low doses (2.5–6 mg/kg) given in one to two divided doses
- **Immunomodulators**
  - Target immune-mediated mechanism of psoriasis
  - Options include T-cell agents (alefacept, efalizumab) and TNF- $\alpha$  inhibitors (infliximab, etanercept, adalimumab, golimumab, ustekinumab)
  - Use limited by adverse effects, monitoring requirements, and toxicity. There is a lack of evidence that they modify the long-term disease process.

**TABLE 41.3 Agents for the Treatment of Severe Psoriasis (>5% Body Surface Area Involvement)**

Treatment Modality	Advantages	Disadvantages
UVA and psoralen (PUVA)	80% efficacy; “suntan” effect is cosmetically desirable	Time-consuming; expensive, office-based therapy (restrictive); sunburn (exacerbates psoriasis); photoaging; both nonmelanoma skin cancer and melanoma; contraindicated during pregnancy and lactation
Acitretin	Not as effective as other systemic agents; efficacy enhanced if given with PUVA or UVB (i.e., RePUVA or ReUVB); less hepatotoxic than methotrexate	Teratogenic (contraception required); contraindicated with liver or renal dysfunction, drug or alcohol abuse, hypertriglyceridemia, hypervitaminosis A
Methotrexate	Effective for both skin lesions and arthritis, as well as psoriatic nail disease	Hepatotoxicity (liver biopsy may be indicated); bone marrow toxicity; folic acid protects against stomatitis (but not against hepatic or pulmonary toxicity); drug interactions; contraindicated during pregnancy and lactation, drug or alcohol abuse; use with caution during acute infections.
Cyclosporine	Toxicities and short-lived remissions; used in patients with extensive disease who are unresponsive to other agents; however, given changing pathophysiology and increasing experience at lower dosages, increasing role in rotational therapy to induce remissions	Renal impairment; suppressive therapy (relapse occurs when discontinued); increased risk of skin cancer, lymphomas, and solid tumors; phototoxic; contraindicated during pregnancy and lactation, and with hypertension, hyperuricemia, hyperkalemia, acute infections
Immunomodulators (alefacept, efalizumab, etanercept, infliximab, adalimumab, golimumab)	Specific, targeted therapy; effective for both moderate to severe skin lesions and arthritis; maintains remission	Expensive; parenteral therapy (often administered in an office-based practice) therapy; long-term safety unknown; increased risk of serious infections

PUVA, psoralens plus ultraviolet A light; RePUVA, retinoid-PUVA; UVA, ultraviolet A; UVB, ultraviolet B.

- **Methotrexate**
  - Effective for skin lesions and psoriatic arthritis
  - Consensus guidelines recommend risk stratification for liver biopsies in all patients with psoriasis at baseline and at intervals of approximately 1 to 1.5 g of cumulative methotrexate dose. Concomitant use with alcohol is a potent hepatotoxic combination.

### PHOTOTHERAPY

- Ultraviolet (UV) light produces comparatively long remissions and is relatively nontoxic. The usual time to induce clearing of lesions is approximately 4 to 6 weeks.
- UVA penetrates the skin more deeply than UVB.
  - UVA and psoralen (PUVA) is used for severe psoriasis (Table 41.3). Measures should be taken to reduce toxicity of UVA light therapy (Table 41.4).
  - UVB is used for maintenance therapy for mild to moderate psoriasis (Table 41.2). Treatments are given three times weekly; pretreatment emollients should not be used.

TABLE 41.4 Guidelines for Isotretinoin Use in Acne

#### PATIENT SELECTION

Severe cystic acne  
 Moderate acne but resistant to combination conventional therapies  
 Usually severe acne variants (conglobate, fulminans)

#### DOSAGE

0.5–1 mg/kg/day  
 Use higher dosage in young patients, male patients, those with severe acne, patients with acne involving the trunk

#### DURATION OF THERAPY

Cumulative dose of 120 mg/kg (usually 3–7 months)

#### RELAPSE RATE

Repeat courses required in 15%–20% of patients  
 Retreatment usually safe and effective  
 Very rarely, patients may require 3–5 courses.



# Photosensitivity, Photoaging, and Burn Injuries\*

## General Principles

- Ultraviolet radiation (UVR) has been linked to many diseases, including malignant melanoma and cataracts. It is divided into four categories on the basis of wavelength: UVA<sub>1</sub>, UVA<sub>2</sub>, UVB, and UVC. UVB is the most erythemogenic and melanogenic.
- The UV index, with a scale of 1 (*low exposure*) to 11+ (*extremely high exposure*), forecasts the probable intensity of skin-damaging UVR expected to reach the surface at noon when the sun is at its highest position. The amount of UVR is influenced by elevation, clouds, and the amount of ozone in the stratosphere.
- Excessive exposure of the skin to UVR results in an inflammatory erythematous reaction. Patients can be classified into six sun-reactive skin types on the basis of their response to initial sun exposure, skin color, tendency to sunburn, ability to tan, and personal history of sunburn (Table 42.1).
- Drug-induced photosensitivity can be subdivided into phototoxic and photoallergic reactions.

## Patient Assessment

- Patient assessment should include determination of the patient's skin type (Table 42.1). People with blond, red, or light brown hair or blue or green eyes tend to have greater skin reactivity to sunlight than do people with darker colored hair or eyes.
- **Sunburn** is a self-limiting condition. Medical care should be sought when a sunburn is accompanied by constitutional symptoms (fever, chills, nausea, vomiting), when infection is present, or when there is a second- or third-degree burn.
- **Phototoxicity** usually has a rapid onset (often within several hours after UVR exposure) and presents as exaggerated or intensified sunburn with erythema, pain, prickling, or burning on UVR-exposed areas.
- **Photoallergy** is when a medication or chemical agent is altered in the presence of UVR to become antigenic or to become a hapten. It produces an intensely pruritic, eczematous form of dermatitis.

TABLE 42.1 Suggested SPF for Various Skin Types

Complexion	Skin Type	Skin Characteristics	Suggested Product SPF
Very fair	I	Always burns easily; never tans	20–30
Fair	II	Always burns easily; tans minimally	15–20
Light	III	Burns moderately; tans gradually	10–15
Medium	IV	Burns minimally; always tans well	8–10
Dark	V	Rarely burns; tans profusely	8
Very dark	VI	Never burns; deeply pigmented	8

SPF, sun protection factor.

\*The reader is referred to Chapter 42, Photosensitivity, Photoaging, and Burn Injuries, written by Katherine R. Gerrald, PharmD, BCPS, and Timothy J. Ives, PharmD, MPH, FCCP, BCPS, in the 10th edition of *Applied Therapeutics: The Clinical Use of Drugs* for a more in-depth discussion. All notations to reference numbers are based on the reference list at the end of that chapter. The editor of this handbook expresses her thanks to Drs. Gerrald and Ives and acknowledges that this chapter is based on their work.

- **Photoaging** is photodamaged skin that is characterized by being wrinkled, yellowed, and sagging.
- **Burn injuries** are classified by the depth of the tissue damage. Severity is proportional to the percentage of body surface area (BSA) involved and the wound depth.
  - **First-Degree Burn:** a superficial thickness burn that does not form blisters and heals within 3 to 4 days without scarring (e.g., mild sunburn)
  - **Second-Degree Burn:** partial-thickness to superficial burn that involves the epidermis and the upper layer of the dermis. The burn may be erythematous, blistered, weeping, painful, and very sensitive to stimuli.
  - **Third-Degree Burn:** partial-thickness to deep burn that entails complete destruction of the full thickness of the skin, including all skin elements.
  - **Fourth-Degree Burn:** full-thickness burn that is similar to a third-degree burn but also extends into the subcutaneous tissue, fascia, and bone.

## Risk Factors

- Risks for development of long-term effects of UVR include congenital pigmentation (skin type, hair color, and eye color), excessive sun exposure (especially in early childhood), history of frequent sunburn or intermittent high-intensity exposures, a large number of moles, and positive family history.

## Goals of Therapy

- Goals for first- and second-degree burns are to relieve pain, to prevent desiccation and deepening of the wound and infection, and to provide a protective environment for healing.

## Treatment

- Appropriate use of sunscreens or other photoprotective behaviors (e.g., protective clothing, sunglasses) can help mitigate the incidence of adverse effects from UVR. Although sunscreens are widely used to prevent sunburn and prevent premature aging, clothing and avoiding direct sunlight offer the best protection. Sunscreens and their UVR absorption are shown in Table 42.2.
- **Sunburn:** Prevention through the use of sunscreen or other photoprotection (clothing, sunglasses) is important. Sun protection in early childhood is essential as most of a person's lifetime sun exposure occurs in childhood and the harmful effects of UVR are cumulative. Protective clothing is rated by the ultraviolet protection factor (UPF; Table 42.3). Treatment of sunburn includes symptom management with oral (e.g., ibuprofen, aspirin) or topical (e.g., camphor, menthol) analgesics, topical anti-inflammatory agents (e.g., hydrocortisone cream, aloe vera gel), or cooling compresses. Topical anesthetics (e.g., benzocaine, lidocaine) provide only transient analgesia for up to 45 minutes.
- **Phototoxicity/Photoallergy:** General management includes removal of exposure to the potential photosensitizer and reduced exposure to the sun.
- **Photoaging:** Topical retinoid therapy for patients 50 to 70 years of age with moderate to severe photoaging may partially reverse some of the clinical and histological changes seen.
- **Burn Injuries:** Most burn injuries are minor and can be managed in the ambulatory setting. Major second- and third-degree burns should be immediately triaged to a health system with a multidisciplinary team that can manage potential complications (e.g., fluid loss, infection, inhalation injury). Three treatment categories for burn injuries are recommended by the American Burn Association (Table 42.4). Criteria for when a patient should be transferred to a burn center are shown in Table 42.5.

## Drug Therapy

- **Sunscreens:** The effectiveness of a sunscreen is based on its sun protection factor (SPF) and substantivity (measure of its effectiveness, ability to be absorbed by or adhere to skin while

TABLE 42.2 Sunscreens and UVR Absorption

Sunscreen	Absorption (nm)
<b>ANTHRANILATES</b>	
Meradimate (menthyl anthranilate)	260–380
<b>BENZOPHENONES</b>	
Dioxybenzone	250–390
Oxybenzone (benzophenone-3)	270–350
Sulisobenzone (Eusolex 4360)	260–375
<b>CINNAMATES</b>	
Cinoxate (diethanolamine <i>p</i> -methoxycinnamate)	280–310
Octocrylene	250–360
Octinoxate (octyl methoxycinnamate, Parsol MCX)	290–320
<b>DIBENZOYLMETHANES</b>	
Avobenzone (butyl methoxydibenzoylmethane, Parsol 1789)	320–400
<b>AMINOBENZOIC ACID AND ESTER DERIVATIVES</b>	
Para-aminobenzoic acid (PABA)	260–313
Padimate O (octyl dimethyl PABA)	290–315
<b>SALICYLATES</b>	
Homosalate	295–315
Octisalate (octyl salicylate)	280–320
Trolamine salicylate	260–320
<b>CAMPHOR DERIVATIVES</b>	
Ecamsule (terephthalylidene dicamphor sulfonic acid; Mexoryl)	290–400
<b>OTHERS</b>	
Ensulizole (phenylbenzimidazole sulfonic acid)	290–340
<b>PHYSICAL SUNSCREENS</b>	
Titanium dioxide	290–700
Zinc oxide	290–700

UVR, ultraviolet radiation.

TABLE 42.3 Relative Ultraviolet Protection Factor (UPF) by Ultraviolet Ray (UVR) Transmission and Absorption

UVR Transmitted (%)	UVR Absorbed (%)	UPF	Protection Category
10	90.0	10	Moderate protection
5	95.0	20	High protection
3.3	96.7	30	Very high protection
2.5	97.5	40	Extremely high protection
<2.0	>98.0	50	Maximal protection

swimming or perspiring). In 2006, FDA introduced regulations on sunscreen labeling for the terms sunscreen, water resistant, and very water resistant. Sunscreens should not be applied to children less than 6 months of age because of possible absorption and decreased ability to metabolize some chemicals. Sunscreens should be reapplied after profuse sweating or water activity.

- **Topical Retinoids:** Agents used for the management of photoaging include topical tretinoin (cream, gel, liquid), tazarotene (cream), adapalene (cream, gel). They can lessen fine wrinkles, mottled pigmentation, and tactile roughness associated with photoaged skin.

- **Topical antimicrobial agents** for the management of burns include the following:
  - **Silver Sulfadiazine:** agent of choice because it has broad-spectrum gram-positive and gram-negative antibacterial activity.
  - **Mafenide Acetate:** a water-soluble agent that is the best choice for patients that has a heavily contaminated burn wound, if treatment is delayed for several days after the burn, or if a dense bacterial population already exists.
  - **Silver Nitrate:** a 0.5% soak that is applied by soaking multilayered occlusive gauze dressings.

TABLE 42.4 Treatment Categories for Burn Injuries

- *Major burn injuries* are second-degree burns with >25% BSA involvement in adults (20% in children); all third-degree burns with ≥10% BSA involvement; all burns involving the hands, face, eyes, ears, feet, and perineum that may result in functional or cosmetic impairment; high-voltage electrical injury; and burns complicated by inhalation injury, major trauma, or poor-risk patients (elderly patients and those with debilitating disease).
- *Moderate, uncomplicated burns* are second-degree burns with 15%–25% BSA involvement in adults (10%–20% in children); third-degree burns with 2%–10% BSA involvement; and burns not involving risk to areas of specialized function such as the eyes, ears, face, hands, feet, or perineum.
- *Major or moderate, uncomplicated burns* necessitate admission, and surgical referral is recommended for patients of all ages who have deep second- or third-degree burns covering ≥3% of the TBSA.
- *Minor burn injuries* include second-degree burns with <15% BSA involvement in adults (10% in children), third-degree burns with <2% BSA, and burns not involving functional or cosmetic risk to areas of specialized function. Patients with burns of this category may be treated on an outpatient basis if no other trauma is present; if circumferential burns of the neck, trunk, arms, or legs are not present; and if the patient is able to comply with therapy. After initial evaluation by a health care provider, patients may self-treat a second- or third-degree burn only if <1% BSA is involved.

BSA, body surface area; TBSA, total body surface area.

TABLE 42.5 Criteria for Transfer to Burn Centers

The American Burn Association and the American College of Surgeons recommend transfer to a burn center for all acutely burned patients who meet any of the following criteria:

- Partial-thickness burns ≥20% TBSA in patients aged 10–50 years
- Partial-thickness burns ≥10% TBSA in children aged 10 or adults aged 50 years
- Full-thickness burns ≥5% TBSA in patients of any age
- Patients with partial- or full-thickness burns of the hands, feet, face, eyes, ears, perineum, and/or major joints
- Patients with high-voltage electrical injuries, including lightning injuries
- Patients with significant burns from caustic chemicals
- Patients with burns complicated by multiple trauma in which the burn injury poses the greatest risk of morbidity or mortality (in such cases, if the trauma poses the greater immediate risk, the patient may be treated initially in a trauma center until stable before being transferred to a burn center)
- Patients with burns who suffer an inhalation injury
- Patients with significant ongoing medical disorders that could complicate management, prolong recovery, or affect mortality
- Patients who were taken to hospitals without qualified personnel or equipment for the care of children
- Burn injury in those patients who will require special social/emotional and/or long-term rehabilitative support, including cases involving suspected child abuse, substance abuse, and so on.

TBSA, total body surface area.

## Osteoarthritis\*

### General Principles

- Osteoarthritis (OA) is a chronic, progressive condition, primarily affecting women, that causes loss of articular cartilage in the hands, knees, hips, and cervical and lumbar spine.
- Regular exercise and physical activity do not increase the risk of OA in normal joints and are necessary to maintain cartilage.
- OA causes significant pain and functional disability.

### Patient Assessment

- A characteristic joint space narrowing seen by radiograph without joint destruction.
- Clinical presentation is usually unilateral pain and stiffness of the knee, hip, or cervical or lumbar spine. OA tends to affect more than one joint.
- Patients typically present with complaints of increased pain or stiffness lasting <30 minutes upon awakening or after long periods of immobility. Kneeling, stair climbing, and walking tend to be limited.

### Risk Factors

- Risk factors can be modifiable (obesity, joint trauma) or nonmodifiable (advancing age, gender, genetics).
- Metabolic conditions (hemochromatosis, acromegaly, deposition of crystalline calcium), leg length discrepancies, joint or hip dislocations, and chronic repetitive joint injury can all contribute to the development of OA.

### Goals of Therapy

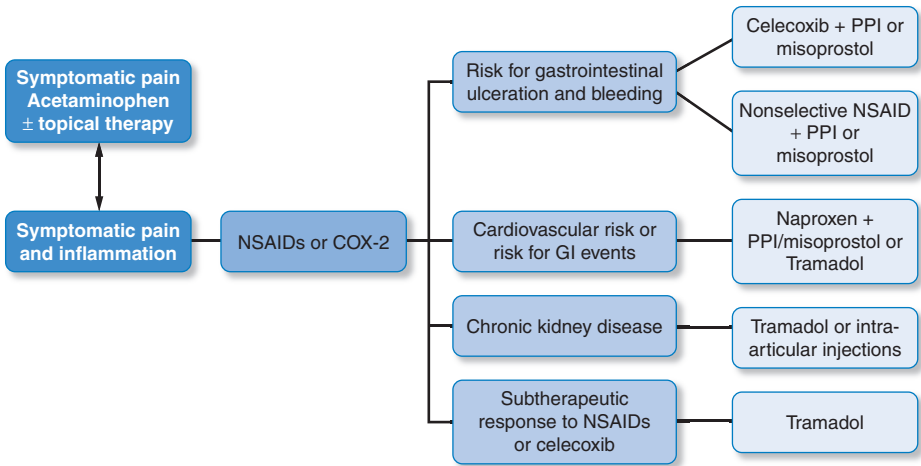
- Goals of therapy are to provide analgesia to support activities of daily living, facilitate participation in physical or occupational therapies, engage in appropriate self-managed exercise programs, minimize disability, and improve overall quality of life.

### Treatment

- An overview of the pharmacologic therapy for OA is shown in Figure 43.1. There are no disease-mitigating strategies for the treatment of OA.
- Nonpharmacologic management (weight loss, aerobic activity, strength training, physical and occupational therapy) should be used whenever possible as pharmacologic strategies have untoward effects and modest efficacy in OA management. A 6-month trial of dietary supplements (glucosamine, chondroitin, or cat's claw) may offer an alternative to prescription medications in some patients.

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\*The reader is referred to Chapter 43, Osteoarthritis, written by Dominick P. Trombetta, PharmD, BCPS, CGP, FASCP, in the 10th edition of *Applied Therapeutics: The Clinical Use of Drugs* for a more in-depth discussion. All notations to reference numbers are based on the reference list at the end of that chapter. The editor of this handbook expresses her thanks to Dr. Trombetta and acknowledges that this chapter is based on his work.



**Figure 43.1** Overview of pharmacologic therapy for treatment of osteoarthritis. COX-2, cyclo-oxygenase-2 inhibitor; GI, gastrointestinal; NSAID, nonsteroidal anti-inflammatory drug; PPI, proton-pump inhibitor. (Adapted from multiple references.)<sup>11,21–24,36,37</sup>

- Treatment is not required during periods when symptoms are absent or too minimal to be bothersome to the patient, as available interventions have not shown to be disease modifying.
- In patients with OA lacking signs or symptoms of inflammation, initial pharmacological treatment for pain and stiffness is a 2- to 3-week trial of acetaminophen (1,000 mg orally, every 6 hours up to 3 g/day, or 650 mg every 6 hours up to four times/day). The dose limit of 3 g/day is consistent with labeling developed by the brand name manufacturer.
- Nonsteroidal anti-inflammatory drugs (NSAIDs) may offer better efficacy in patients who have pain and inflammation. However, they carry the risk of increased blood pressure, gastrointestinal (GI) ulceration, and reduction in renal function. Recommendations for NSAID selection based on GI and cardiovascular risk factors are shown in Tables 43.1 and 43.2. No data suggest one NSAID is more effective than another.
- NSAIDs should be initiated in low doses on an as-needed basis to minimize risk of adverse events, but may be increased to regular daily anti-inflammatory doses if required for symptom relief and permitted by patient's comorbid medical condition.
- Topical therapies may be beneficial for patients unable to tolerate oral NSAIDs or who may be at increased risk of adverse effects with the use of oral NSAIDs. Options include capsaicin, diclofenac gel, and diclofenac solution, used either alone or in combination with other pharmacologic therapies. Oral NSAIDs should not be used concomitantly with topical NSAIDs (diclofenac) due to safety concerns.
  - Capsaicin is applied to hands or knees three to four times daily. Benefits may not be seen for a few weeks. Burning or stinging may occur with application.
  - Diclofenac gel is applied according to dosing cards in either 2- or 4-g measurements. Diclofenac solution with DMSO is approved for OA of the knee.
- Tramadol may be a useful option for pain control in patients who have failed or have contraindications to NSAIDs. Its use should be avoided in patients with a history of seizures or when possible drug interactions exist (Table 43.3). Dosing adjustment is needed with renal dysfunction.
- Oral or transdermal opioids or opioid/acetaminophen can be cautiously considered for pain control in patients who are resistant to initial pharmacotherapy. Their benefits are mild to moderate, so risk:benefit must be assessed.

- Oral glucocorticoids are not currently recommended for the treatment of OA.
- In patients presenting with effusions of the knee who fail oral or topical therapies, aspiration of the affected joint and intra-articular injections (corticosteroids or hyaluronic acid) may be helpful.

**TABLE 43.1 Risk Factors for GI Complications with NSAIDs**

Age >65
NSAID dose
Concurrent steroid use
Previous GI adverse event
Oral antiplatelet agents (aspirin, clopidogrel)
Oral anticoagulant therapy
History of
PUD
Upper GI bleeding
GI hospitalization
Dyspepsia
Cardiovascular disease

GI, gastrointestinal; NSAID, nonsteroidal anti-inflammatory drug; PUD, peptic ulcer disease.

**TABLE 43.2 Recommendations for NSAID Selection Based on Gastrointestinal and Cardiovascular Risks**

Risk Category	Low GI Risk	Moderate GI Risk	High GI Risk
	0 risk factors	1–2 risk factors	Multiple risk factors, history of previous ulcer events, or continued use of corticosteroids or anticoagulants
Low CV risk	NSAID alone	NSAID + PPI/ misoprostol	Alternative therapy or COX-2 + PPI/ misoprostol
High CV risk (low-dose aspirin required)	Naproxen + PPI/ misoprostol	Naproxen + PPI/ misoprostol	Alternative therapy recommended

COX-2, cyclo-oxygenase-2 inhibitor; CV, cardiovascular; NSAID, nonsteroidal anti-inflammatory drug; PPI, proton-pump inhibitor.

**TABLE 43.3 Tramadol Drug Interactions**

Precipitant Drug	Object Drug <sup>a</sup>	Description
Carbamazepine	Tramadol	↓ Coadministration may significantly reduce the analgesic effect of tramadol. Because carbamazepine increases the metabolism and because of the seizure risk associated with tramadol, coadministration is not recommended. <sup>b</sup>
CNS depressants (e.g., alcohol, other opioids)	Tramadol	↑ Coadministration may increase the risk of CNS and respiratory depression. Use tramadol with caution and in reduced dosages. <sup>b</sup>
CYP2D6 inhibitors (e.g., fluoxetine, paroxetine, amitriptyline)	Tramadol	↑ Coadministration may inhibit some of the metabolism of tramadol to various degrees. The full pharmacological impact of these alterations is unknown. <sup>b</sup>
CYP3A4 inducers (e.g., rifampin, phenytoin)	Tramadol	↓ May produce increased clearance of tramadol; use with caution. <sup>b</sup>

TABLE 43.3 Tramadol Drug Interactions (Continued)

Precipitant Drug	Object Drug <sup>a</sup>	Description
CYP3A4 inhibitors (e.g., ketoconazole, erythromycin)	Tramadol	↑ Coadministration may produce increased tramadol concentrations. <sup>b</sup>
TCA's and other tricyclic compounds (e.g., cyclobenzaprine, promethazine)	Tramadol	↑ Concomitant use increases the risk of seizures. <sup>b</sup>
Tramadol	Digoxin	↑ Postmarketing surveillance revealed rare reports of digoxin toxicity. <sup>b</sup>
Tramadol	MAOIs	↑ Tramadol inhibits norepinephrine and serotonin reuptake.
MAOIs	Tramadol	Concomitant use increases the risk of adverse reactions, including seizures and serotonin syndrome. <sup>b</sup>
Tramadol	SSRIs	↑ The serotonergic effects of these agents may be addictive.
SSRIs	Tramadol	The risk of seizures is also increased with coadministration. <sup>b,c</sup>
Tramadol	Warfarin	↑↓ Postmarketing reports revealed alteration of warfarin effects, including elevation of prothrombin times. Use with caution and monitor international normalized ratio. <sup>b,c</sup>

<sup>a</sup>↑, object drug increased; ↓, object drug decreased.

<sup>b</sup>Ultram ER [package insert]. Raritan, NJ: Ortho-McNeil Pharmaceutical Inc.; 2006.

<sup>c</sup>Tramadol. *Drug Interaction Facts*. Facts & Comparisons [database online]. 2003. St. Louis, MO: Wolters Kluwer Health Inc. Accessed August 21, 2006.

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# Rheumatoid Arthritis\*

## General Principles

- **Rheumatoid arthritis (RA)** is a chronic systemic inflammatory disorder characterized by potentially deforming polyarthritis and a wide spectrum of extracellular manifestations.
  - The onset of RA typically occurs between the third and fourth decades of life.
  - RA is a systemic disease that involves multiple organ systems (pleuropulmonary and cardiac involvement, vasculitis, ophthalmic, connective tissue).
- **Juvenile idiopathic arthritis (JIA)** presents before the age of 16 and includes symptoms such as joint inflammation, swelling, pain, limited range of motion, warmth, and erythema.

## Goals of Therapy

- The goal of treatment is disease remission (Table 44.1). Because sustained remission is uncommon, other goals include minimizing disease activity to provide pain relief, maintaining activities of daily living, maximizing quality of life, preserving joint function, and slowing joint damage.

**TABLE 44.1 Provisional Criteria for Rheumatoid Arthritis Remission in Clinical Trials from the American College of Rheumatology/European League Against Rheumatism**

A patient with rheumatoid arthritis is considered to be “in remission” if either of the following applies:

**1. Boolean-based definition:**

At any time, patient must satisfy ALL of the following:

Tender joint count  $\leq 1^a$

Swollen joint count  $\leq 1^a$

C-reactive protein  $\leq 1$  mg/dL

Patient global assessment  $\leq 1$  (on a 0–10 scale)<sup>b</sup>

**2. Index-based definition:**

At any time, patient must have a Simplified Disease Activity Index score of  $\leq 3.3^c$

<sup>a</sup>For tender and swollen joint counts, use of a 28-joint count may miss actively involved joints, especially in the feet and ankles, and it is preferable to include feet and ankles also when evaluating remission.

<sup>b</sup>For the assessment of remission, the following format and wording is suggested for the global assessment questions. *Format:* a horizontal 10-cm visual analog or Likert scale with the best anchor and lowest score on the left side and the worst anchor and highest score on the right side. *Wording of question and anchors:* For patient global assessment, “Considering all of the ways your arthritis has affected you, how do you feel your arthritis is today?” (anchors: very well–very poor). For physician or assessor global assessment, “What is your assessment of the patient’s current disease activity?” (anchors: none–extremely active).

<sup>c</sup>Defined as the simple sum of the tender joint count (using 28 joints), swollen joint count (using 28 joints), patient global assessment (0–10 scale), physician global assessment (0–10 scale), and C-reactive protein level (mg/dL).

Source: Felson DT et al. American College of Rheumatology/European League Against Rheumatism provisional definition of remission in rheumatoid arthritis for clinical trials. *Arthritis Rheum.* 2011;63:573.

\*The reader is referred to Chapter 44, Rheumatoid Arthritis, written by Steven W. Chen, PharmD, FASHP, Rory E. O’Callaghan, PharmD, and Alison M. Reta, PharmD, in the 10th edition of *Applied Therapeutics: The Clinical Use of Drugs* for a more in-depth discussion. All notations to reference numbers are based on the reference list at the end of that chapter. The editor of this handbook expresses her thanks to Drs. Chen, O’Callaghan, and Reta and acknowledges that this chapter is based on their work.

# RHEUMATOID ARTHRITIS

## Patient Assessment

- The diagnosis of RA is based primarily on clinical criteria (Table 44.2); no single chemical or laboratory test is specific for this disease.
- RA usually begins with nonspecific symptoms (fatigue, malaise, diffuse musculoskeletal pain, morning stiffness). Progressive disease is characterized by irreversible joint deformities.
- The cause of RA involves many factors including genetic susceptibility, environmental influences, advancing age, and immune factors. Cigarette smoking is associated with RA.
- Recommendations to reduce cardiovascular risk in patients with RA are shown in Table 44.3.
- Drug therapy for RA should involve use of tools that objectively evaluate disease activity and track disease progression over time (Table 44.4).

## Treatment

- Treatment for RA involves a combination of interventions including rest, exercise (e.g., cycling, swimming, walking), physical therapy, emotional support, occupational therapy, and medications (Figure 44.1). Symptoms of RA can generally be controlled by conservative management. More aggressive therapy is needed to prevent disease progression and disability.
- Most patients with RA are treated with at least one disease-modifying antirheumatic drug (DMARD) and a nonsteroidal anti-inflammatory drug (NSAID). Combination DMARD therapy is indicated for more severe or more advanced RA.
- DMARDs should be initiated in all patients with RA to minimize loss of joint integrity and function and reduce the risk of cardiovascular disease related to RA.

**TABLE 44.2 Criteria for Diagnosis of Rheumatoid Arthritis**

Criteria	Score <sup>a</sup>
<b>JOINT INVOLVEMENT</b>	
1 large joint	0
2–10 large joints	1
1–3 small joints	2
4–10 small joints	3
>10 small joints	5
<b>SEROLOGY</b>	
Negative RF and negative anti-CCP	0
Low-positive RF or low-positive anti-CCP	2
High-positive RF or high-positive anti-CCP	3
<b>ACUTE-PHASE REACTANTS</b>	
Normal CRP and normal ESR	0
Abnormal CRP or abnormal ESR	1
<b>DURATION OF SYMPTOMS</b>	
<6 weeks	0
≥6 weeks	1

<sup>a</sup>Score-based algorithm: add score of all categories; score of ≥6/10 needed to classify patient as having definite RA. anti-CCP, anti-cyclic citrullinated peptide; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; RA, rheumatoid arthritis; RF, rheumatoid factor.

Source: Aletaha D et al. 2010 rheumatoid arthritis classification criteria: an American College of Rheumatology/European League Against Rheumatism collaborative initiative [published correction appears in *Ann Rheum Dis*. 2010;69:1892]. *Ann Rheum Dis*. 2010;69:1580.

**TABLE 44.3 Recommendations for Reducing Cardiovascular Risk<sup>a</sup> in Patients with Rheumatoid Arthritis (Evidence/Strength Rating)<sup>b</sup>**

1. Rheumatoid arthritis should be considered as a disease in which cardiovascular risk is elevated because of both an increased prevalence of traditional cardiovascular risk factors and the inflammatory burden. Although the evidence base is less, this may also apply to ankylosing spondylitis and psoriatic arthritis (2b–3/B).
2. To lower cardiovascular risk, adequate control of arthritis disease activity is necessary (2b–3/B).
3. All patients with rheumatoid arthritis should undergo annual cardiovascular risk evaluation with use of national guidelines. This should also be considered for all patients with ankylosing spondylitis and psoriatic arthritis. When antirheumatic treatment has been changed, risk assessments should be repeated (3–4/C).
4. For patients with rheumatoid arthritis, risk score models should be adapted by introducing a 1.5 multiplication factor when the patient meets two of the following three criteria: disease duration of more than 10 years, rheumatoid factor or anti-cyclic citrullinated peptide positivity, and the presence of certain extra-articular manifestations (3–4/C).
5. When using the Systematic Coronary Risk Evaluation model for determination of cardiovascular risk, triglyceride to high-density lipoprotein cholesterol ratio should be used (3/C).
6. Intervention for cardiovascular risk factor management should be performed according to national guidelines (3/C).
7. Preferred treatment options are statins, angiotensin-converting enzyme inhibitors, or angiotensin II blockers (2a–3/C–D).
8. The effect of cyclo-oxygenase-2 inhibitors and most nonsteroidal anti-inflammatory drugs on cardiovascular risk is not completely determined and should be studied further. Clinicians should therefore be very cautious in prescribing these drugs, especially to patients with cardiovascular risk factors or with documented cardiovascular disease (2a–3/C).
9. When corticosteroids are prescribed, this should be at the lowest possible dose (3/C).
10. Patients should be actively encouraged to stop smoking (3/C).

<sup>a</sup>Cardioprotective treatment is recommended when 10-year cardiovascular risk is above the threshold of “moderate” that is established for each country (i.e., either 10% or 20%).

<sup>b</sup>Level of Evidence: Category 1A, from meta-analysis of randomized, controlled trials; 1B, from at least one randomized, controlled trial; 2A, from at least one controlled study without randomization; 2B, from at least one type of quasi-experimental study; 3, from descriptive studies, such as comparative studies, correlation studies, or case-control studies; 4, from expert committee reports or opinions or from clinical experience of respected authorities; strength of recommendation directly based on: A, category 1 evidence; B, category 2 evidence or extrapolated recommendations from category 1 evidence; C, category 3 evidence or extrapolated recommendations from category 1 or 2 evidence; D, category 4 evidence or extrapolated recommendations from category 2 or 3 evidence.

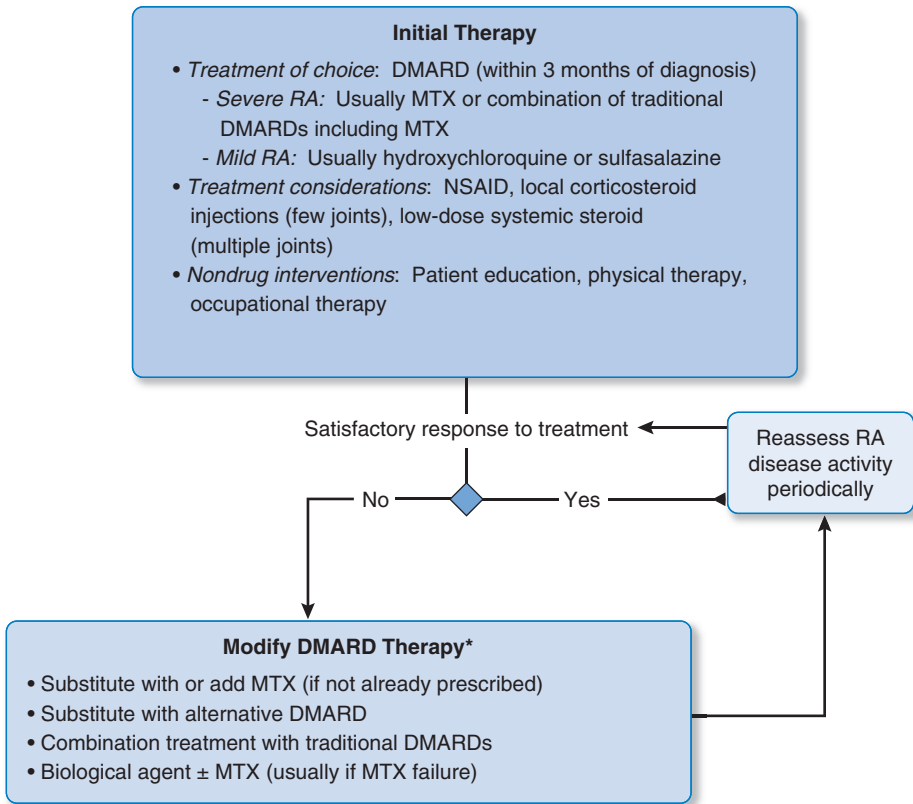
Source: Peters MJ et al. EULAR evidence-based recommendations for cardiovascular risk management in patients with rheumatoid arthritis and other forms of inflammatory arthritis. *Ann Rheum Dis*. 2010;69:325.

**TABLE 44.4 Tools Used to Measure Disease Activity in Rheumatoid Arthritis<sup>a</sup>**

Measurement Tool	Score Range	Thresholds of Disease Activity		
		Low	Moderate	High
Disease Activity Score in 28 joints	0–9.4	≤3.2	>3.2 and ≤5.1	>5.1
Simplified Disease Activity Index	0.1–86.0	≤11	>11 and ≤26	>26
Clinical Disease Activity Index	0–76.0	≤10	>10 and ≤22	>22
Rheumatoid Arthritis Disease Activity Index	0–10	≤2.2	>2.2 and ≤4.9	>4.9
Patient Activity Scale (PAS) or PASII	0–10	≤1.9	>1.9 and ≤5.3	>5.3
Routine Assessment Patient Index Data	0–30	≤6	>6 and ≤12	>12

<sup>a</sup>Tools incorporate multiple variables such as number of swollen joints and tender joints, erythrocyte sedimentation rate, and measures of general health or global disease activity.

Source: Saag KG et al. American College of Rheumatology 2008 recommendations for the use of nonbiologic and biologic disease-modifying antirheumatic drugs in rheumatoid arthritis. *Arthritis Rheum*. 2008;59:762.



\*Consider local corticosteroid injection(s) or low-dose systemic steroids if appropriate

**Figure 44.1** Overview of rheumatoid arthritis (RA) drug therapy from the American College of Rheumatology 2002 guidelines. DMARD, disease-modifying antirheumatic drug; MTX, methotrexate; NSAID, nonsteroidal anti-inflammatory drug. (American College of Rheumatology Subcommittee on Rheumatoid Arthritis Guidelines. Guidelines for the management of rheumatoid arthritis: 2002 update. *Arthritis Rheum.* 2002;46:328.)

- Traditional DMARDs include methotrexate (MTX), hydroxychloroquine, sulfasalazine, leflunomide, minocycline, gold, azathioprine, and D-penicillamine. Their onset is generally slow. MTX is the initial treatment of choice for most patients.
- Biologic DMARDs are shown in Table 44.5. TNF- $\alpha$  biologics are recommended for patients who fail to achieve an adequate response with either MTX alone or MTX in combination with other traditional DMARDs, or for patients who are intolerant to MTX.
- Corticosteroids are reserved for brief periods of active disease (low-dose oral therapy) or isolated joint flares (local intra-articular injections) because of serious adverse effects associated with long-term use.

TABLE 44.5 Biologic Disease-Modifying Antirheumatic Drug Dosing Information

Generic (Brand)	Mechanism of Action	Dosage Range	Administration Schedule	Routes of Administration	Can Be Self-Administered?
Infliximab (Remicade)	TNF- $\alpha$ inhibitor	3 mg/kg <sup>a</sup>	Weeks 0, 2, and 6 and then every 8 weeks	IV	No
Etanercept (Enbrel)	TNF- $\alpha$ inhibitor	25 mg twice weekly or 50 mg once weekly	One to two doses/week	SC	Yes
Adalimumab (Humira)	TNF- $\alpha$ inhibitor	40 mg	Every 14 days	SC	Yes
Certolizumab pegol (Cimzia)	TNF- $\alpha$ inhibitor	Initial: 400 mg SC $\times$ 1 on weeks 0, 2, 4 Subsequent: 200 mg every 2 weeks or 400 mg every 4 weeks	Weeks 0, 2, and 4, then every 2 or 4 weeks	SC	Yes
Golimumab (Simponi)	TNF- $\alpha$ inhibitor	50 mg/0.5 mL	Every 4 weeks	SC	Yes
Abatacept (Orencia)	Costimulation modulator, T-cell activation inhibitor	Weight based: <60 kg = 500 mg 60–100 kg = 750 mg >100 kg = 1,000 mg	Weeks 0, 2, and 4 and then every 4 weeks	IV	No
Rituximab (Rituxan)	CD20 + B-cell inhibitor	1,000 mg IV infusion: Initial: 50 mg/hour, may increase every 30 minutes to a max rate 400 mg/hour Subsequent: 100 mg/hour, may increase every 30 minutes to max rate 400 mg/hour <sup>b</sup>	Repeat in 14 days, then discontinue	IV	No
Tocilizumab (Actemra)	IL-6 inhibitor	Initial: 4 mg/kg every 4 weeks Subsequent: Titrate to 8 mg/kg based on clinical response Max: 800 mg/dose (8 mg/kg)	Every 4 weeks	IV	No
Anakinra (Kineret)	IL-1 inhibitor	100 mg	Once daily	SC	Yes

<sup>a</sup>For incomplete response, may increase dose to 10 mg/kg or decrease dosing interval to every 4 weeks.

<sup>b</sup>Max: total of two doses, safety data unknown past two doses. Premedicate with corticosteroid, acetaminophen, and an antihistamine before each dose. IL, interleukin; IV, intravenous; SC, subcutaneous; TNF, tumor necrosis factor.

Source: Clinical Pharmacology Online. Elsevier Ltd; 2011. <http://www.clinicalpharmacology.com>. Accessed January 2, 2011.

TABLE 44.6 Some Nonsteroidal Anti-inflammatory Drugs

NSAID Generic Name (Brand Name)	Product Availability	Usual Dosing Interval	Maximum Daily Dose (mg)
<b>SALICYLATES (ACETYLATED AND NONACETYLATED)<sup>a</sup></b>			
Aspirin, enteric-coated <sup>b</sup>	Tablets: 325 mg; 325, 500, 800, 975 mg SR	QID	4,000
Salsalate (Disalcid) <sup>b</sup>	Tablets: 500, 750 mg	BID–TID	4,800
Magnesium choline salicylate (Trilisate) <sup>b</sup>	Tablets: 500, 750, 1,000 mg  Liquid: 500 mg/5 mL	Daily–TID	4,800
<b>PROPIONIC ACID DERIVATIVES</b>			
Fenoprofen (Nalfon) <sup>b</sup>	Capsules: 200, 300 mg	TID–QID	3,200
Flurbiprofen (Ansaid) <sup>b</sup>	Tablets: 50, 100 mg	BID–QID	300
Ibuprofen (Motrin) <sup>b</sup>	Tablets: 200, 400, 600, 800 mg Suspension: 100 mg/5 mL	TID–QID	3,200
Naproxen (Naprosyn) <sup>b</sup>	Tablets: 250, 375, 500 mg; 375, 500 mg SR Suspension: 125 mg/5 mL	BID	1,500
Naproxen sodium (Anaprox) <sup>b</sup>	Tablets: 275, 550 mg	BID	1,375
Oxaprozin (Daypro) <sup>b</sup>	Tablet or capsule: 600 mg	Daily	1,800
<b>ACETIC ACID DERIVATIVES</b>			
Diclofenac (Voltaren XR) <sup>b</sup>	Tablets: 25, 50, 75 mg DR; 100 mg XR	BID–TID	200
Etodolac (Lodine, Lodine XL) <sup>b</sup>	Capsules: 200, 300 mg Tablets: 400, 500 mg; 400, 500, 600 mg XL	BID–TID  XL: Daily	1,200  XL: 1,000
Indomethacin (Indocin, Indocin SR) <sup>b</sup>	Capsules: 25, 50 mg; 75 mg SR  Suppository: 50 mg Suspension: 25 mg/5 mL	TID–QID	200
Ketorolac (Toradol) <sup>b</sup>	Tablet: 10 mg	SR: Daily–BID	SR: 150
Nabumetone (Relafen) <sup>b</sup>	Tablet: 500, 750 mg	QID	40
Sulindac (Clinoril) <sup>b</sup>	Tablets: 150, 200 mg	Daily	2,000
Tolmetin (Tolectin) <sup>b</sup>	Tablets: 200, 600 mg Capsules: 400 mg	BID	400
		TID–QID	1,800
<b>OXICAM DERIVATIVES</b>			
Piroxicam (Feldene) <sup>b</sup>	Capsule: 10, 20 mg	Daily	20
Meloxicam (Mobic) <sup>b</sup>	Tablets: 7.5, 15 mg	Daily	15
<b>COX-2 INHIBITORS</b>			
Celecoxib (Celebrex)	Capsules: 50, 100, 200, 400 mg	BID	400

<sup>a</sup>Highly variable half-life; anti-inflammatory doses associated with salicylate serum concentrations from 15 to 30 mg/dL.

<sup>b</sup>Generic version available.

BID, twice a day; COX-2, cyclo-oxygenase-2; DR, delayed release; NSAID, nonsteroidal anti-inflammatory drug; QID, four times a day; SR, sustained release; TID, three times a day; XL/XR, extended release.

Source: [No authors listed]. Drugs for rheumatoid arthritis. *Treat Guidel Med Lett.* 2009;7:37.

## Drug Therapy

- **NSAIDs:** provide pain relief and reduce inflammation, but they do not prevent or slow joint destruction. No significant difference exists in efficacy between agents (Table 44.6).
- **Corticosteroids:** given orally at low doses (equivalent of prednisone 10 mg/day or less) to manage pain and inflammation of acute attacks. Intra-articular injections are useful when flares occur in one or a few joints.

**TABLE 44.7 Selection Recommendations for Nonbiologic Disease-Modifying Antirheumatic Drugs**

Poor Prognosis Features? <sup>a</sup>	Disease Duration (months)							MTX +	MTX +	MTX +	SSZ +	MTX +
		MTX	LEF	SSZ	HCQ	MIN	HCQ	LEF	SSZ	HCQ	SSZ + HCQ	
<b>LOW DISEASE ACTIVITY (SEE TABLE 44.5)</b>												
Yes	<6	X	X	X								
	6–24	X	X	X								X
	>24	X	X	X			X	X				X
No	<6	X	X	X	X	X						
	6–24	X	X	X	X							
	>24	X	X	X			X					
<b>MODERATE OR HIGH DISEASE ACTIVITY (SEE TABLE 44.5)</b>												
Yes	<6	X	X				X		X			X
	6–24	X	X	X			X	X	X			X
	>24	X	X				X	X	X			X
No	<6	X	X	X			X					
	6–24	X	X	X			X	X	X	X		X
	>24	X	X	X			X	X	X			X

<sup>a</sup>Indicators of poor rheumatoid arthritis prognosis include functional limitation using standard measurement scales (e.g., Health Assessment Questionnaire score), extra-articular manifestations (e.g., rheumatoid nodules, vasculitis, rheumatoid arthritis–related lung disease), positive rheumatoid factor, positive anti–cyclic citrullinated peptide antibodies, radiographic evidence of bone erosions.

HCQ, hydroxychloroquine; LEF, leflunomide; MIN, minocycline; MTX, methotrexate; SSZ, sulfasalazine.

Source: Saag KG et al. American College of Rheumatology 2008 recommendations for the use of nonbiologic and biologic disease-modifying antirheumatic drugs in rheumatoid arthritis. *Arthritis Rheum.* 2008;59:762.

- **Traditional DMARDs:** choice of agent is based on disease activity, presence of poor prognostic findings, and disease duration (Table 44.7).
  - **MTX:** recommended first-line therapy with relatively rapid onset. Initiate oral therapy at 7.5 mg once weekly (or 2.5 mg every 12 hours for three doses). May increase dose to 15 mg/week if no response after 1 to 2 months (maximum dose 25 mg/week). Folic acid (1 mg/day or 7 mg once weekly) reduces incidence of MTX toxicity.
  - **Leflunamide:** alternative for first-line therapy. Initiate with 100 mg loading dose for 3 days, followed by 20 mg/day. Dose may be reduced to 10 mg/day if not tolerated.
  - **Hydroxychloroquine (200–400 mg/day), Minocycline (100 mg twice daily), Sulfasalazine (2–3 g/day, titrated slowly):** recommended for relatively mild cases of RA.
  - Rarely used agents include cyclophosphamide, gold, and azathioprine. D-penicillamine is no longer used due to dosing complexity and serious toxicities.
- **Biological DMARDs:** choice of agent is driven by cost, insurance coverage, provider preference, and patient-specific factors (Table 44.8). Agents, their mechanism of action, route of administration, and usual dosing are shown in Table 44.5. Combinations of two biologic DMARDs do not show additional benefit versus biologic DMARD monotherapy, and the risk for serious adverse events increases considerably.

## JUVENILE IDIOPATHIC ARTHRITIS

### Patient Assessment

- Morning stiffness may manifest as increased irritability, guarding of involved joints, or refusal to walk (as children often cannot articulate complaints).
- Systemic JIA has hallmark features including rash, lymphadenopathy, or cyclical high-spiking fever.

**TABLE 44.8 Selection Recommendations for Biologic Disease-Modifying Antirheumatic Drugs**

Biologic DMARDs	Disease Duration <sup>a</sup>	Disease Activity <sup>b</sup>	Poor Prognostic Factors <sup>c</sup>	Previous or Concurrent Therapies
TNF- $\alpha$ inhibitors	Early	High	+	With MTX
	Intermediate/Long	Moderate	+	Must have failed MTX monotherapy
	Intermediate/Long	High	+/-	Must have failed MTX monotherapy
	Intermediate/Long	Moderate/High	+/-	Must have failed MTX + nonbiologic DMARD
Abatacept	Not specified	Moderate/High	+	Must have failed MTX + nonbiologic DMARD
Rituximab	Not specified	High	+	Must have failed MTX + nonbiologic DMARD
Biologic combination	Not recommended in any patients based on data indicating increased risk of adverse events or lack of additive efficacy			

<sup>a</sup>Disease duration: early, <6 months; intermediate, 6 to 24 months; long, >24 months.

<sup>b</sup>Disease activity: low, moderate, high.

<sup>c</sup>Poor prognostic factors: (+) poor prognostic factors present, (-) without poor prognostic factors, (+/-) recommendation independent of prognostic factors.

DMARD, disease-modifying antirheumatic drug; MTX, methotrexate.

Source: Saag KG et al. American College of Rheumatology 2008 recommendations for the use of nonbiologic and biologic disease-modifying antirheumatic drugs in rheumatoid arthritis. *Arthritis Rheum.* 2008;59:762.

## Treatment

- Choice of medication requires consideration of type of JIA, current treatment, degree of disease progression, level of disease activity, and prognosis.
- NSAIDs are first-line treatment to manage joint inflammation and febrile episodes. Naproxen (10–15 mg/kg/day, maximum 750 mg/day) given in two divided doses is most commonly used. Ibuprofen (30–50 mg/kg/day, maximum 2.4 g/day) given in three to four divided doses is an alternative. Other NSAIDs have also been used. Aspirin is seldom used in children due to its association with Reye syndrome.
- Low-dose corticosteroids (0.5–1 mg/kg/day) may be needed for disease flares. The lowest effective dose for the shortest duration possible should be used to avoid long-term side effects. Intra-articular steroid injections can be used when isolated joints are affected.
- MTX (10–15 mg/m<sup>2</sup> once weekly, given orally or by SQ injection) is the DMARD of choice for polyarthritic JIA.
- Sulfasalazine (30–50 mg/kg/day, maximum 2 g/day) given in two divided doses is often the second-line treatment behind MTX.
- Biologic DMARDs (etanercept, adalimumab, and abatacept) are FDA approved for JIA. Other biologic agents have been studied.



# Gout and Hyperuricemia\*

## General Principles

- Gout is a disorder of uric acid metabolism that typically manifests as recurrent episodes of acute joint pain and inflammation secondary to deposition of monosodium urate (MSU) crystals in the synovial fluid and lining. Patients with gout cycle between flares of acute joint pain and inflammation and periods of quiescence with no disease symptoms.
- Although gout is commonly associated with hyperuricemia, elevated serum uric acid (SUA) is not a prerequisite for the condition. Gout is a clinical diagnosis; hyperuricemia is a biochemical diagnosis. The two terms are not synonymous or interchangeable. Increased SUA concentrations can result from an increase in production or a decrease in renal excretion of uric acid (or a combination of both).

## Risk Factors

- Hypertension, type 2 diabetes, hyperlipidemia, cardiovascular diseases including heart failure and obesity have all been associated with hyperuricemia and gout. Overindulgence of alcohol has also been linked to gout attacks.

## Patient Assessment

- Criteria for the diagnosis of gout are shown in Table 45.1; 6 of the 13 criteria must be present to confirm the diagnosis. The presence of MSU crystals from an inflamed joint also confirms diagnosis.
- Symptoms of acute gout include severe, acute pain and an obviously inflamed joint. Pain usually reaches its maximum within 6 to 12 hours of onset. A single joint is affected 85% to 90% of the time. Acute gouty arthritis commonly begins at night, with attacks being more common during episodes of increased physical exercise.
- Review of a patient's complete medication list should occur to rule out drug-induced hyperuricemia (Table 45.2).

## Goals of Therapy

- The primary goal of therapy is to relieve pain and inflammation. It is not necessary to treat the hyperuricemia in the acute situation.
- Goals for lowering SUA concentrations are elimination of acute gout attacks and mobilization of urate crystals from soft tissue. The SUA concentration in a patient who has clinical gout should be decreased to 6 mg/dL or less.

## Treatment

- Gout can be successfully treated and even cured in many patients. Evidence-based recommendations are shown in Table 45.3.

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\*The reader is referred to Chapter 45, Gout and Hyperuricemia, written by KarenBeth H. Bohan, PharmD, BCPS, in the 10th edition of *Applied Therapeutics: The Clinical Use of Drugs* for a more in-depth discussion. All notations to reference numbers are based on the reference list at the end of that chapter. The editor of this handbook expresses her thanks to Dr. Bohan and acknowledges that this chapter is based on her work.

**TABLE 45.1 Proposed Criteria for Acute Arthritis of Primary Gout (Now Accepted as the 1977 American College of Rheumatology Criteria for Diagnosis of Gout)**

1. More than one attack of acute arthritis
2. Maximum inflammation developed within 1 day
3. Monoarthritis attack
4. Redness observed over joints
5. First metatarsophalangeal joint painful or swollen
6. Unilateral first metatarsophalangeal joint attack
7. Unilateral tarsal joint attack
8. Tophus (proven or suspected)
9. Hyperuricemia
10. Asymmetric swelling within a joint on x-ray<sup>d</sup>
11. Subcortical cysts without erosions on x-ray
12. Monosodium urate monohydrate microcrystals in joint fluid during attack
13. Joint fluid culture negative for organisms during attack

<sup>d</sup>This criterion could logically be found on examination as well as on x-ray. However, the protocol did not request this information in regard to examination.

Source: Reprinted with permission from Wallace SL et al. Preliminary criteria for the classification of the acute arthritis of primary gout. *Arthritis Rheum.* 1977;20:895.

- Nonpharmacologic interventions include application of ice on the affected joint, reduction of alcohol consumption, and minor diet modifications.
- Acute gouty arthritis often can be effectively treated with nonsteroidal anti-inflammatory agents (NSAIDs), colchicine, or corticosteroids.
- Drug therapy to lower SUA concentrations is warranted in patients who have recurrent gout attacks (at least two per year), arthropathy, tophi, or radiographic changes related to gout.

**TABLE 45.2 Drugs Associated with Hyperuricemia**

Drug	Mechanism
Certain antiretrovirals <sup>68-71</sup>	Catabolic effect; NRTIs may increase urate through mitochondrial toxicity
Cyclosporine <sup>72,73</sup>	Decreased urate renal clearance, either via a tubular mechanism or decrease in GFR
Cytotoxic chemotherapy <sup>74</sup>	Rapid cell lysis
Diuretics <sup>75-79</sup>	Secondary to volume contraction and increased uric acid reabsorption in the proximal tubules for all diuretics; thiazides may also competitively inhibit proximal tubular secretion
Ethambutol <sup>80</sup>	Decreased urate renal clearance
Ethanol <sup>62,81</sup>	Increased uric acid production owing to adenine nucleotide turnover, lead-tainted moonshine, or high purine content in some alcoholic beverages, such as beer
Filgrastim <sup>82</sup>	Increased WBC production
Isotretinoin <sup>83</sup>	Hypervitaminosis A
Levodopa <sup>84</sup>	Inhibition of urate excretion
Niacin <sup>85,86</sup>	Decreased excretion of urate
Pancreatic enzymes: pancreatin and pancrelipase <sup>87</sup>	Ingestion of pancreatic enzyme products having high purine content
Pyrazinamide <sup>88,89</sup>	Inhibition of renal tubular urate secretion
Ribavirin and interferon <sup>90</sup>	Mechanism unclear; commonly associated with hemolysis
Aspirin (low dose) <sup>91</sup>	Inhibition of proximal tubular secretion of urate
Tacrolimus <sup>92,93</sup>	Reduced urate excretion
Teriparatide <sup>94</sup>	Mechanism unknown
Theophylline <sup>95,96</sup>	Interference with uric acid assay

GFR, glomerular filtration rate; NRTI, nucleoside reverse transcriptase inhibitor; WBC, white blood cell.

**TABLE 45.3 Comparison of EULAR and BSR/BHPR Guidelines for Gout**

EULAR Propositions for Gout Management <sup>39</sup>	A + B (%) <sup>a</sup>	BSR/BHPR Guidelines for Management of Gout <sup>38</sup> : Summary of Selected Recommendations	SOR (Grade) <sup>b</sup>
<b>TREATMENT OF ACUTE GOUT</b>			
Oral NSAIDs or colchicine are first-line agents for systemic treatment of acute gout. In the absence of contraindications, an NSAID is a convenient and well-accepted treatment.	100	Treat acute gout as soon as possible with an NSAID, colchicine, or corticosteroid and continue until attack is terminated (1–2 weeks).	A
		NSAIDs are drug of choice provided no contraindications for use.	A
		All NSAIDs are equally effective when given in optimal doses.	A
		In patients at risk for GI toxicity from NSAIDs, appropriate GI protection should be used.	A
High doses of colchicine cause side effects and low doses (e.g., 0.5 mg TID) can be sufficient. (The more recent AGREE <sup>40</sup> trial showed colchicine 1.2 mg orally followed by 0.6 mg 1 hour later to be as effective and safer than larger doses.)	82	Colchicine is effective for acute gout, but slower to work than NSAIDs.	A
		Use colchicine in doses of 0.5 mg two to four times daily; avoid dosing more frequently (every 2 hours) to prevent adverse effects (diarrhea).	C; B
Intra-articular aspiration and injection of a long-acting steroid are effective and safe treatments for an acute attack.	88	Corticosteroids are effective for acute gout in patients who cannot tolerate NSAIDs or are refractory to other therapy: may use intramuscularly, intravenously, or intra-articularly; the latter is highly effective in monoarticular gout.	A; B
<b>TREATMENT OF HYPERURICEMIA TO PREVENT RECURRENT GOUT</b>			
ULT is indicated in patients with recurrent acute attacks, arthropathy, tophi, or radiographic changes of gout.	100	Allopurinol should not be started in an acute attack; it may prolong or precipitate further attack.	B
		Start long-term ULT in uncomplicated gout only if two or more attacks occur per year.	B
		Long-term ULT may be started as soon as acute gout has resolved in patients with comorbidities (CrCl <80 mL/minute, uric acid stones, continued diuretic use).	B
The therapeutic goal of ULT (i.e., SUA less than or equal to the saturation point for MSU of 6 mg/dL) is to promote crystal dissolution and prevent crystal formation.	100	Plasma urate goal is <300 mmol/L (<5 mg/dL).	C
Allopurinol, an appropriate long-term urate-lowering agent, should be initiated at 100 mg/day and increased by 100 mg every 2–4 weeks, if required. The dose must be adjusted in patients with renal impairment. If toxicity occurs, options include other xanthine oxidase inhibitors, a uricosuric agent, or allopurinol desensitization (if mild rash).	100	Initial ULT should be allopurinol starting with 50–100 mg/day and increasing by 50–100 mg every few weeks until therapeutic goal of SUA <300 mmol/L to a maximum of 900 mg/day allopurinol (adjust as necessary for renal dysfunction).	B

TABLE 45.3 Comparison of EULAR and BSR/BHPR Guidelines for Gout (Continued)

EULAR Propositions for Gout Management <sup>39</sup>	A + B (%) <sup>a</sup>	BSR/BHPR Guidelines for Management of Gout <sup>38</sup> : Summary of Selected Recommendations	SOR (Grade) <sup>b</sup>
Uricosuric agents (e.g., probenecid, sulfapyrazone) can be alternatives to allopurinol in patients with normal renal function, but are relatively contraindicated in patients with urolithiasis. Benzbromarone can be used in patients with moderate renal insufficiency, but carries a small risk of hepatotoxicity.	94	Uricosuric agents should be used only as a second-line drug in those underexcreting urate and in those resistant to or intolerant of allopurinol.	B
Prophylaxis against acute attacks for up to 6 months of initiation of ULT with colchicine (0.5–1 mg/day) or NSAID (with gastroprotection, if indicated).	100	When initiating allopurinol, prevent gout attacks by giving colchicine 0.5 mg twice daily for up to 6 months; if patient cannot tolerate colchicine, NSAIDs or COX-2 inhibitors can be substituted but limit to 6 weeks. If an acute attack occurs while on allopurinol, do not stop allopurinol but treat acute attack as usual with NSAIDs, colchicine, or corticosteroids.	A; C  A
<b>ADJUNCTIVE THERAPY TO PREVENT RECURRENT GOUT</b>			
When gout is associated with diuretic therapy, discontinue the diuretic if possible; consider losartan for hypertension and fenofibrate for hyperlipidemia because of their modest uricosuric effects.	100	If diuretics are being used to treat hypertension, consider alternative agents according to hypertension guidelines, with the exception of the treatment of heart failure.	C
Associated comorbidity and risk factors (e.g., hyperlipidemia, HTN, hyperglycemia, obesity, smoking) should be addressed.	94	Losartan for hypertension and fenofibrate or atorvastatin for hyperlipidemia may be merited for their uricosuric effect (atorvastatin has a smaller effect than fenofibrate).	B
Optimal treatment of gout requires nonpharmacologic and pharmacologic modalities tailored to specific risk factors (SUA levels, prior attacks); clinical phase of gout; and general risk factors (age, comorbidity, drug interactions).	100	Dietary management: include skim milk and yogurt; favor soybeans and vegetable proteins; restrict intake of high-purine food (<200 mg/day); avoid liver, kidneys, shellfish, and yeast extracts; reduce intake of red meat; favor cherries, fresh or preserved.	B
Patient education and lifestyle modifications (e.g., weight loss if obese, reduced beer and other alcohol consumption) are important.	100	Alcohol consumption <sup>c</sup> : restrict to <21 units/week (men) and <14 units/week (women); two 125-mL glasses of wine per day are usually safe; two 25-mL glasses of spirits per day are safer than 1/2 pint of many beers.	B

<sup>a</sup>A + B (%) is the percentage of fully (A) and strongly (B) recommended, based on EULAR ordinal scale.<sup>b</sup>SOR is the strength of recommendation (Grade A based on randomized controlled trials, Grade B based on nonrandomized controlled studies, Grade C based on expert opinion).<sup>c</sup>1 unit equals 10 mL of pure alcohol, so the number of units per drink depends on its alcohol content; generally, 6 ounces of wine is about 2 units, a 12-ounce beer is 1.5 units, and a 2-ounce shot is about 1.2 units.

BSR/BHPR, British Society for Rheumatology/British Health Professionals in Rheumatology; COX-2, cyclo-oxygenase-2; CrCl, creatinine clearance; EULAR, European League Against Rheumatism; GI, gastrointestinal; HTN, hypertension; MSU, monosodium urate; NSAID, nonsteroidal anti-inflammatory drug; SUA, serum uric acid; TID, three times daily; ULT, urate-lowering therapy.

Options include xanthine oxidase inhibitors (allopurinol, febuxostat) and uricosuric agents (probenecid). Xanthine oxidase inhibitors are first-line treatment hyperuricemia.

- Vitamin C may be considered an option for adjunct therapy for patients requiring additional urate lowering.

## Drug Therapy

- **NSAIDs** are the preferred first-line therapy for reduction of acute gouty inflammation, given on a scheduled basis (e.g., naproxen 500 mg twice daily or indomethacin 50 mg three times daily). No one NSAID has been found to be more effective than another; choice of agent should be determined by patient risk factors for gastrointestinal (GI) bleeding and inhibition of platelet aggregation. COX-2 inhibitors are an option when GI bleeding is a concern.
- **Colchicine** has been successfully used to treat acute gouty attacks for many years. Dosing for Colcris, the only FDA-approved colchicine product, is 1.2 mg followed by 0.6 mg in 1 hour for the treatment of acute gout, and 0.6 mg once to twice daily for gout prophylaxis (maximum dose of 1.2 mg daily). Colchicine should be used with caution in patients with reduced renal function (CrCl <30 mL/minute) or in patients taking other drugs that inhibit either cytochrome P450 or P-glycoprotein (Table 45.4).

TABLE 45.4 Colchicine Drug Interactions

Precipitant Drug	Object Drug <sup>a</sup>	Description
Acidifying agents	Colchicine	↓ The action of colchicine is inhibited by acidifying agents. Avoid coadministration. <sup>b</sup>
Alkalinizing agents	Colchicine	↑ The action of colchicine is potentiated by alkalinizing agents. Avoid coadministration. <sup>b</sup>
Digoxin Colchicine	Colchicine Digoxin	↑ The risk for myopathy or rhabdomyolysis may be increased. If coadministration cannot be avoided, monitor the patient for signs of any unexplained muscle pain, tenderness, or weakness. If colchicine toxicity is suspected, discontinue colchicine. <sup>c</sup>
Cyclosporine Colchicine	Colchicine Cyclosporine	↑ The risk for myopathy or rhabdomyolysis may be increased. If coadministration cannot be avoided, monitor the patient for signs of any unexplained muscle pain, tenderness, or weakness. If colchicine toxicity is suspected, discontinue colchicine. <sup>c</sup>
Fibric acids (e.g., fenofibrate, gemfibrozil) Colchicine	Colchicine Fibric acids (e.g., fenofibrate, gemfibrozil)	↑ The risk for myopathy or rhabdomyolysis may be increased. If coadministration cannot be avoided, monitor the patient for signs of any unexplained muscle pain, tenderness, or weakness. If colchicine toxicity is suspected, discontinue colchicine. <sup>c</sup>
HMG-CoA reductase inhibitors (e.g., atorvastatin, fluvastatin, pravastatin, simvastatin) Colchicine	Colchicine HMG-CoA reductase inhibitors (e.g., atorvastatin, fluvastatin, pravastatin, simvastatin)	↑ The risk for myopathy or rhabdomyolysis may be increased. If coadministration cannot be avoided, monitor the patient for signs of any unexplained muscle pain, tenderness, or weakness. If colchicine toxicity is suspected, discontinue colchicine. <sup>c</sup>

TABLE 45.4 Colchicine Drug Interactions (Continued)

Precipitant Drug	Object Drug <sup>a</sup>	Description
Moderate CYP3A4 inhibitors (e.g., aprepitant, diltiazem, erythromycin, fluconazole, fosamprenavir, verapamil)	Colchicine	↑ Colchicine plasma concentrations may be elevated, increasing the risk of toxicity (e.g., myopathy). Coadminister with caution, starting at reduced colchicine doses and increased monitoring of creatine phosphokinase and for adverse reactions. If colchicine toxicity is suspected, discontinue colchicine. <sup>c</sup>
P-glycoprotein inhibitors (e.g., cyclosporine, ranolazine)	Colchicine	↑ Life-threatening and fatal drug interactions have been reported in patients receiving colchicine and a P-glycoprotein inhibitor. Coadministration of colchicine and a P-glycoprotein inhibitor to patients with renal or hepatic impairment is contraindicated. If treatment with a P-glycoprotein inhibitor is needed in patients with healthy renal and hepatic function, the colchicine dose may need to be reduced or withheld. If colchicine toxicity is suspected, discontinue colchicine. <sup>c</sup>
Strong CYP3A4 inhibitors (e.g., atazanavir, clarithromycin, indinavir, itraconazole, ketoconazole, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin, voriconazole)	Colchicine	↑ Life-threatening and fatal drug interactions have been reported in patients receiving colchicine and a strong CYP3A4 inhibitor. Coadministration of colchicine and a strong CYP3A4 inhibitor to patients with renal or hepatic impairment is contraindicated. If treatment with a strong CYP3A4 inhibitor is needed in patients with healthy renal and hepatic function, the colchicine dose may need to be reduced or withheld. If colchicine toxicity is suspected, discontinue colchicine. <sup>c</sup>
Colchicine	CNS depressants	↑ Colchicine may increase sensitivity to the action of CNS depressants. Monitor the patient and adjust the CNS depressant dose as needed. <sup>b</sup>
Colchicine	Sympathomimetics	↑ The action of sympathomimetics may be increased. Monitor the patient and adjust the sympathomimetic dose as needed. <sup>b</sup>

<sup>a</sup>↑ = object drug increased; ↓ = object drug decreased.

CNS, central nervous system; CYP, cytochrome P-450; HMG-CoA,  $\beta$ -hydroxy- $\beta$ -methylglutaryl-CoA.

<sup>b</sup>Colchicine [package insert]. Corona, CA: Watson; June 2001.

<sup>c</sup>Colcris [package insert]. Philadelphia, PA: AR Scientific; December 2009.

Reprinted with permission from Facts & Comparisons eAnswers. <http://online.factsandcomparisons.com/MonoDisp.aspx?monoID=fandc-hcp12251&quick=275331%7c5&search=275331%7c5&isstemmed=True>. Accessed November 14, 2010.

- **Corticosteroids** are considered second-line therapy for management of an acute gout attack, being particularly useful in the elderly, those with renal disease, or those who cannot tolerate NSAIDs or colchicine and are not candidates for intra-articular glucocorticoid injection because of polyarticular disease. Glucocorticoids should be used with caution in patients with heart failure, poorly controlled hypertension, or glucose intolerance, but they may be used in patients with moderate to severe renal insufficiency. Prednisone (or other equivalent

glucocorticoid) in doses of 30 to 50 mg once daily or in two divided doses until flare resolution begins, and we then taper the dose of glucocorticoids, usually over 7 to 10 days.

- **Xanthine oxidase inhibitors** inhibit the production of uric acid. Guidelines recommend that febuxostat be used only in patients who are intolerant of or have contraindications to allopurinol therapy, or for those who do not achieve an adequate response to allopurinol.
  - **Allopurinol** is initiated at 50 to 100 mg/day with the dose increased in 50- to 100-mg increments every 2 to 4 weeks until SUA concentrations are at the desired goal of <6 mg/dL or the patient develops intolerance.
  - **Febuxostat** is initiated at 40 mg once daily with a dose increase to 80 mg daily if SUA concentrations is not <6 mg/dL by 2 weeks of therapy.
- **Uricosuric agents** increase the excretion of uric acid. They should not be used in patients with impaired renal function or urolithiasis.
  - **Probenecid** is initiated at 250 mg twice daily for one week; the dose may be increased to 500 mg twice daily with a maximum dose of 2 g/day.
- **Recombinant urate oxidase drugs (uricase)** convert uric acid into allantoin, which is readily excreted into urine.
  - **Pegloticase**, 8 mg given IV over 2 hours every 2 weeks, is used for the treatment of chronic gout in adult patient who are refractory to or unable to tolerate conventional therapy. Considerable risk for anaphylaxis and infusion site reactions exists; premedication with an antihistamine and corticosteroids is needed.

## Connective Tissue Disorders\*

### General Principles

- Connective tissue disorders (CTDs) and rheumatic diseases encompass a wide range of disorders that are inflammatory in nature and are related to the immune system.
- CTDs that are encountered in clinical practice include systemic lupus erythematosus (SLE), scleroderma, polymyalgia rheumatica, temporal arteritis, Reiter syndrome, polymyositis, and dermatomyositis.
- Patient-reported history of symptoms, results of the physical examination, and laboratory testing help guide the diagnosis of CTD.

### Systemic Lupus Erythematosus

- SLE is a complex autoimmune disease where autoantibody formation related to immunoglobulin G occurs, resulting in immune complexes and tissue damage. Multiple organ systems can be affected (Table 46.1). Genetic and environmental factors likely lead to the disease becoming active.
- Diagnosis is made when 4 of the 11 criteria in Table 46.2 are present.
- There is no cure for SLE; treatment involves controlling acute symptoms and providing maintenance therapy to prevent exacerbations and keep clinical manifestations at acceptable levels.
- Nonpharmacologic treatment includes the use of sunscreen, protective clothing, avoiding ultraviolet (UV) light, stress management, and exercise. Ice therapy can help relieve pain and swelling of joints.

TABLE 46.1 Signs and Symptoms of Systemic Lupus Erythematosus

Organ System	Sign
Cutaneous	Malar rash, discoid rash, mouth/nasal sores, Raynaud phenomenon, cutaneous vasculitis, alopecia
Musculoskeletal	Arthritis, arthralgia, myositis
Renal	Proteinuria, hematuria, red blood cell casts, nephrotic syndrome, elevated creatinine
Cardiopulmonary	Pericarditis, pleurisy, pleural effusions, pneumonitis, pulmonary emboli, pulmonary hypertension, myocardial infarction
Hematologic	Anemia, leukopenia, thrombocytopenia, antiphospholipid syndrome
Neurologic	Seizure, psychosis, stroke, transverse myelitis, peripheral neuropathy
Gastrointestinal	Esophageal dysmotility, intestinal vasculitis, nausea, abdominal pain
Constitutional	Fever, weight loss, lymphadenopathy

Source: Guidelines for referral and management of systemic lupus erythematosus in adults. American College of Rheumatology Ad Hoc Committee on Systemic Lupus Erythematosus Guidelines. *Arthritis Rheum.* 1999;42:1785.

\*The reader is referred to Chapter 46, Connective Tissue Disorders, written by Julie L. Olenak, PharmD, and Jonathan D. Ference, PharmD, BCPS, in the 10th edition of *Applied Therapeutics: The Clinical Use of Drugs* for a more in-depth discussion. All notations to reference numbers are based on the reference list at the end of that chapter. The editor of this handbook expresses her thanks to Drs. Olenak and Ference and acknowledges that this chapter is based on their work.



TABLE 46.2 1997 Revised Criteria for Classification of Systemic Lupus Erythematosus

Criteria	Explanation <sup>a</sup>
Malar rash	Fixed erythema, flat or raised
Discoid rash	Erythematous raised patches with adherent keratotic scaling and follicular plugging; atrophic scarring may occur in older lesions
Photosensitivity	Skin rash resulting from an unusual reaction to sunlight by patient history or observed by physician
Oral ulcers	Painless oral or nasopharyngeal ulcers observed by physician
Arthritis	Nonerosive arthritis involving two or more peripheral joints; characterized by tenderness, swelling, or effusion
Serositis	Evidence of pleuritis or pericarditis documented by ECG or rub heard by physician or evidence of pericardial effusion
Renal disorder	As manifested by persistent proteinuria (>0.5 g/day or >3+) or cellular casts
Neurologic disorder	Seizures or psychosis occurring without any other explanation
Hematologic disorder	Leukopenia (<4,000/ $\mu$ L), or hemolytic anemia, or lymphopenia (<1,500/ $\mu$ L), or thrombocytopenia (<100,000/ $\mu$ L)
Immunologic disorder	Anti-double-stranded DNA antibody, or anti-Smith antibody, or antiphospholipid antibodies
Antinuclear antibody	An abnormal ANA titer in the absence of drugs known to be associated with drug-induced lupus

<sup>a</sup>The diagnosis of systemic lupus erythematosus is made when a patient has 4 or more of the 11 criteria at any time during the course of the disease with 95% specificity and 85% sensitivity.

ANA, antinuclear antibody; ECG, electrocardiogram.

Source: Adapted with permission from Tan EM et al. The 1982 revised criteria for the classification of systemic lupus erythematosus. *Arthritis Rheum.* 1982;25:1271; Hochberg MC. Updating the American College of Rheumatology revised criteria for the classification of systemic lupus erythematosus [letter]. *Arthritis Rheum.* 1997;40:1725; Guidelines for Referral and Management of Systemic Lupus Erythematosus in Adults. American College of Rheumatology Ad Hoc Committee on Systemic Lupus Erythematosus Guidelines. *Arthritis Rheum.* 1999;42:1785.

- Pharmacological therapy is selected on the basis of disease severity. Treatments include nonsteroidal anti-inflammatory drugs (NSAIDs), antimalarials, corticosteroids, and immunosuppressant medications (Table 46.3). NSAIDs help relieve pain and swelling. Hydroxychloroquine helps treat skin manifestations and constitutional symptoms. Immunosuppressants are indicated for severe disease if organ damage is occurring or if symptoms are not responding to other therapies. Belimumab is indicated in patients who are autoantibody positive who have active disease.

## Drug-Induced Lupus

- Many medications have been associated with lupus (Table 46.4); autoantibodies develop and patients present with symptoms similar to lupus. Musculoskeletal (arthralgias, myalgias) and constitutional (fatigue, fever) symptoms are most common.
- The risk of developing drug-induced lupus increases with increasing duration of exposure or increasing dose.
- Symptoms usually resolve within days to weeks after stopping the offending drug. NSAIDs can help resolve severe symptoms. No additional treatment is usually needed or warranted.

## Systemic Sclerosis (Scleroderma)

- Scleroderma is a CTD associated with autoimmunity characterized by excessive extracellular matrix deposition and vascular injury to the skin and other visceral organs.
- The most common subsets include limited cutaneous and diffuse cutaneous (Table 46.5). Manifestations of systemic sclerosis differ on the basis of organ system involved (Table 46.6).
- No specific therapy exists; treatment generally targets the specific organ affected (Table 46.7).

TABLE 46.3 Common Doses of Medications in Treatment of Systemic Lupus Erythematosus

Medication	Dose
Hydroxychloroquine <sup>a,b</sup>	200–400 mg orally divided twice daily
Prednisone (or equivalent) <sup>c,d</sup>	0.125–2 mg/kg orally once daily or divided twice daily if high dose
Mycophenolate mofetil <sup>a,b,d</sup>	1–3 g orally divided twice daily
Azathioprine <sup>d</sup>	1–3 mg/kg once or twice daily
Cyclophosphamide <sup>b,d</sup>	IV: 0.5–1 g/m <sup>2</sup> monthly for initial dose plus 6 months, then quarterly for 1 year once remission achieved Oral: 1–2 mg/kg/day
Belimumab <sup>a</sup>	10 mg/kg IV every 2 weeks for the first three doses and then monthly
Methotrexate <sup>a,d</sup>	5–15 mg orally as a single weekly dose or as three divided doses per week every 12 hours (i.e., 2.5 mg × three doses 12 hours apart)

IV, intravenous.

<sup>a</sup>Facts and Comparison database online. <http://online.factsandcomparisons.com/>. Accessed June 15, 2011

<sup>b</sup>Lexi-comp database online. <http://www.crlonline.com/crlsql/servlet/crlonline>. Accessed June 15, 2011.

<sup>c</sup>Kirou K et al. Systemic glucocorticoid therapy in systemic lupus erythematosus. In: Wallace D, Hahn BH, eds. *Dubois' Lupus Erythematosus*. 7th ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2007:1181.

<sup>d</sup>Tassiulas I, Boumpas D. Clinical features and treatment of systemic lupus erythematosus. In: Firestein G et al, eds. *Kelley's Textbook of Rheumatology*. 8th ed. Philadelphia, PA: Saunders Elsevier; 2009:1263.

TABLE 46.4 Medications Associated with Drug-Induced Lupus

Risk	Medications
High	Procainamide, hydralazine, and tumor necrosis factor- $\alpha$ blockers
Moderate	Quinidine
Low	Methyldopa, captopril, enalapril, acebutolol, chlorpromazine, isoniazid, minocycline, carbamazepine, propylthiouracil, interferon- $\alpha$ , D-penicillamine, and sulfasalazine

Source: Tassiulas I, Boumpas D. Clinical features and treatment of systemic lupus erythematosus. In: Firestein G et al, eds. *Kelley's Textbook of Rheumatology*. 8th ed. Philadelphia, PA: Saunders Elsevier; 2009:1263; Rubin R. Drug-induced lupus. In: Wallace D, Hahn BH, eds. *Dubois' Lupus Erythematosus*. 7th ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2007:870.

TABLE 46.5 Common Clinical Features of Systemic Sclerosis

Subset	Skin Fibrosis	Lung Involvement	Visceral Organ Involvement	Physical Examination Findings
Limited cutaneous	Areas distal to the elbows and knees <sup>a</sup>	Pulmonary arterial hypertension	Severe GERD and Raynaud phenomenon	Telangiectasia, calcinosis cutis, sclerodactyly, digital ischemic complications
Diffuse cutaneous	Areas proximal or distal to the elbows and knees <sup>a</sup>	Interstitial lung disease	Scleroderma renal crisis	Tendon friction rubs, pigment changes

<sup>a</sup>May affect the face.

GERD, gastroesophageal reflux disease.

Source: Adapted with permission from Hinchcliff M, Varga J. Systemic sclerosis/scleroderma: a treatable multisystem disease. *Am Fam Physician*. 2008;78:961.

TABLE 46.6 Manifestations of Systemic Sclerosis

Organ System	Manifestations
Cardiovascular	Abnormal cardiac conduction, congestive heart failure, pericardial effusion, digital ischemic changes, Raynaud phenomenon
Gastrointestinal	Barrett esophagitis or strictures, gastroesophageal reflux disease, dysphagia, halitosis, chronic cough, dental erosions
Genitourinary	Sexual dysfunction, dyspareunia, impotence
Musculoskeletal	Flexion contractures, muscle atrophy, puffy hands, inability to make a tight fist, weakness
Pulmonary	Interstitial lung disease, pulmonary arterial hypertension, basilar and course crackles, dyspnea on exertion
Renal	Renal crisis
Skin	Calcinosis, pruritus, thickened skin, tight skin, excoriations, scabbing, loss of pigmentation

Source: Adapted with permission from Hinchcliff M, Varga J. Systemic sclerosis/scleroderma: a treatable multisystem disease. *Am Fam Physician*. 2008;78:961.

TABLE 46.7 Treatment Options for Manifestations of Systemic Sclerosis

Manifestation	Treatment Options
Raynaud phenomenon	Nifedipine, verapamil, losartan, prazosin, iloprost
Pulmonary hypertension	Bosentan, sildenafil, enalapril, iloprost
Interstitial lung disease	Cyclophosphamide, prednisone
Renal crisis	Angiotensin converting enzyme inhibitors, dialysis or kidney transplant
Skin fibrosis	Methotrexate, cyclosporine, D-penicillamine
Arthralgias	Acetaminophen and NSAIDs
GERD	Proton pump inhibitors, H <sub>2</sub> antagonists, prokinetic agents
Pruritus	Antihistamines, low-dose topical steroids

GERD, gastroesophageal reflux disease; NSAID, nonsteroidal anti-inflammatory drug; H<sub>2</sub>, Type 2 histamine receptor.

Source: Adapted with permission from Usatine RP, Diaz L. Scleroderma (progressive systemic sclerosis). Ebell MH et al. Database online. October 15, 2009. John Wiley & Sons. Accessed March 18, 2011.

## Polymyalgia Rheumatica (PMR) and Temporal Arteritis (Giant Cell Arteritis)

- Polymyalgia rheumatica (PMR) and giant cell arteritis (GCA) are two closely related syndromes that usually affect the elderly and frequently occur together. PMR is characterized by aching and morning stiffness in the cervical region, and shoulder and pelvic girdles. GCA, the most common vasculitis in the elderly, often manifests as a new headache or one that has occurred for 2 to 3 months. Common findings associated with both conditions are shown in Table 46.8.
- The primary risk factor for both conditions is increasing age and female gender.
- Prednisone is considered first-line therapy, with higher doses needed if GCA is present. IV steroids for 3 days should be considered if patients are exhibiting visual symptoms in order to prevent blindness. Oral therapy should continue until symptoms resolve and erythrocyte sedimentation rate (ESR) returns to normal.

## Reiter Syndrome

- Reiter syndrome is a form of reactive arthritis defined as peripheral arthritis often accompanied by one of more extra-articular manifestations (Table 46.9).

**TABLE 46.8 Common Findings Associated with Polymyalgia Rheumatica and Giant Cell Arteritis**

Polymyalgia Rheumatica	Giant Cell Arteritis
Age $\geq$ 50 years	Age $\geq$ 50 years
ESR > 50 mm/hour	ESR > 50 mm/hour
Anemia (mild, normochromic, normocytic)	Anemia
Aching, pain, and morning stiffness in the shoulders and upper arms, hips and thighs, or neck and torso	Headache: temporal with temporal artery involvement, or occipital with occipital artery involvement
Symptoms of systemic inflammation	Visual symptoms or jaw claudication Fever, weight loss, depression, fatigue Arthralgias

ESR, erythrocyte sedimentation rate.

Source: Adapted with permission from Unwin B et al. Polymyalgia rheumatica and giant cell arteritis. *Am Fam Physician.* 2006;74:1547.

**TABLE 46.9 Clinical Manifestations of Reiter Syndrome**

Manifestation Type	Manifestations
Arthritic	Asymmetric, lower extremities, enthesitis, sacroiliitis
Cardiac	Aortitis, aortic insufficiency, heart block
Genitourinary	Nonspecific urethritis, cervicitis, cystitis
Ocular	Conjunctivitis, acute anterior uveitis
Skin	Keratoderma, balanitis circinata, tongue ulcerations

Source: Adapted with permission from Barth WF, Segal K. Reactive arthritis (Reiter's syndrome). *Am Fam Physician.* 1999;60:499.

- Reactive arthritis usually occurs after an infection in a genetically susceptible person. Patients present with mucocutaneous lesions, joint stiffness, myalgia, and low back pain that is worse at rest.
- Oral NSAIDs can be used for pain management. Intra-articular corticosteroid injections may be helpful with joint pain and swelling. Antibiotics should be used for patients with documented infection.

## Polymyositis and Dermatomyositis

- Polymyositis (PM) and dermatomyositis (DM) are idiopathic autoimmune and inflammatory disorders characterized by the presence of inflammatory myopathies (Table 46.10). DM involves specific skin manifestations as well.

**TABLE 46.10 Classification of Polymyositis and Dermatomyositis**

Polymyositis	Dermatomyositis
<ul style="list-style-type: none"> <li>• Adult</li> <li>• Pediatric</li> <li>• Inclusion-body myositis</li> <li>• Overlap (myositis associated with another CTD)</li> </ul>	<ul style="list-style-type: none"> <li>• Without muscle weakness:             <ul style="list-style-type: none"> <li>• Amyopathic dermatomyositis or dermatomyositis sine myositis</li> </ul> </li> <li>• With muscle weakness:             <ul style="list-style-type: none"> <li>• Adult: associated with cancer or not associated with cancer</li> <li>• Pediatric</li> </ul> </li> </ul>

CTD, connective tissue disorder.

Source: Adapted with permission from Drake LA et al. Guidelines of care of dermatomyositis. *J Am Acad Dermatol.* 1996;34(5 Pt 1):824.

- Symptom onset is insidious with patients complaining of muscle weakness of the trunk, shoulders, hip girdles, upper arms, thighs, neck, and pharynx. Frequent falls, fatigue, malaise, weight loss, shortness of breath, and low-grade fever are also often present.
- Goals of therapy are to improve muscle weakness and improve activities of normal living. Therapy is aimed at reducing the risk of respiratory failure, renal failure, and cardiomyopathy.
- Initial therapy is high-dose corticosteroids for several months followed by a slow taper to the lowest effective dose. Supportive therapy (bed rest, physiotherapy, warm baths, moist heat application to the affected area) can improve muscle stiffness.

## Contraception\*

### General Principles

- Proper use and understanding of contraceptives is important for preventing unintended pregnancies.
- Hormonal contraceptives can include combinations of estrogens and progestins (combination hormonal contraceptives [CHC]) or progestins only.
  - Estrogens prevent development of the dominant follicle by suppressing follicle-stimulating hormone secretion and stabilizing the endometrial lining. Large postcoital doses of estrogens inhibit ovum implantation, accelerate ovum transport, decrease time available for fertilization, and break down the corpus luteum.
  - Progestins prevent ovulation by suppressing luteinizing hormone. They also hamper transport of sperm by thickening cervical mucus.

### Goals of Therapy

- The goal of contraceptive therapy is to prevent unintended pregnancies.

### Patient Assessment

- Contraceptive choice is based on several factors including formulation, hormone content, effectiveness, side-effect profile, cost, accessibility, past medical history, concomitant medication use, privacy of use, prevention of sexually transmitted diseases, and return of fertility time.
- Risks associated with CHC use include thromboembolic events, myocardial infarction (with higher estrogen doses), ischemic stroke (in those with a history of migraines), hypertension, hepatotoxicity, and gallstones. All patients using CHCs should be counseled about the venous thromboembolism (VTE) warning signs (Table 47.1). Women 35 years of age and older and who smoke 15 or more cigarettes a day should not use CHCs as a method of contraception.
- Concomitant therapy with various medications can interfere with CHC efficacy (Table 47.2).

TABLE 47.1 Pill Early Danger Signs (ACHES)

Signals	Possible Problem
Abdominal pain (severe)	Gallbladder disease, hepatic adenoma, blood clot, pancreatitis
Chest pain (severe), shortness of breath, or coughing up blood	Blood clot in lungs or myocardial infarction
Headaches (severe)	Stroke, hypertension, or migraine headache
Eye problems: blurred vision, flashing lights, or blindness	Stroke, hypertension, or temporary vascular problem
Severe leg pain (calf or thigh)	Blood clot in legs

\*The reader is referred to Chapter 47, Contraception, written by Shareen Y. El-Ibiary, PharmD, BCPS, and Jennifer L. Hardman, PharmD, in the 10th edition of *Applied Therapeutics: The Clinical Use of Drugs* for a more in-depth discussion. All notations to reference numbers are based on the reference list at the end of that chapter. The editor of this handbook expresses her thanks to Drs. El-Ibiary and Hardman and acknowledges that this chapter is based on their work.

TABLE 47.2 Common Combined Oral Contraceptive Drug<sup>a</sup> Interactions

Drugs That Increase Effect of CHCs or Side Effects of CHCs	Drugs/Herbals That Decrease the Effect of CHCs	Drugs That <i>May</i> Decrease the Effect of CHCs (controversial)	Metabolism or Clearance Altered by CHCs (levels of drug listed may either increase or decrease depending on patient)
Acetaminophen	Amprenavir	Amoxicillin	Acetaminophen
Ascorbic acid	Aprepitant	Ampicillin	Amprenavir
Atazanavir	Barbiturates	Ciprofloxacin	Antidepressants, tricyclic
Atorvastatin	Bexarotene	Clarithromycin	Benzodiazepines
Ginseng	Bosentan	Colesevelam	$\beta$ -blockers
Indinavir	Carbamazepine	Doxycycline	Caffeine
Red clover <sup>b</sup>	Darunavir	Erythromycin	Clofibric acid
Rosuvastatin	Efavirez	Fluconazole	Corticosteroids
Tranexamic acid	Felbamate	Itraconazole	Cyclosporine
Voriconazole	Griseofulvin	Ketoconazole	Lamotrigine
	Isotretinoin	Metronidazole	Levothyroxine
	Lopinavir	Minocycline	Morphine
	Modafinil	Penicillins	Paclitaxel
	Mycophenolate mofetil	Phenylbutazone	Salicylic acid
	Nelfinavir	Ofloxacin	Selegiline
	Nevirapine	Tetracyclines	Tacrine
	Oxcarbazepine	Topiramate	Tacrolimus
	Phenobarbital		Theophyllines
	Phenytoin/ Fosphenytoin		Tizanidine
	Pioglitazone		Valproic acid
	Primidone		Voriconazole
	Red clover <sup>b</sup>		Warfarin <sup>c</sup>
	Rifamycins		
	Ritonavir		
	Rufinamide		
	Saquinavir		
	St. John's wort		
	Tipranavir		

<sup>a</sup>Drug list is not all inclusive. Some drug interactions may exist that are not cited in this table.

<sup>b</sup>Indicates drug may have variable effect on CHC, either increasing or decreasing effect.

<sup>c</sup>May decrease anticoagulant effect of warfarin, not warfarin drug levels.

CHC, combined hormonal contraceptive.

Source: Borgelt L et al., eds. *Women's Health Across the Lifespan: A Pharmacotherapeutic Approach*. Washington DC: American Society of Health Systems Pharmacists; 2010.

## Therapy

- The effectiveness of any contraceptive method depends on several factors. First-year failure rates of the various contraceptive options are shown in Table 47.3.
- Noncontraceptive benefits of CHCs include improving acne, regulating menstrual cycles, managing premenstrual syndrome and premenstrual dysphoric disorder, and protecting against endometrial cancer.
- Effects of estrogens and progestins are shown in Table 47.4. Adverse effects of CHCs include breakthrough bleeding, spotting, amenorrhea, nausea, headache, and weight gain.

## Hormonal Contraceptives

- Combined oral contraceptives (COCs) are available in varying strengths of estrogens and progestins, in different hormone phases, and in a variety of cycle lengths (Table 47.5). Mono-phasic pills are preferred when continuous ovarian suppression is desired.

**TABLE 47.3 Percentage of Women Experiencing an Unintended Pregnancy During the First Year of Typical Use and the First Year of Perfect Use of Contraception and the Percentage Continuing Use at the End of the First Year: United States**

Method	% of Women Experiencing an Unintended Pregnancy within the First Year of Use		% of Women Continuing Use at 1 Year <sup>c</sup>	Relative Cost <sup>k</sup>
	Typical Use <sup>a</sup>	Perfect Use <sup>b</sup>		
Chance <sup>d</sup>	85	85	—	
Periodic abstinence	25	—	51	None
Calendar	—	9	—	
Ovulation method	—	3	—	
Symptothermal <sup>e</sup>	—	2	—	
Postovulation	—	1	—	
Withdrawal	19	4	—	
Spermicides <sup>f</sup>	29	18	42	\$–\$\$
Barrier methods				
Cap <sup>g</sup>				\$\$\$
Parous women	32	20	46	
Nulliparous women	16	9	57	
Sponge				\$\$
Parous women	40	20	42	
Nulliparous women	20	9	57	
Diaphragm <sup>g</sup>	16	6	57	\$\$\$
Condom <sup>h</sup>				\$
Female (Reality)	21	5	49	
Male	15	2	53	
Hormonal contraceptives				
Injectable MPA (Depo-Provera)	3	0.3	56	\$\$\$ <sup>l</sup>
Pill				
Progestin-only	8	0.3	68	\$\$
Combined	8	0.3	68	\$\$
Transdermal patch	8	0.3	68	\$\$
Vaginal ring	8	0.3	68	\$\$
IUD/IUS	—	—	—	\$\$\$ <sup>l</sup>
Copper (ParaGard T 380 A)	0.8	0.6	78	
Levonorgestrel (Mirena)	0.2	0.2	80	

Continued on following page



**TABLE 47.3 Percentage of Women Experiencing an Unintended Pregnancy During the First Year of Typical Use and the First Year of Perfect Use of Contraception and the Percentage Continuing Use at the End of the First Year: United States (Continued)**

Method	% of Women Experiencing an Unintended Pregnancy within the First Year of Use		% of Women Continuing Use at 1 Year <sup>c</sup>	Relative Cost <sup>k</sup>
	Typical Use <sup>a</sup>	Perfect Use <sup>b</sup>		
Female sterilization	0.5	0.5	100	\$\$\$\$ <sup>m</sup>
Male sterilization	0.15	0.10	100	\$\$\$\$ <sup>m</sup>
Emergency contraceptive pills				\$\$\$
Treatment initiated within 72 hours after unprotected intercourse reduces the risk of pregnancy by at least 75%. <sup>i</sup>				
LAM				None
LAM is a highly effective, temporary method of contraception. <sup>j</sup>				

<sup>a</sup>Among typical couples who initiate use of a method (not necessarily for the first time), the percentage who experience an accidental pregnancy during the first year if they do not stop use for any other reason.

<sup>b</sup>Among couples who initiate use of a method (not necessarily for the first time) and who use it perfectly (both consistently and correctly), the percentage who experience an accidental pregnancy during the first year if they do not stop use for any other reason. For patch and ring, the percentage comes from the package insert.

<sup>c</sup>Among couples attempting to avoid pregnancy, the percentage who continue to use a method for 1 year.

<sup>d</sup>The percentages becoming pregnant in the first year are based on data from populations in which contraception is not used and from women who cease using contraception to become pregnant. Among such populations, about 89% become pregnant within 1 year. This estimate was lowered slightly (to 85%) to represent the percentages who would become pregnant within 1 year among women now relying on reversible methods of contraception if they abandoned contraception altogether.

<sup>e</sup>Cervical mucus (ovulation) method supplemented by calendar in the preovulatory and basal body temperature in the postovulatory phases.

<sup>f</sup>Foams, creams, gels, vaginal suppositories, and vaginal film.

<sup>g</sup>With spermicidal cream or jelly.

<sup>h</sup>Without spermicides.

<sup>i</sup>The treatment schedule is one dose within 72 hours after unprotected intercourse, and a second dose 12 hours after the first dose. The US Food and Drug Administration has declared the following brands of oral contraceptives to be safe and effective for emergency contraception: Ovral or Ogestrel (one dose is two white pills); Alesse, Lessina, or Levlite (one dose is five pink pills); Nordette or Leven (one dose is four light-orange pills); Lo/Ovral, Lo/Ogestrel, Crystelle, Levora, or Quasence (one dose is four white pills); Triphasil or Tri-Levlen (one dose is four yellow pills); Jolesa, Portia, Seasonale, or Trivora (one dose is four pink pills); Seasonique (one dose is four light blue-green pills); Lutera (one dose is five white pills); Aviane (one dose is five orange pills); Enpresse (one dose is four orange pills).

<sup>j</sup>However, to maintain effective protection against pregnancy, another method of contraception must be used as soon as menstruation resumes, the frequency or duration of breast-feeding is reduced, bottle feeds are introduced, or the baby reaches 6 months of age.

<sup>k</sup>\$ up to \$10 per item, \$\$ up to \$50 per unit, \$\$\$ up to \$80 per unit, \$\$\$\$ more than \$80 per unit (These are approximate costs and may vary based on location of purchase and patient insurance.)

<sup>l</sup>Administration or clinic costs not included. Initial cost of product reported but over time similar to \$\$ cost (e.g., injectable MPA 150 mg/mL suspension one syringe approximately \$95, but works for 3 months, making its monthly cost similar to COCs or POPs, which range from \$20 to \$45 per pack; copper IUD and levonorgestrel IUS may cost more initially but will work for up to 10 and 5 years, respectively).

<sup>m</sup>Initial cost for procedure but over time may be more cost-effective than other products used frequently (e.g., monthly contraceptives, condoms, or spermicides).

IUD, intrauterine device; IUS, intrauterine system; LAM, lactational amenorrhea method; MPA, medroxyprogesterone acetate.

Source: Adapted with permission from Hatcher RA et al. *Contraceptive Technology*. 19th ed. New York, NY: Ardent Media Inc; 2007:24, Table 3.2; includes additional information from www.drugstore.com (accessed May 13, 2011), <http://www.americanpregnancy.org/preventingpregnancy/diaphragm.html> (accessed May 13, 2011), and <http://www.plannedparenthood.org/health-topics/birth-control/cervical-cap-20487.htm> (accessed May 13, 2011).

TABLE 47.4 Estrogenic, Progestogenic, and Combined Effects of Oral Contraceptive Pills

## Achieving Proper Hormonal Balance in an Oral Contraceptive

Estrogen		Progestin	
Excess	Deficiency	Excess	Deficiency
Nausea, bloating	Early or mid-cycle breakthrough bleeding	Increased appetite	Late breakthrough bleeding
Cervical mucorrhea, polyposis	Increased spotting	Weight gain	Amenorrhea
Melasma	Hypomenorrhea	Tiredness, fatigue	Hypermenorrhea
Hypertension		Hypomenorrhea	
Migraine headache		Acne, oily scalp <sup>a</sup>	
Breast fullness or tenderness		Hair loss, hirsutism <sup>a</sup>	
Edema		Depression	
		Monilial vaginitis	
		Breast regression	

<sup>a</sup>Result of androgenic activity of progestins.

Source: Reprinted with permission from Facts and Comparisons eAnswers. <http://online.factsandcomparisons.com/index.aspx>.

- Information to guide selection of an initial COC is shown in Figure 47.1. No COC has been shown to be superior to another.
- Backup contraception may be needed when first initiating COCs or when doses are missed (see manufacturer's directions).
- Progestin-only pills (minipill) offer the advantage of reduced estrogen side effects but may result in more breakthrough bleeding. Minipill must be taken same time every day. If >3 hours have passed from the scheduled time to take the pill, the patient will need to use a backup method.

### Contraceptive Patch and Ring

- The patch is applied once weekly for 3 consecutive weeks, followed by 1 week of no patch. Efficacy is reduced in patients >90 kg. If avoiding menses is desired, the patch-free week may be skipped and a new patch applied in week 4 for an extended-use regimen.
- The ring is inserted vaginally, kept in place for 3 weeks, and then removed for 1 week before a new ring is inserted. Extended use can be achieved by skipping the ring-free week and inserting a new ring on week 4.
- Risks and benefits of the patch and ring are similar to those of COCs. The patch may have an increased risk of VTE relative to COCs.

### Progestin Injections

- Medroxyprogesterone acetate (MPA) is available as a depot intramuscular or subcutaneous injection.
- Depot-Provera (150 mg IM) is given every 11 to 13 weeks. Depo-subQ provera (104 mg SQ) is given every 12 to 14 weeks.
- Benefits of the depot injections are ease of use, lack of estrogen side effects, and reduced dysmenorrhea and monthly blood loss. They should not be used in patients with breast cancer and should be used with caution in women with unexplained vaginal bleeding. Please keep in mind the blackbox warning associated with this medication and the risk of osteoporosis.

TABLE 47.5 Oral Contraceptives and Relative Progestin, Estrogen, and Androgen Activities

Ingredients	Brand Name Examples	Progestin Activity	Estrogen Activity	Androgen Activity	Unique Properties
<b>MONOPHASIC FORMULATIONS</b>					
Levonorgestrel 0.1 mg/EE 20 mcg	Alesse, Aviane, Lessina, Levlite, LoSeasonique, Lutera, Sronyx	Low	Low	Low	LoSeasonique contains 84 active pills; contains 7 pills of EE 10 mcg instead of placebos
Levonorgestrel 0.09 mg/EE 20 mcg	Lybrel	Low	Low	Low	Lybrel is a 1-year continuous formulation available in packs of 28 active pills
Norgestimate 0.25 mg/EE 35 mcg	MonoNessa, Ortho-Cyclen, Previfem, Sprintec	Low	Intermediate	Low	
Norethindrone 0.5 mg/EE 35 mcg	Brevicon, Modicon, Necon 0.5/35, Nortrel 0.5/35	Low	High	Low	
Norethindrone 0.4 mg/EE 35 mcg	Blaziva, Femcon Fe, Ovcon-35, Ovcon-35 Chewable, Zenchent	Low	High	Low	Femcon Fe and Ovcon-35 Chewable are chewable pills
Levonorgestrel 0.15 mg/EE 30 mcg	Levlen, Levora, Introvale, Jolessa, Nordette-28, Portia, Quasence, Seasonale, Seasonique	Intermediate	Low	Intermediate	Introvale and Seasonale contain 84 active pills, 7 placebo pills; Seasonique contains 84 active pills, 7 pills of EE 10 mcg instead of placebos
Norgestrel 0.3 mg/EE 30 mcg	Cryselle, Lo-Ovral, Low-Ogestrel	Intermediate	Low	Intermediate	
Norethindrone 1 mg/mestranol 50 mcg	Necon 1/50, Norinyl 1+50, Ortho-Novum 1/50	Intermediate	Intermediate	Intermediate	
Norethindrone 1 mg/EE 35 mcg	Genora 1/35, Cyclafem 1/35, Necon 1/35, Norethin 1/35, Norinyl 1+35, Nortrel 1/35, Ortho-Novum 1/35	Intermediate	High	Intermediate	
Norethindrone 1 mg/EE 50 mcg	Ovcon-50	Intermediate	High	Intermediate	
Norethindrone acetate 1 mg/EE 20 mcg	Junel Fe 1/20, Junel 21 Day 1/20, Loestrin 21 1/20, Loestrin Fe 1/20, Loestrin 24 Fe, Microgestin Fe 1/20	High	Low	Intermediate	“Fe” contains 75 mg ferrous fumarate instead of placebos; Loestrin 24 Fe contains 24 active pills and 4 pills of ferrous fumarate
Norethindrone acetate 1.5 mg/EE 30 mcg	Junel 1/35, Loestrin 21 1.5/30, Loestrin Fe 1.5/30, Microgestin Fe 1.5/30	High	Low	High	“Fe” contains 75 mg ferrous fumarate instead of placebos
Ethinodiol diacetate 1 mg/35 mcg EE	Demulen 1/35, Kelnor 1/35, Zovia 1/35E	High	Low	Low	
Desogestrel 0.15 mg/EE 20 mcg	Kariva, Mircette	High	Low	Low	Only 2 days of placebos; other 5 days contain EE 10 mcg
Desogestrel 0.15 mg/EE 30 mcg	Apri, Desogen, Ortho-Cept, Reclipsen, Solia	High	Intermediate	Low	

<b>Ingredients</b>	<b>Brand Name Examples</b>	<b>Progestin Activity</b>	<b>Estrogen Activity</b>	<b>Androgen Activity</b>	<b>Unique Properties</b>
Ethinodiol diacetate 1 mg/EE 50 mcg	Demulen 1/50, Zovia 1/50 E	High	Intermediate	Low	
Norgestrel 0.5 mg/EE 50 mcg	Ovral, Ogestrel	High	High	High	
Norethindrone 0.8 mg/EE 25 mcg	Generess Fe	No data	No data	No data	"Fe" contains 75 mg ferrous fumarate instead of placebo; Generess Fe contains 24 active pills and 4 pills of ferrous fumarate, chewable formulation
Norethindrone 1 mg/EE 10 mcg	Lo Loestrin Fe	No data	No data	No data	Lo Loestrin Fe contains 24 active pills, 2 pills of 10 mcg EE, and 2 pills of 75 mg ferrous fumarate
Drospirenone 3 mg/EE 20 mcg/levomefolate calcium 0.451 mg	Beyaz	No data	No data	None <sup>a</sup>	Provides folate supplementation; FDA-approved use for treatment of acne and PMDD; 24 active pills and 4 days of 0.451 mg of levomefolate calcium instead of placebo
Drospirenone 3 mg/EE 20 mcg	Gianvi, YAZ, Loryna	No data	No data	None <sup>a</sup>	Antimineralocorticoid properties; FDA-approved use for treatment of acne and PMDD; only 4 days of placebo
Drospirenone 3 mg/EE 30 mcg/levomefolate calcium 0.451 mg	Safyral	No data	Intermediate	None <sup>a</sup>	Provides folate supplementation; 21 active pills and 7 days of 0.451 mg of levomefolate calcium instead of placebo
Drospirenone 3 mg/EE 30 mcg	Ocella, Yasmin, Zarah, Syeda	No data	Intermediate	None <sup>a</sup>	Antimineralocorticoid properties

#### **BIPHASIC FORMULATIONS**

Norethindrone 0.5, 1 mg/EE 35 mcg	Necon 10/11, Ortho-Novum 10/11	Intermediate	High	Low	
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#### **TRIPHASIC FORMULATIONS**

Norgestimate 0.18, 0.215, 0.25 mg/EE 25 mcg	Ortho Tri-Cyclen Lo	Low	Low	Low	
Norgestimate 0.18, 0.215, 0.25 mg/EE 35 mcg	Ortho Tri-Cyclen, Tri-Previfem, Tri-Sprintec	Low	Intermediate	Low	FDA-approved use for treatment of acne
Levonorgestrel 0.05, 0.075, 0.125 mg/EE 30, 40, 30 mcg	Enpresse, Levonest, Tri-Levlen, Triphasil, Trivora	Low	Intermediate	Low	
Norethindrone 0.5, 1, 0.5 mg/EE 35 mcg	Aranelle, Leena, Tri-Norinyl	Low	High	Low	

*Continued on following page*

TABLE 47.5 Oral Contraceptives and Relative Progestin, Estrogen, and Androgen Activities (Continued)

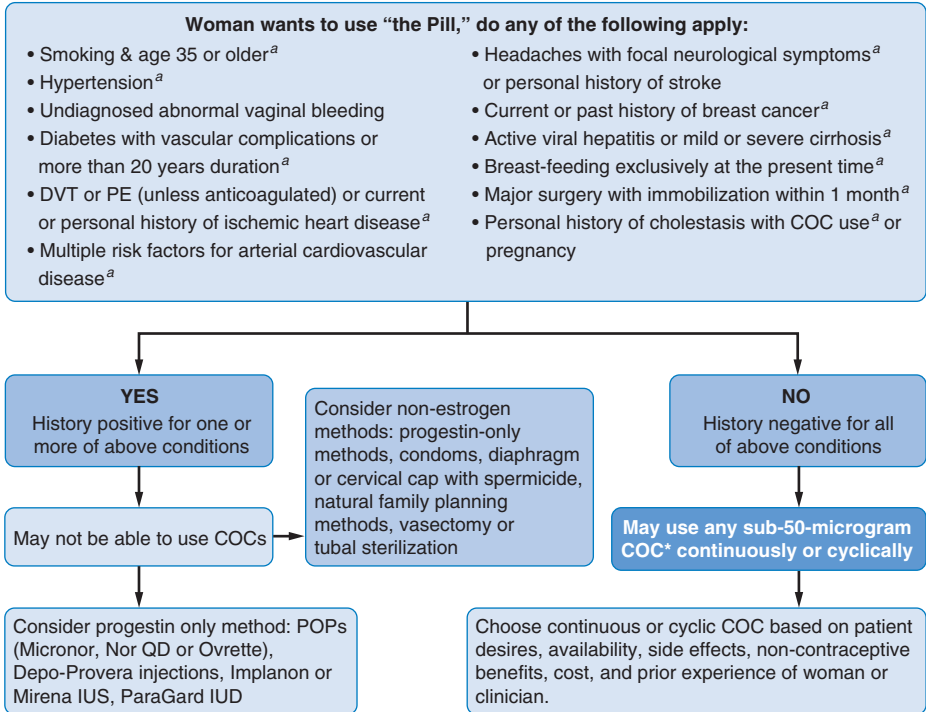
Ingredients	Brand Name Examples	Progestin Activity	Estrogen Activity	Androgen Activity	Unique Properties
Norethindrone 0.5, 0.75, 1 mg/EE 35 mcg	Cyclafem 7/7/7, Necon 7/7/7, Ortho-Novum 7/7/7	Intermediate	High	Low	
Norethindrone 1 mg/EE 20, 30, 35 mcg	Estrostep 21, Estrostep Fe	High	Low	Intermediate	Estrophasic (estrogen content changes); FDA-approved use for treatment of acne; "Fe" contains 75 mg ferrous fumarate instead of placebos
Desogestrel 0.1, 0.125, 0.15 mg/EE 25 mcg	Cyclessa, Velivet	High	Low	Low	
<b>QUADRIPHASIC FORMULATION</b>					
Dienogest 0, 2, 3, 0 mg/ estradiol valerate 3, 2, 2, 1 mg	Natazia	No data	Low	No data	Has 2 placebo pills; has 2 pills with 3 mg of estradiol valerate only, 5 pills with 2 mg of dienogest and 2 mg of estradiol valerate, 17 pills with 3 mg of dienogest and 2 mg of estradiol valerate, and 2 pills of 1 mg estradiol valerate
<b>PROGESTIN-ONLY</b>					
Norethindrone 0.35 mg	Camila, Errin, Jolivette, Micronor, Nor-QD, Nora-BE	Low	None	Low	No placebos; 28 days of active pills
dl-Norgestrel	Ovrette	No data	None	No data	No placebos; 28 days of active pills

<sup>a</sup>Preclinical studies have shown that drospirenone has no androgenic, estrogenic, glucocorticoid, antiglucocorticoid, or antiandrogenic activity.

EE, ethinyl estradiol; FDA, US Food and Drug Administration; PMDD, premenstrual dysphoric disorder.

Source: Facts and Comparisons eAnswers. <http://online.factsandcomparisons.com/index.aspx>

## Choosing a Pill



• The World Health Organization and the Food and Drug Administration both recommend using the lowest dose pill that is effective. All combined pills with less than 50 mcg of estrogen are considered “low-dose” and are effective and safe.

• There are no studies demonstrating a decreased risk for deep vein thrombosis (DVT) in women on 20-mcg pills. Data on higher dose pills have demonstrated that the less the estrogen dose, the lower the risk for DVT.

• All COCs lower free testosterone. Class labeling in Canada for all combined pills states that use of pills may improve acne.

• To minimize discontinuation due to spotting and breakthrough bleeding, warn women in advance, reassure that spotting and breakthrough bleeding become better over time.

<sup>a</sup>These are conditions that receive a WHO:3 or a WHO:4 (based on WHO Medical Eligibility Criteria for Contraceptive Use, 4th ed. 2009, Category 3—A condition in which theoretical or proven risks usually outweigh the benefit of contraceptive method use, Category 4—A condition that represents an unacceptable health risk if contraceptive method is used).

**Figure 47.1** Choosing a pill. ACE, angiotensin-converting enzyme; COC, combined oral contraceptive; DVT, deep venous thrombosis; IUD, intrauterine device; IUS, intrauterine system; NSAIDs, nonsteroidal anti-inflammatory drugs; PE, pulmonary embolism; POP, progestin-only pill. (Adapted with permission from Ziemann M et al. *Managing Contraception for Your Pocket 2010–2012*. Tiger, GA: Bridging the Gap Communications; 2010:108, Figure 26.2.)

TABLE 47.6 Comparison of Vaginal Spermicides

Formulation	Brand Name Examples	How to Use	Onset of Action	Duration of Action
Gel	Conceptrol, Gynol II	Fill applicator, insert applicator vaginally as far as it will comfortably go, press plunger of applicator to deposit spermicide near the cervix.	Immediate	1 hour
Film	VCF	Fold film in half, fold over finger, use finger to insert as far as it will comfortably go.	15 minutes	3 hours
Foam	Delfen, VCF	Shake foam canister, fill applicator, insert applicator vaginally as far as it will comfortably go, press plunger of applicator to deposit spermicide near the cervix.	Immediate	1 hour
Suppository	Encare	Unwrap, use finger to insert as far as it will comfortably go.	15 minutes	1 hour

## Inserted Contraceptive Options

- Implanon, a contraceptive implant that is inserted subdermally in the upper arm using a needle and local anesthetic, is effective for 3 years. Its advantage is quick return to fertility after product removal. Disadvantages are weight gain and irregular bleeding.
- ParaGard T 380A (a copper intrauterine device [IUD]) and Mirena (intrauterine system that contains levonorgestrel) must be inserted by a healthcare provider. The copper IUD may be left in place 10 years after insertion; Mirena may be left in place for 5 years after insertion. The copper IUD offers the advantage of a nonhormonal method of contraception. A benefit of Mirena is the patient would not have her period versus she would have very heavy periods that last for 7 days with the ParaGard.

## Nonhormonal Contraception

- The diaphragm is a soft latex or silicone rubber cap with a metal spring that is inserted vaginally to mechanically block access of sperm to the cervix. The cervical cap is a small, flexible, cuplike device that closely fits around the base of the cervix. Both must be used with a spermicide.
- The vaginal sponge is a barrier method that contains a spermicide. It serves as a mechanical barrier and also absorbs semen.
- Male condoms are effective when properly used. Their primary benefit is in the prevention of sexually transmitted infections.
- Vaginal spermicides are available in a variety of formulations (Table 47.6).

## Emergency Contraception

- Emergency contraception (or morning-after pill) is postcoital contraception useful for women who did not use a contraceptive or whose method failed.
- Emergency contraceptive pills (Next Choice, Plan B-One Step) are progestin-only pills taken as soon as possible and within 72 hours of unprotected intercourse. Next Step is a two-dose regimen, with the second dose taken 12 hours after the first dose. Plan B-One Step is a single-dose regimen.
- Regular COCs may be used for emergency contraception provided they contain levonorgestrel or norgestrel as the progestin.

# Infertility\*

## General Principles

- Infertility is defined as the inability to conceive after 1 year of unprotected intercourse.
- Female factors (primarily ovulatory function) are most common but male factors (impaired sperm production or function) are present in up to 40% of cases.

## Risk Factors

- Factors that affect infertility rates include increasing age, history of conditions associated with infertility (amenorrhea, endometriosis, pelvic inflammatory disease) or anovulation (thyroid dysfunction, hyperprolactinemia, polycystic ovary syndrome), lifestyle choices (tobacco or illicit drug use, caffeine intake, obesity), and occupational or environmental exposure to pesticides, heavy metals, and toxins.

## Patient Assessment

- Evaluation of infertility in women incorporates data from physical examination and laboratory assessments of pituitary and ovarian function. Ovulatory function can be assessed by methods such as basal body temperature monitoring and home ovulation test kits. The clomiphene citrate challenge is used to assess ovarian reserve.
- Evaluation in men involves semen analysis (Table 48.1) and laboratory assessments of hormonal levels to assess gonadal function.
- Unexplained infertility is diagnosed after a thorough evaluation of both the man and the woman reveals no identifiable cause.

## Goals of Therapy

- The goal of ovulatory stimulation is the development of a single dominant follicle.
- The goal of controlled ovarian stimulation is to develop multiple ovarian follicles.

## Treatment

- All couples pursuing pregnancy are encouraged to avoid tobacco, alcohol, and illicit substances and to limit caffeine intake.
- Treatment of unexplained infertility is empiric and often combines controlled ovarian stimulation and intrauterine insemination or in vitro fertilization (IVF).
- There are two approaches focused on ovulation:
  - **Ovulation Induction:** used in patients who are not ovulating
  - **Controlled Ovarian Stimulation:** used in women who have ovulatory cycles but are experiencing infertility
- Assisted reproductive technology is the manipulation of oocytes and embryos (Table 48.2).
- The basic steps of IVF include controlled ovarian stimulation, oocyte retrieval, fertilization, embryo culture, and embryo transfer. Medications are primarily used during the three main stages of IVF (Tables 48.3, 48.4, and 48.5).

\*The reader is referred to Chapter 48, Infertility, written by Erin C. Raney, PharmD, BCPS, in the 10th edition of *Applied Therapeutics: The Clinical Use of Drugs* for a more in-depth discussion. All notations to reference numbers are based on the reference list at the end of that chapter. The editor of this handbook expresses her thanks to Dr. Raney and acknowledges that this chapter is based on her work.



TABLE 48.1 Semen Analysis: Lower Reference Limits for Selected Parameters

Parameter	Lower Reference Limit (5th Percentile with 95% Confidence Interval)
Semen volume (mL)	1.5 (1.4–1.7)
Total sperm number (10 <sup>6</sup> per ejaculate)	39 (33–46)
Sperm concentration (10 <sup>6</sup> per mL)	15 (12–16)
Total motility (progressive + nonprogressive, %)	40 (38–42)
Progressive motility (%)	32 (31–34)
Vitality (live spermatozoa, %)	58 (55–63)
Sperm morphology (normal forms, %)	4 (3–4)

Source: Reprinted with permission from World Health Organization, Department of Reproductive Health and Research. *WHO Laboratory Manual for the Examination and Processing of Human Semen*. 5th ed. Geneva, Switzerland: World Health Organization Press; 2010:224.

TABLE 48.2 Description of Select Infertility Procedures

Classification	Procedure	Description
Insemination	Intrauterine, intracervical, intravaginal	Delivery of a prepared semen sample to the intended site (vagina, cervix, uterus) during ovulation
Assisted reproductive technology	Assisted hatching	Mechanical or chemical separation of the blastocyst from the zona pellucida (membrane surrounding the oocyte) during embryonic development in vitro
	Embryo cryopreservation	Freezing and storage of embryos for future ART cycles
	Gamete intrafallopian transfer	Laparoscopic transfer of the unfertilized oocytes and sperm to the fallopian tube for fertilization
	In vitro fertilization—embryo transfer	Transfer of one or more embryos resulting from in vitro fertilization into the uterus through the cervix
	Intracytoplasmic sperm injection	In vitro injection of the sperm into the oocyte
	Preimplantation genetic diagnosis/screening	Examination of oocytes, zygotes, or embryos for specific genetic conditions (diagnosis) or for general genetic alterations (screening)
	Zygote intrafallopian transfer	Laparoscopic transfer of the fertilized oocyte (zygote) into the fallopian tube

ART, assisted reproductive technology.

Source: Zegers-Hochschild F et al. The International Committee for Monitoring Assisted Reproductive Technology (ICMART) and the World Health Organization (WHO) revised glossary on ART terminology, 2009. *Hum Reprod*. 2009;24:2683.

TABLE 48.3 Role of Medications in an in Vitro Fertilization Cycle

IVF Stage	Medications <sup>a</sup>	Role
Stage One: Controlled ovarian stimulation	Oral contraceptives	Control the onset of menses and the start of controlled ovarian stimulation
	GnRH agonists or GnRH antagonists	Prevent a premature LH surge or disruption of controlled ovarian stimulation
	Gonadotropins (FSH or FSH plus LH)	Stimulate development of multiple ovarian follicles for oocyte retrieval
Stage Two: Oocyte retrieval	hCG	Induce final follicular maturation to prepare for oocyte retrieval
Stage Three: Luteal phase support	Progesterone	Maintain the endometrium for embryo transfer and implantation

<sup>a</sup>This list reflects the medications most commonly used during each stage. Alternate regimens vary widely by specialist. FSH, follicle stimulating hormone; GnRH, gonadotropin releasing hormone; hCG, human chorionic gonadotropin; LH, luteinizing hormone.

TABLE 48.4 Gonadotropin Releasing Hormone Analogs for in Vitro Fertilization

Analogue	Product Name	Strength/Dosage Form	Route of Administration
GnRH agonist	Nafarelin acetate (Synarel)	2 mg/mL solution (200 mcg/spray)	Intranasal
	Leuprolide acetate	1 mg/0.2 mL solution	SC
GnRH antagonist	Cetrorelix acetate <sup>a</sup> (Cetrotide)	0.25-mg, 3-mg kit	SC
	Ganirelix acetate <sup>a</sup>	250 mcg/0.5 mL solution	SC

<sup>a</sup>FDA-labeled for use with assisted reproductive technology procedures.

GnRH, gonadotropin releasing hormone; SC, subcutaneous.

Source: Adapted with permission from Facts & Comparisons eAnswers. <http://online.factsandcomparisons.com/MonoDisp.aspx?monoID=fandc-hcp10444>; <http://online.factsandcomparisons.com/MonoDisp.aspx?monoID=fandc-hcp10921>; <http://online.factsandcomparisons.com/MonoDisp.aspx?monoID=fandc-hcp11447>; <http://online.factsandcomparisons.com/MonoDisp.aspx?monoID=fandc-hcp11213>. Accessed November 4, 2011.

TABLE 48.5 Commercially Available Progesterone Products Used in Assisted Reproductive Technology

Product Name	Strength/Dosage Form	Route of Administration
Crinone	8% vaginal gel <sup>a</sup>	Vaginal
Endometrin	100-mg vaginal insert <sup>a</sup>	Vaginal
FIRST-Progesterone VGS	25-, 50-, 100-, 200-, 400-mg vaginal suppository (compounding kit)	Vaginal
Progesterone	50 mg/mL (oil)	Intramuscular
Prometrium	100-, 200-mg capsule	Oral

<sup>a</sup>FDA-labeled for luteal phase support.

Source: Adapted with permission from Facts & Comparisons eAnswers. <http://online.factsandcomparisons.com/MonoDisp.aspx?monoID=fandc-hcp11740>. Accessed November 4, 2011.

- Ovarian hyperstimulation syndrome (OHSS) is a rare but serious complication of controlled ovarian stimulation that can result in ovarian rupture, thromboembolism, renal failure, and adult respiratory distress syndrome.

## Drug Therapy

- **Clomiphene citrate** stimulates release of GnRH. An intact hypothalamic–pituitary–ovarian axis must exist. Typical initial dosing is 50 mg once daily for 5 days starting on day 5 of the menstrual cycle. Dose increases may be necessary.
- **Aromatase inhibitors** (letrozole, anastrozole) are alternative agents to stimulate ovulation.
- **Gonadotropins:** Injectable agents (Table 48.6) can be used to induce ovulation if oral agents are unsuccessful. The goal of gonadotropin therapy is to guide development of multiple follicles for oocyte retrieval.

TABLE 48.6 Gonadotropins for Ovulation Induction/Controlled Ovarian Hyperstimulation

Ingredient	Product Name	Strength/Dosage Form	Route of Administration
hMG (menotropin)	Repronex	Powder for reconstitution: 75 international units FSH activity and 75 international units LH activity/vial	IM or SC
hMG (menotropin)	Menopur	Powder for reconstitution: 75 international units FSH activity and 75 international units LH activity/vial	SC
Urinary FSH (urofollitropin)	Bravelle	Powder for reconstitution: 75 international units FSH activity/vial	IM or SC
Recombinant FSH (follitropin alfa)	Gonal-f Multi-Dose	Powder for reconstitution: 450 or 1,050 international units FSH activity/vial	SC
	Gonal-f RFF 75 international units	Powder for reconstitution: 75 international units FSH activity/vial	SC
	Gonal-f RFF pen	Solution: 300, 450, or 900 international units FSH/pen	SC
Recombinant FSH (follitropin beta)	Follistim AQ Vial	Solution: 75 or 150 international units FSH/vial	IM or SC
	Follistim AQ Cartridge for Follistim Pen	Solution: 175, 350, 650, or 975 international units/ cartridge (delivers 150, 300, 600, or 900 international units FSH)	SC
Recombinant LH (lutropin alfa)	Luveris	Powder for reconstitution: 75 international units LH/vial	SC
Urinary hCG	Chorionic gonadotropin (generic)	Powder for reconstitution: 10,000 international units LH activity/vial	IM
	Pregnyl	Powder for reconstitution: 10,000 international units LH activity/vial	IM
	Novarel	Powder for reconstitution: 10,000 international units LH activity/vial	IM
Recombinant chorionic gonadotropin alfa	Ovidrel	Prefilled syringe: 250 mcg r-hCG	SC

FSH, follicle stimulating hormone; hCG, human chorionic gonadotropin; hMG, human menopausal gonadotropin; IM, intramuscular; LH, luteinizing hormone; r-hCG, recombinant human chorionic gonadotropin; SC, subcutaneous.

Source: Adapted with permission from Facts & Comparisons eAnswers. <http://online.factsandcomparisons.com/MonoDisp.aspx?monoID=fandc-hcp10484>; <http://online.factsandcomparisons.com/MonoDisp.aspx?monoID=fandc-hcp11267>; <http://online.factsandcomparisons.com/MonoDisp.aspx?monoID=fandc-hcp11305>; <http://online.factsandcomparisons.com/MonoDisp.aspx?monoID=fandc-hcp10483>; <http://online.factsandcomparisons.com/MonoDisp.aspx?monoID=fandc-hcp10893>; <http://online.factsandcomparisons.com/MonoDisp.aspx?monoID=fandc-hcp10894>; <http://online.factsandcomparisons.com/MonoDisp.aspx?monoID=fandc-hcp12150>. Accessed November 4, 2011.

# Obstetric Drug Therapy\*

## General Principles

- **Parity** and **gravid**a are terms used to describe a pregnant woman. Parity refers to the number of deliveries after 20-week gestation. Gravidia refers to the number of pregnancies a woman has had, regardless of outcome.
- The average pregnancy is 40 weeks long and is divided into 3 trimesters of approximately 13 weeks each. The first trimester is the critical period of organogenesis.
- The **perinatal period** is the time between the end of the 20th week of gestation and the end of the 28th day after birth.
- A term infant is a fetus delivered between 37- and 42-week gestation. A preterm infant is delivered between 20 and 37 weeks. A postterm birth occurs after the beginning of week 42.

## Pregnancy

- Timing and quality of prenatal care can influence an infant's health and survival. Predicting date of deliver is important to ensure proper prenatal care.
- A balanced diet with multiple B vitamins, oil-soluble vitamins, folic acid, and minerals should be encouraged. Prenatal vitamins should be taken months before conception.
  - Iron requirements increase during pregnancy; 18 to 21 mg of iron/day are needed.
  - Folic acid is essential to prevent neural tube defects; 0.4 to 0.8 mg/day should be taken during the first trimester.
  - Calcium is needed for adequate mineralization of fetal skeleton and teeth.
- **Drug Use during Pregnancy**
  - Pregnancy-induced pharmacokinetic changes can occur (e.g., alterations in drug absorption, protein binding, metabolism and elimination).
  - Maternal and fetal drug concentrations are dependent on the amount of drug that crosses the placenta, extent of metabolism by the placenta, and fetal distribution and elimination of the drug. Highly protein-bound drugs do not cross the placenta.
  - Risk for congenital malformations is the biggest concern with drug use in pregnancy. **Teratogens** are agents that have the potential to produce abnormal development of the fetus (Table 49.1).
  - Factors to consider when assessing potential teratogenicity include the critical stage of exposure (embryonic period when organogenesis occurs during days 14–56 after fertilization), dose–response curve, extrapolation from animal data, genetic variability, and placental transfer of drugs.
  - Factors that influence the rate of drug transfer across the placenta include molecular weight, lipid solubility, ionization, protein binding, uterine and umbilical blood flow, and maternal diseases.

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\*The reader is referred to Chapter 49, Obstetric Drug Therapy, written by Kimey D. Ung, PharmD, BCPS, and Jennifer McNulty, MD, in the 10th edition of *Applied Therapeutics: The Clinical Use of Drugs* for a more in-depth discussion. All notations to reference numbers are based on the reference list at the end of that chapter. The editor of this handbook expresses her thanks to Drs. Ung and McNulty and acknowledges that this chapter is based on their work.

TABLE 49.1 Drugs with Suspected or Proven Teratogenic Effects in Humans<sup>a,b</sup>

Alcohol	Growth restriction, mental retardation, midfacial hypoplasia, renal and cardiac defects
Androgens (testosterone)	Masculinization of female fetus
Angiotensin-converting enzyme inhibitors and angiotensin receptor blockers	Pulmonary hypoplasia, hypocalvaria, oligohydramnios, fetal kidney anuria, and neonatal renal failure
Antithyroid drugs	Fetal and neonatal goiter with iodine use; small risk of aplasia cutis with methimazole
$\beta$ -Blockers	IUGR and decrease in placental weight in $\beta$ -blockers with intrinsic sympathomimetic activity if used in second and third trimesters
Carbamazepine	Neural tube defects, minor craniofacial defects, fingernail hypoplasia
Cigarette smoking	IUGR, functional and behavioral deficits
Cocaine	Bowel atresias; heart, limbs, face, and genitourinary tract malformations; microcephaly; cerebral infarctions; growth restriction
Corticosteroids (systemic)	Oral cleft lip and palates if used during organogenesis
Cyclophosphamide	Craniofacial, eye, and limb defects; IUGR; neurobehavioral deficits
Diethylstilbestrol	Vaginal carcinoma and other genitourinary defects
Lamotrigine	Oral cleft lip and cleft palate <sup>38</sup>
Lithium	Ebstein anomaly
Methotrexate	CNS and limb malformations
Misoprostol	Möbius sequence (high doses) and spontaneous abortions
Nonsteroidal anti-inflammatory drugs	Constriction of the ductus arteriosus, oral clefts, cardiac defects, and possible spontaneous abortion
Paroxetine	Cardiovascular defects <sup>39</sup>
Phenytoin	Fetal hydantoin syndrome, growth retardation, CNS deficits
Streptomycin and kanamycin	Hearing loss, eighth cranial damage; no ototoxicity reported with gentamicin, tobramycin, amikacin
Systemic retinoids (isotretinoin and etretinate)	CNS, craniofacial, cardiovascular defects
Tetracycline	Permanent discoloration of deciduous teeth
Thalidomide	Limb and skeletal shortening defects, internal organ defects
Topiramate	Cleft lip and cleft palate <sup>40</sup>
Trimethoprim	Neural tube defects and cardiac defects
Vaccines (live)	Live attenuated vaccines can potentially cause fetal infection
Valproic acid	Neural tube defects, developmental delay and deficits
Vitamin A	Microtia, anotia, thymic aplasia, cardiovascular defects (high dose)
Warfarin	Fetal warfarin syndrome with nasal hypoplasia, stippled epiphyses, and skeletal and CNS defects

<sup>a</sup>Teratogenic effects include the four major manifestations of abnormal fetal development, which include growth alterations, functional deficits, structural malformations, and fetal death.

<sup>b</sup>Only drugs that are teratogenic when used at clinically recommended doses are listed. List is not all inclusive. CNS, central nervous system; IUGR, intrauterine growth restriction.

Sources: Briggs G et al. *Drugs in Pregnancy and Lactation: A Reference Guide to Fetal and Neonatal Risk*. 9th ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2011; Koren G et al. *Drugs in pregnancy*. *N Engl J Med*. 1998;338:1128.

- Environmental factors account for about 10% of malformations. Rubella is the best known teratogenic virus. *Toxoplasma gondii*, which can be present in cat litter, is a teratogenic protozoan. Women should avoid handling cat litter while pregnant.

## Complications

### • Nausea and Vomiting of Pregnancy (NVP)

- While common during weeks 5 to 12, for most women it is a self-limiting condition.
- Antiemetics are indicated for moderate to severe NVP that fails to respond to nonpharmacologic intervention or when NVP threatens the mother's metabolic or nutritional status. Common antiemetics used for NVP are shown in Table 49.2.
- The goal of antiemetic therapy is to maintain nutrition and hydration status while ensuring fetal safety.

TABLE 49.2 Common Antiemetics Used for Nausea and Vomiting during Pregnancy

Drug	Dose	Comments
Vitamin B <sub>6</sub> (pyridoxine)	10–25 mg PO TID	First-line therapy <sup>52</sup> Documented safety in pregnancy
Vitamin B <sub>6</sub> (pyridoxine)—doxylamine combination	Pyridoxine 10–25 mg PO TID–QID; Doxylamine 12.5 mg PO TID–QID	First-line therapy Available OTC Well-documented safety in pregnancy through large meta-analysis <sup>54</sup>
<b>ANTI-HISTAMINES</b>		
Diphenhydramine	25–50 mg PO every 8 hours	First-line therapy
Meclizine	25 mg PO every 6 hours	Antihistamines have not been shown to be teratogenic. <sup>43,55</sup>
Hydroxyzine	25–50 mg PO every 4–6 hours	
Dimenhydrinate	50–100 mg PO every 4–6 hours	
<b>PHENOTHIAZINES</b>		
Promethazine	12.5–25 mg PO, PR every 6 hours	Second line of therapy
Prochlorperazine	5–10 mg PO every 6–8 hours	Available as suppositories Also suppositories and buccal tablets Usually add phenothiazine or metoclopramide to therapy if antihistamines fail <sup>52</sup> Can cause EPS
<b>DOPAMINE ANTAGONISTS</b>		
Metoclopramide	10 mg PO every 6 hours	Usually add phenothiazine or metoclopramide to therapy if antihistamines fail <sup>52</sup> Avoid treatment >12 weeks' duration, risk of tardive dyskinesia Can cause EPS
Droperidol	1.25–2.5 mg IV/IM or Continuous infusion 1 mg/hour for treatment of hyperemesis gravidarum <sup>56</sup>	Boxed warning regarding torsades de pointes; may need ECG during administration Continuous infusion of droperidol requires concomitant diphenhydramine 50 mg IV every 6 hours.
<b>5-HT<sub>3</sub> RECEPTOR ANTAGONISTS</b>		
Ondansetron	4–8 mg IV/PO every 6–8 hours	Available as ODT tablets Does not cause sedation Studies suggest low risk in pregnancy. <sup>43</sup>
<b>GLUCOCORTICOIDS</b>		
Methylprednisolone	16 mg PO every 8 hours × 3 days, then taper over 2 weeks	For refractory cases, last line of therapy Avoid use before 10th week of gestation, associated with oral cleft and palate. <sup>43,52</sup>
Ginger extract	125–250 mg PO every 6 hours	Available OTC as food supplement

ECG, electrocardiogram; EPS, extrapyramidal symptoms; IM, intramuscular; IV, intravenous; ODT, oral disintegrating tablet; OTC, over the counter; PO, by mouth; QID, four times a day; TID, three times a day.

Sources: Briggs G et al. *Drugs in Pregnancy and Lactation: A Reference Guide to Fetal and Neonatal Risk*. 9th ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2011; Niebyl JR. Clinical practice. Nausea and vomiting in pregnancy. *N Engl J Med*. 2010;363:1544; McKeigue PM et al. Bendectin and birth defects: I. A meta-analysis of the epidemiologic studies. *Teratology*. 1994;50:27; Seto A et al. Pregnancy outcome following first trimester exposure to antihistamines: meta-analysis. *Am J Perinatol*. 1997;14:119.

- **Hyperemesis gravidarum** is severe NVP that persists and can be detrimental to the mother or fetus. It often requires hospitalization for parenteral fluid and electrolyte replacement, vitamin supplementation, and antiemetic therapy.
- **Reflux Esophagitis (Heartburn)**
  - Symptoms include substernal burning worsened by eating, lying down, or bending over.
  - Lifestyle and dietary modifications should be tried first. If unsuccessful, calcium carbonate antacids may help. H<sub>2</sub>-receptor antagonists and proton-pump inhibitors are alternatives if antacids do not help relieve symptoms. PPIs are pregnancy category C while agents such as zantac are pregnancy category B.
- **Urinary Tract Infections (UTI)**
  - UTIs can present as either **asymptomatic bacteriuria** (i.e., presence of significant bacterial on two consecutive clean catch samples) or **acute cystitis** (i.e., infection of the bladder that includes symptoms of urgency, frequency, dysuria, and hematuria without fever or evidence of systemic illness). **Pyelonephritis** is an infection of the upper urinary tract involving the kidneys.
  - Table 49.3 lists common antibiotics used for UTIs during pregnancy. A 7-day course should be used when possible.
- **Diabetes Mellitus (DM)**
  - Diabetes during pregnancy can be either **pregestational diabetes** (diabetes before pregnancy) or **gestational diabetes** (carbohydrate intolerance first detected during pregnancy).
  - Pregestational diabetes care should begin 6 months before conception with the goal of good glycemic control (Hgb A<sub>1c</sub> levels close to normal). Women receiving angiotensin-converting-enzyme inhibitor (ACEI) therapy should be converted to an alternate therapy as ACEI are contraindicated in pregnancy.
  - Treatment of diabetes during pregnancy should include dietary management, appropriate maternal weight gain, insulin therapy, and exercise. Insulin is the treatment of choice during pregnancy because it does not cross the placenta. Insulin requirements vary depending on the trimester. Oral hypoglycemic agents are rarely used as monotherapy during pregnancy.
  - Most women with gestational diabetes can control glucose with dietary modifications and exercise. Medications should be considered if these measures fail to maintain fasting blood glucose concentrations at 90 mg/dL or less.
- **Hypertension, Preeclampsia, and Eclampsia**
  - Hypertension in pregnancy is defined as a systolic blood pressure (BP) of  $\geq 140$  mm Hg or a diastolic BP of  $\leq 90$  mm Hg on two occasions 6 hours apart.
  - **Chronic hypertension** existed before conception or before the 20th week of gestation. See Table 49.4 for drug therapies for the treatment options.
  - **Preeclampsia** is a pregnancy-specific condition that usually occurs after 20-week gestation that includes hypertension and proteinuria. Symptoms of severe preeclampsia include headaches, visual disturbances, and upper abdominal pain. Drug therapy is needed to lower BP and prevent eclampsia and cerebral complications. BP should be reduced gradually to avoid a reduction in uteroplacental perfusion. Hydralazine, labetalol, and nifedipine are treatment options. Magnesium sulfate prophylaxis is used to prevent eclamptic seizures (4–6 g IV loading dose followed by 2 g/hour continuous infusion).
  - **Eclampsia** is the term used when a woman with preeclampsia develops seizures. Magnesium sulfate, lorazepam, diazepam, and phenytoin have all been used.
  - **Gestational hypertension** occurs when BP is increased during pregnancy or in the first 24 hours post partum in a woman without preeclampsia or preexisting hypertension.

## Labor and Delivery

- **Induction of Labor**
  - Labor induction, artificial stimulation of uterine contractions that leads to labor and delivery, is indicated when the benefits to either the mother or the fetus outweigh continuing

TABLE 49.3 Fetal Risk Assessment of Common Antibiotics Used during Pregnancy

Drug	Fetal Risk	Comments
Aminoglycosides (gentamicin)	Low risk	Gentamicin used for many indications during pregnancy (i.e., chorioamnionitis, pyelonephritis) Dose to target peak of 8 mcg/mL and trough of < 1 mcg/mL Ototoxicity reported with older aminoglycosides (kanamycin, streptomycin). No reports with gentamicin
Cephalosporins	Compatible	First-line therapy for UTI
Clindamycin	Compatible	Used for many indications during pregnancy
Erythromycin	Compatible	Excludes estolate salt, can cause maternal hepatotoxicity
Fluoroquinolones	Animal data suggest risk; human data suggest low risk	Reports of fetal cartilage damage and arthropathies in animal studies; not confirmed in human data Avoid use in first trimester. Reserve use only if needed for drug-resistant organisms (not susceptible to first-line agents).
Metronidazole	Animal data suggest risk; human data suggest low risk	Mutagenic in bacteria and carcinogenic in rodents Avoid use in first trimester. Acceptable to use in second and third trimesters
Nitrofurantoin	Low risk	First-line therapy for UTI Avoid use close to term in third trimester if possible. May induce hemolytic anemia in G6PD-deficient women and neonates who are deficient in glutathione
Penicillins	Compatible	Resistance to <i>Escherichia coli</i> is high. Can use if GBS is cultured in urine
Trimethoprim-sulfamethoxazole	Contraindicated in first trimester Caution use in third trimester	Avoid use in first trimester because folate antagonism of trimethoprim can cause NTDs. Avoid use close to term in third trimester owing to theoretical risk of kernicterus in newborns from competitive binding between bilirubin and sulfonamides, to plasma albumin.
Tetracyclines	Contraindicated in all trimesters	Permanent discoloration of deciduous teeth
Vancomycin	Compatible	Reserve use for drug-resistant gram-positive organisms not sensitive to first-line agents.

GBS, group B Streptococcus; G6PD, glucose-6-phosphate dehydrogenase; NTDs, neural tube defects; UTI, urinary tract infection.

Source: Briggs G et al. *Drugs in Pregnancy and Lactation: A Reference Guide to Fetal and Neonatal Risk*. 9th ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2011.

the pregnancy. Contraindications to labor induction exist (e.g., active genital herpes infection, placenta previa, transverse fetal lie, prolapsed umbilical cord).

- Cervical ripening can be done mechanically (membrane sweeping or intracervical balloons) or pharmacologically.
- *Misoprostol* is an oral prostaglandin E<sub>1</sub> that can be inserted into the posterior vaginal fornix (25 mcg, repeated as needed every 3–6 hours).
- *Dinoprostone* is available as a cervical gel or slow-release vaginal insert.
- *Oxytocin* is used to stimulate uterine contractions for either induction or augmentation of labor.
- **Preterm Labor**
  - Symptoms of preterm labor include backache and uterine contractions that are typically not painful.
  - Risk factors include maternal age <18 or >35 years, low maternal birth weight, smoking, multiple gestation, and prior preterm birth.
  - Treatment is directed at slowing or stopping contractions (tocolysis).



TABLE 49.4 Drugs for Treatment of Chronic Hypertension in Pregnancy and Lactation

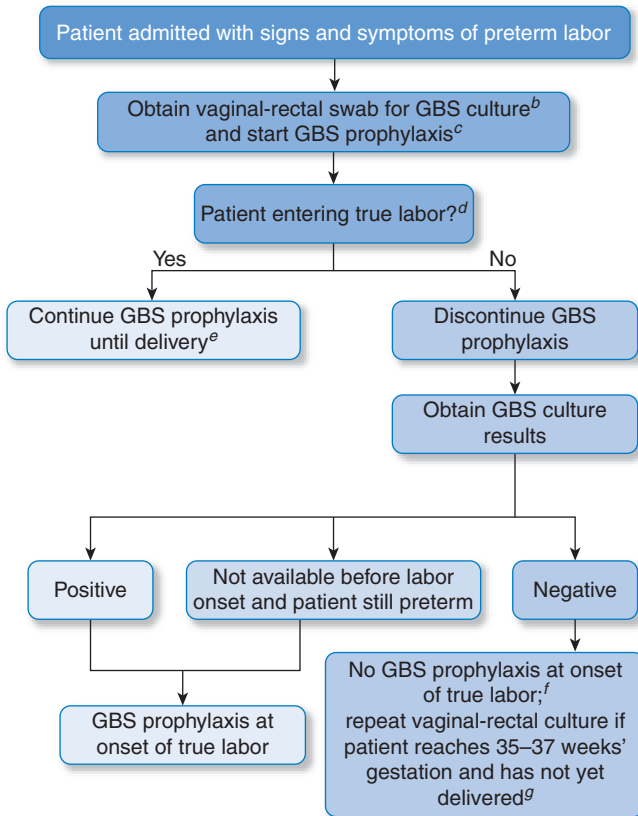
Drug	Dose	Comments
Methyldopa	750–1,000 mg/day start twice a day, increase up to 2–3 g/day, divided in three to four doses if needed <sup>99</sup>	Longest safety record in pregnancy. Considered a first-line drug. <sup>91</sup> Dizziness, sedation, and lack of energy are common symptoms, which tend to resolve. Can cause liver toxicity. Low breast milk concentrations, so considered safe in breast-feeding
Labetalol	200–400 mg/day start, increase to up to 2,400 mg/day, divided in two or sometimes three doses	Combined $\alpha$ - and $\beta$ -receptor antagonist properties. Considered a first-line drug. <sup>91</sup> Increasingly preferred to methyldopa owing to fewer side effects. Neonatal effects could include bradycardia and hypotension. Low concentration in breast milk and generally considered safe in breast-feeding <sup>101</sup>
Other $\beta$ -blockers	Various	Atenolol in particular associated with decreased placental weight and IUGR. <sup>102,103</sup> IUGR thought to be related to $\beta$ -blocker–induced increased vascular resistance in mother and fetus. Atenolol, acebutolol, metoprolol, nadolol, and sotalol can have high milk-to-plasma ratios and accumulate in breast milk, creating potential risk for neonatal blockade. <sup>104,105</sup> Propranolol found in only small amounts in breast milk and generally considered safe, but infants should be monitored for hypotension, bradycardia, and blood glucose changes
Nifedipine, long-acting	30 mg/day start, increase to up to 120 mg/day, once daily	Limited pregnancy data on nifedipine or other calcium-channel blockers such as verapamil, diltiazem, and amlodipine. Concentrations of nifedipine in breast milk are low and considered compatible with breast-feeding. <sup>101,106</sup>
Diuretics	Various	Not first-line agents, although probably safe. <sup>88</sup> Concern regarding potential interference with normal blood volume expansion in pregnancy. Avoid if pre-eclampsia or IUGR already present. Concentration low in breast milk, but may decrease milk production
ACEI or ARB	Contraindicated	Contraindicated in pregnancy in all trimesters. Fetal renal failure when used after first trimester, resulting in oligohydramnios, limb contractures, pulmonary hypoplasia, skull hypoplasia, and irreversible neonatal renal failure. <sup>43</sup> Increased risk major birth defects with first-trimester ACEI exposure. <sup>79</sup> Minimal amounts of captopril and enalapril in breast milk and both considered compatible with breast-feeding. <sup>101</sup> Minimal amounts of benazepril in breast milk

ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; IUGR, intrauterine growth restriction.

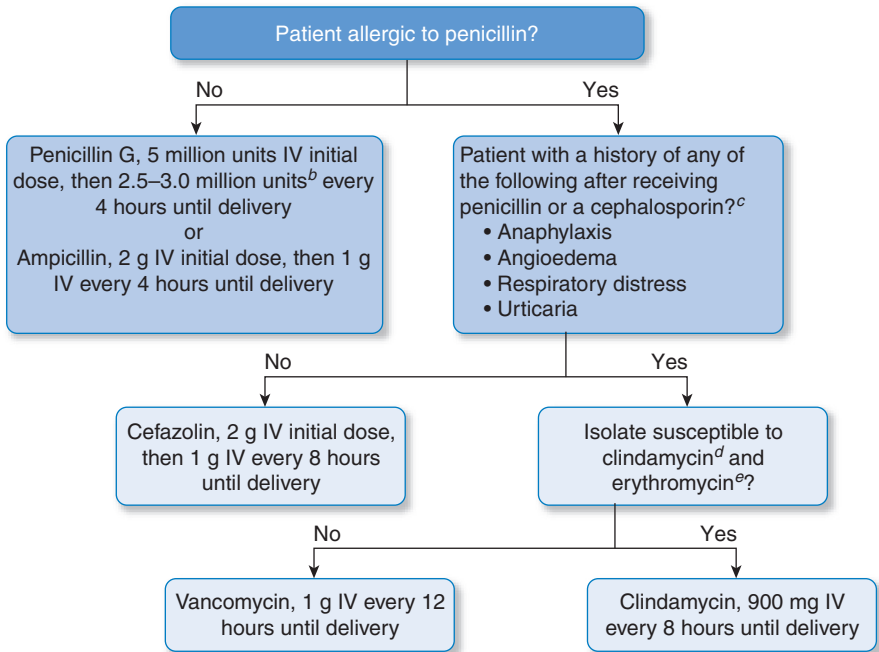
- Magnesium sulfate is the most commonly used parenteral tocolytic.  $\beta$ -Adrenergic agonists (e.g., ritodrine, terbutaline) are second-line options. Indomethacin may be an option for women with contraindications to other tocolytics.
- When delivery is needed before 34 weeks gestation with intact membranes or before 32 weeks with ruptured membranes, antenatal corticosteroids should be given to facilitate fetal lung maturation. Antenatal betamethasone or dexamethasone is recommended for all women in preterm labor between 24- and 34-week gestations. They are not recommended for women who are more than 34-week gestation unless there is an indication of fetal lung immaturity.

## Infections Complications during Pregnancy, Labor, and Breast-Feeding

- **Preterm Premature Rupture of Membranes (PPROM):** Intrauterine infection is associated with about 80% of preterm deliveries. A short course of antibiotics can prolong the time between PPRM and delivery and decrease neonatal morbidity.
- **Group B Streptococcus Intrapartum Prophylaxis:** Antibiotics should be given to women if delivery is anticipated from either preterm labor with intact membranes or after PPRM to prevent group B streptococcal infection in the newborn. A treatment algorithm that has been shown to prevent early-onset group B streptococcal infection is shown in Figure 49.1. Antibiotics for intrapartum antimicrobial prophylaxis are shown in Figure 49.2.



**Figure 49.1** Sample algorithm for group B streptococcus (GBS) prophylaxis for women with threatened preterm delivery. <sup>a</sup>If patient has undergone vaginal-rectal GBS culture within the preceding 5 weeks, the results of that culture should guide management. GBS-colonized women should receive intrapartum antibiotic prophylaxis. No antibiotics are indicated for GBS prophylaxis if a vaginal-rectal screen within 5 weeks was negative. <sup>b</sup>See Figure 49.2 for recommended antibiotic regimens. <sup>c</sup>Patient should be regularly assessed for progression to true labor; if the patient is considered not to be in true labor, discontinue GBS prophylaxis. <sup>d</sup>If GBS culture results become available prior to delivery and are negative, then discontinue GBS prophylaxis. <sup>e</sup>Unless subsequent GBS culture prior to delivery is positive. <sup>f</sup>A negative GBS screen is considered valid for 5 weeks. If a patient with a history of PTL is readmitted with signs and symptoms of PTL and had a negative GBS screen >5 weeks prior, she should be rescreened and managed according to this algorithm at that time. (Reprinted from Verani JR et al. Prevention of perinatal group B streptococcal disease—revised guidelines from CDC, 2010. *MMWR Recomm Rep.* 2010;59(RR-10):1.)



**Figure 49.2** Intrapartum antibiotic prophylaxis to prevent perinatal group B streptococcus (GBS) disease. Indications for intrapartum antibiotic prophylaxis to prevent perinatal GBS disease under a universal prenatal screening strategy based on combined vaginal and rectal cultures collected at 35 to 37 weeks' gestation from all pregnant women. IV, intravenously. <sup>a</sup>Doses ranging from 2.5 to 3.0 million units are acceptable for the doses administered every 4 hours following the initial dose. The choice of dose within that range should be guided by which formulations of penicillin G are readily available to reduce the need for pharmacies to specially prepare doses. <sup>b</sup>Penicillin-allergic patients with a history of anaphylaxis, angioedema, respiratory distress, or urticaria following administration of penicillin or a cephalosporin are considered to be at high risk for anaphylaxis and should not receive penicillin, ampicillin, or cefazolin for GBS intrapartum prophylaxis. For penicillin-allergic patients who do not have a history of those reactions, cefazolin is the preferred agent because pharmacologic data suggest it achieves effective intraamniotic concentrations. Vancomycin and clindamycin should be reserved for penicillin-allergic women at high risk for anaphylaxis. <sup>f</sup>If laboratory facilities are adequate, clindamycin and erythromycin susceptibility testing should be performed on prenatal GBS isolates from penicillin-allergic women at high risk for anaphylaxis. If no susceptibility testing is performed, or the results are not available at the time of labor, vancomycin is the preferred agent for GBS intrapartum prophylaxis for penicillin-allergic women at high risk for anaphylaxis. <sup>d</sup>Resistance to erythromycin is often, but not always, associated with clindamycin resistance. If an isolate is resistant to erythromycin, it might have inducible resistance to clindamycin, even if it appears susceptible to clindamycin. If a GBS isolate is susceptible to clindamycin and resistant to erythromycin, and testing for inducible clindamycin resistance has been performed and is negative (no inducible resistance), then clindamycin can be used for GBS intrapartum prophylaxis instead of vancomycin. (Reprinted from Verani JR et al. Prevention of perinatal group B streptococcal disease—revised guidelines from CDC, 2010. *MMWR Recomm Rep*. 2010;59 (RR-10):1.)

- **Chorioamnionitis** is an infection of the amniotic fluid, membranes, and placenta occurring before, during, or immediately after birth. Maternal fevers are a common clinical presentation; tachycardia (maternal or fetal), uterine tenderness, foul odor from amniotic fluid, and maternal leukocytosis may also occur. Early administration of broad-spectrum antibiotics immediately after the diagnosis has maternal and neonatal benefit.

- **Human Immunodeficiency Virus (HIV):** Current recommendations state that all HIV-infected pregnant women should receive intrapartum zidovudine (AZT), and their infants should receive neonatal AZP immediately after delivery for 6 weeks regardless of the antiretroviral therapy (ART) regimen taken during pregnancy (Table 49.5). Generally if a woman on ART becomes pregnant, she should continue on therapy throughout pregnancy. Women who did not require ART before becoming pregnant should start ART prophylaxis after the first trimester but not later than 28 weeks of gestation. Breast-feeding is not recommended for HIV-infected women in the United States due to safe and affordable formula alternatives. Prophylactic ART in the infant and mother does not eliminate the risk of perinatal transmission through breast milk.

## Postpartum Hemorrhage

- Oxytocin is routinely given after delivery of the placenta to promote uterine contraction and vasoconstriction. Misoprostol can be given orally in the third stage of labor to prevent postpartum hemorrhage.
- Atony, the condition in which the uterus fails to contract after delivery of the placenta, is the most common cause of postpartum hemorrhage.
- Table 49.6 shows medications used for postpartum hemorrhage.

## Prevention of RhD Alloimmunization

- Blood group incompatibility between a pregnant woman and her fetus can result in alloimmunization of the mother and hemolytic anemia in the fetus. This occurs when the mother is exposed to a small amount of the fetus's red blood cells and antigens are formed against the fetus's antigen.

TABLE 49.5 Intrapartum Maternal and Neonatal Zidovudine Dosing for Prevention of Perinatal Human Immunodeficiency Virus Transmission

Drug	Dose	Duration
Maternal zidovudine (intravenous)	<b>LOAD:</b> 2 mg/kg (actual body weight) intravenously for 1 hour <b>MAINTENANCE:</b> Continuous infusion of 1 mg/kg/hour	Onset of labor until delivery of infant
Neonatal zidovudine (oral syrup) <sup>a</sup>	>35 weeks' gestation: 4 mg/kg/dose orally every 12 hours >30 weeks' but <35 weeks' gestation: 2 mg/kg/dose orally every 12 hours, then after 2 weeks, advanced to every 8 hours <30 weeks' gestation: 2 mg/kg/dose orally every 12 hours, then after 4 weeks, advanced to every 8 hours	Start within 6–12 hours of birth and continue for 6 weeks Start within 6–12 hours of birth and continue for 6 weeks Start within 6–12 hours of birth and continue for 6 weeks
Neonatal combination therapy (zidovudine + nevirapine) <sup>b</sup>	Zidovudine 4 mg/kg/dose orally every 12 hours Nevirapine (total of three doses given orally in first week of life: at birth, at 48 hours, and 96 hours after second dose) Birthweight 1.5–2 kg: 8 mg/dose Birthweight: >2 kg: 12 mg/dose	Start within 6–12 hours of birth and continue AZT for 6 weeks. Nevirapine given only during first week of life

<sup>a</sup>Intravenous neonatal zidovudine dose of 1.5 mg/kg/dose every 6 hours if oral zidovudine cannot be given.

<sup>b</sup>In mothers who have not received antepartum ARV medication, infants will need combination ARV therapy.

Source: Panel on Treatment of HIV-Infected Pregnant Women and Prevention of Perinatal Transmission. Recommendations for Use of Antiretroviral Drugs in Pregnant HIV-1-Infected Women for Maternal Health and Interventions to Reduce Perinatal HIV Transmission in the United States. Sept. 14, 2011; pp. 1–207. <http://aidsinfo.nih.gov/ContentFiles/PerinatalGL.pdf>. Accessed November 7, 2011.

TABLE 49.6 Uterotonic Medications Used for Postpartum Obstetric Hemorrhage

Drug	Dose	Comments
Oxytocin (Pitocin)	40 international units in 1 L NS or lactated Ringer solution 10 international units IM if no IV site available	Do not give as undiluted IV bolus, can cause hypotension
Methylergonovine maleate (Methergine)	0.2 mg IM every 2–4 hours	Contraindicated in hypertensive patients
Carboprost tromethamine (Hemabate)	0.25 mg IM every 15–90 minutes, not to exceed eight doses	Caution in use with patients with asthma, can cause bronchoconstriction
Misoprostol	1,000 mcg rectally given once	Can also be given orally or sublingually, but PR is preferred route

IM, intramuscular; IV, intravenous; NS, normal saline; PR, per rectum.

Source: Cunningham FG et al. Obstetrical hemorrhage. In: *Williams Obstetrics*. 23rd ed. New York, NY: McGraw-Hill; 2010:757.

- An RhD-negative mother becomes immunized after exposure to fetal erythrocytes that carry the D antigen.
- Antepartum prophylaxis with Rho(D) immune globulin before or shortly after exposure to fetal RhD-positive blood will prevent alloimmunization of the mother. A second dose of Rho(D) immune globulin should be given within 72 hours of delivery.
- Rho(D) immune globulin should be given after all clinical events or procedures where fetomaternal hemorrhage is a risk when there is Rh-incompatible pregnancy.

## Lactation

- The most effective stimulation for lactation is suckling by the infant.
- Metoclopramide has been used to stimulate lactation in women with decreased or inadequate milk production.

TABLE 49.7 Factors Affecting the Fate of Drugs in Milk and the Nursing Infant

<b>Maternal Parameters</b>	<ul style="list-style-type: none"> <li>• Drug dosage and duration of therapy</li> <li>• Route and frequency of administration</li> <li>• Metabolism</li> <li>• Renal clearance</li> <li>• Blood flow to the breasts</li> <li>• Milk pH</li> </ul>
<b>Drug Parameters</b>	<ul style="list-style-type: none"> <li>• Milk composition</li> <li>• Oral bioavailability (to mother and infant)</li> <li>• Molecular weight</li> <li>• <math>pK_a</math></li> <li>• Lipid solubility</li> <li>• Protein binding</li> </ul>
<b>Infant Parameters</b>	<ul style="list-style-type: none"> <li>• Age of the infant</li> <li>• Feeding pattern</li> <li>• Amount of breast milk consumed</li> <li>• Drug absorption, distribution, metabolism, elimination</li> </ul>

$pK_a$ , dissociation constant.

Sources: Anderson PO. Drugs and breast milk [letter]. *Pediatrics*. 1995;95:957; Dillon AE et al. Drug therapy in the nursing mother. *Obstet Gynecol Clin North Am*. 1997;24:675; Begg EJ et al. Studying drugs in human milk: time to unify the approach. *J Hum Lact*. 2002;18:323; Bennett PN, ed. *Drugs and Human Lactation*. 2nd ed. New York, NY: Elsevier; 1996; Hale TW. *Medications and Mothers' Milk*. 13th ed. Amarillo, TX: Pharmasoft Medical Publishing; 2008.

TABLE 49.8 Reducing Risk of Infant Exposure to Drugs in Breast Milk

A drug should be used only if medically necessary and treatment cannot be delayed until the infant is ready to be weaned.

#### DRUG SELECTION

Consider whether the drug can be safely given directly to the infant.  
 Select a drug that passes poorly into breast milk with the lowest predicted M/P ratio, and an RID <10%.  
 Avoid long-acting formulations (e.g., sustained-release).  
 Consider possible routes of administration that can reduce drug excretion into milk.  
 Determine length of therapy and if possible avoid long-term use.

#### FEEDING PATTERN

Avoid nursing during times of peak drug concentration.  
 If possible, plan breast-feeding before administration of the next dose.

#### OTHER CONSIDERATIONS

Always observe the infant for unusual signs (e.g., sedation, irritability, rash, decreased appetite, failure to thrive).  
 Discontinue breast-feeding during the course of therapy if the risks to the fetus outweigh the benefits of nursing.  
 Provide adequate patient education to increase understanding of risk factors.

M/P, milk to plasma ratio; RID, relative infant dose.

Sources: Anderson PO. Drugs and breast milk [letter]. *Pediatrics*. 1995;95:957; Begg EJ et al. Studying drugs in human milk: time to unify the approach. *J Hum Lact*. 2002;18:323; Howard CR, Lawrence RA. Drugs and breastfeeding. *Clin Perinatol*. 1999;26:447.

- Suppression of lactation may also be indicated. Breast engorgement will occur over several days before lactation stops. Pain from engorgement can be managed with mild analgesics and application of ice packs to the breasts.
- Drug Excretion in Breast Milk
  - Overall risk to the infant depends on the amount of drug bioavailable to the mother, the amount reaching breast milk, and the actual amount of drug injected and bioavailable to the nursing infant.
  - The extent of drug passage into breast milk is often expressed quantitatively as the milk-to-plasma (M/P) ratio. Several parameters affect drug excretion into breast milk (Table 49.7).
  - Factors to consider to reduce risk of infant exposure to drugs in breast milk are shown in Table 49.8.
  - Table 49.9 lists some drugs that are contraindicated during lactation.

TABLE 49.9 Drugs Considered Contraindicated During Lactation<sup>a</sup>

Drug or Drug Class	Effects on Nursing Infants
Amphetamines <sup>b</sup>	Accumulate in breast milk and may cause irritability and poor sleep patterns
Antineoplastics	Potential for immune suppression; cytotoxic effects of drugs on dividing cells in infants unknown <sup>2</sup>
Cocaine <sup>b</sup>	Excreted in milk; contraindicated because of CNS stimulation and intoxication
Ergotamine	Potential for suppressing lactation; vomiting, diarrhea, and convulsions have been reported. <sup>217</sup> Considered contraindicated by some clinicians. AAP recommends using with caution
Heroin <sup>b</sup>	Possible addiction if sufficient amounts ingested
Immunosuppressants	Potential for immune suppression
Lithium	Milk and serum concentrations average 40% of maternal serum levels. Potential for toxicity exists. Considered contraindicated by some clinicians. AAP recommends using with caution.

*Continued on following page*

TABLE 49.9 Drugs Considered Contraindicated During Lactation<sup>a</sup> (Continued)

Drug or Drug Class	Effects on Nursing Infants
Lysergic acid diethylamide (LSD) <sup>b</sup>	Probably excreted in milk
Marijuana <sup>b</sup>	Excreted in milk
Misoprostol	Excretion in milk has not been studied but contraindicated because of potential for severe diarrhea in infant
Phencyclidine <sup>b</sup>	Potent hallucinogenic properties
Phenidone	Massive scrotal hematoma and wound oozing after herniotomy in one infant; contraindicated

## REQUIRING TEMPORARY CESSATION OF BREAST-FEEDING

Radiopharmaceuticals	Halt breast-feeding temporarily to allow clearance of radioactivity from milk. Suggested times for individual agents are <sup>244</sup> : copper-64 ( <sup>64</sup> Cu) 50 hours; gallium-67 ( <sup>67</sup> Ga) 2 weeks; indium-111 ( <sup>111</sup> In) 20 hours; iodine-123 ( <sup>123</sup> I) 36 hours; iodine-125 ( <sup>125</sup> I) 12 days; iodine-131 ( <sup>131</sup> I) 2–14 days; radioactive sodium 96 hours; technetium-99m ( <sup>99m</sup> Tc) 15 hours–3 days; ( <sup>99m</sup> TcO <sub>4</sub> ) ( <sup>99m</sup> Tc macroaggregates) 15 hours–3 days
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<sup>a</sup>This list is not all-inclusive. Selected drugs are listed by drug class and not by individual names.

<sup>b</sup>All drugs of abuse are contraindicated during lactation.

Sources: Briggs G et al. *Drugs in Pregnancy and Lactation: A Reference Guide to Fetal and Neonatal Risk*. 9th ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2011; American Academy of Pediatrics Committee on Drugs. Transfer of drugs and other chemicals into human milk. *Pediatrics*. 2001;108:776; Hale TW. *Medications and Mothers' Milk*. 13th ed. Amarillo, TX: Pharmasoft Medical Publishing; 2008.

# Disorders Related to the Menstrual Cycle\*

## General Principles

- Biologic feedback mechanisms involving the hypothalamus, anterior pituitary gland, ovaries, and endometrial lining of the uterus control the average 28-day menstrual cycle.
- The menstrual cycle is divided into three phases: follicular phase, ovulation, and luteal phase.

## Polycystic Ovarian Syndrome

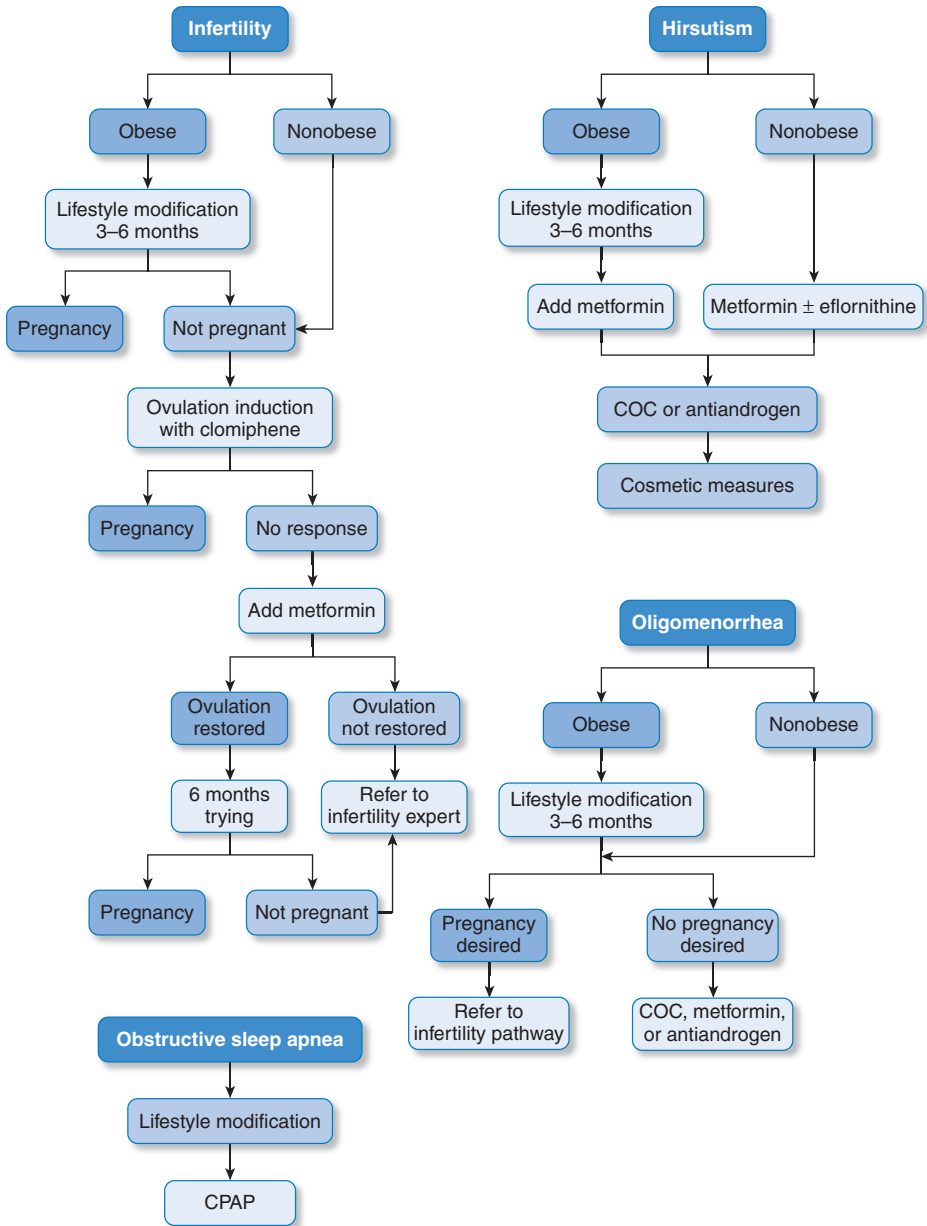
- Polycystic ovarian syndrome (PCOS) is the leading cause of anovulatory infertility.
- Uniform criteria for diagnosis have not been firmly established. Clinical signs of PCOS include hirsutism, acne, and alopecia. Ovulatory dysfunction is typically described as oligo-ovulation or anovulation, presenting as irregular menstrual cycles.
- Patient assessment should include menstrual history, signs and symptoms of hyperandrogenism, time course of symptoms, weight history, previous agents tried, and family history.
- **Treatment**
  - Treatment goals should include short- and long-term objectives. Figure 50.1 shows a treatment algorithm.
  - Lifestyle modification, including weight reduction through appropriate diet and exercise is effective for reducing the metabolic state.
  - Several different pharmacologic options exist (Table 50.1).
  - Clomiphene citrate can be used to induce ovulation in anovulatory women.

## Dysmenorrhea

- Dysmenorrhea is painful cramping that occurs at the onset and during the first few days of menstruation.
- Table 50.2 shows the differences between primary (without underlying uterine pathology) and secondary (with underlying uterine pathology) dysmenorrhea. Dysmenorrhea occurring several years after menarche is most likely secondary disease.
- No specific diagnostic criteria exist for primary dysmenorrhea. Typical symptoms include cramping pain in the suprapubic area, nausea, and diarrhea. Some women also experience vomiting, fatigue, headache, lightheadedness, flushing, loss of appetite, irritability, nervousness, and insomnia.
- **Treatment**
  - Goals of therapy include reduction in pain and associated symptoms.
  - Nonpharmacologic therapies include aerobic exercise, heat therapy, tobacco cessation, omega-3 polyunsaturated fatty acids, and high-frequency transcutaneous electrical nerve stimulation.
  - Nonsteroidal anti-inflammatory drugs (NSAIDs) provide relief from symptoms for primary dysmenorrhea for most women. Over-the-counter (OTC) products may not be sufficient;

\*The reader is referred to Chapter 50, Disorders Related to the Menstrual Cycle, written by Laura M. Borgelt, PharmD, BCPS, FCCP, and Karen M. Gunning, PharmD, BCPS, FCCP, in the 10th edition of *Applied Therapeutics: The Clinical Use of Drugs* for a more in-depth discussion. All notations to reference numbers are based on the reference list at the end of that chapter. The editor of this handbook expresses her thanks to Drs. Borgelt and Gunning and acknowledges that this chapter is based on their work.





**Figure 50.1** Treatment algorithm for polycystic ovary syndrome (PCOS). (Adapted with permission from Borgelt LM, Cheang KI. Polycystic ovary syndrome. In: Borgelt LM et al, eds. *Women's Health Across the Lifespan: A Pharmacotherapeutic Approach*. Bethesda, MD: American Society of Health-System Pharmacists; 2010:247.)

**TABLE 50.1 Adverse Reactions with Danazol and the Gonadotropin-Releasing Hormone Agonists**

	Danazol (%)	Nafarelin (%)	Leuprolide (%)	Goserelin (%)
<b>ANTIESTROGENIC EFFECTS</b>				
Hot flashes	67–69	90	84	96
Vaginal dryness or vaginitis	7–43	19	28	75
Abnormal vaginal bleeding <sup>a</sup>	+	+	28	+
Breast atrophy	16–42	10	6	33
Decreased libido	7–44	22	11	61
<b>ANDROGENIC EFFECTS</b>				
Weight gain	23–28	8	13	3
Voice alteration	8	NR	<5	3
Hirsutism	6–7	2	<5	15
Acne	20–42	13	10	55
<b>CENTRAL NERVOUS SYSTEM EFFECTS</b>				
Sleep disturbances	4	8	<5	11
Headaches	21–63	19	32	75
Depression or emotional lability	18–60	9–15	22	54–56
<b>OTHER</b>				
Peripheral edema	34	8	7	21
Nausea	14	NR	13	8
Seborrhea	17–52	8	10	26
Nasal irritation	NR	10	NR	NR
Injection site reactions	NR	NR	<5	6
Joint pain	+	<1	<8	+

<sup>a</sup>Amenorrhea is an expected consequence of these medications.

+, Reported but percentages not given; NR, not reported.

**TABLE 50.2 Primary Versus Secondary Dysmenorrhea**

Characteristic	Primary Dysmenorrhea	Secondary Dysmenorrhea
Onset	Around menarche	Any age (while menstruating)
Timing in menstrual cycle	Worse on day 1, lasts 24–48 hours	Increases in severity, may last days
Change over time	Stable, predictable	Increasing pain with increasing age
Symptoms	Low back pain, premenstrual syndrome, nausea, bloating	Low back pain, dyspareunia, diarrhea or constipation, dysuria, infertility
Signs	Normal pelvic examination	Fixed retroverted uterus, tenderness, but may be completely normal

Source: Reddish S. Dysmenorrhea. *Aust Fam Physician*. 2006;35:82.

prescription strength NSAIDs may be needed. No significant difference in efficacy between NSAIDs has been found.

- Acetaminophen is of limited benefit compared with NSAIDs or hormonal contraception.
- Hormonal contraceptives are an option if prescription NSAIDs are inadequate or in women who also want contraceptive protection.

## Endometriosis

- Endometriosis is defined as the presence of functional endometrial tissue outside of the uterine cavity. It is the most common cause of secondary dysmenorrhea.
- Diagnosis can be difficult due to similar symptoms to other conditions. Characteristic symptoms include short menstrual cycle length with prolonged flow. Symptoms based on location are shown in Table 50.3.

**TABLE 50.3 Location of Endometriosis and Associated Symptoms**

Sites	Symptoms
<b>PELVIC</b>	
Cervix	Abnormal uterine bleeding
Ovaries	Dysmenorrhea
Peritoneum	Dyspareunia
Rectovaginal septum	Infertility
Uterosacral ligaments	Pelvic pain
<b>INTESTINAL</b>	
Abdominal scars	Intestinal obstruction
Sigmoid colon	Midabdominal pain
Small intestines	Nausea
	Painful defecation
	Rectal bleeding
<b>URINARY TRACT</b>	
Bladder	Cyclic flank pain
Ureter	Hematuria
	Hydronephrosis
	Hydroureter

Source: American College of Obstetricians and Gynecologists. ACDG Practice Bulletin No. 114. Management of endometriosis. *Obstet Gynecol.* 2010;116:223.

• **Treatment**

- Goals of therapy are to relieve symptoms and, if desired, preserve or improve fertility. Therapy should be individualized and should consider desire for future fertility, severity of symptoms, extent of disease, and potential for infertility.
- NSAIDs may help with pain relief for mild symptoms; they should not be the only therapy offered to patients with confirmed endometriosis.
- Combined hormonal contraceptives are a reasonable next step in women desiring contraception, used either alone or in combination with NSAIDs. Continuous dosing (no placebo week) may be preferred.
- Progestins are useful if estrogen use is contraindicated. They have increased side effects compared with combined hormonal contraceptives.
- Gonadotropin-releasing hormone agonist use is limited by the high cost and adverse effects (Table 50.4), making these agents second-line choices behind oral contraceptives and progestins.
- Aromatase inhibitors (anastrozole, letrozole) should be reserved for patients with severe disease who have failed other therapies.
- Danazol use should be limited to 6 months of therapy and should only be initiated in women after all other therapies have failed due to its safety concerns.

**TABLE 50.4 Gonadotropin-Releasing Hormone Agonists**

GnRH Agonist (Brand Name)	Strength	Dosage Form	Dosage Regimen
Nafarelin (Synarel)	2 mg/mL delivers 200 mcg/spray	Intranasal	200–800 mcg BID
Leuprolide (Lupron)	3.75 mg, 11.25 mg	IM depot	3.75 mg/month or 11.25 mg every 3 months
Goserelin (Zoladex)	3.6 mg, 10.8 mg	SC implant	3.6 mg implant every month or 10.8 mg implant every 3 months

BID, twice daily; GnRH, gonadotropin-releasing hormone; IM, intramuscular; SC, subcutaneous.

TABLE 50.5 ACOG Diagnostic Criteria for Premenstrual Syndrome<sup>a</sup>

Affective Symptoms	Somatic Symptoms
Depression	Breast tenderness
Angry outbursts	Abdominal bloating
Irritability	Headache
Anxiety	Swelling of extremities
Confusion	
Social withdrawal	

<sup>a</sup>(1) Diagnosis made if at least one affective and one somatic symptom is reported in the three prior menstrual cycles during the 5 days before the onset of menses. (2) The symptoms must resolve within 4 days of onset of menses and do not recur until after day 12 of the cycle. (3) The symptoms must be present in at least two cycles during prospective recording. (4) The symptoms must adversely affect social or work-related activities.

ACOG, American College of Obstetricians and Gynecologists.

