

8. Hypertension

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1. Disease Overview

- Hypertension is defined as a systolic blood pressure >140 mm Hg, a diastolic blood pressure >90 mm Hg, or any patient requiring antihypertensive therapy.
- 65 million Americans are affected by hypertension.
 - * Approximately 3 of every 4 hypertensive Americans are not well controlled (Table 1).
- Increased incidence with increasing age
- Its onset is most commonly in third to fifth decades of life; lifetime risk of hypertension is 90% for those surviving to an age of 80 years.
- Prevalence differs by ethnic group, socioeconomic group, and by geographical region (Table 2).

Classification

- Classification of hypertension is based on the Seventh Report of the Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure (JNC-VII) (Table 3).

Clinical Presentation and Complications

Cardiovascular effects

- Left ventricular hypertrophy (LVH)
- Congestive heart failure (CHF)
- Peripheral arterial disease
- Angina pectoris
- Myocardial infarction
- Sudden death

Renal effects

- Nephropathy
- Renal failure
- Requirements for dialysis

Cerebrovascular effects

- Transient ischemic attacks (TIAs)
- Stroke

Ophthalmologic effects

- Retinal hemorrhage
- Retinopathy
- Blindness

Pathophysiology and Etiology

- Blood pressure = (stroke volume \times heart rate) \times peripheral resistance (Figure 1)

Table 1

Trends in Awareness, Treatment, and Control of High Blood Pressure in Adults Ages 18-74

	NATIONAL HEALTH AND NUTRITION EXAMINATION SURVEY, PERCENT			
	II (1976-80)	III (PHASE 1) 1988-91	III (PHASE 2) 1991-94	1999-2000
Awareness	51	73	68	70
Treatment	31	55	54	59
Control†	10	29	27	34

†SBP <140 mm Hg and DBP <90 mm Hg.

High blood pressure is systolic blood pressure (SBP) ≥ 140 mm Hg or diastolic blood pressure (DBP) ≥ 90 mm Hg or taking antihypertensive medication.

Sources: Unpublished data for 1999-2000 computed by M. Woltz, National Heart, Lung, and Blood Institute.

Adapted from JNC-7 Express. Source: National Heart, Lung, and Blood Institute.

Sympathetic nervous system activation

Central activation

- Presynaptic α_2 stimulation is a negative feedback mechanism, leading to decreased norepinephrine release.
- Presynaptic β stimulation leads to increased norepinephrine release.

Peripheral activation

- β_1 Stimulation leads to increased heart rate and contractility, causing increased cardiac output.
- β_2 Stimulation leads to arterial vasodilation.
- * β Stimulation also causes increased renin release, causing increased angiotensin II production.
- α_1 Stimulation leads to arterial and venous vasoconstriction.

Renin-angiotensin-aldosterone system

- Decreased renal perfusion pressure causes increases in renin levels.

Table 2

Prevalence of Hypertension by Ethnic Group for Adults Aged 20-74

	Male	Female
Caucasians	24%	19%
African-Americans	35%	34%
Mexican-Americans	25%	22%
Asian-Americans	13%	13%

Figure 1.

Sympathetic nervous system activation.

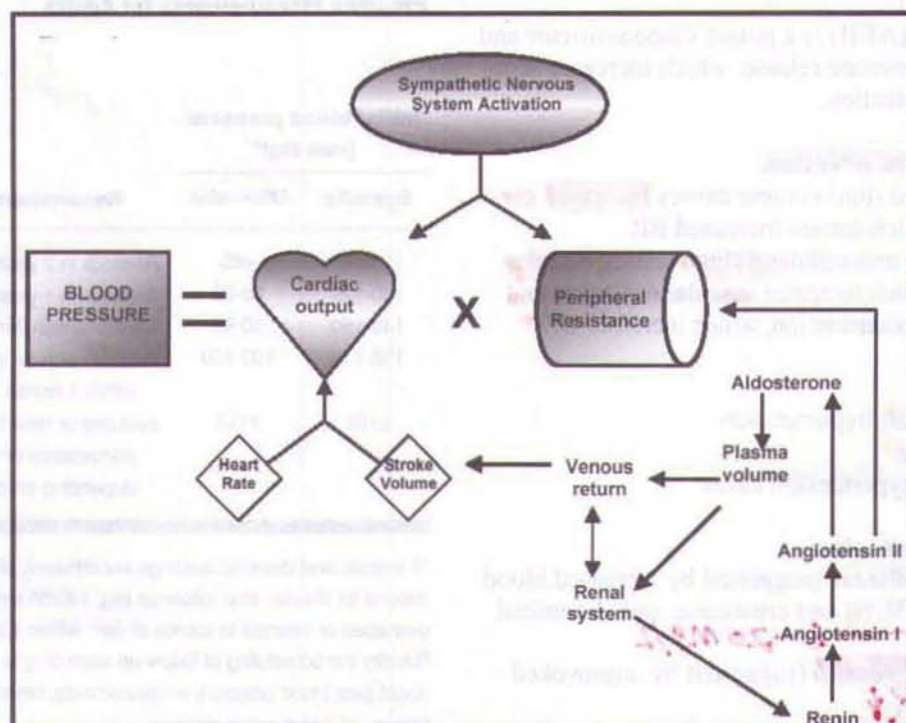


Table 3

Classification and Management of Blood Pressure for Adults

BP CLASSIFICATION	SBP* mmHg	DBP* mmHg	LIFESTYLE MODIFICATION	INITIAL DRUG THERAPY	
				WITHOUT COMPELLING INDICATION	WITH COMPELLING INDICATIONS (SEE TABLE 8)
NORMAL	<120	and <80	Encourage		
PREHYPERTENSION	120-139	or 80-89	Yes	No antihypertensive drug indicated.	Drug(s) for compelling indications. [‡]
STAGE 1 HYPERTENSION	140-159	or 90-99	Yes	Thiazide-type diuretics for most. May consider ACEI, ARB, BB, CCB, or combination.	Drug(s) for the compelling indications. [‡] Other antihypertensive drugs (diuretics, ACEI, ARB, BB, CCB) as needed.
STAGE 2 HYPERTENSION	≥160	or ≥100	Yes	Two-drug combination for most [†] (usually thiazide-type diuretic and ACEI or ARB or BB or CCB).	

Treatment determined by highest BP category.

[†]Initial combined therapy should be used cautiously in those at risk for orthostatic hypotension.

[‡]Treat patients with chronic kidney disease or diabetes to BP goal of <130/80 mm Hg.

ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BB, β-blocker; CCB, calcium channel blocker; DBP, diastolic blood pressure; SBP, systolic blood pressure

Adapted from JNC-7 Express. Source: National Heart, Lung, and Blood Institute.

We have to
monitor chronic
Kidney + Diabetes
to prevent
HTN

monitoring
Common BP Examen

- Renin reacts with angiotensinogen to produce angiotensin I (AT-I).
- Angiotensin converting enzyme (ACE) causes AT-I to become AT-II.
- Angiotensin II (AT-II) is a potent vasoconstrictor and stimulates aldosterone release, which increases sodium and fluid retention.

Water and sodium retention

- Acute: increased fluid volume causes increased cardiac output, which causes increased BP.
- Chronic: excess intracellular sodium causes vascular hypertrophy, which increases vascular resistance and response to vasoconstriction, which increases BP.

Etiology

Primary (essential) hypertension

- Unknown cause
- 85-95% of all hypertension cases

Secondary hypertension

- **Renovascular disease** (suggested by increased blood urea nitrogen [BUN] and creatinine, and abdominal bruits) *6-20 M9/L*
- **Primary aldosteronism** (suggested by unprovoked hypokalemia) *K↓*
- **Cushing's syndrome** (suggested by unprovoked hypokalemia and truncal obesity with purple striae)
- **Pheochromocytoma** (suggested by increased urinary catecholamine excretion [ie, vanillylmandelic acid and metanephrine] accompanied by headache, palpitations, and perspiration)
- **Aortic coarctation** (suggested by delayed or absent femoral pulses and decreased blood pressure in the lower extremities) *الأطراف*

Drug-induced

- * Steroids and estrogens (including oral contraceptives)
- * Alcohol
- * Cocaine
- * Cyclosporine and tacrolimus *macrolides*
- * Sympathomimetics *Adrenergic*
- * Erythropoietin *Regulate production RBC*
- * Licorice (in chewing tobacco)
- * Monoamine oxidase (MAO) inhibitors
- * Tricyclic antidepressants
- * NSAIDs

Diagnostic Criteria

- Diagnosis and treatment begin with proper blood pressure measurement, assessment, and follow-up planning (Table 4):
- 1. Patient should avoid smoking or caffeine for 30 minutes prior to BP measurement.

Table 4

Recommendations for Follow-Up Based on Initial Blood Pressure Measurements for Adults

Initial blood pressure (mm Hg) ¹		Recommended follow-up ²
Systolic	Diastolic	
<130	<85	Recheck in 2 years
130-139	85-89	Recheck in 1 year ³
140-159	90-99	Confirm within 2 months ³
160-179	100-109	Evaluate or refer to source of care within 1 month
≥180	≥110	Evaluate or refer to source of care immediately or within 1 week depending on clinical situation

¹If systolic and diastolic readings are different, follow recommendations for shorter time follow-up (eg, 160/86 mm Hg should be evaluated or referred to source of care within 1 month).

²Modify the scheduling of follow-up according to reliable information about past blood pressure measurements, other cardiovascular risk factors, or target organ disease.

³Provide advice about lifestyle modifications.

Adapted from JNC-7 Express. Source: National Heart, Lung, and Blood Institute.

2. Patient should be resting for 5 minutes before measuring BP.
3. Position arm (brachial artery) at heart level.
4. Uncover arm; do not put cuff over clothes.
5. Determine proper size cuff:

Upper arm circumference	Cuff size required
16-22.5 cm	pediatric cuff
22.6-30 cm	regular adult cuff
30.1-37.5 cm	large adult cuff
37.6-43.7 cm	thigh cuff

6. Position cuff 1 inch above antecubital crease.
7. Ask patient about previous readings.
8. Place stethoscope over brachial artery (medial to the center).
9. Inflate cuff rapidly to approximately 30 mm Hg above previous readings.
10. Deflate cuff slowly.
11. Remember to deflate cuff completely when done.
12. Wait 1-2 minutes before repeating.
13. Take pressure in both arms.
14. If orthostatic hypotension is suspected, take BP sitting, standing, and supine.

15. Two readings separated by at least 2 minutes should be averaged.
16. If readings differ by >5 mm Hg, additional readings should be taken.

Treatment Principles and Goals

Goals of therapy (Figure 2A and B)

- Reduce end-organ damage
- Minimize or control other risk factors for cardiovascular disease
- Maintain blood pressure, with minimal side effects, at or below the level appropriate for the patient's risk:
 - * 140/90 with uncomplicated hypertension
 - * 140/90 with target organ damage or CV disease
 - * $<130/80$ with diabetes and chronic kidney disease
 - * $<125/75$ with proteinuria >1 g/24 h

Monitoring and Evaluation

Goals of initial evaluation of patients with hypertension (Table 5)

- Identify known causes of high blood pressure.
- Assess presence or absence of target organ damage and CV disease, extent of the disease, and the response to therapies (Figure 3).
- Identify other CV risk factors or concomitant disorders that may affect prognosis and guide therapy (Figure 3).

Initial evaluation

History

- Duration and levels of elevated blood pressure
- History or symptoms of CHD, heart failure, cerebrovascular disease, pulmonary vascular disease, diabetes mellitus, renal disease, dyslipidemia
- Family history of hypertension, premature CHD, stroke, diabetes, dyslipidemias, or renal disease
- Symptoms suggesting the cause of hypertension
- Recent weight changes, physical activity levels, smoking or other tobacco use
- **Dietary assessment: intake of sodium, alcohol, saturated fat, and caffeine**
- Complete medication history including prescription, over-the-counter, and herbal/natural products that may increase blood pressure or decrease effectiveness of antihypertensive agents
- Results and adverse effects of previous antihypertensive therapy
- Psychosocial/environmental factors that may influence hypertension control

Examination

- **Two or more blood pressure measurements separated by at least 2 minutes**
- Measurement of height, weight, and waist circumference
- Funduscopic exam for **hypertensive retinopathy**
- Exam of neck for carotid bruits, distended veins, or an enlarged thyroid gland

Table 5

Identifiable Causes, Diagnostic Tests, and Clinical Findings for Secondary Hypertension

Cause/diagnosis

Chronic kidney disease

Coarctation of the aorta

Cushing's syndrome and other glucocorticoid

excess states including chronic steroid therapy

Drug-induced or drug-related

Pheochromocytoma

Primary aldosteronism and other mineralocorticoid excess states

Renovascular hypertension

Sleep apnea

Thyroid/parathyroid disease

Diagnostic test (clinical finding)

Estimated GFR (abdominal or flank mass for polycystic kidney disease)

CT angiography (delayed or absent femoral pulse)

History/dexamethasone suppression test (truncal obesity, moon facies, buffalo hump, abdominal striae, hirsutism)

History; drug screening

24-hour urinary metanephrine and normetanephrine (headache, palpitations, sweating)

24-hour urinary aldosterone level or specific measurements of other mineralocorticoids (hypokalemia)

Doppler flow study; magnetic resonance angiography (abdominal bruit)

Sleep study with oxygen saturation (obesity, snoring, tired during waketime)

TSH; serum PTH (goiter; hypercalcemia)

CT, computed tomography; GFR, glomerular filtration rate; PTH, parathyroid hormone; TSH, thyroid-stimulating hormone.

Figure 2A.

Algorithm for the treatment of hypertension.

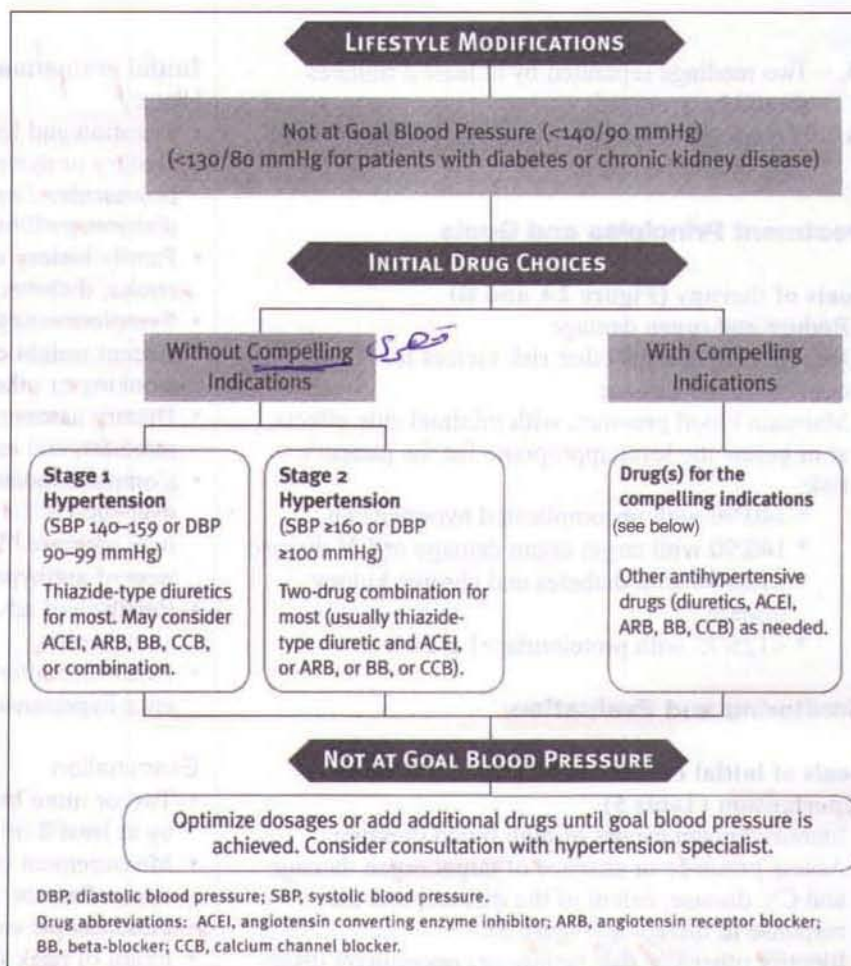


Figure 2B.

Clinical trial and guideline basis for compelling indications for individual drug classes.

COMPELLING INDICATION*	RECOMMENDED DRUGS†						CLINICAL TRIAL BASIS‡
	DIURETIC	BB	ACEI	ARB	CCB	ALDO ANT	
Heart failure	•	•	•	•		•	ACC/AHA Heart Failure Guideline, MERIT-HF, COPERNICUS, CIBIS, SOLVD, AIRE, TRACE, ValHEFT, RALES
Postmyocardial infarction		•	•			•	ACC/AHA Post-MI Guideline, BHAT, SAVE, Capricorn, EPHEsus
High coronary disease risk	•	•	•		•		ALLHAT, HOPE, ANBP2, LIFE, CONVINCE
Diabetes	•	•	•	•	•		NKF-ADA Guideline, UKPDS, ALLHAT
Chronic kidney disease			•	•			NKF Guideline, Captopril Trial, RENAAL, IDNT, REIN, AASK
Recurrent stroke prevention	•		•				PROGRESS

* Compelling indications for antihypertensive drugs are based on benefits from outcome studies or existing clinical guidelines; the compelling indication is managed in parallel with the BP.

† Drug abbreviations: ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; Aldo ANT, aldosterone antagonist; BB, beta-blocker; CCB, calcium channel blocker.

‡ Conditions for which clinical trials demonstrate benefit of specific classes of antihypertensive drugs.

Figure 3.**Cardiovascular risk factors.****Major risk factors**

- Hypertension¹
- Cigarette smoking
- Obesity¹ (body mass index ≥ 30 kg/m²)
- Physical inactivity
- Dyslipidemia¹
- Diabetes mellitus¹
- Microalbuminuria or estimated GFR < 60 mL/min
- Age (> 55 for men, > 65 for women)
- Family history of premature cardiovascular disease (men under age 55, women under 45)

Target organ damage**Heart**

- Left ventricular hypertrophy
- Angina or prior myocardial infarction
- Prior coronary revascularization
- Heart failure

Brain

- Stroke or transient ischemic attack
- Chronic kidney disease
- Peripheral arterial disease
- Retinopathy

GFR, glomerular filtration rate.

¹Components of the metabolic syndrome.

Adapted from JNC-7 Express. Source: National Heart, Lung, and Blood Institute.

- Exam of heart for abnormalities in rate and rhythm, increased size, precordial heave, clicks, murmurs, and third and fourth heart sounds
- Exam of lungs for rales and evidence of bronchospasm
- Exam of abdomen for bruits, enlarged kidneys, masses, and abnormal aortic pulsation
- Exam of extremities for decreased or absent peripheral arterial pulsations, bruits, and edema
- Neurologic assessment

Laboratory**Routine tests**

- Urinalysis
- Complete blood cell count
- Blood chemistries (sodium, potassium, creatinine, BUN, glucose)
- Fasting lipid profile (total cholesterol, triglycerides, HDL, LDL)
- ECG

Optional tests

- Creatinine clearance
- Microalbuminuria
- 24-Hour urinary protein
- Blood calcium
- Uric acid
- Glycosylated hemoglobin
- Thyroid-stimulating hormone
- Limited echocardiography
- Ankle-brachial index (ABI)
- Plasma renin activity/urinary sodium determination

Follow-up evaluation

- Follow-up evaluation includes any of the previous exams completed during the initial evaluation as required to monitor both response to and possible adverse effects from prescribed antihypertensive therapies, in addition to assessment of any new symptoms of target organ damage and the assessment of patient adherence to therapy (Figure 4).

Figure 4.**General guidelines to improve patient adherence to antihypertensive therapy.**

- Be aware of signs of patient nonadherence to antihypertensive therapy.
- Establish the goal of therapy: to reduce blood pressure to nonhypertensive levels with minimal or no adverse effects.
- Educate patients about the disease, and involve them and their families in its treatment. Have them measure blood pressure at home.
- Maintain contact with patients; consider telecommunication.
- Keep care inexpensive and simple.
- Encourage lifestyle modifications.
- Integrate pill-taking into routine activities of daily living.
- Prescribe medications according to pharmacologic principles, favoring long-acting formulations.
- Be willing to stop unsuccessful therapy and try a different approach.
- Anticipate adverse effects, and adjust therapy to prevent, minimize, or ameliorate side effects.
- Continue to add effective and tolerated drugs, stepwise, in sufficient doses to achieve the goal of therapy.
- Encourage a positive attitude about achieving therapeutic goals.
- Consider using nurse case management.

Adapted from JNC-7 Express. Source: National Heart, Lung, and Blood Institute.

2. Nondrug Therapy

- Lifestyle modifications are recommended to improve both blood pressure and overall cardiovascular health (Figure 5).
- Research has shown that diets rich in fruits, vegetables, and low-fat dairy foods, and with reduced saturated and total fats, significantly lower blood pressure (Figures 6 and 7).

Figure 5.

Lifestyle modifications to manage hypertension.

MODIFICATION	RECOMMENDATION	APPROXIMATE SBP REDUCTION (RANGE)
Weight reduction	Maintain normal body weight (body mass index 18.5–24.9 kg/m ²).	5–20 mmHg/10 kg weight loss
Adopt DASH eating plan	Consume a diet rich in fruits, vegetables, and lowfat dairy products with a reduced content of saturated and total fat.	8–14 mmHg
Dietary sodium reduction	Reduce dietary sodium intake to no more than 100 mmol per day (2.4 g sodium or 6 g sodium chloride).	2–8 mmHg
Physical activity	Engage in regular aerobic physical activity such as brisk walking (at least 30 min per day, most days of the week).	4–9 mmHg
Moderation of alcohol consumption	Limit consumption to no more than 2 drinks (1 oz or 30 mL ethanol; e.g., 24 oz beer, 10 oz wine, or 3 oz 80-proof whiskey) per day in most men and to no more than 1 drink per day in women and lighter weight persons.	2–4 mmHg ^a

DASH, Dietary Approaches to Stop Hypertension.

For overall cardiovascular risk reduction, stop smoking.

The effects of implementing these modifications are dose and time dependent, and could be greater for some individuals.

Adapted from JNC-7 Express. Source: National Heart, Lung, and Blood Institute.

Figure 6.

Dietary suggestions for hypertensive patients.

Food group	Daily servings	Serving sizes	Examples and notes	Significance of each food group to the DASH diet pattern
Grains and grain products	7-8	1 slice bread; $\frac{1}{2}$ c. dry cereal; $\frac{1}{2}$ c. cooked rice, pasta, or cereal	Whole wheat bread, english muffins, pita bread, bagel, cereals, grits, oatmeal	Major sources of energy and fiber
Vegetables	4-5	1 c. raw leafy vegetable; $\frac{1}{2}$ c. cooked vegetable; 6 oz. vegetable juice	Tomatoes, potatoes, carrots, peas, squash, broccoli, turnip greens, collards, kale, spinach, artichokes, beans, sweet potatoes	Rich sources of potassium, magnesium, and fiber
Fruits	4-5	6 oz. fruit juice; 1 medium fruit; $\frac{1}{4}$ c. dried fruit; $\frac{1}{4}$ c. fresh, frozen or canned fruit	Apricots, bananas, dates, grapes, oranges, orange juice, grapefruit, grapefruit juice, mangoes, melons, peaches, pineapple, prunes, raisins, strawberries, tangerines	Important sources of potassium, magnesium, and fiber
Low-fat or nonfat dairy foods	2-3	8 oz. milk; 1 c. yogurt; 1.5 oz. cheese	Skim or 1% milk, skim or low-fat buttermilk, nonfat or low-fat yogurt, part-skim mozzarella cheese, nonfat cheese	Major sources of calcium and protein
Meats, poultry, and fish	2 or less	3 oz. cooked meats, poultry, or fish	Select only lean; trim away visible fats; broil, roast, or boil, instead of frying; remove skin from poultry	Rich sources of protein and magnesium
Nuts, seeds, and legumes	4-5 per week	1.5 oz. or $\frac{1}{3}$ c. nuts; $\frac{1}{2}$ oz. or 2 T. seeds; $\frac{1}{2}$ c. cooked legumes	Almonds, filberts, mixed nuts, peanuts, walnuts, sunflower seeds, kidney beans, lentils	Rich sources of energy, magnesium, potassium, protein, and fiber

Adapted from JNC-7 Express. Source: National Heart, Lung, and Blood Institute.
DASH, Dietary Approaches to Stop Hypertension.

Figure 7.**The DASH diet sample menu based on 2000 calories/day.**

Food	Amount	Servings provided	Total number of servings in 2000-calorie-per-day menu	
Breakfast			Food group	Servings
Orange juice	6 oz.	1 fruit	Grains	= 8
1% Lowfat milk	8 oz. (1 c.)	1 dairy	Vegetables	= 4
Cornflakes (with 1 t. sugar)	1 c.	2 grains	Fruits	= 5
Banana	1 medium	1 fruit	Dairy foods	= 3
Whole wheat bread (with 1 T. jelly)	1 slice	1 grain	Meats, poultry, and fish	= 2
Soft margarine	1 t.	1 fat	Nuts, seeds, and legumes	= 1
Lunch			Fats and oils	= 2.5
Chicken salad	$\frac{3}{4}$ c.	1 poultry	Tips on eating the DASH way	
Pita bread	$\frac{1}{2}$ large	1 grain	<ul style="list-style-type: none"> • Start small. Make gradual changes in your eating habits. • Center your meal around carbohydrates, such as pasta, rice, beans, or vegetables. • Treat meat as one part of the whole meal, instead of the focus. • Use fruits or low-fat, low-calorie foods such as sugar-free gelatin for desserts and snacks. 	
Raw vegetable medley: Carrot and celery sticks	3-4 sticks each		REMEMBER! If you use the DASH diet to help prevent or control high blood pressure, make it part of a lifestyle that includes choosing foods lower in salt and sodium, keeping a healthy weight, being physically active, and if you drink alcohol, doing so in moderation.	
Radishes	2	1 vegetable		
Loose-leaf lettuce	2 leaves			
Part-skim mozzarella cheese	1.5 slice (1.5 oz.)	1 dairy		
1% lowfat milk	8 oz. (1 c.)	1 dairy		
Fruit cocktail in light syrup	$\frac{1}{2}$ c.	1 fruit		
Dinner				
Herbed baked cod	3 oz.	1 fish		
Scallion rice	1 c.	2 grains		
Steamed broccoli	$\frac{1}{2}$ c.	1 vegetable		
Stewed tomatoes	$\frac{1}{2}$ c.	1 vegetable		
Spinach salad:				
Raw spinach	$\frac{1}{2}$ c.			
Cherry tomatoes	2	1 vegetable		
Cucumber	2 slices			
Light Italian salad dressing	1 T.	$\frac{1}{2}$ fat		
Whole wheat dinner roll	1 small	1 grain		
Soft margarine	1 t.	1 fat		
Melon balls	$\frac{1}{2}$ c.	1 fruit		
Snacks				
Dried apricots	1 oz. ($\frac{1}{4}$ c.)	1 fruit		
Minipretzels	1 oz. ($\frac{3}{4}$ c.)	1 grain		
Mixed nuts	1.5 oz. ($\frac{1}{3}$ c.)	1 nuts		
Diet ginger ale	12 oz.	0		

Adapted from JNC-7 Express. Source: National Heart, Lung, and Blood Institute.
DASH, Dietary Approaches to Stop Hypertension.

3. Drug Therapy

- All patient factors (severity of blood pressure elevation, presence of target organ damage, and presence of CV disease or other risk factors) must be considered when initiating therapy.

