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APPENDICES

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PREFACE

The 12th edition of this companion to *DiPiro's Pharmacotherapy: A Pathophysiologic Approach* is designed to provide practitioners and students with critical information to guide medication decision-making in collaborative, interprofessional healthcare settings. To ensure brevity, clarity, and portability, a bulleted format provides essential textual information along with key tables, figures, and treatment algorithms.

Corresponding to the major sections in *DiPiro's Pharmacotherapy* textbook, medical conditions are alphabetized within the following sections: Bone and Joint Disorders; Cardiovascular Disorders; Dermatologic Disorders; Endocrinologic Disorders; Gastrointestinal Disorders; Gynecologic and Obstetric Disorders; Hematologic Disorders; Infectious Diseases; Neurologic Disorders; Nutrition Support; Oncologic Disorders; Ophthalmic Disorders; Psychiatric Disorders; Renal Disorders; Respiratory Disorders; and Urologic Disorders. The *Handbook* includes nine tabular appendices involving: (1) pediatric pharmacotherapy, nutrition, and neonatal critical care; (2) geriatric assessment and pharmacotherapy; (3) critical care patient assessment and pharmacotherapy; (4) drug allergy; (5) drug-induced hematologic disorders; (6) drug-induced liver disease; (7) drug-induced pulmonary disease; (8) drug-induced kidney disease; and (9) drug-induced ophthalmic disorders. This edition also includes new chapters on coronavirus disease and multiple sclerosis.

Each chapter is organized in a consistent format:

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

The Treatment section may include goals of treatment, general approach to treatment, nonpharmacologic therapy, drug selection guidelines, dosing recommendations, adverse effects, pharmacokinetic considerations, and important drug–drug interactions. For more in-depth information, the reader is encouraged to refer to the corresponding chapter in the primary textbook, *DiPiro's Pharmacotherapy: A Pathophysiologic Approach,* 12th edition. These chapters also provide guidance on application of the Pharmacists' Patient Care Process for specific conditions.

It is our hope that students and practitioners find this book to be helpful on their daily journey to provide the highest quality individualized, patient-centered care. We invite your comments on how we may improve subsequent editions of this work; you may write to pharmacotherapy@mcgraw-hill.com. Please indicate the author and title of this handbook in the subject line of your e-mail.

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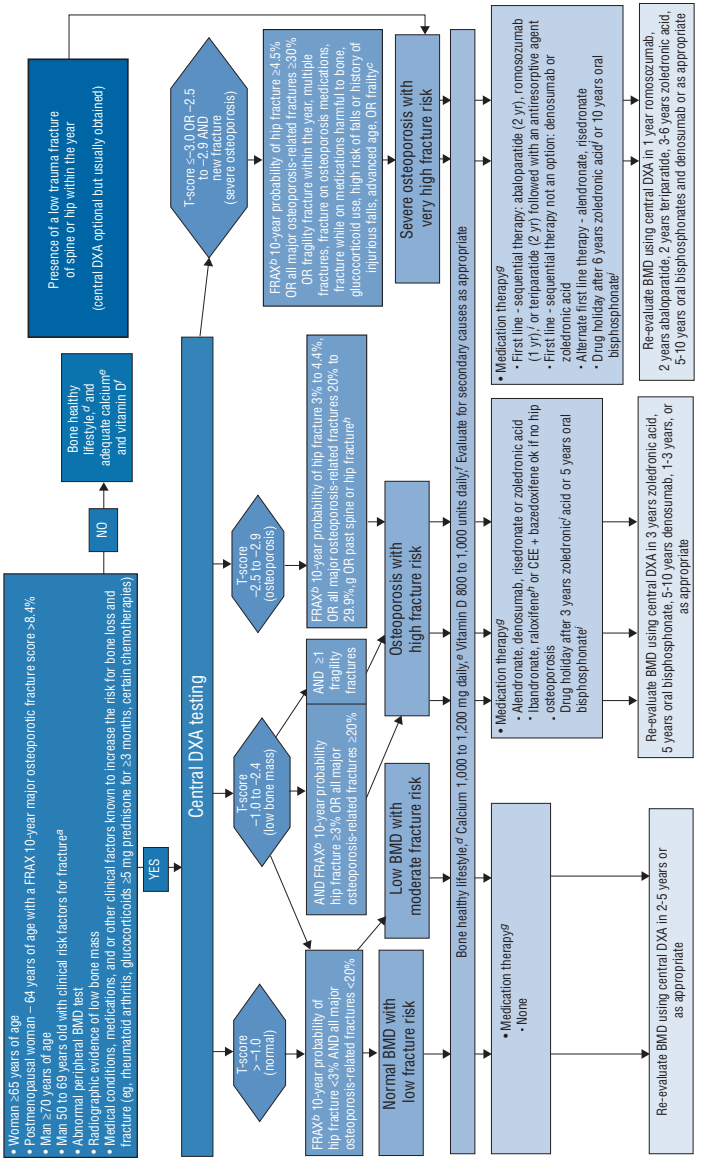


[a]Major clinical risk factors for fracture: advanced age, current smoker, low body weight or body mass index, personal history of fracture as an adult (after age 50 years), history of osteoporosis/low trauma fracture in a first-degree relative, excessive alcohol intake.
[b]Some providers use age adjusted FRAX thresholds versus set thresholds for all age groups.
[c]Fragility fracture is high risk for ES guidelines, and very high risk for AACE/ACE guideline.
[d]Bone-healthy lifestyle includes well-balanced diet with adequate calcium, vitamin D, and protein intakes; smoking cessation; limited alcohol intake; weight-bearing/resistance exercises; and fall prevention.

(*Continued*)

[e]Dietary calcium preferred. If diet is inadequate, supplement as necessary.
[f]Higher vitamin D doses might be needed to achieve 25-hydroxyvitamin D concentrations >30 ng/mL.
[g]Some increased BMD effects will be seen for women using menopausal hormonal therapy and for men using testosterone for hypogonadism. For women and men on hormonal therapy and at high risk or very high risk for osteoporotic fractures, an osteoporosis medication will also be prescribed, creating a case for combination therapy.
[h]Raloxifene option for postmenopausal women <60 years old with low hip fracture, stroke, and venous thromboembolic risk and high breast cancer risk.
[i]Restart therapy when BMD goes below T-score ≤−2.5 or a fracture; alternative is to use raloxifene or denosumab, or in some cases a bone formation medication during the drug holiday.
[j]Do not use romosozumab in patients with at high risk for or past myocardial infarction and/or stroke.

BMD, bone mineral density; DXA, dual-energy x-ray absorptiometry; FRAX, World Health Organization Fracture Risk Assessment Tool.

FIGURE 3-1. Algorithm for the management of osteoporosis in postmenopausal women and men aged 50 and older.

PHARMACOLOGIC THERAPY

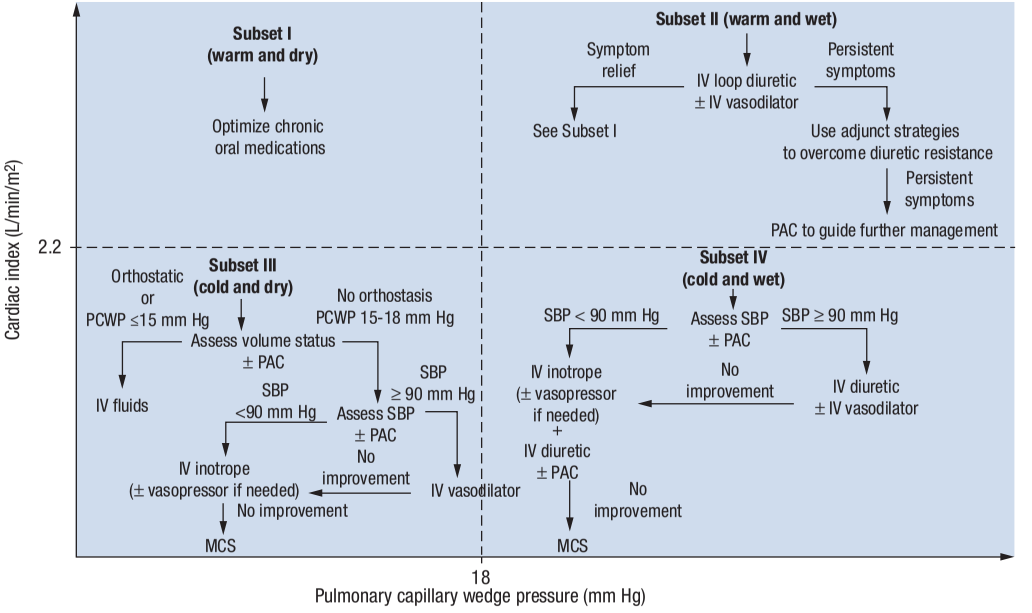
GENERAL APPROACH

- Alendronate, risedronate, zoledronic acid, and denosumab reduce both hip and vertebral fracture risks.
- Abaloparatide, calcitonin, ibandronate, raloxifene, romosozumab, and teriparatide reduce vertebral but not hip fracture risks.
- Calcitonin is the last-line therapy.
- Estrogen and testosterone are not used for osteoporosis treatment, but can have a positive bone effect when prescribed for other conditions.

TABLE 3-1 Calcium and Vitamin D RDAs and Tolerable Upper Intake Levels

Group and Ages	Elemental Calcium RDA (mg)	Calcium Tolerable Upper Intake Level (mg)	Vitamin D RDA (Units)[a]	Vitamin D Tolerable Upper Intake Level (Units)
Infants				
Birth–6 months	200[b]	1000	400[b]	1000
7–12 months	260[b]	1500	400[b]	1500
Children				
1–3 years	700	2500	600	2500
4–8 years	1000	2500	600	3000
9–18 years	1300	3000	600	4000
Adults				
19–50 years	1000	2500	600[b,c]	4000
51–70 years (men)	1000	2000	600[b,c]	4000
51–70 years (women)	1200	2000	600[b,c]	4000
>70 years	1200	2000	800[b,c]	4000

RDA, recommended dietary allowance.
[a]Some guidelines recommend intake to achieve a 25-hydroxyvitamin D concentration >30 ng/mL (mcg/L; 75 nmol/L), which is higher than the Institute of Medicine goal of >20 ng/mL (mcg/L; 50 nmol/L).
[b]Adequate intake (evidence insufficient to determine an RDA).
[c]Guidelines recommend 800–1000 units or 1000–2000 units for adults with osteoporosis.



IV, intravenous; MCS, mechanical circulatory support; PAC, pulmonary artery catheter; PCWP, pulmonary capillary wedge pressure; SBP, systolic BP.