Sources: American College of Obstetricians and Gynecologists. ACOG Practice Bulletin. Clinical management guidelines for obstetrician-gynecologists. Premenstrual syndrome. April 2000. *Obstet Gynecol.* 2000;95(4); Mishell DR. Premenstrual disorders: epidemiology and disease burden. *Am J Manag Care.* 2005;11:S473.

## Premenstrual Syndrome and Premenstrual Dysphoric Disorder

- Premenstrual syndrome (PMS) can be diagnosed if at least one affective and one somatic symptom are present (Table 50.5). Unlike normal premenstrual symptoms, work or social activities are adversely affected with PMS.
- Diagnostic criteria for premenstrual dysphoric disorder (PMDD) are shown in Table 50.6. There is a higher level of dysfunction (mood and mental health symptoms) compared with PMS.
- **Treatment**
  - Treatment of physical symptoms of PMS includes acetaminophen and NSAIDs, although mood symptoms will not be relieved. Evidence for use of calcium, magnesium, pyridoxine, and chasteberry are lacking. Nonpharmacological agents such as heating pads may also help with leg/back aches.
  - Treatment of PMDD includes lifestyle modifications, psychosocial interventions, and pharmacologic therapy (Table 50.7). Combination oral contraceptives may also be considered.

TABLE 50.6 Diagnostic Criteria for Premenstrual Dysphoric Disorder

- In most menstrual cycles during the past year, at least five of the subsequent symptoms (including one core symptom) were present for most of the time 1 week before menses (luteal phase), began to remit within a few days after the onset of menses, and were absent the week after menses (follicular phase).
  - Core symptoms
  - Markedly depressed mood, feelings of hopelessness, or self-deprecating thoughts
  - Persistent and marked anger or irritability or increased interpersonal conflicts
  - Marked anxiety, tension
  - Marked affective lability (i.e., feeling suddenly sad or tearful)
- Other symptoms
  - Decreased interest in usual activities (e.g., friends, hobbies)
  - Subjective sense of difficulty in concentrating
  - Lethargy, easy fatigability, or marked lack of energy
  - Marked change in appetite, overeating, or specific food cravings
  - Hypersomnia or insomnia
  - A subjective sense of being overwhelmed or out of control
  - Other physical symptoms (e.g., breast tenderness, bloating, weight gain, headache, joint or muscle pain)

*Continued on following page*

TABLE 50.6 Diagnostic Criteria for Premenstrual Dysphoric Disorder (Continued)

- The symptoms seriously interfere with work or school, usual activities, or relationships with others.
- Symptoms are not merely an exacerbation of another disorder, such as major depression, panic disorder, dysthymia, or a personality disorder (although it may be superimposed on any of these disorders).
- Three of these major criteria are confirmed by prospective daily self-ratings for at least two consecutive symptomatic cycles.

Source: Adapted with permission from American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders, DSM-IV-TR*. 4th ed. Washington, DC: APA; 2000.

TABLE 50.7 Psychotropic Drugs for the Management of Premenstrual Syndrome or Premenstrual Dysphoric Disorder

Drug (Brand Name)	Daily Dosing Regimen (mg)	Intermittent Dosing Regimen (mg) <sup>a</sup>
<b>SSRI</b>		
Citalopram (Celexa)	5–30	10–30
Escitalopram (Lexapro)	10–20	10–20
Fluoxetine (Prozac or Sarafem <sup>b</sup> )	20–60	20 or 90 weekly
Fluvoxamine (Luvox)	50–150	NS
Paroxetine (Paxil)	10–30	NS
Paroxetine controlled release (Paxil CR) <sup>b</sup>	12.5–25	12.5–25
Sertraline (Zoloft) <sup>b</sup>	50–150	100
<b>OTHER SEROTONERGIC ANTIDEPRESSANTS</b>		
Nefazodone (Serzone)	200–600	NS
Venlafaxine (Effexor)	50	NS
<b>ANXIOLYTICS</b>		
Alprazolam (Xanax)	NS	1–2 <sup>c</sup>
Bupirone (BuSpar)	NS	25–60

<sup>a</sup>Day 14 until onset of menses.

<sup>b</sup>Medication has FDA-approved indication for premenstrual dysphoric disorder.

<sup>c</sup>Dose to be tapered during 2 days after onset of menses to prevent withdrawal symptoms.

NS, not studied; SSRI, selective serotonin reuptake inhibitors.

# The Transition Through Menopause\*

## General Principles

- Menopause is a natural progression of reproductive aging in women characterized by declining ovarian function and decreased synthesis of sex hormones.
- Postmenopausal estrogen production is approximately 10% of premenopausal levels.

## Patient Assessment

- Menopause is usually identified retrospectively after 12 months of amenorrhea and typically occurs 4 to 5 years after the onset of perimenopause. The average age for menopause is 51 years.
- Clinical symptoms that can result from the decrease in estrogen production include hot flashes, genitourinary atrophy, irritability, inability to concentrate, forgetfulness, headaches, dizziness, joint stiffness, and fatigue.
- Vasomotor symptoms (hot flashes) are experienced by 50% to 85% of women during the menopause transition, with prevalence highest during the first 2 years of menopause. Triggers can include increased environmental temperature, mental stress, or ingestion of hot liquids or alcohol.
- Symptoms of atrophic vaginitis include dryness, itching, pain, and dyspareunia (painful coitus).

## Goals of Therapy

- The goal of drug therapy in symptomatic postmenopausal women is to relieve symptoms and improve quality of life without increasing the risk of serious adverse outcomes related to therapy.

## Treatment

- Lifestyle modifications (avoiding known triggers, wearing layered clothing, use of cooling devices) are first-line treatment.
- Estrogen therapy is the most effective treatment for menopausal symptoms but it is associated with risks. All women should be evaluated for contraindications and counseled about possible risks and benefits (Table 51.1).
- Current guidelines on systemic hormone therapy recommend use only in women with moderate to severe hot flashes (Figure 51.1).
- Several hormonal therapies are available (Table 51.2). Oral and transdermal estrogens are equally efficacious. A combination of estrogen/progesterone therapy should be used in a woman with a uterus due to the increased risk of endometrial cancer with estrogen monotherapy in this population. Progestogen monotherapy appears to be similar to estrogen in relieving symptoms of hot flashes.

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\*The reader is referred to Chapter 51, The Transition Through Menopause, written by Louise Parent-Stevens, PharmD, BCPS, in the 10th edition of *Applied Therapeutics: The Clinical Use of Drugs* for a more in-depth discussion. All notations to reference numbers are based on the reference list at the end of that chapter. The editor of this handbook expresses her thanks to Dr. Parent-Stevens and acknowledges that this chapter is based on her work.

TABLE 51.1 Risks and Benefits of Postmenopausal Hormone Therapy

	Evidence	Absolute or Relative Contraindications and Patient Considerations	References
<b>ESTABLISHED BENEFITS<sup>a</sup></b>			
Vasomotor symptoms	Systemic ET (in women without a uterus) or EPT (in women with a uterus) is considered the most effective therapy for hot flashes. There may be a dose–response relationship. Oral and TD estrogen are equally effective.	This is the primary indication for the use of systemic hormone therapy.	34,35
Osteoporosis	Numerous clinical trials support reduced risk of vertebral and hip fractures with use of estrogen.	Not a primary indication for use but will provide bone protection during use of HT for menopausal symptoms.	32,36
Vaginal atrophy	Numerous studies show both local and systemic estrogen reverse the atrophy induced by menopause.	Localized therapy should be used for patients with symptoms related solely to vaginal atrophy.	37,38
<b>ESTABLISHED RISKS<sup>a</sup></b>			
Thromboembolic disease	Increased risk of DVT and PE, greatest within the first year of use, risk with EPT possibly greater than with ET. Transdermal estrogen appears to have lower risk than oral estrogen.	<b>Absolute contraindication:</b> current tobacco use, history of thrombosis <b>Relative contraindication:</b> obesity, women 65 years and older Therapy should be discontinued before surgery or anticipated period of immobilization.	33,39,50,52,55
Breast cancer	Numerous clinical trials indicate risk increased ~25% after 5 years of use, increases with continued use. Greater risk with shorter exposure gap, seen with both EPT and ET	<b>Absolute contraindication:</b> personal history of breast cancer <b>Relative contraindication:</b> strong family history of breast cancer	32,47–49
Cardiovascular disease	Increased risk of MI, especially when started >10 years after menopause or in women ≥60 years old (see also unconfirmed benefit)	<b>Relative contraindication:</b> age 60 years or older, >10 years postmenopause	39,40
Endometrial cancer	Risk related to dose and duration of use Addition of progestogen reduces or eliminates risk	Rationale for use of concomitant progestogen in women with uterus <b>Absolute contraindication:</b> undiagnosed postmenopausal vaginal bleeding, prior history of endometrial cancer	43,44
Ischemic stroke	~30%–40% increased risk for ischemic stroke seen. Risk seen with both ET and EPT and may be dose related. Risk increased with increasing age (because of underlying age-related risk of stroke). HT does not appear to affect risk of hemorrhagic stroke.	<b>Absolute contraindication:</b> history of stroke or transient ischemic attacks, current tobacco use <b>Relative contraindication:</b> obesity, uncontrolled hypertension, uncontrolled diabetes	32,45,46,51,56

TABLE 51.1 Risks and Benefits of Postmenopausal Hormone Therapy (Continued)

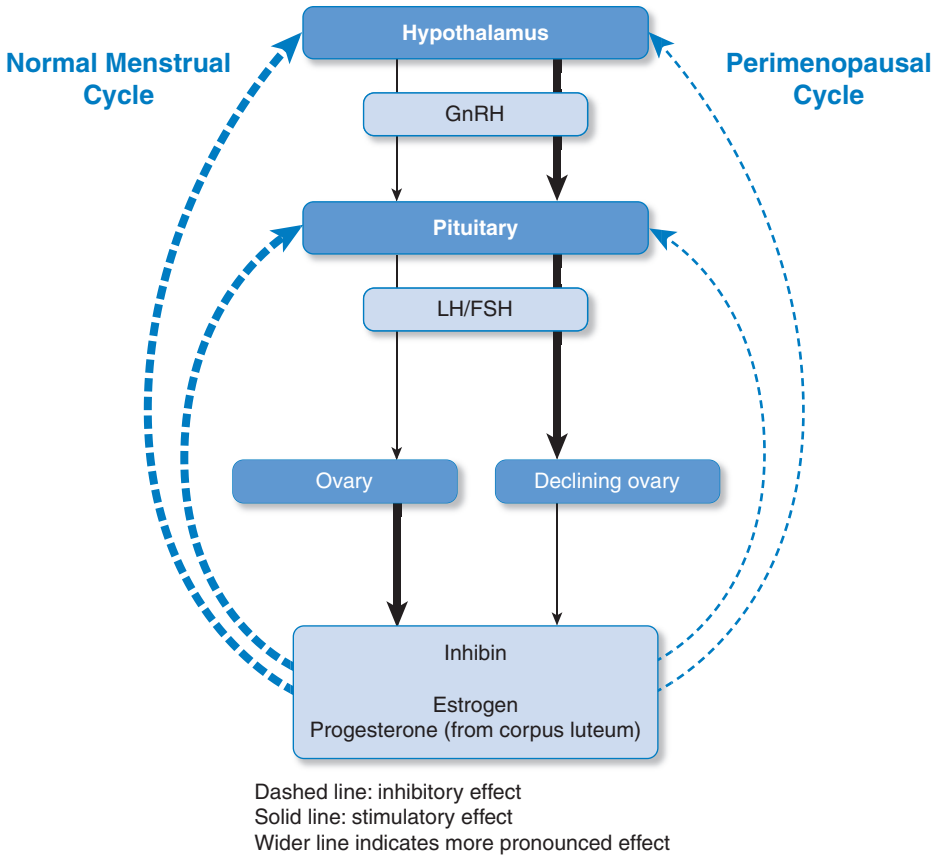
	Evidence	Absolute or Relative Contraindications and Patient Considerations	References
Gallbladder disease	~60% increased risk of cholecystitis and cholelithiasis (gallstones) seen with ET and EPT, also increased risk for gallbladder surgery	<b>Relative contraindication:</b> history of gallbladder disease	33,53
Hypertriglyceridemia	Oral estrogen increases triglycerides. Transdermal estrogen has a less pronounced effect, and EPT may have less effect than ET alone owing to attenuating effect of progestogen.	<b>Relative contraindication:</b> hypertriglyceridemia If estrogen is to be used in woman with elevated TG, select transdermal route, monitor TG levels.	44,54,57
<b>UNCONFIRMED BENEFITS<sup>b</sup></b>			
Cardiovascular disease	No increased risk or possible decreased risk when initiated soon after menopause (see also established risk)	Prevention of CVD is not a primary indication for use; this information can reassure patient needing HT for menopause symptoms or replacement for women with premature ovarian failure.	41,42
Colorectal cancer	Decreased risk is seen with EPT but not with ET.	May be secondary benefit in women using for hot flashes	39,58
Recurrent UTIs	Low-dose localized estrogen treatment can decrease risk for recurrent UTIs.	May be secondary benefit in women using localized therapy for vaginal atrophy	59
Diabetes mellitus	Decreased incidence of new-onset diabetes in women taking EPT or ET	This suggests that DM is not a contraindication for women who wish to use EPT/ET.	56
<b>UNCONFIRMED RISKS<sup>b</sup></b>			
Ovarian cancer	Increased risk seen with ET and EPT and increased duration is associated with greater risk.	<b>Relative contraindication:</b> strong family history of ovarian cancer	60–63
Lung cancer	Studies showed increased risk of lung cancer diagnosis and mortality with EPT but not ET. Risk seen primarily in current smokers and older women	<b>Absolute contraindication:</b> current tobacco use (owing to increased risk of TED)	64–66
Urinary incontinence	Systemic estrogen caused or worsened urinary incontinence	Avoid systemic estrogen in women with urinary incontinence, monitor for new onset in women taking HT.	59,67,68
Cognitive effects	Studies report worsening of dementia in women with preexisting dementia and no improvement or protection in older women taking HT.	<b>Absolute contraindication:</b> patients with evidence of dementia Avoid use in women ≥65 years.	69–71
Migraine headaches	HT may cause worsening of migraine headaches.	<b>Absolute contraindication:</b> migraine with aura (increased risk of stroke) <b>Relative contraindication:</b> migraine without aura—monitor for changes in HA frequency	72

<sup>a</sup>Well-documented risk or benefit supported by multiple clinical studies.

<sup>b</sup>Possible risk or benefit shown in limited clinical trials; additional data needed to confirm.

CVD, cardiovascular disease; DM, diabetes mellitus; DVT, deep venous thrombosis; EPT, estrogen and progestogen therapy; ET, estrogen-only therapy; HA, headache; HT, hormone therapy; MI, myocardial infarction; PE, pulmonary embolism; TD, transdermal; TED, thromboembolic disease; TG, triglycerides; UTI, urinary tract infection.





**Figure 51.1** Perimenopausal changes in hypothalamus–pituitary–ovary axis.  
 FSH, follicle-stimulating hormone; GnRH, gonadotropin-releasing hormone; LH, luteinizing hormone.

- Abrupt discontinuation of hormone therapy should be avoided as it may trigger recurrence of hot flashes. Tapering is recommended (e.g., increasing the dosing interval or decreasing the dose to the next available dosage strength).
- Nonhormonal agents are modestly effective in reducing hot flush frequency and severity and offer an alternative in women who are unable or unwilling to take hormone therapy (Table 51.3).
- Vaginal moisturizers can be used to improve vaginal symptoms, but they do not reverse atrophy.

TABLE 51.2 Agents Labeled for Use in ET and EPT Therapy

Drug (Brand Name)	Route Initial Dosage
<b>ESTROGENS, SYSTEMIC<sup>b</sup></b>	
Conjugated equine estrogens (Premarin) <sup>a</sup>	PO 0.3 mg
Synthetic conjugated estrogens (A: Cenestin, B: Enjuvia)	PO 0.3 mg
Estopipate (piperazine estrone sulfate) (Ogen, Ortho-Est) <sup>a,c</sup>	PO 0.625 mg
Micronized estradiol (Estrace, Gynodiol) <sup>a,c</sup>	PO 0.5 mg
Estradiol transdermal system (various brand name products) <sup>a</sup>	TD 0.014–0.025 mg/24 hour patch applied weekly or twice weekly
Esterified estrogen (Menest) <sup>a</sup>	PO 0.3 mg
Estradiol acetate tablet (Femtrace) <sup>c</sup>	PO 0.45 mg
Estradiol acetate vaginal ring (Femring) <sup>c</sup>	HDV 0.05 mg/24 hour ring inserted vaginally every 90 days
Estradiol topical emulsion/gel/solution (Divigel, Elestrin, Estrogel, Estrasorb, Evamist) <sup>c</sup>	TD 0.0125 mg to 0.75 mg (product dependent)
<b>PROGESTOGENS</b>	
Medroxyprogesterone acetate (Provera generic and combo products)	PO 5 mg for cyclic regimens; 2.5 mg for continuous regimens
Norethindrone acetate (Aygestin generic and combo products)	PO 2.5 mg for cyclic regimens; 0.5 mg for continuous regimens
Micronized progesterone (Prometrium) <sup>c</sup>	PO 200 mg for cyclic regimens; 100 mg for continuous regimens
Progesterone vaginal gel (Prochieve, Crinone) <sup>c</sup>	V 1 full applicator of 4% gel every other day
Progesterone vaginal suppository (First Progesterone VGS)	V 200 mg/day for 12 days
Levonorgestrel-releasing IUD (Mirena)	IU 0.02 mg/day
<b>ESTROGEN AND PROGESTOGEN COMBINATIONS</b>	
Prempro <sup>a</sup>	PO 0.3 mg CEE and 1.5 mg MPA
Premphase <sup>a</sup>	PO 0.625 mg CEE for 28 days with 5 mg MPA for last 14 days
CombiPatch	TD 0.05 mg estradiol with 0.14 mg norethindrone
Femhrt <sup>a</sup>	PO 0.0025 mg ethinyl estradiol and 0.1 mg norethindrone acetate
Activella <sup>a</sup>	PO 0.5 mg estradiol and 0.1 mg norethindrone acetate
Prefest <sup>a</sup>	PO 1 mg estradiol and 0.09 mg norgestimate (3 days of ET alternating with 3 days of EPT)
Climara Pro <sup>a</sup>	TD 0.045 mg estradiol/0.015 mg levonorgestrel/24-hour patch once weekly
Angeliq	PO 1 mg estradiol and 0.5 mg drospirenone
<b>ESTROGEN AND ANDROGEN COMBINATIONS<sup>b</sup></b>	
Esterified estradiol and Methyltestosterone (Estratest, Covaryx)	PO 0.625 mg esterified estrogens and 1.25 mg MT
<b>LOW-DOSE VAGINAL ESTROGENS (LOCALIZED EFFECT ONLY)</b>	
Conjugated Equine Estrogen cream (Premarin)	LDV Initial: 0.5–2 g cream (0.3125–1.25 mg CEE) daily Maintenance: 0.5–2 g cream (0.3125–1.25 mg CEE) once/twice weekly based on severity
Estradiol cream (Estrace) <sup>c</sup>	LDV Initial: 2–4 g cream (0.2–0.4 mg estradiol) daily Maintenance: 1 g cream (0.1 mg estradiol) twice weekly
Estradiol ring (Estring) <sup>c</sup>	LDV 2-mg ring (0.0075 mg/day) every 90 days
Estradiol hemihydrate tablets (Vagifem and Vagifem LD)	LDV one tablet (0.01 mg) daily for 2 weeks, then one tablet twice weekly

<sup>a</sup>Approved by the US Food and Drug Administration for prevention of osteoporosis.

<sup>b</sup>Requires addition of progestogen in women with a uterus.

<sup>c</sup>FDA-approved bioidentical hormone.

CEE, conjugated equine estrogens; HDV, high-dose vaginal estrogen, sufficient absorption to produce systemic estrogenic effect (i.e., for treatment of hot flashes); IU, intrauterine; IUD, intrauterine device; LDV, low-dose vaginal estrogen, provides localized estrogenic effect (i.e., for vaginal atrophy), owing to low dose, minimal systemic absorption; MPA, medroxyprogesterone acetate; MT, methyltestosterone; PO, oral; TD, transdermal; V, vaginal.

Source: Adapted with permission from Facts & Comparisons eAnswers. <http://online.factsandcomparisons.com/index.aspx?> Accessed November 28, 2011.

TABLE 51.3 Nonhormonal Agents for the Management of Vasomotor Symptoms<sup>14,15,17,23,92-99</sup>

Drug	Recommended Dosage	Adverse Reactions Reported
<b>SEROTONERGIC ANTIDEPRESSANTS</b>		
Citalopram (Celexa)	10–30 mg	Dry mouth, ↓ libido, rash/hives, insomnia, somnolence, bladder spasm, palpitations, arthralgias
Desvenlafaxine (Pristiq)	50–100 mg	Asthenia, chills, anorexia, nausea, vomiting, constipation, diarrhea, dizziness, nervousness, mydriasis, dry mouth
Escitalopram (Lexapro)	10–20 mg	Dizziness, lightheadedness, nausea, vivid dreams, increased sweating
Fluoxetine (Prozac)	10–20 mg	Nausea, dry mouth
Paroxetine (Paxil, PaxilCR)	10–20 mg 12.5–25 mg (CR)	Headache, nausea, insomnia, drowsiness
Sertraline (Zoloft)	50 mg	Nausea, fatigue/malaise, diarrhea, anxiety/nervousness
Venlafaxine (Effexor, Effexor XR)	37.5–75 mg 37.5–150 mg XR	Dry mouth, ↓ appetite, nausea, constipation, possible increase in blood pressure at higher doses
<b>ANTISEIZURE AGENTS</b>		
Gabapentin (Neurontin)	900 mg, possibly up to 2,400 mg	Somnolence, fatigue, dizziness, rash, palpitations, peripheral edema
Pregabalin (Lyrica)	150–300 mg	Dizziness, sleepiness, weight gain, cognitive difficulty
<b>ANTIHYPERTENSIVE AGENTS</b>		
Clonidine	PO: 0.05–0.15 mg TD: 0.1 mg/24 hour	Headache, dry mouth, drowsiness Skin reaction/itching (patch only), risk of rebound HTN if stopped abruptly

HTN, hypertension; PO, orally; TD, transdermally.

## Thyroid Disorders\*

### General Principles

- Triiodothyronine ( $T_3$ ) and thyroxine ( $T_4$ ) are the two biologically active thyroid hormones produced by the thyroid gland.  $T_3$  is four times more potent than  $T_4$ . About 80% of daily  $T_3$  production results from conversion from  $T_4$ . The major circulating thyroid hormone is  $T_4$ , most of which is protein bound.
- Low levels of thyroid hormone stimulate thyrotropin-releasing hormone (TRH) from the hypothalamus, which, in turn, stimulates release of thyrotropin (thyroid-stimulating hormone, TSH) from the pituitary.
- TSH is the most accurate indicator of euthyroidism.
- Both hyperthyroidism and hypothyroidism can alter metabolism of coadministered medications (e.g., warfarin, digoxin).

### Laboratory Assessment

- Thyroid function tests are essential to confirm the presence of thyroid disorders (Table 52.1). The primary tests recommended in the initial evaluation of thyroid disorders are TSH and free  $T_4$  ( $FT_4$ ) levels.
- Test results can be altered by acute and chronic illness, and by certain drugs (Table 52.2).

### Hypothyroidism

- Hypothyroidism is a clinical syndrome that results from a deficiency of thyroid hormone. Clinical and laboratory findings are shown in Table 52.3.
- Common causes of hypothyroidism are shown in Table 52.4. The most common cause of primary hypothyroidism is Hashimoto's thyroiditis, an autoimmune disorder.
- **Myxedema coma** is the end stage of long-standing, uncorrected hypothyroidism. Emergency medical care and hospitalization are required.
- Hypothyroid patients with congestive heart failure require careful management due to increased sensitivity to digoxin and risk of hypotension or syncope with nitrates.
- Early (before 3 months of age) diagnosis and treatment of congenital hypothyroidism is critical to allow for normal growth and mental development.
- **Treatment**
  - The goal of therapy is to reverse the signs and symptoms of hypothyroidism and normalize the TSH and  $FT_4$  levels.
  - Thyroid preparations can be either synthetic or natural (Table 52.5). Desiccated thyroid should not be considered a treatment of choice due to variable potency and potential for allergic reactions. Triiodothyronine ( $T_3$ ) is not recommended for routine thyroid replacement because of its short half-life requiring multiple daily doses and potential for cardiotoxicity.

\*The reader is referred to Chapter 52, Thyroid Disorders, written by Betty J. Dong, PharmD, FASHP, FCCP, and Eric F. Schneider, PharmD, BCPS, in the 10th edition of *Applied Therapeutics: The Clinical Use of Drugs* for a more in-depth discussion. All notations to reference numbers are based on the reference list at the end of that chapter. The editor of this handbook expresses her thanks to Drs. Dong and Schneider and acknowledges that this chapter is based on their work.

TABLE 52.1 Common Thyroid Function Tests

Tests	Measures	Normal Values <sup>a</sup>	Assay Interference	Comments
<b>MEASUREMENT OF CIRCULATING HORMONE LEVELS</b>				
FT <sub>4</sub>	Direct measurement of free thyroxine	0.7–1.9 ng/dL (9–24 pmol/L)	No interference by alterations in TBG	Most accurate determination of FT <sub>4</sub> levels; might be higher than normal in patients on thyroxine replacement
FT <sub>4</sub> I	Calculated free thyroxine index	<i>T<sub>4</sub> uptake method:</i> 6.5–12.5 <i>TT<sub>4</sub> × T<sub>3</sub>RU method:</i> 1.3–4.2	Nonthyroidal illness	Estimates direct FT <sub>4</sub> measurement; compensates for alterations in TBG
TT <sub>4</sub>	Total free and bound T <sub>4</sub>	4.8–10.4 mcg/dL (62–134 nmol/L)	Alterations in TBG (Table 52.2)	Specific and sensitive test if no alterations in TBG
TT <sub>3</sub>	Total free and bound T <sub>3</sub>	79–149 ng/dL (1.2–2.3 nmol/L)	Alterations in TBG levels; T <sub>4</sub> to T <sub>3</sub> (Table 52.2). Nonthyroidal illness	Useful in detecting early, relapsing, and T <sub>3</sub> toxicosis. Not useful in evaluation of hypothyroidism
FT <sub>3</sub>	Direct measurement of free T <sub>3</sub>	145–348 pg/dL (2.2–5.4 pmol/L)	No interference by alterations in TBG	Most accurate determination of FT <sub>3</sub> levels; might be lower than normal in patients on thyroxine replacement
FT <sub>3</sub> I	Calculated free T <sub>3</sub> index	17.5–46	Nonthyroidal illness	Estimates direct FT <sub>3</sub> measurement; compensates for alterations in TBG
<b>TESTS OF THYROID GLAND FUNCTION</b>				
RAIU	Gland's use of iodine after trace dose of either <sup>123</sup> I or <sup>131</sup> I	5%–35%	False decrease with excess iodide intake; false elevation with iodide deficiency	Useful in hyperthyroidism to determine RAI dose in Graves disease; does not provide information about hormone synthesis
Scan	Gland size, shape, and tissue activity after <sup>123</sup> I or <sup>99m</sup> Tc	—	<sup>123</sup> I scan blocked by antithyroid/thyroid medications	Useful in nodular disease to detect "cold" or "hot" areas
<b>TEST OF HYPOTHALAMIC–PITUITARY–THYROID AXIS</b>				
TSH	Pituitary TSH level	0.4–4.0 microunits/mL	Dopamine, glucocorticoids, metoclopramide, thyroid hormone, amiodarone, metformin (Table 52.2)	Most sensitive index for hyperthyroidism, hypothyroidism, and replacement therapy

TABLE 52.1 Common Thyroid Function Tests (Continued)

Tests	Measures	Normal Values <sup>a</sup>	Assay Interference	Comments
<b>TESTS OF AUTOIMMUNITY</b>				
TgAb	Thyroglobulin autoantibodies	<20 international units/mL	Nonthyroidal autoimmune disorders	Present in autoimmune thyroid disease; undetectable during remission
TPA	Thyroid peroxidase antibodies	<0.8 international units/mL	Nonthyroidal autoimmune disorders	More sensitive of the two antibodies; titers detectable even after remission
TSI or TRAb	Thyroid receptor or thyroid-stimulating antibody	<125%	—	Confirms Graves disease; detects risk of neonatal Graves disease
<b>MISCELLANEOUS</b>				
Thyroglobulin	Colloid protein of normal thyroid gland	<56 ng/mL	Goiters; inflammatory thyroid disease	Marker for recurrent thyroid cancer or metastases in thyroidectomized patients

<sup>a</sup>At University of California laboratories.

FT<sub>4</sub>, free thyroxine; FT<sub>4</sub>I, free thyroxine index; FT<sub>3</sub>, free triiodothyronine; FT<sub>3</sub>I, free triiodothyronine index; RAI, radioactive iodine; RAIU, radioactive iodine uptake; TBG, thyroxine-binding globulin; T<sub>4</sub>, thyroxine; TgAb, thyroglobulin auto antibody; TPA, thyroid peroxidase antibody; TRAb, thyroid receptor antibody; TSH, thyroid-stimulating hormone; TSI, thyroid-stimulating antibody; T<sub>3</sub>, triiodothyronine; T<sub>3</sub>RU, triiodothyronine resin uptake; TT<sub>4</sub>, total thyroxine; TT<sub>3</sub>, total triiodothyronine.

TABLE 52.2 Factors that Can Significantly Alter Thyroid Function Tests in Euthyroid Patients

Factors	Drugs/Situations
<b>↑ TBG BINDING CAPACITY</b>	
↑ TT <sub>4</sub>	Estrogens, <sup>1,2</sup> tamoxifen, <sup>3</sup> raloxifene <sup>4</sup>
↑ TT <sub>3</sub>	Oral contraceptives <sup>5</sup>
Normal TSH	Heroin <sup>6</sup>
Normal FT <sub>4</sub> I, FT <sub>4</sub>	Methadone maintenance <sup>6</sup>
Normal FT <sub>3</sub> I, FT <sub>3</sub>	Genetic ↑ in TBG Clofibrate Active hepatitis <sup>7</sup>
<b>↓ TBG BINDING CAPACITY/DISPLACEMENT OF T<sub>4</sub> FROM BINDING SITES</b>	
↓ TT <sub>4</sub>	Androgens <sup>5</sup>
↓ TT <sub>3</sub>	Salicylates, <sup>5,8,9</sup> disalacid, <sup>9</sup> salsalate <sup>9</sup>
Normal TSH	High-dose furosemide
Normal FT <sub>4</sub> I, FT <sub>4</sub>	↓ TBG synthesis-cirrhosis/hepatic failure
Normal FT <sub>3</sub> I, FT <sub>3</sub>	Nephrotic syndrome <sup>5,7</sup> Danazol <sup>5,7</sup> Glucocorticoids <sup>5,7,10</sup>
<b>↓ PERIPHERAL T<sub>4</sub> → T<sub>3</sub> CONVERSION</b>	
↓ TT <sub>3</sub>	PTU
Normal TT <sub>4</sub>	Propranolol <sup>11</sup>

Continued on following page

TABLE 52.2 Factors that Can Significantly Alter Thyroid Function Tests in Euthyroid Patients (Continued)

Factors	Drugs/Situations
Normal FT <sub>4</sub> I, FT <sub>4</sub> Normal TSH	Glucocorticoids <sup>5,10,12</sup>
<b>↓ PITUITARY AND PERIPHERAL T<sub>4</sub> → T<sub>3</sub></b>	
↓ TT <sub>3</sub> ↑ TT <sub>4</sub> ↑ TSH (transient) ↑ FT <sub>4</sub> I	Iodinated contrast media (e.g., sodium ipodate) <sup>13–17</sup> Amiodarone <sup>18–20</sup> Nonthyroidal illness <sup>21–23</sup>
<b>↑ T<sub>4</sub> CLEARANCE BY ENZYME INDUCTION/↑ FECAL LOSS<sup>a</sup></b>	
↓ TT <sub>4</sub> ↓ FT <sub>4</sub> I Normal or ↓ FT <sub>4</sub> Normal or ↓ TT <sub>3</sub> Normal or ↑ TSH	Phenytoin <sup>24,25</sup> Phenobarbital <sup>24</sup> Carbamazepine <sup>24–29</sup> Cholestyramine, colestipol <sup>30</sup> Rifampin <sup>24</sup> Bexarotene <sup>31</sup>
<b>↓ TSH SECRETION</b>	
	Dopamine, <sup>5,7</sup> dobutamine <sup>32</sup> Levodopa, <sup>5</sup> cabergoline <sup>33</sup> Glucocorticoids <sup>5,10,12</sup> Bromocriptine, <sup>5,12</sup> pramipexole, <sup>10,34</sup> ropinirole <sup>10,34</sup> Octreotide <sup>35</sup> Metformin <sup>36,37</sup> Bexarotene <sup>38</sup>
<b>↓ TSH SECRETION</b>	
	Metoclopramide <sup>5,7,12</sup> Domperidone <sup>5,7,12</sup>

<sup>a</sup>Can also cause hypothyroidism in patients receiving levothyroxine therapy.

FT<sub>4</sub>, free thyroxine; FT<sub>4</sub>I, free thyroxine index; FT<sub>3</sub>, free triiodothyronine; FT<sub>3</sub>I, free triiodothyronine index; PTU, propylthiouracil; TBG, thyroxine-binding globulin; T<sub>4</sub>, thyroxine; TSH, thyroid-stimulating hormone; T<sub>3</sub>, triiodothyronine; TT<sub>4</sub>, total thyroxine; TT<sub>3</sub>, total triiodothyronine.

TABLE 52.3 Clinical and Laboratory Findings of Primary Hypothyroidism

Symptoms	Physical Findings	Laboratory
General: weakness, tiredness, lethargy, fatigue	Thin brittle nails	↓ TT <sub>4</sub>
Cold intolerance	Thinning of skin	↓ FT <sub>4</sub> I
Headache	Pallor	↓ FT <sub>4</sub>
Loss of taste/smell	Puffiness of face, eyelids	↓ TT <sub>3</sub>
Deafness	Yellowing of skin	↓ FT <sub>3</sub> I
Hoarseness	Thinning of outer eyebrows	↓ TSH
No sweating	Thickening of tongue	Positive antibodies (in Hashimoto's)
Modest weight gain	Peripheral edema	↑ Cholesterol
Muscle cramps, aches, pains	Pleural/peritoneal/pericardial effusions	↑ CPK
Dyspnea	↓ DTRs	↓ Na
Slow speech	“Myxedema heart”	↑ LDH
Constipation	Bradycardia (↓ HR)	↑ AST
Menorrhagia	Hypertension	↓ Hct/Hgb
Galactorrhea	Goiter (primary hypothyroidism)	

AST, aspartate aminotransferase; CPK, creatine phosphokinase; DTRs, deep tendon reflexes; FT<sub>4</sub>, free thyroxine; FT<sub>4</sub>I, free thyroxine index; FT<sub>3</sub>I, free triiodothyronine index; Hct, hematocrit; Hgb, hemoglobin; HR, heart rate; LDH, lactate dehydrogenase; Na, sodium; TSH, thyroid-stimulating hormone; TT<sub>3</sub>, total triiodothyronine; TT<sub>4</sub>, total thyroxine.

TABLE 52.4 Causes of Hypothyroidism

## NONGOITROUS (NO GLAND ENLARGEMENT)

## PRIMARY HYPOTHYROIDISM (DYSFUNCTION OF THE GLAND)

Idiopathic atrophy  
 Iatrogenic destruction of thyroid  
 Surgery  
 Radioactive iodine therapy  
 X-ray therapy  
 Postinflammatory thyroiditis  
 Cretinism (congenital hypothyroidism)

## SECONDARY HYPOTHYROIDISM

Deficiency of TSH caused by pituitary dysfunction  
 Deficiency of TRH caused by hypothalamic dysfunction

## GOITROUS HYPOTHYROIDISM (ENLARGEMENT OF THYROID GLAND)

Dyshormonogenesis: defect in hormone synthesis, transport, or action  
 Hashimoto's thyroiditis  
 Congenital cretinism: maternally induced  
 Iodide deficiency  
 Natural goitrogens: rutabagas, turnips, cabbage

## DRUG-INDUCED

Aminoglutethimide<sup>5</sup>  
 Amiodarone<sup>18-20</sup>  
 Bexarotene<sup>31,38</sup>  
 Ethionamide<sup>39</sup>  
 Iodides and iodide-containing preparations<sup>40</sup>  
 Rifampin<sup>41</sup>  
 Tyrosine kinase inhibitors (e.g., imatinib, sunitinib, sorafenib)<sup>42-45</sup>  
 Interleukin<sup>46,47</sup>  
 Interferon- $\alpha$ <sup>48-51</sup>  
 Lithium<sup>52-54</sup>  
 Thiocyanates, phenylbutazone, sulfonylureas<sup>4</sup>

TRH, thyrotropin-releasing hormone; TSH, thyroid-stimulating hormone.

TABLE 52.5 Thyroid Preparations

Drug/Dosage Forms	Composition	Dosage Equivalent	Comments
Thyroid USP (Armour)	Desiccated hog, beef, or sheep thyroid gland	1 grain <sup>a</sup>	Unpredictable T <sub>4</sub> :T <sub>3</sub> ratio; supraphysiologic elevations in T <sub>3</sub> levels might produce toxic symptoms; Armour brand preferred
Tab: 0.25, 0.5, 1, 1.5, 2, 3, 4, and 5 grains	Standardized iodine content	—	
L-Thyroxine (Levoxy, Levothroid, Synthroid, Unithroid, various)	Synthetic T <sub>4</sub>	60 mcg <sup>a</sup>	Stable, predictable potency; well absorbed; more potent than desiccated thyroid. When changing from >2 grains desiccated thyroid to L-T <sub>4</sub> , a lower dosage of L-T <sub>4</sub> might be needed to avoid toxicity. Weight should be considered in dosing (1.6–1.7 mcg/kg/day). L-T <sub>4</sub> absorption
Tab: 0.013, 0.025, 0.050, 0.075, 0.088, 0.112, 0.125, 0.137, 0.15, 0.175, 0.2, and 0.3 mg	—	—	
Inj: 200 and 500 mcg	—	—	

Continued on following page



TABLE 52.5 Thyroid Preparations (Continued)

Drug/Dosage Forms	Composition	Dosage Equivalent	Comments
L-Triiodothyronine (Cytomel) Tab: 5, 25, and 50 mcg Inj: 10 mcg/mL (Triostat)	Synthetic T <sub>3</sub> — —	25–37.5 mcg — —	can be impaired by iron, aluminum-containing products (e.g., antacids, sucralfate), Kayexalate, calcium preparations, proton-pump inhibitors, cholesterol resin and phosphate binders, raloxifene, soy, bran, coffee, fiber-enriched foods. L-T <sub>4</sub> metabolism increased by anticonvulsants, rifampin, imatinib, bexarotene, and pregnancy Complete absorption; requires multiple daily dosing; toxicity similar to all T <sub>3</sub> -containing products; see desiccated thyroid comments
Liatrix (Thyrolar) Tab: 0.25, 0.5, 1, 2, and 3 grains	60 mcg T <sub>4</sub> :15 mcg T <sub>3</sub> 50 mcg T <sub>4</sub> :12.5 mcg T <sub>3</sub>	Thyrolar-1 —	No need for liatrix because T <sub>4</sub> is converted to T <sub>3</sub> peripherally; expensive, stable, and predictable content

<sup>a</sup>60 mg (1 grain) of desiccated thyroid = 60 mcg of T<sub>4</sub>.<sup>70</sup>

Inj, injection; I-T<sub>4</sub>, levothyroxine; Tab, tablet; T<sub>4</sub>, thyroxine; T<sub>3</sub>, triiodothyronine; USP, United States Pharmacopeia.

- **Levothyroxine (L-thyroxine)** is the preferred thyroid-replacement preparation. The average replacement dose is 1.6 to 1.7 mcg/kg/day, with dose adjustments needed in some patient populations (Table 52.6). Dose decreases with age (Table 52.7). The optimal dose must be administered for 6 to 8 weeks before steady-state levels are reached.
- Levothyroxine should be administered on an empty stomach. Medications that interfere with T<sub>4</sub> absorption (e.g., iron, aluminum-containing antacids, phosphate binders, etc.) should be separated by at least 4 hours from concomitant levothyroxine.
- Unresponsiveness to levothyroxine therapy may be the result of nonadherence, poor absorption, subpotent medication, rapid metabolism, and tissue resistance.
- Overreplacement of levothyroxine is associated with osteoporosis and cardiac changes (e.g., atrial fibrillation, heart failure, tachycardia).
- Myxedema coma should be treated with a large initial loading dose of intravenous (IV) levothyroxine (e.g., 400–500 mcg × 1 in patients <55 years without cardiac disease). The IV route is preferred due to impaired oral absorption caused by myxedema.
- Pregnant patients typically require a 30% to 50% increase in the prepregnancy T<sub>4</sub> dose to maintain euthyroidism during the first trimester. Separate dosing of thyroid-replacement products by 4 hours from prenatal vitamins.

## Hyperthyroidism

- Hyperthyroidism, or thyrotoxicosis, is the hypermetabolic syndrome that occurs when the production of thyroid hormone is excessive. Clinical and laboratory findings are shown in Table 52.8. Symptoms may be absent in the elderly.

TABLE 52.6 Treatment of Hypothyroidism

Patient Type/ Complications	Dose (l-Thyroxine)	Comment
Uncomplicated adult	1.6–1.7 mcg/kg/day; 100–125 mcg/day average replacement dose; usual increment 25 mcg every 6–8 weeks	<i>Onset of action:</i> 2–3 weeks; <i>max effect:</i> 4–6 weeks. Reversal of skin and hair changes may take several months. An FT <sub>4</sub> and TSH should be checked 6–8 weeks after initiation of therapy because T <sub>4</sub> has a half-life of 7 days and three to four half-lives are needed to achieve steady state. Levels obtained before steady state can be very misleading. Because 80% is bioavailable, adjust IV doses downward. Small changes can be made by varying dose schedule (e.g., 150 mcg daily except Sunday).
Elderly	≤1.6 mcg/kg/day (50–100 mcg/day)	Initiate T <sub>4</sub> cautiously. Elderly may require less than younger patients and are sensitive to small dose changes. A few patients older than 60 years require ≤50 mcg/day.
Cardiovascular disease (angina, CAD)	Start with 12.5–25 mcg/day. ↑ by 12.5–25 mcg/day every 2–6 weeks as tolerated	These patients are very sensitive to cardiovascular effects of T <sub>4</sub> . Even subtherapeutic doses can precipitate severe angina, MI, or death. Replace thyroid deficit slowly, cautiously, and sometimes even suboptimally.
Long-standing hypothyroidism (>1 year)	Dose slowly. Start with 25 mcg/day. ↑ by 25 mcg/day every 4–6 weeks as tolerated	Sensitive to cardiovascular effects of T <sub>4</sub> . Steady state may be delayed because of ↓ clearance of T <sub>4</sub> . <sup>a</sup> Correct replacement dose is a compromise between prevention of myxedema and avoidance of cardiac toxicity.
Pregnancy	Most will require 45% ↑ in dose to ensure euthyroidism	Evaluate TSH, TT <sub>4</sub> , and FT <sub>4</sub> I. <i>Goal:</i> normal TSH and TT <sub>4</sub> /FT <sub>4</sub> I in upper-normal range to prevent fetal hypothyroidism. TSH should be no higher than 2.5 μ/mL during the first trimester and 3.0 μ/mL in the second and third trimesters.
Pediatric (0–3 months)	10–15 mcg/kg/day	Hypothyroid infants can exhibit skin mottling, lethargy, hoarseness, poor feeding, delayed development, constipation, large tongue, neonatal jaundice, pig-like facies, choking, respiratory difficulties, and delayed skeletal maturation (epiphyseal dysgenesis). The serum T <sub>4</sub> should be increased rapidly to minimize impaired cognitive function. In the healthy term infant, 37.5–50 mcg/day of T <sub>4</sub> is appropriate. Dose decreases with age (Table 52.7).

<sup>a</sup>In severely myxedematous patients, steady state may require ≥6 months. In patients who are clinically euthyroid but have ↑ TT<sub>4</sub> and FT<sub>4</sub>I, use TT<sub>3</sub> and TSH as guide to dose adjustments.

CAD, coronary artery disease; FT<sub>4</sub>, free thyroxine; FT<sub>4</sub>I, free thyroxine index; IV, intravenous; MI, myocardial infarction; T<sub>4</sub>, thyroxine; TSH, thyroid-stimulating hormone; TT<sub>4</sub>, total thyroxine.

- Common causes of hyperthyroidism are shown in Table 52.9. The most common cause of hyperthyroidism is Graves disease, an autoimmune disorder.
- Untreated hyperthyroidism can progress to **thyroid storm**, a life-threatening form of hyperthyroidism characterized by exaggerated symptoms of thyrotoxicosis and the acute onset of high fever.

TABLE 52.7 T<sub>4</sub> Recommended Replacement Dose

Age	Daily mcg/kg T <sub>4</sub>
3–6 months	10–15
6–12 months	5–7
1–10 years	3–6
>10 years	2–4

T<sub>4</sub>, thyroxine.

TABLE 52.8 Clinical and Laboratory Findings of Hyperthyroidism

## SYMPTOMS

Heat intolerance  
 Weight loss common, or weight gain caused by ↑ appetite  
 Palpitations  
 Pedal edema  
 Diarrhea/frequent bowel movements  
 Amenorrhea/light menses  
 Tremor  
 Weakness, fatigue  
 Nervousness, irritability, insomnia

## PHYSICAL FINDINGS

Thinning of hair (fine)  
 Proptosis, lid lag, lid retraction, stare, chemosis, conjunctivitis, periorbital edema, loss of extraocular movements  
 Diffusely enlarged goiter, bruits, thrills  
 Wide pulse pressure  
 Pretibial myxedema  
 Plummer nails<sup>d</sup>  
 Flushed, moist skin  
 Palmar erythema  
 Brisk DTRs

## LABORATORY FINDINGS

↑ TT<sub>4</sub>  
 ↑ TT<sub>3</sub>  
 ↑ FT<sub>4</sub>I/FT<sub>4</sub>  
 ↑ FT<sub>3</sub>I/FT<sub>3</sub>  
 Suppressed TSH  
 TSI present  
 TgAb present  
 TPA present  
 RAIU > 50%  
 ↓ Cholesterol  
 ↑ Alkaline phosphatase  
 ↑ Calcium  
 ↑ AST

<sup>d</sup>The fingernail separates from its matrix, but only one or two nails are generally affected.

AST, aspartate aminotransferase; DTRs, deep tendon reflexes; FT<sub>4</sub>, free thyroxine; FT<sub>4</sub>I, free thyroxine index; FT<sub>3</sub>, free triiodothyronine; FT<sub>3</sub>I, free triiodothyronine index; RAIU, radioactive iodine uptake; TgAb, thyroglobulin autoantibodies; TPA, thyroid peroxidase antibody; TSI, thyroid-stimulating immunoglobulin; TSH, thyroid-stimulating hormone; TT<sub>3</sub>, total triiodothyronine; TT<sub>4</sub>, total thyroxine.

TABLE 52.9 Causes of Hyperthyroidism

Graves disease (toxic diffuse goiter); may be caused by polymorphisms in the TSH receptor<sup>55</sup>  
 Toxic uninodular goiter (Plummer disease)  
 Toxic multinodular goiter  
 Nodular goiter with hyperthyroidism caused by exogenous iodine (Jod-Basedow)  
 Exogenous thyroid excess through self-administration (factitious hyperthyroidism)  
 Tumors (thyroid adenoma, follicular carcinoma, thyrotropin-secreting tumor of the pituitary, and hydatidiform mole with secretion of a thyroid-stimulating substance)  
 Drug-induced (iodides,<sup>56</sup> amiodarone,<sup>18–20</sup> interleukin,<sup>5,46</sup> interferon- $\alpha$ ,<sup>48,51</sup> lithium<sup>57,58</sup>)

• **Treatment**

- Treatment options include antithyroid drugs (thioamides), radioiodine, and surgery (Table 52.10). All three modalities are effective. Treatment of choice is determined by etiology, size of the goiter, presence of ophthalmopathy, coexisting conditions, patient age, and patient and physician preference.
- Thioamides (methimazole, propylthiouracil) are used as primary therapy and as adjunctive short-term therapy to produce euthyroidism before surgery or radioactive iodine. Thioamides prevent hormone synthesis but do not deplete existing stores; symptoms will persist for 4 to 6 weeks after initiating therapy. Methimazole is the thioamide of choice in most patients. Propylthiouracil should be reserved for use in the first trimester of pregnancy, in thyroid storm, and in those who cannot tolerate methimazole. Thioamide toxicity includes gastrointestinal symptoms, rash, agranulocytosis, and hepatitis.

TABLE 52.10 Treatment for Hyperthyroidism

Modality	Drug/Dosage	Mechanism of Action	Toxicity	Indication
<b>PRIMARY TREATMENT</b>				
<b>THIOAMIDES</b>				
Methimazole (Tapazole) 5-, 10-mg tablet; rectal suppositories can be made <sup>180</sup>	Methimazole 30–40 mg PO daily or in two divided doses (max: 60 mg/day) for 6–8 weeks or until euthyroid, then maintenance of 5–10 mg/day PO × 12–18 months	Blocks organification of hormone synthesis, does not block conversion of T <sub>4</sub> –T <sub>3</sub>	Skin rashes, GI symptoms, arthralgias, cholestatic jaundice, agranulocytosis, aplasia cutis and embryopathy syndrome in pregnancy (methimazole only)	DOC in adults/children except in thyroid storm and first trimester of pregnancy (see PTU). Once-daily dosing can improve adherence
PTU 50-mg tablet; rectal formulation can be made <sup>181,182</sup>	100–200 mg PO every 6–8 hours (max: 1,200 mg/day) for 6–8 weeks or until euthyroid; then maintenance of 50–150 mg daily PO × 12–18 months	Similar to methimazole, and blocks peripheral conversion of T <sub>4</sub> –T <sub>3</sub> (PTU only)	Hepatitis, some fatal Similar to methimazole	DOC in thyroid storm, first trimester of pregnancy
Surgery	Preoperative preparation with iodides, thioamides, or β-blockers before surgery; see specific operative agent	Near-total thyroidectomy	Hypothyroidism, cosmetic scarring, hypoparathyroidism, risks of surgery and anesthesia, vocal cord damage	Obstruction, choking, malignancy, pregnancy in second trimester, contraindication to RAI or thioamides
RAI	<sup>131</sup> I radioactive isotope; 80–100 μCi/g thyroid tissue. Average dose, ≈10 mCi; pretreatment with corticosteroids indicated in patients with ophthalmopathy	Destruction of the gland	Hypothyroidism; worsening of ophthalmopathy; fear of radiation-induced leukemia; genetic damage; malignancy; rarely, radiation sickness	Adults, older patients who are poor surgical risks or have cardiac disease; patients with a history of prior thyroid surgery; contraindications to thioamide usage; increasingly used in children

Continued on following page

TABLE 52.10 Treatment for Hyperthyroidism (Continued)

Modality	Drug/Dosage	Mechanism of Action	Toxicity	Indication
<b>ADJUNCTS TO PRIMARY USAGE</b>				
<b>IODIDES</b>				
Lugol iodine solution 8 mg/drop (5% iodine, 10% potassium iodide; saturated [SSKI] 50 mg/drop)	5–10 drops TID PO for 10–14 days before surgery; minimal effective dose 6 mg/day	↓ Vascularity of gland and ↑ firmness; blocks release of thyroid hormone	Hypersensitivity reactions, skin rashes, mucous membrane ulcers, anaphylaxis, metallic taste, rhinorrhea, parotid and submaxillary swelling; fetal goiters and death	Preoperative preparation before surgery; thyroid storm, provides symptomatic relief of symptoms. <i>Do not use before RAI or chronically during pregnancy</i>
<b>β-BLOCKERS</b>				
Propranolol or equivalent β-blocker. Avoid those with ISA	Propranolol 10–40 mg PO every 6 hours or PRN to control HR <100 beats/minute; IV 0.5–1 mg slowly	Blocks effects of thyroid hormone peripherally, no effect on underlying disease; blocks T <sub>4</sub> –T <sub>3</sub> conversion	Related to β-blockade; bradycardia, CHF, blocks hyperglycemic response to hypoglycemia, bronchospasm, CNS symptoms at high doses; fetal bradycardia	Symptomatic relief while awaiting onset of thioamides, RAI; preoperative preparation for surgery; thyroid storm
<b>CALCIUM-CHANNEL BLOCKERS</b>				
	Diltiazem 120 mg PO TID–QID or verapamil 80–120 mg PO TID–QID PRN to control HR <100 beats/minute	Blocks effects of thyroid hormone peripherally, no effect on underlying disease	Bradycardia, peripheral edema, CHF, headache, flushing, hypotension, dizziness	Alternative for symptomatic relief of hyperthyroid symptoms in patients who cannot tolerate β-blockers
<b>CORTICOSTEROIDS</b>				
	Prednisone or equivalent corticosteroids 50–140 mg PO daily in divided doses; IV hydrocortisone 50–100 mg every 6 hours or equivalent for thyroid storm	↓ TSI, suppression of inflammatory process; blocks T <sub>4</sub> –T <sub>3</sub> conversion	Complications of steroid therapy	Ophthalmopathy, thyroid storm (use IV steroid), pretibial myxedema, pretreatment before RAI therapy in patients with ophthalmopathy

CHF, congestive heart failure; CNS, central nervous system; DOC, drug of choice; GI, gastrointestinal; HR, heart rate; ISA, intrinsic sympathomimetic activity; IV, intravenous; PO, orally (by mouth); PRN, as needed; PTU, propylthiouracil; QID, four times a day; RAI, radioactive iodine; SSKI, saturated solution of potassium iodide; T<sub>3</sub>, triiodothyronine; T<sub>4</sub>, thyroxine; TID, three times a day; TSI, thyroid-stimulating immunoglobulin.<sup>91–93</sup>

- Radioactive iodine is best for older patients and those with coexisting cardiac disease, ophthalmopathy, and hyperthyroidism secondary to a toxic multinodular goiter. Safety precautions are required after radioactive iodine dosing to minimize exposure of others (e.g., avoid close contact with children for 5 days and pregnant women for 10 days, avoid airplane and public transportation, use of sole bathroom facilities). Iatrogenic hypothyroidism is a risk to radioactive iodine therapy.

- Surgery is preferable if obstructive symptoms are present or if concomitant malignancy is suspected. The patient should be in a euthyroid state at the time of surgery to avoid precipitation of thyroid storm.
- Pregnant patients can be managed with thioamides or surgery (in the second trimester); radioactive iodine is contraindicated in pregnancy.
- $\beta$ -Blockers can provide symptomatic relief of hyperthyroid symptoms (e.g., nervousness, palpitations, fatigue, weight loss, diaphoresis, heat intolerance). Diltiazem or verapamil are effective alternatives when  $\beta$ -blockers are contraindicated.
- Thyroid storm requires intensive, continuous, and immediate treatment directed at decreasing the synthesis and release of thyroid hormones, reversing the peripheral effects of thyroid hormones and catecholamines, providing supportive treatment of vital functions, and eliminating precipitating causes of the storm.

## Nodular Goiters

- Thyroid nodules can present as hot (hyperfunctioning), cold (hypofunctioning), or multinodular.
- Malignancy should be considered if there is recent growth in a “cold” single or dominant nodule, a firm nodule clinically suspicious for cancer, a history of thyroid irradiation, or a strong family history of medullary thyroid carcinoma.
- Thyroid function tests, including TSH and FT<sub>4</sub> levels, and antibodies should be obtained.
- Treatment options include surgery, radioactive iodine, and thyroid-replacement therapy, if needed to correct hypothyroidism. Thyroid-suppression therapy is not recommended for benign nodules.

# Diabetes Mellitus\*

## General Principles

- Diabetes is a chronic condition caused by an absolute or relative lack of insulin as a result of impaired insulin secretion and action.
- The incidence of type 2 diabetes in the United States is considered epidemic. The increased incidence is primarily related to obesity and decreased physical activity.
- Most of the morbidity and mortality associated with diabetes occurs over many years and relates to microvascular (e.g., nephropathy, neuropathy, retinopathy) and macrovascular (e.g., coronary heart disease, stroke, peripheral vascular disease) complications. The incidence and severity of microvascular complications has a strong correlation with long-term glycemic control. Macrovascular complications, while influenced by glycemic control, are influenced by multiple factors (e.g., dyslipidemia, hypertension, smoking).

## Classification

- Diabetes is most commonly classified as type 1 or type 2 (Table 53.1).

## Patient Assessment

- Classic symptoms of type 1 diabetes include polyuria, polydipsia, weight loss, and fatigue. Clinical characteristics include hyperglycemia and alterations in lipid and protein metabolism.
- Patients with type 2 diabetes are often diagnosed incidentally as they do not show the typical clinical presentation of type 1 diabetes. Presentation in the elderly is often different than in younger patients (Table 53.2).
- Patients with diabetic ketoacidosis (DKA) present with moderate to high glucose concentrations (Table 53.3). Patient education for DKA is important (Table 53.4).
- Tests used to diagnose diabetes include a glycosylated hemoglobin (A1C) level, fasting plasma glucose, and oral glucose tolerance test (Table 53.5). Ketone testing is recommended for patients with gestational and type 1 diabetes.
- Exercise has varying effects in patients with diabetes (Table 53.6).
- A1C is the gold standard for measuring chronic glycemia and is the clinical marker for predicting long-term complications. Several factors can affect A1C (Table 53.7).
- Patient education around many points is needed when a diagnosis of diabetes is given (Table 53.8).
- Self-monitoring of blood glucose should be done by all patients with type 1 diabetes and most patients with type 2 diabetes (Tables 53.9 and 53.10). Several factors can alter self-monitored blood glucose tests (Table 53.11) or alter blood glucose control (Table 53.12).

## Risk Factors

- Risk factors for type 2 diabetes are shown in Table 53.13.

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\*The reader is referred to Chapter 53, Diabetes Mellitus, written by Lisa A. Kroon, PharmD, CDE, and Craig Williams, PharmD, in the 10th edition of *Applied Therapeutics: The Clinical Use of Drugs* for a more in-depth discussion. All notations to reference numbers are based on the reference list at the end of that chapter. The editor of this handbook expresses her thanks to Drs. Kroon and Williams and acknowledges that this chapter is based on their work.

TABLE 53.1 Type 1 and Type 2 Diabetes

Characteristics	Type 1	Type 2
Other names	Previously, type I; insulin-dependent diabetes mellitus (IDDM); juvenile-onset diabetes mellitus	Previously, type II; non-insulin-dependent diabetes mellitus (NIDDM); adult-onset diabetes mellitus
Percentage of diabetic population	5%–10%	90%
Age at onset	Usually <30 years; peaks at 12–14 years; rare before 6 months; some adults develop type 1 during the fifth decade	Usually >40 years, but increasing prevalence among obese children and young adults
Pancreatic function	Usually none, although some residual C-peptide can sometimes be detected at diagnosis, especially in adults	Insulin present in low, “normal,” or high amounts
Pathogenesis	Associated with certain HLA types; presence of islet cell antibodies suggests autoimmune process	Defect in insulin secretion; tissue resistance to insulin; ↑ hepatic glucose output
Family history	Generally not strong	Strong
Obesity	Uncommon unless “overinsulinized” with exogenous insulin	Common (60%–90%)
History of ketoacidosis	Often present	Rare, except in circumstances of unusual stress (e.g., infection)
Clinical presentation	Moderate to severe symptoms that generally progress relatively rapidly (days to weeks): polyuria, polydipsia, fatigue, weight loss, ketoacidosis	Mild polyuria, fatigue; often diagnosed on routine physical or dental examination
Treatment	MNT Physical activity Insulin Amylin mimetic (pramlintide)	MNT Physical activity Antidiabetic agents (biguanides, glinides, sulfonylureas, thiazolidinediones, $\alpha$ -glucosidase inhibitors, incretin mimetics/analogs, DPP-4 inhibitors) Insulin Amylin mimetic (pramlintide)

DPP-4, dipeptidyl peptidase-4; HLA, human leukocyte antigen; MNT, medical nutrition therapy.

TABLE 53.2 Presentation of Diabetes Mellitus in Elderly Patients Compared with Younger Patients

Metabolic Abnormality	Symptoms in Young Patients	Symptoms in Elderly Patients
Serum osmolality	Polydipsia	Dehydration, confusion, delirium
Glucosuria	Polyuria	Incontinence
Catabolic state owing to insulin deficiency	Polyphagia	Weight loss, anorexia



TABLE 53.3 Common Laboratory Abnormalities in Diabetic Ketoacidosis

Glucose	250 mg/dL
Serum osmolarity	Variable, can be $>320$ mOsm/kg in presence of coma
Sodium	Low, normal, or high <sup>a</sup>
Potassium	Normal or high
Ketones	Present in urine and blood
pH	Mild: 7.25–7.30 Moderate: 7.00–7.24 Severe: $<7.00$
Bicarbonate	Mild: 15–18 mEq/L Moderate: 10 to $<15$ mEq/L Severe: $<10$ mEq/L
WBC count	15,000–40,000 cells/ $\mu$ L even without evidence of infection

<sup>a</sup>Total body sodium is always low.

WBC, white blood cell.

TABLE 53.4 Diabetic Ketoacidosis: Patient Education

*Definition:* DKA occurs when the body has insufficient insulin.

#### QUESTIONS TO ASK

1. Has insulin use been discontinued or a dose skipped for any reason?
2. If an insulin pump is being used, is the tubing clogged or twisted? Has the catheter become dislodged?
3. Has the insulin being used lost its normal activity? Is the bottle of rapid-acting/regular or basal insulin cloudy? Does the bottle of NPH look frosty?
4. Have insulin requirements increased owing to illness or other forms of stress (infection, pregnancy, pancreatitis, trauma, hyperthyroidism, or MI)?
5. Can the patient measure and/or administer insulin accurately?

#### WHAT TO LOOK FOR

1. Signs and symptoms of hyperglycemia: thirst, excessive urination, fatigue, blurred vision, consistently elevated blood glucose concentrations ( $>300$  mg/dL)
2. Signs of acidosis: fruity breath odor, deep and difficult breathing
3. Signs of dehydration: dry mouth; warm, dry skin; fatigue
4. Others: stomach pain, nausea, vomiting, loss of appetite

#### WHAT TO DO

1. Review “sick day management” (Table 53.17)
2. Test blood glucose  $\geq 4$  times daily
3. Test urine for ketones when blood glucose concentration is  $>300$  mg/dL
4. Drink plenty of fluids (water, clear soups)
5. Continue taking insulin dose
6. Contact physician or other healthcare provider immediately

DKA, diabetic ketoacidosis; MI, myocardial infarction; NPH, neutral protamine Hagedorn.

**TABLE 53.5 Normal and Diabetic Plasma<sup>a</sup> Glucose Levels in mg/dL (mmol/L) and Glycosylated Hemoglobin and Normal and Diabetic Plasma Glucose Levels for the Oral Glucose Tolerance Test<sup>7</sup>**

	FPG	A1C (%)	OGTT
Normal	<100 (5.6)	≤5.6	<140 (7.8)
Prediabetes (i.e., impaired fasting glucose, impaired glucose tolerance)	100–125 (5.6–6.9)	≥5.7–6.4	140–199 (7.8–11.0)
Diabetes (nonpregnant adult)	≥126 (7.0)	≥6.5	≥200 (11.1)

<sup>a</sup>Equivalent venous whole blood glucose concentrations are approximately 12% to 15% lower. Arterial samples are higher than venous samples postprandially because glucose has not yet been removed from peripheral tissues. Capillary whole blood samples contain a mixture of arterial and venous blood. Fasting levels are equivalent to whole blood venous samples.

A1C, glycosylated hemoglobin; FPG, fasting plasma glucose; OGTT, oral glucose tolerance test.

**TABLE 53.6 Exercise in Patients with Diabetes**

1. Test blood glucose before, during, and after exercise.
2. For moderate exercise (e.g., bicycling or jogging for 30–45 minutes), ↓ the preceding dose of regular or rapid-acting insulin by approximately 30%–50%. If glucose concentration is normal or low before exercise, supplement the diet with a snack containing 10–15 g of carbohydrate.
3. To avoid ↑ absorption of regular insulin by exercise, inject into the abdomen or exercise 30–60 minutes after injection. Avoid exercise when rapid-acting insulin is peaking.
4. Individuals with low glycogen stores may be predisposed to the hypoglycemic effects of exercise. Examples include alcoholics, fasted individuals, or patients on extremely hypocaloric (<800 calories), low-carbohydrate (<10 g/day) diets.
5. Patients taking insulin are more susceptible to hypoglycemia than those taking oral insulin secretagogues (sulfonylureas, glinides). Patients with type 2 diabetes treated with diet are unlikely to develop hypoglycemia.
6. Watch for postexercise hypoglycemia. Individuals who have been exercising during the day will likely need to ↑ their carbohydrate intake and should test their blood glucose during the night to detect nocturnal hypoglycemia. Hypoglycemia can occur 8–15 hours after exercise.
7. If the glucose concentration is >240–300 mg/dL, the patient should not exercise. This indicates severe insulin deficiency. These patients are predisposed to hyperglycemia secondary to exercise.
8. Patients with severe proliferative retinopathy or retinal hemorrhage should avoid jarring exercise or exercise that involves moving the head below the waist.

**TABLE 53.7 Factors Affecting A1C**

Cause	Effect on A1C
Hemoglobinopathies (sickle cell trait, acetylated or carbamylated <sup>a</sup> hemoglobin)	Decreased or increased
Anemias	
Hemolytic	Decreased
Iron deficiency	Increased
Blood loss	Decreased
Blood transfusion	Decreased
Erythropoietin-stimulating agents	Decreased
Antioxidants	Decreased <sup>b</sup>

<sup>a</sup>Carbamylated hemoglobin equaling 0.063% of total hemoglobin is formed for every 1 mmol/L of serum urea.

<sup>b</sup>Reported with vitamins C (1 g/day) and E (1,200 mg/day). Possible mechanism is competitive inhibition of hemoglobin glycosylation.

A1C, glycosylated hemoglobin; RBC, red blood cell.

A detailed listing of factors that interfere with A1C test results is available at <http://www.ngsp.org/factors.asp>

TABLE 53.8 Areas of Patient Education

*Diabetes:* Pathogenesis and the complications

*Hyperglycemia:* Signs and symptoms

*Ketoacidosis:* Signs and symptoms

*Hypoglycemia:* Signs, symptoms, and appropriate treatment (Table 53.20)

*Exercise:* Effect on blood glucose concentrations and insulin dose (Table 53.6)

*Diet:* See text. Emphasis placed on carbohydrate counting because the carbohydrate is responsible for 90% of the rise in blood glucose after a meal.

*Insulins:*

Injection technique

Types of insulin

Time action profiles (onset, peak, and duration)

Storage and expiration once in use

Stability (look for crystallization and precipitation with NPH insulin)

*Therapeutic goals:* A1C, fasting, preprandial and postprandial blood glucose levels, cholesterol, triglyceride, blood pressure

*SMBG testing:* Table 53.10

*Interpretation of SMBG testing results*

*Foot care:* Inspect feet daily; wear well-fitted shoes; avoid self-care of ingrown toenails, corns, or athlete's foot; see a podiatrist

*Sick day management:* Table 53.17

*Cardiovascular risk factors:* Tobacco use, high blood pressure, obesity, elevated cholesterol

*Importance of annual ophthalmologic examinations; tests for microalbuminuria; keeping up-to-date with immunizations*

A1C, glycosylated hemoglobin; NPH, neutral protamine Hagedorn; SMBG, self-monitored blood glucose.

TABLE 53.9 Self-Monitored Blood Glucose Testing: Areas of Patient Education

### When and How Often to Test

#### Technique

How and when to calibrate the glucose monitor.

Review all “buttons” and their purposes. Identify battery type. Review cleaning procedures, if applicable.

Preparation

1. Calibrate monitor/set code for batch of test strips, if required.
2. Insert test strip to turn machine on (some meters require user to turn machine on).
3. Prepare all materials: tissue, strip, lancet.
4. Remember to close the lid of the strip container immediately. Strips exposed to air and moisture can deteriorate rapidly.
5. Wash hands with warm water. *Dry thoroughly.* A wet finger causes blood to spread rather than form a drop. Rub hands together or milk the finger from the base to ensure an adequate flow of blood.
6. Lance the tip of the finger. Avoid the pads of the finger where nerve endings are concentrated.
7. Hold the finger *below* the heart with the lanced area pointing toward the floor.
8. Once a sufficient amount of blood is available, *quickly* apply blood to designated area of the test strip. Depending on the strip type, the blood sample is placed in an area on the surface of the strip or it is applied to the side of the strip where it is taken up by capillary action.

**Record Results in a Log Book and Bring to All Clinician Visits. Include relevant information regarding diet or exercise.**

**Storage of test strips and device.**

**How To Use Results To Achieve Glycemic Targets; Educate Patients on What To Do With Their Blood Glucose Readings (e.g., adjust their insulin dose; modify their carbohydrate content).**

TABLE 53.10 Interpreting Self-Monitored Blood Glucose Concentrations<sup>a</sup>

Test Time	Target Insulin Dose	Target Meal/Snack
Prebreakfast (fasting)	Predinner/bedtime intermediate-acting or basal insulin	Dinner or bedtime snack
Prelunch	Prebreakfast regular or rapid-acting insulin	Breakfast or midmorning snack
Predinner	Prebreakfast intermediate-acting insulin or prelunch regular or rapid-acting insulin	Lunch or midafternoon snack
Bedtime	Predinner regular or rapid-acting insulin	Dinner
2-hour postprandial	Premeal regular or rapid-acting insulin	Preceding meal or snack
2–3 AM or later	Predinner intermediate-acting insulin or basal insulin if given in AM	Dinner or bedtime snack

<sup>a</sup>Considerations: (a) Assumes a regular meal pattern. For patients who travel, have odd working or sleeping hours, or have irregular meal patterns, these guidelines may not apply. (b) Assumes administration of regular insulin 30 to 60 minutes before meals or rapid-acting insulin 0 to 15 minutes before meals and a normal pattern of insulin response (see Table 53.23 for factors that can alter insulin absorption and response). (c) If prebreakfast concentrations are high, rule out reactive hyperglycemia (Somogyi reaction or posthypoglycemic hyperglycemia). Consider contribution of dawn phenomenon as well. Whenever blood glucose concentrations are high, consider reactive hyperglycemia (excessive insulin doses). (d) Consider accuracy of reported test results: (i) Do they correlate with the glycosylated hemoglobin and patient's signs and symptoms? (ii) What is the patient's medication adherence? Could results be fabricated? (iii) Is the patient's technique appropriate? Check timing, adequate blood sample, machine, strips, and calibration (Table 53.9). (iv) Are insulin kinetics altered? (v) What is the carbohydrate content, quality, and regularity of meals?

TABLE 53.11 Factors that Can Alter Self-Monitored Blood Glucose Test Results: Troubleshooting

Glucose monitor not coded for batch of test strips<sup>a</sup>  
 An inadequate amount of blood applied to test strip<sup>b</sup>  
 Improper storage of test strips (temperature and humidity)<sup>a</sup>  
 Dirty glucose monitor<sup>a</sup>  
 Low battery<sup>a</sup>  
 Test performed outside of altitude, temperature, and humidity operating conditions<sup>a</sup>  
 Low<sup>c</sup> or high<sup>b</sup> hematocrit  
 Dehydration<sup>b</sup>  
 Hyperosmolar, nonketotic state<sup>b</sup>  
 Lipemia<sup>a</sup>  
 Interfering substances  
 Nonglucose sugars (e.g., maltose, xylose, galactose) in meters using GDH-PQQ test strips<sup>139</sup>  
 Large amounts of acetaminophen<sup>c</sup>  
 Large amounts of ascorbic acid or salicylates (rare)<sup>b</sup>

<sup>a</sup>Effect unpredictable.

<sup>b</sup>Values tend to be lower.

<sup>c</sup>Values tend to be higher.

GDH-PQQ, glucose dehydrogenase pyrroloquinolinequinone.

Source: Heinemann L. Quality of glucose measurement with blood glucose meters at the point-of-care: relevance of interfering factors. *Diabetes Technol Ther.* 2010;12:847.

**TABLE 53.12 Factors that Can Alter Blood Glucose Control**

**DIET**

Insufficient calories (e.g., alcoholism, eating disorders, anorexia, nausea, and vomiting)  
 Overeating (e.g., during the holidays)  
 Irregularly spaced, skipped, or delayed meals  
 Dietary content (e.g., fiber, carbohydrate content)

**PHYSICAL ACTIVITY**

See Table 53.6

**STRESS**

Infection  
 Surgery/trauma  
 Psychological

**DRUGS**

Certain medications can increase or decrease blood glucose levels. It is important to assess for potential effects on the blood glucose when starting new medications.

**HORMONAL CHANGES**

Menstruation: Glucose concentrations may increase premenstrually and return to normal after menses.  
 Pregnancy  
 Puberty: hyperglycemia probably related to high growth hormone levels

**GASTROPARESIS**

Delays gastric emptying time. Peak insulin action and meal-related glucose excursions may become mismatched.

**ALTERED INSULIN PHARMACOKINETICS**

See Table 53.23

**INSULIN INJECTION TECHNIQUE**

Measuring  
 Timing  
 Technique

**INACTIVE INSULIN**

Outdated insulin  
 Improperly stored insulin (heat or cold)  
 Crystallized insulin

**TABLE 53.13 Risk Factors for Type 2 Diabetes Mellitus**

<b>Adults</b>	<b>Children<sup>a</sup></b>
Overweight ( $\geq 25$ kg/m <sup>2</sup> )	Overweight (BMI >85th percentile for age and sex; or weight >120% of ideal for height)
Family history of diabetes (first-degree relative)	Family history of diabetes (first- or second-degree relative)
Physical inactivity	
Ethnic predisposition <sup>b</sup>	Ethnic predisposition <sup>b</sup>
Previous IFG, IGT, or A1C $\geq 5.7\%$	
History of PCOS, GDM, or macrosomia	Maternal history of diabetes (including GDM)
Clinical conditions associated with insulin resistance (e.g., severe obesity and acanthosis nigricans)	Signs of insulin resistance (e.g., acanthosis nigricans)
Hypertension ( $\geq 140/90$ mm Hg or on antihypertensive therapy)	Conditions associated with insulin resistance (e.g., hypertension, dyslipidemia, or PCOS)
Dyslipidemia	
HDL-C < 35 mg/dL (0.90 mmol/L)	
Triglyceride >250 mg/dL (2.82 mmol/L)	
Cardiovascular disease	

<sup>a</sup>Children are younger than 18 years of age.

<sup>b</sup>Ethnic predisposition includes individuals of African American, Latino, Native American, Asian, or Pacific Islander descent. A1C, glycosylated hemoglobin; BMI, body mass index; GDM, gestational diabetes mellitus; HDL-C, high-density lipoprotein cholesterol; IFG, impaired fasting glucose; IGT, impaired glucose tolerance; PCOS, polycystic ovarian syndrome.

## Goals of Therapy

- The overall goal of therapy is to prevent acute and chronic complications.
- The primary metabolic goals for diabetes are an A1C <7%, a systolic blood pressure <140 mm Hg, and a low-density lipoprotein (LDL) cholesterol <100 mg/dL (Table 53.14).
- Glycemic goals should be individualized (Table 53.15). More aggressive goals (i.e., A1C <6%) can be considered for patients with a new diagnosis, long life expectancy, and no significant vascular disease.
- Less stringent A1C goals should be considered for patients with existing vascular disease, other significant micro- or macrovascular disease, a history of hypoglycemia, or limited life expectancy.
- The current recommended blood glucose in hospitalized patients is 140 to 180 mg/dL once insulin has been initiated. Very tight glucose control in the acutely ill is not recommended due to safety concerns and risk for hypoglycemia.

## Treatment

- There are three major components to treatment: diet, exercise, and medications. Medical nutrition therapy and physical activity are the cornerstones of treatment.
- Basal-bolus insulin regimens should be used for patients with type 1 diabetes, administered either by multiple daily injections or by an insulin pump. There are several components of physiological insulin therapy (Table 53.16). Insulin requirements increase in the presence of an infection or acute illness (Table 53.17).
- Management of DKA is shown in Table 53.18.

**TABLE 53.14 American Diabetes Association Metabolic Goals<sup>a</sup> for Adults with Diabetes Mellitus**

Glycemic goals	
• A1C	<7.0% (normal, 4%–6%) <sup>b</sup>
• Preprandial plasma glucose	70–130 mg/dL (3.9–7.2 mmol/L) <sup>c</sup>
• Postprandial plasma glucose	<180 mg/dL (<10.0 mmol/L) <sup>d</sup>
Blood pressure	<140/80 mm Hg
Lipids	
• Low-density lipoprotein cholesterol	<100 mg/dL (<2.6 mmol/L) <sup>e</sup>
• Triglycerides	<150 mg/dL (<1.7 mmol/L)
• High-density lipoprotein cholesterol	
• Men	>40 mg/dL (>1.0 mmol/L)
• Women	>50 mg/dL (>1.3 mmol/L)

<sup>a</sup>Goals must be individualized to the patient.

<sup>b</sup>More stringent goals (i.e., <6%) can be considered for select individuals. American Association of Clinical Endocrinologists/American College of Endocrinology recommends A1C goal of  $\leq$ 6.5%.

<sup>c</sup>American Association of Clinical Endocrinologists recommends a fasting blood glucose goal of <110 mg/dL (6.1 mmol/L).<sup>46</sup>

<sup>d</sup>American Association of Clinical Endocrinologists/American College of Endocrinology recommends goal of <140 mg/L (7.8 mmol/L).<sup>46</sup>

<sup>e</sup>More stringent goals (i.e., <70 mg/dL [1.8 mmol/L]) may be considered for individuals with overt cardiovascular disease. A1C, glycosylated hemoglobin.

TABLE 53.15 Goals of Physiological (Basal-Bolus) Insulin Therapy<sup>a</sup>

Monitoring Parameter	Adults (mg/dL)	School Age (6–12 years) (mg/dL)	Adolescents and Young Adults (13–29 years) (mg/dL)	Pregnancy (mg/dL)
Premeals	70–130	90–180	90–130	60–99
2-hour postprandial plasma glucose	<180	Not routinely recommended	Not routinely recommended	100–129
Bedtime/overnight (2–4 AM) plasma glucose	>70	100–180	90–150	60–99
A1C <sup>b</sup>	<7.0% <sup>c</sup>	<8.0%	<7.5% <sup>d</sup>	<6%
Urine ketones <sup>e</sup>	Absent to rare	Absent to rare	Absent to rare	Rare

<sup>a</sup>Basal-bolus insulin therapy is a complete therapeutic program of diabetes management and requires a team approach.

<sup>b</sup>A1C, glycosylated hemoglobin, referenced to a nondiabetic range of 4% to 6% using a Diabetes Control and Complications Trial (DCCT)-based assay.

<sup>c</sup>Acceptable values should be individualized to levels that are attainable without creating undue risk for hypoglycemia.

These results are similar to the results achieved in the DCCT trial. The American Diabetes Association recommends consideration for a lower goal (e.g., <6%) in individuals with a short duration of diabetes, long life expectancy, and no significant cardiovascular disease. Less stringent goals may be appropriate for patients with hypoglycemic unawareness, history of severe hypoglycemia, counterregulatory insufficiency, advanced microvascular or macrovascular complications, or other complicating features (Table 53.27).

<sup>d</sup>A lower goal (<7%) is reasonable if it can be achieved without creating excessive risk for hypoglycemia.

<sup>e</sup>Does not apply to type 2 diabetes patients.

Source: Modified and extrapolated from American Diabetes Association. Standards of medical care in diabetes—2011.

*Diabetes Care.* 2011;34(Suppl 1):S11; American Diabetes Association. Preconception care of women with diabetes. *Diabetes Care.* 2004;27(Suppl 1):S76; Kitzmiller JL et al. Managing preexisting diabetes for pregnancy: summary of evidence and consensus recommendations for care. *Diabetes Care.* 2008;31:1060; The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. The Diabetes Control and Complications Trial Research Group. *N Engl J Med.* 1993;329:977.

TABLE 53.16 Components of Physiological Insulin Therapy

Multicomponent insulin regimen of basal plus prandial insulin doses
Balance of carbohydrate intake, exercise, and insulin dosage
Daily, multiple self-monitoring of blood glucose levels
Patient self-adjustment of carbohydrate intake and insulin dosage with use of correction or supplemental rapid- or short-acting insulin according to a predetermined plan
Individualized target blood glucose and A1C levels
Frequent contact between patient and diabetes team
Intensive patient education
Psychological support
Regular objective assessment (as measured by A1C)

A1C, glycosylated hemoglobin.

Source: Skyler JS. Tactics for type 1 diabetes. *Endocrinol Metab Clin North Am.* 1997;26:647.

TABLE 53.17 Sick Day Management

1. Continue taking your basic dose of insulin even if you are not eating well or have nausea or vomiting.
2. Test your blood glucose more frequently: every 3–4 hours.
3. If indicated, give yourself extra doses (high-sugar correction) of lispro, aspart, glulisine, or regular insulin: for example, 1–2 units for every 30–50 mg/dL over an agreed-on target glucose concentration (e.g., 150 mg/dL). Correction doses must be individualized on the basis of the patient's sensitivity to insulin (Table 53.25).
4. Begin testing your ketones (urine or blood) if you have type 1 diabetes. If you have type 2 diabetes, begin testing especially when glucose readings exceed 300 mg/dL.
5. Try to drink plenty of fluids (1/2 cup/hour for adults) and maintain your caloric intake (50 g carbohydrate every 4 hours). Foods such as gelatin, noncarbonated soft drinks, crackers, soup, and soda may be used.
6. Call a physician if your blood glucose concentration remains >300 mg/dL, or your urine ketones remain high after two or three supplemental doses of insulin, or your blood glucose level remains >240 mg/dL for >24 hours.

TABLE 53.18 Management of Diabetic Ketoacidosis

**FLUID ADMINISTRATION**

Start IV fluids using normal saline (0.9% NaCl) unless patient has cardiac compromise.

Rate is 15–20 mL/kg body weight or 1–1.5 L during first hour.

Then, if corrected sodium is normal or elevated, use 0.45% NaCl at a rate of 4–14 mL/kg/hour (250–500 mL/hour). Use 0.9% NaCl if corrected sodium is low.

Once serum glucose reaches 200 mg/dL, change to 5% dextrose with 0.45% NaCl at 150–250 mL/hour.

**INSULIN**

Continuous IV infusion of regular insulin is preferred. Use IM route only if infusion is not available.

*Bolus dose:* 0.1 units/kg IV

*Maintenance dose:* 0.1 units/kg/hour IV

If blood glucose level has not decreased by 50–75 mg/dL after 1 hour, double infusion rate.

Once blood glucose reaches 200 mg/dL, reduce infusion rate to 0.05–0.1 units/kg/hour and change fluid to 5% dextrose with 0.45% NaCl (do not stop insulin infusion).

When SC insulin can be initiated, administer dose 1–2 hours before discontinuing IV infusion.

For uncomplicated DKA, SC rapid-acting insulin can be considered. A bolus dose of 0.2 units/kg followed by 0.1 units/kg every hour *or* an initial dose of 0.3 units/kg followed by 0.2 units/kg every 2 hours until the blood glucose reaches <250 mg/dL; then the SC insulin dose is decreased by half (to either 0.05 or 0.1 units/kg every 1–2 hours).

**POTASSIUM**

Establish adequate renal function (urine output ~50 mL/hour). If K is <3.3 mEq/L, hold insulin and give 20–40 mEq/hour until K >3.3 mEq/L. If K is >5.5 mEq/L, do not give K and check serum K every 2 hours. If K is >3.3 but <5.3 mEq/L, give 20–30 mEq in each liter of IV fluid to maintain K between 4 and 5 mEq/L.

**PHOSPHATE**

Initiate if level <1 mg/dL, or in patients with cardiac dysfunction, anemia, or respiratory depression. Use potassium phosphate salt, 20–30 mEq added to replacement fluid. Rarely needed.

**BICARBONATE**

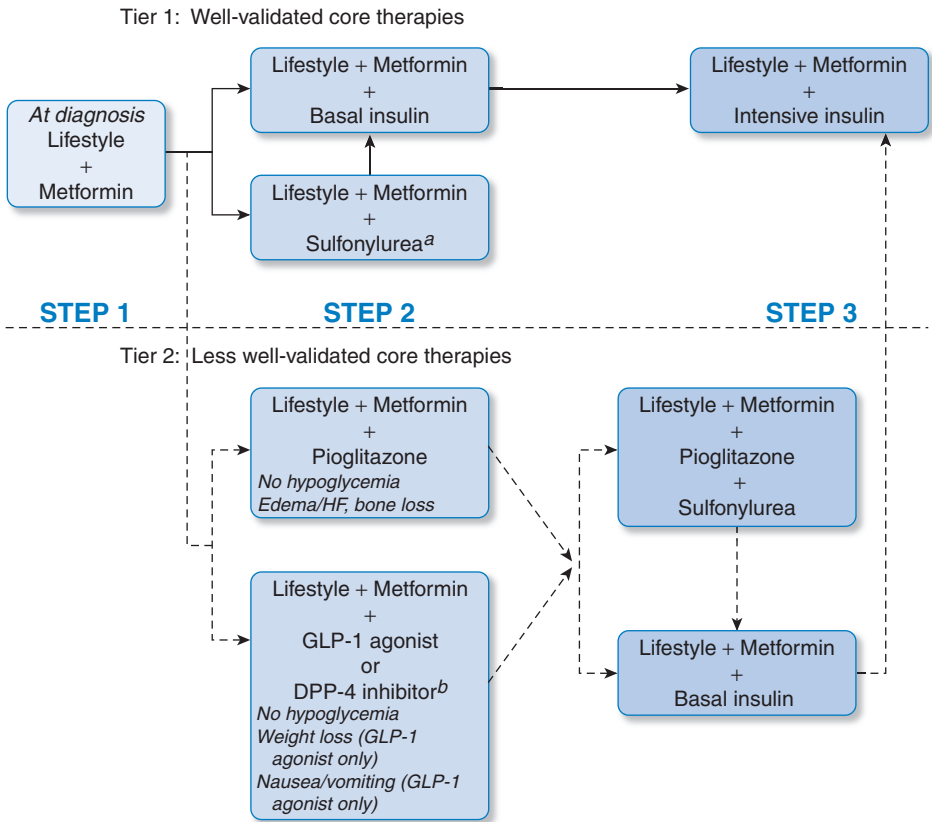
Replacement is controversial and may be dangerous.

For adults with pH <6.9, 100 mmol of sodium bicarbonate may be added to 400 mL of sterile water with 20 mEq of KCl; infuse for 2 hours (200 mL/hour). For adults with pH of 6.9–7.0, 50 mmol of sodium bicarbonate diluted in 200 mL of sterile water with 10 mEq of KCl; infuse for 1 hour (200 mL/hour). No bicarbonate is necessary if pH >7.0.

DKA, diabetic ketoacidosis; IM, intramuscular; IV, intravenous; SC, subcutaneous.

- Figure 53.1 shows a suggested treatment algorithm for glycemic management of type 2 diabetes. Table 53.19 summarizes treatment under special circumstances.
- Metformin is considered first-line therapy for type 2 diabetes unless there is a contraindication to its use or it is not tolerated by the patient. It should be started at the time of diagnosis along with lifestyle changes.
- A second antidiabetic agent should be added to the regimen if a patient fails monotherapy. Choice of agent depends on factors including A1C goal, reduction in A1C needed, kidney and liver function, medication side effects, and cost.
- Insulin therapy should be considered in patients with type 2 diabetes who are no longer able to achieve A1C goals with noninsulin therapy, when the A1C is severely uncontrolled (e.g., >10%), during pregnancy or when the A1C is >8.5% to 9% despite combination oral therapy.





**Figure 53.1** Suggested treatment algorithm for glycemic management of type 2 diabetes. Lifestyle interventions should be reinforced at every visit. The glycosylated hemoglobin (A1C) should be checked every 3 months until the patient’s goal is achieved (e.g., <7%) and then at least every 6 months. The interventions should be changed if the A1C is greater than goal ( $\geq 7\%$ ). <sup>a</sup>Sulfonylureas other than chlorpropamide. <sup>b</sup>Dipeptidyl peptidase-4 (DPP-4) inhibitors added to this category. (Nathan DM et al. Medical management of hyperglycemia in type 2 diabetes: a consensus algorithm for the initiation and adjustment of therapy: a consensus statement of the American Diabetes Association and the European Association for the Study of Diabetes. *Diabetes Care*. 2009;32:193.)

- Patients should be instructed on how to recognize and treat hypoglycemia (Table 53.20).
- Management of cholesterol should include a statin. Management of hypertension should include an angiotensin-converting enzyme inhibitor or angiotensin II receptor blocker.

### Drug Therapy

- **Insulin**
  - Insulins are classified as rapid-, short-, intermediate-, or long-acting (Table 53.21). They differ by their pharmacokinetic properties (Table 53.22).
  - Several factors can alter the onset and duration of insulin action (Table 53.23).
  - Premixed insulins are useful for patients who have difficulty measuring and mixing insulins (Table 53.24).

TABLE 53.19 Treating Type 2 Diabetes under Special Circumstances

Circumstance	Avoid	Consider
Patients with decreased renal function	Acarbose <sup>a</sup> Long-acting SFUs (e.g., glyburide) Metformin	Glipizide Glimepiride Glinides DPP-4 inhibitors (require dose adjustment) Pioglitazone Insulin
Patients with impaired liver function	Acarbose <sup>a</sup> Metformin TZDs SFUs (severe liver dysfunction)	Insulin Repaglinide <sup>b</sup> Exenatide DPP-4 inhibitors Miglitol
Patients who are obese or gaining excessive weight	Insulin <sup>c</sup> Sulfonylureas Repaglinide TZDs <sup>d</sup>	DPP-4 inhibitors GLP-1 agonists Metformin
Patients with preexisting edema	TZDs	SFUs Glinides DPP-4 inhibitors GLP-1 agonists
Patients with heart failure	Metformin (severe heart failure) TZDs	SFUs Glinides DPP-4 inhibitors GLP-1 agonists Insulin
Patients experiencing hypoglycemia owing to irregular eating patterns	Insulin Long-acting SFUs Metformin	Acarbose Glinides Short-acting SFU (e.g., tolbutamide) Pioglitazone DPP-4 inhibitors GLP-1 agonists
Patients with osteoporosis or reduced bone density	TZDs	All other antidiabetic agents

<sup>a</sup>This is a labeled recommendation. Although very little acarbose is absorbed into the systemic circulation, the small amount available relies on the kidneys for elimination. This accumulation and doses  $\geq 300$  mg/day rarely have been associated with elevated liver enzymes. Plasma concentrations of miglitol in renally impaired volunteers were proportionally increased relative to the degree of renal dysfunction.

<sup>b</sup>The manufacturer recommends more cautious dose titration in these cases.

<sup>c</sup>This recommendation presumes that the patient can be controlled on other antidiabetic agents. Often by the time insulin is required in type 2 diabetes, pancreatic function may have deteriorated considerably.

<sup>d</sup>Rosiglitazone and pioglitazone are associated with mild to moderate weight gain owing to fluid retention and fat accumulation. However, because of their mechanism of action, they are effective in improving glycemic control in insulin-resistant patients who are often overweight or obese.

DPP-4, dipeptidyl peptidase-4; GLP-1, glucagon-like peptide-1; SFUs, sulfonylureas; TZDs, thiazolidinediones.

- For patients with type 1 diabetes, a total daily dose of insulin is estimated empirically or by guidelines (Tables 53.25 and 53.26). The use of an insulin pump is the most precise way to mimic normal insulin secretion, but use should be limited to very motivated patients.
- Indications and precautions for basal-bolus insulin are shown in Table 53.27.
- Primary sites for injecting insulin are the lateral thigh, abdomen, and upper arm (Figure 53.2).
- Several noninsulin antidiabetic drugs are available for the management of type 2 diabetes (Tables 53.28 and 53.29).

TABLE 53.20 Hypoglycemia

**DEFINITION**

Blood glucose concentration <60 mg/dL: Patient may or may not be symptomatic.

Blood glucose <40 mg/dL: Patient is generally symptomatic.

Blood glucose <20 mg/dL: Can be associated with seizures and coma.

**SIGNS AND SYMPTOMS**

Blurred vision, sweaty palms, generalized sweating, tremulousness, hunger, confusion, anxiety, circumoral tingling, and numbness. Patients vary with regard to their symptoms. Behavior can be confused with alcohol inebriation.

Patients become combative and use poor judgment.

*Nocturnal hypoglycemia*: nightmares, restless sleep, profuse sweating, morning headache, morning “hangover.” Not all patients have symptoms during nocturnal hypoglycemia.

**CLINICAL CONSIDERATIONS**

Irregular eating patterns

↑ Physical exercise

Gastroparesis (delayed gastric emptying)

Defective counterregulatory responses

Excessive dose of insulin or insulin secretagogues (sulfonylureas, glinides)

Alcohol ingestion

Drugs

**TREATMENT**

Ingest 10–20 g of rapidly absorbed carbohydrate. Repeat in 15–20 minutes if glucose concentration remains <60 mg/dL or if patient is symptomatic. Follow with complex carbohydrate/protein snack if mealtime is not imminent.

The following are examples of food sources that provide 15 g of carbohydrate:

Orange, grapefruit, or apple juice; regular, nondiet soda	1/2 cup
Fat-free milk	1 cup
Grape juice, cranberry juice cocktail	1/3 cup
Sugar	1 tsp or 3 cubes
Lifesavers	5–6 pieces
Glucose tablets	3–4 tablets

If patient is unconscious, the following measures should be initiated:

Glucagon 1 mg SC, IM, or IV (generally administered IM in outpatient setting; mean response time, 6.5 minutes)

Glucose 25 g IV (dextrose 50%, 50 mL; mean response time, 4 minutes)

IM, intramuscular; IV, intravenous; SC, subcutaneous.

TABLE 53.21 Insulins Available in the United States<sup>a</sup>

Type/Duration of Action	Brand Name	Manufacturer
<b>RAPID-ACTING</b>		
Insulin lispro	Humalog	Lilly
Insulin aspart	NovoLog	Novo Nordisk
Insulin glulisine	Apidra	sanofi-aventis
<b>SHORT-ACTING</b>		
Regular	Humulin R <sup>b</sup> Novolin R	Lilly Novo Nordisk
<b>INTERMEDIATE-ACTING</b>		
NPH (isophane insulin suspension)	Humulin N Novolin N	Lilly Novo Nordisk
<b>LONG-ACTING</b>		
Insulin glargine	Lantus	sanofi-aventis
Insulin detemir	Levemir	Novo Nordisk
<b>PREMIXED INSULINS</b>		
NPH/regular (70%/30%)	Humulin 70/30 Novolin 70/30	Lilly Novo Nordisk
Insulin aspart protamine suspension/insulin aspart (70%/30%)	NovoLog Mix 70/30	Novo Nordisk
Insulin lispro protamine suspension/insulin lispro (75%/25%)	Humalog Mix 75/25	Lilly
Insulin lispro protamine suspension/insulin lispro (50%/50%)	Humalog Mix 50/50	Lilly

<sup>a</sup>Insulin is made through recombinant DNA technology. Only regular and NPH are human insulin. All other insulins are human insulin analogs. All insulins available in the United States have a concentration of 100 units/mL (U-100), except as noted.

<sup>b</sup>A U-500 concentration is available for use in rare circumstances in patients with severe insulin resistance requiring very large insulin doses.

NPH, neutral protamine Hagedorn, or isophane insulin suspension.

TABLE 53.22 Insulin Pharmacodynamics<sup>a</sup>

Insulin	Onset (hours)	Peak (hours)	Duration (hours)	Appearance
Rapid-acting (insulin aspart, glulisine, and lispro)	5–15 minutes	30–90 minutes	<5	Clear
Regular	0.5–1	2–4	5–7	Clear
NPH	2–4	4–12	12–18	Cloudy
Insulin glargine	1.5	No pronounced peak	20–24	Clear <sup>b</sup>
Insulin detemir	0.8–2	Relatively flat	5.7–23.2	Clear <sup>b</sup>

<sup>a</sup>The onset, peak, and duration of insulin activity may vary considerably from times listed in this table. See text and Table 53.27.

<sup>b</sup>Should not be mixed with other insulins. Some patients require twice-daily dosing.

Sources: Levemir [package insert]. Bagsværd, Denmark: Novo Nordisk Inc; July 2009; DeWitt DE, Hirsch IB. Outpatient insulin therapy in type 1 and type 2 diabetes mellitus: scientific review. *JAMA*. 2003;289:2254.

**TABLE 53.23 Factors Altering Onset and Duration of Insulin Action**

Factor	Comments										
Route of administration	Onset of action more rapid and duration of action shorter for IV > IM > SC. <sup>111,112</sup> Intrapulmonary insulin has onset and duration comparable to SC rapid-acting insulins. <sup>113</sup>										
<i>Factors altering clearance</i>											
Renal function	Renal failure lowers insulin clearance; may prolong and intensify action of exogenous and endogenous insulin. <sup>86</sup>										
Insulin antibodies	IgG antibodies bind insulin as it is absorbed and release it slowly, thereby delaying or prolonging its effect. <sup>114</sup>										
Thyroid function	Hyperthyroidism increases clearance, but also increases insulin action, making control difficult; patients stabilize as they become euthyroid. <sup>115</sup>										
<i>Factors altering SC absorption</i>											
Site of injection	Rate of absorption is fastest from the abdomen, intermediate from the arm, and slowest from the thigh. <sup>112</sup> Less variation is observed in type 2 diabetes patients; less variation is observed with current rapid-acting and long-acting insulins.										
	<table border="1"> <thead> <tr> <th>Site</th> <th>Half-life absorption (minutes)</th> </tr> </thead> <tbody> <tr> <td>Abdomen</td> <td>87 ± 12</td> </tr> <tr> <td>Arm</td> <td>141 ± 23</td> </tr> <tr> <td>Hip</td> <td>153 ± 28</td> </tr> <tr> <td>Thigh</td> <td>164 ± 15</td> </tr> </tbody> </table>	Site	Half-life absorption (minutes)	Abdomen	87 ± 12	Arm	141 ± 23	Hip	153 ± 28	Thigh	164 ± 15
Site	Half-life absorption (minutes)										
Abdomen	87 ± 12										
Arm	141 ± 23										
Hip	153 ± 28										
Thigh	164 ± 15										
Exercise of injected area	Strenuous exercise of an injected area within 1 hour of injection can increase absorption rate; rate of absorption of regular insulin is increased, but little effect on intermediate-acting insulin. <sup>116,117</sup>										
Ambient temperature	Heat (e.g., hot weather, hot bath, sauna) increases absorption rate; cold has opposite effect. <sup>117-119</sup>										
Local massage	Massaging injected area for 30 minutes substantially increases absorption rate of regular insulin as well as longer-acting insulins. <sup>115</sup>										
Smoking	Controversial; vasoconstriction may decrease absorption rate. <sup>89</sup>										
Jet injectors	Insulin absorption is more rapid, probably secondary to increases in surface area for absorption. <sup>120,121</sup>										
Lipohypertrophy	Insulin absorption is delayed from lipohypertrophic sites. <sup>122</sup>										
Insulin preparation	More soluble forms of insulin are absorbed more rapidly and have shorter durations of action (see Table 53.22 and text); human insulin may have shorter action than animal insulin.										
Insulin mixtures	The short-acting properties of rapid-acting insulins may be blunted if mixed with NPH insulin.										
Insulin concentration	More dilute solutions (e.g., U-40, U-10) are absorbed more rapidly than more concentrated forms (U-100, U-500).										
Insulin dose	Lower doses are absorbed more rapidly and have a shorter duration of action than larger doses.										

IgG, immunoglobulin G; IM, intramuscular; IV, intravenous; NPH, neutral protamine Hagedorn; SC, subcutaneous.

**TABLE 53.24 Compatibility of Insulin Mixtures**

Mixture	Proportion	Comments
Regular + NPH <sup>147</sup>	Any proportion	The pharmacodynamic profiles of regular and NPH insulin are unchanged when premixed and stored in vials or syringes for up to 3 months.
Regular + normal saline	Any proportion	Use within 2-3 hours of preparation.
Regular + insulin diluting solution	Any proportion	Stable indefinitely.
Rapid-acting + NPH <sup>93-95</sup>	Any proportion	The absorption rate and peak action of the rapid-acting insulins are blunted; total bioavailability is unaltered. Rapid-acting insulin and NPH should be mixed just before use (within 15 minutes).
Insulin glargine and detemir <sup>97,107</sup>	Do not mix with other insulins	Pharmacodynamics could be modified.

NPH, neutral protamine Hagedorn.

TABLE 53.25 Empiric Insulin Doses

## ESTIMATING TOTAL DAILY INSULIN REQUIREMENTS

These are initial doses only; they must be adjusted using SMBG results. Patients may be particularly resistant to insulin if their blood glucose concentrations are high (glucose toxicity); once glucose concentrations begin to drop, insulin requirements often decrease precipitously. The weight used is actual body weight. Insulin dose requirements can change dramatically with time depending on circumstances (e.g., a growth spurt, modest weight gain or loss, changes in physical activity, stress or illness).

*Type 1 diabetes*

Initial dose	0.3–0.5 units/kg
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Honeymoon phase	0.2–0.5 units/kg
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With ketosis, during illness, during growth	1.0–1.5 units/kg
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*Type 2 diabetes*

With insulin resistance	0.7–1.5 units/kg
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## ESTIMATING BASAL INSULIN REQUIREMENTS

These are empiric doses only and should be adjusted using appropriate SMBG results (fasting or premeal). Basal requirements vary throughout the day, often increasing during the early morning hours. The basal requirement also is influenced by the presence of endogenous insulin, the degree of insulin resistance, and body weight. Basal requirements are approximately 50% of total daily insulin needs. Thus, basal insulin dose is approximately 50% of TDD. A conservative approach is to reduce the calculated 50% basal dose by 20% to avoid hypoglycemia.<sup>127</sup>

## ESTIMATING PREMEAL INSULIN REQUIREMENTS

The premeal insulin requirements are approximately 50% of the TDD, usually divided equally into three doses initially, taken with each meal (i.e., breakfast, lunch, and dinner), and then each premeal dose is individually adjusted on the basis of BG readings.

The “500 rule” estimates the number of grams of carbohydrate that will be covered by 1 unit of rapid-acting insulin. The rule is modified to the “450 rule” if using regular insulin.

$$500/\text{TDD of insulin} = \text{number of grams covered}$$

*Example:* For a patient using 50 units/day,  $500/50 = 10$ . Therefore, 10 g of carbohydrate would be covered by 1 unit of insulin lispro, glulisine, or aspart. This equation works very well for type 1 diabetes patients in estimating their premeal insulin requirements. Because patients with type 2 diabetes have insulin resistance, the rule may underestimate their insulin requirements.

## DETERMINING THE “CORRECTION FACTOR”

Supplemental doses of rapid-acting insulin are administered to acutely lower glucose concentrations that exceed the target glucose concentration. These doses must be individualized for each patient and again are based on the degree of sensitivity to insulin action. For example, if the premeal blood glucose target is 120 mg/dL and the patient’s value is 190 mg/dL, additional units of rapid-acting insulin could be added to the premeal dose. The correction factor determines how far the blood glucose drops per unit of insulin given and is known as the “1,700 rule.” For regular insulin, the rule is modified to the “1,500 rule.” The equation is as follows:

$$1,700/\text{TDD} = \text{point drop in blood glucose per unit of insulin}$$

*Example:* If a patient uses 28 units/day of insulin, their correction factor (or insulin sensitivity) would be  $1,700/28 = 60$  mg/dL. Therefore, the patient can expect a 60-mg/dL drop for every unit of rapid-acting insulin administered. Patients with a higher sensitivity factor have lower insulin requirements. Individuals with a lower sensitivity factor (higher insulin requirements) typically achieve a smaller reduction in blood glucose per unit of insulin.

SMBG, self-monitored blood glucose; TDD, total daily dose.

*Sources:* DeWitt DE, Hirsch IB. Outpatient insulin therapy in type 1 and type 2 diabetes mellitus: scientific review. *JAMA*. 2003;289:2254; Walsh J, Roberts R. *Pumping Insulin: Everything You Need For Success On A Smart Insulin Pump*. 4th ed. San Diego, CA: Torrey Pines Press; 2006; Walsh J et al. *Using Insulin: Everything You Need for Success With Insulin*. San Diego, CA: Torrey Pine Press; 2003.

TABLE 53.26 Guidelines for Dosing Insulin

**BASIC INSULIN DOSES**

First, adjust the basic insulin dose (i.e., the dose that the patient will be instructed to take daily).

Only adjust insulin doses if a *pattern* of response is observed under stable diet and exercise circumstances. That is, the same response to insulin is observed for  $\geq 3$  days, particularly for the basal insulin dose. It is important to verify the stability of diet and exercise. Consider adjusting these variables as well.

Unless all levels are  $>200$  mg/dL, try to adjust one component of insulin therapy at a time.

Start with the insulin component affecting the FBG concentration. This glucose level often is the most difficult to control and often affects all other glucose concentrations measured throughout the day. The basal insulin dose is often what is adjusted to control the FBG. However, if the dinner insulin dose (of rapid-acting or short-acting insulin) is not adequate, this can result in hyperglycemia that can persist into the morning. The basal dose is typically adjusted by 2–4 units, no sooner than every 3 days.<sup>138</sup>

Prandial/mealtime insulin dose:

- For patients eating a set amount of carbohydrate at meals: Typically adjust the basic insulin dose by 1–2 units at a time. The amount given is based on the individual patient's response to insulin. This can be determined by looking at the patient's total daily dose using the "500 rule" (see the following, and Table 53.25).
- For patients using the insulin-to-carbohydrate method (i.e., 1 unit rapid-acting or short-acting insulin for every x g of carbohydrate), adjust the "ratio" based in the patient's response to insulin (e.g., 1:8, 1:10, 1:12, 1:15, 1:18, 1:20).

**General Principles**

Assumes that diet and physical activity are stable. Set a reasonable goal initially. This may mean the upper limits of the acceptable concentrations may be high initially (e.g.,  $<200$  mg/dL). Move toward a more ideal goal slowly.

**SUPPLEMENTARY INSULIN DOSES (WITH RAPID-ACTING OR SHORT-ACTING INSULIN)**

Once the basic dose of prandial insulin has been established, supplemental doses of rapid- or short-acting insulin can be prescribed to correct *preprandial* hyperglycemia. For example, if the goal is 140 mg/dL and the glucose value is 190 mg/dL, administer one additional unit. Supplemental doses also can be used when the patient is ill (Table 53.17).

Algorithms for correction doses are based on the patient's sensitivity to insulin using the "1,500 or 1,700 rule" (Table 53.25). These are population averages which can be used when patient-specific data are not available.

If premeal glucose concentrations are  $<60$ – $70$  mg/dL, the dose of aspart, glulisine, lispro, or regular insulin administered before the meal is  $\downarrow$  by 1–2 units; insulin administration is delayed until just before the meal; the meal should include an extra 15 g of glucose if the value is  $<50$  mg/dL.

If supplemental doses before a given meal are required for  $\geq 3$  days, the basic insulin dose should be adjusted appropriately. For example, if a patient taking lispro before meals requires an extra 2 units before lunch for  $\geq 3$  days, 2 units should be added to the prebreakfast dose, or the insulin-to-carbohydrate ratio at breakfast should be adjusted (e.g., if patient was using a 1:15 ratio, a 1:12 ratio could be used).

**ANTICIPATORY INSULIN DOSES (WITH RAPID-ACTING OR SHORT-ACTING INSULIN)**

The basic insulin dose is  $\uparrow$  or  $\downarrow$  based on the anticipated effects of diet or physical activity.

$\uparrow$  Aspart/glulisine/lispro or regular insulin by 1 unit for each additional 15 g of carbohydrate ingested (e.g., holiday meal) or  $\downarrow$  the usual dose by 1–2 units if the meal is smaller than usual (Table 53.25).

See Table 53.6 for recommended insulin adjustments for exercise.

FBG, fasting blood glucose.

TABLE 53.27 Basal-Bolus (Physiological) Insulin Therapy: Indications and Precautions

## PATIENT SELECTION CRITERIA

Type 1 diabetes, otherwise healthy patients (>7 years of age) who are highly motivated, engaged in diabetes self-management, and are able to adhere to a complex insulin regimen. Must be willing to test blood glucose concentrations multiple times daily and inject four doses of insulin daily, on average

Women with diabetes who plan to conceive

Pregnant patients with diabetes (preexisting)

Patients poorly controlled on conventional therapy, 2–3 injections daily (includes type 2 diabetes patients)

Technical ability to test blood glucose concentrations

Intellectual ability to interpret blood glucose concentrations and adjust insulin doses appropriately

Access to trained and skilled medical staff to direct treatment program and provide close supervision

## AVOID OR USE CAUTIOUSLY IN PATIENTS WHO ARE PREDISPOSED TO SEVERE HYPOGLYCEMIC REACTIONS OR IN WHOM SUCH REACTIONS COULD BE FATAL

Patients with counterregulatory insufficiency

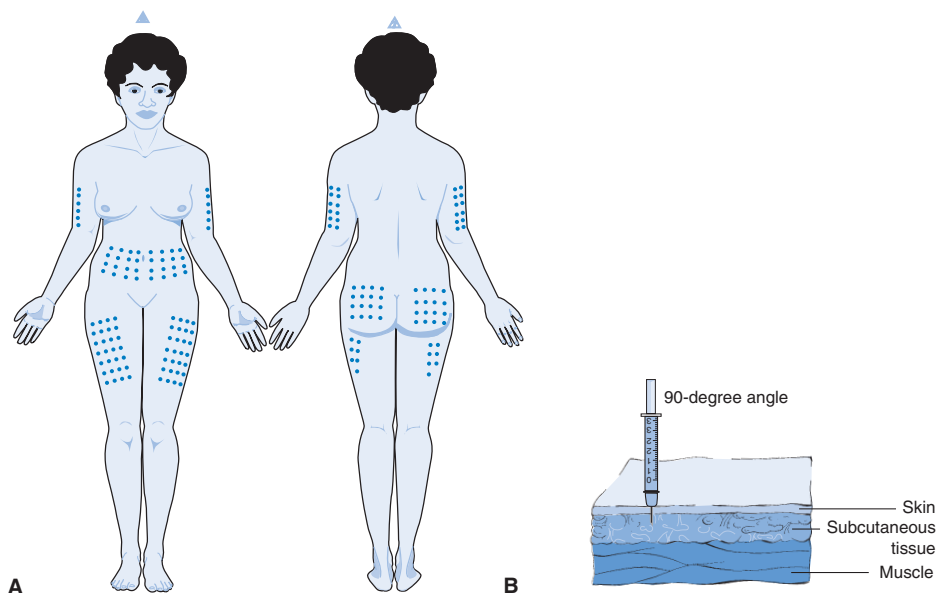
$\beta$ -Adrenergic blocker therapy

Autonomic insufficiency

Adrenal or pituitary insufficiency

Patients with coronary or cerebral vascular disease (*Note:* Counterregulatory hormones released in response to hypoglycemia may have adverse effects in these individuals.)

Unreliable, nonadherent individuals, including those who abuse alcohol or drugs and those with psychiatric disorders.



**Figure 53.2** Selecting insulin injection sites. **A:** Areas of the body most suitable for insulin injections. The actual point of injection should be varied each time within a chosen body area. Give injections at least one inch apart. Patients should consult with their provider or diabetes educator about which area is most appropriate for use. LifeART image © 2011. Lippincott Williams & Wilkins. All rights reserved. **B:** The site where insulin should be injected. Insulin is injected in the subcutaneous tissue (between the skin and the muscle layer). If the skin is pinched up and the needle is pushed all the way in, the needle will reach the proper space under the skin. (Adapted with permission from Springhouse. *Lippincott's Visual Encyclopedia of Clinical Skills*. Philadelphia, PA: Wolters Kluwer Health, 2009.)



TABLE 53.28 Comparative Pharmacology of Antidiabetic Agents

Agent/Generic Name (Brand Name)/Mechanism	FDA Indications	A1C Efficacy <sup>a</sup>	Adverse Effects	Comments
<b>Insulin</b> Replaces or augments endogenous insulin	Monotherapy; combined with any oral agent	↓ A1C <sup>b</sup> ↓ FPG <sup>b</sup> ↓ PPG <sup>b</sup> ↓ TG	Hypoglycemia, weight gain, lipodystrophy, local skin reactions	Offers flexible dosing to match lifestyle and glucose concentrations. Rapid onset. Safe in pregnancy, renal failure, and liver dysfunction. Drug of choice when patients do not respond to other antidiabetic agents
<b>INSULIN-AUGMENTING AGENTS</b>				
<b>Nonsulfonylurea secretagogues (glinides)</b> Repaglinide (Prandin) Nateglinide (Starlix) Stimulates insulin secretion	Monotherapy; combined with metformin or TZD	Monotherapy: ↓ A1C ~1% (repaglinide) ↓ A1C ~0.5% (nateglinide) Combination: additional 1% ↓ A1C	Hypoglycemia, weight gain	Take only with meals. If a meal is skipped, skip a dose. Flexible dosing with lifestyle. Safe in renal and liver failure. Rapid onset. Useful to lower PPG
<b>Sulfonylureas</b> Various; see Table 53.29. Stimulates insulin secretion. May decrease hepatic glucose output and enhance peripheral glucose utilization	Monotherapy; combined with metformin; combined with insulin (glimepiride)	Monotherapy: ↓ A1C ~1% Combination: additional 1% ↓ in A1C	Hypoglycemia, especially long-acting agents; weight gain (5–10 pounds); rash, hepatotoxicity, alcohol intolerance, and hyponatremia rare	Very effective agents. Some can be dosed once daily. Rapid onset of effect (1 week)
<b>INCRETIN-BASED THERAPIES</b>				
<b>Glucagonlike peptide-1 receptor agonists/incretin mimetic</b> Exenatide (Byetta) Liraglutide (Victoza) Stimulates insulin secretion, delays gastric emptying, reduces postprandial glucagon levels, improved satiety	Monotherapy (exenatide only) Combined with metformin, SFU, or TZD, combined with metformin + SFU; combined with metformin + TZD	Monotherapy: ↓ A1C 0.8%–0.9% Combination: additional 1% ↓ in A1C	GI: nausea, vomiting, diarrhea; hypoglycemia (with SFUs); weight loss; reports of acute pancreatitis	Weight loss Exenatide: Take within 60 minutes before morning and evening meals or before two main meals of the day (≥6 hours apart). Liraglutide: Do not use if personal or family history of medullary thyroid carcinoma or in patients with multiple endocrine neoplasia syndrome type 2. Do not use in patients with gastroparesis or severe GI disease. Administered by SC injection; pen device in use does not need to be refrigerated. Rare cases of pancreatitis with both drugs

<b>DPP-4 inhibitors</b> Sitagliptin (Januvia) Saxagliptin (Onglyza) Linagliptin (Tradjenta) Stimulates insulin secretion and reduces postprandial glucagon levels	Monotherapy; combined with metformin, SFU, or TZD; insulin (sitagliptin only)	Monotherapy: ↓ A1C 0.5%–0.8% Combination: ↓ A1C 0.5%–0.9%	Headache, nasopharyngitis, hypoglycemia (with SFU), rash (rare)	Dosed once daily. Taken with or without food. No weight gain or nausea. Need to adjust sitagliptin and saxagliptin dose in renal dysfunction. Reduce dose of SFU when combined. Rare reports of pancreatitis.
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#### AMYLIN RECEPTOR AGONISTS

<b>Amylin mimetic</b> Pramlintide (Symlin) Stimulates insulin secretion, delays gastric emptying, reduces postprandial glucagon levels, improved satiety	Type 1: Adjunct to mealtime insulin Type 2: Adjunct to mealtime insulin; ± SFU and metformin	T1: ↓ A1C 0.33% T2: ↓ A1C 0.40%	GI: nausea, decreased appetite Headache; hypoglycemia; weight loss (mild)	Take only immediately before meals; administered by SC injection. Do not use in patients with gastroparesis.
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#### INSULIN SENSITIZERS

<b>Biguanides</b> Metformin (Glucophage) ↓ Hepatic glucose output; ↑ peripheral glucose uptake	Monotherapy; combined with SFU or TZD; or with insulin	Monotherapy: ↓ A1C ~1% Combination: additional 1% ↓ in A1C	GI: nausea, cramping, diarrhea; lactic acidosis (rare)	Titrate dose slowly to minimize GI effects. No hypoglycemia or weight gain; weight loss possible. Mild reduction in cholesterol. Do not use in patients with renal or severe hepatic dysfunction.
<b>Thiazolidinediones</b> Rosiglitazone (Avandia) Pioglitazone (Actos) Enhances insulin action in periphery; increases glucose utilization by muscle and fat tissue; decreases hepatic glucose output	Monotherapy; combined with SFU, TZD, or insulin; combined with SFU + TZD	Monotherapy: ↓ A1C ~1% Combination: additional 1% ↓ in A1C	Mild anemia; fluid retention and edema, weight gain, macular edema, fractures (in women)	Can cause or exacerbate HF; do not use in patients with symptomatic HF or class III or IV HF. Rosiglitazone may increase risk of MI. Increased risk of distal fractures in older women. Pioglitazone may increase risk of bladder cancer when used for >1 year. Slight reduction in TG with pioglitazone; slight increase in LDL-C with rosiglitazone. LFTs must be measured at baseline and periodically thereafter. Slow onset (2–4 weeks).

*Continued on following page*

TABLE 53.28 Comparative Pharmacology of Antidiabetic Agents (Continued)

Agent/Generic Name (Brand Name)/Mechanism	FDA Indications	A1C Efficacy <sup>a</sup>	Adverse Effects	Comments
<b>DELAYERS OF CARBOHYDRATE ABSORPTION</b>				
<b><math>\alpha</math>-Glucosidase inhibitors</b> Acarbose (Precose) Miglitol (Glyset) Slow absorption of complex carbohydrates	Monotherapy; combined with SFUs, metformin, or insulin	Monotherapy: $\downarrow$ A1C $\sim$ 0.5% Combination: additional $\sim$ 0.5% $\downarrow$ A1C	GI: flatulence, diarrhea. Elevations in LFTs seen in doses $>$ 50 mg TID of acarbose	Useful for PPG control ( $\downarrow$ PPG 25–50 mg/dL). LFTs should be monitored every 3 months during the first year of therapy and periodically thereafter. Because miglitol is not metabolized, monitoring of LFTs is not required. Titrate dose slowly to minimize GI effects. No hypoglycemia or weight gain. If used in combination with hypoglycemic agents, advise patients to treat hypoglycemia with glucose tablets because absorption is not inhibited as with sucrose.
<b>Bile acid sequestrant</b> Colesevelam (Welchol)	Combined with metformin, SFU, or insulin	$\downarrow$ A1C 0.3%–0.4%	Constipation, dyspepsia, and nausea; $\uparrow$ TG	Added benefit of $\downarrow$ LDL-C (by 12%–16%). Administer certain drugs 4 hours before. Take with a meal and liquid.

<sup>a</sup>Comparative effectiveness data provided for SFUs, glinides, TZDs, and  $\alpha$ -glucosidase inhibitors.<sup>307</sup>

<sup>b</sup>Theoretically, unlimited glucose lowering with insulin therapy.

A1C, glycosylated hemoglobin; DPP-4, dipeptidyl peptidase-4; FDA, Food and Drug Administration; FPG, fasting plasma glucose; GI, gastrointestinal; HF, heart failure; LDL-C, low-density lipoprotein cholesterol; LFTs, liver function tests; MI, myocardial infarction; PPG, postprandial glucose; SC, subcutaneously; SFU, sulfonylureas; TG, triglycerides; TID, three times a day; T1, type 1 diabetes; T2, type 2 diabetes; TZD, thiazolidinediones.

**TABLE 53.29 Antidiabetic Pharmacokinetic Data**

<b>Drug (Brand Name), Available Tablet Strengths (mg)</b>	<b>Typical Dosing Regimen (mg)</b>	<b>Usual Minimum and Maximum Total Daily Dose/How Divided</b>	<b>Mean Half-Life</b>	<b>Approximate Duration of Activity</b>	<b>Bioavailability, Metabolism, and Excretion</b>	<b>Comments</b>
<b><i>α</i>-GLUCOSIDASE INHIBITORS</b>						
Acarbose (Precose) 25, 50, 100 mg	25–100 mg with first bite of each meal Begin with 25 mg; ↑ by 25 mg/meal every 4–8 weeks	Minimum: 25 mg TID Maximum dose is 50 mg TID if ≤60 kg; 100 mg TID if >60 kg	2.8 hours	Affects absorption of complex carbohydrates in a single meal	F = 0.5%–1.7%; extensively metabolized by GI amylases to inactive products; 50% excreted unchanged in the feces	Titrate doses slowly to avoid GI effects.
Miglitol (Glyset) 25, 50, 100 mg	25–100 mg with first bite of each meal Begin with 25 mg; ↑ by 25 mg/meal every 4–8 weeks	Minimum: 25 mg TID Maximum: 100 mg TID	2 hours	Affects absorption of complex carbohydrates in a single meal	Dose of 25 mg is completely absorbed; dose of 100 mg 50%–70% absorbed; elimination by renal excretion as unchanged drug	
<b>BIGUANIDES</b>						
Metformin (Glucophage) 500, 850, 1,000 mg; 500 mg/mL liquid	Begin with 500 mg daily or BID; ↑ by 500 mg daily every 1–2 weeks	0.5–2.5 g BID or TID	Plasma, 6.2 hours Whole blood, 17.6 hours	6–12 hours	F = 50%–60%; excreted unchanged in urine	Take with food. Avoid in patients with renal dysfunction or those who could be predisposed to lactic acidosis (e.g., alcoholism, severe HF, severe respiratory disorders, liver failure).
Metformin extended-release (Glucophage XR) 500, 750, 1,000 mg	500–1,000 mg daily with evening meal; ↑ by 500 mg every 1–2 weeks	1,500–2,000 mg daily	As for metformin, but active drug is released slowly	24 hours	As for metformin	As for metformin

*Continued on following page*

TABLE 53.29 Antidiabetic Pharmacokinetic Data (Continued)

Drug (Brand Name), Available Tablet Strengths (mg)	Typical Dosing Regimen (mg)	Usual Minimum and Maximum Total Daily Dose/How Divided	Mean Half-Life	Approximate Duration of Activity	Bioavailability, Metabolism, and Excretion	Comments
<b>NONSULFONYLUREA INSULIN SECRETAGOGUES (GLINIDES)</b>						
Repaglinide (Prandin) 0.5, 1, 2 mg	If A1C is <8% or if this is the first drug, begin with 0.5 mg with each meal. For others, begin with 1–2 mg/meal	0.5–4 mg with each meal (16 mg/day) TID or QID	1 hour	C <sub>max</sub> is at 1 hour; duration is approximately 2–3 hours	F = 56%; 92% metabolized to inactive products by the liver; 8% excreted as metabolites unchanged in the urine	Take only with meals. Skip dose if meal is skipped. Maximum dose per meal is 4 mg.
Nateglinide (Starlix) 60, 120 mg	120 mg TID 1–30 minutes before meals; 60 mg TID for patients with near-normal A1C at initiation	60 or 120 mg TID	1.5 hours	Onset, 20 minutes; peak, 1 hour; duration, 2–4 hours	F = 73%; metabolized to inactive products (predominantly) that are excreted in the urine (83%) and feces (10%)	Skip dose if meal is skipped.
<b>FIRST-GENERATION SULFONYLUREAS</b>						
Acetohexamide (Dymelor) 250, 500 mg	250 or 500 mg daily; ↑ by 250 mg daily every 1–2 weeks	0.25–1.5 g daily or BID	5 hours (active metabolite)	12–18 hours	Activity of metabolite greater than parent drug. Metabolite excreted, in part, by kidney	Caution in elderly and patients with renal disease. Significant uricosuric effects
Chlorpropamide (Diabinese) 100, 250 mg	100 or 250 mg daily; ↑ by 100 or 250 mg every 1–2 weeks	0.1–0.5 g daily	≥35 hours	24–72 hours	Inactive and weakly active metabolites; 20% excreted unchanged; varies widely	Caution in elderly and patients with renal impairment. Highest frequency of side effects relative to other sulfonylureas
Tolazamide (Tolinase) 100, 250, 500 mg	100–250 mg daily; ↑ by 100 or 250 mg every 1–2 weeks	0.2–1 g daily or BID	7 hours (4–25)	12–24 hours	Some metabolites with moderate activity excreted via kidney	Active metabolites may accumulate in renal failure
Tolbutamide (Orinase) 250, 500 mg	250 mg BID before meals; ↑ by 250 mg daily every 1–2 weeks	0.5–3 g BID or TID	7 hours	6–12 hours	Metabolized to compounds with negligible activity	No special precautions. Shortest-acting sulfonylurea

**SECOND-GENERATION SULFONYLUREAS**

Glimepiride (Amaryl) 1, 2, 4 mg	1–2 mg daily initially; usual maintenance dose is 1–4 mg	1–8 mg daily	9 hours	24 hours	F = 100% completely metabolized by liver. Principal metabolite is slightly active (30% of parent compound). Excreted by the urine (60%) and feces (40%)	Probably safe in patients with renal failure, but low initial doses recommended for older patients and those with renal insufficiency. Incidence of hypoglycemia may be lower than other long- acting sulfonylureas.
Glipizide (Glucotrol) 5, 10 mg	2.5 mg daily in elderly, 5 mg daily in others; ↑ by 2.5 or 5 mg every 1–2 weeks	2.5–40 mg daily or BID <sup>a</sup>	2–4 hours	12–24 hours	Metabolized to inactive compounds	No special precautions daily dose >15 mg should be divided. Dose 30 minutes before meals
Glipizide extended- release (Glucotrol XL) 5 mg	5 mg daily; ↑ by 5 mg every 1–2 weeks	5–20 mg daily	4–13 hours	24 hours	Same as glipizide	Use with caution in patients with preexisting GI narrowing owing to possible obstruction.
Glyburide (Diabeta, Micronase) 1.25, 2.5, 5 mg	1.25 mg daily in elderly, 2.5 mg daily in others; ↑ by 1.25 or 2.5 mg every 1–2 weeks	1.25–20 mg daily or BID	4–13 hours	12–24 hours	Metabolized to inactive or weakly inactive compounds; 50% excreted in urine and 50% in feces	Caution in elderly patients with renal failure and others predisposed to hypoglycemia. Daily doses >10 mg should be divided.
Micronized glyburide (Glynase presTab) 1.5, 3 mg	1.5 mg daily; ↑ by 1.5 mg every 1–2 weeks	1.0–12 mg daily	4 hours	24 hours	Metabolized to inactive or weakly inactive compounds; 50% excreted in urine and 50% in feces	Daily doses >6 mg should be divided. ↑ Bioavailability relative to original formulation. Resulted in reduced dose

*Continued on following page*

TABLE 53.29 Antidiabetic Pharmacokinetic Data (Continued)

Drug (Brand Name), Available Tablet Strengths (mg)	Typical Dosing Regimen (mg)	Usual Minimum and Maximum Total Daily Dose/How Divided	Mean Half-Life	Approximate Duration of Activity	Bioavailability, Metabolism, and Excretion	Comments
<b>THIAZOLIDINEDIONES</b>						
Rosiglitazone (Avandia) 2, 4, 8 mg	4 mg daily; ↑ to 8 mg daily (or 4 mg BID)	4–8 mg daily in single or divided doses	3–4 hours	Onset and duration poorly correlated with half-life because of mechanism of action. Onset at 3 weeks; max at ≥4 weeks. Offset likely to be similar	F = 99%; extensively metabolized in liver into inactive metabolites; excreted 2/3 in urine and 1/3 in feces	Food has no effect on absorption. BID dosing may have greater A1C lowering effect. No dose adjustments required in renal failure. Avoid in patients with liver disease and heart failure.
Pioglitazone (Actos) 15, 30, 45 mg	15–30 mg daily; ↑ to 45 mg daily. If used with insulin, ↓ insulin dose by 10%–25% once FPG <120 mg/dL	15–45 mg daily	3–7 hours (16–24 hours for all metabolites)	Same as previous	Extensively metabolized in liver; 15%–30% excreted in urine, remainder eliminated in the feces	Food delays absorption but is not clinically significant. No dose adjustments required in renal disease. Avoid in patients with liver disease and heart failure.
<b>GLP-1 RECEPTOR AGONISTS/INCRETIN MIMETICS</b>						
Exenatide (Byetta)	5 mcg SC BID; ↑ to 10 mcg SC BID after 1 month	5–10 mcg BID	2.4 hours	C <sub>max</sub> is at 2.1 hours; duration 10 hours	Glomerular filtration	Inject within 60 minutes before morning and evening meal. Nausea usually subsides with time.
Liraglutide (Victoza)	0.6 mg daily for 1 week; ↑ to 1.2 mg daily	0.6–1.8 mg daily	13 hours	24 hours; C <sub>max</sub> is 8–12 hours after dosing	Metabolized as other large proteins	Inject daily without regard to meals. Nausea usually subsides with time.

### DPP-4 INHIBITORS

Sitagliptin (Januvia)	100 mg daily CrCl $\geq 30$ to $< 50$ mL/ minute: 50 mg daily CrCl $< 30$ mL/minute: 25 mg daily	100 mg daily	12.4 hours	24 hours	F = 87%; ~79% excreted unchanged in urine	Requires dose adjustment in renal insufficiency
Saxagliptin (Onglyza)	5 mg daily CrCl $\leq 50$ mL/minute: 2.5 mg daily	2.5–5 mg daily	2.5 hours (3.1 hours for active metabolite)	24 hours	Metabolized by CYP 3A4/5 Excreted by renal and hepatic pathways	Active metabolite is 1/2 as potent Reduce dose to 2.5 mg with strong CYP 3A4/5 inhibitors
Linagliptin (Tradjenta)	5 mg daily	5 mg daily	12 hours	24 hours	F = 30%; ~90 excreted unchanged (80% enterohepatic system, 5% urine). Small fraction metabolized to inactive metabolite	No dose adjustment needed in liver or renal disease

### AMYLIN MIMETICS

Pramlintide (Symlin)	Type 1 DM: 15 mcg SC before major meals; $\uparrow$ by 15-mcg increments after minimum of 3 days Type 2 DM: 60 mcg SC before major meals; $\uparrow$ to 120 mcg after 3–7 days	Type 1: 15–60 mcg before major meals Type 2: 60 or 120 mcg before major meals	48 minutes	$C_{\max}$ is 20 minutes	F = 30%–40%; metabolized by kidneys	Reduce mealtime insulin dose by 50%. Titrate dose if no significant nausea.
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### BILE ACID SEQUESTRANTS

Colesevelam (Welchol)	Six tablets once daily or three tablets BID (625 mg tablets)	3.75 g	N/A	N/A	Drug is not absorbed systemically and not metabolized	Take with food and liquid. Do not use if history of bowel obstruction, TG $> 500$ mg/dL, or history of pancreatitis from $\uparrow$ TG.
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A1C, glycosylated hemoglobin; BID, twice a day;  $C_{\max}$ , maximal concentration; CrCl, creatinine clearance; CYP, cytochrome P-450; DM, diabetes mellitus; DPP-4, dipeptidyl peptidase-4; F, bioavailability; FPG, fasting plasma glucose; GI, gastrointestinal; GLP-1, glucagonlike peptide-1; HF, heart failure; N/A, not available; QID, four times a day; SC, subcutaneously; TG, triglycerides; TID, three times a day. For a table of the oral combination medications, go to <http://thepoint.lww.com/AT10e>



## Eye Disorders\*

### General Principles

- The eye is a complex organ composed of various parts, all of which must function together to permit vision. Common ocular conditions including glaucoma, ocular emergencies, ocular infectious and inflammatory conditions, and ocular effects of drugs are discussed below.

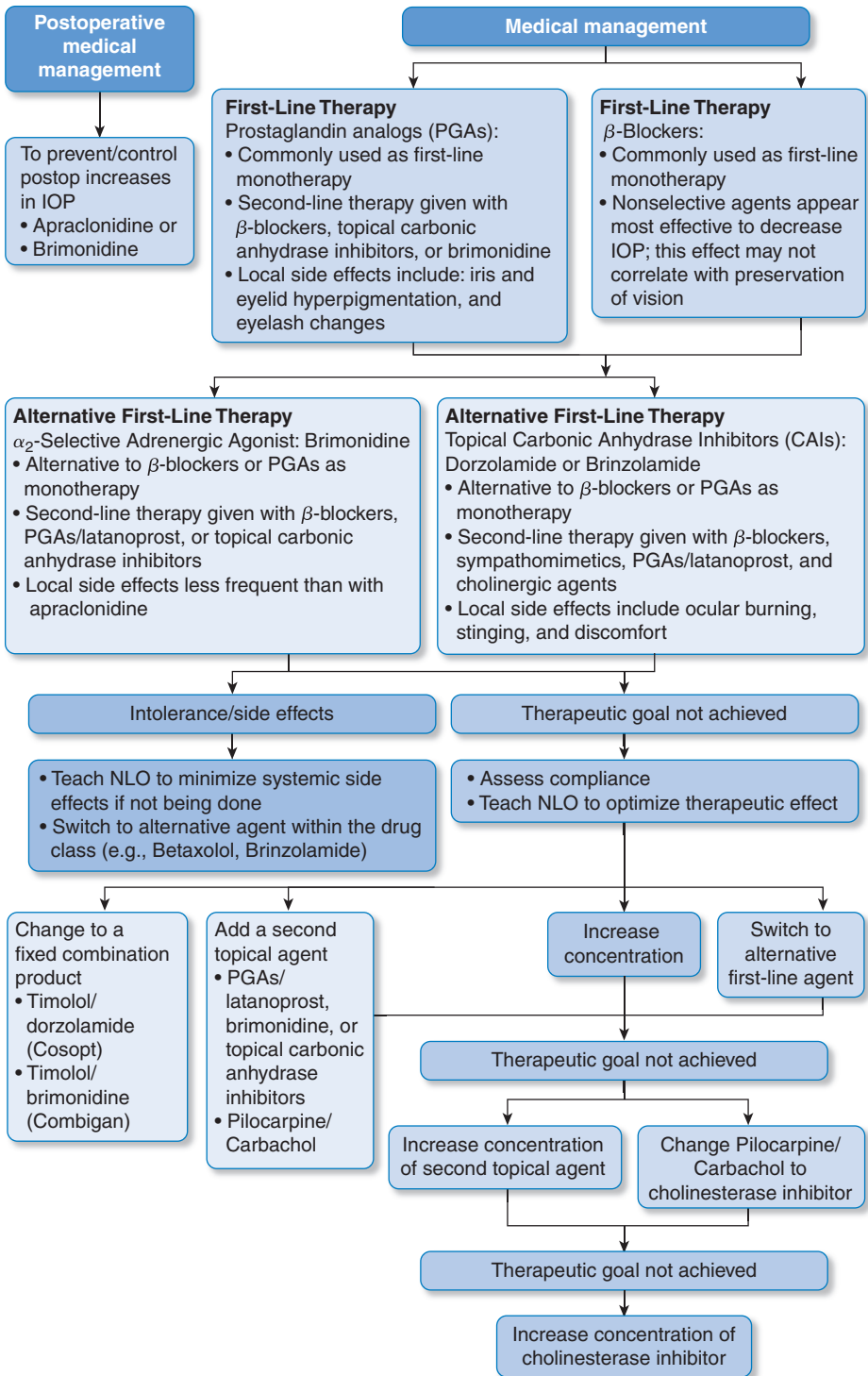
### Glaucoma

- Glaucoma is a nonspecific term used for a group of diseases that can irreversibly damage the optic nerve, resulting in visual field loss.
- Increased intraocular pressure (IOP) is the most common risk factor for developing glaucoma. IOP is influenced by the production and outflow of aqueous humor. An IOP of 10 to 20 mm Hg is considered normal.
- **Open-Angle Glaucoma:** Aqueous humor outflow from the anterior chamber is continuously subnormal. Primary open-angle glaucoma is associated with a positive family history and is more prevalent and aggressive in African Americans.
  - Medical management is shown in Figure 54.1. First-line treatment is with  $\beta$ -blockers or prostaglandin analogs.
  - Table 54.1 illustrates commonly used topical agents for open-angle glaucoma.
- **Angle-Closure Glaucoma:** Elevated IOP is caused by closure of the anterior chamber angle. It is a medical emergency that usually presents as an acute attack with a rapid increase in IOP, blurring or sudden vision loss, appearance of halos around lights, and pain that is often severe.
  - Medical treatment consists of pilocarpine 2% to 4% (1 drop every 5 minutes for 4–6 doses). Covering the puncta will decrease systemic absorption.
  - Hyperosmotic agents (Table 54.2) act by creating an osmotic gradient between plasma and ocular fluids. Intravenous agents work faster than oral agents.

### Ocular Emergencies

- Any loss of vision (sudden, complete, or transient), flashes of light, pain, or photophobia can signify potentially damaging ocular disorders (e.g., retinal artery occlusion, optic neuritis, retinal detachment). Prompt care is needed.
- **Chemical burns** require immediate attention. Copious irrigation using the most accessible water source is critical, followed by prompt medical care.
- **Corneal trauma** can occur from abrasion or foreign bodies. The patient often complains of a gritty, scratchy feeling.
- **Gonococcal conjunctivitis** is an ocular emergency that requires prompt medical attention to minimize the potential for corneal perforation.

\*The reader is referred to Chapter 54, Eye Disorders, written by Steven R. Abel, PharmD, FASHP, and Suellyn J. Sorensen, PharmD, BCPS, in the 10th edition of *Applied Therapeutics: The Clinical Use of Drugs* for a more in-depth discussion. All notations to reference numbers are based on the reference list at the end of that chapter. The editor of this handbook expresses her thanks to Drs. Abel and Sorensen and acknowledges that this chapter is based on their work.



**Figure 54.1** Medical management of glaucoma. IOP, intraocular pressure; NLO, nasolacrimal occlusion.

TABLE 54.1 Common Topical Agents Used in the Treatment of Open-Angle Glaucoma

Generic	Mechanism	Strength	Usual Dosage	Comments
<b><math>\beta</math>-BLOCKERS</b>				
Betaxolol (Betoptic [solution], Betoptic S [suspension])	Sympatholytic	0.25% (suspension)	1 drop BID	Effective with few associated ocular side effects. BID dosage enhances compliance.
	Sympatholytic	0.5% (solution)	1 drop BID	Considered $\beta$ -blocker of choice in patients with preexisting HF or pulmonary disease because of $\beta_1$ -adrenergic specificity. Patient response may be less than that seen with timolol.
Carteolol (Ocupress)	Sympatholytic	1%	1 drop BID	Effective with few associated side effects. BID dosage enhances compliance. Use with caution in patients with preexisting HF or pulmonary disease.
Levobunolol (Betagan)	Sympatholytic	0.25%, 0.5%	1 drop daily or BID	Effective with few associated ocular side effects. Daily and BID dosage enhances compliance. Use with caution in patients with preexisting HF or pulmonary disease.
Metipranolol (OptiPranolol)	Sympatholytic	0.3%	1 drop BID	Effective with few associated side effects. BID dosage enhances compliance. Use with caution in patients with preexisting HF or pulmonary disease.
Timolol (Timoptic)	Sympatholytic	0.25%, 0.5%	1 drop BID	Effective with few associated ocular side effects. BID dosage enhances compliance. Use with caution in patients with preexisting HF or pulmonary disease. Proven long-term effectiveness, with well-defined side-effect profile
Timolol Gel Forming Solution (Timoptic XE)	Sympatholytic	0.25%, 0.5%	1 drop daily	Once-daily timolol formulation. The ophthalmic vehicle, gellan gum (Gelrite), prolongs precorneal residence time and $\uparrow$ ocular bioavailability, allowing once-daily administration.
<b><math>\alpha_2</math>-SELECTIVE ADRENERGIC AGONISTS</b>				
Apraclonidine (Iopidine)	Sympathomimetic	0.5%, 1%	1 drop preoperatively and postoperatively or 1 drop BID to TID	May be used preoperatively and postoperatively for the prevention of $\uparrow$ IOP after anterior-segment laser procedures. Use of NLO minimizes systemic side effects and allows for BID dosing. Does not penetrate

TABLE 54.1 Common Topical Agents Used in the Treatment of Open-Angle Glaucoma (Continued)

Generic	Mechanism	Strength	Usual Dosage	Comments
Brimonidine (Alphagan)	Sympathomimetic	0.15%, 0.2%	1 drop BID to TID	the blood–brain barrier; therefore, negligible systemic hypotension. Local adverse effects fairly common. Tachyphylaxis may be observed Effective long-term monotherapy or adjunctive therapy. Use of NLO minimizes systemic side effects and allows for BID dosing. Penetrates the blood–brain barrier; therefore, may cause mild systemic hypotension and lethargy. Local adverse effects less common than with apraclonidine.
Brimonidine (Alphagan P)	Sympathomimetic	0.1%, 0.15%	1 drop BID to TID	Contains PURITE preservative. PURITE preservative and lower concentrations may improve tolerability.
<b>TOPICAL CARBONIC ANHYDRASE INHIBITORS</b>				
Brinzolamide (Azopt)	Decreased aqueous humor production	1%	1 drop TID	Effective long-term monotherapy or adjunctive therapy. Well tolerated with few systemic side effects. Less burning and stinging compared with dorzolamide
Dorzolamide (Trusopt)	Decreased aqueous humor production	2%	1 drop TID	Effective long-term monotherapy or adjunctive therapy. Well tolerated with few systemic side effects
<b>PROSTAGLANDIN ANALOGS</b>				
Latanoprost (Xalatan)	Prostaglandin $F_{2\alpha}$ agonist	0.005%	1 drop once a day at bedtime	BID dosing may be less effective than once-a-day-at-bedtime dosing. May cause increased pigmentation of the iris and eyelid. Systemic side effects are rare, but may cause muscle, joint, back pain, headaches, migraines, and skin rash. Effective monotherapy or adjunctive therapy. Store unopened bottles in refrigerator. Opened bottles may be stored at room temperature up to 6 weeks.
Travoprost (Travatan Z)	Prostaglandin $F_{2\alpha}$ agonist	0.004%	1 drop once a day at bedtime	BID dosing may be less effective than once-a-day-at-bedtime dosing.

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**TABLE 54.1 Common Topical Agents Used in the Treatment of Open-Angle Glaucoma (Continued)**

Generic	Mechanism	Strength	Usual Dosage	Comments
Bimatoprost (Lumigan)	Prostamide	0.01%, 0.03%	1 drop once a day at bedtime	<p>May cause increased pigmentation of the iris and eyelid. Systemic side effects are rare, but may include colds and upper respiratory tract infections. Effective monotherapy or adjunctive therapy with timolol. May be more effective than timolol and latanoprost and more effective in African Americans. Benzalkonium chloride preservative-free. Contains a preservative that may be better tolerated.</p> <p>BID dosing may be less effective than QHS dosing. May cause increased pigmentation of the iris and eyelid. Systemic side effects are rare but include colds and upper respiratory tract infections and headache. May be more effective than timolol and latanoprost.</p>
<b>MIOTICS</b>				
Pilocarpine (Isopto Carpine)	Parasympathomimetic	1%, 2%, 4% (ointment)	1–2 drops TID or QID ½ inch in cul-de-sac daily at bedtime	<p>Long-term proven effectiveness. Little rationale for administration more frequently than every 4 hours. Side effects of miosis with decreased vision and brow ache are common sources of patient complaints. Once-daily administration of ointment may increase compliance. Effectiveness for 24 hours should be assessed in patients receiving the ointment. Ointment may cause a visual haze and blurred vision.</p>
Carbachol (Isopto Carbachol)	Parasympathomimetic	1.5%, 3%	1–2 drops TID or QID	<p>Used in patients allergic to or intolerant of other miotics. May be used as frequently as every 4 hours. Corneal penetration is enhanced by benzalkonium chloride in commercial preparations. Side effects are similar to those of pilocarpine.</p>

TABLE 54.1 Common Topical Agents Used in the Treatment of Open-Angle Glaucoma (Continued)

Generic	Mechanism	Strength	Usual Dosage	Comments
Echothiophate iodide (Phospholine iodide)	Anticholinesterase	0.125%	1 drop BID	Long duration, although usually dosed BID, which enhances compliance. Available as powder + diluent; after reconstitution, stable 30 days at room temperature, 6 months refrigerated. Side effects similar to those of pilocarpine. Increased cataract formation has been associated with its use.

## COMBINATION PRODUCTS

Brimonidine tartrate 0.2%/timolol 0.5% (Combigan)	Sympathomimetic/ Sympatholytic	0.2%/0.5%	1 drop BID	Combination products may improve adherence. Eliminates the 5- to 10-minute wait between instillation of drops
Dorzolamide 2%/timolol 0.5% (Cosopt)	Decreased aqueous humor production/ sympathomimetic	2%/0.5%	1 drop BID	Combination products may improve adherence. Eliminates the 5- to 10-minute wait between instillation of drops

BID, twice daily; HF, heart failure; IOP, intraocular pressure; NLO, nasolacrimal occlusion; QHS, every day at bedtime; QID, four times a day; TID, three times a day.

## Common Ocular Disorders

- **Stye:** an infection of the hair follicles or sebaceous glands of the eyelids, typically by *Staphylococcus aureus*. Treatment includes hot, moist compresses and may include topical antibiotics.
- **Conjunctivitis:** inflammation of the conjunctiva, usually associated with a diffusely reddened eye, purulent or serous discharge, and itching, stinging, or a foreign-body sensation. It can be bacterial, fungal, parasitic, viral, or allergic in origin.
  - Typical treatment of bacterial conjunctivitis (pinkeye) is empiric antibiotics and mechanical cleaning of the eyelids.
  - Allergic conjunctivitis is managed with topical vasoconstrictors, with or without antihistamines. Cromolyn sodium is an alternative for patients who do not respond to more conservative measures.

TABLE 54.2 Hyperosmotic Agents

Generic	Mode of Administration	Strength	Onset	Peak	Duration	Dose	Ocular	
							Penetration	Distribution
Mannitol	IV	5%, 10%, 15%, 20%	30–60 minutes	1 hour	6–8 hours	1–2 g/kg	Very poor	E
Glycerin	PO	50%	10–30 minutes	30 minutes	4–5 hours	1–1.5 g/kg	Poor	E
Isosorbide	PO	45%	10–30 minutes	1 hour	5 hours	1.5–2 g/kg	Good	TBW

E, Extracellular water; IV, intravenous; PO, orally; TBW, total body water.

- **Corneal Ulcers:** Initial choice of therapy for bacterial corneal ulcers is commonly based on a Gram stain and clinical impression of the ulcer. Topical antimicrobials can be prepared using parenteral agents or by fortifying commercially available products with the addition of parenteral agents.

### Ocular Herpes Simples Virus Infection

- Ocular herpes can be caused by herpes simplex virus or, less commonly, by varicella zoster virus.
- Infections typically affect the eyelids, conjunctiva, and cornea. Patients present with symptoms of pain, tearing, eye redness, sensitivity to light, and irritation or foreign-body sensation.
- Antiviral therapy (trifluridine, acyclovir, ganciclovir) is necessary.

### Age-Related Macular Degeneration

- Age-related macular degeneration is a leading cause of blindness.
- Two forms exist. The dry form is most common and results from the breakdown of light-sensitive cells in the macula. Symptoms include blurred vision and ability to see details less clearly. The wet form, which is more serious, is associated with abnormal growth of blood vessels behind the retina. The first symptom is typically the appearance of straight lines as wavy. Treatments are directed at inhibiting angiogenesis, decreasing permeability of the vascular bed, and decreasing inflammation.

### Ophthalmic Medications

- **Corticosteroids:** Topical ophthalmic corticosteroids are used for a variety of conditions associated with inflammation of the conjunctiva, cornea, and within the anterior segment of the eye. They work by decreasing aqueous humor outflow. Increased IOP can result. Available agents are shown in Table 54.3. Salt form affects corneal penetration.
- **Nonsteroidal Anti-inflammatory Agents:** act by inhibiting prostaglandin synthesis and reducing prostaglandin-mediated ocular effects. Agents are shown in Table 54.4.

### Ocular Side Effects of Drugs

- Table 54.5 outlines some of the more common ocular side effects associated with systemic medication use.

Low Potency	Intermediate Potency	High Potency
Dexamethasone 0.05% (Decadron Phosphate)	Clobetasone 0.1% <sup>a</sup>	Clobetasone 0.5% <sup>a</sup>
Dexamethasone 0.1% (Decadron Phosphate)	Dexamethasone alcohol 0.1% (Maxidex)	Fluorometholone acetate 0.1% (Flarex)
Medrysone 1% (HMS)	Fluorometholone 0.1% (FML)	Prednisolone acetate 1% (Pred Forte)
	Fluorometholone 0.25% (FML Forte)	Rimexolone 1% (Vexol)
	Loteprednol 0.2% (Lotemax)	
	Loteprednol 0.5% (Alrex)	
	Prednisolone acetate 0.12% (Pred Mild)	
	Prednisolone sodium phosphate 0.125% (Inflamase Mild)	
	Prednisolone sodium phosphate 1% (Inflamase Forte)	

<sup>a</sup>Not commercially available in the United States.

TABLE 54.4 Ocular Nonsteroidal Anti-inflammatory Drugs

Indication	Drug/Approval Status for Indication	Dosage(s)
Inhibition of intraoperative miosis	Diclofenac 0.1% (Voltaren, U) <sup>149</sup>	Three reported regimens; 1 drop every 15–30 minutes for four doses; 1 drop TID for 2 preoperative days; 1 drop at 2 hours, 1 hour, and 15 minutes before surgery
	Flurbiprofen 0.03% (Ocufen, A) <sup>150</sup>	1 drop every 30 minutes for 2 hours before surgery
	Ketorolac 0.5% (Acular, U)	1 drop every 15 minutes beginning 1 hour before surgery
Anti-inflammatory after cataract surgery	Bromfenac 0.09% (Xibrom, A)	1 drop BID beginning 24 hours after surgery and continuing through the 2 weeks of the postoperative period
	Diclofenac 0.1% (A) <sup>151</sup>	1 drop BID to QID, including 24 hours preoperative administration
	Nepavanac 0.1% (Nevanac, A)	1 drop TID beginning 1 day before cataract surgery, continued on the day of surgery and through the first 2 weeks of the postoperative period (Nevanac prescribing information. Alcon Laboratories, November 2006).
	Ketorolac 0.5% (A) <sup>152</sup>	1 drop TID, including 24 hours preoperative administration
Prevention/treatment of cystoid macular edema	Diclofenac 0.1% (U) <sup>153</sup>	2 drops 5 times preoperatively, followed by 1 drop 3–5 times daily
	Ketorolac 0.5% (U) <sup>152,154</sup>	1 drop TID or QID, including 24 hours preoperative administration
Ocular inflammatory conditions (iritis, iridocyclitis, episcleritis)	Diclofenac 0.1% (U)	1 drop QID
Seasonal allergic/vernal conjunctivitis	Bromfenac 0.1% (U)	1 drop BID
	Diclofenac 0.1% (U)	1 drop every 2 hours for 48 hours; then QID
	Ketorolac 0.5% (A) <sup>155,156</sup>	1 drop QID

A, approved use; BID, twice daily; QID, four times a day; TID, three times a day; U, unapproved use.

TABLE 54.5 Ocular Side Effects of Systemic Medications

Drug Class	Effect(s)	Clinical Remarks
<b>ANALGESICS</b>		
Ibuprofen	Reduced vision	Rare; blurred vision reported in patients taking from four 200-mg tablets/week to six tablets/day; changes in color vision rarely reported <sup>86</sup>
Narcotics, including pentazocine	Miosis	Miosis often with morphine in normal doses; slight with other agents; effect secondary to CNS action on the pupilloconstrictor center <sup>80</sup>
	Tearing Irregular pupils Paresis of accommodation Diplopia	Effects associated with narcotic withdrawal <sup>80</sup>

**ANTIARRHYTHMICS**

Amiodarone	Keratopathy	Dose and duration related; resembles chloroquine keratopathy. Corneal deposits are bilateral, reversible, and unassociated with visual symptoms. Patients taking 100–200 mg/day have only minimal deposits. Deposits occur in almost 100% of patients receiving 400 mg/day. <sup>80–83</sup>
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TABLE 54.5 Ocular Side Effects of Systemic Medications (Continued)

Drug Class	Effect(s)	Clinical Remarks
	Cataracts	Previously reported as insignificant, anterior subcapsular lens opacities have been associated with amiodarone therapy. Rarely, such opacities may progress, increasing in density and in the diffuse distribution of the deposits, ultimately covering an area somewhat larger than the undilated pupil's aperture. The mechanism for this effect is unclear, but like chlorpromazine, amiodarone is a photosensitizing agent. Given that the lens changes are limited largely to the pupillary aperture, light exposure may result in the lens changes. <sup>80-83</sup>
	Optic neuropathy	Approximately 2% of patients experience optic neuropathy. <sup>85</sup>
<b>ANTICHOLINERGICS</b>		
Atropine Dicyclomine Glycopyrrolate Propantheline Scopolamine Trihexyphenidyl	Mydriasis Cycloplegia with ↓ accommodation Photophobia	Systemic and transdermal anticholinergic agents may cause mydriasis and, less frequently, cycloplegia. Mydriasis may precipitate angle-closure glaucoma. Photophobia is related to the mydriasis. Accommodation for near objects <sup>80,87</sup>
<b>ANTICONVULSANTS</b>		
Carbamazepine	Diplopia Blurred vision	Ocular adverse reactions when dosage >1–2 g/day; disappear when dosage is reduced <sup>80</sup>
Phenytoin	Nystagmus Cataracts	Nystagmus in patients with high blood levels (>20 mcg/mL); rarely occurs with other hydantoin. Cataracts may occur rarely with prolonged therapy. <sup>80,88</sup>
Topiramate	Acute myopia Secondary angle-closure glaucoma	Topiramate has been associated with angle-closure glaucoma. Symptoms including ocular pain, headache, nausea, vomiting, hyperemia, visual field defects, and blindness have been reported. This process is usually bilateral, but if symptoms are recognized and the drug is stopped in a timely manner, adverse outcomes may be minimized. <sup>85</sup>
Trimethadione	Visual glares	A prolonged glare or dazzle occurs when eyes are exposed to light. The glare is reversible, occurs at the retinal level, and is more common in adolescents and adults; occurs rarely in young children <sup>80</sup>
Vigabatrin	Visual field abnormalities	Visual field abnormalities including bilateral, symmetrical, and irreversible peripheral constriction occur in up to 30% of patients. Most patients are asymptomatic and <0.1% of patients are clinically affected. <sup>85</sup>
<b>ANESTHETICS</b>		
Propofol	Inability to open eyes	6 of 50 patients undergoing ENT procedures using standardized anesthesia with propofol were unable to open their eyes either spontaneously or in response to verbal commands. This effect lasted from 3 to 20 minutes after the end of anesthetic administration. Two patients showed complete loss of ocular motility. This was a transient, myasthenia-like weakness. <sup>89</sup>
<b>ANTIDEPRESSANTS</b>		
Tricyclic antidepressants (TCAs)		Mydriasis is the most common ocular side effect of TCAs. Cycloplegia is rare. Reports of precipitation of angle-closure glaucoma. <sup>80</sup>

TABLE 54.5 Ocular Side Effects of Systemic Medications (Continued)

Drug Class	Effect(s)	Clinical Remarks
Fluoxetine	Mydriasis Cycloplegia Eye tics	Administration of fluoxetine 20–40 mg/day has been associated with paroxysmal contractions of the muscles around the lateral aspect of the eye. This effect occurred 3–4 weeks after initiation of fluoxetine therapy and resolved within 2 weeks of discontinuation. <sup>90</sup>
<b>ANTI-HISTAMINES</b>		
Chlorpheniramine	Blurred vision Mydriasis, decreased lacrimal secretions	Blurred vision occurs rarely (about 1% of patients taking 12–14 mg/day). <sup>80</sup> Rare. <sup>80</sup>
<b>ANTI-HYPERTENSIVES</b>		
Clonidine	Miosis Dry itchy eyes	Miosis is seen in overdose. <sup>80</sup> Rare <sup>80</sup>
Diazoxide	Lacrimation	About 20% experience lacrimation, which may continue after drug is discontinued. <sup>80</sup>
Guanethidine	Miosis Ptosis Conjunctivitis Blurred vision	Sporadically documented. One study reported a 17% incidence of blurred vision in patients taking guanethidine 70 mg/day. <sup>80</sup>
Reserpine	Miosis Conjunctivitis	Miosis is slight, but can last up to 1 week after a single dose. <sup>80</sup> Common, secondary to dilation of conjunctival blood vessels <sup>80</sup>
<b>ANTI-INFECTIVES</b>		
Amantadine	Corneal lesions	Diffuse, white punctate subepithelial corneal opacities have been reported, occasionally associated with superficial punctate keratitis. Onset has been 1–2 weeks after initiation of therapy with dosages of 200–400 mg/day. Resolves with drug discontinuation. <sup>91</sup>
Chloramphenicol	Optic neuritis	Rare unless a total dose of 100 g and duration >6 weeks are exceeded. Vision usually improves after the drug is discontinued. <sup>80</sup>
Chloroquine	Corneal deposits  Retinopathy (macular degeneration)	Some patients using ordinary doses may develop corneal deposits in a few months. The deposits are visible with use of a biomicroscope and appear as white-yellow in color, but are of no consequence. <sup>80</sup> Serious retinopathy when total dose >100 g. Usually develops after 1–3 years; can occur in 6 months. Visual loss may be peripheral, with progression to central vision loss and disturbance of color vision. Rarely, effects such as blurred vision are seen earlier when larger doses (500–700 mg/day) are used. Macular changes may progress after drug is discontinued. These agents concentrate in pigmented tissue. <sup>80</sup>
Ethambutol	Retrobulbar neuritis	At dosages of 15 mg/kg/day, virtually void of ocular side effects. Such effects are rare at dosages of 25 mg/kg/day for a duration of a few months. Patients treated for prolonged periods should have routine visual examinations including visual fields. Most effects are reversible after the drug is discontinued, but optic neuritis may continue to progress for 1–2 months after the drug has been discontinued. <sup>80,85</sup>
Gentamicin Isoniazid	Pseudotumor cerebri Optic neuritis	Rare, but has been well documented with secondary papilledema and visual loss. <sup>8</sup> Prevalence not well defined, but appears to be significantly less than peripheral neuritis. Evaluation difficult because most patients are malnourished, chronic alcoholics, or receiving multiple medications. Preexisting eye disease does not appear to be a predisposing factor. <sup>80</sup>

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TABLE 54.5 Ocular Side Effects of Systemic Medications (Continued)

Drug Class	Effect(s)	Clinical Remarks
Nalidixic acid	Visual sensations	Most common ocular side effect. Main feature is a brightly colored appearance of objects; occurs soon after the drug is taken. Although quinolone antibiotics are nalidixic acid derivatives, they have rarely been associated with these ocular side effects. <sup>80</sup>
	Visual loss	Temporary effect (30 minutes–3 days)
	Papilledema	Primarily in infants and young children and secondary to intracranial pressure; reversible on withdrawal of the drug
Sulfonamides	Myopia	Acute and reversible; most common ocular side effect <sup>80</sup>
	Conjunctivitis	Primarily with topical sulfathiazole, 4% incidence between 5 and 9 days of therapy <sup>80</sup>
	Optic neuritis	Even in low dosages. Usually reversible with complete recovery of vision <sup>80</sup>
	Photosensitivity	Associated with use of sulfisoxazole lid margin therapy <sup>92,93</sup>
Tetracyclines	Myopia	Appears to be acute, transient, and rare <sup>80</sup>
	Papilledema	More common in children and infants than adults; rare <sup>80</sup>
Voriconazole	Altered visual perception	May be associated with higher doses or plasma concentrations <sup>94</sup>
	Blurred vision	
<b>ANTI-INFLAMMATORY AGENTS (ALSO SEE ANALGESICS; CORTICOSTEROIDS)</b>		
Cyclo-oxygenase-2 inhibitors	Blurred vision	Discontinuation of therapy leads to resolution without long-term effects. <sup>85</sup>
	Conjunctivitis	
Gold	Corneal	Deposition in the conjunctiva and superficial cornea more common than in the lens or deep cornea. Incidence in cornea of 40%–80% in total doses of 1.5 g; visual acuity is unaffected. One reported case after oral therapy <sup>80</sup>
	Conjunctival deposits	
Indomethacin	Decreased vision	Rare; also changes in color vision have been rarely reported <sup>80</sup>
Phenylbutazone	Decreased vision	Most common ocular side effect with this drug may be caused by lens hydration. <sup>80</sup>
	Conjunctivitis	Occurs less often than vision. The conjunctivitis may be associated with development of Stevens-Johnson syndrome or an allergic reaction. <sup>80</sup>
	Retinal hemorrhage	
<b>ANTILIPEMIC AGENTS</b>		
Lovastatin	Cataracts	The crystalline lenses of hypercholesteremic patients were assessed before and after 48 weeks of treatment with lovastatin 20–80 mg/day. Statistical analyses of the distribution of cortical, nuclear, and subcapsular opacities at 48 weeks showed no significant differences between placebo-treated and lovastatin-treated groups. Visual acuity assessments also were not significantly different among the groups. <sup>95</sup>
<b>ANTINEOPLASTIC AGENTS</b>		
Busulfan	Cataracts	Reported with high dosages <sup>80</sup>
Carmustine	Arterial narrowing	These ocular side effects are not well established. Evidence of delayed bilateral ocular toxicity developed in 2 of 50 patients treated with high-dose IV carmustine (800 mg/m <sup>2</sup> ). Symptoms of ocular toxicity became evident 4 weeks after IV treatment. Evidence of delayed ocular toxicity (mean onset 6 weeks) ipsilateral to the site of infusion developed in 7 of 10 patients treated with intra-arterial carotid doses of carmustine to a cumulative minimum of 450 mg/m <sup>2</sup> in two treatments. <sup>96</sup>
	Nerve fiber-layer infarcts	
	Intraretinal hemorrhages	
Cytarabine	Keratoconjunctivitis	Corneal toxicity and conjunctivitis have been reported with high-dose (3 g/m <sup>2</sup> ) therapy. <sup>97</sup>
	Ocular burning	
	Photophobia	
	Blurred vision	

TABLE 54.5 Ocular Side Effects of Systemic Medications (Continued)

Drug Class	Effect(s)	Clinical Remarks
Doxorubicin	Conjunctivitis Excessive tearing	May last for several days after treatment <sup>80</sup>
Fluorouracil	Ocular irritation Lacrimation	Reversible and seldom interfere with continued therapy <sup>80</sup>
Tamoxifen	Corneal opacities Decreased vision	Generally occurs in patients receiving more than 1 year of treatment when a total dose exceeding 100 g has been taken <sup>80</sup>
Vinca alkaloids (especially vincristine)	Retinopathy Extraocular muscle paresis (EMP) Ptosis	The onset of EMP or paralysis may be seen as early as 2 weeks. Dose related. Most recover fully when drug is discontinued. <sup>80</sup>
<b>BARBITURATES</b>		
	Miosis Mydriasis Disturbances in ocular movement Ptosis	Most significant ocular side effects occur in chronic users or in toxic states. Pupillary responses are variable; miosis seen most frequently except in toxicity when mydriasis predominates. Nystagmus and weakness in extraocular muscles may be seen. Chronic abusers have a characteristic ptosis. <sup>80</sup>
<b>BISPHOSPHONATES (ALENDRONATE, ETIDRONATE, PAMIDRONATE, RISEDRONATE)</b>		
	Blurred vision, pain, photophobia, conjunctivitis, scleritis, uveitis	Adverse events more common with pamidronate. Scleritis and uveitis are of greatest concern. After persistent reduction in vision of sustained ocular pain, refer patient to an ophthalmologist. Ocular NSAID treatment may be of symptomatic benefit. <sup>85</sup>
<b>CALCIUM-CHANNEL BLOCKERS</b>		
	Blurred vision Transient blindness	Primarily blurred vision; transient blindness at peak concentrations has been observed in several patients. <sup>98</sup>
<b>CORTICOSTEROIDS</b>		
	Cataracts	Posterior subcapsular cataracts have been associated with systemic corticosteroids in patients who have received >15 mg/day of prednisone or its equivalent daily for periods >1 year. <sup>99,100</sup> Rare reports of bilateral posterior subcapsular cataracts associated with nasal aerosol or inhalation of beclomethasone dipropionate have been received. Most patients had received therapy for >5 years, often in higher than the recommended dosage. Approximately 40% of patients were also receiving systemic corticosteroids. <sup>101</sup>
	↑ Intraocular pressure	More common with topical corticosteroids than with systemic therapy. Of little consequence in patients without preexisting glaucoma. Glaucoma patients should be monitored routinely if receiving systemic corticosteroids. <sup>80</sup>
	Papilledema	Intracranial hypertension or pseudotumor cerebri from systemic corticosteroids has been well documented. The incidence appears to be greater in children than in adults; primarily associated with chronic therapy
<b>DIGITALIS</b>		
	Altered color vision, visual acuity	Changes in color vision. A glare phenomenon and a snowy appearance in objects have been associated primarily with digitalis intoxication. In a small number of cases, reversible reduction in visual acuity has been noted. Also associated with changes in the visual fields. <sup>80</sup>
	Decreased intraocular pressure	Digitalis derivatives can decrease intraocular pressure, but clinical use for glaucoma is not practical because the therapeutic systemic dose for this effect is very near the toxic dose. <sup>80</sup>

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TABLE 54.5 Ocular Side Effects of Systemic Medications (Continued)

Drug Class	Effect(s)	Clinical Remarks
<b>DIURETICS</b>		
Carbonic anhydrase inhibitors Thiazides	Myopia	Acute myopia that may last from 24 to 48 hours. Probably caused by an increase in the anteroposterior diameter of the lens, which may be reversible even if drug use is continued. <sup>80</sup>
<b>ESTROGENS</b>		
Clomiphene	Blurred vision Mydriasis Visual field changes Visual sensations	5%–10% experience ocular side effects. Blurred vision is the most common effect, although visual sensations such as flashing lights, distortion of images, and various colored lights (primarily silver) may occur. <sup>80</sup>
Oral contraceptives (OCs)	Optic neuritis Pseudotumor cerebri Retrobulbar neuritis	Quite rare. In patients with retinal vascular abnormalities, use of OCs is questionable. Numerous other possible ocular side effects are associated with these agents, and further documentation is required. <sup>80</sup>
<b>HYPOURICEMICS</b>		
Allopurinol	Cataracts	Conflicting reports have suggested allopurinol may be associated with anterior and posterior lens capsule changes and with anterior subcapsular vacuoles; 42 cases of cataracts have been reported; these have been observed primarily in age groups in whom normal lens aging changes would not be expected. No cause-and-effect relationship has been proven. <sup>80,102</sup>
<b>IMMUNE MODULATORS</b>		
Imatinib	Visual deficits	Ocular symptoms include blurred vision, conjunctivitis, dry eyes, epiphora, and periorbital edema. The latter occurs in up to 74% of treated patients. <sup>103</sup>
Interleukin 2	Visual deficits	Interleukin 2 visual complications have occurred during the first or second treatment cycle, usually within 5–6 days of initiation of therapy. Ocular symptoms included diplopia, binocular negative scotomas (isolated areas of varying size and shape in which vision is absent or depressed; these are not perceived ordinarily, but would be apparent on completion of a visual field examination), and palinopsia (abnormal recurring visual imagery). In most cases, treatment was continued for the entire planned duration of therapy. Symptoms resolved after discontinuation <sup>104</sup>
<b>PHENOTHIAZINES</b>		
Chlorpromazine	Deposits on the lens	Rare when total dose <0.5 kg. Visible after a total dose of 1 kg in most cases; incidence may increase to 90% after ≥2.5 kg. Usually, deposits do not affect vision appreciably. The cornea and conjunctiva may be affected after the lens shows pigment changes. <sup>80</sup>
	Retinal pigment deposits	The number of reported cases is small; further documentation is necessary. <sup>80</sup>
Thioridazine	Pigmentary retinopathy	Primarily associated with maximal daily dosages or average doses >1,000 mg. Daily dosages up to 600 mg are relatively safe; 600–800 mg is uncertain, but rarely suspect. If >800 mg/day is used, periodic ophthalmoscopic examinations may uncover problems before visual acuity is compromised. <sup>80</sup>

TABLE 54.5 Ocular Side Effects of Systemic Medications (Continued)

Drug Class	Effect(s)	Clinical Remarks
<b>THERAPY FOR ERECTILE DYSFUNCTION</b>		
Sildenafil Tadalafil Vardenafil $\alpha$ -Blockers	Changes in color or light perception, blurred vision, conjunctival hyperemia, ocular pain, photophobia	Color vision alterations are mild to moderate. Blurred vision does not impair visual acuity. Visual alterations usually subside within 4 hours after the dose. <sup>105–107</sup> Ocular adverse effects are uncommon, dose dependent, and fully reversible to date. Incidence is not related to age, but is related to blood concentration. Peak visual effects usually occur within 60 minutes after ingestion. <sup>85</sup>
Alfuzosin	Visual defects	Amblyopia, blurred vision, and floppy iris have been reported. <sup>108</sup>
Tamsulosin	Floppy iris	Approximately 3% of patients taking tamsulosin for benign prostatic hyperplasia (BPH) experience floppy iris during cataract surgery. Modification of the surgical procedure usually results in successful surgery. <sup>109</sup>

CNS, central nervous system; ENT, ear, nose, and throat; NSAID, nonsteroidal anti-inflammatory drug.

## Multiple Sclerosis\*

### General Principles

- Multiple sclerosis (MS) is a chronic inflammatory and degenerative disease of the central nervous system (CNS) in which demyelination and axonal damage occur. Diagnosis typically occurs between 20 and 50 years, with the mean age at onset of 30 years.

### Classification

- MS is generally characterized as one of three main types distinguished by their natural histories.
  - **Relapsing-Remitting MS (RRMS):** the most common initial diagnosis of MS (80%–90% of patients) in which clinical disease activity alternates with periods of symptom remission
  - **Secondary-Progressive MS:** occurs in approximately 80% of patients with RRMS and is characterized by fewer relapses as disability continues to progress
  - **Primary-Progressive MS:** occurs in approximately 10% to 15% of patients and is progressive from onset with occasional minor improvements or periods of stabilization

### Patient Assessment

- Symptoms are shown in Table 55.1. The most common clinical symptoms are sensory disturbances (particularly of the extremities), partial or complete visual loss, motor dysfunction of the limbs, diplopia, and gait dysfunction.
- A number of painful neurogenic conditions have been described in association with MS (Table 55.2).
- The Expanded Disability Status Scale (EDSS) may be used to measure the level of disability and progression of disease (Table 55.3). Abnormalities on magnetic resonance imaging (MRI) and cerebrospinal fluid findings may be used for diagnosis.

### Risk Factors

- Many environmental and genetic factors have been associated with MS (Table 55.4). However, the causal nature of any of these factors has yet to be established.

### Treatment

- Currently available therapies, loosely categorized as immunomodulating agents, target the inflammatory response of disease (rather than the neurodegeneration).
- Corticosteroids are used for treatment of acute relapses to control inflammation and reduce time to recovery.

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\*The reader is referred to Chapter 55, Multiple Sclerosis, written by Melody Ryan, PharmD, MPH, in the 10th edition of *Applied Therapeutics: The Clinical Use of Drugs* for a more in-depth discussion. All notations to reference numbers are based on the reference list at the end of that chapter. The editor of this handbook expresses her thanks to Dr. Ryan and acknowledges that this chapter is based on her work.

TABLE 55.1 Common Symptoms in Chronic Multiple Sclerosis

Symptom	Prevalence (%)
Sexual dysfunction <sup>42</sup>	85
Walking problems or impaired ambulation <sup>43</sup>	64
Pain <sup>44</sup>	30–90
Bladder dysfunction <sup>45</sup>	75
Fatigue <sup>46</sup>	74
Cognitive dysfunction <sup>47</sup>	70
Spasticity <sup>44</sup>	60
Bowel dysfunction <sup>45</sup>	50
Depression <sup>48</sup>	50
Dysphagia or dysarthria <sup>49</sup>	40
Pseudobulbar affect <sup>50</sup>	10

TABLE 55.2 Types of Neurogenic Pain Associated with Multiple Sclerosis<sup>44,86</sup>

Trigeminal neuralgia—sudden, usually unilateral, severe, brief, stabbing, recurrent episodes of pain in the distribution of one or more branches of the trigeminal nerve <sup>87</sup>
Lhermitte's phenomenon—sudden onset, brief, electric shock-like sensation traveling rapidly down to the spine or into the arms or legs. Usually caused by flexing the neck. Sometimes occur occasionally for short periods
Tonic spasms
Burning dysesthesia of the limbs and trunk
Migraine headache

TABLE 55.3 Expanded Disability Status Scale

Score	Symptoms
0.0	Normal neurological examination
1.0	No disability, minimal signs in one functional system <sup>a</sup>
1.5	No disability, minimal signs in more than one functional system
2.0	Minimal disability in one functional system
2.5	Minimal disability in two functional systems
3.0	Moderate disability in one functional system or mild disability in three or four functional systems though fully ambulatory
3.5	Fully ambulatory but with moderate disability in one functional system and one or two functional systems with minimal disability OR two functional systems with moderate disability OR five functional systems with minimal disability
4.0	Fully ambulatory without aid, self-sufficient, up and about some 12 hours a day despite relatively severe disability in one functional system OR a combination of lesser disabilities that exceed previous steps; able to walk without aid or rest some 500 m
4.5	Fully ambulatory without aid, up and about much of the day, able to work a full day, may otherwise have some limitation of full activity or require minimal assistance; characterized by relatively severe disability in one functional system OR a combination of lesser disabilities that exceed previous steps; able to walk without aid or rest some 300 m
5.0	Ambulatory without aid or rest for about 200 m; disability severe enough to impair full daily activities
5.5	Ambulatory without aid for about 100 m; disability severe enough to preclude full daily activities
6.0	Intermittent or unilateral constant assistance (cane, crutch, brace) required to walk about 100 m with or without resting
6.5	Constant bilateral assistance (canes, crutches, braces) required to walk about 20 m without resting
7.0	Unable to walk beyond approximately 5 m even with aid, essentially restricted to wheelchair; wheels self in standard wheelchair and transfers alone; up and about in wheelchair some 12 hours a day
7.5	Unable to take more than a few steps; restricted to wheelchair; may need aid in transfer; wheels self but cannot carry on in standard wheelchair a full day; may require motorized wheelchair

Continued on following page



TABLE 55.3 Expanded Disability Status Scale (Continued)

Score	Symptoms
8.0	Essentially restricted to bed or chair or perambulated in wheelchair, but may be out of bed itself much of the day; retains many self-care functions; generally has effective use of arms
8.5	Essentially restricted to bed much of the day; has some effective use of arm(s); retains some self-care functions
9.0	Helpless bed patient; can communicate and eat
9.5	Totally helpless bed patient; unable to communicate effectively or eat and swallow
10.0	Death attributable to MS

\*Functional systems are categorized as pyramidal, cerebellar, brainstem, sensory, bowel and bladder, visual, and cerebral or mental.

Source: Adapted with permission from Kurtzke JF. Rating neurologic impairment in multiple sclerosis: an expanded disability status scale (EDSS). *Neurology*. 1983;33:1444.

TABLE 55.4 Factors Associated with Multiple Sclerosis

Female sex <sup>3,29</sup>	Low sun exposure <sup>30,31</sup>
Caucasians <sup>32</sup>	Low serum concentrations of vitamin D (25-hydroxyvitamin D) <sup>31</sup>
Higher latitudes of residence <sup>33</sup>	Northern European heritage <sup>22</sup>
High serum antibody titers to the Epstein–Barr virus nuclear antigens <sup>34,35</sup>	Tobacco smoking <sup>36</sup>

TABLE 55.5 Patient Characteristics and Other Factors Associated with Reduced Adherence to Beta-Interferons or Glatiramer Acetate<sup>126–128</sup>

Secondary-progressive MS	Younger age
Female sex	Cognitive impairment
Depression	Perceived lack of efficacy
Unrealistic expectations	Adverse effects
Inconvenience	Needle phobia
Lifestyle or economic instability	Lack of family or other support

MS, multiple sclerosis.

- FDA-approved agents for the treatment of RRMS include beta-interferons, glatiramer acetate, mitoxantrone, natalizumab, and fingolimod. Patient characteristics and other factors associated with poor adherence are shown in Table 55.5.
- No treatment is FDA-approved for the treatment of primary-progressive MS.
- Rates of relapse for women with MS decreases during pregnancy, increases in the first 3 months after delivery, and then returns to the prepregnancy rate. No treatment for MS is recommended for use during pregnancy. In general, MS therapy should be discontinued before conception.

## Drug Therapy

- **Beta-interferons** work through several different mechanisms of immune modulation. Two types of beta-interferons are available: interferon  $\beta$ -1a and interferon  $\beta$ -1b. These products exist as three different preparations (Table 55.6).
  - Interferon  $\beta$ -1a (subcutaneous route) has a dose titration (20% of full dose for 2 weeks, 50% of full dose for 2 weeks, then 100% of full dose thereafter).