Initial Therapy

- Candidates for therapy (Figure 2A and 2B)
- Use of lifestyle modifications should continue to be stressed to patients after the decision to initiate drug therapy has been made (Figure 5) to further decrease the risk of complications from cardiovascular disease.
- Prehypertension represents a new classification in JNC-VII (Table 3) and represents a significant risk for future development of stage 1 hypertension. Lifestyle modifications should be stressed for this classification, and medication therapy should only be used for patients with compelling indications.
- **β -Blockers and diuretics are considered the initial agents for treatment of hypertension** by JNC-VI unless compelling indications for the use of other medication classes exist or the patient has comorbid conditions that would suggest the use of classes other than β -blockers and diuretics (Figure 2A and 2B and Table 6).
- Recent data suggest that angiotensin-converting enzyme inhibitors (**ACEIs**), calcium channel blockers (**CCBs**), and possibly angiotensin II receptor blockers (**ARBs**) might also be considered as initial agents for treatment of hypertension.
- For patients who are 20/10 mm Hg greater than their goal blood pressure, **2-drug combination** therapy (one drug a diuretic) should be strongly considered.
- If a patient requires a second agent for treatment of hypertension, it is strongly recommended to be a diuretic if one is not chosen as the initial agent.
- All causes for inadequate response should be addressed before additional agents are added to a patient's antihypertensive regimen (Figure 8).
- **Vasodilators, α_1 -receptor antagonists, α_2 -receptor agonists, and postganglionic adrenergic neuron blockers** should be avoided as initial agents for hypertension.

Diuretics

Thiazide and thiazide-like diuretics (Table 7)

Mechanism of action

- **Direct arteriole dilation**
- **Reduction of total fluid volume through the inhibition of sodium reabsorption in the distal tubules,**

which causes increased excretion of sodium, water, potassium, and hydrogen

- Increase the effectiveness of other antihypertensive agents by preventing re-expansion of plasma volume
- Significant decrease in efficacy in renal failure (serum creatinine >2 mg/dL or GFR <30 mL/min)

Adverse drug events (Table 7)

Patient instructions and counseling

- **Can be taken with food or milk**
- **Take early in the day to avoid nocturia.**
- Patients may become more sensitive to sunlight; consider using sunscreen with SPF >15 .
- May increase blood glucose in diabetics
- **Report problems with muscle cramps that may indicate decreased potassium level.**

Drug-drug and drug-disease interactions

- **Steroids: cause salt retention and antagonize thiazide action**
- **NSAIDs: blunt thiazide response**
- Class IA or III antiarrhythmics (that prolong the QT interval) may cause torsades de pointes with diuretic-induced hypokalemia.
- **Probenecid and lithium: block thiazide effects by interfering with thiazide excretion into the urine**
- Lithium: thiazides decrease lithium renal clearance and increase risk of lithium toxicity

Parameters to monitor

- Blood pressure
- Weight
- Serum electrolytes and uric acid
- BUN and creatinine
- Cholesterol levels

Loop diuretics (Table 7)

Mechanism of action

- **Reduction of total fluid volume through the inhibition of sodium and chloride reabsorption in the ascending loop of Henle, which causes increased excretion of water, sodium, chloride, magnesium, and calcium**
- **Are more effective than thiazides in patients with renal failure (serum creatinine >2 mg/dL or GFR <30 mL/min)**
- Diuretics are also available in combination with other drugs (Table 8).

Adverse drug events (Table 7)

Patient instructions and counseling

- Can be taken with food or milk
- Take early in the day to avoid nocturia.

Table 6

Considerations for Individualizing Antihypertensive Drug Therapy¹**Indication****Drug therapy****Compelling indications unless contraindicated**

Diabetes mellitus (type 1) with proteinuria

Heart failure

Isolated systolic hypertension (older patients)

Myocardial infarction

ACEI

ACEI, diuretics

Diuretics (preferred), calcium antagonists (long-acting DHP)

β-Blockers (non ISA), ACEI (with systolic dysfunction)**May have favorable effects on comorbid conditions²****Angina**

Atrial tachycardia and fibrillation

Cyclosporine-induced hypertension (caution with the dose of cyclosporine)

Diabetes mellitus (types 1 and 2) with proteinuria

Diabetes mellitus (type 2)

Dyslipidemia

Essential tremor

Heart failure

Hyperthyroidism

Migraine

Myocardial infarction

Osteoporosis

Preoperative hypertension

Prostatism (benign prostatic hyperplasia)

Renal insufficiency (use caution in renovascular hypertension and if creatinine ≥ 265.2 micromole/L [3 mg/dL])**β-Blockers, calcium antagonists**

β-Blockers, calcium antagonists (non-DHP)

Calcium antagonists

ACEI (preferred), calcium antagonists

Low-dose diuretics

α-Blockers

β-Blockers (non-CS)

Carvedilol, losartan potassium

β-Blockers

β-Blockers (non-CS), calcium antagonists (non-DHP)

Diltiazem hydrochloride, verapamil hydrochloride

Thiazides

β-Blockers

α-Blockers

ACEI

May have unfavorable effects on comorbid conditions^{2,3}

Bronchospastic disease

Depression

Diabetes mellitus (types 1 and 2)

Dyslipidemia

Gout

Second- or third-degree heart block

Heart failure

β-Blockers⁴β-Blockers, central α-agonist, reserpine⁴

β-Blockers, high-dose diuretics

β-Blockers (non-ISA), diuretics (high-dose)

Diureticsβ-Blockers,⁴ calcium antagonists (non-DHP)⁴

β-Blockers (except carvedilol), calcium antagonists (except amlodipine besylate, felodipine)

Labetalol hydrochloride, methyldopa⁴

β-Blockers

ACEI,⁴ angiotensin II receptor blockers⁴

Potassium-sparing agents

ACEI, angiotensin II receptor blockers

ACEI, angiotensin-converting enzyme inhibitors; DHP, dihydropyridine; ISA, intrinsic sympathomimetic activity; non-CS, noncardioselective.

¹For initial drug therapy recommendations, see Tables 7-15.²Conditions and drugs are listed in alphabetical order.³These drugs may be used with special monitoring unless contraindicated.⁴Contraindicated.

Adapted from JNC-7 Express. Source: National Heart, Lung, and Blood Institute.

Figure 8.**Causes of inadequate responsiveness to therapy.****Pseudoresistance**

- "White-coat hypertension" or office elevations
- Pseudohypertension in older patients
- Use of regular cuff on a very obese arm

Nonadherence to therapy**Volume overload**

- Excess salt intake
- Progressive renal damage (nephrosclerosis)
- Fluid retention from reduction of blood pressure
- Inadequate diuretic therapy

Drug-related causes

- Doses too low
- Wrong type of diuretic
- Inappropriate combinations
- Rapid inactivation (eg, hydralazine)
- Drug actions and interactions
 - Sympathomimetics
 - Nasal decongestants
 - Appetite suppressants
 - Cocaine and other illicit drugs
 - Caffeine
 - Oral contraceptives
 - Adrenal steroids
 - Licorice (as may be found in chewing tobacco)
 - Cyclosporine, tacrolimus
 - Erythropoietin
 - Antidepressants
 - Nonsteroidal anti-inflammatory drugs

Associated conditions

- Smoking
- Increasing obesity
- Sleep apnea
- Insulin resistance/hyperinsulinemia
- Ethanol intake of more than 1 oz. (30 mL) per day
- Anxiety-induced hyperventilation or panic attacks
- Chronic pain
- Intense vasoconstriction (arteritis)
- Organic brain syndrome (eg, memory deficit)

Identifiable causes of hypertension

Adapted from JNC-7 Express. Source: National Heart, Lung, and Blood Institute.

- May become more sensitive to sunlight; consider using sunscreen with SPF >15
- May increase blood glucose in diabetics
- Report problems with muscle cramps that may indicate decreased potassium level.
- Rise slowly from a lying or sitting position.

Drug-drug and drug-disease interactions

- **Aminoglycosides: combined with loop diuretics can precipitate ototoxicity**
- NSAIDs: blunt diuretic response
- Class IA or III antiarrhythmics (that prolong the QT interval) may cause torsades de pointes with diuretic-induced hypokalemia.
- **Probenecid: blocks loop diuretic effects by interfering with excretion into the urine**

Parameters to monitor

- Weight
- Serum electrolytes
- BUN and creatinine
- Uric acid
- Hearing (in high doses)

Potassium-sparing diuretics (Table 7)**Mechanism of action**

- **Interferes with potassium/sodium exchange in the distal tubule; decreases calcium excretion, increases magnesium loss**

Adverse drug events (Table 7)**Patient instructions and counseling**

- Take early in day to avoid nocturia.
- Take after meals.
- **Avoid excessive ingestion of foods high in potassium and use of salt substitutes.**
- May increase blood glucose in diabetics.
- Report problems with muscle cramps that may indicate decreased potassium levels.
- Sexual dysfunction

Drug-drug and drug-disease interactions

- ACE inhibitors: **may increase risk of hyperkalemia**
- Indomethacin: combination with triamterene can cause decrease in renal function
- Cimetidine: increases bioavailability and decreases clearance of triamterene

Parameters to monitor

- Weight
- Serum electrolytes (especially potassium)
- BUN and creatinine

Table 7

Thiazide Diuretics, Thiazide-Like Diuretics, Loop Diuretics, Potassium-Sparing Agents, and Aldosterone-Receptor Blocker

Drug	Trade name	Usual dose range, total mg/d (frequency per day)	Adverse events and comments ¹
Thiazide diuretics			
Bendroflumethiazide	Naturetin	2.5-5 (1)	Short-term: increased cholesterol and glucose Biochemical: decreased potassium, sodium, and magnesium; increased uric acid and calcium Rare: blood dyscrasias, photosensitivity, pancreatitis, hyponatremia, sulfonamide-type immune reactions Other: impotence, fatigue, headache, rash, vertigo
Benzthiazide	Aquatag , Exna	12.5-50 (1)	
Chlorothiazide	Diuril	125-500 (1)	
Chlorthalidone	Hygroton , Hylidone	12.5-25 (1)	
Hydrochlorothiazide	HydroDIURIL , Microzide	12.5-50 (1)	
	Saluron , Diucardin		
Hydroflumethiazide		25-50 (1)	
Methyclothiazide	Renese	2.5-5 (1)	
Polythiazide	Metahydrin , Naqua	2-4 (1)	
Trichlormethiazide		2-4 (1)	
Thiazide-like diuretics			
Metolazone	Mykrox	2.5-10 (1)	(Less or no hypercholesterolemia compared to other thiazides; decreased microalbuminuria in diabetes)
Metolazone	Zaroxolyn	2.5-5 (1)	
Indapamide	Lozol	2.5-5 (1)	
Loop diuretics			
Bumetanide	Bumex		Ototoxicity at high doses (Short duration, no hypercalcemia) (Short duration, no hypercalcemia)
Bumetanide	Lasix	0.5-2 (2)	
Furosemide	Demadex	20-80 (2)	
Torsemide		2.5-10 (1)	
Potassium-sparing agents²			
Amiloride	Midamor	5-10 (1-2)	Hyperkalemia (Avoid with history of kidney stones or hepatic disease)
Triamterene	Dyrenium	50-100 (1-2)	
Aldosterone-receptor blocker			
Spironolactone	Aldactone	25-50 (1-2)	

¹Side effects listed are for the class of drugs except where noted for individual drugs (in parentheses).

²See Table 8 for combination products.

Adapted from JNC-7 Express. Source: National Heart, Lung, and Blood Institute.

Adrenergic Inhibitors

Postganglionic adrenergic neuron blockers (Table 9)

- **This medication class is best avoided unless necessary to treat refractory hypertension unresponsive to all other agents, as they are poorly tolerated.**

Mechanism of action

- Causes presynaptic inhibition of the release of neurotransmitter from peripheral neurons by **agonistic**

activity on the α_2 receptor and depletion of neurotransmitter through competitive uptake into the neurosecretory vesicles.

Adverse drug events (Table 9)

Patient instructions and counseling

- Report symptoms of dizziness or hypotension.
- Don't take OTC cold products without first asking the doctor or pharmacist.

Table 8

Combination Drugs for Hypertension

COMBINATION TYPE*	FIXED-DOSE COMBINATION, mg†	TRADE NAME
ACEIs and CCBs	Amlodipine/benazepril hydrochloride (2.5/10, 5/10, 5/20, 10/20)	Lotrel
	Enalapril maleate/felodipine (5/5)	Lexxel
	Trandolapril/verapamil (2/180, 1/240, 2/240, 4/240)	Tarka
ACEIs and diuretics	Benazepril/hydrochlorothiazide (5/6.25, 10/12.5, 20/12.5, 20/25)	Lotensin HCT
	Captopril/hydrochlorothiazide (25/15, 25/25, 50/15, 50/25)	Capozide
	Enalapril maleate/hydrochlorothiazide (5/12.5, 10/25)	Vaseretic
	Lisinopril/hydrochlorothiazide (10/12.5, 20/12.5, 20/25)	Prinzide
	Moexipril HCl/hydrochlorothiazide (7.5/12.5, 15/25)	Uniretic
	Quinapril HCl/hydrochlorothiazide (10/12.5, 20/12.5, 20/25)	Accuretic
ARBs and diuretics	Candesartan cilexetil/hydrochlorothiazide (16/12.5, 32/12.5)	Atacand HCT
	Eprosartan mesylate/hydrochlorothiazide (600/12.5, 600/25)	Teveten/HCT
	Irbesartan/hydrochlorothiazide (150/12.5, 300/12.5)	Avalide
	Losartan potassium/hydrochlorothiazide (50/12.5, 100/25)	Hyzaar
	Telmisartan/hydrochlorothiazide (40/12.5, 80/12.5)	Micardis/HCT
	Valsartan/hydrochlorothiazide (80/12.5, 160/12.5)	Diovan/HCT
BBs and diuretics	Atenolol/chlorthalidone (50/25, 100/25)	Tenoretic
	Bisoprolol fumarate/hydrochlorothiazide (2.5/6.25, 5/6.25, 10/6.25)	Ziac
	Propranolol LA/hydrochlorothiazide (40/25, 80/25)	Inderide
	Metoprolol tartrate/hydrochlorothiazide (50/25, 100/25)	Lopressor HCT
	Nadolol/bendrofluthiazide (40/5, 80/5)	Corzide
	Timolol maleate/hydrochlorothiazide (10/25)	Timolide
Centrally acting drug and diuretic	Methyldopa/hydrochlorothiazide (250/15, 250/25, 500/30, 500/50)	Aldoril
	Reserpine/chlorothiazide (0.125/250, 0.25/500)	Diupres
	Reserpine/hydrochlorothiazide (0.125/25, 0.125/50)	Hydropres
Diuretic and diuretic	Amiloride HCl/hydrochlorothiazide (5/50)	Moduretic
	Spirolactone/hydrochlorothiazide (25/25, 50/50)	Aldactazide
	Triamterene/hydrochlorothiazide (37.5/25, 50/25, 75/50)	Dyazide, Maxzide

*Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BB, β -blocker; CCB, calcium channel blocker.

†Some drug combinations are available in multiple fixed doses. Each drug dose is reported in milligrams.

Adapted from JNC-7 Express. Source: National Heart, Lung, and Blood Institute.

- Rise slowly from a lying or sitting position.
- Report new fluid retention.
- Sexual dysfunction

Drug-drug and drug-disease interactions

- OTC sympathomimetics: may potentiate an acute hypertensive effect
- Tricyclic antidepressants/chlorpromazine: antagonize therapeutic effects of guanethidine
- Pheochromocytoma is a contraindication to this class of medications.

- Should be avoided in patients with CHF, angina, and cerebrovascular disease

Parameters to monitor

- History of depression (reserpine)
- Sleep disturbances, drowsiness, lethargy (reserpine)
- Symptoms of peptic ulcer (reserpine)

Table 9

Postganglionic Adrenergic Neuron Blockers

Drug	Trade name	Usual dose range, total mg/d (frequency per day)	Adverse events and comments
Guanadrel	Hylorel	10-75 (2)	Postural hypotension, diarrhea
Guanethidine monosulfate	Ismelin	10-150 (1)	Postural hypotension, diarrhea
Reserpine ¹	Serpasil	0.05-0.25 (1)	Nasal congestion, sedation, depression, activation of peptic ulcer, dizziness, lethargy, memory impairment, sleep disturbances, weight gain

¹Also acts centrally.

Adapted from JNC-7 Express. Source: National Heart, Lung, and Blood Institute.

Centrally active α -agonists (Table 10)

Mechanism of action

- Causes decreased sympathetic outflow to the cardiovascular system by agonistic activity on central α_2 receptors

Patient instructions and counseling

- Report symptoms of dizziness or hypotension
- Sedation precautions
- Fever and flu-like symptoms may represent hepatic dysfunction (methyldopa).
- Report new fluid retention
- Sexual dysfunction

Drug-drug and drug-disease interactions

- Use cautiously with other sedating medications.
- Use cautiously in patients with angina, recent MI, CVA, and hepatic or renal disease (guanabenz and guanfacine).

Parameters to monitor

- CBC, positive Coombs' test in 25%, less than 1% develop hemolytic anemia (methyldopa)

Table 10

Centrally Active α_2 -Agonists

Drug	Trade name	Usual dose range, total mg/d (frequency per day)	Adverse events and comments ¹
Clonidine HCl ²	Catapres	0.1-0.8 (2)	Sedation, dry mouth, bradycardia, withdrawal hypertension, orthostatic hypotension, depression, impotence, sleep disturbances (More withdrawal)
Guanabenz acetate	Wytensin	8-32 (2)	
Guanfacine HCl	Tenex	1-3 (1)	(Less withdrawal)
Methyldopa	Aldomet	250-1000 (2)	(Hepatic and "autoimmune" disorders)

¹Side effects listed are for the class of drugs except where noted for individual drugs (in parentheses).²Also available as a once-weekly transdermal patch.

Adapted from JNC-7 Express. Source: National Heart, Lung, and Blood Institute.

- Sleep disturbances, drowsiness, dry mouth
- Symptoms of depression
- Impotence
- Pulse
- Rebound hypertension

Peripherally acting α_1 -adrenergic blockers (Table 11)

Mechanism of action

- Blocks peripheral α_1 postsynaptic receptors, which causes vasodilation of both arteries and veins (indirect vasodilators)
- Causes less reflex tachycardia than direct vasodilators (hydralazine/minoxidil)

Adverse drug events (Table 11)

Patient instructions and counseling

- Take first dose of no more than 1 mg of any agent and take at bedtime.
- Rise slowly from a lying or sitting position.
- May cause dizziness
- Priapism

Drug-drug and drug-disease interactions

- NSAIDs: decreased antihypertensive effects of α_1 blockers
- Increased antihypertensive effects with diuretics and β -blockers

Parameters to monitor

- Blood pressure and pulse
- Peripheral edema

β -Blockers (Table 12)

Mechanism of action

- Competitively blocks response to β -adrenergic stimulation:
 - * Blocked secretion of renin
 - * Decreased cardiac contractility, thereby decreases cardiac output
 - * Decreased central sympathetic output
 - * Decreased heart rate, thereby decreasing cardiac output

Adverse drug events (Table 12)

Patient instructions and counseling

- Report symptoms of dizziness or hypotension.
- Sedation precautions (with lipid-soluble compounds)
- Abrupt withdrawal of the drug should be avoided.
- Sexual dysfunction

Drug-drug and drug-disease interactions

- Use with caution in patients with diabetes.
- Use with caution in patients with Raynaud's phenomenon or peripheral vascular disease.
- Sulfonylureas: β -blockers may decrease effectiveness of sulfonylureas.
- Nondihydropyridines: may increase effect/toxicity of β -blockers

Parameters to monitor

- ECG
- Rebound hypertension
- Cholesterol levels
- Pulse (apical and radial)
- Glucose levels

Table 11

Peripherally Acting α_1 -Blockers

Drug	Trade name	Usual dose range, total mg/d (frequency per day)	Adverse events and comments
Doxazosin	Cardura	1-16 (1)	Postural hypotension, syncope episode with first dose, postural hypotension, diarrhea, weight gain, peripheral edema, dry mouth, urinary urgency, constipation, priapism, nausea, dizziness, headache, palpitations, and sweating; no effects on glucose or cholesterol
mesylate	Minipress	2-20 (2-3)	
Prazosin HCl	Hytrin	1-20 (1-2)	
Terazosin HCl			

Table 12

 β -Blockers and Combination α - and β -Blockers

Generic name (trade name)	Lipid solubility/primary (secondary) routes of elimination	Usual dose range, total mg/d (frequency per day)	Adverse events and comments ³
β-Blockers			
Acebutolol (Sectral) ^{1,2}	low/H (R)	200-800 (1)	Bronchospasm, bradycardia, heart failure, may mask insulin-induced hypoglycemia; <i>less serious</i> : impaired peripheral circulation, insomnia, fatigue, decreased exercise tolerance, hypertriglyceridemia (except agents with intrinsic sympathomimetic activity)
Atenolol (Tenormin) ¹	low/R (H)	25-100 (1)	
Betaxolol (Kerlone) ¹	low/H (R)	5-20 (1)	
Bisoprolol fumarate (Zebeta) ¹	low/R (H)	2.5-10 (1)	
Carteolol HCl (Cartrol) ²	low/R	2.5-10 (1)	
Metoprolol tartrate ¹ (Lopressor)	moderate/H (R)	50-100 (2)	
Metoprolol succinate ¹ (Toprol-XL)	moderate/H (R)	50-100 (1)	
Nadolol (Corgard)	low/R	40-120 (1)	
Penbutolol sulfate (Levitol) ²	high/H (R)	10-20 (1)	
Pindolol (Visken) ²	moderate/H (R)	10-60 (2)	
Propranolol HCl (Inderal)	high/H	40-160 (2)	
(Inderal LA)		60-180 (1)	
Timolol maleate (Blocadren)	low-moderate/H (R)	20-40 (2)	
Postural hypotension, bronchospasm			
Combined α- and β-blockers			
Carvedilol (Coreg)	moderate/bile into feces	12.5-50 (2)	
Labetalol (Normodyne, Trandate)	moderate/R (H)	200-800 (2)	

H, hepatic; R, renal.

¹Cardioselective.²Intrinsic sympathomimetic activity.³Side effects listed are for the class of drugs except where noted for individual drugs (in parentheses).

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Direct Vasodilators

- This medication class is **best avoided** (second-line agents) unless necessary to treat refractory hypertension unresponsive to all other agents.
- These agents should **NOT be used alone secondary to increases in plasma renin activity, cardiac output, and heart rate, and should therefore be used only when β -blockers and diuretics are part of the antihypertensive regimen.**

Mechanism of action

- These agents cause **direct relaxation of peripheral arterial smooth muscle and thereby significantly decrease peripheral resistance.**

Adverse drug events (Table 13)**Patient instructions and counseling**

- Report symptoms of dizziness or hypotension.
- Hirsutism (minoxidil)

Table 13

Direct Vasodilators

Drug	Trade name	Usual dose range, total mg/d (frequency per day)	Adverse events and comments ¹
Hydralazine HCl	Apresoline	25-100 (2)	Headaches, fluid retention, tachycardia, peripheral neuropathy, postural hypotension
Minoxidil	Loniten	2.5-80 (1-2)	(Lupus syndrome) (Hirsutism)

¹Side effects listed are for the class of drugs except where noted for individual drugs (in parentheses).

Adapted from JNC-7 Express. Source: National Heart, Lung, and Blood Institute.

- Report any new symptoms of fatigue, malaise, low-grade fever, and joint aches.
- Report rapid weight gain (>5 lb), unusual swelling, and pulse increases of >20 beats/min above normal.
- Rise slowly from a lying or sitting position.

Drug-drug and drug-disease interactions

- Use with caution in patients with pulmonary hypertension.
- Use with caution in patients with significant renal failure or CHF.
- Use with caution in patients with CAD or a recent MI.

Parameters to monitor

- Weight (fluid status)
- Blood pressure and pulse
- CBC with ANA (hydralazine)

Calcium Antagonists

- Low-renin hypertensive, black, and elderly patients respond well to this class of medications.

Mechanism of action

- Inhibit the influx of calcium ions through slow channels in vascular smooth muscle and cause relaxation of both coronary and peripheral arteries
- Sinus (SA) and atrioventricular (AV) nodal depression and decrease in myocardial contractility (nondihydropyridines)

Adverse drug events (Table 14)**Patient instructions and counseling**

- Report symptoms of dizziness or hypotension.
- Constipation (verapamil)

- Report any new symptoms of shortness of breath, fatigue, or increased swelling of the extremities.
- Rise slowly from a lying or sitting position.

Drug-drug and drug-disease interactions

- Use with caution in patients on β -blockers (nondihydropyridines) which may increase CHF and bradycardia; this combination can also cause conduction abnormalities to the AV node.
- Use with extreme caution in patients with conduction disturbances in the SA or AV nodes.
- Grapefruit juice may increase the levels of some dihydropyridines.

Parameters to monitor

- ECG
- Peripheral edema
- Blood pressure and pulse
- Bowel habits
- Symptoms of conduction disturbances

Angiotensin-Converting Enzyme Inhibitors (ACEIs) and Angiotensin II Receptor Blockers (ARBs)

- Ethnic differences in the response to these classes of medications exist. These agents are relatively ineffective as monotherapy in black patients. However, the addition of diuretic therapy has been shown to sensitize black patients to these agents to obtain similar responses as in non-black patients.

Mechanism of action**ACEIs**

- Inhibit the conversion of angiotensin I to angiotensin II (a potent vasoconstrictor; see Figure 1)

Table 14

Calcium Antagonists

Drug	Trade name	Usual dose range, total mg/d (frequency per day)	Adverse events and comments ¹
Nondihydropyridines			
Diltiazem HCl	Cardizem SR, Cardizem CD, Dilacor XR, Tiazac	180-420 (1) 120-360 (1)	Conduction defects, worsening of systolic dysfunction, gingival hyperplasia (Nausea, headache)
Verapamil immediate- release	Calan, Isoptin	80-320 (2)	
Verapamil long-acting	Calan SR, Isoptin SR	120-360 (1-2)	
Verapamil—Coer	Covera HS, Verelan PM	120-360 (1)	(Constipation)
Dihydropyridines			
Amlodipine besylate	Norvasc	2.5-10 (1)	Edema of the ankle, flushing, headache, gingival hyperplasia
Felodipine	Plendil	2.5-20 (1)	
Isradipine	DynaCirc	2.5-10 (2)	
	DynaCirc CR	5-20 (1)	
Nicardipine	Cardene SR	60-120 (1)	
Nifedipine	Procardia XL, Adalat CC	30-60 (1)	
Nisoldipine	Sular	10-40 (1)	

¹Side effects listed are for the class of drugs except where noted for individual drugs (in parentheses).

Adapted from JNC-7 Express. Source: National Heart, Lung, and Blood Institute.

- Indirectly inhibit fluid volume increases by inhibiting angiotensin II—stimulated release of aldosterone

ARBs

- Inhibit the binding of angiotensin II to the angiotensin II receptor, thereby inhibiting the vasoconstrictive properties of angiotensin II as well its ability to stimulate release of aldosterone
- Currently considered as alternative therapy in patients not able to tolerate ACEIs due to cough

Adverse drug events (Table 15)

Patient instructions and counseling

- Report symptoms of dizziness or hypotension.
- Symptoms of swelling of the lips, mouth, or face should be considered an emergency, and the patient should immediately report to a doctor's office or emergency department.
- Report new rashes (especially with captopril).
- Do not use salt substitutes containing potassium, and do not take OTC potassium supplements.
- Rise slowly from a lying or sitting position.

Drug-drug and drug-disease interactions

- NSAIDs will decrease the effectiveness of ACEIs

and ARBs.

- Potassium-sparing diuretics, potassium supplements, and salt substitutes will increase the risk of hyperkalemia when used in combination with ACEIs and ARBs.
- ACEIs and ARBs should be avoided in patients with bilateral renal artery stenosis or stenosis in a single kidney.
- ACEIs and ARBs should be avoided in pregnant patients.