FIGURE 9-2. General management algorithm for acute decompensated heart failure based on clinical presentation. Patients may be categorized into a hemodynamic subset based on signs and symptoms or invasive hemodynamic monitoring. Adjunct strategies for overcoming diuretic resistance include increasing the dose of loop diuretic; switching to a continuous infusion; adding a diuretic with an alternative mechanism of action, an IV vasodilator, or an IV inotrope; and in select patients, adding mechanical circulatory support.

sometimes combined with traditional inotropes so each drug can be adjusted independently to achieve the desired hemodynamic response, although little data exist to support that practice.

✓ Norepinephrine stimulates α_1- and β_1-adrenergic receptors. Stimulation of β_1-receptors in myocardial tissue increases HR, contractility, and therefore CO, but peripheral α_1-receptor-induced vasoconstriction is the predominant clinical hemodynamic effect. Lack of affinity for β_2-receptors may be responsible for the limited impact of norepinephrine on CO.

✓ Dopamine is an endogenous precursor of norepinephrine that stimulates α_1, β_1, β_2, and D_1 (vascular dopaminergic) receptors. Positive inotropic effects mediated primarily by β_1-receptors are prominent with doses of 2–5 mcg/kg/min. The CI is increased with minimal changes in SVR. At doses between 5 and 10 mcg/kg/min, chronotropic and α_1-mediated vasoconstriction become more prominent and MAP usually increases as a result of increases in both CI and SVR.

✓ Administration of low doses of dopamine (ie, 2–5 mcg/kg/min), does not consistently improve congestive symptoms or diuresis but increases the risk of tachyarrhythmias. Because of β-mediated effects at lower infusion rates, dopamine likely does not provide any advantages over a traditional inotrope in this setting.

EVALUATION OF THERAPEUTIC OUTCOMES

CHRONIC HEART FAILURE

- Ask patients about the presence and severity of symptoms and how symptoms affect daily activities.
- Evaluate efficacy of diuretic treatment by disappearance of the signs and symptoms of excess fluid retention. Focus the physical examination on body weight, extent of JVD, presence of HJR, and presence and severity of pulmonary congestion (crackles, dyspnea on exertion, orthopnea, and PND) and peripheral edema.
- Other outcomes are improvement in exercise tolerance and fatigue, decreased nocturia, and decreased HR.
- Monitor BP to ensure that symptomatic hypotension does not develop as a result of drug therapy.
- Body weight is a sensitive marker of fluid loss or retention, and patients should weigh themselves daily and report changes of 3–5 lb (1.4–2.3 kg) to their healthcare provider so adjustments can be made in diuretic doses.
- Symptoms may worsen initially on β-blocker therapy, and it may take weeks to months before patients notice symptomatic improvement.
- Routine monitoring of serum electrolytes (especially potassium and magnesium) and renal function (BUN, serum creatinine, eGFR) is mandatory in patients with HF.

ACUTE DECOMPENSATED HEART FAILURE

- Assess the efficacy of drug therapy with daily monitoring of weight, strict fluid intake and output measurements, and HF signs/symptoms. Monitor frequently for electrolyte depletion, symptomatic hypotension, and renal dysfunction. Assess vital signs frequently throughout the day.
- Patients should not be discharged until optimal volume status is achieved, they have been successfully transitioned from IV to oral diuretics, and IV inotropes and vasodilators have been discontinued for at least 24 hours.
- Optimize GDMT in hemodynamically stable patients without contraindications, including reinitiation of therapies withheld earlier in the admission. Low-dose β-blockers may be safely initiated at discharge without increasing the risk of readmission. Transitioning eligible patients to the ARNI sacubitril/valsartan may also be considered.

NONPHARMACOLOGIC THERAPY

- Implement lifestyle modifications in all patients with elevated BP or stage 1 or 2 hypertension. These measures alone are appropriate initial treatment for patients with elevated BP or stage 1 hypertension who are at low risk of ASCVD (ie, primary prevention with a 10-year ASCVD risk <10%). Start drug therapy for these patients when BP is ≥140/90 mm Hg. For patients with stage 1 or 2 hypertension who already have ASCVD (secondary prevention) or an elevated 10-year ASCVD risk ≥10%, the threshold for starting drug therapy is ≥130/80 mm Hg with a goal BP of <130/80 mm Hg.
- Lifestyle modifications shown to lower BP include (1) weight loss if overweight or obese, (2) the Dietary Approaches to Stop Hypertension (DASH) eating plan, (3) reduced salt intake, ideally to 1.5 g/day sodium (3.8 g/day sodium chloride), (4) physical activity (90–150 min/week of aerobic or dynamic resistance training), and (5) moderation of alcohol intake (≤2 drinks/day in men and ≤1 drink/day in women). Although smoking cessation does not control BP, it reduces CV disease risk and should be encouraged.

PHARMACOLOGIC THERAPY

General Approach to Treatment

- Initial drug selection depends on the degree of BP elevation and presence of compelling indications for certain drugs.
- Use a single first-line drug as initial therapy in most patients with newly diagnosed stage 1 hypertension. Start combination drug therapy (preferably with two first-line drugs) as the initial regimen in patients with newly diagnosed stage 2 hypertension (**Fig. 10-1**).
- The four first-line options are **angiotensin-converting enzyme inhibitors (ACEi)**, **angiotensin II receptor blockers (ARBs)**, **calcium channel blockers (CCBs)**, and **thiazide diuretics**.
- **β-Blockers** should be reserved to treat a specific compelling indication or in combination with a first-line antihypertensive agent for patients without a compelling indication.
- Other antihypertensive drug classes (**α_1-blocker**, **mineralocorticoid receptor antagonist [MRA]**, **central α_2-agonist**, adrenergic inhibitor, and **direct arterial vasodilator**) may be used for select patients after implementing first-line agents. They are generally reserved for resistant hypertension or as add-on therapy with multiple other first-line agents. However, they either lack convincing evidence showing reduced morbidity and mortality in hypertension or have a high incidence of adverse effects that hinders tolerability.

COMPELLING INDICATIONS

- Compelling indications are specific comorbid conditions for which clinical trial data support using specific antihypertensive drug classes to treat both hypertension and the compelling indication (**Fig. 10-2**). Selection of drug therapy should follow an evidence-based order.

Heart Failure with Reduced Ejection Fraction (HFrEF)

- Guideline-directed medical therapy consists of an ACE inhibitor or ARB (although ARB with a neprilysin inhibitor [also called angiotensin receptor neprilysin inhibitor; ARNI] is preferred ahead of an ACEi or ARB alone), an evidence-based β-blocker (ie, bisoprolol, carvedilol, metoprolol succinate) titrated to the maximum dose, and then possibly an MRA.
- Start an ACE inhibitor or ARB in low doses to avoid orthostatic hypotension because of the high renin state in HF.
- Diuretics reduce edema, and loop diuretics are often needed, especially in patients with advanced HF and/or CKD.

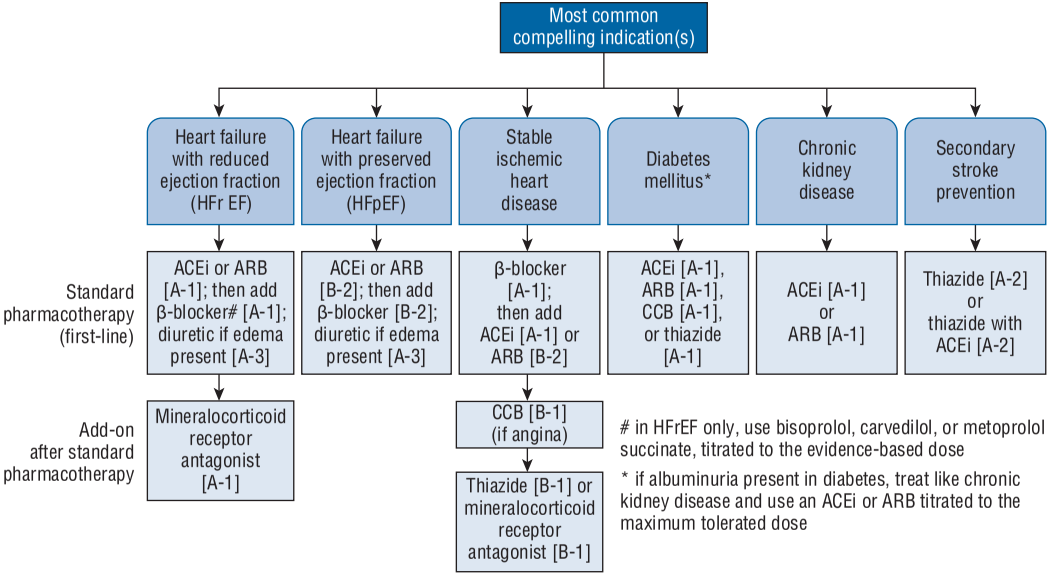


FIGURE 10-2. Compelling indications for individual drug classes. Recommendations are evidence-based from outcome studies or clinical guidelines. The order of drug therapies is a general guidance that should be balanced with clinical judgment and patient response. Add-on recommendations are used when additional medications are needed to lower BP to goal values. BP control should be managed concurrently with the compelling indication. Drug therapy recommendations are graded with strength of recommendation and quality of evidence in brackets. Strength of recommendations: A, B, and C are good, moderate, and poor evidence to support recommendation, respectively. Quality of evidence: (1) evidence from more than one randomized controlled trial; (2) evidence from at least one well-designed clinical trial with randomization, from cohort or case-controlled analytic studies or multiple time series, or dramatic results from uncontrolled experiments or subgroup analyses; (3) evidence from opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert communities.

- Start with low doses and evaluate the serum creatinine soon after starting therapy to minimize the risk of rapid and profound BP drops that could precipitate acute kidney injury (AKI).

Secondary Stroke Prevention

- A thiazide diuretic, either alone or combined with an ACE inhibitor, is recommended for patients with history of stroke or transient ischemic attack. Implement antihypertensive drug therapy only after patients have stabilized after an acute cerebrovascular event.
- The threshold for starting antihypertensive drug therapy in patients with a history of stroke is when BP is >140/90 mm Hg. Once therapy is initiated, patients should be treated to a goal of <130/80 mm Hg.