TABLE 55.6 Interferon  $\beta$  Preparations Used in the Treatment of Multiple Sclerosis<sup>62–64</sup>

Interferon Type	Route of Administration	Frequency of Injection
Interferon $\beta$ -1a	Intramuscular	Weekly
Interferon $\beta$ -1a	Subcutaneous	Three times weekly
Interferon $\beta$ -1b	Subcutaneous	Every other day

- Interferon  $\beta$ -1b requires a dose titration (25% of the full dose for 2 weeks, 50% of full dose for 2 weeks, 75% of full dose for 2 weeks, then full dose thereafter).
- Adverse effects with interferon  $\beta$  include leucopenia, injection site reactions, necrosis, flulike symptoms, breakthrough menstrual bleeding, and increased liver function tests.
- **Corticosteroids:** The most common IV regimen for acute relapses is methylprednisolone 500 to 1,000 mg daily for 3 to 5 days with or without a subsequent regimen of tapering using oral steroids for 1 to 3 weeks. The recommended oral dose for acute relapses is prednisone 1,250 mg every other day for 5 doses.
- **Fingolimod** is the first oral medicine for MS that acts by suppressing T-cell activity. Patients with preexisting sinus bradycardia or heart block without pacemakers should not receive therapy. Baseline testing and monitoring recommendations are shown in Table 55.7.
- **Dalfampridine** is an oral potassium channel blocker approved for the treatment in improving walking in patients with MS. Dalfampridine is associated with a dose-dependent risk of seizure. Seizures may occur within days to weeks after treatment initiation and have been reported more frequently in patients with no history of seizure (Table 55.8).
- **Glatiramer acetate** decreases type 1 helper T cells while increasing type 2 helper T cells.
  - Glatiramer is dosed at 20 mg SQ daily, with no dosage titration needed.
  - See Table 55.9 for important counseling points.
  - Common adverse events are injection site reactions and postinjection systemic reactions (facial flushing, chest tightness, dyspnea palpitations, tachycardia, anxiety).
- **Mitoxantrone** works as a general immunomodulator, decreasing monocytes and macrophages and inhibiting T and B cells. It is dosed at 12 mg/m<sup>2</sup> given as a 5- to 15-minute

TABLE 55.7 Baseline Testing and Monitoring Associated with Fingolimod<sup>141</sup>**BASELINE**

- Varicella zoster immunity evaluation or vaccination
- Ophthalmology evaluation for macular edema
- Dermatologic evaluation for melanomas
- Forced expiratory volume in 1 second (FEV<sub>1</sub>) or full pulmonary function testing, if patient has history of asthma or COPD
- Pulse and blood pressure
- Complete blood count
- Liver function tests

**MONITORING**

- Observe in clinical area for 6 hours after initial dose with monitoring of blood pressure and pulse
- Ophthalmology evaluation at 4 months and as needed thereafter
- Complete blood count every 6 months
- Liver function tests every 6 months
- Dermatologic evaluation as needed
- FEV<sub>1</sub> as needed

COPD, chronic obstructive pulmonary disease.

intravenous infusion every 3 months. Cardiotoxicity limits the lifetime dose to 140 mg/m<sup>2</sup>. Common adverse effects include nausea, menstrual abnormalities, alopecia, upper respiratory and urinary tract infections, neutropenia, and temporary blue color change to urine and sclera. See Table 55.10 for monitoring requirements.

- **Natalizumab** is a humanized monoclonal antibody that blocks T-cell entry into the CNS. Recommendations for use are shown in Table 55.11. Adverse effects include fatigue, liver dysfunction, infections, hypersensitivity reactions, and infusion-related reactions.

TABLE 55.8 Baseline Testing and Monitoring Associated with Dalfampridine

**BASELINE**

- Renal function
- History of seizure

**MONITORING**

Renal function annually  
 EEG  
 Walking ability  
 Seizure occurrence

TABLE 55.9 Patient Counseling Points for Interferon  $\beta$  and Glatiramer Acetate Products<sup>62–64</sup>

**FOR ALL PRODUCTS:**

Use clean technique—wash hands with soap and water, clean injection site with an alcohol swab, do not touch site or needle tip to other surfaces or with fingers.

Choose an appropriate site:

For subcutaneous injection—fleshy part of upper back arm, front of thighs, lower abdomen, fleshy area of upper hip.

For intramuscular injection—front of thigh, side of thigh, upper arm.

Rotate between injection sites to avoid overuse of any one site.

Examine the reconstituted product for particles, cloudiness, or color changes. The products should be colorless to light yellow.

For subcutaneous injection—pinch up a fold of skin between index finger and thumb for the injection.

For intramuscular injection—stretch the skin between index finger and thumb for the injection.

Insert the needle at a 90° angle to the skin.

Release the skin.

Steadily push down on the plunger until all of the medicine is injected.

Pull needle straight out of skin and dispose of it in a hard-walled plastic container.

TABLE 55.10 Monitoring Required for Mitoxantrone Use<sup>152</sup>

**BASELINE AND BEFORE EACH DOSE**

- Left ventricular ejection fraction
- Complete blood count
- Liver function tests
- Pregnancy test, in women

**ONGOING**

- Left ventricular ejection fraction yearly to monitor for late development of cardiotoxicity

TABLE 55.11 Recommendations for Use of Natalizumab<sup>146,150,155</sup>**PATIENTS WHO SHOULD NOT RECEIVE NATALIZUMAB**

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- Immunocompromised
  - Active viral hepatitis
  - Active malignancy that requires treatment
  - Inability to get MRI
- 

**RECOMMENDATIONS FOR USE**

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- Monotherapy with natalizumab only
  - After failure of interferon or glatiramer acetate
  - Therapy-free interval of 14 days after interferon or glatiramer acetate, 3 months after azathioprine, or 6 months after mitoxantrone
- 

**BASELINE TESTING**

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- Clinical neurological examination
  - Human immunodeficiency virus testing
  - Complete blood count
  - Liver function tests
  - MRI with IV contrast
- 

**MONITORING**

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- Neurological examination at 3 months, 6 months, and then yearly
  - MRI with IV contrast at 6 months and then yearly
- 

IV, intravenous; MRI, magnetic resonance imaging.

# Headache\*

## General Principles

- Headache is a symptom caused by a variety of disorders.

## Classification

- **Primary headache disorders** are characterized by the lack of an identifiable and treatable underlying cause (e.g., migraine, tension-type, cluster headaches). Classification of primary headaches is shown in Table 56.1.
- **Secondary headache disorders** are associated with a variety of organic causes (e.g., trauma, cerebrovascular malformations, brain tumors, central nervous system [CNS] infection).

## Treatment

- Drug therapy for headache is divided into two types: (1) abortive therapy to provide relief during an acute attack and (2) prophylactic therapy to prevent or reduce severity of recurrent attacks.

## Migraine

- Migraines are defined as paroxysmal attacks of moderate-to-severe, throbbing headache with associated symptoms that may include nausea, vomiting, and photophobia or phonophobia. They are subclassified according to the presence or absence of aura symptoms (a complex of focal neurologic symptoms that accompany the migraine attack).
- Head pain usually begins as a dull ache that intensifies over minutes to hours to a throbbing headache that may last up to 72 hours. Pain is usually intense enough to interfere with daily activities.
- **Treatment**
  - Eliminate or avoid factors that can precipitate an attack (Table 56.2).
  - Abortive therapy is aimed at relieving headache pain and associated symptoms. Options include triptans, ergot derivatives, analgesics, sedatives, and antiemetic agents. Selection of agents is based on level of disability and presence of associated symptoms.
  - Intractable migraine with associated vomiting usually requires parenteral therapy with ergot derivatives, sumatriptan, or potent narcotic analgesics (Table 56.3). While parenteral narcotic analgesics relieve intractable migraine headache pain, their use should be reserved for patients who fail to respond to parenteral therapies for migraine.
  - **Triptans** (Table 56.4) are considered first-line therapy for patients who do not respond to nonprescription agents. They are effective when given 4 hours or longer after the onset of headache. Repeat dosing may be needed for recurrent attacks. The potential for drug interactions should be considered. A nonoral option (e.g., subcutaneous, intranasal) should be used if vomiting is present.

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\*The reader is referred to Chapter 56, Headache, written by Brian K. Alldredge, PharmD, in the 10th edition of *Applied Therapeutics: The Clinical Use of Drugs* for a more in-depth discussion. All notations to reference numbers are based on the reference list at the end of that chapter. The editor of this handbook expresses her thanks to Dr. Alldredge and acknowledges that this chapter is based on his work.

TABLE 56.1 Classification of Primary Headaches

**MIGRAINE**

Migraine without aura  
Migraine with aura

**TENSION-TYPE HEADACHE**

Episodic tension-type headache  
Chronic tension-type headache

**CLUSTER HEADACHE**

Episodic cluster headache  
Chronic cluster headache

**OTHER PRIMARY HEADACHES**

Cough headache  
Exertional headache

TABLE 56.2 Factors that May Precipitate Migraine Headache

Stress  
Emotion  
Glare  
Hypoglycemia  
Altered sleep pattern  
Menses  
Exercise  
Alcohol  
Carbon monoxide  
Excess caffeine use or withdrawal  
Foods containing:  
  MSG (e.g., Chinese food, canned soups, seasonings)  
  Tyramine (e.g., red wine, ripened cheeses)  
  Nitrites (e.g., cured meat products)  
  Phenylethylamine (e.g., chocolate, cheese)  
  Aspartame (e.g., artificial sweeteners, diet sodas)  
Drugs  
  Excess use or withdrawal (ergots, triptans, analgesics)  
  Estrogens (e.g., oral contraceptives)  
  Cocaine  
  Nitroglycerin

MSG, monosodium glutamate.

TABLE 56.3 Drug Treatment of Acute Migraine Headache<sup>a</sup>

Drug	Route	Dose	Contraindications	Adverse Effects	Comments
Sumatriptan (Imitrex)	PO, IN, SC	6 mg SC stat; may repeat in 1 hour	Ischemic heart disease, within 24 hours of ergot alkaloids	Heavy sensation in head or chest, tingling pain at injection site	First-line therapy for moderate to severe headaches; SC for intractable migraine
Ketorolac	IV, IM	30 mg IV or 60 mg IM	Aspirin- or NSAID-related bronchospasm	N, V, bleeding, renal dysfunction	First-line therapy for moderate to severe headaches

*Continued on following page*

TABLE 56.3 Drug Treatment of Acute Migraine Headache<sup>a</sup> (Continued)

Drug	Route	Dose	Contraindications	Adverse Effects	Comments
Dihydroergotamine (Migranal)	IN, IM, IV	2 mg IN stat; repeat in 15 minutes	See Ergotamine	Rhinitis, dizziness, N, V	For moderate to severe headaches; parenteral use for intractable migraine
Ergotamine tartrate (Cafergot)	PO, SL, PR	1–4 mg stat, then 1–2 mg every 30 minutes to maximum of 6 mg/attack or 10 mg/week	CV disease, sepsis, liver or kidney disease, arterial insufficiency, pregnancy, breast-feeding, concomitant macrolide use	N, V, anorexia, limb paresthesias or pain	Use at HA onset for max effect; ↓ N and V by using smallest effective dose
Prochlorperazine (Compazine)	IM, IV	10 mg stat	CV disease	Extrapyramidal reactions, sedation, dizziness	IV/IM for adjunctive antiemetic therapy; IV for antimigraine effect in intractable migraine
Chlorpromazine (Thorazine)	IM	1 mg/kg	CV disease, history of seizures	Extrapyramidal reactions, sedation, hypotension	For intractable migraine; also has antiemetic properties
Metoclopramide (Reglan)	PO, IM	10 mg stat	GI hemorrhage or obstruction; pheochromocytoma	Extrapyramidal reactions, sedation, restlessness	For adjunctive antiemetic therapy; prochlorperazine also effective

<sup>a</sup>See text for references and additional details. See Table 56.4 for additional information on sumatriptan and other triptan agents.

CV, cardiovascular; GI, gastrointestinal; HA, headache; ICP, intracranial pressure; IM, intramuscular; IN, intranasal; IV, intravenous; N, nausea; NSAID, nonsteroidal anti-inflammatory drug; PO, oral; PR, rectal; SC, subcutaneous; SL, sublingual; V, vomiting.

- **Ergotamine** is an alternative agent that must be taken at the earliest sign of an attack. While typically more affordable than triptans, its use is limited by potentially serious side effects (contraindicated in patients with cardiac, peripheral, and cerebrovascular disease; sepsis, liver, and kidney disease; pregnancy and lactation). Nausea, vomiting, and anorexia are common side effects.
- **Antiemetics:** Metoclopramide is the antiemetic of choice (10 mg orally as soon as possible; IV therapy for severe attacks). Phenothiazine antiemetics are also effective.
- **Nonsteroidal anti-inflammatory agents (NSAIDs)** and combination analgesics are reasonable treatment options for patients with mild-to-moderate headache or for patients with severe attacks who have responded to these agents in the past. Concomitant use of metoclopramide can enhance their absorption, providing more effective and rapid pain relief.

TABLE 56.4 Clinical and Pharmacokinetic Features of the Triptans for Acute Migraine Headache

Drug	Route	Bioavailability (%)	T <sub>max</sub> (hours)	Half-Life (hours)	Response Rate at 2 hours (%)	HA Recurrence within 24–48 hours (%)	Dose/Attack (mg)	Maximal Dose in 24 hours (mg)
Sumatriptan (Imitrex)	PO	14	1.2–2.3	2.5	50–69	25–41	25–100	200
	IN	—	1–1.5	2.5	62–78	10–40	5–40	40
	SC	96	0.2	2.5	63–82	10–40	6–12	12
Zolmitriptan (Zomig)	PO <sup>a</sup>	40–46	1.5	3	62–67	22–37	2.5–10	10
	IN	100	3	3	69	—	5–10	10
Naratriptan (Amerge)	PO	60–70	3–5	6	43–49	17–28	1–5	5
Rizatriptan (Maxalt)	PO <sup>a</sup>	40–45	1.3	2–3	60–77	35–47	5–20	30
Almotriptan (Axert)	PO	70	1–3	3–4	55–65	18–30	6.25–25	25
Frovatriptan (Frova)	PO	20–30	2–4	26	37–46	7–25	2.5–5	7.5
Eletriptan (Relpax)	PO	50	2	4	47–65	6–34	20–40	80

<sup>a</sup>Also available in an orally disintegrating wafer dosage form.

HA, headache; IN, intranasal; PO, oral; SC, subcutaneous.

Sources: Headache Classification Subcommittee of the International Headache Society. The international classification of headache disorders: 2nd ed. *Cephalalgia*. 2004;24(Suppl 1):9; Géraud G et al. Migraine headache recurrence: relationship to clinical, pharmacological, and pharmacokinetic properties of triptans. *Headache*. 2003;43:376.



- **Prophylaxis**

- Effective prophylactic therapy can reduce the frequency of migraine attacks and the severity of ensuing attacks. Prophylaxis is recommended for patients with headaches that affect life despite use of abortive therapy, headaches occurring more than twice monthly, disabling headaches that are unresponsive to abortive therapy, and frequent, prolonged, or bothersome auras.
- Drugs that are more established for migraine prophylaxis are shown in Table 56.5.
- Medication overuse, defined as use of migraine therapies 10 or more days per month, can increase the frequency and intensity of migraine and other headache types. In general, abortive therapies should not be used more than twice weekly.

TABLE 56.5 Drugs Useful for Migraine Headache Prophylaxis<sup>a</sup>

Drug	Dose	Dosage Forms/ Strengths	Effectiveness	Comments
Propranolol (Inderal)	20 mg BID–TID; gradually ↑ dose at weekly intervals to effect or maximum of 320 mg/day	Tab: 10, 20, 40, 60, 80, 90 mg ER Cap: 60, 80, 120, 160 mg	50%–80% obtain complete or partial relief; comparable to methysergide	First-line therapy; atenolol, metoprolol, and timolol also effective
Amitriptyline (Elavil)	10–25 mg HS; ↑ by 10–25 mg/day at weekly intervals to maximum of 150 mg/day; most should benefit from 50–75 mg/day	Tab: 10, 25, 50, 75, 100, 150 mg	Effectiveness comparable to propranolol and methysergide	First-line therapy; effective for prophylaxis of migraine and tension-type headache
Valproate (Depakote)	250 mg BID; ↑ by 250 mg/day at weekly intervals to effect or adverse effects; most should benefit from 1,000–2,000 mg/day	Cap <sup>b</sup> : 250 mg DR Tab <sup>c</sup> : 125, 250, 500 mg ER Tab: 250, 500 mg SCaps: 125 mg	50% obtain complete or partial relief	First-line therapy
Topiramate (Topamax)	25 mg daily (in evening); ↑ by 25 mg/day up to 100 mg/day (given BID)	Tabs: 25, 50, 100 mg SCaps: 15, 25 mg	Headache frequency significantly reduced; efficacy comparable to propranolol	First-line therapy
Verapamil (Isoptin, Calan)	80 mg TID. If needed, ↑ dose gradually to max of 480 mg/day	Tabs: 40, 80, 120 mg ER Cap: 120, 240 mg ER Tab: 180, 240 mg	50% obtain complete or partial relief	Second-line therapy Delay of 1–2 months for maximal effect
Naproxen sodium	550 mg BID	Tab: 220, 275, 550 mg	30% obtain complete or partial relief	Second-line therapy Modest efficacy; effective for menstrual migraine; naproxen, flurbiprofen, ketoprofen, mefenamic acid also effective

<sup>a</sup>See text for references and additional details.<sup>b</sup>Valproic acid capsules.<sup>c</sup>Divalproex sodium delayed-release tablets.

BID, twice daily; Cap, capsules; DR, delayed release; ER, extended release; HS, every evening at bedtime; SCap, sprinkle capsules containing coated particles; Tab, tablets; TID, three times a day.

## Cluster Headaches

- Cluster headaches are headaches of short duration (typically 15–180 minutes) that present as severe, unrelenting, unilateral pain occurring behind the eye with radiation to the territory of the ipsilateral trigeminal nerve (temple, cheek, or gum). Aura and nausea/vomiting are not present.
- Precipitating factors can include alcohol, vasodilating drugs, stress, warm weather, missed meals, or excessive sleep.
- **Treatment**
  - Treatment of choice is sumatriptan (subcutaneous); zolmitriptan (nasal) and oxygen inhalation are alternatives (Table 56.6).
- **Prophylaxis**
  - Drugs for prophylaxis are shown in Table 56.7.

## Tension-Type Headaches

- Tension-type headache is characterized by a dull, aching sensation bilaterally that occurs in a hatband distribution around the head. Pain is usually mild to moderate in severity (not usually of sufficient severity to interfere with daily activities) and has a nonpulsating quality. Aura and nausea/vomiting are not present.
- Three subtypes exist based on frequency of attacks: infrequent, frequent-episodic, and chronic.
- **Treatment**
  - Nondrug techniques (e.g., massage, physical therapy, hot baths, acupuncture) are often effective adjuncts to drug therapy.
  - Analgesics are the drugs of choice for acute attacks. Acetaminophen, aspirin, and NSAIDs are all often effective.
  - Sedatives (e.g., butalbital), anxiolytics (e.g., meprobamate, diazepam), and skeletal muscle relaxants (e.g., orphenadrine) have been used.
- **Prophylaxis**
  - Antidepressants are the most useful agents for prophylaxis. Amitriptyline is the drug of choice (initiated at 10–25 mg/day at bedtime, increasing gradually as needed). Mirtazapine (30 mg/day) or venlafaxine (150 mg/day) are reasonable alternatives for patients who fail to respond to or are intolerant of amitriptyline.

TABLE 56.6 Drugs Recommended for Acute Treatment of Cluster Headache<sup>a</sup>

Drug	Route	Dose	Contraindications	Adverse Effects	Comments
Sumatriptan (Imitrex)	SC	6 mg at HA onset	Ischemic heart disease, within 24 hours of ergot alkaloids	Heavy sensation in head or chest, tingling pain at injection site	Not an FDA-approved indication; costly but well tolerated
Zolmitriptan (Zomig)	IN	5–10 mg at HA onset	Ischemic heart disease, within 24 hours of ergot alkaloids	Bad taste, nasal irritation, somnolence	Not an FDA-approved indication; onset likely slower than SC sumatriptan although no direct comparisons performed
Oxygen	Inhalation	6–12 L/minute for 15 minutes			Fast onset of effect

<sup>a</sup>Class I randomized controlled trials document the effectiveness of these therapies. See text for references and additional details.

FDA, Food and Drug Administration; HA, headache; IN, intranasal; SC, subcutaneous.

TABLE 56.7 Drugs for Prophylaxis of Cluster Headache<sup>a</sup>

Drug	Dose	Route	Comments
Suboccipital steroid injection	12.46 mg betamethasone dipropionate and 5.26 mg betamethasone disodium phosphate with 0.5 mL 2% lidocaine	Suboccipital injection (near periosteum)	RCT demonstrated efficacy compared with placebo. Response evident within 72 hours
Civamide	100 $\mu$ L of 0.025% civamide into each nostril daily $\times$ 7 days	IN	Civamide is investigational agent that may become available soon. RCT demonstrated efficacy compared with placebo. Response lasts for 20 days after treatment.
Verapamil	360 mg/day divided TID–QID	PO	Two RCTs support efficacy for reduction in cluster headache. Verapamil may be more effective than lithium
Lithium carbonate	800–900 mg daily	PO	RCTs support some efficacy
Melatonin	10 mg daily $\times$ 2 weeks	PO	Efficacy demonstrated in 1 RCT; patients with chronic cluster headache did not respond
Prednisone	20 mg every other day	PO	Supportive evidence is limited. May be considered for short bouts of cluster HA owing to long-term adverse effects

<sup>a</sup>See text for references and additional details.

IN, intranasal; HA, headache; PO, oral; QID, four times a day; RCT, randomized controlled trial; TID, three times a day.

# Parkinson Disease and Other Movement Disorders\*

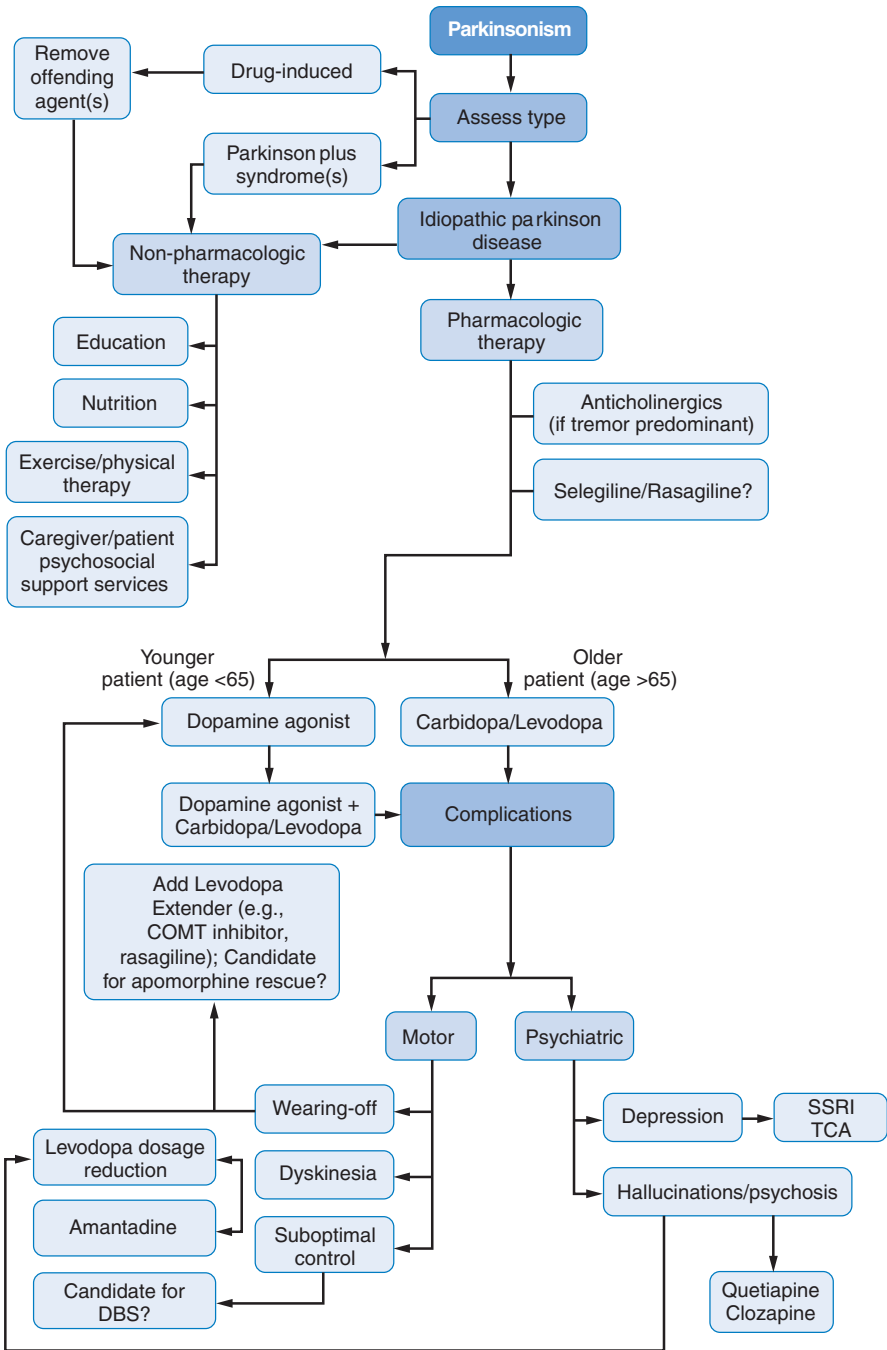
## Parkinson Disease

- Parkinson disease is a chronic, progressive movement disorder resulting from loss of dopamine from the nigrostriatal tracts in the brain. Age of onset is variable (mean of 55 years; range, 50–80 years).
- Effective symptomatic treatments improve quality of life and life expectancy; no cure exists.
- **Patient Assessment**
  - Diagnosis requires a careful history and physical examination. A therapeutic trial of levodopa can confirm the diagnosis.
  - Classic features include tremor, limb rigidity, bradykinesia, and postural disturbances. Patients may develop a masked face or blank stare with reduced eye blinking. Symptoms are progressive, with significant immobility seen in most patients within 10 to 20 years (Table 57.1).
  - Advanced disease is characterized by motor fluctuations including a gradual decline in “on time” and the development of troubling dopaminergic-induced dyskinesias.
  - Drugs that antagonize dopaminergic D<sub>2</sub>-receptors (e.g., neuroleptics, prochlorperazine, and metoclopramide), valproate, amiodarone, phenytoin, and lithium may cause a state of drug-induced parkinsonism.
- **Treatment** should begin when the patient begins to experience functional impairment. An algorithm for management is shown in Figure 57.1. Supportive care including exercise, physiotherapy, nutritional support, psychological support, and support of family members is vital to the overall treatment plan.
  - Drug therapy is aimed primarily at replenishing the supply of dopamine (Table 57.2) through one or a combination of mechanisms.
  - Guidelines support either dopamine agonists (Table 57.3) or levodopa as initial therapy. Levodopa remains the most effective agent; monotherapy is limited by response fluctuations, declining efficacy with disease progression, and undesirable side effects. Levodopa drug interactions must also be considered (Table 57.4).
  - Catechol-O-methyltransferase (COMT) inhibitors can increase the amount of levodopa available (Table 57.5).

TABLE 57.1 Staging of Disability in Parkinson Disease

Stage 1	Unilateral involvement only; minimal or no functional impairment
Stage 2	Bilateral involvement, without impairment of balance
Stage 3	Evidence of postural imbalance; some restriction in activities; capable of leading independent life; mild to moderate disability
Stage 4	Severely disabled, cannot walk and stand unassisted; significantly incapacitated
Stage 5	Restricted to bed or wheelchair unless aided

\*The reader is referred to Chapter 57, Parkinson Disease and Other Movement Disorders, written by Michael E. Ernst, PharmD, BCPS, FCCP, and Mildred D. Gottwald, PharmD, in the 10th edition of *Applied Therapeutics: The Clinical Use of Drugs* for a more in-depth discussion. All notations to reference numbers are based on the reference list at the end of that chapter. The editor of this handbook expresses her thanks to Drs. Ernst and Gottwald and acknowledges that this chapter is based on their work.



**Figure 57.1** Suggested treatment algorithm for the management of Parkinson disease. DBS, deep brain stimulation. (Modified with permission from the American College of Clinical Pharmacy. Ernst ME. Parkinson’s disease. In: Dunsworth T et al, eds. *Pharmacotherapy Self-Assessment Program*. 6th ed. Lenexa, KS: American College of Clinical Pharmacy; 2007:22. Neurology and Psychiatry module.)

TABLE 57.2 Medications Used for the Treatment of Parkinson Disease

Generic (Trade) Name	Dosage Unit	Titration Schedule	Usual Daily Dose	Adverse Effects
Amantadine (Symmetrel)	100-mg capsule Liquid: 50 mg/5 mL	100 mg every day; increased by 100 mg 1–2 weeks	100–300 mg	Orthostatic hypotension, insomnia, depression, hallucinations, livedo reticularis, xerostomia
<b>ANTICHOLINERGIC AGENTS</b>				
Benzotropine (Cogentin)	0.5-, 1-, and 2-mg tablets Injection: 2 mL (1 mg/mL)	0.5 mg/day increased by 0.5 mg every 3–5 days	1–3 mg given every day to BID	Constipation, xerostomia, dry skin, dysphagia, confusion, memory impairment
Trihexyphenidyl (Artane)	2- and 5-mg tablets Liquid: 2 mg/5 mL	1–2 mg/day increased by 1–2 mg every 3–5 days	6–15 mg divided TID to BID	Constipation, xerostomia, dry skin, dysphagia, confusion, memory impairment
<b>COMBINATION AGENTS</b>				
Carbidopa-Levodopa (immediate-release)/Entacapone (Stalevo)	12.5/50/200, 25/100/200, and 37.5/150/200 mg tablets	Titrate with individual dosage forms (carbidopa/levodopa and entacapone) first, then switch to combination tablet	Varies (see listings for individual drugs)	See listing for individual drugs
<b>DOPAMINE REPLACEMENT</b>				
Carbidopa-Levodopa (Regular) (Sinemet)	10/100, 25/100, and 25/250 tablets	25/100 mg BID, increased by 25/100 weekly to effect and as tolerated	30/300 to 150/1,500 divided TID to QID	Nausea, orthostatic hypotension, confusion, dizziness, hallucinations, dyskinesias, blepharospasm
Carbidopa-Levodopa (CR) (Sinemet CR)	25/100 and 50/200 tablets	25/100 mg BID (spaced at least 6 hours apart), increased every 3–7 days	50/200 to 500/2,000 divided QID	Same as regular Sinemet
Carbidopa-Levodopa ODT (Parcopa)	10/100, 25/100, and 25/250 mg tablets	25/100 BID, increased every 1–2 days; if transferring from regular levodopa (<1,500 mg/day), start 25/100 mg TID to QID (start 25/250 mg TID to QID if already on >1,500 mg/day of regular levodopa)	25/100 to 200/2,000 divided TID to QID	Same as regular Sinemet; may occur more rapidly than with regular Sinemet
<b>DOPAMINE AGONISTS</b>				
Bromocriptine (Parlodel)	2.5-mg tablet, 5-mg capsule	1.25 HS, titrate slowly as tolerated for 4–6 weeks	10–40 mg divided TID	Orthostatic hypotension, confusion, dizziness, hallucinations, nausea, leg cramps; retroperitoneal, pleural, pericardial fibrosis; cardiac valve thickening

Continued on following page

TABLE 57.2 Medications Used for the Treatment of Parkinson Disease (Continued)

Generic (Trade) Name	Dosage Unit	Titration Schedule	Usual Daily Dose	Adverse Effects
Pramipexole (Mirapex, Mirapex ER)	0.125-, 0.25-, 0.50-, 1-, 1.5-mg tablets 0.375-, 0.75-, 1.5-, 3-, 4.5-mg tablets (ER)	0.375 divided TID; titrate weekly by 0.125–0.25 mg/dose	1.5–4.5 mg divided TID	Orthostatic hypotension, confusion, dizziness, hallucinations, nausea, somnolence
Ropinirole (Requip, Requip XL)	0.25-, 0.5-, 1-, 2-, 4-, 5-mg tablet 2-, 4-, 6-, 8-, 12-mg tablets (XL)	Titrate weekly by 0.25 mg/dose	3–12 mg divided TID	Orthostatic hypotension, confusion, dizziness, hallucinations, nausea, somnolence
Apomorphine (Apokyn)	10 mg/mL injection	Initial 2-mg test dose, then begin 1 mg less than tolerated test dose; increase by 1 mg every few days; approved for “rescue” during periods of hypomobility	2–6 mg TID	Nausea, vomiting; administer with trimethobenzamide (not 5-hydroxytryptamine-3 [5-HT <sub>3</sub> ] antagonists)
Rotigotine (Neupro) <sup>a</sup>	2-, 4-, 6-mg/24 hour transdermal delivery system	2 mg/24 hour; titrate weekly by 2 mg/24 hour until response noted or maximal dose of 6 mg/24 hour reached. Application site should be rotated daily between abdomen, thigh, hip, flank, shoulder, or upper arm	4–6 mg/24 hour	Hallucinations, abnormal dreaming, insomnia, somnolence, nausea, vomiting, application site reactions; avoid in patients with known sulfite sensitivity
<b>COMT INHIBITORS</b>				
Entacapone (Comtan)	200-mg tablet	One tablet with each administration of levodopa/carbidopa, up to 8 tablets daily	3–8 tablets daily	Diarrhea, dyskinesias, abdominal pain, urine discoloration
Tolcapone (Tasmar)	100-, 200-mg tablet	100–200 mg TID	300–600 mg divided TID	Diarrhea, dyskinesias, abdominal pain, urine discoloration, hepatotoxicity
<b>MAO-B INHIBITORS</b>				
Selegiline (Eldepryl) <sup>b</sup>	5-mg tablet, capsule	5 mg AM; may increase to 5 mg BID	5–10 mg (take 5 mg with breakfast and 5 mg with lunch)	Insomnia, dizziness, nausea, vomiting, xerostomia, dyskinesias, mood changes; use caution when coadministered with sympathomimetics or serotonergic agents (increased risk of serotonin syndrome); avoid tyramine-containing foods

TABLE 57.2 Medications Used for the Treatment of Parkinson Disease (Continued)

Generic (Trade) Name	Dosage Unit	Titration Schedule	Usual Daily Dose	Adverse Effects
Selegiline ODT (Zelapar)	1.25-mg tablet	1.25 mg every day; may increase to 2.5 mg every day after 6 weeks	1.25–2.5 mg every day	Insomnia, dizziness, nausea, vomiting, xerostomia, dyskinesias, mood changes; use caution when coadministered with sympathomimetics or serotonergic agents (increased risk of serotonin syndrome); avoid ingestion of large amounts of tyramine-containing foods
Rasagiline (Azilect)	0.5-mg tablet	0.5 mg every day; may increase to 1 mg every day	0.5–1 mg/day	Similar to selegiline

<sup>a</sup>Not currently available in the United States.

<sup>b</sup>A transdermal formulation is also available, but not approved for use in PD.

BID, twice daily; COMT, catechol-O-methyltransferase; HS, bedtime; MAO-B, monoamine oxidase type B; ODT, orally disintegrating tablet; QID, four times daily; TID, three times daily.

TABLE 57.3 Pharmacologic and Pharmacokinetic Properties of Dopamine Agonists

	Bromocriptine	Pramipexole	Ropinirole	Apomorphine	Rotigotine <sup>a</sup>
Type of compound	Ergot derivative	Nonergoline	Nonergoline	Nonergoline	Nonergoline
Receptor specificity	D <sub>2</sub> , D <sub>1</sub> , <sup>b</sup> α <sub>1</sub> , α <sub>2</sub> , 5-HT	D <sub>2</sub> , D <sub>3</sub> , D <sub>4</sub> , α <sub>2</sub>	D <sub>2</sub> , D <sub>3</sub> , D <sub>4</sub>	D <sub>1</sub> , D <sub>2</sub> , D <sub>3</sub> , D <sub>4</sub> , D <sub>5</sub> , α <sub>1</sub> , α <sub>2</sub> , 5-HT <sub>1</sub> , 5-HT <sub>2</sub>	D <sub>1</sub> , D <sub>2</sub> , D <sub>3</sub> , 5-HT <sub>1</sub>
Bioavailability	8%	>90%	55% (first-pass metabolism)	<5% orally; 100% subcutaneous	<1% orally
T <sub>max</sub> (minutes)	70–100	60–180	90	10–60	15–18 (hours); no characteristic peak observed
Protein binding	90%–96%	15%	40%	>99.9%	89.5%
Elimination route	Hepatic	Renal	Hepatic	Hepatic and extrahepatic	Hepatic
Half-life (hours)	3–8	8–12	6	0.5–1	3

<sup>a</sup>Not currently available in the United States.

<sup>b</sup>Antagonist.

5-HT, serotonin.

TABLE 57.4 Levodopa Drug Interactions

Drug	Interaction	Mechanism	Comments
Anticholinergics	↓ Levodopa effect	↓ Gastric emptying, thus ↑ degradation of levodopa in gut, and ↓ amount absorbed	Watch for ↓ levodopa effect when anticholinergics used in doses sufficient to ↓ GI motility. When anticholinergic therapy discontinued in a patient on levodopa, watch for signs of levodopa toxicity.

*Continued on following page*



TABLE 57.4 Levodopa Drug Interactions (Continued)

Drug	Interaction	Mechanism	Comments
Benzodiazepines	↓ Levodopa effect	Mechanism unknown	Anticholinergics can relieve symptoms of parkinsonism and might offset the reduction of levodopa bioavailability. Overall, interaction of minor significance. Use together with caution; discontinue if interaction observed.
Ferrous sulfate	↓ Levodopa oral absorption by 50%	Formation of chelation complex	Avoid concomitant administration.
Food	↓ Levodopa effect	Large, neutral amino acids compete with levodopa for intestinal absorption	Although levodopa usually taken with meals to slow absorption and ↓ central emetic effect, high-protein diets should be avoided.
MAOI (e.g., phenelzine, tranylcypromine)	Hypertensive crisis	Peripheral dopamine and norepinephrine	Avoid using together; selegiline and levodopa used successfully together. Carbidopa might minimize hypertensive reaction to levodopa in patients receiving an MAOI.
Methyldopa	↓ or ↓ levodopa effect	Acts as central and peripheral decarboxylase inhibitor	Observe for response; may need to switch to another antihypertensive.
Metoclopramide	↓ Levodopa effect	Central dopamine blockade	Avoid using together.
Neuroleptics (e.g., butyrophenones, phenothiazines)	↓ Levodopa effect	Central blockade of dopamine neurotransmission	Important interaction; avoid using these drugs together.
Phenytoin	↓ Levodopa effect	Mechanism unknown	Avoid using together if possible.
Pyridoxine	↓ Levodopa effect	Peripheral decarboxylation of levodopa	Not observed when levodopa given with carbidopa.
TCA	↓ Levodopa effect	Levodopa degradation in gut because of delayed emptying	TCA and levodopa have been used successfully together; use with caution.

GI, gastrointestinal; MAOI, monoamine oxidase inhibitor; TCA, tricyclic antidepressants.

TABLE 57.5 Pharmacologic and Pharmacokinetic Properties of Catechol-O-Methyltransferase Inhibitors

	Tolcapone	Entacapone
Bioavailability	65%	30%–46%
T <sub>max</sub> (hours)	2.0	0.7–1.2
Protein binding	99.9%	98%
Metabolism	Glucuronidation; CYP3A4, 2CYP4A6 Acetylation; methylated by COMT	Glucuronidation
Half-life (hours)	2–3	1.6–3.4
Time to reverse COMT inhibition (hours)	16–24	4–8
Maximal COMT inhibition at 200-mg dose	80%–90%	60%
Increase in levodopa AUC	100%	30%–45%
Increase in levodopa half-life	75%	60%–75%
Dosing method	TID, spaced 6 hours apart	With every administration of levodopa

AUC, area under the curve; COMT, catechol-O-methyltransferase; CYP, cytochrome P-450; TID, three times daily.

- Monoamine oxidase type B (MAO-B) inhibitors (selegiline, rasagiline) prevent the metabolism of dopamine.
- Anticholinergics are rarely used due to undesirable side effects and poor efficacy relative to levodopa.
- Surgical therapies have been used in patients with advanced disease who cannot be adequately treated or controlled with medications.
- Supportive drug treatment for nonmotor symptoms is shown in Table 57.6.

## Restless Leg Syndrome and Periodic Limb Movements of Sleep

- *Restless leg syndrome* (RLS) is a sensorimotor disorder that results in an almost irresistible urge to move the legs. Clinical features are shown in Table 57.7. Most patients with mild symptoms will not require treatment.
  - A treatment algorithm for RLS is shown in Figure 57.2. Several classes of medications are effective for RLS. Dopamine agonists are the preferred dopaminergic class for RLS (ropinerole 0.25 mg initially, up to 0.5–8 mg/day; pramipexole 0.125 mg initially, up to 0.5–1.5 mg/day).
  - Nonpharmacologic therapies and behavioral techniques (discontinuing aggravators, good sleep hygiene, massage, hot baths) should also be considered.

TABLE 57.6 Summary of Pharmacological Treatments for Common Nonmotor Symptoms of Parkinson Disease<sup>10,18,124,126</sup>

Domain	Symptom	Possible Treatments	Adverse Effect Considerations
Cognitive	Dementia	Rivastigmine, donepezil	Deterioration of motor function (tremor), sialorrhea, excessive lacrimation, incontinence, nausea, vomiting, and orthostasis
Psychiatric	Depression	Dopamine agonists (pramipexole), TCAs (amitriptyline, desipramine, nortriptyline), SSRIs (citalopram, paroxetine)	Impulse control disorders (dopamine agonists); anticholinergic adverse effects (TCAs) on cognition, urinary symptoms, autonomic nervous system (orthostasis, falls); tremorogenic (SSRIs)
	Anxiety	Benzodiazepines	Decreased attention, cognition; increased risk of falls
	Psychosis	Clozapine, quetiapine	White cell count monitoring for clozapine (agranulocytosis)
Autonomic	Falls	If possible, avoid using medications that increase risk of falls	N/A
	Erectile dysfunction	Sildenafil	N/A
	Constipation	Polyethylene glycol, fiber, stool softeners	N/A
	Droling	Botulinum toxin, glycopyrrolate	Focal weakness
Sleep	Orthostatic hypotension	Midodrine, fludrocortisone	Hypertension, piloerection (midodrine)
	Excessive daytime sleepiness	Modafinil	Dizziness, insomnia, anxiety
	Insomnia	Melatonin, benzodiazepines	Sedation, dizziness, falls, ataxia, cognitive dysfunction (benzodiazepines)
Miscellaneous	Periodic limb movements of sleep	Carbidopa/levodopa, dopamine agonists	Impulse control disorders, psychosis
	Fatigue	Methylphenidate	Tachycardia, weight loss, nausea

N/A, not applicable; SSRI, selective serotonin reuptake inhibitor; TCA, tricyclic antidepressant.

**TABLE 57.7 Clinical Features of Restless Legs Syndrome**

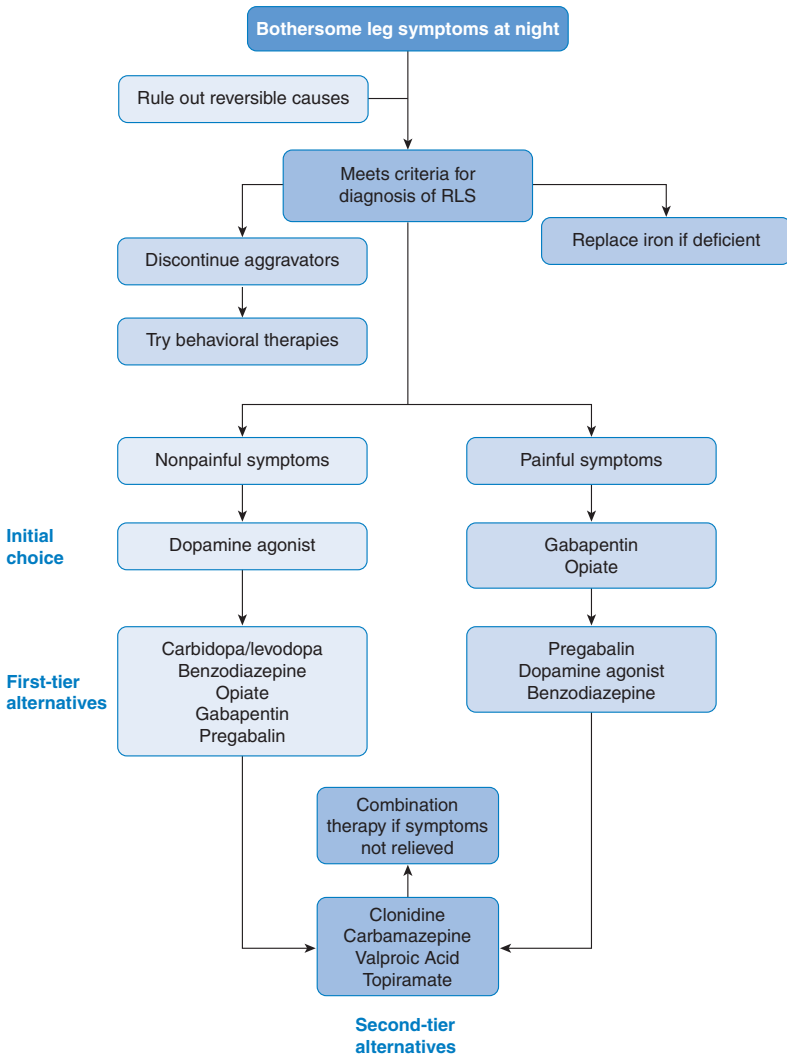
**ESSENTIAL CRITERIA**

- Urge to move legs, associated with paresthasias or dysesthasias
- Relief of symptoms with movement
- Onset or exacerbation of symptoms at rest
- Onset or worsening of symptoms during nighttime

**SUPPORTIVE CLINICAL FEATURES**

- Accompanying sleep disturbance (sleep-onset insomnia)
- Periodic leg movements
- Positive response to dopaminergic therapy
- Positive family history of RLS
- Otherwise normal physical examination

RLS, restless legs syndrome.



**Figure 57.2** Approach to the treatment of restless legs syndrome.

- *Periodic limb movements of sleep* (PLMS; nocturnal myoclonus) is an involuntary clonic-type movement of the lower extremities while sleeping that usually involves bilateral ankle dorsiflexion, knee flexion, and hip flexion.

## Essential Tremor

- Essential tremor describes a kinetic tremor for which no definite cause has been found.
- Diagnostic criteria are shown in Table 57.8. Differentiating between essential tremor and Parkinson disease is important (Table 57.9) as treatments differ.
- A thorough medication history is essential to rule out drug-induced causes of tremor.
- Pharmacotherapy for essential tremor is shown in Table 57.10. Treatment should occur at the lowest dose and longest interval.

TABLE 57.8 Diagnostic Criteria for Essential Tremor

### INCLUSION CRITERIA

Bilateral postural tremor with or without kinetic tremor, involving hands and forearms, that is visible and persistent

Duration >5 years

### EXCLUSION CRITERIA

Other abnormal neurological signs (except Froment sign)

Presence of known causes of increased physiological tremor

Concurrent or recent exposure to tremorogenic drugs or the presence of a drug withdrawal state

Direct or indirect trauma to the nervous system within 3 months before the onset of tremor

Historical or clinical evidence of psychogenic origins

Convincing evidence of sudden onset or evidence of stepwise deterioration

TABLE 57.9 Differentiation of Essential Tremor and Parkinson Disease

Characteristic	Essential Tremor	Parkinson Disease
Kinetic tremor in arms, hands, or head	++	++
Hemibody (arm and leg) tremor	0	++
Kinetic tremor > resting tremor	++	+
Resting tremor > kinetic tremor	0	++
Rigidity or bradykinesia	0	++
Postural instability	0	++
Usual age of onset (years)	15–25, 45–55	55–65
Symmetry	Bilateral	Unilateral > Bilateral
Family history of tremor	+++	+
Response to alcohol	+++	0
Response to anticholinergics	0	++
Response to levodopa	0	+++
Response to pramipexole	+++	0
Response to propranolol	+++	+
Handwriting analysis	Large, tremulous script	Micrographia

0, not observed; +, rarely observed; ++, sometimes observed; +++, often observed.

TABLE 57.10 Pharmacotherapy for Essential Tremor

Drug	Initial Dose	Usual Therapeutic Dose	Adverse Effects
<b><math>\beta</math>BLOCKERS</b>			
Propranolol	10 mg every day to BID	160–320 mg divided every day to BID	Bradycardia, fatigue, hypotension, depression, exercise intolerance
Atenolol	12.5–25 mg every day	50–150 mg every day	Bradycardia, fatigue, hypotension, exercise intolerance
Nadolol	40 mg every day	120–240 mg every day	Bradycardia, fatigue, hypotension, exercise intolerance
<b>ANTICONVULSANTS</b>			
Primidone	12.5 mg every day	50–750 mg divided every day to TID	Sedation, fatigue, nausea, vomiting, ataxia, dizziness, confusion, vertigo
Gabapentin	300 mg every day	1,200–3,600 mg divided TID	Nausea, drowsiness, dizziness, unsteadiness
Topiramate	25 mg every day	200–400 mg divided BID	Appetite suppression, weight loss, paresthesias, concentration difficulties
Pregabalin	75 mg BID	75–300 mg divided BID	Weight gain, dizziness, drowsiness
<b>BENZODIAZEPINES</b>			
Alprazolam	0.125 mg every day	0.75–3 mg divided TID	Sedation, fatigue, potential for abuse
Clonazepam	0.25 mg every day	0.5–6 mg divided every day to BID	Sedation, fatigue, ataxia, dizziness, impaired cognition
<b>MISCELLANEOUS</b>			
Botulinum toxin A	Varies by injection site: 50–100 units/arm for hand tremor; 40–400 units/neck for head tremor; 0.6–15 units/vocal cords for voice tremor; retreat no sooner than every 3 months (extend as long as possible)		Hand weakness (with wrist injection); dysphagia, hoarseness, breathiness (with neck or vocal cord injection)

BID, two times daily; TID, three times daily.

# Seizure Disorders\*

## General Principles

- A **seizure** is the transient occurrence of signs and/or symptoms due to abnormal, excessive, or synchronous neuronal activity in the brain. Signs or symptoms may include alterations of consciousness, motor, sensory, autonomic, or psychic events.
- **Epilepsy** is a condition characterized by the occurrence of two or more seizures that are not acutely provoked by other illnesses or conditions.
- Medications control rather than cure the seizure disorder. Adherence to the medication regimen is important.

## Classification

- Epilepsy can be classified on the basis of seizure type (Table 58.1). Many epilepsy syndromes have been described (Table 58.2).
- **Generalized tonic-clonic seizures are common seizures** where the patient loses consciousness and falls at the onset. After the clonic phase, the patient returns to consciousness but may remain lethargic and confused (postictal state).
- **Absence seizures** occur primarily in children and often remit during puberty. There is a brief loss of consciousness (usually lasting several seconds); muscle tone is maintained and patients do not fall. Consciousness returns immediately after the seizure.
- **Simple partial (focal motor or sensory) seizures** occur in area localized in a single cerebral hemisphere or portion of the hemisphere. They are brief and not associated with a loss of consciousness. Various motor, sensory, or psychic manifestations can occur.
- **Complex partial seizures** result from the spread of focal discharges to involve a larger area. Consciousness is impaired and patient may exhibit complex but inappropriate behaviors (e.g., lip smacking, aimless wandering).
- **Status epilepticus** is defined as either continuous seizures lasting at least 5 minutes, or two or more discrete seizures between which there is incomplete recovery of consciousness.
- **Febrile seizures** occur in up to 8% of children between 6 months and 6 years of age. Long-term treatment or prophylaxis for simple febrile seizures is not recommended.

## Patient Assessment

- Accurate diagnosis of epilepsy syndromes is needed in order to provide optimal treatment. Neurologic exam, medical history, and diagnostic tests (e.g., electroencephalogram [EEG], computed tomography [CT], magnetic resonance imaging [MRI]) help to make an accurate diagnosis.
- Individual patient response to pharmacologic treatment (i.e., seizure frequency and severity, toxicity) is the major focus of therapy assessment.

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\*The reader is referred to Chapter 58, Seizure Disorders, written by James W. McAuley, PhD, FAPhA, Rex S. Lott, PharmD, BCPP, and Brian K. Alldredge, PharmD, in the 10th edition of *Applied Therapeutics: The Clinical Use of Drugs* for a more in-depth discussion. All notations to reference numbers are based on the reference list at the end of that chapter. The editor of this handbook expresses her thanks to Drs. McAuley, Lott, and Alldredge and acknowledges that this chapter is based on their work.

TABLE 58.1 Classification of Epileptic Seizures

**PARTIAL SEIZURE (FOCAL)****Simple Partial Seizures (Without Impairment of Consciousness)**

- Motor symptoms
- Special sensory or somatosensory symptoms
- Autonomic symptoms
- Psychic symptoms

**Complex Partial Seizures (With Impairment of Consciousness)**

- Progressing to impairment of consciousness
  - With no other features
  - With features as in simple partial seizures
  - With automatisms
- With impaired consciousness at onset
  - With no other features
  - With features as in simple partial seizures
  - With automatisms

**Partial Seizures That Evolve to Generalized Seizures**

- Simple partial seizures evolving to generalized seizures
- Complex partial seizures evolving to generalized seizures
- Simple partial seizures evolving to complex partial seizures to generalized seizures

**GENERALIZED SEIZURES (CONVULSIVE OR NONCONVULSIVE)****Absence Seizures**

- Typical seizures (impaired consciousness only)
- Atypical absence seizures

**Myoclonic Seizures****Clonic Seizures****Tonic Seizures****Tonic-Clonic Seizures****Atonic (Astatic or Akinetic) Seizures****UNCLASSIFIED EPILEPTIC SEIZURES**

All seizures that cannot be classified because of inadequate or incomplete data and some that cannot be classified in previously described categories

**Goals of Therapy**

- Goals of therapy are to reduce seizure frequency and severity without producing significant dose-related side effects.

**Treatment**

- Early control of epileptic seizures is important in order to normalize lives and prevent acute physical harm and long-term morbidity associated with recurrent seizures. The decision to treat with medication is based on the likelihood of recurrence.
- Adjuncts to pharmacotherapy may be helpful in some patients. These can include dietary modifications (e.g., ketogenic diet), surgery, and the vagus nerve stimulator device.
- Pharmacotherapy is the mainstay of treatment for epilepsy. Choice of appropriate antiepileptic drug (AED) depends on seizure and syndrome type, patient age, gender, life style, concomitant medications, AED tolerability, and cost.
- Preferred drugs for specific seizures or syndromes are listed in Tables 58.2 and 58.3.
- Agents for the treatment of partial and generalized tonic-clonic seizures are shown in Table 58.4 and for absence seizures in Table 58.5.
- Most experts advocate use of a single AED (monotherapy) whenever possible. Addition of a second drug may be needed in some patients. Polytherapy should be reserved for patients with multiple seizure types or for patients in whom first-line AEDs have failed.

**TABLE 58.2 Selected Epilepsy Syndromes**

Syndrome	Seizure Patterns and Characteristics	Preferred AED Therapy	Comments
Juvenile myoclonic epilepsy	Myoclonic seizures often precede generalized tonic-clonic seizures. Myoclonic and generalized tonic-clonic episodes on awakening. Absence seizures also common. ↓ sleep, fatigue, and alcohol commonly precipitate seizures.	Valproate. Levetiracetam FDA-approved as adjunct for myoclonic seizures. Phenytoin possibly an adjunct to valproate in resistant cases. Carbamazepine reported to exacerbate seizures in some patients	5%–10% of all epilepsies; 85%–90% response to valproate. Lifelong therapy usually needed. High relapse rate with attempts to discontinue AED therapy
Lennox-Gastaut syndrome	Generalized seizures: atypical absence, atonic/akinetic, myoclonic, and tonic most common. Abnormal interictal EEG with slow spike–wave pattern. Cognitive dysfunction and mental retardation. Status epilepticus common	Valproate and benzodiazepines may be effective. Lamotrigine, rufinamide and topiramate FDA-approved. Felbamate also may be effective, but potential hematologic toxicity limits use. Poorly responsive to AED	Oversedation with aggressive AED trials may ↑ seizure frequency. Tolerance to benzodiazepines limits their usefulness.
Childhood absence epilepsy	Typical absences often in clusters of multiple seizures. Tonic-clonic seizures in ~40%. Onset usually between ages 4 and 8 years. Significant genetic component. EEG shows classic 3-Hz spike-and-wave pattern.	Ethosuximide or valproate. Lamotrigine probably effective	80%–90% response rate to AED therapy. Good prognosis for remission. Tonic-clonic seizures may persist.
Reflex epilepsy	Tonic-clonic seizures most common. Induced by flicker or patterns (photosensitivity) most commonly. Reading also may precipitate partial seizures affecting the jaw, which may generalize. Some cases involve precipitation of underlying seizures; some seem primary.	AED specific to underlying seizures. Avoidance of precipitating stimuli when possible. Valproate usually effective for cases of spontaneous seizures precipitated by photosensitivity.	Relatively rare; seizures may be precipitated by television or video games.
Temporal lobe epilepsy	Complex partial seizures with automatisms. Simple partial seizures (auras) common; secondary generalized seizures occur in 50%.	Carbamazepine, phenytoin, valproate, gabapentin, lamotrigine, topiramate, tiagabine, levetiracetam, oxcarbazepine, zonisamide, pregabalin, lacosamide	Often incompletely controlled with current AEDs. Emotional stress may precipitate seizures; psychiatric disorders seen with temporal lobe epilepsy; surgical resection can be effective when patient is identified as a good surgical candidate.

AED, antiepileptic drug; EEG, electroencephalogram; FDA, US Food and Drug Administration.

Sources: Dreifuss FE. The epilepsies: clinical implications of the international classification. *Epilepsia*. 1990;31(Suppl 3):S3; Serratosa JM. Juvenile myoclonic epilepsy. In: Wyllie E et al, eds. *The Treatment of Epilepsy: Principles and Practice*. 3rd ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2001:491; Farrell K. Secondary generalized epilepsy and Lennox-Gastaut syndrome. In: Wyllie E et al, eds. *The Treatment of Epilepsy: Principles and Practice*. 3rd ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2001:525; Kotagal P. Complex partial seizures. In: Wyllie E et al, eds. *The Treatment of Epilepsy: Principles and Practice*. 3rd ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2001:309; Berkovic SF et al. Absence seizures. In: Wyllie E et al, eds. *The Treatment of Epilepsy: Principles and Practice*. 3rd ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2001:357; Zifkin BG et al. Epilepsy with reflex seizures. In: Wyllie E et al, eds. *The Treatment of Epilepsy: Principles and Practice*. 3rd ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2001:537.



TABLE 58.3 Antiepileptic Drugs Useful for Various Seizure Types<sup>a</sup>

Primary Generalized Tonic-Clonic	Secondarily Generalized Tonic-Clonic	Simple or Complex Partial	Absence	Myoclonic, Atonic/Akinetic
<b>MOST EFFECTIVE WITH LEAST TOXICITY</b>				
Valproate	Carbamazepine	Carbamazepine	Ethosuximide	Valproate
Carbamazepine	Oxcarbazepine	Oxcarbazepine	Valproate	Clonazepam
Lamotrigine	Levetiracetam	Levetiracetam	Lamotrigine <sup>b</sup>	Rufinamide
	Valproate	Valproate	(Topiramate) <sup>b</sup>	(Lennox-Gastaut syndrome)
				Levetiracetam (Juvenile myoclonic epilepsy)
(Levetiracetam) <sup>b</sup>	(Gabapentin) <sup>b</sup>	Lamotrigine		Lamotrigine <sup>b</sup>
(Oxcarbazepine) <sup>b</sup>	Lamotrigine	(Gabapentin) <sup>b</sup>		(Topiramate) <sup>b</sup>
(Topiramate) <sup>b</sup>	(Topiramate) <sup>b</sup>	(Levetiracetam) <sup>b</sup>		
(Zonisamide) <sup>b</sup>	(Tiagabine) <sup>b</sup>	(Topiramate) <sup>b</sup>		
	(Zonisamide) <sup>b</sup>	(Tiagabine) <sup>b</sup>		
	(Levetiracetam) <sup>b</sup>	(Pregabalin) <sup>b</sup>		
	(Pregabalin) <sup>b</sup>	(Zonisamide) <sup>b</sup>		
	(Lacosamide) <sup>b</sup>	(Lacosamide) <sup>b</sup>		
<b>EFFECTIVE, BUT OFTEN POORLY TOLERATED OR CAUSE UNACCEPTABLE TOXICITY</b>				
Phenobarbital	Phenobarbital	Clorazepate	Clonazepam	(Felbamate) <sup>c</sup>
Primidone	Primidone	Phenobarbital		
(Felbamate) <sup>c</sup>	(Felbamate) <sup>c</sup>	Primidone		
Phenytoin	Phenytoin	(Felbamate) <sup>c</sup>		
		Phenytoin		
<b>OF LITTLE VALUE</b>				
Ethosuximide	Ethosuximide	Ethosuximide	Phenytoin	
			Carbamazepine	
			Phenobarbital	
			Primidone	
			Oxcarbazepine	
			Levetiracetam	
			Lacosamide	
			Rufinamide	
			Tiagabine	

<sup>a</sup>Drugs are listed in general order of preference within each category. Recommendations by various authorities may differ, especially regarding the relative place of valproate and the role of phenytoin as a first-line AED. The use of phenobarbital and primidone is now discouraged.

<sup>b</sup>The place of gabapentin, lacosamide, rufinamide, lamotrigine, oxcarbazepine, levetiracetam, topiramate, tiagabine, pregabalin, and zonisamide is yet to be determined. They are placed on this table only to indicate the types of seizures for which they appear to be effective. More clinical experience is needed before their roles as possible primary AEDs are clarified.

<sup>c</sup>The place of felbamate is yet to be determined. It is placed on this table only to indicate the types of seizures for which it appears to be effective. Felbamate has been associated with aplastic anemia and hepatic failure; until a possible causative role is clarified, felbamate cannot be recommended for treatment of epilepsy unless all other, potentially less toxic, treatment options have been exhausted.

Sources: French JA et al. Efficacy and tolerability of the new antiepileptic drugs I: treatment of new onset epilepsy: report of the Therapeutics and Technology Assessment Subcommittee and Quality Standards Subcommittee of the American Academy of Neurology and the American Epilepsy Society. *Neurology*. 2004;62:1252; French JA et al. Efficacy and tolerability of the new antiepileptic drugs II: treatment of refractory epilepsy: report of the Therapeutics and Technology Assessment Subcommittee and Quality Standards Subcommittee of the American Academy of Neurology and the American Epilepsy Society. *Neurology*. 2004;62:1261; Pellock JM. Efficacy and adverse effects of antiepileptic drugs. *Pediatr Clin North Am*. 1989;36:435; Mattson RH et al. Comparison of carbamazepine, phenobarbital, phenytoin, and primidone in partial and secondarily generalized tonic-clonic seizures. *N Engl J Med*. 1985;313:145; Mattson RH et al. A comparison of valproate with carbamazepine for the treatment of complex partial seizures and secondarily generalized tonic-clonic seizures in adults. The Department of Veterans Affairs Epilepsy Cooperative Study No. 264 Group. *N Engl J Med*. 1992;327:765; Fisch BJ et al. Generalized tonic-clonic seizures. In: Wyllie E et al, eds. *The Treatment of Epilepsy: Principles and Practice*. 3rd ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2001:369.

**TABLE 58.4 Drugs Used for the Treatment of Partial and Generalized Tonic-Clonic Seizures**

AED	Regimen	Adverse Effects	Comments
Carbamazepine (Tegretol, Tegretol XR, Carbatrol, Equetro)	Initial 200 mg BID and weekly until therapeutic response or target serum concentrations. Usual maintenance doses 800–1,200 mg/day. Maximum recommended doses: 1,600 mg/day	Sedation, visual disturbance may limit dosage. Severe blood dyscrasias extremely rare. Mild leukopenia more common. Laboratory monitoring of little value. Asian patients positive for HLA-B*1502 are at 10-fold higher risk for Stevens-Johnson syndrome/toxic epidermal necrolysis. Hepatotoxicity rare. May cause hyponatremia. Long-term use may cause osteomalacia.	Usually little sedation and minimal interference with cognitive function or behavior. Preferred by most for partial or secondarily generalized seizures. Extended-release products may allow less frequent dosing with fewer peak serum concentration-related side effects. These products may also facilitate adherence.
Phenytoin (Dilantin, Phenytek)	Oral loading dose: 15–20 mg/kg. Usual maintenance dose range 300–600 mg daily in three divided doses	Nystagmus, ataxia, sedation may limit dosage. Gum hyperplasia, hirsutism common. Long-term use may cause osteomalacia. Peripheral neuropathy, hypersensitivity with liver damage rare. Possible increased risk of Stevens-Johnson syndrome/toxic epidermal necrolysis in Asian patients positive for HLA-B*1502	Clearance and half-life change with dose. Small ↑ in dose (30-mg capsule) recommended as plasma concentrations exceed 7–10 mcg/mL. Cautious use of suspension; dose measurement and potential mixing difficulties. IM administration not recommended. Potential precipitation in IV solutions. Fosphenytoin (Cerebyx) recommended for IM and IV use due to faster administration rate, admixture compatibility and lower rate of injection site complications
Valproate (Depakene, Depakote, Depakote-ER) Phenobarbital	See Table 58.5. Initial 1 mg/kg/day; titrate to therapeutic response. 2–3 weeks between dose ↑	— Sedation (chronic), behavior disturbances common, especially in children. Possibly impairs learning and intellectual performance. Long-term use may cause osteomalacia.	— Considered outmoded for AED therapy in most patients; adverse effects outweigh benefits. IV use for refractory status epilepticus
Pregabalin (Lyrica)	Initial 75 mg BID, then titrate to therapeutic response with maximal daily dose at 600 mg/day in divided doses (BID or TID)	Potential side effects include dizziness, blurred vision, and weight gain.	No significant interactions with other AEDs. Can be useful for patients with concomitant pain disorders
Gabapentin (Neurontin)	Initial 300 mg/day with titration to 900–1,800 mg/day for 1–2 weeks. Doses of 2,400 mg/day and higher have been well tolerated. Owing to short half-life, TID or QID dosing recommended.	Sedation, dizziness, and ataxia relatively common with initiation of therapy. Gabapentin therapy usually not associated with prominent side effects. Commonly associated with weight gain	Excreted unchanged by kidneys. No significant drug–drug interactions. Absorption dose dependent; fraction absorbed ↓ as size of individual dose ↑

*Continued on following page*

TABLE 58.4 Drugs Used for the Treatment of Partial and Generalized Tonic-Clonic Seizures (Continued)

AED	Regimen	Adverse Effects	Comments
Lamotrigine (Lamictal)	<p><i>When added to enzyme inducers alone:</i> Initiate at 50 mg daily HS or 50 mg BID. Daily dose can be ↑ by 50–100 mg every 7–14 days. Usual maintenance doses of 400–500 mg/day. BID dosing may be necessary with enzyme inducer cotherapy.</p> <p><i>When added to valproate alone:</i> Initiate at 25 mg QOD HS. Daily dose can be ↑ by 25 mg every 14 days. Usual maintenance doses of 100–200 mg/day.</p> <p><i>When added to valproate and enzyme inducers:</i> Initiate at 25 mg QOD HS. Daily dose can be ↑ by 25 mg every 14 days. Usual daily doses of 100–200 mg/day</p>	Dizziness, diplopia, sedation, ataxia, and blurred vision can be common with initiation of therapy; limit speed of titration. Incidence of serious rash ranges from 0.8–8.0 per 1,000.	Significant ↑ in clearance of lamotrigine when coadministered with enzyme inducers. Significant ↓ in clearance when coadministered with valproate. Slow, gradual titration of dose may reduce risk of skin rash. Estrogen increases clearance.
Tiagabine (Gabitril)	Initial 4 mg/day. ↑ by 4 mg/day at 7 days. Then ↑ daily dose by 4–8 mg every week. Maximal recommended dose of 32 mg/day in adolescents or 56 mg/day in adults. BID to QID dosing recommended	Drowsiness, nervousness, difficulty with concentration or attention, tremor. Nonspecific dizziness described by some patients	Increased clearance when given with enzyme inducers. TID or QID doses probably needed. Potential for protein-binding displacement interactions with other highly protein-bound drugs (e.g., valproate). Significance of protein-binding displacement not known. Substrate for CYP3A4
Topiramate (Topamax)	Initial 50 mg HS. ↑ daily dose by 50 mg every 7 days. 200–400 mg/day recommended as target dosage range. Larger daily doses associated with increased CNS side effects. BID dosing recommended	Sedation, dizziness, difficulty concentrating, confusion. May be dose related. Possible weight loss. Weak CA inhibitor; may cause or predispose to kidney stones; CA inhibition also possibly related to paresthesias in up to 15%. Risk of hypohidrosis and hyperthermia, especially in children. Rarely associated with angle closure glaucoma	Approximately 70% renal elimination. Phenytoin and carbamazepine may reduce topiramate plasma concentrations and potentially increase dosage requirements. Topiramate may cause small ↑ in phenytoin plasma concentration. Advise patients to drink plenty of fluids. May affect oral contraceptives above 200 mg/day

Levetiracetam (Keppra)	Initial 250–500 mg BID. ↑ by 500–1,000 mg/day every 2 weeks. Usual maximal dose is 3,000 mg/day. Doses up to 4,000 mg/day have been used. BID dosing recommended	Somnolence, dizziness, asthenia are commonly reported. Behavioral symptoms (agitation, emotional lability, hostility, depression, and depersonalization) reported	No hepatic (CYP450 or UGT) metabolism. 66% excreted unchanged in urine. Less than 10% protein bound. No significant drug interactions reported
Rufinamide	Initial: In adults 400–800 mg/day given BID. ↑ by 400–800 mg/day every 2 days. Target dose of 3,200 mg/day. In children, initiate at 10 mg/kg/day given BID. ↑ by 10 mg/kg/day every other day. Target dose of 45 mg/kg/day or 3,200 mg/day	Sedation, dizziness, vomiting and headache. Shortens QT interval	Presently only approved for treatment of seizures in Lennox-Gastaut syndrome in patients older than 4 years of age. Extensively metabolized through enzymes other than CYP. Weakly induces CYP3A; may decrease effectiveness of hormonal contraceptives. VPA significantly decreases rufinamide clearance; potentially significant increases in rufinamide clearance caused by carbamazepine, phenytoin, and phenobarbital
Lacosamide	Initiate at 50 mg BID. Increase weekly by 100 mg/day. Target doses of 200–400 mg/day. Maximum recommended dose is 400 mg/day.	Dizziness, ataxia, diplopia, headache, nausea. May slow cardiac conduction. Caution is advised in patients with second-degree AV block. Syncope has been reported.	Currently only indicated for treatment of partial seizures in adults. IV form available; currently only approved for short-term replacement of oral therapy. Little evidence of significant risk of drug–drug interactions. Some hepatic metabolism by CYP2C19; significant renal elimination
Oxcarbazepine (Trileptal)	<i>Monotherapy:</i> Initial 300 mg BID. ↑ weekly up to 1,200 mg/day. Can increase to 2,400 mg/day <i>Adjunctive therapy:</i> Initial 300 mg BID. ↑ weekly up to 1,200 mg/day	Dizziness, somnolence, diplopia, nausea, and ataxia are commonly reported. May cause hyponatremia; most cases asymptomatic; more common in elderly. A 25% cross-sensitivity reported between oxcarbazepine and carbamazepine	Parent is a prodrug; the MHD is the active component. Readily converted to MHD via omnipresent cytosolic enzymes. Lacks autoinduction properties. In doses >1,200 mg/day, may affect oral contraceptives
Zonisamide (Zonegran)	Initial 100 mg daily. ↑ by 100 mg/day every 2 weeks. Usual maintenance doses of 200–400 mg/day; maximum 600 mg/day	Somnolence, nausea, ataxia, dizziness, headache, and anorexia are common. Weight loss and nephrolithiasis reported. Serious skin eruptions, oligohidrosis, and hyperthermia have also occurred.	Broad spectrum, long half-life. 35% of dose is excreted unchanged in the urine. Also a substrate of CYP3A4; enzyme induction may increase clearance. Advise patients to drink plenty of fluids.

AED, antiepileptic drugs; AV, atrioventricular; BID, twice daily; CA, carbonic anhydrase; CNS, central nervous system; CYP, cytochrome P-450; GI, gastrointestinal; HS, at bedtime; IM, intramuscular; IV, intravenous; MHD, monohydroxy derivative; PE, phenytoin sodium equivalent; QID, four times daily; QOD, every other day; SIADH, syndrome of inappropriate antidiuretic hormone secretion; TID, three times daily; UGT, uridine diphosphate glucuronosyltransferase; VPA, valproic acid.

TABLE 58.5 Common Drugs for the Treatment of Absence Seizures

AED	Regimen	Adverse Effects	Comments
Valproate (Depakene, Depakote, Depakote-ER)	Initial 5–10 mg/kg/day (sprinkle caps or syrup); then ↑ by 5–10 mg/kg/day weekly to therapeutic effect or target serum concentration. Manufacturer's recommended usual maximal dose of 60 mg/kg/day often must be exceeded clinically (especially for patients receiving enzyme-inducing AED) to achieve optimal clinical results. Daily dosing recommended for ER product; doses should be 8%–20% higher than non-ER products.	GI upset, hair loss, appetite stimulation, and weight gain common. Tremor may occur. Serious hepatotoxicity extremely rare with monotherapy and in patients younger than 2 years of age	Enteric-coated tablets or capsules or ER tablets may ↓ GI toxicity. Time to peak serum concentrations delayed for 3–8 hours with enteric coating; longer delay if given with food; serum concentrations must be interpreted carefully. Also effective against primarily generalized tonic-clonic seizures
Lamotrigine (Lamictal)	See Table 58.4.		
Ethosuximide (Zarontin)	Initial 20 mg/kg/day or 250 mg daily or BID; then ↑ by 250 mg/day every 2 weeks to therapeutic effect or target serum concentration.	GI upset and sedation common with large single dose, especially on initiation. Daily divided doses may be necessary despite long half-life. Leukopenia (mild, transient) in up to 7%; serious hematologic toxicity extremely rare	Parents/patient should be informed that GI effects and sedation may occur but tolerance usually develops. No good evidence it precipitates tonic-clonic seizures. Up to 50% of patients with absence may exhibit tonic-clonic seizures independent of ethosuximide.

AED, antiepileptic drug; BID, twice daily; ER, extended release; GI, gastrointestinal.

- For some, but not all, AEDs, there is a good correlation between serum concentration and therapeutic response/toxicity. Pharmacokinetic properties of AEDs are shown in Table 58.6.
- Individual patients often differ dramatically in their response to a particular drug concentration. Therapeutic concentrations should only be considered guidelines. Serum concentrations should be considered in the following situations:
  - Seizures are uncontrolled despite higher than average doses.
  - Seizures recur in a patient who was previously controlled.
  - Patient shows signs of dose-related AED toxicity.
  - Assessment of adherence is necessary.
  - Documentation of desired results from a dose change or other therapeutic maneuver is needed.
  - Precise dose changes are required.
  - Patient is pregnant.
- Several considerations exist for women with epilepsy including contraceptive interactions with AEDs, teratogenicity, pharmacokinetic changes during pregnancy, breast-feeding, and menstrual cycle influences on seizure activity. Prepregnancy planning and counseling are important for women of childbearing potential.
- **Discontinuation of Therapy.** Patients who are seizure free for 2 years while receiving medication may be able to stop therapy. Risk factors for seizure recurrence are shown in Table 58.7.

TABLE 58.6 Pharmacokinetic Properties of Antiepileptic Drugs

Drug	Oral Absorption (%)	Half-Life (hours)	Time to Steady State	Dosage Schedule	Usual Therapeutic Serum Concentration	Plasma Protein Binding (%)	Volume of Distribution (L/kg)
Carbamazepine	90–100	<i>Chronic:</i> 5–25	2–4 days	BID to TID	5–12 mcg/mL	75 (50–90)	0.8–1.6
Ethosuximide	90–100	<i>Pediatric:</i> 30 <i>Adult:</i> 60 12–20	5–10 days	Daily (BID)	40–100 mcg/mL	0	0.7
Felbamate	90		3–4 days	BID to TID	50–110 mcg/mL	24	0.7–0.8
Gabapentin	40–60; ↓ with ↑ dose	<i>Normal renal function:</i> 5–9; ↑ with ↓ renal function	<i>Normal renal function:</i> 1–1.5 days	TID to QID (every 6–8 hours)	2 mcg/mL (proposed)	0	≈0.8
Lacosamide	100	13 ↑ slightly with renal impairment	2–3 days	BID	Not determined	<15	0.6
Lamotrigine	90–100	<i>Monotherapy:</i> 24–29 <i>Enzyme inducers:</i> 15 <i>Enzyme inhibitor (VPA):</i> 59	4–9 days	BID	4–18 mcg/mL (proposed)	55	0.9–1.2
Levetiracetam	100	<i>Normal renal function:</i> 6–8; ↑ with ↓ renal function	<i>Normal renal function:</i> 1–1.5 days	BID	Not determined	<10	≈0.7
Oxcarbazepine	100	8–13	2–3 days	BID to TID	Not determined	40	
Phenobarbital	90–100	2–4 days	8–16 days	Daily	15–40 mcg/mL	50	0.5–0.6
Phenytoin	90–100	Varies with dose	5–30 days	Daily to BID	10–20 mcg/mL	95	0.5–0.7
Pregabalin	≥90	<i>Normal renal function:</i> 6; ↑ with ↓ renal function	24 hours	BID to TID	Not determined	0	0.5
Rufinamide	85	9	1–2 days	BID	Not determined	<35	Dose dependent
Tiagabine	90	<i>Monotherapy:</i> 7–9 <i>Enzyme inducers:</i> 4–7	1–2 days	BID to QID	Not determined	96	1.1
Topiramate	≥80	12–24	3–4 days	BID	Not determined	10–15	0.7
Valproate	100 (≈ 80% with divalproe × ER)	10–16	2–3 days	BID to QID (daily with divalproe × ER)	50–150 mcg/mL	90+	0.09–0.17
Vigabatrin	80–90	8–12 (not clinically important. Irreversible enzyme inhibitor)	NA	Daily to BID	NA	NA	NA
Zonisamide	≈80	<i>Monotherapy:</i> ≈60 <i>Enzyme inducers:</i> 27–36	2 weeks	Daily to BID	Not determined	50–60	1.3

<sup>a</sup>Based on four half-lives. This lag time should allow determination of steady-state serum concentrations within limits of most assay sensitivities. BID, twice daily; NA, not applicable; QID, four times daily; VPA, valproic acid.

**TABLE 58.7 Risk Factors Possibly Predicting Seizure Recurrence after Antiepileptic Drug Withdrawal**

- <2 years seizure-free before withdrawal
- Onset of seizures after age 12
- History of atypical febrile seizures
- Family history of seizures
- 2–6 years before seizures controlled
- Large number of seizures (>30) before control or total of >100 seizures
- Partial seizures (simple or complex)
- History of absence seizures
- Abnormal EEG persisting throughout treatment
- Slowing on EEG before medication withdrawal
- Organic neurologic disorder
- Moderate to severe mental retardation
- Withdrawal of valproate or phenytoin (higher rate of recurrence than withdrawal of other AED)

AED, antiepileptic drug; EEG, electroencephalogram.

- Nonadherence is common in patients taking AEDs. Rapid discontinuation of therapy can precipitate status epilepticus.
- **Status Epilepticus**
  - Ensuring ventilation and terminating current seizure activity are essential. IV access should be established.
  - Thiamine 100 mg or vitamin B complex should be given before 25 g of glucose (50 mL of a 50% dextrose solution) by IV push. Thiamine is given to prevent Wernicke's encephalopathy.
  - Lorazepam, diazepam, phenytoin, and fosphenytoin are the agents most commonly used as IV therapy for initial treatment.
  - Lorazepam 0.1 mg/kg IV at 2 mg/minute
  - Diazepam 0.2 mg/kg IV at 5 mg/minute
  - Phenytoin (20 mg/kg IV at 50 mg/minute) or fosphenytoin (20 mg/kg of phenytoin-equivalents IV at 150 mg/minute)
  - Continued effective seizure control is important.
- Skin rash is a relatively common side effect related to AED therapy (seen in 2%–3% of patients). It is most commonly associated with phenytoin, lamotrigine, carbamazepine, and phenobarbital.
- Several drug interactions with AEDs are possible; therapy should be monitored accordingly.

# Cerebrovascular Disorders\*

## General Principles

- Cerebrovascular disease is a broad term encompassing many disorders of the blood vessels of the central nervous system (CNS). These disorders result from either inadequate blood flow to the brain (i.e., cerebral ischemia) with subsequent infarction of the involved portion of the CNS, or hemorrhage into the parenchyma or subarachnoid space of the CNS and subsequent neurologic dysfunction.
- Infarction of brain tissue and neuronal death is similar for both embolic and thrombotic events. Disorders like atrial fibrillation, mitral or aortic valve disease, patent foramen ovale, or coagulopathies are associated with the formation of clots that may embolize to the brain.
- Stroke is a term used to describe a cerebral vascular event when neurologic deficits persist for at least 24 hours.

## Types of Cerebrovascular Disorders

- **Transient Ischemic Attack (TIA):** a temporary focal neurologic injury that can present with any type of neurologic symptom (Table 59.1), including slurred speech, aphasia, facial droop, weakness or paralysis of a limb, or blindness. Patients rarely lose consciousness. Symptoms appear rapidly and are temporary, lasting <24 hours.
- **Cerebral Infarction:** a permanent neurologic disorder characterized by symptoms similar to TIA. Neurological deficits are caused by death of neurons in a focal area of the brain. The two primary causes are atherosclerosis and emboli. Cerebral infarction can present in three forms: stable infarction, improving infarction, or progressing infarction.
- **Cerebral Hemorrhage:** involves escape of blood from blood vessels into the brain and surrounding structures. Clinical symptoms are similar to those associated with TIA or cerebral infarction. Primary causes include cerebral artery aneurysm, arteriovenous malformation, hypertensive hemorrhage, trauma, and adverse drug reactions.

## Patient Assessment

- Rapid recognition of stroke symptoms and immediate initiation of treatment are essential to the management of ischemic or hemorrhagic stroke.
- Proper education regarding the symptoms of stroke is essential for any patient at increased risk for stroke. Patients should be instructed to seek immediate medical attention if they experience any weakness or paralysis, speech impairment, numbness, blurred vision or sudden vision loss, or altered level of consciousness.
- Prognosis after ischemic stroke depends on factors including age, hypertension, coma, cardiopulmonary complications, hypoxia, and neurogenic hyperventilation. Neurologic deficits in stroke patients are not considered stable or fixed until at least 8 to 12 months have elapsed.

## Risk Factors

- Risk factors for stroke are shown in Table 59.2.

\*The reader is referred to Chapter 59, Cerebrovascular Disorders, written by Timothy E. Welty, PharmD, FCCP, in the 10th edition of *Applied Therapeutics: The Clinical Use of Drugs* for a more in-depth discussion. All notations to reference numbers are based on the reference list at the end of that chapter. The editor of this handbook expresses her thanks to Dr. Welty and acknowledges that this chapter is based on his work.



TABLE 59.1 Symptoms Associated with Transient Ischemic Attacks

Symptom	Right Carotid	Left Carotid	Vertebrobasilar
Aphasia	Possible	Yes	No
Ataxia	No	No	Yes
Blindness	Right	Left	Right or left side
Clumsiness	Yes	Yes	Yes
Diplopia	No	No	Yes
Dysarthria	Yes	Yes	No
Paralysis	Left side	Right side	Any limb
Paresthesia	Left side	Right side	Any limb
Vertigo	No	No	Yes

### Goals of Therapy

- The immediate goal of therapy is to reestablish adequate blood flow to affected cerebral vessels. Longer-range objectives are to prevent reocclusion, decrease the risk of future symptomatic TIAs, and prevent cerebral infarction.

TABLE 59.2 Risk Factors for Ischemic Stroke

Modifiable	Potentially Modifiable	Nonmodifiable
Cardiovascular disease (coronary heart disease, heart failure, peripheral arterial disease)	Metabolic syndrome	Age (doubling each 10 years after age 55)
Hypertension	Alcohol abuse ( $\geq 5$ drinks daily)	Race (blacks > Hispanics > whites)
Cigarette smoking	Hyperhomocysteinemia	Sex (men > women)
Diabetes	Drug abuse (e.g., cocaine, amphetamine, methamphetamine)	Low birth weight (<2,500 g)
Asymptomatic carotid stenosis	Hypercoagulability (e.g., anticardiolipin, factor V Leiden, protein C deficiency, protein S deficiency, antithrombin III deficiency)	Family history of stroke (paternal > maternal)
Atrial fibrillation		
Sickle cell disease		
Dyslipidemia (high total cholesterol, low HDL)	Oral contraceptive use (women 25–44 years old)	
Dietary factors (sodium intake <2,300 mg/day; potassium intake <4,700 mg/day)	Inflammatory processes (e.g., periodontal disease, cytomegalovirus, <i>Helicobacter pylori</i> seropositive)	
Obesity	Acute infection (e.g., respiratory infection, urinary tract infection)	
Physical inactivity	CD40 ligand >3.71 ng/mL in women free of cardiovascular disease	
Postmenopausal hormone therapy (women 50–74 years old)	IL-18 upper tertile	
	hs-CRP >3 mg/L in women 45 years or older	
	Migraine headaches	
	High Lp(a)	
	High Lp-PLA2	
	Sleep-disordered breathing	

HDL, high-density lipoprotein; hs-CRP, high sensitivity C-reactive protein; IL, interleukin; Lp(a), lipoprotein(a); Lp-LPA<sub>2</sub>, lipoprotein associated phospholipase A<sub>2</sub>.

Source: Goldstein LB et al. Primary prevention of ischemic stroke: a guideline from the American Heart Association/American Stroke Council: cosponsored by the Atherosclerotic Peripheral Vascular Disease Interdisciplinary Working Group; Cardiovascular Nursing Council; Clinical Cardiology Council; Nutrition Physical Activity, and Metabolism Council; and the Quality of Care and Outcomes Research Interdisciplinary Working Group: The American Academy of Neurology affirms the value of this guideline [published correction appears in *Stroke*. 2007;38:207]. *Stroke*. 2006;37:1583.

TABLE 59.3 Primary Prevention of Ischemic Stroke

Factor	Goal	Recommendation
Hypertension	Blood pressure <140/90 mm Hg; with diabetes <140/90 mm Hg	Follow JNC-8 guidelines; after lifestyle modification thiazide-type diuretic, calcium-channel blocker, angiotensin-converting enzyme inhibitor, or angiotensin receptor blocker
Atrial fibrillation	When warfarin is used, INR 2–3	Aspirin 75–325 mg/day or warfarin as determined by the use of the CHADS <sub>2</sub> score
Dyslipidemia	National Cholesterol Education Program III goals	Lifestyle modification, HMG-CoA reductase inhibitor
Women (>65 years, history of hypertension, hyperlipidemia, diabetes, or 10-year cardiovascular risk ≥10%)	Reduce risk without bleeding complications	Aspirin 75–325 mg/day; use the lowest possible dose
Cigarette smoke	Elimination of cigarette smoke	Smoking cessation; avoidance of environmental tobacco smoke
Physical inactivity	≥30 minutes daily of moderate-intensity activity	Establish exercise program of aerobic activity
Excessive alcohol intake	Moderation	≤2 drinks/day for men or ≤1 drink/day for nonpregnant women
Diet and nutrition	≤2.3 g/day of sodium; ≥4.7 g/day of potassium	Institute a diet that is high in fruits and vegetables and low in saturated fats
Elevated lipoprotein(a)	Reduction of lipoprotein(a) by ≥25%	Niacin 2,000 mg/day as tolerated

HMG-CoA,  $\beta$ -hydroxywy- $\beta$ -methylglutaryl-CoA; INR, international normalized ratio; JNC-7, Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. Source: Goldstein LB et al. Primary prevention of ischemic stroke: a guideline from the American Heart Association/American Stroke Council: cosponsored by the Atherosclerotic Peripheral Vascular Disease Interdisciplinary Working Group; Cardiovascular Nursing Council; Clinical Cardiology Council; Nutrition Physical Activity, and Metabolism Council; and the Quality of Care and Outcomes Research Interdisciplinary Working Group: The American Academy of Neurology affirms the value of this guideline [published correction appears in *Stroke*. 2007;38:207]. *Stroke*. 2006;37:1583.

## Treatment

- **Prevention** of TIA or stroke involves controlling or reducing risk factors (Table 59.3). Lifestyle modification is the mainstay of primary prevention. Pharmacotherapy for primary prevention is limited to select high-risk populations. The CHADS<sub>2</sub> score (Table 59.4) can be used to determine whether aspirin can be used as an alternative to warfarin in patients with atrial fibrillation. Secondary prevention involves the use of antiplatelet agents (Table 59.5).

TABLE 59.4 CHADS<sub>2</sub> Score: Primary Stroke Prevention in Atrial Fibrillation

**Add Points for the following items. If score is <2, aspirin can be considered. If score is ≥2, then warfarin is recommended.**

Congestive heart failure = 1 point

Hypertension = 1 point

Age > 75 years = 1 point

Diabetes mellitus = 1 point

Prior stroke or TIA = 2 points

TIA, transient ischemic attack.

Sources: Gage BF et al. Validation of clinical classification schemes for predicting stroke: results from the National Registry of Atrial Fibrillation. *JAMA*. 2001;285:2864; Gage BF et al. Selecting patients with atrial fibrillation for anticoagulation: stroke risk stratification in patients taking aspirin. *Circulation*. 2004;110:2287.

TABLE 59.5 Drugs for Preventing Transient Ischemic Attacks and Ischemic Stroke

Drug	Action	Dose	Adverse Effects
Aspirin	Antiplatelet	50–1,300 mg/day	Diarrhea, gastric ulcer, GI upset
Dipyridamole	Antiplatelet (use in combination with aspirin)	200 mg sustained-release twice daily	GI upset
Ticlopidine	Antiplatelet	500 mg/day	Diarrhea, neutropenia, rash
Clopidogrel	Antiplatelet	75 mg/day	Thrombocytopenia, neutropenia
Warfarin	Anticoagulant	Titrate to INR 2–3	Bleeding, bruising, petechiae

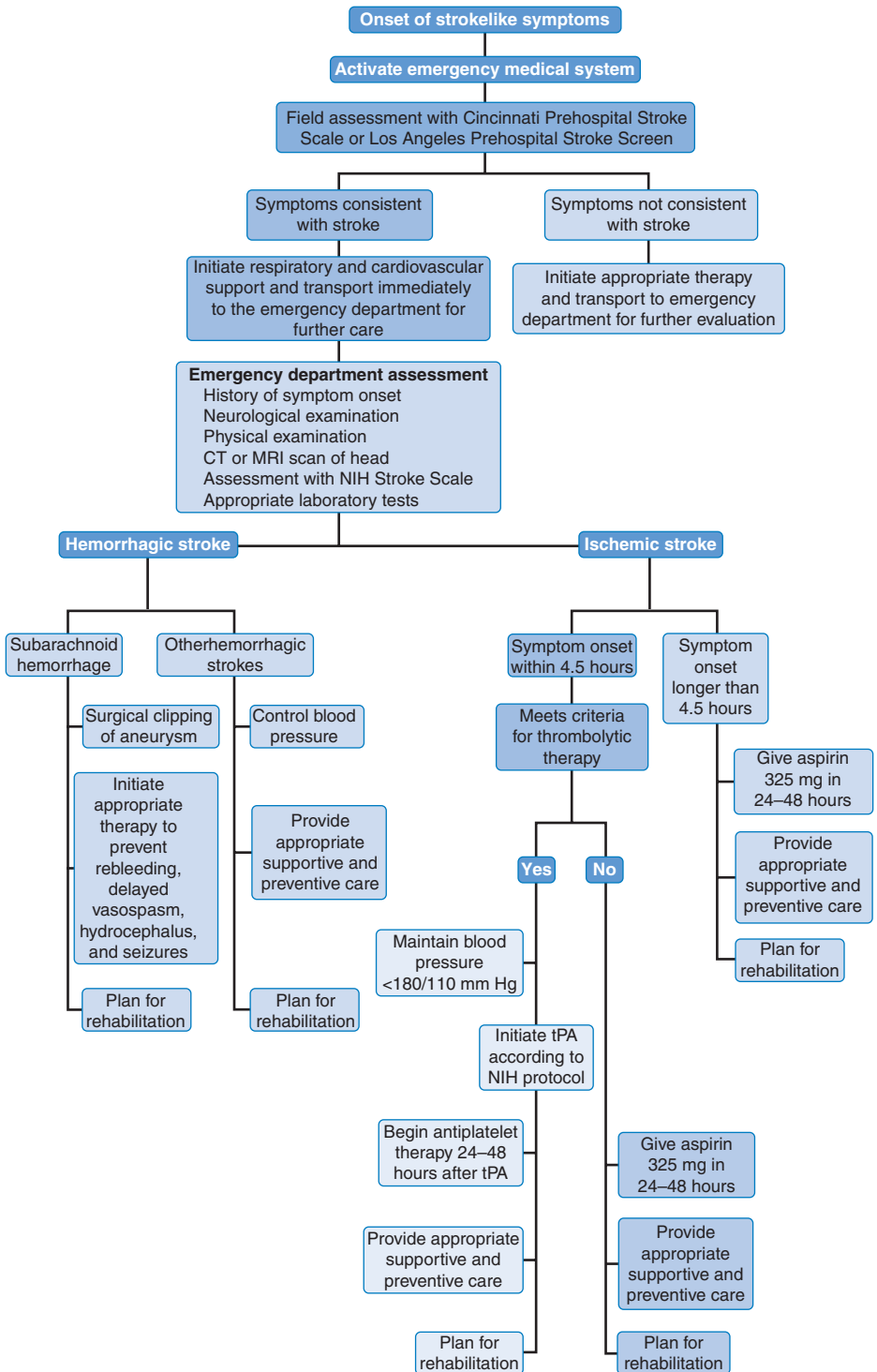
GI, gastrointestinal; INR, international normalized ratio.

- Appropriate pharmacotherapy requires a precise diagnosis; an inaccurate diagnosis of ischemic versus hemorrhagic stroke could lead to use of drugs that may cause severe morbidity or mortality. A well-designed evaluation and treatment algorithm can help address assessment and care of patients (Figure 59.1).
- **Treatment of ischemic stroke** requires acute management, chronic management of the effects of the stroke, and prevention of further events.
  - Rapid reestablishment of blood flow to the ischemic area can delay, prevent, or limit the onset of infarction, improving the outcome of the acute stroke. If blood flow is restored quickly, neurons in this area will survive. Criteria for the use of alteplase in the acute treatment of ischemic stroke are shown in Table 59.6.
  - Surgical interventions (e.g., carotid endarterectomy, balloon angioplasty, carotid artery angioplasty and stenting) are designed to either remove the source for an embolism or improve circulation to ischemic areas of the brain.
- **Treatment of hemorrhagic stroke** involves supportive therapy to maximize neurological function, prevent further hemorrhagic events, and manage complications. Careful management of blood pressure, pulmonary function, fluid and electrolytes, and elimination of drugs

TABLE 59.6 Criteria for Alteplase Use in Treatment of Acute Stroke

Inclusion Criteria	Exclusion Criteria
18 years of age or older	Minor or rapidly improving symptoms
Clinical diagnosis of stroke with clinically meaningful neurologic deficit	CT signs of intracranial hemorrhage
Clearly defined onset within 180 minutes before treatment	History of intracranial hemorrhage
Baseline CT with no evidence of intracranial hemorrhage	Seizure at onset of stroke
	Stroke or serious head injury within 3 months
	Major surgery or serious trauma within 2 weeks
	GI or urinary tract hemorrhage within 3 weeks
	Systolic BP >185 mm Hg, diastolic BP >110 mm Hg
	Aggressive treatment to lower BP
	Glucose 400 mg/dL
	Symptoms of subarachnoid hemorrhage
	<b>Additional Exclusion Criteria for Alteplase Use 3–4.5 hours After Onset of Symptoms</b>
	Age >80 years
	NIHSS score >22
	Major ischemic infarction with 30% of the middle cerebral artery involved

BP, blood pressure; CT, computed tomography; GI, gastrointestinal; NIHSS, National Institutes of Health Stroke Scale.



**Figure 59.1** Treatment algorithm for management of patient with acute stroke-like symptoms. CT, computed tomography; MRI, magnetic resonance imaging; NIH, National Institutes of Health; t-PA, alteplase. (Adams HP et al. Antifibrinolytic therapy in patients with aneurysmal subarachnoid hemorrhage: a report of the cooperative aneurysmal study. *Arch Neurol.* 1981;38:25.)

TABLE 59.7 Therapy for Subarachnoid Hemorrhage Complications

Rebleeding	Hydrocephalus	Delayed Ischemia
Surgical clip	Ventricular drain	Nimodipine 60 mg every 4 hours for 21 days
Aminocaproic acid 5 g loading dose and 1–2 g/hour	Ventricular-peritoneal shunt	Hypervolemia PCWP 12–15 mm Hg Hypertension Systolic BP 170–220 mm Hg

BP, blood pressure; PCWP, pulmonary capillary wedge pressure.

that inhibit coagulation is needed. There are no proven therapies for hemorrhagic events. Treatment of complications associated with subarachnoid hemorrhage is shown in Table 59.7.

- Deep vein thrombosis and pulmonary embolism are common complications in patients following a stroke. Recommendations to prevent these events are shown in Table 59.3.
- Rehabilitation is directed at managing daily functions, enhancing existing neurologic function, and attempting to regain lost function.

## Principles of Infectious Diseases\*

### General Principles

- Infection is commonly associated with an increased white blood cell count, fever, and localizing signs. Symptoms may be absent in less severe disease.
- Severe infection may be associated with hypotension, disseminated intravascular coagulation, and end-organ dysfunction.
- **Sepsis** is a term used to describe a poorly defined syndrome that generally suggests a more systemic infection with the presence of pathogenic microorganisms or their toxins in the blood.
- Other diseases, particularly autoimmune disease and malignancy, may mimic infectious diseases. Drug-induced fever should be ruled out as well.
- The minimum inhibitory concentration (MIC) is the minimum concentration at which an antimicrobial agent inhibits growth of an organism. The minimum bactericidal concentration (MBC) is the minimal concentration at which an antimicrobial agent kills an organism.
- Postantibiotic effect is a term referring to delayed regrowth of bacteria after exposure to an antibiotic.

### Classification

- All organisms are classified according to morphology (e.g., cocci, bacilli), growth characteristics (e.g., aerobic vs. anaerobic), and other qualities (e.g., gram-positive or -negative). Choice of therapy is often based on morphology and growth patterns (Table 60.1).
- Classification of antibacterial agents is shown in Table 60.2.

### Patient Assessment

- Patient assessment must include identification of the most likely site of infection by focusing on signs and symptoms.
- Site-specific signs and symptoms and host factors help predict the most likely pathogens. Empiric therapy should be directed at those pathogens most likely to be at the site of infection (Table 60.3).
- Isolation of an organism may reflect infection. However, colonization (bacteria present at the site that are not causing infection) and contamination (isolates identified that are not at the site of infection) must be ruled out to avoid unnecessary antimicrobial exposure.
- Independent of the presumed site of infection, in septic patients a series of blood samples for culture tests should be drawn to assess the presence of bacteremia.
- **Urosepsis**, the most common cause of nosocomial infection, can range from a urinary tract infection associated with dysuria, flank pain, and abnormal urinalysis to sepsis from a urinary infection.
- **Pulmonary** infection is associated with tachypnea, increased sputum production, altered chest x-ray, and hypoxemia.
- **Infected IV lines** are associated with pain, erythema, and purulent discharge around the IV catheter.
- Once a pathogen is identified, susceptibility tests (e.g., disk diffusion or broth dilution) can help identify the most active antimicrobial agents (Tables 60.4–60.6).

\*The reader is referred to Chapter 60, Principles of Infectious Diseases, written by B. Joseph Guglielmo, PharmD, in the 10th edition of *Applied Therapeutics: The Clinical Use of Drugs* for a more in-depth discussion. All notations to reference numbers are based on the reference list at the end of that chapter. The editor of this handbook expresses her thanks to Dr. Guglielmo and acknowledges that this chapter is based on his work.

TABLE 60.1 Classification of Infectious Organisms

1. Bacteria
  - Aerobic
    - Gram-positive**
      - Cocci
        - Streptococci: pneumococcus, viridans streptococci; group A streptococci
        - Enterococcus
        - Staphylococci: *Staphylococcus aureus*, *Staphylococcus epidermidis*
      - Rods (bacilli)
        - Corynebacterium*
        - Listeria*
    - Gram-negative**
      - Cocci
        - Moraxella*
        - Neisseria* (*Neisseria meningitidis*, *Neisseria gonorrhoeae*)
      - Rods (bacilli)
        - Enterobacteriaceae (*Escherichia coli*, *Klebsiella*, *Enterobacter*, *Citrobacter*, *Proteus*, *Serratia*, *Salmonella*, *Shigella*, *Morganella*, *Providencia*)
        - Campylobacter*
        - Pseudomonas*
        - Acinetobacter*
        - Helicobacter*
        - Haemophilus* (cocci/bacilli morphology)
        - Legionella*
  - Anaerobic
    - Gram-positive**
      - Cocci
        - Peptococcus*
        - Peptostreptococcus*
      - Rods (bacilli)
        - Clostridia (*Clostridium perfringens*, *Clostridium tetani*, *Clostridium difficile*)
        - Propionibacterium acnes*
    - Gram-negative**
      - Cocci
        - None
      - Rods (bacilli)
        - Bacteroides* (*Bacteroides fragilis*, *Bacteroides melaninogenicus*)
        - Fusobacterium*
        - Prevotella*
2. Fungi
  - Aspergillus*, *Candida*, *Coccidioides*, *Cryptococcus*, *Histoplasma*, *Mucor*, *Tinea*, *Trichophyton*
3. Viruses
  - Influenza; hepatitis A, B, C, D, E; human immunodeficiency virus; rubella; herpes; cytomegalovirus; respiratory syncytial virus; Epstein-Barr virus; severe acute respiratory syndrome (SARS) virus
4. Chlamydiae
  - Chlamydia trachomatis*
  - Chlamydia psittaci*
  - Chlamydia pneumoniae*
5. Rickettsiae
  - Rickettsiae rickettsia*
  - Rickettsiae prowazekii*
  - Rickettsiae typhus*
6. Mycoplasmas
  - Mycoplasma pneumoniae*
  - Mycoplasma hominis*
  - Ureaplasma*
7. Spirochetes
  - Treponema pallidum*
  - Borrelia burgdorferi*
8. Mycobacteria
  - Mycobacterium tuberculosis*
  - Mycobacterium avium intracellulare*

TABLE 60.2 Classification of Antibacterials

<i>β</i> -Lactam Antibiotics	<i>β</i> -Lactam Antibiotics
<i>Cephalosporins</i>	<i>Penicillinase-resistant penicillins</i>
First generation	Isoxazolyl penicillins (dicloxacillin, oxacillin, cloxacillin)
Cefadroxil	Nafcillin
Cefazolin	<i>Combination with β-lactamase inhibitors</i>
Cephalexin	Ampicillin/clavulanate Amoxicillin plus clavulanic acid
Second generation	Ticarcillin/clavulanate Ticarcillin plus clavulanic acid
Cefaclor	Ampicillin/sulbactam Ampicillin plus sulbactam
Cefamandole	Piperacillin/tazobactam Piperacillin plus tazobactam
Cefonicid	<i>Aminoglycosides</i>
Ceforanide	Amikacin
Cefotetan	Gentamicin
Cefoxitin	Neomycin
Cefprozil	Netilmicin
Cefuroxime	Streptomycin
Cefuroxime axetil	Tobramycin
Third generation	<i>Protein synthesis inhibitors</i>
Cefdinir	Azithromycin
Cefditoren	Clarithromycin
Cefixime	Clindamycin
Cefotaxime	Chloramphenicol
Cefpodoxime proxetil	Dalpofristin/Quinupristin
Ceftazidime	Dirithromycin
Ceftibuten	Erythromycin
Ceftizoxime	Linezolid
Ceftriaxone	Telithromycin
Fourth generation	Tetracyclines (doxycycline, minocycline, tetracycline)
Cefepime	Tigecycline
Fifth generation	<i>Folate inhibitors</i>
Ceftaroline	Sulfadiazine
<i>Carbacephems</i>	Sulfadoxine
Loracarbef	Trimethoprim
<i>Monobactams</i>	Trimethoprim-sulfamethoxazole
Aztreonam	<i>Quinolones</i>
<i>Penems</i>	Ciprofloxacin
Doripenem	Gemifloxacin
Ertapenem	Levofloxacin
Imipenem	Moxifloxacin
Meropenem	Norfloxacin
<i>Penicillins</i>	Ofloxacin
<i>Natural penicillins</i>	Daptomycin
Penicillin G	Televancin
Penicillin V	Vancomycin
<i>Aminopenicillins</i>	Metronidazole
Ampicillin (Omnipen)	
Amoxicillin (Amoxil)	
Bacampicillin (Spectrobid)	



TABLE 60.3 Site of Infection: Suspected Organisms

Site/Type of Infection	Suspected Organisms
<b>1. RESPIRATORY</b>	
Pharyngitis	Viral, group A streptococci
Bronchitis, otitis	Viral, <i>Haemophilus influenzae</i> , <i>Streptococcus pneumoniae</i> , <i>Moraxella catarrhalis</i>
Acute sinusitis	Viral, <i>Streptococcus pneumoniae</i> , <i>Haemophilus influenzae</i> , <i>Moraxella catarrhalis</i>
Chronic sinusitis	Anaerobes, <i>Staphylococcus aureus</i> (as well as suspected organisms associated with acute sinusitis)
Epiglottitis	Viral, <i>Haemophilus influenzae</i>
Pneumonia	
Community-acquired	
Normal host	<i>Streptococcus pneumoniae</i> , viral, mycoplasma
Aspiration	Normal aerobic and anaerobic mouth flora
Pediatrics	<i>Streptococcus pneumoniae</i> , <i>Haemophilus influenzae</i>
COPD	<i>Streptococcus pneumoniae</i> , <i>Haemophilus influenzae</i> , <i>Legionella</i> , <i>Chlamydia</i> , <i>Mycoplasma</i>
Alcoholic	<i>Streptococcus pneumoniae</i> , <i>Klebsiella</i>
Hospital-acquired	
Aspiration	Mouth anaerobes, aerobic gram-negative rods, <i>Staphylococcus aureus</i>
Neutropenic	Fungi, aerobic gram-negative rods, <i>Staphylococcus aureus</i>
HIV	Fungi, <i>Pneumocystis</i> , <i>Legionella</i> , <i>Nocardia</i> , <i>Streptococcus pneumoniae</i> , <i>Pseudomonas</i>
<b>2. URINARY TRACT</b>	
Community-acquired	<i>Escherichia coli</i> , other gram-negative rods, <i>Staphylococcus aureus</i> , <i>Staphylococcus epidermidis</i> , enterococci
Hospital-acquired	Resistant aerobic gram-negative rods, enterococci
<b>3. SKIN AND SOFT TISSUE</b>	
Cellulitis	Group A streptococci, <i>Staphylococcus aureus</i>
IV catheter infection	<i>Staphylococcus aureus</i> , <i>Staphylococcus epidermidis</i>
Surgical wound	<i>Staphylococcus aureus</i> , gram-negative rods
Diabetic ulcer	<i>Staphylococcus aureus</i> , gram-negative aerobic rods, anaerobes
Furuncle	<i>Staphylococcus aureus</i>
<b>4. INTRA-ABDOMINAL</b>	<i>Bacteroides fragilis</i> , <i>Escherichia coli</i> , other aerobic gram-negative rods, enterococci
<b>5. GASTROENTERITIS</b>	<i>Salmonella</i> , <i>Shigella</i> , <i>Helicobacter</i> , <i>Campylobacter</i> , <i>Clostridium difficile</i> , ameba, <i>Giardia</i> , viral, enterotoxigenic-hemorrhagic <i>Escherichia coli</i>
<b>6. ENDOCARDITIS</b>	
Preexisting valvular disease	<i>Viridans streptococci</i>
IV drug user	<i>Staphylococcus aureus</i> , aerobic gram-negative rods, enterococci, fungi
Prosthetic valve	<i>Staphylococcus epidermidis</i> , <i>Staphylococcus aureus</i>
<b>7. OSTEOMYELITIS AND SEPTIC ARTHRITIS</b>	<i>Staphylococcus aureus</i> , aerobic gram-negative rods
<b>8. MENINGITIS</b>	
<2 months	<i>Escherichia coli</i> , group B streptococci, <i>Listeria</i>
2 months–12 years	<i>Streptococcus pneumoniae</i> , <i>Neisseria meningitidis</i> , <i>Haemophilus influenzae</i>
Adults	<i>Streptococcus pneumoniae</i> , <i>Neisseria meningitidis</i>
Hospital-acquired	<i>Streptococcus pneumoniae</i> , <i>Neisseria meningitidis</i> , aerobic gram-negative rods
Postneurosurgery	<i>Staphylococcus aureus</i> , aerobic gram-negative rods

COPD, chronic obstructive pulmonary disease; IV, intravenous.

TABLE 60.4 In Vitro Antimicrobial Susceptibility: Aerobic Gram-Positive Cocci

Drugs	Staphylococcus aureus	Staphylococcus aureus (MR)	Staphylococcus epidermidis	Staphylococcus epidermidis (MR)	Streptococci <sup>a</sup>	Enterococci <sup>b</sup>	Pneumococci
Ampicillin	+		+		+++	++	+++
Ampicillin/clavulanate	+++	+	+++		+++	++	+++
Aztreonam							
Cefazolin	+++		+++		+++		++
Cefepime	+++		+++		+++		+++
Cefoxitin/Cefotetan	++		++		++		+
Cefuroxime	+++		+++		+++		+++
Ciprofloxacin <sup>c</sup>	+++	++	+++	++	+	+	++
Clindamycin	+++	+	+++	+	+++		+++
Trimethoprim/sulfamethoxazole	+++	+++	++	+	++	+	+
Daptomycin <sup>d</sup>	+++	++++	+++	+++	+++	+++	+++
Erythromycin (azithromycin/clarithromycin)	++		+		++		++
Imipenem	+++		+++		+++	++	+++
Levofloxacin (gemifloxacin, moxifloxacin)	+++	++	+++	++	+++	++	+++
Linezolid <sup>e</sup>	+++	++++	+++	+++	+++	+++	+++
Nafcillin	+++		+++		+++		++
Penicillin	+		+		+++	++	+++
Quinupristin/dalfopristin <sup>d,f</sup>	+++	++++	+++	+++	+++	+++	+++
TGC <sup>c</sup>	+++		++		+++		+++
Televancin	+++	+++	+++	+++	+++	+++	+++
Tigecycline <sup>f</sup>	+++	+++	+++	+++	+++	+++	+++
Ticarcillin/clavulanate	+++		+++		+++	+	+
Ampicillin/sulbactam	+++		+++		+++	++	+++
Vancomycin	+++	+++	+++	+++	+++	+++	+++
Piperacillin/tazobactam	+++		+++		+++	++	+++

<sup>a</sup>Nonpneumococcal streptococci.

<sup>b</sup>Usually requires combination therapy (e.g., ampicillin and an aminoglycoside) for serious infection.

<sup>c</sup>Levofloxacin (gatifloxacin, gemifloxacin, moxifloxacin) is more active than ciprofloxacin against staphylococci and streptococci.

<sup>d</sup>Active against *E. faecium* but unpredictable against *E. faecalis*.

<sup>e</sup>Cefotaxime, ceftizoxime, ceftriaxone, cefoperazone. Ceftazidime has comparatively inferior antistaphylococcal and antipneumococcal activity. Cefotaxime and ceftriaxone are the most reliable cephalosporins versus *S. pneumoniae*.

<sup>f</sup>Active versus vancomycin-resistant *Enterococcus faecium*.

MR, methicillin resistant; TGC, third-generation cephalosporin.

TABLE 60.5 In Vitro Antimicrobial Susceptibility: Gram-Negative Aerobes

Drugs	<i>Escherichia coli</i>	<i>Klebsiella pneumoniae</i>	<i>Enterobacter cloacae</i>	<i>Proteus mirabilis</i>	<i>Serratia marcescens</i>	<i>Pseudomonas aeruginosa</i>	<i>Haemophilus influenzae</i>	<i>Haemophilus influenzae</i> <sup>a</sup>
Ampicillin	++			+++			+++	
Ampicillin/clavulanate	+++	++		+++			+++	+++
Aztreonam	++++	++++	+	+++	++++	++++	+++	+++
Cefazolin	+++	+++		+++			+	
Cefepime	++++	++++	+++	+++	+++	+++	+++	+++
Ceftazidime	++++	++++	+	+++	+++	+++	+++	+++
Cefuroxime	+++	+++		+++	+		+++	+++
Trimethoprim/sulfamethoxazole	++	+++	+++	+++	+++		+++	+++
Ertepenem	++++	++++	+++	+++	+++	+	+++	+++
Gentamicin	++++	++++	+++	+++	+++	+++	++	+
Imipenem/meropenem/doripenem	++++	++++	+++	+++	+++	+++	+++	+++
Quinolones	+++	+++	+++	+++	+++	++	+++	+++
TGC <sup>b</sup>	++++	++++	+	+++	+++	+	+++	+++
Tigecycline	++++	+++	+++	++	+++	-	+++	+++
Ticarcillin/clavulanate	+++	+	+	+++	++	++	+++	+++
Tobramycin	+++	+++	+++	+++	++	+++	++	+
Ampicillin/sulbactam	+++	+++		+++	++		+++	+++
Piperacillin/tazobactam	+++	+++	++	+++	+++	+++	+++	+++

<sup>a</sup> $\beta$ -Lactamase-producing strains.<sup>b</sup>Cefataxime, ceftizoxime, ceftriaxone.

TGC, third-generation cephalosporin.

TABLE 60.6 Antimicrobial Susceptibility: Anaerobes

Drugs	Bacteroides fragilis	Peptococcus	Peptostreptococcus	Clostridia
Ampicillin	+	++++	++++	+++
Aztreonam				
Cefazolin		+++	+++	
Cefepime	+	+++	+++	+
Cefotaxime	++	+++	+++	+
Cefoxitin	+++	+++	++++	+
Ceftazidime		+	+	+
Ceftizoxime	+++	+++	+++	+
Ciprofloxacin	+	+	+	+
Clindamycin	+++	++++	++++	++
Moxifloxacin	+++	+++	+++	++
Imipenem (doripenem/ ertapenem/meropenem)	++++	++++	++++	++
Metronidazole	++++	+++	++	+++
Penicillin	+	++++	++++	++++
Ticarcillin/clavulanate	++++	+++	+++	+++
Ampicillin/sulbactam	++++	++++	++++	++++
Vancomycin		+++	+++	+++
Piperacillin/tazobactam	++++	++++	+++	+++

## Treatment

- The proper choice, dose, and duration of antimicrobial therapy are based on several factors. These include site and severity of infection, suspected pathogen, spectrum of activity, established clinical efficacy, adverse effect profile, pharmacokinetic disposition, and cost considerations.
- Table 60.7 outlines antimicrobials of choice in the treatment of bacterial infection. Dosing guidelines are shown in Table 60.8.
- Before initiating therapy an accurate drug and allergy history should be taken. Antibiotic adverse effects are shown in Table 60.9.
- Antimicrobial failure may be related to inadequate dosing, insufficient penetration into the site of infection, or inadequate duration of therapy. Failure can also be related to host factors including the presence of prosthetic material, an undrained focus of infection, and immune status.

TABLE 60.7 Antimicrobials of Choice in the Treatment of Bacterial Infection

Organism	Drug of Choice	Alternatives	Comments
<b>AEROBES</b>			
<i>Gram-positive cocci</i>			
<i>Streptococcus pyogenes</i> (group A streptococci)	Penicillin	Clindamycin, macrolide, cephalosporin	Clindamycin is the most reliable alternative for penicillin-allergic patients.
<i>Streptococcus pneumoniae</i>	Ceftriaxone, ampicillin, oral amoxicillin	Macrolide, cephalosporin, doxycycline	Although the incidence of penicillin-nonsusceptible pneumococci is 20%–30%, high-dose penicillin or amoxicillin is active against most of these isolates except in the central nervous system. Penicillin-resistant pneumococci commonly demonstrate resistance to other agents, including erythromycin, tetracyclines, and cephalosporins. Antipneumococcal quinolones (gemifloxacin, levofloxacin, moxifloxacin), ceftriaxone, and cefotaxime are options for treatment of high-level penicillin-resistant isolates.
<i>Enterococcus faecalis</i>	Ampicillin ± gentamicin	Piperacillin-tazobactam; vancomycin ± gentamicin; daptomycin, linezolid, tigecycline	Most commonly isolated enterococcus (80%–85%). Most reliable antienterococcal agents are ampicillin (penicillin, piperacillin-tazobactam), vancomycin, and linezolid. Monotherapy generally inhibits but does not kill the enterococcus. Daptomycin is unique in its bactericidal activity against enterococci. Aminoglycosides must be added to ampicillin or vancomycin to provide bactericidal activity. High-level aminoglycoside resistance should be determined for endocarditis.
<i>Enterococcus faecium</i>	Vancomycin ± gentamicin	Linezolid, daptomycin, dalfopristin/quinupristin (D/Q), tigecycline	Second most common enterococcal organism (10%–20%) and is more likely than <i>E. faecalis</i> to be resistant to multiple antimicrobials. Most reliable agents are daptomycin, D/Q, and linezolid. Monotherapy generally inhibits but does not kill the enterococcus. Aminoglycosides must be added to cell wall-active agents to provide bactericidal activity. Ampicillin and vancomycin resistance is common. Daptomycin, D/Q, and linezolid are drugs of choice for vancomycin-resistant isolates.

<i>Staphylococcus aureus</i> (nafcillin-susceptible)	Nafcillin	Cefazolin, vancomycin, clindamycin, trimethoprim-sulfamethoxazole	10%–15% of isolates inhibited by penicillin. Most isolates susceptible to nafcillin, cephalosporins, trimethoprim-sulfamethoxazole, and clindamycin. First-generation cephalosporins are equal to nafcillin. Most second- and third-generation cephalosporins adequate in the treatment of infection (exceptions include ceftazidime and cefonicid). Methicillin-resistant <i>S. aureus</i> must be treated with vancomycin; however, trimethoprim-sulfamethoxazole, daptomycin, D/Q, linezolid, or minocycline can be used.
	Vancomycin	Trimethoprim-sulfamethoxazole, minocycline, daptomycin, tigecycline, telavancin	
<i>Staphylococcus epidermidis</i> (nafcillin-susceptible)	Nafcillin	Cefazolin, vancomycin, clindamycin	Most isolates are $\beta$ -lactam-, clindamycin-, and trimethoprim-sulfamethoxazole-resistant. Most reliable agents are vancomycin, daptomycin, D/Q, and linezolid. Rifampin is active and can be used in conjunction with other agents; however, monotherapy with rifampin is associated with development of resistance.
	Vancomycin	Daptomycin, linezolid, D/Q	
Gram-positive Bacilli Diphtheroids <i>Corynebacterium jeikeium</i>	Penicillin	Cephalosporin	
	Vancomycin	Erythromycin, quinolone	
<i>Listeria monocytogenes</i>	Ampicillin ( $\pm$ gentamicin)	Trimethoprim-sulfamethoxazole	
Gram-negative Cocci <i>Moraxella catarrhalis</i>	Trimethoprim-sulfamethoxazole	Amoxicillin-clavulanic acid,	
		erythromycin, doxycycline, second- or third-generation cephalosporin	
<i>Neisseria gonorrhoeae</i>	Cefixime	Ceftriaxone	
<i>Neisseria meningitidis</i>	Penicillin	Third-generation cephalosporin	
Gram-negative bacilli <i>Campylobacter fetus</i> <i>Campylobacter jejuni</i>	Imipenem	Gentamicin	
	Quinolone, erythromycin	A tetracycline, amoxicillin-clavulanic acid	
Enterobacter	Trimethoprim-sulfamethoxazole	Quinolone, carbapenem, aminoglycoside	Not predictably inhibited by third-generation cephalosporins. Carbapenems, quinolones, trimethoprim-sulfamethoxazole, cefepime, and aminoglycosides are most active agents.
<i>Escherichia coli</i>	Third-generation cephalosporin	First- or second-generation cephalosporin, gentamicin	Extended-spectrum $\beta$ -lactamase (ESBL)-producers should be treated with a carbapenem.
<i>Haemophilus influenzae</i>	Third-generation cephalosporin	$\beta$ -Lactamase inhibitor combinations, second-generation cephalosporin, trimethoprim-sulfamethoxazole	

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TABLE 60.7 Antimicrobials of Choice in the Treatment of Bacterial Infection (Continued)

Organism	Drug of Choice	Alternatives	Comments
<i>Helicobacter pylori</i>	Amoxicillin + clarithromycin + omeprazole	Tetracycline + metronidazole + bismuth subsalicylate	
<i>Klebsiella pneumoniae</i>	Third-generation cephalosporin	First- or second-generation cephalosporin, gentamicin, trimethoprim-sulfamethoxazole	Extended-spectrum $\beta$ -lactamase (ESBL)-producers should be treated with a carbapenem.
<i>Legionella</i>	Fluoroquinolone	Erythromycin $\pm$ rifampin, doxycycline	
<i>Proteus mirabilis</i>	Ampicillin	First-generation cephalosporin, trimethoprim-sulfamethoxazole	
Other <i>Proteus</i>	Third-generation cephalosporin	$\beta$ -Lactamase inhibitor combination, aminoglycoside, trimethoprim-sulfamethoxazole	
<i>Pseudomonas aeruginosa</i>	Antipseudomonal penicillin (or ceftazidime or cefepime) $\pm$ aminoglycoside (or ciprofloxacin or levofloxacin)	Quinolone or imipenem $\pm$ aminoglycoside	Most active agents include aminoglycosides, doripenem, imipenem, meropenem, ceftazidime, cefepime, aztreonam, and the extended-spectrum penicillins. Monotherapy is adequate for most pseudomonal infections.
<i>Salmonella typhi</i>	Quinolone	Ceftriaxone	
<i>Serratia marcescens</i>	Third-generation cephalosporin	Trimethoprim-sulfamethoxazole, aminoglycoside	
<i>Shigella</i>	Quinolone	Trimethoprim-sulfamethoxazole, ampicillin	
<i>Stenotrophomonas maltophilia</i>	Trimethoprim-sulfamethoxazole	Ceftazidime, minocycline, $\beta$ -lactamase inhibitor combination (Ticarcillin/clavulanate)	
<b>ANAEROBES</b>			
<i>Bacteroides fragilis</i>	Metronidazole	$\beta$ -Lactamase inhibitor combinations, penems	Most active agents (95%–100%) include metronidazole, the $\beta$ -lactamase inhibitor combinations (ampicillin-sulbactam, piperacillin-tazobactam, ticarcillin-clavulanic acid), and penems. Clindamycin, cefoxitin, cefotetan, cefmetazole, and ceftizoxime have good activity but not to the degree of metronidazole. Aminoglycosides and aztreonam are inactive.
<i>Clostridia difficile</i>	Metronidazole	Vancomycin	Oral vancomycin is the drug of choice for severe infection.
<i>Fusobacterium</i>	Penicillin	Metronidazole, clindamycin	

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**OTHER OROPHARYNGEAL**

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<i>Prevotella</i>	$\beta$ -Lactamase inhibitor combination	Metronidazole, clindamycin	Most $\beta$ -lactams active (exceptions include aztreonam, nafcillin, ceftazidime)
<i>Peptostreptococcus</i>	Penicillin	Clindamycin, cephalosporin	

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**OTHER**

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<i>Actinomyces israelii</i>	Penicillin	Tetracyclines
<i>Nocardia</i>	Trimethoprim-sulfamethoxazole	Amikacin, minocycline, imipenem
<i>Chlamydia trachomatis</i>	Doxycycline	Azithromycin
<i>Chlamydia pneumoniae</i>		Azithromycin, clarithromycin
<i>Mycoplasma pneumoniae</i>	Doxycycline	Azithromycin, clarithromycin
<i>Borrelia burgdorferi</i>	Doxycycline	Ampicillin, second- or third-generation cephalosporin
<i>Treponema pallidum</i>	Penicillin	Doxycycline

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TABLE 60.8 UCSF/Mt. Zion Medical Center Adult Antimicrobial Dosing Guidelines

Approved by the Antibiotic Advisory Subcommittee and the Pharmacy and Therapeutics Committee 7/10 Department of Pharmaceutical Services

Drug	CrCl >50 mL/minute	CrCl 10–50 mL/minute	CrCl <10 mL/minute (ESRD not on HD)	Dialysis (HD or CRRT)
<b>ACYCLOVIR</b>	<i>Herpes simplex infections</i> 5 mg/kg/dose IV every 8 hours <i>HSV encephalitis/Herpes zoster</i> 10 mg/kg/dose IV every 8 hours	5 mg/kg/dose IV every 12–24 hours 10 mg/kg/dose IV every 12–24 hours	2.5 mg/kg IV every 24 hours 5 mg/kg IV every 24 hours	HD: 2.5 mg/kg IV × 1 now then 2.5 mg/kg every evening (give after HD on HD days) CRRT: 5 mg/kg every 24 hours HD: 5 mg/kg IV × 1 now then 5 mg/kg every evening (give after HD on HD days) CRRT: 5–10 mg/kg every 12–24 hours
<b>AMPHOTERICIN B</b>	0.6–1.0 mg/kg IV every 24 hours	No change	No change	No change
Dosage reductions in renal disease unnecessary; however, due to the drug's nephrotoxicity, consider reducing the dose or holding the drug in the setting of a rising SCr.				
<b>AMBISOME</b>	<i>Invasive mold infections</i> 3–5 mg/kg IV every 24 hours Doses up to 10 mg/kg have been used for invasive mucormycosis <i>Invasive yeast infections</i> 3 mg/kg IV every 24 hours <i>Prophylaxis (heme-onc)</i> 1 mg/kg IV every 24 hours	No change	No change	No change
<b>AMIKACIN</b>	≥60 mL/minute 15–20 mg/kg/dose IV every 24 hours	See below	See below	

Consultation with ID/ID pharmacy recommended before use. Dose is based on ideal body weight (IBW) except in obese patients or those under their ideal body weight. Use actual body weight if patient weight is less than IBW. Use adjusted body weight (ABW) in patients who are obese. Amikacin is generally used as a second-line aminoglycoside because of its increased cost and need to send out levels. The total daily dose of amikacin can be administered as a single daily dose in patients with normal renal function (CrCl ≥ 60 mL/minute). Patients with decreased renal function or abnormal body composition should have doses adjusted according to the recommendations below. Turnaround time on amikacin levels is usually 2–4 days. Peak levels are not useful with this dosing regimen; trough levels are recommended and should be <5 mg/L.

<u>40–60 mL/minute</u>	<u>20–40 mL/minute</u>	<u>&lt;20 mL/minute</u>	HD: 5 mg/kg × 1, then 3 mg/kg IV after HD
5–7.5 mg/kg IV every 12 hours	5 mg/kg IV every 12–24 hours	5 mg/kg loading dose (Consult pharmacy for maintenance dose)	CRRT: 5 mg/kg × 1, then 3 mg/kg IV every 24 hours

With traditional dosing of amikacin, peak (20–30 mg/L) and trough (<8 mg/L) levels are recommended in patients anticipated to receive aminoglycosides for severe gram-negative infection. Those patients with CrCl <60 mL/minute, obesity, or increased fluid volume should be monitored with serum amikacin levels.

<b>AMPICILLIN</b>	1–2 g IV every 4–6 hours	1–1.5 g IV every 6 hours	1 g IV every 8–12 hours	HD: 1–2 g IV every 12 hours CRRT: 1–2 g IV every 6 hours
<b>AMPICILLIN/SULBACTAM</b>	1.5–3 g IV every 6 hours	1.5 g IV every 6–8 hours	1.5 g IV every 12 hours	HD: 1.5 g IV every 12 hours CRRT: 1.5 g IV every 6 hours
<b>AZTREONAM</b>	2 g IV every 8 hours	2 g IV every 12 hours	1 g IV every 12 hours	HD: 1 g IV × 1 now then 1 g every evening (give after HD on HD days) CRRT: 2 g IV every 12 hours
<b>CEFAZOLIN</b>	1–2 g IV every 8 hours	1–2 g IV every 12 hours	1 g IV every 24 hours	HD: 2 g after HD only CRRT: 2 g IV every 12 hours
<b>CASPOFUNGIN</b> Severe hepatic dysfunction: 70 mg LD, then 35 mg IV daily	LD: 70 mg × 1, then 50 mg every 24 hours Increase maintenance dose to 70 mg when given with phenytoin, rifampin, carbamazepine, dexamethasone, nevirapine, efavirenz	No change	No change	No change
<b>CEFEPIME</b> Febrile neutropenia, meningitis, pseudomonas infections, critically ill patients	>60 mL/minute 2 g IV every 12 hours 2 g IV every 8 hours	30–60 mL/minute 2 g IV every 24 hours 2 g IV every 12 hours	10–30 mL/minute 1 g IV every 24 hours 2 g IV every 24 hours	<10 mL/minute 500 mg IV every 24 hours 1 g IV every 24 hours HD: 2 g after HD only CRRT: 2 g IV every 12 hours

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TABLE 60.8 UCSF/Mt. Zion Medical Center Adult Antimicrobial Dosing Guidelines (Continued)

Approved by the Antibiotic Advisory Subcommittee and the Pharmacy and Therapeutics Committee 7/10 Department of Pharmaceutical Services

Drug	CrCl >50 mL/minute	CrCl 10–50 mL/minute		CrCl <10 mL/minute (ESRD not on HD)	Dialysis (HD or CRRT)
<b>CEFTAZIDIME</b>	2 g IV every 8 hours	2 g IV every 12–24 hours		0.5 g IV every 24 hours	HD: 1 g after HD only CRRT: 2 g IV every 12 hours
<b>CEFTRIAXONE</b> Meningitis: 2 g every 12 hours Endocarditis and osteomyelitis: 2 g every 24 hours	1 g IV every 24 hours	No change		No change	No change
<b>CIPROFLOXACIN<sup>IV-PO</sup></b> Pseudomonas infections	400 mg IV every 12 hours 500–750 mg PO every 12 hours 400 mg IV every 8 hours 750 mg PO every 12 hours	30–50 mL/ minute No change No change	10–30 mL/ minute 200–400 mg IV every 12 hours 250–500 mg PO every 12 hours	200 IV every 12 hours 250 mg PO every 12 hours	HD: 400 mg IV every 24 hours or 500 mg PO every 24 hours CRRT: 400 mg IV every 12 hours
<b>CLINDAMYCIN</b>	600–900 mg IV every 8 hours	No change		No change	No change
<b>COLISTIN</b> Consultation with ID pharmacy recommended	2.5 mg/kg IV every 12 hours	2.5 mg/kg IV every 12–24 hours		1.5 mg/kg IV every 24 hours	HD: 1.5 mg/kg every 24 hours CRRT: 1.5 mg/kg every 24 hours
<b>DAPTOMYCIN</b> Dose on total body weight	4–10 mg/kg IV every 24 hours Dose depends on indication	<u>&lt;30 mL/minute</u> 4–10 mg/kg IV every 48 hours			HD: 4–10 mg/kg IV every 48 hours CRRT: 4–10 mg/kg IV every 48 hours
<b>DOXYCYCLINE<sup>IV-PO</sup></b>	100 mg IV/PO every 12 hours	No change		No change	No change
<b>ERTAPENEM</b>	1 g IV every 24 hours	<u>&lt;30 mL/minute</u> 500 mg IV every 24 hours			HD: 500 mg every 24 hours CRRT: 500 mg every 24 hours
<b>ETHAMBUTOL</b>	15–20 mg/kg PO every 24 hours	<u>&lt;30 mL/minute</u> 15–25 mg/kg three times per week			HD: 15–25 mg/kg three times per week (after HD) CRRT: 15–25 mg/kg three times per week

<b>FLUCONAZOLE<sup>IV-PO</sup></b>	100–400 mg IV/PO every 24 hours	50–200 mg IV/PO every 24 hours	50–100 mg IV/PO every 24 hours	HD: 400 mg after HD only CRRT: 400–800 mg every 24 hours
<b>FLUCYTOSINE (5FC)</b>	25 mg/kg/dose PO every 6 hours	<u>25–50 mL/minute</u> 25 mg/kg/dose PO every 12 hours	<u>10–25 mL/minute</u> 25 mg/kg/dose PO every 24 hours	12.5 mg/kg/dose PO every 24 hours HD: 12.5–25 mg/kg PO every 24 hours CRRT: 12.5–37.5 mg/kg/dose PO every 12–24 hours
<b>GANCICLOVIR</b>	<u>≥70 mL/minute</u> 5 mg/kg/dose IV every 12 hours	<u>50–69 mL/minute</u> 2.5 mg/kg/dose IV every 12 hours	<u>25–49 mL/minute</u> 2.5 mg/kg IV every 24 hours	<u>10–24 mL/minute</u> 1.25 mg/kg IV every 24 hours HD: 1.25 mg/kg after HD only CRRT: 2.5–5 mg/kg every 24 hours
<b>GENTAMICIN</b>	<u>≥60 mL/minute</u> 5 mg/kg/dose IV every 24 hours	See below	See below	

Dose is based on ideal body weight (IBW) except in obese patients or those under their ideal body weight. Use actual body weight if patient weight is less than IBW. Use adjusted body weight (ABW) in patients who are obese. The total daily dose of gentamicin can be administered as a single daily dose in patients with normal renal function (CrCl ≥60 mL/minute). Peak levels are not useful in this regimen; however, trough levels are recommended and in most cases will be undetectable. Patients with decreased renal function or abnormal body composition should have doses adjusted according to the recommendations below.

Alternative: 1.6 mg/kg iv every 8 hours (total 5 mg/kg/day) for clinically tenuous patients or patients with changing volume status	<u>40–60 mL/minute</u> 1.2–1.5 mg/kg IV every 12 hours	<u>20–40 mL/minute</u> 1.2–1.5 mg/kg IV every 12–24 hours	<u>≤20 mL/minute</u> 2 mg/kg loading dose (Consult pharmacy for maintenance dose)	HD: 2 mg/kg × 1, then 1 mg/kg IV after HD CRRT: 2 mg/kg × 1, then 1.5 mg/kg IV every 24 hours
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With traditional dosing of gentamicin, peak (5–8 mg/L) and trough (<2 mg/L) levels are recommended for patients receiving aminoglycosides for severe gram-negative infection. Lower doses (1 mg/kg/dose every 8 hours) are suggested when aminoglycosides are used synergistically in gram-positive infections. Those patients with CrCl <60 mL/minute, obesity, or increased fluid volume should be monitored with serum gentamicin levels. Goals for gram-positive synergy dosing peak (3–4 mg/L) and trough (<1 mg/L)

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TABLE 60.8 UCSF/Mt. Zion Medical Center Adult Antimicrobial Dosing Guidelines (Continued)

Approved by the Antibiotic Advisory Subcommittee and the Pharmacy and Therapeutics Committee 7/10 Department of Pharmaceutical Services

Drug	CrCl >50 mL/minute	CrCl 10–50 mL/minute	CrCl <10 mL/minute (ESRD not on HD)	Dialysis (HD or CRRT)
<b>IMIPENEM</b>	500 mg IV every 6–8 hours <i>max 50 mg/kg/day</i>	500 mg IV every 8 hours	≤20 mL/minute 250–500 mg IV every 12 hours	HD: 250 mg IV every 12 hours CRRT: 500 mg IV every 8 hours
<b>ISONIAZID</b>	300 mg PO every 24 hours	No change	No change	No change
<b>LEVOFLOXACIN</b> <sup>IV-PO</sup> Nosocomial pneumonia/Pseudomonas infections	250–500 mg IV/PO every 24 hours 750 mg IV/PO every 24 hours	500 mg × 1, then 250 mg IV/PO every 24 hours 750 mg × 1; then 750 IV/PO every 48 hours	500 mg × 1, then 250 mg IV/PO every 48 hours 750 mg × 1, then 500 mg IV/PO every 48 hours	HD: 500 mg × 1, then 250 mg every 48 hours CRRT: 500 mg × 1, then 250–500 mg every 24 hours
<b>LINEZOLID</b> <sup>IV-PO</sup>	600 mg IV/PO every 12 hours	No change	No change	No change
<b>MEROPENEM</b> Meningitis/documented or suspected <i>Pseudomonas</i> infections or critically ill	0.5–1 g IV every 8 hours 2 g IV every 8 hours	<u>25–50 mL/minute</u> 0.5–1 g IV every 12 hours 2 g IV every 12 hours	<u>10–25 mL/minute</u> 0.5 g IV every 12 hours 1 g IV every 12 hours	0.5 g IV every 24 hours 1 g IV every 24 hours HD: 500 mg IV × 1 now then 500 mg every evening (give after HD on HD days) CRRT: 1 g IV every 12 hours
<b>METRONIDAZOLE</b> <sup>IV-PO</sup>	500 mg IV/PO every 8 hours	500 mg IV/PO every 8 hours	500 mg IV/PO every 12 hours ESRD not on HD	500 mg IV/PO every 8 hours
<b>MOXIFLOXACIN</b> <sup>IV-PO</sup>	400 mg IV/PO every 24 hours	No change	No change	No change
<b>NAFCILLIN</b>	1–2 g IV every 4–6 hours	No change	No change	No change
<b>PENICILLIN G</b>	2–3 MU IV every 4–6 hours	1–2 MU IV every 4–6 hours	1 MU IV every 6 hours	HD: 1 MU IV every 6 hours CRRT: 2 MU IV every 4–6 hours

<b>PIP/TAZO (PIPERACILLIN/ TAZOBACTAM)</b> Documented/suspected <i>Pseudomonas</i> infections	3.375–4.5 g IV every 6–8 hours 4.5 g every 6 hours for ClCr >20 mL/minute	3.375–4.5 g every 6–8 hours	2.25–3.375 g every 8 hours	HD: 2.25 g IV every 8 hours CRRT: 4.5 g IV every 8 hours or 3.375 g IV every 6 hours
<b>POSACONAZOLE</b> Must be administered with high-fat meal or nutritional shake (i.e., Ensure)	400 mg PO every 12 hours or 200 mg PO every 6 hours	No change	No change	No change
<b>PYRAZINAMIDE</b>	20–25 mg/kg/day PO every 24 hours	<30 mL/minute 25–35 mg/kg three times per week		HD: 25–35 mg/kg three times per week after HD CRRT: 25–35 mg/kg three times per week
<b>RIFAMPIN</b> Endocarditis Prosthetic infection	600 mg PO every 24 hours 300 mg PO every 8 hours 450 mg PO every 12 hours	No change	No change	No change
<b>TIGECYCLINE</b> Severe hepatic disease: 100 mg IV × 1, then 25 mg IV every 12 hours	100 mg IV × 1, then 50 mg IV every 12 hours	No change	No change	No change
<b>TOBRAMYCIN</b>	See Gentamicin	See Gentamicin	See Gentamicin	See Gentamicin
<b>TMP/SMX<sup>IV-PO</sup></b> When switching to oral therapy, consider that a single-strength tablet has 80 mg of TMP and a double- strength tablet 160 mg of TMP.	<u>Systemic GNR infections</u> 10 mg TMP/kg/day IV divided every 6–12 hours <u>Pneumocystis pneumonia</u> 15–20 mg TMP/kg/day IV divided every 6–12 hours	5–7.5 mg TMP/kg/day IV divided every 12–24 hours 10–15 mg TMP/kg/day IV divided every 12–24 hours	2.5–5.0 mg TMP/kg IV every 24 hours 5–10 mg TMP/kg IV every 24 hours	HD: 2.5–5 mg TMP/kg/day every 24 hours CRRT: 5–7.5 mg TMP/kg/ day divided every 12–24 hours

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TABLE 60.8 UCSF/Mt. Zion Medical Center Adult Antimicrobial Dosing Guidelines (Continued)

Approved by the Antibiotic Advisory Subcommittee and the Pharmacy and Therapeutics Committee 7/10 Department of Pharmaceutical Services

Drug	CrCl >50 mL/minute	CrCl 10–50 mL/minute	CrCl <10 mL/minute (ESRD not on HD)	Dialysis (HD or CRRT)	
<b>VORICONAZOLE</b> <sup>IV-PO</sup>	LD = 400 mg every 12 hours × 1 day, then 200 mg every 12 hours (PO)	No change	No change*	No change*	
<b>VANCOMYCIN</b>	<p>≥60 mL/minute</p> <p>10–15 mg/kg IV every 12 hours<sup>1</sup></p> <p>15–20 mg/kg IV every 8–12 hours<sup>2</sup></p>	<p>40–60 mL/minute</p> <p>10–15 mg/kg IV every 12–24 hours</p>	<p>20–40 mL/minute</p> <p>5–10 mg/kg IV every 24 hours</p>	<p>10–20 mL/minute</p> <p>5–10 mg/kg IV every 24–48 hours</p>	<p>≤10 mL/minute</p> <p>10–15 mg/kg IV loading dose × 1; redose according to serum levels</p> <p>HD: 15–20 mg/kg load, then 500 mg IV after HD only CRRT: 10–15 mg/kg IV every 24 hours</p>

PO should be used when possible, as oral bioavailability >95%. IV dose: LD = 6 mg/kg/dose every 12 hours × 1 day, then 4 mg/kg/dose every 12 hours. \*The use of the IV formulation should be avoided in patients with CrCl <50 mL/minute owing to accumulation of IV vehicle and is contraindicated in ESRD and hemodialysis. May require dose adjustment in hepatic dysfunction. ID approval required except for heme-onc and lung transplant services.

Round dose to 250 mg, 500 mg, 750 mg, 1 g, 1.25 g, 1.5 g, 1.75 g, or 2 g (maximum 2 g/dose). Trough levels should be obtained within 30 minutes before fourth dose of a new regimen or dosage change. Vancomycin troughs are not recommended in patients in whom anticipated duration of therapy is ≤3 days.

<sup>1</sup>For patients with uncomplicated infections requiring vancomycin, trough levels of 10–15 mcg/mL are recommended.

<sup>2</sup>For patients with serious infections caused by MRSA (central nervous system infections, endocarditis, ventilator-associated pneumonia, bacteremia, or osteomyelitis), trough levels of 15–20 mcg/mL are recommended. ID CONSULT IS RECOMMENDED.

<sup>a</sup>Doses are those recommended for systemic infections commonly treated with these agents.

CrCl, creatinine clearance; CRRT, continuous renal replacement therapy (assumes an ultrafiltration rate of 2 L/hour with continuous venovenous hemofiltration and an ultrafiltration rate of 1 L/hour and dialysate flow rate of 1 L/hour with continuous venovenous hemodiafiltration and residual native glomerular filtration rate <10 mL/minute); ESRD, end-stage renal disease; HD, intermittent (high-flux) hemodialysis (when administering a daily dose with HD, the drug should be administered after the HD session); HSV, herpes simplex virus; IV, intravenous; IV-PO, high oral bioavailability (consider initiating with or switching to PO therapy when patient tolerating orals); LD, loading dose; MRSA, methicillin-resistant *Staphylococcus aureus*; PO, by mouth; SCr, serum creatinine.

Estimate of renal function using Cockcroft and Gault equation: 
$$\text{CrCl (mL/minute)} = \frac{(140 - \text{Age}) \times \text{Wt(kg)}}{(72) \times \text{SCr (mg/dL)}}$$

(for females multiply by 0.85)

Females: IBW = 45.5 + 2.3 kg for each inch over 5 feet.

Adjusted body weight: ABW = IBW + 0.4 (actual weight - IBW).

TABLE 60.9 Antibiotic Adverse Effects and Toxicities

Antibiotic	Side Effects	Comments
$\beta$ -Lactams (penicillin, cephalosporins, monobactams, penems)	Allergic: anaphylaxis, urticaria, serum sickness, rash, fever	Many patients will have “ampicillin rash” or “ $\beta$ -lactam rash” with no cross-reactivity with any other penicillins/ $\beta$ -lactams. Most commonly observed in patients with concomitant EBV disease. Likelihood of IgE-mediated cross-reactivity between penicillins and cephalosporins approximately 5%–10%. Most recent data strongly suggest minimal IgE cross-reactivity between penicillins and imipenem/meropenem. No IgE cross-reactivity between aztreonam and penicillins.
	Diarrhea	Particularly common with ampicillin, Ampicillin/clavulanate, ceftriaxone, and cefoperazone. Antibiotic-associated colitis can occur with most antimicrobials.
	Hematologic: anemia, thrombocytopenia, antiplatelet activity, hypotherbinemia	Hemolytic anemia more common with higher doses. Antiplatelet activity (inhibition of platelet aggregation) most common with the antipseudomonal penicillins and high serum levels of other $\beta$ -lactams
	Hepatitis or biliary sludging	Hypotherbinemia more often associated with those cephalosporins with the methyltetraazolethiol side chain (cefamandole, cefotetan). Reaction preventable and reversible with vitamin K
	Phlebitis	Hepatitis most common with oxacillin. Biliary sludging and stones reported with ceftriaxone
	Seizure activity	Associated with high levels of $\beta$ -lactams, particularly penicillins and imipenem
	Potassium load	Penicillin G ( $K^+$ )
	Nephritis	Most common with methicillin; however, occasionally reported for most other $\beta$ -lactams.
	Neutropenia	Nafcillin
	Disulfiram reaction	Associated with cephalosporins with methyltetraazolethiol side chain (cefamandole, cefotetan)
Aminoglycosides (gentamicin, tobramycin, amikacin, netilmicin)	Hypotension, nausea	Associated with fast infusion of imipenem
	Nephrotoxicity	Averages 10%–15% incidence. Generally reversible, usually occurs after 5–7 days of therapy. <i>Risk factors:</i> dehydration, age, dose, duration, concurrent nephrotoxins, liver disease
	Ototoxicity	1%–5% incidence, often irreversible. Both cochlear and vestibular toxicity occur
Macrolides (erythromycin, azithromycin, clarithromycin)	Neuromuscular paralysis	Rare, most common with large doses administered via intraperitoneal instillation or in patients with myasthenia gravis
	Nausea, vomiting, “burning” stomach	Oral administration. Azithromycin and clarithromycin associated with less nausea than erythromycin
	Cholestatic jaundice	Reported for all erythromycin salts, most common with estolate
Telithromycin	Ototoxicity	Most common with high doses in patients with renal or hepatic failure
	Hepatotoxicity; upper GI	Severe, sometime fatal hepatotoxicity associated with telithromycin
Clindamycin	Diarrhea	Most common adverse effect. High association with antibiotic-associated colitis

Continued on following page



TABLE 60.9 Antibiotic Adverse Effects and Toxicities (Continued)

Antibiotic	Side Effects	Comments
Tetracyclines (including tigecycline)	Allergic Photosensitivity Teeth and bone deposition and discoloration GI Hepatitis Renal (azotemia)	Avoid in pediatrics (<8 years old), pregnancy, and breast-feeding Upper GI predominates Primarily in pregnancy or the elderly Tetracyclines have antianabolic effect and should be avoided in patients with ↓ renal function. Less problematic with doxycycline
Vancomycin	Vestibular Ototoxicity Nephrotoxicity Hypotension, flushing Phlebitis	Associated with minocycline, particularly high doses Only with receipt of concomitant ototoxins such as aminoglycosides or macrolides Nephrotoxic only with high doses or in combination with other nephrotoxins Associated with rapid infusion of vancomycin. More common with increased doses Needs large volume dilution
Dalfopristin/ quinupristin	Phlebitis Myalgia Increased bilirubin	Generally requires central line administration Moderate to severe in many patients
Daptomycin	Myalgia	Primarily at high doses and reversible
Linezolid	Thrombocytopenia, neutropenia, anemia, MAO inhibition, tongue discoloration	
Televancin	Renal toxicity, prolonged QT	
Sulfonamides	GI Hepatic Rash Hyperkalemia Bone marrow Kernicterus	Nausea, diarrhea Cholestatic hepatitis, ↑ incidence in HIV Exfoliative dermatitis, Stevens-Johnson syndrome. More common in HIV Only with trimethoprim (as a component of trimethoprim-sulfamethoxazole) Neutropenia, thrombocytopenia. More common in HIV Caused by unbound drug in the neonate. Premature liver cannot conjugate bilirubin. Sulfonamide displaces bilirubin from protein, resulting in excessive free bilirubin and kernicterus
Chloramphenicol	Anemia Gray syndrome	Idiosyncratic irreversible aplastic anemia (rare). Reversible dose-related anemia Caused by inability of neonates to conjugate chloramphenicol
Quinolones	GI Prolonged QT Drug interactions CNS Cartilage toxicity Tendonitis or tendon rupture	Nausea, vomiting, diarrhea Moxifloxacin; possibly all quinolones as a class ↓ Oral bioavailability with multivalent cations Altered mental status, confusion, seizures Toxic in animal model. Despite this toxicity, appears safe in children including patients with cystic fibrosis Common in elderly, renal failure, concomitant glucocorticoids

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**ANTIFUNGALS**

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Amphotericin B products	Nephrotoxicity	Common. May depend on patient's sodium load. Caution with concomitant nephrotoxins (e.g., aminoglycosides, cyclosporine)
	Hypokalemia	Predictable. Probably caused by renal tubular excretion of potassium. More common in patients receiving concomitant piperacillin-tazobactam
	Hypomagnesemia	Less commonly observed than hypokalemia
	Anemia	Long-term adverse effect. Similar to anemia of chronic disease
Caspofungin, micafungin, anidulofungin	Mild LFT increase with concomitant cyclosporine; anidulofungin is reconstituted with alcohol (about the equivalent of a beer)	
Flucytosine	Neutropenia, thrombocytopenia	Secondary to metabolism of flucytosine to fluorouracil. More commonly observed with flucytosine levels >100 mg/mL. More common in patients with HIV
	Hepatitis	Usually moderate ↑ in LFT. Rarely clinical hepatitis
Ketoconazole (fluconazole, itraconazole, posaconazole, voriconazole)	Drug interactions	↓ Oral bioavailability of ketoconazole tablet, and itraconazole capsules with ↑ gastric pH. Azoles are CYP450 substrates and also inhibitors of CYP450 3A4 and other CYP isoenzymes
	Hepatitis	Ranges from mild ↑ in LFT to occasional fatal hepatitis
	Gynecomastia, ↓ libido	More common with high-dose ketoconazole (>400 mg/day). Less common with other azoles
	Visual disturbance	Unique to voriconazole, particularly first week of therapy

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**ANTIVIRALS (EXCLUDING ANTIRETROVIRALS)**

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Acyclovir	Phlebitis	Caused by poor solubility of IV preparation. Reported in 1%–20% of cases
	Renal failure	Low solubility of acyclovir associated with renal failure. Dehydrated patients, as well as rapid infusions, predispose to toxicity
Foscarnet	CNS	1% incidence in AIDS. ↑ Incidence with dose in >10 mg/kg/day
	Nephrotoxicity	Occurs in up to 60% of patients. May be prevented with normal saline bolus before dose. Frequent monitoring of renal function imperative
	Mineral and electrolyte abnormalities	↑ and ↓ calcium or phosphate may be observed. Hypocalcemia, hypo- and hyperphosphatemia, hypomagnesemia, hypokalemia. ↑ Risk of cardiomyopathy and seizures
	Anemia	Anemia in 33%; usually manageable with transfusions and discontinuation of foscarnet
	Nausea, vomiting	
Ganciclovir	Neutropenia, thrombocytopenia	↑ Incidence in AIDS. ↑ Incidence with doses in excess of 10 mg/kg/day
	Hepatitis	Usually mild to moderate in LFT
Oseltamavir	Nausea	

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AIDS, acquired immunodeficiency syndrome; CNS, central nervous system; EBV, Epstein–Barr virus; GI, gastrointestinal; HIV, human immunodeficiency virus; IV, intravenous; LFT, liver function tests; MAO, monoamine oxidase.

# Antimicrobial Prophylaxis for Surgical Procedures\*

## General Principles

- Surgical site infection occurs when a pathogenic organism multiplies in a surgical wound leading to local or systemic signs and symptoms. Surgical infections are costly and can increase morbidity and mortality.
- Surgical antibiotic prophylaxis is indicated for patients at high risk of infection or in those at high risk of complications from postoperative infection.

## Classification

- Current recommendations for surgical prophylaxis pertain to clean surgeries. Standard classification based on the risk of intraoperative bacterial contamination is shown in Table 61.1.
- Surgical site infections are classified as either superficial (involving the skin and subcutaneous fat) or deep incisional (involving fascia and muscle).

## Risk Factors

- The likelihood for development of postoperative site infection is related to the degree of bacterial contamination during surgery, virulence of the infecting organism, and host

TABLE 61.1 National Research Council Wound Classification

Classification	Criteria	Infection Rate (%)
Clean	No acute inflammation or entry into GI, respiratory, GU, or biliary tracts; no break in aseptic technique occurs; wounds primarily closed	>5
Clean-contaminated	Elective, controlled opening of GI, respiratory, biliary, or GU tracts without significant spillage; clean wounds with major break in sterile technique	>10
Contaminated	Penetrating trauma (>4 hours old); major technique break or major spillage from GI tract; acute, nonpurulent inflammation	15–20
Dirty	Penetrating trauma (<4 hours old); purulence or abscess (active infectious process); preoperative perforation of viscera	30–40

GI, gastrointestinal; GU, genitourinary.

Source: Adapted with permission from Berard F, Gandon J. Postoperative wound infections: the influence of ultraviolet irradiation of the operating room and of various other factors. *Ann Surg.* 1964;160(Suppl 2):1.

\*The reader is referred to Chapter 61, Antimicrobial Prophylaxis for Surgical Procedures, written by Daniel J. G. Thirion, PharmD, FCSHP, in the 10th edition of *Applied Therapeutics: The Clinical Use of Drugs* for a more in-depth discussion. All notations to reference numbers are based on the reference list at the end of that chapter. The editor of this handbook expresses her thanks to Dr. Thirion and acknowledges that this chapter is based on his work.

TABLE 61.2 Suggested Prophylactic Antimicrobial Regimens for Surgical Procedures

Procedure	Predominant Organism(s)	Antibiotic Regimen (Alternative)	Adult Preoperative IV Dose (Alternative)
<b>CLEAN</b>			
Neurosurgery	<i>Staphylococcus aureus</i> , <i>Staphylococcus epidermidis</i>	Cefazolin (vancomycin <sup>b</sup> )	1–2 g (1 g) <sup>a</sup>
Cardiac (all with sternotomy, cardiopulmonary bypass, pacemaker and automated defibrillator placement)	<i>S. aureus</i> , <i>S. epidermidis</i>	Cefazolin (vancomycin <sup>b</sup> )	1–2 g (1 g) <sup>a</sup>
Thoracic	<i>S. aureus</i> , <i>S. epidermidis</i> , gram-negative enterics	Cefazolin (vancomycin <sup>b</sup> )	1–2 g (1 g) <sup>a</sup>
Vascular (aortic resection, groin incision, prosthesis)	<i>S. aureus</i> , <i>S. epidermidis</i> , gram-negative enterics	Cefazolin (vancomycin <sup>b</sup> )	1–2 g (1 g) <sup>a</sup>
Orthopedic (total joint replacement, internal fixation of fractures)	<i>S. aureus</i> , <i>S. epidermidis</i>	Cefazolin (vancomycin <sup>b</sup> )	1–2 g (1 g) <sup>a</sup>
<b>CLEAN-CONTAMINATED</b>			
Head and neck (involving incisions through mucosa)	<i>S. aureus</i> , oral anaerobes, streptococci	Cefazolin (clindamycin-gentamicin)	2 g (600 mg clindamycin–1.5 mg/kg gentamicin)
Gastroduodenal (only for procedures entering the stomach)	Gram-negative enterics, <i>S. aureus</i> , mouth flora	Cefazolin	1–2 g <sup>a</sup>
Appendectomy (uncomplicated)	Gram-negative enterics, anaerobes ( <i>Bacteroides fragilis</i> ), enterococci	Cefoxitin	1–2 g
Biliary tract (only for high-risk procedures)	Gram-negative enterics, <i>Enterococcus faecalis</i> , <i>Clostridia</i>	Cefazolin	1–2 g <sup>a</sup>
Colorectal	Gram-negative enterics, anaerobes ( <i>B. fragilis</i> ), enterococci	Oral neomycin-erythromycin base (IV cefoxitin)	1 g each at 1 PM, 2 PM, and 11 PM day before surgery (1 g)
Cesarean section	Group B streptococci, enterococci, anaerobes, gram-negative enterics	Cefazolin	2 g before umbilical cord clamped
Hysterectomy	Group B streptococci, enterococci, anaerobes, gram-negative enterics	Cefazolin or cefoxitin	1–2 g <sup>a</sup>
Abortion (only for high-risk in first trimester)	Group B streptococci, enterococci, anaerobes, gram-negative enterics	Aqueous penicillin G (doxycycline) (first trimester) Cefazolin (second trimester)	2 million units (100 mg PO before and 200 mg PO after) 1–2 g <sup>a</sup>
Genitourinary (only for high-risk procedures)	Gram-negative enterics, enterococci	Ciprofloxacin <sup>b</sup>	400 mg

<sup>a</sup>Cefazolin should be dosed at 2 g in patients weighing more than 80 kg.

<sup>b</sup>Vancomycin and ciprofloxacin require longer infusion times and should be administered within 2 hours before surgery.

defenses. Risk factors can be classified according to procedure-specific factors and patient characteristics.

## Goals of Therapy

- The goal of surgical antimicrobial prophylaxis is to prevent morbidity and mortality associated with infections secondary to a surgical procedure.

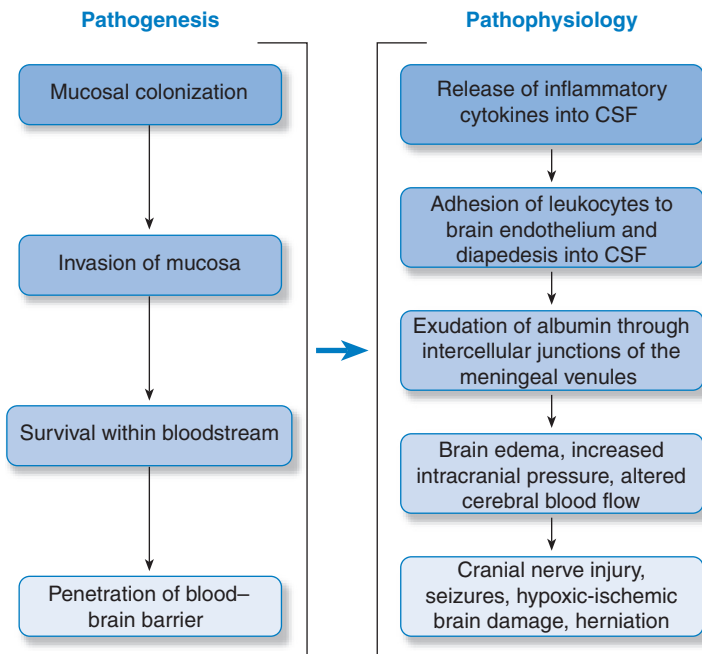
## Treatment

- The choice of agent is based on the spectrum of activity of the agent, the most likely pathogens associated with the surgical procedure (Table 61.2), pharmacokinetic characteristics, adverse-event profile, impact on bacterial resistance, and cost. In general, oral administration of surgical antimicrobial prophylaxis is not recommended due to unreliable or poor absorption of oral agents in the anesthetized bowel. Oral nonabsorbable agents are effective for gastrointestinal (GI) decontamination.
- To achieve adequate drug levels and maximize the benefit of prophylaxis, antibiotics should be given within 1 hour of the incision.
- Single-dose preoperative prophylaxis is sufficient for most surgical procedures. Prophylaxis using antibiotics with short half-lives may require administration of additional intraoperative doses in prolonged surgical cases.
- The shortest effective prophylactic course should be used (e.g., single dose preoperatively or not more than 24 hours postoperatively for most procedures). Postoperative doses after wound closure are usually not required. Continuation of postoperative prophylaxis for up to 48 hours may be appropriate in cardiac surgeries. Continuation beyond this period is not associated with improved outcomes and can increase the risk of resistance and adverse effects.

# Central Nervous System Infections\*

## General Principles

- The brain and spinal cord are ensheathed by a protective covering known as the meninges and suspended in cerebrospinal fluid (CSF). The blood–brain barrier plays a crucial role in protecting the brain and maintaining homeostasis within the central nervous system (CNS).
- Meningitis is a common type of CNS infection. It is generally a disease of the very young and very old. Pathogenesis is shown in Figure 62.1.
- Brain abscess is associated with a different spectrum of pathogens. The barrier from the blood to the brain differs from that between the blood and the CSF so the choice of antimicrobial for brain abscess may differ from that associated with meningitis.
- Pharmacotherapy for CNS infections presents numerous challenges due to limited antibiotic penetration and inadequate host defenses to contain infection.



**Figure 62.1** Summary of the pathogenesis and pathophysiology of bacterial meningitis. (Adapted with permission from Quagliarello VJ, Scheld WM. New perspectives on bacterial meningitis. *Clin Infect Dis.* 1993;17:603; Quagliarello VJ, Scheld WM. Bacterial meningitis: pathogenesis, pathophysiology, and progress. *N Engl J Med.* 1992;327:864.)

\*The reader is referred to Chapter 62, Central Nervous System Infections, written by Gregory A. Eschenauer, PharmD, BCPS, Brian A. Potoski, PharmD, and Victoria J. Dudas, PharmD, in the 10th edition of *Applied Therapeutics: The Clinical Use of Drugs* for a more in-depth discussion. All notations to reference numbers are based on the reference list at the end of that chapter. The editor of this handbook expresses her thanks to Drs. Eschenauer, Potoski, and Dudas and acknowledges that this chapter is based on their work.

## Patient Assessment

- Prompt recognition of meningitis and early initiation of therapy are essential to ensuring beneficial outcomes. Bacterial causes of meningitis correlate with age and underlying conditions (e.g., head trauma, recent neurosurgery) (Table 62.1).
- Clinical features of meningitis are shown in Table 62.2. The most common symptoms of meningitis include the triad of fever, stiff neck, and altered mental status. In neonates and infants, irritability and poor feeding may be reported along with fever. In the elderly, signs may be absent or more subtle.
- Laboratory evaluation should include serum chemistries, a hemogram, and a detailed examination of the CSF (Table 62.3).
- Predisposing characteristics and microbiology for bacterial brain abscess are shown in Table 62.4. Evolution of brain abscess involves two stages: cerebritis and capsule formation. Stage of abscess development has important implications for therapy.
- Brain abscess presents as a focal neurologic process. Headache is the most common symptom. Fever occurs in <50% of patients.

TABLE 62.1 Microbiology of Bacterial Meningitis

Age Group or Predisposing Condition	Most Likely Organisms <sup>a</sup>
Neonates (<1 month)	Group B streptococcus ( <i>Streptococcus agalactiae</i> ), <i>E. coli</i> , ( <i>Klebsiella species</i> , <i>Listeria monocytogenes</i> )
Infants and children (1–23 months)	<i>Streptococcus pneumoniae</i> , <i>Neisseria meningitidis</i> , <i>S. agalactiae</i> , <i>Haemophilus influenzae</i> , <sup>b</sup> <i>E. coli</i>
Children and adults (2–50 years)	<i>N. meningitidis</i> , <i>S. pneumoniae</i>
Adults (>50 years)	<i>S. pneumoniae</i> , <i>N. meningitidis</i> , <i>L. monocytogenes</i> , <i>E. coli</i> , <i>Klebsiella species</i> , and other aerobic gram-negative bacilli
Postneurosurgical	<i>Staphylococcus aureus</i> , aerobic gram-negative bacilli (e.g., <i>E. coli</i> , <i>Klebsiella species</i> , <i>Pseudomonas aeruginosa</i> ), <i>Staphylococcus epidermidis</i> <sup>c</sup>
Closed head trauma	<i>S. pneumoniae</i> , <i>H. influenzae</i> , group A $\beta$ -hemolytic streptococci
Penetrating trauma	<i>S. aureus</i> , <i>S. epidermidis</i> , aerobic gram-negative bacilli (e.g., <i>E. coli</i> , <i>Klebsiella species</i> , <i>P. aeruginosa</i> )
CSF shunt	Coagulase-negative staphylococci (particularly <i>S. epidermidis</i> ), <i>S. aureus</i> , aerobic gram-negative bacilli (including <i>P. aeruginosa</i> ), <i>Propionibacterium acnes</i>
Presence of risk factor (alcoholism and altered immune status)	<i>S. pneumoniae</i> , <i>L. monocytogenes</i> , <i>H. influenzae</i> , <i>N. meningitidis</i>

<sup>a</sup>Organisms listed in descending order of frequency.

<sup>b</sup>Need to consider this pathogen only in children not vaccinated with Hib.

<sup>c</sup>Most commonly seen in association with prosthetic devices (e.g., cerebrospinal fluid shunts). CSF, cerebrospinal fluid.

TABLE 62.2 Signs and Symptoms of Acute Bacterial Meningitis

Fever	Anorexia
Nuchal rigidity (stiff neck)	Headache
Altered mental status	Photophobia
Seizures	Nausea and vomiting
Brudzinski sign <sup>a</sup>	Focal neurologic deficits
Kernig sign <sup>a</sup>	Septic shock
Irritability <sup>b</sup>	

<sup>a</sup>See text for description of sign.

<sup>b</sup>Symptoms seen in infants with meningitis.

TABLE 62.3 Cerebrospinal Fluid Findings in Various Types of Meningitis

Microbial Etiology	WBC Count (cells/ $\mu$ L)	Predominant Cell Type	Protein	Glucose
Bacterial	>500	PMN	Elevated	Decreased
Fungal	10–500	MN	Elevated	Variable
Viral	10–200	PMN or MN	Variable	Normal

MN, mononuclear cells; PMN, polymorphonuclear neutrophils; WBC, white blood cell.

TABLE 62.4 Predisposing Conditions, Microbiology, and Recommended Therapy for Bacterial Brain Abscess

Predisposing Condition	Usual Location of Abscess	Most Likely Organisms	Recommended Therapy
<b>CONTIGUOUS SITE</b>			
Otitis infection	Temporal lobe or cerebellum	Streptococci (anaerobic and aerobic), <i>Bacteroides fragilis</i> , gram-negative bacilli	Penicillin G + metronidazole + cefotaxime or ceftriaxone
Sinusitis	Frontal lobe	Streptococci (predominantly), <i>Bacteroides</i> species, gram-negative bacilli, <i>Staphylococcus aureus</i> , <i>Haemophilus</i> species	Penicillin G + metronidazole + cefotaxime or ceftriaxone
Dental infection	Frontal lobe	<i>Fusobacterium</i> species, <i>Bacteroides</i> species, and streptococci	Penicillin G + metronidazole
<b>PRIMARY INFECTION</b>			
Head trauma or neurosurgery	Related to site of wound	Gram-negative bacilli, staphylococci, streptococci, diphtheroids	Vancomycin + cefepime

## Treatment

- Empiric therapy must be instituted promptly to reduce morbidity and mortality. The regimen should consider patient age, predisposing conditions, results from the CSF Gram stain, history of allergy, and presence of organ dysfunction (Table 62.5). Definitive therapies are shown in Table 62.6, with recommended dosing regimens in Table 62.7.
- Recommended treatment duration for uncomplicated cases of bacterial meningitis varies by pathogen (Table 62.8).
- Factors to consider when selecting an antibiotic include penetration into the CSF, activity against the known or suspected pathogen, and bactericidal effect. Penetration into the CSF is affected by lipid solubility, degree of ionization, molecular weight, protein binding, and susceptibility to active transport systems operative within the choroid plexus. Penetration is generally increased when the meninges are inflamed. Table 62.9 summarizes CSF penetration of various antimicrobials.
- Corticosteroids, particularly dexamethasone, can be used as adjunctive therapy to reduce cerebral edema and lower intracranial pressure.
- Intraventricular antibiotics, in combination with systemic therapy, should be considered for patients with meningitis who have an external drainage device in place.
- Clinical signs and symptoms attributable to disease should be monitored for resolution. Temperature and mental status should be assessed often.
- Vaccinations for prevention of meningitis:
  - All children older than 2 months of age should receive the *Haemophilus influenzae* (Hib) vaccination series (Table 62.10).



TABLE 62.5 Empiric Therapy for Bacterial Meningitis

Age Group or Predisposing Condition	Recommended Therapy	Alternative Therapy
Neonates (<1 month)	Ampicillin + cefotaxime	Ampicillin + gentamicin
Infants and children (1–23 months)	Cefotaxime or ceftriaxone + vancomycin	Vancomycin + rifampin + aztreonam
Older children and adults (2–50 years)	Cefotaxime or ceftriaxone + vancomycin	Vancomycin + rifampin + aztreonam
Elderly (>50 years)	Ampicillin + cefotaxime, or ceftriaxone + vancomycin	Vancomycin + TMP-SMX + aztreonam
Postneurosurgical	Vancomycin + ceftazidime	Vancomycin + cefepime or meropenem
Closed head trauma	Cefotaxime or ceftriaxone + vancomycin	Vancomycin + rifampin + aztreonam
Penetrating head trauma	Vancomycin + ceftazidime	Vancomycin + cefepime or meropenem
Presence of risk factor (alcoholism and altered immune status)	Vancomycin + ceftriaxone or cefotaxime + ampicillin	Vancomycin + TMP-SMX + aztreonam

TMP-SMX, trimethoprim-sulfamethoxazole.

TABLE 62.6 Definitive Therapy for Bacterial Meningitis

Pathogen	Recommended Treatment	Alternative Agents
<i>Haemophilus influenzae</i> $\beta$ -Lactamase-negative	Ampicillin	Cefotaxime or ceftriaxone; aztreonam
$\beta$ -Lactamase-positive <i>Neisseria meningitidis</i>	Cefotaxime or ceftriaxone Penicillin MIC <0.1 mcg/mL: Penicillin G or ampicillin Penicillin MIC 0.1–1.0 mcg/mL: Cefotaxime or ceftriaxone	Aztreonam Cefotaxime or ceftriaxone
<i>Streptococcus pneumoniae</i>	Penicillin MIC $\leq$ 0.06 mcg/mL: Penicillin G or ampicillin Penicillin MIC $\geq$ 0.12 mcg/mL: Cefotaxime or ceftriaxone if susceptible	Cefotaxime or ceftriaxone Vancomycin
	Penicillin and cefotaxime/ceftriaxone nonsusceptible: Vancomycin + cefotaxime/ceftriaxone $\pm$ rifampin	Vancomycin + meropenem
<i>Streptococcus agalactiae</i>	Penicillin G or ampicillin + gentamicin	Cefotaxime or ceftriaxone
<i>Listeria monocytogenes</i>	Penicillin G or ampicillin $\pm$ gentamicin	TMP-SMX
Enterobacteriaceae <sup>a</sup> <i>E. coli</i> , <i>Klebsiella</i> species	Cefotaxime or ceftriaxone	Cefepime; aztreonam; meropenem
<i>Enterobacter</i> , <i>Serratia</i> species	Cefepime; meropenem	TMP-SMX; aztreonam
<i>Pseudomonas aeruginosa</i>	Cefepime or ceftazidime; meropenem	Aztreonam
<i>Staphylococcus aureus</i> <sup>a</sup> Methicillin-susceptible (MSSA)	Nafcillin or oxacillin	Vancomycin $\pm$ rifampin; meropenem; linezolid
Methicillin-resistant (MRSA)	Vancomycin $\pm$ rifampin	TMP-SMX; linezolid
<i>Staphylococcus epidermidis</i> <sup>a</sup>	Vancomycin $\pm$ rifampin	TMP-SMX; linezolid

<sup>a</sup>Concomitant intrathecal therapy may be required for optimal response (most commonly an intrathecal aminoglycoside for gram-negative or intrathecal vancomycin for gram-positive infections).

MIC, minimum inhibitory concentration; TMP-SMX, trimethoprim-sulfamethoxazole.

TABLE 62.7 Suggested Antibiotic Dosing Regimens for Treatment of Central Nervous System Infections

Antibiotic	Daily Dose (interval in hours) <sup>a</sup>			
	Neonates		Infants and Children	Adults
	0–7 Days Old	8–28 Days Old		
Ampicillin	150 mg/kg (8)	200 mg/kg (6–8)	300 mg/kg (6)	12 g (4)
Aztreonam				8 g (6)
Nafcillin	75 mg/kg (8–12)	100–150 mg/kg (6–8)	200 mg/kg (6)	12 g (4)
Penicillin G	0.15 million units/kg (8–12)	0.2 million units/kg (6–8)	0.3 million units/kg (4–6)	24 million units (4)
Meropenem			120 mg/kg (8)	6 g (8)
<b>CEPHALOSPORINS</b>				
Cefotaxime	100–150 mg/kg (8–12)	150–200 mg/kg (6–8)	225–300 mg/kg (6–8)	12 g (4)
Ceftriaxone			80–100 mg/kg (12–24)	4 g (12)
Cefazidime	100–150 mg/kg (8–12)	150 mg/kg (8)	150 mg/kg (8)	6 g (8)
Cefepime			150 mg/kg (8)	6 g (8)
<b>AMINOGLYCOSIDE<sup>b,c</sup></b>				
Gentamicin	5 mg/kg (12)	7.5 mg/kg (8)	7.5 mg/kg (8)	5–7 mg/kg (24)
Tobramycin	5 mg/kg (12)	7.5 mg/kg (8)	7.5 mg/kg (8)	5–7 mg/kg (24)
Amikacin	15–20 mg/kg (12)	30 mg/kg (8)	20–30 mg/kg (8)	15 mg/kg (24)
Linezolid				1,200 mg (12)
Rifampin		10–20 mg/kg (12)	10–20 mg/kg (12–24)	600 mg (24)
TMP-SMX <sup>d</sup>			10–20 mg/kg (6–12)	10–20 mg/kg (6–12)
Vancomycin <sup>e</sup>	20–30 mg/kg (8–12)	30–45 mg/kg (6–8)	60 mg/kg (6)	30–45 mg/kg (8–12)

<sup>a</sup>Recommended daily dose when renal and hepatic functions are normal.

<sup>b</sup>Concurrent intraventricular doses of 5–10 mg (gentamicin, tobramycin) or 20 mg (amikacin) often required when treating gram-negative bacillary meningitis.

<sup>c</sup>Dose should be individualized based on serum level monitoring.

<sup>d</sup>Dose is based on the trimethoprim component.

<sup>e</sup>Concurrent intraventricular doses of 5–20 mg recommended if response to intravenous therapy is inadequate.

TMP-SMX, trimethoprim-sulfamethoxazole.

Source: Tunkel AR et al. Practice guidelines for the management of bacterial meningitis. *Clin Infect Dis*. 2004;39:1267.

TABLE 62.8 Duration of Therapy for Bacterial Meningitis

Etiology	Duration of Therapy (days)
<i>Haemophilus influenzae</i>	7
<i>Neisseria meningitidis</i>	7
<i>Streptococcus pneumoniae</i>	10–14
Group B streptococci ( <i>Streptococcus agalactiae</i> )	14–21
<i>Listeria monocytogenes</i>	≥21
Gram-negative bacilli	21

**TABLE 62.9 Cerebrospinal Fluid Penetration Characteristics of Various Antimicrobials**

**VERY GOOD<sup>a</sup>**

Chloramphenicol, metronidazole, TMP-SMX, linezolid

**GOOD<sup>a</sup>**

*Penicillins:* Penicillin G, ampicillin, nafcillin

*Other β-lactams:* Aztreonam, clavulanic acid, imipenem, meropenem, sulbactam

*Cephalosporins:* Cefepime, cefotaxime, ceftazidime, ceftizoxime, ceftriaxone

*Other agents:* Rifampin

**FAIR TO POOR<sup>c</sup>**

*Aminoglycosides:* Amikacin, gentamicin, tobramycin

*Other agents:* Azithromycin, clarithromycin, clindamycin, erythromycin, vancomycin, daptomycin

<sup>a</sup>Penetrates CSF well regardless of meningeal inflammation.

<sup>b</sup>Adequate CSF penetration achieved when the meninges are inflamed.

<sup>c</sup>Penetration often inadequate even when the meninges are inflamed.

CSF, cerebrospinal fluid; TMP-SMX, trimethoprim-sulfamethoxazole.

**TABLE 62.10 Recommended Vaccination Schedule for Haemophilus influenzae Protein Conjugated Vaccines**

Vaccine (Trade Name)	Schedule				
	2 Months	4 Months	6 Months	12–15 Months	15–18 Months
PRP-T (ActHIB) <sup>a,b</sup>	Dose 1	Dose 2	Dose 3	Booster	
PRP-T/DTaP/IPV (Pentacel) <sup>c</sup>	Dose 1	Dose 2	Dose 3		Booster
PRP-OMP (PedvaxHIB) <sup>d</sup>	Dose 1	Dose 2	—	Booster	

<sup>a</sup>Also approved for reconstitution with diphtheria-tetanus-acellular pertussis vaccine (DTaP/PRP-T, TriHIBit), but only for administration as a booster dose in children 15 months and older (i.e., not as initial doses in vaccination series).

<sup>b</sup>Also available as PRP-T (Hiberix), but only for administration as a booster dose in children 15 months to 4 years (i.e., not as initial doses in vaccination series).

<sup>c</sup>Combination vaccine with diphtheria-tetanus-acellular pertussis (DTaP) vaccine and inactivated poliovirus (IPV) vaccine.

<sup>d</sup>Also available in combination with hepatitis B vaccine (PRP-OMP/hepatitis B, Comvax).

- Meningococcal vaccine is recommended for young adolescents (11–12 years of age) with a booster at age 16 years. All persons aged 21 years or younger should have received a dose within 5 years of enrollment of college.
- Pneumococcal vaccine (e.g., Pneumovax 23) should be given to those at high risk for pneumococcal infection. A 13-valent conjugate vaccine (Prevnar-13, PCV13) is recommended for all children.
- Recommended therapy for bacterial brain abscess must be sufficiently broad to cover the most likely pathogens (Table 62.4). A combined medical and surgical approach is the best form of therapy. High-dose IV antibiotic therapy should continue for at least 6 to 8 weeks.
  - Metronidazole is the drug of choice for anaerobic gram-negative bacterial brain abscess.
  - Vancomycin and carbapenems also penetrate sufficiently into brain abscess fluid.
  - Adjunctive corticosteroid therapy for bacterial brain abscess is controversial. Anticonvulsants should be used in the acute setting when seizures are present.