Parameters to monitor

- Serum electrolytes (especially creatinine and potassium)
- Symptoms of angioedema
- Blood pressure
- Symptoms of hypotension
- CBC (especially with captopril and enalapril) for neutropenia, which is more common in patients with preexisting renal impairment
- Cough
- Urinary proteins

Table 15

Angiotensin-Converting Enzyme Inhibitors (ACEIs) and Angiotensin II Receptor Blockers (ARBs)

Drug	Trade name	Usual dose range, total mg/d (frequency per day)	Adverse events and comments
ACEIs			
Benazepril HCl	Lotensin	10-40 (1-2)	Common: cough Rare: angioedema, hyperkalemia, rash, loss of taste, leukopenia Other: vertigo; headache; fatigue; first-dose hypotension; minor GI disturbances; acute renal insufficiency in patients with predisposing factors such as renal stenosis and coadministration with thiazide diuretics; proteinuria (especially in patients with history of renal disease)
Captopril	Capoten	25-100 (2-3)	
Enalapril maleate	Vasotec	2.5-40 (1-2)	
Fosinopril	Monopril	10-40 (1-2)	
Lisinopril	Prinivil, Zestril	10-40 (1)	
Moexipril	Univasc	7.5-30 (1)	
Perindopril	Aceon	4-8 (1-2)	
Quinapril HCl	Accupril	10-40 (1-2)	
Ramipril	Altace	1.25-20 (1)	
Trandolapril	Mavik	1-4 (1)	
ARBs			
Candesartan	Atacand	8-32 (1)	Angioedema, hyperkalemia
Eprosartan	Teveten	400-800 (1-2)	
Irbesartan	Avapro	150-300 (1)	
Losartan	Cozaar	25-100 (1-2)	
Olmesartan	Benicar	20 (1)	
Telmisartan	Micardis	40-80 (1)	
Valsartan	Diovan	80-320 (1)	

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4. Hypertensive Urgencies and Emergencies

- The classification of hypertensive urgencies and emergencies is determined by the presence or absence of acute target organ damage, not by blood pressure, and determines the appropriate treatment approach.
- The relative rise and rate of increase in blood pressure is more important than the actual blood pressure.

Hypertensive Emergencies

- Acute elevations of blood pressure (>180 mm Hg systolic or >120 mm Hg diastolic) with the presence of acute or ongoing target organ damage constitutes a hypertensive emergency (Table 16).
- This requires immediate lowering of blood pressure to prevent or minimize target organ damage.

Treatment (Table 17)

- Initial goal: reduce mean arterial pressure (MAP) by no more than 25% within minutes to hours; reach 160/100 mm Hg within 2-6 hours.

- Measure BP every 5-10 minutes until goal MAP is reached and life-threatening target organ damage resolves.
- Maintain goal BP for 1-2 days, and further reduce BP toward normal over several weeks.
- Excessive falls in BP may precipitate renal, cerebral, or coronary ischemia.
- IV agents are preferred due to the ability to titrate dosages based on BP response; however, specific agents should be chosen based on patient findings (Table 18).

Hypertensive Urgencies

- These are accelerated, malignant, or perioperative elevations in blood pressure in the absence of new or progressive target organ damage; therefore immediate lowering of BP is not required.

Treatment (Table 19)

- There is no agent of choice; medications should be selected based on patient characteristics.
- Oral therapy is preferred.
- Onset of action should be in 15-30 minutes, and peak effects seen in 2-3 hours.

Table 16

Clinical Findings of Target Organ Damage**Target organ damage:**

Hypertensive encephalopathy

Intracranial hemorrhage

Unstable angina

Acute myocardial infarction

Acute left ventricular failure with pulmonary edema

Dissecting aortic aneurysm

Eclampsia

Clinical findings:**Funduscopy:** papilledema, hemorrhage, exudates**Neurologic:** somnolence, confusion, seizures, coma, visual deficits or blindness**Cardiac:** S₄ gallop, ischemic changes on ECG, chest x-ray consistent with pulmonary edema, chest pain**Renal:** oliguria, progressive azotemia, hematuria, proteinuria**Other:** dyspnea

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- Check BP every 15-30 minutes to ensure response.
- Use of immediate-release nifedipine is inappropriate to lower blood pressure in patients with hypertensive urgencies.

5. Key Points

- Hypertension is defined as a systolic blood pressure >140 mm Hg, a diastolic blood pressure >90 mm Hg, or any patient requiring antihypertensive therapy.
- Prehypertension (120-139/80-89 mm Hg) represents a new classification in JNC-VII that significantly increases the risk of developing stage 1 hypertension. Lifestyle modifications should be stressed for this classification, and medication therapy should only be used for patients with compelling indications.
- Secondary causes of hypertension include: renovascular disease, primary aldosteronism, Cushing's syndrome, pheochromocytoma, aortic coarctation, and drugs (steroids/estrogens, alcohol, cocaine, cyclosporine/tacrolimus, sympathomimetics, erythropoietin, licorice, MAO inhibitors, TCA antidepressants, NSAIDs).
- Recommended lifestyle modifications both to improve blood pressure and overall cardiovascular health include: lose weight; limit alcohol intake; increase aerobic physical activity; reduce sodium intake; maintain adequate dietary intake of potassium, magnesium, and calcium; stop smoking; and reduce dietary cholesterol and saturated fat intake.
- Diuretics are considered by JNC-VII to be the initial agent for treatment of hypertension in most patients unless compelling indications for the use of other medication classes exist or the patient has comorbid conditions that would suggest the use of classes other than diuretics.
- JNC-VII considers angiotensin-converting enzyme inhibitors (ACEIs), angiotensin II receptor blockers (ARBs), β -blockers (BBs), and calcium channel blockers (CCBs) equivalent choices as initial therapy for hypertension.
- Vasodilators, α_1 -receptor antagonists, α_2 -receptor agonists, and postganglionic adrenergic neuron blockers should be avoided as initial agents for hypertension.
- Antihypertensive drug therapy should be individualized, and there are classifications of recommendations from JNC-VII based on the level of evidence, which include: compelling indication unless contraindicated, may have favorable effects on comorbid conditions, and may have unfavorable effects on comorbid conditions.
- The classification and treatment of hypertensive urgencies and emergencies is determined by the presence or absence of acute target organ damage and not on blood pressure.

Table 17

Parenteral Drugs for Treatment of Hypertensive Emergencies¹

Drug	Dose ²	Onset of action	Duration of action	Adverse effects ³	Special indications
Vasodilators					
Sodium nitroprusside	0.25-10 mcg/kg per min as IV infusion ⁴ (maximal dose for 10 min only)	Immediate	1-2 min	Nausea, vomiting, muscle twitching, sweating, thiocyanate and cyanide intoxication	Most hypertensive emergencies; caution with high intracranial pressure or azotemia
Nicardipine hydrochloride	5-15 mg/h IV	5-10 min	1-4 h	Tachycardia, headache, flushing, local phlebitis	Most hypertensive emergencies except acute heart failure; caution with coronary ischemia
Fenoldopam mesylate	0.1-0.3 mcg/kg per min IV infusion	<5 min	30 min	Tachycardia, headache, nausea, flushing	Coronary ischemia
Nitroglycerin	5-100 mcg/min as IV infusion ⁴	2-5 min	3-5 min	Headache, vomiting, methemoglobinemia, tolerance with prolonged use	Acute left ventricular failure; avoid in acute myocardial infarction
Enalaprilat	1.25-5 mg every 6 h IV	15-30 min	6 h	Precipitous fall in pressure in high-renin states; response variable	Eclampsia
Hydralazine hydrochloride	10-20 mg IV; 10-50 mg IM	10-20 min; 20-30 min	3-8 h	Tachycardia, flushing, headache, vomiting, aggravation of angina	Now obsolete; when no intensive monitoring available
Diazoxide	50-100 mg IV bolus repeated, or 15-30 mg/min infusion	2-4 min	6-12 h	Nausea, flushing, tachycardia, chest pain	
Adrenergic inhibitors					
Labetalol hydrochloride	20-80 mg IV bolus every 10 min; 0.5-2.0 mg/min IV infusion	5-10 min	3-6 h	Vomiting, scalp tingling, burning in throat, dizziness, nausea, heart block, orthostatic hypotension	Most hypertensive emergencies except acute heart failure
Esmolol hydrochloride	250-500 mcg/kg/min for 1 min, then 50-100 mcg/kg/min for 4 min; may repeat sequence	1-2 min	10-20 min	Hypotension, nausea	Aortic dissection, perioperative
Phentolamine	5-15 mg IV	1-2 min	3-10 min	Tachycardia, flushing, headache	Catecholamine excess

¹These doses may vary from this in the *Physicians' Desk Reference* (51st ed.).²IV indicates intravenous; IM, intramuscular.³Hypotension may occur with all agents.⁴Requires special delivery system.

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- All causes for inadequate response should be addressed before additional agents are added to a patient's antihypertensive regimen (ie, pseudo-resistance, nonadherence, volume overload, drug-related causes, associated conditions, and secondary causes of hypertension).

Table 18

Selected Agents for Specific Hypertensive Emergencies

Emergency	Recommended therapy	Comments
Encephalopathy	Labetalol; nicardipine; nitroprusside	Avoid: methyldopa (sedation); diazoxide (reduces cerebral blood flow); reserpine (sedation); hydralazine (increases intracranial pressure)
Myocardial infarction (MI)/unstable angina	Nitroglycerin; esmolol	Reduce BP until pain is relieved, use in conjunction with conventional therapy for MI/angina Avoid: Diazoxide and hydralazine (increases oxygen demand); dihydropyridines (may worsen angina); nitroprusside (coronary steal)
Congestive heart failure	Nitroprusside; nitroglycerin; enalaprilat	Avoid: labetalol, esmolol, other β -blockers (reduces cardiac output)
Subarachnoid hemorrhage, intracerebral hemorrhage, stroke	Nitroprusside	BP reduction is controversial as it may cause hypoperfusion; generally recommended for severe hypertension (systolic >220 or diastolic >120 mm Hg)
Dissecting aortic aneurysm	Trimethaphan; esmolol; nitroprusside	Avoid: diazoxide and hydralazine (increase shear force)
Pheochromocytoma, cocaine overdose	Phentolamine; labetalol	Anecdotal reports of increased BP with labetalol; unopposed β blockade may worsen crisis
Renal insufficiency	Nitroprusside; calcium channel blocker; labetalol	Monitor cyanide and thiocyanate levels
Postoperative hypertension	Nitroprusside; nicardipine; labetalol	

Table 19

Agents Used to Treat Hypertensive Urgencies

Drug	Dose	Onset	Duration	Adverse effects
Captopril	25 mg, repeat in 1-2 hours as needed	5-15 minutes	4-6 hours	Hypotension, acute renal failure, angioedema
Clonidine	0.1-0.2 mg, repeat in 1-2 hours as needed (up to 0.6 mg)	5-15 minutes	6-12 hours	Hypotension, drowsiness, sedation, dry mouth
Labetalol	100-400 mg, repeat in 2-3 hours as needed	15-30 minutes	4-6 hours	Hypotension, heart block, bronchoconstriction

6. Questions and Answers

1. All of the following agents are suitable as initial therapy for the treatment of uncomplicated hypertension according to the Seventh Report of the Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure (JNC-VII) EXCEPT
 - A. hydrochlorothiazide
 - B. chlorthalidone
 - C. indapamide
 - D. hydralazine
 - E. atenolol
2. Hyperkalemia is a possible adverse effect of all the following medications EXCEPT
 - A. trandolapril
 - B. Teveten
 - C. doxazosin
 - D. amiloride
 - E. captopril
3. A 48-year-old patient presents with a new diagnosis of hypertension. The patient is also noted to have congestive heart failure (CHF) with an ejection fraction of 28%. Which agent would be an appropriate choice as initial therapy in this patient based on JNC-VII?
 - A. Clonidine
 - B. Guanethidine
 - C. Diltiazem
 - D. Perindopril
 - E. Nisoldipine
4. A 62-year-old patient with a history of hypertension and gout presents to begin pharmacotherapy for hypertension. Which agent is the most appropriate choice as initial therapy based on JNC-VII?
 - A. Chlorothiazide
 - B. Torsemide
 - C. Tenormin
 - D. Chlorthalidone
 - E. Metolazone
5. All of the following medications can cause bradycardia EXCEPT
 - A. terazosin
 - B. verapamil
 - C. diltiazem
 - D. Ziac®
 - E. clonidine
6. A patient requires a cardioselective β -blocker in their outpatient medication regimen after recent discharge from the hospital with a new myocardial infarction. You suggest:
 - A. Labetalol
 - B. Esmolol
 - C. Propranolol
 - D. Atenolol
 - E. Carvedilol
7. A patient presents to your ambulatory clinic with a blood pressure of 210/125 mm Hg. Past medical history is significant for type 2 diabetes, CHF, and renal insufficiency. Which of the following would cause the patient to be classified as a hypertensive emergency?
 - A. Blood glucose levels >300 mg/dL, which increase the patient's risk for acute renal failure
 - B. A serum creatinine of 3 mg/dL
 - C. Nausea, vomiting, and diarrhea for 3 days
 - D. S₄ gallop and a chest x-ray consistent with pulmonary edema
 - E. Polyuria combined with polydipsia
8. What are the treatment goals for the patient with hypertensive emergency described in the Question 7?
 - A. Systolic pressure should be reduced to 120 mm Hg within the first hour of treatment to reduce the risk of further end organ damage
 - B. Diastolic pressure should be reduced to 80 mm Hg within the first hour of treatment to reduce the risk of further end organ damage
 - C. Reduce blood pressure to 160/100 mm Hg in the first 2-6 hours of therapy
 - D. Reduce mean arterial pressure by at least 50% within the first minutes to hours of therapy
 - E. Reduce blood pressure to no lower than 180/110 mm Hg in the first hour, as excessive falls in blood pressure may precipitate coronary ischemia

9. What would be the recommended treatment for the patient with hypertensive emergency in Question 7?
- Clonidine orally 0.1-0.2 mg, repeat in 1-2 hours as needed (up to 0.6 mg)
 - Labetalol orally 100-400 mg, repeat in 2-3 hours as needed
 - Nifedipine sublingually 10 mg, repeat in 0.5-1 hours as needed (up to 60 mg)
 - Labetalol intravenously 20- to 80-mg bolus, followed by 0.5-2 mg/min infusion
 - Enalaprilat intravenously 1.25-5 mg every 6 hours
10. Which of the following antihypertensive agents can cause first-dose syncope, palpitations, peripheral edema, and priapism?
- Hydralazine
 - Nitroprusside
 - Prazosin
 - Verapamil
 - Moexipril
11. Which of the following antihypertensive agents is most likely to cause lupus syndrome, postural hypotension, and peripheral neuropathy?
- Atenolol
 - Hydralazine
 - Guanfacine
 - Mibefradil
 - Nitroprusside
12. Which of the following medications is not associated with drug-induced hypertension?
- Prednisone
 - Indomethacin
 - Rosiglitazone
 - Cocaine
 - Cyclosporine
13. What is the best recommendation for antihypertensive medication in a patient who has atrial fibrillation, CAD with angina, and hyperthyroidism?
- Minoxidil
 - Betaxolol
 - Telmisartan
 - Nicardipine
 - Amiloride
14. What antihypertensive agent should not be used in a patient with essential hypertension and a history of depression with suicidal ideation?
- Captopril
 - Prazosin
 - Metolazone
 - Reserpine
 - Amlodipine
15. All of the following are secondary causes of hypertension EXCEPT
- renovascular disease
 - pheochromocytoma
 - systemic lupus erythematosus
 - primary aldosteronism
 - aortic coarctation

Answer Questions 16-20 based on the patient medication profile provided on the next page.

- I only is correct
 - III only is correct
 - I and II are both correct
 - II and III are both correct
 - I, II, and III are correct
16. Possible complications that the patient is at risk of developing secondary to uncontrolled hypertension include:
- Hyperaldosteronism
 - Myocardial infarction
 - Blindness
17. Education regarding lifestyle modification issues in this patient should include:
- Limit smoking to $\frac{1}{2}$ pack per day and alcohol intake to no more than 2 drinks per day
 - Maintain adequate intake of dietary magnesium, calcium, and sodium
 - Increase aerobic physical activity, lose weight, and limit dietary saturated fat and cholesterol
18. Possible reasons for the patient's blood pressure being uncontrolled include:
- Use of NSAIDs causes decreased effectiveness of ACE inhibitor therapy
 - Possible problems with adherence to antihypertensive therapy
 - Lack of blood pressure response to ACE inhibitor therapy, which should not be used in combination with diuretics in an African-American patient

DATE: 04/12/03		PATIENT MEDICATION PROFILE						
PATIENT'S NAME	Buddy Manwich				NOTES: + tobacco - 1 1/2 ppd.			
ADDRESS	61 Heavenly Highway				4-5 cups of coffee / day			
Phone No.	555-8181				ETOH - 2 drinks / week			
Date of Birth	4/14/44				Race: African American			
Known diseases:	DM (15 yrs), HTN (20 yrs),				Ht: 5'11"			
	Obstructive Sleep Apnea (5yrs), Osteoarthritis				Wt: 248 lbs			
Allergies/Sensitivities	NKDA				OTC use: Aleve, Actron			

DATE	Rx#	MEDICATION/ STRENGTH	ROUTE	QUANTITY	REGIMEN	REFILLS	PHARMACIST	PRESCRIBER
1/15/03	001	Glipizide 5mg	PO	30	1 qd	5	BCE	NTE
1/15/03	002	Lisinopril 5mg	PO	30	1 qd	5	BCE	NTE
1/15/03	003	Hydrodiuril 12.5mg	PO	30	1 qd	5	BBC	NPR
1/20/03	004	Ibuprofen 800mg	PO	90	1 tid	5	REM	FTD
2/11/03	001-RF	Glipizide 5mg	PO	30	1 qd	4	BCE	NTE
2/11/03	003-RF	Hydrodiuril 12.5mg	PO	30	1 qd	4	BBC	NPR
2/11/03	004-RF	Ibuprofen 800mg	PO	90	1 tid	4	REM	FTD
3/13/03	001-RF	Glipizide 5mg	PO	30	1 qd	3	BCE	NTE
3/13/03	002-RF	Lisinopril 5mg	PO	30	1 qd	3	BCE	NTE
3/13/03	004-RF	Ibuprofen 800mg	PO	90	1 tid	3	REM	FTD

19. The appropriate initial antihypertensive agent in this patient could be

- I. benazepril
 - II. terazosin
 - III. minoxidil
20. If the patient is not able to tolerate lisinopril due to adverse effects such as cough, an appropriate alternative agent would be

- I. telmisartan
- II. labetalol
- III. guanabenz

Answers

1. D. Appropriate choices for initial agents in the treatment of uncomplicated hypertension include β -blockers and diuretics. Hydralazine is a direct vasodilator, which would never be considered a first-line agent in the treatment of hypertension.
2. C. Hyperkalemia is a possible side effect with angiotensin-converting enzyme inhibitors, angiotensin II receptor antagonists, and potassium-sparing diuretics. Doxazosin is a peripherally acting α_1 blocker, which does not cause hyperkalemia.
3. D. For patients who have hypertension and congestive heart failure, JNC-VII recommends the use of ACE inhibitors, diuretics, β -blockers, and aldosterone antagonists (see Table 6). The only listed ACE inhibitor is perindopril.
4. C. For patients who have hypertension and gout, JNC-VI recommends not using diuretic therapy, which increases the risk of gouty attacks (see Table 6). The only medication listed that is not a diuretic is atenolol, which is a β -blocker.

5. A. Verapamil and diltiazem are nondihydropyridine calcium channel blockers; Ziac (bisoprolol/hydrochlorothiazide) is a β -blocker; and clonidine is a centrally acting α_2 agonist, and all these have negative inotropic effects on the myocardium. Terazosin is a peripherally acting α_1 blocker, which does not cause bradycardia.
6. D. Labetalol, propranolol, and carvedilol are all nonselective β -blockers. Esmolol is a cardioselective agent only available in injectable form, and therefore would not be for outpatient use. Atenolol is a cardioselective β -blocker that is available as an oral tablet, and therefore can be used for outpatient dosing.
7. D. The classification of hypertensive urgencies and emergencies is determined by the presence or absence of acute target organ damage and not by the actual blood pressure measurement. Presence of an S_4 gallop and a chest x-ray consistent with pulmonary edema suggests acute left ventricular failure with pulmonary edema, which represents defined target organ damage, which means this patient should be classified as a hypertensive emergency.
8. C. According to JNC-VII, the initial goal of blood pressure lowering in patients with hypertensive emergencies is a drop in mean arterial pressure (MAP) of no more than 25% within minutes to hours, and to 160/100 mm Hg within 2-6 hours.
9. E. In a patient with CHF and a hypertensive emergency, recommended treatments include nitroglycerin, nitroprusside, and enalaprilat (Table 18). Clonidine and labetalol (PO) are incorrect choices because the patient requires IV therapy. Nifedipine SL is not indicated for immediate reduction of blood pressure. Labetalol IV is not an appropriate choice in this patient with CHF, as it could decrease cardiac output.
10. C. Possible side effects of peripherally acting α_1 blockers (prazosin) include first-dose syncope, palpitations, peripheral edema, and priapism (Table 11).
11. B. Possible side effects of direct vasodilators (hydralazine) include postural hypotension and peripheral neuropathy. However, lupus syndrome is unique to hydralazine and does not occur with minoxidil (Table 13).
12. C. All agents listed are possible causes of drug-induced hypertension through multiple mechanisms except rosiglitazone (Figure 8).
13. B. The diagnoses of atrial fibrillation, CAD with angina, and hyperthyroidism are all considered comorbid conditions with hypertension in which the use of β -blockers may have favorable effects.
14. D. Because of its possible increased risk of depression, reserpine should not be used in patients in whom the risk for depression and/or suicide already exists.
15. C. All listed diseases are possible causes of secondary hypertension through various mechanisms, except systemic lupus erythematosus.
16. D. Uncontrolled hypertension causes multiple organ system problems, including cardiovascular (CHF, MI, PAD), ophthalmologic (retinopathy, blindness), cerebrovascular (TIA, CVA), and renovascular (nephropathy, renal failure, dialysis). Therefore this patient is at risk for MI and blindness, not hyperaldosteronism.
17. B. Lifestyle modification issues to be considered in hypertensive patients include weight loss; limit of alcohol intake; increased aerobic activity; reduced sodium intake; maintenance of adequate dietary potassium, calcium, and magnesium intake; and smoking cessation.
18. C. Possible causes for inadequate responsiveness to therapy are listed in Figure 8.
19. A. In patients with hypertension and comorbid conditions of CHF and diabetes, the initial agent should be an ACE inhibitor (Table 6).
20. A. In patients who cannot tolerate ACE inhibitor therapy secondary to the adverse effect of cough, angiotensin II receptor antagonists are considered good alternative agents.

7. References

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9. Heart Failure

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Contents

1. Overview
2. Drug Therapy of Heart Failure
3. Drug Therapy of Advanced or Decompensated Heart Failure
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5. Key Points
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1. Overview

Heart failure is a clinical syndrome resulting from a variety of cardiac disorders that impair the ability of the ventricle to fill with or eject blood. This in turn results in the heart being unable to pump blood at a sufficient rate to meet the metabolic demands of the body.

- Nearly 5 million people in the U.S. have heart failure, with 550,000 new patients diagnosed each year.
- It is the only major cardiovascular disease that is increasing in prevalence.
- Approximately 300,000 patients die from heart failure each year. At the time of heart failure diagnosis, the 5-year mortality rate is nearly 50%.
- A large majority of patients are elderly; approximately 10% of individuals over the age of 75 have heart failure.
- Heart failure is the most common hospital discharge diagnosis for Medicare patients. More Medicare dollars are spent for diagnosis and treatment of heart failure than for any other disorder.

Classification

- The New York Heart Association Functional Classification has been widely used for many years. It primarily reflects the severity of symptoms based on a subjective assessment by the provider. A patient's functional class can change frequently over a short period due to changes in medications, diet, or intercurrent illnesses. This classification scheme does not recognize preventive measures or the progressive nature of heart failure.

* **Functional class I** includes patients with cardiac disease but without limitations of physical activity. Ordinary physical activity does not cause undue fatigue, dyspnea, or palpitations.

* **Functional class II** includes patients with cardiac disease that results in slight limitations of physical activity. Ordinary physical activity results in fatigue, palpitations, dyspnea, or angina.

* **Functional class III** includes patients with cardiac disease that results in marked limitation of physical activity. Although patients are comfortable at rest, less than ordinary activity will lead to symptoms.

* **Functional class IV** includes patients with cardiac disease that results in an inability to carry on physical activity without discomfort. Symptoms of heart failure are present even at rest. With any physical activity increased discomfort is experienced.

- The most recent guidelines for evaluation and management of heart failure from the American College of Cardiology (ACC)/American Heart Association (AHA) recommend an additional classification scheme that emphasizes both the evolution and progression of the disease. It more objectively identifies patients within the course of the disease and links to treatments that are appropriate for each stage.

* **Stage A** includes patients at high risk of developing heart failure because of the presence of conditions that are strongly associated with heart failure. These patients have no known cardiac abnormalities and no heart failure signs or symptoms. Examples include patients with hypertension, coronary artery disease, and diabetes mellitus.

* **Stage B** includes patients who have developed structural heart disease that is strongly associated with the development of heart failure but who have never shown signs or symptoms of heart failure. Some examples include previous myocardial infarction, left ventricular hypertrophy, and/or impaired left ventricular function.

* **Stage C** includes patients who have current or prior symptoms of heart failure associated with underlying structural heart disease. Examples include patients with dyspnea or fatigue due to left ventricular systolic dysfunction and asymptomatic patients who are undergoing treatment for prior symptoms of heart failure. Most patients with heart failure are in this stage.

* **Stage D** includes patients with advanced structural heart disease and marked symptoms of heart failure at rest despite maximal medical therapy and who require specialized interventions. Examples include patients who are frequently hospitalized for heart failure and cannot be safely discharged from the hospital, patients in the hospital awaiting heart transplantation, and patients supported with a mechanical circulatory assist device.

Advanced or decompensated heart failure

- Patients with advanced heart failure have persistent limiting symptoms despite therapy with drugs of proven efficacy. Decompensated heart failure is defined as an exacerbation of previously stable symptoms (usually due to volume overload and/or hypoperfusion) and frequently requires hospitalization for acute treatment.
- Causes include medication and dietary noncompliance, atrial fibrillation, myocardial ischemia, and progression of heart failure.
- Assignment to one of four hemodynamic profiles assists in determining approach to therapy.

- حفظ مفاهيم كان
- * Warm and dry: adequate perfusion (ie, cardiac output) and no signs or symptoms of volume overload
 - * Warm and wet: adequate perfusion but signs or symptoms of volume overload
 - * Cold and dry: inadequate perfusion and no signs or symptoms of volume overload
 - * Cold and wet: inadequate perfusion and signs or symptoms of volume overload
 - Most patients (about 70%) present with the warm and wet classification.

Clinical Presentation

- * dyspnea
- FR →
Plum+
Peri Edema
- The primary manifestations of heart failure are dyspnea and fatigue that may limit exercise tolerance, and fluid retention that may lead to pulmonary and peripheral edema. Both abnormalities can limit a patient's functional capacity and quality of life, but do not necessarily occur at the same time. Some patients may have marked exercise intolerance but little evidence of fluid retention, whereas others have prominent edema with few symptoms of dyspnea or fatigue.

- خبر النفس
الاضطراب
- تجمع السوائل / انتفاخ جدار الرئة / جفاف ليلي
- Other symptoms may include paroxysmal nocturnal dyspnea, orthopnea, tachypnea, cough, ascites, and nocturia.
 - Other signs include jugular venous distension, hepatojugular reflux, hepatomegaly, bibasilar rales, pleural effusion, tachycardia, pallor, and S₃ gallop.
 - Symptoms in advanced heart failure are similar but may be more severe.

Pathophysiology

- Heart failure can result from any disorder (see below) that impairs the heart's systolic (ie, pumping ability) or diastolic (impaired cardiac relaxation) function. Many patients have manifestations of both abnormalities. In either case, a decrease in cardiac output is the initiating event in heart failure. The reduction in cardiac output results in activation of a number of compensatory mechanisms that attempt to maintain an adequate cardiac output.
- The beneficial effects of ACE inhibitors (ACEIs), β-blockers, and aldosterone antagonists on reducing mortality and slowing heart failure progression resulted in the neurohormonal model of heart failure pathophysiology.
 - * The decrease in cardiac output leads to activation of systems that release a number of neurohormones including angiotensin II, norepinephrine, aldosterone, proinflammatory cytokines, and vasopressin. These neurohormones can increase renal sodium and water retention,

vasoconstriction, tachycardia, and ventricular hypertrophy and remodeling.