FIRST-LINE ANTIHYPERTENSIVE AGENTS (TABLE 10-2)

Angiotensin-Converting Enzyme Inhibitors

- ACE inhibitors block conversion of angiotensin I to angiotensin II, a potent vasoconstrictor and stimulator of aldosterone secretion. ACE inhibitors also block degradation of bradykinin and stimulate synthesis of other vasodilating substances (prostaglandin E_2 and prostacyclin).
- Starting doses should be low with slow dose titration. Acute hypotension may occur at the onset of therapy, especially in patients who are sodium or volume depleted, in HF exacerbation, very elderly, or on concurrent vasodilators or diuretics. Starting doses in such patients should be half the normal dose followed by slow dose titration.
- ACE inhibitors decrease aldosterone and can increase serum potassium concentrations. Hyperkalemia occurs primarily in patients with CKD or those also taking potassium supplements, potassium-sparing diuretics, MRAs, ARBs, or direct renin inhibitors.
- AKI is an uncommon but serious side effect; preexisting kidney disease increases risk. Bilateral renal artery stenosis or unilateral stenosis of a solitary functioning kidney renders patients dependent on the vasoconstrictive effect of angiotensin II on efferent arterioles, making them particularly susceptible to AKI.
- GFR decreases somewhat when ACE inhibitors are started because of inhibition of angiotensin II vasoconstriction on efferent arterioles. Serum creatinine concentrations often increase, but modest elevations (eg, absolute increases <1 mg/dL [88 μmol/L]) do not warrant treatment changes. Discontinue therapy or reduce dose if larger increases occur.
- Angioedema occurs in <1% of patients. Drug withdrawal is necessary, and some patients may require drug treatment and/or emergent intubation to support respiration. An ARB can generally be used in patients with a history of ACE inhibitor-induced angioedema, with careful monitoring.
- A persistent dry cough occurs in up to 20% of patients and is thought to be due to inhibition of bradykinin breakdown.
- ACE inhibitors (as well as ARBs and direct renin inhibitors) are contraindicated in pregnancy.

Angiotensin II Receptor Blockers

- Angiotensin II is generated by the renin–angiotensin pathway (which involves ACE) and an alternative pathway that uses other enzymes such as chymases. ACE inhibitors block only the renin–angiotensin pathway, whereas ARBs inhibit angiotensin II generated by either pathway. The ARBs directly block the angiotensin II type 1 receptor that mediates the effects of angiotensin II.
- Unlike ACE inhibitors, ARBs do not block bradykinin breakdown. Although this accounts for the lack of cough as a side effect, some of the antihypertensive effect of ACE inhibitors may be due to bradykinin.

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

Class	Subclass	Medication (Brand Name)	Usual Dose Range (mg/day)	Daily Frequency
Diuretic	Thiazide	Chlorthalidone (Thalitone)	12.5–25	1
		Hydrochlorothiazide (Microzide)	12.5–50	1
		Indapamide (Lozol)	1.25–2.5	1
		Metolazone (Zaroxolyn)	2.5–10	1
	Loop	Bumetanide (Bumex)	0.5–4	2
		Furosemide (Lasix)	20–80	2
		Torsemide (Demadex)	5–10	1
	Potassium sparing	Amiloride (Midamor)	5–10	1 or 2
		Amiloride/Hydrochlorothiazide (Moduretic)	5–50	1
		Triamterene (Dyrenium)	50–100	1 or 2
		Triamterene/Hydrochlorothiazide (Dyazide, Maxide)	37.5–75/25–50	1
	Mineralocorticoid receptor antagonist	Eplerenone (Inspra)	50–100	1 or 2
		Spironolactone (Aldactone, CaroSpir)	25–50	1 or 2
β-Blocker	Cardioselective	Atenolol (Tenormin)	25–100	1 or 2
		Betaxolol (Kerlone)	5–20	1
		Bisoprolol (Zebeta)	2.5–10	1
		Metoprolol tartrate (Lopressor)	100–200	2
		Metoprolol succinate extended release (Toprol XL)	50–200	1
		Nebivolol (Bystolic)	5–20	1
	Nonselective	Nadolol (Corgard)	40–120	1
		Propranolol (Inderal)	160–480	2
		Propranolol long acting (Inderal LA, Inderal XL, InnoPran XL)	80–320	1
		Timolol (Blocadren)	10–40	1
	Mixed α- and β-blockers	Carvedilol (Coreg)	12.5–50	2
		Carvedilol phosphate (Coreg CR)	20–80	1
		Labetalol (Normodyne, Trandate)	200–800	2

CHAPTER 11

Ischemic Heart Disease

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

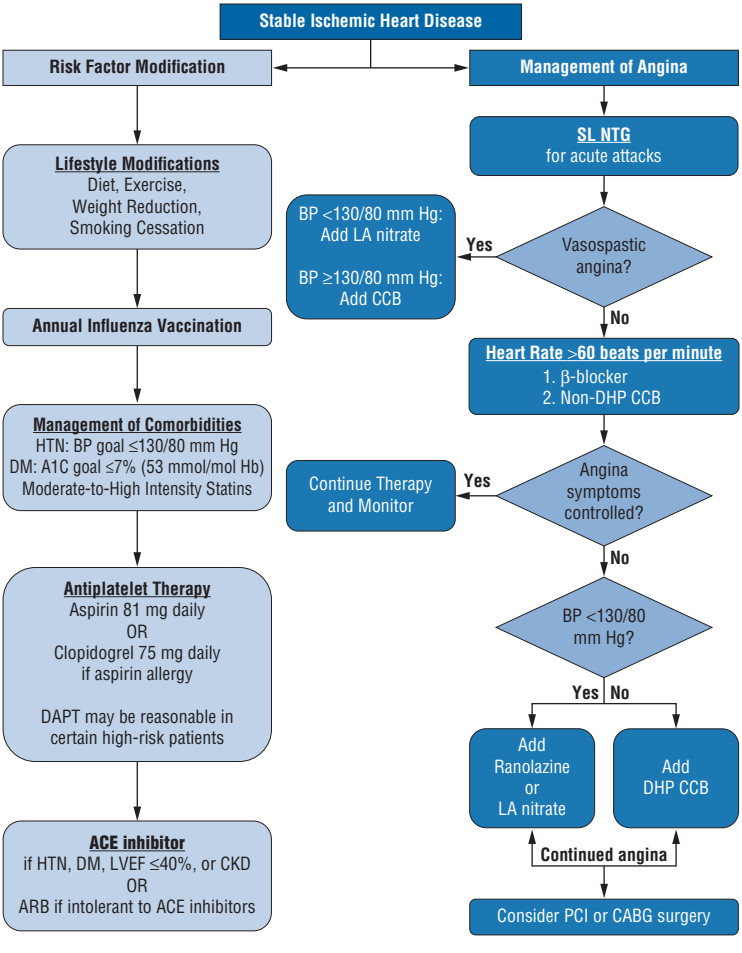
PATHOPHYSIOLOGY

- Angina pectoris usually results from increased myocardial oxygen demand (MVO_2) in the setting of a fixed decrease in myocardial oxygen supply because of atherosclerotic plaque.
- Major determinants of MVO_2 are heart rate (HR), myocardial contractility, and intramyocardial wall tension during systole. A doubling in any of these individual parameters requires a 50% increase in coronary flow to maintain myocardial supply.
- Coronary atherosclerotic plaques typically develop in larger epicardial (R_1 or conductance) vessels, which normally offer little resistance to myocardial flow. As plaques grow and narrow the lumen, the affected vessel begins to provide considerable resistance to blood flow. Smaller endocardial (R_2 or resistance) vessels provide most resistance to flow in normal coronary arteries and can contract and dilate to maintain blood flow based on metabolic demands of the myocardium (referred to as autoregulation). As a result, coronary plaques that occupy less than 50%–70% of the vessel luminal diameter rarely produce ischemia or angina. However, smaller plaques have a lipid-rich core and thin fibrous cap and are more prone to rupture and cause acute thrombosis. When the luminal diameter of epicardial vessels is reduced by 70% or more, endocardial vessels are maximally dilated, much of the coronary flow reserve has been used to preserve resting coronary blood flow, and minimal physical exertion may result in a flow deficit with myocardial ischemia and often angina. When epicardial stenosis exceeds 90%, endocardial flow reserve is exhausted (referred to as critical stenosis).
- When coronary stenosis exceeds 70%, ischemic episodes lead to production of vascular endothelial growth factor and basic fibroblast growth factor which, combined with endogenous vasodilators (eg, nitrous oxide, prostacyclin), cause native collateral vessels to increase in diameter (arteriogenesis) to maintain perfusion. New collateral vessels can also develop (angiogenesis).
- Inflammation also plays a role in IHD; macrophages and T-lymphocytes produce cytokines, chemokines, and growth factors that activate endothelial cells, increase vasoreactivity, and cause proliferation of vascular smooth muscle cells. C-reactive protein may be elevated and correlates with adverse cardiovascular events.
- Some patients have plaque that causes a fixed decrease in supply but also have reduced myocardial oxygen supply transiently due to vasospasm at the site of the plaque. Vasospasm is typically caused by endothelial damage induced by the plaque. Patient symptoms depend on the extent of the fixed obstruction and the degree of dynamic change in coronary arterial tone. The pattern of ischemic symptoms can change due to a variable amount of vasospasm under certain conditions (referred to as *variable threshold angina*). Ischemic episodes may be more common in the morning hours (due to circadian release of vasoconstrictors) and be precipitated by cold exposure and emotional or mental stress.
- Patients with *variant (Prinzmetal) angina* usually do not have a coronary flow-obstructing plaque but instead have significant reduction in myocardial oxygen supply due to vasospasm in epicardial vessels.

and treatment for depression if appropriate), limitation of alcohol intake, and avoiding exposure to air pollution.
- Surgical revascularization options for select patients include coronary artery bypass grafting (CABG) or percutaneous coronary intervention (PCI) with or without stent placement.

PHARMACOLOGIC THERAPY

- Guideline-directed medical therapy (GDMT) reduces the rates of death and MI similar to revascularization therapy. See **Fig. 11-1** for a treatment algorithm based



ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; BP, blood pressure; CABG, coronary artery bypass graft; CCB, calcium channel blocker; CKD, chronic kidney disease; DAPT, dual antiplatelet therapy; DHP, dihydropyridine; DM, diabetes mellitus; Hb, hemoglobin; HTN, hypertension; LA, long-acting; LVEF, left ventricular ejection fraction; PCI, percutaneous coronary intervention; SL NTG, sublingual nitroglycerin.

FIGURE 11-1. Algorithm for treatment of stable ischemic heart disease (guideline-directed medical therapy).