# Endocarditis\*

## General Principles

- Infective endocarditis (IE) is a microbial infection of the heart valves or other endocardial tissue, often associated with an underlying cardiac defect. Any structural cardiac defect that leads to the turbulence of blood flow predisposes to the development of IE.
- Endocarditis can result in life-threatening hemodynamic disturbances and embolic episodes. Without antimicrobial therapy and surgical intervention, IE is virtually 100% fatal.
- Streptococci and staphylococci are the cause of 80% to 90% of cases of IE. The site of heart valve involvement is determined by the underlying cardiac defect and the infecting organism. Multiple valves may be affected simultaneously.

## Classification

- Classification is based on the causative organism as this provides information regarding the course of disease, likelihood of underlying heart disease, and appropriate antimicrobial regimen.

## Patient Assessment

- IE should be suspected in any patient who has a documented fever and heart murmur. Diagnostic criteria for IE are shown in Tables 63.1 and 63.2.
- Clinical presentation of IE is highly variable and can involve almost any organ system. Non-specific complaints include fatigue, weight loss, fever (typically low grade and remittent), night sweats, and arthralgias. The most common presenting complaints in the elderly are confusion, anorexia, fatigue, and weakness.
- Blood culture is the most important diagnostic workup for IE. All patients with suspected IE should have echocardiography on admission and repeated during their course, as needed.
- **Prosthetic valve endocarditis** (PVE), a life-threatening infectious complication of artificial heart valve implantation, may be categorized as early (within 2 months after surgery) or late (>2 months after surgery). Surgical antibiotic prophylaxis is indicated because complications of infection are severe. Selection of the most appropriate prophylactic antibiotic should consider Surgical Care Improvement Project (SCIP) antibiotic recommendations and patient- and institution-specific factors.
- **Fungal endocarditis** is a rare but life-threatening infection that is difficult to diagnose and treat. Most cases are caused by *Candida* and *Aspergillus* species.

## Treatment

- Because IE is associated with significant mortality and long-term morbidity, prevention in patients with certain cardiac conditions is indicated (Table 63.3). Recommendations for antibiotic prophylaxis before common medical procedures are shown in Table 63.4.

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\*The reader is referred to Chapter 63, Endocarditis, written by Annie Wong-Beringer, PharmD, FCCP, FIDSA, and Michelle Lee, PharmD, in the 10th edition of *Applied Therapeutics: The Clinical Use of Drugs* for a more in-depth discussion. All notations to reference numbers are based on the reference list at the end of that chapter. The editor of this handbook expresses her thanks to Drs. Wong-Beringer and Lee and acknowledges that this chapter is based on their work.

TABLE 63.1 **Definition of Infective Endocarditis (IE) According to the Modified Duke Criteria<sup>a</sup>**

**Definite Infective Endocarditis**

**PATHOLOGIC CRITERIA**

Microorganisms: Demonstrated by culture or histology examination of a vegetation, a vegetation that has embolized, or an intracardiac abscess specimen, *or*

Pathologic lesions: Vegetation or intracardiac abscess confirmed by histologic examination showing active endocarditis

**CLINICAL CRITERIA**

Using specific definitions listed in Table 63.2; two major criteria or one major and three minor criteria *or* five minor criteria

**Possible Infective Endocarditis**

**One major criterion and one minor criterion; or three minor criteria**

**Rejected**

Firm alternative diagnosis explaining evidence of IE; *or*

Resolution of IE syndrome with antibiotic therapy for <4 days; *or*

No pathologic evidence of infective endocarditis at surgery or autopsy, with antibiotic therapy for <4 days; or not meet criteria for possible IE as above

<sup>a</sup>Modifications shown in bold.

Source: Reprinted with permission from Li JS et al. Proposed modifications to the Duke criteria for the diagnosis of infective endocarditis. *Clin Infect Dis.* 2000;30:633.

TABLE 63.2 **Definitions of Terminology Used in the Modified Duke Criteria for the Diagnosis of Infective Endocarditis (IE)<sup>a</sup>**

**MAJOR CRITERIA**

**BLOOD CULTURE POSITIVE FOR INFECTIVE ENDOCARDITIS**

- Typical microorganisms consistent with IE from two separate blood cultures
  1. *Viridans streptococci*, *Streptococcus bovis*, HACEK group, *or*
  2. ***Staphylococcus aureus*** or community-acquired enterococci in the absence of a primary focus, *or*
- Microorganisms consistent with IE from persistently positive blood cultures defined as follows:
  1. At least two positive blood cultures drawn >12 hours apart, *or*
  2. All of three or a majority of four separate cultures of blood (with first and last sample drawn at least 1 hour apart)
- **Single positive blood culture for *Coxiella burnetii* or antiphase 1 IgG antibody titer >1:800**

**EVIDENCE OF ENDOCARDIAL INVOLVEMENT**

- Echocardiogram positive for IE (**TEE recommended for patients with prosthetic valves, rated at least “possible IE” by clinical criteria or complicated IE [paravalvular abscess]; TEE as first test in other patients**) defined as follows:
  1. Oscillating intracardiac Masson valve or supporting structures, in the path of regurgitant jets, or on implanted material in the absence of an alternative anatomic explanation; *or*
  2. Abscess, *or*
  3. New partial dehiscence of prosthetic valve
- New valvular regurgitation (worsening or changing of preexisting murmur not sufficient)

**MINOR CRITERIA**

- Predisposition: Predisposing heart condition or intravenous drug use
- Fever >38°C (100.4°F)
- **Vascular Phenomena:** Major arterial emboli, septic pulmonary infarcts, mycotic aneurysm, intracranial hemorrhage, conjunctival hemorrhages, Janeway lesions
- **Immunologic Phenomena:** Glomerulonephritis, Osler nodes, Roth spots, rheumatoid factor
- **Microbiologic Evidence:** Positive blood culture but not meeting major criterion as noted above<sup>b</sup> or serologic evidence of active infection with organism consistent with IE
- **Echocardiographic minor criteria eliminated**

<sup>a</sup>Modifications shown in bold.

<sup>b</sup>Excludes single positive cultures for coagulase-negative staphylococci and organisms that do not cause endocarditis.

HACEK, Haemophilus species, Actinobacillus actinomycetemcomitans, Cardiobacterium hominis, Eikenella species, and Kingella kingae; TEE, transesophageal echocardiography.

Source: Reprinted with permission from Li JS et al. Proposed modifications to the Duke criteria for the diagnosis of infective endocarditis. *Clin Infect Dis.* 2000;30:633.

TABLE 63.3 Cardiac Conditions for Which Prophylaxis Is Recommended

## Cardiac Conditions

## Prophylaxis Recommended

- Prosthetic cardiac valves
- Previous bacterial endocarditis
- Congenital heart disease
  - Unrepaired cyanotic CHD, including palliative shunts and conduits
  - Completely repaired congenital heart defect with prosthetic material device during the first 6 months after the procedure
  - Repaired CHD with residual defects at or adjacent to the site of the prosthetic device or patch
  - Mitral valve prolapse with valvular regurgitation and/or thickened leaflets
- Cardiac transplantation recipients who develop cardiac valvulopathy

CHD, congenital heart disease.

Source: Wilson W et al. Prevention of infective endocarditis: guidelines from the American Heart Association: a guideline from the American Heart Association Rheumatic Fever, Endocarditis, and Kawasaki Disease Committee, Council on Cardiovascular Disease in the Young, and the Council on Clinical Cardiology, Council on Cardiovascular Surgery and Anesthesia, and the Quality of Care and Outcomes Research Interdisciplinary Working Group. American Heart Association [published correction appears in *Circulation*. 2007;116:e376]. *Circulation*. 2007;116:1736.

TABLE 63.4 Endocarditis Prophylaxis Regimen Indicated for Patients with Cardiac Conditions<sup>a</sup>

Drug	Dose
Dental or upper respiratory tract procedures	Single dose 30 to 60 minutes before procedure
<b>STANDARD REGIMEN</b>	
Amoxicillin	Adult: 2 g Pediatric: 50 mg/kg
Allergic to penicillin or ampicillin	
Clindamycin	Adult: 600 mg Pediatric: 20 mg/kg
or	
Cephalexin <sup>b,c</sup>	Adult: 2 g Pediatric: 50 mg/kg
or	
Azithromycin or clarithromycin	Adult: 500 mg Pediatric: 15 mg/kg
<b>UNABLE TO TAKE ORAL MEDICATIONS</b>	
Ampicillin	Adult: 2 g IM or IV Pediatric: 50 mg/kg IM or IV
<b>ALLERGIC TO PENICILLIN OR AMPICILLIN</b>	
Clindamycin	Adult: 600 mg Pediatric: 20 mg/kg IV
or	
Cefazolin <sup>b</sup>	Adult: 1 g IM or IV Pediatric: 50 mg/kg IM or IV

<sup>a</sup>See Table 63.3.

<sup>b</sup>Cephalosporins should not be used in individuals with immediate-type hypersensitivity reaction (e.g., urticaria, angioedema, or anaphylaxis) to penicillins or ampicillin.

<sup>c</sup>Other first- or second-generation oral cephalosporins in equivalent adult or pediatric dose.

IM, intramuscular; IV, intravenous.

Source: Wilson W et al. Prevention of infective endocarditis: guidelines from the American Heart Association: a guideline from the American Heart Association Rheumatic Fever, Endocarditis, and Kawasaki Disease Committee, Council on Cardiovascular Disease in the Young, and the Council on Clinical Cardiology, Council on Cardiovascular Surgery and Anesthesia, and the Quality of Care and Outcomes Research Interdisciplinary Working Group. American Heart Association [published correction appears in *Circulation*. 2007;116:e376]. *Circulation*. 2007;116:1736.

**TABLE 63.5 Suggested Regimens for Therapy of Native Valve Endocarditis Caused by *Streptococcus viridans* and *Streptococcus bovis***

Antibiotic	Dose <sup>a,b</sup> and Route	Duration
<b>PENICILLIN-SUSCEPTIBLE (MINIMUM INHIBITORY CONCENTRATION = 0.12 MCG/ML)</b>		
Aqueous crystalline penicillin G <sup>c</sup>	<i>Adult:</i> 12–18 million units/24 hours IV either continuously or in four to six equally divided doses <i>Pediatric:</i> 200,000 units/kg/24 hours IV (max: 20 million units/24 hours) either continuously or in four to six equally divided doses	4 weeks
Ceftriaxone sodium <sup>c</sup>	<i>Adult:</i> 2 g once daily IV or IM <i>Pediatric:</i> 100 mg/kg once daily IV or IM	4 weeks
Aqueous crystalline penicillin G	<i>Adult:</i> 12–18 million units/24 hours IV either continuously or in six equally divided doses <i>Pediatric:</i> 200,000 units/kg/24 hours IV (max: 20 million units/24 hours) either continuously or in six equally divided doses	2 weeks
Ceftriaxone sodium	<i>Adult:</i> 2 g once daily IV or IM <i>Pediatric:</i> 100 mg/kg once daily IV or IM	
With gentamicin sulfated	<i>Adult:</i> 3 mg/kg once daily IV or IM <i>Pediatric:</i> 3 mg/kg once daily IV or IM or in three equally divided doses	2 weeks
<b>RELATIVELY PENICILLIN G RESISTANT (MINIMUM INHIBITORY CONCENTRATION &gt;0.1 MCG/ML AND &lt;0.5 MCG/ML)</b>		
Aqueous crystalline penicillin G <sup>c</sup>	<i>Adult:</i> 24 million units/24 hours IV either continuously or in four to six equally divided doses <i>Pediatric:</i> 200,000–300,000 units/kg/24 hours IV (max: 20 million units/24 hours) either continuously or in four to six equally divided doses	4 weeks
Ceftriaxone sodium	<i>Pediatric:</i> 100 mg/kg once daily IV or IM	
With gentamicin sulfate <sup>d</sup>	<i>Adult:</i> 3 mg/kg once daily IV or IM <i>Pediatric:</i> 3 mg/kg once daily IV or IM or in three equally divided doses	2 weeks
<b>β-LACTAM ALLERGIC PATIENTS</b>		
Vancomycin hydrochloride <sup>f</sup>	<i>Adult:</i> 30 mg/kg/24 hours IV in two equally divided doses (max: 2 g/24 hours unless serum concentrations are monitored) <i>Pediatric:</i> 40 mg/kg/24 hours IV in two or three equally divided doses (max: 2 g/24 hours unless serum concentrations are monitored)	4 weeks

<sup>a</sup>Pediatric doses should not exceed that of a normal adult.

<sup>b</sup>Antibiotic doses for patients with impaired renal function should be modified appropriately. Vancomycin dosage should be reduced in patients with renal dysfunction; cephalosporin dosage may need to be reduced in patients with moderate to severe renal dysfunction.

<sup>c</sup>Preferred in most patients >65 years of age and in those with impairment of the eighth nerve or renal function.

<sup>d</sup>Two-week regimen not intended for patients with known cardiac or extracardiac abscess or for those with creatinine clearance of <20 mL/minute, impaired eighth cranial nerve function or *Abiotrophia*, *Granulicatella*, or *Gemella* infection. Gentamicin dosage should be adjusted to achieve peak serum concentrations of 3 to 4 mcg/mL and trough serum concentrations of <1 mcg/mL when three divided doses are used; nomogram used for single daily dosing. Other potential nephrotoxic drugs should be used with caution in patients receiving gentamicin therapy.

<sup>e</sup>Cefazolin or other first-generation cephalosporins may be substituted for penicillin in patients whose penicillin hypersensitivity is not of the immediate type.

<sup>f</sup>Vancomycin dosage should be reduced in patients with impaired renal function. Vancomycin given on a milligram-per-kilogram basis produces higher serum concentrations in obese patients than in lean patients. Therefore, in obese patients, dosing should be based on ideal body weight. Each dose of vancomycin should be infused for at least 1 hour to reduce the risk of the histamine-release red man syndrome. Peak serum concentrations of vancomycin should be obtained 1 hour after completion of the infusion and should be in the range of 30 to 45 mg/mL. Trough concentrations should be obtained within half an hour of the next dose and be in the range of 10 to 15 mcg/mL.

IM, intramuscular; IV, intravenous.

Source: Baddour LM et al. Infective endocarditis: diagnosis, antimicrobial therapy, and management of complications: a statement for healthcare professionals from the Committee on Rheumatic Fever, Endocarditis, and Kawasaki Disease, Council on Cardiovascular Disease in the Young, and the Councils on Clinical Cardiology, Stroke, and Cardiovascular Surgery and Anesthesia, American Heart Association: endorsed by the Infectious Diseases Society of America. *Circulation*. 2005; 111:e394.

- High doses of parenteral bactericidal antibiotics are required to treat IE. Cure of infection requires prolonged therapy of 4 to 6 weeks with relapse not uncommon. Risk for relapse may be higher in patients who have had symptoms for longer than 3 months.
- Patients with endocarditis caused by penicillin-sensitive strains of viridians streptococci and nonenterococcal group D streptococci can be treated with one of three regimens (Table 63.5).
- Treatment options for Staphylococcal endocarditis are shown in Table 63.6.
- Therapy of endocarditis caused by Enterococci is shown in Table 63.7.

TABLE 63.6 Treatment of Staphylococcal Endocarditis

Antibiotic	Dosage and Route	Duration
<b>WITHOUT PROSTHETIC MATERIAL<sup>a</sup></b>		
<b>OXACILLIN-SUSCEPTIBLE STAPHYLOCOCCI</b>		
<b>NONPENICILLIN-ALLERGIC PATIENTS</b>		
Nafcillin or	<i>Adult:</i> 2 g IV every 4 hours <i>Pediatric:</i> 150–200 mg/kg/24 hours IV (max: 12 g/24 hours) in four to six equally divided doses	4–6 weeks
Oxacillin	<i>Adult:</i> 2 g IV every 4 hours <i>Pediatric:</i> 200 mg/kg/24 hours IV (max: 12 g/24 hours) in four to six equally divided doses	4–6 weeks
With optional addition of gentamicin <sup>b,c</sup>	<i>Adult:</i> 3 mg/kg IV or IM in two or three equally divided doses <i>Pediatric:</i> 3 mg/kg IV or IM in three equally divided doses	3–5 days
<b>PENICILLIN-ALLERGIC PATIENTS</b>		
1. Cefazolin <sup>d</sup>	<i>Adult:</i> 2 g IV every 8 hours <i>Pediatric:</i> 100 mg/kg/24 hours IV (max: 6 g/24 hours) in equally divided doses every 8 hours	4–6 weeks
With optional addition of gentamicin <sup>b</sup>	<i>Adult:</i> See Nonpenicillin-allergic patient <i>Pediatric:</i> See Nonpenicillin-allergic patient	
2. Vancomycin <sup>b,e,f</sup>	<i>Adult:</i> 30 mg/kg/24 hours IV in two or four equally divided doses (max: 2 g/24 hours unless serum levels monitored) <i>Pediatric:</i> 40 mg/kg/24 hours IV in two or four equally divided doses (max: 2 g/24 hours unless serum levels monitored)	4–6 weeks
<b>METHICILLIN-RESISTANT STAPHYLOCOCCI</b>		
Vancomycin <sup>b,e,f</sup>	<i>Adult:</i> 30 mg/kg/24 hours IV in two or four equally divided doses (max: 2 g/24 hours unless serum levels monitored) <i>Pediatric:</i> 40 mg/kg/24 hours IV in two or four equally divided doses (max: 2 g/24 hours unless serum levels monitored)	4–6 weeks
<b>WITH PROSTHETIC VALVE OR OTHER PROSTHETIC MATERIAL<sup>g</sup></b>		
<b>METHICILLIN-RESISTANT STAPHYLOCOCCI</b>		
Vancomycin <sup>b,e,g</sup>	<i>Adult:</i> 30 mg/kg/24 hours IV in two or three equally divided doses (max: 2 g/24 hours unless serum levels monitored) <i>Pediatric:</i> 40 mg/kg/24 hours IV in two or four equally divided doses (max: 2 g/24 hours unless serum levels monitored)	≥6 weeks
With rifampin <sup>h</sup> and	<i>Adult:</i> 300 mg IV/PO every 8 hours <i>Pediatric:</i> 20 mg/kg/24 hours PO (max: 900 mg/24 hours) in two equally divided doses	≥6 weeks
With gentamicin <sup>b,g,i,j</sup>	<i>Adult:</i> 3 mg/kg IV or IM in two or three equally divided doses <i>Pediatric:</i> 3 mg/kg IV or IM in three equally divided doses	2 weeks

Continued on following page



TABLE 63.6 Treatment of Staphylococcal Endocarditis (Continued)

Antibiotic	Dosage and Route	Duration
<b>METHICILLIN-SUSCEPTIBLE STAPHYLOCOCCI</b>		
Nafcillin or oxacillin <sup>k</sup>	<i>Adult:</i> 2 g IV every 4 hours <i>Pediatric:</i> 150–200 mg/kg/24 hours (max: 12 g/24 hours) in four to six equally divided doses	≥6 weeks
With rifampin <sup>h</sup> and	<i>Adult:</i> 300 mg IV/PO every 8 hours <i>Pediatric:</i> 20 mg/kg/24 hours PO (max: 900 mg/24 hours) in three equally divided doses	≥6 weeks
With gentamicin <sup>b,g,i,j</sup>	<i>Adult:</i> 3 mg/kg IV or IM in two or three equally divided doses <i>Pediatric:</i> 3 mg/kg IV or IM in three equally divided doses	2 weeks

<sup>a</sup>Antibiotic doses should be modified appropriately for patients with impaired renal function. Shorter antibiotic courses have been effective in some drug addicts with right-sided endocarditis caused by *S. aureus*. (See text for comments on the use of daptomycin and rifampin.)

<sup>b</sup>Dosing of aminoglycosides and vancomycin on a milligram-per-kilogram basis will give higher serum concentrations in obese than in lean patients.

<sup>c</sup>The benefit of additional aminoglycoside has not been established. The risk of toxic reactions because of these agents is increased in patients >65 years of age or those with renal or eighth-nerve impairment.

<sup>d</sup>There is potential cross-allergenicity between penicillins and cephalosporins. Cephalosporins should be avoided in patients with immediate-type hypersensitivity to penicillin.

<sup>e</sup>Peak serum concentrations of vancomycin should be obtained 1 hour after infusion and should be in the range of 30 to 45 mcg/mL for twice-daily dosing and 20 to 30 mcg/mL for four-times-a-day dosing. Trough serum concentrations should be obtained within half an hour of the next dose and should be in the range of 10 to 15 mcg/mL. (See text for detailed discussion on the need for high trough target of 15 to 20 mcg/mL for strains with reduced susceptibility to vancomycin. Each vancomycin dose should be infused for 1 hour.)

<sup>f</sup>See text for consideration of optional addition of gentamicin.

<sup>g</sup>Vancomycin and gentamicin doses must be modified appropriately in patients with renal failure.

<sup>h</sup>Rifampin is recommended therapy for infections caused by coagulase-negative staphylococci. Its use in coagulase-positive staphylococcal infections is controversial. Rifampin increases the amount of warfarin sodium required for antithrombotic therapy.

<sup>i</sup>Serum concentration of gentamicin should be monitored and the dose should be adjusted to obtain a peak level of approximately 3 mcg/mL.

<sup>j</sup>Use during initial 2 weeks. (See text on alternative aminoglycoside therapy for organisms resistant to gentamicin.)

<sup>k</sup>First-generation cephalosporins or vancomycin should be used in penicillin-allergic patients. Cephalosporins should be avoided in patients with immediate-type hypersensitivity to penicillin and those infected with methicillin-resistant staphylococci.

IM, intramuscular; IV, intravenous; PO, orally.

Source: Baddour LM et al. Infective endocarditis: diagnosis, antimicrobial therapy, and management of complications: a statement for healthcare professionals from the Committee on Rheumatic Fever, Endocarditis, and Kawasaki Disease, Council on Cardiovascular Disease in the Young, and the Councils on Clinical Cardiology, Stroke, and Cardiovascular Surgery and Anesthesia, American Heart Association: endorsed by the Infectious Diseases Society of America. *Circulation*. 2005;111:e394.

- Gram-negative bacillary endocarditis caused by *Pseudomonas aeruginosa* requires a bactericidal combination of antibiotics (e.g., ceftazidime 2 g IV every 8 hours with tobramycin 3 mg/kg IV every 8 hours) for 4 to 6 weeks.
- Management of fungal endocarditis generally requires early valve replacement and aggressive fungicidal therapy with amphotericin B (0.6–1 mg/kg/day) with or without 5-flucytosine (25 mg/kg orally four times daily). Liposomal formulations of amphotericin can be used as an alternative in patients with poor renal function.

**TABLE 63.7 Therapy for Endocarditis Caused by Enterococci (or Streptococci viridans with an MIC  $\geq 0.5$  mcg/mL)<sup>a,b</sup>**

Antibiotic	Dose and Route	Duration
<b>NONPENICILLIN-ALLERGIC PATIENT</b>		
1. Penicillin G	<i>Adult:</i> 18–30 million units/24 hours IV given continuously or in six equally divided doses	4–6 weeks
	<i>Pediatric:</i> 300,000 units/kg/24 hours IV (max: 30 million units/24 hours) given continuously or in four to six equally divided doses	4–6 weeks
With gentamicin <sup>c,d,e</sup> or	<i>Adult:</i> 1 mg/kg IM or IV every 8 hours	4–6 weeks
	<i>Pediatric:</i> 1 mg/kg IM or IV every 8 hours	4–6 weeks
2. Ampicillin	<i>Adult:</i> 12 g/24 hours IV given continuously or in six equally divided doses	4–6 weeks
	<i>Pediatric:</i> 300 mg/kg/24 hours IV (max: 12 g/24 hours) in four to six equally divided doses	4–6 weeks
With gentamicin <sup>c,d,e</sup>	<i>Adult:</i> 1 mg/kg IM or IV every 8 hours	4–6 weeks
	<i>Pediatric:</i> 1 mg/kg IM or IV every 8 hours	4–6 weeks
<b>PENICILLIN-ALLERGIC PATIENTS<sup>f</sup></b>		
Vancomycin <sup>e</sup>	<i>Adult:</i> 30 mg/kg/24 hours IV in two equally divided doses (max: 2 g/24 hours unless serum levels monitored)	6 weeks
	<i>Pediatric:</i> 40 mg/kg/24 hours IV in two to three equally divided doses (max: 2 g/24 hours unless serum levels monitored)	6 weeks
With gentamicin <sup>c,d</sup>	<i>Adult:</i> 1 mg/kg IM or IV (max: 80 mg) every 8 hours	6 weeks
	<i>Pediatric:</i> 1 mg/kg IM or IV (max: 80 mg) every 8 hours	6 weeks

<sup>a</sup>Antibiotic doses should be modified appropriately in patients with impaired renal function.

<sup>b</sup>Enterococci should be tested for high-level resistance (gentamicin: MIC  $\geq 500$  mcg/mL).

<sup>c</sup>Serum concentration of gentamicin should be monitored and dosage adjusted to obtain a peak level of approximately 3 mcg/mL. (For shorter course gentamicin therapy for enterococcal endocarditis, see comment in text.)

<sup>d</sup>Dosing of aminoglycosides and vancomycin on an mg/kg basis gives higher serum concentrations in obese than in lean patients.

<sup>e</sup>Peak serum concentrations of vancomycin should be obtained 1 hour after infusion and should be in the range of 30 to 45 mcg/mL for twice-daily dosing and 20 to 30 mcg/mL for four-times-a-day dosing. Trough serum concentrations should be obtained within half an hour of the next dose and should be in the range of 10 to 15 mcg/mL. Each dose should be infused over 1 hour; 6 weeks of vancomycin therapy recommended because of decreased activity against enterococci.

<sup>f</sup>Desensitization should be considered; cephalosporins are not satisfactory alternatives.

IM, intramuscular; IV, intravenous; MIC, minimum inhibitory concentration.

*Source:* Baddour LM et al. Infective endocarditis: diagnosis, antimicrobial therapy, and management of complications: a statement for healthcare professionals from the Committee on Rheumatic Fever, Endocarditis, and Kawasaki Disease, Council on Cardiovascular Disease in the Young, and the Councils on Clinical Cardiology, Stroke, and Cardiovascular Surgery and Anesthesia, American Heart Association: endorsed by the Infectious Diseases Society of America. *Circulation*. 2005;111:e394.

# Respiratory Tract Infections\*

## Acute Bronchitis

- An acute, self-limiting respiratory illness of the upper bronchi accompanied by cough for more than 5 days that can last up to 3 weeks.
- Patient Assessment
  - Fever is rare; purulent sputum production may or may not be present.
  - Sputum assessment for culture is not routinely done. Most identified pathogens have no specific treatment and isolated organisms are often not true pathogens.
  - Acute bronchitis should be distinguished from pneumonia through imaging tests (e.g., chest x-ray) if specific clinical features are present (e.g., fever, tachycardia, tachypnea, rales, hypoxemia, mental status changes).
  - Most cases of acute bronchitis are caused by viruses. Common pathogens and the incubation period for particular pathogens are shown in Table 64.1.
- Treatment
  - Symptom-guided therapy includes inhaled  $\beta$ -agonists (albuterol) for shortness of breath; inhaled or systemic corticosteroids for persistent cough; nonsteroidal anti-inflammatory agents, aspirin, or acetaminophen for myalgias and fever; and antihistamines (brompheniramine), antitussives (codeine, dextromethorphan), or mucolytics (guaifenesin) for cough.
  - Antimicrobials do not significantly reduce the symptoms of acute bronchitis. Guidelines recommend against the use of antimicrobial agents.

## Chronic Bronchitis

- Daily symptoms of sputum production on most days for 3 or more consecutive months for greater than 2 successive years.
- Chronic bronchitis is a component of chronic obstructive pulmonary disease (COPD). Primary precipitating factors for acute exacerbation of COPD (AECOPD) are infection of the bronchial tree and air pollution.
- Patient Assessment
  - Common features include breathlessness, increased cough, increased sputum volume, and increased sputum purulence.
  - Risk factors for poor outcome include presence of atrial fibrillation and severe COPD, frequent exacerbations, and use of antimicrobials for respiratory illness in the last 3 months.
  - Table 64.2 describes microorganisms most commonly associated with AECOPD based on risk factors and disease severity. Purulent sputum is often associated with an acute bacterial infection.

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\*The reader is referred to Chapter 64, Respiratory Tract Infections, written by Heather M. Arnold, PharmD, BCPS, Eli N. Deal, PharmD, BCPS, Steven Gelone, and Scott T. Micek, PharmD, BCPS, FCCP, in the 10th edition of *Applied Therapeutics: The Clinical Use of Drugs* for a more in-depth discussion. All notations to reference numbers are based on the reference list at the end of that chapter. The editor of this handbook expresses her thanks to Drs. Arnold, Deal, Gelone, and Micek and acknowledges that this chapter is based on their work.

TABLE 64.1 Causes of Acute Bronchitis

Pathogen	Comments
<b>VIRUS</b>	
Influenza	Quick onset with fever, chills, headache, and cough. Myalgias are common and may be accompanied by myopathy.
Parainfluenza	Epidemics in autumn. Outbreaks may occur in nursing homes. Croup in child at home suggests presence of the organism.
Respiratory syncytial virus	About 45% of family members exposed to infant with bronchiolitis become infected. Outbreaks prominent in winter or spring. Twenty percent of adults have ear pain.
Coronavirus	Can cause severe respiratory symptoms in elderly. Epidemics present in military recruits.
Adenovirus	Similar presentation as influenza; abrupt onset of fever
Rhinovirus	Fever is uncommon and infection is generally mild.
<b>ATYPICAL BACTERIA</b>	
<i>Bordetella pertussis</i>	Incubation period of 1–3 weeks. Whooping occurs in a minority of patients, and fever is uncommon. Marked leukocytosis with lymphocytic predominance can occur.
<i>Mycoplasma pneumoniae</i>	Incubation period is 2–3 weeks. Outbreak cases in military and students have been reported.
<i>Chlamydomphila pneumoniae</i>	Incubation period is 3 weeks. Onset of symptoms, which include hoarseness before cough, is gradual. Outbreaks have been reported in nursing homes, college students, and military personnel.

Source: Wenzel RP, Fowler AA 3rd. Clinical practice. Acute bronchitis. *N Engl J Med*. 2006;355:2125.

- Assess patient understanding of the role of medications (maintenance vs. rescue therapies), ability to use inhalers properly, access to prescribed medications, and pulmonary rehabilitation.
- Treatment
  - Nonpharmacological considerations include decisions regarding site of care and level of respiratory support.
  - Pharmacotherapy includes short-acting bronchodilators (albuterol or ipratropium) and supplemental oxygen to alleviate hypoxemia, antimicrobial therapy, and corticosteroids. There is no role for long-acting bronchodilators.
  - Guidelines recommend antibacterials when two or three cardinal symptoms are present (increased dyspnea, increased sputum volume, and increased sputum purulence); when two cardinal symptoms are present with one of them being increased sputum purulence; or in all patients who require mechanical ventilation. Recommended treatments are shown in Table 64.2.

## Community-Acquired Pneumonia (CAP)

- Pneumonia acquired outside of the hospital or extended-care facility in patients without recent exposure to the healthcare system.
- Patient Assessment
  - Diagnosis requires the presence of clinical features that develop over hours to days in conjunction with radiological evidence of an infiltrate.
  - Patients typically manifest acutely with high fever, chills, tachycardia, and productive cough. Physical findings include crackles, rhonchi, bronchial breath sounds, dullness, or egophony.

TABLE 64.2 Microorganisms Common in Exacerbations of Chronic Obstructive Pulmonary Disease and Recommended Treatment

Group	Microorganisms	Oral Treatment	Parenteral Treatment
Exacerbation with no risk factors for poor outcomes <sup>a</sup>	<i>Haemophilus influenzae</i> <i>Streptococcus pneumoniae</i> <i>Moraxella catarrhalis</i> <i>Chlamydomphila pneumoniae</i> Viruses	$\beta$ -Lactam <sup>b</sup> or $\beta$ -lactam/ $\beta$ -lactamase inhibitor combination Tetracyclines (doxycycline) Trimethoprim- sulfamethoxazole Macrolides (azithromycin) Cephalosporins from second- or third- generation (cefuroxime or cefpodoxime)	
Exacerbations with risk factors for poor outcomes	Above microorganisms plus: Drug-resistant <i>Streptococcus pneumoniae</i> <i>Klebsiella pneumoniae</i> <i>Escherichia coli</i> <i>Proteus</i> sp. <i>Enterobacter</i> sp.	$\beta$ -Lactam/ $\beta$ -lactamase inhibitor combination Fluoroquinolone (moxifloxacin)	$\beta$ -Lactam/ $\beta$ -lactamase inhibitor combination (ampicillin/sulbactam) Cephalosporins from third-generation (ceftriaxone) Fluoroquinolone (moxifloxacin)
Exacerbations with risk factors for <i>Pseudomonas aeruginosa</i> <sup>c</sup>	Above microorganisms plus: <i>P. aeruginosa</i>		$\beta$ -Lactam with <i>P.</i> <i>aeruginosa</i> activity (cefepime) or Ciprofloxacin (added to options above if necessary)

<sup>a</sup>Risk factors for poor outcomes include the following: medical comorbidities (cardiac disease), forced expiratory volume in 1 second of 50% of predicted or less (severe chronic obstructive pulmonary disease), frequent exacerbations (>3 per year), age  $\geq$ 65 years, and antimicrobial use within last 3 months.

<sup>b</sup>High-dose  $\beta$ -lactams should be used in areas with high incidence of drug-resistant *S. pneumoniae*;  $\beta$ -lactams should not be used without a  $\beta$ -lactamase inhibitor in areas with high rates of *H. influenzae* or *M. catarrhalis* resistant to penicillin owing to  $\beta$ -lactamase production.

<sup>c</sup>Risk factors for *P. aeruginosa* include the following: recent hospitalization, severe chronic obstructive pulmonary disease exacerbations, or isolation of *P. aeruginosa* during previous exacerbation or colonization during a stable period.

Source: Global Initiative for Chronic Obstructive Lung Disease (GOLD). Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Lung Disease 2010. <http://www.goldcopd.org/guidelines-global-strategy-for-diagnosis-management.html>.

TABLE 64.3 Microorganisms Common in Community-Acquired Pneumonia

Ambulatory	Hospitalized, Non-ICU	Hospitalized, ICU
<i>Streptococcus pneumoniae</i>	<i>S. pneumoniae</i>	<i>S. pneumoniae</i>
<i>Mycoplasma pneumoniae</i>	<i>M. pneumoniae</i>	<i>S. aureus</i>
<i>Haemophilus influenzae</i>	<i>C. pneumoniae</i>	<i>Legionella</i> species
<i>Chlamydomphila pneumoniae</i>	<i>Staphylococcus aureus</i>	Gram-negative bacilli
Respiratory viruses <sup>a</sup>	<i>H. influenzae</i>	<i>H. influenzae</i>
	<i>Legionella</i> species	
	Respiratory viruses <sup>a</sup>	

<sup>a</sup>Influenza A and B, adenovirus, respiratory syncytial virus, and parainfluenza.

Source: Mandell LA et al. Infectious Diseases Society of America/American Thoracic Society consensus guidelines on the management of community-acquired pneumonia in adults. *Clin Infect Dis.* 2007;44(Suppl 2):S27.

- Pretreatment blood cultures and a respiratory sample should be obtained.
- Common microorganisms are shown in Table 64.3. Epidemiological factors may favor certain bacterial pathogens (Table 64.4).

## Treatment

- Determination of whether hospitalization is needed is important (Table 64.5).
- Antibiotic therapy is empirical and should cover pneumococcus and atypical pathogens (Figure 64.1). Patients should be treated for 48 to 72 hours after they become afebrile (minimum of 5 days).

TABLE 64.4 Community-Acquired Pneumonia: Underlying Conditions and Commonly Encountered Pathogens

Condition	Commonly Encountered Pathogen(s)
Alcoholism	Oral anaerobes, <i>Klebsiella pneumoniae</i> , <i>Acinetobacter</i> sp., <i>Mycobacterium tuberculosis</i>
COPD or smoking	<i>Pseudomonas aeruginosa</i> , <i>Legionella</i> sp.
Aspiration	Gram-negative enteric pathogens, oral anaerobes
Lung abscess	CA-MRSA, oral anaerobes, endemic fungal pneumonia, <i>M. tuberculosis</i> , atypical mycobacteria
Exposure to bat or bird droppings	<i>Histoplasma capsulatum</i>
Exposure to birds	<i>Chlamydomphila psittaci</i> (if poultry; avian influenza)
Exposure to rabbits	<i>Francisella tularensis</i>
Exposure to farm animals or parturient cats	<i>Coxiella burnetii</i> (Q fever)
HIV infection (early)	<i>M. tuberculosis</i>
HIV infection (late)	<i>M. tuberculosis</i> , <i>Pneumocystis jiroveci</i> , <i>Cryptococcus</i> sp., <i>Histoplasma</i> sp., <i>Aspergillus</i> sp., atypical mycobacteria (especially <i>Mycobacterium kansasii</i> ), <i>Pseudomonas aeruginosa</i>
Hotel or cruise ship stay in previous 2 weeks	<i>Legionella</i> sp.
Travel to or residence in southwestern United States	<i>Coccidioides</i> sp., hantavirus
Travel to or residence in Southeast and East Asia	<i>Burkholderia pseudomallei</i> , avian influenza, SARS
Cough >2 weeks with whoop or posttussive vomiting	<i>Bordetella pertussis</i>
Structural lung disease (e.g., bronchiectasis)	<i>P. aeruginosa</i> , <i>Burkholderia cepacia</i> , <i>Staphylococcus aureus</i>
Injection drug use	<i>S. aureus</i> , anaerobes, <i>M. tuberculosis</i>
Endobronchial obstruction	Anaerobes, <i>S. aureus</i>
In context of bioterrorism	<i>Bacillus anthracis</i> (anthrax), <i>Yersinia pestis</i> (plague), <i>F. tularensis</i> (tularemia)

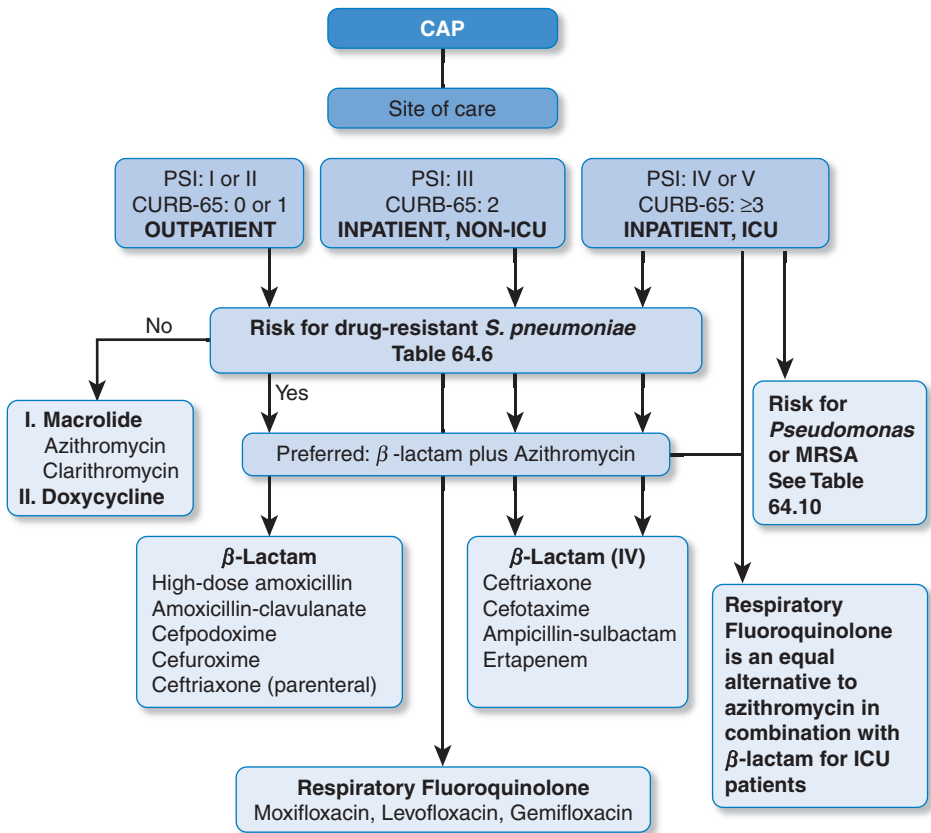
CA-MRSA, community-acquired methicillin-resistant *Staphylococcus aureus*; COPD, chronic obstructive pulmonary disease; HIV, human immunodeficiency virus; SARS, severe acute respiratory syndrome.

**TABLE 64.5 Predicted Mortality and Recommended Site of Care**

System and Score	Predicted 30-Day Mortality (%)	Recommended Site of Care
PSI strata 1–2	0.1–0.7	Outpatient
PSI strata 3	0.9–2.8	Admit to ward
PSI strata 4–5	9.3–27	Admit; consider ICU
CURB-65 score 0–1	0.7–2.1	Outpatient
CURB-65 score 2	9.2	Admit to ward
CURB-65 score ≥3	14.5–57.0	Admit to ICU

CURB-65, confusion, uremia, increased respiratory rate, low blood pressure, and age ≥65 years; ICU, intensive care unit; PSI, pneumonia severity index.

- Delayed antibiotic therapy is associated with increased length of stay and decreased survival. Guidelines recommend the first dose of antibiotic be given in the ED. Risk factors for resistant organisms are shown in Table 64.6.
- Patients at high risk for influenza (Table 64.7) should receive antiviral therapy (Table 64.8) within 48 hours of symptom onset.



**Figure 64.1** Approach to empiric antibiotic therapy in patients with community-acquired pneumonia. CAP, community-acquired pneumonia; CURB-65, confusion, uremia, respiratory rate, blood pressure, and age of at least 65 years; IV, intravenous; MRSA, methicillin-resistant *Staphylococcus aureus*; PSI, pneumonia severity index.

TABLE 64.6 Risk Factors for  $\beta$ -Lactam-Resistant *Streptococcus pneumoniae*

Age <2 or >65 years
$\beta$ -Lactam therapy within the previous 3 months (also at risk for organisms associated with HCAP)
Alcoholism
Medical comorbidities
Immunosuppressive illness or therapy (also at risk for organisms associated with HCAP)
Exposure to a child in a day-care center

HCAP, health care–associated pneumonia.

TABLE 64.7 Patients at High Risk of Complications from Influenza

Unvaccinated infants aged 12–24 months
Persons with asthma or other chronic pulmonary diseases (e.g., COPD, cystic fibrosis)
Persons with hemodynamically significant cardiac disease
Persons who have immunosuppressive disorders or who are receiving immunosuppressive therapy
HIV-infected persons
Persons with sickle cell anemia and other hemoglobinopathies
Persons with diseases that require long-term, high-dose aspirin therapy, such as rheumatoid arthritis
Persons with chronic renal dysfunction
Persons with cancer
Persons with chronic metabolic disease, such as diabetes mellitus
Persons with central nervous system disorders that may compromise the handling of secretions such as neuromuscular disorders, cerebral vascular accidents, or seizure disorders
Adults aged $\geq 65$ years
Residents of any age of nursing homes or other long-term care institutions

COPD, chronic obstructive pulmonary disease; HIV, human immunodeficiency virus.

TABLE 64.8 Comparison of Current Neuraminidase Inhibitors for Influenza

	Oseltamivir	Zanamivir
Influenza activity	A and B	A and B
Route of administration	Oral	Oral inhalation
Treatment dosage	Adults: 75 mg PO BID  Children $\geq 12$ months: $\leq 15$ kg: 30 mg PO BID 15–23 kg: 45 mg PO BID 24–40 kg: 60 mg PO BID $\geq 60$ kg: 75 mg PO BID	Adults: Two inhalations (5 mg each) PO BID Children $\geq 7$ years: Two inhalations (5 mg each) PO BID
Side effects	Nasal and throat discomfort, headache, bronchospasm	Nausea, vomiting, headache

BID, twice a day; PO, by mouth.

## Hospital-Acquired, Healthcare-Associated, and Ventilator-Associated Pneumonia

- Hospital-acquired pneumonia (HAP) occurs at least 48 hours after admission and is not incubating at the time of hospitalization. It is diagnosed on the basis of radiographic findings and clinical features (new or progressive infiltrates, fever, leucopenia or leukocytosis, purulent sputum).
- Healthcare-associated pneumonia (HCAP) occurs within 48 hours of admission in patients with previous risk factors for infection caused by potentially drug-resistant pathogens.



- Ventilator-associated pneumonia (VAP) refers to pneumonia that arises 48 to 72 hours after endotracheal intubation.
- Treatment
  - Empiric therapy is shown in Tables 64.9 and 64.10.
  - Vancomycin or linezolid should be added if methicillin-resistant *Staphylococcus aureus* (MRSA) risk factors are present.
  - 7 to 8 days of therapy is recommended for patients with uncomplicated HAP, VAP, or HCAP who have received appropriate empiric antibiotics with a satisfactory clinical response. Patients with nonfermenting gram-negative bacilli may benefit from longer courses (≥14 days) to prevent recurrence.

**TABLE 64.9 Empiric Therapy for Hospital-Acquired Pneumonia, Health Care–Associated Pneumonia, and Ventilator-Associated Pneumonia in Patients with No Known Risk Factors for Multidrug-Resistant Pathogens and Onset <5 Days**

Possible Pathogens	Recommended Therapy	Dosage
<i>Streptococcus pneumoniae</i> <sup>a</sup> <i>Haemophilus influenzae</i> MSSA	Ceftriaxone or Levofloxacin, moxifloxacin, or ciprofloxacin	1 g IV every 24 hours 500–750 mg PO/IV every 24 hours 400 mg PO/IV every 24 hours
Antibiotic-sensitive enteric GNB <i>Escherichia coli</i> <i>Klebsiella pneumoniae</i> <i>Enterobacter</i> sp. <i>Proteus</i> sp. <i>Serratia marcescens</i>	or Ampicillin/Sulbactam or Ertapenem	500–750 mg PO every 12 hours or 400 mg IV every 8–12 hours 1.5–3 g IV every 6 hours 1 g IM/IV every 24 hours

<sup>a</sup>The frequency of penicillin-resistant *S. pneumoniae* and multidrug-resistant *S. pneumoniae* is increasing; levofloxacin or moxifloxacin are preferred to ciprofloxacin.

GNB, gram-negative bacilli; IM, intramuscular; IV, intravenous; MSSA, methicillin-sensitive *Staphylococcus aureus*; PO, orally.

**TABLE 64.10 Empiric Therapy for Hospital-Acquired Pneumonia, Health Care–Associated Pneumonia, and Ventilator-Associated Pneumonia in Patients with Late-Onset Infection (≥5 days) or Risk Factors for Multidrug-Resistant Pathogens**

Possible Pathogens	Combination Recommended Therapy	Adult Dosage <sup>a</sup>
Pathogens listed in Table 60.1 and MDR pathogens	Antipseudomonal cephalosporin cefepime	1–2 g IV every 8–12 hours
<i>Pseudomonas aeruginosa</i>	Ceftazidime	2 g IV every 8 hours
	Or	500 mg IV every 6 hours or 1 g IV every 8 hours
	Antipseudomonal carbapenem imipenem	
	Doripenem	500 mg IV every 6–8 hours
	Meropenem	
<i>Klebsiella pneumoniae</i> (ESBL <sup>+</sup> ) <sup>b</sup>	Or	1 g IV every 8 hours
	$\beta$ -Lactam/ $\beta$ -Lactamase inhibitor piperacillin-tazobactam	
	Plus	4.5 g IV every 6 hours <sup>c</sup>
	Antipseudomonal fluoroquinolone <sup>d</sup> Ciprofloxacin	400 mg IV every 8 hours
	Or	750 mg IV every 24 hours
	Aminoglycoside	

**TABLE 64.10 Empiric Therapy for Hospital-Acquired Pneumonia, Health Care–Associated Pneumonia, and Ventilator-Associated Pneumonia in Patients with Late-Onset Infection ( $\geq 5$  days) or Risk Factors for Multidrug-Resistant Pathogens (Continued)**

Possible Pathogens	Combination Recommended Therapy	Adult Dosage <sup>a</sup>
<i>Acinetobacter</i> sp. <sup>b</sup>	Amikacin	15–20 mg/kg IV every 24 hours <sup>e</sup>
	Gentamicin	
	Tobramycin	
MRSA <sup>d</sup>	Plus	5–7 mg/kg IV every 24 hours <sup>e</sup>
	Linezolid	5–7 mg/kg IV every 24 hours <sup>e</sup>
	Vancomycin	600 mg/kg every 12 hours <sup>f</sup>
<i>Legionella pneumophila</i> <sup>g</sup>	Azithromycin	15 mg every 12 hours
		500 mg IV every 24 hours

<sup>a</sup>Dosages are based on normal renal and hepatic function.

<sup>b</sup>If an ESBL<sup>+</sup> strain, such as *K. pneumoniae*, or an *Acinetobacter* sp. is suspected, a carbapenem is a reliable choice.

<sup>c</sup>Studied infusion times range from 30 minutes to 4 hours.

<sup>d</sup>If MRSA risk factors are present, or there is a high incidence locally.

<sup>e</sup>Trough levels for gentamicin and tobramycin should be  $<1$  mcg/mL; for amikacin, they should be  $<4$  to 5 mcg/mL.

<sup>f</sup>Trough levels for vancomycin should be 15 to 20 mcg/mL.

<sup>g</sup>If *L. pneumophila* is suspected, a combination antibiotic regimen including a macrolide (e.g., azithromycin) or a fluoroquinolone (e.g., ciprofloxacin or levofloxacin) should be used.

ESBL, extended-spectrum  $\beta$ -lactamase; IV, intravenous; MDR, multidrug-resistant; MRSA, methicillin-resistant *Staphylococcus aureus*.

# Tuberculosis\*

## General Principles

- Tuberculosis (TB), an infectious disease caused by *Mycobacterium tuberculosis*, is transmitted through the air by aerosolized droplet nuclei when a person with pulmonary or laryngeal TB coughs, sneezes, speaks, or sings. The most common site of infection is the lungs.
- A high index of suspicion for TB, rapid pathogen identification, susceptibility testing, patient isolation, and appropriate antimicrobial therapy are critical to prevent development and spread of multidrug-resistant TB (MDR-TB).
- Inadequate treatment of TB is a primary reason for treatment failure and development of acquired drug resistance.
  - MDR-TB—resistance to both isoniazid and rifampin.
  - Extensive drug-resistant TB (XDR-TB)—resistance to isoniazid and rifampin among first-line agents, resistance to any fluoroquinolone, and resistance to at least one second-line injectable drug.
  - Totally drug-resistant TB (TDR-TB)—resistance to all first- and second-line agents.

## Classification

- **Latent infection** occurs when the tubercle bacilli are inhaled into the body. The patient is often asymptomatic with no radiographic evidence of infection.
- **Active disease** typically results from reactivation of a previously controlled latent infection.

## Risk Factors

- Risk factors for TB include immune suppression, exposure to close contacts, and smoking. The elderly, adolescents, and children younger than 5 years of age are at increased risk of developing active disease.
- Risk factors for drug-resistant TB are shown in Table 65.1. Risk factors for XDR-TB include HIV infection, homelessness, and alcohol use.

**TABLE 65.1 Conditions and Risk Factors for Persons with Increased Risk of Drug-Resistant Tuberculosis**

History of treatment for latent tuberculosis infection or active disease
Patients from areas with high prevalence of initial or primary drug resistance (urban population, northeast United States, Florida, California, Texas, United States–Mexico border)
Foreign-born persons from areas with high prevalence of drug-resistant tuberculosis (southeast Asia, Mexico, South America, Africa)
Contact with persons with active infection caused by drug-resistant <i>Mycobacterium tuberculosis</i>
Tuberculosis in persons who are homeless, abusers of intravenous drugs, and HIV infected
Patients with positive sputum smears and cultures after 2 months of treatment

HIV, human immunodeficiency virus.

\*The reader is referred to Chapter 65, Tuberculosis, written by Michael B. Kays, PharmD, FCCP, in the 10th edition of *Applied Therapeutics: The Clinical Use of Drugs* for a more in-depth discussion. All notations to reference numbers are based on the reference list at the end of that chapter. The editor of this handbook expresses her thanks to Dr. Kays and acknowledges that this chapter is based on his work.

## Patient Assessment

- Diagnosis of active disease includes tuberculin skin testing (PPD), chest radiography, and sputum collection for acid-fast bacilli stain and culture. Nucleic acid amplification tests and interferon-gamma release assays may aid in the diagnosis of TB.
- A positive tuberculin skin test (PPD) confirms that a patient has been previously infected with TB, not that active disease is present. Positive culture confirms the diagnosis.
- Active disease is characterized by fever, chills, night sweats, weight loss, and changes on chest radiograph. The sputum may contain blood (hemoptysis) in patients with advanced disease. Classic TB symptoms may be absent in the elderly.
- Human immunodeficiency virus (HIV) screening is recommended for all patients with TB.
- Hospitalized patients with suspected or confirmed TB should be placed in respiratory isolation.

## Goals of Therapy

- Goals of therapy include curing the patient and preventing transmission of *M. tuberculosis*.
- Drug therapy should provide rapid bacterial killing, prevention of emergence of drug resistance, and elimination of persistent tubercle bacilli to prevent relapse.

## Treatment

- Treatment of active disease should be individualized to clinical and social circumstances to ensure adherence and completion of therapy.
- Treatment of active pulmonary disease requires use of multidrug therapy for a minimum of 26 weeks. Directly observed therapy (i.e., watching the patient take each dose) is a core management strategy for all patients to ensure adherence to therapy.
- Current guidelines for active disease recommend four drugs for the initial 8-week treatment phase (Table 65.2). Dosages and side effects of the drugs used for TB are in Table 65.3.
- At least two, and preferentially three, new drugs to which susceptibility can be inferred should be added to the regimen of a patient who is not responding to therapy.
- Principles of treatment of TB in the elderly are the same as any other age group.
- Treatment in pregnancy should be essentially the same as in nonpregnant women, except that pyrazinamide and streptomycin are not recommended. All pregnant women receiving isoniazid should receive pyridoxine 25 mg/day.
- Regimens recommended for children are the same as for adults, except that ethambutol is not routinely used in children. Pyridoxine is recommended if isoniazid is used.
- A pretreatment complete blood count, platelet count, blood urea nitrogen, hepatic enzymes, bilirubin, and serum uric acid should be obtained. Symptoms of hepatotoxicity from drug therapy should be assessed. Sputum cultures should be ordered every 2 to 4 weeks initially and then monthly after sputum cultures become negative. Chest radiograph should be obtained at the completion of therapy.
- BCG (bacilli Calmette-Guerin) is a live vaccine used in many foreign countries with a high prevalence of TB to prevent disease in persons who are tuberculin negative. Its use is generally not recommended in the United States because risk of exposure to TB is low. BCG vaccination is contraindicated in pregnancy and in patients who are or will become immunocompromised.
- Treatment of latent TB infection is effective in preventing active TB in persons with positive tuberculin skin tests and those at risk for reactivation for TB. Daily isoniazid for 6 months and twice weekly isoniazid for 6 to 9 months are options for latent TB.

TABLE 65.2 Treatment Regimens for Pulmonary Tuberculosis Caused by Drug-Susceptible Organisms

Initial Phase			Continuation Phase			Rating (Evidence) <sup>a</sup>			
Regimen	Drugs	Interval and Doses (Minimal Duration)	Regimen	Drugs	Interval and Doses (Minimal Duration) <sup>b</sup>	# Total Doses (Minimal Duration)	HIV–	HIV+	
1	INH	7 day/week for 56 doses (8 weeks) OR	1a	INH/RIF	7 day/week for 126 doses (18 weeks) OR	182–130 (26 weeks)	A (I)	A (II)	
	RIF	5 day/week for 40 doses (8 weeks) <sup>c</sup>							5 day/week for 90 doses (18 weeks) <sup>c</sup>
	PZA EMB								
2	INH	7 day/week for 14 doses (2 weeks) then	2a	INF/RIF	Twice weekly for 36 doses (18 weeks)	62–58 (26 weeks)	A (II)	B (II) <sup>d</sup>	
	RIF	twice weekly for 12 doses (6 weeks) OR							Once weekly for 18 doses (18 weeks)
	PZA EMB	5 day/week for 10 doses (2 weeks) <sup>e</sup> then							
3	INH	twice weekly for 12 doses (6 weeks)	2b <sup>e</sup>	INH/RPT	Once weekly for 18 doses (18 weeks)	44–40 (26 weeks)	B (I)	E (I)	
	RIF	twice weekly for 12 doses (6 weeks)							
	PZA EMB								
4	INH	Three times weekly for 24 doses (8 weeks)	3a	INH/RIF	Three times weekly for 54 doses (18 weeks)	78 (26 weeks)	B (I)	B (II)	
	RIF								
	PZA EMB								
4	INH	7 day/week for 56 doses (8 weeks) OR	4a	INH/RIF	7 d/week for 217 doses (31 weeks) OR	273–195 (39 weeks)	C (I)	C (II)	
	RIF	5 day/week for 40 doses (8 weeks) <sup>c</sup>							5 d/week for 155 doses (31 weeks) <sup>e</sup>
	EMB								

<sup>a</sup>Definitions of evidence ratings: A, preferred; B, acceptable alternative; C, offer when A and B cannot be given; E, should never be given; I, randomized clinical trial; II, data from clinical trials that were not randomized or were conducted in other populations; III, expert opinion.

<sup>b</sup>Patients with cavitation on initial chest radiograph and positive cultures at completion of 2 months of therapy should receive a 7-month continuation phase (31-weeks; either 217 doses [daily] or 62 doses [twice weekly]).

<sup>c</sup>Five-day-a-week administration is always given by directly observed therapy (DOT). Rating for 5-day/week regimens is A (III).

<sup>d</sup>Not recommended for HIV-infected patients with CD4<sup>+</sup> cell counts <100 cells/ $\mu$ L.

<sup>e</sup>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 the initial chest radiograph.

EMB, ethambutol; INH, isoniazid; PZA, pyrazinamide; RIF, rifampin; RPT, rifapentine.

TABLE 65.3 Drugs Used in the Treatment of Tuberculosis in Adults and Children

Drug	Dosing (Maximum Dose)	Primary Side Effects	Dose Adjustment in Renal Impairment	Comments
<b>FIRST-LINE AGENTS</b>				
Isoniazid	Adults: 5 mg/kg (300 mg) daily; 15 mg/kg (900 mg) once, twice, or thrice weekly Children: 10–15 mg/kg (300 mg) daily; 20–30 mg/kg (900 mg) twice weekly	Increased aminotransferases (asymptomatic), clinical hepatitis, peripheral neuropathy, CNS effects, lupus-like syndrome, hypersensitivity reactions	No	Peripheral neuropathy preventable with pyridoxine 10–25 mg; serum level of phenytoin. Hepatitis more common in older patients and alcoholics
Rifampin	Adults: 10 mg/kg (600 mg) once daily, twice weekly, or thrice weekly Children: 10–20 mg/kg (600 mg) once daily or twice weekly	Pruritus, rash, hepatotoxicity, GI (nausea, anorexia, abdominal pain), flulike syndrome, thrombocytopenia, renal failure	No	Orange-red discoloration of body secretions (sweat, saliva, tears, urine). Drug interactions due to induction of hepatic microsomal enzymes (warfarin, antiretroviral agents, corticosteroids, diazepam, lorazepam, triazolam, quinidine, oral contraceptives, methadone, sulfonyleureas)
Rifabutin	Adults: 5 mg/kg (300 mg) once daily, twice weekly, or thrice weekly Children: unknown	Neutropenia, uveitis, GI symptoms, polyarthralgias, hepatotoxicity, rash	No	Orange-red discoloration of body secretions (sweat, saliva, tears, urine). Weaker inducer of hepatic microsomal enzymes than rifampin
Rifapentine	Adults: 10 mg/kg (600 mg) once weekly during continuation phase Children: not approved	Similar to rifampin	Unknown	Drug interactions due to induction of hepatic microsomal enzymes (see rifampin)
Pyrazinamide	Adults: 40–55 kg: 1 g daily, 2 g twice weekly, 1.5 g thrice weekly; 56–75 kg: 1.5 g daily, 3 g twice weekly, 2.5 g thrice weekly; 76–90 kg: 2 g daily, 4 g twice weekly, 3 g thrice weekly Children: 15–30 mg/kg (2 g) daily; 50 mg/kg (2 g) twice weekly	Hepatotoxicity, nausea, anorexia, polyarthralgias, rash, hyperuricemia, dermatitis	Yes	Monitor aminotransferases monthly.
Ethambutol	Adults: 40–55 kg: 800 mg daily, 2 g twice weekly, 1.2 g thrice weekly; 56–75 kg: 1.2 g daily, 2.8 g twice weekly, 2 g thrice weekly; 76–90 kg: 1.6 g daily, 4 g twice weekly, 2.4 g thrice weekly Children: 15–20 mg/kg (1 g) daily; 50 mg/kg (2.5 g) twice weekly	Optic neuritis, skin rash, drug fever	Yes	Routine vision tests recommended; 50% excreted unchanged in urine

Continued on following page

TABLE 65.3 Drugs Used in the Treatment of Tuberculosis in Adults and Children (Continued)

Drug	Dosing (Maximum Dose)	Primary Side Effects	Dose Adjustment in Renal Impairment	Comments
<b>SECOND-LINE AGENTS</b>				
Cycloserine	Adults: 10–15 mg/kg/day (1 g), usually 500–750 mg/day in two divided doses Children: 10–15 mg/kg/day (1 g)	CNS toxicity (psychosis, seizures), headache, tremor, fever, skin rashes	Yes	May exacerbate seizure disorders or mental illness. Some toxicity preventable by pyridoxine (100–200 mg/day). Monitor serum concentrations (peak 20–35 mcg/mL desirable).
Ethionamide	Adults: 15–20 mg/kg/day (1 g), usually 500–750 mg/day in one daily dose or two divided doses Children: 15–20 mg/kg/day (1 g)	GI effects (metallic taste, nausea, vomiting, anorexia, abdominal pain), hepatotoxicity, neurotoxicity, endocrine effects (alopecia, gynecomastia, impotence, hypothyroidism), difficulty in diabetes management	Yes	Must be given with meals and antacids. Monitor aminotransferases and thyroid-stimulating hormone monthly.
Streptomycin	Adults: 15 mg/kg/day (1 g); ≥60 years, 10 mg/kg/day (750 mg) Children: 20–40 mg/kg/day (1 g)	Vestibular or auditory dysfunction of eighth cranial nerve, renal dysfunction, skin rashes, neuromuscular blockade	Yes	Audiometric and neurologic examinations recommended; 60%–80% excreted unchanged in urine. Monitor renal function.
Amikacin	Adults: 15 mg/kg/day (1 g); ≥60 years, 10 mg/kg/day (750 mg) Children: 15–30 mg/kg/day (1 g)	Ototoxicity, nephrotoxicity	Yes	Less vestibular toxicity than streptomycin. Monitoring similar to streptomycin
Capreomycin	Adults: 15 mg/kg/day (1 g); ≥60 years, 10 mg/kg/day (750 mg) Children: 15–30 mg/kg/day (1 g) as single dose or twice-weekly dose	Nephrotoxicity, ototoxicity	Yes	Monitoring similar to streptomycin
p-Aminosalicylic acid (PAS)	Adults: 8–12 g/day in two to three doses Children: 200–300 mg/kg/day in two to four divided doses	GI intolerance, hepatotoxicity, malabsorption syndrome, hypothyroidism	Yes	Liver enzymes and thyroid function should be monitored.
Levofloxacin	Adults: 500–1,000 mg/day	Nausea, diarrhea, abdominal pain, anorexia, headache, dizziness, QT prolongation, tendon pain or rupture	Yes	Do not give with divalent or trivalent cations (aluminum, magnesium, iron, etc.).
Moxifloxacin	Adults: 400 mg/day	Nausea, diarrhea, abdominal pain, anorexia, headache, dizziness, QT prolongation, tendon pain or rupture	No	See levofloxacin.

CNS, central nervous system; GI, gastrointestinal.

# Infectious Diarrhea\*

## General Principles

- Diarrhea is defined as three or more loose stools, or any loose stool with blood, during a 24-hour period. It may be accompanied by nausea, vomiting, or abdominal cramping. Acute symptoms are present for less than 2 weeks, persistent symptoms last for more than 14 days, and chronic symptoms last longer than 30 days.
- Infectious diarrhea is caused by the ingestion of food or water contaminated with pathogenic microorganisms (e.g., bacteria, viruses, protozoa, or fungi).
- Good hand hygiene and proper food handling are essential to prevent the spread of enteropathogens.
- Infection caused by toxin-producing bacteria (e.g., *Escherichia coli*, *Clostridium difficile*) can result in irritation, inflammation, and sloughing of bowel mucosa.

## Classification

- Classification of infectious diarrhea as either inflammatory or noninflammatory provides the basis guiding the diagnostic and therapeutic plan.
  - Inflammatory: diarrhea (may include bloody or mucoid stools) with or without dysentery, abdominal pain, and fever. Management is typically with supportive therapy and antimicrobial agents directed at the causative pathogen.
  - Noninflammatory: watery diarrhea that results from bacterial endotoxins which stimulate secretion of water and electrolytes into the intestinal lumen, or by viruses that infect the absorptive villus tip. Management is typically with supportive therapy.

## Patient Assessment

- Predisposing factors, symptoms, diagnostic evaluations, and treatment options for various types of infectious diarrhea are shown in Table 66.1.
- Use of some medications can increase the risk of gastrointestinal infection (Table 66.2) or risk for developing *Clostridium difficile*-associated diarrhea (Table 66.3).
- Infectious diarrhea is typically a self-limiting illness. Medical evaluation is warranted for patients with profuse watery diarrhea with dehydration, bloody stools, temperature over 101.3°F, or illness lasting more than 48 hours.
- The most common complication of diarrhea is loss of fluids and electrolytes, which can lead to hypovolemia, shock, and death.
- Infection with *E. coli* O157:H7, a specific toxin-producing strain of bacteria, can lead to hemolytic uremic syndrome.

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\*The reader is referred to Chapter 66, Infectious Diarrhea, written by Gail S. Itokazu, PharmD, David T. Bearden, PharmD, and Larry H. Danziger, PharmD, in the 10th edition of *Applied Therapeutics: The Clinical Use of Drugs* for a more in-depth discussion. All notations to reference numbers are based on the reference list at the end of that chapter. The editor of this handbook expresses her thanks to Drs. Itokazu, Bearden, and Danziger and acknowledges that this chapter is based on their work.



TABLE 66.1 Predisposing Factors, Symptoms, and Therapy of Gastrointestinal Infections

Pathogen	Predisposing Factors	Symptoms	Diagnostic Evaluations	Drug of Choice <sup>a,c</sup>	Alternatives <sup>a,c</sup>
<i>Salmonella</i> (nontyphoidal) <sup>b</sup>	Ingestion of contaminated poultry, raw milk, custards, and cream fillings; foreign travel	Nausea, vomiting, diarrhea, cramps, fever, tenesmus Incubation: 6–72 hours	Fecal leukocytes, stool culture	Fluoroquinolone, azithromycin, third-generation cephalosporins	Amoxicillin, TMP-SMX
<i>Salmonella</i> (typhoidal)	Ingestion of contaminated food, foreign travel	High fever, abdominal pain, headache, dry cough	Fecal leukocytes, stool culture, blood culture	Fluoroquinolone, azithromycin, third-generation cephalosporins	TMP-SMX, amoxicillin
<i>Shigella</i>	Ingestion of contaminated food, foreign travel	Fever, dysentery, cramps, tenesmus Incubation: 24–48 hours	Fecal leukocytes, stool culture	Fluoroquinolone, azithromycin, ceftriaxone	TMP-SMX, ampicillin
<i>Campylobacter</i>	Contaminated eggs, raw milk, or poultry; foreign travel	Mild to severe diarrhea; fever, systemic malaise Incubation: 24–72 hours	Fecal leukocytes, stool culture	Erythromycin, azithromycin	—
<i>Clostridium difficile</i>	Antibiotics, antineoplastics	Mild to severe diarrhea, cramps	<i>C. difficile</i> toxin, <i>C. difficile</i> culture, colonoscopy	Metronidazole	Vancomycin
Staphylococcal food poisoning	Custard-filled bakery products, canned food, processed meat, ice cream	Nausea, vomiting, salivation, cramps, diarrhea; usually resolves in 8 hours Incubation: 2–6 hours	—	Supportive therapy only	—
Travelers' diarrhea (Enterotoxigenic <i>Escherichia coli</i> , <i>Campylobacter</i> )	Contaminated food (vegetables and cheese), water, foreign travel	Nausea, vomiting, mild to severe diarrhea, cramps	Stool culture	See Table 66.4	—
Shiga toxin–producing <i>Escherichia coli</i> ( <i>E. coli</i> O157:H7)	Beef, raw milk, water	Diarrhea, headache, bloody stools Incubation: 48–96 hours	Stool cultures on MacConkey's sorbitol	Supportive therapy only	—
Cryptosporidiosis	Immunosuppression, day-care centers, contaminated water, animal handlers	Mild to severe diarrhea (chronic or self-limited); large fluid volume	Stool screening for oocytes, PCR, ELISA	See Chapter 74	—
Viral gastroenteritis	Community-wide outbreaks, contaminated food	Nausea, diarrhea (self-limited), cramps Incubation: 16–48 hours	Special viral studies	Supportive therapy only	—

ELISA, enzyme-linked immunosorbent assay; PCR, polymerase chain reaction; TMP-SMX, trimethoprim-sulfamethoxazole.

<sup>a</sup>Sources: Navaneethan U, Giannella RA. Mechanisms of infectious diarrhea. *Nat Clin Pract Gastroenterol Hepatol*. 2008;5:637; DuPont HL. Clinical practice. Bacterial diarrhea. *N Engl J Med*.

2009;361:1560. See text for doses and duration of therapy.

<sup>b</sup>Not all cases require antibiotic therapy. See text for details.

<sup>c</sup>If susceptible. See text for details.

TABLE 66.2 Pharmacologic Agents that May Promote Gastrointestinal Infection

Drug	Mechanism
Antacids, H <sub>2</sub> -receptor antagonists, proton-pump inhibitors	Increased gastric pH; viable pathogens passed to lower gut
Antibiotics	Eradication of normal (anaerobic) flora
Antidiarrheals	Decreased gut motility; bacterial growth
Immunosuppressives	Inhibition of gut immune defenses

## Treatment

- Fluid and electrolyte replacement is essential to prevent or reverse losses; choice of oral or parenteral route depends on degree of dehydration.
- Antidiarrheal agents should be used only in mild cases and for no more than 3 days.
  - Loperamide slows intestinal transit time and has antisecretory properties.
  - Diphenoxylate/atropine slows intestinal transit time.
  - Bismuth subsalicylate has antisecretory properties. It is not recommended for chronic disease where absorption of salicylate may be increased.
- Probiotics are live microbial mixtures of bacteria and yeast that are used to restore normal intestinal flora.
- Antibacterial therapy directed at the pathogen is often required to decrease the duration and severity of illness, prevent progression to invasive infection, and prevent person-to-person transmission of pathogens (Table 66.1). Antimicrobials are generally recommended for severe illness, when conditions that compromise normal enteric defenses are present, for immunocompromised patients, and for extraintestinal infections.

TABLE 66.3 Medications Implicated in *Clostridium difficile*-Associated Diarrhea

### COMMONLY IMPLICATED

Cephalosporins  
Clindamycin  
Ampicillin  
Fluoroquinolones

### LESS COMMONLY IMPLICATED

Erythromycin  
Clarithromycin  
Azithromycin  
Other penicillins  
Trimethoprim-sulfamethoxazole

### RARELY IMPLICATED

Aminoglycosides  
Rifampin  
Tetracycline  
Vancomycin  
Metronidazole  
Antineoplastic agents

Sources: Owens RC Jr et al. Antimicrobial-associated risk factors for *Clostridium difficile* infection. *Clin Infect Dis*. 2008;46(Suppl 1):S19; Cohen SH et al. Society for Healthcare Epidemiology of America; Infectious Diseases Society of America. Clinical practice guidelines for *Clostridium difficile* infection in adults: 2010 update by the society for healthcare epidemiology of America (SHEA) and the infectious diseases society of America (IDSA). *Infect Control Hosp Epidemiol*. 2010;31:431.

TABLE 66.4 Therapy for Travelers' Diarrhea in Adults

Drug	Treatment
Ciprofloxacin	500 mg twice daily for 1–3 days <sup>a</sup>
Levofloxacin	500 mg daily for 1–3 days <sup>a</sup>
Azithromycin	1,000 mg in a single dose
Rifaximin	200 mg three times daily for 3 days

<sup>a</sup>Single dose may be effective. If diarrhea improves 12 to 24 hours after the first dose, the antibiotic can be stopped; otherwise, antibiotic may be continued for up to 3 days.

Sources: Hill DR, Beeching NJ. Travelers' diarrhea. *Curr Opin Infect Dis.* 2010;23:481; DuPont HL et al. Expert review of the evidence base for self-therapy of travelers' diarrhea. *J Travel Med.* 2009;16:161.

TABLE 66.5 Costs of Oral Drug Therapy for *Clostridium difficile*-Associated Diarrhea

Drug	Regimen	Cost <sup>a</sup>
Metronidazole tablets (generic)	500 mg TID × 10 days	\$8.51/10 days
Vancomycin capsules (Vancocin)	125 mg QID × 10 days	\$707.16/10 days
Vancomycin solution (generic) <sup>b</sup>	125 mg QID × 10 days	\$45.50/10 days
Nitazoxanide (Alinia)	125 mg BID × 10 days	\$345.63/10 days

<sup>a</sup>AWP Red Book 2010.

<sup>b</sup>Prepared from intravenous formulation.

- Patients traveling to areas at high risk for traveler's diarrhea should bring a travel kit that includes medications (e.g., loperamide, antimicrobials) and instructions for self-treatment at the onset of illness. Choice of antimicrobial depends on the area of travel. Table 66.4 outlines treatment options for traveler's diarrhea.
- Treatment regimens for *C. difficile*-associated diarrhea are shown in Table 66.5.

# Intra-abdominal Infections\*

## General Principles

- Intra-abdominal infections are contained within the peritoneal cavity. They can persist as localized infection (appendicitis), a diffuse inflammation throughout the peritoneum (peritonitis), or as abscesses (which can form anywhere within the abdomen).
- Common pathogens seen in intra-abdominal infections are shown in Table 67.1.

## Biliary Tract Infections

- **Cholecystitis:** acute inflammation of the gallbladder
  - Clinical presentation of fever and prolonged constant abdominal pain typically localized to the right upper quadrant, followed by nausea and vomiting
  - Lab findings include leukocytosis with increased neutrophils and mild elevations in transaminases.
- **Cholangitis:** acute inflammation of the common bile duct
  - Clinical presentation is Charcot's triad (fever, jaundice, right upper quadrant pain)
  - Lab findings include leukocytosis, and increased bilirubin and alkaline phosphatase.

## Peritoneal Infections

- Peritonitis is inflammation of the peritoneum as a result of infectious or chemical inflammation within the peritoneal cavity.
- **Primary:** infection in the absence of intra-abdominal pathology (also known as spontaneous bacterial peritonitis, SBP)
  - Clinical presentation of fever, abdominal pain, altered mental status, changes in gastrointestinal (GI) motility, vomiting, diarrhea, and ileus.
- **Secondary:** infection from contamination with gastrointestinal or genitourinary organisms as a result of loss of mucosal barrier integrity
  - Clinical presentation of pain, voluntary guarding of abdomen, faint/absent bowel sounds, rapid/shallow breaths
  - Table 67.2 shows common pathogens
- **Tertiary:** clinical peritonitis with signs of sepsis and multiorgan dysfunction after the treatment of secondary peritonitis
- Peritonitis is a major complication of peritoneal dialysis (CAPD). Symptoms include abdominal pain and tenderness, nausea, vomiting, diarrhea, and fever. The dialysate will typically be cloudy with a WBC count  $\geq 100$  cells/ $\mu$ L.

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\*The reader is referred to Chapter 67, Intra-Abdominal Infections, written by Carrie A. Sincak, PharmD, BCPS, and Sheila K. Wang, PharmD, BCPS (AQ-ID), in the 10th edition of *Applied Therapeutics: The Clinical Use of Drugs* for a more in-depth discussion. All notations to reference numbers are based on the reference list at the end of that chapter. The editor of this handbook expresses her thanks to Drs. Sincak and Wang and acknowledges that this chapter is based on their work.

TABLE 67.1 Common Pathogens in Intra-abdominal Infection

Disease	Pathogens	Comments
Primary peritonitis	<i>Escherichia coli</i> , <i>Klebsiella pneumoniae</i> , <i>Streptococcus pneumoniae</i> , <i>Streptococcus pneumoniae</i> species, occasional anaerobes	Predominately in spontaneous bacterial peritonitis in cirrhotic patients. Anaerobes less likely than aerobes.
Secondary peritonitis	<i>E. coli</i> , <i>Bacteroides fragilis</i> , other aerobic gram-negative rods and anaerobes, <i>Enterococcus</i>	Generally polymicrobial with both aerobic and anaerobic pathogens. <i>Enterococcus</i> species are associated with nosocomial infections and chronic surgical infections, particularly in patients receiving broad-spectrum antimicrobials.
Chronic ambulatory peritoneal dialysis	<i>S. epidermidis</i> , <i>Staphylococcus aureus</i> , diphtheroids, gram-negative rods	Dwell time of exchange with intraperitoneal antibiotics must be a minimum of 6 hours.
Cholecystitis, cholangitis	<i>E. coli</i> , <i>K. pneumoniae</i> , other gram-negative rods, <i>Enterococcus</i> , and anaerobes	Unnecessary to use antimicrobials that achieve high biliary concentrations

## Treatment

### BILIARY INFECTIONS

- Empiric antibiotic therapy should be initiated as soon as an intra-abdominal infection is suspected. Choice of agent is based on common causative pathogens (Table 67.3).
- Definitive therapy must involve source control (surgery, percutaneous drainage, or endoscopic intervention) to eliminate infection and restore normal physiological function.
- Supportive measures include fluid and electrolyte supplementation and analgesia.

TABLE 67.2 Bacteriology of Intra-abdominal Infections

Bacteria	Patients (%)
<b>FACULTATIVE AND AEROBIC GRAM-NEGATIVES</b>	
<i>Escherichia coli</i> <sup>a</sup>	71
<i>Klebsiella</i> species	14
<i>Pseudomonas aeruginosa</i>	14
<i>Proteus mirabilis</i>	5
<i>Enterobacter</i> species	5
<b>ANAEROBES</b>	
<i>Bacteroides fragilis</i> <sup>a</sup>	35
Other <i>Bacteroides</i> species	71
<i>Clostridium</i> species	29
<i>Prevotella</i> species	12
<i>Peptostreptococcus</i> species	17
<i>Fusobacterium</i> species	9
<b>AEROBIC GRAM-POSITIVES</b>	
<i>Streptococcus</i> species	38
<i>Enterococcus faecalis</i>	12
<i>Enterococcus faecium</i>	3
<i>Staphylococcus aureus</i>	4

<sup>a</sup>Most common in community-acquired intra-abdominal infections.

TABLE 67.3 Empiric Treatment of Biliary Infections

Infection	Regimen
Community-acquired acute cholecystitis (mild-to-moderate)	Cefazolin, cefuroxime, or ceftriaxone
Community-acquired acute cholecystitis with severe physiologic disturbance, advanced age, or immunocompromised state	1. Imipenem-cilastatin, meropenem, doripenem, piperacillin-tazobactam monotherapy
Acute cholangitis associated with biliary-enteric anastomosis	2. Ciprofloxacin, levofloxacin, or cefepime PLUS metronidazole <sup>d</sup>
Health care–associated biliary infection	Vancomycin <sup>b</sup> may be added to each regimen in the setting of health care–associated biliary infections.

<sup>a</sup>Selection of fluoroquinolones should be based on local antibiogram or susceptibility reports.

<sup>b</sup>Given for suspected MRSA or ampicillin-resistant enterococcal infection.

### PERITONEAL INFECTIONS

- Initial antibacterial therapy for patients with SBP is typically empiric. Third-generation cephalosporins (cefotaxime, ceftriaxone) are generally first line; fluoroquinolones (levofloxacin, moxifloxacin) are an option in patients with  $\beta$ -lactam allergy. Prophylactic antimicrobial therapy may be needed as recurrence rate for SBP is high.
- Intraperitoneal delivery of antimicrobials is the preferred route of administration for the treatment of CAPD-associated peritonitis. While clinical response is expected within 48 hours of initiating appropriate antimicrobials, therapy is recommended for at least 2 weeks (3 weeks for severe cases). Dosing guidelines for peritonitis associated with CAPD are shown in Tables 67.4 and 67.5.

TABLE 67.4 Intraperitoneal Antibiotic Intermittent Dosing Recommendations for CAPD Patients<sup>a</sup>

	Intermittent Dosing <sup>b</sup>
Amikacin	2 mg/kg
Ampicillin-sulbactam	2 g every 12 hours
Cefazolin	15 mg/kg
Cefepime	1,000 mg
Ceftazidime	1,000–1,500 mg
Ceftizoxime	1,000 mg
Fluconazole	200 mg every 24–28 hours
Gentamicin	0.6 mg/kg
Imipenem-cilastatin	1 g twice daily
Levofloxacin	500 mg PO every 48 hours <sup>c</sup>
Linezolid	200–300 mg PO daily
Meropenem	500–1,000 mg daily
Polymixin B	150,000 units (IV) every 12 hours
Quinupristin-dalfopristin	25 mg/L in alternate bags <sup>d</sup>
Tobramycin	0.6 mg/kg
Vancomycin	15–30 mg/kg every 5–7 days

<sup>a</sup>Empiric doses for patients with residual renal function (>100 mL/day urine output) should be increased by 25%.

<sup>b</sup>Per exchange, once daily.

<sup>c</sup>Oral levofloxacin is recommended to be given with weekly IP vancomycin in centers with low fluoroquinolone resistance.

<sup>d</sup>Given in conjunction with 500 mg intravenous twice daily.

CAPD, continuous ambulatory peritoneal dialysis; LD, loading dose; MD, maintenance dose; IV, intravenous.

Source: Li PK et al. Peritoneal dialysis-related infections recommendations: 2010 update. *Perit Dial Int.* 2010;30:393.

**TABLE 67.5 Intraperitoneal Antibiotic Continuous Dosing Recommendations for CAPD Patients<sup>a</sup>**

	Continuous Dosing <sup>b</sup> (mg/L)	
	LD	MD
Amikacin	25	12
Amoxicillin	250–500	50
Amphotericin		1.5
Ampicillin		125
Ampicillin-sulbactam	1,000	100
Aztreonam	1,000	250
Cefazolin	500	125
Cefepime	500	125
Ceftazidime	500	125
Ceftizoxime	250	125
Ciprofloxacin	50	25
Daptomycin	100	20
Gentamicin	8	4
Imipenem-cilastatin	250	50
Nafcillin		125
Oxacillin		125
Penicillin G	50,000 units	25,000 units
Tobramycin	8	4
Vancomycin	1,000	25

<sup>a</sup>Empiric doses for patients with residual renal function (>100 mL/day urine output) should be increased by 25%.

<sup>b</sup>All exchanges.

CAPD, continuous ambulatory peritoneal dialysis; LD, loading dose; MD, maintenance dose.

Source: Li PK et al. Peritoneal dialysis-related infections recommendations: 2010 update. *Perit Dial Int.* 2010;30:393.

- Fungal peritonitis, while rare, is associated with significant morbidity and mortality. CAPD catheters should be removed and broad antifungal therapy given for at least 2 weeks post-catheter removal.
- Therapy for secondary peritonitis includes source control and early administration of antimicrobial agents directed at gram-negative bacteria and anaerobes (Table 67.6) with treatment continuing for 4 to 7 days.

### INFECTIONS FROM ABDOMINAL TRAUMA

- Acute penetrating abdominal trauma requires a short course (<24 hours) of antimicrobial therapy if instituted promptly. Delay of therapy or development of infection requires a 5-to-7-day course of therapy.

### Antimicrobial Penetration

- Antimicrobial penetration into tissues and abscess cavities depends on serum-to-tissue fluid concentration gradient.
- Surgical drainage is often required for abscesses as antibiotic penetration into an abscess is poor.

TABLE 67.6 Treatment of Intra-abdominal Infections

Regimen	Dosage
<b>COMBINATION THERAPY</b>	
1. Metronidazole Plus Aminoglycoside (gentamicin or tobramycin)	500 mg IV every 8–12 hours 5–7 mg/kg/day (normal renal function)
Amikacin	15–20 mg/kg/day (normal renal function)
2. Metronidazole Plus Aztreonam	500 mg IV every 8–12 hours 1–2 g IV every 6–8 hours
3. Metronidazole Plus Ceftriaxone	500 mg IV every 8–12 hours 1–2 g IV every 12–24 hours
Or Cefotaxime	1–2 g IV every 6–8 hours
Or Cefepime	2 g IV every 8–12 hours
4. Metronidazole Plus Ciprofloxacin	500 mg IV every 8–12 hours 400 mg IV every 12 hours
Or Levofloxacin	750 mg IV every 24 hours
Or Moxifloxacin	400 mg IV every 24 hours
<b>MONOTHERAPY</b>	
Cefoxitin	2 g IV every 6 hours
Cefazolin	1–2 g IV every 8 hours
Cefepime	2 g IV every 8–12 hours
Cefotaxime	1–2 g IV every 6–8 hours
Ceftazidime	2 g IV every 8 hours
Ceftriaxone	1 g IV every 24 hours
Cefuroxime	1.5 g IV every 8 hours
Ertapenem	1 g IV every 24 hours
Imipenem-cilastatin	500 mg IV every 6 hours or 1 g every 8 hours
Meropenem	1 g IV every 8 hours
Doripenem	500 mg IV every 8 hours
Piperacillin-tazobactam	3.375 g IV every 4–6 hours or 4.5 g IV every 6 hours
Ticarcillin-clavulanic acid	3.1 g IV every 6 hours
Tigecycline	100 mg initial, then 50 mg IV every 12 hours
Vancomycin	15–20 mg/kg IV every 8–12 hours (normal renal function)

IV, intravenous.



# Urinary Tract Infections\*

## General Principles

- Urinary tract infection (UTI) is an acute or chronic infection, usually bacterial in origin, that may affect any part of the upper or lower urinary system.
- **Cystitis** is an infection of the bladder.
- **Pyelonephritis** is an infection involving the parenchyma of the kidneys.
- **Acute urethral syndrome** is defined as symptoms consistent with lower UTI but with no organisms on Gram stain or culture.
- **Prostatitis** is an acute inflammatory condition affecting the prostate.
- An important distinction in the characterization and treatment of UTI is that of uncomplicated versus complicated infection.
  - Uncomplicated: infection in patients with normal structure and function almost always caused by a single organism
  - Complicated: infection associated with conditions that increase the risk for acquiring infection potentials for serious outcomes, or risk for therapy failure

## Risk Factors

- Risk factors for developing UTI include extremes of age, female gender, sexual activity, use of contraception, pregnancy, urinary tract instrumentation (catheterization), urinary tract obstruction, neurologic dysfunction, renal disease, and previous antimicrobial use.

## Patient Assessment

- Most UTIs are caused by gram-negative aerobic bacilli from the intestinal tract.
- Clinical signs and symptoms correlate poorly with either the presence or extent of infection. Symptoms commonly associated with cystitis include burning on urination (dysuria), frequent urination, suprapubic pain, blood in the urine (hematuria), and back pain. Symptoms of acute pyelonephritis may also include loin pain, costovertebral angle (CVA) tenderness, fever, chills, nausea, and vomiting. Most elderly patients are asymptomatic.
- The gold standard for diagnosis is urine culture with a positive urinalysis.
- Recurrent infections develop in up to 30% of women with acute cystitis. Relapse refers to recurrence with the same organism. Reinfection implies recurrence with a different organism.
- Chronic UTI in adults can be managed by treating recurrent infections or by administering chronic, low-dose prophylactic therapy (Table 68.1).
- Treatment of prostatitis is complicated by poor penetration of antibiotics into the prostate.

## Goals of Therapy

- Eradicate the infection, prevent associated complications, and minimize adverse events and costs associated with drug therapy.

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\*The reader is referred to Chapter 68, Urinary Tract Infections, written by Douglas N. Fish, PharmD, in the 10th edition of *Applied Therapeutics: The Clinical Use of Drugs* for a more in-depth discussion. All notations to reference numbers are based on the reference list at the end of that chapter. The editor of this handbook expresses her thanks to Dr. Fish and acknowledges that this chapter is based on his work.

**TABLE 68.1 Antimicrobial Agents Commonly Used for Chronic Prophylaxis against Recurrent UTIs<sup>1,2,4,81–83,87</sup>**

Agent	Adult Dose	Comments <sup>a</sup>
Nitrofurantoin	50–100 mg nightly	Contraindicated in infant <1 month of age. <i>To be taken with food or milk. May cause brown or rust-yellow discoloration of urine.</i>
Trimethoprim	100 mg nightly	Not recommended in children <12 years of age.
Trimethoprim 80 mg + Sulfamethoxazole 400 mg	0.5–1 tablet nightly Or 3/week	Not recommended for use in infants <2 months. <i>To be taken on an empty stomach with a full glass of water. Photosensitivity may occur.</i>
Norfloxacin	200 mg/day	<i>Avoid antacids; monitor theophylline levels.</i>
Cephalexin	125–250 mg/day	
Cefaclor	250 mg/day	
Cephadrine	250 mg/day	
Sulfamethoxazole	500 mg/day	

<sup>a</sup>Includes unique patient consultation information in italics.

## Treatment

- The cornerstone of effective treatment is appropriate selection and use of antibiotics. Drug therapy for lower UTI is often started before culture results are back and is based probably on organisms and susceptibility to therapy (Table 68.2).
- Guidelines for the treatment of acute, uncomplicated cystitis and pyelonephritis exist (Table 68.3). Hospitalization for treatment of pyelonephritis may be needed, particularly for patients who cannot maintain adequate fluid intake or tolerate oral medications.

**TABLE 68.2 Overview of Treatment of Urinary Tract Infections**

Organisms Commonly Found	Antibacterial of Choice
<b>UNCOMPLICATED UTI</b>	
<i>Escherichia coli</i>	TMP-SMX <sup>a</sup>
<i>Proteus mirabilis</i>	TMP-SMX <sup>a</sup>
<i>Klebsiella pneumoniae</i>	TMP-SMX <sup>a</sup>
<i>Enterococcus faecalis</i>	Ampicillin, amoxicillin
<i>Staphylococcus saprophyticus</i>	First-generation cephalosporin or TMP-SMX
<b>COMPLICATED UTI<sup>b,c</sup></b>	
<i>Escherichia coli</i>	First-, second-, or third-generation cephalosporin; TMP-SMX <sup>c</sup>
<i>Proteus mirabilis</i>	First-, second-, or third-generation cephalosporin
<i>Klebsiella pneumoniae</i>	First-generation cephalosporin; fluoroquinolone
<i>Enterococcus faecalis</i>	Ampicillin or vancomycin ± aminoglycoside
<i>Pseudomonas aeruginosa</i>	Antipseudomonal penicillin ± aminoglycoside; ceftazidime; cefepime; fluoroquinolone; carbapenem
<i>Enterobacter</i>	Fluoroquinolone; TMP-SMX; carbapenem
Indole-Positive <i>Proteus</i>	Third-generation cephalosporin; fluoroquinolone
<i>Serratia</i>	Third-generation cephalosporin; fluoroquinolone
<i>Acinetobacter</i>	Carbapenem; TMP-SMX
<i>Staphylococcus aureus</i>	Penicillinase-resistant penicillin; vancomycin

<sup>a</sup>Caution in communities with increased resistance (>10%–20%).

<sup>b</sup>Drug selection based on culture and susceptibility testing when possible.

<sup>c</sup>Oral therapy when appropriate. Nitrofurantoin, fosfomycin, fluoroquinolone, or cephalosporins should be used in areas with increased TMP-SMX resistance.

TMP-SMX, trimethoprim-sulfamethoxazole; UTI, urinary tract infection.

**TABLE 68.3 Summary of Evidence-Based Recommendations for Treatment of Acute Uncomplicated Cystitis and Pyelonephritis<sup>19</sup>**

Recommendations	Recommendation Grades <sup>a</sup>
<b>CYSTITIS</b>	
<i>Preferred Agents</i>	
Nitrofurantoin monohydrate/macrocrystals 100 mg PO twice daily × 5 days	A-1
TMP-SMX 160/800 mg (1 double-strength tablet) PO twice daily × 3 days	A-1
Trimethoprim 100 mg PO twice daily × 3 days is considered equivalent to TMP-SMX and is the preferred agent in some regions.	A-3
Fosfomycin trometamol 3 g PO × one dose	A-1, but appears to have inferior microbiological efficacy compared with standard short-course therapies with agents such as trimethoprim or nitrofurantoin
Pivmecillinam 400 mg PO twice daily × 3–7 days (not commercially available in the United States)	A-1, but may have inferior efficacy compared with other available therapies
<b>RESISTANCE CONSIDERATIONS</b>	
A specific antibiotic is no longer recommended for empirical treatment when the prevalence of resistance is ≥20%.	B-3 for TMP-SMX No recommendation for other agents
<i>Alternative agents</i>	
<b>FLUOROQUINOLONES</b>	
Fluoroquinolones (ofloxacin, ciprofloxacin, or levofloxacin) PO × 3 days are highly efficacious for acute cystitis.	A-1
Fluoroquinolones should be reserved for other important clinical uses due to propensity for collateral damage.	A-3
<b>β-LACTAMS</b>	
β-Lactams (including amoxicillin-clavulanate, cefdinir, cefaclor, and cefpodoxime-proxetil) PO × 3–7 days are appropriate when other recommended agents cannot be used.	B-1
Other β-lactams such as cephalexin are less well studied but may also be appropriate in certain settings.	B-3
β-Lactams generally have inferior efficacy and more adverse effects compared with other antimicrobials for UTI.	B-1
<b>PYELONEPHRITIS</b>	
<i>All Patients</i>	
Urine culture and susceptibility testing should be performed and initial empirical antibiotic therapy tailored appropriately based on results.	A-3
<i>Outpatient Treatment</i>	
<b>FLUOROQUINOLONES</b>	
Ciprofloxacin 500 mg PO twice daily × 7 days, ± an initial IV dose of ciprofloxacin 400 mg, a long-acting parenteral cephalosporin (e.g., ceftriaxone 1 g) or a consolidated 24-hour dose of an aminoglycoside (e.g., gentamicin 5–7 mg/kg)	A-1
Ciprofloxacin 1,000 mg extended release tablet PO once daily × 7 days, or levofloxacin 750 mg PO once daily × 5 days	B-2
If the local prevalence of fluoroquinolone resistance among uropathogens is >10%, an initial one-time IV dose of a long-acting parenteral cephalosporin or a consolidated 24-hour dose of an aminoglycoside should be administered.	B-3
<i>Alternative agents</i>	
TMP-SMX 160/800 mg (1 double-strength tablet) PO twice daily × 14 days	A-1

**TABLE 68.3 Summary of Evidence-Based Recommendations for Treatment of Acute Uncomplicated Cystitis and Pyelonephritis (Continued)**

Recommendations	Recommendation Grades <sup>a</sup>
If TMP-SMX susceptibility is not known, an initial IV dose of a long-acting parenteral cephalosporin or a consolidated 24-hour dose of an aminoglycoside should be administered.	B-2 for a cephalosporin B-3 for an aminoglycoside
Oral $\beta$ -lactams $\times$ 10–14 days are less effective than other available agents.	B-3
If an oral $\beta$ -lactam is used, an initial IV dose of a long-acting parenteral cephalosporin or a consolidated 24-hour dose of an aminoglycoside should be administered.	B-2 for a cephalosporin B-3 for an aminoglycoside
<i>Hospitalized Patients</i>	
One of the following antibiotic options may be used initially, based on local resistance data and tailored based on susceptibility results: IV fluoroquinolone; IV aminoglycoside $\pm$ IV ampicillin; extended-spectrum IV cephalosporin or extended-spectrum IV penicillin $\pm$ aminoglycoside; or IV carbapenem.	B-3

<sup>a</sup>Strength of recommendations: A, B, C = good, moderate, and poor evidence to support recommendation for or against use, respectively.

Quality of evidence: 1 = evidence from  $\geq 1$  properly randomized, controlled trial; 2 = evidence from  $\geq 1$  well-designed clinical trial without randomization, from cohort or case-control 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 committees.

IV, intravenous; PO, orally; TMP-SMX, trimethoprim-sulfamethoxazole; UTI, urinary tract infection.

- Treatment of UTI in patients with renal failure carries the challenge of achieving adequate urine concentrations without causing systemic toxicity.

## Drug Therapy

- See tables for dosing regimens for commonly used oral antimicrobial agents (Table 68.4) and parenteral agents (Table 68.5).
- Phenazopyridine, 200 mg three times daily for 1 to 2 days, may be used in conjunction with antibiotics for symptomatic relief of dysuria.

**TABLE 68.4 Commonly Used Oral Antimicrobial Agents for Acute Urinary Tract Infections<sup>1,2,4,27,48,49,96</sup>**

Drug	Usual Dose		Pregnancy <sup>a</sup>	Breast Milk <sup>a</sup>	Comments <sup>b</sup>
	Adult	Pediatric			
Amoxicillin	250 mg every 8 hours or 3 g single dose	20–40 mg/kg/day in three doses	Crosses placenta (cord) = 30% (maternal) <sup>c</sup>	Small amount present	High resistance rates, not for empiric use
Amoxicillin + potassium clavulanate	500 + 125 mg every 12 hours	20 mg/kg/day (amoxicillin content) in three doses	Unknown	Unknown	
Ampicillin	250–500 mg every 6 hours	50–100 mg/kg/day in four doses	Crosses placenta	Variable amount (milk) = 1%–30% (serum) <sup>c</sup>	High resistance rates, not for empiric use. Should be taken on an empty stomach

*Continued on following page*

**TABLE 68.4 Commonly Used Oral Antimicrobial Agents for Acute Urinary Tract Infections<sup>1,2,4,27,48,49,96</sup> (Continued)**

Drug	Usual Dose		Pregnancy <sup>a</sup>	Breast Milk <sup>a</sup>	Comments <sup>b</sup>
	Adult	Pediatric			
Cefadroxil	0.5–1 g every 12 hours	15–30 mg/kg/day in four doses	Crosses placenta	Enters breast milk (milk) = 20% (serum) <sup>c</sup>	Alternate choices for patients allergic to penicillins, although cross-hypersensitivity can occur. May be associated with high failure rates
Cephalexin	250–500 mg every 6 hours	15–30 mg/kg/day in four doses	Crosses placenta		
Cephradine	250–500 mg every 6 hours	15–30 mg/kg/day in four doses	Crosses placenta (cord) = 10% (maternal) <sup>c</sup>		
Norfloxacin <sup>d</sup>	400 mg every 12 hours	Avoid	Arthropathy in immature animals	Unknown	Useful for pseudomonas infection. <i>Avoid antacids, divalent and trivalent cations, and sucralfate. May cause dizziness<sup>e</sup></i>
Ciprofloxacin <sup>d</sup>	250–500 mg every 12 hours	Avoid	Arthropathy in immature animals	Unknown	Alternate choices for patients allergic to $\beta$ -lactams
Levofloxacin	250 mg every 24 hours	Avoid	Arthropathy in immature animals	(milk) = 100% (serum) <sup>c</sup>	
Nitrofurantoin	100 mg every 12 hours	5–7 mg/kg/day in two to four doses	Hemolytic anemia in newborn	Variable amounts; not detectable to 30%; may cause hemolysis in G6PD-deficient baby	Alternate choice. <i>To be taken with food or milk. May cause brown or rust-yellow discoloration of urine</i>
Sulfisoxazole	0.5–1 g every 6 hours	50–100 mg/kg/day in four doses	Crosses placenta; hemolysis in newborn with G6PD deficiency; displacement of bilirubin may lead to hyperbilirubinemia and kernicterus; teratogenic in some animal studies	Enters breast milk; displacement of bilirubin may lead to neonatal jaundice; may cause hemolysis in G6PD-deficient baby	Alters bowel flora to favor resistant organisms. <i>To be taken on an empty stomach with a full glass of water. Photosensitivity may occur</i>
Sulfamethoxazole (SMX)	1 g every 12 hours	60 mg/kg/day in two doses			

**TABLE 68.4 Commonly Used Oral Antimicrobial Agents for Acute Urinary Tract Infections<sup>1,2,4,27,48,49,96</sup> (Continued)**

Drug	Usual Dose		Pregnancy <sup>a</sup>	Breast Milk <sup>a</sup>	Comments <sup>b</sup>
	Adult	Pediatric			
Trimethoprim (TMP)	100 mg every 12 hours		Crosses placenta (cord) = 60%; (maternal) folate antagonism; teratogenic in rats	(milk) >1 (serum) <sup>c</sup>	Alternate choice
TMP-SMX	160 + 800 mg every 12 hours or 0.48 + 2.4 g single dose	10 mg/kg/day (TMP component in two doses)	Crosses placenta (cord) = 60%; (maternal) folate antagonism; teratogenic in rats	(milk) >1 (serum) <sup>c</sup>	<i>To be taken on an empty stomach with a full glass of water. Photosensitivity may occur. Monitor HIV-infected patients closely for development of adverse hematologic reactions. First-line agent for prostatitis</i>
Fosfomycin	3 g single dose	No data	Crosses placenta	Unknown	Recommended option for uncomplicated cystitis

<sup>a</sup>Also see Chapter 49.

<sup>b</sup>Includes unique patient consultation information in italics.

<sup>c</sup>Denotes drug concentration.

<sup>d</sup>May increase theophylline concentrations when given concurrently. Carefully monitor theophylline serum concentrations during quinolone use.

<sup>e</sup>Same comments apply to all fluoroquinolones.

G6PD, glucose-6-phosphate dehydrogenase; HIV, human immunodeficiency virus; TMP-SMX, trimethoprim-sulfamethoxazole.

**TABLE 68.5 Parenteral Antimicrobial Agents Commonly Used in the Treatment of Urinary Tract Infections**

Class	Drug	Average Adult Daily Dose		Usual Dosage Interval <sup>a</sup>	Comments
		UTI	Sepsis		
Penicillins	Ampicillin	2–4 g	8 g	Every 4–6 hours	Use should be based on local susceptibility patterns
	Ampicillin-sulbactam	6 g	12 g	Every 6 hours	
Extended-spectrum penicillin	Ticarcillin-clavulanate	9–12 g	18 g	Every 4–6 hours	
	Piperacillin-tazobactam	9 g	18 g	Every 4–6 hours	
First-generation cephalosporins	Cefazolin	1.5–3 g	6 g	Every 8–12 hours	More effective than second- or third-generation cephalosporins against gram-positive organisms

*Continued on following page*

**TABLE 68.5 Parenteral Antimicrobial Agents Commonly Used in the Treatment of Urinary Tract Infections (Continued)**

Class	Drug	Average Adult Daily Dose		Usual Dosage Interval <sup>a</sup>	Comments
		UTI	Sepsis		
Second-generation cephalosporins	Cefoxitin	3–4 g	8 g	Every 4–8 hours	Intermediate between first- and third-generation cephalosporins against gram-negative organisms
	Cefuroxime	2.25 g	4.5 g	Every 8 hours	
	Cefotetan	1–4 g	6 g	Every 12 hours	
Third-generation cephalosporins	Cefotaxime	3–4 g	8 g	Every 6–8 hours	Better coverage than first- and second-generation cephalosporins against gram-negative organisms Ceftazidime and cefepime are most effective against <i>Pseudomonas</i> . All generations of cephalosporins are ineffective against <i>Enterococcus faecalis</i> and methicillin-resistant staphylococci.
	Ceftizoxime	2–3 g	8 g	Every 8–12 hours	
	Ceftriaxone	1 g	2 g	Every 12–24 hours	
	Ceftazidime	1.5–3 g	6 g	Every 8–12 hours	
Fourth-generation cephalosporins	Cefepime	1–2 g	4 g	Every 12 hours	Has activity against methicillin-resistant staphylococci
	Ceftaroline	0.6 g	0.6 g	Every 12 hours	
Carbapenems	Imipenem-cilastatin	1 g	2 g	Every 6 hours	The most broad-spectrum coverage of any antibiotics listed. Ertapenem not active against <i>Pseudomonas</i> . Resistance may develop especially with <i>Pseudomonas</i> . Toxic in some pregnant animals
	Meropenem	1.5–3 g	3 g	Every 8 hours	
	Doripenem	0.5 g	0.5 g	Every 8 hours	
	Ertapenem	0.5–1 g	1 g	Every 24 hours	
Monobactam	Aztreonam	1–2 g	6–8 g	Every 8–12 hours	Active against gram-negative aerobic pathogens, including <i>Pseudomonas</i> sp.
Aminoglycosides	Gentamicin	3 mg/kg	5 mg/kg	Every 8 hours	Potent against gram-negative bacteria including <i>Pseudomonas</i> . Associated with possible eighth nerve toxicity in the fetus. Amikacin should be reserved for multiresistant bacteria.
	Tobramycin	3 mg/kg	5 mg/kg	Every 8 hours	
	Amikacin	7.5 mg/kg	15 mg/kg	Every 12 hours	
Quinolones	Ciprofloxacin	400–800 mg	800 mg	Every 12 hours	Use for resistant organisms. Change to oral therapy when indicated.
	Levofloxacin	250–500 mg	500–750 mg	Every 24 hours	

<sup>a</sup>Assuming normal renal function.  
UTI, urinary tract infection.

# Sexually Transmitted Diseases\*

## General Principles

- Differentiation between the sexually transmitted diseases (STDs) has only occurred in the last several decades. Common STDs are described herein.
- Prevention focuses on education. Proper condom use provides a high degree of protection against STDs.

## Gonorrhea

- Gonorrhea is caused by *Neisseria gonorrhoeae*, a gram-negative diplococcus.
- **Infection in Men:** Symptoms, including a purulent discharge with dysuria, appear 1 to 7 days after contact with an infected source. Asymptomatic patients (rare in males) may serve as a reservoir for infection.
- **Infection in Women:** Symptoms include abnormalities of the cervix, purulent or mucopurulent endocervical discharge, erythema, friability, and edema of the zone of ectopy. Pelvic inflammatory disease is a serious complication that can lead to infertility and chronic pelvic pain. Complications in pregnancy include spontaneous abortion, premature rupture of the fetal membranes, premature delivery, and acute chorioamnionitis. Asymptomatic patients (common in females) may serve as a reservoir for infection.
- Pharyngeal and anorectal gonococcal infections are often asymptomatic. Rectal gonorrhea can produce a syndrome of proctitis with anorectal pain, mucopurulent anorectal discharge, constipation, tenesmus, and anorectal bleeding.
- Table 69.1 shows the Centers for Disease Control and Prevention (CDC) recommendations for treatment of uncomplicated infection. Co-treatment for presumed Chlamydia infection is

TABLE 69.1 CDC Recommendations for Treatment of Uncomplicated Gonorrhea

Presentation	Drugs of Choice (% Cured)	Dosage	Alternative Regimens
Urethritis, cervicitis, rectal <sup>a</sup>	Ceftriaxone (98.9) Cefixime (97.4) <sup>b</sup>	250 mg IM once 400 mg PO once	Cephalosporin single-dose regimens <sup>c</sup>
Pharyngeal	Ceftriaxone	250 mg IM once	

<sup>a</sup>Because a high percentage of patients with gonorrhea have coexisting *Chlamydia trachomatis* infections, the CDC recommends treating all patients with gonorrhea with a 7-day course of doxycycline or single-dose azithromycin for treatment of *Chlamydia*.

<sup>b</sup>Available in an oral suspension (100 mg/5 mL or 200 mg/5 mL) or tablet (400 mg) dosage form.

<sup>c</sup>Additional cephalosporin regimens include ceftizoxime 500 mg IM, cefoxitin 2 g IM (administered with probenecid 1 g PO), and cefotaxime 500 mg IM. Limited evidence suggests that cefpodoxime 400 mg and cefuroxime axetil 1 g might be oral alternatives.

Source: Adapted from Workowski KA et al. Sexually transmitted diseases treatment guidelines, 2010. *MMWR Recomm Rep.* 2010;59(RR-12):1.

\*The reader is referred to Chapter 69, Sexually Transmitted Diseases, written by Jeffery A. Goad, PharmD, MPH, and Karl M. Hess, PharmD, FCPA, in the 10th edition of *Applied Therapeutics: The Clinical Use of Drugs* for a more in-depth discussion. All notations to reference numbers are based on the reference list at the end of that chapter. The editor of this handbook expresses her thanks to Drs. Goad and Hess and acknowledges that this chapter is based on their work.



**TABLE 69.2 Treatment of Disseminated Gonococcal Infection<sup>a</sup>**

<b>No Penicillin Allergy</b>
<b>PARENTERAL</b>
<b>Recommended</b> —Ceftriaxone 1 g IV or IM every 24 hours
<b>Alternative</b> —Cefotaxime 1 g IV every 8 hours or ceftizoxime 1 g IV every 8 hours
<b>ORAL<sup>b</sup></b>
Cefixime 400 mg PO twice daily

<sup>a</sup>Parenteral treatment should be continued for 24 to 48 hours beyond clinical improvement.

<sup>b</sup>Treat for 7 days after switching from parenteral therapy.

Source: Adapted from Workowski KA et al. Sexually transmitted diseases treatment guidelines, 2010. *MMWR Recomm Rep.* 2010;59(RR-12):1.

recommended (see below). Sexual partners within the past 60 days should be treated. Pregnant women can be treated with cephalosporins.

- Complicated gonorrhea can result in disseminated gonococcal infection (DGI) with symptoms that include fever, occasional chills, mild tenosynovitis of the small joints, and skin lesions. Treatment for DGI is shown in Table 69.2.
- Gonococcal endocarditis and meningitis require high-dose IV therapy (e.g., ceftriaxone 1–2 g IV every 12 hours) for 10 to 14 days (meningitis) or 4 weeks (endocarditis).
- Neonatal DGI and meningitis is treated with cefotaxime 25 mg/kg (IV or IM) every 12 hours for 7 days (DGI) or 10 to 14 days (meningitis). Ceftriaxone is an alternative.

### Pelvic Inflammatory Disease (PID)

- PID refers to a variety of inflammatory disorders of the upper female reproductive tract. Most cases are caused by *N. gonorrhoeae* or *C. trachomatis*.
- Symptoms are often nonspecific (vaginal discharge, menorrhagia, dysuria, dyspareunia). Clinical sequelae can include abscess formation in the fallopian tubes, chronic abdominal pain, and ectopic pregnancy.
- Recommended treatments (Table 69.3) should be initiated immediately after diagnosis to prevent sequelae.

**TABLE 69.3 Antimicrobial Regimens Recommended by the CDC for Treatment of Acute Pelvic Inflammatory Disease**

Treatment Setting, Drugs, Schedule	Advantage	Disadvantage	Clinical Considerations
<b>INPATIENT (PARENTERAL) THERAPY</b>			
<b>REGIMEN A</b>			
Cefotetan 2 g IV every 12 hours or cefoxitin 2 g IV every 6 hours plus doxycycline 100 mg IV or PO every 12 hours <sup>a</sup>	Optimal coverage of <i>N. gonorrhoeae</i> (including resistant strains) and <i>C. trachomatis</i>	Possible suboptimal anaerobic coverage	Penicillin-allergic patients also may be allergic to cephalosporins; doxycycline use in pregnant patients may cause reversible inhibition of skeletal growth in the fetus and discoloration of teeth in young children.
Continue doxycycline (100 mg PO twice daily) after discharge to complete 14 days of therapy			

**TABLE 69.3 Antimicrobial Regimens Recommended by the CDC for Treatment of Acute Pelvic Inflammatory Disease (Continued)**

Treatment Setting, Drugs, Schedule	Advantage	Disadvantage	Clinical Considerations
<b>REGIMEN B</b>			
Clindamycin 900 mg IV every 8 hours plus gentamicin loading dose IV or IM (2 mg/kg) followed by a maintenance dose of 1.5 mg/kg every 8 hours <sup>b</sup>	Optimal coverage of anaerobes and gram-negative enteric rods	Possible suboptimal coverage of <i>N. gonorrhoeae</i> and <i>C. trachomatis</i>	Patients with decreased renal function may not be good candidates for aminoglycoside treatment or may need a dosage adjustment.
<b>ALTERNATIVE REGIMEN</b>			
Ampicillin/sulbactam 3 g IV every 6 hours plus doxycycline 100 mg PO or IV every 12 hours	Optimal coverage of <i>N. gonorrhoeae</i> and <i>C. trachomatis</i>	Inadequate coverage of anaerobes necessitates use of metronidazole or ampicillin/sulbactam	Not appropriate in pregnancy or in young children
<b>OUTPATIENT (ORAL) THERAPY<sup>c</sup></b>			
<b>REGIMEN A</b>			
Ceftriaxone 250 mg IM in a single dose plus doxycycline 100 mg PO twice daily for 14 days with or without metronidazole 500 mg PO twice daily for 14 days OR cefoxitin 2 g IM in a single dose and probenecid 1 g PO administered concurrently in a single dose plus doxycycline 100 mg PO twice daily for 14 days with or without metronidazole 500 mg PO twice daily for 14 days OR other parenteral third-generation cephalosporins (e.g., ceftizoxime or cefotaxime) plus doxycycline 100 mg PO twice daily for 14 days with or without metronidazole 500 mg PO twice daily for 14 days	Good to excellent coverage of <i>N. gonorrhoeae</i> and optimal coverage of <i>C. trachomatis</i>	Possible suboptimal anaerobic coverage necessitating the addition of metronidazole	Optimal cephalosporin is unclear; more complicated regimen requiring combination of parenteral and oral therapies

<sup>a</sup>Considering the oral bioavailability of doxycycline, PO therapy should be preferentially used over IV.

<sup>b</sup>Single daily dosing may be substituted.

<sup>c</sup>Consider for mild-to-moderate acute PID.

Source: Adapted from Workowski KA et al. Sexually transmitted diseases treatment guidelines, 2010. *MMWR Recomm Rep.* 2010;59(RR-12):1.

## Chlamydia Trachomatis

- Women are three times more likely to be infected than men. Untreated infection in women can lead to serious sequelae including PID, ectopic pregnancy, and infertility.
- Routine screening is recommended for sexually active women 25 years of age and older women with risk factors for infection (multiple partners or a new partner).
- **Nongonococcal urethritis** (NGU), the most common STD in men frequently caused by *C. trachomatis*, typically produces less severe and less frequent dysuria and penile discharge compared with gonococcal infections.

- Treatment options include azithromycin (a single 1-g oral dose) or doxycycline (100 mg twice daily for 7 days). Erythromycin, ofloxacin, and levofloxacin are alternatives; ciprofloxacin should be avoided due to documented treatment failures. Sexual partners of men with NGU should receive treatment for Chlamydia.
- NGU that persists or recurs should be retreated with the initial regimen if the patient was noncompliant or if the sexual partner was not treated. Combination therapy including azithromycin with metronidazole is recommended for patients who were compliant.
- *Lymphogranuloma venereum* (LGV) is usually caused by *C. trachomatis*. Treatment includes doxycycline 100 mg twice daily or erythromycin base 500 mg four times daily for 21 days.

**Syphilis**

- Syphilis, caused by *Treponema pallidum*, exists in stages. Initially a painless papule (chancre) that becomes ulcerated and indurated develops at the site of infection. Left untreated, it resolves spontaneously. Secondary-stage syphilis with skin lesions occurs in untreated patients about 6 weeks after the chancre first appeared. This is followed by a latent stage and subsequent tertiary stage that is associated with serious morbidity and mortality. Infection can involve the skin, bones, central nervous system, and cardiovascular system.
- CDC recommends penicillin G for all stages of syphilis (Table 69.4). Skin testing and desensitization should be used in patients with a true penicillin allergy.

Stage	Recommended Regimen	Alternative Regimen
Early (primary, secondary, or early latent) <sup>a</sup>	Benzathine penicillin G 2.4 million units single dose IM	Doxycycline 100 mg PO BID for 14 days <i>or</i> Tetracycline 500 mg PO QID for 14 days <i>or</i> Ceftriaxone 1 g IM/IV every day for 8–10 days <i>or</i> Azithromycin 2 g PO × 1 dose
Late latent or latent syphilis of unknown duration	Lumbar puncture If CSF normal: benzathine penicillin G 2.4 million units/week × 3 weeks IM If CSF abnormal: treat as neurosyphilis	Lumbar puncture If CSF normal: doxycycline 100 mg PO BID for 28 days If CSF abnormal: treat as neurosyphilis
Neurosyphilis (asymptomatic or symptomatic) <sup>b</sup>	Aqueous crystalline penicillin G 18–24 million units IV every day × 10–14 days <sup>c</sup>	Procaine penicillin 2.4 million units IM every day plus probenecid 500 mg PO QID, both for 10–14 days
Congenital	Aqueous crystalline penicillin G 100,000–150,000 units/kg/day, administered as 50,000 units/kg/dose IV every 12 hours during the first 7 days of life, and every 8 hours thereafter for a total of 10 days <sup>d</sup> Or Procaine penicillin G 50,000 units/kg/dose IM a day in a single dose for 10 days	If CSF normal: benzathine penicillin G 50,000 units/kg/dose IM in a single dose
Syphilis in pregnancy	According to stage	According to stage

<sup>a</sup>Some experts recommend repeating this regimen after 7 days for HIV-infected patients.  
<sup>b</sup>Because of the shorter duration of therapy as compared with latent syphilis, some experts recommend giving benzathine penicillin G, 2.4 million units/week for up to 3 weeks, after the completion of these neurosyphilis regimens to provide a comparable total duration of therapy.  
<sup>c</sup>Administered as 3 to 4 million units IV every 4 hours or continuous infusion.  
<sup>d</sup>All infants born to women treated during pregnancy with erythromycin must be treated with penicillin at birth.  
 Source: Adapted from Workowski KA et al. Sexually transmitted diseases treatment guidelines, 2010. *MMWR Recomm Rep.* 2010;59(RR-12):1.

- Pregnant women should be treated as soon as possible to prevent spread to the fetus. Infants born to women who were treated for syphilis during pregnancy should receive treatment, even if they are asymptomatic.
- Neurosyphilis can occur in any stage of syphilis. Aqueous crystalline penicillin G is the drug of choice. Patients should be monitored until cerebrospinal fluid (CSF) examinations are normal.
- Jarisch-Herxheimer reaction (JHR) is a benign, self-limited complication of antibiotic therapy for syphilis that presents as fever, chills, headache, myalgias, tachycardia, and hypotension.

## Chancroid

- Chancroid, caused by *Haemophilus ducreyi*, causes a painful genital ulcer 3 to 10 days after exposure; it becomes pustular and ulcerates within 2 days of developing. Risk for chancroid is increased in uncircumcised men.
- Treatment options include azithromycin (single 1-g oral dose), ceftriaxone (250 mg IM once), ciprofloxacin (500 mg twice daily for 3 days), or erythromycin base (500 mg three times daily for 7 days).

## Vaginitis

- Vaginitis refers to nonspecific vaginal symptoms (itching, burning, irritation, and abnormal discharge) that may be caused by infection or other mechanical conditions. The most common vaginal infections are bacterial vaginosis, vulvovaginal candidiasis, and trichomoniasis. Table 69.5 shows the different characteristics of vaginal discharge.
- **Bacterial Vaginosis:** Nonpregnant women with symptomatic disease require treatment (intravaginal metronidazole or clindamycin, or oral metronidazole). If treatment is required during pregnancy, CDC recommends oral therapy with metronidazole or clindamycin. Routine treatment of sexual partners is not recommended.
- **Vulvovaginal candidiasis**, most commonly caused by *Candida albicans*, is not usually described as an STD as celibate women can be affected. Signs and symptoms include vulvar and vaginal pruritis, vaginal soreness, vulvar burning, dyspareunia, and a thick white vaginal discharge that appears curdlike.
  - Nonprescription and prescription products are available for treatment (Table 69.6). Complicated cases (e.g., recurrent infection, severe symptoms, or infection in those who are pregnant, immunocompromised, or with diabetes) should be referred to a medical practitioner.
  - Treatment of recurrent infection should include a prolonged course (7–14 days) of topical therapy or a three-dose regimen of oral fluconazole. A 6-month maintenance regimen after remission should be given (Table 69.7).

TABLE 69.5 Characteristics of Vaginal Discharge

Characteristics	Normal	Candidiasis	Trichomoniasis	Bacterial Vaginosis
Color	White or clear	White	Yellow-green	White to gray
Odor	Nonodorous	Nonodorous	Malodorous	Fishy smell
Consistency	Floccular	Floccular	Homogeneous	Homogeneous
Viscosity	High	High	Low	Low
pH	<4.5	4–4.5	5–6.0	>4.5
Other characteristics		Thick, curdlike	Frothy	Thin

Sources: Ries AJ. Treatment of vaginal infections: candidiasis, bacterial vaginosis, and trichomoniasis. *J Am Pharm Assoc (Wash)*. 1997;NS37:563; Sobel JD. Vaginitis. *N Engl J Med*. 1997;337:1896; Carr PL et al. Evaluation and management of vaginitis. *J Gen Intern Med*. 1998;13:335.

TABLE 69.6 Products Available for the Treatment of *Candida* Vulvovaginitis

Drug	Availability	Trade Names	Dosing Regimens
<b>NONPRESCRIPTION PRODUCTS</b>			
Butoconazole	2% vaginal cream <sup>a</sup>	Femstat 3	<i>Nonpregnant women:</i> Administer one applicatorful intravaginally at bedtime for 3 consecutive days. <i>Pregnant women during second and third trimesters:</i> Administer one applicatorful intravaginally at bedtime for 7 consecutive days.
Clotrimazole	1% vaginal cream <sup>a</sup>	Gyne-Lotrimin 7; Mycelex-7; Clotrimazole 7; various generics	Administer one applicatorful intravaginally at bedtime for 7 consecutive days.
	2% vaginal cream <sup>a</sup>	Gyne-Lotrimin 3; various generics	Administer one applicatorful intravaginally at bedtime for 3 consecutive days.
	100-mg vaginal suppositories <sup>a</sup>	Mycelex-7; various generics	Insert one suppository intravaginally at bedtime for 7 consecutive days.
Miconazole	200-mg vaginal suppositories <sup>a</sup>	Gyne-Lotrimin 3; various generics	Insert one suppository intravaginally at bedtime for 3 consecutive days.
	2% cream <sup>a</sup>	Monistat 7; Femizol-M; various generics	Administer one applicatorful intravaginally at bedtime for 7 consecutive days.
	4% cream <sup>a</sup>	Monistat 3; various generics	Administer one applicatorful intravaginally at bedtime for 3 consecutive days.
	100-mg vaginal suppositories <sup>a</sup>	Monistat 7	Insert one suppository intravaginally at bedtime for 7 consecutive days.
	200-mg vaginal suppositories <sup>a</sup>	Monistat 3	Insert one suppository intravaginally at bedtime for 3 consecutive days.
Tioconazole	1,200-mg vaginal suppositories <sup>a</sup>	Monistat 1 Daytime Ovule	Insert one suppository intravaginally at bedtime for one dose only.
	6.5% vaginal ointment	Vagistat-1, generics	Administer one applicatorful intravaginally at bedtime for one dose only.
<b>PRESCRIPTION PRODUCTS</b>			
Butoconazole (sustained release)	2% vaginal cream <sup>a</sup>	Gynazole 1	<i>Nonpregnant women:</i> Administer one applicatorful at bedtime for one dose only.
Fluconazole	150-mg oral tablet	Diflucan tablet	Take one tablet PO for one dose only.
Nystatin <sup>b</sup>	100,000 units vaginal tablet	Mycostatin; Nystatin; various generics	Insert one tablet intravaginally at bedtime for 14 consecutive days.
Terconazole	0.4% vaginal cream <sup>a</sup>	Terazol 7	Administer one applicatorful intravaginally at bedtime for 7 consecutive days
	0.8% vaginal cream <sup>a</sup>	Terazol 3	Administer one applicatorful intravaginally at bedtime for 3 consecutive days
	80-mg vaginal suppositories <sup>a</sup>	Terazol 3	Insert one suppository intravaginally at bedtime for 3 consecutive days

<sup>a</sup>The CDC states that the use of vaginally administered oil-based preparations may weaken latex products such as condoms and diaphragms.<sup>b</sup>All topically applied azole medications are superior to nystatin.Source: Adapted from Workowski KA et al. Sexually transmitted diseases treatment guidelines, 2010. *MMWR Recomm Rep.* 2010;59(RR-12):1.

TABLE 69.7 Maintenance Regimens for Recurrent Vulvovaginal Candidiasis

	Dose	Frequency
<b>TOPICAL AGENTS<sup>a</sup></b>		
Clotrimazole	200 mg	Intermittently
Clotrimazole vaginal suppositories	500 mg	Intermittently
<b>Oral agents</b>		
Fluconazole tablets	100, 150, or 200 mg	Weekly for 6 months

<sup>a</sup>Given as examples only, CDC does not indicate a preferred regimen.

Source: Adapted from Workowski KA et al. Sexually transmitted diseases treatment guidelines, 2010. *MMWR Recomm Rep.* 2010;59(RR-12):1.

- **Trichomoniasis** is caused by the protozoan *T. vaginalis*. Men are usually asymptomatic. Classic symptoms in women include diffuse, yellow-green discharge with pruritis, dysuria, and a “strawberry” cervix. Infection during pregnancy can result in premature rupture of the membranes, preterm delivery, and low birth weight. Treatment options include metronidazole or tinidazole (both as a 2-g single oral dose). Sexual partners should be treated simultaneously.

## Genital Herpes

- Two distinct herpes serotypes exist: HSV-1 and HSV-2. Genital and neonatal herpes are primarily caused by HSV-2.
- Most initial episodes of genital herpes are asymptomatic, especially in males. Prodromal signs of tingling, itching, paresthesia, or genital burning occur about 1 week after initial exposure. Numerous vesicles that eventually erupt then develop, resulting in painful genital ulcers.
- Transmission occurs by direct contact; virus shedding begins during the prodromal phase with lesions being most contagious in the ulcerative phase.
- There is no cure for HSV. Oral antivirals can speed healing and symptom resolution (Table 69.8).

TABLE 69.8 Antiviral Chemotherapy of Genital HSV-2 Infections

	Acyclovir	Valacyclovir	Famciclovir	Duration	Comments
First clinical episode	400 mg PO TID or 200 mg PO five times per day	1 g PO BID	250 mg PO TID	7–10 days	May extend treatment duration if healing is incomplete
Episodic recurrent infection	400 mg PO TID or 800 mg PO BID or 800 mg PO TID × 2 days	1 g every day or 500 mg PO BID × 3 days	125 mg PO BID or 1 g PO BID × 1 day or 500 mg PO × 1 day, then 250 mg BID × 2 days	5 days	Most effective if initiated within the first 24 hours of onset of lesions or during the prodrome
Daily suppressive therapy	400 mg PO BID <sup>a</sup>	500 mg PO every day <sup>b</sup> or 1 g PO every day	250 mg PO BID	Daily	Reduces the frequency of genital herpes recurrences by ≥75% among patients who have frequent recurrences (i.e., ≥6 recurrences per year); use should be reevaluated at 1 year

Continued on following page

TABLE 69.8 Antiviral Chemotherapy of Genital HSV-2 Infections (Continued)

	Acyclovir	Valacyclovir	Famciclovir	Duration	Comments
Severe disseminated	5–10 mg/kg IV every 8 hours	Not indicated	Not indicated	Variable	Hospitalize and treat until clinical resolution of symptoms. Follow-up IV therapy with PO acyclovir to complete 10 days
HIV-infected: episodic	400 mg PO TID or 200 mg 5 per day	1 g PO BID <sup>f</sup>	500 mg PO BID	5–10 days	Treat until clinical resolution of lesions
HIV-infected: suppressive	400–800 mg PO BID or TID	500 mg PO BID <sup>d</sup>	500 mg PO BID		

<sup>a</sup>Safety and efficacy up to 6 years have been documented with the use of acyclovir.

<sup>b</sup>Valacyclovir 500 mg every day seems less effective in patients with more than 10 episodes per year. Thus, 1 g every day should be used in these patients.

<sup>c</sup>Dosages up to 8 g/d have been used, but an association with a syndrome resembling either hemolytic uremic syndrome or thrombotic thrombocytopenic purpura was observed.

<sup>d</sup>Effective in decreasing both the rate of recurrences and the rate of subclinical shedding among HIV-infected patients.

Source: Regimen recommendations derived from Workowski KA et al. Sexually transmitted diseases treatment guidelines, 2010. *MMWR Recomm Rep.* 2010;59(RR-12):1.

## Genital Warts

- Human papillomavirus (HPV), the cause of genital warts (*condylomata acuminata*), affects men and women. Types 6 and 11 account for over 90% of genital warts; types 16 and 18 are associated with cervical cancer.
- Treatment is directed at removal of symptomatic warts. Vaccines to prevent HPV types 6, 11, 16, and 18 are available.

# Osteomyelitis and Septic Arthritis\*

## General Principles

- **Osteomyelitis** is an inflammation of the bone marrow and surrounding bone associated with infection. Any bone can be involved, and it can affect all age groups.
- Bone may be infected by three routes: hematogenous spread, direct infection of bone from an adjacent or contiguous source, and infection secondary to vascular insufficiency.
- Patients with recurrent osteomyelitis are considered to have chronic osteomyelitis.
- **Septic arthritis** (or infectious arthritis) is usually acquired hematologically. It can occur from spread of osteomyelitis into the joint.

## Patient Assessment

- Table 70.1 summarizes characteristics associated with osteomyelitis including age of onset, site of infection, risk factors, common pathogens, and clinical findings.
- Hematogenous osteomyelitis usually involves a single pathogen; polymicrobial infection is common in contiguous-spread osteomyelitis and vascular insufficiency.
- Osteomyelitis secondary to vascular insufficiency is most common in patients with diabetes mellitus.
- Patients with impaired blood flow may develop osteomyelitis in the toes or small bones of the feet. Infection often first presents as cellulitis, progressing to deep ulcers, and finally to underlying bone.
- Predisposing factors for septic arthritis include trauma or underlying systemic disorders (diabetes mellitus, rheumatoid arthritis, osteoarthritis, chronic granulomatous disease, cancer, or chronic liver disease).
- **Nongonococcal arthritis** is associated with monoarticular joint pain and swelling, and reduced range of motion and fever.
- **Gonococcal arthritis** typically affects multiple joints and is associated with fever, dermatitis, and tenosynovitis.

## Treatment

- **Hematogenous Osteomyelitis:** Table 70.2 summarizes the common causative organisms of acute hematogenous osteomyelitis in children and their recommended therapy. Initial empiric therapy should be directed at gram-positive cocci. Early, aggressive therapy gives the best change for cure; IV antibiotics should be given initially. Oral therapy (Table 70.3) should not be given until the effectiveness of IV therapy is known. A total of at least 4 weeks of therapy should be given.

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\*The reader is referred to Chapter 70, Osteomyelitis and Septic Arthritis, written by Bridgette Kram, PharmD, and Ralph H. Raasch, PharmD, FCCP, BCPS, in the 10th edition of *Applied Therapeutics: The Clinical Use of Drugs* for a more in-depth discussion. All notations to reference numbers are based on the reference list at the end of that chapter. The editor of this handbook expresses her thanks to Drs. Kram and Raasch and acknowledges that this chapter is based on their work.



**TABLE 70.1 Features of Osteomyelitis**

Feature	Hematogenous	Adjacent Site of Infection	Vascular Insufficiency
Usual age of onset (years)	<20; >50	>40	>40
Sites of infection	Long bones, vertebrae	Femur, tibia, skull, mandible	Feet
Risk factors	Bacteremia	Surgery, trauma, cellulitis, joint prosthesis	Diabetes, peripheral vascular disease
Common bacteria	<i>Staphylococcus aureus</i> , gram-negative bacilli; usually one organism	<i>S. aureus</i> , gram-negative bacilli; anaerobic organisms; often polymicrobial	<i>S. aureus</i> , coagulase-negative staphylococci, streptococci, gram-negative and anaerobic organisms; usually polymicrobial
Clinical findings			
Initial episode	Fever, chills, local tenderness, swelling; limitation of motion	Fever, warmth, swelling; unstable joint	Pain, swelling, drainage, ulcer formation
Recurrent episode	Drainage	Drainage, sinus tract	As above

- Vascular Insufficiency:** Optimal duration of antibiotic therapy is patient dependent; 6 weeks or longer are needed, with chronic suppressive therapy considered thereafter. Cure rates are low and radical surgery (e.g., amputation) is often necessary to cure chronic infection. Duration of antibiotic therapy after amputation varies from days to weeks depending on residual soft tissue infection.

**TABLE 70.2 Empiric Intravenous Antibiotics for Acute Osteomyelitis in Children**

Host	Likely Organisms	Antibiotics	Dosage	
			(mg/kg/day)	(doses/day)
Neonate	<i>S. aureus</i> Group B streptococci Gram-negative bacilli	Oxacillin (or nafcillin) +	100	4
		Cefotaxime	150	3
<3 years	<i>S. aureus</i> or streptococci (if vaccinated for <i>Haemophilus influenzae</i> type b) <i>Haemophilus influenzae</i> type b (if not vaccinated)	Oxacillin (or nafcillin) or	150	4
		Cefazolin	100	3
		Cefuroxime	50	2
≥3 years	<i>S. aureus</i>	Oxacillin (or nafcillin) or	150	4
		Cefazolin or	100	3
		Vancomycin (if severe $\beta$ -lactam allergy or MRSA suspected) or	45–60	4
		Clindamycin	30–40	3
After puncture wound through shoe	<i>Pseudomonas aeruginosa</i>	Ceftazidime	150	3
Child with sickle cell disease	<i>Salmonella</i> sp., <i>S. aureus</i>	Oxacillin (or nafcillin) +	150	4
		Cefotaxime or	100	4
		Vancomycin (if $\beta$ -lactam severe allergy or MRSA suspected) +	45–60	4
		Cefotaxime	100	4

**TABLE 70.3 Oral Antibiotic Doses for the Treatment of Osteomyelitis in Children**

<b>Drug</b>	<b>Dosage (mg/kg/day)</b>	<b>Interval between Doses (Hours)</b>
Penicillin V	125	4
Dicloxacillin	100	6
Amoxicillin	100	6
Cephalexin	150	6
Cefaclor	150	6
Clindamycin	40	8

- Local delivery of antibiotics (e.g., plaster pellets, impregnated bone cement, etc.) allows for delivery of high concentrations at the site of infection. Local delivery should never replace systemic antibiotics for the treatment of chronic osteomyelitis.
- Infection associated with prosthetic material requires surgical removal of the prosthesis and long-term antibiotic administration.
- Drainage of purulent joint fluid and appropriate antibiotic therapy (at least 2 weeks of IV antibiotics followed by 4 or more weeks of oral therapy) is required for nongonococcal arthritis.

# Traumatic Skin and Soft Tissue Infections\*

## General Principles

- Skin and soft tissue infections can involve any or all layers of the skin, subcutaneous fat, fascia, or muscle.
- Potential causative organisms are shown in Table 71.1.
- Treatment is often empiric and based on the severity and site of infection, underlying immunocompetence, and triggering event.
- Tetanus prophylaxis should be a component of routine wound management (Table 71.2).

## Cellulitis

- Cellulitis is an acute inflammation of the skin and subcutaneous fat characterized by local tenderness, pain, swelling, warmth, and erythema with or without a definite entry point.
- Local treatment (cleaning or irrigation of the site with soap and water) is sufficient for mild cellulitis in patients with no evidence of systemic infection. More serious infections require antibiotics in addition to local wound care.
- Oral cloxacillin, dicloxacillin, or flucloxacillin are appropriate empiric therapy for cellulitis in an otherwise healthy patient. Treatment should cover community-acquired

TABLE 71.1 Potential Organisms Causing Skin and Soft Tissue Infections

	Gram-Positive		Gram-Negative		Anaerobes		
	Staphylococcal	Streptococcal	<i>Escherichia coli</i> , <i>Klebsiella</i> species, <i>Proteus</i> species		<i>Eikenella corrodens</i>	Oral Anaerobes	<i>Clostridium</i> species <i>Bacteroides fragilis</i>
			<i>Pasteurella multocida</i>				
Cellulitis	X	X					
Diabetic soft tissue	X	X	X				X
Necrotizing infections	X	X	X			X	X
Erysipelas		X					
Animal bites	X	X	X	X		X	
Human bites	X	X	X		X	X	

X, organisms that should be covered empirically with appropriate antibiotic therapy.

\*The reader is referred to Chapter 71, Traumatic Skin and Soft Tissue Infections, written by James P. McCormack, BSc Pharm, PharmD, and Glen R. Brown, PharmD, in the 10th edition of *Applied Therapeutics: The Clinical Use of Drugs* for a more in-depth discussion. All notations to reference numbers are based on the reference list at the end of that chapter. The editor of this handbook expresses her thanks to Drs. McCormack and Brown and acknowledges that this chapter is based on their work.

TABLE 71.2 Tetanus Prophylaxis in Routine Wound Management: Adults

History of Adsorbed Tetanus Toxoid	Clean, Minor Wounds		All Other Wounds <sup>a</sup>	
	Td <sup>b</sup>	TIG	Td <sup>b</sup>	TIG
Unknown or <3 doses	Yes	No	Yes	Yes
≥3 doses	No <sup>c</sup>	No	Yes <sup>d</sup>	No

<sup>a</sup>Including, but not limited to, wounds contaminated with dirt, feces, soil, and saliva; puncture wounds, avulsions, and wounds resulting from missiles; crushing, burns, frostbite.

<sup>b</sup>For children <7 years of age, diphtheria-tetanus-pertussis (DTP) is preferred to tetanus toxoid alone. For persons ≥7 years of age, Td is preferred to tetanus toxoid alone.

<sup>c</sup>Yes, if >10 years since last dose.

<sup>d</sup>Yes, if >5 years since last dose. (More frequent boosters are not needed and can accentuate the side effects.)

Td, tetanus and diphtheria toxoid; TIG, tetanus immune globulin.

Methicillin-resistant *Staphylococcus aureus* (MRSA) in areas where this organism is prevalent. Clindamycin or moxifloxacin are options for patients with documented penicillin or cephalosporin allergy. The usual recommended treatment duration is 10 days.

- Treatment for severe infection (covering a large area or when lymphangitis is present) where hospitalization is required should be with either nafcillin or cefazolin. Oral therapy to complete a 10-to-14-day course can begin after the patient is afebrile and has improved for 2 days.

### Soft Tissue Infection in Diabetic Patients

- Diabetic patients are at particular risk for foot infections. Proper foot care is essential (Table 71.3). Infected wounds (e.g., purulent drainage, erythema, pain, and swelling) should be treated with antibiotics.
- Pedal and popliteal pulses can influence oral or intravenous treatment as well as the duration of therapy.
- Mild diabetic foot infections should be treated empirically with a penicillinase-resistant penicillin (e.g., cloxacillin, nafcillin) or cephalexin. Metronidazole or clindamycin should be added if anaerobes are suspected.
- Moderate diabetic foot infections should be treated empirically with moxifloxacin or cefoxitin or ampicillin-sulbactam or ertapenem or levofloxacin plus metronidazole or third-generation cephalosporin plus metronidazole.
- Uncontrollable or life-threatening infections may require amputation.

### Necrotizing Soft Tissue Infections

- Necrotizing infections exist when inflammation rapidly progresses and necrosis of the skin or underlying tissue exists. Redness, tenderness, and edema beyond the edges of the infection may be the only presenting signs.
- Flesh-eating disease is usually caused by toxin-producing strains of group A streptococci. High-dose penicillin G (3 million units every 4 hours) plus clindamycin (900 mg IV every 8 hours) are drugs of choice.

TABLE 71.3 Foot Care for the Diabetic Patient

Inspect feet daily for cuts, blisters, or scratches. Pay particular attention to the area between the toes and use a mirror to examine the bottom of the foot.

Wash feet daily in tepid water and dry thoroughly.

Apply lotion to feet to prevent calluses and cracking.

Ensure that shoes fit properly (not too tight or too loose), and inspect them daily.

Trim nails regularly, making sure to cut straight across the nail.

Do not use chemical agents to remove corns or calluses.

## Erysipelas

- Erysipelas is a superficial skin infection caused by streptococci. Skin lesions are accompanied by systemic symptoms (fever, chills, rigors, general malaise). Treatment with oral or parenteral penicillin is appropriate.

## Acute Traumatic Wounds

- Routine oral antibiotic therapy is not indicated unless there are signs of infection or when the patient is immunocompromised, pus is present, contamination by feces is suspected, or there was a delay in wound cleaning (>3 hours). Prophylactic antibiotics do not decrease the chance of infection.

## Bite Wounds

- Any bite wound should be examined to ensure no underlying tissue damage occurred.
- Copious irrigation of the wound should occur for all bites. The need for antibiotics depends on wound characteristics; given antibiotics when the wound involves the hand or is near joints, if the puncture wound is deep or difficult to irrigate, if the patient is immunocompromised, or if the wound is not well perfused.
- Antibiotics are not required for some dog bites (e.g., no deep tissue injury); all cat bites should be treated with antibiotics. Prophylaxis for rabies is required only if the animal is from an area with endemic rabies or if the bite was an unprovoked attack by a wild animal.
- Parenteral antibiotics should be given for severe human bites (e.g., those involving subcutaneous tissue, a joint, or a large area) or in patients who are unlikely to be compliant with oral therapy.

# Prevention and Treatment of Infections in Neutropenic Cancer Patients\*

## General Principles

- A consequence of select cancer chemotherapy is neutropenia, defined as an absolute neutrophil count  $<500$  cells/ $\mu\text{L}$  or anticipated to drop to this level within 48 hours. Neutropenia (also referred to as granulocytopenia) predisposes a host to infection.
- Fever is defined as a single oral temperature of  $>38.3^\circ\text{C}$  ( $101^\circ\text{F}$ ) or a temperature  $\geq 38^\circ\text{C}$  ( $100.4^\circ\text{F}$ ) for  $>1$  hour.
- Bacteria are the primary pathogens associated with infection in febrile neutropenic patients.
- Duration of neutropenia is the most important factor affecting outcome.

## Patient Assessment

- Fever is usually the earliest, and often the only, sign of infection.
- The most common sites for documented infection are skin; mouth and throat; esophagus; sinuses; abdomen, rectum, and liver; vascular access; lungs; and urinary tract.
- An accurate history and complete physical exam should be completed. This should include cancer type, treatment regimen, new signs of infection, antimicrobial prophylaxis, prior infections, and comorbidities.
- Two sets of blood cultures should be obtained before antibiotics are started. Additional Gram stain and cultures should be obtained from other suspected sites of infection (e.g., stool, urine, skin, IV site, respiratory).
- Chest radiograph and oximetry should be done if signs of a respiratory infection exist.
- Other assessments include a complete blood count, serum electrolytes, coagulation, C-reactive protein, urinalysis, and organ function.

## Risk Factors

- Risk factors for infection include neutropenia and impairment in both humoral (antibody and complement) and cell-mediated immune defenses.

## Goals of Therapy

- Prophylactic regimens are intended to reduce pathogenic endogenous microflora or prevent the acquisition of new microorganisms.

## Treatment

- All febrile neutropenic patients or afebrile neutropenic patients with signs of infection should undergo a risk assessment for the possibility of life-threatening infection. Risk stratification can identify patients most likely to experience significant infection-related complications.

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\*The reader is referred to Chapter 72, Prevention and Treatment of Infections in Neutropenic Cancer Patients, written by Richard H. Drew, PharmD, MS, BCPS, FCCP, in the 10th edition of *Applied Therapeutics: The Clinical Use of Drugs* for a more in-depth discussion. All notations to reference numbers are based on the reference list at the end of that chapter. The editor of this handbook expresses her thanks to Dr. Drew and acknowledges that this chapter is based on his work.

- Patients at highest risk are those with prolonged (>7 days) and profound (<100 cells/ $\mu$ L) neutropenia or select comorbidities. Antibacterial and antifungal prophylaxis should be considered in these patients.
- In the absence of site- or pathogen-specific etiology, initial empiric monotherapy is most commonly an antipseudomonal third-generation cephalosporin (e.g., ceftazidime), a fourth-generation cephalosporin (e.g., cefepime), or an antipseudomonal carbapenem (e.g., imipenem-cilastatin, meropenem). Additional agents may be added in patients who are hemodynamically unstable (e.g., vancomycin, aminoglycoside, fluoroquinolone).
- Defervescence and clinical stability (usually within 2–4 days) should guide therapy modification.
- High-risk patients unresponsive to initial empiric antibacterial therapy should be considered for the addition of antifungal therapy at days 4 to 7. Low-risk patients who are clinically stable do not routinely need antifungal therapy.
- Antiviral therapy is generally restricted to patients with serologic or clinical evidence of viral infection.

### Drug Therapy

- Table 72.1 outlines antibacterial regimens in patients with neutropenia and fever.
- Hematopoietic colony-stimulating factors (CSFs) may be used as adjunctive therapy to reduce the duration of neutropenia.

TABLE 72.1 **Antibacterials in Patients with Neutropenia and Fever<sup>a</sup>**

Condition	Therapy <sup>b</sup>
<b>INITIAL EMPIRIC THERAPY</b>	
<i>Low Risk (Anticipated Neutropenia <math>\leq</math>7 Days, Clinically Stable, No Medical Comorbidities)</i>	
Candidate for oral therapy	Adults: ciprofloxacin <sup>a</sup> + amoxicillin-clavulanate (alternate clindamycin if penicillin allergic) Children: cefixime
Requires IV therapy	(see <i>High Risk</i> below)
<i>High Risk (Anticipated Neutropenia &gt;7 Days, Clinically Unstable, or Medical Comorbidities)</i>	
	Piperacillin-tazobactam, antipseudomonal carbapenem, <sup>c</sup> ceftazidime, or cefepime Clinically unstable: consider addition of aminoglycoside, fluoroquinolone, or vancomycin to regimen above

#### MODIFICATIONS OF INITIAL THERAPY

##### *Unexplained Fever*

Defervescence with negative cultures	Continue antibiotics
Persistent fever (2–4 days) without clinical or microbiological evidence of infection	Low-risk patients: if IV therapy initially, consider switch to oral therapy Clinically stable: continue antibiotics Unstable: hospitalize (if outpatient), IV therapy (if initially treated with oral), broaden antibacterial coverage to include anaerobes, resistant gram-negative rods, and resistant gram-positive organisms. Consider antifungal therapy for <i>Candida</i> species, or antimold therapy if previously receiving azole prophylaxis. Consider empiric antifungal therapy on days 4–7, especially if neutropenia is expected to continue >7 days or the patient has other risk factors for fungal infections. If initial regimen did not include vancomycin, reevaluate risk factors for gram-positive infection and consider adding vancomycin.

##### *Documented Infection(s)*

Multidrug-resistant pathogen	MRSA: add vancomycin, linezolid or daptomycin VRE: add linezolid or daptomycin ESBLs: switch to a carbapenem; carbapenemase-producing Enterobacteriaceae: polymyxin-colistin or tigecycline
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TABLE 72.1 **Antibacterials in Patients with Neutropenia and Fever<sup>a</sup>** (Continued)

Condition	Therapy <sup>b</sup>
<i>Head, Eyes, Ears, Nose, Throat</i>	
Necrotizing ulceration, gingivitis	If initial regimen did not include anaerobic therapy (carbapenem or $\beta$ -lactam/ $\beta$ -lactamase inhibitor; i.e., piperacillin-tazobactam), consider adding clindamycin or metronidazole or switch to antipseudomonal carbapenem (imipenem-cilastatin or meropenem). Consider adding antifungal or antiviral therapy.
Oral vesicular lesions	Add antiviral therapy for herpes simplex virus.
Oral thrush	Add systemic (e.g., fluconazole) antifungal therapy.
Sinus tenderness, periorbital cellulitis, nasal ulceration	If suspicion of mold infection: add lipid amphotericin B formulation. Vancomycin for periorbital cellulitis Reassess antistaphylococcal activity of empiric regimen; consider vancomycin
<i>Gastrointestinal Tract</i>	
Esophagitis	Add antifungal agent (see text); if no response, add acyclovir. Assess CMV risk and (if high) consider ganciclovir or foscarnet
Acute abdominal pain/perianal	If initial regimen did not include carbapenem or $\beta$ -lactam/ $\beta$ -lactamase inhibitor (i.e., piperacillin-tazobactam), consider adding metronidazole, or switch to imipenem-cilastatin or meropenem. Assure pseudomonal coverage for perirectal infection. For perirectal pain: consider enterococcal coverage for infection (not colonization) Consider antifungal.
Diarrhea	Add metronidazole if <i>Clostridium difficile</i> documented or suspected. Oral vancomycin should be used for severe <i>C. difficile</i> infections. Contact isolation of rotavirus documented
Liver abnormalities	Consider anaerobic and enterococcal coverage. Antifungal or antiviral therapy added on the basis of results of diagnostic studies
<i>Respiratory Tract</i>	
Pneumonia	Add vancomycin or linezolid. Add an aminoglycoside and switch to antipseudomonal carbapenem PCP: institute TMP-SMX or (for sulfa-allergic patients) pentamidine Atypical pathogens ( <i>Mycoplasma</i> , <i>Legionella</i> ): Add fluoroquinolone or macrolide CMV: add ganciclovir if high risk Consider influenza during outbreaks. Oseltamivir (preferred) or other directed therapies when indicated
Focal lesion on chest radiograph	If evidence of mold infection, add mold-active antifungal (such as voriconazole [preferred] or amphotericin B formulations) Consider growth factors (G-CSF, GM-CSF) Consider antibiotic coverage for pathogen causing atypical pneumonia
Vesicular lesions	HSV, VZV treatment: acyclovir, famciclovir, or valacyclovir
Cellulitis, wound infection	Consider adding vancomycin therapy
Vascular access device infection, tunnel tract infection	Remove catheter whenever possible. Add empiric vancomycin therapy. Adjust on the basis of culture and susceptibility results.
Central nervous system	Antipseudomonal $\beta$ -lactam (cefepime, ceftazidime, meropenem [imipenem if meropenem not available]) + vancomycin. Add ampicillin if meropenem not used
Encephalitis	Consider high-dose acyclovir.
Urinary tract	Change on the basis of pathogen identification and susceptibility.
Bloodstream infections	Gram-negative: add aminoglycoside and switch to antipseudomonal carbapenem Gram-positive: add vancomycin, linezolid, or daptomycin

<sup>a</sup>Exclude option if patient received fluoroquinolone prophylaxis.

<sup>b</sup>All modifications should be based on clinical and microbiologic data.

<sup>c</sup>Antipseudomonal carbapenem is imipenem-cilastatin or meropenem. Doripenem provides comparable in vitro activity, but has not been investigated in this patient population.

CMV, cytomegalovirus; ESBL, extended-spectrum  $\beta$ -lactamase; G-CSF, granulocyte colony-stimulating factor; GM-CSF, granulocyte-macrophage colony-stimulating factor; HSV, herpes simplex virus; IV, intravenous; KPCs, *Klebsiella* producing carbapenemases, MRSA, methicillin-resistant *Staphylococcus aureus*; PCP, *Pneumocystis jirovecii*; TMP-SMX, trimethoprim-sulfamethoxazole; VRE, vancomycin-resistant enterococcus; VZV, varicella-zoster virus.

Sources: National Comprehensive Cancer Network. Clinical Practice Guidelines in Oncology. Prevention and treatment of cancer-related infections (V2.2009). [http://www.nccn.org/professionals/physician\\_gls/pdf/infections.pdf](http://www.nccn.org/professionals/physician_gls/pdf/infections.pdf). Accessed June 21, 2010; Freifeld A et al. Clinical practice guideline for the use of antimicrobial agents in neutropenic patients with cancer: 2010 update by the Infectious Diseases Society of America. *Clin Infect Dis*. 2011;52:e56.



# Pharmacotherapy of Human Immunodeficiency Virus Infection\*

## General Principles

- Human immunodeficiency virus (HIV) can be acquired through unprotected sexual intercourse (both anal and vaginal), injectable drug use, receipt of tainted blood products, and mother-to-infant transmission.
- Without intervention, the natural progression of HIV infection results in depletion of 50 to 100 T cells/ $\mu\text{L}$ /year but may be accelerated in early and late stages.
- Not every patient with HIV has a diagnosis of AIDS. The diagnosis of AIDS is made when a significant amount of immune deterioration occurs, either by depletion of CD4<sup>+</sup> cells to  $\leq 200$  cells/ $\mu\text{L}$  (Table 73.1) or because of the development of new opportunistic infections (Table 73.2).

## Patient Assessment

- Infections (e.g., shingles, tuberculosis, thrush, recurrent candidal vaginal infection) uncommon in an otherwise immunocompetent healthy person warrant further evaluation for the possibility of HIV infection.
- Infections such as *Pneumocystis jiroveci* pneumonia, *Mycobacterium avium* bacteremia, and cytomegalovirus retinitis generally occur in patients with severely compromised immune systems and strongly suggest HIV infection.

TABLE 73.1 1993 Revised Classification System for HIV Infection and the Expanded CDC Surveillance Case Definition for AIDS in Adults and Adolescents<sup>a</sup>

CD4 <sup>+</sup> T-Cell Categories	Clinical Categories		
	(A) Asymptomatic, Acute (Primary) HIV	(B) Symptomatic, Not (A) or (C) Conditions	(C) AIDS-Indicator Conditions
500/ $\mu\text{L}$	A1	B1	C1
200–499/ $\mu\text{L}$	A2	B2	C2
<200/ $\mu\text{L}$ (AIDS indicator T-cell count)	A3	B3	C3

<sup>a</sup>The modifications to the prior 1986 Surveillance Case Definition, which have been included in the 1993 revision, include the use of CD4 cell count (<200 cells/ $\mu\text{L}$ ) or CD4 cell percentage (<14%) and the additional AIDS-indicating conditions of pulmonary tuberculosis, recurrent pneumonia, and invasive cervical cancer (see Table 73.2).

AIDS, acquired immunodeficiency syndrome; CDC, Centers for Disease Control and Prevention; HIV, human immunodeficiency virus.

\*The reader is referred to Chapter 73, Pharmacotherapy of Human Immunodeficiency Virus Infection, written by Jessica L. Adams, PharmD, Julie B. Dumond, PharmD, BCPS, AAHIVE, and Angela D. M. Kashuba, BScPharm, PharmD, DABCP, in the 10th edition of *Applied Therapeutics: The Clinical Use of Drugs* for a more in-depth discussion. All notations to reference numbers are based on the reference list at the end of that chapter. The editor of this handbook expresses her thanks to Drs. Adams, Dumond, and Kashuba and acknowledges that this chapter is based on their work.

TABLE 73.2 Conditions Included in the 1993 Surveillance Case Definition

## CATEGORY A

Asymptomatic human immunodeficiency virus (HIV) infection  
 Persistent generalized lymphadenopathy  
 Acute HIV infection with accompanying illness or history of HIV infection

## CATEGORY B

Bacillary angiomatosis  
 Candidiasis, oropharyngeal (thrush)  
 Candidiasis, vulvovaginal; persistent, frequent, or poorly responsive to treatment  
 Cervical dysplasia or carcinoma in situ  
 Constitutional symptoms, such as fever  $>38^{\circ}\text{C}$  or diarrhea  $>1$  month  
 Hairy leukoplakia  
 Herpes zoster (shingles), involving at least two distinct episodes or more than one dermatome  
 Idiopathic thrombocytopenic purpura  
 Listeriosis  
 Pelvic inflammatory disease, particularly if complicated by tubo-ovarian abscess  
 Peripheral neuropathy

## CATEGORY C

Candidiasis of bronchi, trachea, or lungs  
 Candidiasis, esophageal  
 Cervical cancer, invasive  
 Coccidioidomycosis, disseminated or extrapulmonary  
 Cryptococcosis, extrapulmonary  
 Cryptosporidiosis, chronic intestinal ( $>1$  month)  
 Cytomegalovirus disease (other than liver, spleen, or nodes)  
 Cytomegalovirus retinitis (with loss of vision)  
 Encephalopathy, HIV-related  
 Herpes simplex: chronic ulcer(s) ( $>1$  month); or bronchitis, pneumonitis, or esophagitis  
 Histoplasmosis, disseminated or extrapulmonary  
 Isosporiasis, chronic intestinal (duration  $>1$  month)  
 Kaposi sarcoma  
 Lymphoid interstitial pneumonia, pulmonary lymphoid hyperplasia, or both<sup>d</sup>  
 Lymphoma, Burkitt (or equivalent term)  
 Lymphoma, immunoblastic (or equivalent term)  
 Lymphoma, primary, of brain  
*Mycobacterium avium*–intracellular complex or *Mycobacterium kansasii*, disseminated or extrapulmonary  
*Mycobacterium tuberculosis*, any site (pulmonary<sup>b</sup> or extrapulmonary)  
*Mycobacterium*, other species or unidentified species, disseminated or extrapulmonary  
*Pneumocystis carinii* pneumonia  
 Pneumonia, recurrent<sup>b</sup>  
 Progressive multifocal leukoencephalopathy  
 Salmonella septicemia, recurrent  
 Toxoplasmosis of brain  
 Wasting syndrome resulting from HIV

<sup>d</sup>Children  $<13$  years of age.

<sup>b</sup>Added in the 1993 expansions of the acquired immunodeficiency syndrome surveillance case definition for adolescents and adults.

- The severity of immune damage and potential for disease progression must be assessed to determine whether therapeutic interventions are needed. The risk for T-cell destruction and opportunistic infections increases with increased viral load.
- Criteria to determine whether an antiretroviral (ARV) regimen is effective are clinical assessment, surrogate marker response, and regimen tolerability.

## Goals of Therapy

- Goals of therapy are to maximally and durably suppress viral load; preserve the strength of the immune system; limit drug adverse events, promote adherence, and improve quality of life; minimize HIV-related morbidity and mortality; and prevent transmission.

## Treatment

- Highly active antiretroviral therapy (HAART) decreases viral replication and dramatically alters the natural course of infection by prolonging the time to opportunistic infection and death (Table 73.3). ARV regimens may improve quality and duration of life but they are not without risks. Once therapy is initiated, therapy is a lifetime commitment.
- HAART initiation is recommended for all individuals identified as infected with HIV, with stronger evidence supporting initiation in those with lower pretreatment T-cell counts. Risks versus benefits of treatment must be considered when deciding when and which ARV regimen to initiate. Table 73.4 provides guidelines on when to consider ARV therapy in HIV-infected patients. Treatment is strongly recommended for any patient who has a T-cell count  $<350$  cell/ $\mu\text{L}$  or who is symptomatic (e.g., new opportunistic infections or constitutional symptoms) regardless of T-cell count and viral load measurements.
- Recommended ARV agents for initial treatment of established HIV infection are shown in Table 73.5.
- The following steps should be followed when selecting a patient-specific regimen:
  - Carefully review the advantages and disadvantages of each strategy (Table 73.6).
  - Optimize the agents in the regimen.
  - Assess quality-of-life issues, potential adverse reactions, and patient preference.
- Up to 25% of HAART will fail within the first year. Patients should be counseled to always take the medications as prescribed. Factors associated with compliance are the number of medications, complexity of the regimen, special storage requirements, interference with daily routine, and poor communication with healthcare providers.
- Carefully assess for possible drug interactions (Table 73.7).
- General rules for changing therapy due to virologic failure:
  - Causes of virologic failure should be identified if possible and include suboptimal adherence, medication adverse effects/intolerance, pharmacokinetic issues, or presence of drug resistance.
  - Resistance testing is recommended to guide selection of future drug regimens.
  - If possible, the new regimen should contain at least two and ideally three fully active ARV agents. Selection should be based on the patient's past HAART history, resistance testing, or the inclusion of a new drug class.
  - Changes to therapy should occur close to the time of treatment failure.
  - To prevent development of resistance, never add one new drug to a failing regimen.
  - If possible, do not initiate a regimen that failed in the past.
  - Switching virologically suppressed patients may occur for reasons including simplification of regimens, to manage adverse effects/intolerances or drug interactions, or for pregnancy. Risk and benefit of the switch should be assessed along with the patient's ARV usage history, resistance profile, and past adverse effects and intolerances.
  - If an agent in a given regimen must be stopped, it is recommended that all agents in the regimen be stopped and restarted simultaneously to prevent development of resistance.
- Current prenatal HIV guidelines recommend that women receiving and tolerating a suppressive regimen when they become pregnant continue that regimen. Although efavirenz may not be recommended to be part of a regimen for women of child-bearing age seeking to become pregnant, efavirenz-based regimens may be continued in a pregnant women

**TABLE 73.3 Characteristics of Antiretroviral Agents for the Treatment of Adult Human Immunodeficiency Virus Infection**

<b>Drug</b>	<b>Dose</b>	<b>Pharmacokinetic Parameters</b>	<b>Administration Considerations</b>
<b>NUCLEOSIDE REVERSE TRANSCRIPTASE INHIBITORS</b>			
<b>ZDV</b> <b>Retrovir</b> <i>Preparations</i> Oral Solution: 10 mg/mL Capsule: 100 mg Tablet: 300 mg IV Solution: 10 mg/mL	300 mg twice daily or 200 mg three times daily	<i>Oral bioavailability:</i> 60% <i>Serum t<sub>1/2</sub>:</i> 1.1 hours <i>Intracellular t<sub>1/2</sub>:</i> 3 hours <i>Elimination:</i> hepatic glucuronidation; renal excretion of glucuronide metabolite	Can be administered without regard to meals (manufacturer recommends administration 30 minutes before or 1 hour after a meal)
<b>ddI</b> <b>Videx</b> <i>Preparations</i> Videx EC (R): 125, 200, 250, 400 mg capsule Pediatric powder for oral solution (when reconstituted as solution containing antacid): 10 mg/mL Generic ddI enteric- coated capsule also available	>60 kg: 400 mg daily (with TDF, use 250 mg daily) <60 kg: 250 mg daily (with TDF, use 200 mg daily)	<i>Oral bioavailability:</i> 30%–40% <i>Serum t<sub>1/2</sub>:</i> 1.6 hours <i>Intracellular t<sub>1/2</sub>:</i> 25–40 hours <i>Elimination:</i> renal excretion ~50%	Food decreases absorption (↓ 55%); administer ddI on empty stomach (1 hour before or 2 hours after meal) Separate ATV and TPV/r administration by at least 2 hours
<b>d4T</b> <b>Zerit</b> <i>Preparations</i> Solution: 1 mg/mL Capsules: 15, 20, 30, 40 mg	>60 kg: 40 mg twice daily <60 kg: 30 mg twice daily Sustained release: >60 kg use 100 mg daily; <60 kg use 75 mg daily	<i>Oral bioavailability:</i> 86% <i>Serum t<sub>1/2</sub>:</i> 1.0 hour <i>Intracellular t<sub>1/2</sub>:</i> 3.5 hours <i>Elimination:</i> renal excretion ~50%	Can be administered without regard to meals
<b>3TC</b> <b>Epivir</b> <i>Preparations</i> Solution: 10 mg/mL Tablets: 150 mg, 300 mg	150 mg PO twice daily or 300 mg PO daily	<i>Oral bioavailability:</i> 86% <i>Serum t<sub>1/2</sub>:</i> 5–7 hours <i>Intracellular t<sub>1/2</sub>:</i> 18–22 hours <i>Elimination:</i> 70% unchanged in urine	Can be administered without regard to meals
<b>FTC</b> <b>Emtriva</b> <i>Preparations</i> Capsules: 200 mg Oral solution: 10 mg/mL	200 mg daily for patients with calculated CrCl >50 mL/minute	<i>Oral bioavailability:</i> 93% <i>Serum t<sub>1/2</sub>:</i> 10 hours <i>Intracellular t<sub>1/2</sub>:</i> >20 hours <i>Elimination:</i> 86% recovered in urine	Can be administered without regard to meals
<b>TDF</b> <b>Viread</b> <i>Preparations</i> Tablets: 300 mg	300 mg daily for patients with CrCl >50 mL/ minute	<i>Oral bioavailability:</i> 25% fasting; 39% with high- fat meal <i>Serum t<sub>1/2</sub>:</i> 17 hours <i>Intracellular t<sub>1/2</sub>:</i> >60 hours <i>Elimination:</i> primarily by glomerular filtration and active tubular secretion	Can be administered without regard to meals
<b>ABC</b> <b>Ziagen</b> <i>Preparations</i> Tablets: 300 mg Oral solution: 20 mg/mL	300 mg every 12 hours, or 600 mg daily	<i>Oral bioavailability:</i> 83% <i>Serum t<sub>1/2</sub>:</i> 1.5 hours <i>Intracellular t<sub>1/2</sub>:</i> 12–26 hours <i>Elimination:</i> alcohol dehydrogenase and glucuronyltransferase; 82% renal elimination of metabolites	Can be administered without regard to meals Alcohol raises abacavir exposure by 41% HLA testing required before administration

Continued on following page

**TABLE 73.3 Characteristics of Antiretroviral Agents for the Treatment of Adult Human Immunodeficiency Virus Infection (Continued)**

<b>Drug</b>	<b>Dose</b>	<b>Pharmacokinetic Parameters</b>	<b>Administration Considerations</b>
<b>NRTI FIXED-DOSE COMBINATIONS</b>			
<b>Combivir</b> ZDV 300 mg + 3TC 150 mg	<b>1 tablet twice daily</b>		Can be administered without regard to meals
<b>Trizivir</b> ZDV 300 mg + 3TC 150 mg + ABC 300 mg	<b>1 tablet twice daily</b>		Can be administered without regard to meals
<b>Truvada</b> TDF 300 mg + FTC 200 mg	As Truvada: one tablet daily Truvada not for patients with CrCl <50 mL/minute		Can be administered without regard to meals
<b>Epzicom</b> ABC 600 mg + 3TC 300 mg	<b>1 tablet daily</b>		Can be administered without regard to meals
<b>NON-NUCLEOSIDE REVERSE TRANSCRIPTASE INHIBITORS<sup>a</sup></b>			
<b>NVP</b> <b>Viramune</b> <i>Preparations</i> Suspension: 50 mg/5 mL Tablets: 200 mg	200 mg PO daily × 14 days, then 200 mg PO twice daily	<i>Oral bioavailability:</i> >90% <i>Serum t<sub>1/2</sub>:</i> 25–30 hours <i>Intracellular t<sub>1/2</sub>:</i> unknown <i>Elimination:</i> metabolized by CYP2B6 and CYP3A4 (also a CYP3A4 inducer) with 80% excreted in urine as the glucuronide metabolite	Can be administered without regard to meals
<b>EFV</b> <b>Sustiva</b> <i>Preparations</i> Capsules: 50, 100, 200 mg Tablets: 600 mg	600 mg at bedtime	<i>Oral bioavailability:</i> ~60%–70% <i>Serum t<sub>1/2</sub>:</i> 40–55 hours <i>Intracellular t<sub>1/2</sub>:</i> unknown <i>Elimination:</i> hepatically metabolized by CYP2B6 and CYP3A4 (also CYP3A4 mixed inhibitor/inducer)	Avoid taking with high-fat meals, concentrations ↑ 50% (increased risk for CNS toxicity)
<b>ETV</b> <b>Intellec</b> <i>Preparations</i> Tablets: 100, 200 mg	200 mg twice daily	<i>Oral bioavailability:</i> unknown <i>Serum t<sub>1/2</sub>:</i> 40 ± 20 hours <i>Intracellular t<sub>1/2</sub>:</i> unknown <i>Elimination:</i> hepatically metabolized by CYP3A4, CYP2C9, CYP2C19 (also 3A4 inducer, 2C9 and 2C19 inhibitor)	Take after a meal
<b>DLV</b> <b>Rescriptor</b> <i>Preparations</i> Tablets: 100, 200 mg	400 mg three times daily (four 100-mg tabs in at least 3 ounces of water to produce slurry); 200-mg tablets should be taken intact	<i>Oral bioavailability:</i> 85% <i>Serum t<sub>1/2</sub>:</i> 5.8 hours <i>Intracellular t<sub>1/2</sub>:</i> unknown <i>Elimination:</i> metabolized by CYP3A4 (also a CYP3A4 inhibitor) with 51% excreted in urine as metabolites	Can be administered without regard to meals

**TABLE 73.3 Characteristics of Antiretroviral Agents for the Treatment of Adult Human Immunodeficiency Virus Infection (Continued)**

<b>Drug</b>	<b>Dose</b>	<b>Pharmacokinetic Parameters</b>	<b>Administration Considerations</b>
<b>RPV</b> <b>Edurant</b> <i>Preparations</i> Tablets: 25 mg	25 mg daily	<i>Oral bioavailability:</i> not established <i>Serum t<sub>1/2</sub>:</i> ~50 hours <i>Intracellular t<sub>1/2</sub>:</i> unknown <i>Elimination:</i> hepatic metabolism primarily by CYP3A4 with 85% fecal excretion	Take with moderate- to high-calorie meal (increases absorption 40%)
<b>PROTEASE INHIBITORS</b>			
<b>IDV</b> <b>Crixivan</b> <i>Preparations</i> Capsule: 200, 333, 400 mg	800 mg every 8 hours (twice daily dosing ineffective when sole protease inhibitor) IDV/RTV: IDV 800 mg + 100 mg or 200 mg RTV twice daily	<i>Oral bioavailability:</i> 65% <i>Serum t<sub>1/2</sub>:</i> 1.5–2 hours <i>Intracellular t<sub>1/2</sub>:</i> unknown <i>Elimination:</i> hepatically metabolized via CYP3A4 (also inhibitor of CYP3A4)	Must be taken on empty stomach (1 hour before or 2 hours after a meal); may take with skim milk or low-fat meal Adequate hydration necessary (at least 1.5 L/24 hours of liquid) to minimize risk of nephrolithiasis
<b>RTV</b> <b>Norvir</b> <i>Preparations</i> Oral solution: 80 mg/mL Capsules: 100 mg Tablets: 100 mg	Current primary use is as a pharmacokinetic enhancer for other PIs, using 100–400 mg/day in one to two divided doses	<i>Oral bioavailability:</i> Not determined <i>Serum t<sub>1/2</sub>:</i> 3–5 hours <i>Intracellular t<sub>1/2</sub>:</i> unknown <i>Elimination:</i> extensive hepatic metabolism via CYP3A4 (also potent CYP3A4 inhibitor and mixed inhibitor/inducer of other isozymes)	Take with food if possible to improve tolerability Dose should be titrated upward to minimize gastrointestinal adverse events Refrigerate capsules but not liquid or tablets
<b>NFV</b> <b>Viracept</b> <i>Preparations</i> Powder for oral suspension: 50 mg per one level scoop (200 mg per one level teaspoon) Tablets: 250 and 625 mg	750 mg three times daily or 1,250 mg twice daily	<i>Oral bioavailability:</i> 20%–80% <i>Serum t<sub>1/2</sub>:</i> 3.5–5 hours <i>Intracellular t<sub>1/2</sub>:</i> unknown <i>Elimination:</i> hepatic metabolism via CYP3A4	Administer with meal or light snack (exposure increased twofold to threefold)
<b>SQV</b> <b>Invirase</b> (hard gel capsules) <i>Preparations</i> Hard gel capsule: 200 mg Tablets: 500 mg	Unboosted saquinavir not recommended Saquinavir/ritonavir: 1,000/100 twice daily; 1,600/100 daily under investigation	<i>Oral bioavailability:</i> 4% (as the sole PI) <i>Serum t<sub>1/2</sub>:</i> 1–2 hours <i>Intracellular t<sub>1/2</sub>:</i> unknown <i>Elimination:</i> hepatic metabolism via CYP3A4 (inhibitor)	Take within 2 hours of a meal and take with RTV
<b>FPV</b> <b>Lexiva</b> Tablet: 700 mg	ARV-naïve patients: FPV 1,400 mg twice daily or FPV 1,400 mg + RTV 200 mg daily or FPV 700 mg + RTV 100 mg twice daily PI-experienced patients: FPV 700 mg + RTV 100 mg twice daily	<i>Oral bioavailability:</i> not determined <i>Serum t<sub>1/2</sub>:</i> 7.1–10.6 hours (APV) <i>Intracellular t<sub>1/2</sub>:</i> unknown <i>Elimination:</i> hepatic metabolism via CYP3A4 (inhibitor)	Can be taken without regard to meals but should not be taken with high-fat meals

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**TABLE 73.3 Characteristics of Antiretroviral Agents for the Treatment of Adult Human Immunodeficiency Virus Infection (Continued)**

Drug	Dose	Pharmacokinetic Parameters	Administration Considerations
<b>LPV/RTV</b> <b>Kaletra</b> <i>Preparations</i> Tablet: LPV 200 mg + RTV 50 mg Solution: LPV 80 mg + RTV 20 mg per mL	Treatment-naïve: Four tablets or 10 mL daily Treatment-experienced: Two tablets or 5 mL twice daily	<i>Oral bioavailability:</i> not determined <i>Serum t<sub>1/2</sub>:</i> 5–6 hours <i>Intracellular t<sub>1/2</sub>:</i> unknown <i>Elimination:</i> hepatic metabolism via CYP3A4 (inhibitor)	Take with food (increases AUC by 48%). Tablet stable at room temperature
<b>ATV</b> <b>Reyataz</b> <i>Preparations</i> Capsules: 100, 150, 200, 300 mg	Treatment-naïve: 400 mg daily or ATV 300 mg + RTV daily Treatment-experienced: ATV 300 mg + RTV 100 mg	<i>Oral bioavailability:</i> 60%–70% <i>Serum t<sub>1/2</sub>:</i> 6–7 hours <i>Intracellular t<sub>1/2</sub>:</i> unknown <i>Elimination:</i> hepatic metabolism via CYP3A4 (modest inhibitor)	Take with food, and avoid acid suppressing agents (which prevent ATV solubility and absorption)
<b>DRV</b> <b>Prezista</b> <i>Preparations</i> Tablet: 300 mg, 600 mg, 800 mg	Treatment-naïve: 800 mg DRV 800 mg + RTV 100 mg once daily Treatment-experienced: 600 mg DRV + 100 mg RTV twice daily Should always be administered with RTV	<i>Oral bioavailability:</i> 37% alone, 82% with RTV <i>Serum t<sub>1/2</sub>:</i> 15 hours <i>Intracellular t<sub>1/2</sub>:</i> unknown <i>Elimination:</i> hepatic metabolism via CYP3A4 (inhibitor)	Food ↑ C <sub>max</sub> and AUC by 30%: administer with food
<b>TPV</b> <b>Aptivus</b> Capsules: 250 mg	TPV 500 mg + RTV 200 mg twice daily <b>DO NOT USE WITHOUT RTV</b>	<i>Oral bioavailability:</i> not determined <i>Serum t<sub>1/2</sub>:</i> 6 hours <i>Intracellular t<sub>1/2</sub>:</i> unknown <i>Elimination:</i> hepatic metabolism via CYP3A4 (inhibitor and inducer)	Administer with food to increase bioavailability

#### ENTRY INHIBITORS

<b>T-20</b> <b>Fuzeon</b>	90 mg SC twice daily in upper arm, thigh, or abdomen	<i>Oral bioavailability:</i> 84.3% compared with IV <i>Serum t<sub>1/2</sub>:</i> 3.8 hours <i>Intracellular t<sub>1/2</sub>:</i> not applicable <i>Elimination:</i> nonrenal, nonhepatic	Reconstitute with 1.1 mL sterile water for injection; gently tap vial for 10 seconds and then roll gently between hands to avoid foaming and ensure all drug is off vial walls. After reconstitution, use immediately or refrigerate for 24 hours. Refrigerated T-20 should be brought to room temperature before injection.
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**TABLE 73.3 Characteristics of Antiretroviral Agents for the Treatment of Adult Human Immunodeficiency Virus Infection (Continued)**

<b>Drug</b>	<b>Dose</b>	<b>Pharmacokinetic Parameters</b>	<b>Administration Considerations</b>
<b>CHEMOKINE RECEPTOR ANTAGONISTS (CCR5)</b>			
<b>MVC</b> <b>Selzentry</b> <i>Preparations</i> Tablet: 150, 300 mg	300 mg twice daily (with all NRTIs, NVP, TPV, ENF), 150 mg twice daily with CYP3A inhibitors (with or without a CYP3A inducer) including protease inhibitors (except tipranavir/ritonavir), delavirdine, ketoconazole, itraconazole, clarithromycin, and other strong CYP3A inhibitors (e.g., nefazodone, telithromycin) 600 mg twice daily with CYP3A inducers (without a strong CYP3A inhibitor) including efavirenz, etravirine (TMC125), rifampin, carbamazepine, phenobarbital, and phenytoin	<i>Oral bioavailability:</i> ~33% <i>Serum t<sub>1/2</sub>:</i> 14–18 hours <i>Elimination:</i> hepatic metabolism by CYP3A; 20% recovered in urine, 76% recovered in feces	Can be administered without regard to meals (high-fat meal decreases C <sub>max</sub> and AUC by ~30%) Trofile assay must be performed before administration
<b>INTEGRASE INHIBITORS</b>			
<b>RAL</b> <b>Isentress</b> <i>Preparations</i> Tablet: 400 mg Chewable tablet: 25 mg, 100 mg (pediatric)	400 mg twice daily	<i>Oral bioavailability:</i> not established <i>Serum t<sub>1/2</sub>:</i> 9 hours <i>Elimination:</i> hepatic metabolism by UGT1A1 glucuronidation; 32% recovered in urine, 51% recovered in feces	Can be administered without regard to meals (high-fat meal decreases C <sub>max</sub> by ~34% and increases AUC by ~19%) Tablet and chewable tablet are not bioequivalent
<b>DTG</b> <b>Tivicay</b> <i>Preparations</i> Tablet: 50 mg	Integrase-Inhibitor naïve: 1 tablet daily Integrase-Inhibitor experienced: 1 tablet twice daily	<i>Oral bioavailability:</i> not established <i>Serum t<sub>1/2</sub>:</i> 14 hours <i>Elimination:</i> hepatic metabolism by UGT1A1, some CYP3A; 31% as metabolite recovered in urine, 53% as unchanged drug recovered in feces	Can be administered without regard to meals

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**TABLE 73.3 Characteristics of Antiretroviral Agents for the Treatment of Adult Human Immunodeficiency Virus Infection (Continued)**

Drug	Dose	Pharmacokinetic Parameters	Administration Considerations
<b>SINGLE-TABLET FIXED-DOSE REGIMENS</b>			
<b>Atripla</b> EFV 600 mg + TDF 300 mg + FTC 200 mg	1 tablet at bedtime Not for patients with CrCl <50 mL/minute		Avoid taking with high-fat meals, concentrations ↑ 50% (increased risk for CNS toxicity)
<b>Complera</b> RPV 25 mg + TDF 300 mg + FTC 200 mg	1 tablet daily Not for patients with CrCl <50 mL/minute		Take with moderate- to high-calorie meal (increases absorption 40%)
<b>Stribild</b> ETG 150 mg + Cobi 150 mg + TDF 300 mg + FTC 200 mg	1 tablet daily Not indicated for pretreatment CrCl <70 mL/minute		Administer with food

<sup>a</sup>In clinical trials, the NNRTIs was discontinued because of rash in 7% of patients taking nevirapine, 4.3% of patients taking delavirdine, and 1.7% of patients taking efavirenz. Rare cases of Stevens–Johnson syndrome have been reported with all three NNRTIs.