- نوع مرضي
- * Activation of the compensatory systems results in a systemic disorder that is not just confined to the heart, whose progression is largely mediated by these neurohormones.

Specific Causes of Heart Failure

- Coronary artery disease is the cause of heart failure in about 65% of patients with left ventricular systolic dysfunction. Other causes include nonischemic cardiomyopathy (eg, due to hypertension, thyroid disease, or valvular disease). Most of these patients have a reduced left ventricular ejection fraction (usually <40%).
- Approximately 20%-50% of patients with heart failure have preserved (normal) left ventricular systolic function and their heart failure is secondary to diastolic dysfunction. This is most often seen in elderly patients.
- A number of drugs can precipitate or worsen heart failure.

Drugs with negative inotropic effects

- سوء على القلب
- * Antiarrhythmics: disopyramide, flecainide, propafenone
 - * β-Blockers
 - * Calcium channel blockers: verapamil and diltiazem
 - * Oral antifungals: itraconazole and terbinafine
 - Cardiotoxic drugs
 - * Doxorubicin
 - * Daunorubicin
 - * Cyclophosphamide
 - * Alcohol
 - Sodium and water retention
 - * NSAIDs (including the COX-2 inhibitors) also can attenuate the efficacy and increase the toxicity of diuretics and ACEIs.
 - * Glucocorticoids
 - * Rosiglitazone and pioglitazone

Diagnostic Criteria

- There is no single diagnostic test for heart failure; it is a clinical diagnosis based on history, signs and symptoms, and physical examination.
- A rapid bedside assay for B-type natriuretic peptide (BNP) is often used in acute care settings (eg, emergency departments) as an aid in the diagnosis of suspected heart failure. BNP is synthesized and released from the ventricles in response to pressure or volume overload. BNP counteracts the increased sympathetic nervous and renin-angiotensin-

LVH

aldosterone system activity by increasing diuresis, renal sodium excretion, and vasodilation. The degree of elevation of **BNP** correlates with prognosis. The test is useful to differentiate between heart failure exacerbations and other causes of dyspnea (eg, **COPD**, **asthma**, or **infection**). Patients with dyspnea secondary to heart failure will have elevated plasma **BNP** concentrations.

- The echocardiogram is one of the most useful diagnostic tests in patients with heart failure.
- Patients with a left ventricular ejection fraction <40% are generally considered to have systolic dysfunction.
- Note that in general there is a poor correlation between the ejection fraction and symptoms.

Treatment Principles and Goals of Therapy

- Goals of therapy are to improve the patient's quality of life, reduce symptoms, reduce hospitalizations for heart failure exacerbations, slow progression of the disease, and improve survival.
- ACC/AHA guidelines for heart failure treatment according to stage are shown in Figure 1. Therapy in stages A and B is primarily targeted toward prevention of heart failure development, whereas stages C and D focus on treatment of patients with symptomatic heart failure.
- An algorithm for treatment of patients with advanced or decompensated heart failure is shown in Figure 2.

2. Drug Therapy of Heart Failure

- The following section on drug therapy focuses on treatment of stage C heart failure patients (ie, patients with left ventricular dysfunction with current or prior symptoms). This is also commonly referred to as outpatient treatment of patients with heart failure. These patients should be routinely managed with a combination of three drugs: a diuretic, an ACE inhibitor or an angiotensin receptor blocker (ARB), and a β -blocker. Drug therapies that can be considered in selected patients include digoxin, aldosterone antagonists, and hydralazine/isosorbide dinitrate.

Loop Diuretics

- Most heart failure patients require use of the more potent loop diuretics versus thiazide diuretics (Table 1).

Mechanism of action

- Reduce the sodium retention associated with heart failure by inhibiting reabsorption of sodium and chloride in the loop of Henle

Patient instructions and counseling

- Patients allergic to sulfa-containing medications may also be allergic to these medications.
- Take once a day in the morning, or if taking twice daily, take in the morning and afternoon.
- Can cause frequent urination
- Patients should weigh themselves daily (best in the morning after urinating). Patients who gain more than 1 pound per day for several consecutive days or 3-5 pounds in a week should contact their health care provider.
- Report muscle cramps, dizziness, excessive thirst, weakness, or confusion, as these may be signs of overdiuresis.
- Photosensitivity: patients should use sunscreen and/or avoid sun exposure.

Adverse drug events

- Electrolyte depletion: hypokalemia and hypomagnesemia
- Hypotension
- Renal insufficiency

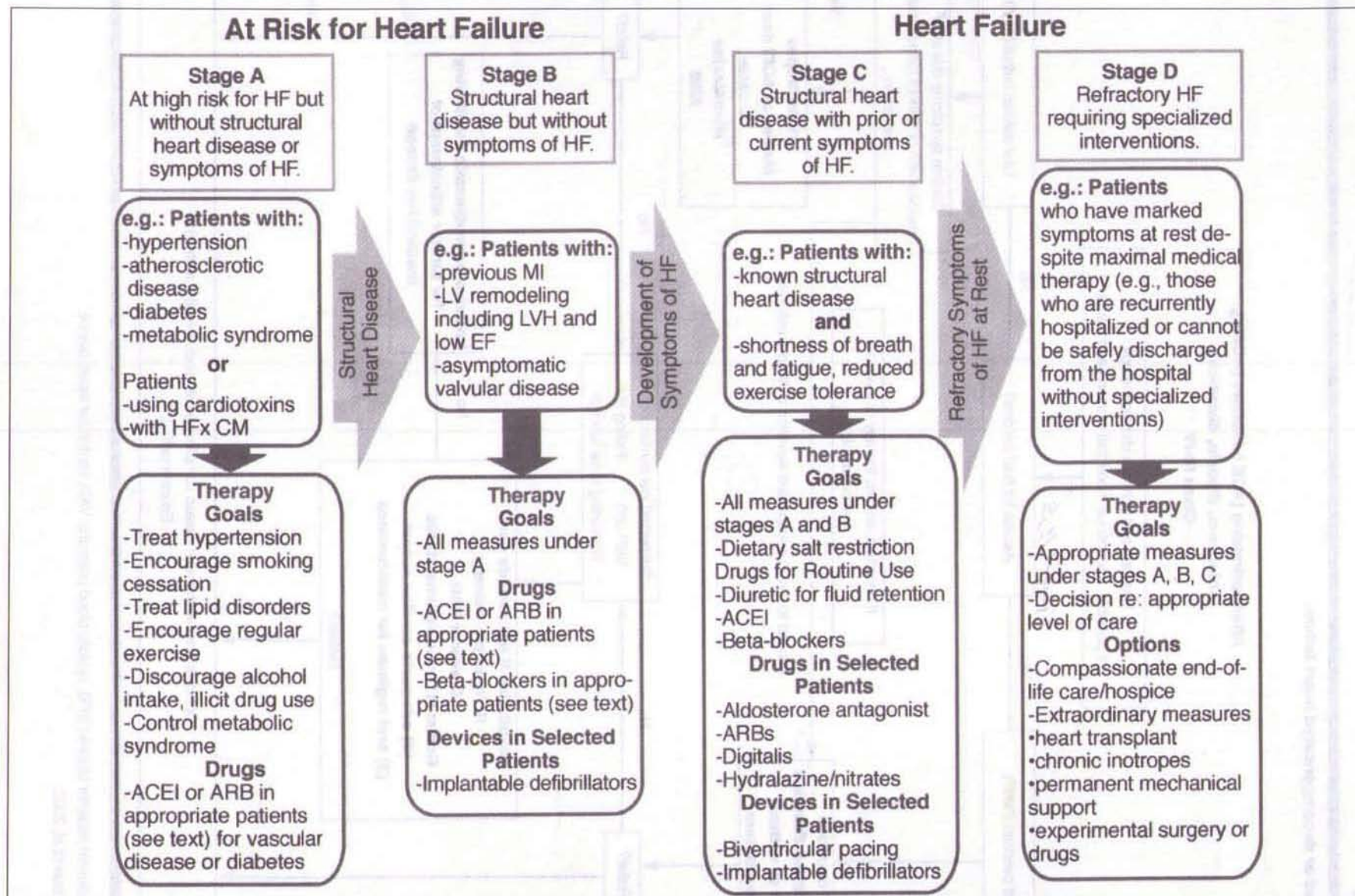
Drug-drug and drug-disease interactions

- Furosemide bioavailability and its diuretic effect are decreased by food and it should be taken on an empty stomach. Food does not affect torsemide absorption.

Figure 1.

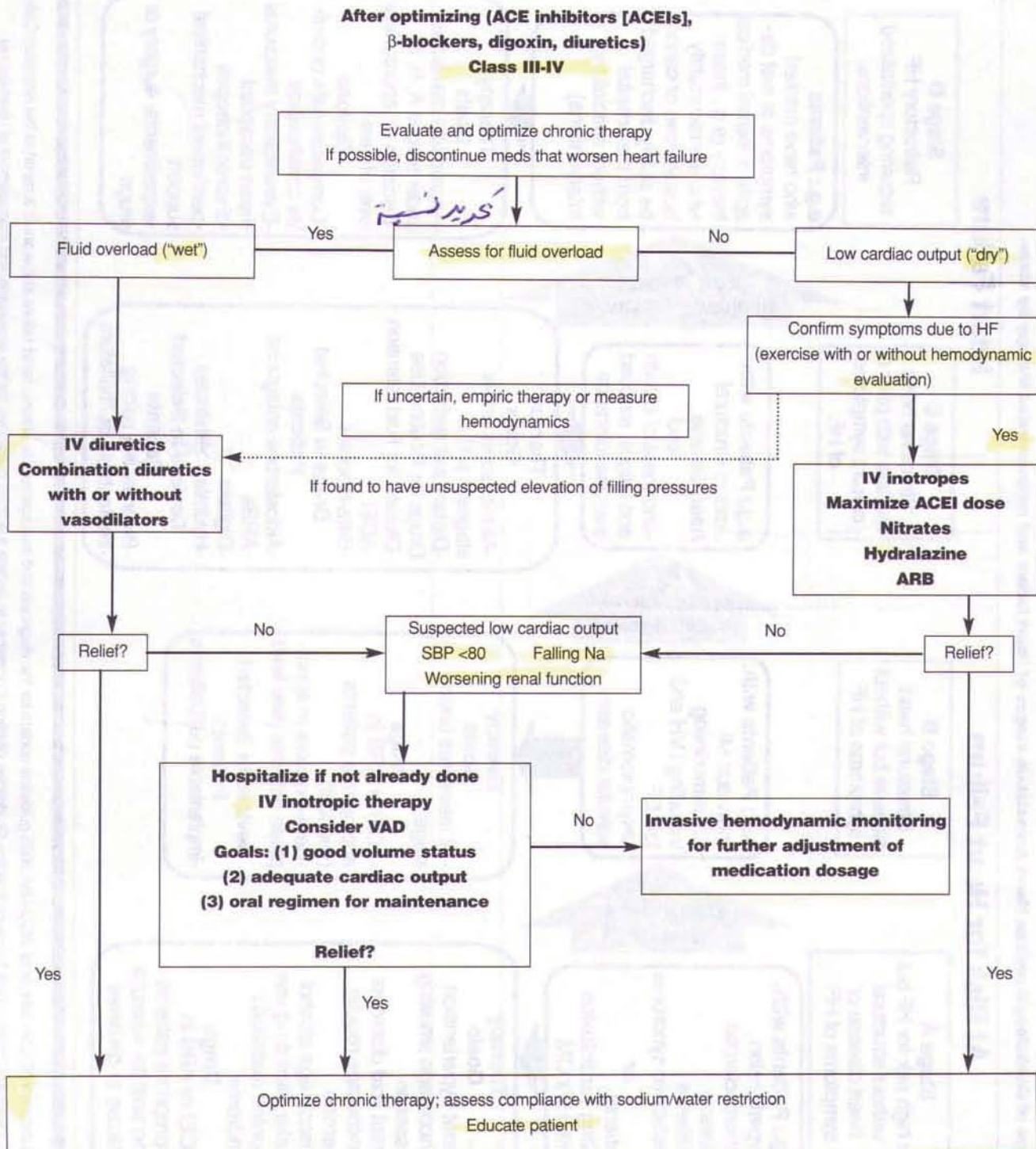
Summary

American College of Cardiology/American Heart Association stages of heart failure and recommended therapy by stage.



Source: Hunt SA, Abraham WT, Chin MH, et al. ACC/AHA 2005 guideline update for the diagnosis and management of chronic heart failure in the adult: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to update the 2001 guidelines for the evaluation and management of heart failure).

Figure 2.

Advanced or decompensated heart failure.

ARB, angiotensin receptor blocker; SPB, systolic blood pressure; VAD, ventricular assist device.
From Johnson et al, 2002.

Table 1

Loop Diuretics

Generic name (trade name)	Dosage form	Dosage range and frequency
Furosemide (Lasix®)	Oral tablet	20-160 mg qd-bid
Bumetanide (Bumex®)	Oral tablet	0.5-5 mg qd-bid
Torsemide (Demadex®)	Oral tablet	10-100 mg qd-bid

- The absorption of oral furosemide is significantly slowed in patients with decompensated heart failure, resulting in decreased diuretic response. Therefore, these individuals will usually require the use of IV furosemide.
- NSAIDs may diminish the diuretic effect.
- Potassium supplementation may not be required in patients also receiving ACE inhibitors, ARBs, and/or aldosterone antagonists.

Parameters to monitor

- Serum sodium, potassium, magnesium, creatinine, and BUN
- Patient weight: loss of 0.5-1.0 kg daily is desired until the patient achieves their dry weight.
- Urine output
- Blood pressure
- Improvement in heart failure symptoms: dyspnea, peripheral edema

Kinetics

- Bioavailability of torsemide is less variable than that of furosemide and is not affected by food.

Angiotensin-Converting Enzyme Inhibitors (ACEIs)

- These are the cornerstone of therapy in heart failure patients (Table 2). Clinical trials in over 7000 patients consistently demonstrate that ACEIs alleviate symptoms, improve clinical status and quality of life, and improve mortality. Current guidelines recommend that all patients with heart failure due to left ventricular systolic dysfunction should receive an ACEI unless contraindicated.

Mechanism of action

- They interfere with the renin-angiotensin system by inhibiting angiotensin-converting enzyme that is responsible for the conversion of angiotensin I to the potent vasoconstrictor angiotensin II. This results in

Table 2

Angiotensin-Converting Enzyme Inhibitors

Generic name (trade name)	Dosage form	Dosage range and frequency
Captopril (Capoten®)	Oral tablet	6.25-50 mg tid
Enalapril (Vasotec®)	Oral tablet	2.5-20 mg bid
Fosinopril (Monopril®)	Oral tablet	5-40 mg qd
Lisinopril (Zestril®, Prinivil®)	Oral tablet	2.5-40 mg qd
Quinapril (Accupril®)	Oral tablet	10-40 mg bid
Ramipril (Altace®)	Oral capsule	2.5-5 mg bid
Trandolapril (Mavik®)	Oral tablet	0.5-4 mg qd

a decrease in plasma angiotensin II and aldosterone concentrations, thus reducing the adverse effects of these neurohormones. Inhibition of angiotensin-converting enzyme also prevents the breakdown of the endogenous vasodilator bradykinin.

- They improve hemodynamics by increasing cardiac output and reducing left ventricular filling pressures, systemic vascular resistance, blood pressure, and heart rate.
- They improve heart failure symptoms and reduce hospitalizations for heart failure.
- They reduce mortality by 20%-30% and slow the progression of heart failure.

Patient instructions and counseling

- Patients that are pregnant or breast-feeding should not take ACEIs. If they become pregnant while taking an ACEI, they should contact their physician immediately.
- Captopril should be taken on an empty stomach, 1 hour before or 2 hours after meals.
- Use salt substitutes that contain potassium cautiously.
- Call your doctor immediately if you experience swelling of the face, eyes, lips, tongue, arms, or legs, or if you have difficulty breathing or swallowing.
- May cause cough

Adverse drug events

- Hypotension
- Dizziness
- Renal insufficiency
- Cough
- Angioedema
- Hyperkalemia
- Rash
- Taste disturbances

Drug-drug and drug-disease interactions

- NSAIDs (including the COX-2 inhibitors) can increase the risk of renal insufficiency and attenuate the beneficial hemodynamic effects of ACEIs.
- Use potassium supplements or potassium-sparing diuretics with caution in patients receiving ACEIs.
- Cyclosporine and tacrolimus may increase the risk of nephrotoxicity and hyperkalemia.
- Diuretics increase the risk of hypotension.

Parameters to monitor

- Blood pressure
- Renal function (ie, serum BUN and creatinine)
- Serum potassium
- Heart failure symptoms
- Dose: therapy should be initiated at low doses followed by gradual increases if lower doses are well tolerated.

Other

- Pregnancy category C (first trimester) and D (second and third trimesters); ACEIs can cause fetal and neonatal morbidity and death when administered to pregnant women.

Angiotensin Receptor Blockers (ARBs)

- ACEIs remain the drugs of choice for inhibiting the renin-angiotensin-aldosterone system in patients with chronic heart failure. Recent clinical trials confirm the efficacy and safety of candesartan and valsartan in the treatment of heart failure. Whether other ARBs are equally effective is unknown. Current guidelines recommend the use of candesartan or valsartan in patients that are intolerant to ACEIs—both of these agents are approved for use in patients with heart failure. Intolerance is most often due to cough or angioedema, although caution is advised when used in patients that have angioedema secondary to an ACEI. Note that ARBs are just as likely as ACEIs to cause impaired renal function, hyperkalemia, or hypotension. (Table 3)

Mechanism of action

- Interfere with the renin-angiotensin system by blocking the angiotensin-1 receptor thus attenuating the detrimental effects of this hormone.
- Unlike ACEIs, the ARBs do not affect the kinin system and thus are not associated with cough.
- Reduce hospitalizations and improve survival.

Patient instructions and counseling

- Patients that are pregnant or breast-feeding should not take ARBs. If they become pregnant while taking an ARB, they should contact their physician immediately.
- Use salt substitutes that contain potassium cautiously.
- Dizziness or light-headedness may occur, especially in patients taking diuretics.

Adverse drug events

- Hypotension
- Dizziness
- Renal insufficiency
- Hyperkalemia

Drug-drug and drug-disease interactions

- Use potassium supplements or potassium-sparing diuretics with caution in patients receiving ARBs.
- Diuretics: increase risk of hypotension

Parameters to monitor

- Blood pressure
- Renal function (ie, serum BUN and creatinine)
- Serum potassium
- Heart failure symptoms
- Dose: therapy should be initiated at low doses followed by gradual increases if lower doses are well tolerated.

Other

- Pregnancy category C (first trimester) and D (second and third trimesters). Can cause fetal and neonatal morbidity and death when administered to pregnant women.

Table 3**Angiotensin Receptor Blockers (ARBs)**

Generic name (trade name)	Dosage form	Dosage range and frequency
Candesartan (Atacand®)	Oral tablet	4-32 mg qd
Valsartan (Diovan®)	Oral tablet	20-160 mg bid

Beta-Blockers

- Because of their negative inotropic effects, β -blockers were classically considered to be contraindicated in patients with heart failure. However, by inhibiting the deleterious effects of long-term activation of the sympathetic nervous system in heart failure, these agents have been repeatedly shown to provide hemodynamic, symptomatic, and survival benefits. Metoprolol succinate (extended-release metoprolol), bisoprolol, and carvedilol have all been shown to be effective and one of these three agents should be used for the treatment of heart failure (Table 4).

Mechanism of action

- Blockade of β -receptors by these agents antagonizes the increase in sympathetic nervous system activity that is one of the important mechanisms responsible for progression of heart failure. Bisoprolol and metoprolol succinate are β_1 -selective agents, whereas carvedilol blocks β_1 -, β_2 -, and α_1 -receptors. It remains uncertain whether these differences in pharmacologic actions have any important effects on outcomes in patients with heart failure.
- Treatment with β -blockers reduces symptoms, improves the clinical status, and decreases the risk of death and hospitalization.
- β -Blockers should be used in all patients with stable heart failure due to left ventricular systolic dysfunction unless they have a contraindication or have been shown not to tolerate them.
- In general, β -blockers should be used in combination with ACEIs and diuretics.

Patient instructions and counseling

- May cause fluid retention or worsening of heart failure with initiation of therapy or an increase in dose. Report any cases of body or leg swelling or increased shortness of breath. Patients should weigh themselves daily and if they gain more than 1 pound per day for several consecutive days or 3-5 pounds in a week, they should contact their health care provider.
- Fatigue or weakness may occur in the first few weeks of treatment, but will usually resolve spontaneously.
- Report any cases of dizziness, lightheadedness, or blurred vision. These may be caused by blood pressure being too low or from bradycardia or heart block.
- Take carvedilol with food.
- It is important not to miss doses or abruptly stop taking these medications.
- If patients have diabetes, β -blockers may cause their blood sugar to rise and mask the signs of hypoglycemia except for sweating.

Adverse drug events

- The adverse events listed below are the most common observed in heart failure patients receiving β -blockers. For other adverse effects of β -blockers, see the chapters on hypertension and ischemic heart disease.
 - * Fluid retention and worsening heart failure
 - * Fatigue
 - * Bradycardia and heart block
 - * Hypotension
 - * Abrupt withdrawal can lead to hypertension, tachycardia, or myocardial ischemia.

Drug-drug and drug-disease interactions

- Amiodarone and calcium channel blockers (verapamil and diltiazem): increased risk of bradycardia, heart block, hypotension
- Quinidine, fluoxetine, paroxetine, and other inhibitors of cytochrome P450 2D6: inhibit hepatic metabolism of metoprolol and carvedilol and may result in increased plasma concentrations and enhanced effects.
- Ophthalmic β -blockers increase risk of bradycardia, heart block, and hypotension.
- May cause bronchoconstriction in patients with asthma or COPD
- Should not use in patients with symptomatic bradycardia or heart block unless a pacemaker is present
- May worsen blood glucose control in diabetics and mask the signs of hypoglycemia

Parameters to monitor

- Blood pressure and heart rate
- Heart failure symptoms
- Weigh daily

Table 4

Beta-Blockers

Generic name (trade name)	Dosage form	Dosage range and frequency
Bisoprolol (Zebeta®)	Oral tablet	1.25-10 mg qd-bid
Carvedilol (Coreg®)	Oral tablet	3.125-50 mg bid
Metoprolol succinate extended-release (Toprol-XL®)	Oral tablet	12.5-200 mg qd

Kinetics

- **Bisoprolol** is eliminated about 50% by the kidneys, so dosage adjustment may be required in patients with **renal insufficiency**.
- Both **metoprolol** and **carvedilol** are metabolized by the **liver**.

Other

- Patients must be stable (ie, minimal evidence of fluid overload or volume retention) before β -blocker treatment is initiated.
- Treatment should be initiated with low doses and titrated slowly upward until the target dose is reached. Doses are usually increased no more frequently than every 2 weeks with close monitoring of symptoms required during this titration period.
- Fluid accumulation during dose titration can usually be managed by adjusting diuretic doses.
- Staggering the schedule of other heart failure medications that lower blood pressure (eg, ACEIs and diuretics) may help reduce risk of hypotension.
- A recent study comparing the effects of carvedilol with immediate-release metoprolol (metoprolol tartrate) in patients with heart failure found that survival was improved in patients receiving carvedilol. Whether carvedilol is superior to extended-release metoprolol (Toprol-XL, metoprolol succinate) is unknown. Therefore these results strongly argue that only β -blockers proven to improve survival (carvedilol, metoprolol succinate, and bisoprolol) should be used in these patients.

Aldosterone Antagonists

- Elevated plasma aldosterone plays an important detrimental role in the pathophysiology and progression of heart failure. Although short-term treatment with ACEIs or ARBs lowers circulating aldosterone concentrations, this suppression is not sustained with long-term therapy. In low doses, the aldosterone antagonists spironolactone and eplerenone reduce the risk of death and hospitalization in patients with moderate to severe heart failure. Current guidelines recommend the addition of aldosterone antagonists in patients with moderately severe to severe symptoms of heart failure and reduced left ventricular ejection fraction that can be closely monitored for renal function and serum potassium (Table 5).

Mechanism of action

- Antagonism of aldosterone results in reduced renal potassium excretion.

Patient instructions and counseling

- Avoid potassium-containing salt substitutes.
- Call physician immediately for muscle weakness or cramps; numbness or tingling in hands, feet, or lips; or slow or irregular heartbeat
- Spironolactone may cause swollen or painful breasts in men

Adverse drug events

- Hyperkalemia
- Gynecomastia (only with spironolactone)
- Irregular menses

Drug-drug and drug-disease interactions

- **ACE inhibitors**, **ARBs**, **NSAIDs** increase risk of hyperkalemia.
- Spironolactone can increase digoxin plasma concentrations
- Potassium supplements
- Patients with diabetes as well as the elderly are at increased risk of hyperkalemia
- Erythromycin, clarithromycin, verapamil, ketoconazole, fluconazole, itraconazole, and other inhibitors of cytochrome P450 3A4: inhibit hepatic metabolism of eplerenone and may result in increased plasma concentrations and enhanced effects.

Parameters to monitor

- Serum creatinine: should be **<2.5 mg/dL** in men or **<2.0 mg/dL** in women before therapy is initiated
- Serum potassium: should be **<5.0 mEq/L** before therapy is initiated. Potassium should be evaluated in three days and one week after therapy is started and at least monthly for the **first 3 months** of therapy.

Table 5

Aldosterone Antagonists

Generic name (trade name)	Dosage form	Dosage range and frequency
Spironolactone (Aldactone®)	Oral tablet	25-50 mg qd or qod
Eplerenone (Inspra®)	Oral tablet	25-50 mg qd

Digoxin

- Unlike ACEIs or β -blockers, digoxin does not improve mortality, but does appear to produce symptomatic benefits (Table 6).

Mechanism of action

- Inhibits the $\text{Na}^+\text{-K}^+\text{-ATPase}$ pump, which results in an increase in intracellular calcium, that in turn causes a positive inotropic effect.
- Recent evidence indicates that digoxin reduces sympathetic outflow from the central nervous system, thus blunting the excessive sympathetic activation that occurs in heart failure. These effects occur at low plasma concentrations where little positive inotropic effect is seen.

Patient instructions and counseling

- The patient should report to the health care provider if any of the following occur:
 - Dizziness, lightheadedness, fatigue
 - Changes in vision (blurred or yellow vision)
 - Irregular heartbeat
 - Loss of appetite
 - Nausea, vomiting, or diarrhea

Adverse drug events

- Major adverse effects involve three systems:
 - Cardiovascular: cardiac arrhythmias, bradycardia, and heart block
 - Gastrointestinal: anorexia, abdominal pain, nausea, and vomiting
 - Neurological: visual disturbances, disorientation, confusion, fatigue
- Toxicity is more commonly associated with serum digoxin concentrations >2 ng/mL but may occur at lower levels if patients have hypokalemia, hypomagnesemia, and in the elderly.

Table 6

Digoxin

Generic name (trade name)	Dosage form	Dosage range and frequency
Digoxin (Lanoxin®)	Oral tablet, IV, elixir	0.125-0.25 mg qd
Digoxin (Lanoxicaps®)	Oral capsule	0.1-0.2 mg qd

Drug-drug and drug-disease interactions

- Drugs that increase serum digoxin concentrations:
 - Quinidine, verapamil, amiodarone: the dose of digoxin should be decreased by 50% if these medications are added
 - Propafenone
 - Flecainide
 - Macrolide antibiotics: erythromycin and clarithromycin
 - Itraconazole, ketoconazole
 - Spironolactone
 - Cyclosporine
- Drugs that decrease serum digoxin concentrations:
 - Antacids
 - Cholestyramine, colestipol
 - Kaolin-pectin
 - Metoclopramide
- Diuretics: increase the risk of digoxin toxicity in the presence of hypokalemia or hypomagnesemia
- Digoxin clearance is reduced in patients with renal insufficiency (see section on kinetics).