Venous Thromboembolism

CHAPTER 14

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

PATHOPHYSIOLOGY

- Risk factors for VTE include increasing age, history of VTE, and aspects related to Virchow's triad: (1) blood stasis (eg, immobility and obesity); (2) vascular injury (eg, surgery, trauma, venous catheters); and (3) hypercoagulability (eg, malignancy, coagulation factor abnormalities, antiphospholipid antibodies, certain drugs).
- The most common inherited hypercoagulability disorder is activated protein C (aPC) resistance (Caucasian prevalence 2%–7%), which increases the risk of VTE threefold. Most aPC resistance results from a factor V gene mutation (known as factor V Leiden) that renders it resistant to degradation by aPC.
- The prothrombin G20210A mutation is the second most frequent inherited hypercoagulability disorder (Caucasian prevalence 2%–4%) and imparts a threefold increased risk of VTE. The mutation increases circulating prothrombin, enhancing thrombin generation.
- Inherited deficiencies of protein C, protein S, and antithrombin occur in <1% of the population and may increase the lifetime VTE risk by as much as sevenfold.
- Normal hemostasis maintains circulatory system integrity after blood vessel damage. Disruption of the endothelial cell lining with injury results in platelet activation and tissue-factor–mediated clotting factor cascade initiation, culminating in thrombin formation and ultimately a fibrin clot. In contrast to physiologic hemostasis, pathologic VTE often occurs without gross vessel wall damage and may be triggered by tissue factor (TF) brought to the growing thrombus by circulating microparticles. Clots causing VTE impair blood flow and often cause complete vessel occlusion.
- Exposure of blood to damaged vessel endothelium causes platelets to become activated after binding to adhesion proteins (eg, von Willebrand factor, collagen). Activated platelets recruit additional platelets, causing growth of the platelet thrombus. Activated platelets change shape and release components that sustain further thrombus formation at the site. Activated platelets express the adhesion molecule P-selectin, which facilitates capture of TF-bearing microparticles, resulting in fibrin clot formation via the coagulation cascade.
- The conceptual coagulation cascade model involves reactions that occur on cell surfaces in three overlapping phases (**Fig. 14-1**):
  - ✓ *Initiation*: A TF/VIIa complex (known as extrinsic tenase or X-ase) on cells bearing TF that have been exposed after vessel injury or captured via P-selectin activates limited amounts of factors IX and X. Factor Xa then associates with factor Va to form the prothrombinase complex, which cleaves prothrombin (factor II) to generate a small amount of thrombin (factor IIa), which activates factors V, VIII, and XI on platelet surfaces. Factor IXa moves to the surface of activated platelets in the growing platelet thrombus. Tissue factor pathway inhibitor (TFPI) regulates TF/VIIa-induced coagulation, rapidly terminating the initiation phase.
  - ✓ *Amplification:* Thrombin produced during the initiation phase activates factors V and VIII, which bind to platelet surfaces and support the large-scale thrombin generation occurring during the propagation phase. Platelet-bound factor XI is also activated by thrombin during amplification.
  - ✓ *Propagation:* A burst of thrombin generation occurs as factor VIIIa/IXa complex (known as intrinsic tenase) promotes factor Xa formation and prothrombinase complexes assemble on the surface of activated platelets, accelerating thrombin generation. Thrombin generation is further supported by factor XIa bound to platelet surfaces, which activates factor IX to form additional intrinsic tenase.

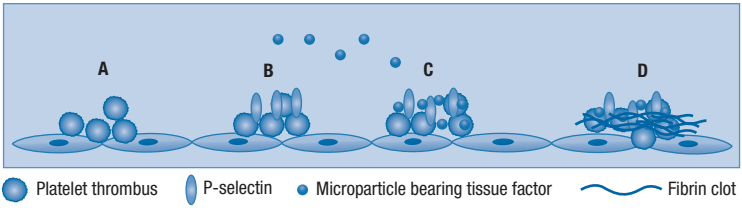


FIGURE 14-1. Model of pathologic thrombus formation: (A) activated platelets adhere to vascular endothelium; (B) activated platelets express P-selectin; (C) pathologic microparticles express active tissue factor and are present at a high concentration in the circulation—these microparticles accumulate, perhaps by binding to activated platelets expressing P-selectin; and (D) tissue factor can lead to thrombin generation, and thrombin generation leads to platelet thrombus formation and fibrin generation.

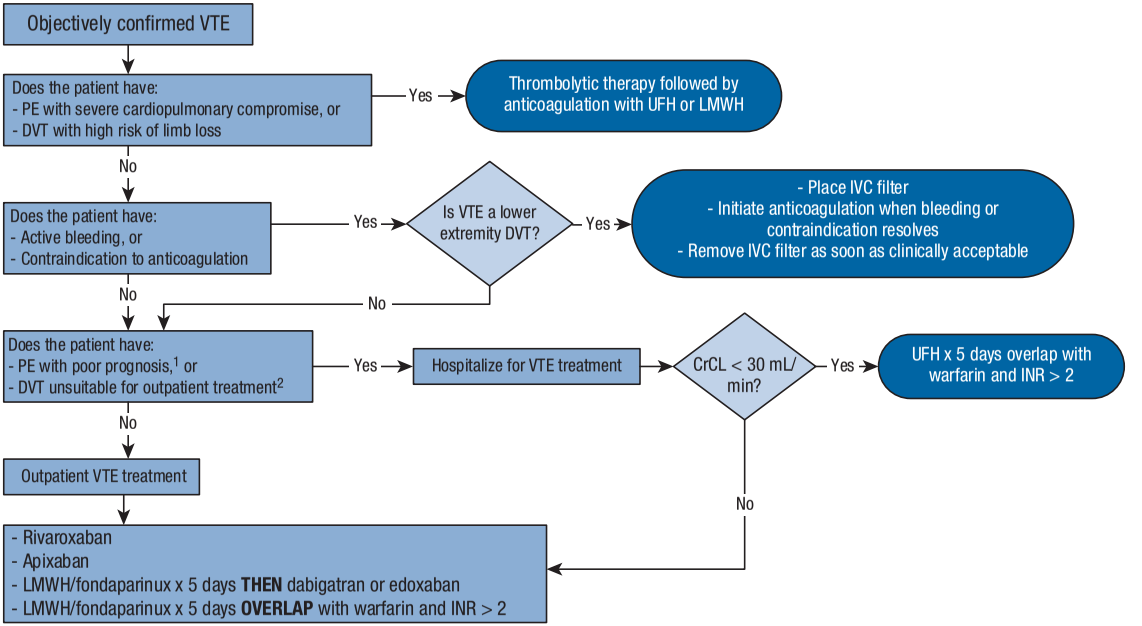
- Thrombin then converts fibrinogen to fibrin monomers that precipitate and polymerize to form fibrin strands. Factor XIIIa (also activated by thrombin) covalently bonds these strands to form an extensive meshwork that encases the aggregating platelet thrombus and red cells to form a stabilized fibrin clot.
- Hemostasis is controlled by antithrombotic substances produced by intact endothelium adjacent to damaged tissue. Thrombomodulin modulates thrombin activity by converting protein C to its activated form (aPC), which joins with protein S to inactivate factors Va and VIIIa. This prevents coagulation reactions from spreading to uninjured vessel walls. In addition, circulating antithrombin inhibits thrombin and factor Xa. Heparan sulfate is secreted by endothelial cells and accelerates antithrombin activity. These self-regulatory mechanisms limit fibrin clot formation to the zone of vessel injury.
- The fibrinolytic system dissolves formed blood clots; inactive plasminogen is converted to plasmin by tissue plasminogen activator (tPA). Plasmin is an enzyme that degrades the fibrin mesh into soluble end products (known as fibrin degradation products including D-dimer).
- Most venous thrombi begin in the leg(s). Isolated calf vein thrombi seldom embolize; those involving the popliteal and larger veins above the knee are more likely to embolize and lodge in the pulmonary artery or one of its branches, occluding blood flow to the lung and impairing gas exchange. Without treatment, the affected lung area becomes necrotic and oxygen delivery to other vital organs may decrease, potentially resulting in fatal circulatory collapse.

CLINICAL PRESENTATION

- Some patients with DVT are asymptomatic. Symptoms may include unilateral leg swelling, pain, tenderness, erythema, and warmth. Physical signs may include a palpable cord and a positive Homan sign.
- Symptoms of PE may include cough, chest pain or tightness, shortness of breath, palpitations, hemoptysis, dizziness, or lightheadedness. Signs of PE include tachypnea, tachycardia, diaphoresis, cyanosis, hypotension, shock, and cardiovascular collapse.
- Postthrombotic syndrome may produce chronic lower extremity swelling, pain, tenderness, skin discoloration, and ulceration.

DIAGNOSIS

- Assessment should focus on identifying risk factors (see section Pathophysiology).
- Compression ultrasound (CUS) and computed tomography pulmonary angiography (CTPA) are used most often for initial evaluation of suspected VTE.



CrCl, creatinine clearance via Cockcroft and Gault equation; DVT, deep vein thrombosis; INR, international normalized ratio; IVC, inferior vena cava; LMWH, low-molecular-weight heparin; PE, pulmonary embolism; UFH, unfractionated heparin; VTE, venous thromboembolism [includes DVT and PE].

FIGURE 14-2. Acute treatment of venous thromboembolism (VTE).

relatively high recurrence rate. In patients with VTE and active cancer, extended therapy is rarely stopped because of a high recurrence risk.

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- Encourage patients to ambulate as much as symptoms permit.
- Ambulation in conjunction with graduated compression stockings results in a faster reduction in pain and swelling than strict bedrest with no increase in embolization rate.
- Inferior vena cava filters should only be used when anticoagulants are contraindicated due to active bleeding.
- Elimination of the obstructing thrombus via thrombolysis or thrombectomy may be warranted in life- or limb-threatening DVT.

PHARMACOLOGIC THERAPY

Direct Oral Anticoagulants (DOACs)

- **Rivaroxaban**, **apixaban**, and **edoxaban** are oral selective inhibitors of both free and clot-bound factor Xa and do not require antithrombin to exert their anticoagulant effect. **Dabigatran** is an oral selective, reversible, direct factor IIa (thrombin) inhibitor.
- See **Table 14-1** for DOAC indications and dosing. Use DOACs with caution in patients with renal dysfunction.
- Single-drug oral therapy with rivaroxaban or apixaban produces similar rates of recurrent VTE compared to traditional therapy with warfarin overlapped with enoxaparin and perhaps less major bleeding. Both drugs are initiated with a higher dose and subsequently reduced to a maintenance dose. Neither drug requires routine anticoagulation monitoring, but the high acquisition cost may be a barrier for some patients.
- Edoxaban and dabigatran must be given only after at least 5 days of subcutaneous (SC) anticoagulation with UFH, LMWH, or fondaparinux. These regimens were noninferior to warfarin in patients with acute VTE for the outcome of recurrent VTE. Compared to warfarin, dabigatran caused similar major bleeding and edoxaban caused significantly less bleeding.
- Bleeding is the most common adverse effect with DOAC therapy. Patients experiencing significant bleeding should receive routine supportive care and discontinuation of anticoagulant therapy. **Idarucizumab** (Praxbind) 5 g IV rapidly reverses the dabigatran anticoagulant effect when needed during emergency situations (eg, life-threatening bleeding) and when there is need for urgent surgical intervention. **Recombinant coagulation factor Xa** (also known as **andexanet alfa**; Andexxa) can reverse life-threatening bleeding in patients taking rivaroxaban or apixaban. Adding aspirin to DOAC therapy nearly doubles bleeding rates and should be avoided in most patients with VTE. All DOACs are P-gp substrates and subject to changes in anticoagulant effect when coadministered with P-gp inhibitors or inducers. Rivaroxaban and apixaban are subject to interactions involving inhibitors or inducers of CYP 3A4.