ABC, abacavir; ARV, antiretroviral; ATV, atazanavir; AUC, area under the curve; Cobi, Cobicistat; CNS, central nervous system; CrCl, creatinine clearance; ddi, didanosine; d4T, stavudine; DLV, delavirdine; DRV, darunavir; DTG, dolutegravir; EFV, efavirenz; ENF, enfuvirtide; ETG, elvitegravir; ETV, etravirine; FPV, fosamprenavir; FTC, emtricitabine; HLA, human leukocyte antigen; IDV, indinavir; IV, intravenous; LPV, lopinavir; MVC, maraviroc; NFV, nelfinavir, NNRTI, non-nucleoside reverse transcriptase inhibitor; NRTIs, nucleoside reverse transcriptase inhibitors; NVP, nevirapine; PI, protein inhibitor; PO, orally; QID, four times daily; RAL, raltegravir; RPV, rilpivirine; RTV, ritonavir; SC, subcutaneously; SQV, saquinavir; 3TC, lamivudine; TDF, tenofovir disoproxil fumarate; TPV, tipranavir; TPV/r, tipranavir/ritonavir; T-20, enfuvirtide; ZDV, zidovudine.

**TABLE 73.4 Indications for the Initiation of Antiretroviral Therapy in the Chronically HIV-1–Infected Patient<sup>a</sup>**

Clinical Category	CD4 <sup>+</sup> T-Cell Count	Plasma HIV RNA	Recommendation
Symptomatic (AIDS, severe symptoms)	Any value	Any value	Treat
Asymptomatic	<350/ $\mu$ L	Any value	Treat
Asymptomatic	350–500/ $\mu$ L	Any value	Treatment should be offered
Asymptomatic	>500/ $\mu$ L	>100,000 copies/mL	Treatment should be offered
Asymptomatic	>500/ $\mu$ L	<100,000 copies/mL	Treatment should be offered

<sup>a</sup>The optimal time to initiate therapy in asymptomatic individuals with >500 CD4<sup>+</sup> cells/ $\mu$ L is not known. This table provides general guidance rather than absolute recommendations for an individual patient. All decisions to initiate therapy should be based on prognosis as determined by the CD4<sup>+</sup> T-cell count and plasma HIV RNA, the potential benefits and risks of therapy shown in Table 73.6, and the willingness of the patient to accept therapy.

AIDS, acquired immunodeficiency syndrome; HIV, human immunodeficiency virus.

**TABLE 73.5 Recommended Antiretroviral Agents for Initial Treatment of Established Human Immunodeficiency Virus Infection<sup>a</sup>**

RECOMMENDED FOR ANY PRETREATMENT VIRAL LOAD	
NNRTI-based	Efavirenz <sup>b</sup> /tenofovir/emtricitabine (Atripla)
PI-based	Atazanavir/ritonavir <sup>c</sup> + tenofovir/emtricitabine Darunavir/ritonavir once daily + tenofovir/emtricitabine
Integrase inhibitors-based	Raltegravir twice daily + tenofovir/emtricitabine Elvitegravir/cobicistat/tenofovir/emtricitabine <sup>d</sup> (Stribild) Dolutegravir + tenofovir/emtricitabine Dolutegravir + abacavir/lamivudine <sup>e</sup>
RECOMMENDED ONLY FOR PRETREATMENT VIRAL LOADS <100,000 COPIES/ML	
NNRTI-based	Efavirenz + abacavir/lamivudine <sup>e</sup> Rilpivirine/tenofovir/emtricitabine <sup>f</sup>
PI-based	Atazanavir/ritonavir + abacavir/lamivudine <sup>e</sup>
Not recommended: Should not be offered	All monotherapies, dual-nucleoside regimens, triple-NRTI regimens

<sup>a</sup>This table provides a guide to the use of available treatment regimens for individuals with no prior or limited experience on HIV therapy. In accordance with the established goals of HIV therapy, priority is given to regimens in which clinical trial data suggest the following: sustained suppression of HIV plasma RNA (particularly in patients with high baseline viral load), sustained increase in CD4<sup>+</sup> T-cell count (in most cases >48 weeks), and favorable clinical outcome (i.e., delayed progression to AIDS and death). Additional consideration is given to the regimen's pill burden, dosing frequency, food requirements, convenience, toxicity, and drug interaction profile compared with other regimens. It is important to note that all antiretroviral agents have potentially serious toxic and adverse events associated with their use.

<sup>b</sup>Except in women with high pregnancy potential (women who are trying to conceive or who are not using effective and consistent contraception).

<sup>c</sup>When used with tenofovir, atazanavir should be combined with ritonavir 100 mg/d.

<sup>d</sup>Not recommended for pretreatment CrCl <70 mL/minute

<sup>e</sup>Patient should have HLA-B\*5701 negative test prior to initiation of abacavir

<sup>f</sup>Patient T-cell count should also be greater than 200 cells/mL

AIDS, acquired immunodeficiency syndrome; HIV, human immunodeficiency virus; NRTI, nucleos(t)ide analog reverse transcriptase inhibitor; NNRTI, non-nucleos(t)ide analog reverse transcriptase inhibitor; PI, protease inhibitor.

presenting in her first trimester. It is recommended that HIV-positive women not breast-feed in settings where clean water and formula are reasonably available.

- Tenofovir/emtricitabine fixed-dose combination (Truvada), when used with safer sex practices, has been approved for use in high-risk HIV-negative adults to reduce the risk of sexually acquired HIV-1. The HIV-negative status of the individual should be confirmed at baseline and at least every 3 months while on the regimen.
- Occupational postexposure prophylaxis should be started as soon as possible after exposure, should contain three or more active ARVs, and should continue for 4 weeks.
- Nonoccupational postexposure prophylaxis is recommended for individuals seeking care with 72 hours of exposure to blood, genital secretions, or other infectious fluids from a known HIV-infected person.

**TABLE 73.6 Advantages and Disadvantages of Antiretroviral Components for Initial Antiretroviral Therapy<sup>a</sup>**

ARV Class		Possible Advantages	Possible Disadvantages
Dual NRTI	ABC/3TC	<ul style="list-style-type: none"> <li>Once-daily dosing</li> <li>No food requirement</li> <li>Minimal side effects</li> </ul>	<ul style="list-style-type: none"> <li>Not recommended in baseline viral loads <math>\leq 100,000</math> copies/mL <i>except</i> with dolutegravir</li> <li>HLA-B*5701 testing required prior to initiation to identify potential for hypersensitivity reaction</li> <li>Inconclusive association with cardiovascular events</li> </ul>
	TD/F/FTC	<ul style="list-style-type: none"> <li>Recommended in HAART regimens regardless of baseline viral load</li> <li>Once-daily dosing</li> <li>No food requirement</li> <li>Co-formulated with multiple fixed-dose tablet regimens</li> <li>Active against HBV</li> </ul>	<ul style="list-style-type: none"> <li>Potential for renal toxicity</li> <li>Potential for bone mineral density reduction</li> <li>Requires adjustment in renal impairment</li> </ul>
NNRTIs	EFV	<ul style="list-style-type: none"> <li>Virologic response regardless of baseline viral load</li> <li>Similar or better efficacy to comparator regimens</li> <li>Once-daily dosing</li> <li>No food requirement</li> <li>Co-formulated with TDF/FTC</li> </ul>	<ul style="list-style-type: none"> <li>Low genetic barrier to resistance</li> <li>Potential for CYP-450 drug interactions</li> <li>Transmitted resistance to NNRTIs more common than with PIs</li> <li>Adverse effects: CNS, rash, dyslipidemias</li> <li>Avoid use in women of child-bearing potential</li> <li>Should be dosed on empty stomach</li> </ul>
	RPV	<ul style="list-style-type: none"> <li>Co-formulated with TDF/FTC</li> <li>Once-daily dosing</li> <li>Well tolerated</li> </ul>	<ul style="list-style-type: none"> <li>Not recommended in patients with baseline viral loads <math>&gt;100,000</math> copies/mL or CD4 counts <math>&lt;200</math> cells/mm<sup>3</sup></li> <li>Low genetic barrier to resistance</li> <li>Potential for cytochrome P-450 drug interactions</li> <li>Transmitted resistance to NNRTIs more common than with PIs</li> <li>Specific caloric intake requirement</li> <li>Interactions with gastric acid-modifying agents</li> </ul>
	ATV/RTV	<ul style="list-style-type: none"> <li>Once-daily dosing</li> <li>PI resistance uncommon with failure (boosted PIs)</li> <li>Higher genetic barrier to resistance</li> </ul>	<ul style="list-style-type: none"> <li>CYP-450 substrates, inhibitors, and inducers</li> <li>Take with food</li> <li>Interactions with gastric acid-modifying agents</li> <li>Adverse effects: nausea, diarrhea, dyslipidemias, nephrolithiasis, hyperbilirubinemia leading to scleral icterus or jaundice, nephrotoxicity</li> </ul>
	DRV/RTV	<ul style="list-style-type: none"> <li>Once-daily dosing</li> <li>PI resistance uncommon with failure (boosted PIs)</li> <li>Higher genetic barrier to resistance</li> </ul>	<ul style="list-style-type: none"> <li>CYP-450 substrates, inhibitors, and inducers</li> <li>Take with food</li> <li>Adverse effects: rash, nausea, diarrhea, dyslipidemias</li> </ul>

**TABLE 73.6 Advantages and Disadvantages of Antiretroviral Components for Initial Antiretroviral Therapy (Continued)**

ARV Class		Possible Advantages	Possible Disadvantages
INSTIs	DTG	<ul style="list-style-type: none"> <li>Higher rates of virologic suppression versus EFV-based and DRV/RTV-based regimens, likely due to drug discontinuations</li> <li>Once-daily dosing</li> <li>Higher genetic barrier to resistance than EVG or RAL</li> <li>Efficacious with both dual NRTI backbones regardless of baseline viral load</li> <li>No food requirement</li> <li>Few CYP-450 drug interactions</li> <li>50 mg twice-daily dosing in INSTI-experienced patients and depending on INSTI-resistance pattern</li> <li>Generally well tolerated</li> </ul>	<ul style="list-style-type: none"> <li>Inhibits secretion of creatinine leading to increased creatinine clearance; does not affect glomerular filtration</li> <li>Absorption may be decreased with coadministration of products containing polyvalent cations including <math>Al^{3+}</math>, <math>Ca^{2+}</math>, <math>Fe^{2+}</math>, and <math>Mg^{2+}</math>; administering in with food may minimize this interaction</li> <li>Drug interactions: UGT substrate</li> </ul>
	EVG	<ul style="list-style-type: none"> <li>Co-formulated with Cobi/TDF/FTC</li> <li>Once-daily dosing</li> <li>Noninferior to EFV-based and ATV/RTV-based regimens</li> <li>Generally well tolerated</li> </ul>	<ul style="list-style-type: none"> <li>Only indicated in patients with baseline creatinine clearance <math>\geq 70</math> mL/minute</li> <li>CYP-450 drug interactions due to Cobi</li> <li>Cobi inhibits secretion of creatinine leading to increased creatinine clearance; does not affect glomerular filtration</li> <li>Low genetic barrier to resistance</li> <li>Food requirement</li> <li>Absorption may be decreased with coadministration of <math>Al^{3+}</math>- or <math>Mg^{2+}</math>-containing antacids.</li> <li>EVG is not currently available as single agent.</li> </ul>
	RAL	<ul style="list-style-type: none"> <li>No food requirement</li> <li>Minimal CYP-450 drug interactions</li> <li>Generally well tolerated</li> </ul>	<ul style="list-style-type: none"> <li>Twice-daily dosing</li> <li>Low barrier to resistance</li> <li>Potential for UGT-related drug interactions</li> <li>Reports of creatine kinase elevation, myopathy, and rhabdomyolysis</li> <li>Absorption may be decreased with coadministration of <math>Al^{3+}</math>- or <math>Mg^{2+}</math>-containing antacids.</li> </ul>

<sup>a</sup>Adapted from DHHS treatment guidelines January 2014.

ABC, abacavir; ARV, antiretroviral; DHHS, Department of Health and Human Services; Cobi, cobicistat; CYP, cytochrome P-; DTG, dolutegravir; EVG, elvitegravir; FTC, emtricitabine; HBV, hepatitis B virus; NNRTI, non-nucleoside reverse transcriptase inhibitors; NRTI, nucleoside reverse transcriptase inhibitor; PI, protease inhibitor; INSTI, integrase strand transfer inhibitor; RAL, raltegravir; RVP, rilpivirine; TDF, tenofovir disoproxil fumarate; 3TC, lamivudine.

TABLE 73.7 Drugs that Should Not Be Coadministered with Antiretrovirals (Otherwise Indicated)

	Cardiac Agents	Lipid-Lowering Agents	Anti-Infectants	Gastrointestinal Drugs	Psychotropic Agents	Anticonvulsants	Pulmonary Agents	Herbs	Others	ARV Agents
ATV ± RTV	Bosentan <sup>d</sup>	Lovastatin Simvastatin	Rifampin Rifapentine Voriconazole <sup>b</sup>	Cisapride PPIs <sup>c</sup>	Midazolam Triazolam		Salmeterol Sildenafil (for PAH) Fluticasone <sup>d</sup>	St. John's wort	Alfuzosin Irinotecan Buprenorphine <sup>e</sup>	ETR NVP
DRV/RTV		Lovastatin Simvastatin	Rifampin Rifapentine Voriconazole <sup>b</sup>	Cisapride	Midazolam Triazolam		Salmeterol Sildenafil (for PAH) Fluticasone <sup>e</sup>	St. John's wort	Alfuzosin	
FPV ± RTV	Flecainide Propafenone	Lovastatin Simvastatin	Rifampin Rifapentine Voriconazole <sup>b</sup>	Cisapride	Midazolam Triazolam		Salmeterol Sildenafil (for PAH) Fluticasone <sup>e</sup>	St. John's wort	Alfuzosin	ETR
LPV/r		Lovastatin Simvastatin	Rifampin Rifapentine Voriconazole <sup>b</sup>	Cisapride	Midazolam Triazolam	Carbamazepine <sup>f</sup> Phenobarbital <sup>f</sup> Phenytoin <sup>f</sup>	Salmeterol Sildenafil (for PAH) Fluticasone <sup>e</sup>	St. John's wort	Alfuzosin	
TPV/r	Amiodarone Flecainide Propafenone Quinidine	Lovastatin Simvastatin	Rifampin Rifapentine Voriconazole <sup>b</sup>	Cisapride	Midazolam Triazolam		Salmeterol Sildenafil (for PAH) Fluticasone <sup>e</sup>	St. John's wort	Alfuzosin	ETR
EFV			Rifapentine Voriconazole <sup>b</sup>	Cisapride	Midazolam Triazolam			St. John's wort		Other NNRTIs
ETR			Rifampin Rifapentine			Carbamazepine Phenobarbital Phenytoin		St. John's wort	Clopidogrel	Unboosted PIs ATV/r, FPV/r, or TPV/r Other NNRTIs DTG when not coadministered with a boosted PI
NVP			Rifapentine Ketoconazole					St. John's wort		ATV ± RTVDTG Other NNRTIs

RVP			Rifabutin Rifampin Rifapentine	Proton-pump inhibitors		Carbamazepine Oxycarbazepine Phenobarbital Phenytoin	St. John's wort		Other NNTRIs
MVC EVG/Cobi/ TDF/FTC		Lovastatin Simvastatin	Rifapentine Rifabutin Rifampin Rifapentine	Cisapride	Midazolam Triazolam		Salmeterol Sildenafil for PAH	St. John's wort St. John's Wort	Alfuzosin Dihydroergotamine Ergotamine Methylethylgiovine
DTG	Dofetilide		Rifapentine			Carbamazepine Oxycarbazepine Phenobarbital Phenytoin	St. John's Wort		NVP ETV when not coadministered with a boosted PI

<sup>a</sup>Bosentan not recommended if ATV is unboosted.

<sup>b</sup>Do not coadminister with boosted PIs unless benefit outweighs risk and do not coadminister with EFV at standard doses (voriconazole 400 mg twice daily, EFV 300 mg daily).

<sup>c</sup>PPIs are not recommended if ATV is unboosted or in treatment-experienced patients.

<sup>d</sup>Do not coadminister inhaled or intranasal fluticasone with boosted PIs unless benefit outweighs risk of systemic corticosteroid adverse effects.

<sup>e</sup>Do not coadminister with unboosted ATV.

<sup>f</sup>Not recommended if LPV/r is given once daily.

Source: Adapted from DHHS treatment guidelines, January 2014

ATV, atazanavir; DRV/r, darunavir/ritonavir; DTG, dolutegravir; EFV, efavirenz; ETR, etravirine; FPV, fosamprenavir; LPV/r, lopinavir/ritonavir; MVC, maraviroc; NVP, nevirapine; RVP, rilpivirine; RTV, ritonavir; TPV/r, tipranavir/ritonavir; PAH, Pulmonary arterial hypertension.

# Opportunistic Infections in HIV-Infected Patients\*

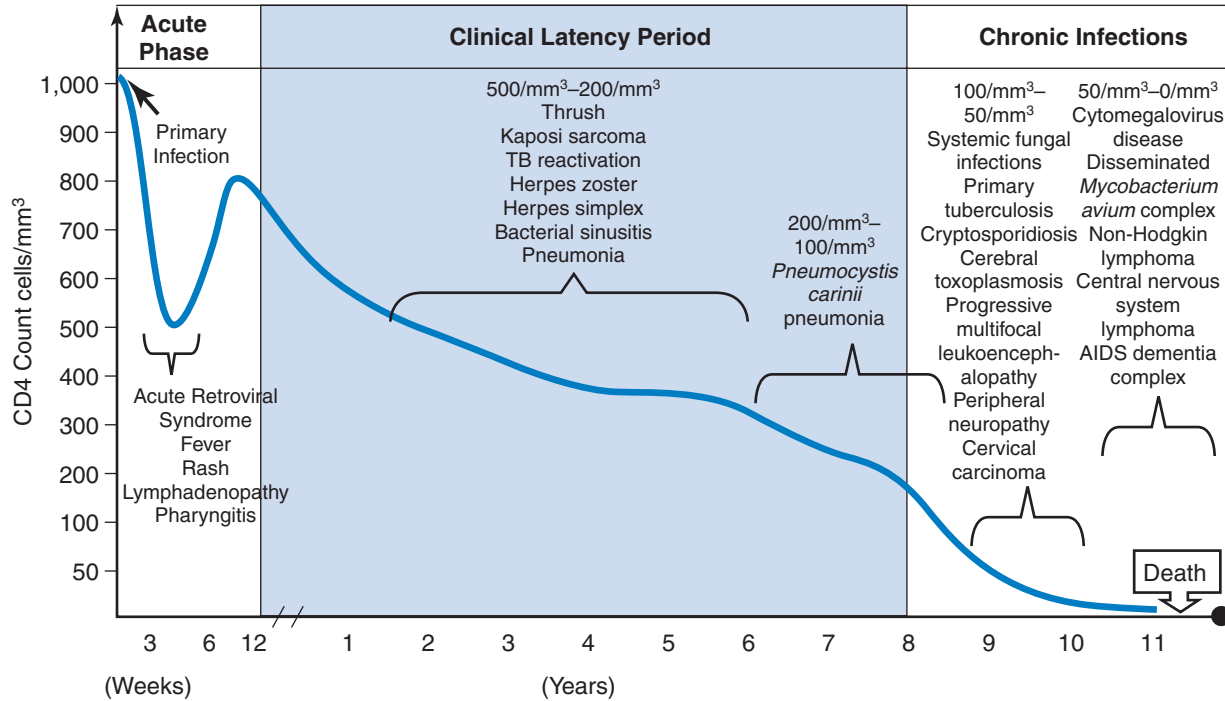
## General Principles

- Long-standing immunosuppression from HIV infection can result in opportunistic infections. Risk for specific opportunistic infections (OI) varies with the degree of immunosuppression and CD4 T-cell counts (Figure 74.1).
- Highly active antiretroviral therapy (HAART) regimens that reduce the viral load and allow for immune recovery have reduced the incidence of opportunistic infections.
- With the initiation of HAART and subsequent immune recovery, immune reconstitution inflammatory syndrome (IRIS) may occur in patients with low pre-treatment CD4 T-cell counts ( $<50$  to  $100$  cells/mm<sup>3</sup>). Certain OIs may require a delay between the initiation of treatment for the OI and the initiation of HAART (e.g., *Mycobacterium tuberculosis* [TB] infection or cryptococcal meningitis).

## Treatment

- Guidelines for prevention of opportunistic infections in HIV-infected patients include preventing exposure to opportunistic pathogens; preventing first episodes of disease by chemoprophylaxis (primary prophylaxis), screening, and vaccination; or preventing disease recurrence (secondary prophylaxis).
- Patients should be screened for TB infection, syphilis, and hepatitis A and B. Those testing positive for latent TB or who are close contacts to a person infected with TB will require treatment, as would those with evidence of recent exposure to syphilis and chronic hepatitis B.
- Vaccination is recommended against influenza, pneumococcal infection, hepatitis A and B. Varicella zoster virus vaccine is recommended for patients with CD4 T-cell counts  $> 200$  cells/mm<sup>3</sup> who have not been vaccinated or have no history of chicken pox or herpes zoster, or are seronegative for VZV. Postexposure prophylaxis with varicella-zoster immune globulin (VariZIG™) in susceptible or unvaccinated close contacts to chickenpox or herpes zoster.
- Guidelines strongly recommend primary chemoprophylaxis against PCP, toxoplasmosis, and *Mycobacterium avium* complex (MAC). Treatment of latent TB may also be considered here. It may be possible to discontinue chemoprophylactic therapy when CD4 T-cell counts rise above the threshold associated with risk for infection (Table 74.1). Primary prophylaxis against Cryptococcal meningitis, CMV, and mucosal candidiasis are not recommended. Chronic maintenance therapy or secondary prophylaxis may be required for OIs (e.g., PCP, toxoplasmosis, MAC, ocular microsporidiosis, CMV retinitis, and infections caused by endemic fungi and Cryptococcal meningitis) after initial treatment in patients with immunosuppression *and maybe be discontinued upon specific immune recovery guidelines for each OI (Table 74.1)*. Guidelines strongly recommend restarting secondary prophylaxis for certain OIs on the basis of level of immunosuppression. These include PCP (CD4 count

\*The reader is referred to Chapter 74, Opportunistic Infections in HIV-Infected Patients, written by Amanda H. Corbett, PharmD, BCPS, FCCP, AAHIVE, and Emily L. Heil, PharmD, BCPS, in the 10th edition of *Applied Therapeutics: The Clinical Use of Drugs* for a more in-depth discussion. All notations to reference numbers are based on the reference list at the end of that chapter. The editor of this handbook expresses her thanks to Drs. Corbett and Heil and acknowledges that this chapter is based on their work.



**Figure 74.1** Natural history of CD4<sup>+</sup> cell count in the average HIV patient without antiretroviral therapy, from the time of HIV transmissions to death. (Illustration by Mary Van, PharmD.)



TABLE 74.1 Primary Prophylaxis of Opportunistic Infections in HIV-Infected Adults and Adolescents

Pathogen	Indication	Preventive Regimens		D/C Primary Prophylaxis
		First Choice	Alternatives	
<i>Pneumocystis jiroveci</i> pneumonia (PCP)	<ul style="list-style-type: none"> <li>• CD4<sup>+</sup> count &lt;200 cells/mm<sup>3</sup> or</li> <li>• Oropharyngeal candidiasis</li> </ul>	<ul style="list-style-type: none"> <li>• TMP-SMX, 1 DS PO daily or</li> <li>• TMP-SMX 1 SS PO daily</li> </ul>	<ul style="list-style-type: none"> <li>• TMP-SMX 1 DS three times per week or</li> <li>• Dapsone 50 mg twice daily or</li> <li>• Dapsone 100 mg daily or</li> <li>• Aerosolized pentamidine 300 mg monthly via Respirgard II nebulizer,</li> <li>• Atovaquone 1,500 mg PO daily</li> <li>• Note: weekly oral pyrimethimine (50–75 mg) PO + leucovorin 25 mg may be added to certain dapsone or atovaquone regimens</li> </ul>	Patients on HAART with sustained CD4 <sup>+</sup> >200 cells/mm <sup>3</sup> for ≥3 months may discontinue PCP prophylaxis. Reintroduce if CD4 <sup>+</sup> <200 cells/mm <sup>3</sup> .
<i>Mycobacterium tuberculosis</i> (treatment of LTBI)	<ul style="list-style-type: none"> <li>• (+) LTBI screen; no evidence of active TB; no prior treatment for active TB or LTBI; or</li> <li>• Close contact with person with infectious TB; no evidence of active TB regardless of screening test results</li> </ul>	<ul style="list-style-type: none"> <li>• Isoniazid 300 mg PO daily or</li> <li>• Isoniazid 900 mg PO twice per week × 9 months both with pyridoxine 50 mg PO daily</li> </ul>	<ul style="list-style-type: none"> <li>• Rifampin 600 mg PO daily × 4 months or</li> <li>• Rifabutin dose adjusted for antiretroviral therapy × 4 months</li> </ul>	
<i>Toxoplasma gondii</i> encephalitis	<ul style="list-style-type: none"> <li>• IgG antibody to <i>Toxoplasma</i> and CD4<sup>+</sup> count &lt;100 cells/mm<sup>3</sup></li> </ul>	<ul style="list-style-type: none"> <li>• TMP-SMX, 1 DS PO daily</li> </ul>	<ul style="list-style-type: none"> <li>• TMP-SMX, 1 SS PO daily or</li> <li>• TMP-SMX 1 DS PO three times per week or</li> <li>• dapsone 50 mg PO daily + pyrimethamine 50 mg PO weekly + leucovorin 25 mg PO weekly or</li> <li>• Weekly dapsone 200 mg PO + pyrimethimine 75 mg PO + leucovorin 25 mg PO or</li> <li>• Atovaquone 1,500 mg PO daily with or without pyrimethamine 25 mg PO daily + leucovorin 10 mg PO daily</li> </ul>	Patients on HAART with sustained CD4 <sup>+</sup> >200 cells/mm <sup>3</sup> for ≥3 months may discontinue toxoplasmosis prophylaxis. Restart if CD4 <sup>+</sup> <100–200.
MAC	<ul style="list-style-type: none"> <li>• CD4<sup>+</sup> count &lt;50 after ruling out active MAC infection</li> </ul>	<ul style="list-style-type: none"> <li>• Azithromycin, 1,200 mg PO weekly or</li> <li>• Clarithromycin 500 mg PO twice daily or</li> <li>• Azithromycin 600 mg PO twice daily</li> </ul>	<ul style="list-style-type: none"> <li>• Rifabutin, 300 mg PO daily or dose adjusted for antiretroviral therapy</li> </ul>	Patients on HAART with sustained CD4 <sup>+</sup> >100 cells/mm <sup>3</sup> for ≥3 months may discontinue MAC prophylaxis. Restart if CD4 <50 cells/mm <sup>3</sup> .

<200 cells/mm<sup>3</sup>), toxoplasmosis (CD4 count <200 cells/mm<sup>3</sup>), MAC (CD4 count <100 cells/mm<sup>3</sup>), CMV retinitis (CD4 count <100 cells/mm<sup>3</sup>), and Cryptococcal meningitis (CD4 count <100 cells/mm<sup>3</sup>).

## Treatment of Specific Opportunistic Infections

- Prompt diagnosis and timely initiation of therapy are essential for management of acute OIs. (See Tables 74.2–74.9 for treatment of select OIs).
- Timing of initiation of antiretroviral therapy should be considered depending on the OI (e.g., Cryptococcal infections, *Mycobacterium tuberculosis* infections). Delaying antiretroviral therapy may limit immune reconstitution inflammatory syndrome (IRIS) and improve outcomes in certain OIs.
- The primary treatment modality for certain OIs is the initiation of ART (e.g., cryptosporidiosis, progressive multifocal leukoencephalopathy [PML]).
- Drug–drug interactions are common among agents that treat OIs, HIV, or other comorbidities. Caution should be taken when initiating or changing therapies in these patients.

TABLE 74.2 Commonly Administered Vaccines in HIV-Infected Adults and Adolescents

Pathogen	Indication	Recommendation
<i>Streptococcus pneumoniae</i>	Individuals not previously receiving pneumococcal vaccine, regardless of CD4 cell count. To be followed by: <ul style="list-style-type: none"> <li>• if CD4 cell count <math>\geq 200</math> cell/mm<sup>3</sup></li> <li>• if CD4 cell count &lt;200 cells/mm<sup>3</sup></li> </ul> Individuals already received pneumococcal vaccine Revaccination: Age >18 years and $\geq 5$ years since initial or previous PPV23 dose	PCV13 0.5 mL IM $\times$ 1 PPV23 0.5 mL IM at minimum 8 weeks after PCV13 vaccine PPV23 offered at minimum 8 weeks after receiving PCV13 or until CD4 count > 200 cells/mm <sup>3</sup> PCV13 0.5 mL IM $\times$ 1 dose given at minimum 1 year after PPV23 administration PPV23 0.5 mL IM $\times$ 1
HBV	All susceptible (anti-HBc-negative) patients	Hepatitis B vaccine 3 doses
Influenza virus	All patients (annually before influenza season)	Inactivated trivalent influenza virus vaccine 0.5 mL/year IM
HAV	All susceptible (anti-HAV-negative) patient at increased risk for HAV or patients with chronic liver disease (including HBV or HCV)	Hepatitis A vaccine; 2 doses

DS, double strength; HAART, highly active antiretroviral therapy; HAV, hepatitis A virus; HBc, hepatitis B core; HBV, hepatitis B virus; INH, isoniazid; MAC, *Mycobacterium avium* complex; PO, orally; RIF, rifampin; SC, subcutaneously; SS, single strength; TMP-SMX, trimethoprim-sulfamethoxazole; TST, tuberculin skin test.

Source: Panel on Opportunistic Infections in HIV-Infected Adults and Adolescents. Guidelines for the prevention and treatment of opportunistic infections in HIV-infected adults and adolescents: recommendations from the Centers for Disease Control and Prevention, the National Institutes of Health, and the HIV Medicine Association of the Infectious Diseases Society of America. Available at [http://aidsinfo.nih.gov/contentfiles/lvguidelines/adult\\_oi.pdf](http://aidsinfo.nih.gov/contentfiles/lvguidelines/adult_oi.pdf). Accessed July 22, 2014.

TABLE 74.3 Treatment of *P. jiroveci* Pneumonia

Regimen	Duration	Adverse Effects/Comments
TMP-SMX 15–20 mg/kg TMP (75–100 mg/kg SMX) daily administered IV or PO every 6–8 hours or 2 DS tabs TID (drug of choice)	21 days	Hypersensitivity, hyperkalemia, rash, fever, neutropenia $\uparrow$ LFTs, nephrotoxicity (15 mg/kg/day preferred to 20 mg/kg/day because of reduced toxicity)

Continued on following page

**TABLE 74.3 Treatment of *P. jiroveci* Pneumonia (Continued)**

Regimen	Duration	Adverse Effects/Comments
<b>ALTERNATIVE AGENTS</b>		
Pentamidine 4 mg/kg IV daily for 60–90 minutes Atovaquone 750 mg PO twice daily with meals (suspension) TMP <sup>b</sup> PO 15 mg/kg/day + dapsone 100 mg PO daily	21 days	Pancreatitis, hypotension, hypoglycemia, hyperglycemia, nephrotoxicity Headache, nausea, diarrhea, rash, fever, ↑LFTs TMP: Pruritus, GI intolerance, bone marrow suppression Dapsone: Methemoglobinemia, hemolytic anemia (contraindicated in G6PD deficiency)
Clindamycin 600 mg IV every 8 hours or 300–450 mg PO every 6 hours + primaquine 15–30 mg (base) PO daily		Clindamycin: Rash, diarrhea Primaquine: Methemoglobinemia, hemolytic anemia (contraindicated in G6PD deficiency)
Adjunctive Therapy for PaO <sub>2</sub> < 70 mm Hg or A-a gradient >35 mm Hg; Should begin as soon as possible and within 72 hours of therapy for PCP		
<sup>a</sup> Prednisone	Oral steroid taper: 40 mg every twice daily × 5 days, then 40 mg daily × 5 days, then 20 mg/day × 11 days	

A-a, alveolar-arterial gradient; BID, twice a day; CNS, central nervous system; DS, double strength; GI, gastrointestinal; G6PD, glucose-6 phosphate dehydrogenase; IV, intravenous; PCP, *P. jiroveci* pneumonia; PO, oral; PaO<sub>2</sub>, arterial partial pressure of oxygen; LFTs, liver function tests; TMP-SMX, trimethoprim-sulfamethoxazole.  
 Source: Panel on Opportunistic Infections in HIV-Infected Adults and Adolescents. Guidelines for the prevention and treatment of opportunistic infections in HIV-infected adults and adolescents: recommendations from the Centers for Disease Control and Prevention, the National Institutes of Health, and the HIV Medicine Association of the Infectious Diseases Society of America. Available at [http://aidsinfo.nih.gov/contentfiles/lvguidelines/adult\\_oi.pdf](http://aidsinfo.nih.gov/contentfiles/lvguidelines/adult_oi.pdf). Accessed July 22, 2014.

**TABLE 74.4 Pharmacologic Treatment of Cryptococcal infection**

Preferred Agent/Regimen	Induction (2 weeks)	Consolidation (8 weeks)	Chronic Maintenance
Alternative Regimens	<ul style="list-style-type: none"> <li>Liposomal amphotericin B 3–4 mg/kg IV daily</li> </ul> PLUS <ul style="list-style-type: none"> <li><sup>a</sup>Flucytosine 25 mg/kg PO four times daily</li> </ul>	<ul style="list-style-type: none"> <li>Fluconazole 400 mg PO/IV daily</li> </ul>	<ul style="list-style-type: none"> <li>Fluconazole 200 mg PO daily for at least 12 months</li> </ul>
	<ul style="list-style-type: none"> <li>Amphotericin B deoxycholate 0.7 mg/kg IV daily or amphotericin B lipid complex 5 mg/kg IV daily</li> </ul> PLUS <ul style="list-style-type: none"> <li>Flucytosine 25 mg/kg PO four times daily</li> <li>Liposomal Amphotericin B 3–4 mg/kg IV daily or Amphotericin B deoxycholate 0.7 mg/kg IV daily</li> </ul> PLUS <ul style="list-style-type: none"> <li>Fluconazole 800 mg IV/PO daily</li> <li>Fluconazole 800 mg IV/PO daily + flucytosine 25 mg/kg four times daily</li> <li>Fluconazole 1,200 mg IV/PO daily</li> </ul>	<ul style="list-style-type: none"> <li>Itraconazole 200 mg PO twice daily (less effective than fluconazole)</li> </ul>	No alternative recommended

<sup>a</sup>Flucytosine dose may need to be adjusted for renal dysfunction or cytopenia.  
 Source: Panel on Opportunistic Infections in HIV-Infected Adults and Adolescents. Guidelines for the prevention and treatment of opportunistic infections in HIV-infected adults and adolescents: recommendations from the Centers for Disease Control and Prevention, the National Institutes of Health, and the HIV Medicine Association of the Infectious Diseases Society of America. Available at [http://aidsinfo.nih.gov/contentfiles/lvguidelines/adult\\_oi.pdf](http://aidsinfo.nih.gov/contentfiles/lvguidelines/adult_oi.pdf). Accessed July 22, 2014.

**TABLE 74.5 Treatment of *M. avium* Complex Infection**

Agents	Duration	Toxicities
<b>INITIAL THERAPY AGENTS (SUSCEPTIBILITY TESTING MAY BE REQUIRED)</b>		
Clarithromycin 500 mg PO twice daily Or Azithromycin 500–600 mg PO daily <i>Plus</i> Ethambutol 15 mg/kg/day PO	Treatment continued for at least 12 months and until asymptomatic and CD4 count >100 cells/mm <sup>3</sup> for >6 months	Clarithromycin: nausea, vomiting, diarrhea, abdominal pain, serum transferase elevations, bitter taste; drug interactions Azithromycin: nausea, vomiting, diarrhea, abdominal pain, serum transferase elevations Ethambutol optic neuritis, <sup>a</sup> nausea, and vomiting
<b>SECONDARY AGENTS (ADDITION OF THIRD OR FOURTH AGENTS DEPENDENT ON DISEASE SEVERITY AND IMMUNOSUPPRESSION)</b>		
Rifabutin <sup>b</sup> 300 mg PO daily		Rifabutin: nausea, vomiting, diarrhea, serum transferase elevations, hepatitis, neutropenia, thrombocytopenia, rash, orange discoloration of body fluids, uveitis; drug–drug interactions
Ciprofloxacin 500–750 mg PO twice daily or Moxifloxacin 400 mg PO daily or Levofloxacin 500 mg PO daily		Nausea, vomiting, diarrhea, abdominal pain, headache, rare insomnia, hallucinations, seizures
Amikacin 10–15 mg/kg/day IV		Nephrotoxicity, ototoxicity

<sup>a</sup>Visual testing should be done monthly in patients receiving >15 mg/kg/day.

<sup>b</sup>Rifabutin dose may need to be adjusted depending on concomitant agents/drug–drug interactions.

Source: Panel on Opportunistic Infections in HIV-Infected Adults and Adolescents. Guidelines for the prevention and treatment of opportunistic infections in HIV-infected adults and adolescents: recommendations from the Centers for Disease Control and Prevention, the National Institutes of Health, and the HIV Medicine Association of the Infectious Diseases Society of America. Available at [http://aidsinfo.nih.gov/contentfiles/lvguidelines/adult\\_oi.pdf](http://aidsinfo.nih.gov/contentfiles/lvguidelines/adult_oi.pdf). Accessed July 22, 2014.

**TABLE 74.6 Treatment of Mucocutaneous Candidal Infections**

	Preferred	Alternative (Select One of the Following Agents)	Considerations
Oral candidiasis <i>Duration</i> 7–14 days	<ul style="list-style-type: none"> <li>Fluconazole 100 mg PO daily or</li> <li>Clotrimazole troches 10 mg PO five times daily or</li> <li>Miconazole mucoadhesive buccal 50 mg tablets daily applied topically to mucosal surface of canine fossa</li> </ul> Duration: 7–14 days	<ul style="list-style-type: none"> <li>Itraconazole oral solution 200 mg PO daily</li> <li>Posaconazole oral solution 400 mg PO twice daily × 1 day, then 400 mg daily</li> <li>Nystatin suspension 4–6 mL four times daily</li> </ul>	<ul style="list-style-type: none"> <li>Suppressive therapy not generally recommended; only in frequent for severe recurrences</li> <li>Azole resistance has been noted</li> </ul>
Esophageal candidiasis <i>Duration:</i> 14–21 days	<ul style="list-style-type: none"> <li>Fluconazole 100–400 mg IV/PO daily or</li> <li>Itraconazole oral solution 200 mg PO daily</li> </ul>	<ul style="list-style-type: none"> <li>Voriconazole 200 mg IV/PO twice daily</li> <li>Posaconazole 400 mg PO twice daily</li> <li>Anidulafungin 100 mg IV × 1, then 50 mg IV daily</li> <li>Caspofungin 50 mg IV daily</li> <li>Micafungin 150 mg IV daily</li> <li>Amphotericin B deoxycholate 0.6 mg/kg IV daily</li> <li>Lipid formulation of amphotericin B 3–4 mg/kg IV daily</li> </ul>	

Source: Panel on Opportunistic Infections in HIV-Infected Adults and Adolescents. Guidelines for the prevention and treatment of opportunistic infections in HIV-infected adults and adolescents: recommendations from the Centers for Disease Control and Prevention, the National Institutes of Health, and the HIV Medicine Association of the Infectious Diseases Society of America. Available at [http://aidsinfo.nih.gov/contentfiles/lvguidelines/adult\\_oi.pdf](http://aidsinfo.nih.gov/contentfiles/lvguidelines/adult_oi.pdf). Accessed July 22, 2014.

TABLE 74.7 Treatment of Cytomegalovirus Retinitis

Preferred Agent/Regimen	Induction	Chronic Maintenance	Notes
	<ul style="list-style-type: none"> <li>Valganciclovir 900 mg PO twice daily for 14–21 days</li> </ul> PLUS (for immediate sight-threatening lesions only) <ul style="list-style-type: none"> <li>Ganciclovir 2 mg OR foscarnet 2.4 mg intravitreal injection by 1–4 doses over 7–10 days</li> </ul> Note: valganciclovir requires dose adjustment for renal impairment	<ul style="list-style-type: none"> <li>Valganciclovir 900 mg PO daily</li> </ul>	Considerations for treatment include location and severity of lesions, level of immunosuppression, concurrent medications and adherence Regular eye exams should follow discontinuation of maintenance therapy
Alternative Drug/Regimen	<ul style="list-style-type: none"> <li>Ganciclovir 5 mg/kg IV every 12 hours by 14–21 days or</li> <li>Foscarnet 90 mg/kg IV every 12 hours or 60 mg/kg every 8 hours for 14–21 days or</li> <li>Cidofovir 5 mg/kg/week IV for 2 weeks with pre- and posttherapy saline hydration plus probenecid 2 gm PO 3 hours prior to dose and 1 gm PO 2 and 8 hours after dose (total 4 gm)</li> </ul>	<ul style="list-style-type: none"> <li>Ganciclovir 5 mg/kg IV 5–7 times weekly or</li> <li>Foscarnet 90–120 mg/kg IV daily or</li> <li>Cidofovir 5 mg/kg IV every other week with saline hydration and probenecid (as with induction)</li> </ul>	<ul style="list-style-type: none"> <li>Ganciclovir, foscarnet and cidofovir require dose adjustment for renal impairment</li> </ul>

Source: Panel on Opportunistic Infections in HIV-Infected Adults and Adolescents. Guidelines for the prevention and treatment of opportunistic infections in HIV-infected adults and adolescents: recommendations from the Centers for Disease Control and Prevention, the National Institutes of Health, and the HIV Medicine Association of the Infectious Diseases Society of America. Available at [http://aidsinfo.nih.gov/contentfiles/lvguidelines/adult\\_oi.pdf](http://aidsinfo.nih.gov/contentfiles/lvguidelines/adult_oi.pdf). Accessed July 22, 2014.

TABLE 74.8 Tuberculosis Treatment Recommendations for Patients Coinfected with HIV and Isoniazid Susceptible *M. tuberculosis*

Induction	Maintenance	Comments
INH/RIF <sup>a</sup> (OR RFB <sup>b</sup> )/PZA/EMB (or SM) 5–7 times per week × 2 months	INH/RIF <sup>a</sup> (or RFB <sup>b</sup> ) 5–7 times per week (duration dependent on location of TB)	RIF-containing regimens used with caution with protease inhibitors and NNRTIs

<sup>a</sup>Concurrent use of rifampin and HIV protease inhibitors and certain NNRTIs not recommended.

<sup>b</sup>Dose adjustment may be required for rifabutin and/or HIV PIs and NNRTIs if used concurrently.

EMB, ethambutol; INH, isoniazid; NNRTI, nonnucleoside reverse transcriptase inhibitor; PI, protease inhibitor; PZA, pyrazinamide; RFB, rifabutin; RIF, rifampin; SM, streptomycin.

Source: Panel on Opportunistic Infections in HIV-Infected Adults and Adolescents. Guidelines for the prevention and treatment of opportunistic infections in HIV-infected adults and adolescents: recommendations from the Centers for Disease Control and Prevention, the National Institutes of Health, and the HIV Medicine Association of the Infectious Diseases Society of America. Available at [http://aidsinfo.nih.gov/contentfiles/lvguidelines/adult\\_oi.pdf](http://aidsinfo.nih.gov/contentfiles/lvguidelines/adult_oi.pdf). Accessed July 22, 2014.

TABLE 74.9 Treatment Summaries for Other Opportunistic Infections

Enteric Infections	Treatment
<b>FUNGAL</b>	
<i>Histoplasmosis</i>	Moderate-severe: liposomal amphotericin 3 mg/kg daily for 2 weeks or clinical improvement, then itraconazole 200 mg TID × 3 days, then BID at least 12 months Less severe: Itraconazole 200 mg PO TID × 3 days, then 200 mg PO BID × at least 12 months (liquid formulation has better absorption, limited data available on IV)
<b>VIRAL</b>	
CMV	Esophagitis or colitis: Ganciclovir 5 mg/kg IV every 12 hours for 21–42 days (may switch to oral valganciclovir 900 mg PO twice daily if tolerating oral agents)
HSV <sup>a</sup>	Severe mucocutaneous: Valacyclovir 1 g PO BID; acyclovir 400 mg or acyclovir 5 mg/kg IV every 8 hours × 5–14 days (switch to oral therapy when tolerating); treat until lesions have completely healed. May require chronic suppressive therapy
<b>BACTERIAL</b>	
<i>Salmonella</i> spp.	Ciprofloxacin 500–750 mg PO/IV BID 7 days to 6 weeks (depending on CD4 <sup>+</sup> count) or TMP-SMX 5–10 mg/kg/day PO/IV BID × 2–4 weeks; levofloxacin 750 mg daily × 2–4 weeks; or third-generation cephalosporin treatment may be extended to 4–6 weeks
<i>Shigella</i> spp.	Ciprofloxacin 500 mg PO/IV BID × 3–14 days; TMP-SMX 1 DS PO BID × 3–7 days; azithromycin 500 mg × 1 day, then 250 mg daily × 4 days; antiperistaltic agents (atropine/diphenoxylate or loperamide) are contraindicated
<i>Campylobacter jejuni</i>	Ciprofloxacin 500 mg PO BID × 7 days or azithromycin 500 mg daily × 7 days
<i>Clostridium difficile</i>	Metronidazole 250–500 mg PO QID × 10–14 days or vancomycin 125 mg PO QID 10–14 days; antiperistaltic agents (atropine/diphenoxylate or loperamide) are contraindicated
<b>PROTOZOA</b>	
<i>Isospora</i>	TMP-SMX 1 DS QID or 2 DS BID Alternative: pyrimethamine 50–75 mg with leucovorin 5–10 mg or fluoroquinolone
<i>Cyclospora</i>	TMP-SMX 1 DS BID
<i>Microsporidia</i>	Albendazole 400 PO BID until CD4 <sup>+</sup> >200 Alternative: itraconazole, nitazoxanide
<i>Cryptosporidia</i>	No effective treatment; paromomycin, nitazoxanide, octreotide, azithromycin (marginal benefits and no cure); best treatment approach is antiretroviral therapy to increase CD4 <sup>+</sup> >100

<sup>a</sup>Primarily esophagitis

BID, twice a day; DS, double strength; HSV, herpes simplex virus; IV, intravenously; PO, orally; QID, four times a day; TID, three times a day; TMP-SMX, trimethoprim-sulfamethoxazole.

Source: Jacobson MA et al. Retinal and gastrointestinal disease due to cytomegalovirus in patients with the acquired immune deficiency syndrome: prevalence, natural history, and response to ganciclovir therapy. *QJM*. 1988;67:473; Vakili NB et al. Biliary cryptosporidiosis in HIV-infected people after the waterborne outbreak of cryptosporidiosis in Milwaukee. *N Engl J Med*. 1996;334:19; Panel on Opportunistic Infections in HIV-Infected Adults and Adolescents. Guidelines for the prevention and treatment of opportunistic infections in HIV-infected adults and adolescents: recommendations from the Centers for Disease Control and Prevention, the National Institutes of Health, and the HIV Medicine Association of the Infectious Diseases Society of America. Available at [http://aidsinfo.nih.gov/contentfiles/lvguidelines/adult\\_oi.pdf](http://aidsinfo.nih.gov/contentfiles/lvguidelines/adult_oi.pdf). Accessed July 22, 2014.

# Fungal Infections\*

## General Principles

- A morphological classification of fungi is shown in Table 75.1.
- Fungal infections are best classified by the area of the body infected (Table 75.2).

## Risk Factors

- The most common risk factors for acquiring mycotic infections include immunocompromised host, use of broad-spectrum antibacterials, and breakdown of physical barriers (including invasive catheterization).

## Treatment

- Selection of antifungal therapy should be based on the extent and type of infection.
- Patients at high risk for mycotic infection may benefit from prophylactic regimens (Table 75.3).
- Empiric antifungal therapy (amphotericin B) in a neutropenic host should be initiated when a patient is febrile for more than 96 hours on appropriate anti-infectives.

## Drug Therapy

- Many FDA-approved topical and systemic antimycotic agents for the treatment of fungal infections exist (Table 75.4). Amphotericin is available in several different formulations (Table 75.5).

TABLE 75.1 Organism Classification

### HYPHAE (MOLDS)

#### Hyalohyphomycoses

*Aspergillus* species, *Pseudallescheria boydii*

*Dermatophytes*: *Epidermophyton floccosum*, *Trichophyton* species, *Microsporum* species

#### Phaeohyphomycoses

*Alternaria* species, *Anthopsis deltoidea*, *Bipolaris hawaiiensis*, *Cladosporium* species, *Curvularia geniculata*, *Exophiala* species, *Fonsecaea pedrosoi*, *Phialophora* species, *Fusarium* species

#### Zygomycetes

*Absidia corymbifera*, *Mucor indicus*, *Rhizomucor pusillus*

### DIMORPHIC FUNGI

*Blastomyces* species, *Coccidioides* species, *Paracoccidioides* species, *Histoplasma* species, *Sporothrix* species

### YEASTS

*Candida* species, *Cryptococcus neoformans*

\*The reader is referred to Chapter 75, Fungal Infections, written by John D. Cleary, PharmD, Stanley W. Chapman, PharmD, MD, and Margaret M. Pearson, PharmD, MS, in the 10th edition of *Applied Therapeutics: The Clinical Use of Drugs* for a more in-depth discussion. All notations to reference numbers are based on the reference list at the end of that chapter. The editor of this handbook expresses her thanks to Drs. Cleary, Chapman, and Pearson and acknowledges that this chapter is based on their work.

TABLE 75.2 Clinical Classification of Mycoses

Classification	Site Infected	Example	Potential Gene Deficiency
Superficial	Outermost skin and hair	Malasseziasis (tinea versicolor)	
Cutaneous	Deep epidermis and nails	Dermatophytosis	
Subcutaneous	Dermis and subcutaneous tissue	Sporotrichosis	
Systemic	Disease of more than one internal organ		
Opportunistic		Candidiasis Cryptococcosis Aspergillosis Mucormycosis	Mannose Binding Lectin-1 Dectin-1
Nonopportunistic		Histoplasmosis Blastomycosis Coccidioidomycosis	Interferon- $\gamma$ receptor 1 Dectin-1 Mannose binding lectin-1

TABLE 75.3 Antimycotic Prophylaxis Regimens and Approximate Costs

Agent	Dose/Day	Formulation	Recommended Regimen	Cost (\$)/Day <sup>a</sup>
<b>SELECTIVE GI DECONTAMINATION</b>				
Amphotericin B	400 mg	Oral suspension	Swish and swallow QID	9.75
Nystatin	4–12 million units	Oral suspension	Swish and swallow QID	38.50–115.25
<b>SYSTEMIC</b>				
Clotrimazole	30–80 mg	Trouche	TID–QID	125–450
Ketoconazole	200–400 mg	Oral	Daily	0.75–1.50
Itraconazole	200–400 mg	Oral	Daily	18–36.25
Fluconazole	50–400 mg	Oral	Daily	4.50–35.25

<sup>a</sup>Average wholesale price, on average.

Source: Red Book. Montvale, NJ: PDR Network, LLC; 2011.

GI, gastrointestinal; QID, four times daily; TID, three times daily.

TABLE 75.4 Antifungal Agents Approved for Use

Agent (Brand Name)	Formulation
<b>SYSTEMIC AGENTS</b>	
Amphotericin B (Abelcet, AmBisome, Amphotec)	IV
Amphotericin B (generic)	IV
Anidulafungin (Eraxis)	IV
Caspofungin (Cancidas)	IV
Fluconazole (Diflucan)	IV, tablet, oral suspension
Fluorocytosine [Flucytosine] (Ancobon)	Capsule
Griseofulvin (generic)	Tablet, oral suspension
Itraconazole (Sporanox)	IV, capsule, oral solution
Ketoconazole (Nizoral)	Tablet
Micafungin (Mycamine)	IV
Posaconazole (Noxafil)	Oral suspension
Potassium iodide	Solution
Terbinafine (Lamisil)	Tablet, oral granules
Voriconazole (Vfend)	IV, tablet, oral suspension

Continued on following page



TABLE 75.4 Antifungal Agents Approved for Use (Continued)

Agent (Brand Name)	Formulation
<b>TOPICALS, CLASS I</b>	
Amphotericin B	Cream, lotion, ointment, oral suspension <sup>d</sup>
Butenafine	Cream
Butoconazole	Vaginal cream
Ciclopirox	Cream, gel, lotion, shampoo, solution, suspension
Clioquinol	Cream, ointment
Clotrimazole	Cream, lotion, lozenge, solution, tablet, vaginal cream
Econazole	Cream
Ketoconazole	Cream, foam, gel, shampoo
Miconazole	Aerosol liquid and powder, buccal tablet, cream, lotion, ointment, powder, suppository, vaginal tablet
Naftifine	Cream, gel
Nystatin	Cream, mouthwash, ointment, powder, suspension, tablet
Oxiconazole	Cream, lotion
Povidone iodine	Aerosol, douche, gel, ointment, solution, suppository
Sodium thiosulfate	Lotion
Sulconazole	Cream, solution
Terbinafine	Cream, spray
Terconazole	Cream, suppository
Tioconazole	Ointment
Tolnaftate	Aerosol, cream, gel, powder, solution
Undecylenic acid	Powder

<sup>d</sup>No longer available in United States.  
IV, intravenous.

- Conventional amphotericin is associated with significant infusion-related reactions, nephrotoxicity, and electrolyte abnormalities. Other agents (e.g., triazoles, echinocandins, and lipid-based amphotericin) are drugs of choice for deep-seated fungal infections.
- Pharmacokinetic properties of systemically administered agents are shown in Table 75.6.
- Significant drug interactions may occur with antifungal agents (Table 75.7).

## Treatment of Specific Fungal Infections

- Superficial and cutaneous mycoses
  - Infections should initially be treated topically. Any follicular, nail, or widespread infection should be treated systemically.
  - Onychomycosis (tinea unguium) can be treated with terbinafine (250 mg/day) or itraconazole (200 mg/day) for 6 (fingernails) to 12 (toenails) weeks.
- Subcutaneous mycoses
  - Sporotrichosis causes lymphocutaneous disease. Itraconazole is the drug of choice.
- Systemic mycoses
  - *Candida* species are the most common pathogens. Characteristics of systemic disease are subtle (fever, chills, hypotension). Prompt treatment is essential as delaying therapy increases mortality. Treatment options should be individualized and based on competence of the host defenses. Patients who cannot receive an echinocandin or azole can be treated with amphotericin B (regular or lipid formulation). Treatment duration is based on severity of infection and immunocompetence of the patient.
  - *Histoplasmosis*: Treatment guidelines are shown in Table 75.8.
  - *Aspergillosis*: Treatment options are shown in Table 75.9.

TABLE 75.5 Amphotericin B Formulations

Category	Amphotericin B (Fungizone)	Amphotericin B Lipid Complex (Abelcet)	Amphotericin B Colloidal Dispersion (Amphotec)	Liposomal Amphotericin B (AmBisome)	Amphotericin B in Lipid Emulsion	
<b>FORMULATION</b>						
Sterol	None	None	Cholesterol sulfate	Cholesterol sulfate (5) <sup>a</sup>	Safflower and soybean oils	
Phospholipid	None	DMPC and DMPG (7:3) <sup>a</sup>	None	EPC and DSPG (10:4) <sup>a</sup>	10–20 g/100 mL EPC >2.21 g/100 mL Glycerin >258 g/100 mL	
Amphotericin B (Mole %)	34	33	50	10	Variable	
Particle size (nm)	<10	1,600–11,000	122 (± 48)	80–120	333–500	
Stability	1 week at 2–8 °C or 24 hours at 27 °C	15 hours at 2–8 °C or 6 hours at 27 °C	24 hours at 2–8 °C	24 hours at 2–8 °C	Unstable	
Dosage and rate	0.3–0.7 mg/kg/day during 1–6 hours <sup>b</sup>	5 mg/kg/day at 2.5 mg/kg/hours	3–4 mg/kg/day during 2 hours	3–5 mg/kg/day during 2 hours	Investigational: 1 mg/kg/day during 1–8 hours	
Lethal dose 50%	3.3 mg/kg	10–25 mg/kg	68 mg/kg	175 mg/kg	Unknown	
<b>PHARMACOKINETIC PARAMETERS</b>						
Dose	0.5 mg/kg	5 mg/kg × 7 days	5 mg/kg × 7 days	2.5 mg/kg × 7 days	5 mg/kg × 7 days	0.8 mg/kg/day × 13 days
<b>SERUM CONCENTRATIONS</b>						
Peak	1.2 mcg/mL	1.7 mcg/mL	3.1 mcg/mL	31.4 mcg/mL	83.0 mcg/mL	2.13 mcg/mL
Trough	0.5 mcg/mL	0.7 mcg/mL		4.0 mcg/mL		0.42 mcg/mL
Half-life	91.1 hours	173.4 hours	28.5 hours	6.3 hours	6.8 hours	7.75 hours
Volume of distribution	5.0 L/kg	131.0 L/kg	4.3 L/kg	0.16 L/kg	0.10 L/kg	0.45 L/kg
Clearance	38.0 mL/hour/kg	436.0 mL/hour/kg	0.117 mL/hour/kg	22.0 mL/hour/kg	11.0 mL/hour/kg	37.0 mL/hour/kg
AUC	14 mcg/mL·hour	17 mcg/mL·hour	43.0 mcg/mL·hour	197 mcg/mL·hour	555 mcg/mL·hour	26.37 mcg/mL·hour

<sup>a</sup>Molar ratio of each component, respectively.

<sup>b</sup>No benefit for longer infusions.

<sup>c</sup>Doses >10 mg/kg have no benefit.

AmB, amphotericin B; AUC, area under the curve; DMPC, dimyristoyl phosphatidylcholine; DMPG, dimyristoyl phosphatidylglycerol; DSPG, distearoylphosphatidylglycerol; EPC, egg phosphatidylcholine; FDA, US Food and Drug Administration; FUO, fever of unknown origin; NA, not applicable.

TABLE 75.6 Pharmacokinetic Properties of Systemically Active Antifungals

Characteristic	Imidazoles			Triazoles				Echinocandins			Other	
	MCZ <sup>a</sup>	KCZ <sup>a</sup>	ITZ <sup>a</sup>	FCZ <sup>a</sup>	PCZ <sup>a</sup>	RCZ <sup>a</sup>	VCZ <sup>a</sup>	AFG <sup>a</sup>	CFG <sup>a</sup>	MFG <sup>a</sup>	5FC <sup>a</sup>	TBF <sup>a</sup>
<b>ABSORPTION</b>												
Relative bioavailability	<10	75 <sup>b</sup>	99.8 (40) <sup>b</sup>	(85–92) <sup>b</sup>		ND	>90 <sup>d</sup>	<10	<10	<10	75–90 <sup>b</sup>	70
C <sub>max</sub> (mcg/mL)	1.9	3.29	0.63	1.4	0.851	0.76	2.3–4.7 <sup>d</sup>	7.5	12	7.1	70–80	1.34–1.7
T <sub>max</sub> (hours)	1.0	2.6	4.0	1.0–4.0	3	ND	<2	1	1	1	<2	1.5
AUC <sup>c</sup> (mcg/hour/mL)	ND	12.9 (13.6)	1.9 (0.7)	42	8.619	13.84–119.12	9–11 (13) <sup>d</sup>	104.5	97.63–100.5	59.9	ND	4.74–10.48
<b>DISTRIBUTION</b>												
Protein binding (%)	91–93	99	99.8	11	ND	95	58	80	96.5	99.5	2–4	>99
CSF or serum concentration (%)	<10	<10	<10	60	ND	ND	~50	ND	ND	ND	60	<10
<b>EXCRETION</b>												
$\beta$ t <sub>1/2</sub> (hours)	2.1	8.1 <sup>d</sup>	17 <sup>d</sup>	23–45	11.9	157	6	25.6	10	13	2.5–6.0	36
Active drug in urine (%)	1	2	<10	60–80	13	ND	<2	<1	2	1	0	80

<sup>a</sup>Given parameters are estimated from the administration of currently recommended doses. Miconazole (MCZ) 7.4 to 14.2 mg/kg/day (500–1,000 mg) parenterally; ketoconazole (KTZ) 2.8 mg/kg/day orally (200 mg); itraconazole (ITZ) 1.4 to 2.8 mg/kg/day orally (100–200 mg); fluconazole (FCZ) 0.7 to 1.4 mg/kg/day orally; voriconazole (VCZ) and posaconazole (PCZ) 400 mg twice daily orally; ravuconazole (RCZ) 400 mg/day orally; anidulofungin (AFG) 200 mg parenterally; caspofungin (CFG) 70 (50) mg parenterally on day 1 (2–14); micafungin (MFG) 70 mg parenterally; flucytosine (5FC) 150 mg/day parenterally; and terbinafine (TBF) 250 mg/day orally.

<sup>b</sup>With meals (fasting), absorption altered by gastric acidity.

<sup>c</sup>Dose-dependent and/or infusion-dependent.

<sup>d</sup>Absorption decreased when administered with high-fat meal; C<sub>max</sub> and AUC reduced by 34% and 24%, respectively.

AUC, area under the concentration–time curve; C<sub>max</sub>, maximum concentration; CSF, cerebrospinal fluid; ND, no data; T<sub>max</sub>, time of maximum concentration; t<sub>1/2</sub>, half-life.

TABLE 75.7 Significant Drug Interactions

Antifungal	Interacting Agent(s)	Class <sup>a</sup>	Onset	Manifestation
AmB	Acetazolamide	2	R	Severe hyperchloremic acidosis secondary to additive or synergistic renal effects
	<b>Chemotherapeutic agents</b>			
	Doxorubicin, carmustine, cyclophosphamide, fluorouracil	2	D	Enhanced chemotherapeutic effect secondary to ↑ cellular uptake
	Cyclosporine	2	D	Enhanced nephrotoxicity
	Digoxin	2	D	AmB-induced hypokalemia leading to ↑ digoxin toxicity
	Leukocyte transfusion	1	R	Severe pulmonary leukostasis with potential for respiratory failure
	NSAID	2	R	Additive or synergistic nephrotoxicity
	Pentamidine	2	D	Additive or synergistic nephrotoxicity
	Potassium-sparing diuretics	2	D	Spironolactone ↓ potassium requirements preventing hypokalemia in neutropenic patients receiving AmB
	AFG, CFG	Cyclosporine	2	D
CFG	<b>CYP450 inducers</b>			
	Carbamazepine, phenytoin, mephenytoin, dexamethasone, efavirenz, nevirapine	3	D	↓ CFG concentrations through CYP450 induction; use of 70 mg of CFG should be considered
CFG	Rifampin	3	D	Hepatic uptake transporters of CFG might be induced by rifampin; administer CFG 70 mg/day when coadministered with rifampin
CFG	Tacrolimus	2	D	Tacrolimus peak blood concentrations ↓ by 20%; monitor tacrolimus whole blood trough concentrations and adjust dose as warranted
MFG	Nifedipine	3	D	Nifedipine serum concentrations ↑; monitor for adverse effects
MFG	Sirolimus	2	D	Sirolimus serum concentrations ↑; monitor for toxicity and reduce dose as warranted
Griseofulvin	<b>Sedative/Hypnotics</b>			
	Benzodiazepines, ethanol, barbiturates	3	D	↑ Griseofulvin clearance with concomitant barbiturate or ethanol consumption
KI	Oral contraceptives	1	D	↓ Oral contraceptive efficacy
	ACE inhibitors	2	D	Hyperkalemia
	Lithium	2	D	Hypothyroidism
	Potassium-sparing diuretics	2	D	Hyperkalemia
<b>Azole Antifungal Interactions</b>				
<b>Effect of other drugs on azole(s)</b>				
Azole	Interacting Agent(s)	Class	Onset	Manifestation
KCZ	Isoniazid	2	D	↓ Serum antifungal concentration and potential treatment failure
KCZ	Anticholinergics	2	R	↓ Antifungal absorption; antifungal should not be administered concomitantly.
KCZ	Sucralfate	2	R	20% ↓ in KCZ concentration
KCZ, ITZ	Didanosine	2	R	Acid neutralizing agents in didanosine prevent ITZ absorption; KCZ extrapolated
ITZ	Dexamethasone	2	D	Dexamethasone hepatically induces metabolism of ITZ.
ITZ	Fluoxetine	3	D	Norfluoxetine inhibits CYP3A4, ↑ ITZ concentrations

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TABLE 75.7 Significant Drug Interactions (Continued)

Azole	Interacting Agent(s)	Class	Onset	Manifestation
ITZ	Micafungin	3	D	ITZ AUC and $C_{max}$ ↑ by 22% and 11%; monitor for ITZ toxicity and reduce dose as warranted
FCZ	Hydrochlorothiazide	2	D	Significant ↑ in FCZ concentrations; changes attributed to ↓ FCZ renal clearance
KCZ, ITZ, FCZ	Antacids	2	R	Poor dissolution of dosage form, therefore ↓ azole availability; administer KCZ and ITZ 2 hours after antacid dose; note drug formulations containing antacid buffers
KCZ, ITZ, FCZ	H <sub>2</sub> -blockers <sup>b</sup>	2	R	↓ Antifungal absorption; antifungal should not be administered with H <sub>2</sub> -blockers.
FCZ, PCZ, VCZ	Cimetidine	2	R	Alteration of gastric pH ↓ FCZ, and PCZ absorption; VCZ concentrations noted slightly ↑, possibly through nonspecific CYP450 inhibition by cimetidine
KCZ, ITZ, FCZ, VCZ	Carbamazepine	2	D	↓ ITZ serum concentrations and therapeutic failures have occurred; carbamazepine likely to significantly ↓ VCZ concentration via potent CYP450 induction; coadministration contraindicated
KCZ, ITZ, FCZ, VCZ	Rifampin	2	D	Rifampin-potent CYP450 inducer; significant ↓ in serum antifungal concentrations, potentially leading to treatment failure—doubling VCZ dose does not restore adequate antifungal exposure; coadministration contraindicated
PCZ	Esomeprazole	2	D	↓ PCZ concentrations; monitor for breakthrough fungal infections
PCZ	Metoclopramide	2	D	↓ PCZ concentrations; monitor for breakthrough fungal infections
VCZ	Barbiturates	3	D	Long-acting barbiturates likely to significantly ↓ VCZ concentrations; coadministration contraindicated
VCZ	St. John's wort	3	D	St. John's wort CYP450 and P-gp inducer; long-term use could lead to ↓ VCZ concentrations; concomitant use contraindicated
<b>Azole effects on other drugs</b>				
KCZ, ITZ	Corticosteroids	2	D	Twofold ↑ in serum methylprednisolone observed with concomitant KCZ; similar reaction with prednisone has been observed; ↑ systemic effects of inhaled budesonide after ITZ
ITZ	Fexofenadine	2	R	Significant ↑ fexofenadin AUC not related to dose of ITZ suggesting mechanism related to inhibition of gastrointestinal P-glycoprotein
KCZ, FCZ	Theobromines	2	R	Inhibition of theophylline absorption
FCZ	Oral contraceptives	1	D	↓ Oral contraceptive efficacy
KCZ, ITZ, FCZ, VCZ	Warfarin	1	D	↓ Warfarin protein binding and hydroxylation by liver (poor documentation) leading to ↑ in prothrombin time response; interaction with VCZ proposed via CYP2C9 inhibition
KTZ, FCZ, VCZ	Pimozide Quinidine	1	D	Azoles result in inhibition of metabolism of these drugs; ↑ plasma concentrations can lead to QT prolongation and rarely <i>torsade de pointes</i> ; coadministration of VCZ contraindicated; coadministration of FCZ and terfenadine contraindicated

TABLE 75.7 Significant Drug Interactions (Continued)

Azole	Interacting Agent(s)	Class	Onset	Manifestation
KCZ, ITZ, FCZ, PCZ, VCZ	<b>Immunologic agents</b> Cyclosporine, sirolimus, tacrolimus	2	D	Azole inhibition of CYP3A4 produce significant ↑ in serum immunosuppressant concentration and ↑ toxicity; monitor cyclosporine and tacrolimus whole blood trough concentrations frequently during and at discontinuation of antifungal therapy. Coadministration of PCZ or VCZ and sirolimus contraindicated; data extrapolated for sirolimus and ITZ
KCZ, ITZ, FCZ	Sulfonylureas	2	D	Significantly ↑ sulfonylurea concentrations; data extrapolated for VCZ
PCZ, VCZ, KCZ, ITZ, FCZ, PCZ, VCZ	Benzodiazepines	3	D	20% ↓ in clordiazepoxide clearance demonstrated with KCZ. Inhibition of CYP3A4 by azole significantly ↑ serum concentrations of benzodiazepines metabolized by this enzyme; monitor adverse effects frequently and consider dose reduction.
PCZ	Digoxin	1	D	↑ Plasma concentrations of digoxin; monitor digoxin plasma concentrations.
FCZ, VCZ	NSAIDs	3	D	VCZ ↑ serum concentrations of ibuprofen and diclofenac; FCZ ↓ flubiprofen clearance by 55%; mechanism is CYP2C9 inhibition by FCZ and VCZ
PCZ, VCZ	Calcium-channel blockers	3	D	↑ Plasma concentrations of calcium-channel blockers metabolized by CYP3A4
PCZ, VCZ	Statins	2	D	VCZ inhibits lovastatin metabolism in vitro (CYP3A4 inhibition). PCZ ↑ simvastatin concentration ~10-fold; coadministration contraindicated; PCZ data extrapolated to other HMG-CoA reductase inhibitors; monitor for rhabdomyolysis.
PCZ, VCZ	Vinca alkaloids	3	D	↑ Plasma concentrations of vinca alkaloids (CYP3A4 substrates) leading to neurotoxicity
PCZ, VCZ	Ergot alkaloids	1	D	Ergotism; coadministration of VCZ with ergot alkaloids contraindicated; data extrapolated to PCZ
VCZ	Methadone	2	D	R-methadone and S-methadone serum concentrations ↑ via VCZ inhibition of CYP2C9, CYP2C19, and CYP3A4; monitor for methadone toxicity (QT prolongation).
VCZ	Alfentanil, fentanyl, oxycodone	3	D	↑ Plasma concentration of opiates (CYP3A4 substrate); heterophoria and miosis noted with oxycodone; ↓ dose of opiates metabolized by CYP3A4 and monitor for respiratory and other opiate adverse effects
<b>Two-way interactions</b> KCZ, ITZ, FCZ, PCZ, VCZ	Phenytoin, mephenytoin	2	D	Phenytoin induction of UDP-G metabolism decreases PCZ concentrations; ↓ VCZ concentrations thought due to phenytoin as CYP2C9 substrate and CYP450 inducer; avoid concomitant phenytoin and PCZ use; ↑ VCZ maintenance dose

Continued on following page

TABLE 75.7 Significant Drug Interactions (Continued)

Azole	Interacting Agent(s)	Class	Onset	Manifestation
PCZ, VCZ	Rifabutin	2	D	Phenytoin serum concentrations ↑ after FCZ, PCZ, or VCZ administration; postulated mechanism via CYP3A4 inhibition; monitor plasma phenytoin concentrations ↓ PCZ concentrations via UDP-6 induction; ↓ VCZ concentrations via potent CYP450 induction ↑ Rifabutin concentrations due to inhibition of CYP3A4 by PCZ and VCZ may ↑ rifabutin adverse effects; avoid concomitant PCZ and rifabutin; coadministration with VCZ contraindicated
PCZ, VCZ	Ritonavir	2	D	Ritonavir-potent CYP450 inducer and both substrate for and inhibitor of CYP3A4; ritonavir plasma concentrations ↑ by PCZ and ↓ by VCZ in dose-dependent manner; VCZ serum concentrations ↓ by ritonavir in dose-dependent manner; VCZ coadministration with high-dose ritonavir contraindicated and should be avoided with low-dose ritonavir.
PCZ, VCZ	Efavirenz	1	D	Efavirenz is a CYP450 inducer, CYP3A4 substrate and inhibitor. Concomitant administration results in ↓ VCZ and ↑ efavirenz concentrations; if coadministered, ↑ VCZ dose and ↓ efavirenza dose; PCZ serum concentrations ↓ through UDP-6 induction of efavirenz; avoid concomitant PCZ and efavirenz; VCZ in vitro data for other non-nucleoside reverse transcriptase inhibitors; monitor for drug toxicity or antifungal failure.
VCZ	Omeprazole	2	R	↑ Omeprazole and VCZ concentrations via CYP2C19 inhibition; reduce omeprazole doses of ≥40 mg by one-half. Metabolism of other proton-pump inhibitors CYP2C19 substrates may also be inhibited by VCZ.
VCZ	Oral contraceptives	2	D	↑ Oral contraceptive and VCZ concentrations via CYP2C19 inhibition; monitor for oral contraceptive and VCZ adverse events.
VCZ	<b>HIV protease inhibitors</b> Saquinavir, amprenavir, nelfinavir	2	D	VCZ and protease inhibitors cause inhibition of CYP3A4 metabolism (in vitro); monitor patients for toxicity.

<sup>a</sup>Classification: 1, major; 2, moderate; 3, minor.

<sup>b</sup>Clinically significant interaction that the authors recommend the reader should focus upon.

ACE, angiotensin-converting enzyme; AFG, anidulofungin; AmB, amphotericin B; AUC, area under the curve; CFG, casopfungin; CYP, cytochrome P; D, delayed; FCZ, fluconazole; HIV, human immunodeficiency virus; ITZ, itraconazole; KCZ, ketoconazole; KI, potassium iodide; MFG, micofungin; NSAID, nonsteroidal anti-inflammatory drugs; PCZ, posaconazole; R, rapid; UDP-G, uridine diphosphate 6-deoxygalactose; VCZ, voriconazole.

TABLE 75.8 Treatment of Histoplasmosis

Disease	Primary	Secondary
<b>ACUTE PULMONARY</b>		
Prolonged symptomatology (>2 weeks)	Resolves spontaneously	N/A
Immunocompromised <sup>a</sup>	ITZ 50–100 mg/day (3–6 months) <sup>b</sup>	AmB 0.3–0.5 mg/kg/day <sup>b</sup>
Respiratory distress (Pao <sub>2</sub> <70 mm Hg)	AmB lipid formulation 3–5 mg/kg/day <sup>d</sup> AmB 0.5–1.0 mg/kg/day (TD 250–500 mg) ± corticosteroids (methylprednisolone 0.5–1 mg/kg) × 1–2 weeks	AmB 0.3–0.5 mg/kg/day ITZ 1.5–2.8 mg/kg/day (≥6 months) <sup>b</sup> ITZ (has not been investigated in life-threatening situations)
<b>CHRONIC PULMONARY</b>		
Active	ITZ (1.5–2.8 mg/kg/day 9 months) <sup>b,c</sup>	AmB 0.5 mg/kg/day <sup>c</sup>
Inactive		Or KTZ 400 mg/day (≈6 months)
Histoplasmosis	No treatment	N/A
Mediastinal fibrosis	Surgery <sup>d</sup>	N/A
<b>SYSTEMIC DISEASE</b>		
	AmB (TD recommended: 35 mg/kg) or lipid AmB then ITZ 2.8 mg/kg/day × up to 12 months <sup>b</sup>	Fluconazole 400–800 mg/day <sup>c</sup>

<sup>a</sup>Lipid formulations of amphotericin B are preferable to generic amphotericin B in HIV-infected patients.<sup>148</sup>

<sup>b</sup>Treatment should be continued until the patient is symptom-free and culture negative for 3 months. The recommendations for duration of therapy or total doses should be used only as guides for initial therapy based on the IDSA 2007 Guideline.<sup>147</sup>

<sup>c</sup>Indicated only for serious symptoms (i.e., hemoptysis).

<sup>d</sup>ITZ 200 mg daily or twice a day for 6 to 18 months for most patients.

<sup>e</sup>Fluconazole should only be used in patients who cannot take ITZ.

AmB, amphotericin B deoxycholate; ITZ, itraconazole; KTZ, ketoconazole; TD, total dose.

TABLE 75.9 Therapeutic Options for Treatment of Aspergillosis

Disease	Primary	Secondary
<b>HYALOPHYCOMYCETES</b>		
Aspergillosis		
Allergic bronchopulmonary	Prednisone 1 mg/kg/day followed by 0.5 mg/kg/day or every other day × 3–6 months; no antifungal therapy	ITZ 200 mg BID × 4 months <sup>a</sup>
Aspergilloma	Observation	Surgery <sup>b</sup>
Systemic (invasive) Serious	Voriconazole 6 mg/kg/day LD, 4 mg/kg/day divided twice daily	Amphotericin B lipid formulation, <sup>d</sup> or AmB 1.0–1.5 mg/kg/day <sup>c</sup>
Mild or moderate	Voriconazole 6 mg/kg/day LD, 4 mg/kg/day divided twice daily	Amphotericin B lipid formulation, <sup>d</sup> or AmB 0.5–0.6 mg/kg/day <sup>c</sup> Or ITZ 200 mg TID loading dose × 3 days, then 200 mg BID with meals (6 months, minimum)

<sup>a</sup>Treatment should be continued until the patient is symptom-free and culture negative for 3 months. Noted durations or total doses should be used only as a compass to help guide therapy.

<sup>b</sup>Indicated only for serious symptoms (e.g., hemoptysis).

<sup>c</sup>Lipid formulations of amphotericin B should be utilized preferentially in these patients.

<sup>d</sup>Liposomal amphotericin B at doses up to 15 mg/kg/day appear safe in phase I/II trials.<sup>184</sup>

AmB, amphotericin B; BID, twice daily; ITZ, itraconazole; LD, loading dose; TID, three times daily.



# Viral Infections\*

## General Principles

- An estimated 60% of illnesses in developed countries result from viruses, compared with only 15% from bacteria.

## Treatment

- Several antiviral agents are available. Treatment options for the various viral infections described below are shown in Table 76.1. The pharmacokinetic parameters of antiviral agents are shown in Table 76.2 and adverse effects are shown in Table 76.3.

## Herpes Simplex Virus (HSV) Infections

- Herpes infections are responsible for a wide spectrum of disease from life-threatening to chronic, recurrent infection.
- **Herpes encephalitis** is associated with significant morbidity and mortality. It typically occurs in patients 6 months to 20 years of age, or older than 50 years. Symptoms include fever, headache, disorientation, decreased consciousness, and seizures. Intravenous acyclovir for 21 days is the therapy of choice. Oral acyclovir is not appropriate due to its poor oral absorption.
- **Neonatal herpes** is typically acquired from infected genital secretions at the time of delivery. The drug of choice is IV acyclovir for a minimum of 14 days (longer if CNS involvement is present).
- **Oral-facial herpes (herpes labialis)** infections present with fever, malaise, myalgia, inability to eat, and irritability; infections can also be asymptomatic. Cold sores are the most common lesions. Antiviral therapy is indicated only when the patient has a primary infection, an underlying illness, or a compromised immune system that may lead to prolonged illness or dissemination. Topical agents must be applied within 1 hour of the first sign/symptom of a cold sore and then every 2 hours for 4 days while awake. Daily suppressive therapy (oral acyclovir 400 mg twice daily for 4 months) may be appropriate in patients with six or more recurrences per year or in patients with severe episodes.

## Varicella-Zoster Virus (VZV) Infection

- **Chickenpox** is highly contagious; vaccination is now considered routine in children. Adolescents and adults are more likely than children to develop complications (e.g., pneumonia, encephalitis). Acyclovir therapy should be considered in these patients.
- **Shingles** is caused by reactivation of dormant VZV in sensory neurons. Incidence increases with age. Symptoms include deep aching or burning pain, sensitivity to touch, and rash. Postherpetic neuralgia (PHN) is pain that occurs 1 month after onset of rash. Acyclovir should be started within 72 hours of rash onset. Options for PHN include capsaicin (cream, gel, or patch), topical lidocaine 5% patch, and oral gabapentin or pregabalin.

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\*The reader is referred to Chapter 76, Viral Infections, written by Milap C. Nahata, PharmD, MS, Neeta Bahal O'Mara, PharmD, BCPS, CCP, and Sandra Benavides, PharmD, in the 10th edition of *Applied Therapeutics: The Clinical Use of Drugs* for a more in-depth discussion. All notations to reference numbers are based on the reference list at the end of that chapter. The editor of this handbook expresses her thanks to Drs. Nahata, Bahal O'Mara, and Benavides and acknowledges that this chapter is based on their work.

**TABLE 76.1 US Food and Drug Administration (FDA)–Indicated Drugs for Various Viral Infections**

Disease	Drug	Dosage (Age Group)	Route	Duration
Herpes encephalitis	Acyclovir (Zovirax) <sup>d</sup>	>12 years: 10 mg/kg every 8 hours	IV	21 days
		3 months–12 years: 20 mg/kg every 8 hours	IV	21 days
Neonatal herpes	Acyclovir (Zovirax)	Birth–3 months: 10–20 mg/kg every 8 hours <sup>a</sup>	IV	14–21 days
Oral-facial herpes (for treatment of recurrent infection)	Acyclovir (Zovirax)	Adults: 400 mg 5×/day	PO	5 days
	Famciclovir (Famvir)	Adults: 1,500 mg	PO	1 dose
	Valacyclovir (Valtrex)	Adults: 2,000 mg BID	PO	1 day
Oral-facial herpes <sup>b</sup> (immunocompromised patients)	Acyclovir (Zovirax)	>12 years: 5 mg/kg every 8 hours	IV	7 days
	Acyclovir (Zovirax)	<12 years: 10 mg/kg every 8 hours	IV	7 days
	Famciclovir (Famvir)	Adults: 500 mg BID	PO	7 days
Herpes zoster <sup>b</sup> (immunocompetent patients)	Acyclovir (Zovirax)	Adults: 800 mg 5×/day	PO	7–10 days
	Acyclovir (Zovirax)	Adult: 500 mg every 8 hours	PO	7 days
	Famciclovir (Famvir)	Adult: 1,000 mg every 8 hours	PO	7 days
	Valacyclovir (Valtrex)			
Herpes zoster <sup>b</sup> (immunocompromised patients)	Acyclovir (Zovirax)	>12 years: 10 mg/kg every 8 hours	IV	7 days
		<12 years: 20 mg/kg every 8 hours	IV	7 days
Varicella (immunocompetent patient)	Acyclovir (Zovirax)	>40 kg: 800 mg QID	PO	5 days
		>2 years and <40 kg: 20 mg/kg (max. 800 mg) QID	PO	5–10 days
Varicella (immunocompromised patients)		>12 years: 10 mg/kg every 8 hours	IV	7–10 days
		<12 years: 500 mg/m <sup>2</sup> every 8 hours	IV	7–10 days
Cytomegalovirus retinitis (immunocompromised patients)	Ganciclovir (Cytovene)	5 mg/kg every 12 hours; then 5 mg/kg/day or 6 mg/kg, 5 days a week	IV	14–21 days for induction;
	Cidofovir (Vistide)	5 mg/kg every week for 2 weeks, then every 2 weeks	IV	maintenance
	Foscarnet (Foscavir)	90 mg/kg every 12 hours, then 90 mg/kg every day	IV	Maintenance
	Valganciclovir (Valcyte)	900 mg BID, 900 mg every day	PO	Induction for 2 weeks; maintenance
Influenza A	Amantadine <sup>c</sup> (Symmetrel)	>9 years: 100 mg BID	PO	Induction for 21 days; maintenance
				10 days (treatment), 14–28 days (protection with vaccine), 90 days (protection without vaccine)
	Rimantadine <sup>c</sup> (Flumadine)	1–9 years: 4.4–8.8 mg/kg/day but <150 mg/day	PO	
		>14 years: 100 mg BID	PO	7 days (treatment, not approved children) up to 6 weeks for prophylaxis
		1–13 years: 100 mg BID	PO	Up to 6 weeks for prophylaxis
	1–9 years: 5 mg/kg div. every day BID (max. 150 mg/day)	PO		

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TABLE 76.1 US Food and Drug Administration (FDA)–Indicated Drugs for Various Viral Infections (Continued)

Disease	Drug	Dosage (Age Group)	Route	Duration
Influenza A and B	Oseltamivir (Tamiflu)	>13 years (or >40 kg): 75 mg BID	PO	5 days (treatment)
		>13 years (or >40 kg): 75 mg every day	PO	10 days (prophylaxis)
		24–40 kg: 60 mg BID 16–23 kg: 45 mg BID	PO	Up to 6 weeks (community outbreaks) 5 days (treatment)
	Zanamivir (Relenza)	>1 year–15 kg: 30 mg BID 24–40 kg: 60 mg every day 16–23 kg: 45 mg every day	PO	10 days (prophylaxis)
		>1 year–15 kg: 30 mg every day >7 years: 10 mg (2 inhalations) BID	Inhalation	5 days (treatment)
		Adolescent and adult: 10 mg (2 inhalations) every day >5 years: 10 mg (2 inhalations) every day	Inhalation	10 days (prophylaxis) 28 days (community outbreak) 10 days (prophylaxis)
Respiratory syncytial virus	Ribavirin (Virazole)	6 g in 300 mL for 12–18 hours/day	Inhalation	3–7 days

<sup>a</sup>FDA-approved dose is 10 mg/kg. Although doses of 15 to 20 mg/kg have been used, safety has not been established at these doses.

<sup>b</sup>Foscarnet 40 mg/kg IV every 8 hours is recommended for acyclovir-resistant herpes simplex virus or varicella-zoster virus.

<sup>c</sup>Amantadine and rimantadine are no longer recommended as drugs of choice for either prophylaxis or treatment of influenza A. BID, twice a day; IV, intravenously; PO, orally; QID, four times a day.

## Influenza Virus

- Infection can be difficult to differentiate from the common cold. Systemic symptoms are more prevalent (abrupt onset of fever, chills, headache, myalgias).
- Influenza vaccine should be given yearly to patients at high risk (Table 76.4).
- Vaccination dosing is shown in Table 76.5. A live, attenuated vaccine (FluMist) is an option for healthy, nonpregnant people between 2 and 49 years of age.
- Patients with influenza at high risk for developing complications may benefit from antiviral therapy (oseltamivir, zanamivir) if started within 48 hours of symptom onset.

## Respiratory Syncytial Virus (RSV) Infection

- RSV causes bronchiolitis and bronchopneumonia in infants younger than 2 years. Children who are severely premature, immunocompromised, or with underlying congenital heart disease or lung disease are at increased risk of mortality.
- Goals of therapy are to increase oxygen saturation and decrease airway resistance.
- Ribavirin should be considered in children with, or at risk of developing, severe disease.
- Palivizumab (Synagis) is indicated to prevent RSV infection in children at risk. The first dose is given before the start of the RSV season and continued monthly for 5 months.

## Hantavirus Infection

- Rodents are the primary reservoir hosts (deer mouse). Infection in humans occurs when infected saliva, urine, and feces produced by the rodent are inhaled.
- Clinical features include fever, myalgias, headache, and cough. Abdominal pain, nausea, and vomiting may also be present.
- Supportive treatment (oxygen, vasopressors, and fluids for hypotension) is important. No treatment is available.

**TABLE 76.2 Clinical Pharmacokinetics of Antiviral Drugs**

Drug	Type of Patient	Peak Serum Concentration (mcg/mL)	VD	Elimination			Comments
				% Recovered Unchanged in Urine	Total Clearance	Half-Life (Hours)	
Acyclovir <sup>8,16,17,66-69</sup>	Adults	3.4–22.9 (Based on a dose of 2.5–10 mg/kg IV) 0.83–1.61 (Based on a dose of 200–800 mg PO)	59 L/1.73 m <sup>2</sup>	69–91	327 mL/minute/1.73 m <sup>2</sup>	2.5–3.3	Use 100% of recommended dose, but extend dosage interval to 12 and 24 hours if ClCr ranges from 25–50 and 10–25 mL/minute/1.73 m <sup>2</sup> , respectively; use 50% of recommended dose every 24 hours if ClCr ranges from 0–10 mL/minute/1.73 m <sup>2</sup> .
	Neonates	N/A	24–30 L/1.73 m <sup>2</sup>	N/A	98–122 mL/minute/1.73 m <sup>2</sup>	3.2–4.1	
Amantadine <sup>70</sup>	Adults	0.2–0.5 (Based on a dose of 100–200 mg PO)	3–8 L/kg	52–88	2.5–10.5 L/hour	20–41	Adjust doses in renal failure: 200 mg on day 1, then 100 mg/day if ClCr 30–50; 200 mg on day 1, then 100 mg every other day if ClCr 15–29; 200 mg every 7 days if ClCr <15 mL/minute/1.73 m <sup>2</sup>
Famciclovir <sup>44,71,72</sup>	Adults	0.8–6.6 (Based on a dose of 125–1,000 mg PO)	1.1 L/kg	73–94 <sup>a</sup>	0.37–0.48 L/hour/kg	2.2–3.0	Use 100% of recommended dose, but extend dosage interval to 12 and 24 hours if ClCr ranges from 40–59 and 20–39 mL/minute, respectively; use 250 mg every 24 hours if ClCr <20 mL/minute.
Oseltamivir <sup>73-76</sup>	Adults	0.6–3.5 <sup>b</sup> (Based on a dose of 75 mg PO)	23–26 L	99 <sup>b</sup>	18.8 L/hour	6.0–10	Use 75 mg/day in patients if ClCr 10–30 mL/minute. The effect of hepatic impairment has not been determined.
	Pediatrics (1–12 years)	0.06–0.8 <sup>b</sup> (Based on a dose of 2 mg/kg PO)	N/A	N/A	0.63 L/hour/kg	3.2–7.8	Dosage recommendations are based on body weight and age. Use 30 mg BID if patient is 15 kg and 1–3 years, 45 mg if patient is 15–23 kg and 4–7 years, 60 mg if patient is 23–40 kg and 8–12 years, and normal adult dose if >40 kg and older than 13 years.
	Adolescents	N/A	N/A	N/A	0.32 L/hour/kg	8.1	

*Continued on following page*

TABLE 76.2 Clinical Pharmacokinetics of Antiviral Drugs (Continued)

Drug	Type of Patient	Peak Serum Concentration (mcg/mL)	VD	Elimination			Comments
				% Recovered Unchanged in Urine	Total Clearance	Half-Life (Hours)	
Rimantadine <sup>77</sup>	Adults	0.2–0.7 (Based on a dose of 100–200 mg PO)	17–25 L/kg	20	20–48 L/hour	25–32	Because it undergoes extensive metabolism, dose may have to be adjusted in patients with severe liver disease. Dose adjustments may also be necessary in elderly and in those with severe renal failure (ClCr <10 mL/minute). Manufacturer recommends 50% reduction in such cases.
Valacyclovir <sup>43,78</sup> (see Acyclovir [prodrug of acyclovir])	Adults	5.7–6.7 <sup>c</sup> (Based on a dose of 1,000 mg PO)	N/A	46–80 <sup>c</sup>	N/A	2.5–3.3 <sup>c</sup>	Use 100% of recommended dose, but extend dosage interval to 12 and 24 hours if ClCr ranges from 30–49 and 10–29 mL/minute, respectively; use 500 mg every 24 hours if ClCr <10 mL/minute.
Zanamivir <sup>79–81</sup>	Adults	0.02–0.1 (Based on a dose of 10 mg INH)	15.9 L	7–17	2.5–10.9 L/hour	2.5–5.1	4%–17% of inhaled dose systemically absorbed. Although only limited studies with renal or hepatic impairment, dosing adjustment likely unnecessary

<sup>a</sup>Pharmacokinetic properties of active metabolite penciclovir.

<sup>b</sup>Active metabolite oseltamivir carboxylate.

<sup>c</sup>Pharmacokinetic properties of active metabolite acyclovir.

BID, twice a day; ClCr, creatinine clearance; INH, inhalation; IV, intravenously; N/A, not available; PO, orally; VD, volume of distribution.

**TABLE 76.3 Adverse Effects of US Food and Drug Administration–Indicated Drugs for Various Viral Infections**

Drug	Adverse Effects
Acyclovir	Local irritation, phlebitis (9%); increased SCr, BUN (5%–10%); nausea, vomiting (7%); itching, rash (2%); increased liver transaminases (1%–2%); CNS toxicity (1%), hematologic abnormalities (<1%)
Amantadine	Nausea, dizziness (lightheadedness), insomnia (5%–10%); depression, anxiety, irritability, hallucination, confusion, dry mouth; constipation, ataxia, headache, peripheral edema, orthostatic hypotension (1%–5%); suicide ideation or attempt (<1%)
Cidofovir	Nephrotoxicity (53%); neutropenia (34%); rash (30%); headache (27%); alopecia (25%); anemia (20%); abdominal pain (17%); fever (15%); infection (12%); ocular hypotonia (12%); nausea, vomiting (8%); asthenia (7%); diarrhea (7%)
Famciclovir	Headache (6%–9%); nausea (4%–5%); diarrhea (1%–2%)
Foscarnet	Fever, nausea, vomiting (47%); renal dysfunction (33%); anemia (9%–33%); diarrhea (30%); headache (26%); electrolyte abnormalities (6%–15%); bone marrow suppression (10%); seizure (10%); anorexia (5%); abdominal pain (5%); mental status changes (5%); paresthesia, peripheral neuropathy (5%); cough, dyspnea (5%); rash (5%); first-degree AV block, ECG changes (1%–5%)
Ganciclovir	Increased SCr (35%–69%); anemia (15%–25%); neutropenia, pancytopenia, thrombocytopenia (5%–8%); abdominal pain, anorexia (15%); diarrhea (44%); nausea, vomiting (13%); retinal detachment, vitreous hemorrhage, cataracts, corneal opacification (6%–15%); neuropathy; rash
Oseltamivir	Nausea, vomiting (9%–15%); diarrhea (3%); abdominal pain (2%); dizziness, vertigo, insomnia (1%); self-injury and psychosis
Ribavirin	Worsening of respiratory status, bacterial pneumonia, pneumothorax, apnea, ventilator dependence; cardiac arrest, hypotension; rash; conjunctivitis
Rimantadine	CNS (insomnia, dizziness, headache, nervousness, fatigue); GI (nausea, vomiting, anorexia, dry mouth, abdominal pain) (1%–3%)
Trifluridine	Burning or stinging on instillation (4.6%); palpebral edema (2.8%); keratopathy; hypersensitivity reaction; stromal edema; hyperemia; increased intraocular pressure
Valacyclovir	Headache (14%); nausea (15%); vomiting (6%); dizziness (3%); abdominal pain (3%)
Valganciclovir	Neutropenia (27%); thrombocytopenia (6%); diarrhea (41%); nausea, vomiting (21%–30%); abdominal pain (15%); increased SCr (3%); insomnia (16%); peripheral neuropathy (9%); paresthesias (8%); ataxia, dizziness, seizures, psychosis, hallucinations, confusion, drowsiness (<5%); retinal detachment (15% during treatment of CMV retinitis); hypersensitivity
Zanamivir	Bronchospasm; decline in respiratory function, especially if underlying respiratory disease; nasal or throat irritation or congestion (2%); headache (2%); cough (2%); diarrhea (3%); nausea, vomiting (1%–3%)

AV, atrioventricular; BUN, blood urea nitrogen; CMV, cytomegalovirus; CNS, central nervous system; ECG, electrocardiogram; GI, gastrointestinal; SCr, serum creatinine.

**TABLE 76.4 Persons Who Should Receive the Influenza Vaccine<sup>97</sup>**

- All persons 6 months of age or older
- Nursing home or chronic care facility residents
- Children and adults with chronic pulmonary or cardiovascular disease
- Children and adults who have required medical follow-up because of chronic metabolic diseases (e.g., diabetes mellitus), renal dysfunction, hemoglobinopathies, or immunosuppression (as a result of medications or diseases such as HIV)
- Children and adults who are at risk for aspiration (e.g., cognitive dysfunction, spinal cord injuries, seizures)
- Children (6 months–18 years) receiving long-term aspirin therapy
- Women who will be pregnant during influenza season
- Health care workers
- Household members of persons in high-risk groups (including contacts of infants and children 0–59 months)

TABLE 76.5 Influenza Vaccines<sup>97</sup>

Age	Dosage	Number of Doses
6–35 months	0.25 mL IM <sup>a</sup> inactivated vaccine	1 or 2 <sup>c</sup>
36–59 months	0.5 mL IM <sup>a</sup> inactivated vaccine or 0.2 mL IN <sup>b</sup> live vaccine	1 or 2 <sup>c</sup>
5–49 years	0.5 mL IM <sup>a</sup> inactivated vaccine or 0.2 mL IN <sup>b</sup> live vaccine	1 or 2 <sup>c</sup>
50 years	0.5 mL IM <sup>a</sup> inactivated vaccine	1

<sup>a</sup>The recommended site is the deltoid muscle for adults and older children and the anterolateral aspect of the thigh in infants and young children.

<sup>b</sup>The live vaccine should not be used in patients with chronic pulmonary or cardiovascular disease and in those with underlying immunodeficiencies.

<sup>c</sup>Two doses given at least 1 month apart for children younger than 9 years who are receiving the vaccine for the first time.

IM, intramuscularly; IN, intranasally.

## West Nile Virus

- Infection involves direct inoculation by the infecting mosquito. Birds are the reservoir host.
- Clinical features can range from asymptomatic to fever, encephalitis, or meningitis. Acute symptoms include sudden onset of fever, anorexia, weakness, nausea, vomiting, eye pain, headache, altered mental status, and stiff neck.
- Treatment is supportive; antiviral agents have no activity against the virus.

## Severe Acute Respiratory Distress Syndrome (SARS)

- A highly infectious disease spread by airborne microdroplets. Symptoms include fever, chills, rigor, myalgia, headache, diarrhea, sore throat, or rhinorrhea. Severe illness includes evidence of pneumonia or acute respiratory distress syndrome.
- No treatment guidelines are available due to lack of clinical trials.

## Common Cold

- Rhinovirus is the most common pathogen.
- Treatment is directed at symptoms: nonsteroidal anti-inflammatory agents, oral or intranasal decongestants, antihistamines, and antitussives.

# Viral Hepatitis\*

## General Principles

- Viral hepatitis can present as an acute or chronic illness and is caused by different viruses (Table 77.1). Immunologic characteristics and epidemiologic patterns are shown in Table 77.2. Fecal–oral transmission is the primary mode of infection for hepatitis A virus (HAV) and hepatitis E virus (HEV); percutaneous transmission is characteristic of hepatitis B virus (HBV), hepatitis C virus (HCV), and hepatitis D virus (HDV).
- Acute hepatitis is defined as an illness with a discrete manifestation with jaundice or increased serum aminotransferase concentrations greater than 2.5 times the upper limit of normal. Infection can last up to 6 months.
- Chronic hepatitis involves ongoing hepatocellular necrosis for 6 months or more beyond the acute illness. Chronic hepatitis can result from various etiologies (Table 77.3); HBV or HCV are the most common causes.
- Symptoms of the different hepatitis viruses are similar and include fatigue, weakness, anorexia, nausea, vomiting, scleral icterus, and jaundice.
- The primary causes of acute liver failure are shown in Table 77.4.
- Dosage adjustments for hepatically eliminated drugs may be necessary (Table 77.5). Potentially hepatotoxic medications should be avoided, if possible.

## Patient Assessment

- Serologies are useful in diagnosing viral hepatitis. The presence of antigens specific to the hepatitis virus aids in the diagnosis of infection. Serologic patterns of hepatitis viruses are shown in Table 77.6.

## Hepatitis A Virus

- HAV is often a benign, self-limited infection with recovery within 2 months of disease onset. Infection is related to quality of the water supply, level of sanitation, and age. The primary mode of transmission is the fecal–oral route. Chronic HAV does not exist.
- Risk factors include close contact with an HAV-positive person, employment/attendance at daycare centers, injection drug use, recent travel, and association with a suspected food or water-borne outbreak.
- Prevention of HAV can be achieved through immunization (Table 77.7). Postexposure prophylaxis can be accomplished with the vaccine (for those 12 months to 40 years of age if given within 14 days of exposure to HAV) or with immunoglobulin.
- Drug treatment does not significantly alter the course of disease. Treatment is typically in the outpatient setting. Intravenous fluid and electrolyte replacement, nutritional support, and antiemetic therapy may be helpful in some patients.

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\*The reader is referred to Chapter 77, Viral Hepatitis, written by Curtis D. Holt, PharmD, in the 10th edition of *Applied Therapeutics: The Clinical Use of Drugs* for a more in-depth discussion. All notations to reference numbers are based on the reference list at the end of that chapter. The editor of this handbook expresses her thanks to Dr. Anandan and acknowledges that this chapter is based on his work.



TABLE 77.1 Hepatitis Nomenclature

Hepatitis Type	Antigen	Corresponding Antibody	Comments
A	Hepatitis A virus (HAV)	Hepatitis A antibody (anti-HAV)	RNA virus; present in stool and serum early in course of hepatitis A
B	Hepatitis B surface antigen (HBsAg)	Hepatitis B surface antibody (anti-HBs)	DNA virus; found in serum in >90% of patients with acute hepatitis B, anti-HBs appears after infection and confers immunity
	Hepatitis B core antigen (HBcAg)	Hepatitis B core antibody (anti-HBc)	Anti-HBc detected in serum during and after acute infection
	Hepatitis B envelope antigen (HBeAg)	HB envelope antibody (anti-HBe)	HBeAg correlates with infectivity; suggestive of active viral replication
C	Hepatitis C antigen (HcAg)	Hepatitis C antibody (anti-HCV)	RNA virus; previously known as posttransfusion NANB hepatitis
D	Hepatitis D antigen (HDAg)	Hepatitis D antibody (anti-HDV)	Defective RNA virus; requires presence of HBsAg
E	Hepatitis E antigen (HEAg)	Hepatitis E antibody (anti-HEV)	RNA virus present in stool; cause of enteric NANB hepatitis

NANB, non-A, non-B hepatitis.

TABLE 77.2 Comparison of the Etiologic Forms of Hepatitis A, B, C, D, and E Viruses

Virus	HAV	HBV	HCV	HDV	HEV
Genome	RNA	DNA	RNA	RNA	RNA
Family	Picornavirus	Hepadnaviridae	Flaviviridae	Satellite	Hepeviridae
Size (nm)	27	42	30–60	40	32
Incubation (days) [mean]	15–50 [30]	45–180 [80]	14–180 [45]	21–140 [35]	15–65 [42]

#### TRANSMISSION

Oral	Common	Rare	Rare	No	Yes, common
Percutaneous	Rare	Common	Common	Common	Unknown
Sexual	No	Common	Common	Common	No
Perinatal	No	Common	Rare	Common	Rare
Onset	Sudden	Insidious	Insidious	Insidious	Sudden
Clinical illness	70%–80% adults; 5% children	10%–15%	5%–10%	10%	70%–80% adults

#### ICTERIC PRESENTATION

Children	<10%	30%	25%	Unknown	Unknown
Adults	30%	5%–20%	5%–10%	25%	Common
Peak alanine aminotransferase (ALT) (units/L)	800–1,000	1,000–1,500	300–800	1,000–1,500	800–1,000
Incidence of acute liver failure (%)	<1	<1	<1	2–7.5	<1; higher in pregnant women

#### SERUM DIAGNOSIS

Acute infection	Anti-HAV IgM	HBsAg, anti-HBc IgM	No serologic marker for acute infection	Anti-HDV IgM	Anti-HEV IgG (seroconversion)
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TABLE 77.2 Comparison of the Etiologic Forms of Hepatitis A, B, C, D, and E Viruses (Continued)

Virus	HAV	HBV	HCV	HDV	HEV
Chronic infection	NA	HBsAg, HBeAg	Screening test for anti-HCV; If reactive, HCV-RNA (PCR)	Anti-HDV IgG	NA
Viral markers	HAV RNA	Anti-HBc IgG HBV DNA; DNA polymerase	HCV RNA	HDV RNA	Virus-like particles
Immunity	Anti-HAV IgG	Anti-HBs	NA	NA	Anti-HEV IgG
Case-fatality rate	0.1%–2.7%  0.15%–1.7%	1%–3%	1%–2%	<1% coinfection	0.5%–4%  1.5%–21% pregnant women
Complete recovery	>97%	85%–97%	50%	90%	99%
Incidence of chronic infection	0%	2%–7% >90% neonates	50%	80% superinfection; ≤5% coinfection	0%
Carrier state	No	Yes	Yes	Yes	No
Risk of hepatocellular carcinoma	No	Yes	Yes	Yes	No
Drug treatment	None	Pegylated interferon, interferon, tenofovir, entecavir, adefovir, telbivudine, lamivudine	Sofosbuvir, + pegylated interferon/ ribavirin, or + ribavirin, or + simeprevir +/- ribavirin; OR simeprevir + pegylated interferon/ ribavirin, or + sofosbuvir +/- ribavirin, OR ledipasvir + sofosbuvir	Pegylated interferon, interferon	None

ELISA, enzyme-linked immunosorbent assay; NA, not applicable.

## Hepatitis B Virus

- HBV results in an acute illness with or without a chronic disease state. Transmission occurs primarily via sexual contact, percutaneous or perinatal exposure, and close person-to-person contact allegedly through open cuts and sores.
- High-risk groups include certain ethnic groups (Alaskan natives, Pacific Islanders), first-generation immigrants from hyperendemic areas, injection drug use, men who have sex with men, black Americans, and males.
- Chronic carriers tend to remain infected throughout their lifetime. Asymptomatic HBV carriers have mild disease manifestations with few complications.

**TABLE 77.3 Etiologies of Chronic Hepatitis**

VIRAL INFECTIONS
Hepatitis viruses (B, C, D)
Cytomegalovirus (CMV)
Epstein–Barr virus (EBV)
Rubella virus
DRUG-INDUCED
Methyldopa
Nitrofurantoin
Isoniazid
Sulfonamides
Propylthiouracil
METABOLIC DISORDERS
Wilson disease
$\alpha_1$ -Antitrypsin deficiency
Autoimmune hepatitis

- The most significant complication of acute HBV is acute liver failure. Clinical symptoms develop when the intracranial pressure (IOP) is >30 mm Hg. Prognosis is poor once encephalopathy develops. Primary therapy for acute liver failure is supportive care. Mannitol (0.5–1 g/kg given by rapid IV infusion, repeated after several hours if needed) may reduce IOP.
- Evaluation of patients infected with chronic HBV is shown in Table 77.8.
- Goals of therapy in chronic HBV are to achieve sustained suppression of HBV replication and remission of liver disease. Recommendations for treatment of chronic HBV are shown in Table 77.9. Dosage adjustments for renal function may be needed (Table 77.10).
- Prevention of HBV can be accomplished through vaccination (Tables 77.11 and 77.12). While completion of the vaccination series with the same product is recommended, it is not absolutely necessary. Routine administration of HBV booster doses is not needed for immunocompetent individuals. Immunocompromised patients may require booster doses when annual antibody testing shows low levels (<10 milli-international units/mL).
- Postexposure prophylaxis should be considered after exposure to HBV (Tables 77.13 and 77.14).

**TABLE 77.4 Principal Causes of Acute Liver Failure**

Cause	Agents Responsible
Viral hepatitis	Hepatitis A, B, C, D, E virus
Toxins	Carbon tetrachloride <i>Amanita phalloides</i> Phosphorus
Vascular events	Ischemia Veno-occlusive disease Heatstroke Malignant infiltration
Miscellaneous	Wilson disease Acute fatty liver of pregnancy Reye syndrome
Drug-related injury	Acetaminophen Idiosyncratic

TABLE 77.5 Half-Life Data for Various Agents in Acute Viral Hepatitis Compared with Reference Normal Controls

Drug	Half-life (Hours)	
	Normal Controls	Acute Viral Hepatitis
Acetaminophen	2.1	3.2
Aspirin	0.4	No change <sup>a</sup>
Carbamazepine	12	Increased
Chlordiazepoxide	11.1	91
Chloramphenicol	4.6	11.6
Clofibrate	17.5	No change
Diazepam	37.2	74.5
Lidocaine	3.7	6.4
Lorazepam	21.7	No change
Meperidine	3.4	7
Nitrendipine	2.2	No change
Norfloxacin	4.3	No change
Oxazepam	5.1	No change
Phenobarbital	86	No change
Phenytoin	13.2	No change
Quinine	10	17
Rifampin	2.5	6.5
Theophylline	7.7	19.2
Tolbutamide	5.9	4.0
Warfarin	25	No change

<sup>a</sup>No change indicates that the difference between patients with acute viral hepatitis and normal control patients is not statistically significant.

TABLE 77.6 Common Serologic Patterns of Hepatitis B Virus Infection

HBsAg	HBeAg	Anti-HBs	Anti-HBe	Anti-HBc	Interpretation
+	+	-	-	-	Incubation period
+	+	-	-	+(IgM)	Acute HBV infection (typical case); chronic HBV carrier with high infectivity
-	-	+	-	+(IgG)	Recovery from HBV infection
+	-	-	-	+(IgG)	Chronic HBV carrier; chronic hepatitis B
-	-	+	-	-	Successful immunization with HBV vaccine

Anti-HBc, hepatitis B core antibody; anti-HBe, hepatitis B envelope antibody; anti-HBs, hepatitis B surface antibody; HBeAg, hepatitis B envelope antigen; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; IgG, immunoglobulin G; IgM, immunoglobulin M.

TABLE 77.7 Recommended Doses of Hepatitis A Vaccines

Age at Vaccination	Dose (Volume) <sup>a</sup>	Schedule (Months) <sup>b</sup>
<b>HAVRIX</b>		
Children 12 months–18 years	720 ELISA units (0.5 mL)	0, 6–12
Adults >19 years	1,440 ELISA units (1.0 mL)	0, 6–12
<b>VAQTA</b>		
Children 12 months–18 years	25 units (0.5 mL)	0, 6–18
Adults >19 years	50 units (1.0 mL)	0, 6–18

<sup>a</sup>Enzyme-linked immunosorbent assay (ELISA) units.

<sup>b</sup>Zero months represents timing of the initial dose; subsequent numbers represent months after the initial dose.

TABLE 77.8 Evaluation of Patients with Chronic Hepatitis B

**Initial Evaluation****HISTORY AND PHYSICAL EXAMINATION**

Determine whether the patient will be committed to ongoing adherence with drug therapy and routine disease and treatment response monitoring (if needed)

Laboratory tests to assess liver disease (CBC, platelets, ALT, AST, bilirubin, prothrombin time/INR) and biopsy  
Tests for HBV replication (HBeAg/anti-HBe, HBV DNA)

Tests to rule out coinfection (anti-HCV, anti-HDV, anti-HIV)

Tests to screen for HCC (AFP, and ultrasound for high-risk patients)

**Suggested Follow-up for Patients Not Considered for Treatment (HBeAg+, HBV DNA >20,000 international units/mL, and normal ALT)**

ALT every 3–6 months, increasing frequency if ALT becomes elevated

If ALT >2 × ULN, recheck ALT every 1–3 months; consider liver biopsy if age >40 years, ALT borderline or mildly elevated on serial tests. Consider treatment if biopsy shows moderate or severe inflammation or significant fibrosis

If ALT >2 × ULN for 3–6 months and HBeAg+, HBV DNA >20,000 international units/mL, consider liver biopsy and treatment

Consider screening for HCC in relevant population

**Inactive HBsAg Carrier**

ALT every 3 months for 1 year, if persistently normal, ALT every 6–12 months

If ALT >1–2 × ULN, check serum HBV DNA level and exclude other causes of liver disease. Consider liver biopsy if ALT borderline or mildly elevated in serial tests or if HBV DNA persistently >20,000 international units/mL. Consider treatment if biopsy shows moderate or severe inflammation or significant fibrosis

Consider screening for HCC in relevant population

ALT, alanine aminotransferase; anti-HBe, hepatitis B envelope antibody; anti-HCV, hepatitis C antibody; anti-HDV, hepatitis D antibody; anti-HIV, human immunodeficiency virus antibody; APE,  $\alpha$ -fetoprotein; AST, aspartate aminotransferase; CBC, complete blood count; HBeAg, hepatitis B envelope antigen; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; INR, international normalized ratio; ULN, upper limit of normal.

TABLE 77.9 Recommendations for Treatment of Chronic Hepatitis B

HBsAg	HBV DNA (PCR)	ALT	Treatment Strategy
+	>20,000 international units/mL	$\leq 2 \times$ ULN	<ul style="list-style-type: none"> <li>• Low efficacy with current treatment</li> <li>• Observe, monitor ALT q3 months, consider treatment when ALT becomes elevated.</li> <li>• Consider biopsy in persons &gt;40 years, ALT persistently high normal to <math>2 \times</math> ULN, or family history of HCC</li> <li>• Consider treatment if HBV DNA &gt;20,000 international units/mL and biopsy shows moderate to severe inflammation or significant fibrosis</li> </ul>
+	>20,000 international units/mL	$\geq 2 \times$ ULN	<ul style="list-style-type: none"> <li>• Observe for 3–6 months and treat if no spontaneous HBeAg loss</li> <li>• Consider liver biopsy before treatment if compensated</li> <li>• Immediate treatment if icteric or clinical decompensation</li> </ul> <ol style="list-style-type: none"> <li>1. Interferons:             <ul style="list-style-type: none"> <li>• IFN-<math>\alpha</math> for 16 weeks</li> <li>• PegIFN-<math>\alpha</math> for 48 weeks: Preferred</li> </ul> </li> <li>2. Nucleotide Analogs: treatment for minimum 1 year, continue for at least 6 months after HBeAg seroconversion             <ul style="list-style-type: none"> <li>• ETV or TNF: preferred</li> <li>• ADV: not preferred owing to weak antiviral activity and high 1-year resistance rates</li> </ul> </li> </ol>

TABLE 77.9 Recommendations for Treatment of Chronic Hepatitis B (Continued)

HBeAg	HBV DNA (PCR)	ALT	Treatment Strategy
–	>20,000 international units/mL	$\geq 2 \times$ ULNs	<ul style="list-style-type: none"> <li>• LAM or LdT: not preferred owing to high rate of resistance</li> <li>• End point of treatment: seroconversion from HBeAg to anti-HBe</li> <li>• IFN-<math>\alpha</math> nonresponders/contraindications to IFN-<math>\alpha</math> <math>\rightarrow</math> TNF/EDV</li> <li>• Treat if persistent. Liver biopsy optional               <ol style="list-style-type: none"> <li>1. Interferons: for 1 year duration                   <ul style="list-style-type: none"> <li>• IFN-<math>\alpha</math></li> <li>• PegIFN-<math>\alpha</math>: Preferred</li> </ul> </li> <li>2. Nucleotide Analogs: for &gt;1 year duration                   <ul style="list-style-type: none"> <li>• ETV or TNF: preferred</li> <li>• ADV: not preferred owing to weak antiviral activity and high 1-year resistance rates</li> <li>• LAM or LdT: not preferred owing to high rate of resistance</li> <li>• End point of therapy not defined</li> <li>• IFN-<math>\alpha</math> nonresponders/contraindications to IFN-<math>\alpha</math> <math>\rightarrow</math> TNF/EDV</li> </ul> </li> </ol> </li> </ul>
–	>2,000 international units/mL	1–2 $\times$ ULN	Consider liver biopsy and treat if liver biopsy shows moderate to severe necroinflammation or significant fibrosis
–	<2,000 international units/mL	$\leq$ ULN	Observe, monitor ALT and HBV DNA q3 months and treat if HBV DNA or ALT becomes higher
+/-	Detectable	Cirrhosis	Compensated: <ul style="list-style-type: none"> <li>• HBV DNA &gt;2,000 international units/mL—treat: LAM/ADV/ETV/LdT/TNF may be used as initial therapy; LAM and LdT not preferred owing to high rate of resistance</li> <li>• ADV not preferred owing to weak antiviral activity and high 1-year resistance rates</li> <li>• HBV DNA &lt;2,000 international units/mL—consider treatment if ALT is elevated</li> </ul> Decompensated: <ul style="list-style-type: none"> <li>• Coordinate treatment with transplant center, LAM (or LdT) + ADV, TNF, or ETV preferred. Refer for liver transplant</li> </ul>
+/-	Undetectable	Cirrhosis	Compensated: observe Decompensated: refer for liver transplant

ADV, adefovir; ALT, alanine aminotransferase; ETV, entecavir; HBeAg, hepatitis B envelope antigen; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; IFN- $\alpha$ , interferon- $\alpha$ ; LAM, lamivudine; LdT, telbivudine; PCR, polymerase chain reaction; PegIFN- $\alpha$ , pegylated interferon- $\alpha$ ; TNF, tenofovir; ULN, upper limit of normal.

## Hepatitis C Virus

- HCV is the most common cause of non-A, non-B transfusion-associated hepatitis. Once established, infection persists and is often asymptomatic. Infection leads to progressive liver disease. Most patients with acute HCV are asymptomatic.
- HCV is the primary cause of death from liver disease, and the leading indication for liver transplant in the United States. HCV is transmitted through percutaneous and nonpercutaneous routes.

TABLE 77.10 Adjustment of Adult Dosage of Nucleoside/Nucleotide Analogs in Accordance with Creatinine Clearance

Creatinine Clearance (mL/min)	Recommended Dose	
<b>Lamivudine</b>		
≥50	100 mg every day	
30–49	100 mg first dose then 50 mg every day	
15–29	100 mg first dose, then 25 mg every day	
5–14	35 mg first dose, then 15 mg every day	
<5	35 mg first dose, then 10 mg every day	
<b>Adefovir</b>		
≥50	10 mg daily	
30–49	10 mg every other day	
10–29	10 mg every third day	
Hemodialysis patients	10 mg every week after dialysis	
<b>Entecavir</b>		
	Nucleoside naïve	Lamivudine refractory/resistant
≥50	0.5 mg every day	1.0 mg every day
30–49	0.25 mg every day or 0.5 mg every 48 hours	0.5 mg every day or 1 mg every 48 hours
10–29	0.15 mg every day or 0.5 mg every 72 hours	0.3 mg every day or 1 mg every 72 hours
<10 or hemodialysis or continuous ambulatory peritoneal dialysis	0.05 mg every day or 0.5 mg every 7 days	0.1 mg every day or 1 mg every 7 days
<b>Telbivudine</b>		
≥50	600 mg daily	
30–49	600 mg once every 48 hours	
<30 (not requiring dialysis)	600 mg once every 72 hours	
End-stage renal disease	600 mg once every 96 hours (give after dialysis)	
<b>Tenofovir</b>		
≥50	300 mg every 24 hours	
30–49	300 mg every 48 hours	
10–29	300 mg every 72–96 hours	
<10 (with hemodialysis)	300 mg once a week or after 12 hours of hemodialysis (give dose after dialysis)	
<10 without dialysis	No recommendation	

- Goals of therapy are to eradicate the virus, decrease HCV-associated morbidity and mortality, normalize biochemical markers, improve symptoms, prevent spread of disease, prevent progression of disease, and prevent development of end-stage liver disease.
- The American Association for the Study of Liver Diseases (AASLD) and Infectious Diseases Society of America (IDSA) recommendations for testing, managing, and treating hepatitis C are available at [www.hcvguidelines.org](http://www.hcvguidelines.org). Please refer to this website for the most updated information. HCV infection may spontaneously clear in 20% to 50% of patients; therefore, it may be decided to delay treatment initiation in patients with acute infection, while monitoring for

TABLE 77.11 Recommended Doses of Currently Licensed Hepatitis B Vaccines.<sup>a, 61, 54, 85</sup>

Group	Single-Antigen Vaccine				Combination Vaccine					
	Recombivax HB		Engerix-B		Comvax		Pediatrix		Twinrix	
	Dose (mcg)	(mL)	Dose (mcg)	(mL)	Dose (mcg)	(mL)	Dose (mcg)	(mL)	Dose (mcg)	(mL)
Infants (<1 year)	5	(0.5)	10	(0.5)	5	(0.5)	0	(0.5)	—	—
Children (1–10 years)	5	(0.5)	10	(0.5)	5 <sup>e</sup>	(0.5)	10 <sup>f</sup>	(0.5)	—	—
Children and adolescents 11–19 years	5	(0.5)	10	(0.5)	—	—	—	—	—	—
Adolescents 11–15 years <sup>b</sup>	10	(1.0)	—	—	—	—	—	—	—	—
Adults ≥20 years	10	(1.0)	20	(1.0)	—	—	—	—	20 <sup>g</sup>	(1.0)
Dialysis patients and other immunocompromised hosts <20 years	5	(0.5)	10	(0.5)	—	—	—	—	—	—
Dialysis patients and other immunocompromised hosts ≥20 years	40 <sup>c</sup>	(1.0)	40 <sup>d</sup>	(2.0)	—	—	—	—	—	—

<sup>a</sup>One dose administered three times: at time 0, 1 month, and 6 months.

<sup>b</sup>One dose administered two times: at 0 and 4–6 months.

<sup>c</sup>Dialysis formulation administered in a 3-dose schedule at 0, 1, and 6 months.

<sup>d</sup>Two 1 mL doses administered at one site on a 4-dose schedule at 0, 1, 2, and 6 months.

<sup>e</sup>Cannot be administered at birth, before age 6 weeks, or after 71 months.

<sup>f</sup>Cannot be administered at birth, before age 6 weeks, or at age > 7 years.

<sup>g</sup>Recommended for persons aged >18 years who are at increased risk for both hepatitis B virus and hepatitis A virus infections.

TABLE 77.12 Recommended Schedules of Hepatitis B Vaccination for Infants Born to HBsAg (–) Mothers

Hepatitis B Vaccine	Age of Infant
<b>OPTION 1</b>	
Dose 1	Birth (before hospital discharge)
Dose 2	1–2 months <sup>a</sup>
Dose 3	6–18 months <sup>a</sup>
<b>OPTION 2</b>	
Dose 1	1–2 months <sup>a</sup>
Dose 2	4 months <sup>a</sup>
Dose 3	6–18 months <sup>a</sup>

<sup>a</sup>Hepatitis B vaccine can be administered simultaneously with diphtheria-tetanus-pertussis, *Haemophilus influenzae* type b conjugate, measles-mumps-rubella, and oral polio vaccines.

spontaneous clearance for a minimum of 6 months. If it is decided to treat during the acute infection period, monitoring for spontaneous clearance for at least 12 to 16 weeks is recommended before starting therapy. The same regimens for chronic HCV infection are recommended for acute infection.

- The standard therapy for chronic HCV has been peginterferon alfa (PEG) plus ribavirin (RBV; two formulations of peginterferon are listed in Table 77.15). Direct-acting antivirals (DAA), sofosbuvir (400 mg once daily), and simeprevir (150 mg once daily) were FDA-



TABLE 77.13 Guide to Postexposure Immunoprophylaxis for Exposure to Hepatitis B Virus

Type of Exposure	Immunoprophylaxis
Perinatal	Vaccination + HBIG
Sexual—acute infection	Vaccination + HBIG
Sexual—chronic carrier	Vaccination
Household contact—chronic carrier	Vaccination
Household contact—Acute case	None unless known exposure
Household contact—Acute case, known exposure	HBIG +/- vaccination
Infant (<12 months) acute case in primary caregiver	HBIG + vaccination
Inadvertent (percutaneous or permucosal)	Vaccination +/- HBIG

HBIG, hepatitis B immunoglobulin.

TABLE 77.14 Recommendations for Hepatitis B Prophylaxis after Percutaneous Exposure

Exposed Person	Treatment When Source Is Found to Be		
	HBsAg-Positive	HBsAg-Negative	Unknown or Not Tested
Unvaccinated	Administer HBIG × 1 <sup>a</sup> and initiate hepatitis vaccine series	Initiate hepatitis B vaccine series <sup>b</sup>	Initiate hepatitis B vaccine series <sup>b</sup>
<b>PREVIOUSLY VACCINATED</b>			
Known responder	Test exposed person for anti-HBs <sup>c</sup> 1. If inadequate, hepatitis B vaccine booster dose 2. If adequate, no treatment	No treatment	No treatment
Known nonresponder	HBIG × 1 <sup>a</sup> as soon as possible, repeat in 1 month OR HBIG × 1 <sup>a</sup> plus one dose of hepatitis B vaccine	No treatment	If known high-risk source, may treat as if source were HBsAg positive
Response unknown	Test exposed person for anti-HBs <sup>c</sup> 1. If inadequate, HBIG × 1 <sup>a</sup> plus hepatitis B vaccine booster dose 2. If adequate, no treatment	Test exposed person for anti-HBs <sup>c</sup> 1. If inadequate, Hepatitis B vaccine and anti-HBs testing 1–2 months later; if still inadequate, re-vaccinate with two more doses 2. If adequate, no treatment	Test exposed person for anti-HBs <sup>c</sup> 1. If inadequate, hepatitis B vaccine booster dose 2. If adequate, no treatment

<sup>a</sup>HBIG dose 0.06 mL/kg given intramuscularly.

<sup>b</sup>For dosing information, see Table 77.11.

<sup>c</sup>Adequate anti-HBs is ≥10 milli-international units.

HBIG, hepatitis B immunoglobulin; HBs, hepatitis B surface; HBsAg, hepatitis B surface antigen.

TABLE 77.15 Comparative Pharmacokinetics of Pegylated Interferons

Parameter	Interferon- $\alpha$	PEG- $\alpha$ 2b (12 kDa)	PEG- $\alpha$ 2a (40 kDa)
Absorption	Rapid	Rapid	Sustained
Distribution	Wide	Wide	Blood, organs
Clearance	—	10-fold reduction (hepatic/renal)	100-fold reduction (hepatic)
Elimination half-life (hours)	3–5	30–50	50–80
Weight-based dosing	No	Yes	No
Increased concentration with multiple dosing	No	Yes	Yes
Protected from degradation	No	Probable	Yes

PEG, peginterferon alfa.

approved for the treatment of chronic HCV infection. Sofosbuvir is indicated for HCV genotype 1 to 4 infections, whereas simeprevir is indicated for genotype 1 infection. Current guidelines recommend sofosbuvir use in combination with PEG/RBV or with RBV, depending on the HCV genotype being treated. More recently, ledispavir and sofosbuvir combination therapy was approved for the management of HCV in genotype 1 infection, offering the first PEG- and RBV-free regimen for HCV management.

- No vaccine is available for HCV. Prevention is focused on identifying high-risk uninfected persons and counseling them on risk-reducing strategies. Immunoglobulin is not recommended for postexposure prophylaxis of HCV due to lack of efficacy.

## Hepatitis D Virus

- Hepatitis D virus replication is dependent on coinfection with HBV. Successful immunization with HBV vaccine also prevents HDV infection.
- Coinfection with HBV and HDV is correlated with a higher risk of severe or fulminant liver disease. Patients with chronic HDV are at risk for developing cirrhosis and hepatic decompensation.
- Treatment is directed at eradicating HDV and HBV. Supportive care is the general strategy used to treat HDV. In patients with decompensated cirrhosis caused by HDV, liver transplantation is the most appropriate intervention.

## Hepatitis E Virus

- Transmission of HEV is via the fecal–oral route, most commonly through contaminated water.
- Recovery from acute illness occurs; however, mortality in pregnant women is significant.
- No immunoprophylactic measures exist for HEV; effective prevention strategies are dependent on improved sanitation in endemic areas.

## Parasitic Infections\*

### General Principles

- Multiple parasitic infections exist, with common ones described below. Table 78.1 lists the drugs of choice for these parasitic infections.
- **Malaria** is transmitted primarily by the female mosquito. Symptoms include chills and fever. *Plasmodium falciparum* is the most severe form and has the highest mortality rate. Failure to comply with chemosuppressive regimens, delays in seeking therapy, misdiagnosis, and inappropriate treatment can lead to fatality. Travelers to endemic areas should receive chemoprophylaxis for malaria.
- **Amebiasis**, caused by the protozoan parasite *Entamoeba histolytica*, results in amebic dysentery and hepatic abscess. Infection occurs through ingestion of cysts present in contaminated water or food.
- **Giardiasis**, caused by the protozoan *Giardia lamblia*, manifests as nausea, abdominal cramping, and diarrhea. Waterborne outbreaks are more common than foodborne outbreaks. Symptoms include profuse watery stools, abdominal distension, and cramping.
- **Enterobiasis**, caused by ingestion of the pinworm *Enterobius vermicularis*, usually infects all household members. Intense pruritis in the perianal area is common.
- **Cestodiasis**, or tapeworm infection, is caused by ingestion of poorly cooked meat. Symptoms range from mild epigastric or abdominal pain to a burning sensation, general weakness, weight loss, headache, constipation, and diarrhea.
- **Pediculosis** (lice infections) can be caused by head, body, or crab lice. Head and body lice are transmitted through personal and clothing contact; crab lice are transmitted by sexual contact. Common symptoms are pruritus (scalp, ears, neck, or other body parts).
- Scabies is caused by the female mite that burrows into the skin of the host and lays eggs, which hatch into larvae after 72 to 84 hours. The classic symptom is intense itching with erythematous papules and excoriations. Transmission is by intimate contact.

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\*The reader is referred to Chapter 78, Parasitic Infections, written by J. V. Anandan, PharmD, in the 10th edition of *Applied Therapeutics: The Clinical Use of Drugs* for a more in-depth discussion. All notations to reference numbers are based on the reference list at the end of that chapter. The editor of this handbook expresses her thanks to Dr. Anandan and acknowledges that this chapter is based on his work.

**TABLE 78.1 Drug Therapy of Parasitic Infection**<sup>2,7,9,10,11,14,18,22,26–29,32,35,36,39,57,61,64,79,82,100,107,110,111,116,119,120,124–126,130</sup>

Drug of Choice	Dosage	Adverse Effects
<b>AMEBIASIS (INCLUDING CYST PASSERS)</b>		
Asymptomatic Iodoquinol	Adults: 650 mg PO TID × 20 days	Rash, acne, thyroid enlargement
Or	Children: 30–40 mg/kg/day PO TID × 20 days	
Diloxanide furoate	Adults: 500 mg PO TID × 10 days	Flatulence, abdominal pain
Or	Children: 20 mg/kg/day PO TID × 10 days	
Paromomycin	Adults: 25–35 mg/kg/day PO TID × 7 days	Nausea, vomiting
	Children: Same as adults	
<b>MILD TO MODERATE GASTROINTESTINAL DISEASE</b>		
Metronidazole	Adults: 750 mg PO TID × 10 days	Nausea, headache, metallic taste, disulfiram reaction with alcohol, paresthesia
Or	Children: 35–50 mg/kg/day PO TID × 10 days	
Tinidazole followed by	Adults: 2 g once daily × 3 days	Metallic or bitter taste, anorexia, nausea, vomiting, epigastric discomfort, weakness, seizures, peripheral neuropathy
	Children: 50 mg/kg (max. 2 g) × 3 days	
Iodoquinol	Adults: 650 mg PO TID × 20 days	Rash, acne, thyroid enlargement
	Children: 30–40 mg/kg/day PO TID × 20 days	
<b>SEVERE GASTROINTESTINAL DISEASE</b>		
Metronidazole	Adults: 750 mg PO TID × 10 days	Nausea, headache, metallic taste, disulfiram reaction with alcohol, paresthesia
Or	Children: 35–50 mg/kg/day PO TID × 10 days	
Tinidazole followed by	Adults: 2 g once daily × 5 days	Metallic taste or bitter taste, nausea, vomiting, epigastric discomfort, anorexia, and weakness
	Children: 50 mg/kg/day (max. 2 g) × 5 days	
Iodoquinol	Adults: 650 mg PO TID × 20 days	Rash, acne, thyroid enlargement
	Children: 30–40 mg/kg/day PO TID × 20 days	
<b>AMEBIC LIVER ABSCESS</b>		
Metronidazole	Adults: 750 mg PO TID × 10 days	Nausea, headache, metallic taste, disulfiram reaction with alcohol, paresthesia
Or	Children: 35–50 mg/kg/day PO TID × 10 days	
Tinidazole followed by	Adults: 2 g once daily × 5 days	
	Children: 50 mg/kg (max. 2 g) × 5 days	
Iodoquinol	Adults: 650 mg PO TID × 20 days	Rash, acne, thyroid enlargement
Or	Children: 30–40 mg/kg/day PO TID × 20 days	
Diloxanide furoate <sup>b</sup>	Adults: 500 mg PO TID × 10 days	
Or	Children: 20 mg/kg/day PO TID × 10 days	
Paromomycin	Adults: 25–30 mg/kg/day PO TID × 7 days	Nausea, vomiting
	Children: Same as adults	
<b>ASCARIASIS (ROUNDWORM)</b>		
Albendazole	Adults and children: 400 mg once	Nausea and headache
Or		
Mebendazole	Adults and children: 100 mg BID PO × 3 days	Diarrhea, abdominal pain
<b>ENTEROBIASIS (PINWORM)</b>		
Mebendazole	Adults and children: 100 mg once; repeat in 2 weeks	Diarrhea, abdominal pain
Pyrantel pamoate	Adults and children: 11 mg/kg PO once (max. 1 g), repeat in 2 weeks	Nausea, headache, dizziness, rash, fever
Or		

Continued on following page

**TABLE 78.1 Drug Therapy of Parasitic Infection**<sup>2,7,9,10,11,14,18,22,26–29,32,35,36,39,57,61,64,79,82,100,107,110,111,116,119,120,124–126,130</sup> (Continued)

Drug of Choice	Dosage	Adverse Effects
Albendazole	Adults and children: 400 mg once; repeat in 2 weeks	Abdominal pain, reversible alopecia, increased transaminases, rarely leukopenia
<b>FILARIASIS</b>		
Diethylcarbamazine	Adults: Day 1, 50 mg PO; day 2, 50 mg TID; day 3, 100 mg TID; days 4–14, 6 mg/kg/day in 3 doses Children: Day 1, 25–50 mg; day 2, 25–50 mg TID; day 3, 50–100 mg TID; days 4–14, 6 mg/kg/day in 3 doses	Severe allergic or febrile reactions, gastrointestinal disturbance, rarely encephalopathy
<b>FLUKES (TREMATODES)<sup>d</sup></b>		
Praziquantel	Adults and children: 75 mg/kg/day in 3 doses × 2 days (exceptions: <i>Clonorchis sinensis</i> and <i>Paragonimus westermani</i> , × 2 days)	Malaise, headache, dizziness, sedation, fever, eosinophilia
<b>GIARDIASIS</b>		
Metronidazole Or	Adults: 250 mg PO TID with meals × 5–7 days Children: 15 mg/kg/day PO TID × 5–7 days	Nausea, headache, metallic taste, disulfiram reaction with alcohol, paresthesia
Quinacrine <sup>b</sup>	Adults: 100 mg PO TID × 5 days Children: 2 mg/kg TID × 5 days (max. 300 mg/day)	Gastrointestinal yellow staining of skin and psychosis
Nitazoxanide <sup>c</sup>	Children: 12–47 months 100 mg (5 mL) every 12 hours × 3 days 4–11 years 200 mg (10 mL) every 12 hours × 3 days	Abdominal pain, diarrhea, vomiting, and headache
<b>HOOKWORM</b>		
Mebendazole	Adults and children: 100 mg PO BID × 3 days	Diarrhea, abdominal pain
<b>LICE</b>		
1% Permethrin (NIX) Or	Topical administration	Occasional allergic reaction, mild stinging, erythema
Ivermectin	Adults and children: 200 mcg/kg × 3, day 1, day 2, and day 10	Fever, pruritus, sore lymph nodes, headache, joint pains, rarely hypotension
<b>LEISHMANIASIS</b>		
Sodium stibogluconate	Adults: 20 mg SB/kg IV or IM × 20–28 days	Gastrointestinal, malaise, headache arthralgias, myalgias, anemia, neutropenia, thrombocytopenia; ECG abnormalities (ST- and T-wave changes)
Or Liposomal Amphotericin B	Children: Same as adults Adults: 3 mg/kg/day (days 1–5) and 3 mg/kg/day (days 14 and 21) Children: Same as adult	Hypotension, chills, headache, anemia, thrombocytopenia, fever, and elevated serum creatinine
<b>MALARIA</b>		

All *Plasmodia* except chloroquine-resistant

**TABLE 78.1 Drug Therapy of Parasitic Infection**<sup>2,7,9,10,11,14,18,22,26–29,32,35,36,39,57,61,64,79,82,100,107,110,111,116,119,120,124–126,130</sup> (Continued)

Drug of Choice	Dosage	Adverse Effects
<b>PARENTERAL THERAPY</b>		
Quinidine gluconate Or	Adults: Loading dose 10 mg/kg of salt (6.2 mg base) diluted in 250 mL of normal saline and infused IV for 2 hours, followed by a continuous IV infusion of 0.02 mg/kg/minute (0.012 mg base) for 72 hours; switch to oral quinine 650 mg every 8 hours as soon as possible	ECG: Q-T and QRS prolongation; hypotension, syncope, arrhythmias; cinchonism
Artesunate <sup>d</sup>	2.4 mg/kg per dose every 12 hours for 3 days. Children: Same as adults.	Pruritus, hypotension, dizziness, nausea, vomiting, diarrhea, and bitter metallic taste
<b>ORAL THERAPY</b>		
Chloroquine phosphate	Adults: 1 g (600 mg base), then 500 mg 6 hours later, then 500 mg at 24 and 48 hours later Children: 10 mg base (max. 600 mg base) then 5 mg base/kg 6 hours later, then 5 mg/base at 24 and 48 hours	Gastrointestinal, headache, pruritus, malaise, and cinchonism
<b>CHEMOPROPHYLAXIS</b>		
Chloroquine phosphate	Adults: 500 mg (base) once weekly (beginning 1–2 weeks before departure and continuing through stay and up to 4 weeks after returning) Children: 5 mg/kg base once weekly up to adult dose (300 mg base)	Dose-related: vertigo, nausea, dizziness, light-headedness, headache, visual disturbances, toxic psychosis, and seizures
<b>CHLOROQUINE-RESISTANT THERAPY (CRF)</b>		
Mefloquine	Adults: 750 mg followed by 500 mg 12 hours later	Nausea, vomiting, abdominal pain, arthralgias, chills, dizziness, tinnitus, and A-V block
Or	Children: 15 mg/kg followed 8–12 hours later by 10 mg/kg	
Atovaquone/ Proguanil Or	Adults: 2 tablets BID × 3 days Children: 11–20 kg: 1 adult tablet/day × 3 days; 21–30 kg: 2 adult tablets/day × 3 days; 31–40 kg: 3 adult tablets/day × 3 days; >40 kg: 2 adult tablets BID × 3 days	Rash, nausea, diarrhea, increased aminotransferases, cholestasis
Artemether 20 mg lumefantrine 120 mg (Coartem)	3-day regimen of 6 doses based on body weight: initial dose, followed by 8 hours later and one dose twice daily × 2 days; 5–<15 kg: 1 tablet per dose; 15–<25 kg: 2 tablets per dose; 25–<35 kg: 3 tablets per dose; >35 kg: 4 tablets per dose	
<b>CHEMOPROPHYLAXIS-CRF</b>		
Mefloquine	Adults: 250 mg once weekly beginning 1–2 weeks before departure, continuing through stay and for 1–4 weeks after return	
Or	Children: <15 kg: 5 mg/kg once weekly; 15–19 kg: 1/4 tablet once weekly; 20–30 kg: 1/2 tablet once weekly; 31–45 kg: 3/4 tablet once weekly; >45 kg: 1 tablet once weekly	
Doxycycline	Adults: 100 mg daily beginning 1–2 days before departure continuing during stay and 1 week after return	Nausea, diarrhea, and monilial rash

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**TABLE 78.1 Drug Therapy of Parasitic Infection**<sup>2,7,9,10,11,14,18,22,26–29,32,35,36,39,57,61,64,79,82,100,107,110,111,116,119,120,124–126,130</sup> (Continued)

Drug of Choice	Dosage	Adverse Effects
Quinine sulfate (Qualaquin) <i>Plus</i> Pyrimethamine-sulfadoxine (Fansidar) Or Mefloquine	Adults: 650 PO TID × 3 days  Children: 25 mg/kg/day PO TID × 3 days Adults: 3 tablets at once (withhold until febrile episode)  Children: 1/2–2 tablets (depends on age) <sup>c</sup> Adults: 1,250 mg once Children: 25 mg/kg once (>45 kg)	Cinchonism  Gastrointestinal, erythema multiforme, Stevens–Johnson syndrome, toxic epidermal necrolysis  Dose-related: vertigo, nausea, dizziness, light-headedness, headache, visual disturbances, toxic psychosis seizures
<b>PREVENTION OF RELAPSES (<i>P. vivax</i> and <i>P. ovale</i>)</b>		
Primaquine phosphate	Adults: 52.6 mg/day (30 mg base) × 14 days; this follows chloroquine or mefloquine regimen	Abdominal cramps, nausea, hemolytic anemia in G6PD
<b>SCABIES</b>		
5% Permethrin (Elimite cream)	Topical administration	Rash, edema, erythema
<b>ALTERNATIVES</b>		
Ivermectin	Adults: 200 mcg/kg PO; repeat in 2 weeks	Nausea, diarrhea, dizziness, vertigo, and pruritus
Lindane (Kwell)	Apply topically once	Not recommended in pregnant women, infants, and patients with massively excoriated skin. Second-line therapy when other alternatives have failed
Crotamiton 10% (Eurax)	Topically	Local skin irritation
<b>TAPEWORM<sup>e</sup></b>		
Praziquantel	Adults and children: 5–10 mg/kg PO × 1 dose	Malaise, headache, dizziness, sedation, eosinophilia, fever
<b>HYDATID CYSTS<sup>f</sup></b>		
Albendazole	Adults: 400 mg BID × 8–30 days, repeat if necessary Children: 15 mg/kg/day × 28 days, repeat if necessary (surgical resection may precede drug therapy)	Diarrhea, abdominal pain, rarely hepatotoxicity, leukopenia
<b>TRICHOMONIASIS</b>		
Metronidazole	Adults: 2 g PO × 1 day or 250 mg PO TID × 7 days Children: 15 mg/kg/day PO TID × 7 days	Nausea, headache, metallic taste, disulfiram reaction with alcohol, paresthesia

<sup>a</sup>*Schistosoma haematobium*, *Schistosoma mansoni*, *Schistosoma japonicum*, *Clonorchis sinensis*, *Paragonimus westermani*.

<sup>b</sup>Quinacrine is available in the United States: Panorama Compounding Pharmacy, 6744 Balboa Blvd, Van Nuys, CA 91406 (1-800-247-9767). Diloxanide furoate is not available in the United States or Canada.

<sup>c</sup>Same dose is recommended in children with *Cryptosporidium parvum*.

<sup>d</sup>Obtained from CDC under an Investigational New Drug (IND) protocol for patients intolerant of intravenous quinidine or when intravenous quinidine is not readily available. Therapy should be followed by oral therapy with antimalarials (see above and text).

<sup>e</sup>*Diphyllobothrium latum* (fish), *Taenia solium* (pork), and *Dipylidium caninum* (dog), except for *Hymenolepis nana*, in which the dose is 25 mg/kg × 1 dose.

<sup>f</sup>*Echinococcus granulosus*, *Echinococcus multilocularis*. For neurocysticercosis: 400 mg BID 8 to 30 days.

BID, twice daily; ECG, electrocardiograph; G6PD, glucose-6-phosphate dehydrogenase; IM, intramuscularly; PO, orally; SB, sodium stibogluconate; TID, three times daily.

## Tick-Borne Diseases\*

### General Principles

- Disease spread by ticks either by transmission of microorganisms or injection of tick toxin into a host.
- Bacterial, rickettsial, protozoal, and viral disease pathogens can be transmitted from ticks to humans (Table 79.1).

### Lyme Disease

- Caused by *Borrelia burgdorferi*, a spirochete transmitted to humans via a tick bite.
- A multisystem condition affecting the skin, joints, and cardiovascular and central and peripheral nervous systems. Clinical manifestations are shown in Table 79.2.
- Preventive measures include personal protection and tick avoidance. Tick repellents (e.g., DEET) can be applied to skin or clothing. Prophylactic antibiotic preventative therapy (a single dose of oral doxycycline) can be given if exposure is suspected.
- Treatment strategy should be governed by clinical manifestations of disease (Table 79.3). A nondoxycycline regimen is preferred in pregnant or breast-feeding women and in children below 8 years of age.

### Endemic Relapsing Fever

- Caused by a bacterial spirochete (*B. recurrentis*) that is transmitted between humans by the human body louse.
- Disease is characterized by abrupt onset of high fever with occasional additional symptoms including shaking chills, headache, and tachycardia. Fever usually breaks in 3 to 6 days in untreated patients.
- Treatment includes 7 to 10 days of doxycycline (100 mg twice daily) or erythromycin (500 mg four times daily).

### Tularemia

- Caused by the gram-negative coccobacillus, *Francisella tularensis*. Transmission is primarily via tick or fly bites.
- Clinical manifestations fall into two main groups:
  - Ulceroglandular—the most common form of tularemia. An ulcer forms at the site of entry.
  - Typhoidal—characterized by fever, chills, headache, debilitation, abdominal pain
- Treatment is streptomycin 7.5 to 10 mg/kg/dose IM or IV every 12 hours for 7 to 14 days. Higher doses are needed for pediatric patients.

### Rocky Mountain Spotted Fever (RMSF)

- Caused by a coccobacillus (*Rickettsia rickettsii*) and transmitted by a tick bite, RMSF is the most prevalent and virulent rickettsial disease in the United States.

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\*The reader is referred to Chapter 79, Tick-Borne Diseases, written by Thomas E. Christian, BS Pharm, BCPS, in the 10th edition of *Applied Therapeutics: The Clinical Use of Drugs* for a more in-depth discussion. All notations to reference numbers are based on the reference list at the end of that chapter. The editor of this handbook expresses her thanks to Dr. Christian and acknowledges that this chapter is based on his work.



**TABLE 79.1 Tick-Borne Diseases**

Disease	Causative Agent	Tick Vector	Host	Region
Lyme	<i>Borrelia burgdorferi</i>	<i>Ixodes</i>	Wild rodents	Worldwide
Relapsing fever (endemic)	<i>Borrelia</i> species	<i>Ornithodoros</i>	Wild rodents	Worldwide
Southern tick-associated rash illness	<i>Borrelia lonestari?</i>	<i>Amblyomma</i>	?	South-central to Northeast United States
Tularemia	<i>Francisella tularensis</i>	<i>Dermacentor</i> <i>Amblyomma</i>	Rabbits, ticks	North America
Rocky Mountain spotted fever	<i>Rickettsia rickettsii</i>	<i>Dermacentor</i>	Wild rodents, ticks	Western Hemisphere
Spotted fever group	<i>Rickettsia parkeri</i> , others	<i>Rhipicephalus</i> <i>Amblyomma</i>	Horses?	Arizona
Boutonneuse fever	Various rickettsia	Various species	?	United States
	<i>Rickettsia conorii</i>	<i>Ixodes</i>	Wild rodents, dogs	Worldwide
North Asian tick typhus	<i>Rickettsia sibirica</i>	<i>Ixodes</i>	Wild rodents	Africa, India, Mediterranean
Queensland tick typhus	<i>Rickettsia australis</i>	<i>Ixodes</i>	Wild rodents, marsupials	Mongolia, Siberia
Q fever	<i>Coxiella burnetii</i>	<i>Dermacentor</i>	Sheep, goats, cattle, ticks, cats	Australia
		<i>Amblyomma</i>		Worldwide
Babesiosis	<i>Babesia</i> species	<i>Ixodes</i>	Mice, voles	Europe, North America
Human monocytic ehrlichiosis	<i>Ehrlichia chaffeensis</i>	<i>Amblyomma</i>	Deer, dogs	United States, Mexico, Europe, Africa, Middle East
		<i>Dermacentor</i>	Deer	
Human granulocytic anaplasmosis	<i>Anaplasma phagocytophilum</i>	<i>Ixodes pacificus</i>	Deer, elk, wild rodents	United States, Europe
		<i>Ixodes</i>		
Human ehrlichial ewingii	<i>Ehrlichia ewingii</i>	<i>Amblyomma</i>	Dogs?	United States
Colorado tick fever	<i>Coltivirus</i> species	<i>Dermacentor</i>	Wild rodents, mammals	North America
Tick-borne encephalitis	<i>Flavivirus</i>	<i>Ixodes</i>	Rodents	Eurasia, Far East
Tick paralysis	Neurotoxin	<i>Dermacentor</i> , others	N/A	Worldwide

N/A, not applicable.

**TABLE 79.2 Lyme Disease Clinical Manifestations**

EARLY LOCALIZED INFECTION
Erythema migrans skin rash
EARLY DISSEMINATED DISEASE
Heart (<4% of untreated patients in United States)
Myocarditis or pericarditis
Conduction defects, varying degrees of atrioventricular or bundle-branch block, but permanent pacing not indicated
Nervous System (Neuroborreliosis)
Cranial nerve (Bell's) palsy
Meningitis, lymphocytic
Radiculoneuritis, myelitis
Sensory or motor peripheral neuropathy

TABLE 79.2 Lyme Disease Clinical Manifestations (Continued)

**Skin**

Multiple secondary erythema migrans lesions; lymphocytoma (lymphadenosis benigna cutis) rare in the United States, but 1% in Europe

**E DISEASE****Musculoskeletal (less common in Europe)**

Persistent (<10% of untreated in United States) or intermittent arthritis of >1 large joint, especially the knee

**Skin (10% in Europe; rare in the United States)**

Acrodermatitis chronica atrophicans (unique to Lyme disease)

**Late Neurologic**

Peripheral neuropathy, subacute encephalopathy (memory impairment, sleep disturbance, dementia), and in Europe, progressive encephalomyelitis

- Disease is associated with generalized vasculitides, which in severe infection is associated with hypotension and intravascular coagulation. Dehydration is an early sign of RMSF; myalgia or muscular tenderness is common. Fulminant disease can be rapidly fatal.
- Recommended treatment is doxycycline 100 mg PO/IV twice daily for 5 to 7 days. Chloramphenicol is reserved for use in the first or second trimesters of pregnancy (but should not be used in the third trimester).

**Ehrlichiosis and Anaplasmosis**

- Human monocytic ehrlichiosis (HME) is caused by *Ehrlichia chaffeensis* and human granulocytic anaplasmosis (HGA) is caused by *Anaplasma phagocytophilum*.
- Both diseases share similar clinical features: fever, malaise, myalgia, and headache.
- Doxycycline 100 mg PO twice daily for 10 to 14 days is the drug of choice.

**Babesiosis**

- Caused by a parasite: *Babesia microti*, *B. divergens*, or *B. bovis*. Diagnosis is confirmed by the presence of protozoa inside of red blood cells.
- Most patients are asymptomatic. Fever, headache, and sweats can be present. Severe infection is associated with hemolytic anemia and can be life-threatening.

TABLE 79.3 Treatment Recommendations for Lyme Disease

**ERYTHEMA MIGRANS**

**Adults:** Doxycycline (Vibramycin) 100 mg PO BID × 10 days

Or

Amoxicillin (Polymox) 500 mg PO TID × 14–21 days

Or

Cefuroxime axetil (Ceftin) 500 mg PO BID × 14–21 days

**Children (<8 years):** Amoxicillin 50 mg/kg/day PO in 3 divided doses (maximum, 500 mg/dose) × 14–21 days or

cefuroxime 30 mg/kg/day PO in 2 divided doses (maximum, 500 mg/dose) × 14–21 days

**Children (>8 years):** May use doxycycline 4 mg/kg PO in 2 divided doses (maximum, 100 mg/dose) × 14–21 days

**Cardiac Disease:** second- or third-degree heart block, PR interval >0.3 seconds

**Adults:** Ceftriaxone (Rocephin) 2 g IV daily × 14–21 days

Or

Penicillin G (Pfizerpen) 3–4 million units IV every 4 hours × 14–21 days

Or

For first- or second-degree heart block, PR interval <0.3 seconds: doxycycline or amoxicillin in doses as noted above × 14–21 days

BID, twice daily; IV, intravenous; PO, by mouth; TID, three times daily.

- Treatment of choice is 7 to 10 days of atovaquone (750 mg PO every 12 hours) plus azithromycin (500–1,000 mg on day 1 and 250 mg–1,000 mg on subsequent days). For severe disease, 7 to 10 days of IV clindamycin (300–600 mg every 6 hours) plus quinine (650 mg PO every 6–8 hours).

### Colorado Tick Fever

- A viral illness (*Coltivirus*) transmitted by the bite of an infected tick.
- Most common initial symptoms are fever of rapid onset, headache, chills without true rigors, and myalgias.
- Treatment is supportive care.

# Anxiety Disorders/Obsessive-Compulsive Disorder/Trauma and Stressor-Related Disorder\*

## General Principles

- Anxiety, an uncomfortable feeling of vague fear or apprehension accompanied by characteristic physical sensations, is a normal reaction to a perceived threat of physical or psychological well-being.
- Anxiety disorder occurs when anxiety is without an external cause, is out of proportion to the actual threat, or lasts beyond the presence of the threat.
- While obsessive-compulsive disorder is closely related to anxiety disorders, it is classified separately in DSM 5.
- Posttraumatic stress disorder is now classified under trauma- and stressor-related disorder in DSM 5 and has undergone significant changes from DSM-IV.

## Classification

- Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM 5) classifies generalized anxiety disorder, panic disorder, and phobic disorder under the category of anxiety disorders, giving obsessive-compulsive disorder (OCD) a separate classification. Posttraumatic stress disorder (PTSD) and acute stress disorder are now classified under trauma and stressor-related disorders. Many secondary causes of anxiety exist (Table 80.1).

## Patient Assessment

### TREATMENT

- A summary of the comparative treatment options for anxiety disorders is in Table 80.2.

## Generalized Anxiety Disorder

- For diagnostic criteria, please refer to DSM 5.
- Onset is usually gradual, and the condition is typically chronic and recurrent.
- Nonpharmacologic therapies include psychotherapy, cognitive therapy, relaxation training, and meditation.
- Antidepressants (e.g., selective serotonin reuptake inhibitors [SSRIs]) are the recommended first-line treatment for most patients. Gradual dose titration is appropriate. Allow at least 8 weeks to assess response.

\*The reader is referred to Chapter 80, Anxiety Disorders, written by Sally K. Guthrie, PharmD, and Jolene R. Bostwick, PharmD, BCPS, BCPP, in the 10th edition of *Applied Therapeutics: The Clinical Use of Drugs* for a more in-depth discussion. All notations to reference numbers are based on the reference list at the end of that chapter. The editor of this handbook expresses her thanks to Drs. Guthrie and Bostwick and acknowledges that this chapter is based on their work.

**TABLE 80.1 Secondary Causes of Anxiety**

<b>MEDICAL ILLNESSES</b>
<i>Endocrine and metabolic disorders:</i> hyperthyroidism, hypoglycemia, Addison disease, Cushing disease, pheochromocytoma, PMS, electrolyte abnormalities, acute intermittent porphyria, anemia
<i>Neurologic:</i> seizure disorders, multiple sclerosis, chronic pain syndromes, traumatic brain injury, CNS neoplasm, migraines, myasthenia gravis, Parkinson disease, vertigo, essential tremor
<i>Cardiovascular:</i> mitral valve prolapse, CHF, arrhythmias, post-MI, hyperdynamic $\beta$ -adrenergic state, hypertension, angina pectoris, post-cerebral infarction
<i>GI:</i> PUD, Crohn's disease, ulcerative colitis, irritable bowel syndrome
<i>Respiratory:</i> COPD, asthma, pneumonia, pulmonary edema, respirator dependence, pulmonary embolus
<i>Others:</i> HIV infection, systemic lupus erythematosus
<b>PSYCHIATRIC</b>
Depression, mania, schizophrenia, adjustment disorder, personality disorders, delirium, dementia, eating disorders
<b>DRUGS</b>
<i>CNS stimulants:</i> amphetamines, caffeine, cocaine, diethylpropion, ephedrine, MDMA (Ecstasy), methylphenidate, nicotine (and withdrawal), PCP, phenylephrine, pseudoephedrine
<i>CNS depressant withdrawal:</i> barbiturates, benzodiazepines, ethanol, opiates
<i>Psychotropics:</i> antipsychotics (akathisia), bupropion, buspirone, SNRIs, SSRIs, TCAs
<i>Cardiovascular:</i> captopril, enalapril, digoxin, disopyramide, hydralazine, procainamide, propafenone, reserpine
<i>Others:</i> albuterol, aminophylline, baclofen, bromocriptine, cycloserine, dapsone, dronabinol, efavirenz, fluoroquinolones, interferon- $\alpha$ , isoniazid, isoproterenol, levodopa, lidocaine, mefloquine, metoclopramide, monosodium glutamate, nicotinic acid, NSAIDs, pergolide, quinacrine, sibutramine, statins, steroids, theophylline, thyroid hormone, triptans, vinblastine, yohimbine

CHF, congestive heart failure; CNS, central nervous system; COPD, chronic obstructive pulmonary disease; GI, gastrointestinal; HIV, human immunodeficiency virus; MDMA, 3,4-methylenedioxymethamphetamine; MI, myocardial infarction; NSAIDs, nonsteroidal anti-inflammatory drugs; PCP, phencyclidine; PMS, premenstrual syndrome; PUD, peptic ulcer disease; SNRIs, serotonin and norepinephrine reuptake inhibitors; SSRIs, selective serotonin reuptake inhibitors; TCAs, tricyclic antidepressants.

**TABLE 80.2 Summary of Comparative Medication Treatment Options for Anxiety Disorders**

Disorder	First-Line Treatments <sup>a</sup>	Second-Line Treatments	Possible Alternatives
Generalized anxiety disorder	Venlafaxine XR Buspirone Benzodiazepines Paroxetine Escitalopram Duloxetine	Sertraline Citalopram	Tricyclic antidepressants <sup>b</sup> Pregabalin Fluoxetine Mirtazapine Atypical antipsychotics <sup>c</sup>
Panic disorder	Paroxetine Sertraline Fluoxetine Venlafaxine Alprazolam Clonazepam	Fluvoxamine Citalopram Escitalopram Clomipramine Lorazepam	Nefazodone <sup>b</sup> Mirtazapine Imipramine Valproic acid Diazepam
Social anxiety disorder	Paroxetine Sertraline Venlafaxine XR Fluvoxamine CR	Citalopram Escitalopram Fluoxetine Alprazolam Clonazepam	Phenelzine <sup>b</sup> Nefazodone Bupropion Duloxetine Gabapentin Pregabalin Atypical antipsychotics <sup>c</sup>

<sup>a</sup>US Food and Drug Administration–approved indications.  
<sup>b</sup>Documented efficacy, but not recommended for first-line treatment because of undesirable clinical properties (side effects, potential toxicity, drug interactions).  
<sup>c</sup>Adjunctive therapy only.

- Benzodiazepines are widely prescribed anxiolytic agents that act quickly and are effective for short-term therapy (Tables 80.3 and 80.4). Several physiological factors can influence their pharmacokinetics (Table 80.5); drug interactions exist (Table 80.6). Physical dependence can occur; limit use to 2 to 6 weeks of therapy. Abrupt discontinuation can cause withdrawal symptoms (Table 80.7).
- Buspirone is a nonbenzodiazepine anxiolytic treatment option that has minimal potential for abuse. Drug interactions are possible (Table 80.8).
- Atypical antipsychotics are options in patients who fail first-line treatment or who have a comorbid psychotic illness.
- Effective treatment should be continued for at least 6 to 12 months after response.

## Panic Disorder

- For diagnostic criteria, please view DSM 5.
- Panic attacks are the hallmark symptom, but their occurrence does not always indicate panic disorder.
- Nonpharmacologic management includes cognitive behavior therapy (CBT).

TABLE 80.3 Clinical Comparison of Benzodiazepine Agents

Drug (Trade Name, Generic)	FDA-Approved Indications	Usual Dosage Range Through 65 Years of Age	Maximal Recommended Dosage Through 65 Years of Age	Approximate Dosage Equivalencies
Alprazolam (Xanax, Xanax XR, Niravam orally disintegrating tablets, Intensol oral solution, generic)	Anxiety, anxiety associated with depression, panic disorder	0.5–6 mg/day (up to 10 mg/day for panic disorder)	2 mg/day	1
Chlordiazepoxide (Librium, Limbitrol <sup>a</sup> , Librax <sup>b</sup> , generic)	Anxiety, preoperative anxiety, acute alcohol withdrawal	15–100 mg/day	40 mg/day	50
Clonazepam (Klonopin, Klonopin wafer, generic)	Anticonvulsant, panic disorder	0.5–12 mg/day	3 mg/day	0.5
Clorazepate (Tranxene, Tranxene-SD, generic)	Anxiety, alcohol withdrawal, anticonvulsant	15–60 mg/day	30 mg/day	15
Diazepam (Valium, Intensol oral solution, Injection solution, generic)	Anxiety, muscle relaxant, acute alcohol withdrawal, preoperative anxiety, anticonvulsant	4–40 mg/day	20 mg/day	10
Estazolam (ProSom, generic)	Sedative-hypnotic	1–2 mg HS	1 mg HS	2
Flurazepam (Dalmane, generic)	Sedative-hypnotic	15–30 mg HS	15 mg HS	30
Lorazepam (Ativan, oral solution, injection solution, generic)	Anxiety, anxiety associated with depression, anticonvulsant, premedication for anesthetic procedure	2–6 mg/day	3 mg/day	1.5–2
Oxazepam (Serax, generic)	Anxiety, alcohol withdrawal	30–120 mg/day	60 mg/day	30
Quazepam (Doral)	Sedative-hypnotic	7.5–15 mg HS	7.5 mg HS	15
Temazepam (Restoril, generic)	Sedative-hypnotic	15–30 mg HS	15 mg HS	30
Triazolam (Halcion, generic)	Sedative-hypnotic	0.125–0.25 mg HS	0.125 mg HS	0.25

<sup>a</sup>Combination product containing amitriptyline.

<sup>b</sup>Combination product containing clidinium bromide (classified as a gastrointestinal antispasmodic agent). FDA, US Food and Drug Administration; HS, at bedtime.

TABLE 80.4 Pharmacokinetic Comparison of Benzodiazepine Agents

Drug	Elimination Half-Life (hours) <sup>a</sup>	Active Metabolites	Protein Binding	Pathway of Metabolism	Rate of Onset After Oral Administration
Chlordiazepoxide	>100	Desmethyldiazepam	96%	Oxidation	Intermediate
Diazepam	>100	Desmethyldiazepam	98%	Oxidation (CYP3A4, CYP2C19)	Very fast
Oxazepam	5–14	None	87%	Conjugation	Slow
Flurazepam	>100	Desalkylflurazepam, hydroxyethylflurazepam	97%	Oxidation	Fast
Clorazepate	>100	Desmethyldiazepam	98%	Oxidation	Fast
Lorazepam	10–20	None	85%–90%	Conjugation	Intermediate
Alprazolam	12–15	Insignificant	80%	Oxidation (CYP3A4)	Fast
Temazepam	10–20	Insignificant	98%	Conjugation	Intermediate
Triazolam	1.5–5	Insignificant	90%	Oxidation (CYP3A4)	Intermediate
Quazepam	47–100	2-Oxoquazepam, N-desalkyl-2-oxoquazepam	>95%	Oxidation	Fast
Estazolam	24	Insignificant	93%	Oxidation	Intermediate
Clonazepam	20–50	Insignificant	85%	Oxidation, reduction (CYP3A4)	Intermediate
Midazolam	1–4	None	97%	Oxidation (CYP3A4)	NA

<sup>a</sup>Parent drug + active metabolite.

CYP, cytochrome P-450; NA, not applicable.

- First-line medication treatments are SSRIs and venlafaxine. Low starting doses are recommended to minimize side effects, with the dose titrated to response. At least 6 weeks of optimal dosing should be allowed before assessing response.
- Benzodiazepines are effective but not recommended as first-line therapy because of their abuse liability and inability to treat concomitant depression.
- Effective treatment should be continued for at least 6 to 12 months after acute response.

## Social Anxiety Disorder

- For diagnostic criteria, please see DSM 5.
- Early detection and treatment is vital to reduce lifelong functional consequences.
- Pharmacotherapy is first line; nonpharmacologic treatment (e.g., cognitive behavior therapy) can be useful.
- SSRIs at standard antidepressant doses are considered the primary treatment option. Monoamine oxidase inhibitors are reserved for SSRI nonresponders.
- Benzodiazepines are considered second-line therapy. High-potency benzodiazepines (e.g., clonazepam) may be useful in some patients.
- $\beta$ -Adrenergic blockers are useful for nongeneralized social phobia involving performance-related situations.
- Effective treatment should be continued for at least 1 year after acute response.

## Posttraumatic Stress Disorder and Acute Stress Disorder

- For diagnostic criteria, please view DSM 5. Acute stress disorder is a separate diagnosis in which symptoms last less than 1 month.

TABLE 80.5 Physiological Factors Influencing Benzodiazepine Pharmacokinetics

Factor	Physiological and Pharmacokinetic Effects	Clinical Significance or Comments
Aging	Increased elimination half-life as a result of increased Vd of all benzodiazepines	Lower benzodiazepine dosages, and possibly less-frequent dosing intervals, recommended in the elderly
	Decreased clearance of benzodiazepines that undergo oxidative hepatic metabolism (Table 80.5)	Benzodiazepines that undergo glucuronidation (lorazepam, oxazepam) preferred in the elderly
	Decreased plasma proteins may lead to increased free fraction of highly protein-bound benzodiazepines	Possible increased clinical effects
	Decreased gastric acidity may lead to increased rate of benzodiazepine absorption	Possible faster onset of clinical effects
Sex	Age-related decrease in hepatic oxidative metabolism of benzodiazepines more pronounced in men	Elderly men may require especially low benzodiazepine dosages
	Increased CYP 3A4 and CYP 2C19 activity in premenopausal women may result in higher clearance of drugs that undergo oxidative metabolism	Possible decreased plasma benzodiazepine concentrations and shorter duration of clinical effects of oxidatively metabolized agents in premenopausal women
	Decreased glucuronidation in women may result in slower clearance of benzodiazepines metabolized by conjugation	Women may have longer elimination half-lives of lorazepam and temazepam and may require less-frequent dosing
	Increased Vd in women owing to lower lean body mass and increased adipose tissue	Possible longer elimination half-lives in women, especially the elderly, and greater drug accumulation
Obesity	Lower plasma protein binding in women	Clinical significance unknown
	Increased benzodiazepine elimination half-lives owing to increased Vd	Increased chance of drug accumulation in obese patients; dosage reductions may be indicated
Liver disease	Decreased clearance and increased elimination half-lives of long-acting benzodiazepines and alprazolam in cirrhosis and hepatitis; no changes with oxazepam or triazolam	Avoid long-acting benzodiazepines, or use significantly lower doses to avoid drug accumulation
	Increased elimination half-life of lorazepam in cirrhosis but not acute hepatitis	Decreased lorazepam dose or increased dosing interval recommended in cirrhosis
Kidney disease	Decreased plasma protein binding may lead to increased free fraction of highly protein-bound benzodiazepines	Dosage reductions may be necessary
Ethnicity	Decreased oxidative metabolism (via CYP 2C19) of diazepam and alprazolam in Asians	Asians may require lower doses of diazepam, alprazolam, and possibly other benzodiazepines

CYP, cytochrome P-450; Vd, volume of distribution.

- Pharmacotherapy, either alone or in combination with psychological therapy, is recommended for patients with moderate or severe illness. Nonpharmacologic therapies alone are reserved for patients with mild symptoms.
- First-line medication treatments are SSRIs, initiated at low doses and titrated to response. Other antidepressants may also be useful.
- Goals of therapy are to reduce core symptoms of reexperiencing, avoidance, negative alterations in mood, and hyperarousal. Other goals are decreasing detrimental behaviors and treating comorbid psychiatric conditions.
- Response is more likely when treatment is started within 3 months of trauma. Effective treatment should continue for at least 6 to 12 months for acute cases, and 12 to 24 months for chronic cases.



TABLE 80.6 Drug Interactions with Benzodiazepines

Interacting Drug(s)	Effect on Object Drug	Clinical Significance or Comments
Hepatic enzyme inducers: carbamazepine, phenobarbital, phenytoin, and rifampin	Decreased Cps and clinical effects of benzodiazepines	Triazolam and midazolam may be ineffective in patients taking rifampin. Carbamazepine greatly decreases the Cps and clinical effects of midazolam, alprazolam, and clonazepam, possibly rendering them ineffective.
Hepatic CYP 3A4 inhibitors: ketoconazole, itraconazole, nefazodone, fluvoxamine, fluoxetine, erythromycin, clarithromycin, cimetidine, oral contraceptives, diltiazem, nelfinavir, indinavir, ritonavir, saquinavir, verapamil	Significantly increased Cps of benzodiazepines that undergo oxidative metabolism (alprazolam, triazolam, diazepam, chlordiazepoxide, clonazepam)	Benzodiazepine dosage reductions may be required because of increased clinical effects such as sedation and psychomotor impairment; effects are greatest on alprazolam, triazolam, and midazolam. Ketoconazole and itraconazole should be avoided in patients taking alprazolam or triazolam. Benzodiazepine dosage reductions are recommended when nefazodone, fluoxetine, or fluvoxamine are added to alprazolam, diazepam, or triazolam.
Ritonavir	Initial inhibition of alprazolam and triazolam metabolism, followed by later induction of metabolism	Reduced benzodiazepine dosage is needed initially if ritonavir is added to therapy; a dosage increase may be required later.
Grapefruit juice	Increased Cps of diazepam, alprazolam, and triazolam	Increased benzodiazepine clinical effects (sedation, psychomotor impairment) are possible.
Omeprazole	Increased diazepam Cp and prolonged half-life	Increased benzodiazepine clinical effects (sedation, psychomotor impairment) are possible.
Valproic acid, probenecid	Significantly decreased clearance of lorazepam	Lorazepam dosage reductions may be required.
Estrogen-containing oral contraceptives	Decreased Cps of benzodiazepines that undergo glucuronidation (lorazepam, oxazepam, temazepam) and increased Cps of benzodiazepines that undergo oxidative CYP 3A4 metabolism (alprazolam)	Decreased or increased clinical effects of benzodiazepines are possible.
Central nervous system depressants (alcohol, barbiturates, and opioids)	Increased central nervous system depressant effects of benzodiazepines (sedation, psychomotor impairment)	Avoid use of alcohol with benzodiazepines; exercise caution with use of other depressants.
Alprazolam	Increased digoxin Cp	Digoxin toxicity is possible; monitoring of digoxin level and possible digoxin dosage reduction are recommended.
Benzodiazepines	Respiratory depression and adverse cardiovascular effects reported on addition of benzodiazepines in several patients taking clozapine Possible decreased efficacy of levodopa in Parkinson disease Increased or decreased efficacy of neuromuscular blocking agents.	Caution with benzodiazepine use in patients taking clozapine.  Drug interaction is not well established; monitor for possible effect. Drug interaction is not well established; monitor for possible effect

CP, plasma concentration; CYP, cytochrome P-450.

TABLE 80.7 Symptoms of Benzodiazepine Withdrawal

Common	Less Common	Rare
Anxiety	Nausea	Confusion
Insomnia	Depression	Delirium
Irritability	Ataxia	Psychosis
Muscle aches or weakness	Hyperreflexia	Seizures
Tremor	Blurred vision	Catatonias
Loss of appetite	Fatigue	

TABLE 80.8 Buspirone Drug Interactions

Interacting Drug(s)	Clinical Significance or Comments
CYP 3A4 inhibitors: nefazodone, fluoxetine, fluvoxamine, erythromycin, itraconazole, ketoconazole, diltiazem, verapamil, grapefruit juice, and ritonavir	Significant increases in buspirone Cp have been reported with these agents, but adverse clinical effects are not always apparent. Buspirone dosage reductions are recommended when coadministered with erythromycin, fluvoxamine, nefazodone, fluoxetine, or itraconazole.
Rifampin	Highly significant decreases in buspirone Cp; avoid concurrent use.
Haloperidol	Buspirone may increase haloperidol Cp, but one study found no interaction.
Monoamine oxidase inhibitors	Possible serotonin syndrome; avoid concurrent use.

Cp, plasma concentration; CYP, cytochrome P-450.

## Obsessive-Compulsive Disorder

- For diagnostic criteria, please refer to DSM 5. An obsession is an intrusive or recurrent thought, image, or impulse that incites anxiety and cannot be ignored or suppressed voluntarily. A compulsion is a behavior or ritual that is performed in a repetitive or stereotypical way to reduce anxiety associated with obsessions.
- Course and severity of OCD are highly variable and unpredictable; serious detrimental effects on functional ability can occur.
- Identification of comorbidities is important as it can influence choice of treatment.
- Medication and behavioral therapies (cognitive behavior therapy) are effective treatment.
- SSRIs are first-line medication treatments. No evidence supports one agent over another. Switching to a second SSRI is recommended before initiating clomipramine therapy. Usual SSRI starting doses are appropriate; allow at least 4 weeks of therapy before exceeding the minimal effective dose.
- Current guidelines recommend reserving clomipramine for patients who fail at least two SSRIs.
- Risperidone (2–4 mg/day), olanzapine (10–20 mg/day), and quetiapine (up to 600 mg/day) have all been used to augment SSRI therapy in treatment-resistant OCD.
- Benzodiazepines are generally not effective for OCD.
- Response to medication is gradual and delayed. Maximal response may take 5 to 6 months.
- The primary treatment goal is to reduce obsessions and compulsions to a level at which the person can function normally. Complete elimination of symptoms is rare.
- Effective treatment should continue for at least 1 year after response to reduce the risk of relapse. Therapy should be withdrawn gradually (approximately 25% every 1–2 months). Continuous monitoring for signs of relapse is required.

# Sleep Disorders\*

## General Principles

- Untreated sleep disorders are associated with reduced mental and physical functioning and poor quality of life. Major sleep disorders are shown in Table 81.1.
- **Insomnia** is defined as requiring longer than 30 minutes to fall asleep, awakenings throughout the night without immediate return to sleep, early morning awakening, or total sleep time of less than 6 hours. It is not just a symptom of a medical or psychiatric illness but also a condition that contributes to the severity of that disease or disorder. Insomnia concurrent with medical illness is frequently chronic (>1 month).
- **Sleep apnea** is a neurologic disorder characterized by mini episodes of cessation of breathing, which can occur 10 to 200 times per hour.
- **Narcolepsy** is an incurable neurologic disease characterized by irrepressible sleep attacks (up to 5 times daily) and cataplexy (loss of muscle tone in face or limb muscles).

## Classification

- Sleep disorders are categorized largely on the basis of pathophysiology and presumed etiology; four main categories are useful for clinical assessment (Table 81.2).

## Patient Assessment

- Asking the right questions to explore the type of insomnia (trouble falling asleep, staying asleep, early morning awakening), possible causes (lifestyle issues, medications), resulting impairment, and concomitant conditions is essential to proper management.
- Numerous medical disorders and primary sleep disorders are associated with difficulty falling asleep and maintaining sleep (Tables 81.3 and 81.4).
- Sleep apnea is characterized by excessive snoring, gasping for air, and weight gain.

TABLE 81.1 Incidence of Major Sleep Disorders

Sleep Disorder	Incidence (%)
Insomnia	30–35
Transient (few days)	
Short-term (up to 1 month)	
Chronic (>1 month)	
Sleep apnea	5–15
PLMS (nocturnal myoclonus)	5–15
RLS	5–15
Narcolepsy	0.06

PLMS, periodic limb movements during sleep; RLS, restless legs syndrome.

\*The reader is referred to Chapter 81, Sleep Disorders, written by Julie A. Dopheide, PharmD, BCPP, and Glen L. Stimmel, PharmD, BCPP, in the 10th edition of *Applied Therapeutics: The Clinical Use of Drugs* for a more in-depth discussion. All notations to reference numbers are based on the reference list at the end of that chapter. The editor of this handbook expresses her thanks to Drs. Dopheide and Stimmel and acknowledges that this chapter is based on their work.

TABLE 81.2 Classification of Sleep Disorders

**DYSSOMNIAS<sup>a</sup>**

Intrinsic: idiopathic insomnia, narcolepsy, sleep apnea, periodic limb movements during sleep  
 Extrinsic: inadequate sleep hygiene, substance-induced sleep disorder  
 Circadian rhythm sleep disorders: jet lag, shift work, delayed sleep-phase syndrome

**PARASOMNIAS<sup>b</sup>**

Arousal: confusional arousals, sleepwalking, sleep terrors  
 Sleep-wake transition disorders: sleep talking, nocturnal leg cramps  
 Associated with REM: nightmares, sleep paralysis, impaired sleep-related penile erections  
 Other: primary snoring, sudden infant death syndrome, sleep bruxism

**MEDICAL, PSYCHIATRIC, AND SUBSTANCE-INDUCED SLEEP DISORDERS**

Associated with mental disorders: mood disorders, anxiety disorders, psychotic disorders  
 Associated with neurologic disorders: Parkinson disease, Huntington disease, dementia  
 Associated with other medical disorders: heart disease, renal insufficiency, pulmonary disease  
 Associated with a substance: medication/substance abuse (e.g., phenylpropranolamine, cocaine)

**PROPOSED SLEEP DISORDERS**

Menstrual-associated sleep disorder, pregnancy-associated sleep disorder, short or long sleeper

<sup>a</sup>Any sleep pattern that is abnormal (e.g., insomnia or excessive sleepiness).