Parameters to monitor

- Digoxin serum concentration
 - There is little relationship between serum digoxin concentration and therapeutic effects in heart failure.
 - Current guidelines suggest a target range of 0.5-1.0 ng/mL.
- Heart rate
- Serum potassium and magnesium
- Renal function: serum BUN and creatinine
- Heart failure symptoms

Kinetics (Table 7)

- Approximately 60%-80% of the dose is eliminated unchanged in the kidney. Dosage adjustment is

Table 7

Digoxin Pharmacokinetics

Oral bioavailability

Tablets	0.5-0.9 (average 0.65)
Elixir	0.75-0.85 (average 0.80)
Capsules	0.9-1.0 (average 0.95)

Elimination half-life

Normal renal function	36 hours
Anuric patients	5 days
Volume of distribution	7 L/kg
Fraction excreted unchanged in urine	0.65-0.70

required in patients with renal insufficiency.

- Lower doses (0.125 mg daily or every other day) should be used in the elderly or patients with a low lean body mass.
- No loading dose is needed in the treatment of heart failure.
- Because of the long distribution phase after either oral or intravenous digoxin administration, blood samples for determination of serum digoxin concentrations should be collected at least 6 and preferably 12 hours or more after the last dose.

Hydralazine-Isosorbide Dinitrate

- These were initially combined because of complementary hemodynamic actions. An early clinical trial reported reduced mortality compared to placebo with this combination. A comparison with an ACEI showed that the ACEI was superior to hydralazine-isosorbide dinitrate. Adverse effects with the combination are common (primarily headache and gastrointestinal complaints), and result in many patients discontinuing therapy. Current guidelines indicate this combination can be considered a therapeutic option in patients who cannot be given an ACEI or an ARB due to drug intolerance, hypotension, or renal insufficiency.
- A recent clinical trial found that the combination of hydralazine-isosorbide dinitrate, when added to standard background therapy (ACEIs or ARBs, β -blockers, diuretics, digoxin), reduced mortality by 40% compared to placebo in African-Americans with heart failure. Whether these benefits are specific for African-Americans remains to be determined. The current heart failure treatment guidelines indicate that the addition of hydralazine and a nitrate is reasonable in patients with persistent heart failure symptoms despite therapy with ACEIs and β -blockers.
- A fixed-dose combination product is now available (BiDil®).

3. Drug Therapy of Advanced or Decompensated Heart Failure

- Patients with advanced or decompensated heart failure are usually admitted to the hospital for aggressive treatment with IV diuretics, vasodilators, or positive inotropic drugs. Treatment goals are to reduce volume overload and improve cardiac output. The approach to treatment is dictated by the patient's hemodynamic profile.

Warm and dry

- No specific therapy is needed.

Warm and wet

- The goal is to reduce volume overload and minimize congestive symptoms.
- IV loop diuretics are often used. For patients unresponsive to loop diuretics, addition of supplemental thiazide diuretics (eg, metolazone) may be helpful.
- Addition of IV vasodilators (nitroglycerin, nitroprusside, and nesiritide) can also reduce symptoms.
- Inotropic therapy is usually not necessary.

Cold and dry

- May be clinically stable and often do not present with acute symptoms
- Need to rule out volume depletion from overdiuresis as the cause of decreased cardiac output
- Gradual introduction of β -blockers may be helpful.

Cold and wet

- Improve cardiac output first (ie, before removing excess volume).
- Cardiac output can be increased by IV vasodilators and/or inotropes.
- The relative roles of vasodilators and inotropes are this patient population is controversial.

Vasodilators

- See Table 8.

Inotropes

- See Table 9.

Table 8

Vasodilators

Generic name (trade name)	Mechanism of action	Dose ¹	Adverse effects and comments
Nitroprusside (Nipride®)	Arterial and venous dilator	Initial dose 0.1-0.25 mcg/kg per min and titrate to response	Hypotension, headache, tachycardia, cyanide and thiocyanate toxicity, myocardial ischemia
Nitroglycerin (Nitro-Bid®, Nitrostat®)	Venous dilator but also an arterial dilator at higher doses	Initial dose 5-10 mcg/min and titrate to response	Hypotension, headache, tachycardia, tolerance to hemodynamic effects
Nesiritide (Natrecor®)	B-type natriuretic peptide that increases diuresis and is an arterial and venous dilator	Initially 2 mcg/kg bolus followed by 0.01 mcg/kg per min infusion; can increase to 0.03 mcg/kg per min	Hypotension, headache when used in combination with diuretics

¹All are given by continuous IV infusion.

Table 9

Inotropes

Generic name (trade name)	Mechanism of action	Dose ¹	Adverse effects and comments
Dopamine (Intropin®)	Dose-dependent agonist of dopamine and β and α_1 receptors	0-3 mcg/kg per min: stimulates dopamine receptors (may improve urine output) 3-10 mcg/kg per min: stimulates β_1 and β_2 receptors to increase cardiac output >10 mcg/kg per min: stimulates α_1 receptors to increase blood pressure	Increases heart rate, contractility, myocardial oxygen demand, myocardial ischemia, arrhythmias, and systemic vascular resistance; should only be used in patients with marked systemic hypotension or cardiogenic shock
Dobutamine (Dobutrex®)	β_1 - and β_2 -receptor agonist and weak α_1 agonist; increases cardiac output and vasodilates	2.5-20 mcg/kg per min	Increases heart rate, contractility, myocardial oxygen demand, myocardial ischemia, arrhythmias; not useful to increase blood pressure in hypotensive patients
Milrinone (Primacor®)	Inhibits phosphodiesterase III, resulting in positive inotropic and vasodilating effects	50 mcg/kg loading dose over 10 min, followed by 0.375 mcg/kg per min; can titrate to 0.75 mcg/kg per min based on response	Arrhythmias, hypotension, headache; alternative to patients not responding to dobutamine or dopamine; may be useful in patients receiving β -blockers since its positive inotropic effects are not mediated by β receptors; adjust dose in patients with renal insufficiency; preferred over amrinone because of decreased risk of thrombocytopenia

¹All are given by continuous IV infusion.

4. Nondrug Therapy

Intra-aortic balloon pump

Left ventricular assist devices

Biventricular pacing

Implantable cardioverter-defibrillator (ICD)

Cardiac transplantation

5. Key Points

- Heart failure is a clinical syndrome caused by the inability of the heart to pump sufficient blood to meet the needs of the body.
- Although there are many causes of heart failure, the most common are coronary artery disease and hypertension.
- A number of compensatory mechanisms are activated to help maintain adequate cardiac output, and activation of these systems is responsible for heart failure symptoms and contributes to disease progression. Medications that improve patient outcomes antagonize these compensatory mechanisms.
- Drugs that can precipitate or worsen heart failure should be avoided (eg, NSAIDs, verapamil, diltiazem).
- All patients with stage C (symptomatic) heart failure should be treated with diuretics, ACEIs, and β -blockers.
- The goal of treatment with diuretics is to eliminate signs of fluid retention, thus minimizing symptoms.
- ACEIs are an integral part of heart failure pharmacotherapy. They improve survival and slow disease progression. ARBs are the preferred alternative for patients intolerant to ACEIs.
- β -Blockers are recommended for all patients with systolic dysfunction and mild to moderate symptoms. They improve survival, decrease hospitalizations, and slow disease progression. The agents with proven benefits are bisoprolol, carvedilol, and metoprolol extended-release. They should be started at low doses with slow upward titration to the target dose.
- Digoxin does not improve survival in patients with heart failure but does provide symptomatic benefits. The goal plasma concentration is 0.5-1.0 ng/mL.
- Spironolactone and eplerenone improve survival in patients with moderate to severe heart failure.
- Patients with advanced or decompensated heart failure often require hospitalization and aggressive therapy with IV diuretics, vasodilators, and positive inotropic drugs.

6. Questions and Answers

- Which of the following combinations represents optimal pharmacotherapy of heart failure?
 - Furosemide, clonidine, hydrochlorothiazide, and propranolol
 - Furosemide, lisinopril, and carvedilol
 - Carvedilol, verapamil, amlodipine, and nesiritide
 - Diltiazem, hydrochlorothiazide, digoxin, and furosemide
 - Dobutamine, milrinone, furosemide, and nitroglycerin
- Which of the following mechanisms most likely contributes to the benefits of β -blockers in the treatment of heart failure?
 - Stimulation of β_2 receptors
 - Increased heart rate and decreased blood pressure
 - Increased plasma norepinephrine
 - Blockade of increased sympathetic nervous system activity
 - Blockade of angiotensin II receptors
- Appropriate monitoring parameters for enalapril therapy of heart failure include
 - serum creatinine
 - serum potassium
 - serum calcium
 - I only
 - III only
 - I and II only
 - II and III only
 - I, II, and III
- Patients taking eplerenone for heart failure should avoid taking
 - potassium supplements
 - ACEIs
 - β -blockers
 - Furosemide
 - calcium supplements
- All of the following are adverse effects of digoxin EXCEPT
 - nausea
 - anorexia
 - confusion
 - arrhythmias
 - acute renal failure
- Heart failure may be exacerbated by which of the following medications?
 - Naproxen
 - Glipizide
 - Simvastatin
 - I only
 - III only
 - I and II only
 - II and III only
 - I, II, and III
- Cough is an adverse effect associated with which of the following medications?
 - Enalapril
 - Valsartan
 - Carvedilol
 - Torsemide
 - Eplerenone
- Which of the following ACEIs has the shortest duration of action?
 - Ramipril
 - Captopril
 - Lisinopril
 - Monopril
 - Fosinopril
- Candesartan can be used for treating heart failure in patients intolerant to
 - Milrinone
 - Torsemide
 - Enalapril
 - Metoprolol
 - Bisoprolol
- A significant interaction can occur if digoxin is administered with
 - Clarithromycin
 - Fosinopril
 - Glyburide
 - Pravastatin
 - Warfarin

11. All of the following medications can cause bradycardia EXCEPT
 - A. Carvedilol
 - B. Amiodarone
 - C. Digoxin
 - D. Verapamil
 - E. Dobutamine
12. Which of the following is contraindicated in patients with a history of lisinopril-induced angioedema?
 - A. Captopril
 - B. Bumetanide
 - C. Spironolactone
 - D. Milrinone
 - E. Aspirin
13. Nesiritide would be indicated in
 - A. patients with asymptomatic left ventricular dysfunction.
 - B. patients with acute decompensated heart failure not responsive to IV diuretics.
 - C. patients with stage B heart failure.
 - D. patients with type 2 diabetes.
 - E. patients intolerant to digoxin.
14. All of the following are true about the use of furosemide in heart failure EXCEPT:
 - A. The drug reduces mortality and slows heart failure progression.
 - B. Hypokalemia is a common adverse effect.
 - C. Response can be evaluated by monitoring patient weight.
 - D. Oral absorption is slowed in patients with advanced or decompensated heart failure.
 - E. The bioavailability is reduced by food.
15. Which of the following is an important consideration when using β -blockers for treating heart failure?
 - A. They are only effective in post-MI patients.
 - B. All β -blockers are equally effective for the treatment of heart failure.
 - C. Therapy should be initiated at the target dose.
 - D. Patients with fluid overload are the optimal candidates for initiating therapy.
 - E. Therapy should be initiated at low doses and titrated upward slowly.
16. The dose of which of the following medications should be reduced in patients with renal insufficiency?
 - A. Metoprolol
 - B. Carvedilol
 - C. Digoxin
 - D. Nitroglycerin
 - E. Dobutamine
17. The plasma concentration of digoxin is NOT affected by
 - A. renal function
 - B. Amiodarone
 - C. Quinidine
 - D. Metoprolol
 - E. Bismuth subsalicylate
18. Which of the following β -blockers also blocks α_1 receptors and is effective for treating heart failure?
 - A. Metoprolol
 - B. Carvedilol
 - C. Bisoprolol
 - D. Propranolol
 - E. Atenolol
19. Patients with heart failure who experience fluid retention after β -blocker initiation should have
 - A. the β -blocker dose increased.
 - B. the digoxin dose increased.
 - C. the β -blocker discontinued.
 - D. their ACEI discontinued.
 - E. adjustment of their diuretic dose.
20. Which of the following agents should be used in patients with advanced or decompensated heart failure and hypotension?
 - A. Dopamine
 - B. Milrinone
 - C. Nitroprusside
 - D. Dobutamine
 - E. Hydralazine

Use Patient Profile #1 to answer Questions 21 and 22.

21. Which of the following medications should be added to Mr. Johnson's regimen?
- Lisinopril and metoprolol
 - Valsartan and prazosin
 - Torsemide and amlodipine
 - Verapamil and gemfibrozil
 - Clonidine and hydrochlorothiazide
22. Mr. Johnson's serum potassium level of 2.0 mEq/L (normal 4.0-5.0 mEq/L) could
- increase the risk of lanoxin toxicity
 - be treated by increasing the dose of Lasix
 - be considered a side effect of therapy with EC aspirin
 - be caused by an interaction between Zocor and Lanoxin
 - increase his blood pressure

Patient Profile #1

Patient Name William Johnson
 Age 64
 Sex Male
 Allergies NKA

Height 5'11"
 Weight 185 lbs

DIAGNOSIS Myocardial infarction 1999
 Hypertension
 Heart failure
 Hyperlipidemia

LABORATORY AND DIAGNOSTIC TESTS

Echocardiogram in 12/02 showed LV ejection fraction 30%
 Blood pressure on 4/1/03: 145/90 mm Hg
 Heart rate on 4/1/03: 88 bpm
 Lipid profile on 4/1/03:
 Total cholesterol 160 mg/dL
 LDL cholesterol 95 mg/dL
 HDL cholesterol 50 mg/dL
 Triglycerides 100 mg/dL
 Serum potassium 2.0 mg/dL

MEDICATION RECORD

Date	Rx #	Physician	Drug/Strength	Quantity	Sig	Refills
4/1	1000	Smith	Lanoxin 0.125 mg	90	1 tab qd	2
4/1	1001	Smith	Lasix 40 mg	60	1 tab q AM	3
4/1	1002	Smith	KCl 20 mEq	90	1 tab q AM	1
4/1	1003	Smith	Zocor® 40 mg	90	1 tab qhs	3
4/1	1004	Smith	EC aspirin 325 mg	90	1 tab q AM	2

Use Hospital Inpatient Profile #2 to answer Questions 23 and 24.

23. Based on her profile, the recent worsening of Mrs. Jones's heart failure is most likely related to

A. zestril
 B. ibuprofen
 C. subtherapeutic serum digoxin concentration.
 D. furosemide
 E. drug interaction between zestril and furosemide.

24. Toprol-XL is an agent that

A. is contraindicated in heart failure.
 B. blocks β_1 , β_2 , and α_1 receptors.
 C. blocks only β_1 receptors.
 D. should not be used in combination with Zestril.
 E. increases the serum digoxin concentration.

Answers

1. **B.** Furosemide, lisinopril (an ACEI), and carvedilol (a β -blocker) in combination should routinely be used in patients with heart failure.
2. **D.** Activation of the sympathetic nervous system plays an important role in the initiation and progression of heart failure. The benefits of β -blockers are thought to be due to blockade of this increased activity of the sympathetic nervous system.
3. **C.** Enalapril, as well as other ACEIs, can cause renal insufficiency and an increase in serum potassium. Thus serum creatinine and potassium should be monitored.
4. **A.** Use of eplerenone is associated with renal potassium retention. Concomitant use of potassium supplements significantly increases the risk of hyperkalemia.

Hospital Inpatient Profile #2

Patient Name	Ellen Smith	Height	5'4"
Age	71	Weight	150 lbs
Sex	Female		
Allergies	NKA		

DIAGNOSIS	Heart failure exacerbation with 20-lb weight gain over last 3-4 weeks
	Hypertension
	Osteoarthritis

LABORATORY AND DIAGNOSTIC TESTS

Echocardiogram in 2/03 showed LV ejection fraction 25%
 Blood pressure on 4/1/03: 130/85 mm Hg
 Heart rate on 4/1/03: 80 bpm
 Serum digoxin concentration on 4/1/03: 0.8 ng/mL

MEDICATION RECORD

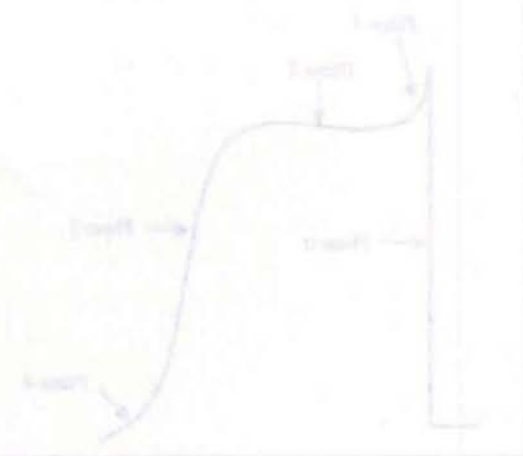
Date	Rx #	Physician	Drug/Strength	Quantity	Sig	Refills
2/1	100	Jones	Lanoxin 0.125 mg	90	1 tab qd	2
3/1	101	Jones	Furosemide 80 mg	60	1 tab q AM	3
1/1	102	Jones	Zestril 20 mEq	90	1 tab q AM	1
1/1	103	Jones	Toprol-XL 50 mg	90	1 tab qd	3
3/1	1004	Nelson	Ibuprofen 600 mg	90	1 tab qid with food	3

5. **E.** Nausea, anorexia, confusion, and arrhythmias are all common signs and symptoms of digoxin toxicity. Digoxin does not affect renal function.
6. **A.** Naproxen, an NSAID, can worsen heart failure by increasing renal sodium and water retention and by attenuating the efficacy and enhancing the toxicity of ACEIs and diuretics. Neither glipizide or simvastatin affect heart failure.
7. **A.** Cough is a frequently encountered adverse effect of ACEIs.
8. **B.** Captopril must be given three times daily in patients with heart failure. The other agents can be given once daily.
9. **C.** The angiotensin receptor blocker candesartan is an alternative agent for patients intolerant to ACEIs.
10. **A.** The macrolide antibiotic clarithromycin is associated with a 50%-100% increase in serum digoxin concentrations.
11. **E.** Dobutamine is a β -receptor agonist and is associated with an increase in heart rate. The other choices all slow heart rate through various mechanisms.
12. **A.** Lisinopril is an ACEI and angioedema is a known adverse effect of all agents in this class. Thus captopril, which is also an ACEI, should not be used in this situation.
13. **B.** Nesiritide is only indicated for use in patients with severe or decompensated heart failure. It can only be given intravenously.
14. **A.** Although furosemide plays an important role in patients with heart failure by interfering with sodium and water retention, they only provide symptomatic benefit. Neither furosemide nor other diuretics improve survival or affect heart failure progression.
15. **E.** When used in heart failure, β -blocker therapy should be started at low doses and gradually titrated upward to the target dose that was established in clinical trials to improve survival. Starting at the target dose or initiating treatment in patients with fluid overload increases the risk of worsening heart failure. Only carvedilol, bisoprolol, and metoprolol extended-release are proven to be effective in heart failure.
16. **C.** Only digoxin is eliminated by the kidneys.
17. **D.** Renal insufficiency reduces digoxin clearance and results in increased plasma concentrations. Amiodarone and quinidine both increase digoxin concentrations by 50%-100%. Bisumth subsalicylate can reduce digoxin concentrations by binding it in the gut, thus reducing absorption.
18. **B.** Only carvedilol blocks α_1 receptors and has been shown to be effective in patients with heart failure.
19. **E.** Some patients with heart failure may experience increases in fluid retention after initiation of β -blocker therapy. This can usually be best managed by adjustment of the diuretic dose and close monitoring of patient weight.
20. **A.** Dopamine is a β - and α -receptor agonist and is useful in patients with severe heart failure and hypotension. The other agents listed all have vasodilatory effects and are not useful for increasing blood pressure.
21. **A.** An ACEI and β -blocker are indicated in this patient with heart failure to improve survival and slow disease progression.
22. **A.** Hypokalemia increases the risk of digoxin toxicity.
23. **B.** The addition of the NSAID ibuprofen ~3-4 weeks before admission is the likely cause of this episode of decompensated heart failure. NSAIDs can increase sodium and water retention and negate the effects of diuretics and ACEIs.
24. **C.** Toprol-XL (metoprolol succinate) is a cardioselective β -blocker. It blocks only the β_1 receptor at usual therapeutic doses.

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10. Cardiac Arrhythmias



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Contents

1. Cardiac Arrhythmias
2. Drug and Nondrug Therapy
3. Key Points
4. Questions and Answers
5. References

1. Cardiac Arrhythmias

- Cardiac arrhythmias are abnormal heart rhythms resulting from alterations in impulse formation and/or conduction.

Electrophysiology

Impulse generation (automaticity) and conduction

- Initiation and propagation of the electrical impulse in cardiac cells is dependent on regulation of the action potential.
- Conduction velocity is determined by regulation of action potential, specifically the slope of phase 0 depolarization (Figure 1 and Table 1).
- The **absolute refractory period** is the time during which cardiac cells cannot conduct or propagate an action potential (Figure 1 and Table 1).
- The **relative refractory period** is the time during which cardiac cells may conduct and propagate action potentials secondary to strong electrical stimuli.

Normal conduction system

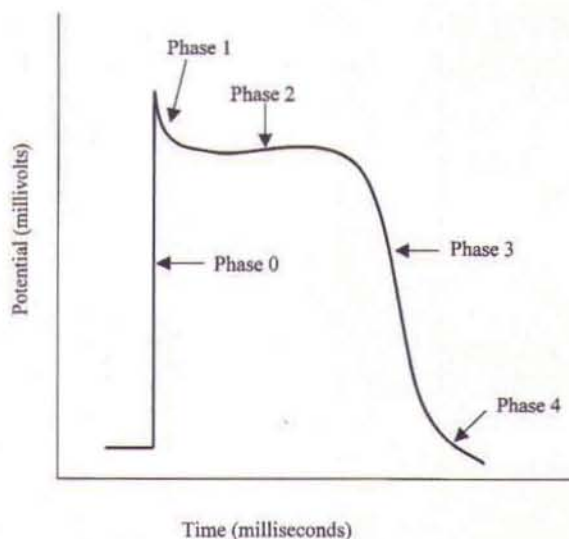
- The sinoatrial (SA) node, located in the right atrium, initiates an impulse, which:
 - Stimulates the left atrium and atrioventricular (AV) node, which
 - Stimulates the left and right bundle branches via the bundle of His, which then
 - Stimulates Purkinje fibers and causes ventricular contraction.

Mechanisms of Arrhythmia

- Cardiac arrhythmias arise secondary to disorders of:
 - Automaticity (impulse generation)
 - Latent pacemaker (non-SA node pacemaker)

Figure 1.

Action potential for atrial and ventricular tissue.



- Triggered automaticity (early or late after-depolarizations)
- Reentry
- Impulse conduction
- Automaticity and impulse conduction

Clinical Manifestations

Symptoms

- Except for ventricular tachycardia (VT) and ventricular fibrillation (VF), the patient may be asymptomatic. VT may be asymptomatic, but it can also

Table 1

Phases of Atrial and Ventricular Tissue Action Potential

Phase	Process	Ion flow	Corresponding ECG
0	Depolarization	Na ⁺ fast channel opens, Na ⁺ enters cell	Atrial: P wave; ventricular: QRS
1	Initial repolarization	Na ⁺ channel closes; passive Cl ⁻ influx	
2	Prolongs depolarized state	Predominantly Ca ²⁺ enters cell	ST segment
3	Repolarization	Rapid efflux of K ⁺ out of cell	T wave, QT interval
4	Repolarization	Na ⁺ leaks into cell, K ⁺ pumped out of cell	

result in hypotension, syncope, or death. VF produces no cardiac output and is the cause of most cases of sudden cardiac death.

- Symptoms generally related to poor cardiac output include dizziness, syncope, chest pain, fatigue, confusion, and exacerbation of heart failure.
- Patients with tachyarrhythmias may report palpitations.
- With atrial fibrillation/flutter, patients may also experience signs and symptoms of transient ischemic attack (TIA) or stroke.

* Signs

- Electrocardiogram (ECG) abnormalities
- Ventricular rate can be assessed by documenting the heart rate from the radial artery or carotid palpation.

Diagnostic Criteria and Therapy According to Arrhythmia Classification

Arrhythmias are defined by:

- Anatomic location
 - * Supraventricular: these arise from abnormalities in the SA node, atrial tissue, the AV node, or bundle of His.
 - * Ventricular: these arrhythmias originate from below the bundle of His.
- Ventricular rate
 - * Bradycardia: heart rate <60 bpm
 - * Tachycardia: heart rate >100 bpm

Supraventricular Arrhythmias

Bradyarrhythmias

Sinus bradycardia

Diagnostic criteria and characteristics

- * HR <60 bpm; otherwise normal ECG

Mechanism of arrhythmia

- * Decreased SA node automaticity

Clinical etiology

- * Acute myocardial infarction, hypothyroidism, drug-induced (β -blockers, digoxin, calcium channel blockers [diltiazem, verapamil], clonidine, amiodarone, and cholinergic agents), hyperkalemia

Treatment goals

- * Restore normal sinus rhythm if the patient is clinically symptomatic.

Drug and nondrug therapy

- * Intermittent symptomatic episodes: atropine 0.5-1 mg IV repeated up to maximum dose of 3 mg

- * For persistent episodes or if atropine nonresponsive: place transvenous or transcutaneous pacemaker.

Atrioventricular (AV) block

Diagnostic criteria and characteristics

- * First-degree: prolonged PR interval >0.20 seconds, 1:1 atrioventricular conduction
- * Second-degree Mobitz type I: gradual prolongation of PR interval followed by P wave without ventricular conduction
- * Second-degree Mobitz type II: constant PR interval with intermittent P wave without ventricular contraction; often widened QRS complex
- * Third-degree: HR 30-60 bpm; no temporal relation between atrial and ventricular contraction; ventricular contraction initiated by AV junction or ventricular tissue.

Mechanism of arrhythmia

- * Prolonged conduction

Clinical etiology

- * AV nodal disease, acute myocardial infarction, myocarditis, increased vagal tone, drug-induced (β -blockers, digoxin, calcium channel blockers [diltiazem and verapamil], clonidine, amiodarone, cholinergic agents), hyperkalemia

Treatment goals

- * Restore sinus rhythm if the patient is symptomatic.

Drug and nondrug therapy

- * If the cause is reversible, treat with a temporary pacemaker or intermittent atropine; if chronic, implant a permanent pacemaker.