Low-Molecular-Weight Heparin

- LMWH fragments produced by either chemical or enzymatic depolymerization of UFH are heterogeneous mixtures of sulfated glycosaminoglycans with approximately one-third of the mean UFH molecular weight. LMWH prevents thrombus propagation by accelerating the activity of antithrombin similar to UFH.
- LMWH given SC in fixed, weight-based doses is at least as effective as UFH given IV for VTE treatment. LMWH has largely replaced UFH for initial VTE treatment due to improved pharmacokinetic and pharmacodynamic profiles and ease of use. Advantages of LMWH over UFH include: (1) predictable anticoagulation dose response; (2) improved SC bioavailability; (3) dose-independent clearance; (4) longer biologic half-life; (5) lower incidence of thrombocytopenia; and (6) less need for routine laboratory monitoring.

TABLE 14-1 Approved Indications and Dosing for the Direct Oral Anticoagulants

Generic (Brand) Name	VTE Prophylaxis	Acute VTE Treatment	Reduction in Risk of Recurrent VTE in Patients at Continued Risk
Dabigatran (Pradaxa)	Hip replacement surgery: CrCl >30 mL/min: 110 mg the first day beginning 1–4 hours after surgery once hemostasis is achieved, then 220 mg once daily for 28–35 days CrCl ≤30 mL/min or on dialysis: Dosing recommendations cannot be provided	150 mg PO twice daily with or without food FOLLOWING at least 5 days of parenteral anticoagulant therapy	150 mg PO twice daily with or without food
Rivaroxaban (Xarelto)	Hip or knee replacement surgery: 10 mg PO once daily with or without food beginning 6–10 hours after surgery once hemostasis is achieved and continuing for 12 (knee) to 35 (hip) days	15 mg PO twice daily with food for days 1–21, then 20 mg PO once daily with food beginning on day 22	10 mg PO once daily with or without food
Apixaban (Eliquis)	Hip or knee replacement surgery: 2.5 mg PO twice daily with or without food beginning 12–24 hours after surgery and continuing for 12 (knee) or 35 (hip) days	10 mg PO twice daily with or without food on days 1–7, then 5 mg PO twice daily beginning on day 8	2.5 mg PO twice daily with or without food
Edoxaban (Savaysa)	Not approved for use	60 mg PO once daily with or without food FOLLOWING at least 5 days of parenteral anticoagulant therapy; 30 mg once daily with CrCl 15–50 mL/min (0.25–0.83 mL/sec) or body weight ≤60 kg or who use certain P-gp inhibitors	Not approved for use
Betrixaban (Bevyxxa)	Adults hospitalized for acute medical illness: Initial single dose of 160 mg PO with food, followed by 80 mg once daily with food for 35–42 days	Not approved for use	Not approved for use

PO, by mouth; CrCl, creatinine clearance; P-gp, P-glycoprotein; VTE, venous thromboembolism.

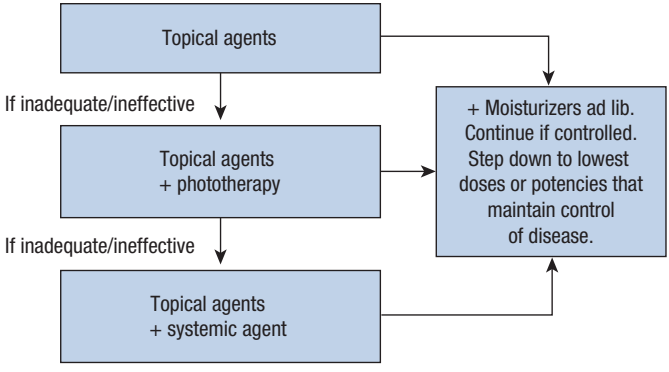
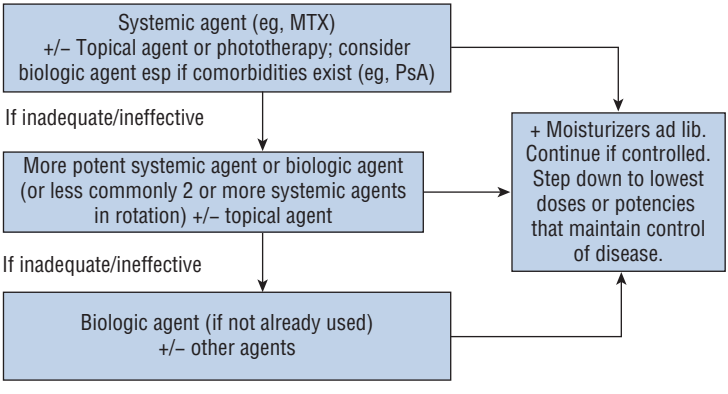


FIGURE 17-1. Treatment algorithm for mild-to-moderate psoriasis.



MTX, methotrexate; PsA, psoriatic arthritis.

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

cost-effective treatment, provide appropriate counseling (eg, stress reduction), and maintain or improve quality of life.

- See **Figs. 17-1** and **17-2** for psoriasis treatment algorithms based on disease severity.

NONPHARMACOLOGIC THERAPY

- Nonmedicated moisturizers help maintain skin moisture, reduce skin shedding, control scaling, and reduce pruritus.
- Oatmeal baths further reduce pruritus, and regular use may decrease need for systemic antipruritic drugs. Harsh soaps and detergents should be avoided. Cleansing should involve tepid water, preferably with lipid- and fragrance-free cleansers.
- Sunscreens (preferably sun protection factor [SPF] 30 or higher) should be used when outdoors.
- Stress management can improve extent and severity of psoriasis.

PHARMACOLOGIC THERAPY

Topical Therapies

- **Corticosteroids** (**Table 17-1**) have anti-inflammatory, antiproliferative, immunosuppressive, and vasoconstrictive effects. They are recommended in U.S. treatment guidelines as first-line treatment for limited psoriasis either as monotherapy or with

TABLE 17-1	Topical Corticosteroid Potency Chart
Potency Rating	**Topical Corticosteroid**
Class 1: Superpotent	Betamethasone dipropionate 0.05% ointment (Diprolene and Diprosone ointment) Clobetasol propionate 0.05% lotion/spray/shampoo/foam (Clobex lotion/spray/shampoo, OLUX and OLUX-E foam) Clobetasol propionate 0.05% cream, gel, solution (scalp), ointment (Cormax, Temovate, Dermovate) Diflorasone diacetate 0.05% ointment (Florone, Psorcon, ApexiCon) Flurandrenolide tape 4 mcg/cm^2 (Cordran) Halobetasol propionate 0.05% cream, lotion, ointment (Ultravate)
Class 2: Potent	Amcinonide 0.1% ointment (Cyclocort, Amcort) Betamethasone dipropionate 0.05% cream/gel (Diprolene cream, gel, and Diprosone cream) Desoximetasone 0.25% cream, gel, ointment (Topicort) Diflorasone diacetate 0.05% ointment (ApexiCon, Florone, Psorcon) Fluocinonide 0.05% cream, gel, ointment (Lidex) Halcinonide 0.1% cream (Halog)
Class 3: Upper mid-strength	Amcinonide 0.1% cream (Cyclocort) Betamethasone valerate 0.1% ointment (Betnovate/Valisone) Diflorasone diacetate 0.05% cream (Psorcon, Florone, ApexiCon) Fluticasone propionate 0.005% ointment (Cutivate) Mometasone furoate 0.1% ointment (Elocon) Triamcinolone acetonide 0.5% cream and ointment (Aristocort)
Class 4: Mid-strength	Betamethasone dipropionate 0.05% spray (Sernivo) Betamethasone valerate 0.12% foam (Luxiq) Clocortolone pivalate 0.1% cream (Cloderm) Desoximetasone 0.05% cream and gel (Topicort LP) Fluocinolone acetonide 0.025% ointment (Synalar) Fluocinolone acetonide 0.2% cream (Synalar-HP) Hydrocortisone valerate 0.2% ointment (Westcort) Mometasone furoate 0.1% cream, lotion, solution (Elocon) Triamcinolone acetonide 0.1% ointment (Kenalog)
Class 5: Lower mid-strength	Betamethasone dipropionate 0.05% lotion (Diprosone) Betamethasone valerate 0.1% cream and lotion (Betnovate/Valisone) Desonide 0.05% lotion, ointment, gel (DesOwen, Tridesilon) Fluocinolone acetonide 0.01% shampoo (Capex) Fluocinolone acetonide 0.01%, 0.025%, 0.03% cream (Synalar) Flurandrenolide 0.05% cream and lotion (Cordran) Fluticasone propionate 0.05% cream and lotion (Cutivate) Hydrocortisone butyrate 0.1% ointment, lotion, cream (Locoid, Locoid Lipocream) Hydrocortisone probutate 0.1% cream (Pandel) Hydrocortisone valerate 0.2% cream (Westcort) Prednicarbate 0.1% cream and ointment (Dermatop) Triamcinolone acetonide 0.1% cream, ointment, and lotion (Kenalog)
Class 6: Mild (low potency)	Alclometasone dipropionate 0.05% cream and ointment (Aclovate) Betamethasone valerate 0.05% cream and ointment (Valisone) Desonide 0.05% cream, ointment, gel (DesOwen, Desonate, Tridesilon) Desonide 0.05% foam (Verdeso) Fluocinonide acetonide 0.01% cream and solution (Synalar) Fluocinonide acetonide 0.01% FS oil (Derma-Smoothe)
Class 7: Least Potent	Hydrocortisone 0.5%, 1%, 2%, 2.5% cream, lotion, spray, and ointment (various brands)

Dipeptidyl Peptidase-4 (DPP-4) Inhibitors

- **Alogliptin**, **linagliptin**, **saxagliptin**, and **sitagliptin** prolong the half-life of endogenously produced GLP-1 and GIP, thereby increasing glucose-dependent insulin secretion from the pancreas and reducing inappropriate postprandial glucagon secretion, resulting in lower glucose levels without an increase in hypoglycemia when used as monotherapy. They do not alter gastric emptying, cause nausea, have significant effects on satiety, or cause weight gain/loss.
- DPP-4 inhibitors produce average A1C reductions of 0.5%–0.9% (6–10 mmol/mol Hb) when used at maximum doses. There are no clear differences in efficacy among agents in the class.
- DPP-4 inhibitors are considered second- or third-line therapy. Advantages include once-daily dosing, oral administration, weight neutrality, low risk of hypoglycemia, and good tolerability. However, they have less A1C lowering efficacy than other medication classes and are expensive.
- Adverse effects are uncommon and include stuffy, runny nose; headache; and upper respiratory tract infections. The labeling of saxagliptin and alogliptin includes information about increased risk of hospitalizations for HF. The FDA has also issued a warning on the risk of severe joint pain with DPP-4 inhibitors. Pancreatitis appears to be an established but rare safety concern.
- There is no need to titrate the dose of DPP-4 inhibitors; however, renal dose adjustments are required for alogliptin, saxagliptin, and sitagliptin (**Table 19-3**).