<sup>b</sup>Any unusual behavior that emerges during sleep.

REM, rapid eye movement.

TABLE 81.3 Potential Causes and Contributing Factors for Each Chronic Sleep Complaint

**DFA**

Learned or conditioned activation (primary insomnia): RLS  
 Medications: methylphenidate, modafinil, fluoxetine, bupropion, steroid,  $\beta$ -blocker  
 Substances: caffeine, guarana, alcohol  
 Psychiatric disorders: schizophrenia, depression, anxiety disorder, bipolar disorder  
 Medical disorder: chronic pain, neuropathy, gastrointestinal disorder, cardiopulmonary disorders (particularly if in recumbent position)

**DMA**

Excessive time in bed  
 Psychiatric disorder: major depression, anxiety or bipolar disorder, substance abuse  
 Sleep-disordered breathing: sleep apnea, acute respiratory distress syndrome  
 Cardiac disease: atrial fibrillation, heart failure, angina  
 Neurologic disorder: dementia, Parkinson disease, multiple sclerosis

**EMA**

Major depression  
 Advanced sleep-phase syndrome: learned or conditioned activation (primary insomnia)  
 Forced to get up because of family or work obligations

**EXCESSIVE DAYTIME SLEEPINESS**

Medications: clonidine, antihistamines, antipsychotic, antidepressant, benzodiazepine, chloral hydrate, opioid, anticonvulsant,  $\alpha_1$ -adrenergic blockers  
 Obstructive sleep apnea, central sleep apnea, narcolepsy  
 Chronic sleep deprivation

DFA, difficulty falling asleep; DMA, difficulty maintaining sleep; EMA, early morning awakening, RLS, restless legs syndrome.

**Treatment**

- Treatment of insomnia requires assessment of concomitant conditions and the nature of sleep problems (Figure 81.1). Nonpharmacologic treatments are recommended as first-line therapy for many patients (Table 81.5).

TABLE 81.4 Potential Causes of Chronic Sleep Disorders

## PSYCHIATRIC DISORDERS

Anxiety disorders	Depressive disorders
Bipolar disorder	Psychotic disorders
Personality disorders	Somatoform disorders
Organic mental disorders	Substance abuse

## MEDICAL AND NEUROLOGIC DISORDERS

Angina pectoris	Dementia
Bronchitis	Peptic ulcer disease
Chronic fatigue	Hyperthyroidism and hypothyroidism
Cystic fibrosis	Asthma
Huntington disease	COPD
Parkinson disease	Epilepsy
Hypertension	Gastroesophageal reflux
Arthritis	Renal insufficiency
Cardiac disease	Connective tissue disease
Chronic pain	
Cancer	

## SLEEP DISORDERS

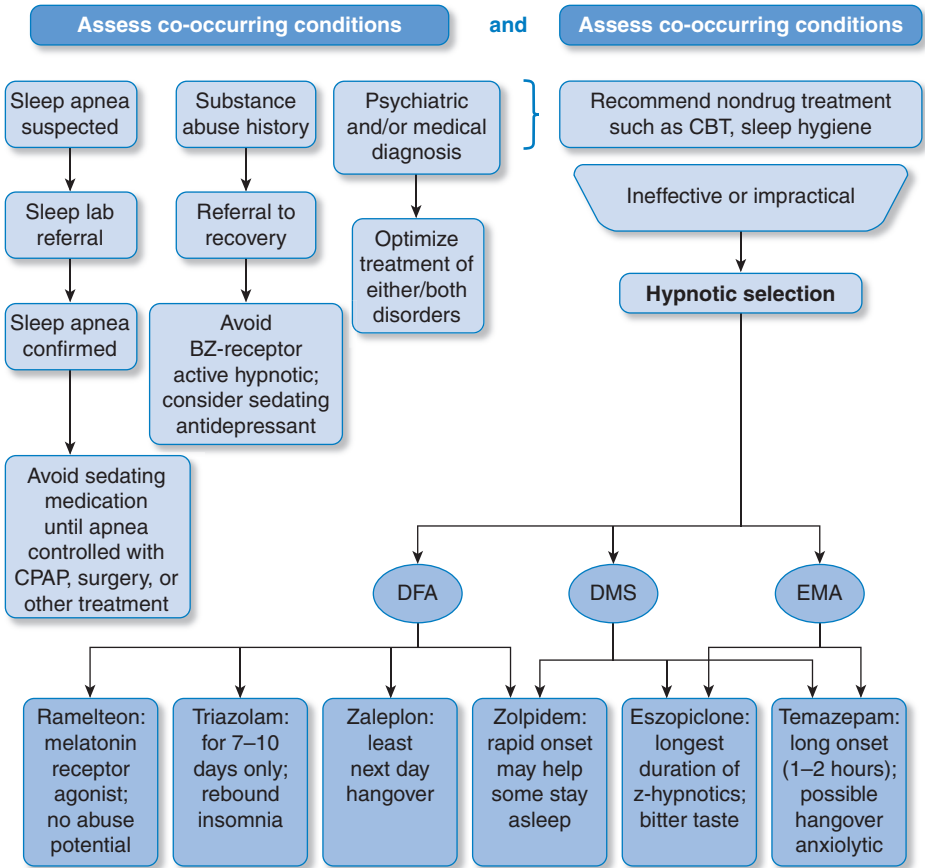
RLS	Sleep apnea (obstructive or central)
PLMS (nocturnal myoclonus)	Primary snoring
Circadian rhythm sleep disorder (jet lag, shift work, delayed sleep phase)	Narcolepsy

## DRUGS ASSOCIATED WITH SLEEP DISTURBANCE

Insomnia	Hypersomnia
Alcohol	Alcohol
Bupropion	Benzodiazepines
Fluoxetine	Antihypertensives
Sertraline	Clonidine
MAO inhibitors	$\alpha$ -Adrenergic blockers
TCA	ACE inhibitors
Thyroid supplements	$\beta$ -Blockers
Calcium-channel blockers	Anticonvulsants
Decongestants	Analgesics
Appetite suppressants	Chloral hydrate
Theophylline	Antipsychotics
Corticosteroids	Antihistamines
Dopamine agonists	Opioids

ACE, angiotensin-converting enzyme; COPD, chronic obstructive pulmonary disease; MAO, monoamine oxidase; PLMS, periodic limb movements during sleep; RLS, restless legs syndrome; TCA, tricyclic antidepressants.

- Hypnotic medications are recommended when nondrug interventions fail or cannot be implemented, or when rapid results are essential. Pharmacologic treatments are selected on the basis of efficacy, tolerability, onset and duration of effect, potential for next-day hangover, and abuse potential.
- Insomnia concurrent with psychiatric illness requires optimization of psychiatric maintenance medications and judicious use of hypnotic medications on the basis of type of sleep complaint and substance abuse potential.
- Management of insomnia in the elderly involves consideration of age-related pharmacodynamic and pharmacokinetic changes and counseling regarding realistic expectations. Medication doses lower than those used in younger patients should be used. Sedating antihistamines should be avoided due to anticholinergic side effects.
- Diphenhydramine is the most commonly used sedative in children. Melatonin may help with falling asleep but not with sustaining sleep.



**Figure 81.1** Algorithm for treatment of insomnia. DFA, difficulty falling asleep; DMS, difficulty maintaining sleep; EMA, early morning awakening.

**TABLE 81.5 Nonpharmacologic Treatments for Insomnia**

1. Cognitive-behavioral therapy: most effective; can be from any trained provider.
  - Cognitive: identify and stop thought patterns that interfere with sleep (e.g., “I’m never going to sleep” or allowing 15 minutes to review a worry list, then putting worries aside).
  - Behavioral: stimulus control, sleep restriction, relaxation, paradoxical intention.
    - a. Stimulus control: train the brain to reassociate the bed and bedroom with sleep and reestablish a consistent sleep–wake schedule.
    - b. Sleep restriction: create “sleep-debt” by curtailing amount of time in bed, then increasing time in bed as sleep efficiency improves.
    - c. Relaxation therapy: progressive tensing and relaxing of muscles, yoga, stretching.
    - d. Paradoxical intention: encourage patient to engage in most feared behavior, “staying awake,” to reduce performance anxiety associated with trying to sleep.
2. Sleep hygiene: not considered effective on its own; useful adjunctive treatment.
  - Avoid caffeine, stimulants, heavy meals, and alcohol at bedtime; exercise early in the day before dinner to relieve stress and prime brain for sleep. Turn the face of the clock away from view; establish a before-bedtime ritual, make sure bedroom is dark, quiet, and comfortable.

- Pregnant patients should be managed with nonpharmacologic measures whenever possible. Short-term (<1 week) use of diphenhydramine is considered safe; doxylamine and hydroxyzine should be avoided. Risk versus benefit must be considered when using benzodiazepines in pregnancy.
- Sleep apnea should be treated with continuous positive airway pressure or surgical interventions. Sedating medications should be avoided as they could be lethal.
- Narcolepsy can be managed with stimulants (e.g., modafinil, armodafinil) to help decrease sleep attacks and promote daytime alertness; they do not help with cataplexy or nocturnal insomnia. Sodium oxybate improves nocturnal sleep but is limited by its high abuse potential and psychiatric side effects.

## Drug Therapy

- Benzodiazepine hypnotics or selective omega-1 selective hypnotics, or Z-hypnotics (zaleplon, zolpidem, eszopiclone), are first-line pharmacologic therapy (Tables 81.6 and 81.7). Triazolam is most commonly associated with rebound insomnia and withdrawal problems. Z-hypnotics are less likely to cause rebound insomnia.
- Melatonin (0.5–10 mg) has shown efficacy for insomnia in children and adolescents with concomitant neuropsychiatric disorders (e.g., autism, attention deficit hyperactivity disorder [ADHD]). Efficacy for chronic insomnia has not been established.
- Ramelteon is approved for insomnia characterized by difficulty falling asleep. It offers the advantage of no abuse potential and little risk of next-day impairment.
- Antidepressants can improve sleep, although some agents may also cause insomnia. Trazodone (50–200 mg) and doxepin (3–6 mg) at bedtime are commonly prescribed.

**TABLE 81.6 Pharmacokinetic Properties of Hypnotics Acting at Benzodiazepine Receptors<sup>33,34,41,45-47</sup>**

Active Substance	Lipid Solubility	T <sub>max</sub> (hours)	Onset (minutes)	Half-Life (hours)	Duration (hours) <sup>a</sup>
Zaleplon	Moderate	1.1	30	1.1	1–2
Zolpidem	Low	1–2	30	2.5	2–4
Zolpidem ER	Low	2	45	2.8	3–5
Eszopiclone	Low	1–1.6	30–45	6	5–8
Triazolam	Moderate	1	15–30	2–5	2–4
Temazepam	Moderate	1.5–2.0	60–120	10–20	8–12
Flurazepam <sup>b</sup>					
Hydroxyethyl <sup>b</sup>	Low	1		2–3	
Aldehyde <sup>b</sup>	Low	1		1	
N-desalkyl <sup>b</sup>	Moderate	10	30–60	50–100	10–30

<sup>a</sup>Time the patient feels the effects after a single dose; usually approximates half-life with multiple doses; individual variability exists; and tolerance may develop with continued use, lessening the duration.

<sup>b</sup>Flurazepam metabolite.

T<sub>max</sub>, time of maximum concentration.

**TABLE 81.7 Hypnotic Dosing Comparison**

Drug	Dose (mg)	Range (mg)
Midazolam (Versed)	15	10–30
Zaleplon (Sonata)	10	5–10
Zolpidem (Ambien, Edluar)	5 (women) 5–10 (men)	5–10
Zolpidem ER (Ambien CR)	6.25 (women) 6.25 or 12.5 (men)	6.25–12.5
Eszopiclone (Lunesta)	1	1–3
Ramelteon (Rozerem)	8	—
Triazolam (Halcion)	0.25	0.125–0.25
Temazepam (Restoril)	15	7.5–30
Flurazepam (Dalmane)	15	15–30

# Schizophrenia\*

## General Principles

- Schizophrenia is typically a lifelong psychiatric disability that requires comprehensive and continuous care over the course of a lifetime.
- Table 82.1 provides a glossary of terms used in schizophrenia.

TABLE 82.1 Glossary of Commonly Used Terms in Schizophrenia

**Affect:** behavior (usually an expression of an emotion) observed by the interviewer. Common types of disturbances in affect include *restricted*—mild decrease in range and intensity of the expression of emotion; *blunted*—significant decrease in intensity of the expression of emotion; *flat*—absence of expression of emotion; *inappropriate*—

incongruency between patient's affect and mood or behavior; and *labile*—abrupt shifts in expression of emotion  
**Akathisia:** syndrome consisting of subjective feelings of anxiety and restlessness, and objective signs of pacing, rocking, and an inability to sit or stand still for extended periods

**Akinesia:** absence or decrease in voluntary movement; may be antipsychotic induced (extrapyramidal side effects) or a manifestation of negative symptoms of schizophrenia

**Alogia:** impoverished thinking usually manifested through speech and language deficits. Speech is brief and lacks spontaneity; replies to questions are very concrete (*poverty of speech*). *Poverty of content* refers to speech that is adequate in amount, but is of little substance (overly abstract), repetitive, or stereotyped

**Anergy:** lack of energy

**Anhedonia:** loss of interest or pleasure

**Avolition:** an inability to initiate and sustain goal-directed activities. The patient may sit for extended periods and show minimal interest in participating in social or work-related activities

**Circumstantiality:** a form of disorganized speech characterized by “talking in circles” or taking an unusually long time in answering a question or expressing one’s point of view

**Delusions:** a false belief that is firmly held despite evidence to refute the belief. The belief does not qualify as a delusion if it is a cultural or religious belief accepted by a group of individuals. Types of delusions include grandiose, persecutory, and somatic

**Executive function:** the ability to design and carry out a solution to a plan when the solution is not obvious. Loss of executive function presents as failure to learn from past experience and failure to plan or organize life events

**Hallucination:** a sensory perception (e.g., auditory, visual, somatic, tactile) experienced in the absence of external stimuli. Hallucinations may be recognized as false sensory perceptions in some, whereas others may believe that the experiences are reality based

**Loose associations:** a form of disorganized, illogical speech characterized by unrelated words, phrases, and sentences used in a fashion that makes comprehension very difficult, if not impossible

**Mood:** a pervasive and sustained emotion that is experienced by the patient. Examples include depressed, anxious, angry, or irritable mood

**Mood-congruent delusions or hallucinations:** delusions or hallucinations that are consistent with a mood or behavior (e.g., delusions or hallucinations of death, guilt, or punishment in the presence of a depressed mood)

**Mood-incongruent delusions or hallucinations:** delusions or hallucinations that are not consistent with a mood or behavior (e.g., delusions or hallucinations of death, guilt, or punishment in the presence of mania)

**Tangentiality:** a form of disorganized speech in which answers are remotely or completely unrelated to questions, and patients’ thoughts frequently shift in an unconnected fashion

**Thought broadcasting:** a delusion that one’s thoughts are being broadcast to others (e.g., a patient feels that others can read his or her mind)

**Thought disorder:** a general term often used to describe any type of abnormal thought process (e.g., delusion, loose association, conceptual disorganization)

**Thought insertion:** a delusion that one’s thoughts are being inserted into one’s mind by others

\*The reader is referred to Chapter 82, Schizophrenia, written by Jonathan P. Lacro, PharmD, BCPS, BCPP, Sanaz Farhadian, PharmD, and Rene A. Endow-Eyer, PharmD, BCPP, in the 10th edition of *Applied Therapeutics: The Clinical Use of Drugs* for a more in-depth discussion. All notations to reference numbers are based on the reference list at the end of that chapter. The editor of this handbook expresses her thanks to Drs. Lacro, Farhadian, and Endow-Eyer and acknowledges that this chapter is based on their work.



## Patient Assessment

- For diagnostic criteria and differential diagnoses, please refer to DSM 5.
- Characteristic symptoms fall into two categories, positive and negative (Table 82.2).
- A complete medical, psychiatric, and medication history, physical exam, laboratory panel, and electrocardiogram (ECG) should be obtained as soon as possible during the acute phase.

## Goals of Therapy

- Goals of therapy are to optimize functional capacity, reduce the frequency and severity of symptom exacerbations, and reduce overall morbidity and mortality.

## Treatment

- Acute phase of illness: Often requires hospitalization or placement in a supervised outpatient setting. Medications are usually required to calm agitated patients (Table 82.3). Initiate antipsychotic therapy as soon as feasible; prolonged psychotic episodes are associated with worsened course of illness.

Positive	Negative
Psychosis	Psychomotor retardation
Hallucinations	Affective flattening
Delusions	Avolition
Disorganization	Lack of socialization
Disorganized speech (loose associations, tangential, blocking)	Alogia
Unusual behavior	Loss of emotional connectedness
Combattiveness, agitation, and hostility	Loss of executive functions

Medication	Dosage Form	Dose (mg)	Onset (minutes)	Half-Life (hours)	Duration of Action (hours)
Lorazepam	PO (tablet), IM, IV	1–2	60–90	720–900 minutes	480–600 minutes
<b>TYPICAL ANTIPSYCHOTICS</b>					
Haloperidol	PO (tablet), IM, IV	5–10	30–60	720–2,160 minutes	Upto 1,440 minutes
<b>ATYPICAL ANTIPSYCHOTICS</b>					
Olanzapine	PO (tablet), IM, ODT	10	15–45	1,800 minutes	1,440 minutes
Risperidone	PO (tablet, liquid), ODT	2	60	1,200 minutes	Not available
Ziprasidone	PO (tablet), IM	20	30–60	120–300 minutes	240 minutes
Aripiprazole	PO (tablet, liquid), IM, ODT	9.75	60–180	4,500–5,640 minutes	Not available

IM, intramuscularly; IV, intravenously; ODT, oral disintegrating tablet; PO, orally.

Sources: Battaglia J. Pharmacological management of acute agitation. *Drugs*. 2005;65:1207; Garza-Trevino ES et al. Efficacy of combinations of intramuscular antipsychotics and sedative-hypnotics for control of psychotic agitation. *Am J Psychiatry*. 1989;146:1598; Altamura AC et al. Intramuscular preparations of antipsychotics: uses and relevance in clinical practice. *Drugs*. 2003;63:493; Brook S et al. Intramuscular ziprasidone compared with intramuscular haloperidol in the treatment of acute psychosis. Ziprasidone I.M. Study Group. *J Clin Psychiatry*. 2000;61:933; Andrienza R et al. Intramuscular aripiprazole for the treatment of acute agitation in patients with schizophrenia or schizoaffective disorder: a double-blind, placebo-controlled comparison with intramuscular haloperidol. *Psychopharmacology (Berl)*. 2006;188:281; Currier GW et al. Acute treatment of psychotic agitation: a randomized comparison of oral treatment with risperidone and lorazepam versus intramuscular treatment with haloperidol and lorazepam. *J Clin Psychiatry*. 2004;65:386; Lesem MD et al. Intramuscular ziprasidone, 2 mg versus 10 mg, in the short-term management of agitated psychotic patients [published correction appears in *J Clin Psychiatry*. 2001;62:209]. *J Clin Psychiatry*. 2001;62:12; Breier A et al. A double-blind, placebo-controlled dose-response comparison of intramuscular olanzapine and haloperidol in the treatment of acute agitation in schizophrenia. *Arch Gen Psychiatry*. 2002;59:441; Abilify (aripiprazole) [package insert]. Princeton, NJ: Bristol Myers Squibb; 2011; Geodon (ziprasidone HCl) [package insert]. New York, NY: Pfizer; 2010; Zyprexa (olanzapine) [package insert]. Indianapolis, IN: Eli Lilly and Company; 2010.

- Stabilization phase: Manage with nonpharmacologic and pharmacologic strategies. Guidelines recommend patients continue the same medication and dosage form received during the acute phase of illness; treatment should continue for at least 6 months.
- The stable phase provides a level of functioning considered optimal for an individual patient. All patients should receive maintenance therapy for at least 1 year, unless antipsychotic agents are not tolerated or the diagnosis is uncertain. Lifelong treatment is indicated in patients who present a significant risk to themselves or others when unmedicated. Antipsychotic polypharmacy should be avoided.
- Nonpharmacologic interventions include individual or group therapy, vocational rehabilitation, social skills training, and cognitive or cognitive-behavioral interventions.
- Antipsychotics are broadly defined as typical (also known as conventional or first-generation agents, major tranquilizers, or neuroleptics) and atypical agents (second-generation antipsychotics). Long-acting agents should be considered in patients who are nonadherent to medications. Dosing guidelines are shown in Tables 82.4 and 82.5.

TABLE 82.4 Antipsychotic Relative Potency and Adult Dosing

Drug and Chemical Class	Dose Equivalence	Usual Starting Dose (mg/day)	Acute Phase Dosage (mg/day)	Maintenance or Stable Phase Dosage (mg/day)
<b>TYPICAL AGENTS—PHENOTHIAZINES</b>				
Aliphatic type				
Chlorpromazine (Thorazine)	100	50–200	300–1,500 <sup>a</sup>	150–800
Piperidine type				
Thioridazine (Mellaril)	100	50–200	300–800	150–600
Piperazine type				
Perphenazine (Trilafon)	10	4–16	32–64 <sup>a</sup>	8–48
Trifluoperazine (Stelazine)	5	2–10	10–80	5–30
Fluphenazine (Prolixin)	2	2–10	5–80	2–20
<b>TYPICAL AGENTS—NONPHENOTHIAZINES</b>				
Thioxanthene				
Thiothixene (Navane)	4	2–10	5–60 <sup>a</sup>	5–30
Butyrophenone				
Haloperidol (Haldol)	2	2–10	5–100	2–20
Dibenzoxazepine				
Loxapine (Loxitane)	10	10–20	50–250	25–100
Dihydroindolone				
Diphenylbutylpiperidine				
Pimozide (Orap)	1	1–2	10–30	2–6
<b>ATYPICAL AGENTS</b>				
Risperidone (Risperdal)	2	1–2	2–16	2–8
Clozapine (Clozaril)	50	12.5–25	150–900	150–600
Olanzapine (Zyprexa)	5	5–10	10–20	10–20
Quetiapine (Seroquel)	75	50–100	300–750	400–600
Ziprasidone (Geodon)	60	40–80	80–200	80–160
Aripiprazole (Abilify)	7.5	10–15	10–30	15–30
Paliperidone (Invega)	3	6	6–12	6–12
lloperidone (Fanapt)	N/A	2	12–24	12–24
Asenapine (Saphris)	N/A	10	10–20	10–20
Lurasidone (Latuda)	N/A	40	40–80	40–80

<sup>a</sup>Dosages can be exceeded with caution, but high-dose therapy is rarely needed.

Sources: Facts & Comparisons eAnswers. <http://online.factsandcomparisons.com/Viewer.aspx?book=DFC&monoID=fandc-hcp15080>. Accessed January 19, 2011; Saphris [package insert]. Whitehouse Station, NJ: Schering Corporation, a subsidiary of Merck & Co, Inc; January 2011; Latuda [package insert]. Marlborough, MA: Sunovion Pharmaceuticals, Inc, a US subsidiary of Daiichi Sankyo Co. Ltd; October 2010.

TABLE 82.5 Long-Acting Injectables (LAI)

	Dose	Frequency	Available	Comments
Haloperidol decanoate	10–20× oral	Every 4 weeks	50 mg/mL	1st injection NTE 100 mg Max: 3 mL/injection site *Sesame oil formulation
	Month 1: 20×		100 mg/mL	
	Month 2: 15× Month 3: 10×			
Fluphenazine decanoate	1.2× oral	Every 3 weeks	25 mg/mL	Titrate by 12.5 mg increments Max: 100 mg/dose *Sesame oil formulation
	12.5–25 mg			
Risperdal Consta	25 mg	Every 2 weeks	12.5 mg	Overlap with PO ×3 weeks *Inject within 2 minutes of reconstituting Wait 4 weeks before ↑ dose Must refrigerate
			25 mg	
			37.5 mg	
			50 mg	
Invega Sustenna	Day 1: 234 mg	Every 4 weeks	39 mg/0.25 mL	3 mg oral = 39–78 mg IM 6 mg oral = 117 mg IM 12 mg oral = 234 mg IM
	Day 8: 156 mg		78 mg/0.50 mL	
	Then, 117 mg		117 mg/0.75 mL	
	monthly		156 mg/1 mL	
			234 mg/1.5 mL	
Zyprexa Relprevv	Weeks 1–8:	Every 2 weeks or Every 4 weeks	210 mg	Postinjection delirium or sedation may occur. Must be given in health care facility with ready access to emergency response services. Patient must be observed for at least 3 hours by health care professional at the facility after each injection.
	10 mg oral: 210 mg every 2 weeks or 405 mg every 4 weeks		300 mg	
	15 mg oral: 300 mg every 2 weeks	405 mg		
	20 mg oral: 300 mg every 2 weeks			
	>8 Weeks:			
	10 mg oral: 150 mg every 2 weeks or 300 mg every 4 weeks			
	15 mg oral: 210 mg every 2 weeks or 405 mg every 4 weeks			
	20 mg oral: 300 mg every 2 weeks			

IM, intramuscular; NTE, not to exceed; PO, by mouth.

Sources: Zyprexa Relprevv (olanzapine extended release injectable suspension) [package insert]. Indianapolis, IN: Eli Lilly and Company; 2010; Risperdal Consta (risperidone long acting injection) [package insert]. Titusville, NJ: Janssen, Division of Ortho-McNeil-Janssen Pharmaceuticals, Inc; 2011; Invega Sustenna [package insert]. Titusville, NJ: Janssen, division of Ortho-McNeil-Janssen Pharmaceuticals, Inc; March 2010.

- Patients receiving antipsychotic therapy should receive regular monitoring (Table 82.6); specific monitoring requirements exist for clozapine (see product labeling).
- Pharmacokinetic parameters (Table 82.7) and potential adverse drug effects (Table 82.8) should be considered. Treatment of antipsychotic-induced Parkinsonism and akathisia may be needed (Table 82.9).

TABLE 82.6 Monitoring Protocol for Atypical Antipsychotics<sup>a</sup>

	Baseline	Week 4	Week 8	Week 12	Quarterly	Annually	Every 5 Years
Personal or family history	X					X	
Weight (BMI)	X	X	X	X	X		
Waist circumference	X					X	
Blood pressure	X			X		X	
Fasting plasma glucose	X			X		X	
Fasting lipids profile	X			X			X

<sup>a</sup>More frequent assessments may be warranted on the basis of clinical status.

Source: Reprinted with permission from American Diabetes Association et al. Consensus Development Conference on Antipsychotic Drugs and Obesity and Diabetes. *Diabetes Care*. 2004;27:596.

TABLE 82.7 Pharmacokinetic Comparisons of Antipsychotics

Antipsychotic Agent	Mean Half-Life (hours)	Major Cytochrome P-450 Pathway	Plasma Concentration Range
Chlorpromazine	24	2D6	Not well defined
Thioridazine	24	2D6	Not well defined
Perphenazine	9–12	2D6	Not well defined
Fluphenazine	18	2D6	0.2–2.8 ng/mL
Fluphenazine decanoate	8 days	2D6	0.2–2.8 ng/mL
Thiothixene	34	2D6	2–15 ng/mL
Haloperidol	18	2D6	4–12 ng/mL
Haloperidol decanoate	21 days	2D6	4–12 ng/mL
Loxapine	8	None	Not well defined
Trifluoperazine	18		Not well defined
Clozapine	16	1A2, 3A4	350–420 mcg/mL suggested
Risperidone	22	2D6	Not well defined
Olanzapine	30	1A2	>23.2 ng/mL at 12 hours after dose
Quetiapine	7	3A4	Not well defined
Ziprasidone	4–5	3A4	Not well defined
Aripiprazole	75–94	2D6, 3A4	Not well defined
Paliperidone	23	Limited 2D6, 3A4	Not well defined
Iloperidone	18–33	2D6, 3A4	Not well defined
Asenapine	24	UGT1A4, 1A2	Not well defined
Lurasidone	18	3A4	Not well defined

UGT1A4, uridine diphosphate glucuronosyltransferase 1 family, polypeptide A4.

Sources: Facts & Comparisons eAnswers. <http://online.factsandcomparisons.com/Viewer.aspx?book=DFC&monoID=fandc-hcp15080>. Accessed January 19, 2011; *Saphris* [package insert]. Whitehouse Station, NJ: Schering Corporation, a subsidiary of Merck & Co, Inc; January 2011; *Latuda* [package insert]. Marlborough, MA: Sunovion Pharmaceuticals, Inc. a US subsidiary of Daiinippon Sumitomo Pharma Co. Ltd; October 2010.

- Nonantipsychotic agents such as benzodiazepines and mood stabilizers (e.g., lithium, carbamazepine, valproic acid) have been used as adjunctive therapy.
- Medication management in pregnant patients should balance the need for continued drug treatment with risks to the unborn child.
- Treatment of first-episode schizophrenia in children requires special consideration of sensitivity to extrapyramidal symptoms and susceptibility to metabolic effects of therapy.

TABLE 82.8 Relative Incidence of Antipsychotic Drug Adverse Effects

	Sedation	EPS	Anticholinergic	Orthostasis	Seizures	Prolactin Elevation	Weight Gain
<b>TYPICAL—LOW POTENCY</b>							
Chlorpromazine	++++	+++	+++	++++	+++	+++	++
Thioridazine	++++	++	++++	++++	++	+++	+++
<b>TYPICAL—HIGH POTENCY</b>							
Trifluoperazine	++	++++	++	++	+++	+++	++
Fluphenazine	++	+++++	++	++	++	+++	++
Thiothixene	++	++++	++	++	++	+++	++
Haloperidol	+	+++++	+	+	++	+++	++
Loxapine	+++	++++	++	+++	++	+++	+
Molindone	+	++++	++	++	++	+++	+
<b>ATYPICALS</b>							
Clozapine	++++	+	++++	++++	++++ <sup>c</sup>	0	++++
Risperidone	+++	+ <sup>a</sup>	++	+++	++	0 to +++ <sup>c</sup>	++
Olanzapine	+++	+ <sup>b</sup>	+++	++	++	+ <sup>c</sup>	+++
Quetiapine	+++	+	++	++	++	0	++
Ziprasidone	++	+	++	++	++	0	+
Aripiprazole	++	+	++	++	++	0	+
Paliperidone	++	+	++	++	++	0 to +++ <sup>c</sup>	++
Iloperidone <sup>d</sup>	++	+	+	++	0 to +	0 to +++	+
Asenapine <sup>d</sup>	++	+	0	++	0 to +	+	++
Lurasidone <sup>d</sup>	+	+	+/0	++	0 to +	+ <sup>c</sup>	+

<sup>a</sup>Very low at dosages <8 mg/day.

<sup>b</sup>With dosages <20 mg/day.

<sup>c</sup>Dose related.

<sup>d</sup>Based on clinical trial data.

0, no effect; +, very low; ++, low; +++, moderate; +++++, high; ++++++, very high; EPS, extrapyramidal side effects.

Sources: Facts & Comparisons eAnswers. <http://online.factsandcomparisons.com/Viewer.aspx?book=DFC&monoID=fandc-hcp15080>. Accessed January 19, 2011; *Saphris* [package insert]. Whitehouse Station, NJ: Schering Corporation, a subsidiary of Merck & Co, Inc; January 2011; *Latuda* [package insert]. Marlborough, MA: Sunovion Pharmaceuticals, Inc. a US subsidiary of Dainippon Sumitomo Pharma Co. Ltd; October 2010.

TABLE 82.9 Agents to Treat Antipsychotic-Induced Parkinsonism and Akathisia

Medication	Equivalent Dose (mg)	Dose/Day (mg/day)
<b>ANTICHOLINERGIC</b>		
Benzotropine (Cogentin) <sup>a</sup>	0.5	2–8
Biperiden (Akineton) <sup>a</sup>	0.5	2–8
Diphenhydramine (Benadryl) <sup>a</sup>	25	50–250
Procyclidine (Kemadrin)	1.5	10–20
Trihexyphenidyl (Artane)	1	2–15
<b>DOPAMINERGIC</b>		
Amantadine	—	100–300
<b>GABAMINERGIC</b>		
Diazepam (Valium)	10	5–40
Clonazepam (Klonopin)	2	1–3
Lorazepam (Ativan) <sup>a</sup>	2	1–3
<b>NORADRENERGIC BLOCKERS</b>		
Propranolol (Inderal)	—	30–120

<sup>a</sup>Oral dose or intramuscular injection can be used.

# Mood Disorders I: Major Depressive Disorder\*

## General Principles

- Depression is a common, chronic, and debilitating illness. Onset is most commonly in the late 20s, but the first episode may present at any age. Acute depressive episodes are often due to a combination of environmental and genetic factors.
- For a diagnosis of depression to be made, symptoms must be present for at least 2 weeks and must not be precipitated or influenced by a medical illness or medication (Tables 83.1 and 83.2).

## Patient Assessment

- Patients should be educated on key points about depression (Table 83.3).
- Table 83.4 contains a mnemonic for target symptoms, but for full diagnostic criteria, please refer to DSM 5. Common features of atypical depression and melancholia are shown in Table 83.5.
- The structured mental status exam is a systematic way of assessing a patient's mental health (Table 83.6). Patients with depressive symptoms should always be assessed for suicidal ideation.
- Establish realistic expectations with the patient for treatment with antidepressants as the onset of side effects usually precedes therapeutic effects.
- Depression in the elderly may be difficult to recognize and may present differently than in younger patients (e.g., more likely to dwell on somatic complaints such as poor sleep, body aches, changes in bowel function).
- Risk for depression is higher during pregnancy and in the postpartum period.

## Goals of Therapy

- The goal of antidepressant therapy is complete amelioration of symptoms (i.e., remission). Therapy should continue for at least 6 months once remission is achieved.

## Treatment

- Treatment should include psychotherapy, medication, and lifestyle adjustments as these interventions work synergistically. For mild to moderate depression, psychotherapy may be comparable to pharmacologic intervention. For severe depression, antidepressants are more effective and may act faster.
- Several forms of psychotherapy are available: cognitive-behavioral, interpersonal, psychoanalytic, and psychodynamic.
- Lifestyle adjustments include reversing unhealthy or destructive behaviors (e.g., alcohol abuse, recreational drug use) and promoting activities that relieve stress.

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\*The reader is referred to Chapter 83, Mood Disorders I: Major Depressive Disorders, written by Patrick R. Finley, PharmD, BCPP, and Kelly C. Lee, PharmD, BCPP, in the tenth edition of *Applied Therapeutics: The Clinical Use of Drugs* for a more in-depth discussion. All notations to reference numbers are based on the reference list at the end of that chapter. The editor of this handbook expresses her thanks to Drs. Finley and Lee and acknowledges that this chapter is based on their work.

**TABLE 83.1 Selected Medical Conditions that May Mimic Depression****CENTRAL NERVOUS SYSTEM**

Alzheimer disease  
 Cerebrovascular accident  
 Epilepsy  
 Multiple sclerosis  
 Parkinson disease

**CARDIOVASCULAR**

Cerebral arteriosclerosis  
 Congestive heart failure  
 Myocardial infarction

**ENDOCRINE**

Addison disease  
 Diabetes mellitus (types 1 and 2)  
 Hypothyroidism

**WOMEN'S HEALTH**

Premenstrual dysphoric disorder  
 Antepartum/postpartum  
 Perimenopause

**OTHER**

Chronic fatigue syndrome  
 Chronic pain syndrome(s)  
 Fibromyalgia  
 Irritable bowel syndrome  
 Malignancies (various)  
 Migraine headaches  
 Rheumatoid arthritis  
 Systemic lupus erythematosus

**TABLE 83.2 Selected Medications that May Induce Depression****CARDIOVASCULAR AGENTS**

$\beta$ -Blockers<sup>a</sup> (?)  
 Clonidine  
 Methyldopa  
 Reserpine

**CENTRAL NERVOUS SYSTEM**

Barbiturates  
 Chloral hydrate  
 Ecstasy (MDMA)  
 Ethanol  
 Varenicline

**HORMONAL AGENTS**

Anabolic steroids  
 Corticosteroids  
 Gonadotropin-releasing hormone  
 Progestins  
 Tamoxifen

**OTHERS**

Efavirenz  
 Interferon  
 Isotretinoin  
 Mefloquine  
 Levetiracetam

<sup>a</sup>Lipophilic  $\beta$ -blockers (e.g., propranolol) may have higher risk but data are conflicting.

TABLE 83.3 **Seven Things Everyone Should Know About Depression**

- **Depression is NOT a personality flaw or a weakness of character.**  
Depression has been associated with a chemical imbalance in the nervous system, which can be easily corrected with antidepressant medications and associated counseling.
- **All antidepressants are equally effective.**  
Approximately 65% of patients receiving a therapeutic trial of any antidepressant medication will have a beneficial response.
- **Most patients receiving antidepressants will experience some side effect(s) initially.**  
Identify an accessible health professional who can answer your questions.
- **Antidepressants should be taken at the same time daily.**  
This will make it easier for you to remember to take the medication and may also minimize side effects.
- **The response to antidepressants is delayed.**  
Several weeks may pass before you begin to feel better, and it may take 4–6 weeks before maximal benefits are evident.
- **Antidepressants must be taken for at least 6–9 months.**  
Even if you are feeling completely better, studies have shown that people who stop their medication during the first 6 months are much more likely to become depressed again.
- **Antidepressants are NOT addictive substances.**  
Antidepressants may elevate the moods of depressed individuals, but they do not act as stimulants and are not associated with craving or other abuse patterns. However, if certain antidepressants are discontinued abruptly, mild withdrawal reactions may occur.

TABLE 83.4 **Depressive Disorder Target Symptom Mnemonic**

D	SIG	E	CAPS
Depressed mood	Sleep (insomnia or hypersomnia) Interest (loss of, including libido) Guilt	Energy loss	Concentration (loss) Appetite (loss or gain) Psychomotor (agitation or retardation) Suicide (ideation)

Source: Adapted with permission from Kellner CH et al. Continuation electroconvulsive therapy vs. pharmacotherapy for relapse prevention in major depression: a multisite study from the consortium for research in electroconvulsive therapy (CORE). *Arch Gen Psychiatry*. 2006;63:1337.

TABLE 83.5 **A Comparison of Atypical Depression and Melancholia**

Feature	Atypical Depression	Melancholia
Onset	Teens (or younger)	Thirties (avg)
Sex	Females > males	Females > males
Course	Chronic	Episodic
Phenomenology		
Appetite/weight	Increased	Decreased
Sleep	Increased	Decreased
Energy	Low with leaden paralysis	Low
Reaction to rejection	Very sensitive	Indifferent
Treatment response	MAOI = SSRI = TCA	MAOI = TCA = SSRI

MAOI, monoamine oxidase inhibitor; SSRI, selective serotonin reuptake inhibitor; TCA, tricyclic antidepressant.



TABLE 83.6 **Mental Status Exam****GENERAL APPEARANCE, BEHAVIOR, SPEECH**

- Apparent age; appear ill or in distress?
- Dress
- General reaction to examination, negativism
- Posture and gait
- Unusual movements
- Facial expression
- Signs of anxiety
- General level of activity
- Repetitious activities (stereotypy, mannerisms, compulsions)
- Disturbances of attention: distractibility
- Speech: mute, word salad, echolalia, clang, neologisms

**MOOD AND AFFECT**

- Quality of prevailing mood; intensity and depth
- Constancy of mood, patient-stated mood
- Affect: range, appropriateness, lability, flatness

**SENSORIUM**

- Orientation for time, place, person, situation
- Memory: recent and remote, immediate recall

**LEVEL OF INTELLECTUAL FUNCTIONING**

- An estimate of current intellectual functioning, not an estimate of original intellectual potential
- General fund of information: presidents, oceans, governor, large cities, current events. Why does the moon appear larger than the stars?
- Vocabulary
- Serial 7 subtractions (also tests attention and sensorium)

**THOUGHT PROCESSES**

- Pattern of associations (tempo, rhythm, organization, distortions, excesses, deficiencies)
- False perceptions (hallucinations, illusions, delusions, distortions of body image, depersonalization)
- Thought content (what patient tells, main concerns, obsessive ideation)
- Abstracting ability (tests by similarities, proverbs)
- Judgment and insight

Source: Adapted with permission from Carlat DJ. *The Psychiatric Interview. Practical Guides in Psychiatry*. Philadelphia, PA: Lippincott Williams & Wilkins; 2004.

- Many patients will seek out complementary and alternative medicines (Table 83.7).
- Several factors guide the selection of antidepressant therapy (Table 83.8). All available antidepressants are equally effective in the general depressed patient and have the same delayed onset of therapeutic benefits (4–6 weeks). See tables for pharmacology (Table 83.9), dosing (Table 83.10), and adverse effects (Table 83.11).
- Antidepressant treatment is broken into three stages (Table 83.12). Selective serotonin reuptake inhibitors (SSRIs) are considered the treatment of choice for most patients. Patients unresponsive or intolerant to one SSRI will often respond to a different SSRI.
- Routine therapeutic blood monitoring is not recommended; serum levels may be useful for evaluating adherence or ruling out serious toxicities.
- Treatment augmentation may be appropriate when a partial response to antidepressant therapy is seen (Table 83.13).
- Detection and management of SSRI-induced sexual dysfunction is important to improve medication adherence (Table 83.14).
- Withdrawal symptoms, which may appear within 48 to 72 hours of stopping treatment and persist for at least 1 week, are possible when discontinuing therapy (Table 83.15).

TABLE 83.7 Complementary and Alternative Medicine Treatments for Depression

Treatment Regimen	Efficacy	Toxicity	Dosing	Drug Interactions	Other Health Benefits
St. John's wort	Monotherapy: superior to placebo, comparable to antidepressants; best studied for mild–moderate depression Augmentation: no data available	Agitation, mania, sun sensitivity	900 mg PO daily (divided)	CYP3A4 inducer; weak evidence of 5-HT syndrome	—
S-Adenosyl-L-Methionine	Monotherapy: superior to placebo, comparable to antidepressants Augmentation: superior to placebo	Nausea, skin rashes, hypoglycemia, theoretical ↑ homocysteine levels	800–1,600 mg PO daily	One probable case of 5-HT syndrome (with clomipramine)	Osteoarthritis
Omega-3 Fatty Acids	Monotherapy: limited data available Augmentation: majority of trials positive	Fishy taste, regurgitation	1–2 g PO daily (EPA + DHA)	None	↓ CV risk; ↓ risk of obstetric complications
Folate	Monotherapy: no evidence available Augmentation: limited number of studies but positive results (especially in women); Methylfolate preferred due to superior CNS penetration (?)	Well tolerated; may mask pernicious anemia	Folic acid: 200–500 mg PO daily Methylfolate: 15–50 mg PO daily	None	Other health benefits: ↓ risk of pregnancy complications; reverse folate deficiency

5-HT, serotonin; CNS, central nervous system; CV, cardiovascular; CYP, cytochrome P-450; DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid; PO, orally.

Source: Adapted with permission from Freeman MP et al. Complementary and alternative medicine in major depressive disorder: the American Psychiatric Association Task Report. *J Clin Psychiatry*. 2010;71:669.

- The potential for several drug interactions exists (Table 83.16). Serotonin syndrome is a rare and potentially fatal drug interaction (Table 83.17); symptoms include anxiety, shivering, diaphoresis, tremor, hyperreflexia, autonomic instability, and malignant hyperthermia. Patients taking monoamine oxidase inhibitor (MAOI) therapy should avoid foods containing tyramine (Table 83.18).

TABLE 83.8 Factors to Consider in Selecting an Antidepressant

- History of prior response (personal or family member)
- Safety in overdose
- Adverse effect profiles
- Patient age
- Concurrent medical/psychiatric conditions
- Concurrent medications (e.g., potential for drug interactions)
- Convenience (e.g., minimal titration, once-daily dosing)
- Cost
- Patient preference

TABLE 83.9 Pharmacology of Antidepressant Medications

Medication	Serotonin	Norepinephrine	Dopamine	Bioavailability (Oral)	Protein Binding	Half-Life (hours) (Active Metabolite)
<b>SELECTIVE SEROTONIN REUPTAKE INHIBITORS</b>						
Fluoxetine	++++	0/+	0	80%	95%	24–72 (146)
Sertraline	++++	0/+	+	>44%	95%	26 (66)
Paroxetine	++++	+	0	64%	99%	24
Citalopram	++++	0	0	80%	<80%	33
Escitalopram	++++	0	0	80%	56%	27–32
<b>SEROTONIN NOREPINEPHRINE REUPTAKE INHIBITORS</b>						
Venlafaxine	++++	+++	0	92%	25%–29%	4 (10)
Desvenlafaxine	+++	+++	0	80%	30%	11 (0)
Duloxetine	++++	++++	0	50%	>90%	12 (8–17)
<b>NOREPINEPHRINE REUPTAKE INHIBITORS</b>						
Bupropion	0/+	+	+	>90%	85%	10–21
<b>TRICYCLIC ANTIDEPRESSANTS</b>						
Desipramine	+	++++	0/+	51%	90%	12–28
Nortriptyline	++	+++	0	46%–56%	92%	18–56
Amitriptyline	++++	++++	0	37%–49%	95%	9–46 (18–56)
Imipramine	+++	++	0/+	19%–35%	95%	6–28 (12–28)
Doxepin	+++	+	0	17%–37%	68%–85%	11–23
<b>OTHERS</b>						
Mirtazapine	+++	++++	0	50%	85%	20–40

0, negligible; +, very low; ++, low; +++, moderate; +++++, high.

TABLE 83.10 Dosage Ranges and Costs of Commonly Prescribed Antidepressant Medications

Medication	Brand Name	Starting Dose (mg/day)	Maximum Dosage (mg/day)	Usual Dosage (mg/day)	Relative Cost <sup>a</sup>
<b>SELECTIVE SEROTONIN REUPTAKE INHIBITORS</b>					
Fluoxetine	Prozac	10	80	10–20 mg daily	\$ <sup>b</sup>
Sertraline	Zoloft	25	200	50 mg daily	\$ <sup>b</sup>
Paroxetine	Paxil	10	50	10–20 mg daily	\$ <sup>b</sup>
Citalopram	Celexa	10	60	20 mg daily	\$\$ <sup>b</sup>
Escitalopram	Lexapro	5	20	10 mg daily	\$\$\$ <sup>b</sup>
<b>SEROTONIN NOREPINEPHRINE REUPTAKE INHIBITORS</b>					
Venlafaxine	Effexor XR	37.5	225	150 mg daily	\$\$\$\$
Desvenlafaxine	Pristiq	50	50	50 mg daily	\$\$\$\$
Duloxetine	Cymbalta	30	120	60 mg daily	\$\$\$\$
<b>NOREPINEPHRINE REUPTAKE INHIBITORS</b>					
Bupropion	Wellbutrin SR	150	400	150 mg BID	\$\$\$ <sup>b</sup>
Bupropion	Wellbutrin XL	150	450	300 daily	\$\$\$ <sup>b</sup>

**TABLE 83.10 Dosage Ranges and Costs of Commonly Prescribed Antidepressant Medications (Continued)**

Medication	Brand Name	Starting Dose (mg/day)	Maximum Dosage (mg/day)	Usual Dosage (mg/day)	Relative Cost <sup>a</sup>
<b>TRICYCLIC ANTIDEPRESSANTS</b>					
Desipramine	Norpramin	25	300	200 mg half-strength	\$
Nortriptyline	Pamelor	10–25	150	100 mg half-strength	\$
<b>OTHERS</b>					
Mirtazapine	Remeron	15	45	15–30 mg half-strength	\$\$ <sup>b</sup>

<sup>a</sup>Based on average wholesale prices for usual therapeutic doses (April 2011).

<sup>b</sup>Price reflects cost of generic formulation.

\$ = \$0–25/month; \$\$ = \$25–50/month; \$\$\$ = \$50–100/month; \$\$\$\$ = more than \$100/month.

BID, twice a day; TID, three times a day.

**TABLE 83.11 Adverse Effects of Antidepressant Medications**

Medication	Sedation	Agitation/Insomnia	Anticholinergic Effects	Orthostasis	GI Effects (Nausea/Diarrhea)	Sexual Dysfunction	Weight Gain
<b>SELECTIVE SEROTONIN REUPTAKE INHIBITORS</b>							
Fluoxetine	+	++++	0/+	0/+	++++	++++	+
Sertraline	+	+++	0/+	0	+++	+++	+
Paroxetine	+++	++	++	0	+++	++++	+++
Citalopram	++	++	0/+	0	+++	+++	+
Escitalopram	+	++	0/+	0	+++	+++	+
<b>SEROTONIN NOREPINEPHRINE REUPTAKE INHIBITORS</b>							
Venlafaxine (Effexor)	++	++	+	0	+++	+++	+
Desvenlafaxine (Pristiq)	++	++	+	+	+++	++	0/+
Duloxetine (Cymbalta)	++	++	+	0	+++	++	0/+
<b>NOREPINEPHRINE REUPTAKE INHIBITORS</b>							
Bupropion (Wellbutrin)	0	+++	+	0	+	0/+	0
<b>TRICYCLIC ANTIDEPRESSANTS</b>							
Desipramine (Norpramin)	++	+	++	+++	0/+	+	++
Nortriptyline (Pamelor)	++	+	++	++	0/+	+	++
Amitriptyline (Elavil)	++++	0/+	++++	++++	0/+	++	+++
Imipramine (Tofranil)	+++	0/+	+++	++++	0/+	++	++
Doxepin (Sinequan)	++++	0/+	++++	++++	0/+	++	++
<b>OTHERS</b>							
Mirtazapine (Remeron)	++++	0	++	0/+	+	0/+	+++

0, negligible; +, very low; ++, low; +++, moderate; +++++, high.

**TABLE 83.12 Duration of Antidepressant Treatment**

Acute treatment phase:	3 months
Continuation treatment phase:	4–9 months
Maintenance treatment phase:	Variable

- Acute and continuation treatment recommended for all patients with major depressive disorder (i.e., minimal duration of treatment = 7 months)
- Decision to prescribe maintenance treatment is based on the following:
  - Number of previous episodes
  - Severity of previous episodes
  - Family history of depression
  - Patient age (worse prognosis if elderly)
  - Response to antidepressant
  - Persistence of environmental stressors
- Indefinite maintenance treatment is recommended if any one of the following criteria are met:
  - Three or more previous episodes (regardless of age)
  - Two or more previous episodes and age older than 50 years
  - One or more previous episodes and age older than 60 years

**TABLE 83.13 Partial Response to Antidepressant Treatment Augmentation Strategies (with SSRIs)**

Ensure completion of full therapeutic trial (4–6 weeks).

Ensure optimal dose of antidepressant.

Consider augmentation therapies:

- Lithium
- Thyroid supplements
- Bupropion
- Buspirone
- Lamotrigine Pindolol (?)
- Modafinil
- Atypical antipsychotics

SSRI, selective serotonin reuptake inhibitor.

**TABLE 83.14 Management of SSRI-Induced Sexual Dysfunction**

- Patience (may improve after 2–4 weeks)
- Reduced dosage (if possible)
- Drug holidays (sertraline, paroxetine, citalopram, escitalopram only)
- Antidotes
  - Bupropion SR 150 mg daily to BID
  - Sildenafil 50–100 mg daily PRN
  - Mirtazapine 7.5–15 mg at bedtime
  - Cyproheptadine 4–12 mg PRN (1 hour prior)
  - Methylphenidate 2.5–5.0 mg daily
  - Others: yohimbine, amantadine, buspirone, ginkgo
- Change of antidepressants (e.g., bupropion, mirtazapine)

BID, twice a day; PRN, as needed.

TABLE 83.15 Discontinuation of Antidepressants

## Withdrawal syndrome

- Worse with paroxetine, venlafaxine
- Symptoms: dizziness, nausea, paresthesias, anxiety/insomnia, flulike symptoms
- Onset: 36–72 hours
- Duration: 3–7 days

## Taper schedule (for patients receiving long-term treatment)

- Fluoxetine: generally unnecessary
- Sertraline: decrease by 25–50 mg every 1–2 weeks
- Paroxetine: decrease by 5–10 mg every 1–2 weeks
- Citalopram: decrease by 5–10 mg every 1–2 weeks
- Escitalopram: decrease by 5 mg every 1–2 weeks
- Venlafaxine: decrease by 25–50 mg every 1–2 weeks
- Nefazodone: decrease by 50–100 mg every 1–2 weeks
- Bupropion: generally unnecessary
- Tricyclics: decrease by 10%–25% every 1–2 weeks

Note: Risk of depression relapse is greatest 1 to 6 months after discontinuation.

TABLE 83.16 Drug Interactions of the Cytochrome P-450 System

Relative Rank	CYP1A2	CYP2C9/19	CYP2D6	CYP3A4
<b>OFFENDING AGENT (INHIBITS ENZYME)</b>				
High	Fluvoxamine	CYP2C9 Fluoxetine Fluvoxamine CYP2C19 Fluvoxamine	Paroxetine Fluoxetine Duloxetine Bupropion	Fluoxetine (norfluoxetine) Fluvoxamine
Moderate	Fluoxetine Paroxetine	CYP2C19 Fluoxetine Sertraline CYP2C9/19	Citalopram Escitalopram Sertraline	
Low	Citalopram Escitalopram Sertraline Venlafaxine Duloxetine  Bupropion	Citalopram Escitalopram Sertraline	Venlafaxine Mirtazapine	Citalopram Escitalopram Paroxetine Sertraline Venlafaxine Desvenlafaxine Duloxetine
<b>OTHER INHIBITORS</b>				
	Quinolones (ciprofloxacin, enoxacin, etc.) Macrolides (erythromycin, clarithromycin) Grapefruit juice	Modafinil (2C9, 2C19)  Cimetidine (2C19)  Omeprazole (2C19)  Imidazoles (2C9, 2C19) (ketoconazole, fluconazole)	Fenfluramine  Yohimbine  Methadone  Quinidine  Celecoxib	Macrolides (erythromycin, clarithromycin) Cimetidine  CCB (verapamil, diltiazem) Imidazoles (ketoconazole, fluconazole) Protease inhibitors Grapefruit juice

Continued on following page

**TABLE 83.16 Drug Interactions of the Cytochrome P-450 System (Continued)**

Relative Rank	CYP1A2	CYP2C9/19	CYP2D6	CYP3A4
<b>OTHER INDUCERS</b>				
	Cigarettes Caffeine	St. John's wort	Modafinil Phenytoin and phenobarbital Carbamazepine Rifampin Prednisone Testosterone	St. John's wort
	St. John's wort			
<b>AFFECTED AGENT (INCREASED CONCENTRATION)</b>				
	TCA-tertiary amines (imipramine, amitriptyline) Phenothiazines (chlorpromazine) Thiothixene Haloperidol Clozapine Olanzapine Caffeine	CYP2C9  Phenytoin  Tolbutamide Warfarin NSAIDs CYP2C19 TCA-tertiary amines (imipramine, amitriptyline)	TCA-secondary amines (desipramine, nortriptyline) Fluoxetine  Paroxetine Venlafaxine Duloxetine Amphetamines Atomoxetine	Fluoxetine  Sertraline  Venlafaxine Modafinil Quetiapine Ziprasidone Aripiprazole
	Theophylline Propranolol	Citalopram Barbiturates	Risperidone Donepezil	Buspirone Benzodiazepines (triazolam, alprazolam)
	Tacrine	Propranolol Omeprazole	Codeine Hydrocodone Tramadol Dextromethorphan  Chlorpheniramine  $\beta$ -Blockers (propranolol, metoprolol)	Zolpidem Carbamazepine Donepezil CCB (verapamil, diltiazem, nifedipine) Sex hormones (estrogen) Corticosteroids Statins (lovastatin, simvastatin) Protease inhibitors Sildenafil

CCB, calcium-channel blockers; NSAIDs, nonsteroidal anti-inflammatory drugs; TCA, tricyclic antidepressant.

- Electroconvulsive therapy (ECT) is a rapid-acting and highly effective therapeutic intervention. Its use is recommended for patients with treatment-resistant depression, severe vegetative depression, psychotic depression, and depression in pregnancy. Response may be seen within the first 2 weeks of therapy; recommended frequency of treatments is variable.
- Phototherapy is effective for relieving irritability and malaise associated with seasonal affective disorder.

TABLE 83.17 Medications Associated with Serotonin Syndrome

**MOST COMMONLY ASSOCIATED<sup>d</sup>**

Monoamine oxidase inhibitors (selegiline, phenelzine, tranylcypromine)

**COMMONLY ASSOCIATED<sup>d</sup>**

SSRI (all)  
 SNRI (all)  
 Clomipramine  
 Sibutramine

**OCCASIONALLY ASSOCIATED<sup>d</sup>**

Tramadol  
 Meperidine  
 Linezolid  
 Dextromethorphan (high dose)

<sup>d</sup>The combination of any two medications from these categories should be strongly discouraged.

TABLE 83.18 Foods Containing Tyramine

**HIGH AMOUNTS OF TYRAMINE<sup>a</sup>**

Smoked, aged, or pickled meat or fish  
 Sauerkraut  
 Aged cheeses (e.g., Stilton, blue cheese)  
 Yeast extracts (e.g., marmite)  
 Fava beans

**MODERATE AMOUNTS OF TYRAMINE<sup>b</sup>**

Beer (microbrewed > commercial)  
 Avocados  
 Meat extracts  
 Red wines such as Chianti

**LOW AMOUNTS OF TYRAMINE<sup>c</sup>**

Caffeine-containing beverages  
 Distilled spirits  
 Chocolate  
 Soy sauce  
 Cottage and cream cheese  
 Yogurt and sour cream

<sup>a</sup>May not consume.<sup>b</sup>May consume in moderation.<sup>c</sup>May consume.

*Source:* Adapted with permission from Shulman KI et al. Dietary restriction, tyramine, and the use of monoamine oxidase inhibitors. *J Clin Psychopharmacol.* 1989;9:397.



## Mood Disorders II: Bipolar Disorders\*

### General Principles

- Bipolar disorder (BD), or manic depression, is a severe cyclical psychiatric condition. Manic/hypomanic episodes are characteristic of BD; however, depressive episodes predominate and are typically the presenting symptom. Suicide and excessive risk-taking behaviors contribute to the high mortality rate.
- Left untreated, severe mania can result in confusion, fever, exhaustion, and death.
- BD is more common in women than men, and risk is increased in first-degree relatives.

### Classification

- Discrete periods of mood disturbance are defined as **manic** (episodes of elevated mood), **hypomanic** (elevated moods less severe than mania), **mixed** (features of both depression and mania), and **major depressive** episodes. A history of manic, hypomanic, or mixed episodes precludes a diagnosis of major depression (see Chapter 83).
- **Bipolar I Disorder**—an individual who has had manic or mixed episodes with or without a depressive episode
- **Bipolar II Disorder**—an individual who has both hypomania and depression without a history of manic or mixed episodes

### Patient Assessment

- Manic episodes usually begin with a change in sleep patterns along with mood elevation. Presenting symptoms develop gradually over several days in three stages (For full criteria of a manic episode, please refer to DSM 5):
  - **Stage I** (hypomania)—euphoria, labile affect, grandiosity, overconfidence, racing thoughts, increased psychomotor activity, and an increased rate/amount of speech.
  - **Stage II** (acute mania)—increased irritability, dysphoria, hostility, anger, delusions, and cognitive disorganization. Many patients progress no further than this stage.
  - **Stage III**—progression of mania to an undifferentiated psychotic state. Individuals experience terror, panic, hallucinations, bizarre behavior, and frenzied activity.
- Patients may present initially with mania, hypomania, depression, or a mixed episode. Medications (Table 84.1) and clinical states that can induce mania should be assessed.

### Goals of Therapy

- Goals include control acute symptoms, symptomatic remission, return to normal level of functioning, prevent relapses, and prevent suicide.
- Medications for treatment of bipolar depression should produce an acute antidepressant response, decrease suicide risk, and prevent future depressive episodes without inducing mania or mood cycling.

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\*The reader is referred to Chapter 84, Mood Disorders II: Bipolar Disorders, written by James J. Gasper, PharmD, in the 10th edition of *Applied Therapeutics: The Clinical Use of Drugs* for a more in-depth discussion. All notations to reference numbers are based on the reference list at the end of that chapter. The editor of this handbook expresses her thanks to Dr. Gasper and acknowledges that this chapter is based on his work.

TABLE 84.1 Selected Drugs Reported to Induce Mania

<b>Anticonvulsants</b>	Gabapentin, lamotrigine, topiramate
<b>Antidepressants</b>	Monoamine oxidase inhibitors, TCAs, SSRIs, SNRIs, bupropion, nefazodone, trazodone, mirtazapine
<b>Antimicrobials</b>	Clarithromycin, ofloxacin, cotrimoxazole, erythromycin, isoniazid, metronidazole, zidovudine, efavirenz
<b>Antiparkinsonian drugs</b>	Levodopa, amantadine, bromocriptine
<b>Anxiolytics/hypnotics</b>	Buspirone, alprazolam, triazolam
<b>Atypical antipsychotics</b>	Aripiprazole, olanzapine, quetiapine, risperidone, ziprasidone
<b>CNS stimulants</b>	Caffeine, cocaine, methylphenidate, amphetamine
<b>Drugs of abuse</b>	Marijuana, PCP, LSD
<b>Endocrine</b>	Corticosteroids, thyroid supplements, androgens
<b>Herbals</b>	St. John's wort, SAMe, ma-huang, omega-3 fatty acids, tryptophan
<b>Sympathomimetics</b>	Ephedrine, phenylpropanolamine, pseudoephedrine, phenylephrine
<b>Miscellaneous</b>	Cimetidine, tramadol, sibutramine

CNS, central nervous system; LSD, lysergic acid diethylamide; PCP, phencyclidine; SAMe, S-adenosyl-L-methionine; SNRI, serotonin and norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor; TCA, tricyclic antidepressant.

## Treatment

- Treatment should be individualized; several medication options exist (Table 84.2). Treatment decisions should take into account presenting symptoms, history of response, patient preference, and comorbid medical or substance use conditions. When drug combinations are used, individual agents should have different mechanisms of action.
- Treatment of mania or hypomania:
  - For initial treatment: use well-established agents—lithium, valproate (VPA), or an atypical antipsychotic (AAP). VPA or AAP are preferred for mixed episodes.
  - Short-term benzodiazepines may help reduce agitation and promote sleep.
  - For severe mania or in those partially responsive to an adequate trial of monotherapy (generally 1–2 weeks): use a two-drug combination of lithium, VPA, or an AAP. Carbamazepine (CBZ), oxcarbazepine, or a typical antipsychotic, alone or in combination with a preferred antimanic drug, are alternatives.

TABLE 84.2 FDA-Approved Medications for Bipolar Disorder

Drug	Mania	Mixed	Depression	Maintenance
Carbamazepine (extended-release capsule)	X	X		
Lamotrigine				X
Lithium	X			X
Valproate (divalproex sodium)	X	X		
Asenapine	X	X		
Aripiprazole	X	X		X
Olanzapine	X	X		X
Olanzapine–fluoxetine			X	
Quetiapine	X		X	X <sup>a</sup>
Quetiapine XR	X	X	X	X <sup>a</sup>
Risperidone long-acting injection				X
Risperidone	X	X		
Ziprasidone	X	X		X <sup>a</sup>

<sup>a</sup>Adjunct to lithium or valproate.

FDA, Food and Drug Administration.

- For treatment of resistant disease: use electroconvulsive therapy (ECT), clozapine, or a three-drug combination of lithium plus an anticonvulsant (CBZ, oxcarbazepine, VPA) plus an AAP.
- Discontinue antidepressants in patients presenting with a manic/mixed manic episode.
- Treatment of bipolar depression:
  - First-line treatments: lithium or lamotrigine. Combination therapy with these agents is appropriate for patients who fail monotherapy.
  - Alternative treatments: quetiapine or the fixed olanzapine-fluoxetine combination. Subsequent trials can include antidepressants (selective serotonin reuptake inhibitors [SSRIs], bupropion, serotonin and norepinephrine reuptake inhibitors [SNRIs]) in combination with an antimanic agent.
  - For severe depression or those who are treatment resistant: ECT
- Maintenance treatment should include continuing acute-phase treatment while simplifying and moving toward monotherapy with lithium, VPA, or lamotrigine. Long-term use of AAPs should be done cautiously due to the risk of metabolic complications.
- Medication adherence is critical to long-term recovery. Patients should maintain regular patterns of daily activities, sleep, meals, and exercise routine to promote stability.

## Drug Therapy

- **Valproate**—correlation between serum concentration and efficacy is not well established. Levels greater than 125 mg/mL are associated with side effects. Obtain baseline tests (complete blood count with differential and platelet count [CBCDP], liver function tests [LFTs], weight, neurological status, pregnancy status) before initiating therapy. Symptoms should improve in approximately 5 days. Adverse effects include gastrointestinal symptoms, sedation, ataxia, tremor, benign hepatic transaminase elevations, and thrombocytopenia. LFTs, serum levels, and CBCDP should be monitored at least monthly for the first 3 months and every 3 to 6 months thereafter.
- **Lithium**—baseline and routine monitoring of labs is required (Table 84.3). Serum levels between 0.5 to 1.2 mEq/L are appropriate for acute mania. Onset of effect may take 1 to 2 weeks; adjunctive therapy to help with acute symptoms may be needed. Monitor adverse effects (Table 84.4) to avoid toxicity. Drug interactions are a common cause of changes in lithium levels (Table 84.5).
- **AAPs**—although equally effective for acute mania, agents differ in adverse effect profiles (see Chapter 82). Table 84.6 shows dosing in acute mania.

TABLE 84.3 Routine Monitoring During Lithium Therapy

	Baseline	Every 1–3 Months	Yearly
CBC	X		
Electrolytes	X		X
Renal function <sup>a</sup>	X		X
ECG <sup>b</sup>	X		X
Urine	X		
Thyroid function	X		X
Lithium level <sup>c</sup>		X	
Weight or BMI	X		X
Pregnancy <sup>d</sup>	X		

<sup>a</sup>Monitor more often in patients with history of kidney disease.

<sup>b</sup>Patients  $\geq 45$  years or those with history of cardiac disease.

<sup>c</sup>Weekly monitoring during the first month of treatment is often recommended.

<sup>d</sup>Women of childbearing potential.

BMI, body mass index; CBC, complete blood count; ECG, electrocardiogram.

TABLE 84.4 Lithium Adverse Effects

Organ System	Clinical Presentation	Comments
Cardiovascular	ECG changes	T-wave suppression, delayed or irregular rhythm, increase in PVCs; SSNS; myocarditis
	Edema	Primarily ankles and feet; transient or intermittent; secondary to effects on sodium and carbohydrate metabolism; caution about diuretics and sodium restriction to avoid lithium toxicity
Dermatologic	Acne	Worsens
	Psoriasis	Treatment-refractory worsening
	Rashes	Maculopapular and follicular
Endocrine	Hypothyroidism	About 5% goiter; about 30% clinically significant hypothyroidism; may diminish sex drive
	Hyperparathyroidism	Clinically not significant
Fetus (teratogenic)	Tricuspid valve malformation, atrial septal defect	Ebstein anomaly
Gastrointestinal	Anorexia, nausea (10%–30%)	Usually early in treatment and usually transient; may be early sign of toxicity
	Diarrhea (5%–20%)	Slow-release preparations may help
Hematologic	Leukocytosis	May be useful in disorders such as Felty syndrome and iatrogenic neutropenia. May counter CBZ-induced leukopenia
	Tremor (10%–65%)	Dose-related; men > women; worse with antidepressants and antipsychotics; reduce dose or use $\beta$ -blocker
Neurologic	Cognitive disruption (10%)	Worsens compliance; perceived as “mental dulling”
	Poor concentration or memory; fatigue or weakness	May be early toxicity; may mimic depression
	Polyuria-polydipsia (nephrogenic diabetes insipidus)	May be an indication of morphological changes; requires adequate hydration

CBZ, carbamazepine; ECG, electrocardiogram; PVC, premature ventricular contraction; SSNS, sick sinus node syndrome.

Source: Reprinted with permission from Janicak PG et al. Treatment with mood stabilizers. In: *Principles and Practice of Psychopharmacotherapy*. 4th ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2006:426.

- **Anticonvulsants**—CBZ is an alternative for acute mania when first-line agents fail. No correlation between serum levels and efficacy for BD has been shown; the recommended target is 4 to 12 mcg/mL. Average daily doses for maintenance therapy are 200 to 1,600 mg. Lamotrigine (in combination with an antimanic agent) is recommended as first-line therapy for bipolar depression.
- **Antidepressants**—should be used in combination with antimanic agents (e.g., VPA, lithium, AAP) to prevent mood switching

**TABLE 84.5 Lithium Drug Interactions of Clinical Significance**

**DRUGS THAT INCREASE LITHIUM LEVELS**

*NSAIDs*

Many NSAIDs have been reported to increase lithium levels as much as 50%–60%. This probably is owing to an enhanced reabsorption of sodium and lithium secondary to inhibition of prostaglandin synthesis.

*Diuretics*

All diuretics can contribute to sodium depletion. Sodium depletion can result in an increased proximal tubular reabsorption of sodium and lithium. Thiazide-like diuretics cause the greatest increase in lithium levels, whereas loop diuretics and potassium-sparing diuretics seem to be somewhat safer.

*ACE inhibitors*

ACE inhibitors and lithium both result in volume depletion and a reduction in glomerular filtration rate. This results in reduced lithium excretion.

**DRUGS THAT DECREASE LITHIUM LEVELS**

*Theophylline, caffeine*

Theophylline and caffeine may increase renal clearance of lithium and result in a decrease in levels in the range of 20%.

*Acetazolamide*

Acetazolamide may impair proximal tubular reabsorption of lithium ions.

*Sodium*

High dietary sodium intake promotes the renal clearance of lithium.

**DRUGS THAT INCREASE LITHIUM TOXICITY**

*Methyl dopa*

Cases of sedation, dysphoria, and confusion owing to the combined use of lithium and methyl dopa have been reported.

*Carbamazepine*

Cases of neurotoxicity involving the combined use of lithium and carbamazepine have been reported in patients with normal lithium levels.

*Calcium-channel antagonists*

Cases of neurotoxicity involving the combined use of lithium and the calcium-channel blockers verapamil and diltiazem have been reported. Lithium interferes with calcium transport across cells.

*Antipsychotics*

Cases of neurotoxicity (encephalopathic syndrome, extrapyramidal effects, cerebellar effect, EEG abnormalities) have been reported owing to the combined use of lithium and various antipsychotics. The interaction may be related to increase in phenothiazine levels, changes in tissue uptake of lithium, or dopamine-blocking effects of lithium. Studies attempting to demonstrate this effect have yielded differing results.

*Serotonin-selective reuptake inhibitors*

Fluvoxamine and fluoxetine have been reported to result in toxicity when added to lithium. Sertraline has been reported to cause nausea and tremor in lithium recipients.

ACE, angiotensin-converting enzyme; EEG, electroencephalogram; NSAIDs, nonsteroidal anti-inflammatory drugs.

**TABLE 84.6 Atypical Antipsychotic Dosing in Acute Mania**

Atypical Antipsychotic	Initial Dose	Titration	Effective Dose Range
Aripiprazole	15 mg/day	Not required	15–30 mg/day
Asenapine	10 mg twice daily	5 mg twice daily	5–10 mg twice daily
Olanzapine	10–15 mg/day	5 mg/day	5–20 mg/day
Quetiapine	50 mg twice daily	50 mg twice daily	200–400 mg twice daily
Quetiapine XR	300 mg/day	300 mg/day	400–800 mg/day
Risperidone	2–3 mg/day	1 mg/day	1–6 mg/day
Ziprasidone	40 mg twice daily	20–40 mg twice daily	40–80 mg twice daily

Sources: *Abilify (aripiprazole)* [package insert]. Tokyo, Japan: Otsuka Pharmaceutical; December 2010; *Saphris (asenapine)* [package insert]. Whitehouse Station, NJ: Merck & Company; November 2010; *Zyprexa (olanzapine)* [package insert]. Indianapolis, IN: Eli Lilly and Company; November 2010; *Seroquel (quetiapine)* [package insert]. Wilmington, DE: Astra Zeneca Pharmaceuticals; May 2010; *Seroquel Extended Release (quetiapine fumarate)* [package insert]. Wilmington, DE: Astra Zeneca Pharmaceuticals; May 2010; *Risperdal (risperidone)* [package insert]. Titusville, NJ: Janssen, LP; August 2010; *Geodon (ziprasidone)* [package insert]. New York, NY: Pfizer; November 2010.

# Attention Deficit Hyperactivity Disorder in Children, Adolescents, and Adults\*

## General Principles

- Attention deficit hyperactivity disorder (ADHD) is a chronic disorder. Symptoms manifest in early childhood and will typically persist into adulthood.
- If left untreated, ADHD can produce significant impairments in academic performance and social functioning.

## Classification

- Three types of ADHD: inattentive, hyperactive/impulsive, and combined inattentive and hyperactive/impulsive.

## Patient Assessment

- Diagnosis is based on DSM 5 criteria, physical examination, and patient/parent interview. Establishing the diagnosis in an adult who was not treated for ADHD as a child is difficult.
- Hyperactive and impulsive behaviors recede during adolescence; inattention predominates in adults.
- Medical conditions (e.g., head injury, seizure disorders, metabolic disorders, cerebral infection, toxic exposure, sleep problems, substance abuse, and hyperthyroidism) should be excluded before initiating therapy.

## Treatment

- Optimal treatment for moderate to severe ADHD should include behavioral and pharmacotherapy interventions.
- Several agents are used to manage ADHD (Table 85.1). Selection of agent is based on duration of action, formulation preference, and cost.
- Stimulants are considered the most effective. Patients who don't respond to one agent may respond to another due to differences in mechanism of action. Stimulant adverse effects can often be managed by dose/dosing schedule adjustments (Table 85.2).
- Nonstimulants are less effective and may require at least 4 weeks to see a response. They are appropriate in patients who fail stimulants or when stimulants are not preferred.
- Tricyclic antidepressants should be reserved for patients with ADHD accompanied by other psychiatric comorbidities.
- $\alpha$ -2 agonists (e.g., clonidine and guanfacine) and atomoxetine have been shown to reduce symptoms of ADHD and tic disorders (e.g., Tourette syndrome).

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\*The reader is referred to Chapter 85, Attention Deficit Hyperactivity Disorder in Children, Adolescents, and Adults, written by Kimberly B. Tallian, PharmD, BCPP, FASHP, FCCP, FCSHP, Patrick R. Finley, PharmD, BCPP, Paul Perry, PhD, and Samuel Kuperman, MD, in the 10th edition of *Applied Therapeutics: The Clinical Use of Drugs* for a more in-depth discussion. All notations to reference numbers are based on the reference list at the end of that chapter. The editor of this handbook expresses her thanks to Drs. Tallian, Finley, Perry, and Kuperman and acknowledges that this chapter is based on their work.

TABLE 85.1 Overview of Common Drugs to Treat Attention Deficit Hyperactivity Disorder

Drug (Generic)	Drug (Brand)	Usual Child Dose	Usual Adult Dose	Availability	Duration of Action	Titration
<b>STIMULANTS</b>						
Methylphenidate C-II	Ritalin IR (generic)	0.3–2 mg/kg in 2–4 divided dosages	20–60 mg/day in 2–4 divided dosages (Max: 60 mg/day)	5-mg, 10-mg, 20-mg tablets	3.5–4 hours	Initiate dose at 2.5–5 mg and increase by 2.5- to 5-mg increments every 7 days until clinical benefit. Titration can be more rapid every 3–5 days depending on tolerance to adverse effects.
	Ritalin SR (generic)	20 mg/day	20 mg/day (Max: 60 mg/day)	20-mg tablets	6–8 hours	For IR products, a second lunchtime dose can be added to control afternoon symptoms if the duration is insufficient. Patient may require a third dose at around 3:30 PM to improve evening symptoms. Metadate CD and Ritalin LA can be sprinkled on applesauce.
	Metadate ER	0.3–2 mg/kg/day	20–60 mg/day (Max: 60 mg/day)	10-mg, 20-mg tablets	6–8 hours	
	Methylin ER	0.3–2 mg/kg/day	20–60 mg/day (Max: 60 mg/day)	10-mg, 20-mg tablets	6–8 hours	
	Metadate CD	0.3–2 mg/kg/day	20–60 mg/day (Max: 60 mg/day)	10-mg, 20-mg, 40-mg, 50-mg, 60-mg capsule	8 hours	
	Concerta (generic)	18–54 mg/day (Max: 72 mg/day)	18–72 mg/day	18-mg, 27-mg, 36-mg, 54-mg capsules	10–12 hours	
	Ritalin LA	0.3–2 mg/kg/day	20–60 mg/day (Max: 60 mg/day)	10-mg, 20-mg, 30-mg, 40-mg capsules	4–5 hours	
	Daytrana	10 mg/9 hours (Max: 30 mg/9 hours)	10 mg/9 hours (Max: 30 mg/9 hours)	10-mg, 20-mg, 15-mg, 30-mg patch	11–12 hours	
Dexmethylphenidate C-II	Focalin (generic)	0.6–1 mg/kg in 2–3 dosages/day	2.5–20 mg/day in 2–3 dosages/day (Max: 20 mg/day)	2.5-mg, 5-mg, 10-mg tablets	4–5 hours	Initiate dose at 2.5-mg 2–3 times/day and increase by 2.5- to 5-mg increments every 7 days until clinical benefit. Initiate dose at 5- to 10-mg/ day increments every 7 days until clinical benefit. Focalin XR can be sprinkled on applesauce.
	Focalin XR	5 mg/day (Max: 20 mg/day)	10 mg/day (Max: 20 mg/day)	5-mg, 10-mg, 20-mg capsules	4–11 hours	Initiate dose of 20 mg/day and titrate every 7 days until clinical benefit.

Amphetamine Dextroamphetamine	Dexedrine spansules	5 mg/day	5–40 mg/day (Max: 40 mg/day)	5-mg, 10-mg, 15-mg spansules	6–8 hours	Initiate dose at 5 mg/day and increase by 5 mg/day every 7 days until clinical benefit.
Lisdexamfetamine C-II	Vyvanse	20 mg/day (Max: 70 mg/day)	20 mg/day (Max: 70 mg/day)	20-mg, 30-mg, 40-mg, 50-mg, 60-mg, 70-mg capsules	8–11 hours	Titration can be more rapid every 3–5 days depending on tolerance to adverse effects.
Amphetamine Dextroamphetamine	Adderall (generic)	0.3–1.5 mg/kg in 2–3 divided dosages	10–30 mg/day in 2–3 divided dosages (Max: 30 mg/day)	5-mg, 10-mg, 20-mg, 30-mg tablets	3.5–8 hours	Initiate dose of 2.5–5 mg and increase by 2.5- to 5-mg increments every 7 days.
Levo- and Dextroamphetamine C-II	Adderall XR (generic)	0.3–1.5 mg/kg/day; titrate weekly	10–30 mg/day; titrate weekly (Max: 30 mg/day)	5-mg, 10-mg, 15-mg, 20-mg, 25-mg, 30-mg capsules	10 hours	For IR products, a second lunchtime dose can be added to control evening symptoms if duration is insufficient. A third dose at around 3:30 PM may be required to improve evening symptoms. ER product can be sprinkled on applesauce.

## NONSTIMULANTS

<b>NORADRENERGICS</b>						
Atomoxetine	Strattera (generic)	0.5–1.4 mg/kg in 1–2 divided dosages	40–100 mg/day in 1–2 divided dosages	10-mg, 18-mg, 25-mg, 40-mg, 60-mg, 80-mg, 100-mg capsules	5–22 hours	In children <70 kg, initiate dose of 0.5 mg/kg/day and increase by 0.5-mg/kg increments weekly until maximal dose or clinical benefit. In patients >70 kg, initiate dose at 40 mg/day and increase by 40-mg increments weekly until maximal dose or clinical benefit.
<b>ANTIDEPRESSANTS</b>						
Imipramine	Tofranil (generic)	2–5 mg/kg in 1–2 divided dosages	100–300 mg/day in 1–2 divided dosages	10-mg, 25-mg, 50-mg, 100-mg tablets	8–16 hours	Start at bedtime and increase every 7 days to clinical effect.
Desipramine	Norpramin (generic)	2–5 mg/kg in 1–2 divided dosages	100–300 mg/day in 1–2 divided dosages	10-mg, 25-mg, 50-mg, 100-mg tablets	7 to >60 hours	

*Continued on following page*



TABLE 85.1 Overview of Common Drugs to Treat Attention Deficit Hyperactivity Disorder (Continued)

Drug (Generic)	Drug (Brand)	Usual Child Dose	Usual Adult Dose	Availability	Duration of Action	Titration
Nortriptyline	Pamelor (generic)	1–3 mg/kg in 1–2 divided dosages	50–200 mg/day in 1–2 divided dosages	10-mg, 25-mg, 50-mg, 100-mg tablets	16 to >90 hours	
Bupropion	Wellbutrin (generic)	3–6 mg/kg in 3 divided dosages	150–450 mg in 3 divided dosages (Max: 450 mg/day)	75-mg, 100-mg tablets	14 hours	In children, increase weekly by 3 mg/kg/day to maximum of 6 mg/kg/day or 400 mg/day (whichever is smaller) to clinical benefit. In adults, initiate 150 mg/day using SR or XL in the morning and increase by 150 mg/day weekly to a maximal dose or clinical benefit.
	Wellbutrin SR (generic)	3–6 mg/kg in 2 divided dosages	150–450 mg in 2 divided dosages (Max: 400 mg/day)	100-mg, 150-mg, 200-mg SR tablets	20 hours	
	Wellbutrin XL (generic)	3–6 mg/kg/day	150–450 mg in 2 divided dosages (Max: 400 mg/day)	150-mg, 300-mg ER tablets	20 hours	
$\alpha_2$ -Agonists Clonidine	Catapres (generic)	3–10 mcg/kg in 2–3 divided dosages	0.1–0.3 mg in 2–3 divided dosages (Max: 0.4 mg/day)	0.1-mg, 0.2-mg, 0.3-mg tablets	6–20 hours	Initiate 0.05 mg at bedtime and increase every 1–2 weeks until clinical benefit. Can switch to patch when optimal dose is established.
	Catapres patch	3–10 mcg/kg/week	0.1–0.3 mg in 2–3 divided dosages (Max: 0.4 mg/day)	0.1-mg, 0.2-mg, 0.3-mg transdermal patch	>7 days	
	Kapvay	0.1–0.4 mg/day	0.1–0.4 mg/day	0.1-mg, 0.2-mg tablets	12–16 hours	
Guanfacine	Tenex (generic)	30–100 mcg/kg in divided dosages	1–3 mg in 2–3 divided dosages (Max: 4 mg/day)	1-mg, 2-mg tablets	24 hours	Initiate 0.5 mg at bedtime and increase every 1–2 weeks until clinical effect or BP prevents further increases.
	Intuniv	0.05–0.08 mg/kg daily (Max: 4 mg/day)	0.05–0.08 mg/kg daily (Max: 4 mg/day)	1-mg, 2-mg, 3-mg, 4-mg tablets	13–19 hours	Initiate 0.05 mg/kg/day and increase weekly by 0.05 mg/kg/day until clinical effect or BP prevents further increases.

BP, blood pressure; ER, extended release; IR, immediate release; SR, sustained release; XR, extended release.

**TABLE 85.2 Managing Adverse Effects of Stimulants Used in Children with Attention Deficit Hyperactivity Disorder**

Adverse Effect	Management
Decreased appetite, nausea, or growth impairment	<ul style="list-style-type: none"> <li>• Take drug after meals</li> <li>• Do not force meals but encourage foods with high caloric density or nutritional supplements</li> <li>• Encourage evening/bedtime snack</li> <li>• Switch from long-acting to short-acting preparation</li> <li>• If severe, consider a drug holiday or different drug</li> </ul>
Sleep disturbance	<ul style="list-style-type: none"> <li>• Administer doses earlier in the day</li> <li>• If using a sustained-release product, consider changing to a short-acting preparation</li> <li>• Discontinue afternoon/evening dose</li> </ul>
Behavioral rebound	<ul style="list-style-type: none"> <li>• If using short-acting preparation, consider changing to a long-acting preparation</li> <li>• Overlap stimulant dosing</li> </ul>
Irritability	<ul style="list-style-type: none"> <li>• Assess time of symptoms:               <ul style="list-style-type: none"> <li>• Related to peak: reduce dose or try long-acting preparation</li> <li>• Related to withdrawal: change to long-acting preparation</li> </ul> </li> <li>• Evaluate for comorbid diagnosis</li> </ul>
Dysphoria, moodiness, agitation, dazed, or withdrawn behavior	<ul style="list-style-type: none"> <li>• Decrease dose or change to long-acting preparation</li> <li>• Consider comorbid diagnosis</li> </ul>
Dizziness	<ul style="list-style-type: none"> <li>• Monitor blood pressure</li> <li>• Encourage fluid intake</li> <li>• Lower dose or change to long-acting preparation to reduce peak effects</li> </ul>
Development or increase in tic disorder	<ul style="list-style-type: none"> <li>• Stop stimulant</li> <li>• Consider trial of clonidine or guanfacine</li> <li>• Consider referral to physician</li> </ul>

## Drug Abuse\*

### General Principles

- **Physical addiction or dependence** occurs when repeated administration of a drug causes an altered physiologic state. A characteristic set of withdrawal symptoms occurs when the drug is abruptly discontinued.
- **Psychological addiction or psychological dependence** refers to a maladaptive pattern of substance uses that leads to significant impairment or distress.
- **Habituation** is a state of either chronic or periodic drug use characterized by a desire (but not a compulsion) to continue using the drug, no tendency to increase the dose, and an absence of physical addiction despite some degree of psychological dependence.
- **Substance use disorder** is used to describe a group of behavioral, cognitive, and physiological symptoms that may indicate ongoing substance abuse despite substantial drug-related problems.
- **Substance-induced disorders** are a result of drug abuse (e.g., intoxication, withdrawal).
- For criteria regarding substance dependence and abuse, please refer to DSM 5.

### Goals of Therapy

- The goal of a detoxification program is to transform the addict into a responsible, drug-free, emotionally stable, and productive member of society.

### Treatment Principles

- Detoxification is the first step; it should be followed by individualized psychosocial treatment (e.g., counseling, cognitive-behavioral therapy, motivational enhancement, voucher-based reinforcement). Multimodal treatment is necessary.

### Opioids

- Abuse includes illicit drugs and nonmedical use of prescription pain relievers.
- Patients addicted to heroin or morphine will typically experience withdrawal symptoms 6 to 12 hours after the last dose. Symptoms may include anxiety, hyperactivity, restlessness, insomnia, sialorrhea, rhinorrhea, lacrimation, nausea, vomiting, and diarrhea. Heart rate and blood pressure may be elevated. Symptoms are seldom life-threatening.
- Opioids with shorter durations of action tend to produce brief, intense abstinence syndromes. Agents eliminated from the body slower produce longer, milder withdrawal syndromes. Mixed agonist-antagonist opioids (e.g., butorphanol) and partial mu agonists (e.g., buprenorphine, tramadol) have less potential for abuse than pure mu agonists (e.g., morphine).
- **Opioid (e.g., Heroin) Overdose**—immediate treatment includes airway management, cardiorespiratory support, and opioid reversal with naloxone (0.4–2.0 mg IV, IM, SubQ, repeat every 2–3 minutes as needed up 10 mg in patients  $\geq 5$  years or  $>20$  kg). If total cumulative

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\*The reader is referred to Chapter 86, Drug Abuse, written by Wendy O. Zizzo, PharmD, and Paolo V. Zizzo, DO, in the 10th edition of *Applied Therapeutics: The Clinical Use of Drugs* for a more in-depth discussion. All notations to reference numbers are based on the reference list at the end of that chapter. The editor of this handbook expresses her thanks to Drs. Zizzo and Zizzo and acknowledges that this chapter is based on their work.

dose exceeds 10 mg, consider alternative causes of respiratory depression. It is not necessary to precipitate opioid withdrawal symptoms; the end point of treatment is stabilization of vital signs.

- **Treatment of Opioid Dependence**—no single treatment modality works for all patients. Options are divided into social model programs and medical model programs. Either may be inpatient or outpatient based.
  - **Social model programs** use a nonmedical approach. Detoxification usually involves abrupt cessation of opioids without supportive therapy (i.e., cold turkey).
  - **Medical model programs** are based on pharmacotherapeutic treatment. Approaches include opioid substitution for detoxification or maintenance; symptomatic treatment of withdrawal; and rapid detoxification precipitated by an opioid antagonist under general anesthesia.
- Methadone detoxification for opioid dependence is federally regulated and is only available through specially licensed opioid treatment programs. Patients are stabilized on a daily methadone dose; the dose is then gradually tapered every 1 to 2 weeks. Psychosocial treatments should be used in conjunction with medical management.
- Buprenorphine detoxification is associated with a milder withdrawal than full opioid agonists. The first dose should be given at least 4 hours after the last dose of a short-acting opioid (e.g., heroin). Limited information supports a time frame for administration after a long-acting opioid (e.g., methadone), but buprenorphine sublingual tablet can be started preferably after moderate objective signs of opioid withdrawal.
- Ultrarapid opiate detoxification involves precipitating withdrawal with an opioid antagonist (e.g., naltrexone). It is performed under heavy sedation or general anesthesia. Risks include vomiting with aspiration, cardiovascular complications, pulmonary edema, and death.
- **Symptomatic Treatment of Opioid Withdrawal:** Clonidine can be used as part of a multi-drug regimen to ameliorate some of the opioid withdrawal symptoms. For treatment options regarding the four primary symptoms, please see DSM 5.
- Methadone maintenance therapy is the most common form of pharmacologic treatment for opioid dependence. Heroin-dependent patients are stabilized on a dose of methadone sufficient to suppress withdrawal symptoms for 12 to 24 hours without producing euphoria.
- Methadone is the standard of care for the management of opioid dependence in pregnancy. Withdrawal from methadone is not recommended for pregnant women.
- Neonatal abstinence syndrome occurs when the newborn experiences opioid withdrawal. Symptoms include restlessness, tremors, high-pitched cry, hypertonicity, increased reflexes, regurgitation, tachypnea, diarrhea, and sneezing. While evidence to support pharmacological treatment is limited, opioids (e.g., morphine) have been suggested as preferred, with phenobarbital as an alternative, and should be considered when symptoms occur; prophylactic therapy is not recommended.

## Sedative-Hypnotics

- Patients who have been on long-term courses of therapeutic doses of sedative-hypnotics may experience withdrawal symptoms with abrupt discontinuation of therapy. Symptoms, which can be life-threatening, include insomnia, anxiety, tremors, headaches, restlessness, nausea, vomiting, hypertension, tachycardia, perceptual distortions, and hypersensitivity to light, sound, and touch.
- Withdrawal symptoms after chronic use of long-acting benzodiazepines typically occur within 5 days of cessation and peak at 1 to 9 days after the last dose.
- Three general medication strategies are used to remove patients from sedative-hypnotics: decreasing the dose of the drug of dependence (i.e., tapering); substitution and gradually tapering phenobarbital for the drug of dependence; or substituting and gradually tapering a long-acting benzodiazepine for the drug of dependence. Phenobarbital substitution is generally applied. It is the preferred option for polydrug users or patients who have lost control of their benzodiazepine use. Hypnotic dose equivalents to phenobarbital are shown in Table 86.1.

TABLE 86.1 Hypnotic Dose Equivalent to 30 mg Phenobarbital

Pure ethanol 30–60 mL	Clonazepam 1–2 mg	Pentobarbital 100 mg
Alprazolam 0.5–1 mg	Diazepam 10 mg	Secobarbital 100 mg
Butalbital 100 mg	Flunitrazepam 1–2 mg <sup>a</sup>	Temazepam 15 mg
Carisoprodol 700 mg	Lorazepam 2 mg	Triazolam 0.25–0.5 mg
Chlordiazepoxide 25 mg	Oxazepam 10–15 mg	Zolpidem 5 mg

<sup>a</sup>Not approved for use in the United States.

Source: Dickinson WE, Eickelberg SJ. Management of sedative-hypnotic intoxication and withdrawal. In: Ries RK et al, eds. *Principles of Addiction Medicine*. 4th ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2009:573.

- Gamma-hydroxybutyric acid (GHB) is abused for its euphoric properties, disinhibition, and enhanced sensuality. Adverse effects include dizziness, nausea, weakness, agitation, hallucinations, seizures, respiratory depression, and coma. Treatment of overdose is primarily supportive.

## Central Nervous System Stimulants

- Abuse of central nervous system (CNS) stimulants typically includes cocaine and amphetamines.
- Cardiac complications associated with cocaine use include hypertension, arrhythmias, myocardial ischemia and infarction, dilated and hypertrophic cardiomyopathy, myocarditis, aortic dissection, and acceleration of atherosclerosis. Medical management of acute coronary syndromes differs when cocaine is the cause; nonselective  $\beta$ -blockers are contraindicated. Nitroglycerine and benzodiazepines are part of first-line therapy.
- Stimulant withdrawal typically manifests within a few hours to several days following discontinuation or reduction of stimulant use. Onset of a dysphoric mood is often observed, with the presence of at least two of the other following manifestations confirming diagnosis of stimulant withdrawal: bradycardia, fatigue, vivid and disturbing dreams, insomnia or hypersomnia, hyperphagia, and psychomotor retardation or agitation. Drug craving and anhedonia may also occur, but are not considered in the diagnosis.
- Acute withdrawal symptoms correspond with abrupt discontinuation after frequent usage of high-dose stimulants and are characterized by an overwhelming depression accompanied by hyperphagia. Most cases of simple withdrawal do not require medical treatment, generally necessitating rest and recuperation. No drug treatment has been proven effective in treating cocaine dependence.
- Chronic methamphetamine abuse can result in someone who is mentally unstable, aggressive, and emotionally labile with unpredictable periods of violent behavior. Chronic users characteristically develop complex paranoid delusional systems with hallucinations. The initial treatment for stimulant-induced adverse psychological effects is nonpharmacologic (e.g., reduce environmental stimuli, reassure the patient that the condition will resolve, talk the patient down). Administration of a benzodiazepine (e.g., diazepam, lorazepam) or a high-potency neuroleptic (e.g., haloperidol, risperidone) may be needed in an extremely agitated, anxious, psychotic user.
- Withdrawal after acute cessation of chronic stimulant use is notable for marked fatigue, depression, and anhedonia. No pharmacologic treatments have been proven effective for methamphetamine dependence.

## Dissociative Drugs

- Dissociative drugs include phencyclidine (PCP), ketamine, and dextromethorphan.
- Symptoms of PCP intoxication are influenced by dose, route, and serum concentration. In low doses, it causes inebriation, ataxia, changes in body image, numbness, and a mind–body dissociative feeling. As the dose increases, the patient may manifest agitation, combativeness, catatonia, and psychosis. CNS depression occurs with large doses.

- Diagnosis of PCP intoxication should be confirmed through a blood or urine specimen.
- There is no approved antidote to PCP; treatment should be supportive. Activated charcoal 1 g/kg has been suggested to prevent further absorption of PCP. Atypical antipsychotics (e.g., olanzapine, ziprasidone) may be utilized for PCP-induced psychosis. Diphenhydramine 50 mg IV or 1 mg/kg may also be implemented for dystonic symptoms that may occur. Environmental stimuli should be minimized, and chemical restraints may be needed for combative patients. Hypertension can be managed with  $\beta$ -blockers and diazepam is useful for seizures.
- Dextromethorphan ingested in large doses produces effects similar to PCP.

## Hallucinogens

- The usual pattern of use is occasional self-administration for enhancement of recreational activities. Lysergic acid diethylamide is considered the prototype agent.
- The most common adverse reaction associated with hallucinogenic drugs is a mental state of acute anxiety and fear (i.e., a bad trip). Initial therapy for a bad trip is talking down the fear and panic. If unsuccessful, sedation with an oral or parenteral benzodiazepine can be considered. Haloperidol can be used if benzodiazepine therapy is insufficient.
- Hallucinogen persisting perceptual disorder, or flashbacks, are characterized by recurrence of part or all of the hallucinogenic drug experiences after a period of normal consciousness in a person who used the drug previously.
- MDMA can cause anxiety, depression, panic attacks, agitation, paranoia, and rarely psychosis. Hyperthermia is the most dangerous physical adverse effect. It can lead to rhabdomyolysis, acute renal and hepatic failure, disseminated intravascular coagulation, and death.
- MDMA does not appear to produce physical dependence, but psychological dependence is possible. Although withdrawal symptoms have been noted, they may not require pharmacologic treatment.

## Marijuana

- Marijuana produces sedation, mental relaxation, euphoria, and mild hallucinogenic effects. Anxiety, paranoia, and panic attacks may cause someone to seek medical treatment. Tolerance to the psychoactive effects of marijuana does develop.
- Dependence is characterized by physical withdrawal syndrome that includes anxiety, depression, irritability, restlessness, anorexia, insomnia, sweating, tremor, nausea, vomiting, or diarrhea. The withdrawal syndrome is generally mild and self-limiting. Pharmacologic treatments are not required.

## Inhalants

- Inhalant use is typically episodic in nature.
- Inhalants are divided into three main categories: volatile solvents (e.g., mostly hydrocarbons), volatile nitrites (e.g., amyl, butyl, isobutyl, cyclohexyl), and nitrous oxide (i.e., laughing gas).
- Toxicity depends on the chemical and the magnitude and duration of exposure.

# Alcohol Use Disorders\*

## General Principles

- **Ethanol** is a central nervous system (CNS) depressant.
- **Alcoholic proof** is a measure of how much ethanol is in an alcoholic beverage; it is twice the percentage of alcohol by volume.
- **Alcohol dependence** is a chronic relapsing disorder with genetic, psychosocial, and environmental factors influencing its development and manifestations. Dependence is characterized by preoccupation with alcohol use; signs of tolerance and withdrawal; and use despite adverse consequences.
- **Alcohol use disorder (AUD)** is clinically significant impairment or distress, due to alcohol use, with at least two of the following signs or symptoms within a 12-month period:
  - Alcohol intake frequently in larger amounts or over a longer period than anticipated
  - Efforts to control or decrease alcohol use continuously desired or unsuccessfully attempted
  - A large amount of time spent obtaining and using alcohol or recovering from its effects
  - Failure to fulfill obligations at work, school, or home due to persistent alcohol use
  - Recurrent alcohol use although persistent social or interpersonal problems exist or are exacerbated by alcohol use
  - Reduction in social, occupational, or recreational activities due to alcohol use
  - Use of alcohol recurrently in physically hazardous situations
  - Continued use of alcohol despite knowledge of physical or psychological problem likely caused or increased by alcohol use
  - Evidence of tolerance or withdrawal
- **Alcohol withdrawal syndrome (AWS)** is defined as cessation or reduction in heavy and prolonged alcohol use and two or more of the following symptoms within several hours to a few days following alcohol cessation:
  - Anxiety, autonomic hyperactivity, grand mal seizures, increased hand tremor, insomnia, nausea or vomiting, psychomotor agitation, transient hallucinations or illusions.
  - Signs or symptoms previously described must affect the ability to function in social, occupational, or other settings and are not associated with another medical condition.
- **Alcohol withdrawal delirium, or delirium tremens**, is a severe manifestation of withdrawal.

## Patient Assessment

- An accurate medical history, including laboratory test results and history of alcohol use, is important (Table 87.1).
- Prescription drug use and interactions with alcohol are common (Table 87.2).
- Blood ethanol concentration often correlates with the clinical presentation (Table 87.3).
- Chronic heavy drinkers can oxidize ethanol at twice the normal rate. Chronic use can produce significant tolerance and characteristic changes in the liver.

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\*The reader is referred to Chapter 87, Alcohol Use Disorders, written by George A. Kenna, PhD, RPh, in the 10th edition of *Applied Therapeutics: The Clinical Use of Drugs* for a more in-depth discussion. All notations to reference numbers are based on the reference list at the end of that chapter. The editor of this handbook expresses her thanks to Dr. Kenna and acknowledges that this chapter is based upon his work.

TABLE 87.1 Useful Screens for Assessing Alcohol Problems

## THE C-A-G-E SCREENING QUESTIONS (CAGE)

Have you ever felt you should cut down on your drinking?  
 Have other people annoyed you by criticizing your drinking?  
 Have you ever felt guilty about drinking?  
 Have you ever taken a drink in the morning to calm your nerves or get rid of a hangover (eye opener)?

## METHODS FOR DETERMINING RECENT ALCOHOL CONSUMPTION

Acute consumption

- Blood alcohol concentration
- Urine (ethyl glucuronide)
- Saliva
- Breath alcohol concentration

Recent heavy consumption

- Gamma-glutamyl transferase (GGT)
- Carbohydrate-deficient transferrin (CDT)
- Mean corpuscular volume (MCV)

TABLE 87.2 Ethanol-Drug Interactions

Acetaminophen	Chronic excessive alcohol consumption increases susceptibility to acetaminophen-induced hepatotoxicity. Acute intoxication theoretically protects against acetaminophen toxicity because less hepatotoxic metabolite is generated.
Anticoagulants (oral)	Chronic ethanol consumption induces hepatic metabolism of warfarin, decreasing hypoprothrombinemic effect. Very large acute ethanol doses (>3 drinks/day) may impair the metabolism of warfarin and increase hypoprothrombinemic effect. Vitamin K-dependent clotting factors may be reduced in alcoholics with liver disease, also affecting coagulation.
Antidepressants	Enhanced sedative effects of alcohol and psychomotor impairment are possible. Acute ethanol impairs metabolism. Fluoxetine, paroxetine, fluvoxamine, and probably other selective serotonin reuptake inhibitors (SSRIs) do not interfere with psychomotor or subjective effects of ethanol.
Ascorbic acid	Ascorbic acid increases ethanol clearance and serum triglyceride levels and improves motor coordination and color discrimination after ethanol consumption.
Barbiturates	Phenobarbital decreases blood ethanol concentration; acute intoxication inhibits pentobarbital metabolism; chronic intoxication enhances hepatic pentobarbital metabolism.
Benzodiazepines	Psychomotor impairment increases with the combination.
Bromocriptine	Ethanol may increase the sensitivity to dopamine receptors, which may increase the side effects of bromocriptine (e.g., constipation, nausea). Additive CNS effects may be seen as well.
Caffeine	Caffeine has no effect on ethanol-induced psychomotor impairment.
Calcium-channel blockers	Verapamil inhibits ethanol metabolism and increases intoxication.
Cephalosporin antibiotics	Ethanol produces flushing, nausea, headaches, tachycardia, and hypotension. Cephalosporin antibiotics that have an ethyltetrahydrothiol side chain produce this disulfiramlike reaction (e.g., cefoperazone, cefamandole, cefotetan).
Chloral hydrate	Elevation of plasma trichloroethanol (a chloral hydrate metabolite) and blood ethanol may occur, combined with central nervous system (CNS) depression, vasodilation, tachycardia, and headache.
Chloroform	Ethanol increases chloroform hepatotoxicity.
Doxycycline	Chronic consumption of ethanol induces hepatic metabolism of doxycycline and may lower serum concentration of the antibiotic.
Erythromycin	Ethanol may interfere with absorption of the ethylsuccinate salt. Effects on other formulations are unknown.
Furazolidone	When ethanol is ingested, nausea, flushing, lightheadedness, and dyspnea may occur (i.e., a disulfiramlike reaction).

*Continued on following page*



TABLE 87.2 Ethanol-Drug Interactions (Continued)

H <sub>2</sub> antagonists	Cimetidine potentiates ethanol effects and increases peak plasma ethanol concentrations and area under the plasma ethanol concentration time curve. CNS toxicity results from increased cimetidine serum concentration. Nizatidine and ranitidine may also increase blood alcohol levels slightly by inhibiting gastric alcohol dehydrogenase. Famotidine does not affect blood alcohol levels.
Isoniazid	Consumption of ethanol with isoniazid increases risk of hepatotoxicity. Tyramine-containing alcoholic beverages may cause hypertensive reaction.
Ketoconazole and metronidazole	When ethanol is ingested, nausea, flushing, lightheadedness, and dyspnea may occur (i.e., a disulfiramlike reaction may occur with metronidazole). A sunburnlike rash has been reported with ethanol consumption and ketoconazole. A similar reaction may occur with itraconazole, although no reports exist.
Meprobamate	Synergistic CNS depression may occur
Metoclopramide	Enhances sedative effects of ethanol
Monoamine oxidase inhibitors	Tyramine-containing alcoholic beverages (e.g., wines, beer) may cause a hypertensive crisis. Pargyline may inhibit aldehyde dehydrogenase and cause a disulfiramlike interaction with ethanol.
Narcotic analgesics	Volume of distribution of intravenous meperidine increases with increasing ethanol consumption. Clinical significance unknown. Potential for enhanced CNS depression
Oral antidiabetic agents	Chlorpropamide, tolbutamide, and tolazamide may cause flushing, lightheadedness, nausea, and dyspnea if alcohol is ingested (i.e., a disulfiramlike reaction). Excessive alcohol consumption may later blood glucose levels. Concomitant metformin and alcohol ingestion may increase risk of lactic acidosis.
Paraldehyde	Possible metabolic acidosis may occur
Phenothiazines	Potentiates psychomotor effects of ethanol
Quinacrine	Possibly inhibits acetaldehyde oxidation
Salicylates	Increases gastric bleeding associated with aspirin; may increase chance of gastrointestinal hemorrhage
Tetrachloroethylene	Combined CNS depression may occur.
Trichloroethylene	Flushing, lacrimation, blurred vision, and tachypnea may occur when patients are exposed to trichloroethylene drink alcohol.

Source: Adapted with permission from Ciraulo D, Shader RI, Greenblatt DJ, et al. *Drug Interactions in Psychiatry*. 3rd ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2006.

## Treatment

- Treatment of alcohol dependence consists mainly of psychological, social, and pharmacotherapy interventions aimed at reducing alcohol-related problems. Pharmacotherapy is intended to be adjunctive to psychosocial treatments (Table 87.4).
- Treatment usually consists of two phases: detoxification and rehabilitation. Detoxification manages the signs and symptoms of withdrawal. Rehabilitation helps avoid future problems with alcohol.

TABLE 87.3 Relationship of Blood Alcohol Concentration to Clinical Status

Blood Ethanol Concentration	Clinical Presentation <sup>a</sup>
50 mg/dL (0.05 mg%)	Motor function impairment observable
80 mg/dL (0.08 mg%)	Moderate impairment; legal definition of intoxication in all states when driving
450 mg/dL (0.45 mg%)	Respiratory depression
500 mg/dL (0.50 mg%)	LD <sub>50</sub> for ethanol

<sup>a</sup>Tolerance to alcohol varies among individuals.

LD<sub>50</sub>, median lethal dose.

TABLE 87.4 Psychosocial and Behavioral Interventions Used with AUD

Type of Therapy	Underlying Processes	Key Components
Cognitive behavioral therapy (CBT)	The foundation is the belief that by identifying and monitoring maladaptive thinking patterns, patients can reduce or eliminate negative feelings and substance use	Alter cognitive processes that lead to maladaptive behaviors of AUD Intervene in the behavioral chain that leads to substance use Help patients deal with acute or chronic substance craving Promote and reinforce the development of social skills and behaviors compatible with abstinence
Motivational enhancement therapy (MET)	Brief treatment is characterized by an empathetic approach in which the therapist helps to motivate the patient by asking about the pros and cons of the target behavior (e.g., substance use)	Develop discrepancy (e.g., comparing given behavior with peer norms) Elicit self-motivational statements Listen with empathy Avoid argumentation Support self-efficacy
Medical management (MM)	Brief 20-minute intervention by a health care professional (e.g., nurse, pharmacist, or physician)	Focus on medication adherence Monitor alcohol use Assess side effects Encourage 12-step meeting attendance Set goals Educate
Brief behavioral compliance enhancement therapy (BBCET)	Brief 10-minute intervention by a health care professional	Focus on medication adherence Monitor alcohol use Assess side effects Allow patient to set goals
12-Step facilitation	Any support group that is a self-help group (e.g., Alcoholics Anonymous)	Find a support group one feels comfortable with Get a sponsor Work the 12 steps to recovery

AUD, alcohol use disorder.

Source: Miller WR et al. Mesa Grande: a methodological analysis of clinical trials of treatments for alcohol use disorders. *Addiction*. 2002;97:265.

- Treatment of alcohol intoxication is essentially supportive (Table 87.5). In highly intoxicated patients, the prolonged slowing of respiratory rate can lead to arrhythmias, cardiac arrest, and death. Immediate supportive care, which may include endotracheal intubation for respiratory support, may be necessary.
- Administration of sodium bicarbonate may be needed when metabolic acidosis is present. Respiratory support is needed to prevent hypercapnea.
- Patients who present in a comatose state should receive naloxone (0.4–2 mg) as alcohol intoxication may be complicated by co-ingestion of opioids.
- Antipsychotics (e.g., haloperidol 2–5 mg IM or IV with caution) can be used for managing hallucinations and severe agitation.
- Gastric lavage may be useful if ingestion of other drugs is suspected or when a recent consumption of large quantities of alcohol is expected. Activated charcoal absorbs ethanol poorly. Dialysis may be considered if the patient cannot be stabilized or has complicating factors.
- Benzodiazepines are considered the drugs of choice for alcohol withdrawal. Choice of agent depends on pharmacokinetic properties, dosage formulation, presence of liver impairment, and ease of dose titration (Table 87.6).

**TABLE 87.5 Acute Alcohol Intoxication: Symptoms and Treatment**

Symptom	Course	Treatment
Respiratory acidosis	Alcohol-induced respiratory depression; blunted response to hypercapnia and hypoxia	Endotracheal intubation for respiratory support
Coma	Alcohol-induced CNS depression; ingestion of other drugs	Gastric lavage (not usually performed), naloxone (Narcan) 1 mg, repeat every 2–3 minutes up to 10 doses, depending on response and suspicion of ingestion. Thiamine and glucose can be considered to prevent or treat Wernicke’s encephalopathy. Dialysis possible
Hypotension	Hypovolemia	IV fluid replacement
Hypoglycemia	Most often occurs in malnourished patients. Pyruvate is converted to lactate, rather than glucose, through gluconeogenesis.	50% glucose (50 mL) by IV push

CNS, central nervous system; IV, intravenous.

- General AWS treatment guidelines are shown in Table 87.7. Elderly patients, those with hepatic or renal dysfunction, and those with medical or psychiatric illnesses require close observation to prevent overmedication.
- Hydration, electrolyte (especially potassium and magnesium) and nutritional status should be assessed. IV fluids, thiamine, and multivitamins should be given, if needed. Thiamine administration should precede glucose to prevent precipitation of Wernicke’s encephalopathy.

### Drug Therapy

- **Disulfiram** blocks alcohol metabolism. It reinforces the desire to stop drinking by providing a disincentive; headache, palpitations, hypotension, flushing, nausea, and vomiting occur when alcohol is consumed. Dosing should start at least 12 hours after abstinence begins. Use should be avoided during the first trimester of pregnancy and in patients with cardiac disease, coronary occlusion, cerebrovascular disease, and renal or hepatic failure. Liver function tests should be monitored when initiating and periodically during therapy. Patients should be informed that exposure to small amounts of any form of alcohol (in food, mouthwash, topical lotions) can cause a reaction.

**TABLE 87.6 Comparison of Benzodiazepines Used for Alcohol Withdrawal**

Benzodiazepine	Onset of Action <sup>a</sup>	Peak Level Onset	Pathway Metabolized	Elimination Half-Life (Hours)	Comparative Dose
Chlordiazepoxide	Intermediate (PO)	1–4 hours (PO)	Hepatic	3–29 (parent drug) 28–100 (metabolite)	25 mg
Diazepam	Rapid (IV or PO)	1–2 hours (PO); 1 hour (IM); 8 minutes (IV)	Hepatic	14–70 (parent drug) 30–200 (metabolites)	5 mg
Lorazepam	Intermediate (PO); Rapid (IV)	1–6 hours (PO); 45–75 minutes (IM/SL); 5–10 minutes (IV)	Hepatic; no active metabolites	8–24	1 mg
Oxazepam	Slow (PO)	1–4 hours (PO)	Hepatic; no active metabolites	3–25	15 mg

<sup>a</sup>Onset of action: rapid, within 15 minutes; intermediate, 15 to 30 minutes; slow, 30 to 60 minutes. IM, intramuscular; IV, intravenous; PO, oral; SL, sublingual.

- **Acamprosate** is a GABA antagonist, which promotes abstinence by reducing cravings. It should be used in combination with a psychosocial program. Side effects include nausea, diarrhea, and bloating. Use should be avoided in patients with impaired kidney function.
- **Naltrexone** is an opioid antagonist used as an adjunct to psychosocial interventions to reduce cravings by reducing the reward associated with alcohol. Treatment can be given orally (50 mg daily) or by deep IM injection every 4 weeks (380 mg). Concurrent use of opioid analgesics is contraindicated. Patients must be opioid free for 7 to 14 days before initiating therapy. Side effects include nausea, dizziness, sedation, headache, anxiety, and blurred vision.

TABLE 87.7 Suggested Treatment Strategies for Alcohol Withdrawal Syndrome

Protocol	Clinical Rationale	Drug	Dosing Regimen (Example)	Considerations
Fixed-Schedule Regimen	The patient receives a fixed dose of medication for 2–3 days regardless of the severity of symptoms. This approach is generally used in severe alcohol withdrawal.	Chlordiazepoxide	50 mg orally every 6 hours × 4 doses followed by 25 mg every 6 hours × 8 doses	Protocol fixed dose and time parameters are decided beforehand. Additional medication is provided as needed when symptoms are not controlled (e.g., the CIWA-Ar score remains at least 8–10).
		Diazepam	10 mg orally every 6 hours × 4 doses, followed by 5 mg every 6 hours × 8 doses	
		Lorazepam	2 mg orally every 6 hours × 4 doses followed by 1 mg every 6 hours × 8 doses	
Symptom-Triggered Regimen	The patient is assessed every hour using the CIWA-Ar to determine the need for medication. The primary advantage of this approach is that less medication is used to achieve the same control and less sedation.	Chlordiazepoxide	50–100 mg	Less abuse potential for outpatients, low cost; long-acting 24–48 hours
		Diazepam	10–20 mg	
		Lorazepam	2–4 mg	

Continued on following page

TABLE 87.7 Suggested Treatment Strategies for Alcohol Withdrawal Syndrome (Continued)

Protocol	Clinical Rationale	Drug	Dosing Regimen (Example)	Considerations
Alternative Therapies	In patients with benzodiazepine allergy or when use of a benzodiazepine is deemed medically inappropriate	Carbamazepine	Taper from 600–800 mg on day 1 down to 200 mg over 5 days 400 mg PO TID for 3 days, then 400 mg PO BID for 1 day, then 400 mg PO for 1 day	Not addictive  Few drug interactions and relatively little cognitive impairment
	May be equally efficacious as benzodiazepines, but more information is needed before routine use in alcohol withdrawal	Baclofen	5 mg PO TID for 3 days, then increase to 10 mg TID	Not addictive. Known to lower the seizure threshold
Adjunctive Therapies	Adrenergic hyperactivity	Clonidine	0.1 mg PO BID as needed	For mild to moderate hyperactivity
	Adrenergic hyperactivity	$\beta$ -Blockers	Atenolol: 50 mg PO daily	May improve vital signs faster than oxazepam alone
		Atenolol Metoprolol	Metoprolol: 2.5–5 mg IV	Up to 3 doses about 2 minutes apart; use parameters for HR and blood pressure
	Agitation, hallucinations, delirium	Haloperidol	0.5–5 mg PO/IM/IV every hour; maximal dose 100 mg/day PO	Rapid onset; QTc prolongation (e.g., >450 ms); recommend baseline ECG before using IV Monitor for orthostatic hypotension before the administration of repeated doses.

BID, twice daily; CIWA-Ar, Clinical Institute Withdrawal Assessment; ECG, electrocardiogram; HR, heart rate; IM, intramuscular; IV, intravenous; PO, oral; TID, three times daily.

Sources: Guirguis AB, Kenna GA. Treatment considerations for alcohol withdrawal syndrome. *US Pharm.* 2005;30:71; Mayo-Smith MF et al. Management of alcohol withdrawal delirium. An evidence-based guideline [published correction appears in *Arch Intern Med.* 2004;164:2068. Dosage error in article text]. *Arch Intern Med.* 2004;164:1405.

# Tobacco Use and Dependence\*

## General Principles

- Tobacco addiction is maintained by nicotine dependence. All forms of tobacco are harmful; there is no safe level of exposure.
- Smoking has a causal or contributory role in the development of a variety of medical conditions (Table 88.1).
- Adverse health consequences of tobacco use have been shown to include cancer of the lung, oral cavity, larynx, esophagus, and pancreas.
- Nicotine meets the criteria for an addictive substance: It induces psychoactive effects, use is in a highly controlled or compulsive manner, and behavioral patterns of use are reinforced by its pharmacological effects.

## Patient Assessment

- Nicotine withdrawal symptoms include anger, anxiety, depressed mood, difficulty concentrating, impatience, increased appetite, insomnia, and restlessness. Symptoms typically manifest within a few days of quitting, peak within a week, and subside within 2 to 3 weeks.
- Several drug interactions with tobacco smoke exist, most of which involve inducing hepatic enzymes (particularly CYP1A2, Table 88.2).
- Guidelines recommend five key components of counseling for tobacco cessation. Clinicians should view quitting as a process that may take months to achieve.
- Several strategies can be used to enhance motivation to quit (Table 88.3).
- Weight gain after quitting is common.

## Goals of Therapy

- The target goal is complete, long-term abstinence from all nicotine-containing products. Decreasing the number of cigarettes smoked per day should be viewed as a positive step toward quitting, but should not be recommended as a target endpoint.

## Treatment

- Successful quitting is more likely to occur in those who receive assistance, although most tobacco users attempt to quit on their own. Treatment requires a multifaceted approach.
- Cognitive and behavioral strategies should be used for tobacco cessation (Table 88.4).
- Many medications are available for tobacco dependence. Their use should be encouraged for all patients attempting to quit smoking, except when medically contraindicated or in populations in which there is insufficient evidence of effectiveness (e.g., pregnant women, smokeless tobacco users, light smokers, adolescents).

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\*The reader is referred to Chapter 88, Tobacco Use and Dependence, written by Robin L. Corelli, PharmD, and Karen Suchanek Hudmon, DrPH, MS, RPh, in the 10th edition of *Applied Therapeutics: The Clinical Use of Drugs* for a more in-depth discussion. All notations to reference numbers are based on the reference list at the end of that chapter. The editor of this handbook expresses her thanks to Drs. Corelli and Hudmon and acknowledges that this chapter is based on their work.

TABLE 88.1 Health Consequences of Smoking

<b>Cancer</b>	Acute myeloid leukemia
	Bladder
	Cervical
	Esophageal
	Gastric
	Kidney
	Laryngeal
	Lung
	Oral cavity and pharyngeal
	Pancreatic
	<b>Cardiovascular disease</b>
Coronary heart disease (angina pectoris, ischemic heart disease, myocardial infarction)	
Cerebrovascular disease (transient ischemic attacks, stroke)	
Peripheral arterial disease	
<b>Pulmonary disease</b>	Acute respiratory illnesses
	Upper respiratory tract (rhinitis, sinusitis, laryngitis, pharyngitis)
	Lower respiratory tract (bronchitis, pneumonia)
	Chronic respiratory illnesses
	Chronic obstructive pulmonary disease
	Respiratory symptoms (cough, phlegm, wheezing, dyspnea)
<b>Reproductive effects</b>	Poor asthma control
	Reduced lung function
	Reduced fertility in women
	Pregnancy and pregnancy outcomes
	Preterm, premature rupture of membranes
	Placenta previa
	Placental abruption
Preterm delivery	
<b>Other effects</b>	Low infant birth weight
	Infant mortality
	Sudden infant death syndrome
	Cataract
	Osteoporosis (reduced bone density in postmenopausal women, increased risk of hip fracture)
	Periodontitis
Peptic ulcer disease (in patients who are infected with <i>Helicobacter pylori</i> )	
Surgical outcomes (poor wound healing, respiratory complications)	

Source: Adapted from National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health. *The Health Consequences of Smoking: A Report of the Surgeon General*. Washington, DC: Office on Smoking and Health, National Center for Chronic Disease Prevention and Health Promotion, Centers for Disease Control and Prevention, US Department of Health and Human Services; 2004.

- Nicotine replacement therapy (NRT) improves cessation rates by reducing the physical withdrawal symptoms while the patient focuses on modifying behavior. Several NRT options exist. Available dose forms, dosing and use guidelines, and adverse effects are shown in Table 88.5.
- Guidelines state that extended use of medications for cessation may be beneficial in patients who report persistent withdrawal symptoms during treatment, those who relapsed shortly after medication discontinuation, or those who are interested in long-term therapy.

TABLE 88.2 Drug Interactions with Smoking<sup>a</sup>

Drug/Class	Mechanism of Interaction and Effects
<b>PHARMACOKINETIC INTERACTIONS</b>	
Alprazolam (Xanax)	<ul style="list-style-type: none"> <li>• Conflicting data on significance of a PK interaction, but possible ↓ plasma concentrations (up to 50%); ↓ half-life (35%)</li> </ul>
Bendamustine (Treanda)	<ul style="list-style-type: none"> <li>• Metabolized by CYP1A2. Manufacturer recommends using with caution in smokers because of likely ↓ bendamustine concentrations, with ↑ concentrations of its two active metabolites.</li> </ul>
Caffeine	<ul style="list-style-type: none"> <li>• ↑ Metabolism (induction of CYP1A2); ↑ clearance (56%)</li> <li>• Likely ↑ caffeine levels after cessation</li> </ul>
Chlorpromazine (Thorazine)	<ul style="list-style-type: none"> <li>• ↓ AUC (36%) and serum concentrations (24%)</li> <li>• ↓ Sedation and hypotension possible in smokers; smokers may need ↑ dosages.</li> </ul>
Clopidogrel (Plavix)	<ul style="list-style-type: none"> <li>• ↑ Metabolism (induction of CYP1A2) of clopidogrel to its active metabolite</li> <li>• Clopidogrel's effects are enhanced in smokers (≥10 cigarettes/day): significant ↑ platelet inhibition, ↓ platelet aggregation; although improved clinical outcomes have been shown, may also ↑ risk of bleeding</li> </ul>
Clozapine (Clozaril)	<ul style="list-style-type: none"> <li>• ↑ Metabolism (induction of CYP1A2); ↓ plasma concentrations (18%)</li> <li>• ↑ Levels on cessation may occur; closely monitor drug levels and reduce dose as required to avoid toxicity.</li> </ul>
Erlotinib (Tarceva)	<ul style="list-style-type: none"> <li>• ↑ Clearance (24%); ↓ trough serum concentrations (twofold)</li> </ul>
Flecainide (Tambacor)	<ul style="list-style-type: none"> <li>• ↑ Clearance (61%); ↓ trough serum concentrations (25%)</li> <li>• Smokers may need ↑ dosages.</li> </ul>
Fluvoxamine (Luvox)	<ul style="list-style-type: none"> <li>• ↑ Metabolism (induction of CYP1A2); ↑ clearance (24%); ↓ AUC (31%); ↓ plasma concentrations (32%)</li> <li>• Dosage modifications not routinely recommended but smokers may need ↑ dosages</li> </ul>
Haloperidol (Haldol)	<ul style="list-style-type: none"> <li>• ↑ Clearance (44%); ↓ serum concentrations (70%)</li> </ul>
Heparin	<ul style="list-style-type: none"> <li>• Mechanism unknown but ↑ clearance and ↓ half-life are observed. Smoking has prothrombotic effects.</li> <li>• Smokers may need ↑ dosages because of PK and PD interactions.</li> </ul>
Insulin, subcutaneous	<ul style="list-style-type: none"> <li>• Possible ↓ insulin absorption secondary to peripheral vasoconstriction; smoking may cause release of endogenous substances that cause insulin resistance.</li> <li>• PK and PD interactions likely not clinically significant; smokers may need ↑ dosages.</li> </ul>
Irinotecan (Camptosar)	<ul style="list-style-type: none"> <li>• ↑ Clearance (18%); ↓ serum concentrations of active metabolite SN-38 (approximately 40%; via induction of glucuronidation); ↓ systemic exposure resulting in lower hematologic toxicity and may reduce efficacy</li> <li>• Smokers may need ↑ dosages.</li> </ul>
Methadone	<ul style="list-style-type: none"> <li>• Possible ↑ metabolism (induction of CYP1A2, a minor pathway for methadone)</li> <li>• Carefully monitor response upon cessation.</li> </ul>
Mexiletine (Mexitil)	<ul style="list-style-type: none"> <li>• ↑ Clearance (25%; via oxidation and glucuronidation); ↓ half-life (36%)</li> </ul>
Olanzapine (Zyprexa)	<ul style="list-style-type: none"> <li>• ↑ Metabolism (induction of CYP1A2): ↑ clearance (98%); ↓ serum concentrations (12%)</li> <li>• Dosage modifications not routinely recommended but smokers may require ↑ dosages</li> </ul>
Propranolol (Inderal)	<ul style="list-style-type: none"> <li>• ↑ Clearance (77%; via side-chain oxidation and glucuronidation)</li> </ul>
Riociguat (Adempas)	<ul style="list-style-type: none"> <li>• ↓ Plasma concentrations (50%–60%)</li> <li>• May require dosages higher than 2.5 mg three times a day; consider dose reduction upon cessation.</li> </ul>
Ropinirole (Requip)	<ul style="list-style-type: none"> <li>• ↓ C<sub>max</sub> (30%) and AUC (38%) in study with patients with restless legs syndrome</li> <li>• Smokers may need ↑ dosages.</li> </ul>
Tacrine (Cognex)	<ul style="list-style-type: none"> <li>• ↑ Metabolism (induction of CYP1A2); ↓ half-life (50%); serum concentrations threefold lower</li> <li>• Smokers may need ↑ dosages.</li> </ul>
Tasimetleon (Hetlioz)	<ul style="list-style-type: none"> <li>• ↑ Metabolism (induction of CYP1A2); drug exposure ↓ 40%</li> <li>• Smokers may need ↑ dosages.</li> </ul>

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TABLE 88.2 Drug Interactions with Smoking<sup>a</sup> (Continued)

Drug/Class	Mechanism of Interaction and Effects
Theophylline (Theo-Dur, etc.)	<ul style="list-style-type: none"> <li>• ↑ Metabolism (induction of CYP1A2); ↑ clearance (58%–100%); ↓ half-life (63%)</li> <li>• Levels should be monitored if smoking is initiated, discontinued, or changed.</li> <li>• ↑ Clearance with secondhand smoke exposure</li> <li>• Maintenance doses are considerably higher in smokers.</li> </ul>
Tricyclic antidepressants (e.g., imipramine, nortriptyline)	<ul style="list-style-type: none"> <li>• Possible interaction with tricyclic antidepressants in the direction of ↓ blood levels, but the clinical significance is not established</li> </ul>
Tizanidine (Zanaflex)	<ul style="list-style-type: none"> <li>• ↓ AUC (30%–40%) and ↓ half-life (10%) observed in male smokers</li> </ul>
Warfarin	<ul style="list-style-type: none"> <li>• ↑ Metabolism (induction of CYP1A2) of R-enantiomer; however, S-enantiomer is more potent and effect on INR is inconclusive. Consider monitoring INR on smoking cessation.</li> </ul>

PHARMACODYNAMIC INTERACTIONS

Benzodiazepines (diazepam, chlordiazepoxide)	<ul style="list-style-type: none"> <li>• ↓ Sedation and drowsiness, possibly caused by nicotine stimulation of central nervous system</li> </ul>
β-Blockers	<ul style="list-style-type: none"> <li>• Less effective antihypertensive and heart rate control effects; might be caused by nicotine-mediated sympathetic activation</li> <li>• Smokers may need ↑ dosages.</li> </ul>
Corticosteroids, inhaled	<ul style="list-style-type: none"> <li>• Smokers with asthma may have less of a response to inhaled corticosteroids.</li> </ul>
Hormonal contraceptives	<ul style="list-style-type: none"> <li>• ↑ Risk of cardiovascular adverse effects (e.g., stroke, myocardial infarction, thromboembolism) in women who smoke and use oral contraceptives. Ortho Evra patch users shown to have twofold ↑ risk of venous thromboembolism compared with oral contraceptive users, likely as a result of ↑ estrogen exposure (60% higher levels)</li> <li>• ↑ Risk with age and with heavy smoking (15 or more cigarettes per day) and is quite marked in women aged 35 and older</li> </ul>
Opioids (propoxyphene, pentazocine)	<ul style="list-style-type: none"> <li>• ↓ Analgesic effect; smoking may ↑ the metabolism of propoxyphene (15%–20%) and pentazocine (40%). Mechanism unknown</li> <li>• Smokers may need ↑ opioid dosages for pain relief.</li> </ul>
Serotonin 5-HT <sub>1</sub> receptor agonists (triptans)	<ul style="list-style-type: none"> <li>• This class of drugs may cause coronary vasospasm; caution for use in smokers due to unrecognized CAD</li> </ul>

<sup>a</sup>Shaded rows indicate the most clinically significant interactions.

AUC, area under the curve; C<sub>max</sub>, maximal concentration; INR, international normalized ratio; PD, pharmacodynamic; PK, pharmacokinetic.

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TABLE 88.3 Enhancing Motivation to Quit: The “5 R’s” for Tobacco Cessation Counseling

- **Relevance**—Encourage patients to think about the reasons why quitting is important. Counseling should be framed such that it relates to the patient’s risk for disease or exacerbation of disease, family or social situations (e.g., having children with asthma), health concerns, age, or other patient factors, such as prior experience with quitting.
- **Risks**—Ask patients to identify potential negative health consequences of smoking, such as acute risks (shortness of breath, asthma exacerbations, harm to pregnancy, infertility), long-term risks (cancer, cardiac, and pulmonary disease), and environmental risks (promoting smoking among children by being a negative role model; effects of secondhand smoke on others, including children and pets).
- **Rewards**—Ask patients to identify potential benefits that they anticipate from quitting, such as improved health, enhanced physical performance, enhanced taste and smell, reduced expenditures for tobacco, less time wasted or work missed, reduced health risks to others (fetus, children, housemates), and reduced aging of the skin.
- **Roadblocks**—Help patients identify barriers to quitting and assist in developing coping strategies (Table 88.4) for addressing each barrier. Common barriers include nicotine withdrawal symptoms, fear of failure, a need for social support while quitting, depression, weight gain, and a sense of deprivation or loss.
- **Repetition**—Continue to work with patients who are successful in their quit attempt. Discuss circumstances in which smoking occurred to identify the trigger(s) for relapse; this is part of the learning process and will be useful information for the next quit attempt. Repeat interventions when possible.

Source: Adapted from Fiore MC et al. *Treating Tobacco Use and Dependence: 2008 Update. Clinical Practice Guideline*. Rockville, MD: Public Health Service, US Department of Health and Human Services; 2008.

**TABLE 88.4 Cognitive and Behavioral Strategies for Tobacco Cessation**

**COGNITIVE STRATEGIES**

Focus on *retraining the way a patient thinks*. Often, patients deliberate on the fact that they are thinking about a cigarette, and this leads to relapse. Patients must recognize that thinking about a cigarette does not mean they need to have one.

Review commitment to quit	Each morning, say, "I am proud that I made it through another day without tobacco." Reminding oneself that cravings and temptations are temporary and will pass. Announce, either silently or aloud, "I want to be a nonsmoker, and the temptation will pass."
Distractive thinking	Deliberate, immediate refocusing of thinking toward other thoughts when cued by thoughts about tobacco use
Positive self-talks, "pep talks"	Saying "I can do this" and reminding oneself of previous difficult situations in which tobacco use was avoided with success
Relaxation through imagery	Centering of mind toward positive, relaxing thoughts
Mental rehearsal, visualization	Preparing for situations that might arise by envisioning how best to handle them. For example, envision what would happen if offered a cigarette by a friend; mentally craft and rehearse a response, and perhaps even practice it by saying it aloud.

**BEHAVIORAL STRATEGIES**

Involve *specific actions to reduce risk for relapse*. These strategies should be considered before quitting, after determining patient-specific triggers and routines or situations associated with tobacco use. Below is a list of some behavioral strategies for several common cues or triggers for relapse.

Stress	Anticipate upcoming challenges at work, at school, or in personal life. Develop a substitute plan for tobacco use during times of stress (e.g., deep breathing, take a break or leave the situation, call a supportive friend or family member, or use nicotine replacement therapy).
Alcohol	Drinking alcohol can lead to relapse. Consider limiting or abstaining from alcohol during the early stages of quitting.
Other tobacco users	Quitting is more difficult when around other tobacco users. This is especially difficult if there is another tobacco user in the household. During the early stages of quitting, limit prolonged contact with individuals who are using tobacco. Ask coworkers, friends, and housemates not to smoke or use tobacco in your presence.
Oral gratification needs	Have nontobacco oral substitutes (e.g., gum, sugarless candy, straws, toothpicks, lip balm, toothbrush, nicotine replacement therapy, bottled water) readily available.
Automatic smoking routines	Anticipate routines that are associated with tobacco use and develop an alternative plan. Examples: <i>Morning coffee with cigarettes</i> : change morning routine, drink tea instead of coffee, take shower before drinking coffee, take a brisk walk shortly after awakening. <i>Smoking while driving</i> : remove all tobacco from car, have car interior detailed, listen to an audio book or talk radio, use oral substitute. <i>Smoking while on the phone</i> : stand while talking, limit call duration, change phone location, keep hands occupied by doodling or sketching. <i>Smoking after meals</i> : get up and immediately do dishes or take a brisk walk after eating, brush teeth, call supportive friend.
Postcessation weight gain	The majority of tobacco users gain weight after quitting. Most quitters will gain <10 pounds, but there is a broad range of weight gain reported, with up to 10% of quitters gaining as much as 30 pounds. Do not attempt to modify multiple behaviors at one time. If weight gain is a barrier to quitting, engage in regular physical activity and adhere to a healthful diet (as opposed to strict dieting). Carefully plan and prepare meals, increase fruit and water intake to create a feeling of fullness, and chew sugarless gum or eat sugarless candies. Consider use of pharmacotherapy shown to delay weight gain (e.g., nicotine gum, lozenge, or sustained-release bupropion).
Cravings for tobacco	Cravings for tobacco are temporary and usually pass within 5–10 minutes. Handle cravings through distractive thinking, take a break, change activities or tasks, take deep breaths.

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TABLE 88.5 Pharmacotherapy Options: Products, Precautions, Warnings, and Contraindications; Dosing; and Adverse Effects

NRT Formulations						
Gum	Lozenge	Transdermal Patch	Nasal Spray	Oral Inhaler	Bupropion SR	Varenicline
<b>PRODUCT</b>						
<b>Nicorette,<sup>a</sup> Generic</b>	<b>Nicorette (Standard And Mini),<sup>a</sup> Generic</b>	<b>NicoDerm CQ,<sup>a</sup> Generic<sup>b</sup></b>	<b>Nicotrol NS<sup>c</sup></b>	<b>Nicotrol Inhaler<sup>c</sup></b>	<b>Zyban,<sup>a</sup> Generic</b>	<b>Chantix<sup>c</sup></b>
OTC	OTC	OTC (NicoDerm CQ, generic)Rx (generic)	Rx	Rx	Rx	Rx
2 mg, 4 mg	2 mg, 4 mg	7 mg, 14 mg, 21 mg (24-hour release)	Metered spray containing 0.5 mg of nicotine in 50- $\mu$ L aqueous nicotine solution	10-mg cartridge that delivers 4 mg of inhaled nicotine vapor	150-mg sustained-release tablet	0.5-mg, 1-mg tablet
Original, cinnamon, fruit, mint, orange	Cherry, mint					
<b>PRECAUTIONS, WARNINGS, AND CONTRAINDICATIONS</b>						
<ul style="list-style-type: none"> <li>Recent (<math>\leq 2</math> weeks) myocardial infarction</li> <li>Serious underlying arrhythmias</li> <li>Serious or worsening angina pectoris</li> <li>Temporomandibular joint disease</li> <li>Pregnancy<sup>d</sup> and breast-feeding</li> <li>Adolescents (&lt;18 years)</li> </ul>	<ul style="list-style-type: none"> <li>Recent (<math>\leq 2</math> weeks) myocardial infarction</li> <li>Serious underlying arrhythmias</li> <li>Serious or worsening angina pectoris</li> <li>Pregnancy<sup>d</sup> and breast-feeding</li> <li>Adolescents (&lt;18 years)</li> </ul>	<ul style="list-style-type: none"> <li>Recent (<math>\leq 2</math> weeks) myocardial infarction</li> <li>Serious underlying arrhythmias</li> <li>Serious or worsening angina pectoris</li> <li>Pregnancy<sup>d</sup> (Rx formulations, category D) and breast-feeding</li> <li>Adolescents (&lt;18 years)</li> </ul>	<ul style="list-style-type: none"> <li>Recent (<math>\leq 2</math> weeks) myocardial infarction</li> <li>Serious underlying arrhythmias</li> <li>Serious or worsening angina pectoris</li> <li>Underlying chronic nasal disorders (rhinitis, nasal polyps, sinusitis)</li> </ul>	<ul style="list-style-type: none"> <li>Recent (<math>\leq 2</math> weeks) myocardial infarction</li> <li>Serious underlying arrhythmias</li> <li>Serious or worsening angina pectoris</li> <li>Bronchospastic disease</li> <li>Pregnancy<sup>d</sup> (category D) and breast-feeding</li> <li>Adolescents (&lt;18 years)</li> </ul>	<ul style="list-style-type: none"> <li>Concomitant therapy with medications or medical conditions known to lower seizure threshold</li> <li>Severe hepatic cirrhosis</li> <li>Pregnancy<sup>d</sup> (category C) and breast-feeding</li> <li>Adolescents (&lt;18 years)</li> </ul>	<ul style="list-style-type: none"> <li>Severe renal impairment (dosage adjustment is necessary)</li> <li>Pregnancy<sup>d</sup> (category C) and breast-feeding</li> <li>Adolescents (&lt;18 years)</li> </ul> <p><b>WARNING:</b></p> <ul style="list-style-type: none"> <li>BLACK-BOXED WARNING for neuropsychiatric symptoms<sup>e</sup></li> </ul> <p><b>CONTRAINDICATIONS:</b></p> <ul style="list-style-type: none"> <li>Seizure disorder</li> <li>Concomitant bupropion (e.g., Wellbutrin) therapy</li> <li>Current or prior diagnosis of bulimia or anorexia nervosa</li> </ul>

## DOSING

<p>First cigarette <math>\leq</math>30 minutes after waking: 4 mg First cigarette &gt;30 minutes after waking: 2 mg</p> <p>Weeks 1–6: 1 piece every 1–2 hours</p> <p>Weeks 7–9: 1 piece every 2–4 hours</p> <p>Weeks 10–12: 1 piece every 4–8 hours</p>	<p>First cigarette <math>\leq</math>30 minutes after waking: 4 mg First cigarette &gt;30 minutes after waking: 2 mg</p> <p>Weeks 1–6: 1 lozenge every 1–2 hours</p> <p>Weeks 7–9: 1 lozenge every 2–4 hours</p> <p>Weeks 10–12: 1 lozenge every 4–8 hours</p>	<p>&gt;10 cigarettes/day: 21 mg/day <math>\times</math> 4 weeks (generic) (NicoDerm CQ) 14 mg/day <math>\times</math> 2 weeks 7 mg/day <math>\times</math> 2 weeks <math>\leq</math>10 cigarettes/day: 14 mg/day <math>\times</math> 6 weeks 7 mg/day <math>\times</math> 2 weeks</p>	<ul style="list-style-type: none"> <li>• Severe reactive airway disease</li> <li>• Pregnancy<sup>d</sup> (category D) and breast-feeding</li> <li>• Adolescents (&lt;18 years)</li> </ul> <p>1–2 doses/hour (8–40 doses/day)</p> <p>One dose = 2 sprays (one in each nostril); each spray delivers 0.5 mg of nicotine to the nasal mucosa</p>	<p>6–16 cartridges/day</p> <p>Individualize dosing; initially use 1 cartridge every 1–2 hours</p>	<p><b>WARNINGS:</b></p> <ul style="list-style-type: none"> <li>• <b>BLACK-BOXED WARNING</b> for neuropsychiatric symptoms<sup>e</sup></li> <li>• Safety and efficacy have not been established in patients with serious psychiatric illness</li> <li>• Cardiovascular adverse events in patients with existing cardiovascular disease</li> </ul> <p>150 mg PO every morning <math>\times</math> 3 days, then increase to 150 mg PO BID</p> <ul style="list-style-type: none"> <li>• Do not exceed 300 mg/day</li> <li>• Begin therapy 1–2 weeks <i>before</i> quit date</li> <li>• Allow at least 8 hours between doses</li> <li>• Avoid bedtime dosing to minimize insomnia</li> </ul>	<ul style="list-style-type: none"> <li>• Simultaneous abrupt discontinuation of alcohol or sedatives (including benzodiazepines)</li> <li>• Monoamine oxidase inhibitor therapy in previous 14 days; concurrent use of reversible MAO agents (e.g., linezolid, methylene blue)</li> </ul> <p>Days 1–3: 0.5 mg PO every morning</p> <p>Days 4–7: 0.5 mg PO BID</p> <p>Weeks 2–12: 1 mg PO BID</p> <ul style="list-style-type: none"> <li>• Begin therapy 1 week <i>before</i> quit date. Alternatively, the patient can begin therapy and then quit smoking between days 8 and 35 of treatment.</li> <li>• Take dose after eating and with a full glass of water</li> <li>• Dose tapering is not necessary</li> </ul>
<ul style="list-style-type: none"> <li>• Maximum, 24 pieces/day</li> <li>• Chew each piece slowly</li> <li>• Park between cheek and gum when peppery or tingling sensation appears (~15–30 chews)</li> <li>• Resume chewing when tingle fades</li> <li>• Repeat chew and park steps until most of nicotine is gone (tingle does not return; generally 30 minutes)</li> </ul>	<ul style="list-style-type: none"> <li>• Maximum, 20 lozenges/day</li> <li>• Allow to dissolve slowly (20–30 minutes for standard; 10 minutes for mini)</li> <li>• Nicotine release may cause a warm, tingling sensation</li> </ul>	<ul style="list-style-type: none"> <li>• May wear patch for 16 hours if patient experiences sleep disturbances (remove at bedtime)</li> <li>• Duration: 8–10 weeks</li> </ul>	<ul style="list-style-type: none"> <li>• Maximum</li> <li>• –5 doses/hour or –40 doses/day</li> <li>• For best results, initially use at least 8 doses/day</li> <li>• Do not sniff, swallow, or inhale through the nose as the spray is being administered</li> </ul>	<ul style="list-style-type: none"> <li>• Best effects with continuous puffing for 20 minutes</li> <li>• Initially use at least 6 cartridges/day</li> <li>• Nicotine in cartridge is depleted after 20 minutes of active puffing</li> <li>• Inhale into back of throat or puff in short breaths</li> </ul>		

Continued on following page

TABLE 88.5 Pharmacotherapy Options: Products; Precautions, Warnings, and Contraindications; Dosing; and Adverse Effects (Continued)

NRT Formulations						
Gum	Lozenge	Transdermal Patch	Nasal Spray	Oral Inhaler	Bupropion SR	Varenicline
<i>DOSING (continued)</i>						
<ul style="list-style-type: none"> <li>• Park in different areas of mouth</li> <li>• No food or beverages 15 minutes before or during use</li> <li>• Duration: up to 12 weeks</li> </ul>	<ul style="list-style-type: none"> <li>• Do not chew or swallow</li> <li>• Occasionally rotate to different areas of the mouth</li> <li>• No food or beverages 15 minutes before or during use</li> <li>• Duration: up to 12 weeks</li> </ul>		<ul style="list-style-type: none"> <li>• Duration: 3–6 months</li> </ul>	<ul style="list-style-type: none"> <li>• Do NOT inhale into the lungs (like a cigarette) but “puff” as if lighting a pipe</li> <li>• Open cartridge retains potency for 24 hours</li> <li>• No food or beverages 15 minutes before or during use</li> <li>• Duration: 3–6 months</li> </ul>	<ul style="list-style-type: none"> <li>• Dose tapering is not necessary</li> <li>• Can be used safely with NRT</li> <li>• Duration: 7–12 weeks, with maintenance up to 6 months in selected patients</li> </ul>	<ul style="list-style-type: none"> <li>• Dosing adjustment is recommended for patients with severe renal impairment</li> <li>• Duration: 12 weeks; an additional 12-week course may be used in selected patients</li> </ul>

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## ADVERSE EFFECTS

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<ul style="list-style-type: none"><li>• Mouth or jaw soreness</li><li>• Hiccups</li><li>• Dyspepsia</li><li>• Hypersalivation</li><li>• Effects associated with incorrect chewing technique:<ul style="list-style-type: none"><li>• Lightheadedness</li><li>• Nausea or vomiting</li><li>• Throat and mouth irritation</li></ul></li></ul>	<ul style="list-style-type: none"><li>• Nausea</li><li>• Hiccups</li><li>• Cough</li><li>• Heartburn</li><li>• Headache</li><li>• Flatulence</li><li>• Insomnia</li></ul>	<ul style="list-style-type: none"><li>• Local skin reactions (erythema, pruritus, burning)</li><li>• Headache</li><li>• Sleep disturbances (insomnia, abnormal or vivid dreams); associated with nocturnal nicotine absorption</li></ul>	<ul style="list-style-type: none"><li>• Nasal or throat irritation (hot, peppery, or burning sensation)</li><li>• Rhinitis</li><li>• Tearing</li><li>• Sneezing</li><li>• Cough</li><li>• Headache</li></ul>	<ul style="list-style-type: none"><li>• Mouth or throat irritation</li><li>• Cough</li><li>• Headache</li><li>• Rhinitis</li><li>• Dyspepsia</li><li>• Hiccups</li></ul>	<ul style="list-style-type: none"><li>• Insomnia</li><li>• Dry mouth</li><li>• Nervousness or difficulty concentrating</li><li>• Rash</li><li>• Constipation</li><li>• Seizures (risk is approximately 0.1%)</li><li>• Neuropsychiatric symptoms (rare; see PRECAUTIONS)</li></ul>	<ul style="list-style-type: none"><li>• Nausea</li><li>• Sleep disturbances (insomnia, abnormal or vivid dreams)</li><li>• Constipation</li><li>• Flatulence</li><li>• Vomiting</li><li>• Neuropsychiatric symptoms (rare; see PRECAUTIONS)</li></ul>
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<sup>a</sup>Marketed by GlaxoSmithKline.

<sup>b</sup>Transdermal patch formulation previously marketed as Habitrol.

<sup>c</sup>Marketed by Pfizer.

<sup>d</sup>The US Clinical Practice Guideline states that pregnant smokers should be encouraged to quit without medication, on the basis of insufficient evidence of effectiveness and theoretical concerns with safety. Pregnant smokers should be offered behavioral counseling interventions that exceed minimal advice to quit.

<sup>e</sup>In July 2009, the FDA mandated that the prescribing information for all bupropion- and varenicline-containing products include a black-boxed warning highlighting the risk of serious neuropsychiatric symptoms, including changes in behavior, hostility, agitation, depressed mood, suicidal thoughts and behavior, and attempted suicide. Clinicians should advise patients to stop taking varenicline or bupropion SR and contact a health care provider immediately if they experience agitation, depressed mood, and any changes in behavior that are not typical of nicotine withdrawal, or if they experience suicidal thoughts or behavior. If treatment is stopped because of neuropsychiatric symptoms, patients should be monitored until the symptoms resolve.

For complete prescribing information, refer to the manufacturers' package inserts.

NRT, nicotine replacement therapy; OTC, over-the-counter (nonprescription); Rx, prescription; SR, sustained-release.

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# Neoplastic Disorders and Their Treatment: General Principles\*

## General Principles

- Cancer (neoplasm, tumor, or malignancy) is a group of diseases characterized by uncontrolled cellular growth, tissue infiltration, and spread of abnormal cells. Cancer cells do not respond to the normal processes that regulate cell growth, proliferation, and survival. They cannot carry out the physiologic functions of their normal differentiated counterparts.
- Cancers can arise in any tissue in the body and may be classified as benign or malignant. If malignant cells are allowed to grow uncontrollably, they can eventually result in patient death. Benign cancer cells cannot spread by tissue invasion or metastasize.
- Carcinogenesis is the process by which normal cells are transformed into cancer cells.
- Metastasis is the ability of cancer cells to disseminate; tumor metastases to distant sites generally have a greater effect than the primary tumor on the frequency of complications and quality of life. Individuals with metastases face a worse prognosis. The blood vessels and the lymphatics are the primary pathways by which cells metastasize (Table 89.1).

TABLE 89.1 Common Sites of Metastases for Selected Tumors

Cancer Type	Sites of Metastases
Breast	Primarily bone, lung, pleura, and liver; less frequently, brain and adrenal. ER-positive tumors preferentially spread to bone; ER-negative tumors metastasize more aggressively to visceral organs.
Lung	The two most common types of lung cancer have different etiologies. Small-cell lung cancer disseminates rapidly to many organs including the liver, brain, adrenals, pancreas, contralateral lung, and bone. Non-small-cell lung carcinomas often spread to the contralateral lung, brain, adrenal glands, liver, and bones.
Prostate	Almost exclusively to bone; forms osteoblastic lesions filling the marrow cavity with mineralized osseous matrix, unlike the osteolytic metastasis caused by breast cancer.
Pancreatic	Aggressive spread to the liver, lungs, and surrounding viscera.
Colon	The portal circulation pattern favors dissemination to the liver and peritoneal cavity, but metastasis also occurs in the lungs.
Ovarian	Local spread in the peritoneal cavity.
Sarcomas	Various types of sarcoma; mesenchymal origin; mainly metastasize to the lungs.
Myeloma	Osteolytic bone lesions, sometimes spreading to other organs.
Glioma	Little propensity for distant organ metastasis, despite aggressively invading the central nervous system.
Neuroblastoma	Bone, liver, and lung metastases, which in some cases spontaneously regress.

ER, estrogen receptor.

Source: Adapted from Nguyen DX, Massague J. Genetic determinants of cancer metastasis. *Nat Rev Genet.* 2007;8:341–352.

\*The reader is referred to Chapter 89, Neoplastic Disorders and Their Treatment: General Principles written by Mark N. Kirstein PharmD, Makala B. Pace, PharmD, BCOP, and Katherine Tipton Patel, PharmD, BCOP, in the 10th edition of *Applied Therapeutics: The Clinical Use of Drugs* for a more in-depth discussion. All notations to reference numbers are based on the reference list at the end of that chapter. The editor of this handbook expresses her thanks to Drs. Kirstein, Pace, and Patel and acknowledges that this chapter is based on their work.

## Risk Factors

- The incidence of cancer and cancer-related deaths can be affected by age and ethnic background. Increased risk for cancer is associated with environmental and lifestyle factors (e.g., cigarette smoking), genetic predisposition, immunosuppression, and exposure to potential carcinogens (Table 89.2).
- Representative genes involved with human cancers are shown in Table 89.3.
- Prevention strategies include vaccines (e.g., human papilloma virus vaccine), healthy lifestyle habits (e.g., diet, exercise, nonsmoking), and limiting sun exposure.

## Patient Assessment

- Standardized screening tests help identify disease in asymptomatic individuals (screening) or diagnose disease in symptomatic individuals (early detection).
- The stage of cancer and histologic diagnosis influence prognosis. Staging, which is done at the time of initial diagnosis and periodically during treatment, is a process that determines the extent or spread of disease. Staging for solid tumors uses the TNM system (size of the primary tumor [T], extent of regional lymph node spread [N], and presence/absence of metastatic spread [M]).
- The initial signs and symptoms of malignant disease are variable and depend on histologic diagnosis and location and size of the tumor (Table 89.4). Paraneoplastic syndromes produced by substances secreted by a tumor may exist (Table 89.5).
- Performance status is a measure of functional capacity of the patient (e.g., ability to ambulate, care for self, and perform daily activities). Different scales are used (Table 89.6).

TABLE 89.2 Selected Carcinogens Associated with an Increased Risk of Cancer

Carcinogenic Risk Factor	Associated Cancer(s)
<b>ENVIRONMENTAL</b>	
Ionizing radiation (radon gas emitted from soil containing uranium deposits)	Leukemia, breast, thyroid, lung
Ultraviolet radiation	Skin melanoma
Viruses	Leukemia, lymphoma, nasopharyngeal, liver, cervix
<b>OCCUPATIONAL</b>	
Asbestos	Lung, mesothelioma
Chromium, nickel	Lung
Vinyl chloride	Liver
Aniline dye	Bladder
Benzene	Leukemia
Radiation	Leukemia, thyroid
<b>LIFESTYLE</b>	
Alcohol	Esophagus, liver, stomach, oropharynx, larynx
Dietary factors	Colon, breast, gallbladder, gastric
Tobacco	Lung, oropharynx, pharynx, larynx, esophagus, bladder
<b>MEDICAL DRUGS</b>	
Diethylstilbestrol	Vaginal (in the offspring of the exposed mother), breast, testes, ovary
Alkylating agents	Leukemia, bladder
Azathioprine, calcineurin inhibitors, mycophenolate	Lymphoma
Phenacetin	Bladder
Estrogens, tamoxifen	Endometrial
Cyclophosphamide, ifosfamide	Bladder
Etoposide	Leukemia



TABLE 89.3 Representative Genes Involved in Human Cancers

## GENES FOR GROWTH FACTORS OR THEIR RECEPTORS

<i>PDGF</i>	Codes for platelet-derived growth factor; involved in glioma (a brain cancer)
<i>ERB-B</i>	Codes for the receptor for epidermal growth factor; involved in glioblastoma (a brain cancer) and breast cancer
<i>ERB-B<sub>2</sub></i>	Also called <i>Her-2</i> or <i>neu</i> ; codes for a growth factor receptor; involved in breast, salivary gland, and ovarian cancers
<i>RET</i>	Codes for a growth factor receptor; involved in thyroid cancer

## GENES FOR CYTOPLASMIC RELAYS IN STIMULATORY SIGNALING PATHWAYS

<i>K-RAS</i>	Involved in lung, ovarian, colon, and pancreatic cancers
<i>N-RAS</i>	Involved in leukemias

## GENES FOR TRANSCRIPTION FACTORS THAT ACTIVATE GROWTH-PROMOTING GENES

<i>C-MYC</i>	Involved in leukemias and breast, stomach, and lung cancers
<i>N-MYC</i>	Involved in neuroblastoma (a nerve cell cancer) and glioblastoma
<i>L-MYC</i>	Involved in lung cancer

## GENES FOR OTHER KINDS OF MOLECULES

<i>BCL-2</i>	Codes for a protein that normally blocks cell suicide; involved in follicular B-cell lymphoma
<i>BCL-1</i>	Also called <i>PRAD1</i> ; codes for cyclin D1, a stimulatory component of the cell-cycle clock; involved in breast, head, and neck cancers
<i>MDM2</i>	Codes for an antagonist of the p53 tumor-suppressor protein; involved in sarcomas (connective tissue cancers) and other cancers

## TUMOR-SUPPRESSOR GENES

## GENES FOR PROTEINS IN THE CYTOPLASM

<i>APC</i>	Involved in colon and stomach cancers
<i>DPC-4</i>	Codes for a relay molecule in a signaling pathway that inhibits cell division; involved in pancreatic cancer
<i>NF-1</i>	Codes for a protein that inhibits a stimulatory (Ras) protein; involved in neurofibroma and pheochromocytoma (cancers of the peripheral nervous system) and myeloid leukemia
<i>NF-2</i>	Involved in meningioma and ependymoma (brain cancers) and schwannoma (affecting the wrapping around peripheral nerves)

## GENES FOR PROTEINS IN THE NUCLEUS

<i>MTS1</i>	Codes for the p16 protein, a braking component of the cell-cycle clock; involved in a wide range of cancers
<i>RB</i>	Codes for the pRB protein, a master brake of the cell cycle; involved in retinoblastoma and bone, bladder, and small-cell lung and breast cancer
<i>p53</i>	Codes for the p53 protein, which can halt cell division and induce abnormal cells to kill themselves; involved in a wide range of cancers
<i>WT1</i>	Involved in Wilms tumor of the kidney

## GENES FOR OTHER PROTEINS

<i>BRCA1</i>	Codes for the breast cancer type 1 susceptibility protein that helps repair damaged DNA or destroy cells if DNA cannot be repaired; involved in breast and ovarian cancers
<i>BRCA2</i>	Codes for the breast cancer type 2 susceptibility protein that helps repair damaged DNA; involved in breast cancer
<i>VHL</i>	Codes for a protein involved in protein degradation when other proteins are no longer needed by the cell; involved in renal cell cancer

**TABLE 89.4 Signs and Symptoms Associated with Common Cancers**

Cancer	Local <sup>a</sup>	Distant <sup>b</sup>
Bladder	Hematuria; bladder irritability; urinary hesitancy, frequency, or urgency; dysuria; flank or pelvic pain	Edema of lower extremities and genitalia
Breast	Breast lumps; nipple retraction, dimpling, discharge; skin changes; axillary lymphadenopathy	Bone pain; elevated LFT; hypercalcemia
Colorectal	Change in bowel habits; in stool caliber; occult bleeding; constipation	Elevated LFT, CEA, and alkaline phosphatase; obstruction; hepatomegaly; perforation
Lung	New cough or change in current cough; hoarseness, hemoptysis, or dyspnea; unresolving pneumonias; chest wall pain; pain; dysphagia; effusion; tracheal obstruction	Anorexia; weight loss; elevated LFT; bone pain, hypercalcemia; jaundice; lymphadenopathy; osteoarthropathy; neurologic (brain metastases and neuromuscular disorders); SIADH
Lymphomas	Painless lymphadenopathy	Fever; night sweats; weight loss; bone or retroperitoneal pain; hepatomegaly; splenomegaly; abnormal CBC
Melanoma	Change in size, color, or shape of a preexisting nevus	Lymphadenopathy; elevated LFT
Ovarian	Abdominal pain, discomfort, or enlargement; postprandial flatulence; vaginal bleeding; abdominal mass; urinary frequency; constipation, nausea; dyspepsia; early satiety	Peripheral neuropathies; pleural effusion; thrombophlebitis; elevated LFT; abdominal distention or pain; Addison or Cushing syndrome
Prostate	Urinary hesitancy; nocturia; poor urine stream; dribbling; terminal hematuria	Bone pain; elevated acid phosphatase, PSA, and alkaline phosphatase
Testicular	Painless enlargement; epididymitis; gynecomastia; back pain; infertility or erectile dysfunction	Elevated $\beta$ hCG, $\alpha$ -fetoprotein, LDH

<sup>a</sup>Local effects include those produced by the primary tumor.

<sup>b</sup>Distant effects include those associated with metastatic spread and paraneoplastic syndromes. Many cancers may not produce symptoms in the early stages, and early diagnosis depends on effective detection and screening efforts. CBC, complete blood cell count; CEA, carcinoembryonic antigen;  $\beta$ hCG, beta human chorionic gonadotropin; LDH, lactate dehydrogenase; LFT, liver function tests; PSA, prostate-specific antigen; SIADH, syndrome of inappropriate antidiuretic hormone secretion.

**TABLE 89.5 Common Paraneoplastic Syndromes Associated with Cancer**

Syndrome	Cancer Type(s)
Sweet syndrome	Hematologic malignancies and various carcinomas
<b>ENDOCRINE</b>	
Addison syndrome	Adrenal carcinoma, lymphomas, and ovarian
Cushing syndrome	Lung, thyroid, testicular, adrenal, and ovarian cancers
Hypercalcemia (not associated with bone metastases)	Lung, multiple myeloma, renal and lymphoma
Syndrome of inappropriate antidiuretic hormone secretion	Lung, head and neck
<b>HEMATOLOGIC OR COAGULATION</b>	
Anemia	Many
Autoimmune hemolytic anemia	Chronic lymphocytic leukemia, lymphomas, ovarian
Disseminated intravascular coagulation	Acute progranulocytic leukemia, lung, and prostate
Thrombophlebitis	Lung, breast, ovarian, prostate, and pancreatic
<b>DERMATOLOGIC</b>	
Acanthosis nigricans	Gastric adenocarcinoma
<b>NEUROMUSCULAR</b>	
Dermatomyositis and polymyositis	Lung and breast
Myasthenic syndrome (Eaton-Lambert syndrome)	Small-cell lung, gastric, and ovarian
Sensory neuropathies	Small-cell lung, breast, and ovarian

Source: Adapted from Pelosof LC, Gerber DE. Paraneoplastic syndromes: an approach to diagnosis and treatment. *Mayo Clin Proc.* 2010;85(9):838–854.

TABLE 89.6 Performance Status Scales

Eastern Cooperative Group (ECOG) <sup>a</sup>		Karnofsky <sup>b</sup>	
Grade	Description	Grade	Description
0	Fully active, able to carry on all predisease performance without restriction	100	Normal, no complaints; no evidence of disease
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature	90	Able to carry on normal activity; minor signs or symptoms of disease
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours	80	Normal activity with effort, some signs or symptoms of disease
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours	70	Cares for self but unable to carry on normal activity or do active work
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.	60	Requires occasional assistance but is able to care for most of personal needs
5	Dead	50	Requires considerable assistance and frequent medical care
		40	Disabled; requires special care and assistance
		30	Severely disabled; hospitalization is indicated although death not imminent
		20	Very ill; hospitalization and active supportive care necessary
		10	Moribund
		0	Dead

<sup>a</sup>[http://www.ecog.org/general/perf\\_stat.html](http://www.ecog.org/general/perf_stat.html)

<sup>b</sup>Péus D, Newcomb N, Hofer S. Appraisal of the Karnofsky Performance Status and proposal of a simple algorithmic system for its evaluation. *BMC Med Inform Decis Mak.* 2013;13:72 at <http://www.biomedcentral.com/1472-6947/13/72>

## Goals of Therapy

- Cure is the goal, when possible. When therapy with curative intent is not possible, therapy becomes palliative with disease control and symptom management the priority.
- Goals of therapy should consider both quantity and quality of life.

## Treatment

- Choice of therapy depends on histology, stage of cancer, and treatment side effects.
- Cancer is primarily treated with three modalities: surgery, radiation, and systemic therapy. Solid tumors are typically treated with localized therapy using surgery or radiation; systemic therapy is the primary modality for hematologic malignancies.
- Surgery can be preventative (e.g., removal of polyps), diagnostic, or used for staging. It can be used to manage localized or advanced tumors.
- Radiation can be curative, adjuvant, or palliative therapy for localized solid tumors. Not all cancers are sensitive to radiation (Table 89.7).
- Systemic cytotoxic chemotherapy kills cancer cells by damaging DNA, interfering with DNA synthesis, or inhibiting cell division. Phase-specific (schedule-dependent) agents act in a specific phase of the cell cycle. Phase-nonspecific (dose-dependent) agents affect the cell at any phase of the cell cycle (Figure 89.1).
- Several factors influence response to chemotherapy:
  - **Schedule Dependency:** Successful treatment requires administration of the next cycle before the tumor has grown to its previous size. The objective of chemotherapy cycles is to decrease tumor mass. Chemotherapy is administered in cycles with recovery periods between the cycles.

TABLE 89.7 Cancers Frequently Treated with Radiation Therapy

Acute lymphocytic leukemia (central nervous system radiation)
Brain
Breast
Head and neck cancers, squamous cell
Lung
• Non–small-cell lung
• Small-cell lung
Lymphomas
Neuroblastoma
Prostate
Rectal
Testicular, seminoma
Central nervous system

- **Dose Intensity:** Chemotherapy dose per unit of time during which treatment is given (e.g., mg/m<sup>2</sup>/week).
- **Drug resistance** is a major impediment to successful treatment with most cancers. It can occur de novo or develop during cell division as a result of mutation.
- **Tumor Size:** Cytotoxic effects of drugs are related to the time the tumor is exposed to an effective drug concentration. Dose, infusion rate, lipophilicity, and protein binding can affect concentration-time product. Larger tumors have less vascularity, making it more difficult for drugs to penetrate the tumor.
- **Pharmacogenetics:** Genetic polymorphisms can affect metabolism and disposition of drug.
- Most tumors show only partial or short response to single-agent therapy. Combination therapy provides broader coverage against resistant cell lines.
- **Induction Therapy:** Primary therapy used as first-line treatment. It can be curative or palliative in nature (Table 89.8).

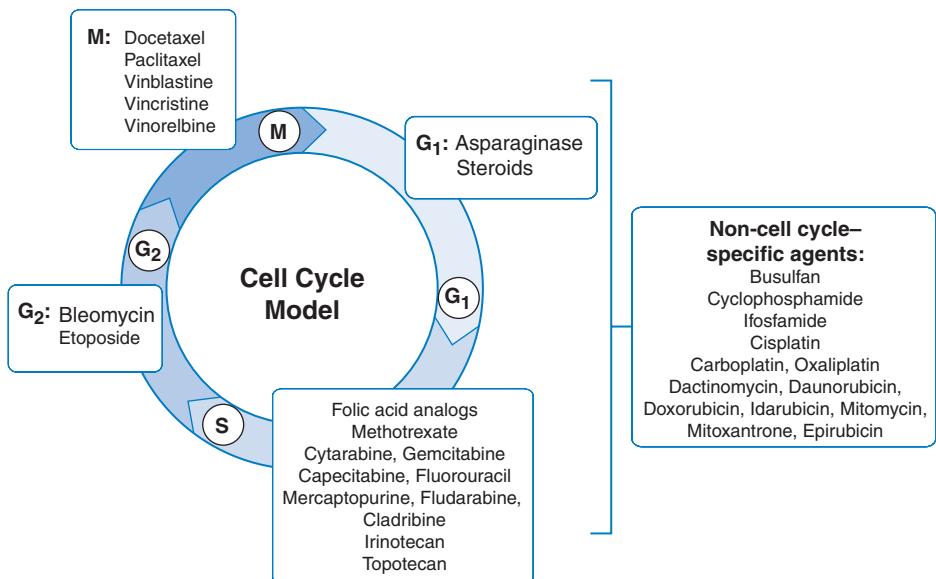


Figure 89.1 Cell cycle and effects of representative cytotoxic drugs on phases of the cell cycle.

**TABLE 89.8 Primary Chemotherapy: Neoplasms for Which Chemotherapy Is a Primary Treatment Modality**

Acute leukemias
Non-Hodgkin lymphoma
Myeloma
Hodgkin lymphoma
Germ cell cancer
Primary central nervous system lymphoma
Ovarian cancer
Small-cell lung cancer
Wilms tumor
Embryonal rhabdomyosarcoma

Source: Reprinted with permission from DeVita VT Jr, Chu E. Principles of medical oncology: basic principles. In: DeVita VT Jr, et al, eds. *DeVita, Hellman, and Rosenberg's Cancer: Principles & Practice of Oncology*. 8th ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2008:338.

- **Salvage Therapy:** Second-line treatment used after the tumor has become refractory to the primary therapy or if the patient cannot tolerate first-line therapy.
- **Consolidation, intensification, or maintenance therapy** refers to the use of additional chemotherapy in an attempt to further eradicate residual disease.
- **Adjuvant Therapy:** Systemic treatment used to eradicate any undetectable tumor (micrometastases or residual disease) (Table 89.9). Duration of adjuvant chemotherapy varies depending on type of cancer and drugs being used.
- **Neoadjuvant Therapy:** Treatment given before the primary treatment (typically surgery or radiation) in patients with locally advanced tumors (e.g., large tumors) to reduce tumor mass (Table 89.10).
- Systemic cytotoxic chemotherapy is most commonly administered by the intravenous route (bolus injection, short infusion, or continuous infusion). Oral, intramuscular, or subcutaneous administration are options for some agents.
- Techniques exist to administer therapy locally to specific sites of the body affected by the tumor, allowing high concentrations at the site of the tumor while minimizing systemic exposure (Table 89.11).

**TABLE 89.9 Adjuvant Chemotherapy: Neoplasms for Which Therapy Is Indicated After Surgery**

Anaplastic astrocytoma
Breast cancer
Colorectal cancer
Gastric cancer
Melanoma
Non-small-cell lung cancer
Osteogenic sarcoma
Ovarian cancer
Osteogenic cancer
Rectal cancer
Soft tissue sarcoma

Source: From DeVita VT Jr, Chu E, Medical oncology. In: DeVita VT Jr, Lawrence TS, Rosenberg SA. *Cancer: Principles & Practice of Oncology*. 9th ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2011:313.

**TABLE 89.10 Neoadjuvant Chemotherapy: Neoplasms for Which Chemotherapy Is Indicated for Locally Advanced Disease**

Anal cancer  
 Bladder cancer  
 Breast cancer  
 Cervical cancer  
 Gastroesophageal cancer  
 Lung cancer  
 Head and neck cancer  
 Ovarian cancer  
 Osteogenic sarcoma  
 Pancreatic cancer

Source: From DeVita VT Jr, Chu E. Principles of medical oncology: basic principles. In: DeVita VT Jr, et al, eds. *DeVita, Hellman, and Rosenberg's Cancer: Principles & Practice of Oncology*. 8th ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2008:338.

**TABLE 89.11 Local or Regional Routes of Chemotherapy Administration**

Route of Administration	Cancer Managed with Alternative Route
Intrathecal or intraventricular	Leukemia, lymphoma
Intravesicular	Bladder
Intraperitoneal	Ovarian
Intrapleural	Malignant pleural effusions
Intra-arterial	Melanoma, sarcoma
Hepatic artery	Liver metastases
Chemoembolization (intra-arterial or intravenous)	Colon, rectal, carcinoid, liver metastases

**TABLE 89.12 Response Criteria for Evaluating Effects of Chemotherapy of Target Lesion (RECIST Version 1.1)****COMPLETE RESPONSE**

Disappearance of all target lesions. Any pathological lymph nodes (whether target or nontarget) must have reduction in short axis to <10 mm.

**PARTIAL RESPONSE**

At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters.

**PROGRESSIVE DISEASE**

At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. The appearance of one or more new lesions is also considered progression.

**STABLE DISEASE**

Neither sufficient shrinkage to qualify for partial response nor sufficient increase to qualify for progressive disease, taking as reference the smallest sum diameters while on study.

**DISEASE-FREE SURVIVAL**

Time from documentation of complete response until disease relapse or death.

**OVERALL SURVIVAL**

Time from treatment until time of death.

Source: <http://www.recist.com/>

- Response to therapy should be assessed (antitumor activity and toxic effects) using physical examination, laboratory tests, and repeat diagnostic tests to stage the cancer. RECIST (Response Evaluation Criteria in Solid Tumors) is one tool to evaluate response (Table 89.12). Tumor markers can also be measured (Table 89.13).
- Systemic therapies used to treat cancer are potentially carcinogenic, teratogenic, or mutagenic. Handling and administering these agents poses a risk to healthcare workers. Appropriate policies and procedures must be in place to maximize safety and minimize risk.

## Drug Therapy

- Mechanisms of action of several agents are shown in Table 89.14.
- Monoclonal antibodies selectively target receptors or ligands known to potentiate cancer pathways (Table 89.15). They minimize toxicity to noncancer cells.
- Tyrosine kinase inhibitors compete with adenosine triphosphate (ATP) for binding to intracellular tyrosine kinase (Table 89.16).
- Additional targeted agents to treat malignancies are shown in Table 89.17.
- Endocrine therapies are used for tumors that arise from hormone-sensitive tissues, inhibiting tumor growth by blocking the receptors or eliminating the endogenous hormone feeding the tumor (Table 89.18).
- Biologic response modifiers are substances that either boost or restore the ability of the immune system to fight cancer. Agents include vaccines, interferon- $\alpha$ , interleukin-2, bacterium bacillus Calmette-Guérin, cancer-killing viruses, gene therapy, and adoptive T-cell transfer.

TABLE 89.13 Clinically Useful Tumor Markers

Tumor Marker	Cancers Commonly Associated with Increased Markers
CA-19-9	Pancreatic
CA-15-3	Breast
CA-27-29	Breast
Neuron-specific enolase	Neuroblastoma, small-cell lung cancer
$\alpha$ -Fetoprotein (AFP)	Liver
CA-125	Ovarian, testicular—nonseminoma
Carcinoembryonic antigen (CEA)	Colon, lung, breast
ER (estrogen receptors) and PR (progesterone receptors)	Breast
Human chorionic gonadotropin (hCG)	Trophoblastic, testicular
$\beta_2$ -Microglobulin	Multiple myeloma
KRAS mutations	All patients with colorectal cancer should be tested for candidacy for anti-epidermal growth factor receptor (EGFR) antibody therapy
Prostate-specific antigen (PSA)	Prostate
Receptor tyrosine-protein kinase human epidermal growth factor receptor 2 (HER-2)	Breast

Source: Hayes D. Biomarkers. In: DeVita VT Jr, Lawrence TS, Rosenberg SA. *Cancer: Principles & Practice of Oncology*. 9th ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2011:698.