Tachyarrhythmias

Atrial fibrillation and atrial flutter

Diagnostic criteria and characteristics

- * Fibrillation: no P waves, irregularly irregular QRS pattern
- * Flutter: sawtooth P-wave pattern; regular QRS pattern

Mechanism of arrhythmia

- * Enhanced automaticity and reentrant circuits

Clinical etiology

- * Rheumatic heart disease, heart failure, hypertension, ischemic heart disease, pericarditis, cardiomyopathy, mitral valve prolapse, cardiac surgery, infection, alcohol abuse, hyperthyroidism, chronic obstructive pulmonary dis-

ease, pulmonary embolism, idiopathic (lone atrial fibrillation)

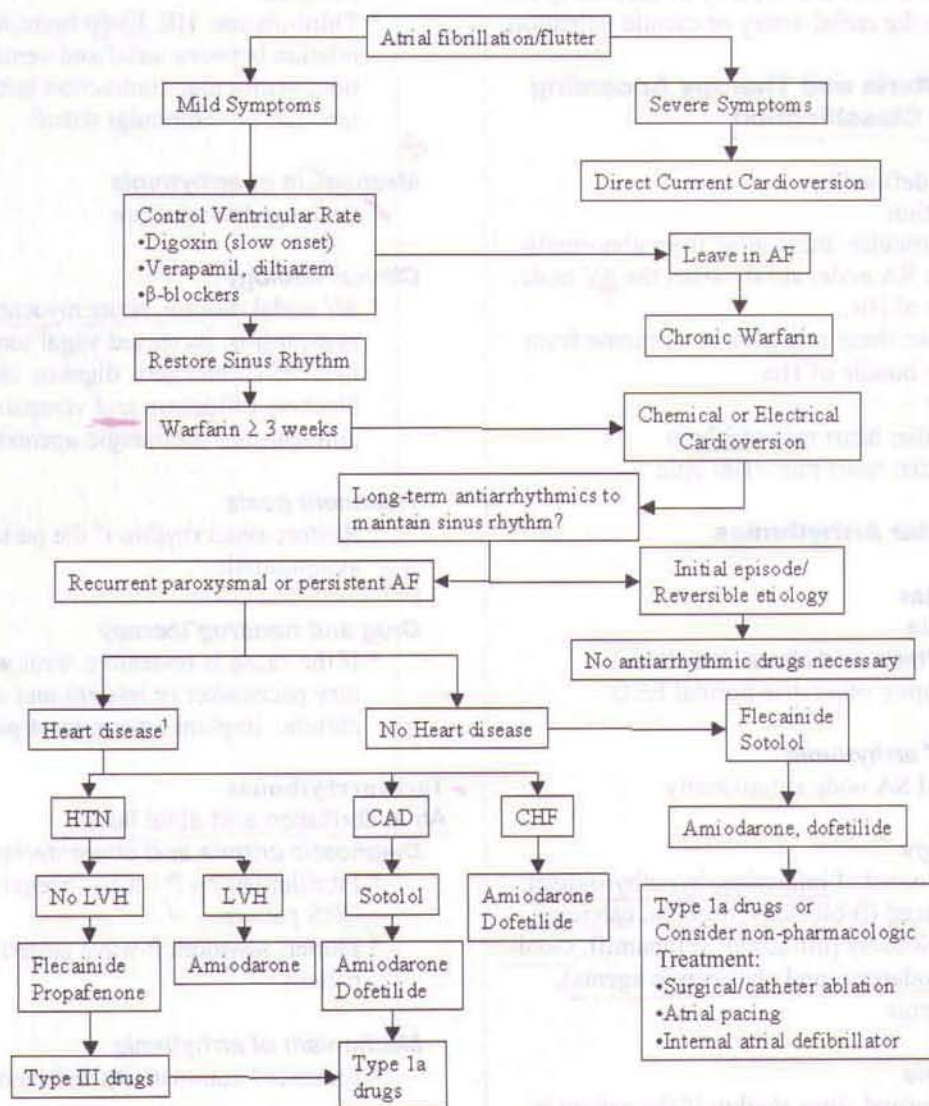
- * The risk of developing atrial fibrillation increases with age.
- * Complications: stroke, heart failure exacerbation

Specific treatment goals for atrial fibrillation (Figure 2)

- Control ventricular rate
 - * Digoxin (slow-onset, poor control in hyperadrenergic-induced AF)
 - * β -Blockers (esmolol, metoprolol, propranolol, others)

Figure 2.

Treatment algorithm for atrial fibrillation.



¹Most patients with heart disease who receive antiarrhythmic drugs to maintain sinus rhythm should also receive chronic warfarin therapy titrated to an INR of 2-3.

CAD, coronary artery disease; CHF, congestive heart failure; HTN, hypertension; LVH, left ventricular hypertrophy.

- * Calcium channel blockers (diltiazem, verapamil)
- * Digoxin, calcium channel blockers, and β -blockers do not restore sinus rhythm.

Restore and maintain sinus rhythm

- * Restoration of sinus rhythm is usually accomplished by electrical cardioversion or administration of antiarrhythmic drugs.
- * An important area of controversy centers on whether chronic antiarrhythmic drug therapy should be administered to maintain sinus rhythm after cardioversion (rhythm control approach) or whether patients should simply be treated with agents to control ventricular response and anticoagulants to prevent thromboembolic stroke (rate control approach).
- * Historically, antiarrhythmic drugs were frequently used to restore and maintain sinus rhythm in patients with atrial fibrillation (rhythm control approach). With chronic therapy, antiarrhythmic drugs approximately double the chances of a patient remaining in sinus rhythm. However, this approach exposes patients to the large number of adverse effects associated with antiarrhythmic drugs. The rationale for this approach includes the possibility of fewer symptoms, lower risk of stroke, improved quality of life, and reduced mortality. However, these benefits had never been proven in large clinical trials.
- * The alternative approach, so called "rate control," involves using drugs to control the ventricular response and chronic anticoagulation, usually with warfarin, for stroke prevention.
- * The rate control and rhythm control approaches have recently been compared and the studies demonstrate no advantage for rhythm control over the rate control approach. Regardless of the approach, adequate anticoagulation is needed to prevent stroke.
- * Chronic antiarrhythmic therapy is usually reserved for patients with recurrent, symptomatic episodes.

Prevent thromboembolism

- * Pharmacologic or direct-current (DC) cardioversion: if atrial fibrillation is present for >48 hours; anticoagulate with warfarin (INR 2-3) for 3-4 weeks prior to cardioversion unless transesophageal echocardiography (TEE) rules out atrial thrombus.
- * Postcardioversion, continue anticoagulation for at least 4 weeks.
- * Risk factors for nonvalvular atrial fibrillation thromboembolism:

- Previous stroke or TIA
- Hypertension
- Congestive heart failure
- Diabetes mellitus
- Age >75 years

Recommended antithrombotic therapy

* Aspirin 325 mg daily:

- Age <65 years and no risk factors
- Age <65 years and coronary artery disease but no risk factors (risk factors: see above)
- Age 65-75 years and no risk factors (warfarin is an acceptable alternative in this group)

* Warfarin (INR 2-3):

- Age ≥ 75
- Any age and presence of risk factors for thromboembolism

Warfarin (Coumadin®)

Dosage forms

- Tablets:
 - * 1 mg (pink), 2 mg (lavender), 2.5 mg (green), 3 mg (tan), 4 mg (blue), 5 mg (peach), 6 mg (teal), 7.5 mg (yellow), 10 mg (white)
- Injections (intravenous):
 - * 5 mg powder for reconstitution (2 mg/mL)

Mechanism of action

- Inhibits vitamin K epoxide-reductase and vitamin K reductase, preventing the conversion of vitamin K-epoxide to vitamin K; ultimately inhibits formation of vitamin K-dependent coagulation factors II, VII, IX, and X, as well as proteins C and S.

Pharmacokinetics

Absorption

- Bioavailability 80-100% following oral administration
- Absorbed in the upper gastrointestinal tract
- Food/enteral feedings may decrease rate and extent of absorption.

Distribution

- 99.0-99.5% protein bound, primarily to albumin

Metabolism and elimination

- Metabolized in the liver via cytochrome P450 (CYP450) 2C9 (S-(-)-enantiomer) and mixed function CYP450 enzymes to inactive metabolites. Genetic differences in the CYP2C9 gene may significantly affect the activity of this enzyme, thus affecting the dose of warfarin needed for adequate anticoagulation.
- Low extraction pharmacokinetic characteristics
- Clearance decreases with increasing age

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- Half-life: R-(+)-enantiomer, 45 hours; S-(–)-enantiomer, 33 hours

Pharmacodynamics

- The S-isomer is approximately 2-5 times more potent than the R-isomer in inhibiting vitamin K reductase.
- Its pharmacodynamic effect (change in INR) is an indirect effect of the decreased formation of the vitamin K-dependent coagulation factors II, VII, IX, and X. The long half-lives of these factors results in delayed onset of action and delayed response to dosage changes.

Adverse effects

- Bleeding, roughly proportional to the degree of anticoagulation
- Skin necrosis related to depletion of or deficiency of protein C; usually occurs within 10 days of warfarin initiation; the incidence is low.
- Purple-toe syndrome: usually occurs 3-8 weeks after warfarin initiation; the incidence is low.

Some common drug interactions

- Medications decreasing warfarin anticoagulant response:
 - * Rifampin
 - * Barbiturates
 - * Carbamazepine
 - * Phenytoin (chronic therapy)

- * Cholestyramine
- * Griseofulvin
- * Nafcillin

- Medications increasing warfarin anticoagulant response:

- * Amiodarone
- * Propafenone
- * Cimetidine
- * Clofibrate
- * Omeprazole (R-enantiomer)
- * Erythromycin, clarithromycin
- * Metronidazole
- * Trimethoprim-sulfamethoxazole
- * Phenytoin (acute therapy)
- * Allopurinol
- * Phenylbutazone
- * Azole antifungal agents
- * Ciprofloxacin
- * Sulfapyrazole
- * Acetaminophen

Dosing management

- Once-daily dose of 1-10 mg orally; patient response is highly variable.
- Management of elevated INR (Table 2)

Monitoring

- The standard for assessing the degree of anticoagulation is the International Normalized Ratio (INR)

Table 2

Management of Elevated International Normalized Ratio

INR	Significant bleeding	Recommendations
<5.0 but above therapeutic range	No	Lower dose or omit single dose and restart at lower dose
>5.0 and <9.0	No	Omit 1-2 doses, resume at lower dose when the INR is in the therapeutic range; alternatively, omit dose and give 1-2.5 mg vitamin K orally (2-4 mg if urgent surgery is required); restart warfarin at lower dose when the INR is therapeutic or clinically appropriate
>9.0	No	Hold warfarin and give 5-10 mg vitamin K orally; resume warfarin at lower dose when the INR is therapeutic
Serious bleeding at any elevation of INR	Yes	Hold warfarin; give 10 mg vitamin K IV via slow infusion ¹ ; supplement with fresh frozen plasma or prothrombin complex concentrate if necessary; repeat vitamin K 10 mg IV q12h if necessary
Life-threatening bleeding at any elevation of INR	Yes, life-threatening	Hold warfarin; give prothrombin complex concentrate with vitamin K 10 mg via IV slow infusion ¹ ; repeat as necessary

¹Infused over at least 10 minutes.

- $INR = (\text{observed prothrombin ratio})^{ISI}$, where ISI is the International Standardized Index, which corrects for variability in thromboplastin sensitivity
- Initially the INR is monitored every 1-2 days until the desired INR is achieved and has stabilized at a given dose. Periodic INR monitoring (ie, monthly) is recommended thereafter unless dosage changes are made.

Paroxysmal supraventricular tachycardia (PSVT)

Diagnostic criteria and characteristics

- PSVT: rate 160-240 bpm that is abrupt in onset and termination with regular QRS interval; 1:1 AV conduction

Mechanism of arrhythmia

- Reentry

Clinical etiology

- Idiopathic, fever, drug-induced (sympathomimetics, anticholinergics, β -agonists)

Treatment goals (Figure 3)

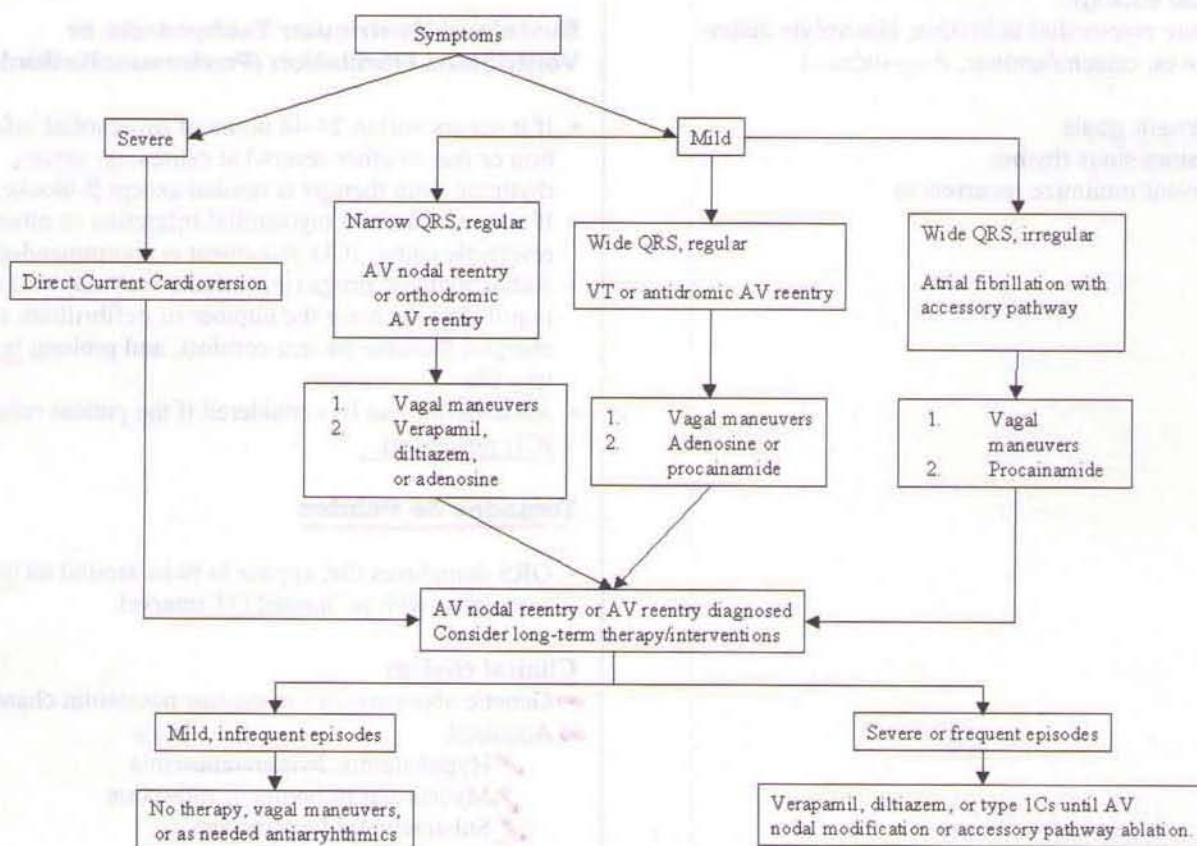
- **Acute:** terminate reentry circuit by prolonging refractoriness and slowing conduction
- **Chronic:** prevent or minimize the number and severity of episodes

*Acute nonpharmacologic therapy

- Vagal maneuvers may terminate PSVT: carotid massage and Valsalva maneuver (most common), squat-

Figure 3.

Treatment algorithm for paroxysmal supraventricular tachycardia.



ting, deep breathing, coughing, inducing eyeball pressure, and diving reflex (less common)

Ventricular Arrhythmias

Major classifications and diagnostic criteria

Ventricular tachycardia (VT)

- Three or more consecutive premature ventricular contractions (PVCs) at rate >100 bpm; wide QRS interval (>0.12 seconds), usually regular pattern
- Nonsustained VT (NSVT): episode lasting <30 seconds
- Sustained VT: episode lasting >30 seconds

Ventricular fibrillation

- Absence of organized cardiac electrical or mechanical activity, no recognizable P waves, QRS complexes, or T waves on the ECG; rapidly results in no effective cardiac output, blood pressure, or pulse

Mechanism of arrhythmia

- Reentry *like it restart more than one time.*

Clinical etiology

- Acute myocardial infarction, electrolyte disturbances, catecholamines, drug-induced

Treatment goals

- Restore sinus rhythm
- Prevent/minimize recurrences

2. Drug and Nondrug Therapy

Nonsustained Ventricular Tachycardia

- Patients with heart disease and ejection fraction $\geq 30\%$
 - * If asymptomatic, no drug therapy is warranted
 - * If symptomatic (palpitations), β -blocker and other therapy to reduce the risk of recurrent cardiovascular events (eg, aspirin, ACE inhibitors, statins)
- Patients with heart disease and ejection fraction $<30\%$
 - * Recent studies indicate these patients are at increased risk for sudden cardiac death (usually from ventricular fibrillation). Use of an implantable cardioverter defibrillator (ICD) improves survival in this group, whereas amiodarone does not affect survival.
 - * Unless contraindicated, these patients should also receive standard background therapy which includes aspirin, ACE inhibitors, β -blockers, statins, and aldosterone antagonists.

Sustained Ventricular Tachycardia or Ventricular Fibrillation (Postresuscitation)

- If it occurs within 24-48 hours of myocardial infarction or due to other reversible causes, no antiarrhythmic drug therapy is needed except β -blockers.
- If not secondary to myocardial infarction or other reversible cause, ICD placement is recommended.
- Antiarrhythmic drugs (ie, amiodarone) may still be required to decrease the number of defibrillator discharges, increase patient comfort, and prolong battery life.
- Amiodarone can be considered if the patient refuses ICD placement.

Torsades de Pointes

- QRS complexes that appear to twist around an axis; associated with prolonged QT interval

Clinical etiology

- Genetic abnormalities in cardiac potassium channels
- Acquired
 - * Hypokalemia, hypomagnesemia
 - * Myocardial ischemia or infarction
 - * Subarachnoid hemorrhage
 - * Hypothyroidism
 - * Myocarditis or cardiomyopathy
 - * Arsenic poisoning

* Drug-induced (known association with torsades de pointes)

- Antiarrhythmics: quinidine, procainamide, disopyramide, sotalol, ibutilide, dofetilide, amiodarone
- Antipsychotics: chlorpromazine, haloperidol, droperidol, mesoridazine, thioridazine, pimozide, quetiapine, risperidone, ziprasidone
- Antidepressants: amitriptyline, desipramine, doxepin, imipramine, nortriptyline
- Antibiotics: erythromycin, clarithromycin, sparfloxacin, gatifloxacin, moxifloxacin, pentamidine, trimethoprim-sulfamethoxazole

Treatment

- Stop the offending drug if possible.
- Administer direct current cardioversion for hemodynamically unstable patients.
- Administer magnesium sulfate 2 g over 1 minute IV.
- Use a pacemaker or isoproterenol infusion to increase heart rate.
- Correct hypokalemia or hypomagnesemia.

Drug therapy (Tables 3, 4, and 5)

- Antiarrhythmic drugs terminate or minimize arrhythmias via:
 - * Decreasing automaticity of abnormal pacemaker tissues
 - * Altering conduction characteristics of reentry
 - Increasing refractory period
 - * Eliminating premature impulses that trigger reentry

Table 3

Effects of Antiarrhythmic Drugs on Cardiac Electrophysiology

Drug class	Ion block	Conduction	Refractory period	Automaticity
Ia	Sodium	↓	↑	↓
Ib	Sodium	0/↓	↓	↓
Ic	Sodium	↓↓	↑	↓
II	Calcium	↓	↑	↓
III	Potassium	0	↑↑	0
IV	Calcium	↓	↑	↓

Sotalol also possesses β -blocking activity.

Amiodarone also possesses sodium and calcium channel blockade.

Patient counseling

- Take medication as prescribed. If a dose is missed, have the patient take the dose as soon as it is remembered, unless it is close to the next scheduled dose. In this case, the patient should skip the missed dose and continue the regular regimen; do not double doses.
- Many drug interactions are possible; patients should inform health care providers of medications prescribed prior to starting new medications, including over-the-counter medications (Table 6).
- Periodic ECG and laboratory assessments may be required to minimize or prevent adverse effects.
- Patients should be educated that complete remission of their arrhythmia is unlikely. However, symptomatic arrhythmias that have increased in frequency or severity should be reported to the physician immediately.
- Patients with atrial fibrillation/flutter should be educated about the importance of antithrombotic therapy as well as the signs and symptoms of stroke. Patients with symptoms including sudden onset of slurred speech, facial drooping, or muscle weakness should seek emergent care.
- Antiarrhythmic drugs that are administered as extended-release formulations should not be crushed, opened, or chewed. Advise patients to swallow the dose whole.

Drug-specific information

Amiodarone

- The FDA now requires that a medication guide be distributed directly to each patient to whom amiodarone is dispensed.
- Visual disturbances are rare but should be reported immediately to the physician.
- Difficulty breathing, shortness of breath, wheezing, or persistent cough should be reported immediately to the physician.
- Nausea or vomiting, passing brown or dark-colored urine, feeling more tired than usual, skin or whites of the eyes turning yellow, or stomach pain should be reported immediately to the physician.
- Cardiac symptoms such as pounding heart, skipping a beat, or very rapid or slow heartbeats, as well as lightheadedness or feeling faint should be reported immediately to the physician.
- Periodic laboratory tests to evaluate thyroid function, liver function, and pulmonary function, as well as diagnostic tests such as chest x-ray, ECG, and eye exams may be necessary to assess and prevent adverse events (Table 7).
- May cause skin photosensitivity. Patients should be advised to wear protective clothing and sunscreen when exposed to sunlight or ultraviolet light.

Table 4

Antiarrhythmic Drug Availability and Standard Dosing Regimens

Generic name (trade name)	Dosage forms	Loading dose	Maintenance dose
Class Ia			328-648 mg PO tid
Quinidine gluconate (Quinaglute Dura-Tabs, Duraquin, Quinalan, Quinatime)	324-mg tablets 80-mg/mL inj	IV: not recommended	
Quinidine sulfate (Quinidex Extentabs, Cin-Quin, Quinora)	200-, 300-mg tablets	PO: 200 mg q 2-3 h for 5-8 doses (sulfate salt only)	200-400 mg PO qid
Quinidine polygalacturate (Cardioquin)	275-mg tablets		275 mg PO bid-tid
Procainamide (Procanbid, Pronestyl)	IR: 250-, 375-, 500-mg capsules/tablets SR: 250-, 500-, 750-, 1000-mg tablets 100- and 500-mg/mL inj	IV: 15-18 mg/kg at 20-50 mg/min	IV: 1-6 mg/min PO: up to 50 mg/kg divided q3-6h for immediate release; divided q6h for sustained release
Disopyramide (Norpace, Norpace CR)	100-, 150-mg capsules 100-, 150-mg capsules		150-300 mg q6h 300-600 mg q12h
Moricizine (Ethmozine)	200-, 250-, 300-mg tablets		200-300 mg q8h
Class Ib			
Lidocaine	10 mg/mL (5 mL and 10 mL) 20 mg/mL (5 mL) IV infusion: 2 (500 mL), 4 (250, 500, 1000 mL), 8 (250, 500 mL) mg/mL in D ₅ W	IV: 100 mg repeat up to 2 times	IV: 1-4 mg/min
Tocainide (Tonocard)	400-, 600-mg tablets		400-600 mg q8h
Mexiletine (Mexitil)	150-, 200-, 250-mg capsules		100-300 mg q8h
Class Ic			
Flecainide (Tambocor)	50-, 100-, 150-mg tablets		50-200 mg q12h
Propafenone (Rythmol)	150-, 225-, 300-mg tablets		150-300 mg q8h
Class II: β-blockers			
Metoprolol (Lopressor, Toprol XL)	50-, 100-mg tablets 25-, 50-, 100-, 200-mg tablets; 1-mg/mL injection	IV: 2.5-5 mg up to 3 doses	25-450 mg PO daily
Propranolol (Inderal, Inderal LA)	10-, 20-, 40-, 60-, 80-mg tablets 60-, 80-, 120-, 160-mg capsules 20-, 40-mg/mL oral solution 1-mg/mL (5 mL) injection	IV: 0.15 mg/kg IV: 0.5 mg/kg	PO: 80-240 mg daily
Esmolol (Brevibloc)	10- and 250-mg/mL injection	0.5 mg/kg/min x 1 min	IV: 0.05-0.2 mg/kg/min
Class III			
Bretylium (Bretylol)	50 mg/mL (10 and 20 mL) for injection In D ₅ W 2 mg/mL (250 mL), 4 mg/mL (250, 500 mL)		IV: 1-4 mg/min
Amiodarone (Cordarone)	200-, 400-mg tablets 50-mg/mL IV solution	800-1600 mg/d in divided doses x 2-4 weeks IV (VT/VF): 150 mg/10 min or 900 mg in 500 mL D ₅ W at 1 mg/min x 6 h IV (cardiac arrest): 300 mg	PO: 100-400 mg qd IV: 0.5 mg/min

(continued)

Table 4

Antiarrhythmic Drug Availability and Standard Dosing Regimens (continued)

Generic name (trade name)	Dosage forms	Loading dose	Maintenance dose
Sotalol (Betapace, Betapace AF)	80-, 120-, 160-, 240-mg tablets		80-320 mg q12h N/A
Ibutilide (Corvert)	0.1-mg/mL (10 mL) injection	1.0 mg IV over 10 min; repeat x 1 if needed	
Dofetilide (Tikosyn)	125-, 250-, 500-mcg capsules		CrCl >60 mL/min = 500 mcg bid; 40-60 mL/min = 250 mcg bid; 20-39 mL/min = 125 mcg bid; <20 mL/min = not recommended
Class IV: calcium channel blockers			
Verapamil (Calan, Calan SR, Isoptin SR, Covera-HS, Verelan, Verelan-PM)	40-, 80-, 120-mg tablets 120-, 180-, 240-mg tablets 180-, 240-mg tablets 120-, 180-, 240-, 360-mg capsules 100-, 200-, 300-mg capsules	2.5-10 mg IV over 2 min	PO: 120-360 mg/d IV: 5-15 mg/h Calan: tid-qid Calan SR, Isoptin SR, Covera-HS, Verelan: qd
Diltiazem (Cardizem, Cardizem CD, Cardizem Monovial, Cardizem Lyo-Ject, Cardizem SR, Cartia XT, Dilacor XR, Diltia XT, Tiazac)	30-, 60-, 190-, 120-mg tablets; 25-mg/mL injection 120-, 180-, 240-, 300-, 360-mg capsules 100-mg/mL injection 25-mg injection 60-, 90-, 120-mg capsules 120-, 180-, 240-, 300-mg capsules 120-, 180-, 240-mg tablets 120-, 180-, 240-, 300-mg capsules	20 mg IV over 2 min	IV: 5-15 mg/h; PO: 120-360 mg/d Cardizem: qid Cardizem SR: bid Cardizem CD, Dilacor XR, Tiazac: qd
Miscellaneous			
Atropine	0.1-, 0.3-, 0.4-, 0.5-, 0.8-, 1.0-mg/mL injection	0.5-1.0 mg q 5 min up to 3 mg total	
Adenosine (Adenocard)	3-mg/mL injection	IV and PO: 0.25 mg q 2 h up to 1.5 mg	Initial dose: 6 mg IV bolus; if necessary, can be followed by 12 mg q 2 min as IV bolus; flush IV line after each administration
Digoxin (Lanoxin)	125-, 250-, 500-mcg tablets 50-mcg/mL elixir 100-, 250-mcg/mL injection		IV and PO: 0.125-0.375 mg qd
Digoxin (Lanoxicaps)	50-, 100-, 200-mcg capsules		

- Prolonged use may cause blue-gray skin discoloration.
- Tell your doctor and pharmacist about all the other medicines you take including prescription and non-

prescription medicine, vitamins, and herbal supplements.