Thiazolidinediones (TZDs)

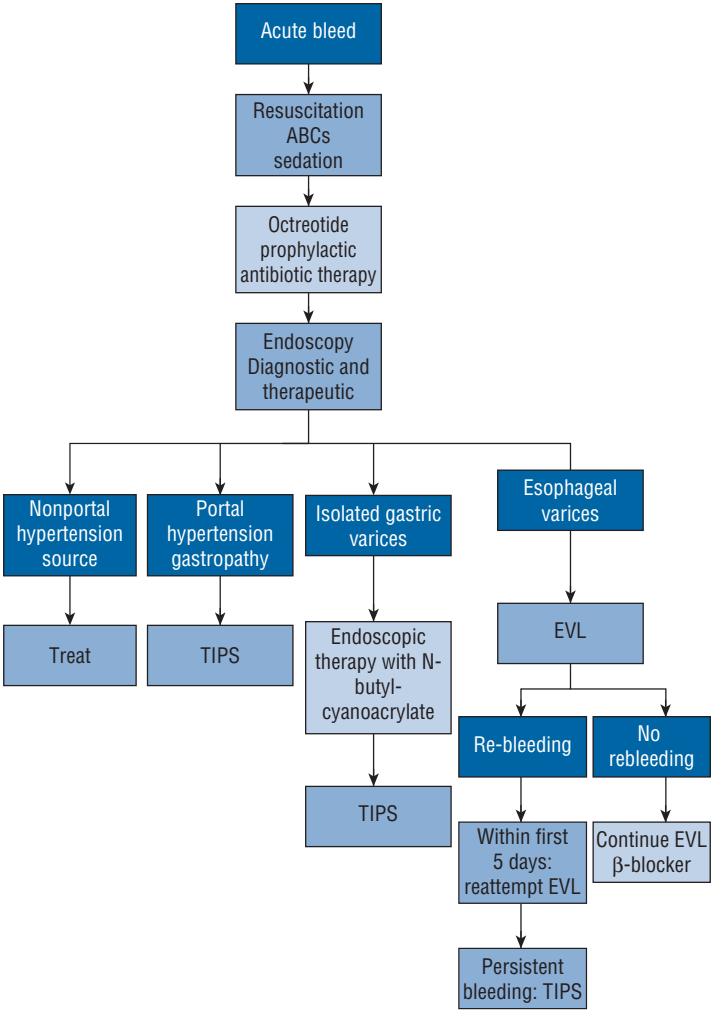
- TZDs bind to the peroxisome proliferator activator receptor-γ (PPAR-γ) located primarily on fat and vascular cells, enhancing insulin sensitivity in muscle, liver, and fat tissues.
- At maximal doses, **pioglitazone** and **rosiglitazone** reduce A1C by 1%–1.5% (11–22 mmol/mol Hb) and FPG by 60–70 mg/dL (3.3–3.9 mmol/L), and they have high durability over time. Maximum effects may not be seen until 3–4 months of therapy.
- TZDs are considered second- or third-line agents and can be used in combination with metformin and other commonly prescribed medications for type 2 DM.
- Pioglitazone decreases plasma triglycerides by 10%–20%, whereas rosiglitazone tends to have no effect. Pioglitazone does not significantly increase LDL-C, whereas rosiglitazone may increase LDL-C by 5%–15%. Both drugs increase HDL-C, but the magnitude may be greater with pioglitazone.
- Fluid retention may occur due to peripheral vasodilation and improved insulin sensitization in the kidney with increased sodium and water retention. This may result in peripheral edema (4%–5% of patients with monotherapy; 15% or more when combined with insulin), HF, hemodilution of hemoglobin and hematocrit, and weight gain. Edema is dose related and if not severe may be managed by dose reduction in most patients. TZDs are contraindicated in patients with New York Heart Association Class III or IV HF and should be used with caution in patients with Class I or II HF.
- Weight gain is dose related and results from both fluid retention and fat accumulation; a gain of 4 kg is not uncommon, and higher gains may require drug discontinuation. TZDs have also been associated with an increased fracture rate in the upper and lower limbs of postmenopausal women. An increased risk of bladder cancer is controversial.
- See **Table 19-3** for TZD dosing information.

Sulfonylureas

- Sulfonylureas enhance insulin secretion by binding to the sulfonylurea receptor SUR1 on pancreatic β-cells. First-generation agents (**chlorpropamide**, **tolazamide**, and **tolbutamide**) are lower in potency than second-generation drugs (**glyburide**, **glipizide**, and **glimepiride**), and are rarely used due to a higher risk of adverse effects.
- All sulfonylureas are equally effective in lowering BG when given in equipotent doses. On average, the A1C falls by 1.5%–2% (16–22 mmol/mol Hb) with FPG reductions of 60–70 mg/dL (3.3–3.9 mmol/L) in drug-naïve patients.

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

Drug/Dosage Form	Content	Relative Dose	Comments/ Equivalency
Thyroid USP Armour Thyroid, Nature-Throid, and Westhroid (T_4:T_3 ratio approximately 4.2:1); Armour, 1 grain = 60 mg; Nature-Throid and Westhroid, 1 grain = 65 mg. Doses include 1/4, 1/2, 1, 2, 3, 4, and 5 grain tablets	Desiccated pork thyroid gland	1 grain (equivalent to 74 mcg of T_4)	High T_3:T_4 ratio; inexpensive
Levothyroxine Synthroid, Levothroid, Levoxyl, Levo-T, Unithroid, and other generics 25, 50, 75, 88, 100, 112, 125, 137, 150, 175, 200, 300 mcg tablets; Tirosint 13–150 mcg liquid in gelatin capsule; Tirosint-Sol liquid solution 13, 25, 50, 75, 88, 100, 112, 137, 150, 175, and 200 mcg in unit-dose ampules; 200 and 500 mcg per vial solution for injection	Synthetic T_4	100 mcg	Stable; predictable potency; generics may be bioequivalent; when switching from natural thyroid to L-thyroxine, lower dose by one-half grain; variable absorption between products; half-life = 7 days, so daily dosing; considered to be drug of choice
Liothyronine Cytomel 5, 25, and 50 mcg tablets	Synthetic T_3	33 mcg (~equivalent to 100 mcg T_4)	Uniform absorption, rapid onset; half-life = 1.5 days, rapid peak and troughs
Liotrix Thyrolar 1/4, 1/2, 1, 2, and 3 grain tablets	Synthetic T_4:T_3 in 4:1 ratio	Thyrolar 1 = 50 mcg T_4 and 12.5 mcg T_3	Stable; predictable; expensive; risk of T_3 thyrotoxicosis because of high ratio of T_3 relative to T_4



ABCs, airway, breathing, and circulation; EVL, endoscopic variceal ligation; TIPS, transjugular intrahepatic portosystemic shunt.

FIGURE 21-1. Management of acute variceal hemorrhage.

- **Propranolol** may be given at 20 mg twice daily (or **nadolol** 40 mg once daily) and titrated weekly to achieve a goal of heart rate 55–60 beats/min or the maximal tolerated dose. Patients should be monitored for evidence of bradycardia, bronchospasm, and hypoglycemia, particularly in patients with insulin-dependent diabetes, as well as symptoms of heart failure and excessive sodium and water retention. Maximum doses of propranolol 320 mg/day for patients without ascites and 160 mg/day for patients with ascites, and nadolol 160 mg/day for patients without ascites and 80 mg/day for patients with ascites are recommended.
- Patients who cannot tolerate or who fail pharmacologic and endoscopic interventions can be considered for tips to prevent bleeding.

TABLE 44-6 Antibiotic Doses for Treatment of Bacterial Pneumonia (*Continued*)

		Antibiotic Dose[a]	
Antibiotic Class	**Antibiotic**	**Pediatric**	**Usual Adult Dose**
Macrolide/Azalide	Clarithromycin	15 orally mg/kg/day orally	0.5–1 g orally once or twice daily
	Erythromycin	30–50 IV or orally mg/kg/day orally	500 mg IV or orally every 6–8 hours
	Azithromycin	10 mg/kg × 1 day (×2 days if parenteral), and then 5 mg/kg days 2–5 IV or orally	500 mg × 1 day (×2 days if parenteral), and then 250 mg days 2–5 IV or orally
Fluoroquinolones[c]	Moxifloxacin	–	400 mg IV or orally daily
	Levofloxacin	8–20 mg/kg/day IV or orally	750 mg IV or orally daily
	Ciprofloxacin	30 mg/kg/day IV or orally	400 mg IV every 8 hours / 750 mg orally twice daily
Tetracycline[d]	Doxycycline	2–5 mg/kg/day IV or orally	100 mg IV or orally twice daily
	Tetracycline HCl	25–50 mg/kg/day orally	–
Aminoglycosides	Gentamicin	7.5–10 mg/kg/day IV	7.5 mg/kg IV daily
	Tobramycin	7.5–10 mg/kg/day IV	7.5 mg/kg IV daily
	Amikacin	15–20 mg/kg/day IV	15–20 mg/kg IV daily
	Plazomicin		15 mg/kg IV daily
Carbapenems	Imipenem	60–100 mg/kg/day IV	500–1000 mg IV every 6–8 hours
	Meropenem	30–60 mg/kg/day IV	500–2000 mg IV every 6–8 hours
	Meropenem–vaborbactam		2 g/2 g IV every 8 hours
	Imipenem-relabactam		1.25 g every 8 hours IV
Polymyxins	Colistin	2.5–5 mg/kg/day IV	IV: 300 mg × 1, then 150 mg daily/Neb: 150 mg every 8 hours
	Polymyxin B	15,000–30,000 units/kg/day IV	IV: 2–2.5 mg/kg × 1, then 1.25–1.5 mg/kg every 12 hours