TABLE 89.14 **Chemotherapy Agents**

Class	Subclass	Agent (Trade Name)	Mechanism of Action	Route of Administration	Pharmacokinetic Characteristics	Major Toxicities	
Alkylating Agents	Alkyl sulfonates	Busulfan (Myleran, Busulfex)	Bifunctional alkylating species; produces DNA cross-links	IV and PO	Well absorbed orally; extensively hepatically metabolized; metabolites elimination primarily renal	Myelosuppression; pulmonary fibrosis; hyperpigmentation; hepatic dysfunction; suppression of testicular, ovarian, and adrenal function; seizures and veno-occlusive disease with high dose	
		Ethyleneimines/methylmelamines		Bendamustine (Treanda)	IV	Highly protein bound; metabolized hepatically; elimination primarily fecal	Myelosuppression; nausea, vomiting, constipation, diarrhea; hepatic dysfunction; pyrexia; fatigue
	Nitrogen mustards		Thiotepa (Thioplex)	Produces DNA cross-links	IV	Intracellular metabolism; minimal urinary excretion	Anaphylaxis, rash, blurred vision; dizziness, alopecia, anorexia, nausea, vomiting
			Chlorambucil (Leukeran)		PO	Well absorbed; extensively protein bound; extensively metabolized hepatically; metabolites spontaneously degrade; minimal renal elimination	Myelosuppression; tremor, twitching, myoclonia, agitation, ataxia, hallucinations; pulmonary fibrosis; hepatic dysfunction
			Cyclophosphamide (Cytosan)		IV and PO	Well absorbed; activated in liver; elimination of metabolites primarily renal	Myelosuppression; hemorrhagic cystitis; nausea, vomiting; alopecia; cardiomyopathy (rare); interstitial pneumonitis; SIADH
			Ifosfamide (Ifex)		IV	Activated in liver; elimination primarily renal	Myelosuppression; hemorrhagic cystitis (should be administered with MESNA); somnolence, confusion, depressive psychosis, hallucinations; nausea, vomiting; alopecia
			Melphalan (Alkeran)		IV and PO	Variable oral absorption; elimination primarily by chemical hydrolysis; minimal renal elimination	Myelosuppression; alopecia; hepatic dysfunction; nausea, vomiting; pulmonary fibrosis

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TABLE 89.14 Chemotherapy Agents (Continued)

Class	Subclass	Agent (Trade Name)	Mechanism of Action	Route of Administration	Pharmacokinetic Characteristics	Major Toxicities
	Nitrosoureas	Carmustine (BiCNU)	Alkylates DNA	IV and brain implant	Crosses the blood–brain barrier effectively; elimination primarily renal	Myelosuppression, pulmonary toxicity, nausea, vomiting, hepatic and renal dysfunction, venous irritant
		Lomustine (CeeNU)		PO	Crosses the blood–brain barrier effectively	Myelosuppression; nausea, vomiting; pulmonary fibrosis; hepatic and renal dysfunction
	Triazines	Dacarbazine (DTIC-Dome)	Prodrug activated by CYP and photodecomposition, forms an ion that inhibits DNA synthesis	IV	Moderate renal elimination	Myelosuppression; nausea, vomiting, anorexia; hepatic dysfunction; flulike syndrome; capsules should be taken on an empty stomach
<i>Imidazotetrazine derivative</i>		Temozolomide (Temodar)	Prodrug of dacarbazine; spontaneously hydrolyzed to active drug	IV and PO	Food affects absorption; moderate renal elimination	Myelosuppression; nausea, vomiting; hepatic dysfunction
<i>Antimetabolites</i>	Folic acid antagonists	Methotrexate (Trexall)	Inhibits DHFR; depletes reduced folates	IV and PO	Variable absorption; “third space” collections of fluid may provide a reservoir for drug accumulation; elimination primarily renal	Myelosuppression; renal and hepatic dysfunction; mucositis, pulmonary toxicity; neurotoxicity
		Pemetrexed (Alimta)	Multitargeted; inhibits TS DHFR, and GARFT	IV	Highly protein bound; elimination primarily renal	Rash; diarrhea; myelosuppression; to minimize toxicity, begin vitamin B <sub>12</sub> and folic acid therapy 1 week prior to treatment
		Pralatrexate (Folotyng)	Inhibits DHFR, folic acid synthetase	IV	Minimal hepatic metabolism; moderate renal elimination	Mucositis; thrombocytopenia; nausea, vomiting; fatigue
		Purine analogs	Cladribine (Leustatin)	Inhibits DNA synthesis by inhibiting several synthesis enzymes (ribonucleotide reductase, etc.) after being activated by dCK	IV	Mild penetration into CSF; poorly protein bound; hepatic metabolism; may undergo renal elimination
	Clofarabine (Clolar)			IV	Intracellular metabolism; moderate renal elimination	Nausea, vomiting; headache; rash, pruritus; anxiety; tachycardia, hypotension

		Fludarabine (Fludara)		IV	Metabolized in the plasma; moderate renal elimination	Myelosuppression; fever, chills; nausea, vomiting; hemolytic anemia
		Mercaptopurine (Purinethol)	Converted to monophosphate forms by hypoxanthineguanine phosphoribosyl transferase → inhibits the first step of the de novo purine synthesis; directly incorporated into nucleic acids of DNA and RNA	PO	Absorption highly variable; hepatic and gastrointestinal mucosa metabolism; elimination primarily hepatic	Myelosuppression; anorexia, nausea, vomiting; hepatic dysfunction; take on an empty stomach
		Thioguanine (Tabloid)		PO	Mean bioavailability 30%; hepatic metabolism; minimal excretion in urine	Myelosuppression, hepatotoxicity (including veno-occlusive disease), hyperuricemia, anorexia, mild nausea and stomatitis
	Pyrimidine analogs	Capecitabine (Xeloda)	Prodrug metabolized to fluorouracil; incorporates into RNA and interferes with RNA function; inhibits TS	PO	Well absorbed; moderately protein bound; extensive hepatic metabolism; primary renal elimination	Nausea, vomiting; stomatitis; hand-foot syndrome; myelosuppression; anorexia
		Cytarabine (Cytosar-U, Ara-C)	Blocks progression of the cells from the G <sub>1</sub> phase to the S phase	IV or intrathecal (liposomal)	Hepatic metabolism; primary renal elimination	Myelosuppression; cytarabine syndrome (fever, myalgia, bone pain, rash, conjunctivitis); hepatic dysfunction; diarrhea; anorexia, nausea, vomiting
		Fluorouracil (Aduvicol)	Incorporates into RNA, interferes with RNA function; inhibits TS	IV	Hepatic metabolism; minimal renal elimination	Mucositis; diarrhea; myelosuppression; dermatologic; nausea, vomiting; hand-foot syndrome
		Gemcitabine (Gemzar)	Inhibits DNA and RNA synthesis by inhibiting ribonucleotide reductase	IV	Intracellular metabolism; primary renal elimination	Myelosuppression; flulike syndrome; nausea, vomiting; edema; hemolytic uremic syndrome
Antimitotic Agents	Epothilones	Ixabepilone (Ixempra)	Binds directly to $\beta$ -tubulin promotes stabilization of treadmilling	IV	Extensive hepatic metabolism; primarily fecally eliminated; moderate renal elimination	Alopecia; diarrhea; musculoskeletal pain; arthralgia/myalgia; peripheral neuropathy; fatigue; stomatitis, nausea, vomiting

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TABLE 89.14 Chemotherapy Agents (Continued)

Class	Subclass	Agent (Trade Name)	Mechanism of Action	Route of Administration	Pharmacokinetic Characteristics	Major Toxicities
Taxanes		Cabazitaxel (Jevtana)	Binds to $\beta$ -tubulin; promotes stabilization of microtubules; suppresses treadmilling and dynamic instability	IV	Highly protein bound; extensive hepatic metabolism; eliminated in feces; minimal renal elimination	Myelosuppression; nausea, vomiting, constipation; peripheral neuropathy; musculoskeletal pain
		Docetaxel (Taxotere)		IV	Highly protein bound; extensive hepatic metabolism; primarily eliminated in feces; minimal renal elimination	Peripheral edema; myelosuppression; hypersensitivity reaction; hand-foot syndrome
		Paclitaxel (Taxol)		IV	Highly protein bound; metabolism primarily hepatic; primary eliminated in feces; minimal renal elimination	Hypersensitivity reactions; peripheral neuropathy; myalgia; arthralgia; myelosuppression; alopecia; hepatic dysfunction
		Paclitaxel, albumin-bound (Abraxane)		IV		Peripheral neuropathy; alopecia; myelosuppression; nausea, vomiting; myalgia; arthralgia; hepatic dysfunction
Vinca alkaloids		Vinblastine (Velban)	Binds to tubulin interfering with microtubule assembly and mitotic spindle formation	IV	Metabolism primarily hepatic; primary biliary elimination	Myelosuppression; CNS toxicity; nausea, vomiting; vesicant
		Vincristine (Oncovin)		IV	Primary hepatic metabolism; primary fecal elimination	Neurotoxicity (sensory and motor); autonomic neuropathies (high dosages); SIADH; vesicant
		Vinorelbine (Navelbine)		IV	Primary hepatic metabolism; primary eliminated in feces; minimal renal elimination	Leukopenia; neurotoxicity; vesicant
		Eribulin (Halaven)	Disruption of microtubule polymerization	IV	Metabolism primarily hepatic	Myelosuppression; alopecia; nausea, constipation, stomatitis; peripheral neuropathy
Other		Estramustine (Emcyt)	Stabilizes microtubule formation	PO	Well absorbed; readily dephosphorylated during absorption to active metabolites; eliminated into bile, feces, and urine	Gynecomastia; hepatic dysfunction; edema; nausea, diarrhea

<i>Antitumor Antibiotics</i>	Anthracyclines	Daunorubicin (Cerubidine)	Stabilizes the cleavable complex between topoisomerase II and DNA, causing single- and double-strand DNA breaks; forms oxygen free radicals	IV	Extensive binding to tissues; metabolism primarily hepatic; moderate biliary excretion; minimal renal elimination	Myelosuppression; mucositis; alopecia; cumulative cardiac toxicity; vesicant
		Daunorubicin, liposomal (DaunoXome)		IV		Myelosuppression, nausea, vomiting, diarrhea, headache, edema, rigors, neuropathy, back pain, dyspnea, hand-foot syndrome
		Doxorubicin (Adriamycin, Rubex)		IV		Myelosuppression; mucositis; alopecia; cumulative cardiac toxicity; vesicant
		Doxorubicin, liposomal (Doxil)		IV		Myelosuppression; nausea, vomiting; fatigue; stomatitis; rash, hand-foot syndrome
		Epirubicin (Ellence)		IV	Highly protein bound; metabolism primarily hepatic; moderate biliary excretion; minimal renal elimination	Myelosuppression; mucositis; alopecia; cumulative cardiac toxicity; vesicant
		Idarubicin (Idamycin)		IV	Extensive extrahepatic metabolism; primarily biliary excretion; minimal renal elimination	Myelosuppression; mucositis; anorexia; nausea, vomiting; diarrhea; fever; alopecia
		Valrubicin (Valstar)		Intravesical	Minimal systemic absorption during the 2-hour dose-retention in bladder; excreted by voiding the instillate	Urinary urgency; urinary frequency, dysuria, hematuria
	Other	Bleomycin (Blenoxane)	Binds to DNA, producing single- and double- strand breaks through generation of oxygen free radicals; inhibits DNA and directed RNA polymerase	IV	Enzymatic degradation by a cytosolic cysteine proteinase enzyme, widely distributed in normal tissues, except lung and skin; elimination primarily renal	Erythema, hyperpigmentation; pulmonary toxicity; fever, chills; vomiting
	Dactinomycin (Cosmegen)		IV	Minimally metabolized; moderate renal and fecal elimination	Myelosuppression; hepatic dysfunction; vesicant; radiation recall	

*Continued on following page*

TABLE 89.14 Chemotherapy Agents (Continued)

Class	Subclass	Agent (Trade Name)	Mechanism of Action	Route of Administration	Pharmacokinetic Characteristics	Major Toxicities
DNA Demethylation Agents		Azacitidine (Vidaza)	Inhibition of DNA methyltransferase; competes for incorporation into RNA	IV or SC	May be metabolized hepatically; elimination primarily renal	Myelosuppression; nausea, vomiting, diarrhea; ecchymosis, injection-site erythema, pyrexia
		Decitabine (Dacogen)		IV	Precise route of metabolism and elimination not known	Myelosuppression; depression; edema; tachycardia
		Nelarabine (Arranon)		IV	Metabolism primarily hepatic; elimination partially renal	Myelosuppression; fatigue; pyrexia; peripheral neuropathies; hyperglycemia
DNA Topoisomerase Inhibitors		Etoposide (VePesid)	Inhibits topoisomerase II, stabilizing the cleavable complex causing double-strand DNA breaks	IV and PO	Variable oral absorption; highly protein bound; moderate renal elimination; minimal bile and fecal elimination	Myelosuppression; nausea, vomiting; alopecia; mucositis; hypotension (related to rapid infusion); hypersensitivity reactions; fever; bronchospasm
		Irinotecan (Camptosar)	Inhibits topoisomerase I, stabilizing the cleavable complex causing double-strand DNA breaks	IV	Moderately protein bound; metabolism primarily hepatic; minimal renal elimination	Diarrhea; cholinergic syndrome; myelosuppression
		Topotecan (Hycamtin)		IV and PO	Bioavailability 40%; metabolism by reversible pH-dependent hydrolysis of its lactone moiety to active form; 20% unchanged drug elimination via urine	Myelosuppression, nausea, vomiting, diarrhea, fatigue, alopecia
Enzymes		Asparaginase (Elspar)	Hydrolyzes serum asparagine to nonfunctional aspartic acid and ammonia, depriving tumor cells of a necessary amino acid	IV	Not well documented	Allergic reactions; reduction of clotting factors; pancreatitis; hepatic and renal dysfunction
Methylhydrazine Derivative		Procarbazine (Matulane)	Inhibition of protein, RNA and DNA synthesis; may attack protein sulfhydryl groups	PO	Well absorbed; primarily metabolized by liver and kidneys; metabolites spontaneously degrade or via renal elimination	Myelosuppression; nausea, vomiting; coma, confusion, nystagmus, headache, dizziness; hepatic dysfunction
Platinum Analogs		Carboplatin (Paraplatin)	Reacts with nucleophilic sites on DNA, causing DNA cross-links	IV	Elimination primarily renal	Myelosuppression; nausea, vomiting; peripheral neuropathy

		Cisplatin (Platinol)		IV	Elimination primarily renal	Nephrotoxicity; nausea, vomiting; peripheral neuropathy; ototoxicity; electrolyte disturbances
		Oxaliplatin (Eloxatin)		IV	Highly protein bound; nonenzymatically biotransformed; elimination primarily renal	Anaphylactic or anaphylactoid reactions; peripheral neuropathy, sensitivity to cold, jaw spasm, dysphagia; nausea, vomiting, diarrhea, fatigue; pulmonary fibrosis
<i>Miscellaneous</i>		Arsenic trioxide (Trisenox)	Causes morphological changes and DNA fragmentation characteristic of apoptosis	IV	Metabolism primarily hepatic; elimination primarily renal	Myelosuppression; cardiac effects; agitation, anxiety, depression, dizziness; dermatitis, pruritus; nausea, vomiting, diarrhea; electrolyte abnormalities
	Substituted urea	Hydroxyurea (Hydrea, Droxia)	Holds cells of the cell cycle in the G <sub>1</sub> or pre-DNA synthesis stage	PO	Well absorbed; hepatic metabolism; elimination primarily renal	Myelosuppression; hyperpigmentation of skin; nausea, vomiting, diarrhea
	Retinoids	Tretinoin (Vesanoid)	Produces an initial maturation of the primitive promyelocytes	PO	Well absorbed; highly protein bound; hepatic metabolism; primary renal elimination; moderate fecal elimination	RA-APL syndrome (fever, dyspnea, respiratory distress, edema, multiorgan failure); dizziness, paresthesia, anxiety, depression, insomnia, confusion, agitation, intracranial hypertension; hemorrhage; malaise; nausea, vomiting
	Retinoid	Bexarotene (Targretin)	Activates transcription factors that regulate the expression of genes that control cellular differentiation and proliferation	PO	Highly protein bound; hepatic metabolism; primary hepatobiliary elimination	Lipid abnormalities; hypothyroidism; nausea; rash; leucopenia; headache; edema

CNS, central nervous system; CSF, cerebrospinal fluid; CYP, cytochrome; dCK, deoxycytidine kinase; DHFR, dihydrofolate reductase; DNA, deoxyribonucleic acid; GARFT, glycinamide ribonucleotide formyltransferase; IV, intravenous; MESNA, 2-mercaptoethane sulfonates sodium; PO, oral; RA-APL, retinoic acid–acute promyelocytic leukemia; RNA, ribonucleic acid; SC, subcutaneous; SIADH, syndrome of inappropriate antidiuretic hormone; TS, thymidylate synthase.

TABLE 89.15 Monoclonal Antibodies<sup>a</sup>

Agent (Trade Name)	Mechanism of Action	Major Toxicities
Ado-trastuzumab emtansine (Kadcyla)	Monoclonal antibody trastuzumab conjugated emtansine (DM1); binding to the HER <sub>2</sub> receptor results in intracellular release of DM1	Infusion reactions; bleeding; anemia; thrombocytopenia; left ventricular dysfunction; nausea; diarrhea; hepatotoxicity
Alemtuzumab (Campath)	Targets CD52 cell surface antigen; binding leads to lysis of CD52-positive leukemic cells	Hypersensitivity reactions; myelosuppression, pancytopenia, opportunistic infection, nausea, vomiting, dyspnea, hypotension
Bevacizumab (Avastin)	Inhibits development of new blood vessels (angiogenesis) by binding to and inhibiting vascular endothelial growth factor (VEGF) from interacting with receptors	Hypertension, diarrhea, constipation; bleeding, thrombosis; gastrointestinal perforation; impaired wound healing; proteinuria; infusion reactions
Brentuximab vedotin (Adcetris)	Anti-CD30 antibody joined by an enzyme cleavable linker to monomethyl auristatin E (MMAE) which releases MMAE upon internalization into CD30-expressing tumor cells	Neutropenia; anemia; neuropathy, upper respiratory infections; diarrhea
Cetuximab (Erbix)	Inhibits cell proliferation by preventing activation of the epidermal growth factor receptor (EGFR)	Anaphylactic or hypersensitivity reactions; papulopustular skin rash; asthenia; nausea, vomiting, hypomagnesemia
Denileukin difitox (Ontak)	Fusion protein containing diphtheria toxin and IL-2 segments; directs cytotoxic action of diphtheria toxin to IL-2 receptor-expressing cells leading to inhibition of protein synthesis and cell death	Nausea, vomiting, diarrhea, fatigue, peripheral edema, pruritus, hypersensitivity reactions, rigors, capillary leak syndrome, loss of visual acuity
Ibritumomab tiuxetan (Zevalin)	Yttrium-90 (Y-90)-linked to rituximab; binds to the CD20 antigen on malignant B lymphocytes; releases radiation ( $\beta$ particles), which induces cell damage and death	Infusion reactions (hypotension, angioedema, hypoxia, bronchospasm); asthenia, chills, nausea; myelosuppression; see major toxicities for rituximab
Obinutuzumab (Gazyva)	Anti-CD20 monoclonal antibody	
Ofatumumab (Arzerra)	Mediates immune effector functions by binding the CD20 molecule to result in B-cell lysis	Cough, diarrhea, dyspnea, fatigue, nausea, neutropenia, anemia, hypersensitivity reactions, pyrexia, rash, infections; hypomagnesemia
Panitumumab (Vectibix)	Same as cetuximab	Papular-pustular rash, pruritus, hypersensitivity reactions, abdominal pain, diarrhea, hypomagnesemia, nausea, paronychia
Pertuzumab (Perjeta)	Inhibits heterodimerization of HER <sub>2</sub> with other HER family members, including EGFR, HER <sub>3</sub> , and HER.	Decreased left ventricular ejection fraction; congestive heart failure; rash; G; neutropenia; headache; infusion reaction
Rituximab (Rituxan)	Lyses B cells by recruiting immune effectors against the CD20 antigen	Tumor lysis; hypersensitivity reactions; mucocutaneous reactions; lymphopenia
Tositumomab (Bexxar)	Iodine-131 (I-131)-linked to rituximab; binds to the CD20 antigen on malignant B lymphocytes; releases radiation and induces apoptosis, complement- or antibody-dependent cell cytotoxicity; inducing cell damage and death	Hypersensitivity reactions; myelosuppression; hypothyroidism; nausea, vomiting, abdominal pain, diarrhea; myelodysplastic syndrome, acute leukemia; see major toxicities for rituximab
Trastuzumab (Herceptin)	Inhibits proliferation of human tumor cells that express HER <sub>2</sub> proto-oncogene	Cardiomyopathy; diarrhea; nausea, vomiting; hypersensitivity reaction

<sup>a</sup>All monoclonal antibodies are administered intravenously.

TABLE 89.16 Tyrosine Kinase Inhibitors<sup>a</sup>

Agent (Trade Name)	Mechanism of Action	Pharmacokinetic Characteristics	Major Toxicities
Afatinib (Gilotrif)	Co-valiantly binds to kinase domains of EGFR (ErbB <sub>1</sub> ) HER <sub>2</sub> (ErbB <sub>2</sub> ), and HER <sub>4</sub> (ErbB <sub>4</sub> )	Substrate of the P-glycoprotein efflux pump	Rash; diarrhea; stomatitis, acne; paronychia; hepatotoxicity
Axitinib (Inlyta)	Inhibition of vascular endothelial growth factor receptors VEGFR-1, VEGF-2, and VEGFR-3	Hepatic metabolism by CYP3A4	Diarrhea; hypertension; nausea; hand-foot syndrome; fatigue; hypothyroidism
Dasatinib (Sprycel)	Inhibits kinases for Bcr-Abl, platelet-derived growth factor (PDGF), c-kit	Hepatic metabolism by CYP3A4; excreted in the feces (19%) and urine (<4%)	Diarrhea, myelosuppression, headache, rash, nausea, fatigue, fluid retention, pleural and pericardial effusions, dyspnea, hemorrhage
Erlotinib (Tarceva)	Epidermal growth factor receptor (EGFR) tyrosine kinase antagonist	Oral bioavailability 60%; hepatic metabolism primarily CYP3A4, also CYP1A1 and CYP1A2	Diarrhea, papulopustular rash, appetite loss, interstitial lung disease
Imatinib mesylate (Gleevec)	Inhibits kinases for Bcr-Abl, platelet-derived growth factor (PDGF), c-kit, and stem cell factor	Mean bioavailability 98%; hepatically metabolized via CYP3A4; eliminated as unchanged drug in feces (20%) and urine (5%)	Fluid retention, edema; nausea, vomiting, diarrhea; rash, fatigue, muscle cramps, musculoskeletal pain; intratumoral bleeding; myelosuppression, hepatic toxicity
Lapatinib (Tykerb)	Inhibitor of EGFR and HER <sub>2</sub>	Primarily metabolized by CYP3A4 and CYP3A5, minor metabolism by CYP2C19 and CYP2C8; excreted in feces (27%) and urine (<2%)	Diarrhea, papulopustular rash, QT prolongation, hepatotoxicity, decrease in left ventricular ejection fraction, interstitial lung disease
Nilotinib (Tasigna)	Inhibits kinases for Bcr-Abl	Oxidation and hydroxylation; excreted in feces (93%)	Rash, pruritus, fatigue, diarrhea, myalgia, QT prolongation, hyperbilirubinemia
Pazopanib (Votrient)	Multikinase inhibitor; inhibits VEGFR, c-kit, PDGFR, FGFR	Primary metabolism by CYP3A4 and minor metabolism by CYP1A2 and CYP2D8; excreted in urine (4%)	Diarrhea, nausea, vomiting, depigmentation of hair and skin, hypertension, dysgeusia, visual disturbances, muscle spasms, alopecia, rash
Sorafenib (Nexavar)	Multikinase enzyme inhibitor; raf kinase inhibitor; VEGFR, PDGFR, Flt3, c-KIT, p-38	Bioavailability 38%–49%; hepatic metabolism primarily CYP3A4 and UGT1A9; long <i>t</i> <sub>1/2</sub> 24–48 hours	Hypertension, rash, hand-foot syndrome, diarrhea, myelosuppression
Sunitinib (Sutent)	Angiogenesis inhibitor; VEGFR, PDGFR, bFGF inhibition	Hepatic metabolism primarily by CYP3A4	Skin discoloration, rash, diarrhea, myelosuppression, prolonged QT interval

<sup>a</sup>All tyrosine kinase inhibitors are administered orally.



TABLE 89.17 Other Targeted and Miscellaneous Agents

Class or Mechanism of Action	Agent (Trade Name)	Route of Administration	Pharmacokinetic Characteristics	Major Toxicities
Histone deacetylase (HDAC) inhibitors	Romidepsin (Istodax)	IV	Extensive metabolism by CYP3A4 with minor metabolism by CYP3A5, CYP1A1, CYP2B6, and CYP2C19	Fatigue, nausea, electrocardiogram changes, constipation, myelosuppression, pruritus, dermatitis, electrolyte abnormalities
	Vorinostat (Zolinza)	PO	Metabolized via glucuronidation and $\beta$ -oxidation after initial hydrolysis; 1% excreted in urine	Fatigue, nausea, vomiting, anorexia, weight loss, diarrhea, dysgeusia, myelosuppression
Proteasome inhibitor	Bortezomib (Velcade)	IV	Metabolized by CYP3A4, CYP2C19, and CYP1A2	Peripheral neuropathy, nausea, vomiting, diarrhea or constipation, myelosuppression, fatigue, cough, pyrexia
mTOR inhibitors	Everolimus (Afinitor)	PO	Metabolized by CYP3A4, substrate of P-glycoprotein; 80% excreted in feces and 5% in urine	Asthenia, cough, diarrhea, fatigue, stomatitis, infections, pneumonitis, anemia, hyperglycemia, hypertriglyceridemia, QT prolongation
	Temsirolimus (Torisel)	IV	Metabolized by CYP3A4; primarily excreted in feces	Anorexia, nausea, asthenia, edema, rash, hyperglycemia, hyperlipidemia, interstitial lung disease, renal failure, bowel perforation
Miscellaneous	Lenalidomide (Revlimid)	PO	Excreted in urine	Thrombocytopenia, neutropenia, pruritus, rash, diarrhea, arthralgias, pyrexia, dizziness, thromboembolism
	Thalidomide (Thalomid)	PO	Bioavailability: 90%; metabolism through nonenzymatic hydrolysis; <1% is excreted in urine	Teratogenic potential, bradycardia, dizziness, orthostatic hypotension, somnolence, hypersensitivity, neutropenia, peripheral neuropathy, thromboembolism

IV, intravenous; PO, oral.

TABLE 89.18 Endocrine Therapies Used for Hormone-Sensitive Tumors

Class	Agent	Cancer Treated	Selected Side Effects
Androgens	Fluoxymesterone (Androxy)	Breast	Deepening voice, alopecia, hirsutism, facial or truncal acne, fluid retention, menstrual irregularities, cholestatic jaundice
Antiandrogens	Abiraterone (Zytiga)	Prostate	Fluid retention, hypertension, electrolyte abnormalities
	Bicalutamide (Casodex)	Prostate	Gynecomastia, hot flashes, breast tenderness, hepatic dysfunction, diarrhea
	Flutamide (Eulexin) Nilutamide (Nilandron)	Prostate Prostate	Diarrhea; hematuria Diarrhea, disulfiram reaction; decreased visual accommodation; interstitial pneumonia
Antiestrogens	Fulvestrant (Faslodex) Tamoxifen (Nolvadex, Soltamox)	Breast	Disease flare, hot flashes, nausea, vomiting, edema, thromboembolism, endometrial cancer
Aromatase inhibitors	Anastrozole (Arimidex) Exemestane (Aromasin) Letrozole (Femara)	Breast	Hot flashes, nausea, fatigue, insomnia, increased risk of bone fractures
Estrogens	Ethinylestradiol (Estradiol) Conjugated estrogens (Premarin)	Breast, prostate	Nausea, vomiting, fluid retention, hot flashes, anorexia, thromboembolism, hepatic dysfunction
Gonadotropin-releasing hormone analogs (LHRH agonists) <sup>a</sup>	Goserelin (Zoladex) Histrelin (Vantas) Leuprolide (Lupron, Eligard) Triptorelin (Trelstar)	Breast, prostate	Amenorrhea, hot flashes, nausea
Progestins	Medroxyprogesterone (Provera)	Breast, prostate	Weight gain, hot flashes, vaginal bleeding, edema, thromboembolism
Immunotherapy	Sipucel-T (Provenge)	Prostate	Infusion reactions, paresthesia, vomiting, hot flush

<sup>a</sup>Leuprolide and triptorelin also available in extended release and depot formulations.

LHRH, luteinizing hormone releasing hormone.

# Adverse Effects of Chemotherapy and Targeted Agents\*

## General Principles

- Cytotoxic and targeted anticancer agents are toxic to cancer cells and also to various host tissues and organs. Toxicities are often the most important factor limiting use of potentially curative doses.
- Factors affecting toxicity include specific agent, dose intensity, treatment duration, and individual susceptibility.
- Therapies can be classified as having common and acute toxicities, specific organ toxicities, and long-term complications.
- Severity of toxicities is classified using the National Cancer Institute (NCI) common terminology for criteria for adverse events.

## Common and Acute Toxicities

- Common and acute toxicities generally occur as a result of inhibition of host cell division. Cells most susceptible include tissues with renewal cell populations (e.g., lymphoid tissues, bone marrow, epithelium of gastrointestinal [GI] tract and skin).

## HEMATOLOGIC TOXICITIES

- Myelosuppression is one of the most common toxicities of cytotoxic chemotherapy. Any of the bone marrow cell lines can be affected. Life-threatening granulocytopenia or thrombocytopenia often requires treatment to minimize the risk of adverse effects with additional courses of cytotoxic chemotherapy. Clinically significant anemia is unlikely if red blood cell (RBC) production is impaired for a short time.
- Factors affecting the degree of cytopenia are agent-related (agent, dose intensity, dose density) and patient-related (advanced age, bone marrow reserve, degree of myelosuppression from previous chemotherapy, ability of liver or kidney to metabolize and excrete administered compounds). The majority of targeted agents do not suppress bone marrow production.
- RBCs survive approximately 120 days in peripheral blood, platelets survive about 10 days, and granulocytes about 6 to 8 hours. With most myelosuppressive agents, white blood cells (WBCs) and platelet counts begin to fall within 5 to 7 days of cytotoxic therapy dosing, reach a nadir within 7 to 10 days, and recover within 14 to 26 days. Some agents have a second nadir 4 to 6 weeks after dosing.
- **Neutropenia** (low WBCs; counts  $<500\text{--}1,000/\text{mm}^3$ ) increases the risk for bacterial infections.
  - Chemotherapy dose reduction can reduce neutropenia but may also compromise treatment response.
  - **Colony-Stimulating Factors (CSFs)**: National Comprehensive Cancer Network (NCCN) Guidelines recommend primary prophylaxis for all patients receiving chemotherapy regimens

\*The reader is referred to Chapter 90, Adverse Effects of Chemotherapy and Targeted Agents, written by Amy Hatfield Seung, PharmD, BCOP, in the 10th edition of *Applied Therapeutics: The Clinical Use of Drugs* for a more in-depth discussion. All notations to reference numbers are based on the reference list at the end of that chapter. The editor of this handbook expresses her thanks to Dr. Seung and acknowledges that this chapter is based on her work.

that cause a 20% incidence of febrile neutropenia. Granulocyte CSFs such as filgrastim 5 mcg daily or tbo-filgrastim 5 mcg daily until Absolute Neutrophil Count (ANC) recovery or pegfilgrastim 6 mg once can be used. Another option is granulocyte-macrophage CSF sargramostim 250 mcg/m<sup>2</sup> daily until ANC recover. These regimens can be given once per cycle. Guidelines support discontinuation of CSF therapy when neutrophil counts reach 2,000 to 4,000 cells/mcL after the chemotherapy nadir. Mild bone pain is a side effect of CSF therapy.

- Guidelines do not support routine use of CSFs for treatment of febrile neutropenia; use should be limited to patients with high-risk features predictive of clinical deterioration. Duration of neutropenia is a significant prognostic factor for morbidity and mortality.
- **Thrombocytopenia** (low platelets; <20,000) can result in bleeding, often from GI and urinary tracts.
  - **Oprelvekin** is indicated to prevent severe thrombocytopenia and reduce the need for platelet transfusions in patients receiving chemotherapy for nonmyeloid malignancies who are at high risk for developing thrombocytopenia. Side effects include peripheral edema, dyspnea, and pleural effusions.
- **Anemia** (low RBCs) is not usually a dose-limiting toxicity of chemotherapy. It commonly occurs secondary to the primary disease. Patients present with fatigue and decreased exercise tolerance. In 2008, the FDA limited the indication of erythropoiesis-stimulating agents (ESAs) to patients receiving chemotherapy for palliative therapy and not for patients who are receiving chemotherapy for the intent of cure. The FDA requires all ESAs to be prescribed and used under the risk evaluation and mitigation strategy (REMS) program to ensure the safe use of these drugs. Under the program, health care providers must do the following:
  - Register and maintain enrollment in the ESA APPRISE Oncology Program (part of the REMS program);
  - Complete a training module on how to use ESAs in cancer patients;
  - Counsel each patient on the risks of ESAs prior to each new course of ESA therapy; and
  - Document that the risk:benefit discussion with each patient has occurred by completing the Acknowledgment Form and providing each patient a copy of the signed form.

The threshold for use of ESA therapy is a hemoglobin of <10 g/dL. The starting dose of epoetin is 150 units/kg subcutaneously three times per week until completion of a chemotherapy course or 40,000 units subcutaneously weekly. Alternatively, darbepoetin alfa 2.25 mcg/kg every week subcutaneously until completion of a chemotherapy course or 500 mcg every 3 weeks subcutaneously until completion of a chemotherapy course can be given.

- **Thrombotic Events:** Risk is increased in patients with cancer due to hypercoagulability, abnormalities in the coagulation cascade, vessel wall damage, and vessel wall compression due to tumor masses. Factors affecting risk include type and stage of cancer, comorbidities, mobility, and type of chemotherapy used.

## GASTROINTESTINAL TRACT TOXICITIES

- GI toxicities include nausea, vomiting, oral complications, esophagitis, and lower bowel disturbances. Emesis usually occurs on the first day of chemotherapy and often persist for several days. Antiemetics given before and after chemotherapy can help control symptoms. The most appropriate antiemetic regimen is based on patient- and agent-specific factors.
- Complications of the oral cavity include mucositis, xerostomia (dry mouth), infection, and bleeding. Incidence of mucositis varies by chemotherapy agent. Infection and bleeding occur when chemotherapy causes myelosuppression (thrombocytopenia and neutropenia).
- **Xerostomia**, a frequent side effect of radiation to the head and neck, can cause caries and a change in ability to taste. *Amifostine* can be used to reduce the incidence of moderate to severe xerostomia; use is limited by adverse effects and cost. Other treatment strategies include stimulation of existing salivary flow using pilocarpine, sucrose-free hard candies, or sugar-free

TABLE 90.1 Guidelines for the Management of Mucositis

1. Remove dentures to prevent further irritation and tissue damage.
2. Maintain gentle brushing of teeth with a soft toothbrush.
3. Avoid mouthwashes or rinses that contain alcohol because they may be painful and cause drying of the mucosa. Consider normal saline or sodium bicarbonate oral swishes.
4. Lubricants, such as artificial saliva, may loosen mucus and prevent membranes from sticking together. Avoid mineral oil and petroleum jelly because they can be aspirated.
5. Apply local anesthetics for localized pain control, especially before meals (may add an antacid or an antihistamine). Systemic opioid analgesics may be required to control pain associated with severe mucositis. Acetaminophen is often avoided because it may mask fevers in neutropenic patients, and ibuprofen is often avoided because it may cause more bleeding in patients with thrombocytopenia.
6. Ensure that adequate hydration and nutrition are maintained:
  - Eat a bland diet, avoiding spiced, acidic, and salted foods.
  - Avoid rough food; process in a blender if necessary.
  - Use sugar-free gum or sugar-free hard candy to stimulate salivation and facilitate mastication.
  - If necessary, provide intravenous nutritional support.
  - Avoid extremely hot or cold foods.
  - Use shakes with nutritional supplements or ice cream.

chewing gum; or replacing lost secretions using saliva substitutes. Meticulous attention to oral hygiene with regular dental checkups is essential.

- **Mucositis and stomatitis** (oral mucositis) typically occur 5 to 7 days after chemotherapy or at almost any point during radiation therapy. Lesions usually resolve in about 1 to 3 weeks. Treatment is usually palliative (Table 90.1). *Palifermin* is a growth factor approved for patients with hematologic malignancies undergoing bone marrow transplant to reduce the incidence and duration of severe oral mucositis.
- **Esophagitis**: Symptomatic management is similar to the management of mucositis. Monitor patients to ensure an adequate intake of fluids and nutrition is occurring.
- **Lower GI tract complications** include malabsorption, diarrhea, and constipation. Constipation can be treated prophylactically with stool softeners and a mild laxative. Diarrhea can be managed with atropine (for early onset symptoms) or loperamide. Late-onset, prolonged diarrhea can lead to dehydration, electrolyte imbalances, and significant morbidity.

## DERMATOLOGIC TOXICITIES

- Dermatologic toxicities include alopecia, hyperpigmentation, radiation recall, photosensitivity, nail changes, hand-food syndrome, acneiform rashes, hypersensitivity reactions, and extravasation.
- **Alopecia** usually begins 7 to 10 days after treatment, with prominent hair loss noted within 1 to 2 months. Hair will begin to regenerate 1 to 2 months after therapy is completed. Although the major consequence is cosmetic, it can be quite distressing for patients.
- **Nail changes** include growth arrest lines that move distally as the nail grows.
- **Dermatologic pigment changes**, particularly hyperpigmentation, are common. Pigment changes typically resolve with time.
- **Hand-foot syndrome** results in erythematous skin on the palms and soles. Discontinuation of the medication will help resolve the reaction; therapy may be restarted at a lower dose once resolved, if desired.
- **Dry skin and fine scaling** can be caused by many cytotoxic agents. Topical emollient creams can provide symptom relief.
- Cytotoxic therapy can interact with radiation therapy or ultraviolet light (Table 90.2). Reactions can produce severe tissue necrosis.
- Chemotherapeutic agents may also produce local toxicities (Table 90.3).

TABLE 90.2 Chemotherapy-Associated and Radiation-Associated Reactions

## RADIATION SENSITIVITY REACTIONS

Bleomycin	Doxorubicin	Hydroxyurea
Dactinomycin	Fluorouracil	Methotrexate
Etoposide	Gemcitabine	

## RADIATION RECALL REACTIONS

All of the above plus		
Vinblastine	Epirubicin	Capecitabine
Etoposide	Paclitaxel	Oxaliplatin
	Docetaxel	

## REACTIONS WITH ULTRAVIOLET LIGHT

**Phototoxic Sensitivity**

Dacarbazine	Thioguanine	Methotrexate
Fluorouracil	Vinblastine	Mitomycin

**Sunburn Reactivation**

Methotrexate

Sources: Payne AS et al. Dermatologic toxicity of chemo-therapeutic agents. *Semin Oncol.* 2006;33:86; Yeo W, Johnson PJ. Radiation-recall skin disorders associated with the use of antineoplastic drugs: pathogenesis, prevalence, and management. *Am J Clin Dermatol.* 2000;1:113; Alley E et al. Cutaneous toxicities of cancer therapy. *Curr Opin Oncol.* 2002;14:212.

TABLE 90.3 Chemotherapeutic Drugs Reported to Produce Local Toxicities

## POTENTIAL VESICANTS

Dactinomycin	Epirubicin
Daunorubicin	Streptozocin
Doxorubicin	Vinblastine
Idarubicin	Vincristine
Mechlorethamine	Paclitaxel
Mitomycin	Oxaliplatin

## POTENTIAL IRRITANTS

Carmustine	Etoposide
Cisplatin	Mitoxantrone
Dacarbazine	Melphalan
Vinorelbine	Vindesine
Cyclophosphamide	Teniposide

Sources: Goolsby TV, Lombardo FA. Extravasation of chemotherapeutic agents: prevention and treatment. *Semin Oncol.* 2006;33:139; Doellman D et al. Infiltration and extravasation: update on prevention and management. *J Infus Nurs.* 2009;32:203.

- **Extravasation** is a potentially serious local reaction, particularly if it occurs with a vesicant. Immediate management should occur (Table 90.4); specific antidotes are recommended for some agents (Table 90.5).
- **Hypersensitivity reactions** typically present with urticaria, angioedema, rash, bronchospasm, abdominal cramping, and hypotension (Table 90.6). Prophylactic and treatment options are shown in Table 90.7.

## Specific Organ Toxicities

- Toxicities are often due to unique uptake or selective toxicity of an agent to the organ.
- **Neurotoxicity** may occur with chemotherapeutic agents (Table 90.8). Recognition of neurotoxicity may be difficult due to comorbidities.

**TABLE 90.4 Suggested Procedures for Management of Suspected Extravasation of Vesicant Drugs**

1. Stop the infusion immediately, but do not remove the needle. Any drug remaining in the tubing or needle, as well as the infiltrated area, should be aspirated.
2. Contact a physician as soon as possible.
3. If deemed appropriate, instill an antidote in the infiltrated areas (via the extravasated intravenous needle if possible).
4. Remove the needle.
5. Apply ice to the site and elevate the extremity for the first 24–48 hours (if vinca or podophyllotoxin, use warm compresses).
6. Document the drug, suspected volume extravasated, and the treatment in the patient's medical record.
7. Check the site frequently for 5–7 days.
8. Consult a surgeon familiar with extravasations early so that the surgeon can periodically review the site, and, if ulceration begins, the surgeon can rapidly assess if surgical debridement or excision is necessary.

Sources: Goolsby TV, Lombardo FA. Extravasation of chemotherapeutic agents: prevention and treatment. *Semin Oncol.* 2006;33:139; Doellman D et al. Infiltration and extravasation: update on prevention and management. *J Infus Nurs.* 2009;32:203.

**TABLE 90.5 Recommended Extravasation Antidotes**

Class/Specific Agents	Local/Systemic Antidote Recommended	Specific Procedure
Alkylating Agents Cisplatin <sup>a</sup> Oxaliplatin Mechloroethamine	1/6-M solution sodium thiosulfate	Mix 4 mL 10% sodium thiosulfate USP with 6 mL of sterile water for injection, USP for a 1/6-M solution. Into site, inject 2 mL for each mg of mechlorethamine or 100 mg of cisplatin extravasated.
Mitomycin-C	Dimethyl sulfoxide 99% (w/v)	Apply 1–2 mL to the site every 6 hours for 14 days. Allow to air dry; do not cover.
Anthracyclines Doxorubicin  Daunorubicin	Cold compresses Dextrazoxane	Apply immediately for 30–60 minutes on first day. Once daily for 3 days. First dose should be given within the first 6 hours. Day 1: 1,000 mg/m <sup>2</sup> IV Day 2: 1,000 mg/m <sup>2</sup> IV Day 3: 500 mg/m <sup>2</sup> IV
Vinca alkaloids  Vinblastine Vincristine	Warm compresses  Hyaluronidase	Apply immediately for 30–60 minutes, then alternate off/on every 15 minutes for 1 day. Inject 150 units into site.
Epipodophyllotoxins <sup>a</sup>	Warm compresses	Apply immediately for 30–60 minutes, then alternate off/on every 15 minutes for 1 day.
Etoposide	Hyaluronidase	Inject 150 units into site.
Taxanes  Docetaxel Paclitaxel	Cold compresses  Hyaluronidase	Apply immediately for 30–60 minutes every 6 hours for 1 day. Inject 150 units into site.

<sup>a</sup>Treatment indicated only for large extravasations (e.g., doses one-half or more of the planned total dose for the course of therapy). IV, intravenous; w/v, weight per volume.

Sources: Goolsby TV, Lombardo FA. Extravasation of chemotherapeutic agents: prevention and treatment. *Semin Oncol.* 2006;33:139; Doellman D et al. Infiltration and extravasation: update on prevention and management. *J Infus Nurs.* 2009;32:203; Totect (dextrazoxane injection) [package insert]. Rockaway, NJ: Topo Target USA, Inc.; 2009.

**TABLE 90.6 Cancer Chemotherapeutic Agents Commonly Causing Hypersensitivity**

<b>Drug</b>	<b>Frequency</b>	<b>Risk Factors</b>	<b>Manifestations</b>	<b>Mechanism</b>	<b>Comments</b>
Asparaginase	10%–20%	Increasing doses; interval (weeks to months) between doses; IV administration; history of atopy or allergy; use without prednisone, mercaptopurine and/or vincristine	Pruritus, dyspnea, agitation, urticaria, angioedema, laryngeal spasm	Type I	Substitute PEG-asparaginase, but up to 32% may demonstrate mild hypersensitivity
Paclitaxel	Up to 10% first or second dose	None known	Rashes, dyspnea, bronchospasm, hypotension	Nonspecific release of mediators; Cremophor	Premedicate with diphenhydramine corticosteroids, and H <sub>2</sub> receptor antagonists Paclitaxel protein-bound particles (Abraxane) may be substituted and better tolerated in some patients
Cisplatin	Up to 20% intravesicular, 5%–10% systemic; case reports of hemolytic anemia	Increasing number of doses Anemia: none known	Rash, urticaria, bronchospasm Anemia: hemolytic anemia	Type I Anemia: type III	Carboplatin may be substituted in some cases but cross-reactivity has been reported
Procarbazine	Up to 15%, case reports	None known	Urticaria pneumonitis	Type I Type III	All patients rechallenged have prompt return of symptoms
Anthracyclines	1%–15% depending on anthracycline	None known	Dyspnea, bronchospasm, angioedema	Unknown; nonspecific release	Cross-reactivity documented, but incidence and likelihood unknown
Bleomycin	Common	Lymphoma	Fever (up to 42°C), tachypnea	Endogenous pyrogen release	Not technically classified as HSR; premedicate with acetaminophen and diphenhydramine
Rituximab	First treatment 80%; subsequent treatments 40%	Female sex, pulmonary infiltrates, CLL or mantle cell lymphoma	Fevers, chills, occasional nausea, urticaria, fatigue, HA, pain, pruritus, bronchospasm, SOB, angioedema, rhinitis, vomiting, ↓ BP, flushing	Unknown; related to manufacturing process	Stop or ↓ infusion rate by 50%; provide supportive care with IV fluids, acetaminophen, diphenhydramine, vasopressors PRN
Trastuzumab	First treatment 40%; subsequent treatments rare	None known	Chills, fever, occasional nausea or vomiting; pain, rigors, HAs, dizziness, SOB, ↓ BP, rash, asthenia	Unknown, related to manufacturing process	Manage with acetaminophen, diphenhydramine, meperidine

*Continued on following page*



TABLE 90.6 Cancer Chemotherapeutic Agents Commonly Causing Hypersensitivity (*Continued*)

Drug	Frequency	Risk Factors	Manifestations	Mechanism	Comments
Cetuximab	First treatment, 15%–20%; grades 3–4, 3%; subsequent treatments uncommon	None known	Airway obstruction (bronchospasm, stridor, hoarseness), urticaria, hypotension, or cardiac arrest		Premedicate with diphenhydramine; stop or decrease infusion rate; provide supportive care with epinephrine, corticosteroids, IV antihistamines, bronchodilators, and oxygen PRN
Alemtuzumab	Approximately 90% with IV administration in first week	None known	Hypotension, rigors, fever, SOB, bronchospasm, chills, rash	Unknown	Dose titration during several days; substitute with SC administration rather than IV; premedicate with acetaminophen, diphenhydramine, meperidine
Docetaxel	0.9% with premedication	None known	↓ BP, bronchospasm, rash, flushing, pruritus, SOB, pain, fever, chills	Unknown	Premedicate with acetaminophen, dexamethasone, and diphenhydramine
Doxorubicin liposomal	6.8%	None known	Flushing, SOB, angioedema, HA, chills, ↓ BP	Unknown, related liposomal components	Stop infusion; restart at a lower rate

Type I: antigen interaction with IgE bound to mast cell membrane causes degranulation. Drug binding to mast cell surface causes degranulation. Activation of classic or alternative complement pathways produces anaphylatoxins. Neurogenic release of vasoactive substances. Type III: antigen–antibody complexes form intravascularly and deposit in or on tissues.

BP, blood pressure; CLL, chronic lymphocytic leukemia; HA, headache; HSR, hypersensitivity reaction; IV, intravenous; PRN, as needed; SC, subcutaneous; SOB, shortness of breath.

**TABLE 90.7 Prophylaxis and Treatment of Hypersensitivity Reactions from Anticancer Drugs**

**PROPHYLAXIS**

IV access must be established.  
BP monitoring must be available.

**PREMEDICATION**

- Administer dexamethasone 20 mg PO and diphenhydramine 50 mg PO 12 and 6 hours before treatment, then the same dose IV immediately before treatment.
- Consider addition of H<sub>2</sub> antagonist with schedule similar to dexamethasone.
- Have epinephrine and diphenhydramine readily available for use in case of a reaction.
- Observe the patient up to 2 hours after discontinuing treatment.

**TREATMENT**

- Discontinue the drug (immediately if being administered IV).
- Administer epinephrine 0.3 mg IM or SC minutes until reaction subsides.
- Administer diphenhydramine 50 mg IV.
- If hypotension is present that does not respond to epinephrine, administer IV fluids.
- If wheezing is present that does not respond to epinephrine, administer nebulized albuterol solution.
- Although corticosteroids have no effect on the initial reaction, they can block late allergic symptoms. Therefore, administer methylprednisolone 125 mg (or its equivalent) IV to prevent recurrent allergic manifestations.

BP, blood pressure; IV, intravenous; PO, orally.

- **Cardiotoxicity** is a dose-dependent toxicity of anthracyclines (doxorubicin, daunorubicin, idarubicin, epirubicin, and mitoxantrone [an anthracenedione]). Total cumulative dose of doxorubicin is the most clearly established risk factor for congestive heart failure (CHF). Prevention is achieved by limiting the total cumulative dose. Cardiac function should be monitored in patients receiving anthracycline therapy. Treatment is similar to that used for cardiomyopathy induced by other means. Dexrazoxane is indicated to reduce the incidence and severity of cardiomyopathy associated with doxorubicin in women with metastatic breast cancer receiving a cumulative dose of 300 mg/m<sup>2</sup>.
  - Cardiotoxicity has also been associated with trastuzumab and multitargeted tyrosine kinase inhibitors.
- **Arrhythmias** (EKG changes) can occur after treatment with anthracyclines, cisplatin, etoposide, paclitaxel, cyclophosphamide, mechlorethamine, and arsenic.
- **Hypertension** has been seen in patients receiving VEGF inhibitors (bevacizumab, sunitinib, sorafenib, pazopanib).
- Fluorouracil has been associated with angina pectoris and myocardial infarction.
- **Nephrotoxicity** is a dose-limiting toxicity of cisplatin. Vigorous hydration helps prevent development of acute renal failure. *Amifostine* may be used as a chemoprotectant in patients receiving cisplatin for advanced ovarian cancer.
- **Renal Insufficiency:** Several agents require dose adjustments or dose omissions (Table 90.9).
- **Renal tubular defects** can be caused by streptozocin, lomustine, carmustine, ifosfamide, and azacytidine.
- **Proteinuria** can be caused by bevacizumab.
- **Acute tubular obstruction** can occur with high-dose methotrexate if appropriate precautions are not taken.
- **Cystitis** (ranging from mild to severe bladder damage and hemorrhage) can be caused by ifosfamide and cyclophosphamide. Guidelines recommend parenteral *mesna* as a preventative measure. Once hemorrhagic cystitis develops, the agent causing the disorder must be discontinued and vigorous hydration started. If these measures fail, surgical intervention to divert urine flow away from the bladder may be needed.

TABLE 90.8 Neurotoxicity of Selected Chemotherapeutic Agents

Acute Encephalopathy	Chronic Encephalopathic Syndrome	Cerebellar Neuropathy	Peripheral Neuropathy	Cranial Neuropathy	Arachnoiditis (Intrathecal Therapy)	Autonomic Neuropathy	SIADH
Asparaginase	Cytarabine	Cytarabine	Bortezomib	Fluorouracil	Cytarabine	Vinblastine	Cyclophosphamide
Cisplatin	Methotrexate	Cisplatin	Cisplatin	Ifosfamide	Methotrexate	Vincristine	Vinblastine
Cytarabine	Nelarabine	Fludarabine	Docetaxel		Thiotepa	Vinorelbine	Vincristine
Fludarabine	Thiotepa	Fluorouracil	Fluorouracil				Vinorelbine
Ifosfamide		Ifosfamide	Ifosfamide				
Methotrexate			Lenalidomide				
Nelarabine			Nelarabine				
Procarbazine			Paclitaxel				
			Thalidomide				
			Vinblastine				
			Vincristine				
			Vinorelbine				

SIADH, syndrome of inappropriate secretion of antidiuretic hormone.

Sources: Sul JK, Deangelis LM. Neurologic complications of cancer chemotherapy. *Semin Oncol.* 2006;33:324; Meyer M. Neurotoxicity of chemotherapy agents. In: Perry MC, ed. *The Chemotherapy Source Book*. 3rd ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2001:504; Arranon (nelarabine injection) [package insert]. Research Triangle Park, NC: GlaxoSmithKline; 2009; Hildebrand J. Neurological complications of cancer chemotherapy. *Curr Opin Oncol.* 2006;18:321.

**TABLE 90.9 Anticancer Agents Requiring Dosage Modifications or Dosage Omissions in Renal Insufficiency**

Bleomycin	Lenalidomide
Capecitabine	Lomustine
Carboplatin	Melphalan
Carmustine	Methotrexate
Cisplatin	Mitomycin
Cytarabine	Pemetrexed
Dacarbazine	Pentostatin
Fludarabine	Topotecan
Ifosfamide	

Sources: Kintzel PE, Dorr RT. Anticancer drug renal toxicity and elimination: dosing guidelines for altered renal function. *Cancer Treat Rev.* 1995;21:33; Launay-Vacher V et al. Prevalence of renal insufficiency in cancer patients and implications for anticancer drug management: the renal insufficiency and anticancer medications (IRMA) study. *Cancer.* 2007;110:1376; Li YF et al. Systemic anticancer therapy in gynecological cancer patients with renal dysfunction. *Int J Gynecol Cancer.* 2007;17:739.

- **Pulmonary toxicity** is associated with many chemotherapy agents (Table 90.10). The most effective management is prevention. If toxicity becomes evident, the suspected agents should be discontinued and symptomatic support should be given.
- **Elevated liver function tests (LFTs)** occur frequently in cancer patients; causes are varied (Table 90.11). Several cancer agents have been associated with hepatocellular damage

**TABLE 90.10 Chemotherapy-Induced Pulmonary Toxicity**

Drug	Histopathology	Clinical Features	Treatment/Outcome
Aldesleukin	Capillary leak, pulmonary edema	<i>Clinical Presentation:</i> ↓ BP, fever, SOB, anorexia, rash, mucositis	Stop infusion; provide supportive care to cause a quick resolution of symptoms.
Bleomycin	Interstitial edema and hyaline membrane formation, mononuclear cell infiltration pneumonitis with progression to fibrosis, eosinophilic infiltrations seen in patients with suspected hypersensitivity-type reactions	Cumulative dose-related toxicity with risk increasing substantially with total dose >450 mg or 200 units/m <sup>2</sup> ; may occur during or after treatment <i>Clinical Presentation:</i> Cough, fever, dyspnea, tachypnea, rales, hypoxemia, bilateral infiltrates, dose-related ↓ in diffusing capacity	Recovery if bleomycin is discontinued while symptoms and radiologic changes still minimal; progressive and usually fatal if symptoms severe. Avoid cumulative doses >200 mg/m <sup>2</sup> ; monitor serial pulmonary function tests. Discontinue therapy if diffusing capacity ≤40% of baseline, FVC <25% of baseline, or if any signs or symptoms suggestive of pulmonary toxicity occur. Steroids may be helpful if toxicity is the result of hypersensitivity.
Busulfan	Pneumocyte dysplasia; mononuclear cell infiltrations, fibrosis	Does not appear to be dose related, but no cases reported with total doses <500 mg <i>Clinical Presentation:</i> Insidious onset of dyspnea, dry cough, fever, tachypnea, rales, hypoxemia, diffuse linear infiltrate, ↓ in diffusing capacity	Fatal in most patients; progressive despite discontinuation of busulfan. High-dose steroids (50–100 mg prednisone daily) have been helpful in a few cases.

*Continued on following page*

TABLE 90.10 Chemotherapy-Induced Pulmonary Toxicity (Continued)

Drug	Histopathology	Clinical Features	Treatment/Outcome
Carmustine		Dose related; usually occurs with doses >1,400 mg/m <sup>2</sup> <i>Clinical Presentation:</i> Dyspnea, tachypnea, dry hacking cough, bibasilar rales, hypoxemia, interstitial infiltrates; spontaneous pneumothorax has been reported	May continue to progress after carmustine discontinued. No evidence that steroids improve or alter incidence. High mortality rate if symptoms severe. Serial pulmonary function studies recommended. Total cumulative dose should not exceed 1,400 mg/m <sup>2</sup> .
Chlorambucil	Pneumocyte dysplasia, fibrosis	Usually occurs after at least 6 months of treatment with total cumulative doses of >2 g <i>Clinical Presentation:</i> Dyspnea, dry cough, anorexia, fatigue, fever, hypoxemia, bibasilar rales, localized infiltrates progressing to diffusing involvement of both lung fields	Fatal in most cases despite discontinuation of chlorambucil and treatment with high-dose steroids
Cyclophosphamide	Endothelial swelling, pneumocyte dysplasia, lymphocyte infiltration, fibrosis	Does not appear to be schedule related or dose related and may occur after discontinuation <i>Clinical Presentation:</i> Progressive dyspnea, fever, dry cough, tachypnea, fine rales, ↓ diffusing capacity and restrictive ventilatory defect, bilateral interstitial infiltrates	Clinical recovery reported in about 50% of patients within 1–8 weeks if therapy stopped. Some of these patients received steroid therapy; however, others have died despite steroid therapy. Occasionally, therapy has been restarted without recurrence.
Cytarabine	Pulmonary edema, capillary leak	<i>Clinical Presentation:</i> Tachypnea, hypoxemia, interstitial or alveolar infiltrates	Not always fatal
Gemcitabine <sup>278</sup>	Pulmonary edema, rare interstitial pneumonitis	Dyspnea was reported in 23% of patients; severe dyspnea in 3%; dyspnea occasionally accompanied by bronchospasm (<2% of patients); rare reports of parenchymal lung toxicity consistent with drug-induced pneumonitis	Treatment is supportive care measures. Symptoms resolve and are usually not seen with rechallenge.
Fludarabine	Interstitial infiltrates, alveolitis, centrilobular emphysema	<i>Clinical Presentation:</i> Fever, dyspnea, cough, hypoxia; onset 3–28 days after third or fourth course; bilateral infiltrates and effusions	Resolves spontaneously during several weeks with or without corticosteroids
Melphalan	Pneumocyte dysplasia	Not dose related <i>Clinical Presentation:</i> Dyspnea, dry cough, fever, tachypnea, rales, pleuritic chest pain, hypoxemia	Most patients die because of progressive pulmonary disease. Most reported cases occurred while patients were receiving concomitant prednisone therapy. Usually progresses rapidly
Methotrexate	Nonspecific changes, occasional fibrosis	No evidence that it is dose related; daily or weekly schedules more likely to cause toxicity than monthly dosing	Most patients recover within 1–6 weeks (some may have persistent infiltrates or ↓ pulmonary function parameters). Steroids may produce more rapid resolution. May resolve despite continuation of methotrexate, but discontinuation may speed resolution. Rarely fatal
Delayed		<i>Clinical Presentation:</i> Headache, malaise prodrome, dyspnea, dry cough, fever, hypoxemia, tachypnea, rales, eosinophilia, cyanosis in up to 50% of patients, interstitial infiltrates, ↓ diffusing capacity, restrictive ventilatory defect	

TABLE 90.10 Chemotherapy-Induced Pulmonary Toxicity (Continued)

Drug	Histopathology	Clinical Features	Treatment/Outcome
Noncardiac pulmonary edema	Acute pulmonary edema	Occurs very rarely 6–12 hours after PO or IT methotrexate	May be fatal
Pleuritic chest pain		Not related to other methotrexate toxicities or serum levels; may not occur with each course of therapy <i>Clinical Presentation:</i> Right-sided chest pain, occasional pleural effusion or collapse of lung, thickened pleural densities	Usually resolves within 3–5 days
Mitomycin	Similar to bleomycin	<i>Clinical Presentation:</i> Dyspnea, dry cough, basilar rales, hypoxemia, bilateral interstitial or finely nodular infiltrates, ↓ diffusing capacity	Fatal in ~50% of cases. Complete resolution reported in some patients, including some who received steroid therapy
Procarbazine	Hypersensitivity pneumonitis with eosinophilia and interstitial fibrosis	<i>Clinical Presentation:</i> Nausea, fever, dry cough, dyspnea within a few hours of ingestion, bilateral interstitial infiltrates, and pleural effusion	Rapid resolution after discontinuation
Vinblastine	Hyperplasia, dysplasia, interstitial edema, and fibrosis	Associated with concomitant treatment with mitomycin <i>Clinical Presentation:</i> Acute respiratory distress, bilateral infiltrates	Initial improvement with subsequent progression

BP, blood pressure; FVC, forced vital capacity; IT, intrathecal; PO, oral; SOB, shortness of breath.

TABLE 90.11 Common Causes of Elevated Liver Function Tests in Patients with Cancer

Primary or metastatic tumor involvement of the liver
Hepatotoxic drugs (e.g., cytotoxics, hormones [estrogens, androgens], antimicrobials [trimethoprim-sulfamethoxazole, voriconazole])
Infections (e.g., hepatic candidiasis, viral hepatitis)
Parenteral nutrition
Portal vein thrombosis
Paraneoplastic syndrome
History of liver disease (including hepatitis B and hepatitis C)

(Table 90.12). Symptoms of hepatotoxicity include nausea, vomiting, jaundice, abdominal pain, and rarely encephalopathy. Agents that are eliminated by the liver may require dosage adjustments and should be administered cautiously (Table 90.13).

## Long-Term Complications

- Long-term complications occur secondary to continued immunodeficiencies or from permanent damage to the organ cells from the specific therapy.
- **Acute leukemia** has been associated with cytotoxic therapies used to treat a variety of malignancies. Cytotoxic agents may also cause secondary lymphoid malignancies.
- Cytotoxic therapy is potentially gonadotoxic in humans.

TABLE 90.12 Hepatotoxicity from Select Antineoplastic Drugs

Drug	Type
Asparaginase <sup>288-290</sup>	Hepatocellular fatty metamorphosis
Busulfan <sup>291</sup>	Veno-occlusive disease
Carmustine <sup>292,293</sup>	Hepatocellular
Clofarabine <sup>294</sup>	Hepatocellular
Cytarabine <sup>295</sup>	Cholestatic
Etoposide <sup>296</sup>	Hepatocellular
Imatinib <sup>297</sup>	Hepatocellular
Mercaptopurine <sup>298,299</sup>	Cholestatic and hepatocellular
Methotrexate <sup>300,301</sup>	Hepatocellular
Streptozocin <sup>302</sup>	Hepatocellular

TABLE 90.13 Select Anticancer Agents<sup>a</sup> Requiring Dose Modification in Hepatic Dysfunction

Anthracyclines	Lapatinib
Capcitabine	Methotrexate
Dasatinib	Nilotinib
Docetaxel	Paclitaxel
Eribulin	Sorafenib
Erlotinib	Thiotepa
Etoposide	Vinblastine
Fluoruracil	Vincristine
Imatinib	Vinorelbine
Ixabepilone	

<sup>a</sup>The agents listed in this table are examples and are not meant to be an exhaustive list of agents that may need dose adjustments. Additionally, specific dose reductions may depend on multiple factors including treatment goals (curative vs. palliative), performance status, and specific protocols.

Sources: Field KM et al. Part I: Liver function in oncology: biochemistry and beyond. *Lancet Oncol.* 2008;9:1092; Field KM, Michael M. Part II: Liver function in oncology: towards safer chemotherapy use. *Lancet Oncol.* 2008;9:1181. Pham T, Holle L. *Cancer Therapy: Prescribing and Administration Basics*. Burlington, MA: Jones & Barlett Learning; 2015.

# Pediatric Malignancies\*

## General Principles

- Cancer is the leading cause of disease-related death for children between 1 to 14 years of age (Table 91.1). Many common pediatric solid tumors are uncommon in adults.
- Acute leukemia is a malignancy of blood-forming cells involving the lymphoid and myeloid cell lines. The two most common types of childhood leukemia are acute lymphoblastic leukemia (ALL) and acute myelogenous leukemia (AML).
- Treatment of pediatric malignancies with alkylators or topoisomerase II inhibitors (e.g., etoposide, doxorubicin) is associated with increased risk of acute leukemia.
- Patient age can be a factor in pediatric cancer prognosis and treatment. It may also be associated with treatment-related toxicity.
- Late effects are toxicities or complications that either persist or occur after therapy is finished. Examples include bone/joint problems, heart failure, secondary malignancies, strokes, or cognitive dysfunction.
- Cancer survivors should keep a record of their treatment to provide to health care providers for the remainder of their lives.

## Pediatric Solid Tumors

### NEUROBLASTOMA

- Neuroblastoma is a tumor that develops from immature cells originating from the sympathetic nervous system. They can be ganglioneuroma (benign), ganglioneuroblastoma (mixed benign and malignant), or pure neuroblastoma. Staging criteria are shown in Table 91.2. Median age of diagnosis is 19 months.
- Urine is screened for vanillylmandelic acid (VMA) and homovanillic acid (HVA) in infants.
- Patients often present with a fixed, hard, abdominal mass noted on physical exam. Gastrointestinal (GI) fullness, discomfort, or dysfunction may also occur.
- Common sites for metastases are bone marrow, bone, liver, and skin.
- Treatment is based on age, stage, N-MYC amplification, histology, and diploidy. Guidelines divide low-risk and intermediate-risk patients into four groups for treatment (Table 91.3). Typical cycles of chemotherapy for low and intermediate risk are shown in Table 91.4. Therapy for high-risk disease generally involves a first surgery for biopsy, aggressive chemotherapy (Table 91.5), second-look surgery for residual tumor resection, either additional aggressive chemotherapy or high-dose chemotherapy with autologous progenitor cell rescue, and then radiation to the tumor bed.

### WILMS TUMOR

- Wilms tumor (nephroblastoma) is a kidney tumor composed of various kidney cell types at different stages of maturation. Peak incidence occurs at 3 to 4 years of age.

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\*The reader is referred to Chapter 91, Pediatric Malignancies, written by David W. Henry, PharmD, MS, BCOP, FASHP, Mark T. Holdsworth, PharmD, and Nicole A. Kaiser, RPh, BCOP, in the 10th edition of *Applied Therapeutics: The Clinical Use of Drugs* for a more in-depth discussion. All notations to reference numbers are based on the reference list at the end of that chapter. The editor of this handbook expresses her thanks to Drs. Henry, Holdsworth, and Kaiser and acknowledges that this chapter is based on their work.



TABLE 91.1 Relative Incidence of Malignancies in Children 0 to 14 Years of Age

Malignancy	Relative Incidence (%)
Acute lymphoblastic leukemia	25.4
Central nervous system	20.6
Neuroblastoma	7.0
Non-Hodgkin lymphoma	5.9
Wilms tumor	5.4
Acute myeloid leukemia	5.0
Hodgkin lymphoma	4.0
Rhabdomyosarcoma	3.4
Retinoblastoma	2.9
Osteosarcoma	2.5
Ewing sarcoma	1.5
Other histologic types	16.4

TABLE 91.2 International Neuroblastoma Staging System (Abbreviated)

Stage 1	Local tumor with complete gross excision
Stage 2A	Unilateral localized tumor with incomplete gross excision
Stage 2B	Unilateral localized tumor, complete or incomplete excision, with ipsilateral nonadherent lymph node spread
Stage 3	Involves both sides of the midline
Stage 4	Distant lymph node or organ involvement
Stage 4S	Infants younger than 1 year of age with localized primary tumor (stage 1 or 2) with dissemination limited to liver, skin, or less than 10% of bone marrow

Source: National Institutes of Health, National Cancer Institute. *Neuroblastoma Treatment (PDQ)*. <http://cancer.gov/wcancertopics/pdq/treatment/neuroblastoma/HealthProfessional>. Accessed January 7, 2011.

TABLE 91.3 Children's Oncology Group Neuroblastoma Risk Groups and Treatment for Low-Risk, Intermediate-Risk, and High-Risk Patients

#### LOW-RISK, GROUP 1; OBSERVATION

All stage 1 patients  
 Patients with stages 2A or 2B, >50% resected and N-MYC not amplified  
 Infants with 4S with N-MYC not amplified, favorable histology, and hyperdiploidy

#### LOW-RISK, GROUP 2; RECEIVE TWO CYCLES OF CHEMOTHERAPY WITH SURGERY

Stage 2A/2B, <50% resected, or biopsy only and N-MYC not amplified  
 Infants with stage 3 or symptomatic 4S, N-MYC not amplified, favorable histology and hyperdiploid; increase one group if loss of heterozygosity at 1p or 11q  
 Stage 3, >1 year old, N-MYC not amplified, favorable histology

#### INTERMEDIATE-RISK, GROUP 3; FOUR CYCLES OF CHEMOTHERAPY WITH SURGERY

Infants with stage 3, N-MYC not amplified, and diploidy or unfavorable histology  
 Infants with stage 4, N-MYC not amplified, favorable histology and hyperdiploid; upstage if loss of heterozygosity at 1p or 11q  
 Infants with stages 4S and N-MYC not amplified, and either diploidy or unfavorable histology

#### INTERMEDIATE-RISK, GROUP 4; EIGHT CYCLES OF CHEMOTHERAPY WITH SURGERY

Infants with stage 4S, unknown biology  
 Infants with stage 4, N-MYC not amplified, with diploidy or unfavorable histology  
 Stage 3, up to 18 months old, N-MYC not amplified and unfavorable histology  
 Stage 4, up to 18 months old, N-MYC not amplified, favorable histology and hyperdiploid

**TABLE 91.3 Children’s Oncology Group Neuroblastoma Risk Groups and Treatment for Low-Risk, Intermediate-Risk, and High-Risk Patients (Continued)**

**HIGH-RISK**

Five to six cycles of chemotherapy per Table 91.5, followed by definitive surgery, high-dose chemotherapy with autologous progenitor cell rescue, radiation to the primary site, and maintenance therapy with isotretinoin. N-MYC amplified and not included in previous groups

See Table 91.4 for details of chemotherapy regimens in low-risk and intermediate-risk patients, and Table 91.5 for chemotherapy in high-risk patients.

Sources: Brodeur GM et al. Neuroblastoma. In: Pizzo PA, Poplack DG, eds. *Principles and Practice of Pediatric Oncology*. 6th ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2010:886; National Institutes of Health, National Cancer Institute. *Neuroblastoma Treatment (PDQ)*. <http://cancer.gov/cancertopics/pdq/treatment/neuroblastoma/HealthProfessional>. Accessed January 7, 2011.

- Patients may present with an asymptomatic abdominal mass, malaise, and pain.
- Metastases, when present at diagnosis, commonly involve the lungs or liver.
- Diagnosis is based on biopsy and computed tomography (CT) of the chest and abdomen to rule out metastatic disease.
- Surgical resection is the primary treatment, followed by adjuvant chemotherapy. Treatment is determined by stage and histology (Table 91.6).

**OSTEOSARCOMA**

- Osteosarcoma is a malignant osteoid-producing bone tumor that occurs most commonly in adolescents or young adults in the second or third decade of life.
- Disease usually occurs close to a joint in long bones; pain or a limp may be present.
- Diagnosis is based on pathology from a biopsy. Typical staging systems are not used.
- Surgery is the main treatment of the primary tumor. Chemotherapy is used to prevent development of metastases (eradicate micrometastases) in patients with high-grade disease. Drugs frequently used include high-dose methotrexate (with leucovorin), cisplatin, doxorubicin, epirubicin, etoposide, gemcitabine, topotecan, and ifosfamide.
- Leucovorin rescue is often used with high-dose methotrexate to reduce toxicities.

**TABLE 91.4 Typical Cycles of Chemotherapy Used in Children’s Oncology Group Low-Risk and Intermediate-Risk Neuroblastoma**

Cycle <sup>a</sup>	Drugs
1	Carboplatin, etoposide
2	Carboplatin, cyclophosphamide, doxorubicin
3	Cyclophosphamide, etoposide
4	Carboplatin, doxorubicin, etoposide
5	Cyclophosphamide, etoposide
6	Carboplatin, cyclophosphamide, doxorubicin
7	Carboplatin, etoposide
8	Cyclophosphamide, doxorubicin

<sup>a</sup>Each row represents a single cycle of therapy. Generally, the first four cycles are used in patients at intermediate risk with favorable histology disease, and all eight for patients with unfavorable histology. Patients at low risk whose disease is potentially organ-threatening may receive the first two to four cycles plus surgery. See Table 91.3 for common chemotherapy guidelines for low-risk and intermediate-risk patients.

Sources: Brodeur GM et al. Neuroblastoma. In: Pizzo PA, Poplack DG, eds. *Principles and Practice of Pediatric Oncology*. 6th ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2010:886; National Institutes of Health, National Cancer Institute. *Neuroblastoma Treatment (PDQ)*. <http://cancer.gov/cancertopics/pdq/treatment/neuroblastoma/HealthProfessional>. Accessed January 7, 2011.

**TABLE 91.5 Typical Cycles of Chemotherapy Used Historically in US Intergroup Trials and Currently in Children's Oncology Group Trials Before Transplant for High-Risk Neuroblastoma**

**A. HISTORICAL<sup>a</sup>**

Cisplatin, etoposide  
 Vincristine, doxorubicin, cyclophosphamide  
 Ifosfamide, etoposide  
 Carboplatin, etoposide  
 Cisplatin, etoposide  
 Ifosfamide, etoposide  
 Vincristine, doxorubicin, cyclophosphamide  
 Cisplatin, etoposide  
 Vincristine, doxorubicin, cyclophosphamide  
 Carboplatin, etoposide

**B. CURRENT<sup>b</sup>**

Cyclophosphamide, doxorubicin, vincristine for cycles 1, 2, 4, 6  
 Cisplatin, etoposide for cycles 3, 5

<sup>a</sup>The second five cycles may be skipped if the patient is ready to proceed to high-dose chemotherapy with progenitor cell rescue after the first five combinations. Patients who are not candidates for autologous progenitor cell rescue receive all 10 cycles of chemotherapy. Primary tumor removal or debulking is performed before progenitor cell rescue. Radiation to the site of the primary tumor most commonly occurs after all chemotherapy and progenitor cell rescue. Patients who are in complete response after this therapy will receive six cycles of isotretinoin (14 of every 28 days).

<sup>b</sup>After five cycles, proceed to definitive surgery, high-dose chemotherapy with autologous progenitor cell rescue, radiation therapy, and maintenance with isotretinoin.

Sources: Brodeur GM et al. Neuroblastoma. In: Pizzo PA, Poplack DG, eds. *Principles and Practice of Pediatric Oncology*. 6th ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2010:886; National Institutes of Health, National Cancer Institute. *Neuroblastoma Treatment (PDQ)*. <http://cancer.gov/cancertopics/pdq/treatment/neuroblastoma/HealthProfessional>. Accessed January 7, 2011.

**TABLE 91.6 National Wilms Tumor Study V Treatment Regimens by Stage and Histology**

**STAGES I AND II, FAVORABLE HISTOLOGY; STAGE I, FOCAL OR DIFFUSE ANAPLASIA**

Surgery followed by 18 weeks of vincristine and dactinomycin. Add abdominal radiation for anaplasia

**STAGE III, FAVORABLE HISTOLOGY; STAGES II AND III, FOCAL ANAPLASIA; STAGE IV, FAVORABLE HISTOLOGY OR FOCAL ANAPLASIA**

Surgery followed by 24 weeks of vincristine, dactinomycin, and doxorubicin, with abdominal radiation

**STAGE IV, FAVORABLE HISTOLOGY OR FOCAL ANAPLASIA**

Add pulmonary radiation if chest radiograph shows metastases

**STAGES II THROUGH IV, DIFFUSE ANAPLASIA; STAGES I TO IV, CLEAR CELL SARCOMA OF THE KIDNEY**

Surgery followed by 24 weeks of vincristine, doxorubicin, etoposide, and cyclophosphamide with mesna, abdominal radiation

**STAGE IV, DIFFUSE ANAPLASIA OR CLEAR CELL SARCOMA OF THE KIDNEY**

Add pulmonary radiation if chest radiograph is positive for metastases

**STAGE V**

Biopsy followed by neoadjuvant vincristine, dactinomycin, and doxorubicin, then complete resection or debulking followed by more chemotherapy and, if a poor response, radiation therapy; more aggressive treatment if unfavorable histology

**STAGES I-IV, RHABDOID TUMOR (UNFAVORABLE HISTOLOGY)**

Surgery followed by 24 weeks of carboplatin, etoposide, and cyclophosphamide with mesna, abdominal radiation, plus or minus vincristine, doxorubicin, and cyclophosphamide, for a total of 30 weeks of treatment

Source: National Institutes of Health, National Cancer Institute. Wilms tumor and other childhood kidney tumors treatment (PDQ). <http://cancer.gov/cancertopics/pdq/treatment/wilms/HealthProfessional>. Accessed January 7, 2010.

- Neoadjuvant chemotherapy is often given for 6 cycles and continued after surgery for 12 more cycles (to 29 weeks); it may improve limb-sparing surgery by shrinking the tumor.

### RHABDOMYOSARCOMA

- Rhabdomyosarcoma is a rare soft tissue tumor of skeletal muscle. The two common histologic types in children are embryonal (cells resemble striated muscle; more common in young children) and alveolar (cells resemble lung parenchyma; more common in older children and adults). Embryonal classification has a better prognosis.
- Clinical presentation varies with location (head and neck, genitourinary, parameningeal, extremity, orbit). The primary site affects resectability, route of spread, and how early the diagnosis is made.
- Diagnosis involves biopsy of the tumor.
- Treatment combines surgery, radiation, and chemotherapy. Complete surgical removal is often difficult. Radiation is generally given after surgery. Chemotherapy for patients at low risk is limited to vincristine and dactinomycin. Those at intermediate risk are treated with vincristine, dactinomycin, and cyclophosphamide.

## Pediatric Hematologic Tumors

### ACUTE LYMPHOBLASTIC LEUKEMIA (ALL)

- ALL, the most common childhood cancer, accounts for approximately 30% of all malignancies. Peak incidence occurs at 2 to 3 years of age. In ALL, normal bone marrow is replaced with a clone of immature lymphoid cells.
- Signs and symptoms of ALL are nonspecific. Frequent findings include fever, bleeding, and bone pain. Patients may have lymphadenopathy, hepatosplenomegaly, and splenomegaly. At least 50% of patients have normal or low white blood cell (WBC) counts. WBC differential shows a low percentage of neutrophils and bands, and marked lymphocytosis.
- Bone marrow aspirate and biopsy are usually necessary to confirm the diagnosis. Certain clinical and laboratory findings present at diagnosis are important predictors of prognosis and are used to determine risk stratification. Age and initial WBC count are most important, with young age (<1 year or >9 years) and high WBC count (>50,000/mm<sup>3</sup>) carrying a poor prognosis.
- ALL is classified by risk of relapse (low, intermediate, high, or very high), immunologic subsets based on cell surface markers present on leukemic lymphoblasts at diagnosis (e.g., mature B-cell, or Burkitt ALL), and cytogenetic variables (e.g., Philadelphia chromosome).
- Early response to treatment, measured by either clearance of blasts from peripheral blood or morphologic bone marrow remission on day 7 to 14 of therapy, is predictive of long-term, disease-free survival. Rapid early response is defined as clearance of bone marrow blasts by day 15 of induction.
- Most patients receive a total duration of 2.5 years of therapy. Treatment is organized into different phases of chemotherapy:
  - **Induction:** Usually includes three to four systemic agents in addition to central nervous system (CNS) preventive therapy (Table 91.7). Treatment is designed to induce complete remission (inability to detect leukemic cells in the peripheral blood or bone marrow by morphologic microscopic evaluation).
  - **Postinduction:** Different intensive chemotherapy given in 2-to-6-week cycles (referred to as consolidation, delayed intensification, or interim maintenance therapy) designed to kill leukemia cells in the cell cycle that were not destroyed during induction therapy (Table 91.8).
  - **Maintenance:** Less intensive therapy lasting approximately 2 years designed to sustain the complete remission achieved by induction therapy. Mercaptopurine and methotrexate are two of the most effective drugs used.

TABLE 91.7 Systemic Induction Regimens for Childhood Acute Lymphocytic Leukemia

Agent	Route	Dose/Schedule
<b>THREE-DRUG INDUCTION REGIMEN</b>		
Prednisone or Dexamethasone <sup>a</sup>	PO	40 mg/m <sup>2</sup> /day × 28 days
with Vincristine and Asparaginase or Pegaspargase	IV	1.5 mg/m <sup>2</sup> /week (max. 2 mg) × 4 doses
	IM	10,000 units/m <sup>2</sup> 3 times weekly × 9 doses
	IM	2,500 units/m <sup>2</sup> × 1 dose
<b>AND (IF FOUR-DRUG INDUCTION)</b>		
Daunorubicin	IV	25 mg/m <sup>2</sup> on days 2, 8, 15

<sup>a</sup>Denotes that this agent is only used in three-drug induction regimens (see text).

IM, intramuscularly; IV, intravenously; PO, orally.

Sources: Bostrom BC et al. Dexamethasone versus prednisone and daily oral versus weekly intravenous mercaptopurine for patients with standard-risk acute lymphoblastic leukemia: a report from the Children's Cancer Group. *Blood*. 2003;101:3809; Clavell LA et al. Four-agent induction and intensive asparaginase therapy for treatment of childhood acute lymphoblastic leukemia. *N Engl J Med*. 1986;315:657; Balis FM et al. Differences in cerebrospinal fluid penetration of corticosteroids: possible relationship to the prevention of meningeal leukemia. *J Clin Oncol*. 1987;5:202; Hurwitz CA et al. Substituting dexamethasone for prednisone complicates remission induction in children with acute lymphoblastic leukemia. *Cancer*. 2000;88:1964; Ortega JA et al. L-asparaginase, vincristine, and prednisone for induction of first remission in acute lymphocytic leukemia. *Cancer Res*. 1977;37:535; Reiter A et al. Chemotherapy in 998 unselected childhood acute lymphoblastic leukemia patients: results and conclusions of the multicenter trial ALL-BFM 86. *Blood*. 1994;84:3122; Kaplan RS, Wiernik PH. Neurotoxicity of antineoplastic drugs. *Semin Oncol*. 1982;9:103.

TABLE 91.8 Acute Lymphoblastic Leukemia Postinduction Regimen Components

Schedule	Reference
Vincristine 1.5 mg/m <sup>2</sup> IV on days 0, 10, 20, 30, and 40	
Methotrexate 100 mg/m <sup>2</sup> IV on days 0, 10, 20, 30, and 40 (escalate by 50 mg/m <sup>2</sup> per dose if tolerated)	
PEG-asparaginase 2,500 units/m <sup>2</sup> IM on days 1 and 21	
Methotrexate IT on days 0 and 30	226
Cyclophosphamide 1 g/m <sup>2</sup> IV on days 0 and 30	
Cytarabine 75 mg/m <sup>2</sup> SC or IV on days 1–4, 8–11, 29–32, and 36–39	
Mercaptopurine 60 mg/m <sup>2</sup> PO daily on days 0–13 and 28–41	
Methotrexate IT on days 1, 8, 15, and 22	
PEG-asparaginase 2,500 units/m <sup>2</sup> IM on days 14 and 42	
Vincristine 1.5 mg/m <sup>2</sup> IV on days 14, 21, 42, and 49	226
Methotrexate 1 g/m <sup>2</sup> IV for 24 hours, every 3 weeks × 6 doses	
Vincristine 1.5 mg/m <sup>2</sup> IV on weeks 8, 9, 17, and 18	
Prednisone 40 mg/m <sup>2</sup> PO daily × 7 days at weeks 8 and 17	224
Dexamethasone 10 mg/m <sup>2</sup> PO daily on days 0–7 and 14–20	
Vincristine 1.5 mg/m <sup>2</sup> IV on days 0, 7, and 14	
PEG-asparaginase 2,500 units/m <sup>2</sup> IM on day 3	
Doxorubicin 25 mg/m <sup>2</sup> IV on days 0, 7, and 14	226

IV, intravenously; IM, intramuscularly; PO, orally; SC, subcutaneously; IT, intrathecally.

- All treatment protocols for childhood ALL should include some form of CNS preventive therapy. Current CNS preventive therapy includes IT methotrexate alone, triple IT chemotherapy (methotrexate, cytarabine, and hydrocortisone), and IT methotrexate combined with systemic dose-intensified methotrexate. High chemotherapy concentrations can be attained within the cerebrospinal fluid with relatively low doses. Age-based dosing regimens are less neurotoxic (Table 91.9).
- Vincristine is associated with autonomic neuropathy, which may substantially reduce GI motility (constipation, colicky abdominal pain, paralytic ileus). Symptoms appear 3 to 10 days after drug administration. Inadvertent intrathecal (IT) administration is almost uniformly fatal.
- Asparaginase toxicity includes severe, sometimes fatal pancreatitis and frequent hypersensitivity reactions. Premedication does not prevent subsequent reactions. Delayed hypersensitivity reactions can occur with intramuscular administration. Pegaspargase appears to be safe and effective in patients with prior reactions to *Escherichia coli* and *Erwinia* asparaginase products.
- Allopurinol is the standard prophylactic regimen for tumor lysis syndrome. Rasburicase is an alternative that obviates the need for allopurinol, hydration, and alkalination.
- Long-term complications of chemotherapy can include late-occurring cardiotoxicity secondary to anthracycline use and loss of bone mineral density.
- Most patients who relapse are asymptomatic with diagnosis done by routine complete blood count (CBC) or lumbar puncture. At least 80% of patients will achieve a second remission with salvage therapy. Allogeneic bone marrow transplantation can be considered after a second remission has been achieved.

### PEDIATRIC NON-HODGKIN LYMPHOMA

- Lymphomas are a collection of diseases originating in cells and organs of the immune system. Non-Hodgkin lymphoma (NHL) is the most common form of lymphoma in children below 10 years of age. Hodgkin lymphoma is more common in children 15 to 19 years of age.
- NHL is classified using histopathology: B-cell, lymphoblastic, and anaplastic large cell. B-cell is further classified as Burkitt, Burkittlike, and large B-cell lymphoma.
- Symptoms in children differ from those in adults.
  - B-cell lymphoma presents with an abdominal tumor, abdominal pain, alterations in bowel function, and nausea/vomiting.
  - Lymphoblastic lymphoma presents with a mediastinal mass or pleural effusions. Pain, dyspnea, or swelling of the face and upper arms may be present.
  - Anaplastic large cell involves the gut or unusual sites (lung, skin, face, CNS).

TABLE 91.9 Dosage Regimen for Intrathecal Chemotherapy Based on Patient Age

Patient Age (Years)	Methotrexate (mg)	Hydrocortisone (mg)	Cytarabine (mg)
<1	6	6	12
1	8	8	16
2	10	10	20
3	12	12	24
≥9	15	15	30

Source: Lobel JS et al. Methotrexate and asparaginase combination chemotherapy in refractory acute lymphoblastic leukemia of childhood. *Cancer*. 1979;43:1089.

- Several staging systems for pediatric NHL exist. The main predictor of outcome is tumor burden at time of presentation.
- Treatment of lymphoblastic (T-cell) lymphoma uses an intensive scheme of multiagent chemotherapy given over 24 months (Table 91.10). All patients are given CNS preventive therapy, regardless of stage.
- Treatment of B-cell lymphoma is shorter in duration (6 months) using intensive therapy with alkylating agents in conjunction with high-dose antimetabolite therapy.
- Large cell lymphoma is treated similar to B-cell lymphoma. Patients who relapse may be reinduced with intensive chemotherapy.

TABLE 91.10 BFM Group Treatment Protocols for T-Cell Lymphoblastic Lymphoma

Drug	Dose	Days of Administration
<b>INDUCTION PROTOCOL I (ALL STAGES)</b>		
Prednisone (PO)	60 mg/m <sup>2</sup>	1–28, then taper
Vincristine (IV)	1.5 mg/m <sup>2</sup> (max. 2 mg)	8, 15, 22, 29
Daunorubicin (IV for 1 hour)	30 mg/m <sup>2</sup>	8, 15, 22, 29
L-asparaginase (IV <sup>a</sup> for 1 hour)	10,000 international units/m <sup>2</sup>	12, 15, 18, 21, 24, 27, 30, 33
Cyclophosphamide <sup>b</sup> (IV for 1 hour)	1,000 mg/m <sup>2</sup>	36, 64
Cytarabine (IV)	75 mg/m <sup>2</sup>	38–41, 45–48, 52–55, 59–62
6-Mercaptopurine (PO)	60 mg/m <sup>2</sup>	36–63
Methotrexate (IT)	12 mg	1, 15, 29, 45, 59
<b>PROTOCOL M (TYPICALLY STAGES I AND II)</b>		
Mercaptopurine (PO)	25 mg/m <sup>2</sup>	1–56
Methotrexate (IV)	5 g/m <sup>2</sup>	8, 22, 36, 50
Methotrexate (IT)	12 mg	8, 22, 36, 50
<b>REINDUCTION PROTOCOL II (STAGES III AND IV ONLY)</b>		
Dexamethasone (PO)	10 mg/m <sup>2</sup>	1–21, then taper
Vincristine (IV)	1.5 mg/m <sup>2</sup> (max. 2 mg)	8, 15, 22, 29
Doxorubicin (IV for 1 hour)	30 mg/m <sup>2</sup>	8, 15, 22, 29
L-asparaginase (IV <sup>a</sup> for 1 hour)	10,000 international units/m <sup>2</sup>	8, 11, 15, 18
Cyclophosphamide <sup>b</sup> (IV for 1 hour)	1,000 mg/m <sup>2</sup>	36
Cytarabine (IV)	75 mg/m <sup>2</sup>	38–41, 45–48
Thioguanine (PO)	60 mg/m <sup>2</sup>	36–49
Methotrexate (IT)	12 mg	38, 45
<b>MAINTENANCE (ALL STAGES)</b>		
Mercaptopurine (PO)	50 mg/m <sup>2</sup>	Daily, until month 24 of therapy
Methotrexate (PO)	20 mg/m <sup>2</sup>	Weekly, until month 24 of therapy

<sup>a</sup>This agent is typically administered intramuscularly in most treatment protocols in the United States.

<sup>b</sup>With mesna.

Note. IT methotrexate doses were adjusted for children younger than 3 years. Ten percent of the 5 g/m<sup>2</sup> methotrexate dose in Protocol M was given for 30 minutes, and 90% was given as a 23.5-hour continuous IV infusion. Leucovorin rescue: 30 mg/m<sup>2</sup> IV at hour 42; 15 mg/m<sup>2</sup> IV at hours 48 and 54.

Additional doses are given on days 8 and 22 for CNS-positive patients.

CNS, central nervous system; IT, intrathecally; IV, intravenously; PO, orally.

Source: Watanabe A et al. Undifferentiated lymphoma, non-Burkitt's type: meningeal and bone marrow involvement in children. *Am J Dis Child.* 1973;125:57.

# Adult Hematologic Malignancies\*

## General Principles

- **Leukemias** are hematologic malignancies that are derived from cytogenic alterations in hematopoietic cells. They are classified on the basis of the cell of origin (myeloid or lymphocytic) and clinical course.
- **Lymphomas** are a heterogeneous group of hematologic malignancies that originate in lymphoid tissues and arise from malignant transformation of lymphocytes (B cells, T cells, or natural killer cells). A lymphoma may arise within a single or multiple lymph nodes or in extranodal sites involving the lymphoid tissue.

## Acute Myeloid Leukemia

- Acute myeloid leukemia (AML) is a group of relatively well-defined hematopoietic neoplasms involving precursor cells committed to the myeloid line of cellular development. Two major groups exist: abnormal (poor prognosis) and normal karyotype (variable prognosis, Table 92.1).
- AML is the most common acute leukemia in adults. Median age at diagnosis is 67 years.
- AML is characterized by a clonal proliferation of myeloid precursors with a reduced capacity to differentiate into more mature cellular elements. Leukemic blasts accumulate in the bone marrow, peripheral blood, and occasionally other tissues.
- Patients present with symptoms related to pancytopenia (anemia, neutropenia, thrombocytopenia), including weakness and easy fatigability, infection, and hemorrhagic findings (gingival bleeding, ecchymoses, epistaxis, menorrhagia).
- Presumptive diagnosis can be made by examination of peripheral blood smear; definitive diagnosis requires a bone marrow aspiration and biopsy (>20% leukemic blasts must be present in the bone marrow aspirate). Morphologic, immunophenotypic, cytogenetic, and molecular studies are critical for making the correct diagnosis, determining prognosis, and identifying optimal treatment.
- The goal of treatment is to rapidly restore normal bone marrow function to produce and maintain complete remission (platelet count >100,000 cells/mL, neutrophil count >1,000 cells/mL, bone marrow specimen <5% blasts).
- **Induction Therapy**—used to clear the bone marrow and peripheral blood of all blast cells in the hope that normal blood cell components can regenerate.
  - Standard induction chemotherapy includes an anthracycline (daunorubicin or idarubicin) and cytarabine (100–200 mg/m<sup>2</sup>/day). The combination is most commonly used for all types of AML except APL or AML-M3. For these subtypes of AML, all-trans-retinoic acid (ATRA) should be added to the regimen, beginning 2 days before conventional chemotherapy.

\*The reader is referred to Chapter 92, Adult Hematologic Malignancies, written by Lynn Weber, PharmD, BCOP, Steve Stricker, PharmD, MS, BCOP, and Casey B. Williams, PharmD, BCOP, in the 10th edition of *Applied Therapeutics: The Clinical Use of Drugs* for a more in-depth discussion. All notations to reference numbers are based on the reference list at the end of that chapter. The editor of this handbook expresses her thanks to Drs. Weber, Stricker, and Williams and acknowledges that this chapter is based on their work.



**TABLE 92.1 Pretreatment Molecular Entities Shown to Predict Disease Outcome in Adults with Acute Myeloid Leukemia and a Normal Karyotype**

Gene	Mutation Frequency (%)	Prognosis
<i>NPM1</i>	45–63	Favorable
<i>FLT3</i>	23–33	Poor
<i>C/EBP<math>\alpha</math></i>	8–19	Favorable
<i>MLL</i>	5–30	Poor

Source: Baldus CD et al. Clinical outcome of de novo acute myeloid leukaemia patients with normal cytogenetics is affected by molecular genetic alterations: a concise review. *Br J Haematol.* 2007;137:387.

- Patients presenting with very high white blood cell (WBC) counts may experience complications with hyperviscosity of the blood (ringing ears, stroke, blindness, headache). Hydroxyurea (2–4 g orally) or leukapheresis can rapidly decrease WBC count.
- Tumor lysis syndrome (TLS) may occur when there is high tumor burden resulting from rapid lysis of leukemic cells. Complications include metabolic abnormalities (hyperuricemia, hyperphosphatemia, hypocalcemia, uremia), arrhythmias, and acute renal failure. IV hydration (3–4 L/day) beginning 24–48 hours before chemotherapy and allopurinol (300–600 mg/day) should be given to prevent or minimize TLS. Serum uric acid and electrolytes should be monitored three to four times daily for 24 to 48 hours. Rasburicase is an alternative to allopurinol.
- Arsenic trioxide can be used for patients in APL subtype patients refractory to or have relapsed with all-trans-retinoic acid and anthracycline chemotherapy.
- **Postremission (Consolidation) Therapy**—used to maintain remission since almost all patients will relapse within a median of 4 to 8 months. Three to four cycles of chemotherapy are given. Regimens usually include high-dose cytarabine (HiDAC; >1g/m<sup>2</sup>/day) alone or in combination with other agents (e.g., anthracycline, etoposide).
- **Maintenance Therapy**—with the exception of the APL subtype, maintenance chemotherapy has not been shown to improve survival in adult AML.
- **Allogeneic Hematopoietic Cell Transplant (HCT)**—provides the best chance of cure in patients who relapse or are refractory to therapy.
- Elderly patients are generally poor candidates for intensive chemotherapy due to the higher risk of morbidity and mortality.

## Chronic Myelogenous Leukemia

- Chronic myelogenous leukemia (CML) is a myeloproliferative disorder characterized by unregulated stem cell proliferation in the bone marrow and an increase in mature granulocytes in the peripheral blood. Median age of diagnosis is 50 to 60 years.
- Presenting symptoms include fatigue, abdominal pain, fever, anorexia, and weight loss. Up to 50% of patients may be asymptomatic. Approximately 50% to 70% will present with a leukocyte count >100,000 cells/mL.
- Diagnosis is confirmed by bone marrow biopsy. The cytogenetic hallmark of CML, present in >95% of cases, is the Philadelphia chromosome (translocation that creates a new protein, BCR-ABL that has unregulated tyrosine kinase activity).
- The natural history of CML is divided into three phases: chronic (<10% blasts and promyelocytes in the bone marrow and peripheral blood; lasts from weeks to years); accelerated (leukocytosis progresses and an increased number of immature leukocytes, blasts, appear in peripheral blood; lasts <6 weeks); and blast (characterized by a predominance of immature cells, with >20% blasts in peripheral blood or bone marrow; survival <3 months).

**TABLE 92.2 Definition of Complete and Partial Hematologic Response in Chronic Myelogenous Leukemia**

	Partial Response	Complete Response
Peripheral leukocyte count	$<10 \times 10^9/L$	$<10 \times 10^9/L$
Platelet count	$<50\%$ pretreatment count (but $>450 \times 10^9/L$ )	$<450 \times 10^9/L$
Immature cells	Present	Absent
Splenomegaly	Present (but $<50\%$ pretreatment extent)	Absent

Source: NCCN National Comprehensive Cancer Network. Clinical Practice Guidelines in Oncology: Chronic Myelogenous Leukemia. 2012; V1.2012. [http://www.nccn.org/professionals/physician\\_gls/f\\_guidelines.asp](http://www.nccn.org/professionals/physician_gls/f_guidelines.asp). Accessed May 2, 2011.

- The initial goal of therapy is to immediately reduce leukocytosis and its related symptoms. Hydroxyurea (2 g/day, orally, with dose titrated to a WBC count  $<20,000$  cells/mcL) is used for initial leukocyte reduction.
- Tyrosine kinase (TK) inhibitors (imatinib, nilotinib, and dasatinib) are first-line therapy in most patients with chronic phase CML even though they are not curative. The goal is to prolong survival, prevent progression of disease, and attain a complete hematologic or cytogenetic remission.
- Treatment of patients who progress to accelerated or blast phase is determined on mutational changes in the BCR-ABL protein and bone marrow cytogenetics.
- Assessment of response is based on hematologic (Table 92.2) and cytogenetic (Table 92.3) factors. Molecular response is defined as undetectable BCR-ABL.
- HCT is the only curative therapy.

## Chronic Lymphocytic Leukemia

- Chronic lymphocytic leukemia (CLL), a disorder of mature but functionally incompetent lymphocytes, is the most common type of leukemia in adults with a median age at diagnosis of 65 years.
- CLL is characterized by overproduction of functionally incompetent B-cell lymphocytes derived from a single stem cell clone in the bone marrow.
- Chronic leukemia follows a relatively insidious onset and course compared with acute leukemia; 40% of patients may be asymptomatic at the time of presentation. Symptomatic patients experience night sweats, fatigue, weight loss, fever, and painful lymphadenopathy. Infections contribute significantly to morbidity and mortality.
- Survival is variable and depends on stage of disease at diagnosis. Staging is based on peripheral lymphocyte count; enlargement of lymph nodes, liver, and spleen; and presence of anemia or thrombocytopenia (Tables 92.4 and 92.5).

**TABLE 92.3 Definition of Cytogenetic Response in Chronic Myelogenous Leukemia**

Cytogenetic Response	Philadelphia (Ph) Chromosome-Positive Metaphase Cells (%)
Complete	0
Partial	1–35
Major (includes complete and partial responses)	0–35
Minor	$>35$

Source: NCCN National Comprehensive Cancer Network. Clinical Practice Guidelines in Oncology: Chronic Myelogenous Leukemia. 2012; V1.2012. [http://www.nccn.org/professionals/physician\\_gls/f\\_guidelines.asp](http://www.nccn.org/professionals/physician_gls/f_guidelines.asp). Accessed May 2, 2011.

TABLE 92.4 Binet Classification

Stage	Lymphocytosis <sup>a</sup>	Anemia <sup>b</sup>	Thrombocytopenia <sup>c</sup>	Number of Involved Nodes (Max. 5) <sup>d</sup>	Median Survival (Years)
A	+	—	—	<3	12
B	+	—	—	≥3	7
C	+	±	±	Any	2–4

<sup>a</sup>Lymphocytes  $>5 \times 10^9/L$  in peripheral blood and  $>30\%$  of total cells in the bone marrow.

<sup>b</sup>Hemoglobin  $<11$  g/dL in men and  $<10$  g/dL in women excluding immune-mediated etiology.

<sup>c</sup>Platelets  $<100,000/\mu L$ .

<sup>d</sup>Maximum of five—cervical, axillary, inguinal, spleen, and liver—are counted as one area.

Source: Binet JL et al. A new prognostic classification of chronic lymphocytic leukemia derived from a multivariate survival analysis. *Cancer*. 1981;48:198.

- An acceptable treatment approach for early-stage disease is conservative, watchful waiting.
- Indications for treatment initiation include significant anemia or thrombocytopenia, progressive disease demonstrated by lymphadenopathy, hepatomegaly, splenomegaly, a lymphocyte doubling time of less than 6 months, persistent B-symptoms (fever, night sweats, weight loss), threatened end-organ function, and recurrent infection.
- Selection of therapy is determined by presence/absence of cytogenetic abnormalities. First-line therapy for patients  $\geq 70$  years of age or with significant comorbidities generally includes chlorambucil with prednisone, or bendamustine with rituximab. For younger patients without comorbidities, three-drug combinations such as fludarabine, cyclophosphamide, and rituximab can be offered.
- Relapsed disease (relapse occurring  $>3$  years after treatment) is often treated with combinations of the same drugs used for initial treatment.
- Refractory disease (relapse occurring  $<2$  years after treatment) should be treated with at least one agent not previously given.
- Younger patients with relapsed disease or high-risk features may benefit from HCT. Allogeneic HCT is the only curative treatment for CLL.

## Multiple Myeloma

- Multiple myeloma (MM) is defined as a malignancy of plasma cells, terminally differentiated B lymphocytes responsible for the production of antibodies and for the rapid response of the immune system to antigen exposure. The average age of diagnosis is 70 years.
- Symptomatic patients present with bone pain, fatigue, and recurrent infections. There may also be end-organ damage (hypercalcemia, renal dysfunction, anemia, and bone lesions).

TABLE 92.5 Modified Rai Classification

Risk	Stage	Lymphocytosis <sup>a</sup>	Anemia <sup>b</sup>	Thrombocytopenia <sup>c</sup>	Lymphadenopathy	Hepatomegaly or Splenomegaly	Median Survival (Years)
Low	0	+	—	—	—	—	10
Intermediate	I	+	—	—	+	—	7
	II	+	—	—	±	+	
High	III	+	+	—	±	±	1.5–4
	IV	+	±	+	±	±	

<sup>a</sup>Lymphocytes  $>5,000/\mu L$  in peripheral blood and  $>30\%$  of total cells in the bone marrow.

<sup>b</sup>Hemoglobin  $<11$  g/dL excluding immune-mediated etiology.

<sup>c</sup>Platelets  $<100,000/\mu L$ .

Source: Rai KR et al. Clinical staging of chronic lymphocytic leukemia. *Blood*. 1975;46:219.

TABLE 92.6 Diagnostic Criteria for Plasma Cell Disorders<sup>a</sup>**MULTIPLE MYELOMA**

1. Presence of a serum or urinary monoclonal immunoglobulin protein
2. Presence of clonal plasma cells in the bone marrow or a plasmacytoma
3. Presence of end-organ damage related to plasma cell proliferation, including:
  - Elevated calcium (1 mg/dL above the upper limit of the normal range, or >11 mg/dL)
  - Renal insufficiency (creatinine >1.9 mg/dL)
  - Anemia (2 g/dL below the lower limit of the normal range, or <10 g/dL)
  - Bone lesions (lytic lesions or osteoporosis with compression fractures)

**ASYMPTOMATIC (SMOLDERING) MULTIPLE MYELOMA**

1. Serum monoclonal immunoglobulin >3 g/dL or bone marrow plasma cells >10%
2. No end-organ damage related to plasma cell proliferation

**MONOCLONAL GAMMOPATHY OF UNDETERMINED SIGNIFICANCE (MGUS)**

1. Serum monoclonal immunoglobulin <3 g/dL
2. Bone marrow plasma cells <10%
3. No end-organ damage related to plasma cell proliferation

<sup>a</sup>All criteria must be met.

Source: International Myeloma Working Group. Criteria for the classification of monoclonal gammopathies, multiple myeloma and related disorders: a report of the International Working Group. *Br J Haematol.* 2003;121:749.

- MM is not considered a curable malignancy. The goal of treatment is to achieve and maintain a clinical response through the combination of induction therapy, HCT, and maintenance therapy.
- Table 92.6 outlines the diagnostic criteria for plasma cell disorders. Staging and prognosis can be predicted from serum  $\beta$ -2 microglobulin (Table 92.7).
- Patients who meet the diagnostic criteria for MM and who are symptomatic are candidates for systemic chemotherapy (Table 92.8). Choice of induction therapy is based on the patient's eligibility for HCT. The most effective treatment is induction chemotherapy to achieve a complete clinical response, defined by elimination of M-protein in plasma and elimination of plasma cells in the bone marrow.
- Autologous HCT is regarded as the current treatment of choice for eligible patients with MM who achieve CR after induction therapy.
- Bortezomib alone or in combination with pegylated liposomal doxorubicin and the combination of lenalidomide and dexamethasone are considered the preferred regimens for management of patients with relapsed or refractory MM.
- Osteolytic bone lesions or osteopenia occur in nearly 80% of patients with MM. Bisphosphonates (pamidronate, zoledronic acid) can be used to prevent skeletal fractures.

**Non-Hodgkin Lymphoma**

- Non-Hodgkin lymphoma (NHL) is a spectrum of diseases marked by different pathological features, natural history, response to treatment, and prognosis (Table 92.9). Disease can be indolent or aggressive.

TABLE 92.7 International Staging System for Multiple Myeloma

- Stage I— $\beta_2$  microglobulin <3.5 mg/L and serum albumin  $\geq$ 3.5 g/dL  
 Stage II—neither stage I nor stage III  
 Stage III— $\beta_2$  microglobulin  $\geq$ 5.5 mg/L

Source: Greipp PR et al. International staging system for multiple myeloma. *J Clin Oncol.* 2005;23:3412.

TABLE 92.8 Multiple Myeloma Treatment Regimens

Regimen	Agents	Comments
<b>INDUCTION THERAPY</b>		
<i>Eligible for High-Dose Chemotherapy with Autologous HCT</i>		
RVD	Lenalidomide 25 mg PO daily, days 1–14  Bortezomib 1.3 mg/m <sup>2</sup> IV days 1, 4, 8, and 11 Dexamethasone 40 mg PO daily, days 1–2, 4–5, 8–9, 11–12 Repeat cycle every 21 days	Antithrombotic prophylaxis is recommended with lenalidomide. Antiviral prophylaxis with acyclovir is recommended with bortezomib.
VTD	Bortezomib 1.3 mg/m <sup>2</sup> IV days 1, 4, 8, and 11  Thalidomide 200 mg PO daily Dexamethasone 40 mg PO daily, days 1–4 and 9–12 Repeat cycle every 21 days	Thalidomide should be given in the evening to minimize sedation. Antithrombotic prophylaxis is recommended.
Bortezomib + Dexamethasone	Bortezomib 1.3 mg/m <sup>2</sup> IV days 1, 4, 8, and 11 Dexamethasone 20 mg PO daily, days 1–2, 4–5, 8–9, 11–12 Repeat cycle every 21 days	
<i>Ineligible for High-Dose Chemotherapy with Autologous Stem Cell Support</i>		
MPB	Melphalan 9–12 mg/m <sup>2</sup> PO daily, days 1–4 Prednisone 60 mg/m <sup>2</sup> PO daily, days 1–4 Bortezomib 1.3 mg/m <sup>2</sup> IV days 1, 4, 8, 11, 22, 25, 29, 32 for the first four cycles, then days 1, 8, 22, 29 in subsequent cycles	
MPT	Melphalan 4 mg/m <sup>2</sup> PO daily, days 1–7 Prednisone 40 mg/m <sup>2</sup> PO daily, days 1–7 Thalidomide 100 mg PO daily Repeat cycle every 28 days	Melphalan should be given on an empty stomach owing to variable absorption when administered with food.
MP	Melphalan 8–10 mg/m <sup>2</sup> PO daily, days 1–4 Prednisone 60 mg/m <sup>2</sup> PO daily, days 1–4 Repeat cycle every 28–42 days	
<b>SALVAGE THERAPY</b>		
Bortezomib	Bortezomib 1.3 mg/m <sup>2</sup> IV days 1, 4, 8, and 11  Repeat cycle every 21 days	Dose reduction to 1 mg/m <sup>2</sup> may be necessary in patients with neuropathy or thrombocytopenia. Addition of dexamethasone may be required in patients who do not respond.
Bortezomib + liposomal doxorubicin	Bortezomib 1.3 mg/m <sup>2</sup> IV once Liposomal doxorubicin 30 mg/m <sup>2</sup> , day 4 Repeat cycle every 21 days	
Lenalidomide + dexamethasone	Lenalidomide 25 mg PO daily, days 1–21 Dexamethasone 40 mg PO daily, days 1–4, 9–12, 17–20 for the first four cycles, then days 1–4 only in subsequent cycles	Consider prophylactic antithrombotics

CIV, continuous intravenous infusion; HCT, hematopoietic cell transplantation; IV, intravenously; MP, melphalan and prednisone; MPB, melphalan, prednisone, and bortezomib; MPT, melphalan, prednisone, and thalidomide; PO, orally; RVD, lenalidomide, bortezomib, and dexamethasone; VTD, bortezomib, thalidomide, and dexamethasone.

TABLE 92.9 World Health Organization Classification of Non-Hodgkin's Lymphoma

**PRECURSOR B- AND T-CELL NEOPLASMS**

Precursor B-lymphoblastic leukemia/lymphoma  
 Precursor T-lymphoblastic leukemia/lymphoma

**MATURE B-CELL NEOPLASMS<sup>a</sup>**

Chronic lymphocytic leukemia/small lymphocytic lymphoma  
 B-cell prolymphocytic leukemia  
 Lymphoplasmacytic lymphoma/Waldenström macroglobulinemia  
 Splenic marginal zone B-cell lymphoma  
 Hairy cell leukemia  
 Splenic B-cell lymphoma/leukemia, unclassifiable  
 Splenic diffuse red pulp small B-cell lymphoma  
 Hairy cell leukemia-variant  
 Plasma cell neoplasms  
 Monoclonal gammopathy of undetermined significance (MGUS)  
 Plasma cell myeloma  
 Solitary plasmacytoma of bone  
 Extracranial plasmacytoma  
 Monoclonal immunoglobulin deposition diseases  
 Extranodal marginal zone B-cell lymphoma (MALT lymphoma)  
 Nodal marginal zone B-cell lymphoma  
 Follicular lymphoma  
 Primary cutaneous follicle center lymphoma  
 Mantle cell lymphoma  
 Diffuse large B-cell lymphoma (DLBCL)  
 T-cell/histiocyte-rich large B-cell lymphoma  
 Primary DLBCL of the central nervous system  
 Primary cutaneous DLBCL, leg type  
 EBV-positive DLBCL of the elderly  
 DLBCL associated with chronic inflammation  
 Lymphomatoid granulomatosis  
 Primary mediastinal (thymic) large B-cell lymphoma  
 Intravascular large B-cell lymphoma  
 ALK-positive large B-cell lymphoma  
 Plasmablastic lymphoma  
 Large B-cell lymphoma arising in HHV8-associated multicentric  
 Castleman disease  
 Burkitt lymphoma/leukemia  
 B-cell lymphoma, unclassifiable, with features intermediate between DLBCL and Burkitt lymphoma  
 B-cell lymphoma, unclassifiable, with features intermediate between DLBCL and classic Hodgkin lymphoma

**MATURE T-CELL AND NK-CELL NEOPLASMS**

T-cell prolymphocytic leukemia  
 T-cell large granular lymphocytic leukemia  
 Chronic lymphoproliferative disorder of NK cells  
 Aggressive NK-cell leukemia  
 Systemic EBV-positive T-cell lymphoproliferative diseases of childhood  
 Hydroa vacciniformelike lymphoma  
 Adult T-cell leukemia/lymphoma  
 Extranodal NK/T-cell lymphoma, nasal type  
 Enteropathy-type T-cell lymphoma  
 Hepatosplenic T-cell lymphoma  
 Subcutaneous panniculitislike T-cell lymphoma  
 Mycosis fungoides  
 Sézary syndrome  
 Primary cutaneous CD30-positive T-cell lymphoproliferative disorders  
 Primary cutaneous anaplastic large cell lymphoma  
 Lymphomatoid papulosis

*Continued on following page*

**TABLE 92.9 World Health Organization Classification of Non-Hodgkin's Lymphoma (Continued)**

Primary cutaneous peripheral T-cell lymphomas, rare subtypes  
 Primary cutaneous gamma-delta T-cell lymphoma  
 Primary cutaneous CD8-positive aggressive epidermotropic cytotoxic T-cell lymphoma  
 Primary cutaneous CD4-positive small/medium T-cell lymphoma  
 Peripheral T-cell lymphoma, not otherwise specified  
 Angioimmunoblastic T-cell lymphoma  
 Anaplastic large cell lymphoma, ALK-positive  
 Anaplastic large cell lymphoma, ALK-negative

**IMMUNODEFICIENCY-ASSOCIATED LYMPHOPROLIFERATIVE DISORDERS**

Lymphoproliferative diseases associated with primary immune disorders  
 Lymphomas associated with HIV infection  
 Posttransplant lymphoproliferative disorders (PTLD)  
 Plasmacytic hyperplasia and infectious mononucleosis–like PTLD  
 Polymorphic PTLD  
 Monomorphic PTLD  
 Classic Hodgkin lymphoma–type PTLD  
 Other iatrogenic immunodeficiency-associated lymphoproliferative disorders

MALT, mucosa-associated lymphoid tissue; ALK, anaplastic lymphoma kinase; HHV8, human herpesvirus-8; NK, natural killer; EBV, Epstein-Barr virus; HIV, human immunodeficiency virus.

\*B- and T/NK-cell neoplasms are grouped according to major clinical presentations (predominantly disseminated/leukemic, primary extranodal, predominantly nodal).

Source: Reprinted with permission from DeVita VT et al, eds. *DeVita, Hellman, and Rosenberg's Cancer: Principles and Practice of Oncology*. 9th ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2011.

- NHL is divided into categories on the basis of cell of origin (B, T, natural killer), histology (low, intermediate, high grade), immunophenotypic characteristics, cytogenetic abnormalities, and natural history. More than 80% of NHLs are B-cell neoplasms.
- Morphologic features of the lymph node (e.g., cell type, size, and appearance) help establish the subtype of lymphoma and best treatment option. Staging is important for selection of therapy (Table 92.10). In general, stage I or II is referred to as limited disease; stage III or IV is considered advanced disease.
- Presenting features of common NHLs are shown in Table 92.11. Fever, night sweats, and weight loss are defined as B-symptoms.

**TABLE 92.10 Ann Arbor Staging System**

Stage	Description <sup>a</sup>
I	Involvement of a single lymph node region or a single extralymphatic organ or site (IE)
II	Involvement of two or more lymph node regions on the same side of the diaphragm (II) or localized involvement of an extralymphatic organ or site (IIE)
III	Involvement of lymph node regions on both sides of the diaphragm (III) or localized involvement of an extralymphatic organ or site (IIIE) or spleen (IIIS) or both (IIISE)
IV	Diffuse or disseminated involvement of one or more extralymphatic organs with or without associated lymph node involvement. Bone marrow and liver involvement are always stage IV.

<sup>a</sup>Identification of the presence or absence of symptoms should be noted with each stage designation: A, asymptomatic; B, fever, sweats, weight loss >10% of body weight.

Source: Reprinted with permission from DeVita VT et al, eds. *DeVita, Hellman, and Rosenberg's Cancer: Principles and Practice of Oncology*. 9th ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2011.

TABLE 92.11 Presenting Clinical Features of the Common Non-Hodgkin Lymphomas

	Frequency %	Age (Years)	Stage %				Extranodal Involvement %	Bone Marrow Involvement %	B-Symptoms %	GI Involvement %	Elevated LDH %	International Prognostic Index %		
			1	2	3	4						0/1	2/3	4/5
Diffuse Large B-Cell	31	64	25	29	13	33	71	16	33	18	53	35	46	9
Follicular	22	59	18	15	16	51	64	42	28	3	30	45	48	7

Source: Armitage JO, Weisenburger DD. New Approach to classifying non-Hodgkin's lymphomas: clinical features of the major histologic subtypes. Non-Hodgkin's Lymphoma Classification Project. *J Clin Oncology*. 1998;16(8):2780. Uses Revised European & American Lymphoma Classification.



- Treatment:
  - Aggressive and highly aggressive B-cell NHLs are potentially curable.
  - Patients with localized, nonbulky (<10 cm) stage I or II DLBC lymphoma without B-symptoms are typically treated with rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) for three to six cycles with or without radiotherapy.
  - The standard treatment of patients with advanced disease (bulky stage II or stage III or IV) is R-CHOP for six cycles.
  - High-dose chemotherapy immediately followed by autologous HCT should be considered for patients who relapse after conventional chemotherapy. Salvage chemotherapy is given before HCT to ensure the disease is sensitive to additional cytotoxic therapy. Allogeneic HCT may be considered for patients who are not good candidates for autologous HCT.
  - Highly aggressive NHL (e.g., lymphoblastic or Burkitt lymphoma) progress rapidly and metastasize to the central nervous system. Regimens similar to those for ALL are used.

## Hodgkin Lymphoma

- Hodgkin lymphoma (HL) is classified into two distinct diseases: classical HL and lymphocyte-predominant HL.
- Patients present with lymphadenopathy typically in a contiguous pattern; extranodal involvement is less common. B-symptoms may also be present (fatigue, cough, loss of appetite, abdominal discomfort).
- Tumor staging is done to guide treatment (Table 92.12).

TABLE 92.12 Cotswolds Staging Classification for Hodgkin Lymphoma

Stage	Description
I	Involvement of a single lymph node region or lymphoid structure (e.g., spleen, thymus, Waldeyer's ring) or involvement of a single extralymphatic site (IE).
II	Involvement of two or more lymph node regions on the same side of the diaphragm (hilar nodes, when involved on both sides, constitute stage II disease); localized contiguous involvement of only one extranodal organ or site and lymph node region(s) on the same side of the diaphragm (IIE). The number of anatomic regions involved should be indicated by a subscript (e.g., II3).
III	Involvement of lymph node regions on both sides of the diaphragm (III), which may also be accompanied by involvement of the spleen (IIIS) or by localized contiguous involvement of only one extranodal organ site (IIIE) or both (IIISE)
III <sub>1</sub>	With or without involvement of splenic, hilar, celiac, or portal nodes
III <sub>2</sub>	With involvement of para-aortic, iliac, and mesenteric nodes
IV	Diffuse or disseminated involvement of one or more extranodal organs or tissues, with or without associated lymph node involvement

### DESIGNATIONS APPLICABLE TO ANY DISEASE STAGE

A	No symptoms
B	Fever (temperature >38°C), drenching night sweats, unexplained loss of >10% body weight within the preceding 6 months
X	Bulky disease (a widening of the mediastinum by more than one-third or the presence of a nodal mass with a maximal dimension >10 cm)
E	Involvement of a single extranodal site that is contiguous or proximal to the known nodal site
CS	Clinical stage
PS	Pathologic stage (as determined by laparotomy)

Source: Reprinted with permission from DeVita VT et al, eds. *DeVita, Hellman, and Rosenberg's Cancer: Principles and Practice of Oncology*. 9th ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2011.

- Treatment:
  - HL is highly responsive to treatment, even in advanced stages.
  - Initial treatment may include radiation, combination chemotherapy, or combined chemotherapy/radiation. The standard of care is doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD). Cycles are given every 28 days; all patients should continue treatment for two cycles beyond documentation of complete remission.
  - Patients with relapsed disease can opt for salvage chemotherapy with or without radiation therapy, or high-dose chemotherapy with stem cell support.

# Breast Cancer\*

## General Principles

- Breast cancer, a hormonally mediated disease, is the most common malignancy in American women and the second leading cause of cancer-related mortality.

## Classification

- Two common histologic types are ductal and lobular. Both may be subclassified as invasive or carcinoma in situ (noninvasive).
- Inflammatory breast cancer is an aggressive form of disease (sudden onset, inflamed breast tissue, redness, and change in skin appearance).

## Risk Factors

- Several risk factors are associated with the development of breast cancer (Table 93.1).

## Patient Assessment

- Standardized screening methods (clinical breast exam, mammography, and breast self-examination) have increased the likelihood of early detection.
- Women considered high risk for breast cancer may undergo prophylactic mastectomy or chemoprevention to reduce, but not eliminate, the risk of developing breast cancer.
- Typical presentation involves identification of a painless lump, nipple discharge or retraction, or skin changes of the breast.
- Workup includes radiographic examination, patient history, and physical examination. Biopsy should be done to diagnose disease. Full radiologic testing should be done to assess for metastatic disease (e.g., CT scan of the chest, abdomen, and pelvis, and bone scan). Common places for metastases are bone, lung, liver, lymph nodes, and brain.

## Goals of Therapy

- Early-stage disease is highly curable. In patients with metastatic disease, the goal is palliation of symptoms and improvement in quality of life.

## Treatment

- Treatment depends on stage of disease (Table 93.2). Other factors include estrogen- or progesterone receptor status (ER, PR) and HER<sub>2</sub> status.
- Treatment options include surgery, radiation, hormonal, biologic, or cytotoxic chemotherapy. Surgery is definitive treatment in early-stage disease. Radiation may be offered in addition to surgery when the tumor is >5 cm in size, if there are >4 positive lymph nodes, or if positive tissue margins are present. Neoadjuvant therapy should be used for large tumors to reduce tumor size.

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\*The reader is referred to Chapter 93, Breast Cancer, written by Kellie L. Jones, PharmD, BCOP, in the 10th edition of *Applied Therapeutics: The Clinical Use of Drugs* for a more in-depth discussion. All notations to reference numbers are based on the reference list at the end of that chapter. The editor of this handbook expresses her thanks to Dr. Jones and acknowledges that this chapter is based on her work.

TABLE 93.1 Risk Factors for Developing Breast Cancer

## KNOWN RISK FACTORS

Gender: female > male  
 Personal history of breast cancer  
 Family history of breast cancer (first-degree relatives)  
 Benign breast “cancer” (i.e., atypical hyperplasia)  
 Early menarche (<12 years of age), late menopause (>55 years of age)  
 Late first pregnancy ( $\geq 30$  years) or no pregnancy  
 Advancing age  
 Long-term use of hormone-replacement therapy (estrogen)  
 Previous chest wall irradiation

## POSSIBLE RISK FACTORS

Alcohol  
 Obesity  
 High-fat diet

Sources: Carlson RW et al. Invasive breast cancer. *J Natl Compr Canc Netw*. 2011;9:136; Chlebowski RT et al. Influence of estrogen plus progestin on breast cancer and mammography in healthy postmenopausal women: the women’s health initiative randomized trial. *JAMA*. 2003;289:3243.

- Systemic adjuvant chemotherapy, hormonal therapy, or biologic therapy is used to manage microscopic disease and diminish the chance of recurrence post-surgery or -radiation (Table 93.3).
- Many combination chemotherapy regimens are used in the adjuvant setting (Table 93.4). Side effects of the various agents are discussed in Chapter 89 (Table 89.14). Anthracycline-containing regimens are most commonly used. Taxanes should be given to patients with lymph node–positive disease. Trastuzumab is used in patients with HER<sub>2</sub>-positive disease. Adjuvant hormonal therapy is the treatment of choice for ER/PR positive disease (Table 93.5). Aromatase inhibitors should only be used in postmenopausal women (Table 93.6).
- **Metastatic Disease**
  - Choice of therapy depends on site of disease and other factors (e.g., ER/PR status). Different agents from those used in the adjuvant setting should be used. Commonly used agents are shown in Table 93.7.

TABLE 93.2 American Joint Committee on Cancer Staging for Breast Cancer

Stage	T	N	M
0	Tis	N0	M0
I	T1	N0	M0
II	T0–T3	N0–N1	M0
IIIA	T0–T3	N1–N2	M0
IIIB	T4	N0–N2	M0
IIIC	Any T	N3	M0
IV	Any T	Any N	M1

M, metastatic disease; N, presence of lymph nodes; N0, no lymph node involvement; N1, movable ipsilateral lymph nodes; N2, ipsilateral axillary lymph nodes (fixed or matted); or clinical ipsilateral internal mammary nodes with no axillary lymph node involvement; N3, ipsilateral infraclavicular lymph nodes, clinical ipsilateral internal mammary lymph nodes, clinical axillary lymph nodes, or ipsilateral supraclavicular lymph nodes with or without axillary or internal mammary lymph node involvement; T, tumor size; Tis, carcinoma in situ; T1,  $\leq 2$  cm; T2,  $>2$  to 5 cm; T3,  $>5$  cm; T4, any size with skin invasion or direct invasion to the chest wall.

Source: Singletary SE et al. Revision of the American Joint Committee on Cancer staging system for breast cancer. *J Clin Oncol*. 2002;20:3628.

**TABLE 93.3 Overview of the Selection of Adjuvant Treatment**

LYMPH NODE–NEGATIVE DISEASE	Adjuvant Hormonal Therapy		Adjuvant Chemotherapy <sup>a</sup>
	ER/PR (+)	ER/PR (–)	
<0.5 cm	Yes	No	No
0.6–1 cm <sup>b</sup>	Yes	No	Consider
>1 cm	Yes	No	Yes
LYMPH NODE–POSITIVE DISEASE	ER/PR (+)	ER/PR (–)	
	Yes	No	Yes

<sup>a</sup>Give trastuzumab therapy if the patient is HER<sub>2</sub> (+) and no contraindications.

<sup>b</sup>Consider Oncotype DX testing: low recurrence score (<18) = adjuvant hormonal therapy; intermediate recurrence score (18–30) = adjuvant hormonal therapy +/- chemotherapy; high recurrence score (≥31) = adjuvant hormonal therapy + chemotherapy.

Source: National Comprehensive Cancer Network. Clinical practice guidelines in oncology. *Breast Cancer*. v2. <http://www.nccn.org>. Accessed June 20, 2011.

- Biologic and targeted therapies (e.g., trastuzumab, lapatinib) are options for metastatic disease.
- Chemotherapy is continued as long as there is benefit and toxicities are tolerated.
- Response to therapy should be monitored periodically; tumor markers are commonly used (see Chapter 89, Table 89.13).

**TABLE 93.4 Common Adjuvant Chemotherapy Regimens**

Regimen	Schedule (No. of Weeks between Cycles)	No. of Cycles
Cyclophosphamide (C)	4	6
Methotrexate (M)		
5-Fluorouracil (F), classic (oral)		
CMF (intravenous)	3	9–12
Cyclophosphamide (C)	4	6
Doxorubicin (A)		
5-Fluorouracil (F) (oral)		
Cyclophosphamide (C)	3–4	6
Doxorubicin (A)		
5-Fluorouracil (F)		
Cyclophosphamide (C)	3	6
Epirubicin (E)		
5-Fluorouracil (F)		
Docetaxel (T)	4	6
Doxorubicin (A)		
Cyclophosphamide (C)		
Doxorubicin (A) →	3 → 3	4 → 8
Cyclophosphamide (C)		
Methotrexate (M)		
5-Fluorouracil (F)		
Doxorubicin (A)	3	4–6
Cyclophosphamide (C)		
Doxorubicin (A)	3 → 3	4 → 4
Cyclophosphamide (C) →		
Paclitaxel (P)		

TABLE 93.4 Common Adjuvant Chemotherapy Regimens (continued)

Regimen	Schedule (No. of Weeks between Cycles)	No. of Cycles
Doxorubicin (A) → Paclitaxel (P) → Cyclophosphamide (C)	3 → 3 → 3	4 → 4 → 4
Dose dense <sup>a</sup> Doxorubicin (A) Cyclophosphamide (C) → Paclitaxel (P)	2 → 2	4 → 4
Dose dense <sup>a</sup> Doxorubicin (A) → Paclitaxel (P) → Cyclophosphamide (C)	2 → 2 → 2	4 → 4 → 4

A, adriamycin; C, cyclophosphamide; E, epirubicin; F, fluorouracil; M, methotrexate; P, paclitaxel; T, docetaxel; →, followed by.

<sup>a</sup>Dose dense, given every 2 weeks instead of every 3 weeks. See source document for specific dosing.

Source: National Comprehensive Cancer Network. Clinical practice guidelines in oncology. *Breast Cancer*. v2. <http://www.nccn.org>. Accessed April 22, 2011.

TABLE 93.5 Overview of Adjuvant Hormonal Therapy

Hormone receptor-positive breast cancer in pre- or perimenopausal patients	Tamoxifen for an initial duration of 5 years	If women become definitively postmenopausal, they should be offered continued tamoxifen for a total duration of 10 years or switching to up to 5 years of an aromatase inhibitor (AI) for a total duration of up to 10 years of adjuvant endocrine therapy.
Postmenopausal at time of therapy initiation should be one of the four options:	<ol style="list-style-type: none"> <li>1. Tamoxifen for a duration of 10 years</li> <li>2. An AI for a duration of 5 years</li> <li>3. Tamoxifen for an initial duration of 5 years, then switching to an AI for up to 5 years, for a total duration of up to 10 years of adjuvant endocrine therapy</li> <li>4. Tamoxifen for a duration of 2–3 years and switching to an AI for up to 5 years, for a total duration of up to 7–8 years of adjuvant endocrine therapy</li> </ol>	

Source: Adjuvant Endocrine Therapy for Women with Hormone Receptor-Positive Breast Cancer. [http://www.asco.org/sites/www.asco.org/files/adj\\_end\\_update\\_summary\\_of\\_recs\\_table\\_2014\\_0.pdf](http://www.asco.org/sites/www.asco.org/files/adj_end_update_summary_of_recs_table_2014_0.pdf)

TABLE 93.6 Aromatase Inhibitors

Type	Dose	Toxicities
<b>NONSTEROIDAL</b>		
Anastrozole	1 mg daily PO	Common toxicities: myalgias/arthralgias, hot flashes, osteoporosis
Letrozole	2.5 mg daily PO	
<b>STEROIDAL</b>		
Exemestane	25 mg daily PO	Common toxicities: myalgias/arthralgias, increased sweating, hot flashes, osteoporosis, insomnia, headache

PO, orally.

Sources: Jones KL, Buzdar AU. A review of adjuvant hormonal therapy in breast cancer. *Endocr Relat Cancer*. 2004;11:391; Buzdar AU, Howell A. Advances in aromatase inhibitors: clinical efficacy and tolerability in the treatment of breast cancer. *Clin Cancer Res*. 2001;7:2620.

**TABLE 93.7 Commonly Used Chemotherapy Agents in the Metastatic Setting**

SEQUENTIAL OR SINGLE AGENT	Doxorubicin, epirubicin Liposomal doxorubicin, paclitaxel Docetaxel, capecitabine Vinorelbine, gemcitabine Albumin-bound paclitaxel, eribulin
COMBINATION CHEMOTHERAPY	FAC/CAF, FEC AC EC Doxorubicin/docetaxel CMF Doxorubicin/paclitaxel, GT Docetaxel/capecitabine Ixabepilone/capecitabine
SINGLE-AGENT CHEMOTHERAPY + TRASTUZUMAB	Docetaxel/trastuzumab TCH Vinorelbine/trastuzumab capecitabine/trastuzumab
IF PREVIOUSLY RECEIVED TRASTUZUMAB	Lapatinib/capecitabine Trastuzumab + other first-line agents Trastuzumab/capecitabine Trastuzumab/lapatinib
SINGLE-AGENT THERAPY USED AFTER FAILING STANDARD OPTIONS LISTED HERE	Cyclophosphamide mitoxantrone Cisplatin etoposide (oral) Vinblastine fluorouracil (continuous infusion) Ixabepilone

A, doxorubicin; C, cyclophosphamide; E, epirubicin; F, fluorouracil; G, gemcitabine; H, trastuzumab; M, methotrexate; T, paclitaxel.

Source: National Comprehensive Cancer Network. Clinical practice guidelines in oncology. *Breast Cancer*. v2. <http://www.nccn.org>. Accessed April 22, 2011.

# Lung Cancer\*

## General Principles

- Lung cancer peaks in the seventh decade of life. It is classified as non–small cell lung cancer (NSCLC) and small cell lung cancer (SCLC); 85% of lung cancers are NSCLC.
  - NSCLC is further classified by tumor tissue histology: squamous cell or nonsquamous cell (adenocarcinoma and large cell).
  - SCLC has a more rapid doubling time and early widespread metastases.
- Chances for survival increase if disease is detected early. No effective screening methods are available.

## Risk Factors

- Smoking is the biggest risk factor; risk is proportional to the number of pack years. Risk decreases over time for former smokers after smoking cessation.
- Other risk factors include occupational or environmental exposures, radon, asbestos, certain metals (chromium, cadmium), various organic chemicals, radiation, air pollution, history of tuberculosis, and genetic factors.

## Patient Assessment

- Initial signs and symptoms vary according to location and stage of disease (Table 94.1). Many patients are asymptomatic on initial diagnosis. Symptoms may be masked by concurrent conditions (e.g., chronic obstructive pulmonary disease).
- Staging is done to determine prognosis and guide treatment (Tables 94.2 and 94.3).
- Patients with SCLC may experience superior vena cava syndrome (a serious complication requiring immediate medical attention) or paraneoplastic syndromes (e.g., SIADH, Cushing syndrome, neurologic paraneoplastic syndrome).

## Treatment

### NON–SMALL CELL LUNG CANCER

- Treatments include surgery, radiotherapy, and chemotherapy. Treatment decisions should be individualized and based on disease stage, tumor histology (e.g., adenocarcinoma, squamous), presence of molecular marker mutations (e.g., epidermal growth factor receptor), performance status, comorbidities, and patient preference.
- Surgery is the best treatment modality for patients with stages I, II, or early stage III disease. Neoadjuvant chemotherapy can be used to reduce tumor burden before surgery.

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\*The reader is referred to Chapter 94, Lung Cancer, by Mark N. Kirstein, PharmD, Robert A. Kratzke, MD, and Arkadiusz Z. Dudek, MD, PhD, in the 10th edition of *Applied Therapeutics: The Clinical Use of Drugs* for a more in-depth discussion. All notations to reference numbers are based on the reference list at the end of that chapter. The editor of this handbook expresses her thanks to Drs. Kirstein, Kratzke, and Dudek and acknowledges that this chapter is based on their work.



**TABLE 94.1 Common Selected Signs and Symptoms for Lung Cancer**

- Cough
- Hemoptysis
- Wheeze
- Dyspnea
- Pain (e.g., chest wall)
- Obstruction of vital structures (e.g., esophagus, superior vena cava)

Note: Symptoms are highly dependent on tumor size, location within the chest cavity, and presence of metastases.

**TABLE 94.2 Definitions for T, N, M Descriptors in the IASLC Staging Classification<sup>a</sup>**

TNM	Descriptions	Subgroup <sup>b</sup>
<b>T (PRIMARY TUMOR)</b>		
T0	No primary tumor	
T1	Tumor $\leq 3$ cm <sup>c</sup> , surrounded by lung or visceral pleura, not more proximal than the lobar bronchus	
T1a	Tumor $\leq 2$ cm <sup>c</sup>	T1a
T1b	Tumor $> 2$ but $\leq 3$ cm <sup>c</sup>	T1b
T2	Tumor $> 3$ but $\leq 7$ cm <sup>c</sup> or tumor with any of the following <sup>d</sup> : Invades visceral pleura, involves main bronchus $\geq 2$ cm distal to the carina, atelectasis/obstructive pneumonia extending to hilum but not involving the entire lung	
T2a	Tumor $> 3$ but $\leq 5$ cm <sup>c</sup>	T2a
T2b	Tumor $> 5$ but $\leq 7$ cm <sup>c</sup>	T2b
T3	Tumor $> 7$ cm <sup>c</sup> or directly invading chest wall, diaphragm, phrenic nerve, mediastinal pleura, parietal pericardium, or tumor in the main bronchus $< 2$ cm distal to the carina <sup>e</sup> , or atelectasis/obstructive pneumonitis of entire lung, or separate tumor nodule(s) in the same lobe	T3 <sup>&gt;7</sup> T3 <sub>inv</sub> T3 <sub>Centr</sub> T3 <sub>Satell</sub>
T4	Tumor of any size with invasion of heart, great vessels, trachea <sup>e</sup> , recurrent laryngeal nerve, esophagus, vertebral body, or carina <sup>e</sup> ; or separate tumor nodule(s) in a different ipsilateral lobe	T4 <sub>Inv</sub>
<b>N (REGIONAL LYMPH NODES)</b>		
N0	No regional node metastasis	
N1	Metastasis in ipsilateral peribronchial and/or perihilar lymph nodes and intrapulmonary nodes, including involvement by direct extension	
N2	Metastasis in ipsilateral mediastinal and/or subcarinal lymph node(s)	
N3	Metastasis in contralateral mediastinal, contralateral hilar, ipsilateral or contralateral scalene or supraclavicular lymph node(s)	
<b>M (DISTANT METASTASIS)</b>		
M0	No distant metastasis	
M1a	Separate tumor nodule(s) in a contralateral lobe; or tumor with pleural nodules or malignant pleural dissemination <sup>f</sup>	M1a <sub>Contr, Nod</sub> M1a <sub>pl, Dissem</sub>
M1b	Distant metastasis	M1b

**TABLE 94.2 Definitions for T, N, M Descriptors in the IASLC Staging Classification (Continued)**

TNM	Descriptions	Subgroup <sup>b</sup>
<b>SPECIAL SITUATIONS</b>		
TX, NX, MX	T, N, or M status not able to be assessed	
Tis	Focus of in situ cancer	Tis
T1 <sup>c</sup>	Superficial spreading tumor of any size but confined to the wall of the trachea or mainstem bronchus	T1 <sub>ss</sub>

<sup>a</sup>Reflects the IASLC Staging Committee's recommendations and not necessarily the UICC 7th Edition Staging System.

<sup>b</sup>These subgroup labels are not defined in the IASLC publications, but are added here to facilitate a clear discussion.

Goldstraw et al. *J Thorac Oncol.* 2007;2:706–714; Rami-Porta et al. *J Thorac Oncol.* 2007;2:593; Postmus et al. *J Thorac Oncol.* 2007;2:686; Rusch et al. *J Thorac Oncol.* 2007;2:603.

<sup>c</sup>In greatest dimension.

<sup>d</sup>T2 tumors with these features are classified as T2a if ≤5 cm.

<sup>e</sup>The uncommon superficial spreading tumor in central airways is classified as T1.

<sup>f</sup>Pleural effusions are excluded that are cytologically negative, nonbloody, transudative, and clinically judged not to be due to cancer.

IASLC, International Association for the Study of Lung Cancer; TNM, tumor, node, metastasis.

Source: Reprinted with permission from Detterbeck FC et al. Anatomy, biology and concepts, pertaining to lung cancer stage classification. *J Thorac Oncol.* 2009;4:437.

- Adjuvant chemotherapy is recommended for patients with stage II or III disease at surgery and for larger (>4 cm) tumors (Table 94.4). Most regimens are cisplatin- or carboplatin-based doublets, given for four to six cycles.
- Targeted therapies (antiangiogenesis and anti-EGFR) are useful for advanced-stage disease (Table 94.5). ALK-positive may receive crizotinib.
- Patients with squamous cell non–small cell lung cancer should not receive bevacizumab.

**TABLE 94.3 Stage Groups in the IASLC Staging Classification<sup>a</sup>**

Stage Group	T	N	M
I			
Ia	T1a, b	N0	M0
Ib	T2a	N0	M0
II			
IIa	T1a, b T2a	N1 N1	M0 M0
IIb	T2b T2b T3	N0 N1 N0	M0 M0 M0
III			
IIIa	T1–3 T3 T4	N2 N1 N0,1	M0 M0 M0
IIIb	T4 T1–4	N2 N3	M0 M0
IV	T <sub>Any</sub>	N <sub>Any</sub>	M1a, b

<sup>a</sup>Reflects the IASLC Staging Committee's recommendations and not necessarily the UICC 7th Edition Staging System. IASLC, International Association for the Study of Lung Cancer; TNM, tumor node metastasis.

Source: Reprinted with permission from Detterbeck FC et al. Anatomy, biology and concepts, pertaining to lung cancer stage classification. *J Thorac Oncol.* 2009;4:437.

TABLE 94.4 Adjuvant Chemotherapy Regimens for Non–Small Cell Lung Cancer

Regimen	Schedule
Cisplatin, days 1 and 8	Every 28 days for four cycles <sup>18</sup>
Vinorelbine, days 1, 8, 15, 22	Every 28 days for four cycles <sup>19,20</sup>
Cisplatin, day 1	Every 21 days for four cycles <sup>18</sup>
Vinorelbine, days 1, 8, 15, 22	Every 28 days for four cycles <sup>19,20</sup>
Cisplatin, day 1	Every 21 days for four cycles <sup>18</sup>
Vinorelbine, days 1, 8	Every 28 days for four cycles <sup>20</sup>
Cisplatin, day 1	Every 28 days for four cycles <sup>20</sup>
Etoposide, days 1–3	Every 21 days for four cycles <sup>20</sup>
Cisplatin, days 1, 22, 43, 64	Every 21 days for four cycles <sup>20</sup>
Vinblastine, days 1, 8, 15, 22, then every 2 weeks after day 43	Every 21 days <sup>21</sup>
Paclitaxel on, day 1	Every 21 days <sup>21</sup>
Carboplatin, day 1	
<b>OTHER ACCEPTABLE REGIMENS</b>	
Cisplatin, day 1	Every 21 days <sup>22</sup>
Gemcitabine, days 1, 8	Every 21 days <sup>23</sup>
Cisplatin, day 1	Every 21 days <sup>23</sup>
Docetaxel, day 1	Every 21 days for four cycles <sup>22</sup>
Pemetrexed, day 1	Every 21 days for four cycles <sup>22</sup>
Cisplatin, day 1 for nonsquamous NSCLC	

NSCLC, non–small cell lung cancer.

TABLE 94.5 Representative Regimens for Advanced or Metastatic Non–Small Cell Lung Cancer

Regimen	Schedule
Cisplatin, day 1	Every 21 days <sup>30</sup>
Paclitaxel, day 1	Every 21 days <sup>30</sup>
Cisplatin, day 1	Every 28 days <sup>30,31</sup>
Gemcitabine, days 1, 8, 15	Every 21 days <sup>30</sup>
Cisplatin, day 1	Every 21 days <sup>30</sup>
Docetaxel, day 1	Every 21 days <sup>30</sup>
Paclitaxel, day 1	Every 21 days <sup>30</sup>
Carboplatin, day 1	Every 21 days <sup>32</sup>
Cisplatin, day 1	Every 21 days <sup>32</sup>
Vinorelbine, days 1, 8	Every 21 days <sup>32</sup>
Cetuximab weekly	Every 21 days <sup>33</sup>
Nonsquamous histology	Every 21 days <sup>33</sup>
Cisplatin, day 1	Every 21 days <sup>33</sup>
Gemcitabine, days 1, 8	Every 21 days <sup>33</sup>
Bevacizumab, day 1	Every 21 days <sup>34</sup>
Paclitaxel, day 1	Every 21 days <sup>34</sup>
Carboplatin, day 1	Every 21 days <sup>34</sup>
Bevacizumab, day 1	Every 21 days <sup>34</sup>
Pemetrexed, day 1	Every 21 days <sup>31</sup>
Cisplatin, day 1	Every 21 days <sup>31</sup>
Erlotinib daily for known EGFR mutation status	Until disease progression or unacceptable toxicity <sup>35</sup>

EGFR, epidermal growth factor receptor.

TABLE 94.6 Representative Chemotherapy Regimens for Small Cell Lung Cancer

**LIMITED-STAGE SCLC (MAXIMUM 4–6 CYCLES)**

Cisplatin, day 1  
 Etoposide, days 1, 2, 3, and then every 21 days<sup>69</sup>  
 Carboplatin, day 1  
 Etoposide, days 1–4, then every 21 days<sup>72</sup>

**EXTENSIVE-STAGE SCLC (MAXIMUM 4–6 CYCLES)**

Cisplatin, day 1  
 Etoposide days 1–4, then every 21 days<sup>72</sup>  
 Carboplatin, day 1  
 Etoposide, days 1, 2, 3, then every 21 days<sup>73</sup>  
 Cisplatin, day 1  
 Irinotecan days 1, 8, 15, then every 28 days<sup>74</sup>  
 Cisplatin, day 1  
 Irinotecan days 1, 8, then every 21 days<sup>75</sup>

**CHEMOTHERAPY FOR RELAPSED DISEASE<sup>58</sup>**

Clinical trial preferred  
 If relapse occurs <2–3 months after first-line and PS 0–2: ifosfamide, paclitaxel, docetaxel, gemcitabine, irinotecan, or topotecan  
 If relapse occurs >2–3 months up to 6 months: topotecan (oral or IV), irinotecan, paclitaxel, docetaxel, oral etoposide, vinorelbine, gemcitabine, or cyclophosphamide/doxorubicin/vincristine  
 If relapse occurs >6 months: original regimen

PS, performance status; SCLC, small cell lung cancer.

**SMALL CELL LUNG CANCER**

- Chemotherapy and radiotherapy are the primary treatments. Surgical resection provides limited benefit. The chemotherapy regimen is based on staging (Table 94.6).
- Most regimens are cisplatin- or carboplatin-based doublets in combination with etoposide or irinotecan for extensive-stage disease.
- Prophylactic cranial irradiation after remission can decrease brain metastases.

# Colorectal Cancer\*

## General Principles

- Colorectal cancer is the malignant growth of tumor that begins from the inner wall of the colon or rectum. Most are classified as adenocarcinomas. Metastases most commonly occur in the liver.
- Colorectal is one of the few cancers that can be prevented by removal of precancerous tissue.

## Risk Factors

- Risk factors include age above 50 years, male sex, history of previous colonic polyps, inflammatory bowel disease, and lifestyle factors (e.g., diet high in red meat, high fat, and low fiber; sedentary lifestyle; obesity; excessive alcohol consumption; and long-term smoking).

## Patient Assessment

- Early detection through screening can reduce cancer-related mortality. Colonoscopy is the gold standard screening method. Other options include fecal screening tests, digital rectal exams, barium enemas, endoscopy, and stool DNA test. Recommendations for screening are shown in Table 95.1.
- Symptoms are often subtle and may include abdominal pain, constipation, diarrhea, bloating, other sudden changes in bowel habits, rectal bleeding, or pencil-thin stools.
- Staging of colorectal cancer is shown in Table 95.2.

## Goals of Therapy

- **Localized Disease**—to reduce risk of relapse and prolong disease-free survival by eradicating residual, undetectable disease
- **Stage IV Metastatic Disease**—prolongation of survival

## Treatment

- Surgery, radiation, and chemotherapy each have roles in localized and advanced disease. Treatment strategy depends on the location and extent of disease and goals of therapy. Surgery is generally preferred for stage I, II or III disease, and select patients with metastatic stage IV disease. Radiation is usually reserved for patients with rectal cancer.
- Adjuvant chemotherapy is typically considered for patients with stage III cancer or in those with stage II disease and high-risk features. Select regimens are shown in Table 95.3.
- Routine surveillance for 5 years after definitive therapy is essential as recurrences usually occurs within the first 2 to 3 years of completing adjuvant therapy. Carcinoembryonic antigen (CEA) can be used to monitor for recurrence of disease.

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\*The reader is referred to Chapter 95, Colorectal Cancer, written by Sachin R. Shah, PharmD, BCOP, FCCP, and Julian Hoyt Slade, III, PharmD, BCOP, in the 10th edition of *Applied Therapeutics: The Clinical Use of Drugs* for a more in-depth discussion. All notations to reference numbers are based on the reference list at the end of that chapter. The editor of this handbook expresses her thanks to Drs. Shah and Slade and acknowledges that this chapter is based on their work.

**TABLE 95.1 American Cancer Society Screening Recommendation for Colorectal Cancer by Age and Risk**

Average Risk	Begin screening at age of 50 years Annual DRE <b>and</b> FOBT/FIT (stool DNA test, interval uncertain) <b>and</b> one of the following: <ul style="list-style-type: none"> <li>• Sigmoidoscopy every 5 years</li> <li>• CT colonography every 5 years</li> <li>• Colonoscopy every 10 years</li> <li>• Barium enema every 5 years</li> </ul>
Family History	Begin screening at age of 40 years or 10 years younger from first-degree relative colorectal cancer diagnosis
Hereditary HNPCC	Begin screening at age of 20–25 years <b>or</b> 10 years younger from first-degree relative colorectal cancer diagnosis
FAP	Begin screening at age of 10–12 years
IBD, CUC, or CC	Begin screening at 8–15 years after diagnosis

CC, Crohn's colitis; CT, computed tomography; CUC, chronic ulcerative colitis; DRE, digital rectal examination; FAP, familial adenomatous polyposis; FIT, fecal immunochemical test; FOBT, fecal occult blood test; HNPCC, hereditary nonpolyposis colon cancer; IBD, inflammatory bowel disease.

- Treatment of advanced colorectal cancer includes single-agent therapy, combination chemotherapy, and biologic therapies (e.g., bevacizumab, cetuximab, panitumumab). The decision of choice of combination therapy for first- or second-line therapy is based on prior therapy, quality of life, preexisting toxicities, and comorbid conditions. Surgery is not typically an option for extensive metastatic disease.
- Use of specific predictive markers helps maximize treatment outcomes. Presence of the *KRAS* mutation is one of the most important predictive molecular markers. Patients with mutated *KRAS* do not see treatment benefit with anti-EGFR monoclonal antibodies. Tumors expressing wild-type *KRAS* often receive benefit from these therapies.

**TABLE 95.2 Colorectal Cancer Staging****T, N, M Definitions****Primary Tumor (T)****TX** Primary tumor cannot be assessed**T0** No evidence of primary tumor**Tis** Carcinoma in situ: intraepithelial or invasion of lamina propria<sup>a</sup>**T1** Tumor invades submucosa**T2** Tumor invades muscularis propria**T3** Tumor invades through the muscularis propria into pericorectal tissues**T4A** Tumor penetrates to the surface of the visceral peritoneum<sup>b</sup>**T4B** Tumor directly invades or is adherent to other organs or structures<sup>b,c</sup>**Regional Lymph Nodes (N)<sup>d</sup>****NX** Regional lymph nodes cannot be assessed**N0** No regional lymph node metastasis**N1** Metastasis in 1–3 regional lymph nodes**N1A** Metastasis in 1 regional lymph node**N1B** Metastasis in 2–3 regional lymph nodes**N1C** Tumor deposit(s) in the subserosa, mesentery, or nonperitonealized pericolic or perirectal tissues without regional nodal metastasis**N2** Metastasis in 4 or more regional lymph nodes**N2A** Metastasis in 4–6 regional lymph nodes**N2B** Metastasis in 7 or more regional lymph nodes**Distant Metastasis (M)****M0** No distant metastasis**M1** Distant metastasis*Continued on following page*

TABLE 95.2 Colorectal Cancer Staging (Continued)

**M1a** Metastasis confined to one organ or site (e.g., liver, lung, ovary, nonregional node)  
**M1b** Metastases in more than one organ or site or the peritoneum

**Anatomic Stage/Prognostic Groups**

Stage	T	N	M	Dukes <sup>a</sup>	MAC <sup>e</sup>
0	Tis	N0	M0	–	–
I	T1	N0	M0	A	A
	T2	N0	M0	A	B1
IIA	T3	N0	M0	B	B2
IIB	T4a	N0	M0	B	B2
IIC	T4b	N0	M0	B	B3
IIIA	T1–T2	N1/N1c	M0	C	C1
	T1	N2a	M0	C	C1
IIIB	T3–T4a	N1/N1c	M0	C	C2
	T2–T3	N2a	M0	C	C1/C2
IIIC	T1–T2	N2b	M0	C	C1
	T4a	N2a	M0	C	C2
	T3–T4a	N2b	M0	C	C2
	T4b	N1–N2	M0	C	C3
IVA	Any T	Any N	M1a	–	–
IVB	Any T	Any N	M1b	–	–

<sup>a</sup>Tis includes cancer cells confined within the glandular basement membrane (intraepithelial) or mucosal lamina propria (intramucosal) with no extension through the muscularis mucosae into the submucosa.

<sup>b</sup>Direct invasion in T4 includes invasion of other organs or other segments of the colorectum as a result of direct extension through the serosa, as confirmed on microscopic examination (e.g., invasion of the sigmoid colon by a carcinoma of the cecum) or, for cancers in a retroperitoneal or subperitoneal location, direct invasion of other organs or structures by virtue of extension beyond the muscularis propria (i.e., a tumor on the posterior wall of the descending colon invading the left kidney or lateral abdominal wall; or a mid or distal rectal cancer with invasion of prostate, seminal vesicles, cervix, or vagina).

<sup>c</sup>Tumor that is adherent to other organs or structures, grossly, is classified cT4b. However, if no tumor is present in the adhesion, microscopically, the classification should be pT1–4a depending on the anatomical depth of wall invasion. The V and L classifications should be used to identify the presence or absence of vascular or lymphatic invasion, whereas the PN site-specific factor should be used for perineural invasion.

<sup>d</sup>A satellite peritumoral nodule in the pericolorectal adipose tissue of a primary carcinoma without histologic evidence of residual lymph node in the nodule may represent discontinuous spread, venous invasion with extravascular spread (V1/2), or a totally replaced lymph node (N1/2). Replaced nodes should be counted separately as positive nodes in the N category, whereas discontinuous spread or venous invasion should be classified and counted in the Site-Specific Factor category Tumor Deposits (TD).

<sup>e</sup>Dukes B is a composite of better (T3 N0 M0) and worse (T4 N0 M0) prognostic groups, as is Dukes C (any T N1 M0 and any T N2 M0). MAC is the modified Astler-Coller classification.

Note: cTNM is the clinical classification, pTNM is the pathologic classification. The y prefix is used for those cancers that are classified after neoadjuvant pretreatment (e.g., ypTNM). Patients who have a complete pathologic response are ypT0N0cM0, which may be similar to Stage Group 0 or I. The r prefix is to be used for those cancers that have recurred after a disease-free interval (rTNM).

Source: Used with the permission of the American Joint Committee on Cancer (AJCC), Chicago, IL. *AJCC Cancer Staging Manual*. 7th ed. Springer-Verlag: New York; 2010. www.springer.com

TABLE 95.3 Select Regimens Used in the Treatment of Localized Colon and Rectal Cancers<sup>a</sup>

Regimen Name	Dosing of Chemotherapy Agents	Cycle Description
<b>COLON AND RECTAL ADJUVANT REGIMENS</b>		
Roswell Park	Leucovorin 500 mg/m <sup>2</sup> IV for 2 hours; One hour after starting the leucovorin administer: 5'-Fluorouracil 500 mg/m <sup>2</sup> IV bolus Administered on days 1, 8, 15, 22, 29, and 36, followed by 2 weeks off	Cycle length = 56 days Repeat × 3 cycles
Mayo Clinic	Leucovorin 20 mg/m <sup>2</sup> IV bolus daily on days 1–5; 5'-Fluorouracil 425 mg/m <sup>2</sup> IV bolus daily on days 1–5	Cycle length = 28 days Repeat × 6 cycles
Simplified Infusional Biweekly 5'-FU/LV <sup>b</sup>	Leucovorin 400 mg/m <sup>2</sup> /day IV for 2 hours on day 1 5'-Fluorouracil 400 mg/m <sup>2</sup> IV bolus on day 1, then 5'-Fluorouracil 1,200 mg/m <sup>2</sup> /day IVCI × 2 days (total 2,400 mg/m <sup>2</sup> IVCI for 46–48 hours)	Cycle length = 14 days Repeat × 12 cycles
Capecitabine	Capecitabine 1,000–1,250 mg/m <sup>2</sup> /day PO BID days 1–14	Cycle length = 21 days Repeat × 8 cycles
FLOX	Leucovorin 500 mg/m <sup>2</sup> IV for 2 hours; One hour after starting the leucovorin administer: 5'-Fluorouracil 500 mg/m <sup>2</sup> IV bolus Administered on days 1, 8, 15, 22, 29, and 36 Oxaliplatin 85 mg/m <sup>2</sup> IV for 2 hours Administered on days 1, 15, and 29	Cycle length = 56 days Repeat × 3 cycles
FOLFOX <sub>4</sub>	Oxaliplatin 85 mg/m <sup>2</sup> IV for 2 hours day 1 Leucovorin 200 mg/m <sup>2</sup> /day IV for 2 hours on days 1 and 2 5'-Fluorouracil 400 mg/m <sup>2</sup> /day IV bolus on days 1 and 2 5'-Fluorouracil 600 mg/m <sup>2</sup> /day IVCI for 22 hours on days 1 and 2	Cycle length = 14 days Repeat × 12 cycles
mFOLFOX <sub>6</sub>	Oxaliplatin 85 mg/m <sup>2</sup> IV for 2 hours day 1 Leucovorin 350–400 mg/m <sup>2</sup> /day IV for 2 hours on day 1 5'-Fluorouracil 400 mg/m <sup>2</sup> IV bolus on day 1, then 5'-Fluorouracil 1,200 mg/m <sup>2</sup> /day IVCI × 2 days (total 2,400 mg/m <sup>2</sup> IVCI for 46–48 hours)	Cycle length = 14 days Repeat × 12 cycles
XELOX <sup>c</sup>	Capecitabine 1,000 mg/m <sup>2</sup> PO BID days 1–14 Oxaliplatin 130 mg/m <sup>2</sup> IV every 21 days	Cycle length = 21 days Repeat × 8 cycles
CAPIRI	Capecitabine 1,000 mg/m <sup>2</sup> bid orally for 14 days and Oxaliplatin 130 mg/m <sup>2</sup> on day 1	Repeat every 21 days
CaPOX	Capecitabine 1,000 mg/m <sup>2</sup> bid orally for 14 days and Oxaliplatin 130 mg/m <sup>2</sup> on day 1	Every 21 days Maximum 8 cycles
<b>RECTAL REGIMENS COMBINED WITH RADIATION</b>		
Infusional 5'-FU	5'-Fluorouracil 225–300 mg/m <sup>2</sup> IVCI	Daily throughout radiation or Monday–Friday throughout radiation
Capecitabine	Capecitabine 825 mg/m <sup>2</sup> PO BID	Daily throughout radiation or Monday–Friday throughout radiation

<sup>a</sup>Disclaimer: Please consult specific regimen protocol for exact dosing recommendation.<sup>b</sup>Recommended as an option in NCCN guidelines.<sup>c</sup>Not in current NCCN recommendations, but data are available supporting its use in stage III disease.

BID, twice daily; 5'-FU, 5'-fluorouracil; IV, intravenous; IVCI, intravenous continuous infusion; LV, leucovorin; NCCN, National Comprehensive Cancer Network; PO, orally.



# Hematopoietic Cell Transplantation\*

## General Principles

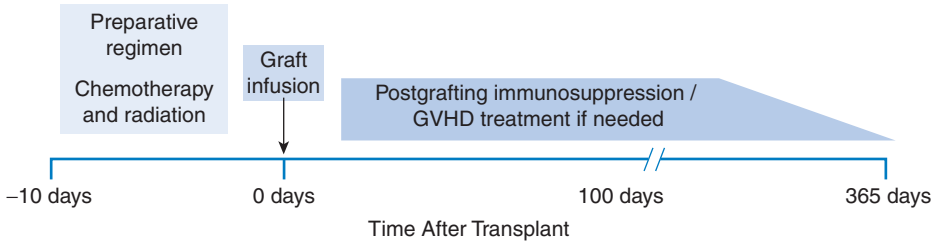
- Hematopoietic cell transplantation (HCT) is a medical procedure involving the administration of chemotherapy followed by infusion of hematopoietic stem cell into a patient to treat disease and/or restore normal hematopoiesis and lymphopoiesis. The basic schema is shown in Figure 96.1. Many diseases are treated with HCT (Table 96.1). A comparison of the types of HCTs is in Table 96.2.
- Sources of hematopoietic stem cells include bone marrow transplant (BMT), peripheral blood progenitor cells transplant (PBPC), and umbilical cord transplant (UCT). The type of transplant depends on factors including type and status of disease, availability of a compatible donor, patient age, performance status, and organ function. PBPC requires less invasive collection methods and grafts that have more rapid neutrophil and platelet recovery, fewer platelet transfusions, fewer days of antibiotics, and shorter duration of hospitalization compared with BMT.
- **Autologous HCT** involves infusion of a patient's own hematopoietic stem cells. It allows for administration of higher doses of chemotherapy, radiation, or both to treat cancer. The hematopoietic stem cells rescue the patient from otherwise dose-limiting hematopoietic toxicity.
- **Allogeneic HCT** involves transplantation of hematopoietic stem cells obtained from a donor's bone marrow, PBPC, or umbilical cord blood to a patient. Genetic compatibility between the donor and recipient, assessed through major histocompatibility complex (MHC) and human leukocyte antigen (HLA), is important to minimize the potential for bidirectional graft rejection. The risk of graft failure decreases with better matches.
- **Graft-versus-Tumor Effect (GVT)**—when the donor's cytotoxic T-lymphocytes suppress or eliminate the recipient's malignancy

## Treatment

- **Mobilization** refers to techniques used to move stem cells out of the bone marrow to increase their numbers in circulation. Hematopoietic growth factors (filgrastim, sargramostim) are used as mobilizing agents for PBPC. Myelosuppressive chemotherapy also stimulates stem cell and progenitor cell proliferation. Plerixafor is an agent approved for use in stem cell mobilization in conjunction with filgrastim. Stem cells are collected via pheresis.
- **Harvesting Allogeneic Hematopoietic Stem Cells:** Harvesting bone marrow entails a surgical procedure and is the major source for allogeneic transplants in children. Peripheral blood has largely replaced marrow for allogeneic transplants in adults. Umbilical cord transplant is an alternative stem cell source in patients who do not have a suitable related donor.

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\*The reader is referred to Chapter 96, Hematopoietic Cell Transplantation, written by Kathleen G. E. Green, MS, PharmD, and John R. Rogosheske, PharmD, in the 10th edition of *Applied Therapeutics: The Clinical Use of Drugs* for a more in-depth discussion. All notations to reference numbers are based on the reference list at the end of that chapter. The editor of this handbook expresses her thanks to Drs. Green and Rogosheske and acknowledges that this chapter is based on their work.



**Figure 96.1** Basic schema for hematopoietic stem cell transplantation. Day 0 = bone marrow, peripheral blood progenitor cell, or umbilical cord blood infusion. Postgraft immunosuppression or graft-versus-host disease (GVHD) prophylaxis for allogeneic grafts only.

- **Preparative or Conditioning Regimen**—the combination of chemotherapy and/or radiation administered before infusion of hematopoietic stem cells. Common regimens and their toxicities are shown in Tables 96.3 and 96.4.
  - **Autologous HCT:** Myeloablative preparative regimens involving the use of near-lethal doses of chemotherapy are used. The goal is to eradicate residual malignancy that is not treatable with standard chemotherapy. Profound aplasia lasts 20 to 30 days after autologous BMT or 7 to 14 days after autologous PBPCT.

**TABLE 96.1 Diseases Commonly Treated with Hematopoietic Stem Cell Transplantation<sup>a</sup>**

ALLOGENEIC	
Nonmalignant	Aplastic anemia Thalassemia major Severe combined immunodeficiency disease Wiskott-Aldrich syndrome Fanconi anemia Inborn errors of metabolism
Malignant	AML Acute lymphoblastic leukemia Chronic myeloid leukemia Myelodysplastic syndrome Myeloproliferative disorders NHL Hodgkin disease Chronic lymphocytic leukemia Multiple myeloma Juvenile myelomonocytic leukemia
AUTOLOGOUS	
Malignant	NHL Multiple myeloma AML Hodgkin disease Neuroblastoma Germ-cell tumors
Other diseases	Autoimmune disorders Amyloidosis

<sup>a</sup>Timing of HCT relative to diagnosis varies with disease. AML, acute myelogenous leukemia; NHL, non-Hodgkin lymphoma. Sources: Copelan EA. Hematopoietic stem-cell transplantation. *N Engl J Med*. 2006;354:1813; Vaughan W et al. The principles and overview of autologous hematopoietic stem cell transplantation. *Cancer Treat Res*. 2009;144:23.

TABLE 96.2 Comparison of Types of Hematopoietic Cell Transplants

Risk <sup>a</sup>	Myeloablative		Nonmyeloablative
	Autologous	Allogeneic	Allogeneic
Relapse after HCT	+++	+	+
Rejection	–	+	++
Delayed engraftment	++	+	+
GVHD	–	+	++
Infection	+	++ to +++ <sup>b</sup>	++ to +++ <sup>b</sup>
Transplant-related morbidity	+	+++	++
Transplant-related mortality	+	++	+
Cost of procedure	++	+++	++ to +++

<sup>a</sup>Risk varies depending on underlying disease, patient characteristics, and previous medical history.

<sup>b</sup>Risk of infection increases with intensity and duration of immunosuppression and/or chronic GVHD. GVHD, graft-versus-host disease; HCT, hematopoietic cell transplants.

- **Allogeneic HCT:** Myeloablative, reduced-intensity, or nonmyeloablative preparative regimens can be used. The goal is to eradicate immunologically active host tissues (lymphoid tissue and macrophages) and to prevent or minimize the development of host-versus-graft reactions. The preparative regimen is tailored to the primary disease and to the HLA compatibility between the recipient–donor pair. Reduced-intensity preparative regimens lead to lower treatment-related mortality rates, but they may be offset by higher relapse rates.
- For most chemotherapy-based preparative regimens, a rest period is needed to allow for elimination of toxic metabolites from the chemotherapy that could damage infused cells.

TABLE 96.3 Representative Myeloablative Preparative Regimens Used in Hematopoietic Stem Cell Transplantation

Type of HCT	Disease State	Regimen	Dose/Schedule
Allogeneic <sup>27</sup>	Hematologic malignancies	CY/TBI	CY 60 mg/kg/day IV on 2 consecutive days before TBI 1,000–1,575 rads fractionated for 1–7 days
Autologous <sup>28,29,30</sup>	Acute and chronic leukemias	BU/CY	BU adult 1 mg/kg/dose PO or 0.8 mg/kg/dose IV every 6 hours for 16 doses BU children <12 kg 1.1 mg/kg/dose IV every 6 hours for 16 doses CY 50 mg/kg/day IV daily for 4 days or 60 mg/kg/day IV daily for 2 days after BU
Autologous <sup>31</sup>	Non-Hodgkin lymphoma, Hodgkin disease	BEAM (carmustine/etoposide/cytarabine/melphalan)	Carmustine 300 mg/m <sup>2</sup> /day IV, 1 dose Etoposide 200 mg/m <sup>2</sup> /day BID IV for 3 days Cytarabine 100 mg/m <sup>2</sup> /day IV BID for 4 days Melphalan 140 mg/m <sup>2</sup> 1 dose

<sup>a</sup>Includes acute myelogenous leukemia, acute lymphocytic leukemia, chronic myelogenous leukemia, non-Hodgkin lymphoma, and Hodgkin disease.

BID, twice a day; BU, busulfan; CY, cyclophosphamide; IV, intravenously; PO, orally; TBI, total body irradiation.

**TABLE 96.4 Common Toxicities Associated with Myeloablative Allogeneic Hematopoietic Stem Cell Transplantation**

Early Posttransplant (<100 days)	Late Posttransplant (>100 days)
Febrile neutropenia	Increased susceptibility to infections
Nausea, vomiting, diarrhea	Endocrine disorders (hypothyroidism, hemorrhagic cystitis, infertility, growth retardation)
Mucositis	Neurocognitive changes
Veno-occlusive disease	
Renal dysfunction	
Cardiotoxicity	
Pneumonitis	Secondary malignant neoplasms
Graft rejection	Chronic GVHD
Acute GVHD	Cataracts

GVHD, graft-versus-host disease.

- **Engraftment**—the point at which a patient can maintain a sustained absolute neutrophil count (ANC) of more than 500 cells/mcL and a sustained platelet count of at least 2,000 mcL lasting 3 consecutive days without transfusions.
- **Immunosuppressive Therapy**
  - Immunosuppression is not needed with autologous HCT because the donor and recipient are the same patient (genetically identical).
  - Numerous immunosuppressive agents, alone or in combination, are used to prevent graft-versus-host disease (GVHD) in allogeneic HCT (Table 96.5). Corticosteroids are more commonly used to treat GVHD.
  - In allogeneic HCT recipients without GVHD, immunosuppressive therapy is slowly tapered and discontinued over the course of 6 to 12 months.
- **Supportive care** is directed at maintaining an adequate complete blood count, preventing or treating infection, and providing adequate nutrition.

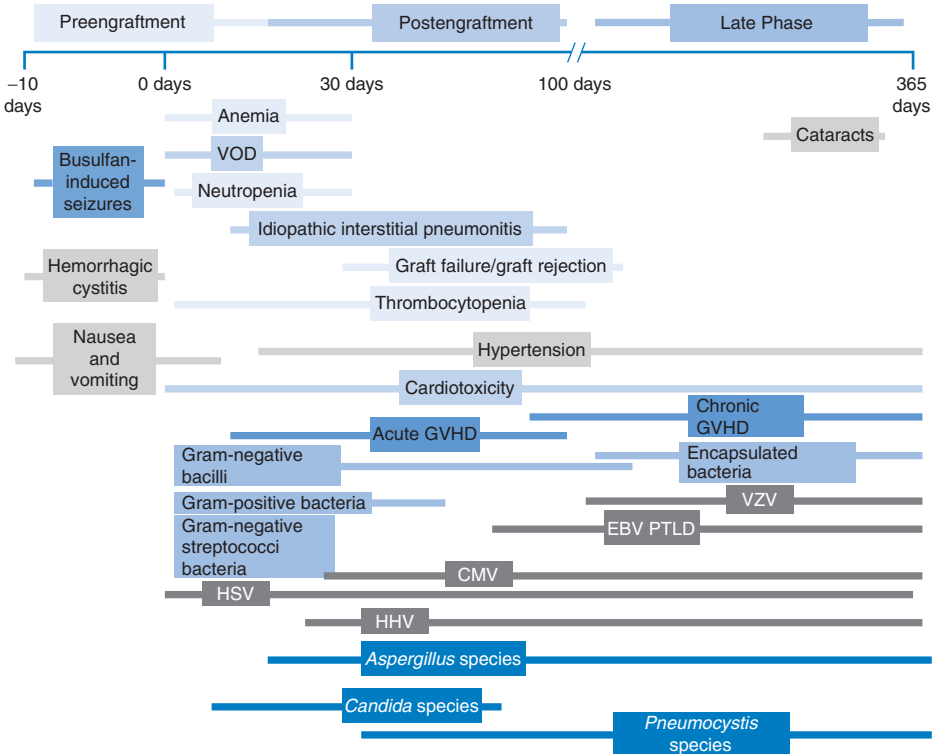
**Complications Associated with HCT**

- Toxicities vary with the preparative regimen used. Table 96.4 shows the range of toxicities that can occur, and Figure 96.2 shows the time course for complications after HCT.
- **Busulfan Seizures:** Seizures occur in about 10% of patients receiving high-dose busulfan for HCT. Seizure prophylaxis therapy is started at least 12 hours before the first busulfan dose and is discontinued 24 to 48 hours after the last dose. Phenytoin, levetiracetam, and benzodiazepines have all been used for prophylaxis.

**TABLE 96.5 Common Reduced Intensity Preparative or Nonmyeloablative Regimens and Postgrafting Immunosuppression**

Preparative Regimens	Postgrafting Immunosuppression
Fludarabine 30 mg/m <sup>2</sup> /day IV on 3 consecutive days (-4, -3, -2), TBI 2 Gy as single fraction on day 0	Cyclosporine 6.25 mg/kg PO BID, days 3 to day +100 with taper from day +100 to +180
Fludarabine 25 mg/m <sup>2</sup> /day IV for 5 days and melphalan 90 mg/m <sup>2</sup> /day IV for 2 days	Mycophenolate mofetil 15 mg/kg PO BID or TID, day +0 to +40 with taper from day +40 to +90
Fludarabine 25–30 mg/m <sup>2</sup> /day IV for 3–5 days, busulfan ≤9 mg/kg/total dose	Tacrolimus to maintain trough blood concentration of 5–10 ng/mL with methotrexate 5 mg/m <sup>2</sup> /day IV days +1, +3, +6, +11

BID, twice a day; IV, intravenous; PO, orally; TBI, total body irradiation; TID, three times a day.



**Figure 96.2** Complications after hematopoietic stem cell transplantation (HCT) by time for patients undergoing myeloablative allogeneic HCT only. CMV, cytomegalovirus; EBV, Epstein–Barr virus; GVHD, graft-versus-host disease; HHV, human herpes virus; HSV, herpes simplex virus; PTLD, posttransplantation lymphoproliferative disease; VOD, veno-occlusive disease; VZV, varicella-zoster virus.

- **Hemorrhagic Cystitis:** Moderate to severe hemorrhagic cystitis occurs in 4% to 20% of HCT patients receiving cyclophosphamide and hydration alone. Guidelines recommend the use of mesna plus saline diuresis or forced saline diuresis to lower the incidence.
- **Gastrointestinal Effects:** Preparative regimens will cause most patients to be nauseated and anorexic until day 10 to 15 post-transplant. Prophylactic therapy with a serotonin antagonist plus a corticosteroid should be given. Guidelines also recommend using aprepitant. Many patients will also experience mucositis; opioids may be needed for pain relief, and parenteral nutrition may be needed to prevent nutritional deficits.
- **Hepatic Veno-Occlusive Disease (VOD)** is a life-threatening complication of HCT that results in marked sinusoidal fibrosis, necrosis of the pericentral hepatocytes, and narrowing and eventual fibrosis of central veins. Signs and symptoms include hyperbilirubinemia ( $>2$  mg/dL), weight gain ( $>5\%$  above baseline), hepatomegaly, azotemia, elevated alkaline phosphatase, ascites, elevated Aspartate transaminase (AST), and encephalopathy. Severe hepatic VOD is usually accompanied by multi-organ system failure. Important risk factors are preparative regimen, radiation dose, high systemic exposure to busulfan and/or cyclophosphamide, and liver inflammation and fibrosis pre-HCT. The mainstay of treatment is managing sodium and water balance, and paracentesis for ascites that is associated with pain and pulmonary compromise.

- **Graft Rejection:** Rejection is less common after allogeneic versus autologous HCT because the donor PBPC or marrow is unmanipulated and free from the damaging effects of prior chemotherapy. In patients receiving myeloablative allogeneic HCT, graft rejection is best managed with immunosuppressants.
- **Graft-versus-Host Disease:** GVHD, the most important complication of allogeneic HCT, is caused by activation of donor lymphocytes leading to immune-mediated damage to the recipient. Histocompatibility differences between donor and recipient necessitate posttransplant immunosuppression after allogeneic HCT.
  - **Acute GVHD** occurs within the first 100 days after allogeneic HCT. Risk is associated with degree of histocompatibility between donor and recipient. Other factors include increasing recipient age, greater intensity of the preparative regimen, use of PBPC rather than bone marrow, and donor/recipient sex mismatch. Primary targets of immune-mediated destruction by donor lymphocytes are the skin (diffuse maculopapular pruritic rash that starts on the palms of hands, soles of feet, or face), gastrointestinal tract (loss of appetite, nausea, vomiting, watery or bloody diarrhea), and liver (increased total bilirubin, alkaline phosphatase, hepatic transaminases). Severity is determined first (Table 96.6) and then overall grade (Table 96.7). Postgrafting immunosuppressive therapy is given to minimize risk of GVHD (Table 96.8). First-line treatment of GVHD is a corticosteroid added to the current immune-suppressive regimen.
  - **Chronic GVHD** occurs after day 100 posttransplant and is the most common reason for nonrelapse morbidity and mortality. Risk factors include older age, diagnosis, lack of an HLA-matched donor, and history of acute GVHD. Signs and symptoms are shown in Table 96.9. No specific prophylactic therapy exists. The mainstay of therapy is long-term immunosuppressive therapy. Trimethoprim-sulfamethoxazole should be given for prophylaxis of *P. jiroveci* and encapsulated organisms. Sunscreens, artificial tears, and artificial saliva can help prevent fissures and cracking of the mucous membranes.
- **Infectious Complications:** Opportunistic infections are a major cause of morbidity and mortality after HCT; risks exist in three general periods (Figure 96.2).
  - Catheter-associated infections have become the leading cause of bacteremia.
  - Measures to minimize the risk of infection include private reverse isolation rooms equipped with positive-pressure high-efficiency particulate air (HEPA) filters, adherence to strict hand washing, low microbial diets (Table 96.10), and good oral hygiene including frequent (4–6 times daily) mouth rinses.

TABLE 96.6 Modified Glucksberg Grading of Acute Graft-versus-Host Disease

Organ Stage	Skin <sup>a</sup>	Liver	Intestinal Tract <sup>b</sup>
1	Maculopapular rash <25% of body surface	Bilirubin 2–2.9 mg/dL	500–1,000 mL/day diarrhea or biopsy-proven upper GI involvement
2	Maculopapular rash 25%–50% body surface	Bilirubin 3–6 mg/dL	1,000–1,500 mL/day diarrhea
3	Maculopapular rash >50% body surface	Bilirubin 6.1–15 mg/dL	1,500–2,000 mL/day diarrhea
4	Generalized erythroderma with bullae	Bilirubin >15 mg/dL	>2,000 mL/day diarrhea or severe abdominal pain with or without ileus

<sup>a</sup>Extent of rash determined by “rule of nines.”

<sup>b</sup>Diarrhea volume applies to adults.

Source: Cutler C, Antin JH. Manifestations and treatment of acute graft-versus-host disease. In: Blume KG et al, eds. *Thomas' Hematopoietic Cell Transplantation*. 4th ed. Malden, MA: Blackwell; 2009:1291.

**TABLE 96.7 Modified Glucksberg versus International Bone Marrow Transplant Registry Overall Grading of Acute Graft-versus-Host Disease Severity**

Organ Stage	Skin	Liver	Gut
<b>GLUCKSBERG GRADING</b>			
I—Mild	Stage 1–2	None	None
II—Moderate	Stage 3 or	Stage 1 or	Stage 1
III—Severe		Stage 2–3 or	Stage 2–4
IV—Life threatening	Stage 4 or	Stage 4	—
<b>IBMTR GRADING</b>			
A—Mild	Stage 1	None	None
B—Moderate	Stage 2	Stage 1 or 2	Stage 1 or 2
C—Severe	Stage 3	Stage 3	Stage 3
D—Life threatening	Stage 4	Stage 4	Stage 4

IBMTR, International Bone Marrow Transplant Registry.

Source: Cutler C, Antin JH. Manifestations and treatment of acute graft-versus-host disease. In: Blume KG et al, eds.

*Thomas' Hematopoietic Cell Transplantation*. 4th ed. Malden, MA: Blackwell; 2009:1291.

- Aggressive use of antibacterial, antifungal, and antiviral therapy, both prophylactically and for documented infection, is important.
- Patients who become febrile should immediately receive broad-spectrum IV antibiotics and prophylaxis should be discontinued.
- Antifungal prophylaxis (e.g., fluconazole 400 mg daily) may be used until day 75 post-transplant.
- When mold prophylaxis is required, either posiconazole or voriconazole may be used.
- Herpes simplex virus (HSV)-seropositive patients may experience reactivation of HSV. Varicella zoster virus-seropositive patients are at risk for developing herpes zoster, particularly after day 100 post-transplantation. Prophylactic acyclovir is commonly used.

**TABLE 96.8 Combination Immunosuppression Regimens for Prophylaxis of Acute Graft-versus-Host Disease in Myeloablative Transplant**

Drug	Dosing Examples
Cyclosporine/short-term methotrexate	1.5 mg/kg IV or 4 mg/kg (Neoral) PO every 12 hours, days –1 to +50, then taper 5% per week and discontinue by day +180 Methotrexate 10 mg/m <sup>2</sup> IV, days +3, +6, +11
Tacrolimus/short-term	Tacrolimus 0.03 mg/kg/day continuous IV infusion or 0.12 mg/kg/day PO BID
Methotrexate <sup>101</sup>	Methotrexate 15 mg/m <sup>2</sup> IV day +1; 10 mg/m <sup>2</sup> IV, days +3, +6, +11
Cyclosporine/methotrexate/prednisone	Cyclosporine 5 mg/kg/day IV continuous infusion, days –2 to +3, then 3–3.75 mg/kg IV until day +35; then 7 mg/kg/day (Neoral) PO, dose adjusted to cyclosporine concentrations (via radioimmunoassay) of 200–400 ng/mL. Taper by 20% every 2 weeks; then discontinue by day +180 Methotrexate 15 mg/m <sup>2</sup> IV day +1; 10 mg/m <sup>2</sup> IV days +3, +6 Methylprednisolone 0.5 mg/kg/day IV day +7 until day +14; then 1 mg/kg/day IV until day +28; then prednisone 0.8 mg/kg/day PO until day +42; then taper slowly and discontinue by day +180

BID, twice a day; IV, intravenous; PO, orally.

TABLE 96.9 Selected Signs and Symptoms of Chronic Graft-versus-Host Disease<sup>a</sup>

Affected Organ	Diagnostic	Distinctive	Other Features <sup>b</sup>	Seen With Both Acute and Chronic GVHD
Eyes		New-onset dry, gritty, or painful eyes <sup>c</sup> Cicatricial conjunctivitis Keratoconjunctivitis sicca <sup>c</sup> Confluent areas of punctate keratopathy, tear formation, dry eyes, burning, photophobia	Photophobia Periorbital hyperpigmentation Erythema of the eyelids with edema	
Gastrointestinal tract	Esophageal web Stricture or stenosis in the upper to mid third of the esophagus <sup>d</sup>		Pancreatic insufficiency	Anorexia Nausea Vomiting Diarrhea Weight loss Failure to thrive (infants and children)
Liver				Total bilirubin, alkaline phosphatase >2 × upper limit of normal <sup>d</sup>
Lung	Bronchiolitis obliterans diagnosis with lung biopsy	Bronchiolitis obliterans diagnosed with pulmonary function tests and radiology <sup>c</sup>		Bronchiolitis obliterans organizing pneumonia
Skin	Poikiloderma	Depigmentation	Seat impairment ichthyosis Keratosis pilaris	Erythema Maculopapular rash Pruritus
	Lichen planuslike features Sclerotic features Morphealike features Lichen sclerosuslike features		Hypopigmentation Hyperpigmentation	

<sup>a</sup>Signs and symptoms for hematopoietic and immune differences, as well as for nails; scalp and body hair; mouth; genitalia; muscles, fascia, and joints; and other organs, are also described by Filipovich et al.<sup>152</sup>

<sup>b</sup>Part of chronic GVHD symptomatology if the diagnosis is confirmed.