- Frequent administration with grapefruit juice may increase oral absorption. Encourage patients to drink

Table 5

Pharmacokinetics of Antiarrhythmic Drugs

Drug	Bioavailability (%)	Protein binding (%)	Primary route of elimination	Substrate for	Inhibitor of	Half-life	Therapeutic range (mg/L)
Quinidine	70-80	80-90	Hepatic	CYP 3A4	CYP 2D6, CYP 3A4, P-gp	5-9 h	2-6
Procainamide	75-95	10-20	Hepatic/renal	NAT		2.5-5.0 h	4-15
Disopyramide	70-95	50-80	Hepatic/renal	CYP 3A4		4-8 h	2-6
Moricizine	34-38	92-95	Hepatic			1-6 h	
Lidocaine	20-40	65-75	Hepatic	CYP 3A4, CYP 2B6, CYP 1A2	CYP 1A2	60-180 min	1.5-5.0
Tocainide	90-95	10-30	Hepatic			12-15 h	4-10
Mexiletine	80-95	60-75	Hepatic	CYP 2D6, CYP 1A2	CYP 1A2	6-12 h	0.8-2.0
Flecainide	90-95	35-45	Hepatic/renal	CYP 2D6	CYP 2D6	13-20 h	0.3-2.5
Propafenone	11-39	85-95	Hepatic	CYP 2D6, CYP 1A2, CYP 3A4	CYP 2D6	12-32 h	
Bretium	15-20	0	Renal	CYP 3A4		5-10 h	0.5-2.0
Amiodarone	22-88	95-99	Hepatic	CYP 3A4	CYP 1A2, CYP 2C9, CYP 2D6, CYP 3A4, P-gp	15-100 d	1.0-2.5
Sotalol	90-95	30-40	Renal			12-20 h	
Ibutilide		40	Hepatic			6	
Dofetilide	>90	60-70	Renal	CYP 3A4		8-10 h	
Digoxin	60-85 (90-100 for lanicaps)	20-30	Renal	P-gp		34-44	0.5-2.2 ng/mL
Diltiazem	35-50	70-85	Hepatic	CYP 3A4	CYP 3A4, P-gp	4-10 h	>0.05
Verapamil	20-40	95-99	Hepatic	CYP 3A4, CYP 1A2	CYP 3A4, P-gp	4-12 h	>0.05

CYP, cytochrome P450 isoenzyme; P-gp, P-glycoprotein.

water with amiodarone or separate grapefruit juice consumption by at least 2 hours.

β-Blockers (including sotalol)

- Patients with asthma and chronic obstructive pulmonary disease should be advised that β-blockers may worsen their symptoms of airway disease. Advise patients to notify physician immediately if this occurs.
- Patients with diabetes should be advised that β-blockers may mask symptoms of hypoglycemia.
- Patients should avoid abrupt withdrawal of β-blocker therapy. If withdrawal of β-blocker therapy is desired, the patient should contact the physician for the dosage tapering regimen, if necessary.

Digoxin

- Refer to "Heart Failure" chapter.

Warfarin

- Warfarin should be avoided at any time during pregnancy.
- To determine the correct dosage, your physician may need to check your blood regularly.
- Encourage patients to maintain consistency in their diet. Abrupt changes, particularly in the intake of green leafy vegetables, may alter the effectiveness of warfarin.
- Minor cuts may take longer to stop bleeding. If a cut or injury fails to stop bleeding, contact your health care provider.
- Excessive alcohol intake may alter the effectiveness of this medication.
- Tell your doctor and pharmacist about all the other medicines you take including prescription and non-prescription medicine, vitamins, and herbal supplements.

Table 6

Antiarrhythmic Drug Interactions and Significant Adverse Effects

Drug	Effect of disease/drugs on antiarrhythmic drug concentrations	Effect of antiarrhythmic on other drug concentrations	Common or severe adverse effects
Quinidine	Elevated: cimetidine, amiodarone, verapamil, diltiazem, ketoconazole, urine alkalinization; reduced: enzyme inducers	Elevated: warfarin, digoxin, β -blockers, disopyramide, procainamide, propafenone, mexiletine, flecainide	QTc prolongation, torsades de pointes, diarrhea
Procainamide	Elevated: cimetidine, trimethoprim, amiodarone		Lupus-like syndrome, QTc prolongation, torsades de pointes, hypotension, dizziness, blurred vision, GI distress
Disopyramide	Reduced: enzyme inducers; elevated: erythromycin, protease inhibitors, cimetidine		Anticholinergic side effects, decreased cardiac contractility, heart failure, QTc prolongation, torsades de pointes, hypoglycemia
Moricizine	Elevated: cimetidine	Elevated: theophylline	Dizziness, nausea, paresthesias, proarrhythmia
Lidocaine	Increased: with decreased cardiac output		CNS toxicity: paresthesias, dizziness, confusion, nausea and vomiting, seizures
Tocainide	Decreased: cimetidine, enzyme inducers		GI distress; CNS: dizziness, paresthesias, confusion, seizures; pulmonary fibrosis/pneumonitis; agranulocytosis
Mexiletine	Reduced: enzyme inducers; elevated: quinidine, amiodarone, ritonavir	Elevated: theophylline	GI distress; CNS: tremor, dizziness, confusion, vertigo, nystagmus, diplopia; hypotension, sinus bradycardia, AV block
Flecainide	Elevated: cimetidine, amiodarone	Elevated: digoxin	Proarrhythmia, prolonged PR interval and QRS complex; dizziness, blurred vision, heart failure
Propafenone	Reduced: enzyme inducers; elevated: cimetidine, quinidine	Elevated: warfarin, digoxin, cyclosporine, theophylline	Metallic/bitter taste; CNS: dizziness, paresthesias, fatigue; GI distress; heart failure, liver injury, agranulocytosis
Bretium			Adrenergic blocking effects: initial hypertension followed by hypotension; GI distress; hyperthermia
Amiodarone ¹		Elevated: quinidine, procainamide, warfarin, digoxin, phenytoin, cyclosporine, lovastatin, simvastatin	IV: phlebitis; general: corneal microdeposits, photophobia, increased liver enzymes, photosensitivity, blue-gray skin discoloration, pulmonary fibrosis, hyper- and hypothyroidism, polyneuropathy
Sotalol			β -blocking effects: bradycardia, fatigue, dyspnea, bronchospasm, heart failure; QTc prolongation, torsades de pointes
Ibutilide			QTc prolongation, torsades de pointes
Dofetilide	Elevated: verapamil, cimetidine, ketoconazole, trimethoprim, megestrol, prochlorperazine		QTc prolongation, torsades de pointes
Digoxin	Elevated: quinidine, amiodarone, verapamil, diltiazem		
Diltiazem	Elevated: cimetidine	Elevated: cyclosporine, carbamazepine, digoxin	Hypotension, bradycardia, heart failure
Verapamil	Reduced: rifampin, phenobarbital	Elevated: theophylline, digoxin, carbamazepine, cyclosporine	Hypotension, bradycardia, heart failure, constipation

¹See Table 7.

Table 7

Suggested Monitoring Guidelines for Amiodarone

Test	Baseline	3 Months	6 Months	12 Months
Electrocardiogram	•	•	•	•
Pulmonary function tests	•	Routine monitoring controversial; may repeat tests if patient becomes symptomatic		
Ophthalmologic examination	•	Periodic exam recommended		
Chest x-ray	•	•	•	•
Thyroid function tests	•	•	•	•
Liver enzymes	•	•	•	•

3. Key Points

- All antiarrhythmic drugs are proarrhythmic.
- Cardiac arrhythmias range from benign to lethal.
- Antiarrhythmic drug therapy should be individualized to patient response while minimizing adverse effects.
- Most antiarrhythmic drugs are hepatically eliminated and are associated with significant drug interactions.
- Nonpharmacologic therapy is an important treatment modality, particularly for life-threatening ventricular tachycardia and ventricular fibrillation.
- Treatment of atrial fibrillation should always include an assessment of antithrombotic therapy.
- Direct current cardioversion is typically the treatment of choice for severely symptomatic arrhythmias.
- Anticoagulant response to warfarin therapy is influenced by numerous factors, including diet, drug interactions, and disease.
- The treatment of excessive anticoagulation secondary to warfarin should be based on the INR, the presence of active bleeding, and the risk of recurrent thromboembolism.
- Patient education and appropriate monitoring are important aspects of successful therapy while minimizing adverse effects.

4. Questions and Answers

- Which of the following is (are) an adverse effect(s) of orally administered amiodarone?
 - Gastrointestinal upset
 - Pulmonary fibrosis
 - Phlebitis
 - I only
 - III only
 - I and II only
 - II and III only
 - I, II, and III
- Which of the following antiarrhythmic agent's mechanism of action is primarily the result of sodium ion transport blockade?
 - Quinidine
 - Ibutilide
 - Sotalol
 - Verapamil
 - Diltiazem
- First-degree atrioventricular heart block can be categorized as a disorder of
 - automaticity
 - reentry
 - conduction
 - I only
 - III only
 - I and II only
 - II and III only
 - I, II, and III

4. Each of the following can be symptoms of atrial fibrillation except
 - A. dizziness
 - B. palpitations
 - C. angina
 - D. hypertension
 - E. sudden-onset slurred speech
5. Each of the following are recommended monitoring tools for patients requiring chronic amiodarone therapy except
 - A. electrocardiogram
 - B. coagulation tests
 - C. thyroid function tests
 - D. liver function tests
 - E. chest x-ray
6. For the treatment of persistent atrial fibrillation, each of the following patients should receive chronic warfarin therapy with a target INR 2.0-3.0 except for
 - A. patients with heart failure
 - B. patients ≥ 65 years old with hypertension
 - C. a 50-year-old male with no risk factors for thromboembolism
 - D. a 77-year-old female with diabetes
 - E. a 63-year-old male who has had a previous stroke
7. Patients with which type of arrhythmia should be educated on performing vagal maneuvers to restore sinus rhythm?
 - A. Paroxysmal supraventricular tachycardia
 - B. Torsades de pointes
 - C. Atrial flutter
 - D. Sinus bradycardia
 - E. Ventricular fibrillation
8. In the absence of an acute myocardial infarction, what is the treatment of choice for resuscitated patients with sustained ventricular tachycardia?
 - A. β -Blocker
 - B. Amiodarone
 - C. No antiarrhythmic therapy
 - D. Digoxin
 - E. Implantable cardioverter defibrillator (ICD)
9. Which of the following medications is (are) associated with torsades de pointes?
 - I. Dofetilide
 - II. Droperidol
 - III. Erythromycin
 - A. I only
 - B. III only
 - C. I and II only
 - D. II and III only
 - E. I, II, and III
10. Which of the following would result in the greatest risk of lidocaine toxicity?
 - A. Rifampin
 - B. Cimetidine
 - C. Amiodarone
 - D. Heart failure
 - E. Bradycardia
11. What is the recommended dosage regimen for dofetilide in a patient with a calculated creatinine clearance of 30 mL/min?
 - A. Dofetilide therapy not recommended
 - B. 125 mcg PO bid
 - C. 125 mg PO bid
 - D. 500 mcg PO bid
 - E. 500 mg PO bid
12. Quinidine is metabolized by and inhibits the metabolism of which cytochrome P450 enzymes, respectively?
 - A. CYP 3A4 and CYP 2D6
 - B. CYP 2D6 and CYP 3A4
 - C. P-gp and CYP 2D6
 - D. P-gp and CYP 3A4
 - E. CYP 1A2 and CYP 3A4
13. Which of the following antiarrhythmic agents does not increase digoxin concentrations when used concomitantly?
 - A. Quinidine
 - B. Lidocaine
 - C. Amiodarone
 - D. Diltiazem
 - E. Verapamil
14. J.S. is a 66-year-old male with a past medical history of congestive heart failure and hypertension for which he is receiving lisinopril 10 mg PO qd, digoxin 0.25 mg PO qd, and spironolactone 25 mg PO qd at home. J.S. now presents to the emergency room with a 1-week history of intermittent palpitations and dizziness. A stat ECG reveals atrial fibrillation with a

ventricular rate of 130 bpm. The decision is made to attempt to restore normal sinus rhythm. Which of the following represents the best therapeutic approach to cardioverting this patient?

- A. Perform transesophageal echocardiography; if no thrombus is present, cardiovert; no need for anticoagulation
 - B. Perform transesophageal echocardiography; if no thrombus is present, cardiovert; anticoagulate for at least 4 weeks post-cardioversion
 - C. Anticoagulate for 4 weeks prior to cardioversion; discontinue anticoagulation post-cardioversion
 - D. Anticoagulate for 2 weeks prior to cardioversion; continue anticoagulation for at least 4 weeks post-cardioversion
 - E. Direct current cardiovert immediately
15. After the initial successful cardioversion, J.S. continues to have recurrent atrial fibrillation episodes. Chronic therapy to maintain sinus rhythm is to be initiated. Which of the following antiarrhythmic drugs would be the best choice to maintain sinus rhythm?
- A. Flecainide
 - B. Amiodarone
 - C. Sotalol
 - D. Ibutilide
 - E. Esmolol
16. In a patient with mildly symptomatic paroxysmal supraventricular tachycardia, verapamil should be used for which rhythm(s)?
- I. Narrow QRS complex, regular interval
 - II. Wide QRS complex, regular interval
 - III. Wide QRS complex, irregular interval
- A. I only
 - B. III only
 - C. I and II only
 - D. II and III only
 - E. I, II, and III
17. R.J. is a 53-year-old male with a past medical history of coronary artery disease and hypertension. He presents to his doctor complaining of short (about 10 seconds in duration), intermittent palpitations during the last 2 days. Tests rule out an acute myocardial infarction and an echocardiogram shows a left ventricular ejection fraction of 52%. The patient is sent home with a Holter monitor to identify

any arrhythmias. The Holter monitor reveals episodes of ventricular tachycardia. What is the most appropriate intervention for R.J.?

- A. No therapy
 - B. Place an implantable cardioverter defibrillator (ICD)
 - C. Start amiodarone
 - D. Start a β -blocker
 - E. Direct current cardioversion
18. Treatment of torsades de pointes may include all of the following except
- A. discontinue any drugs associated with prolonged QT interval
 - B. isoproterenol infusion
 - C. adenosine
 - D. magnesium sulfate
 - E. atrial/ventricular pacing
19. Which of the following antiarrhythmic agents has anticholinergic properties?
- A. Sotalol
 - B. Amiodarone
 - C. Lidocaine
 - D. Disopyramide
 - E. Propafenone
20. Which of the following is not a characteristic of atrial fibrillation?
- A. No discernable P waves
 - B. Ventricular rate 100-130 bpm
 - C. Regular QRS pattern
 - D. Narrow QRS complex
 - E. Chaotic atrial contractions
21. Which of the following would be the best choice for ventricular rate control in atrial fibrillation secondary to hyperthyroidism?
- A. Adenosine
 - B. Digoxin
 - C. Verapamil
 - D. Propranolol
 - E. Atropine
22. A dose-limiting adverse effect of sotalol is
- A. bradycardia
 - B. polyneuropathy
 - C. metallic taste
 - D. agranulocytosis
 - E. lupus-like syndrome

23. Which of the following is not available in both intravenous and oral dosage forms?
- Procainamide
 - Amiodarone
 - Verapamil
 - Digoxin
 - Ibutilide
24. Warfarin dosage adjustment should be considered for the following drugs, except for
- amiodarone
 - sotalol
 - quinidine
 - propafenone
 - diltiazem
5. B. See Table 7 for recommended monitoring parameters and schedule. Coagulation tests are not routinely recommended for patients receiving amiodarone therapy. Coagulation tests may be required if a patient develops severe hepatotoxicity secondary to amiodarone or simply requires concomitant warfarin therapy for atrial fibrillation.
6. C. Patients under age 65 with no thromboembolic risk factors are at low risk of stroke and should be treated with aspirin 325 mg/day rather than warfarin.
7. A. Vagal maneuvers are effective nonpharmacologic therapy for PSVT since the reentry impulse circuit exists in the atrioventricular node. Although vagal maneuvers will slow the rate in atrial fibrillation/flutter, it will not terminate the arrhythmia since the reentry circuit is in the atrial tissue. Vagal maneuvers will have no effect on ventricular arrhythmia since the impulse arises from below the AV node.

Answers

- C. Gastrointestinal upset is common, particularly with larger oral doses (ie, during the loading dose phase), and pulmonary fibrosis occurs during prolonged therapy. Phlebitis would only be expected to occur during intravenous amiodarone infusion, particularly through a peripheral intravenous line. To decrease risk of phlebitis, a central line is preferred.
- A. Quinidine blocks sodium entry into the cardiac cell, slowing depolarization. Ibutilide and sotalol act primarily by blocking potassium transport, whereas verapamil and diltiazem inhibit the calcium channel.
- B. Atrioventricular heart block is caused by slowed conduction through the atrioventricular node.
- D. Due to loss of functional atrial contraction and rapid ventricular rate (producing palpitations), cardiac output may decrease, resulting in decreased perfusion of major organs, particularly the brain (dizziness, confusion, etc) and heart (angina and heart failure exacerbation). Depending on the vascular tone, blood pressure may remain stable or fall as a direct result of decreased cardiac output; however, hypertension would not be expected. Patients with atrial fibrillation are at increased risk of thrombosis, particularly stroke, secondary to pooling of blood in the left atrium and subsequent thrombus formation.
- E. Based on the results of several clinical trials, implantable cardioverter defibrillator (ICD) treatment has a significant mortality benefit over antiarrhythmic drug therapy alone. Antiarrhythmic therapy may be considered if the patient refuses surgical placement of the ICD or to decrease the number of discharges from the ICD if recurrences are frequent.
- E.
- D. Lidocaine is nearly 100% metabolized in the liver. Lidocaine metabolism is dependent upon liver blood flow rather than enzymatic activity (ie, high extraction ratio). Therefore, poor cardiac output secondary to congestive heart failure may decrease lidocaine delivery to the liver for metabolism. Bradycardia typically does not decrease cardiac output secondary to a compensatory increase in left ventricular stroke volume.
- B. Dofetilide is renally eliminated and therefore must be adjusted to decrease the significant risk of torsades de pointes.
- A.
- B.

14. **B.** Since the patient appears to have been in atrial fibrillation for 1 week by history, there is a significant risk of thromboembolism during conversion to sinus rhythm. Proper treatment would require at least 3-4 weeks of anticoagulation (warfarin INR 2-3) prior to cardioversion, followed by at least 4 weeks of anticoagulation post-cardioversion. Alternatively, a transesophageal echocardiogram can be used to rule out an atrial thrombus, allowing immediate cardioversion. Since the atria will require time to recover normal contractile activity, anticoagulation will be required for at least 4 weeks post-conversion.
15. **B.** Since the patient has heart failure, the results of the CAST trials indicate the avoidance of class Ic agents due to increased risk of death. Sotalol may worsen heart failure. Ibutilide is indicated for chemical conversion only, not for maintenance of sinus rhythm. Esmolol will only control the ventricular rate but will have no effect on maintaining sinus rhythm.
16. **A.** A wide QRS complex signifies conduction via an accessory pathway other than the AV node. Since calcium channel blockers prolong conduction in the AV node and not in the accessory pathways, administration of these agents will block the AV node and force impulses to be conducted via the accessory pathways, which have shorter refractory periods. Consequently, the ventricular response will significantly increase.
17. **D.** According to the patient's presentation, he has nonsustained ventricular tachycardia, since the duration of each event is less than 30 seconds. Since he is symptomatic and has no heart failure, the treatment of choice is β -blocker therapy.
18. **C.** Adenosine is typically only used to terminate paroxysmal supraventricular tachycardia. Discontinuation of drugs that prolong the QT interval is essential to terminate torsades de pointes and prevent recurrences. Treatment should consist of intravenous magnesium sulfate and electrical pacing. An isoproterenol infusion can be used while waiting for electrical pacing.
19. **D.**
20. **C.** Atrial fibrillation represents chaotic atrial activity resulting in no identifiable P wave. Since atrial fibrillation originates above the AV node, the QRS complex is narrow and the ventricular rate is typically >100 bpm.
21. **D.** β -Blockers are the preferred rate-controlling agent for hyperthyroidism since they inhibit the adrenergic response and decrease thyroid hormone conversion (especially propranolol). Digoxin is not as effective in controlling the ventricular rate related to an hyperadrenergic state (hyperthyroidism).
22. **A.** Sotalol possesses significant β -blocking activity and therefore the patient may experience adverse effects similar to traditional β -blockers.
23. **E.**
24. **B.** Warfarin is metabolized via multiple cytochrome P450 isoenzymes, including CYP 2C9, CYP 1A2, and CYP 3A4. Amiodarone inhibits CYP 2C9, CYP 1A2, and CYP 3A4, quinidine via unknown mechanisms, propafenone via CYP 1A2 and CYP 3A4, and diltiazem via CYP 3A4. Sotalol is primarily renally eliminated and does not result in cytochrome P450-mediated drug interactions.

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11. Ischemic Heart Disease

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1. Introduction

Definitions

Ischemia

- Lack of oxygen from inadequate perfusion due to an imbalance between oxygen supply and demand

Ischemic heart disease (IHD)

- Disease caused most frequently by atherosclerosis
- May present as silent ischemia, chest pain (at rest or on exertion), or myocardial infarction (MI)

Angina

- Syndrome described as discomfort or pain in the chest, arm, shoulder, back, or jaw
- Frequently worsened by physical exertion or emotional stress and usually relieved by sublingual (SL) nitroglycerin (NTG)
- Patients with angina usually have coronary artery disease (CAD) in at least one large epicardial artery.

Atypical angina

- Transient pain or discomfort lacking one or more of the criteria of classic angina
- More common presentation for women

Acute coronary syndrome (ACS)

- ACS encompasses the following:
 - * Unstable angina (UA)
 - * Non ST-segment myocardial infarction (NSTEMI)
 - * ST-segment myocardial infarction (STEMI)

Coronary artery disease (CAD)

- Chronic disorder that typically cycles in and out of the clinically defined phases of ACS and asymptomatic, stable, or progressive angina

Percutaneous coronary intervention (PCI)

- Procedure to reopen a partially or completely occluded coronary vessel to restore blood flow

Coronary artery bypass graft (CABG)

- Surgical procedure in which a vein is harvested from the leg and attached to the heart as a new coronary vessel in order to bypass a diseased vessel

Epidemiology of IHD

- Leading cause of death in the U.S.
- Causes more deaths than the next five leading causes combined (cancer, chronic lower respiratory diseases, accidents, diabetes mellitus, influenza and pneumonia)

- Approximately 61 million Americans have some type of cardiovascular (CV) disease, which includes high blood pressure, coronary heart disease (CHD), heart failure, stroke, and congenital defects.
- Approximately 950,000 Americans die of CV disease per year; nearly 2600/day.
- Every 34 seconds an American will die of heart disease or stroke.
- Approximately every 26 seconds an American will suffer a coronary event and every minute someone will die from one.
- In 2002, there were 4,648,000 visits to emergency departments and 80,092,000 physician office visits with a primary diagnosis of CV disease.
- In 2005, the estimated direct and indirect cost of CV disease is \$393.5 billion.
- CHD, which includes AMI, angina, atherosclerotic CVD, and all forms of chronic ischemic heart disease, is the single largest killer of American men and women. CHD caused 1 of every 5 deaths in the U.S. in 2002.
- In 2005, an estimated 700,000 people will have a new coronary attack. About 500,000 will have a recurrent attack and approximately 175,000 silent attacks occur per year.

2. Normal Physiology versus Pathophysiology

Normal Physiology

- The arterioles change their resistance and dilate as needed to enable the heart to receive a fixed amount of O_2 .
- In response to physical exertion, an increase in blood pressure (BP), or an increase in myocardial oxygen demand (MVO_2), the arterioles dilate to maintain O_2 supply to the heart.
- **Note:** In atherosclerosis, plaque narrows the conductance vessel causing the arterioles to dilate under normal or resting conditions to prevent ischemia. With stress or exercise, the vasodilator response is minimal, which causes ischemia and angina.

Pathophysiology

Determinants of MVO_2

- Heart rate (HR)
 - * Tachycardia will increase MVO_2 .
- Contractility
 - * Increases will increase MVO_2 .
- Myocardial wall tension
 - * Dependent on ventricular volume and pressure
 - * Increased pressure or enlargement of the ventricle will increase systolic wall force and increase MVO_2 .

Determinants of Myocardial Oxygen Supply and Flow

- Limits of flow: thrombi, spasm, congenital abnormalities, severe anemia, and severe ventricular hypertrophy due to hypertension (HTN) or aortic stenosis (abnormally high oxygen demands)
- Autoregulation of coronary blood flow
 - * Adenosine, a potent vasodilator, is released from myocardial cells in response to decreased O_2 supply (ie, occlusion), increased sympathetic activity (exercise, mental stress, exposure to cold), increased BP, and increased HR, which leads to increased MVO_2 .
- Normal arteries respond to increased demand with increased blood flow and some vasodilation of the large epicardial vessels.
 - * Note: Atherosclerotic vessels lose this vasodilator response and develop constriction.
- Vascular endothelium
 - * Protective surface of the artery wall
 - * Promotes smooth muscle relaxation and inhibits thrombogenesis

* If damaged, the endothelium produces nitric oxide (NO) which produces vasodilation similar to the therapeutic effects of nitroglycerin (NTG).

* Loss of the vascular endothelium due to primary transcatheter coronary angioplasty (PTCA), cigarettes, oxidized LDL, HTN, or atherosclerosis results in loss of NO and the defense mechanism.

• Diastole

* Normally, the distribution of blood flow between the epicardial and endocardial layers is equal during the period when coronary artery filling occurs.

* In atherosclerosis, there is a reduction in subendocardial blood flow.

• Coronary vasospasm

* Reduces blood flow, thereby causing ischemia in areas of atherosclerotic plaques

• Atherosclerosis

* Most common cause of myocardial ischemia

* Decrease in the lumen of coronary arteries due to stenosis leads to reduced myocardial perfusion and subsequent ischemia.

* Segmental atherosclerotic narrowing is most commonly caused by a plaque, which can fissure, hemorrhage, and cause thrombosis, which then worsens the obstruction, reduces blood flow further, and leads to ACS.

3. Diagnostic Procedures

- History and physical examination
- Laboratory work-up (Table 1)
- Resting ECG

Exercise Tolerance Test (ETT, Treadmill)

Drugs that can interfere with test

- Digoxin causes abnormal exercise-induced ST depression in ~30% of healthy patients.
- β -Blockers and vasodilators alter hemodynamic response to BP.
 - * Hold 4-5 half-lives before ETT
 - * Withdraw β -blockers gradually to avoid precipitating an attack.
- Nitrates can attenuate angina.
- Flecainide may cause exercise-induced ventricular tachycardia.

Stress Imaging

Thallium treadmill (exercise thallium test)

Pharmacologic stress imaging

- Drugs "do the exercise" by increasing MVO_2 .

Dobutamine

- High doses up to 40 mcg/kg/min cause positive inotropic and chronotropic effects which increase cardiac demand as a result of positive inotropic and chronotropic effects and lead to ischemia.
- Commonly used with ECHO. Side effects (SE) include nausea, anxiety, tremor, arrhythmias, angina, and headache.

Dipyridamole and adenosine

- Induce coronary vasodilation; used in conjunction with myocardial perfusion scintigraphy

- Dipyridamole SEs occur in up to 50% of patients: angina, headache, nausea, dizziness, flushing, and severe bronchospasm in patients with COPD or asthma.
- Adenosine SEs occur in up to 80% of patients: chest pain, headache, flushing, shortness of breath (SOB), first-degree AV block, and severe bronchospasm in patients with COPD or asthma.

Drug interactions

- Xanthines (theophylline, caffeine) are adenosine receptor antagonists that attenuate the effects of adenosine and dipyridamole.
- β -Blockers interact with dobutamine, but the interaction can be overcome by increasing the dose of dobutamine.

Cardiac Catheterization (Cath, Angiography)

- A catheter is inserted into the femoral artery and guided to the heart.
- Radiocontrast dye is injected directly into the coronary arteries.
- The dye shows which arteries are involved and the extent of occlusion.
- Complications
 - * Allergic reaction to iodine in the dye
 - * Dye is nephrotoxic.
 - * Arterial bleeding from access site, stroke, MI, death (rare)

Table 1

Pertinent Laboratory Tests in Ischemic Heart Disease

Complete blood cell count (CBC) with platelet count
 Serial creatine kinase-myocardial bound (CK-MB) and troponin levels
 (enzyme markers specific for myocardial necrosis)
 Activated partial thromboplastin time (aPTT)
 Prothrombin time (PT) and international normalized ratio (INR)
 Fasting lipid panel (FLP) within 24 hours of admission

4. Chronic Stable Angina, Prinzmetal's (or Variant) Angina, and Silent Ischemia

Clinical Presentation

Chronic stable angina

- Symptoms are caused by decreased O_2 supply due to reduced flow.
- Considered stable if symptoms have been occurring for several weeks without worsening (Table 2)

Prinzmetal's or variant angina (uncommon)

- Usually due to spasm without increased MVO_2
- Most patients have severe atherosclerosis.
- Characterized by recurrent, prolonged attacks of severe ischemia
- Patients are often between 30 and 40 years old.
- Pain usually occurs at rest or awakens the patient from sleep.
- Electrocardiogram (ECG) shows ST segment elevation, which returns to baseline when the patient is given NTG.