(*Continued*)

TABLE 44-6 Antibiotic Doses for Treatment of Bacterial Pneumonia (*Continued*)

Antibiotic Class	Antibiotic	Antibiotic Dose[a]	
		Pediatric	Usual Adult Dose
Other	Vancomycin	45–60 mg/kg/day IV	15–20 mg/kg IV every 8–12 hours
	Linezolid	20–30 mg/kg/day IV or orally	600 mg IV or orally every 12 hours
	Clindamycin	30–40 mg/kg/day IV or orally	600 mg IV or orally every 8 hours or 450 mg orally every 6 hours

[a]Doses can be increased for more severe disease and may require modification for patients with organ dysfunction.
[b]Higher-dose amoxicillin and amoxicillin/clavulanate (eg, 90 mg/kg/day) are used for penicillin-resistant *S. pneumoniae*.
[c]Fluoroquinolones have been avoided for pediatric patients because of the potential for cartilage damage; however, they have been used for MDR bacterial infection safely and effectively in infants and children (see Chapter 35, *Dipiro's Pharmacotherapy: A Pathophysiologic Approach*, 12 edition).
[d]Tetracyclines are rarely used in pediatric patients, particularly in those younger than 8 years because of tetracycline-induced permanent tooth discoloration.

TABLE 44-7 Directed Antimicrobial Therapy for Common Pneumonia Pathogens in Adult Patients

Pathogen	Preferred Antibiotic Therapy	Alternative Antibiotic Therapy
Penicillin-susceptible *S. pneumoniae* (MIC ≤2 mg/L)	Ampicillin, amoxicillin, penicillin G	Ceftriaxone, cefotaxime, macrolide, levofloxacin, moxifloxacin, doxycycline, clindamycin, vancomycin
Penicillin-resistant *S. pneumoniae* (MIC >2 mg/L)	Ceftriaxone, cefotaxime, levofloxacin, moxifloxacin	High-dose amoxicillin (3 g/day), linezolid, clindamycin, vancomycin
Non-β-lactamase-producing *H. influenzae*	Ampicillin (IV), amoxicillin	Fluoroquinolone, doxycycline, azithromycin, clarithromycin
β-Lactamase-producing *H. influenzae*	Ceftriaxone, cefotaxime, ampicillin–sulbactam, amoxicillin–clavulanate	Fluoroquinolone, doxycycline, azithromycin, clarithromycin
Mycoplasma pneumoniae	Macrolide, doxycycline	Fluoroquinolone, doxycycline, azithromycin, clarithromycin
Chlamydophila pneumoniae	Macrolide, doxycycline	Fluoroquinolone
Legionella pneumophila	Fluoroquinolone or azithromycin	Doxycycline
MSSA	Cefazolin, antistaphylococcal penicillin	Clindamycin, vancomycin

(*Continued*)

TABLE 44-7 Directed Antimicrobial Therapy for Common Pneumonia Pathogens in Adult Patients (*Continued*)

Pathogen	Preferred Antibiotic Therapy	Alternative Antibiotic Therapy
MRSA	Vancomycin, linezolid	Telavancin, ceftaroline, quinupristin/dalfopristin, clindamycin, sulfamethoxazole/trimethoprim
P. aeruginosa	Antipseudomonal β-lactam[a] or fluoroquinolone[b] based on antimicrobial susceptibility testing results. Can consider adding aminoglycoside if patient in septic shock or at high mortality risk	IV colistin or polymyxin B + inhaled colistin for isolates resistant to all preferred therapies
Acinetobacter spp.	Carbapenem OR ampicillin–sulbactam based on antimicrobial susceptibility testing results	IV colistin or polymyxin B + inhaled colistin for isolates resistant to all preferred therapies
Extended-spectrum β-lactamase-producing gram-negative bacilli	Carbapenem	Piperacillin–tazobactam or cefepime potential options depending on susceptibility/adequate dosing
Carbapenem-resistant organisms	New β-lactam/β-lactamase inhibitors[c] based on antimicrobial susceptibility testing OR IV colistin or polymyxin B + inhaled colistin	

MIC, minimum inhibitory concentration; MRSA, methicillin-resistant *Staphylococcus aureus*; MSSA, methicillin-sensitive *Staphylococcus aureus*; PCN, penicillin.
[a]Antipseudomonal β-lactam: piperacillin/tazobactam, cefepime, ceftazidime, meropenem, imipenem/cilastatin, doripenem, aztreonam.
[b]Antipseudomonal fluoroquinolone: ciprofloxacin and levofloxacin
[c]New β-lactam/β-lactamase inhibitors: ceftazidime/avibactam, meropenem/vaborbactam, ceftolozane/tazobactam.

- With HAP some resolution of symptoms should be observed within 2 days of instituting antibiotic therapy. If no resolution of symptoms is observed within 2 days of starting seemingly appropriate antibiotic therapy or if the patient's clinical status is deteriorating, the appropriateness of initial antibiotic therapy should be critically reassessed. The clinician should consider the possibility of changing the initial antibiotic therapy to expand antimicrobial coverage not included in the original regimen if the patient's clinical status is worsening or failing to improve after 48–72 hours of therapy.
- De-escalation of antibiotic therapy to be more narrow spectrum in patients with HAP/VAP is strongly recommended. Evidence suggests this approach does not affect clinical outcomes while reducing excess antibiotic use. The recommended duration of therapy for HAP/VAP is 7 days, as the clinical benefit of longer durations of therapy (≥10 days) is not clear based on available clinical evidence.

See Chapter 129, Lower Respiratory Tract Infections, authored by Evan J. Zasowski and Martha G. Blackford, for a more detailed discussion of this topic.

TABLE 54-3 Antiseizure Medication Elimination Pathways and Major Effects on Hepatic Enzymes

Antiepileptic Medications	Major Hepatic Enzymes	Induces	Inhibits
First Generation			
Carbamazepine	CYP3A4	CYP1A2; CYP2B6; CYP2C9/19; CYP3A; GT	None
Clonazepam	CYP3A	None	None
Ethosuximide	CYP3A4; CYP2E1	None	None
Phenobarbital	CYP2C9; CYP2C19	CYP 3A4/2C9/2C19/1A2; GT	None
Phenytoin	CYP2C9; CYP2C19	CYP3A; CYP2C; GT	
Primidone			
Valproate	GT; β-oxidation	None	CYP2C9; GT epoxide hydrolase
Second Generation			
Felbamate	CYP3A4; CYP2E1; other	CYP3A4	CYP2C19; β-oxidation
Gabapentin	None	None	None
Lamotrigine	GT	GT	None
Levetiracetam	None (undergoes nonhepatic hydrolysis)	None	None
Oxcarbazepine (MHD is the active metabolite.)	Cytosolic system	CYP3A4; CYP3A5; GT	CYP2C19
Tiagabine	CYP3A4; CYP1A2; CYP2D6; CYP2C19	None	None
Topiramate	Not known	CYP3A (dose dependent)	CYP2C19
Zonisamide	CYP3A4	None	None
Third Generation			
Brivaracetam	CYP2C19	None	CYP2C19 (weak), GT epoxide hydrolase
Cenobamate	UGT2B7/B4; CYP2E1; CYP2A6; CYP2B6; CYP2C19; CYP3A4/5	CYP2B6; CYP2C8; CYP3A4	CYP 2B6; CYP2C19; CYP3A

TABLE 57-5 Skeletal Muscle Relaxants (*Continued*)

Medication	Dosing	Notes
Cyclobenzaprine	Initial: 5 mg 3 times daily Titrate: increase to 7.5–10 mg 3 times daily × 2–3 weeks Older patients: 5 mg dose with less frequent doses Doses for fibromyalgia 10mg QAM, 20mg QHS	Anticholinergic effects Avoid in older paints and caution in those with cardiac conduction/arrhythmias Avoid closed angle glaucoma Hepatic dose adjustments
Diazepam	Adults: 2–10 mg 3–4 times daily	Long half-life Avoid in older patients and those with renal/hepatic impairment Withdrawal with abrupt discontinuation
Methocarbamol	Initial: 1500 mg 4 times daily × 2–3 days Then: 750–1000 mg 4 times daily	Urine discoloration Respiratory depression with opioids, benzodiazepines, or barbiturates
Metaxalone	800 mg 3–4 times daily	Respiratory depression when used with opioids, benzodiazepines, or barbiturates Contraindicated in severe liver/renal impairment
Orphenadrine	100 mg twice daily	Anticholinergic effects Rare aplastic anemia
Tizanidine	Initial: 4 mg Titrate by 2–4 mg every 6–8 hours Maximum: 36 mg/day	Hypotension Hepatotoxicity Tablets and capsules not bioequivalent Withdrawal syndrome with abrupt discontinuation

Topicals

- Topicals address local symptoms while minimizing systemic exposure and adverse effects (**Table 57-6**). Guidelines suggest use of topical NSAIDs before oral treatment for knee or hand osteoarthritis.
- **Capsaicin** is recommended for peripheral neuropathic pain. It is more effective used on a schedule basis. The burning that may occur with initial application decreases over time with repeated, scheduled use.
- Topical **lidocaine** may be the treatment of choice when CNS adverse effects are a concern.

Emerging Agents

- **Cannabis** has been primarily studied in the treatment of neuropathic pain; however, the route of administration, dose, and monitoring recommendations are still unclear.
- The non-psychoactive cannabinoid, cannabidiol (CBD) may have a role in the treatment of chronic pain, although its utility in the absence of delta-9-tetrahydrocannabinol (THC) is unclear.