<sup>c</sup>Diagnosis of chronic GVHD requires biopsy or radiology confirmation (or Schirmer's test for eyes).

<sup>d</sup>Infection, drug effects, malignancy, or other causes must be excluded.

GVHD, graft-versus-host disease.

- Cytomegalovirus (CMV) can establish lifelong latent infection after primary exposure. CMV infection or disease may occur post-transplantation in seropositive patients. Common manifestations include pneumonitis, fever, and gastrointestinal tract infection. In CMV-seronegative patients, primary CMV infection is prevented by using CMV-negative donors and CMV-negative blood products. If the patient is CMV-positive or a CMV-negative donor received a CMV-positive organ, antiviral drugs are essential to minimize



TABLE 96.10 Foods Posing Infection Risk in Neutropenic Patients

High-Risk Foods to Avoid When Neutropenic	Infection Risk
Salad	Gram-negative bacillus including <i>Pseudomonas aeruginosa</i> and <i>Campylobacter</i>
Tomatoes, radishes, celery, and carrots	<i>Pseudomonas aeruginosa</i>
Raw eggs	<i>Campylobacter jejuni</i> , <i>Salmonella</i>
Unpasteurized cheeses	<i>Listeria monocytogenes</i>
Cold, loose meats	Enterococci <i>Listeria</i> , <i>Clostridium perfringens</i> , <i>Campylobacter jejuni</i>
Undercooked meat	<i>Salmonella</i> , <i>Listeria</i> , <i>Escherichia coli</i>
Uncooked nuts	<i>Aspergillus niger</i> , <i>Aspergillus flavus</i>
Black pepper/uncooked herbs and spices	<i>Aspergillus</i> sp.
Raw shellfish/sushi	<i>Vibrio vulnificus</i> , Norwalk virus
Bottled water	<i>Pseudomonas</i> , <i>Cytophaga</i> , <i>Campylobacter</i>
Prepared foods that are cooked and then eaten chilled	<i>Listeria</i>
Ice machines	<i>P. aeruginosa</i> , <i>Stenophomonas maltophilia</i>

morbidity. Universal prophylaxis is ganciclovir from the time of engraftment until approximately day 100 post-transplant. Foscarnet or cidofovir are alternatives, if needed.

- ***Aspergillus* Infection:** Invasive molds are an increasing cause of morbidity and mortality post-HCT. Treatment consists of conventional amphotericin B (or its lipid formulations), broad-spectrum triazole agents (itraconazole, voriconazole, posaconazole), or echinocandin agents (casposungin, micafungin). Therapy should be tailored to the individual patient on response, tolerability, and cost.
- *P. jiroveci* is a common pathogen that causes *Pneumocystis pneumonia* (PCP); prophylaxis with trimethoprim/sulfamethoxazole is routinely recommended. Dapsone or aerosolized pentamidine are alternatives.

## Pediatric Pharmacotherapy\*

### General Principles

- Commonly used age definitions are shown in Table 97.1.
- Children undergo considerable physiologic changes between birth and adulthood.
- Differences in pharmacokinetics and pharmacodynamics resulting from growth and development can alter therapeutic response and adverse effect profiles of drugs.

### Drug Absorption

- Oral drug absorption is altered by a variety of mechanisms (delayed gastric emptying time, prolonged intestinal transit time, reduced splanchnic blood flow), with the most significant differences noted during the first months of life.
- Intramuscular dosing is affected by reduced muscle size, weaker muscle contractions, and an immature vasculature resulting in erratic blood flow to and from the muscle.
- Transdermal or percutaneous administration results in greater drug absorption in neonates than it does in older children and adults.
- Rectal administration is a useful route of drug delivery for many pediatric patients.

### Drug Distribution

- Drug distribution is affected by changes in organ size, body water content, fat stores, plasma protein concentrations, acid–base balance, cardiac output, and tissue perfusion. Changes occur most notably in the first year of life. A higher volume of distribution often results in higher weight-based dosing for infants.
- Plasma protein binding is reduced in neonates. Greater unbound concentrations of some drugs may exist in neonates versus adults (Table 97.2).
- In neonates, administration of drugs with a high binding affinity for albumin (e.g., sulfonamides) can result in competition with bilirubin for binding sites leading to kernicterus, neurologic damage caused by deposition of bilirubin in the brain.

TABLE 97.1 Commonly Used Age Definitions

Premature neonate	Born at <37 weeks' gestational age
Term neonate	Born at ≥37 weeks' gestational age
Neonate	Birth to 28 days of age
Infant	>28 days to <1 year of age
Child	1–11 years of age
Adolescent	12–17 years of age

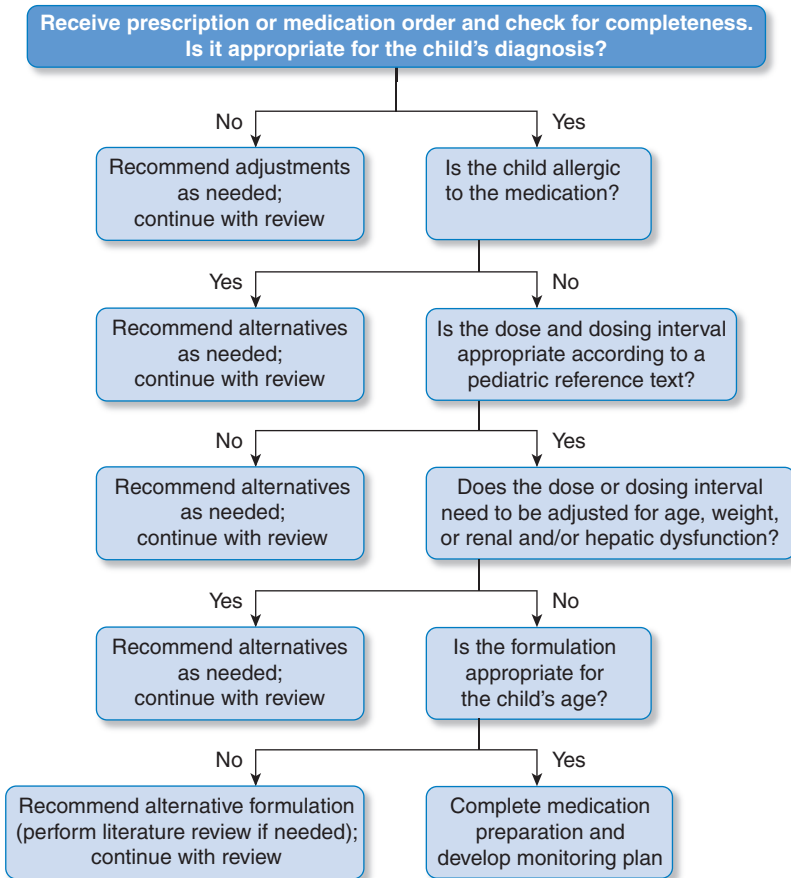
\*The reader is referred to Chapter 97, Pediatric Pharmacotherapy, written by Marcia L. Buck, PharmD, FCCP, FPPAG, in the 10th edition of *Applied Therapeutics: The Clinical Use of Drugs* for a more in-depth discussion. All notations to reference numbers are based on the reference list at the end of that chapter. The editor of this handbook expresses her thanks to Dr. Buck and acknowledges that this chapter is based on her work.

**TABLE 97.2 Examples of Drugs Present in Greater Unbound Concentrations in Neonates than in Adults**

Alfentanil	Digoxin	Penicillin G	Sulfonamides
Ampicillin	Lidocaine	Phenobarbital	Teicoplanin
Ceftriaxone	Ketamine	Phenytoin	Theophylline
Cefuroxime	Morphine	Propranolol	Thiopental
Diazepam	Nafcillin	Salicylates	Valproic acid

**Metabolism**

- Metabolic function is highly dependent on patient age. Metabolic enzyme function does not appear to be complete until after puberty. Considerable interpatient variability exists.
- Phase I (oxidation, reduction, hydroxylation, hydrolysis) and Phase II (glucuronidation, sulfation, acetylation) reactions develop at varying rates during childhood, resulting in a wide range of half-lives for many drugs.
- Alcohol dehydrogenase activity does not approach functional maturity until approximately 5 years of age. Exposure to benzyl alcohol can result in gasping syndrome.



**Figure 97.1** Evaluation of pediatric prescriptions and medication orders. (Modified with permission from the American College of Clinical Pharmacy. Buck ML. Pediatric pharmacotherapy. In: Carter BL et al, eds. *Pharmacotherapy Self-Assessment Program*. 3rd ed. Module 9: Pediatrics. Lenexa, KS: American College of Clinical Pharmacy; 2000:189.)

## Elimination

- The ability of the kidneys to filter, excrete, and reabsorb substances is not maximized until 1 year of age. A rapid rise in glomerular filtration rate (GFR) occurs during the first 2 weeks of life with continual increases until it approaches adult values by 1 year of age.
- Tubular secretion gradually increases during the first year of life.
- Renal function should be closely monitored in children and drug doses adjusted accordingly. Blood urea nitrogen and serum creatinine values are not always useful indicators of renal function in children. Adult equations to estimate creatinine clearance are not appropriate for patients younger than 18 years of age.

## Medication Dosing in Children

- Differences in pharmacokinetics and pharmacodynamics influence the selection of the drug dose and dosing interval. Most doses are based on units per weight (e.g., mg/kg). Several steps should be taken to ensure the appropriate dose for a pediatric patient (Figure 97.1).
- Several methods can help reduce the potential for medication errors (Table 97.3).

**TABLE 97.3 Methods for Reducing Pediatric Medication Errors**

### IMPROVE ORDERING AND PREPARATION

Perform careful medication histories, including assessment of oral liquid concentrations  
 Provide access to current pediatric medication information  
 Include patient weight (in kg) on all medication orders and prescriptions  
 Include dosage calculations on orders and prescriptions  
 Limit the number of concentrations available for high-risk medications  
 Use accurate measuring devices, in both the hospital/clinic and home settings

### IMPLEMENT APPROPRIATE TECHNOLOGY

Adopt weight-based electronic prescribing or dose-checking software  
 Employ barcode technology to reduce patient identification and medication administration errors  
 Use smart pump technology (programmable IV pumps with weight-based dosing limits)

### USE STAFF EXPERTISE

Provide pediatric-specific continuing education for all staff on a routine basis  
 Develop pediatric-specific medication orders and protocols to guide care  
 Assign staff with pediatric expertise to all committees involved in medication management

### INVOLVE FAMILIES AND OTHER CAREGIVERS

Encourage all caregivers to ask questions about their child's medications  
 Recommend that all caregivers know the names and doses of their children's medications or carry information about their medications  
 Remind caregivers to include nutritional supplements, herbal or complementary therapies, and over-the-counter medications when giving a medication history  
 Ensure that caregivers can accurately prepare the medication dose

IV, intravenous.

# Pediatric Fluid, Electrolytes, and Nutrition\*

## General Principles

- Fluid, electrolyte, and nutrient management should be approached in an integrated manner. Requirements for fluid and calories normalized to body weight are much greater in very small children than in older children or adults.
- Growth assessment is an important focus of pediatric healthcare. The most rapid growth occurs in the first year of life.
- Factors used to determine nutritional status in children include dietary history, weight, height, and visceral protein measurements (i.e., albumin, prealbumin).

## Fluid and Electrolyte Maintenance

- Management of fluid and electrolyte disturbances involves providing normal daily maintenance requirements and replacing deficits and ongoing losses.
- Fluid, electrolyte, and nutrient requirements are provided in Table 98.1
- Situations that alter maintenance of fluid needs are shown in Table 98.2. When abnormal losses are present, they must be administered back to the patient daily.
- Replacement fluid is generally 1 mL for every 1 mL lost; more may be needed on the basis of clinical status.
- The composition of a replacement fluid can be estimated on the basis of knowledge of the usual electrolyte distribution of the fluid type being lost (Table 98.3).

## Dehydration

- Clinical signs of dehydration include lethargy, decreased urine output, tearless crying, dry mucous membranes, dry skin with fever, sunken eyes, mild tachycardia with low normal blood pressure, poor skin turgor, and body weight. The extent of dehydration can be approximated from physical findings (Table 98.4).
- Rehydration can be done orally or parenterally. Composition of common oral replacement solutions is provided in Table 98.5. Parenteral replacement should be calculated to provide one-third of the daily maintenance fluid plus one-half of the deficit replacement during the first 8 hours. The remainder of the maintenance fluid (adjusted for fever) and deficit replacement should be administered over the next 16 hours. Serum electrolytes should be monitored every 6 to 8 hours during rehydration therapy.

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\*The reader is referred to Chapter 98, Pediatric Fluid, Electrolytes, and Nutrition, written by Michael F. Chicella, PharmD, and Jennifer W. Chow, PharmD, in the 10th edition of *Applied Therapeutics: The Clinical Use of Drugs* for a more in-depth discussion. All notations to reference numbers are based on the reference list at the end of that chapter. The editor of this handbook expresses her thanks to Drs. Chicella and Chow and acknowledges that this chapter is based on their work.

TABLE 98.1 Daily Parenteral Nutrient Requirements in Children

Nutrient	Weight/Age	Requirement
Fluid	<1.5 kg	150 mL/kg
	1.5–2.5 kg	120 mL/kg
	2.5–10 kg	100 mL/kg
	10–20 kg	1,000 mL + 50 mL/kg for each kg >10 kg
	>20 kg	1,500 mL + 20 mL/kg for each kg >20 kg
Calories	Up to 10 kg	100 kcal/kg
	20 kg	1,000 kcal + 50 kcal/kg for each kg >10 kg
	>20 kg	1,500 kcal + 20 kcal/kg for each kg >20 kg
Protein <sup>a</sup>	Infants	2–3 g/kg
	Children	1.5–2.0 g/kg
	Adolescents and older	1.0–1.5 g/kg
Fat <sup>b</sup>	Infants and children	Initially 0.5–1 g/kg then increase by 0.5–1 g/kg (maximum of 3 g/kg in preterm neonates, 4 g/kg older infants and children) ( $\geq 4\%$ of calories as linoleic acid)
	>50 kg	One 500-mL bottle (100 g fat)

**ELECTROLYTES AND MINERALS<sup>c</sup>**

Sodium	Infants and children	2–4 mEq/kg
Potassium	Infants and children	2–3 mEq/kg
Chloride	Infants and children	2–4 mEq/kg
Magnesium	Preterm and term infants	0.25–0.5 mEq/kg
	Children >1 year (or >12 kg)	4–12 mEq
Calcium	Preterm and term infants	2–3 mEq/kg
	Children >1 year (or >12 kg)	10–20 mEq
Phosphorus	Preterm and term infants	1.0–1.5 mmol/kg
	Children >1 year (or >12 kg)	10–20 mmol

**TRACE ELEMENTS**

Zinc	Preterm infants	400 mcg/kg
	Term infants	
	<3 months	250 mcg/kg
	>3 months	100 mcg/kg
Copper	Children	50 mcg/kg (up to 5 mg)
	Infants and children	20 mcg/kg (up to 300 mcg)
Manganese	Infants and children	1 mcg/kg (up to 50 mcg)
Chromium	Infants and children	0.2 mcg/kg (up to 5 mcg)
Selenium	Infants and children	2 mcg/kg (up to 80 mcg)

VITAMINS	TERM INFANTS AND CHILDREN >11 YEARS		
	PRETERM INFANTS <2.5 KG (2 mL/KG MVI PEDIATRIC)	CHILDREN <11 YEARS (5 mL MVI PEDIATRIC)	CHILDREN >11 YEARS (10 mL MVI-12)
Vitamin A	280 mcg/kg	700 mcg	1 mg
Vitamin D	160 international units/kg	400 international units	200 international units
Vitamin E	2.8 mg/kg	7 mg	10 mg
Vitamin K <sup>d</sup>	80 mcg/kg	200 mcg	None
Thiamine	0.48 mg/kg	1.2 mg	3 mg
Niacin	6.8 mg/kg	17 mg	40 mg
Riboflavin	0.56 mg/kg	1.4 mg	3.6 mg
Pyridoxine	0.4 mg/kg	1 mg	4 mg
Vitamin B <sub>12</sub>	0.4 mcg/kg	1 mcg	5 mcg
Biotin	8 mcg/kg	20 mcg	60 mcg
Vitamin C	32 mg/kg	80 mg	100 mg
Folic acid	56 mcg/kg	140 mcg	400 mcg

<sup>a</sup>“Infant” amino acids contain histidine, taurine, tyrosine, and cysteine, which are essential in infants but not older patients.

TABLE 98.1 Daily Parenteral Nutrient Requirements in Children (Continued)

<sup>b</sup>Because linoleic acid represents 54% of the fatty acid in soy bean oil and 77% in safflower oil, 7% to 10% of calories must be provided as fat emulsion. This can be given daily over the course of 24 hours (preferred in patients predisposed to sepsis and preterm infants) or two to three times weekly.

<sup>c</sup>These doses are guidelines and all patients should be evaluated individually for appropriateness of dosing. For example, patients with short bowel syndrome may require large doses of magnesium, and patients with renal insufficiency may require none to low amounts of potassium, calcium, phosphorus, and magnesium.

<sup>d</sup>For patients receiving MVI-12, it may be desirable to add vitamin K.

MVI, multivitamin.

Sources: Holliday MA, Segar WE. The maintenance need for water in parenteral fluid therapy. *Pediatrics*. 1957;19(5):823–832<sup>1</sup>; Greene HL, Hambidge KM, Schanler R, Tsang RC. Guidelines for the use of vitamins, trace elements, calcium, magnesium, and phosphorus in infants and children receiving total parenteral nutrition: report of the Subcommittee on Pediatric Parenteral Nutrient Requirements from the Committee on Clinical Practice Issues of the American Society for Clinical Nutrition [published corrections appear in *Am J Clin Nutr*. 1989;49(6):1332; *Am J Clin Nutr*. 1989;50(3):560]. *Am J Clin Nutr*. 1988;48(5):1324–1342.<sup>2</sup>

TABLE 98.2 Situations that Alter Maintenance Fluid Requirements

Situation	Mechanism	Extent of Change (%)
Extreme prematurity	↑ Skin losses	Varies
Radiant warmer use	↑ Insensible water loss	20–40
Diarrhea or vomiting	↑ GI loss	Varies
Fever	↑ Insensible water loss	10–15/°C
Renal dysfunction	↑ or ↓ renal loss	Varies
Hyperventilation	↑ Pulmonary evaporative loss	Varies
Phototherapy for hyperbilirubinemia	↑ Insensible water loss	10–20
GI tract suction or ostomy	↑ GI loss	Varies
Mechanical ventilation	↓ Insensible water loss	20–30

GI, gastrointestinal.

TABLE 98.3 Body Fluid Volumes and Electrolyte Content

Source	Volume (L/day)	Na <sup>+</sup> (mEq/L)	K <sup>+</sup> (mEq/L)	Cl <sup>-</sup> (mEq/L)	HCO <sub>3</sub> <sup>-</sup> (mEq/L)
Salivary glands	1.5 (0.5–2)	10 (2–10)	26 (20–30)	10 (8–18)	30
Stomach	1.5 (0.1–4)	60 (9–116)	10 (0–32)	130 (8–154)	—
Duodenum	(0.1–2)	140	5	80	—
Ileum	3 (0.1–9)	140 (80–150)	5 (2–8)	104 (43–137)	30
Colon	—	60	30	40	—
Pancreas	(0.1–0.8)	140 (113–185)	5 (3–7)	75 (54–95)	115
Bile	(0.05–0.8)	145 (131–164)	5 (3–12)	100 (89–180)	35

TABLE 98.4 Clinical Signs of Dehydration

Severity	Dehydration (%)		Mucous Membranes			Anterior Fontanel		Urine Specific Gravity
	Dehydration (%)	Psyche	Thirst	Tears	Skin	Skin		
Mild	<5	Normal	Slight	Normal to dry	Present	Flat	Normal	Slight change
Moderate	6–10	Irritable	Moderate	Dry	±	±	±	Increased
Severe	10–15	Hyperirritable to lethargic	Intense	Parched	Absent	Sunken	Tenting	Greatly increased

TABLE 98.5 Composition of Oral Rehydration Products

Product	Na <sup>+</sup> (mEq/L)	K <sup>+</sup> (mEq/L)	Cl <sup>-</sup> (mEq/L)	Bicarbonate Source (mEq/L)	Carbohydrate (%)
Enfalyte	50	25	45	34 citrate	3
Rehydralyte	75	20	65	30 citrate	2.5
Pedialyte	45	20	35	30 citrate	2.5
Gatorade	23.5	<1	17	—	4.6
WHO salts	90	20	80	30 bicarbonate	2

WHO, World Health Organization.

## Enteral Nutrition

- Caloric requirements of infants can be estimated (Table 98.1). Nutritional support using the gastrointestinal (GI) tract is the preferred approach, when possible. Patients with a condition that prevents adequate oral ingestion can be fed by a GI tube in intermittent boluses or by continuous infusion.
- Infant feeding is divided into three stages: nursing (oral liquids only); transition period (solid foods are introduced but human milk/formula are major source of nutrients); and modified adult period (most nutrition is provided from solid foods).
- **Human milk** is the ideal food for a human infant and should be encouraged to be continued for the first year of life as long as mutually desired by the mother and the child. There are three phases to human milk production:
  - Colostrum, produced during the first 5 days of milk production, is rich in protein, minerals, and other substances (e.g., immunoglobulins) and low in fat.
  - Transitional milk is produced during the next 5 days.
  - Mature human milk is produced thereafter. It provides 70 kcal/100mL and fat accounts for more than 50% of its caloric content.
- **Infant formulas** (Table 98.6) provide adequate nutrition for the first 12 months of life. Infant formulas generally begin with cow's milk where casein is the predominant protein. Soy-based formulas that use soybean as the protein source are an alternative. Elemental formulas are another option for infants intolerant of cow's milk or soy protein. Therapeutic formulas, available for infants with inborn errors of metabolism, are designed to reduce the intake of precursor compounds or to provide the deficient metabolic end product.
- **Solid foods** should not be introduced before 4 months of age because younger infants are unprepared to swallow foods other than liquids. Solids (first cereals, then fruits and vegetables) should be introduced when the child has good control of the head and neck movements (usually at 4–6 months of age).

TABLE 98.6 Infant Formulas

Cow's Milk-Based Formulas	Soy-Based, Lactosefree Formulas	Protein Hydrolysate, Elemental, Premature Infant Formulas
Enfamil with iron	Isomil	Alimentum
Similac with iron	Nursoy	Nutrigen
Gerber Good Start	ProSoBee	Pregestimil
	Alsoy	NeoCate
	Gerber Soy Plus	Neosure Advance
	Similac Sensitive	Enfamil Premature with Lipil
		Similac Special Care



## Parenteral Nutrition

- Parenteral nutrition is indicated for any infant or child unable to take in sufficient nourishment to maintain normal growth. Patients with intrinsic GI disease (Table 98.7) or malabsorption may require total or supplemental parenteral nutrition.
- Basic requirements for a parenteral nutrient program are in Table 98.1. Initiation of a nutrient regimen should be individualized to specific patient needs to ensure sufficient nutrients are available to promote a normal rate of growth without toxicity. Very low-birth-weight infants require specialized nutritional support.
- Administration of parenteral nutrition into a peripheral vein is limited to those patients expected to require short-term parenteral feeding (up to 2 weeks).
- Patients 1 year of age or older tolerate standard adult amino acid preparations. Two specifically designed pediatric amino acid formulations are available for infants (TrophAmine and Aminosyn PF).
- Carnitine is an essential nutrient in neonates and infants; deficiency can adversely affect the central nervous system, and skeletal and cardiac muscles.
- The absence of GI hormones, which depend on enteral feeding for their release, can promote cholestasis. If parenteral nutrition can be discontinued soon after the onset of cholestasis, the prospect of recovery of normal hepatic function improves.

**TABLE 98.7 Indications for Parenteral Nutrition Support**

Extreme prematurity
Respiratory distress
Congenital GI anomalies
Duodenal atresia
Jejunal atresia
Esophageal atresia
Tracheoesophageal fistula
Pyloric stenosis
Congenital webs
Hirschsprung disease
Malrotation
Volvulus
Abdominal wall defects
Omphalocele (herniation of viscera into the umbilical cord base)
Gastroschisis (defect of abdominal wall, any location except umbilical cord)
Congenital diaphragmatic hernia
Necrotizing enterocolitis
Chronic diarrhea
Inflammatory bowel disease
Chylothorax
Pseudoobstruction
Megacystic microcolon
Abdominal trauma involving viscera
Adverse effects of treating neoplastic disease
Radiation enteritis
Nausea and vomiting
Stomatitis, glossitis, and esophagitis
Anorexia nervosa
Cystic fibrosis
Chronic renal failure
Hepatic failure
Metabolic errors

GI, gastrointestinal.

# Common Pediatric Illnesses\*

## General Principles

- Medication administration to children can be challenging. Gently restraining young children may be needed to facilitate accurate and rapid drug administration.
- **Oral Medications:** Dosing syringes or droppers provide the most accurate measurement of the desired dose; household spoons or cups should be avoided. In some cases, crushed tablets or capsule contents can be mixed with small amounts of food. Limiting the volume facilitates the likelihood of delivering the full dose. Most children can swallow oral tablets by 5 to 8 years of age.
- **Otic medications** should be instilled by pulling the auricle down and out in infants and young children. For older children, hold the auricle up and back to straighten the ear canal.
- **Nose and eye drops** are best administered with the child's head lower than the rest of the body. Restraint is often required when giving ophthalmic medications to infants.

## Teething

- Eruption of primary or deciduous teeth rarely begins before 4 to 5 months of age and usually is complete by 36 months of age.
- Symptoms of teething include drooling, restlessness, thumb-sucking, gum-rubbing, and decreased appetite.
- Gentle irrigation with water relieves inflammation around a gum flap. Chewing on a blunt, firm object (e.g., teething ring) or on cracked ice wrapped in a soft cloth can relieve pain. Lidocaine topical anesthetics should be avoided. Ibuprofen or acetaminophen can help relieve pain.

## Diaper Rash

- Irritants (urine, stool, detergents), occlusion, and fungal or bacterial overgrowth can cause diaper rash.
- Diaper rash can appear as a mild, scaling rash in the perianal area; a sharply demarcated confluent erythema; ulceration distributed through the diaper area; or a beefy red confluent erythema with satellite lesions, vesiculopustular lesions, and diffuse involvement of the genitalia (candida infection).
- Stool and urine should be removed from the diaper area by gentle rinsing with plain water. Diaper wipes that contain alcohol should be avoided. A good protective agent (zinc oxide, petrolatum) can create a barrier. Powdered protective agents (e.g., talc, cornstarch) can minimize friction caused by diapers; use cautiously to avoid aspiration of powder particles by the infant.
- Candidal infection typically persists longer than 3 days with diffuse involvement of the genitalia and inguinal folds. Topical antifungal creams (1% clotrimazole, 2% miconazole) should be applied four times daily until the rash is resolved.

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\*The reader is referred to Chapter 99, Common Pediatric Illnesses, written by Michelle Condren, PharmD, AE-C, CDE, and Mark R. Haase, PharmD, FCCP, BCPS, in the 10th edition of *Applied Therapeutics: The Clinical Use of Drugs* for a more in-depth discussion. All notations to reference numbers are based on the reference list at the end of that chapter. The editor of this handbook expresses her thanks to Drs. Condren and Haase and acknowledges that this chapter is based on their work.

## Fever

- Fever is defined as a core temperature of 38°C or higher (37.5°C axillary). Rectal and tympanic measurements are typically 0.3 to 0.6°C higher than oral readings. Rectal temperatures are most reliable in infants younger than 3 months of age.
- Any child <2 months of age who develops a fever requires a complete evaluation (e.g., blood culture, urinalysis).
- Children 3 to 36 months of age with a temperature  $\geq 39^{\circ}\text{C}$  and a white blood cell count  $< 5,000/\text{mm}^3$  or  $> 15,000/\text{mm}^3$  are at increased risk for bacteremia.
- Children of any age with a temperature  $> 41^{\circ}\text{C}$  should be evaluated for bacteremia and meningitis.
- Febrile seizures occur in 2% to 4% of children 6 months to 5 years of age with temperatures  $> 38^{\circ}\text{C}$ .
- Acetaminophen (10–15 mg/kg/dose every 4–6 hours; maximum 90 mg/kg/day) is the most common antipyretic agent used in children.
- Ibuprofen (5–10 mg/kg/dose every 6–8 hours; maximum 40 mg/kg/day) is an alternative.
- Aspirin is not recommended due to its association with Reye's syndrome.

## Cough and Cold

- Children often present with sore throat, nasal congestion, rhinorrhea, sneezing, cough, and irritability.
- Symptomatic relief can be achieved with use of a cool-mist humidifier, saline nasal drops, or bulb suctioning. Cough and cold medications should not be used in children younger than 6 years of age.

## Constipation

- Chronic constipation is defined as delay or difficulty in stooling for at least 2 weeks. It is most commonly idiopathic or functional and may be related to a diet low in fiber, lack of time or routine for toileting, or passage of a painful stool resulting in fear of defecating.
- Proper management is important to avoid negative effects on growth and development.
- After disimpaction, a combination of behavioral, dietary, and medication therapies (Table 99.1) should be initiated to promote regular stool production and prevent impaction.

## Vomiting and Diarrhea

- Vomiting and diarrhea are usually self-limiting but severe cases can result in serious complications (e.g., dehydration, metabolic disturbances, death). Infants and young children are particularly susceptible to complications.
- The most common causes of vomiting beyond the neonatal period are in Table 99.2.
- Acute diarrhea in infants and children generally is abrupt in onset, lasts a few days, and usually is caused by a virus. It is considered chronic if it lasts longer than 2 weeks.

## Viral Gastroenteritis

- Routine use of antiemetics for acute vomiting in children is not recommended. Promethazine is contraindicated in children <2 years of age due to the risk of fatal respiratory depression.
- Medical evaluation is necessary for all infants younger than 6 months of age and for children who exhibit unusual behavior or signs of an ear infection, experience abdominal pain or distension, have red or black vomitus or stool, or if there is a history or suspicion of toxic ingestion or head trauma.
- Gastroenteritis usually resolves within 24 to 48 hours. Fluid and electrolyte replacement in infants is critically important.

TABLE 99.1 Medications for the Treatment of Constipation

Medication	Initial Dosage	Comments
<b>OSMOTIC AGENTS</b>		
Polyethylene glycol	0.5–1.5 g/kg/day	0.5 g/kg initial dose; titrate to effect; do not exceed 17 g/day
Lactulose	1–3 mL/kg/day once or twice daily	
Sorbitol	1–3 mL/kg/day once or twice daily	Less expensive than lactulose
Barley malt extract	2–10 mL/240 mL of milk or juice daily	Useful for infants drinking from a bottle
Magnesium hydroxide	1–3 mL/kg/day using 400 mg/5 mL	Infants are at risk for hypermagnesemia
Phosphate enema	≥2 years of age: 6 mL/kg up to 135 mL	Electrolyte abnormalities more common in children with renal failure or Hirschprung disease. Avoid in children <2 years.
<b>LUBRICANT</b>		
Mineral oil	>1 year of age: Disimpaction: 15–30 mL/year of age up to 240 mL daily Maintenance: 1–3 mL/kg/day	Better tolerated if chilled. Avoid in children <1 year. Lipoid pneumonia may occur if aspirated.
<b>STIMULANTS</b>		
Senna	2–6 years of age: 2.5–7.5 mL/day 6–12 years of age: 5–15 mL/day	Not recommended for chronic use
Bisacodyl	≥2 years old: 0.5–1 suppository or 1–3 tablets per dose	Not recommended for chronic use
Glycerin suppositories	1 suppository per dose	Preferred stimulant for children <2 years of age

TABLE 99.2 Causes of Vomiting in Infants and Children

Causes	Other Signs and Symptoms
<b>DRUG INDUCED</b>	
Cancer chemotherapy	Nausea
Narcotics	
Theophylline or aminophylline	
Antibiotics	
Alcohol	
Anesthetics	
Toxic ingestion	
<b>METABOLIC OR ENDOCRINE DISORDERS</b>	
	Alteration in behavior
<b>INFECTIOUS DISEASES</b>	
	Fever
Otitis media	Symptoms of otitis media
Meningitis	Stiff neck, toxic appearance
Appendicitis	Abdominal pain
Urinary tract infection or pyelonephritis	Dysuria, frequency, and urgency in older children
Viral or bacterial gastroenteritis	Diarrhea
<b>MECHANICAL OBSTRUCTION</b>	
Bowel obstruction	Abdominal distension, green emesis
Pyloric stenosis	Projectile nonbilious vomiting Abdominal pain
<b>INFLAMMATORY</b>	
Pancreatitis	
Inflammatory bowel	Diarrhea
Peptic ulcer disease	Black or red vomitus

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TABLE 99.2 Causes of Vomiting in Infants and Children (Continued)

Causes	Other Signs and Symptoms
<b>PSYCHOLOGIC</b>	
Chemotherapy	
Bulimia	
<b>MISCELLANEOUS</b>	
Gastroesophageal reflux	Usually self-limited; indications for evaluation include recurrent pneumonia, poor growth, gastrointestinal blood loss, dysphagia, or heartburn
Increased intracranial pressure	Mental status alteration
Head injury or trauma	History of trauma, mental status changes
Food or milk intolerance	Irritability, loose stool, blood in stool, or allergy

- Symptoms of dehydration include sunken eyes, parched mucous membranes, prolonged capillary refill (assess by applying pressure on the nail bed to cause blanching and measure refill time, 1 second is normal), cool, mottled extremities, crying without tears, oliguria or anuria, weak or thready pulses, lethargy, poor oral intake, deep respirations, fever without perspiration, thirst, and weight loss (3%–9% mild to moderate dehydration; >9% severe dehydration).
- Treatment goals are to prevent dehydration and restore and maintain adequate fluid and electrolyte balance.
- Fluid losses in stools can be replaced with a glucose-containing oral replacement solution (Table 99.3).
- Reinstitution of a regular diet should not adversely affect mild diarrhea and can be beneficial; continue feeding using an age-appropriate diet while avoiding simple sugars.
- Medications play a minor role in the treatment of acute infantile diarrhea; most episodes are self-limiting. Antibiotics are recommended when systemic bacteremia is suspected, immune defenses are compromised, a persistent enteric infection is sensitive to antibiotics, or specific strains are isolated (e.g., *Shigella*, *Campylobacter*, *Vibrio cholera*, *Clostridium difficile*).

TABLE 99.3 Oral Electrolyte Solutions

Solution	Compositions			
	Sodium (mmol/L)	Potassium (mmol/L)	Carbohydrate (mmol/L)	Osmolarity
<b>REHYDRATION</b>				
Rehydralyte	75	20	140	305
WHO formula (1975)	90	20	111	311
WHO formula (2002)	75	20	75	245
<b>MAINTENANCE</b>				
Enfalyte	50	25	167	200
Pedialyte	45	20	139	250
<b>HOME REMEDIES</b>				
Apple juice	0.4	44	667	730
Gatorade	20	3	255	330
Ginger ale	3	1	500	540
Chicken broth	250	8		500
Cola	1.6		622	730

WHO, World Health Organization.

- Antidiarrheal agents such as loperamide, bismuth subsalicylate preparations, and kaolin-pectin should be avoided.
- Probiotics (e.g., lactobacilli) are most useful in infectious diarrhea when used early in the course of disease; use should be avoided in immunocompromised patients.

## Gastroesophageal Reflux

- Gastroesophageal reflux (GER) affects 50% to 67% of infants with recurrent vomiting and regurgitation during the first 4 months of life.
- Uncomplicated GER usually resolves spontaneously in infants; therapy should focus on providing symptom relief and maintaining normal growth. Mild cases can be treated with dietary measures (thickening foods with cereal, avoiding overfeeding) and by propping infants in an upright position during and 1 hour after feedings.
- Treatment may be needed in some patients as untreated GER can result in esophageal strictures, GI hemorrhage, or chronic respiratory disease. Various agents have been used (Table 99.4). Chronic antacid therapy is not recommended for infants and young children; they are useful for short-term relief of symptoms in older children and adolescents.

TABLE 99.4 Oral Drugs Used to Treat Gastroesophageal Reflux in Infants

Agent	Mode of Action	Oral Dosage
<b>ACID-SUPPRESSING AGENTS</b>		
Antacids (aluminum or magnesium hydroxide)	Neutralizes acid	0.5–1.0 mL/kg/dose before and after feeding (maximum, 15 mL/dose)
<b>PROTON-PUMP INHIBITORS</b>		
	Decrease acid secretion via inhibition of gastric hydrogen-potassium adenosine triphosphatase	
Omeprazole		5 mg daily (5 kg to <10 kg) 10 mg daily (10 kg to ≤20 kg) 20 mg daily (>20 kg) 1 mg/kg daily or twice daily (alternate dosing)
Esomeprazole		10–20 mg daily (1–11 years) >1 mg/kg/day has not been evaluated
Lansoprazole		15 mg daily (weight ≤30 kg) 30 mg daily (weight >30 kg)
Pantoprazole		20 mg daily (0.5–1 mg/kg/day)
Rabeprazole		5 mg daily (weight <15 kg) 10 mg daily (weight ≥15 kg) 20 mg daily (age ≥12 years)
<b>H<sub>2</sub> RECEPTOR ANTAGONISTS</b>		
	Blocks H <sub>2</sub> -receptors; ↓ acid secretion	
Cimetidine		40 mg/kg/day divided QID
Famotidine		0.5–1 mg/kg/day divided daily or BID
Nizatidine		5–10 mg/kg/day divided BID
Ranitidine		4–10 mg/kg/day divided TID or QID
<b>PROKINETIC AGENTS</b>		
Bethanechol	Cholinergic agent; stimulates peristalsis ↑ ↑ LES pressure; ↑ gastric emptying; ↑ colonic motility	0.1–0.2 mg/kg/dose QID given 30–60 minutes before feeding and HS

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TABLE 99.4 Oral Drugs Used to Treat Gastroesophageal Reflux in Infants (Continued)

Agent	Mode of Action	Oral Dosage
Metoclopramide	Dopamine antagonist	0.1–0.2 mg/kg/dose QID given 30 minutes before feeding and HS
Erythromycin	Motilin agonist stimulates smooth muscle contraction	1–3 mg/kg/dose QID

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**SURFACE-ACTIVE AGENTS**

Sucralfate	Forms paste and adheres to damaged esophageal mucosa	40–80 mg/kg/day divided QID
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BID, twice daily; HS, at bedtime; LES, lower esophageal sphincter; QID, four times daily; TID, three times daily.

## Acute Otitis Media

- Acute otitis media (AOM) is most common from ages 3 months to 3 years (highest incidence from 6–9 months of age). AOM is often preceded by an upper respiratory tract infection.
- Risk factors include age younger than 2 years, day-care attendance, bottle propping, cleft palate, immune compromise, and Down syndrome.
- *Streptococcus pneumoniae*, nontypable *Haemophilus influenzae*, and *Moraxella catarrhalis* are the most common pathogens.
- Diagnosis requires acute symptom onset, middle ear effusion, and signs and symptoms of inflammation (Table 99.5).
- Antibiotic therapy should be initiated in children 6 months of age and older who have otorrhea with AOM or unilateral or bilateral AOM with severe symptoms. Severe symptoms are defined as a toxic-appearing child, persistent otalgia more than 48 hours, temperature  $\geq 39^{\circ}\text{C}$  ( $102.2^{\circ}\text{F}$ ) in the past 48 hours, or uncertain access to follow-up.
- Antibiotics should be prescribed for children 6 months to 2 years of age with bilateral AOM without otorrhea. For those 2 years of age or older, observation may also be considered.
- Antibiotics or observation is recommended for children 6 months of age and older who have unilateral AOM without otorrhea.
- Initial antibiotic therapy is amoxicillin (80–90 mg/kg/day). Amoxicillin/clavulanate (90 mg/kg/day) should be used for severe disease. Cephalosporins (e.g., cefdinir, cefuroxime, cefprozime) are options in patients with non-type I allergy to penicillin.
- Treatment should be assessed after 48 to 72 hours.

## Acute Pharyngitis

- Acute pharyngitis is most common in children 5 to 15 years of age; it is rare before 3 years of age. Infection is typically viral but bacteria (e.g., group A  $\beta$ -hemolytic *streptococcus* [GAS]) are also causative organisms.

TABLE 99.5 Evidence of Middle Ear Effusion and Inflammation on Otoloscopic Examination

### MIDDLE EAR EFFUSION

Bulging tympanic membrane  
 Lack of tympanic membrane mobility  
 Presence of air-fluid level in middle ear  
 Otorrhea

### MIDDLE EAR INFLAMMATION

Obvious erythema of tympanic membrane  
 Pain specific to the ear preventing normal activity and sleep

- Symptoms of a GAS infection include sudden onset of throat pain, fever, headache, abdominal pain, nausea, vomiting, tonsillopharyngeal edema/erythema/exudate/ulceration, enlarged anterior cervical lymph nodes, soft palate petechiae, and a scarlatiniform rash.
- A rapid antigen test can be used to determine need for antibiotics; if negative, a throat culture should be done.
- Penicillins are the agents of choice for a GAS infection (Table 99.6).
- Patients with a history of rheumatic fever (characterized by acute generalized inflammation of the heart, joints, brain, or skin) should receive long-term antibiotic prophylaxis to prevent further complications (Table 99.7).

**TABLE 99.6 Medication Regimens for the Treatment of Streptococcal Pharyngitis and Prevention of Rheumatic Fever**

Medication	Dose	Duration
Amoxicillin	50 mg/kg once a day (maximum 1 g)	10 days
Penicillin VK	≤27 kg: 250 mg two or three times a day >27 kg: 500 mg two or three times a day	10 days
Benzathine penicillin G	≤27 kg: 600,000 units IM >27 kg: 1,200,000 units IM	Once

**FOR PATIENTS WITH PENICILLIN ALLERGY**

Cephalexin	12.5–25 mg/kg (up to 500 mg) twice a day	10 days
Cefadroxil	15 mg/kg (up to 1 g) twice a day	10 days
Clindamycin	10 mg/kg three times a day (maximum 1.8 g per day)	10 days
Azithromycin	12 mg/kg once a day (maximum 500 mg)	5 days
Clarithromycin	7.5 mg/kg twice a day (maximum 250 mg per dose)	10 days

IM, intramuscular.

**TABLE 99.7 Medication Regimens for the Prevention of Recurrent Rheumatic Fever**

Medication	Dose	Frequency
Benzathine penicillin G	≤27 kg: 600,000 units IM >27 kg: 1,200,000 units IM	Every 4 weeks
Penicillin V	250 mg oral	Twice a day
Sulfadiazine	≤27 kg: 0.5 g oral >27 kg: 1 g oral	Once a day
If allergic to above agents		
Erythromycin	250 mg oral	Twice a day
Clindamycin	75 mg oral	Twice a day

IM, intramuscular.



# Neonatal Therapy\*

## General Principles

- Every newborn is evaluated and classified at birth according to birth weight, gestational age, and intrauterine growth status. Table 100.1 shows common neonatal terminology.
- Apgar score (normal scores range from 7–10) is a method of evaluating the physical condition of an infant immediately after birth. The score is based on five clinical signs: heart rate, respiratory effort, muscle tone, skin color, and reflex irritability. Scores are taken at 1 and 5 minutes after birth until a score of 7 or higher is reached.

## Respiratory Distress Syndrome

- Respiratory distress syndrome (RDS), a major cause of morbidity and mortality in preterm neonates, results from pulmonary surfactant deficiency.
- Risk factors for RDS include prematurity, male sex, perinatal asphyxia, cesarean section, second-born twins, gestational diabetes, and maternal-fetal hemorrhage.
- RDS is characterized by respiratory failure with atelectasis, hypoxemia, decreased lung compliance, small airway epithelial damage, and pulmonary edema. Clinical signs include tachypnea, cyanosis, retracting respirations, grunting, nasal flaring, hypoxemia, hypercapnia, and a mixed respiratory and metabolic acidosis. Symptoms typically present within the first 6 hours of life.

TABLE 100.1 Common Neonatal Terminology

Term	Definition
Gestational age (GA)	<i>By dates:</i> The number of weeks from the onset of the mother's last menstrual period until birth <i>By examination:</i> Assessment of gestational maturity by physical and neuromuscular examination; gestational age estimates the time from conception until birth
Postnatal age (PNA)	Chronologic age after birth
Postconceptional age (PCA)	Gestational age plus postnatal age
Corrected age	Postconceptional age in weeks minus 40; represents postnatal age if neonate had been born at term (40 weeks' gestational age)
Preterm	<38 weeks' gestational age at birth
Term	38–42 weeks' gestational age at birth
Postterm	≥43 weeks' gestational age at birth
Extremely low-birth-weight (ELBW)	Birth weight <1 kg
Very low-birth-weight (VLBW)	Birth weight <1.5 kg
Low-birth-weight (LBW)	Birth weight <2.5 kg
Small for gestational age (SGA)	Birth weight <10th percentile for gestational age
Appropriate for gestational age (AGA)	Birth weight between 10th and 90th percentiles for gestational age
Large for gestational age (LGA)	Birth weight >90th percentile for gestational age

\*The reader is referred to Chapter 100, Neonatal Therapy, written by Jennifer Tran Pham, PharmD, BCPS, in the 10th edition of *Applied Therapeutics: The Clinical Use of Drugs* for a more in-depth discussion. All notations to reference numbers are based on the reference list at the end of that chapter. The editor of this handbook expresses her thanks to Dr. Pham and acknowledges that this chapter is based on her work.

- Inadequate oxygenation and ventilation and increased work of breathing caused by RDS may result in the need for assisted positive-pressure ventilation.
- Treatment includes intubation and intratracheal administration of exogenous surfactant (Table 100.2). Natural surfactants (calfactant or poractant alpha) are preferred to modified natural surfactant (beractant). Lucinactant is a new synthetic surfactant containing a protein analogue. Surfactant is typically administered after a diagnosis of RDS is established; prophylactic use (e.g., within 10–30 minutes after birth) is also an option.
- Mechanical ventilation can be avoided by using the “INSURE” technique (INTubate-SURfactant-Extubate).
- Adverse effects of surfactant are related to the method of administration (bradycardia, oxygen desaturation secondary to vagal stimulation and airway obstruction, pulmonary hemorrhage).

## Bronchopulmonary Dysplasia

- Bronchopulmonary dysplasia (BPD; also known as chronic lung disease) is the most common form of chronic pulmonary disease in infants and is a significant cause of infant morbidity and mortality.
- The cause is multifactorial: lung immaturity, surfactant deficiency, oxygen toxicity, barotraumas or volutrauma, and inflammation all play important roles.
- BPD is characterized by tachypnea with shallow breathing, intercostal and subcostal retractions, and expiratory wheezing. Other signs and symptoms include rales, rhonchi, cough, airflow obstruction, airway hyperactivity, increased mucus production, hypoxemia, and hypercarbia. Infants with severe BPD eventually experience cardiovascular complications (e.g., pulmonary hypertension, cor pulmonale, systemic hypertension, and left ventricular hypertrophy).
- Infants with BPD have significant growth, nutritional, and neurodevelopmental problems (e.g., learning disabilities, speech delays, vision and hearing impairment, poor attention span). They are also at risk for frequent respiratory infections.
- Prevention of prematurity and other etiologic factors of RDS are the most effective means of preventing BPD. Administration of antenatal steroids to mothers before delivery decreases the incidence of RDS and, potentially, BPD.
- Medical management of BPD includes supplemental oxygen therapy, mechanical ventilation, fluid restriction (120–130 mL/kg/day), and nutritional management (e.g., hypercaloric formulas). Various pharmacologic interventions including diuretics, bronchodilators, and corticosteroids are also used (Table 100.3).

## Patent Ductus Arteriosus

- Normally, the ductus arteriosus (a blood vessel connecting the left pulmonary artery to the aorta) of a term neonate functionally closes within the first days of life. If it fails to close, unoxygenated blood from the right ventricle is shunted to the systemic circulation through the ductus arteriosus. Patent ductus arteriosus (PDA) is a serious cardiovascular disorder.
- Risk factors include prematurity and RDS.
- Signs and symptoms include tachycardia, hyperactive precordium, wide pulse pressure, bounding pulses, and a continuous murmur.
- Complications of PDA include pulmonary edema and heart failure. PDA places the infant at high risk for BPD, intraventricular hemorrhage, and necrotizing enterocolitis.
- Medical management includes fluid management (fluid restriction and diuretic therapy), correction of anemia, and treatment of hypoxia and acidosis.
- Pharmacologic therapy with prostaglandin inhibitors (indomethacin, ibuprofen) may be needed to close the ductus. Ibuprofen is preferred in patients who have or are at risk for decreased renal function.
- Not every infant responds to pharmacologic therapy; surgical ligation of PDA may be required. Response is determined by assessing clinical signs of PDA (tachycardia, widened pulse pressure, bounding pulses, heart murmur, and ability to wean from ventilator support).

TABLE 100.2 Comparison of Currently Marketed Surfactant Products

Variable	Calfactant (Infasurf)	Poractant Alpha (Curosurf)	Beractant (Survanta)
Type and source	Natural surfactant, calf lung wash	Natural surfactant, porcine lung mince extract	Modified natural surfactant, bovine lung mince extract
Phospholipids	Natural DPPC with mixed phospholipids	Natural DPPC with mixed phospholipids	Natural and supplemented DPPC with mixed phospholipids
Proteins	Calf proteins SP-B and SP-C	Porcine proteins SP-B and SP-C	Bovine proteins SP-B and SP-C
Dispersing and adsorption agents	Proteins SP-B and SP-C	Proteins SP-B and SP-C	Proteins SP-B and SP-C
Indications	Prophylaxis and rescue therapy	Rescue therapy	Prophylaxis and rescue therapy
Criteria for prophylaxis	Premature infants <29 weeks' gestational age at high risk for RDS	Not approved	Birth weight <1,250 g or evidence of surfactant deficiency
Recommended dose	3 mL/kg (phospholipids 105 mg/kg)	<i>Initial dose:</i> 2.5 mL/kg (phospholipids 200 mg/kg); <i>Repeat dose:</i> 1.25 mL/kg (phospholipids 100 mg/kg)	4 mL/kg (phospholipids 100 mg/kg)
Recommended regimen for prophylaxis	Give first dose ASAP after birth, preferably within 30 minutes; repeat every 12 hours up to a total of three doses if infant remains intubated or repeat as early as 6 hours up to a total of four doses if infant remains intubated and requires $\text{FiO}_2 \geq 0.3$ with $\text{PaO}_2 \leq 80$ mm Hg	Not approved	Give first dose ASAP after birth, preferably within 15 minutes; repeat as early as 6 hours up to a total of four doses if infant remains intubated and requires $\text{FiO}_2 \geq 0.3$ with $\text{PaO}_2 \leq 80$ mm Hg
Criterion for rescue therapy	Infants $\leq 72$ hours of age with confirmed RDS who require endotracheal intubation	Infants with confirmed RDS who require endotracheal intubation	Infants with confirmed RDS who require endotracheal intubation
Recommended regimen for rescue therapy	Give first dose ASAP after RDS diagnosed, repeat every 12 hours up to a total of three doses if infant still remains intubated or repeat as early as 6 hours up to a total of four doses if infant still remains intubated and requires $\text{FiO}_2 \geq 0.3$ with $\text{PaO}_2 \leq 80$ mm Hg	Give first dose ASAP after RDS diagnosed, repeat every 12 hours up to a total of three doses if infant remains intubated and requires mechanical ventilation with supplemental oxygen	Give first dose ASAP after RDS diagnosed, preferably by 8 hours postnatal age; repeat as early as 6 hours up to a total of four doses if infant remains intubated and requires $\text{FiO}_2 \geq 0.3$ with $\text{PaO}_2 \leq 80$ mm Hg
Recommended administration technique	Administer through side-port of ETT adapter via ventilator; divide dose into two aliquots with position change or through disconnected ETT via 5F catheter; divide dose into four aliquots with position change	Administer through disconnected ETT via 5F catheter; divide dose into two aliquots with position change	Administer through disconnected ETT via 5F catheter; divide dose into four aliquots with position change
Special instructions	Gentle swirling of the vial may be necessary for redispersion; warming to room temperature is not necessary; do not shake	Warm to room temperature before use, do not shake	Warm to room temperature before use; do not shake

TABLE 100.2 Comparison of Currently Marketed Surfactant Products (Continued)

Variable	Calfactant (Infasurf)	Poractant Alpha (Curosurf)	Beractant (Survanta)
Stability	If warmed to room temperature for <24 hours, unopened, unused vials may be returned once to refrigerator; single-use vial contains no preservative; discard unused portion	If warmed to room temperature for <24 hours, unopened, unused vials may be returned only once to refrigerator; single-use vial contains no preservative; discard unused portion	If warmed to room temperature for <24 hours, unopened, unused vials may be returned only once to refrigerator; single-use vial contains no preservative; discard unused portion
Cost per vial	\$413.64 (3 mL), \$732.12 (6 mL) <sup>a</sup>	\$418.71 (1.5 mL), \$819.70 (3 mL) <sup>a</sup>	\$459.60 (4 mL), \$813.46 (8 mL) <sup>a</sup>

<sup>a</sup>Average wholesale price according to 2010 Red Book.

ASAP, as soon as possible; DPPC, dipalmitoylphosphatidylcholine; ETT, endotracheal tube; F, French; Fio<sub>2</sub>, fractional inspired oxygen; Pao<sub>2</sub>, partial pressure of oxygen; RDS, respiratory distress syndrome.

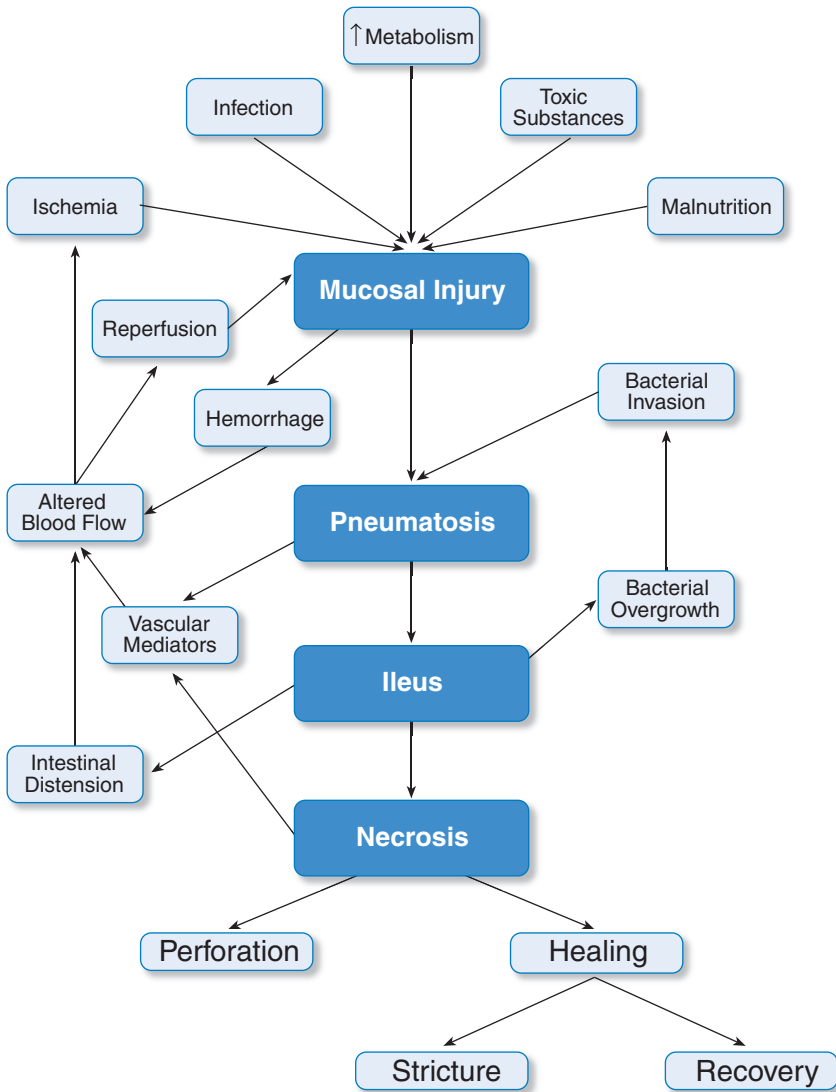
## Necrotizing Enterocolitis

- Necrotizing enterocolitis (NEC) is a type of acute intestinal necrosis and is the most common life-threatening nonrespiratory condition in newborns. It results from the effects of intestinal bacteria and other factors on injured intestinal mucosa (Figure 100.1). The most significant risk factor is prematurity.
- Signs and symptoms include abdominal distension, bloody stools, apnea, metabolic acidosis, gastric retention of feedings, respiratory distress, lethargy, thrombocytopenia, and neutropenia.

TABLE 100.3 Pharmacologic Management of Bronchopulmonary Dysplasia

Drug Therapy	Dosage Regimen
<b>DIURETICS</b>	
Chlorothiazide	<i>Neonates and infants &lt;6 months:</i> PO: 20–40 mg/kg/day in two divided doses; maximum dose: 375 mg/day
Furosemide	PO: 1–4 mg/kg/dose every 12–24 hours IV: 1–2 mg/kg/dose every 12–24 hours <i>Nebulized:</i> 1 mg/kg/dose diluted to a final volume of 2 mL with NS (use IV form)
Hydrochlorothiazide	<i>Neonates and infants &lt;6 months:</i> PO: 2–3 mg/kg/day in two divided doses; maximum dose: 37.5 mg/day
Spirinolactone	PO: 1–3 mg/kg/day every 12–24 hours
<b>INHALED BRONCHODILATORS</b>	
Albuterol	0.03–0.06 mL/kg/dose of 0.5% solution (0.15–0.3 mg/kg/dose) diluted to 1–2 mL of NS; give via nebulization every 2–6 hours or PRN; minimum dose: 0.25 mL (1.25 mg); maximum dose: 1 mL (5 mg)
Ipratropium bromide	<i>Neonates:</i> 0.125 mL/kg/dose of 0.02% solution (25 mcg/kg/dose) diluted to 2–2.5 mL of NS; give via nebulization every 8 hours <i>Infants:</i> 0.625–1.25 mL of 0.02% solution (125–250 mcg/dose) diluted to 2–2.5 mL of NS; give via nebulization every 8 hours
<b>INHALED CORTICOSTEROIDS</b>	
Beclomethasone dipropionate	2 puffs (40 mcg/puff) via face mask and spacer every 12 hours OR 2 puffs (80 mcg/puff) via face mask and spacer every 12 hours
Budesonide	0.25–0.5 mg; give via nebulization every 12 hours
Fluticasone	2–4 puffs (44 mcg/puff) via face mask and spacer every 12 hours

IV, intravenous; NS, normal saline; PO, oral; PRN, as needed.



**Figure 100.1** Necrotizing enterocolitis (NEC). This schematic is a composite of the theories about factors believed to be involved in the pathogenesis of NEC. The progression of this disease is denoted in large type. The factors believed to initiate or propagate the disease process are in smaller type. (Adapted with permission from Crouse DT. Necrotizing enterocolitis. In: Pomerance JJ, Richardson CJ, eds. *Neonatology for the Clinician*. Norwalk, CT: Appleton & Lange; 1993:364.)

NEC may progress to bowel perforation, peritonitis, sepsis, disseminated intravascular coagulopathy, and shock.

- **Stage I:** suspected NEC and mild GI problems (e.g., emesis, ileus)
- **Stage II:** systemic and abdominal signs (abdominal distension, bloody stools) that can be confirmed by the presence of pneumatosis intestinalis on x-ray
- **Stage III:** advanced NEC with peritonitis, shock, and possible intestinal perforation

- Management of NEC depends on the severity of illness. Options include parenteral nutrition, intravenous antibiotics, and bowel resection. Fluid resuscitation and inotropic agents may be needed for Stage III disease.
- Interventions including trophic feedings, breast milk, and probiotics may be used to decrease the incidence of NEC.

## Neonatal Sepsis and Meningitis

- Neonates are at increased risk for infections, and, because of the neonate's decreased immune function, there is a reduced ability to localize infections.
- Bacterial sepsis can be classified as early-onset (presenting in first 5–7 days of life; caused by pathogens colonized from the maternal genital tract) or late-onset (presenting after days 5–7 of life; caused by primary or nosocomial pathogens).
- Meningitis occurs as a complication of bacterial sepsis in up to 30% of septic neonates. Long-term sequelae include hearing loss, abnormal behavior, developmental delay, cerebral palsy, focal motor disability, seizure disorders, and hydrocephalus. Bacterial meningitis should always be considered in infants with neonatal sepsis.
- Risk factors include prematurity, low birth weight, male sex, predisposing maternal conditions (e.g., prolonged rupture of membranes, maternal fever, elevated maternal WBC or left shift, chorioamnionitis, and urinary tract infections), and presence of IV catheters.
- Clinical signs can be subtle and nonspecific especially in preterm infants. The most common signs are poor feeding, temperature instability, lethargy, or apnea. Other signs can include glucose instability, tachycardia, dyspnea or cyanosis, tachypnea, diarrhea, vomiting, feeding intolerance, abdominal distension, metabolic acidosis, or abnormal WBC counts. Hypothermia is more common than fever. Late signs can include jaundice, hepatosplenomegaly, and petechiae. Bulging fontanelle, posturing, or seizures suggest meningitis.
- Empiric treatment with appropriate IV antibiotics must be promptly initiated after collecting blood, cerebrospinal fluid, and urine for cultures and sensitivities. Selection of empiric intravenous antibiotics is the same for sepsis and meningitis; choice depends on nosocomial pathogens commonly isolated in the neonatal intensive care unit, antibiotic resistance patterns, and underlying neonatal risk factors. Empiric antibiotic of choice for early-onset neonatal sepsis and meningitis is ampicillin plus gentamicin (Tables 100.4 and 100.5).

## Congenital Infections

- Certain bacteria, viruses, and protozoa can cause fetal infections that may result in fetal death, congenital anomalies, serious CNS sequelae, intrauterine growth retardation, or preterm birth.

TABLE 100.4 Gentamicin Dosing Guidelines for Neonates and Infants

Traditional Dosing		
Age	Weight	Dosing Regimen
GA <38 weeks	<1,000 g	3.5 mg/kg/dose every 24 hours
PNA 0–4 weeks	<1,200 g	2.5 mg/kg/dose every 18–24 hours
PNA ≤7 days	≥1,200 g	2.5 mg/kg/dose every 12 hours
PNA >7 days	1,200–2,000 g	2.5 mg/kg/dose every 8–12 hours
PNA >7 days	>2,000 g	2.5 mg/kg/dose every 8 hours
Extended-Interval Dosing		
Age	≤29 Weeks GA	30–34 Weeks GA
PNA 0–7 days	5 mg/kg/dose every 48 hours	4.5 mg/kg/dose every 36 hours
PNA 8–28 days	4 mg/kg/dose every 36 hours	4 mg/kg/dose every 24 hours
PNA ≥29 days	4 mg/kg/dose every 24 hours	4 mg/kg/dose every 24 hours

GA, gestational age; PNA, postnatal age.

TABLE 100.5 Antimicrobial Dosage Regimens for Neonates: Dosages and Intervals of Administration

Drug	Weight <1,200 g	Weight 1,200–2,000 g		Weight >2,000 g	
	0–4 Weeks (mg/kg) <sup>a</sup>	0–7 Days (mg/kg) <sup>a</sup>	8–28 Days (mg/kg) <sup>a</sup>	0–7 Days (mg/kg) <sup>a</sup>	8–28 Days <sup>a</sup> (mg/kg) <sup>a</sup>
Amphotericin B					
Deoxycholate	1 every 24 hours	1 every 24 hours	1 every 24 hours	1 every 24 hours	1 every 24 hours
Lipid complex/ Liposomal	5 every 24 hours	5 every 24 hours	5 every 24 hours	5 every 24 hours	5 every 24 hours
Ampicillin					
Meningitis	100 every 12 hours	100 every 8 hours	75 every 6 hours	50 every 8 hours	75 every 6 hours
Other diseases	25 every 12 hours	25 every 12 hours	25 every 8 hours	25 every 8 hours	25 every 6 hours
Cefazolin	25 every 12 hours	25 every 12 hours	25 every 12 hours	25 every 12 hours	25 every 8 hours
Cefepime	30 every 12 hours	50 every 12 hours	30 every 12 hours <sup>b</sup>	50 every 12 hours	30 every 12 hours <sup>b</sup>
Cefotaxime <sup>c</sup>	50 every 12 hours	50 every 12 hours	50 every 8 hours	50 every 12 hours	50 every 8 hours
Ceftazidime <sup>c</sup>	50 every 12 hours	50 every 12 hours	50 every 8 hours	50 every 12 hours	50 every 8 hours
Ceftriaxone <sup>c</sup>	25 every 24 hours	50 every 24 hours	50 every 24 hours	50 every 24 hours	75 every 24 hours
Clindamycin	5 every 12 hours	5 every 12 hours	5 every 8 hours	5 every 8 hours	5 every 6 hours
Erythromycin	10 every 12 hours	10 every 12 hours	10 every 8 hours	10 every 12 hours	13.3 every 8 hours
Fluconazole	6 every 72 hours	12 every 48 hours	12 every 24 hours	12 every 48 hours	12 every 24 hours
Linezolid	10 every 12 hours	10 every 12 hours	10 every 8 hours	10 every 8 hours	10 every 8 hours
Meropenem <sup>c</sup>	20 every 12 hours	20 every 12 hours	20 every 8 hours	20 every 8 hours	30 every 8 hours
Metronidazole	7.5 every 48 hours	7.5 every 24 hours	7.5 every 12 hours	7.5 every 12 hours	15 every 12 hours
Oxacillin	25 every 12 hours	25 every 12 hours	25 every 8 hours	25 every 8 hours	37.5 every 6 hours
Nafcillin	25 every 12 hours	25 every 12 hours	25 every 8 hours	25 every 8 hours	37.5 every 6 hours
Penicillin G					
Meningitis	50,000 U every 12 hours	50,000 U every 12 hours	50,000 U every 8 hours	50,000 U every 12 hours	50,000 U every 8 hours
Other diseases	25,000 U every 12 hours	25,000 U every 12 hours	25,000 U every 8 hours	25,000 U every 12 hours	25,000 U every 8 hours
Piperacillin/ tazobactam	50 every 12 hours	75 every 12 hours	75 every 8 hours	75 every 12 hours	75 every 8 hours
Ticarcillin or Ticarcillin/ clavulanate	75 every 12 hours	75 every 12 hours	75 every 8 hours	75 every 12 hours	75 every 8 hours
Vancomycin	15 every 24 hours <sup>d</sup>	15 <sup>e</sup>	15 <sup>e</sup>	15 <sup>e</sup>	15 <sup>e</sup>

<sup>a</sup>Postnatal age.<sup>b</sup>Cefepime should be given at 30 mg/kg/dose every 12 hours for the first 2 weeks of life, then increase to 50 mg/kg/dose every 12 hours (or 50 mg/kg/dose every 8 hours for *Pseudomonas* infections or meningitis).<sup>c</sup>Higher dosage may be needed for meningitis.<sup>d</sup>If weight <750 g and postnatal age <14 days, use 10 to 12.5 mg/kg every 24 hours.<sup>e</sup>If ≤26 weeks' PCA, use every 18 hours; if 27 to 34 weeks' PCA, use every 12 hours; if >35 weeks' PCA, use every 8 hours.

- Primary clinical manifestations and treatment for selected congenital infections are listed in Table 100.6. The TORCH acronym is used to remember the primary organisms that cause infection (**T**oxoplasmosis, **O**ther [syphilis, gonorrhea, hepatitis B, listeria], **R**ubella, **C**ytomegalovirus, **H**erpes simplex).

## Apnea of Prematurity

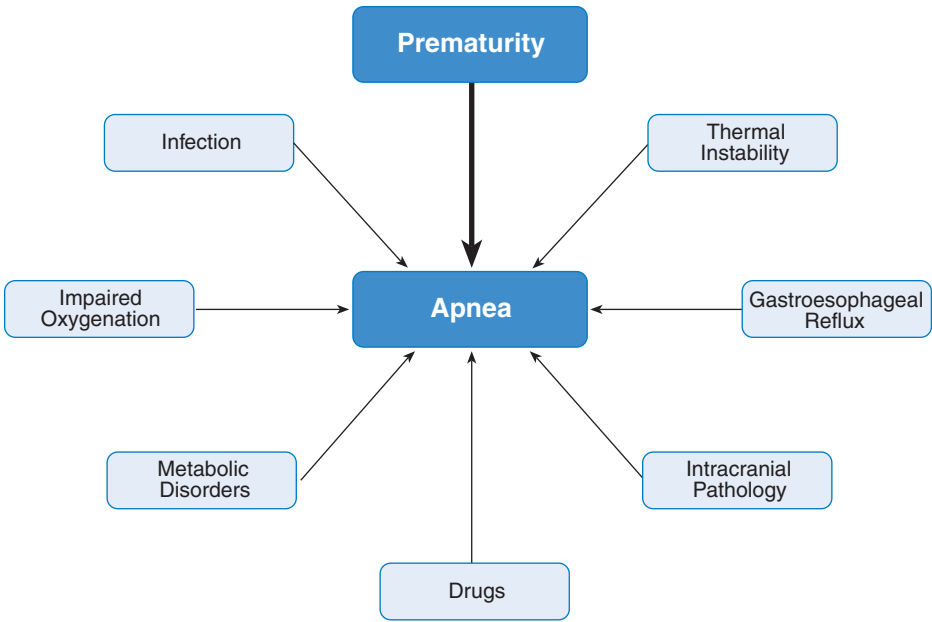
- Apnea in neonates is a life-threatening condition that occurs more frequently in premature newborns and newborns of lower birth weights. Apnea can be caused by prematurity or by severe underlying disease; sepsis must be ruled out (Figure 100.2).
- Clinically significant apnea is defined as cessation of breathing for at least 15 seconds, or less if accompanied by bradycardia (HR <100 beats/minute), significant hypoxemia, or cyanosis. Pallor or hypotonia may also occur.

TABLE 100.6 Selected Congenital and Perinatal Infections in the Neonate

Organism	Primary Clinical Manifestations	Treatment of Proven or Highly Probable Disease
Herpes simplex	Cutaneous vesicles, keratoconjunctivitis, microcephaly, CNS infection, hepatitis, pneumonitis, prematurity, respiratory distress, sepsis, convulsion, chorioretinitis	<i>Acyclovir</i> : 20 mg/kg every 8 hours IV × 14–21 days <i>Ocular involvement</i> : Acyclovir IV plus topical therapy: 1%–2% trifluridine, 1% iododeoxyuridine, or 3% vidarabine
Toxoplasmosis	Chorioretinitis, ventriculomegaly, microcephaly, hydrocephaly, intracranial calcifications, ascites, hepatosplenomegaly, lymphadenopathy, jaundice, anemia, mental retardation	Sulfadiazine 100 mg/kg/day in two divided doses PO for 1 year and pyrimethamine 2 mg/kg/day × 2 days, then 1 mg/kg/day for 2–6 months, then 1 mg/kg QOD to complete 1 year of therapy <i>and</i> leucovorin (folinic acid) 5–10 mg three times/week × 1 year
Treponema pallidum	<i>Early</i> : Osteochondritis, periostitis, hepatosplenomegaly, skin rash (maculopapular or vesiculobullous), rhinitis, meningitis, IUGR, jaundice, hepatitis, anemia, thrombocytopenia, chorioretinitis <i>Late</i> : Hutchinson triad (interstitial keratitis, VIII-nerve deafness, Hutchinson teeth), mental retardation, hydrocephalus, saddle nose, mulberry molars	Aqueous crystalline penicillin G × 10 days IV (preferred) or IM: ≤7 days postnatal age: 50,000 units/kg every 12 hours >7 days postnatal age: 50,000 units/kg every 8 hours OR Procaine penicillin G 50,000 units/kg/day IM every 24 hours × 10 days
Hepatitis B	Prematurity; usually asymptomatic; long-term effects include chronic hepatitis, cirrhosis, liver failure, hepatocellular carcinoma	<i>Perinatal exposure (maternal HbsAg-positive)</i> : HBIG 0.5 mL IM and hepatitis B vaccine IM (different IM sites) within 12 hours after birth; repeat hepatitis B vaccine at 1 and 6 months Supportive care
Rubella	<i>Early</i> : IUGR, retinopathy, hypotonia, hepatosplenomegaly, thrombocytopenic purpura, bone lesions, cardiac effects <i>Late</i> : Hearing loss, mental retardation, diabetes <i>Rare</i> : Myocarditis, glaucoma, microcephaly, hepatitis, anemia	
Cytomegalovirus	Petechiae, hepatosplenomegaly, jaundice, prematurity, IUGR, increased liver enzymes, hyperbilirubinemia, anemia, thrombocytopenia, interstitial pneumonitis, microcephaly, chorioretinitis, intracranial calcifications <i>Late</i> : Hearing loss, mental retardation, learning and motor abnormalities, visual disturbances	IV ganciclovir (optimal dose and duration not established; preliminary data suggest doses of 12 mg/kg/day divided every 12 hours for 6 weeks)
<i>Neisseria gonorrhoeae</i>	Ophthalmia neonatorum, scalp abscess, sepsis, arthritis, meningitis, endocarditis	<i>Nondisseminated (including ophthalmia neonatorum)</i> : Ceftriaxone 25–50 mg/kg IV or IM × 1 (maximum dose: 125 mg); alternative for ophthalmic neonatorum: cefotaxime 100 mg/kg IM or IV × 1; use saline eye irrigations for ophthalmia neonatorum <i>Disseminated</i> : Ceftriaxone 25–50 mg/kg IV or IM every 24 hours; cefotaxime 25–50 mg/kg IV or IM every 12 hours <i>Duration of therapy</i> : • Arthritis or septicemia: 7 days • Meningitis: 10–14 days Use cefotaxime if hyperbilirubinemic

CNS, central nervous system; HBIG, hepatitis B immune globulin; HbsAg, hepatitis B surface antigen; IM, intramuscular; IUGR, intrauterine growth retardation; IV, intravenous; PO, oral; QOD, every other day.





**Figure 100.2** Causes of apnea in the neonate. (Adapted with permission from Martin RJ et al. Pathogenesis of apnea in preterm infants. *J Pediatr.* 1986;109:738.)

- Treatment includes the use of supplemental oxygen, gentle tactile stimulation, environmental temperature control, methylxanthines, nasal continuous positive airway pressure, and positive-pressure ventilation.
- Methylxanthines (caffeine, theophylline, aminophylline) are widely accepted as the initial pharmacologic approach. Therapy is initiated when apneic episodes are frequent, prolonged for 20 seconds or greater, are accompanied by significant bradycardia or cyanosis, or are not controlled by nonpharmacologic means. The goal of therapy is to reduce the number of episodes of apnea and bradycardia.

## Neonatal Seizures

- Neonatal seizure activity is a common manifestation of a life-threatening underlying neurologic process (Table 100.7).
- Seizure activity can be clonic, tonic, myoclonic, or subtle. Autonomic nervous system signs (change in HR, BP, respiration, skin color, oxygenation, salivation, pupil size) may occur.
- Complete evaluation includes assessment of the infant's airway, breathing, and circulation; review of the infant's history, physical examination, and laboratory studies (glucose, electrolytes, blood gases, bilirubin, complete blood count); and infectious disease workup.
- Initial therapy is focused on the treatment of the underlying cause (e.g., hypoglycemia, hypocalcemia, infection) and may not include antiepileptic drug therapy.
- Phenobarbital is the initial antiepileptic drug of choice; phenytoin and lorazepam are usually considered second- and third-choice agents (Table 100.8). The optimal duration of anticonvulsant treatment is not established. Periodic reassessment at 1- and 3-months post-discharge and then every 3 months is recommended for neonates receiving ongoing therapy.

TABLE 100.7 Causes of Neonatal Seizures<sup>118–122</sup>

Metabolic or electrolyte imbalance
Alterations in calcium, glucose, magnesium, or sodium concentrations
Inborn errors of metabolism (e.g., pyridoxine-responsive seizures)
Cerebrovascular injury
Hypoxic or ischemic encephalopathy
Arterial and venous ischemic stroke
Hemorrhage (intracerebral, intraventricular, subarachnoid, or subdural)
CNS infection
Bacterial meningitis
Viral meningoencephalitis
Congenital infections
Drug-related causes
Adverse effects from drugs administered before, during, or after delivery
Withdrawal after maternal drug use
Other
Cerebral dysgenesis
Genetic or syndromic disorders
Familial seizure disorders
Early myoclonic encephalopathy

TABLE 100.8 Pharmacotherapy of Neonatal Seizures<sup>a</sup>

Drug	Loading Dose	Maintenance Dose	Therapeutic Concentration
Phenobarbital	IV: Initial: 20 mg/kg then 5–10 mg/kg every 15–20 minutes if needed until total load of 40 mg/kg	IV PO: Initial: Premature: 3 mg/kg/day Term: 4 mg/kg/day May need to ↑ to 4–5 mg/kg/day by 2–4 weeks of therapy	20–40 mcg/mL
Phenytoin	IV: 15–20 mg/kg	IV: Initial: 5 mg/kg/day May need to ↑ to ≥10 mg/kg/day by 2–4 weeks of therapy	8–15 mcg/mL
Lorazepam	IV: 0.05–0.1 mg/kg	May repeat doses if needed every 10–15 minutes	
Midazolam	IV: Initial bolus dose of 0.15 mg/kg has been used in some studies; however, for safety reasons, this bolus dose should not be given if the neonate has received an IV dose of a benzodiazepine	IV continuous infusion: Initial: 0.05 mg/kg/hour; ↑ by 0.025 mg/kg/hour increments; usual maximum 0.4 mg/kg/hour; some studies reported neonates who required doses up to 1 mg/kg/hour	
Levetiracetam	Dose not established; studies have used the following: IV: Initial: 10 mg/kg given twice daily	IV: ↑ dose by 10 mg/kg/day over 3 days to 30 mg/kg/day given in two divided doses; additional increases up to 45–60 mg/kg/day have been used	
Pyridoxine	IV: 50–100 mg	IV PO: 20–50 mg/day; ↑ dose PRN with age	
Valproic acid	PO: 20 mg/kg	PO: 10 mg/kg/dose every 12 hours	40–50 mcg/mL

<sup>a</sup>See 10th edition of *Applied Therapeutics: The Clinical Use of Drugs* for comments on appropriate IV administration and monitoring.

IV, intravenous; PO, oral; PRN, as needed.

# Care of the Critically Ill Child\*

## General Principles

- The numerous physiologic changes that take place during childhood, and understanding how they affect assessment and patient management (medication selection, dosing, monitoring), create challenges for managing pediatric patients.

## Pediatric Cardiopulmonary Arrest

- The most frequent cause of cardiac arrest in pediatric patients is a terminal result of respiratory failure or shock, not a primary cardiac event.
- Epinephrine is the drug of choice for the management of pediatric asystole.

## Respiratory Distress

- Developmental changes and immaturity of the respiratory system make respiratory distress the most common reason for hospital admission in the first year of life. Anything that impairs diaphragm movement (e.g., large stomach bubble, abdominal distension, peritonitis) can result in respiratory failure in a young child.
- The most common causes of respiratory failure in infants and children are infectious diseases, asthma, malignancies, trauma, poisonings, foreign body aspiration, anatomical upper airway obstruction, cardiogenic shock, and untreated left–right intracardiac shunts.
- Assessment of respiratory distress should include respiratory rate and effort, work of breathing, quality and magnitude of breath sounds, and patient’s mental status. Normal respiratory rates vary with age (Table 101.1).
- Table 101.2 summarizes common respiratory noises in children and their site of origin. Nasal flaring and grunting are unique features of the respiratory examination in infants that indicate respiratory distress.
- Oxygen should be given immediately when respiratory difficulty is suspected.
- **Intubation and Mechanical Ventilation:** Indications for intubation in infants and children include apnea, acute respiratory failure, need to control oxygen delivery, inadequate chest

TABLE 101.1 Normal Respiratory Rates and Definition of Tachypnea for Children, by Age

Age	Respiratory Rate (breaths/minute)	Tachypnea (breaths/minute)
Newborn–2 months	30–60	>60
2 months–12 months	25–40	>50
1–3 years	20–30	>40
3–6 years	16–22	>40
7–12 years	14–20	>40
>12 years	12–20	>40

\*The reader is referred to Chapter 101, Care of the Critically Ill Child, written by Elizabeth Farrington, PharmD, FCCP, FCCM, FPPAG, BCPS, and Marcia L. Buck, PharmD, FCCP, FPPAG, in the 10th edition of *Applied Therapeutics: The Clinical Use of Drugs* for a more in-depth discussion. All notations to reference numbers are based on the reference list at the end of that chapter. The editor of this handbook expresses her thanks to Drs. Farrington and Buck and acknowledges that this chapter is based on their work.

TABLE 101.2 Common Airway Noises, Site of Origin, and Clinical Causes in Children

Respiratory Noise	Definition	Site of Origin	Common Clinical Causes	
			Acute	Persistent
Wheeze	A high-pitched, continuous musical noise, often associated with prolonged expiration (can occur with inspiration or expiration)	Intrathoracic airways	Intermittent asthma/viral-induced wheeze	Persistent asthma
Rattle	This sound is the result of excessive secretions in the large airways, which are presumably moving with normal respirations	Either or both intrathoracic and extrathoracic airways	Acute viral bronchitis	Chronic sputum retention (neuromuscular disorders)
Stridor	This is predominately an inspiratory noise and indicates obstruction to airflow in the extrathoracic airways (upper airways obstruction) (can occur with inspiration or expiration)	Extrathoracic airways	Acute laryngotracheobronchitis (or viral croup)	Laryngomalacia
Snore	The noise arises from an increase to airflow through the upper airways, predominately in the region of the nasopharynx and oropharynx; it is more obvious during inspiration, but may be audible throughout the respiratory cycle	Oronasopharyngeal airway	Acute tonsillitis/pharyngitis	Chronically enlarged tonsils and adenoids, obstructive sleep apnea
Snuffle/snort	These terms describe respiratory noises emanating from the nasal passages; these noises are audible in both inspiration and expiration and are often associated with visible secretions from the nares	Nasal passage/nasopharynx	Acute viral head cold	Allergic rhinitis
Grunt	This sound occurs with closure of the glottis during active exhalation	Alveoli/lung parenchyma	Any alveolar pathology in infants and small children	None

For examples of some of these airway noises, go to the following web links:

Wheeze: <http://www.youtube.com/watch?v=YGO-ukhU1xE&feature=related>

Rattle/rhonchi: <http://www.youtube.com/watch?v=QPBZOohj2a0&feature=related>

Stridor:

Toddler: <http://www.youtube.com/watch?v=Zkau4yHsLLM&feature=related>

Infant: <http://www.youtube.com/watch?v=73zUjcCzgqA&NR=1>

Grunt: [http://www.youtube.com/watch?v=aptwtj6y\\_4](http://www.youtube.com/watch?v=aptwtj6y_4)

wall function, upper airway obstruction, and protection of the airway in a patient whose protective reflexes are absent (e.g., head trauma). Specific patient conditions and recommended agents for intubation are shown in Table 101.3.

TABLE 101.3 Management Examples of Specific Patient Cases

Condition	Treatment Goal During Intubation	Medications
Full stomach	Prevent passive regurgitation and aspiration after airway protective reflexes lost	Rocuronium, succinylcholine
Bronchospasm	Eliminate or treat stimuli that would induce or increase bronchospasm	Ketamine, vecuronium, lidocaine, atropine
Increased intracranial pressure	No increase in heart rate or blood pressure	Thiopental/pentobarbital, etomidate, vecuronium, rocuronium, lidocaine
Pulmonary vascular hypertension	Avoid decreased pulmonary blood flow	Midazolam, fentanyl, vecuronium
Hypocalcemia or depressed cardiac output	Maintain blood pressure without heart rate changes	Etomidate or midazolam with fentanyl

- Pharmacologic therapy is used to produce adequate sedation, analgesia, and amnesia plus a blunting of the physiologic response to airway manipulation (Table 101.4). Patients with inadequate relaxation despite adequate sedation may require neuromuscular blockade.
- Rapid sequence intubation (RSI) is used to gain airway control with an endotracheal tube (ETT) as quickly as possible to prevent aspiration.

TABLE 101.4 Pharmacologic Agents Used for Pediatric Intubation and Continuous Sedation

Drug	Route	Dose	Onset	Duration	Benefits	Adverse Effects
<b>NARCOTICS</b>						
Morphine	IV	0.1 mg/kg/dose (max: initial dose 2 mg) may repeat to a maximum total dose of 15 mg Neonates: 0.05 mg/kg/dose <b>Continuous infusion</b> Children: 20–50 mcg/kg/hour Neonates: 15 mcg/kg/hour Premature neonates: 10 mcg/kg/hour	Peak: 20 minutes	2–4 hours in neonates	Reversible (naloxone)	Histamine release. Respiratory depression, hypotension, peripheral vasodilatation, euphoria, dysphoria, itching, central nausea and vomiting, decreased response to hypercarbia
Fentanyl	IV	1–3 mcg/kg/dose (max: initial dose 100 mcg, may repeat to a total dose of 5 mcg/kg or 250 mcg) <b>Continuous infusion</b> 1–3 mcg/kg/hour (max: initial dose 50–100 mcg/hour) CHD patient with an open chest: 5 mcg/kg/hour	1–3 minutes	30–90 minutes	Rapid onset, short acting, reversible (naloxone), relatively stable hemodynamic profile	Bradycardia, respiratory depression, decreased response to hypercarbia, acute chest wall rigidity, itching
<b>BENZODIAZEPINES</b>						
Diazepam	IV	0.05 mg/kg/dose (max: 5 mg) may repeat in 0.05-mg/kg increments (max: 1 mg) to a total maximum dose of 10 mg	0.5–2 minutes	3 hours	Reversible (flumazenil)	Respiratory depression, lacks analgesic properties, hypotension and bradycardia, local irritation, pain

TABLE 101.4 Pharmacologic Agents Used for Pediatric Intubation (Continued)

Drug	Route	Dose	Onset	Duration	Benefits	Adverse Effects
Lorazepam	IV	0.05–0.15 mg/kg/dose (max: 4 mg)	15–30 minutes	0.5–3 hours	Reversible (flumazenil)	Respiratory depression, lacks analgesic properties, hypotension and bradycardia
Midazolam	IV/ IM	0.05–0.15 mg/kg/dose (max: initial dose 2 mg, may repeat in 1-mg increments to a total dose of 5 mg) <b>Continuous infusion</b> 0.05–0.1 mg/kg/hour (max: initial dose 2 mg/hour)	1–5 minutes	20–30 minutes	Rapid onset, short acting, provides amnesia, reversible (flumazenil)	Respiratory depression, lacks analgesic properties, hypotension and bradycardia
	IN	0.1–0.3 mg/kg/dose (max: 10 mg) Use the 5-mg/mL concentration	2–5 minutes	30–60 minutes		
	PO	0.5–0.75 mg/kg/dose (max: 10–20 mg)	30 minutes	2–6 hours		
<b>BARBITURATES</b>						
Pentobarbital	IV	2 mg/kg/dose (max: 100 mg). May repeat in 1-mg/kg/dose increments to a total dose of 7 mg/kg Do not exceed 200 mg total dose <b>Continuous infusion:</b> 0.5–1 mg/kg/hour	1 minute	15 minutes	Decreases intracranial pressure	Cardiovascular and respiratory depression
	IM/ PO/ PR	2–6 mg/kg/dose	IM: 10–15 minutes PR/PO: 15–60 minutes	1–4 hours		
Thiopental	IV	2–3 mg/kg/dose, repeat as needed	30–60 seconds	5–20 minutes	Ultrashort-acting barbiturate Decreases intracranial pressure	Cardiovascular and respiratory depression
<b>MISCELLANEOUS</b>						
Ketamine	IV	1 mg/kg/dose every 5 minutes titrated to effect  <b>Continuous infusion:</b> 0.5–1 mg/kg/hour	1–2 minutes	10–30 minutes	Rapid onset, airway protective reflexes stay intact, no hypotension or bradycardia Bronchodilation is useful to intubate asthmatics	Increases airway secretions and laryngospasm (blunted with atropine). Elevated intracranial and intraocular pressure. Emergence reactions are possible.
	IM	4–5 mg/kg/dose	3–5 minutes	12–25 minutes		
	PO	6–10 mg/kg (mixed in cola or other beverage)	30 minutes	30–60 minutes		

Continued on following page

TABLE 101.4 Pharmacologic Agents Used for Pediatric Intubation (Continued)

Drug	Route	Dose	Onset	Duration	Benefits	Adverse Effects
Etomidate	IV	0.3 mg/kg/dose initially, then 0.1 mg/kg/dose every 5 minutes to titrate to effect	10–20 seconds	4–10 minutes	Rapid onset Short acting Stable hemodynamic profile, decreased ICP	Potential for adrenal inhibition, nausea, and vomiting on emergence
Propofol	IV	1–2 mg/kg/dose initially, then 0.5–2 mg/kg/dose every 3–5 minutes to titrate to effect  <b>Continuous infusion:</b> Infants and children: 50–150 mcg/kg/minute Adolescents: 10–50 mcg/kg/minute	30–60 seconds	5–10 minutes	Intravenous general anesthetic, rapid onset and recovery	Cardiovascular and respiratory depression, contraindicated in patients with egg allergy, pain on injection
Dexmedetomidine	IV	0.5–1 mg/kg/dose  <b>Continuous infusion:</b> 0.4–0.7 mcg/kg/hour Doses as high as 2.5 mcg/kg/hour have been used	30 minutes	4 hours	Minimal to no respiratory depression	Hypotension and bradycardia Use with caution in patients with advanced heart block
<b>NEUROMUSCULAR BLOCKERS</b>						
Succinylcholine	IV	1 mg/kg/dose	30–60 seconds	4–7 minutes	Rapid onset Short duration	Potentiates hyperkalemia. Contraindicated in head trauma (↑ ICP), crush injury, burns, hyperkalemia. May induce neuroleptic malignant syndrome
Vecuronium	IV	0.1 mg/kg/dose <b>Continuous infusion:</b> 0.1 mg/kg/hour	1–3 minutes	30–40 minutes	Cardiovascular stable	Slower onset Longer duration of action
Rocuronium	IV/ IM	0.6–1 mg/kg/dose	60–75 seconds	20–30 minutes	Cardiovascular stable	
<b>REVERSAL AGENTS</b>						
Naloxone	IV	For opioid overdose: 0.1 mg/kg/dose (max: 2 mg) For reversal of mild respiratory depression: 0.01–0.02 mg/kg/dose (max: 0.4 mg) may repeat every 2–3 minutes	2 minutes	20–60 minutes	Rapid onset	Shorter duration than most opioids, therefore repeated doses may be needed
Flumazenil	IV	0.01 mg/kg/dose (max: 0.2 mg), may repeat 0.005 mg/kg/dose at 1-minute intervals to a max total dose of 1 mg	1–3 minutes	6–10 minutes	Rapid onset	Shorter duration than most benzodiazepines, therefore repeated doses may be needed

CHD, congenital heart disease; ICP, intracranial pressure; IM, intramuscular; IN, intranasal; IV, intravenous; PO, oral.

## Pediatric Shock

- Shock results from inadequate blood flow and oxygen delivery to meet the metabolic demands of tissues. It can be classified as hypovolemic, distributive, cardiogenic, or obstructive. Hypovolemic shock, the most common shock seen in pediatric patients, occurs when circulating intravascular volume decreases such that adequate tissue perfusion can no longer be maintained.
- Signs of compensated shock include tachycardia, cool and pale distal extremities, prolonged (>2 seconds) capillary refill, weak peripheral pulses compared with central pulses, and normal systolic blood pressure. As the ability to compensate is exhausted, the patient will exhibit signs of inadequate end organ perfusion (decreased mental status, decreased urine output, metabolic acidosis, tachypnea, weak central pulses, and mottling of extremities).
- Key definitions of the pediatric sepsis continuum are in Table 101.5. Six clinical and physiologic age categories for defining systemic inflammatory response syndrome (SIRS) exist (Tables 101.6 and 101.7). Definitions of organ dysfunction are modified for children (Table 101.8).
- **Septic Shock:** Due to the immature immune system in the infant, the incidence of septic shock is highest in the first year of life. Common pediatric pathogens and appropriate empiric antibiotic coverage is shown in Table 101.9. Antibiotics should be administered within 1 hour of diagnosis, after the collection of appropriate cultures.
- All patients presenting with shock should be placed on high-flow oxygen and should receive prompt resuscitation of poor perfusion through administration of IV fluids and appropriately targeted inotropic and vasopressor therapy, early empiric antimicrobial therapy, drainage of the infection whenever possible, and continuous monitoring of hemodynamic status. Cardiovascular therapy in children with septic shock must be individualized (Table 101.10).
  - Dopamine is the initial vasopressor of choice in children with shock unresponsive to fluid resuscitation.

**TABLE 101.5 Definitions of Systemic Inflammatory Response Syndrome, Infection, Sepsis, Severe Sepsis, and Septic Shock in Children**

SIRS	The presence of at least two of the following four criteria, one of which must be abnormal temperature or leukocyte count: <ul style="list-style-type: none"> <li>• Core temperature of &gt;38°C or &lt;36°C (must be measured by rectal, bladder, oral, or central catheter probe)</li> <li>• Tachycardia defined as at least 2 standard deviations above normal for age in the absence of external stimulus, chronic drugs, or painful stimuli; or otherwise persistent elevation for a 0.5- to 4-hour time period OR for children &lt;1 year old. Bradycardia, defined as a mean heart rate &lt;10% percentile for age in the absence of external vagal stimulus, <math>\beta</math>-blocker drugs, or congenital heart disease; or otherwise unexplained depression in a half-hour period</li> <li>• Mean respiratory rate &gt;2 standard deviations above normal for age or mechanical ventilation for an acute process not related to underlying neuromuscular disease or receipt of general anesthesia</li> <li>• Leukocyte count elevated or depressed for age (not secondary to chemotherapy-induced neutropenia) or &gt;10% immature neutrophils</li> </ul>
Infection	A suspected or proven (by positive culture, tissue stain, or polymerase chain reaction test) infection caused by any pathogen OR a clinical syndrome associated with a high probability of infection. Evidence of infection includes positive findings on clinical examination, imaging, or laboratory tests (e.g., white blood cells in a normally sterile body fluid, perforated viscus, chest radiograph consistent with pneumonia, petechial or purpuric rash, or purpura fulminans)
Sepsis	SIRS in the presence of or as a result of suspected or proven infection
Severe sepsis	Sepsis plus one of the following: cardiovascular organ dysfunction OR acute respiratory distress syndrome OR dysfunction of two or more other organs, as defined in Table 101.9
Septic shock	Severe sepsis with cardiovascular dysfunction, as defined in Table 101.9

SIRS, systemic inflammatory response syndrome.

Source: Adapted with permission from Goldstein B et al. International pediatric sepsis consensus conference: definitions for sepsis and organ dysfunction in pediatrics. *Pediatr Crit Care Med.* 2005;6(1):4.



TABLE 101.6 Pediatric Age Groups Definitions for Severe Sepsis

Age Category	Definition
Newborn	0 days to 1 week
Neonate	1 week to 1 month
Infant	1 month to 1 year
Toddler and preschool	2 to 5 years
School-age child	6 to 12 years
Adolescent and young adult	13 to <18 years

Source: Reprinted with permission from Goldstein B et al. International pediatric sepsis consensus conference: definitions for sepsis and organ dysfunction in pediatrics. *Pediatr Crit Care Med.* 2005;6(1):3

TABLE 101.7 Age-Specific Vital Signs and Laboratory Variables

Age Group	Heart Rate <sup>a</sup> (beats/minute)		Respiratory Rate (breaths/minute)	Leukocyte Count <sup>a</sup> (per 10 <sup>3</sup> /μL)	Systolic Blood Pressure <sup>a</sup> (mm Hg)
	Tachycardia	Bradycardia			
0 days to 1 week	>180	<100	>50	>34	<65
1 week to 1 month	>180	<100	>40	>19.5 or <5	<75
1 month to 1 year	>180	<90	>34	>17.5 or <5	<100
2 to 5 years	>140	n/a	>22	>15.5 or <6	<94
6 to 12 years	>130	n/a	>18	>13.5 or <4.5	<105
13 to <18 years	>110	n/a	>14	>11 or <4.5	<117

<sup>a</sup>Lower limits of the normal range for heart rate, leukocyte count, and systolic blood pressure for the 5th percentile and upper limits for the 95th percentile.

Source: Reprinted with permission from Goldstein B et al. International pediatric sepsis consensus conference: definitions for sepsis and organ dysfunction in pediatrics. *Pediatr Crit Care Med.* 2005;6(1):4.

TABLE 101.8 Organ Dysfunction Criteria

#### Cardiovascular Dysfunction

Despite administration of isotonic intravenous fluid bolus 40 mL/kg in 1 hour

- Decrease in BP (hypotension) <5th percentile for age or systolic BP <2 standard deviations below normal for age<sup>a</sup> OR
- Need for vasoactive drug to maintain BP in normal range (dopamine >5 mcg/kg/minute or dobutamine, epinephrine, or norepinephrine at any dose) OR
- Two of the following:
  - Unexplained metabolic acidosis: base deficit >5 mEq/L
  - Increased arterial lactate >2 times upper limit of normal
  - Oliguria: urine output <0.5 mL/kg/hour
  - Prolonged capillary refill: >5 seconds
  - Core to peripheral temperature gap >3°C

#### Respiratory<sup>b</sup>

- PaO<sub>2</sub>/Fio<sub>2</sub> <300 in absence of cyanotic heart disease or preexisting lung disease OR
- Paco<sub>2</sub> >65 torr or 20 mm Hg over baseline Paco<sub>2</sub> OR
- Proven need<sup>c</sup> or >50% Fio<sub>2</sub> to maintain saturations >92% OR
- Need for nonelective invasive or noninvasive mechanical ventilation<sup>d</sup>

#### Neurologic

- Glasgow coma scale (see Table 101.12) <11 OR
- Acute change in mental status with a decrease in Glasgow Coma Scale ≥3 points from abnormal baseline

#### Hematologic

- Platelet count <80,000/μL or a decline of 50% in platelet count from highest value recorded in the past 3 days (for chronic hematology/oncology patients) OR
- International normalized ratio of >2

#### Renal

- Serum creatinine >2 times upper limit of normal for age or twofold increase in baseline creatinine

**TABLE 101.8 Organ Dysfunction Criteria (Continued)**

*Hepatic*

- Total bilirubin  $\geq 4$  mg/dL (not applicable for newborn) OR
- ALT 2 times upper limit of normal for age

<sup>a</sup>See Table 101.7

<sup>b</sup>Acute respiratory distress syndrome must include a  $\text{PaO}_2/\text{FiO}_2$  ratio  $< 200$  mm Hg, bilateral infiltrates, acute onset, and no evidence of left heart failure. Acute lung injury is defined identically except the  $\text{PaO}_2/\text{FiO}_2$  ratio must be  $< 300$  mm Hg.

<sup>c</sup>Proven need assumes oxygen requirement was tested by decreasing flow if required.

<sup>d</sup>In postoperative patients, this requirement can be met if the patient has exhibited an acute inflammatory or infectious process in the lungs that prevents him or her from being extubated.

ALT alanine transaminase; BP, blood pressure.

Source: Adapted with permission from Goldstein B et al. International pediatric sepsis consensus conference: definitions for sepsis and organ dysfunction in pediatrics. *Pediatr Crit Care Med.* 2005;6(1):5.

**TABLE 101.9 Causative Pathogens and Recommended Treatments for Pediatric Sepsis**

Age or Risk Factor	Microorganism	Empiric Antibiotic Coverage
Age <30 days	<i>Listeria monocytogenes</i> <i>Escherichia coli</i> Group B <i>Streptococcus</i>	ampicillin + aminoglycoside or ampicillin + cefotaxime
Age 1–3 months	Gram-negative enteric organisms <i>L. monocytogenes</i> <i>E. coli</i> Group B <i>Streptococcus</i> <i>Haemophilus influenzae</i> <i>Streptococcus pneumoniae</i> <i>Neisseria meningitidis</i>	acyclovir (if patient presents with seizures, until HSV ruled out) ampicillin + TGC $\pm$ vancomycin <sup>a</sup>
Age >3 months	<i>H. influenza</i> <i>S. pneumonia</i> <i>N. meningitidis</i>	TGC $\pm$ vancomycin <sup>a</sup>
Immunocompromised child	<i>Pseudomonas aeruginosa</i> <i>Staphylococcus aureus</i> <i>Staphylococcus epidermidis</i>	ceftazidime or cefepime or piperacillin/ tazobactam + vancomycin <sup>a</sup>
Child with a ventriculoperitoneal shunt	<i>S. aureus</i> <i>S. epidermidis</i> Gram-negative enteric organisms	TGC $\pm$ vancomycin <sup>a</sup>

<sup>a</sup>Dosed to maintain trough vancomycin serum concentrations of 15 to 20 mcg/mL.

HSV, herpes simplex virus; TGC, third-generation cephalosporin (i.e., cefotaxime, ceftriaxone, or ceftazidime).

**TABLE 101.10 Summary of Selected Vasoactive Agents**

Agent	Dose Range	Peripheral Vascular Effects			Cardiac Effects
<b>VASOPRESSORS</b>					
		$\alpha$	$\beta_1$	$\beta_2$	
Dobutamine	2–10 mcg/kg/minute	1+	3–4+	1–2+	Less chronotropy and arrhythmias at lower doses; chronotropic advantage compared with dopamine may not be apparent in neonates
Dopamine	2–4 mcg/kg/minute 4–8 mcg/kg/minute >10 mcg/kg/minute	0 0 2–4+	0 1–2+	0 1+	Splanchnic and renal vasodilator, increasing doses create increasing $\alpha$ -effect
Epinephrine	0.03–0.1 mcg/kg/ minute 0.2–0.5 mcg/kg/minute	2+ 4+	2–3+ 2+	2+ 3+	$\beta_2$ effects with lower doses

*Continued on following page*

TABLE 101.10 Summary of Selected Vasoactive Agents (Continued)

Agent	Dose Range	Peripheral Vascular Effects			Cardiac Effects	
Norepinephrine	0.05–0.5 mcg/kg/ minute	4+	2+	0	Increases systemic resistance, moderate inotrophy	
Phenylephrine	0.05–0.5 mcg/kg/ minute	4+	0	0	Increases systemic resistance, moderate inotrophy	
<b>VASODILATORS</b>						
Nitroprusside	0.5–8 mcg/kg/minute	Donates nitric oxide to relax smooth muscles and dilate pulmonary and systemic vessels			Indirectly increases cardiac output by decreasing afterload	Reflex tachycardia
Nitroglycerine	0.5–10 mcg/kg/minute	As a nitric oxide donor, may cause pulmonary vasodilation and enhance coronary vasoreactivity after aortic cross-clamping			Decreases preload; may decrease afterload, reduces myocardial work in relation to change in wall stress	Minimal
<b>MISCELLANEOUS AGENTS</b>						
Milrinone	50 mcg/kg load; then 0.25–1 mcg/kg/ minute	Systemic and pulmonary vasodilator			Diastolic relaxation (lusitrophy)	Minimal tachycardia
Vasopressin	0.003–0.002 units/kg/ minute OR 18–120 milliunits/kg/hour	Potent vasoconstrictor			No direct effect	None known

- Dopamine-resistant shock commonly responds to epinephrine or norepinephrine.
- Dobutamine should be considered if clinical signs or lab values are consistent with poor tissue perfusion, and blood pressure can tolerate some vasodilation.
- Vasodilators (nitroglycerin, nitroprusside) may be required for elevated systemic vascular resistance and normal or decreased cardiac output. Milrinone is an option for long-term therapy.
- Corticosteroids should be reserved for those with catecholamine-resistant shock; severe septic shock and purpura; children who have previously received steroid therapies for a chronic illness; children with pituitary or adrenal abnormalities; and those who previously received etomidate.
  - Prophylaxis to prevent stress-related mucosal bleeding is not routinely done.
  - Routine use of deep-vein thrombosis prophylaxis in children is controversial.
- Hypoglycemia often develops in infants during periods of stress, including shock. Point-of-care glucose testing should be done in any critically ill infant with a history of poor oral intake.

## Congenital Heart Disease

- Functional closure of the ductus arteriosus (DA) typically occurs within the first 10 to 14 hours of life, with complete anatomic closure not occurring until 2 to 3 weeks of age.
- In infants with ductal-dependent congenital heart disease (CHD), closure of the DA results in inadequate delivery of oxygenated blood to the systemic circulation (Table 101.11). Infants present with symptoms of shock.
- If CHD is suspected, an infusion of alprostadil should be initiated to maintain patency of the DA and allow blood to reach the descending aorta. Age-appropriate equipment for intubation and mechanical ventilation should be readily available.

TABLE 101.11 Ductal-Dependent Congenital Heart Lesions

## LESIONS THAT DEPEND ON FLOW VIA THE DUCTUS ARTERIOSUS TO MAINTAIN SYSTEMIC CIRCULATION

Hypoplastic left heart syndrome (HLHS)  
 Coarctation of the aorta  
 Critical aortic stenosis  
 Interrupted aortic arch  
 Total anomalous pulmonary venous return (TAPVR) with obstruction

## LESIONS THAT DEPEND ON FLOW VIA THE DUCTUS ARTERIOSUS TO MAINTAIN PULMONARY CIRCULATION

Pulmonary atresia with intact ventricular septum  
 Critical pulmonic stenosis  
 Tricuspid atresia  
 Tetralogy of Fallot (TOF)  
 Epstein anomaly

## LESIONS THAT DEPEND ON FLOW VIA THE DUCTUS ARTERIOSUS TO MAINTAIN ADEQUATE MIXING OF THE PULMONARY AND SYSTEMIC CIRCULATIONS

Truncus arteriosus  
 Transposition of the great vessels (TGV)  
 Total anomalous pulmonary venous return (TAPVR) without obstruction

## Pediatric Traumatic Brain Injury

- Traumatic brain injury (TBI) is the leading cause of mortality among children. Diffuse injury (diffuse cerebral swelling and subdural hematomas) is more common in infants and young children; focal injury (contusions) is more common in older children and adults.
- The Glasgow Coma Scale (GCS) is a widely accepted method of initially evaluating and characterizing trauma patients with head injuries (Table 101.12). Lower scores represent more serious injury: mild (GCS 13-15), moderate (GCS 9-12), or severe (GCS 3-8). Continued evaluation of GCS scores is the best way to track clinical progress.
- A noncontrast cerebral computed tomography (CT) scan is the radiologic examination of choice for immediate assessment of a child with a severe TBI.
- A skeletal survey (films of extremities, skull, and axial skeletal images) is strongly recommended in all cases of suspected physical abuse in children below 24 months of age, done after the child is stable.
- Initial management of a child with a head injury should focus on basics of resuscitation (securing an airway and supporting circulation). Goals of treatment for TBI are directed at protecting against secondary brain insults.
- All patients should be assumed to have a full stomach and cervical spine injury; intubation should be done with RSI using appropriate short-acting sedatives and muscle relaxants (Tables 101.4 and 101.3).
- Assessment and reassessment of circulatory status, including central and peripheral pulse quality, capillary refill, heart rate, and blood pressure, is critical.
- A significant consequence of TBI is intracranial hypertension. Intracranial pressure (ICP) monitoring is recommended for any child with a GCS score of 8 or less. Uncontrolled increased ICP must be aggressively treated to reduce cerebral ischemia. Options include the following:
  - Drainage of cerebrospinal fluid
  - Hyperosmolar therapy (e.g., mannitol, hypertonic saline 3%)
  - High-dose barbiturate therapy (for hemodynamically stable patients with salvageable severe head injury and refractory intracranial hypertension)

TABLE 101.12 Modified Glasgow Coma Scale

**EYE OPENING**

SCORE	≥1 YEAR	0–1 YEAR
4	Opens eyes spontaneously	Opens eyes spontaneously
3	Opens eyes to verbal command	Opens eyes to shout
2	Opens eyes in response to pain	Opens eyes in response to pain
1	No response	No response

**BEST MOTOR RESPONSE**

SCORE	≥1 YEAR	0–1 YEAR
6	Obeys command	N/A
5	Localizes pain	Localizes pain
4	Flexion withdrawal	Flexion withdrawal
3	Flexion abnormal (decorticate)	Flexion abnormal (decorticate)
2	Extension (decerebrate)	Extension (decerebrate)
1	No response	No response

**BEST VERBAL RESPONSE**

SCORE	>5 YEARS	2–5 YEARS	0–2 YEARS
5	Oriented and able to converse	Uses appropriate words	Cries appropriately
4	Disoriented and able to converse	Uses inappropriate words	Cries
3	Uses inappropriate words	Cries and/or screams	Cries and/or screams inappropriately
2	Makes incomprehensible sounds	Grunts	Grunts
1	No response	No response	No response

Source: Chung CY et al. Critical score of Glasgow Coma Scale for pediatric traumatic brain injury. *Pediatr Neurol.* 2006;34:379.

- Therapeutic hypothermia (for refractory hypertension)
- Decompressive craniectomy (removal of a section of the skull) can be considered in pediatric patients with severe TBI, diffuse cerebral swelling, and intracranial hypertension refractory to intensive medical management.
- Posttraumatic seizures (PTS) can occur early (within 7 days of injury) or late (after 7 days of injury). Prophylactic antiseizure therapy may be considered as a treatment to prevent early PTS. No prophylactic anticonvulsant therapy is recommended to prevent late PTS.

## Geriatric Drug Use\*

### General Principles

- The profile of older Americans is shown in Table 102.1.
- Physiologic changes associated with aging, disease states, and pharmacologic factors can affect pharmacokinetic parameters and alter drug response (Table 102.2).
- Age-related changes in renal function result in more adverse drug reactions than any other age-related physiological alteration. Drugs primarily eliminated by the kidneys require dose adjustment (Table 102.3).
- Pharmacodynamic changes can be defined as alterations in concentration–response relationships or receptor sensitivity.

TABLE 102.1 Profile of Older Americans

#### CURRENT STATUS OF THE OLDER POPULATION

- The older population, persons age 65 years and older, numbered 40 million in 2010, representing 13% of the US population. This means that since 1900, the percentage of Americans age 65 years and older tripled (4.1% in 1900 to 13% in 2008), and their numbers have increased more than 10-fold (from 3.1 million to 40 million in 2010).
- There are more women than men in the older population. Among persons 65 years old in 2010, 57% were women. In the oldest old group, 67% of persons age 85 years and older were women.
- The older population is getting older. The 85 and older age group grew from just above 100,000 in 1900 to 5.5 million in 2010.
- The expected number of years of life increased by approximately 60% since 1900. In 2009, life expectancy was 80.4 years for women and 75.4 years for men.
- In 2020, the most common and costly health conditions among all persons age 65 and older were heart disease, diabetes, stroke, and cancer.
- Among all persons age 65 and older, the five leading causes of death are heart disease, cancer, chronic lower respiratory diseases, stroke, and Alzheimer disease.

#### FUTURE GROWTH OF THE OLDER POPULATION

- Although the rate of growth slowed during the 1990s because of the relatively small number of births during the Great Depression of the 1930s, the most rapid increase is expected between the years 2010 and 2030, when the baby boomer generation reaches age 65.
- By 2030, there will be about 72 million older persons, representing 20% of the total US population. The population age 85 years and older will grow from 5.5 million in 2010 to 19 million by 2050.

Source: Federal Interagency Forum on Aging-Related Statistics. Older Americans 2012: key indicators of well-being. Federal Interagency Forum on Aging-Related Statistics. Washington, DC: US Government Printing Office; August 2012.

\*The reader is referred to Chapter 102, Geriatric Drug Use, written by Judith L. Beizer, PharmD, CGP, FASCP, Jiwon Whitney Kim, PharmD, and May Mak, PharmD, in the 10th edition of *Applied Therapeutics: The Clinical Use of Drugs* for a more in-depth discussion. All notations to reference numbers are based on the reference list at the end of that chapter. The editor of this handbook expresses her thanks to Drs. Beizer, Kim, and Mak and acknowledges that this chapter is based on their work.

TABLE 102.2 Changes Affecting Pharmacokinetic Parameters

Parameter	Physiological Changes	Disease States	Pharmacologic Factors
Absorption (bioavailability, first-pass metabolism)	Gastric pH Absorptive surface Splanchnic blood flow GI motility Gastric emptying rate	Achlorhydria, diarrhea, gastrectomy, malabsorptive syndromes, pancreatitis	Drug interactions, antacids, anticholinergics, cholestyramine, food
Distribution	Cardiac output TBW Lean body mass Serum albumin $\alpha_1$ -Acid glycoprotein Body fat Altered relative tissue perfusion	HF, dehydration, edema, ascites, hepatic failure, malnutrition, renal failure	Drug interactions, protein-binding displacement
Metabolism	Hepatic mass Enzyme activity Hepatic blood flow	HF, fever, hepatic failure, malignancy, malnutrition, thyroid disease, viral infection or immunization	Dietary makeup, drug interactions, insecticides, alcohol, smoking, induction of metabolism, inhibition of metabolism
Excretion	Renal blood flow GFR Tubular secretion Renal mass	Hypovolemia, renal insufficiency	Drug interactions

GFR, glomerular filtration rate; GI, gastrointestinal; HF, heart failure; TBW, total body water.

TABLE 102.3 Drugs Highly Dependent on Renal Function for Elimination<sup>a</sup>

Acetazolamide	Furosemide
Acyclovir	H <sub>2</sub> blockers (most)
Allopurinol	Imipenem
Amantadine	Lisinopril
Amiloride	Lithium
Aminoglycosides	Methotrexate
Amphotericin B	Metoclopramide
Atenolol	Nadolol
Aztreonam	Phenazopyridine
Captopril	Penicillins (most)
Cephalosporins (most)	Procainamide
Clonidine	Pyridostigmine
Colistimethate	Spiro lactone
Digoxin	Sulfamethoxazole
Enalapril	Thiazides
Fluconazole	Trimethoprim
Fluoroquinolones (most)	Vancomycin

<sup>a</sup>This list is not comprehensive; for additional details, see Arnoff GR, et al., eds. *Drug Prescribing in Renal Failure: Dosing Guidelines for Adults*. 5th ed. Philadelphia, PA: American College of Physicians; 2007.

- Certain therapeutic agents are commonly associated with adverse drug reactions that may affect mobility of older patients (Table 102.4). Orthostatic hypotension is often aggravated by drugs with sympatholytic activity.
- Receptor sensitivity can result in an exaggerated response. Drugs with anticholinergic properties are associated with memory loss, confusion, and other cognitive impairments in older patients (Table 102.5).
- Polypharmacy is the primary cause of drug-related adverse events in the older population; monitoring drug therapy is imperative.

TABLE 102.4 Adverse Drug Reactions that May Affect Mobility of the Older Patient

Medication Class	Adverse Drug Reaction
TCA's	Orthostatic hypotension, tremor, cardiac arrhythmias, sedation
Benzodiazepines and sedative hypnotics	Sedation, weakness, coordination, confusion
Narcotic analgesics	Sedation, coordination, confusion
Antipsychotics	Orthostatic hypotension, sedation, extrapyramidal effects
Antihypertensives	Orthostatic hypotension
$\beta$ -Adrenergic blockers	Ability to respond to work load

TCA's, tricyclic antidepressants.

TABLE 102.5 Categories of Anticholinergic Drugs that Can Induce Confusion in Older Patients

Therapeutic Class	Examples (Brand Name)
Antispasmodic	Belladonna (generic) Oxybutynin (Ditropan XL) Dicyclomine (Bentyl)
Antiparkinson	Benztropine (Cogentin)
Antihistamine	Diphenhydramine (Benadryl) Chlorpheniramine (Chlor-Trimeton)
Antidepressant	Paroxetine (Paxil) Amitriptyline (Elavil) Imipramine (Tofranil)
Antiarrhythmic	Quinidine
Antipsychotic	Olanzapine (Zypexa) Clozapine (Clozaril) Asenapine (Saphris)
Hypnotic	Hydroxyzine (Vistaril)
OTC agents	Antidiarrheals Doxylamine Cold remedies

OTC, over the counter.

TABLE 102.6 Predictors of Adverse Drug Events

- More than four prescription medications
- Length of stay in hospital longer than 14 days
- More than four active medical problems
- Admission to a general medical unit vs. a specialized geriatric ward
- History of alcohol use
- Lower mean Mini-Mental State Examination score (confusion, dementia)
- Twenty-four new medications added to medication regimen during hospitalization

Sources: Budnitz DS, et al. National surveillance of emergency department visits for outpatient adverse drug events. *JAMA*. 2006;296:1858; Gray SL, et al. Adverse drug events in hospitalized elderly. *J Gerontol A Biol Sci Med Sci*. 1998;53:M59; and Gurwitz JH, et al. Incidence and preventability of adverse drug events among older persons in the ambulatory setting. *JAMA*. 2003;289:1107.

- Adverse drug reactions can be difficult to detect in older patients because they often present atypically and with nonspecific symptoms (e.g., lethargy, confusion, lightheadedness, falls). Most adverse reactions represent extensions of the drug's pharmacological effects, have identifiable predictors, and are preventable (Table 102.6).
- Various factors can contribute to nonadherence in the older patient (Table 102.7).
- Up to 50% of those above 85 years of age require assistance with everyday activities. Including the caregiver in the counseling and monitoring of daily activities is important.



TABLE 102.7 Factors Influencing the Inability to Adhere with a Medication Regimen

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Three chronic conditions
More than five prescription medications
Twelve medication dosages per day
Medication regimen changed four times during the past 12 months
Three prescribers involved
Significant cognitive or physical impairments (e.g., memory, hearing, vision, color discrimination, child-resistant containers)
Living alone in the community
Recently discharged from the hospital
Reliance on a caregiver
Low literacy
Medication cost
Demonstrated poor adherence history

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Sources: Lamy PP. The elderly, communications, and compliance. *Pharm Times*. 1992;58:33; Bero LA, et al. Characterization of geriatric drug-related hospital readmissions. *Med Care*. 1991;29:989.

TABLE 102.8 Atypical Depressive Symptoms in the Older Adult

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Agitation, anxiety, or worrying
Reduced initiative and problem-solving capacities
Alcohol or substance abuse
Paranoia
Obsessions and compulsions
Irritability
Somatic complaints
Excessive guilt
Marital discord
Social withdrawal
Cognitive impairment
Deterioration in self-care

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Source: Sable JA, et al. Late-life depression: how to identify its symptoms and provide effective treatment. *Geriatrics*. 2002;57:18.

## Disease-Specific Geriatric Drug Therapy

- Heart failure is a common cause of morbidity and mortality in older patients. Loop diuretics are generally more effective than thiazides.  $\beta$ -blockers (carvedilol, metoprolol, bisoprolol), angiotensin-converting enzyme inhibitors, or angiotensin receptor blockers are also used.
- Elevated total cholesterol levels have been shown to increase the risk for coronary heart disease. The drug of choice for treating hyperlipidemia is a statin.
- Hypertension is present in more than two-thirds of those above 65 years of age. Treatment of elderly patients should be based on guidelines for the general adult population. Monitoring is essential to prevent hypotension and bradycardia.
- Diabetes management should focus on reduction of cardiovascular risks with strict control of blood pressure and lipids in addition to avoidance of hypoglycemic events. Metformin and lifestyle modification is the initial management approach. Glyburide is more commonly associated with hypoglycemia; glipizide or glimepiride are better choices.
- Depression is the most common mental illness in adults above 65 years of age. Presenting symptoms of major depression in an older patient are different from those in younger patients (Table 102.8). Selective-serotonin reuptake inhibitors (SSRIs) are better tolerated by elderly patients than the older tricyclic antidepressants (Table 102.9).

TABLE 102.9 Antidepressant Dosing in Older Adults

	Initial Dosage	Maximum Dosage
Citalopram	10 mg every day	20 mg every day
Escitalopram	5 mg every day	10 mg every day
Fluoxetine	5 mg every day	80 mg every day
Fluvoxamine	25 mg at bedtime	300 mg at bedtime
Paroxetine	10 mg every day	40 mg every day
Sertraline	25 mg every day	200 mg every day
Mirtazapine	7.5 mg every day	45 mg every day
Bupropion IR	100 mg twice a day	150 mg three times a day
Bupropion SR	150 mg daily	400 mg every day
Bupropion XL	150 mg daily	450 mg every day
Duloxetine	20 mg twice a day	60 mg every day
Venlafaxine IR	75 mg twice a day	375 mg every day
Venlafaxine XR	75 mg every day	225 mg every day
Desvenlafaxine	50 mg every day	400 mg every day

- Asthma symptoms (wheezing, cough, chest tightness, dyspnea) and management (bronchodilators, anti-inflammatory agents) are similar in older and younger patients. Appropriate use of metered-dose inhalers can be difficult; spacers or a holding chamber device can be helpful.
- Pneumonia is the leading infectious cause of mortality in the elderly. Risk factors for community-acquired pneumonia are alcoholism and asthma. Management may require hospitalization. Influenza and pneumococcal vaccinations are beneficial for the prevention of pneumonia in the older population.
- Urinary tract infection (UTI) is the most common bacterial infection in the elderly. The majority of UTIs do not present typically; there are often nonspecific manifestations (e.g., decline in functional status, cognitive impairment, weakness, falls, urinary incontinence). Oral antibiotics are appropriate for most patients and should be dosed on the basis of kidney function.
- Arthritis is the most common cause of disability in people above 75 years of age. Osteoarthritis is the most common type of joint disease. Acetaminophen is the drug of choice for mild to moderate arthritis pain. Nonsteroidal anti-inflammatory agents should be used with caution due to the potential for renal and gastrointestinal toxicity.

# Geriatric Dementias\*

## General Principles

- Dementia is a syndrome that exhibits impaired short- and long-term memory as its most prominent feature. Multiple cognitive deficits that compromise normal social or occupational function must be present before dementia can be diagnosed. Please refer to DSM 5 for more information.

## Patient Assessment

- Memory loss often accompanies several disease or disorders in elderly individuals. A medical history, physical examination, and medication history are essential to identify possible causes (Table 103.1).
- Laboratory and other tests can be used for dementia screening (Table 103.2).
- Several trigger symptoms are associated with dementia (Table 103.3).
- Evaluation of daily functions (e.g., ability for self-care), living arrangements, safety, and potential for abuse or neglect should occur.

TABLE 103.1 Causes of Dementia Symptoms

Central Nervous System Disorders	Systemic Illness	Medications
Adjustment disorder (e.g., inability to adjust to retirement)	Cardiovascular disease Arrhythmia Heart failure	Anticholinergic agents Anticonvulsants Antidepressants Antihistamines
Amnesic syndrome (e.g., isolated memory impairment)	Vascular occlusion	Anti-infectives
Delirium	Deficiency states Vitamin B <sub>12</sub> Folate Iron	Antineoplastic agents Antipsychotic agents Cardiovascular agents Antiarrhythmics
Depression	Infections	Antihypertensives
Intracranial causes	Metabolic disorders	Corticosteroids
Brain abscess	Adrenal	H <sub>2</sub> -receptor antagonists
Normal pressure	Glucose	Immunosuppressants
Hydrocephalus	Renal failure	Narcotic analgesics
Stroke	Thyroid	Nonsteroidal anti-inflammatory agents
Subdural hematoma		Sedative hypnotics and anxiolytics
Tumor		Skeletal muscle relaxants

\*The reader is referred to Chapter 103, Geriatric Dementias, written by Nicole J. Brandt, PharmD, MBA, CGP, BCPP, FASCP, and Bradley R. Williams, PharmD, in the 10th edition of *Applied Therapeutics: The Clinical Use of Drugs* for a more in-depth discussion. All notations to reference numbers are based on the reference list at the end of that chapter. The editor of this handbook expresses her thanks to Drs. Brandt and Williams and acknowledges that this chapter is based on their work.

TABLE 103.2 Dementia Screening Tests

Test	Rationale for Testing
Complete blood count with sedimentation rate	Anemic anoxia, infection, neoplasms
Metabolic screen	
Serum electrolytes	Hypernatremia, hyponatremia; renal function
Blood urea nitrogen, creatinine	Renal function
Bilirubin	Hepatic dysfunction (e.g., portal systemic encephalopathy, hepatocerebral degeneration)
Thyroid function	Hypothyroidism, hyperthyroidism
Iron, vitamin B <sub>12</sub> , folate, vitamin D	Deficiency states (vitamin B <sub>12</sub> , folate neuropathies, vitamin D deficiency), anemias
Stool occult blood	Blood loss, anemia
HIV and RPR	Infection
Urinalysis	Infection, proteinuria
Chest roentgenogram	Neoplasms, infection, airway disease (anoxia)
Electrocardiogram	Cardiac disease (stagnant anoxia)
Brain scan	Cerebral tumors, cerebrovascular disease
Mental status testing	General cognitive screen
Depression testing	Depression, pseudodementia

TABLE 103.3 Symptoms Suggesting Dementia

Symptom	Evidence
Difficulty learning or retaining new information	Repeats questions; difficulty remembering recent conversations, events, etc.; loses items
Unable to handle complex tasks	Cannot complete tasks that require multiple steps (e.g., difficulty following a shopping list)
Impaired reasoning	Difficulty solving everyday problems; inappropriate social behavior
Impaired spatial orientation and abilities	Gets lost in familiar places; difficulty with driving
Language deficits	Problems finding appropriate words (e.g., difficulty with naming common objects)
Behavior changes	Changes in personality; suspiciousness

Source: Adapted from Costa P et al. Recognition and initial assessment of Alzheimer's disease and related dementias. Clinical Practice Guideline No. 19. Rockville, MD: U.S. Department of Health and Human Services, Public Health Service, Agency for Health Care Policy and Research. AHCPR Publication No. 97-0702. November 1996.

## Alzheimer Disease

- Alzheimer disease (AD), the most common cause of dementia, accounts for more than half of all diagnosed cases.
- Advancing age is the primary risk factor for AD; other risk factors include head trauma, metabolic syndrome, diabetes, hypertension, and family history.
- Criteria for dementia of the Alzheimer type exist (Table 103.4).
- AD follows a predictable course that may progress over the course of 10 or more years (Table 103.5). Maintaining independence as long as possible is an important goal.
- **Treatment:** Agents are available for symptomatic treatment (Table 103.6).
  - Agents that inhibit AChE (donepezil, rivastigmine, galantamine), the enzyme primarily responsible for metabolizing acetylcholine, seldom improve cognition and function and are primarily used to delay symptom progression. Beneficial effects may occur for as long as 3 years. Factors to consider in choice of agent include anticipated response, adverse

**TABLE 103.4 Revised Criteria for Dementia of the Alzheimer Type**

<b>DEFINITE DAT</b>	
Clinical criteria for probable DAT Histopathological evidence for DAT (autopsy or biopsy confirmed)	
<b>PROBABLE DAT</b>	
Dementia established by clinical examination and documented by mental status testing Confirmation of dementia by neuropsychologic tests (e.g., Blessed Dementia Scale and other tests) Insidious and gradual onset during a period of months to years History of worsening cognition established by observation or report Initial and most prominent cognitive deficits are evidenced by problems in either of the following categories: <ul style="list-style-type: none"> <li>• Amnesic presentation, which includes impaired learning or inability to retain recently learned information, plus evidence of impairment in at least one other cognitive domain</li> <li>• Nonamnesic presentations, including (a) language, with deficits in word-finding; (b) visuospatial, with deficits in ability to recognize objects, impaired face recognition, or other similar impairments; and (c) executive dysfunction, evidenced by impaired reasoning, judgment, and problem solving. All are accompanied by deficits in other cognitive domains.</li> </ul> Absence of evidence of significant cerebrovascular disease, core features of dementia with Lewy bodies, or other dementia syndromes or conditions that could have a substantial negative effect on cognition	
<b>POSSIBLE DAT</b>	
Atypical course: Meets all core clinical criteria for DAT but has sudden onset of cognitive impairment or demonstrates insufficient historical detail or objective cognitive documentation of progressive decline Mixed presentation: Meets all core clinical criteria for DAT but has evidence of (a) history of cerebrovascular disease, (b) features of Dementia with Lewy bodies other than dementia itself, and (c) evidence for another neurological disease or nonneurological medical comorbidity or medication use that could have a substantial effect on cognition.	
<b>UNLIKELY DAT</b>	
Does not meet clinical criteria for DAT Sufficient evidence for alternative diagnosis (ex. HIV dementia, Huntington disease dementia) Negative A $\beta$ and neuronal injury biomarkers	
DAT, dementia of the Alzheimer type. Source: McKhann G et al. The diagnosis of dementia due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. <i>Alzheimers Dement.</i> 2011;7:263.	

**TABLE 103.5 Stages of Dementia of the Alzheimer Type**

Stage of Cognitive Decline	Features
No cognitive decline	Normal cognitive state
Very mild cognitive decline	Forgetfulness, subjective complaints only; no objective decline
Mild cognitive decline	Objective decline through psychiatric testing; work and social impairment; mild anxiety and denial
Moderate cognitive decline	Concentration, complex skills decline; flat affect and withdrawal
Moderately severe cognitive decline	Early dementia; difficulty in interactions; unable to recall or recognize people or places
Severe cognitive decline	Requires assistance with bathing, toileting; behavioral symptoms present (agitation, delusions, aggressive behavior)
Very severe cognitive decline	Loss of psychomotor skills and verbal abilities; incontinence; total dependence

Source: Adapted from Reisberg B et al. The global deterioration scale for assessment of primary degenerative dementia. *Am J Psychiatry.* 1982;139:1136.

TABLE 103.6 U.S. Food and Drug Administration–Approved Drugs for Alzheimer Disease (AD)

Generic Drug (Brand Name) and Mechanism	Dosage Form and Dosage	Indication and Effect	Adverse Effects	Other
Donepezil HCl (Aricept) Reversibly inhibits AChE, primarily in CNS	<p>Aricept</p> <ul style="list-style-type: none"> <li>• Tablets 5 mg</li> <li>• Tablets 10 mg</li> <li>• Tablets 23 mg</li> </ul> <p>Aricept RDT</p> <ul style="list-style-type: none"> <li>• Tablets, orally disintegrating 5 mg</li> <li>• Tablets, orally disintegrating 10 mg</li> </ul> <p>Mild to moderate Alzheimer disease: Adults: PO: 5 mg once daily; may increase to 10 mg once daily after 4–6 weeks.</p> <p>Severe Alzheimer Disease: Adults: PO: Start with 5 mg once daily. Increase to 10 mg once daily after 4–6 weeks. A dosage of 23 mg once daily may be given after the patient has been on 10 mg once daily for at least 3 months.</p> <p>General Dosing Information:</p> <ul style="list-style-type: none"> <li>• Orally disintegrating tablets are bioequivalent to tablets.</li> <li>• Administer in the evening, just before bedtime.</li> <li>• May be taken without respect to food.</li> <li>• Allow the oral disintegrating tablet to dissolve on the tongue and follow with water.</li> </ul>	<p>Treatment of mild to severe dementia of the Alzheimer type. Small improvements in cognition and function occur within 12–24 weeks; benefits may last for at least 2 years.</p>	<p>Cholinergic effects, particularly affecting the GI tract (nausea, anorexia, diarrhea); headache; bradycardia may occur.</p>	<p>Completely bioavailable and may be given as a single daily dose owing to long half-life (70 hours). Metabolized by CYP3A4 isoenzymes.</p>
Galantamine HBr (Razadyne and Razadyne ER) Reversibly inhibits AChE, primarily in CNS; also stimulates nicotinic receptors at a site distinct from that of acetylcholine	<p>Razadyne</p> <ul style="list-style-type: none"> <li>• Tablets 4 mg (as base)</li> <li>• Tablets 8 mg (as base)</li> <li>• Tablets 12 mg (as base)</li> <li>• Oral Solution 4 mg/mL</li> </ul> <p>Razadyne ER</p> <ul style="list-style-type: none"> <li>• Capsules, extended-release 8 mg (as base)</li> <li>• Capsules, extended-release 16 mg (as base)</li> <li>• Capsules, extended-release 24 mg (as base)</li> </ul> <p>Immediate-Release Tablets and Oral Solution: Adults: PO: 4 mg twice daily. May increase to 8 mg twice daily after 4 weeks. A further increase to 12 mg twice daily may be attempted after minimum of 4 weeks at previous dose.</p>	<p>Treatment of mild to moderate dementia of the Alzheimer type. Small improvements in cognition and function occur within 12–24 weeks. Benefits may last for more than 1 year.</p>	<p>Cholinergic effects, particularly affecting the GI tract (nausea, anorexia, diarrhea); headache; bradycardia may occur.</p>	<p>Highly bioavailable. Initial dose is not therapeutic; slow titration increases tolerability. Metabolized by CYP2D6 and CYP3A4 isoenzymes.</p>

Continued on following page

TABLE 103.6 U.S. Food and Drug Administration–Approved Drugs for Alzheimer Disease (AD) (Continued)

Generic Drug (Brand Name) and Mechanism	Dosage Form and Dosage	Indication and Effect	Adverse Effects	Other
Rivastigmine tartrate (Exelon) Pseudo-irreversible inhibitor of AChE and butyrylcholinesterase, primarily in the CNS	<p>Extended-Release Capsules: Adults: PO: 8 mg/day. Increase to 16 mg/day after min 4 weeks. A further increase to 24 mg/day may be attempted after minimum of 4 weeks at previous dose.</p> <p>General Dosing Information:</p> <ul style="list-style-type: none"> <li>Administer immediate-release tablets and oral solution twice daily, preferably with morning and evening meal.</li> <li>Administer extended-release tablets once daily in the morning, preferably with food.</li> </ul> <p>Renal/Hepatic Function Impairment:</p> <p>In patients with moderately impaired hepatic function (Child-Turcotte-Pugh score 7–9) and those with moderate renal function impairment, the dose should not exceed 16 mg/day. Not recommended for patients with severe renal (CrCl &lt;9 mL/minute) or severe hepatic function impairment (Child-Turcotte-Pugh score 10–15).</p>	<p>Treatment of mild to moderate dementia of the Alzheimer type; treatment of mild to moderate dementia associated with Parkinson disease.</p> <p>Small improvements in cognition and function occur within 12–24 weeks. Benefits may last for more than 1 year.</p>	<p>Cholinergic effects, particularly affecting the GI tract (nausea, anorexia, vomiting, diarrhea); headache; bradycardia may occur.</p>	<p>Highly bioavailable. Therapeutic effect greatly exceeds biological half-life (1 hour), allowing for twice-daily dosing. Metabolized by hydrolysis. Initial dose is not therapeutic; administration with food and slow titration are necessary to increase tolerability. Effective dose for patch is 9.5 mg/24 hour or 13.3 mg/24 hour; however, for severe AD 13.3 mg/24 hour patch may be most effective.</p>
	<p>Exelon</p> <ul style="list-style-type: none"> <li>Capsules 1.5 mg (as tartrate)</li> <li>Capsules 3 mg (as tartrate)</li> <li>Capsules 4.5 mg (as tartrate)</li> <li>Capsules 6 mg (as tartrate)</li> <li>Solution, oral 2 mg/mL (as tartrate)</li> </ul> <p>Exelon</p> <ul style="list-style-type: none"> <li>Patch, transdermal 4.6 mg/24 hour</li> <li>Patch, transdermal 9.5 mg/24 hour</li> <li>Patch, transdermal 13.3 mg/24 hour</li> </ul> <p>Alzheimer Disease, Parkinson Disease Dementia:</p> <p>Adults: Transdermal: Start with 4.6 mg/24 hour patch. After a minimum of 4 weeks at the initial dose, increase the dose to 9.5 mg/24 hour patch, and 13.3 mg/24 hour after an additional 4 weeks, if needed (recommended max, 13.3 mg/24 hour).</p>			
	<p>If adverse reactions (e.g., diarrhea, nausea, vomiting) cause intolerance to treatment, stop treatment for several days, then restart at the same or next lower dose. If treatment is stopped for more than several days, restart treatment with 4.6 mg/24 hour patch and titrate to 9.5 mg/24 hour or 13.3 mg/24 hour after a minimum of 4 weeks for each dosage escalation.</p> <p>Dementia of the Alzheimer Type:</p> <p>Adults: PO: 1.5 mg twice daily initially, then dose may be increased by increments of 1.5 mg twice daily at intervals of 2 weeks or more (max, 6 mg twice daily).</p>			

Dementia Associated With Parkinson Disease:

Adults: PO: 1.5 mg twice daily initially, then dose may be increased by increments of 1.5 mg twice daily at intervals of 4 weeks or more (max, 6 mg twice daily).

Switching from Capsules or Oral Solution to Transdermal Patch:

Adults: Transdermal: Patients receiving an oral dose of less than 6 mg of rivastigmine daily can be switched to 4.6 mg/24 hour patch. Patients receiving an oral dose of rivastigmine 6–12 mg daily may be switched directly to 9.5 mg/24 hour patch. When switching from oral administration to patch, it is recommended that the first patch be applied on the day after the last oral dose.

General Dosing Information:

Capsules and oral solution:

- Administer with meals in divided doses in the morning and evening.
- Use the provided syringe to withdraw the prescribed amount of oral solution.
- Oral solution may be swallowed directly from the syringe or mixed with a small glass of water, cold fruit juice, or soda. Stir the mixture before drinking.
- Oral solution and capsules may be interchanged at equal doses.

Transdermal patch:

- Apply patch once daily to clean, dry, hairless, intact, healthy skin.
- Apply patch to an area that will not be rubbed against tight clothing.
- The recommended sites for application of patch are the upper or lower back. If these sites are not accessible, patch can be applied to chest or upper arm.
- Do not apply patch to an area that is red, irritated, or cut.
- To avoid irritation, change the site of patch application daily. Avoid application to the same spot for at least 14 days.
- Apply patch by pressing firmly until the edges stick.
- The patch can be used in situations that include bathing and hot weather.
- Do not apply patch to areas where cream, lotion, or powder has recently been applied.
- The patch should be replaced every 24 hours.
- Used transdermal system should be folded, with the adhesive surface pressed together, and discarded safely.



TABLE 103.6 U.S. Food and Drug Administration–Approved Drugs for Alzheimer Disease (AD) (Continued)

Generic Drug (Brand Name) and Mechanism	Dosage Form and Dosage	Indication and Effect	Adverse Effects	Other
Memantine Immediate- and Extended-Release (Namenda and Namenda XR) Uncompetitive antagonist of the <i>N</i> -methyl-D-aspartate type of glutamate receptors	<p>Namenda</p> <ul style="list-style-type: none"> <li>• Tablets 5 mg</li> <li>• Tablets 10 mg</li> </ul> <p>Namenda XR</p> <ul style="list-style-type: none"> <li>• Solution, oral 2 mg/mL</li> <li>• Capsules, ER 7 mg</li> <li>• Capsules, ER 14 mg</li> <li>• Capsules, ER 21 mg</li> <li>• Capsules, ER 28 mg</li> </ul> <p>Adults: Immediate Release: PO: Start with 5 mg daily. Increase the dose in 5-mg increments to 5 mg twice daily, 15 mg/day (5 and 10 mg as separate doses), and 10 mg twice daily. The minimum recommended interval between dose increases is 1 week.</p> <p>ER: PO: Start with 7 mg daily. Increase the dose in 7-mg increments to a maximum of 28 mg daily. The minimum recommended interval between dose increases is 1 week.</p> <p>Conversion from immediate-release to ER: PO: Patients taking immediate-release 10 mg twice daily may switch to ER 28 mg once daily the day after the last dose of an immediate-release 10-mg tablet.</p> <p>Renal Function Impairment:            Adults: Immediate Release:            Severe renal impairment (CrCl 5–29 mL/minute): PO: A target dosage of 5 mg twice daily is recommended. Patients taking 5 mg twice daily may switch to ER 14 mg once daily the day after the last dose of an immediate-release 5-mg tablet.            Mild to moderate renal impairment (CrCl 30–79 mL/minute): PO: No dosage adjustment is recommended.            ER: Severe renal impairment (CrCl 5–29 mL/minute): PO: A target dosage of 14 mg/day is recommended.            Mild to moderate renal impairment (CrCl 30–79 mL/minute): PO: No dosage adjustment is recommended.</p>	<p>Treatment of moderate to severe dementia of the Alzheimer type.</p> <p>Small improvements in cognition and function as well as less burden on caregivers.</p>	<p>Well tolerated, yet can cause headaches, dizziness, insomnia, and agitation.</p>	<p>Can be used as monotherapy or in conjunction with cholinesterase inhibitors.</p>

General Dosing Information:

- Administer without regard to meals.
- ER capsules can be taken intact or may be opened, sprinkled on applesauce, and then swallowed. The entire contents of each capsule should be consumed; the dose should not be divided. Swallow capsules whole. The capsules should not be divided, chewed, or crushed.
- Refer to the patient information for instructions on how to use the oral solution dosing device.

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AChE, acetylcholinesterase; BID, twice daily; CNS, central nervous system; CrCl, creatinine clearance; CYP, cytochrome P-450; ER, extended release; GI, gastrointestinal; ODT, orally disintegrating tablets; PO, orally; QID, four times daily.

Sources: Wilkinson DG et al. Cholinesterase inhibitors used in the treatment of Alzheimer's disease: the relationship between pharmacological effects and clinical efficacy. *Drugs Aging*. 2004;21:453; Masterman D. Cholinesterase inhibitors in the treatment of Alzheimer's disease and related dementias. *Clin Geriatr Med*. 2004;20:59; Winblad B et al. Donepezil in patients with severe Alzheimer's disease: double-blind, parallel-group, placebo-controlled study [published corrections appear in *Lancet*. 2006;367:1980; *Lancet*. 2006;368:1650]. *Lancet*. 2006;367:1057; Farlow MR et al. Effectiveness and tolerability of high-dose (23 mg/day) versus standard-dose (10 mg/day) donepezil in moderate to severe Alzheimer's disease: a 24-week, randomized, double-blind study. *Clin Ther*. 2010;32:1234; Williams BR et al. A review of rivastigmine: a reversible cholinesterase inhibitor. *Clin Ther*. 2003;25:1634; Farlow M et al. A 52-week study of the efficacy of rivastigmine in patients with mild to moderately severe Alzheimer's disease. *Eur Neurol*. 2000;44:236; Grossberg G et al. Safety and tolerability of the rivastigmine patch: results of a 28-week open-label extension. *Alzheimer Dis Assoc Disord*. 2009;23:158; Scott LJ, Goa KL. Galantamine: a review of its use in Alzheimer's disease. *Drugs*. 2000;60:1095; Becker M et al. The effect of cholinesterase inhibitors on risk of nursing home placement among Medicaid beneficiaries with dementia. *Alzheimer Dis Assoc Disord*. 2006;20:147; Wallin AK et al. Donepezil in Alzheimer's disease: what to expect after 3 years of treatment in a routine clinical setting. *Dement Geriatr Cogn Disord*. 2007;23:150; Jarvis B, Figgitt DP. Memantine. *Drugs Aging*. 2003;20:465; Tariot PN et al. Memantine treatment in patients with moderate to severe Alzheimer disease already receiving donepezil: a randomized controlled trial. *JAMA*. 2004;291:317; Monograph Summary for Donepezil HCl Oral and Rivastigmine Tartrate Oral. <http://online.factsandcomparisons.com/ComparativeMonographSummary.aspx?drillDownType=SBS&selectedDrugs=47180|65654&selectedDrugs=|47180|65654|129123|91778|93939&searchSections=1|3|4|5|7|8>. Accessed June 29, 2011; Monograph Summary for Galantamine Hydrobromide Oral and Memantine HCl Oral. <http://online.factsandcomparisons.com/ComparativeMonographSummary.aspx?drillDownType=SBS&selectedDrugs=91778|93939&selectedDrugs=|47180|65654|129123|91778|93939&searchSections=1|3|4|5|7|8>. Accessed June 29, 2011; Exelon Patch [Package Insert]. <http://www.exelonpatch.com/info/alzheimers-dementia-help/alzheimers-medication-dosage.jsp>. Accessed August 25, 2014; Frampton JE. Rivastigmine Transdermal Patch 13.3 mg/24 hour: A review of its use in the management of mild to moderate Alzheimer's dementia. *Drugs Aging*. 2014;31(8):639–649. doi: 10.1007/s40266-014-0197-x.

effects, and adherence. A second agent may be tried if treatment failure occurs with the first agent; if the second agent does not improve or stabilize the condition, there is no value in attempting a third agent.

- Memantine, a noncompetitive N-Methyl-D-aspartic acid OR N-Methyl-D-aspartate (NMDA) receptor antagonist, is an option that works by a different mechanism.

## Lewy Body Dementias

- Lewy bodies are hyaline-containing inclusion bodies typically found in people with Parkinson disease. Up to 25% of patients with dementia have Lewy bodies.
- Patients may display extrapyramidal signs without the classic presentation of Parkinson disease. Please refer to DSM 5 for more information.
- Cholinesterase inhibitors are the only treatment strategy for dementia associated with Parkinson disease and Lewy bodies.

## Vascular Dementia

- Vascular dementia (VaD) is a broad classification of cognitive disorders caused by vascular disease. The most common cause is occlusion of cerebral blood vessels by a thrombus or embolus, leading to ischemic brain injury.
- Risk factors include advancing age, diabetes mellitus, hypertension, heart disease, small vessel cerebrovascular disease, hyperlipidemia, cigarette smoking, and alcohol use.
- VaDs commonly present suddenly after a cerebrovascular insult. Cognitive impairments are variable. (Please see DSM 5 for more information.)
- Several treatment options that modify risk factors for VaDs are available: smoking cessation, treatment of hypertension and hypercholesterolemia, and antiplatelet therapy (for patients with a history of transient ischemic attack (TIA) or atherothrombotic stroke that is not of cardiogenic origin). Use of cholinesterase inhibitors is controversial.
- Physical and occupational therapy may be needed to maintain strength, independence, and safety.

## Behavior Disturbances in Dementia

- Several types of behavior disturbances develop with dementia, particularly in the later stages (Table 103.7).
- Pharmacologic interventions are appropriate when nondrug therapies are unsuccessful or the behavior is severe.
- Nonpsychologic behaviors (e.g., wandering, inappropriate motor activity) respond better to environmental modifications.
- Delusions and hallucinations are common. Behavioral interventions can be tried but are often of limited benefit. Paranoid symptoms respond best to antipsychotic agents; no agent is more effective than another.
- Up to 90% of patients with dementia exhibit at least one disruptive behavior (angry outbursts, screaming, abusive language), typically directed at the caregiver. Verbal abuse and aggressiveness place both the patient and the caregiver at risk for injury and may lead to abuse.
- Depression often accompanies dementia and may significantly impair functional capacity, cognitive abilities, and communication.
- Outside assistance is essential to families caring for a patient with dementia. Institutionalization is often required in the late stages of dementia.

**TABLE 103.7 Behavior Disturbances in Dementia**

Behavior	Typical Presentation	Nonpharmacologic Treatment	Pharmacologic Treatment
General strategies		Safety-proof living areas Issue one-step commands for directions Maintain a daily routine of activities Avoid arguing incorrect statements Avoid startling the patient Limit unusual or overly stimulating environments	
Anxiety	Excessive worrying, sleep disturbances, rumination	Listen to and acknowledge frustrations Redirection Exercise Engage in enjoyable activities Sleep hygiene practices Limit noise and distractions	Trazodone Buspirone (if no insomnia) Short-acting benzodiazepine SSRI antidepressant
Depression	Withdrawal, loss of appetite, irritability, restlessness, sleep disturbances	Exercise Engage in meaningful activities	SSRI antidepressant
General agitation and restlessness	Repeated questions, wandering, pacing	Distraction and redirection Break down tasks into simple steps Provide enclosed area for exercise	Often unresponsive to medications
Paranoid behaviors	Delusions (often of theft), hallucinations, misperceptions	Reassurance Distraction, rather than confrontation Remove potential sources of confusion (e.g., mirrors and other reflective surfaces)	Atypical antipsychotic, if not responsive to other strategies and person is fearful to self or others SSRI antidepressant, if associated with withdrawal, tearfulness, themes of loss
Aggressive behaviors	Physical or verbal aggressiveness toward others, excessive yelling and screaming, manic features	Identify the precipitating cause or situation Focus on the patient's feelings and concerns Avoid getting angry or upset Maintain a simple, pleasant, and familiar environment Use music, exercise, etc., as a calming activity Shift the focus to another activity	Anticonvulsant, such as divalproex or carbamazepine, possibly in combination with an atypical antipsychotic

Sources: Adapted from California Workgroup on Guidelines for Alzheimer's Disease Management. *Guideline for Alzheimer's Disease Management: Final Report*: State of California, Department of Public Health; April 2008; Teri L et al. Nonpharmacologic treatment of behavioral disturbance in dementia. *Med Clin North Am.* 2002;86:641; Tariot PN et al. Pharmacologic therapy for behavioral symptoms of Alzheimer's disease. *Clin Geriatr Med.* 2001;17:359; Herrmann N, Lanctôt KL. Pharmacologic management of neuropsychiatric symptoms of Alzheimer disease. *Can J Psychiatry.* 2007;52:630; Gray KF. Managing agitation and difficult behavior in dementia. *Clin Geriatr Med.* 2004;20:69; Binetti G et al. Delusions in Alzheimer's disease and multi-infarct dementia. *Acta Neurol Scand.* 1993;88:5; Teri L et al. Exercise plus behavioral management in patients with Alzheimer disease: a randomized controlled trial. *JAMA.* 2003;290:2015.

# Geriatric Urologic Disorders\*

## General Principles

- Aging causes structural and functional changes in the lower urinary tract (Table 104.1).
- The most common age-related change in both men and women is involuntary bladder contractions (detrusor muscle instability). Nocturia is a common complaint.

## Urinary Incontinence

- Urinary incontinence is a common disorder in the elderly. Neurologic impairment, immobility, female sex, and history of hysterectomy are independent risk factors for incontinence. Several causes exist (Table 104.2).
- Incontinence can be classified as (1) acute and reversible or (2) chronic and persistent.
- Acute onset incontinence should prompt a review for reversible factors (cystitis, atrophic vaginitis, urethritis, heart failure, polyuria from diabetes, delirium and acute confusional states, immobility, medication side effects).

TABLE 104.1 Age-Related Changes in Urologic Function

↓ Bladder capacity
↑ Residual urine
↑ Uninhibited bladder contractions
↑ Nocturnal sodium and fluid excretion
↓ Urethral resistance in women
↑ Urethral resistance in men
Weakness of pelvic floor muscles in women

TABLE 104.2 Causes of Incontinence

	Resnick's Mnemonic: DIAPPERS
D	Delirium and dementia
I	Infections
A	Atrophic vaginitis, atrophic urethritis, atonic bladder
P	Psychological causes, depression
P	Pharmacologic agents
E	Endocrine (diabetes, hypercalcemia, hypothyroidism)
R	Restricted mobility
S	Stool impaction

Sources: Ouslander JG, Bruskevitz R. Disorders of micturition in the aging patient. *Adv Intern Med.* 1989;34:165; Ouslander JG. Management of overactive bladder. *N Engl J Med.* 2004;350:786; Ouslander JG. Urinary incontinence. In: Osterweil D et al, eds. *Comprehensive Geriatric Assessment.* New York, NY: McGraw-Hill; 2000:555.

\*The reader is referred to Chapter 104, Geriatric Urologic Disorders, written by Michael R Brodeur, PharmD, CGP, FASCP, in the 10th edition of *Applied Therapeutics: The Clinical Use of Drugs* for a more in-depth discussion. All notations to reference numbers are based on the reference list at the end of that chapter. The editor of this handbook expresses her thanks to Dr. Brodeur and acknowledges that this chapter is based on his work.

TABLE 104.3 Drug Therapy of Persistent Urinary Incontinence

Type	Treatment with Initial Doses
Urge	Oxybutynin 2.5 mg every day to TID; 5–30 mg XL once daily Oxybutynin transdermal patch 1 patch 2×/week (available OTC) Oxybutynin 10% topical gel 1 g every day applied to upper arms, abdomen, or thighs Tolterodine 1–2 mg every day; 2–4 LA every day Trospium 20 mg BID; 60 mg ER every day Darifenacin 7.5 mg every day Solifenacin 5 mg every day Fesoterodine 4 mg every day Mirabegron 25 mg every day
Stress	Pseudoephedrine 15–30 mg BID–TID Vaginal estrogen cream 0.5–1.0 g 2–3 times/week Duloxetine 40–80 mg every day or BID
Overflow	Terazosin 1–5 mg every day (usually at bedtime) Doxazosin 1–8 mg every day Tamsulosin 0.4–0.8 mg every day Alfuzosin 10 mg every day Silodosin 4–8 mg every day Bethanechol 10 mg TID
Functional	None

BID, twice daily; LA, long acting; OTC, over the counter; TID, three times daily; XL, extended release.

- Persistent incontinence is classified into four subgroups: urge, stress, overflow, functional.
- **Urge incontinence** is the most common form of incontinence in the elderly. Involuntary voiding is preceded by a warning of a few seconds to a few minutes. Overactive bladder is a medical syndrome defined by symptoms of urgency with or without urge incontinence, usually with frequency and nocturia.
- **Stress incontinence** is involuntary leakage that occurs when an abrupt increase in intra-abdominal pressure overcomes urethral resistance. It is typically characterized by daytime loss of small to moderate amounts of urine. The usual cause is urethral hypermobility due to weakness and laxity of the pelvic floor muscles.
- **Overflow incontinence** occurs when the weight of urine in a distended bladder overcomes outlet resistance. Leakage of small amounts of urine (day and night) is common.
- **Functional incontinence** occurs when a continent individual is unable or unwilling to reach the toilet to urinate.
- Nonpharmacologic options include scheduled voiding, urge-suppression techniques, and pelvic muscle exercises.
- Drug therapy for persistent urinary incontinence is shown in Table 104.3. Therapy is directed at decreasing bladder contractility or increasing bladder outlet resistance.

## Benign Prostatic Hyperplasia

- Benign prostatic hyperplasia (BPH) is a common cause of urinary dysfunction in elderly men.
- Symptoms can be obstructive and irritative (Tables 104.4 and 104.5). Objective symptoms include abdominal tenderness with increased dullness in the hypogastrium; enlarged bladder; enlarged, firm, and rubbery prostate gland; and residual bladder volume. Incontinence is not a common symptom of BPH.
- Prostate-specific antigen (PSA) correlates with prostate weight. Normal age-adjusted ranges are shown in Table 104.6.

TABLE 104.4 Benign Prostatic Hyperplasia Symptom Scoring System (Boyersky Index)<sup>a</sup>

NOCTURIA	
0	Absence of symptoms
1	Urinate 1 time/night
2	Urinate 2–3 times/night
3	Urinate $\geq 4$ times/night
DAYTIME FREQUENCY	
0	Urinate 1–4 times/day
1	Urinate 5–7 times/day
2	Urinate 8–12 times/day
3	Urinate $\geq 13$ times/day
HESITANCE (LASTS $\geq 1$ MINUTE)	
0	Occasional ( $\leq 20\%$ of the time)
1	Moderate (20%–50% of the time)
2	Frequent ( $\geq 50\%$ of the time)
3	Always present
INTERMITTENCY (LASTS $\geq 1$ MINUTE)	
0	Occasional ( $\leq 20\%$ of the time)
1	Moderate (20%–50% of the time)
2	Frequent ( $\geq 50\%$ of the time)
3	Always present
TERMINAL DRIBBLING (AT END OF VOIDING)	
0	Occasional ( $\leq 20\%$ of the time)
1	Moderate (20%–50% of the time)
2	Frequent ( $\geq 50\%$ of the time)
3	Always present (may wet clothes)
URGENCY	
0	Absence
1	Occasionally difficult to postpone urination
2	Frequently difficult to postpone urination
3	Always difficult to postpone urination
IMPAIRMENT OF SIZE AND FORCE OF URINARY STREAM	
0	Absence
1	Impaired trajectory
2	Most of the time size and force are restricted
3	Urinate with great effort and stream is interrupted
DYSURIA	
0	Absence
1	Occasional burning sensation during urination
2	Frequent ( $> 50\%$ of the time) burning sensation
3	Frequent and painful burning sensation during urination
SENSATION OF INCOMPLETE VOIDING	
0	Absence
1	Occasional sensation
2	Frequent ( $> 50\%$ of the time) sensation
3	Constant and urgent sensation, no relief on voiding

<sup>a</sup>Symptom scoring provides the clinician with a tool to measure the relative need for, and efficacy of, different interventions. No specific score is associated with the need for a specific intervention. A low symptom score in the absence of significant urine retention generally indicates that medical management can be attempted before considering surgical intervention.

**TABLE 104.5 American Urological Association Urinary Symptom Index for Prostatism**

Symptom	Score					
	Not at All	<1 in 5 Times	<1/2 the Time	=1/2 Time	>1/2 the Time	Almost Always
1. Over the past month or so, how often have you had a sensation of not emptying your bladder completely after you finished urinating?	0	1	2	3	4	5
2. Over the past month or so, how often have you had to urinate again less than 2 hours after you finished urinating?	0	1	2	3	4	5
3. Over the past month or so, how often have you found you stopped and started several times when you urinated?	0	1	2	3	4	5
4. Over the past month or so, how often have you found it difficult to postpone urination?	0	1	2	3	4	5
5. Over the past month or so, how often have you had a weak urinary stream?	0	1	2	3	4	5
6. Over the past month or so, how often have you had to push or strain to begin urination?	0	1	2	3	4	5
7. Over the past month or so, how many times did you most typically get up to urinate from the time you went to bed at night until the time you got up in the morning?	0 times	1 time	2 times	3 times	4 times	5 times

Interpretation of AUA Symptom Index  
 AUA Symptom Score = Sum of questions 1–7 = \_\_\_\_\_  
 Mild prostatism ≤7  
 Moderate prostatism 8–18  
 Severe prostatism >18  
 Highest possible score 35

AUA, American Urological Association.

Source: Reprinted with permission from Longe RL, Calvert JC. *Physical Assessment: A Guide for Evaluating Drug Therapy*. Vancouver, WA: Applied Therapeutics 1994.

**TABLE 104.6 Age-Adjusted Prostate-Specific Antigen Values**

Age Range (years)	PSA Upper Limit (ng/mL)	PSA Density
40–49	2.5	0.08
50–59	3.5	0.10
60–69	4.5	0.11
70–79	6.5	0.13

PSA, prostate-specific antigen.

- Drug therapy includes the following:
  - $\alpha$ -1 receptor antagonists (terazosin, doxazosin, tamsulosin, alfuzosin, silodosin) that work quickly to provide symptomatic relief
  - 5- $\alpha$ -reductase inhibitors (finasteride, dutasteride) that take longer to work to reduce prostate size
  - Given their different mechanisms of action, combination therapy is reasonable.
- Common surgical treatments are shown in Table 104.7.



TABLE 104.7 Common Procedures for the Management of Benign Prostatic Hyperplasia

Therapy	Brief Description	Comments
Transurethral resection of the prostate (TURP)	A resectoscope is inserted into the urethra and obstructing tissue is removed a piece at a time.	Post-TURP syndrome: potentially life-threatening, caused by the absorption of irrigating fluid. Cerebral edema and seizures may result from hypervolemia and hyponatremia. Late complications: erectile dysfunction (up to 30%), urinary incontinence, bladder neck contractures, and retrograde ejaculation
Transurethral incision of the prostate (TUIP)	Shallow incisions in the prostatic urethra area relieve bladder outflow obstruction	Advantageous in high-risk patients such as the elderly because it can be performed under local anesthesia
Transurethral dilation of the prostate (TUDP)	Balloon catheter is positioned in the prostatic urethra and inflated.	Appropriate for men with smaller prostates who wish to avoid potential side effects of other procedures
Visual laser ablation of the prostate gland (VLAP)	Laser is used to partially remove obstructing prostate.	Used in men with smaller prostates
Transurethral microwave hyperthermia	Local microwave hyperthermia, delivered transurethrally or transrectally	Not as effective as surgical therapy but can be completed as an outpatient procedure in 1 hour

## Sexual Dysfunction

- Major factors that correlate with reduced sexual activity in older adults include poor mental or physical health, marital difficulties, previous negative sexual experiences, and negative attitudes toward sexuality in the aged.
- Aging men may experience andropause, a syndrome consisting of weakness, fatigue, reduced muscle and bone mass, impaired hematopoiesis, oligospermia, sexual dysfunction, and psychiatric symptoms.
- **Erectile dysfunction** (ED) is the inability to achieve and maintain a firm erection sufficient for satisfactory sexual performance. Approximately 80% of all cases of erectile dysfunction are thought to be related to organic disease (Table 104.8).
- A detailed medical and sexual history and thorough physical examination are essential in the evaluation of sexual dysfunction. Drug-induced causes should be ruled out (Table 104.9). Abnormalities of primary or secondary hypogonadism must be ruled out, particularly in patients with decreased libido with or without ED. Testosterone serum concentrations should be measured to assess primary hypogonadism.
- Management of erectile dysfunction:
  - **Level 1**—lifestyle (smoking and alcohol use) and drug therapy modifications. Oral medications for ED can be started, if needed.
  - **Level 2**—vacuum constriction device to elicit an erection, intracavernosal injections, or transurethral inserts
  - **Level 3**—penile prosthesis
- Drug therapy includes phosphodiesterase-5 inhibitors (PDE-5; sildenafil, tadalafil, vardenafil), hormonal therapy (testosterone for primary hypogonadism with severely deficient serum levels of bioavailable testosterone), bromocriptine (for hyperprolactinemia), and prostaglandin E (alprostadil).

TABLE 104.8 Causes of Erectile Dysfunction

**ATHEROSCLEROSIS**

Penile Raynaud phenomenon

**NEUROLOGIC**

Cerebrovascular accident

Spinal cord damage

Autonomic neuropathy

Peripheral neuropathy

**ENDOCRINE**

Diabetes mellitus

Hypogonadism

Prolactinomas

Hyperthyroidism

Hypothyroidism

**IATROGENIC**

Pelvic radiation

Lumbar sympathectomy

Prostatectomy

Renal transplantation

Spinal cord resection

**PSYCHOGENIC**

Performance anxiety

Depression

Widower syndrome

**NEUROGENIC**

Diabetes

Spinal cord injury

Cauda equina lesions

Polyneuropathy

Myelopathy

Multiple sclerosis

Dorsal nerve dysfunction from alcohol abuse or parkinsonism

Radical pelvic surgery

Sources: Morley JE, Kaiser FE. Sexual function with advancing age. *Med Clin North Am.* 1989;73:1483; Whitehead ED et al. Diagnostic evaluation of impotence. *Postgrad Med.* 1990;88:123.

TABLE 104.9 Common Drug-Induced Alterations in Sexual Response

**Drug Categories                      Clinical Considerations****ANTIHYPERTENSIVES**

Diuretic thiazides	Temporal association with sexual dysfunction. Reported incidence varies between 0% and 32% <sup>161–164</sup> ; however, impotence generally is not considered common. Mechanism believed to be a “steal syndrome” whereby blood is routed from erectile tissues to skeletal muscle <sup>165</sup>
Spironolactone	Associated with ↓ libido, impotence, and gynecomastia. Mechanism may be hormone related. Incidence is dose related and reported to be 5%–67% <sup>165</sup> and much more commonly encountered than with the thiazides. May be owing to antiandrogen effects of drug

Continued on following page

TABLE 104.9 Common Drug-Induced Alterations in Sexual Response (Continued)

Drug Categories	Clinical Considerations
<b>SYMPATHOLYTICS</b>	
Methyldopa	Central action mediated causing vasodilation resulting in erectile dysfunction. Reported incidence: 10%. <sup>165,166</sup> Also ↓ libido
Clonidine	Induces erectile dysfunction. Mechanism similar to methyldopa and other central $\alpha_2$ -agonists. Incidence reported to be 4%–70% and dose related. <sup>167–169</sup> Also ↓ libido
Guanabenz, guanfacine	Incidence and mechanism believed to be similar to other central $\alpha_2$ -agonists
<b>NONSELECTIVE <math>\beta</math>-BLOCKERS</b>	
Propranolol	Associated with erectile dysfunction and ↓ libido. Mechanism believed to be caused by ↓ vascular resistance and central effects. Erectile dysfunction reported to begin at doses of 120 mg/day. Incidence may be as high as 100% at higher dosages. <sup>166,170,171</sup>
<b>SELECTIVE <math>\beta</math>-BLOCKERS</b>	
Atenolol, metoprolol, pindolol, timolol	Incidence of erectile dysfunction is significantly less than nonselective $\beta$ -blockers. <sup>172</sup>
<b><math>\alpha</math>-BLOCKERS</b>	
Doxazosin, prazosin, terazosin	Associated with erectile dysfunction and priapism. <sup>166,168</sup> Reported incidence: 0.6%–4%. <sup>166</sup> Mechanism is local $\alpha_1$ -blockade resulting in vasodilation. Erectile dysfunction and priapism appear to be unique to the nonspecific $\alpha_1$ -antagonists.
Phenoxybenzamine	Associated with priapism, retrograde ejaculation, and inhibited emissions during erection. Effects are dose related. <sup>173,174</sup>
<b>DIRECT VASODILATORS</b>	
Hydralazine	Associated with erectile dysfunction. Mechanism is vascular smooth muscle relaxation. Incidence not reported <sup>173</sup>
<b>CALCIUM-CHANNEL BLOCKERS</b>	
Nifedipine	Associated with erectile dysfunction. Mechanism believed to be vasodilation and possibly muscle relaxation. Reported incidence: <2%. <sup>175</sup>
Diltiazem, verapamil	Similar to nifedipine. Reported incidence: <1%.
<b>ANTIARRHYTHMICS</b>	
Class 1A Disopyramide	Associated with erectile dysfunction in patients treated for ventricular arrhythmias. Incidence not reported. Mechanism believed to be caused by strong anticholinergic effect <sup>165,173</sup>
<b>ANTICONSULSANTS</b>	
Carbamazepine, phenytoin	May be associated with sexual dysfunction through decreasing DHEA, which is a precursor to testosterone, estrogen, and pheromones. <sup>19</sup>
<b>ANTIDEPRESSANTS</b>	
Selective serotonin reuptake inhibitors	Drugs with prominent serotonin agonist effects commonly cause delayed ejaculation and anorgasmia. The reported incidence for delayed ejaculation among men is 2%–12%; for anorgasmia among women users, the incidence appears to be <3%. This adverse effect is directly dose related. <sup>19</sup>
Tricyclic antidepressants, monoamine oxidase inhibitors	Associated with impairment of sexual performance in both male and female: ↓ libido, anorgasmia, retrograde ejaculation, erectile dysfunction. Mechanism believed to be caused by anticholinergic and serotonergic effects. Incidence not reported; several case studies in the literature <sup>165</sup>
Trazodone	Associated with priapism in men and ↑ libido in women. Mechanism similar to TCA. Incidence not reported but believed to be dose related. <sup>165</sup> (Note: The literature reports that overall there is less sexual dysfunction with desipramine than with other antidepressants.)

TABLE 104.9 Common Drug-Induced Alterations in Sexual Response (Continued)

Drug Categories	Clinical Considerations
<b>ANTIPSYCHOTICS</b>	
Phenothiazines	Frequently associated with sexual dysfunction. Commonly, ↓ libido is reported. Mechanism is owing to hyperprolactinemia secondary to central dopamine antagonism. Thioridazine is the most often reported offender. Erectile and ejaculatory pain are very common with this drug class; the $\alpha$ -antagonism and anticholinergic effects are responsible. Priapism is common with this drug group, owing to the peripheral $\alpha$ -blockade property. Incidence for all sexual dysfunction with this drug class: approximately 50% of users. <sup>165</sup>
<b>ANXIOLYTICS</b>	
Short-acting barbiturates	Biphasic effect. At low doses, libido ↑, similar to ethanol, and at higher doses, CNS depression causes ↓ libido and performance. <sup>165</sup>
Benzodiazepines	Biphasic effect. At low doses, ↑ libido, whereas at higher dosages, CNS depression causes performance failure. Some reports of anorgasmia (men and women) and ejaculatory failure. <sup>165</sup>
<b>SUBSTANCES OF ABUSE</b>	
Alcohol	Alcohol is thought to impair sexual function through its chronic effects on the nervous system. Short-term use of alcohol can induce erectile dysfunction through its sedative effects. More than 600 mL/week of alcohol increases the probability of erectile dysfunction. <sup>176</sup> At low doses actually may enhance libido. Sexual dysfunction is dose related and caused by CNS depressant effects. <sup>165,166</sup>
Cocaine	Biphasic effect. At low doses, there is enhanced sexual desire (similar to amphetamines) and possibly performance. At higher dosages, there may be arousal dysfunction, ejaculatory dysfunction, anorgasmia. Freebasing has been associated with spontaneous orgasm. Continued use (“on a run”) causes significant loss of sexual interest and performance ability. Chronic use associated with hyperprolactinemia resulting in ↓ libido. <sup>165</sup>
Hallucinogens	Biphasic effect for most drugs in this category. At low doses, libido is enhanced; at higher doses, libido is severely ↓. No reports on chronic use. <sup>165</sup>
Marijuana	Biphasic effect similar to ethanol. With chronic use, there is a ↓ in libido. Mechanism may be owing to ↓ testosterone. Incidence not reported. <sup>165</sup>
Opioids	Associated with sexual dysfunction: erection lubrication, orgasm, and ejaculation. Chronic use associated with ↓ libido. Mechanism may be owing to $\alpha$ -antagonism, alterations in testosterone, and the intoxicating effects. Incidence not reported. <sup>166,177,178</sup>
<b>MISCELLANEOUS</b>	
Amyl nitrate	Associated with intense and prolonged orgasms in both men and women. Impotence has been reported in some cases owing to vasodilation. <sup>165</sup>
Cimetidine, ranitidine	Associated with ↓ libido and erectile dysfunction. Mechanism owing to antiandrogen qualities and drug-induced elevation of prolactin. May be dose related. <sup>166,179</sup>
Metoclopramide	Associated with ↓ libido and erectile dysfunction. Mechanism is through CNS dopamine antagonism, resulting in hyperprolactinemia. Incidence not reported. <sup>166</sup>

CNS, central nervous system; DHEA, dehydroepiandrosterone; TCA, tricyclic antidepressants.

# Osteoporosis\*

## General Principles

- Osteoporosis is a condition of low bone mass and deterioration of bone tissue leading to bone fragility and possible fracture. Many preventable and inherent risk factors exist.
- World Health Organization defines osteoporosis as the presence of bone mineral density (BMD) T-score that is 2.5 standard deviations below the mean peak value for young adults.
- Osteopenia, a lesser degree of bone loss, is defined as a T-score that is between 1 and 2.5 standard deviations below that of the mean peak value for young adults.
- Osteoporosis-related fracture sites primarily include the vertebrae, distal radius, and hips.

## Classification

- Primary osteoporosis is subclassified as type 1 or type 2.
- Type 1, postmenopausal osteoporosis, is associated with increased cortical and cancellous bone loss resulting from increased bone resorption.
- Type 2, senile osteoporosis, occurs in men and women 75 years of age and older.
- Secondary osteoporosis results from various medications or the presence of particular disease states.

## Risk Factors

- Risk factors associated with the development of osteoporosis are shown in Table 105.1.

## Patient Assessment

- Guidelines recommend BMD measurement in women 50 to 65 years of age with 10-year major osteoporotic risk (FRAX) is greater than 9.3%; routine screening should be done in women above 65 years of age in the absence of risk factors. Several techniques exist to measure BMD; DXA is the gold standard (Table 105.2).

TABLE 105.1 Risk Factors Associated with the Development of Osteoporosis

↑Age	Predisposing medical problems (e.g., chronic liver disease, chronic renal failure, hyperthyroidism, primary hyperparathyroidism, Cushing syndrome, insulin dependent diabetes, gastrointestinal resection, malabsorption, irritable bowel disease, chronic obstructive pulmonary disease, and acquired immune deficiency syndrome or human immunodeficiency virus) Drugs (e.g., corticosteroids, long-term anticonvulsant therapy [phenytoin or phenobarbital], excessive use of aluminum-containing antacids, long-term high-dose heparin, furosemide, excessive levothyroxine therapy)
Female sex	
Caucasian or Asian	
Family history	
Small stature	
Low weight	
Early menopause or oophorectomy	
Sedentary lifestyle	
↓Mobility	
Low calcium intake	
Excessive alcohol intake	
Cigarette smoking	

\*The reader is referred to Chapter 105, Osteoporosis, written by Rebecca A. Rottman-Sagebiel, Pharm D, BCPS, CGP, in the 10th edition of *Applied Therapeutics: The Clinical Use of Drugs* for a more in-depth discussion. All notations to reference numbers are based on the reference list at the end of that chapter. The editor of this handbook expresses her thanks to Dr. Rottman-Sagebiel and acknowledges that this chapter is based on her work.

TABLE 105.2 Techniques for Measuring Bone Mineral Density

Technique	Abbreviation	Measurement Sites
Dual-energy x-ray absorptiometry	DXA	Hip, spine, total body bone mineral density
Peripheral dual-energy x-ray absorptiometry	PDXA	Forearm, fingers, heel
Peripheral quantitative computed tomography	PQTC	Forearm
Quantitative ultrasound	QUS	Heel, shin
Quantitative computed tomography	QCT	Spine
Single-energy x-ray absorptiometry	SXA	Heel

- BMD measurement is recommended for any postmenopausal woman who presents with fractures to confirm diagnosis and severity of disease.

## Treatment

- Prevention and treatment focus on modifying preventable risks, providing adequate dietary supplementation of calcium and vitamin D, increasing bone mineral density, and reducing fracture rates.
- Pharmacologic therapy is reserved for patients with a hip or vertebral fracture, a T-score  $\leq -2.5$  at the femoral neck or spine, or low bone mass with a 10-year probability of  $\geq 3\%$  risk of hip fracture or  $\geq 20\%$  risk of major osteoporotic fracture.
- **Preventative measures** include adequate intake of calcium (1,000–1,200 mg daily from diet or supplementation for all adults >50 years of age, Tables 105.3 and 105.4) and vitamin D (800–1,000 international units daily in postmenopausal women), weight-bearing exercise (at least 30 minutes three times weekly), cessation of smoking, and limiting alcoholic beverages.
- **Treatment measures in postmenopausal women** include antiresorptive agents (selective estrogen receptor modulators, bisphosphonates, calcitonin, denosumab, parathyroid hormone), calcium, exercise, and fall prevention.

TABLE 105.3 Calcium Content of Selected Foods

Food	Serving Size	Calcium (mg)
<b>DAIRY PRODUCTS</b>		
Milk, dry nonfat	1 cup	350–450
Yogurt, low-fat	1 cup	345
Milk, skim	1 cup	300
Milk, whole	1 cup	250–350
Cheese, cheddar	1 oz	211
Cheese, cottage	1 cup	211
Cheese, American	1 oz	195
Cheese, Swiss	1 oz	270
Ice cream or ice milk	1/2 cup	50–150
<b>FISH</b>		
Sardines, in oil	8 med	354
Salmon, canned (pink)	3 oz	167
<b>FRUITS AND VEGETABLES</b>		
Calcium-fortified juices	1 cup	100–350
Spinach, fresh cooked	1/2 cup	245
Broccoli, cooked	1 cup	100
Collards, turnip greens	1/2 cup	175
Soybeans, cooked	1 cup	131
Tofu	1 oz	75
Kale	1/2 cup	50–150

TABLE 105.4 Percentage of Calcium in Various Salts

Salt	Percent Calcium
Calcium carbonate	40
Tricalcium phosphate (calcium phosphate, tribasic)	39
Calcium chloride	27
Dibasic calcium phosphate dehydrate	23
Calcium citrate	21
Calcium lactate	13
Calcium gluconate	9

- **Management of glucocorticoid-induced osteoporosis** varies depending on the duration and dose of glucocorticoid therapy and risk factors. Decreases in BMD can be seen as soon as 3 to 6 months after glucocorticoid initiation. Bisphosphonates (alendronate, risedronate, zoledronic acid) and parathyroid hormone (teriparatide) are treatment options. American College of Rheumatology recommends preventative therapy in patients taking glucocorticoids on the basis of risk factors, sex, and age.
- **Treatment of osteoporosis in men** includes oral and intravenous bisphosphonates, denosumab, and parathyroid hormone.

## Drug Therapy

- **Bisphosphonates** (alendronate, risedronate, ibandronate, zoledronic acid) are considered first-line agents for the prevention and treatment of osteoporosis unless patients are unable to tolerate them or have relative contraindications. Bisphosphonates incorporate into bone and interfere with osteoclast-mediated bone resorption; the half-life is estimated to be 1 to 10 years. No consensus exists on duration of treatment. Gastrointestinal complaints are common (acid regurgitation, dysphagia, abdominal distension, gastritis, nausea, dyspepsia, flatulence). Osteonecrosis of the jaw can occur if blood loss in bone tissue is temporarily or permanently impaired. Different formulations exist that allow for varying frequency of administration (e.g., daily, weekly, monthly, biannually); consult product labeling.
- **Estrogen/progestin therapy** (EPT) is approved for prevention, but not treatment, of postmenopausal osteoporosis. EPT should be used for the shortest duration possible due to safety concerns with prolonged use; contraindications to use exist.
- **Selective estrogen receptor modulators** (raloxifene and tamoxifen) are alternative hormone-related agents.
- **Calcitonin**, which acts directly on osteoclasts to inhibit bone resorption, is indicated for treatment but not prevention.
- **Parathyroid hormone** (teriparatide) stimulates new bone formation and activates remodeling, which then results in increased BMD and connectivity.
- **Denosumab** targets RANKL, which is a necessary part of bone-resorbing osteoclasts. It is indicated for treatment of postmenopausal osteoporosis.

# Appendix

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