TABLE 57-6 Topical Analgesics

Medication	Uses	Dosing	Notes
Capsaicin cream (various)	Temporary relief of minor aches and pains of muscles and joints Localized neuropathic pain	Apply 3–4 times daily	Continue scheduled use for 2–4 weeks for best results
Capsaicin 8% patch (Qutenza)	PHN	Apply 1–4 patches to affected area for 60 minutes (PHN) or 30 minutes (DPN) Cleansing gel must be used on application site after patch removal Repeat no more frequently than every 3 months Max: Four patches	Specific administration directions in packaging information Apply topical anesthetic before applying Monitor blood pressure due to transient increase in blood pressure during application
Diclofenac 1% gel (Voltaren)	Pain of osteoarthritis of joints amenable to topical treatment (knees, hands)	Lower extremities: 4 g four times daily, max. 16 g/day Upper extremities: 2 g four times daily, max. 8 g/day Total dose maximum: 32 g/day	Same black box warnings as PO NSAIDs despite low systemic bioavailability (6% of systemic exposure from oral diclofenac) Use dosing card to measure amount
Diclofenac epolamine 1.3% patch (Flector)	Topical treatment of acute pain due to minor strains, sprains, and contusions	1 patch to most painful area twice daily	Systemic effects were <1% after 4 days of repeated dosing
Diclofenac topical solution (Pennsaid)	Pain from osteoarthritis of the knee	1.5%: 40 drops to each affected knee 4 times daily. Apply 10 drops at a time 2%: 2 pumps (40 mg) on each painful knee twice daily	Same black box warnings as PO NSAIDs

(*Continued*)

TABLE 57-6 Topical Analgesics (*Continued*)

Medication	Uses	Dosing	Notes
Lidocaine gel/Ointment/Patch (various)	Neuropathic pain	Cream/Ointment: Apply to affected area 3 times daily Patch: apply 1 patch to affected area up to 12 hours	Apply to intact skin only
Lidocaine 5% patch (Lidoderm, also available over the counter at 4%)	PHN	Apply 1–3 patches to site of pain for 12 hours Maximum: 3 patches	May cut lidocaine patches Apply to intact skin only Severe hepatic impairment increases risk of adverse effects
Menthol/Methyl salicylate (various)	Minor aches and pains of muscles and joints (simple backache, arthritis, strains, bruises, sprains)	Apply topically 3–4 times a day to affected area	Do not apply to damaged skin
Trolamine salicylate cream 10% (various)	Aches and pains of muscles and joints (arthritis, simple backache, bruises, sprains, strains)	Apply topically 3–4 times a day to affected area	Do not apply to damaged skin

DPN, diabetic peripheral neuropathy; NSAIDs, nonsteroidal anti-inflammatory drugs; PHN, postherpetic neuralgia.

- Guidelines for the use of **ketamine** for treating maladaptive pain syndrome are available, but appropriate dose, duration, and patient selection for chronic pain are still unclear.

Opioid Agents

- Opioids are often the next step in the management of acute pain and cancer-related chronic pain.
- Equianalgesic doses, dosing guidelines, and major adverse effects are shown in **Tables 57-7** and **57-8**. Equianalgesic doses are only a guide, and doses must be individualized based on response and adverse effects.
- Combining opioid analgesics with alcohol or other CNS depressants amplifies CNS depression and risk of death.
- Partial agonists and antagonists (eg, **nalbuphine**) compete with agonists for opioid receptor sites and exhibit mixed agonist–antagonist activity. They may produce analgesia with fewer adverse effects.
- Initially give analgesics around-the-clock for acute pain. As pain subsides, as-needed schedules can be used. Around-the-clock administration is also useful for management of chronic pain.
- Patients with severe pain may receive high doses of opioids with no unwanted adverse effects, but as pain subsides, may not tolerate low doses.
- Most opioid-related itching or rash is due to histamine release from cutaneous mast cells, and is not a true allergic response. When opioid allergies occur, an opioid from a different structural class may be cautiously tried. For these purposes, the mixed agonist–antagonist class behaves most like the morphine-like agonists.
- With patient-controlled analgesia (PCA), patients self-administer preset amounts of IV opioids via a syringe pump electronically interfaced with a timing device. PCA provides better pain control, improved patient satisfaction, and relatively few differences in adverse effects compared to traditional as needed administration.
- Administration of opioids directly into the CNS (see **Table 57-9**) (eg, epidural and intrathecal/subarachnoid routes) can be used for acute pain, chronic noncancer pain, and cancer pain. This requires preservative free formulations and careful monitoring for marked sedation, respiratory depression, pruritus, vomiting, urinary retention, and hypotension.

Morphine and Congeners (Phenanthrenes)

- **Morphine** is a first-line agent for moderate-to-severe pain. It may be used for pain associated with myocardial infarction, as it decreases myocardial oxygen demand, but this is controversial.
  - ✓ Tidal exchange and minute volume can be affected by opioids. Patients with underlying pulmonary dysfunction are at increased risk for respiratory depression, which can be reversed by **naloxone**.
  - ✓ Morphine-induced respiratory depression can increase intracranial pressure and cloud the neurologic examination results.
  - ✓ Hypovolemic patients are at risk for morphine-induced orthostatic hypotension.
  - ✓ Most clinicians avoid morphine in patients with creatinine clearance less than or equal to 30 mL/min [0.5 mL/sec] due to accumulation of active metabolites.
- **Hydromorphone** may have fewer adverse effects, especially pruritus, compared with other opioids and **levorphanol** has an extended half-life and purported NMDA glutamate receptor activity.
- **Codeine**, alone or combined with other analgesics (eg, acetaminophen), is commonly used for mild-to-moderate pain. **Oxycodone** is useful for moderate-to-severe pain, especially when combined with nonopioids.
- **Oliceridine** is approved IV for moderate-severe pain and is classified as a biased opioid agonist. It is structurally dissimilar from other opioid analgesics and is associated with fewer tolerability concerns.

TABLE 57-7 Opioid Dosing Guidelines

Agent(s)	Standard Dose Ranges	Equianalgesic Dose in Adults (mg)	Notes
Morphine	PO 5–30 mg every 4 hours[a]	25	Medication of choice in severe pain
	IM 5–20 mg every 4 hours[a]	10	Use immediate-release product with SR product to control breakthrough pain in cancer patients
	IV 5–15 mg every 4 hours[a]	10	Typical patient controlled analgesia IV dose is 1 mg with a 10-minutes lock-out interval
	SR 15–30 mg every 12 hours (may need to be every 8 hours in some patients)		Every 24-hour products available
	Rectal 10–20 mg every 4 hours[a]		
Hydromorphone	PO 2–4 mg every 4–6 hours[a]	7.5	Use in severe pain
	XR 8 mg to 64 mg every 24 hours		More potent than morphine; otherwise, no advantages
	IM 1–2 mg every 4–6 hours[a]	1.5	
	IV 0.5–2 mg every 4 hours[a]	1.5	Typical patient-controlled analgesia IV dose is 0.2 mg with a 10-minute lock-out interval
	Rectal 3 mg every 6–8 hours[a]		Every 24-hour product (Exalgo) available
Oxymorphone	IM 1–1.5 mg every 4–6 hours[a]	1	Use in severe pain
	IV 0.5 mg every 4–6 hours[a]	1	No advantages over morphine
	PO immediate-release 5–10 mg every 4–6 hours[a]	10	Use immediate-release product with controlled-release product to control breakthrough pain in cancer or chronic pain patients
	PO extended-release 5–10 mg every 12 hours[a]		Manufacturer recommends 5 mg every 12 hours in opioid-naïve patients Take ER on empty stomach

TABLE 57-8 Major Adverse Medication Effects of the Opioid Analgesics

Effect	Manifestation
Mood changes	Dysphoria, euphoria
Somnolence	Sedation, inability to concentrate
Chemoreceptor trigger zone stimulation	Nausea, vomiting
Respiratory depression	Decreased respiratory rate, periodic breathing, oxygen desaturation
Decreased gastrointestinal motility	Constipation
Increase in sphincter tone	Biliary spasm, urinary retention (varies among agents)
Histamine release	Urticaria, pruritus, rarely exacerbation of asthma due to bronchospasm (varies among agents)
Tolerance	Larger doses for same effect
Physical Dependence	Withdrawal symptoms upon abrupt discontinuation
Hypogonadism	Fatigue, depression, loss of analgesia, sexual dysfunction, amenorrhea (females)
Sleep	Disrupts sleep–wake cycle, causes dose-dependent rapid eye movement (REM) suppression

TABLE 57-9 Intraspinal Opioids

Medication	Single Dose (mg)	Onset of Pain Relief (minutes)	Duration of Pain Relief (hour)	Continual Infusion Dose (mg/h)
Epidural route				
Morphine	1–6	30	6–24	0.1–1
Hydromorphone	0.8–1.5	5–8	4–8	0.1–0.3
Fentanyl	0.025–0.1	5	2–8	0.025–0.1
Sufentanil	0.01–0.06	5	2–4	0.01–0.05
Subarachnoid route				
Morphine	0.1–0.3	15	8–34	–
Fentanyl	0.005–0.025	5	3–6	–

Doses above should not be interpreted as equianalgesic doses for conversion to or from the specific opioid or route of administration.

Meperidine and Congeners (Phenylpiperidines)

- **Meperidine** is less potent and has a shorter duration of action than morphine.
  - ✓ With high doses or in patients with renal failure, the metabolite normeperidine accumulates, causing tremor, muscle twitching, and possibly seizures. In most settings, meperidine offers no advantages over morphine.
  - ✓ Do not combine meperidine with monoamine oxidase inhibitors because severe respiratory depression or serotonin syndrome may occur.

TABLE 58-2 Dosing of Medications Used in Parkinson Disease[a]

Medication (Brand Name)	Starting Dose[b] (mg/day)	Maintenance Dose[b] (mg/day)
Adenosine-Receptor Antagonist		
Istradefylline	20	20-40
Anticholinergic Medications		
Benztropine	0.5–1	1–6
Trihexyphenidyl	1–2	6–15
Carbidopa/Levodopa products		
Carbidopa/levodopa	300[c]	300–2000[c]
Carbidopa/levodopa ODT	300[c]	300–2000[c]
Carbidopa/levodopa CR	400[c]	400–2000[c]
Carbidopa/levodopa IR/ER	435[c]	435–2450[c]
Carbidopa/levodopa enteral suspension	1000[c]	1000–2000[c]
Carbidopa/levodopa/entacapone	600[d]	600–1600[d]
Carbidopa	25	25–75
Levodopa	84	84–420
Dopamine agonists		
Apomorphine (Apokyn)	1–3	3–12
Apomorphine (Kynmobi)	10	10-150
Bromocriptine	2.5–5	15–40
Pramipexole	0.125	1.5–4.5
Pramipexole ER	0.375	1.5–4.5
Ropinirole	0.75	9–24
Ropinirole XL	2	8–24
Rotigotine	2	2–8
COMT inhibitors		
Entacapone	200–600	200–1600
Ocicapone	25-50	50
Tolcapone	300	300–600
MAO-B inhibitors		
Rasagiline	0.5–1	0.5–1
Safinamide	50	50–100
Selegiline	5–10	5–10
Selegiline ODT	1.25	1.25–2.5

(*Continued*)