Silent ischemia

- Ischemia in the absence of symptoms.
- ~75% of ischemic episodes in patients with stable angina are undetected.
- ECG shows ST segment changes and there is elevation or depression during activity, but patient experiences no symptoms.
- Occurs in ~20-30% of post-MI patients
- 50% of patients with stable angina have silent ischemia; common in diabetics

Table 2

Characteristics of Stable Angina

1. Pain located over sternum and may radiate to left shoulder or arm, jaw, back, right arm, or neck
2. Description of symptoms: pressure or heavy weight on chest, burning, tightness, deep, squeezing, aching, vise-like, suffocating, crushing
3. Duration of 0.5-30 minutes
4. Precipitating factors: exercise, cold weather, postprandial, emotional stress, sexual activity
5. Pain relief: sublingual (SL) nitroglycerin or rest

Pharmacologic Management

Chronic stable angina

Goals of therapy:

- Prevent MI and death
- Reduce symptoms of angina and occurrence of ischemia to improve quality of life

Agents

Antiplatelets

- Aspirin decreases the incidence of MI, adverse CV events, and sudden death.
- Clopidogrel (Plavix®) has a greater antithrombotic effect than ticlopidine (Ticlid®) and has fewer SEs.
- **Note:** Ticlopidine has not been shown to reduce CV events in stable angina.
- Indications for therapy (Table 3)

Table 3

Antiplatelet Use in Stable Angina

- Aspirin (75-325 mg qd) in all patients with acute and chronic IHD (with or without symptoms) in the absence of contraindications
- Clopidogrel is chosen when aspirin is absolutely contraindicated
- Ticlopidine is not recommended due to poor side-effect profile
- The combination of clopidogrel plus aspirin is not indicated in patients with stable disease not undergoing PCI

Anti-ischemic therapy

β-Blockers (BBs)

- Effects on MVO_2
 - * Inhibit catecholamine effects, thereby decreasing MVO_2
 - * Decrease HR (negative chronotrope-decreases conduction through the AV node)
 - * Decreases contractility (negative inotrope-decreases force of contraction)
 - * Reduces BP
- Effects on oxygen supply
 - * No direct improvement on oxygen supply
 - * Increases diastolic perfusion time (coronary arteries fill during diastole) due to decreased HR, which may enhance left ventricle (LV) perfusion
 - * Ventricular relaxation causes increased subendocardial blood flow.
 - * Unopposed alpha stimulation may lead to coronary vasoconstriction.
- Dosing
 - * Start low, go slow.
 - * Titrate to resting HR of 50-60 bpm, maximal exercise HR ≤ 100 .

- * Avoid abrupt withdrawal, which can precipitate more severe ischemic episodes and MI. Taper over 2 days.
- Basis of selection of BBs
 - * Cardiosensitivity to decrease adverse effects; lose cardiosensitivity at higher doses
 - * The intrinsic sympathomimetic activity (ISA) with acebutolol, carteolol, penbutolol, and pinidolol may not be as effective because the reduction in HR would be minimal; therefore, there is a small reduction in MVO_2 . BBs with ISA are generally reserved for patients with low resting HR who experience angina with exercise.
 - * Lipophilicity is associated with more central nervous system (CNS) SEs.
 - * Preferred in young patients who are hypertensive, post-MI, with high resting HR, fixed angina threshold, and mild heart failure (HF)
- Indications for therapy (Table 4)

Nitrates (endothelium-independent vasodilators)

- Effects on MVO_2
 - * Peripheral vasodilation leads to decreased blood return to the heart (preload) which leads to decreased LV volume, decreased wall stress, and decreased O_2 demand.
 - * Arterial vasodilation leads to decreased peripheral resistance (afterload), decreased systolic BP (SBP), and decreased O_2 demand.
 - * Nitrates can cause a reflex increase in sympathetic activity, which may increase HR/contractility and lead to an increase in O_2 demand in some patients. This can be overcome with the use of a BB.

Table 4

β -Blocker Use in Stable Angina

- First-line therapy if not contraindicated in patients with prior MI
- Initial therapy if not contraindicated in patients without prior MI
- More effective than nitrates and calcium channel blockers (CCBs) in silent ischemia
- Effective as monotherapy and in combination with nitrates and/or CCBs
- Avoid in Prinzmetal's angina
- Improves symptoms 80% of the time
- All BBs are effective, but not all are FDA-indicated

- Effects on O_2 supply
 - * Dilatation of large epicardial coronary arteries and collateral vessels in areas with or without stenosis leads to increased O_2 supply.

- Indications for therapy (Table 5)

Calcium channel blockers (CCBs)

- Effects on MVO_2
 - * Primarily by decreasing systemic vascular resistance and arterial BP by vasodilation of systemic arteries
 - * Decreased contractility and O_2 requirement (all CCBs exert varying degrees of negative inotropic effects): verapamil > diltiazem > nifedipine
 - * Verapamil and diltiazem promote additional decreases in MVO_2 by decreasing conduction through the AV node, thereby decreased HR.
- Effects on O_2 supply
 - * Increased diastolic perfusion time due to decreased HR which may enhance LV perfusion
 - * Decreased coronary vascular resistance and increased coronary blood flow by vasodilation of coronary arteries
 - * Coronary vasodilation at sites of stenosis
 - * Prevents/relieves vasospastic angina by dilation of the epicardial coronary arteries
- Indications for therapy (Table 6)

Combination therapy

BBs and nitrates

- BBs can potentially increase LV volume and left ventricular end-diastolic pressure.

Table 5

Nitrate Use in Stable Angina

- Sublingual nitroglycerin or NTG spray for the immediate relief of angina
- Long-acting nitrates as initial therapy to reduce symptoms if BBs are contraindicated
- Long-acting nitrates in combination with BBs when initial treatment with BBs is ineffective
- Long-acting nitrates as a substitute for BBs if BBs cause unacceptable side effects
- In patients with CAD or other vascular disease
- Preferred agents in treatment of Prinzmetal's/vasospastic angina
- Improves exercise tolerance
- In combination with BBs or CCBs, nitrates produce greater effects

Table 6**Calcium Channel Blocker Use in Stable Angina**

- Initial therapy for reduction of symptoms when BBs are contraindicated
- In combination with BBs when initial treatment with BBs is not successful
- As a substitute for BBs if initial treatment with BBs causes unacceptable side effects
- Slow-release/long-acting dihydropyridines and nondihydropyridines are effective in stable angina
- Avoid short-acting dihydropyridines
- Newer-generation dihydropyridines such as amlodipine or felodipine can be used safely in patients with depressed LV systolic function

* Nitrates attenuate this effect.

- Nitrates increase sympathetic tone and may cause a reflex tachycardia.

* BBs attenuate this response.

BBs and CCBs

- BBs and long-acting dihydropyridine CCBs are usually efficacious and well-tolerated.
- CCBs, especially the dihydropyridines, increase sympathetic tone and may cause reflex tachycardia.
- * BBs attenuate this effect.
- BBs and nondihydropyridine CCBs should be used together cautiously as the combination can lead to excessive bradycardia or AV block. The combination can also precipitate symptoms of HF.

ACE-inhibitors (ACEIs)

- Potential CV protective effects:
 - * Reduce the incidence of MI, CV death, and stroke in patients at high risk for vascular disease (data from the Heart Outcomes Prevention Evaluation [HOPE] trial).
- Controversy exists as to whether all ACEIs are equally effective or if "tissue ACEIs" provide better protection.
- Based on a recent clinical trial, low-risk patients with stable CAD and normal or slightly reduced left ventricular function may not benefit from ACEI therapy as greatly as a high-risk patient.
- Indications for therapy (Table 7)

Lipid-lowering therapy

- Clinical trials have proved that lipid-lowering therapy should be recommended in patients with established CAD, including chronic stable angina,

Table 7**Angiotensin-Converting Enzyme Inhibitor Use in Stable Angina**

- In all patients with CAD (by angiography or previous MI) who also have diabetes mellitus (DM) and/or left ventricular dysfunction
- In patients with CAD or other vascular disease
- In all patients with DM who do not have contraindications due to severe renal disease

even if only mild-moderate elevations of LDL cholesterol are present.

- Indications for therapy (Table 8)

Table 8**Low Density Lipoprotein-Lowering Therapy in Stable Angina**

- In patients with documented or suspected CAD or CHD risk equivalents and LDL ≥ 100 mg/dL; target LDL < 100 mg/dL
- In high-risk patients; target LDL < 70 mg/dL may be appropriate

Prinzmetal's or variant angina

- BBs have no role in management and may increase painful episodes.
- BBs may induce coronary vasoconstriction and prolong ischemia.
- Nitrates are often used for acute attacks.
- CCBs may be more effective, may be dosed less frequently, and have fewer SEs than nitrates.
- Nifedipine, diltiazem, or verapamil are all equally effective as single agents.
- Nitrates can be added if there is no response to CCB.
- Combination therapy with nifedipine + diltiazem and nifedipine + verapamil have been reported to be useful.
- Dose titration is recommended to obtain efficacy without unacceptable SEs.
- Treat acute attacks and provide prophylactic treatment for 6-12 months.

Silent ischemia

- Goal is to decrease the number of episodes, both symptomatic and asymptomatic

- Initial step is to modify risk factors for IHD (smoking, hypercholesterolemia, hypertension)
- BBs have shown improvement in patients with ischemic episodes and are preferred in patients post-MI.
- CCBs are somewhat less effective than BBs.

5. Unstable Angina/Non-ST-Segment Elevation Myocardial Infarction (UA/NSTEMI)

Pathophysiology

- The process of ischemic syndromes involves two essential events:
 - * Disruption of an atherosclerotic plaque
 - * Formation of a platelet-rich thrombus
- The clinical manifestation depends on the extent and duration of the thrombotic occlusion.
- In UA/NSTEMI the thrombus does not completely occlude the vessel.
- Pathogenesis and clinical presentations of UA and NSTEMI are similar but differ in severity.

Presentation

- Central/substernal or crushing chest pain that can radiate to the neck, jaws, back, shoulders, and arm(s).
- Patients may present with diaphoresis, nausea, vomiting, arm tingling, weakness, shortness of breath, or syncope.
- Pain may be similar to typical angina except that the occurrences are more severe, may occur at rest, and may be caused by less exertion than typical angina.
- May be incorrectly interpreted as dyspepsia or indigestion
- Pain is not relieved by NTG.
- May evolve into STEMI without treatment.

Diagnosis

- Chest pain persisting longer than 5 minutes that is unrelieved by NTG
- Cardiac enzymes and ECG changes (Table 9)

Table 9

Cardiac Enzymes and Electrocardiographic Changes: UA versus NSTEMI

	UA	NSTEMI
Cardiac enzymes	Negative	Positive
ECG changes:	If present, are transient	Always present
ST-segment,		
T-wave changes		

Goals of Therapy

- Complete restoration of blood flow to the myocardium
- Prevent MI, arrhythmias, and ischemia

Pharmacologic Management of UA/NSTEMI

Morphine, oxygen, nitrates, and aspirin (MONA)

- Indications for therapy (Table 10)

Anti-ischemic therapy

β -Adrenergic blockade

- Preference is for an agent without ISA
- Agents with β_1 selectivity are preferred in patients with bronchoconstrictive disease.
- No evidence that one agent is superior to another
- Initial choices include metoprolol, atenolol, and propranolol.
- Indications for therapy (Table 11)

Nitrates (see MONA, Table 10)

Calcium channel blockers (CCBs)

- There is no mortality benefit from the use of CCBs,

Table 11

β -Blocker Use in UA/NSTEMI

- All patients without contraindications
- In patients with continued chest pain, the first dose should be given IV

therefore they are not recommended as first-line therapy.

- Indications for therapy (Table 12)

Angiotensin-converting enzyme inhibitors

- Indications for therapy (Table 13)

Antiplatelet therapy

Aspirin (see MONA, Table 10)

Table 10

Morphine, Oxygen, Nitrates, and Aspirin (MONA) Therapy

Morphine	<p>Rationale: vasodilatory properties on both arterial and venous sides, therefore decreases both preload and afterload. Pain relief decreases tachycardia, along with decrease in preload and afterload; all work to decrease myocardial O_2 demand</p> <p>Dosing: increments of 2-4 mg IV every 5-15 minutes until pain relief</p> <p>Adverse effects: nausea, vomiting, hypotension, sedation, and respiratory depression</p> <p>Cautions and contraindications: produces a vagotonic effect that may be contraindicated in patients with bradycardia. Watch closely for hypotension, respiratory depression, and allergic reactions.</p>
Meperidine	Can be used in patients who are intolerant to morphine. Has vagolytic effects, so it is the analgesic of choice in patients who are bradycardic; 25-75 mg IV
Oxygen	Supplemental O_2 2-4 L/min by nasal cannula is recommended to correct and avoid hypoxia, particularly within the first 2-3 hours. More aggressive ventilatory support should be considered and given as needed.
Nitroglycerin (NTG)	<ul style="list-style-type: none"> • All patients should receive NTG as a sublingual tablet or spray, followed by IV administration as needed for the relief of ischemia. • Long-acting nitrates (oral, transdermal) should be used as secondary prevention in patients who do not tolerate BBs and CCBs. These nitrates can be used in patients who have continual chest pain despite the use of BBs and CCBs.
Aspirin (ASA)	<ul style="list-style-type: none"> • Aspirin 160-325 mg should be given at the onset of chest pain unless contraindicated. Chew and swallow the first dose. • Daily dose of 75-325 mg for life • Clopidogrel may be substituted if true aspirin allergy is present or if the patient is unresponsive to ASA.

Table 12**Calcium Channel Blocker Use in UA/NSTEMI**

- In patients with contraindications to BBs, a nondihydropyridine CCB (verapamil, diltiazem) should be used in the absence of severe LV dysfunction or other contraindication
- Oral long-acting CCBs provide additional control of anginal symptoms in patients who are already receiving BBs and nitrates
- Avoid short-acting dihydropyridines

Thienopyridines (ie, clopidogrel [Plavix] and ticlopidine [Ticlid])

- * Inhibition of platelet aggregation is irreversible and takes 2-5 days to achieve full effect. Often clopidogrel or ticlopidine is given in a loading dose for a more rapid effect (within 2 hours).
- * Clopidogrel is the preferred agent in this class.
- * Ticlopidine is rarely used as a result of severe toxicities.
- * The mechanism of platelet aggregation for clopidogrel and ASA differ; therefore, their effects are additive.
- Indications for therapy (clopidogrel) (Table 14)

Glycoprotein IIb/IIIa receptor inhibitors (GPIs)

Agents

- Abciximab (ReoPro®)
- Eptifibatide (Integrilin®)
- Tirofiban (Aggrastat®)

Uses

- All of the agents can be used as adjunctive therapy in patients undergoing PCI.

Table 13**Angiotensin-Converting Enzyme Inhibitor Use in UA/NSTEMI**

- Not indicated for the immediate treatment of UA/NSTEMI
- Recommended in patients with HF, DM, patients with high-risk CAD and in patients with persistent hypertension not controlled by the use of BBs or nitrates
- Based on the results from the HOPE trial, which showed a mortality reduction when ramipril was used in patients with vascular disease and no history of HF, may consider in all patients without contraindications

Table 14**Clopidogrel Use in UA/NSTEMI**

- Alternative for patients who are allergic to ASA or who have a gastrointestinal intolerance to ASA
- Clopidogrel should be combined with ASA in patients undergoing stent implantation for at least 1-6 months depending on type of stent used and possibly up to one year.
- Clopidogrel should be combined with ASA in patients without a planned PCI procedure for up to 9 months

- Eptifibatide and tirofiban can also be used in patients who will be managed medically. Medical management can be used in patients who refuse a PCI procedure or in patients who are at high risk of complications related to a PCI procedure.
- In combination with heparin and ASA, eptifibatide and abciximab have been shown to reduce the incidence of combined death, MI, and recurrent ischemia in patients with UA/NSTEMI who undergo PCI.
- Indications for therapy (Table 15)

Anticoagulant therapy

Unfractionated heparin (UFH)

- Indications for therapy (Table 16)

Low molecular weight heparin (LMWH)

- Agents
 - * Enoxaparin (Lovenox®)
 - * Dalteparin (Fragmin®)
- Differ from UFH in size and affinity for thrombin
- Advantages of LMWH over UFH include: better bioavailability, a more predictable response, ease of

Table 15**Glycoprotein IIb/IIIa Receptor Inhibitor Use in UA/NSTEMI**

- In addition to heparin, ASA and clopidogrel should be given to all patients with a planned PCI procedure. The GPI can be given during the interventional procedure just before stent deployment or angioplasty
- Eptifibatide or tirofiban should be given in combination with ASA and LMWH/UFH to patients with ACS who will not undergo a PCI procedure

Table 16

Heparin Use in UA/NSTEMI

- Heparin or LMWH should be given to all patients in combination with ASA and clopidogrel
- Heparin is continued for a total of 24-48 hours or until a PCI procedure is completed
- In patients with a planned CABG within 24 hours, heparin use is preferred to LMWH

Table 17

Low Molecular Weight Heparin (LMWH) Use in UA/NSTEMI

- LMWH or heparin in combination with aspirin and clopidogrel should be given to all patients
- Enoxaparin may be superior to heparin in patients with UA/NSTEMI

administration, fewer SEs, and no recommended routine monitoring.

- A total of four clinical trials have compared UFH to LMWH for the treatment of UA/NSTEMI. Two of the trials showed superiority of enoxaparin over UFH. The remaining two trials with dalteparin showed equivalence to UFH.
- Indications for therapy (Table 17)

Lipid-lowering therapy

- Indications for therapy (Table 18)

Table 18

LDL-Lowering Therapy in UA/STEMI

- In patients with documented or suspected CAD or CHD risk equivalents and LDL ≥ 100 mg/dL: target LDL < 100 mg/dL
- In high-risk patients: target LDL < 70 mg/dL may be appropriate

6. Acute Myocardial Infarction (ST-Segment Elevation MI or STEMI)**Pathophysiology**

- More than 85% of all MIs occur by thrombus formation precipitated by atherosclerotic plaque rupture.
- Aggregated platelets after plaque rupture can serve as a substrate for thrombus propagation, leading to formation of an occlusive thrombus.
- This complete occlusion results in abrupt and persistent ischemia that clinically manifests as ST-segment elevation MI. Left untreated, occlusion of the coronary arteries can lead to sudden cardiac death.

STEMI vs UA/ NSTEMI (Table 19)**Location**

- Patients with RV wall infarction should be managed similarly to LV infarction with the exception that NTG, diuretics, and other preload reducing agents should be avoided in RV wall MIs because these patients are dependent on preload.
- RV MI may require volume loading with IV fluids to maintain preload and cardiac output.

Table 19

STEMI versus UA/NSTEMI

STEMI	NSTEMI
Totally occlusive thrombus	Platelet-rich thrombi, which do not completely block coronary blood flow
More extensive damage	Smaller, less extensive damage
Results in an injury that affects the entire thickness of the myocardial wall	NSTEMI involves only the subendocardial myocardium
Occlusion persists long enough to compromise myocardial function and leads to myocardial necrosis	Unstable angina is ischemia; NSTEMI may still result in necrosis, but not to the extent of STEMI
ST-segment elevation on ECG	ST depression or no ST elevation on ECG
Lytic therapy or primary reperfusion is a main treatment strategy	Antiplatelet agents such as GPIs are used to target platelet-rich thrombus

- Symptoms differ from a LV wall MI in that an RV wall MI can cause hypotension, elevated jugular venous pressure, and cardiogenic shock because of inadequate filling of the LV.

Ventricular remodeling

- Can occur as a result of myocardial necrosis and may continue for months following MI.
- Leads to activation of the neurohormonal and renin-angiotensin systems that will ultimately affect ventricular shape, size, and function
- Precipitates chronic changes in ventricular volume, ventricular dilation, hypertrophy, and eventually heart failure (HF)
- ACEIs and BBs reduce the progression of ventricular remodeling. Carvedilol may reverse ventricular remodeling.

Prognosis

Mortality

- The highest risk of death from MI is generally within the first 48 hours.
- Anterior MIs usually involve a larger area of the myocardium than do inferior MIs, and thereby have a higher mortality.
- An important prognostic factor following MI is LV function, as HF is one of the most serious complications of MI.
- Large anterior wall MIs, LV dysfunction, and complex ventricular ectopy carry the highest mortality rate post-MI.
- Early identification and risk stratification can reduce mortality following MI.

Predictors of death

- High troponin concentration correlates with higher death rates in STEMI and NSTEMI.
- Predictors of death within 30 days post-MI include: age >70 years, HTN, atrial fibrillation (afib), tachycardia, large infarct size, previous MI, and female gender.
- Lower-risk patients include those younger than 71 years of age with an LV ejection fraction (EF) $\geq 40\%$.
- Patients who continue to have frequent ventricular arrhythmias following MI are at a high risk of sudden cardiac death.

Presentation

- Symptoms similar to UA/NSTEMI
- Atypical presentation is common in women, elderly, and in those with DM.

Diagnosis (Table 20)

Table 20

Criteria for the Diagnosis of Myocardial Infarction

(Two of these three must be met)

Chest pain	Generally lasting for >30 minutes
ECG changes	ST-segment elevation of 0.1 mV in two limb leads or 0.1-0.2 mV elevation in at least two precordial leads
Cardiac isoenzymes	Troponin T or I elevation CK-MB elevations

Goals of Therapy in Acute MI

- Limit infarct size
- Reverse myocardial ischemia and thereby salvage myocardium
- Minimize complications.
- Reduce mortality.
- Strict glucose control

Pharmacologic Management of STEMI

Morphine, oxygen, nitrates, aspirin (refer to Table 10 in UA/NSTEMI section)

Nitrates

- Indications for therapy (Table 21)

Table 21

Nitrate Use in STEMI

- Nitrates may be used for the first 24 hours in all patients with MI who do not have hypotension, bradycardia, or tachycardia. Nitrates salvage ischemic myocardium by relaxation of vascular smooth muscle in veins, arteries, and arterioles.
- Insignificant reductions in mortality beyond 48 hours. Use is reserved for those patients with large AMIs, persistent chest discomfort, HF, HTN, or persistent pulmonary congestion.
- Cautions and contraindications: carefully titrate in patients with inferior wall MI because of its frequent association with RV infarction. Such patients are especially dependent on adequate RV preload to maintain cardiac output and can experience profound hypotension during nitrate administration.

Reperfusion therapy

Primary PTCA (see section 7 for more information)

- Intervention designed to reopen a partially or completely occluded coronary artery to reestablish blood flow
- Goal is time to balloon <90 minutes.
- Mechanical reperfusion (PTCA such as balloon angioplasty and coronary stenting) has been shown to be more successful than fibrinolysis.
- In patients who receive a stent, clopidogrel therapy should be added to the regimen as in UA/NSTEMI.

Fibrinolytic therapy (also known as thrombolytic therapy)

- Improves myocardial O₂ supply, limits infarct size, and decreases mortality
- Controversy exists in regard to one lytic agent's superiority over another.
- A door-to-needle time <30 minutes is an important goal.
- Signs of successful reperfusion include relief of CP, resolution of ST-segment changes, and reperfusion arrhythmias, usually ventricular in nature.
- Fibrinolytic therapy is unsuccessful in approximately 22-30% of patients.
- Indications for therapy (Table 22)

Heparin therapy

- Indications for therapy (Table 23)

LMWH

- Indications for therapy (Table 24)

Table 22

Use of Fibrinolytic Therapy in STEMI

- ST-segment elevation >1 mm in two or more contiguous leads or Left Bundle Branch Block (obscuring ST observational changes)
- Presentation within 12 hours or less of symptom onset
- Patient has no contraindications to fibrinolytic therapy and has indications for therapy
- In patients age >75 years may be useful and appropriate
- Can be used in STEMI when time to therapy is 12-24 hours if chest pain is ongoing
- Should not be used if the time to therapy is >24 hours, and the ischemic pain is resolved
- Should not be used for ST depression

Table 23

Heparin Use in STEMI

- Adjunct with fibrinolytics for the prevention of recurrent coronary thrombosis.
- Combination of UFH with streptokinase (SK) is less clear because it is a nonspecific fibrinolytic. UFH may increase the risk of bleeding because of SK's long half-life.
- Patients at high risk for systemic emboli (large or anterior MI, afib, previous emboli, or known LV thrombus) should have UFH held for 6 hours (postthrombolytic) and aPTT monitoring begun at that time. After 48 hours a change to SC heparin, warfarin or ASA alone should be considered.
- IV UFH or LMWH or dalteparin 120 units/kg SC bid in patients at high risk for systemic emboli
- Can use SC UFH (7500 units bid x 7 days or until the patient is fully ambulatory) or LMWH in all patients not treated with a thrombolytic (who have no contraindications to UFH).
- Consider SC UFH or LMWH for DVT prophylaxis.

β-Adrenergic blockade (BB)

- Early BB use post-MI reduces infarct size, CV mortality, reinfarction rate, and nonfatal cardiac arrests, and increases probability of long-term survival.
- Late administration of a BB (at least 24 hours after MI) improves left ventricular diastolic filling and reduces risk of recurrent MI and death
- Indications for therapy (Table 25)

Table 24

LMWH Use in STEMI

- Can be used as an alternative to UFH for patients <75 years of age without significant renal dysfunction (men: SCr >2.5 mg/dl; women: SCr >2 mg/dl) who are receiving fibrinolytic therapy. Enoxaparin (30 mg IV bolus, 1 mg/kg SC q12h until discharge) + tenecteplase (full dose) is the most studied regimen in this population.
- Should not be used in patients >75 years of age or in patients <75 years of age with renal dysfunction
- LMWH or IV UFH in patients at high risk for systemic emboli
- Patients not treated with a thrombolytic without contraindications can be treated with SC or IV UFH or LMWH (enoxaparin 1 mg/kg SC bid or dalteparin 120 units/kg SC bid) for at least 48 hours.
- Consider LMWH or SC UFH for DVT prophylaxis.

Table 25 **β -Blocker Use in STEMI**

Early therapy: BBs should be given to all patients with acute MI who can be treated within 12 hours of MI, regardless of administration of concomitant thrombolytic therapy. IV or PO treatment should be started as soon as possible in all patients within 12-24 hours after onset of symptoms.

Late therapy: BBs should be given to all patients without a clear contraindication to BB therapy. Treatment should begin within a few days of the event (if not initiated early) and be continued indefinitely.

Glycoprotein IIb/IIIa Inhibitors (GPIs)

- The role of platelet GPI in STEMI is rapidly evolving, and trials to date in combination with full- and half-dose fibrinolytic agents have shown a more complete reperfusion at the price of higher bleeding rates, especially in elderly patients.
- Abciximab reduces the incidence of combined death, MI, and recurrent ischemia in patients with STEMI.

Inhibition of the renin-angiotensin-aldosterone (RAA) system (ACEIs, angiotensin receptor blockers [ARBs], and aldosterone inhibitors)

- Primary goal is to limit postinfarction LV dilatation and hypertrophy so that pump function is preserved or improved. ACEIs attenuate the remodeling process and thereby slow the progression to HF post-MI.
- Benefits of ACEIs are clearly most pronounced in patients with evidence of ventricular dysfunction (either objective evidence such as LVEF $\leq 40\%$ or subjective evidence such as HF symptoms).
- Marked benefit of ACEIs in other high-risk patients (previous MI, HF, and anterior MI without thrombolytic therapy)
- Recent studies of ACEI therapy suggest acute treatment should be given to patients considered at higher risk due to a history of HTN, DM, or previous MI, and should be continued indefinitely.
- An ARB can be used for those patients who are intolerant of an ACEI and have either clinical or radiological signs of heart failure and an LVEF of $\leq 40\%$.
- The combination of an ACEI and an ARB may be considered in patients with persistent heart failure. Due to results from clinical trials when this combination is considered, candesartan is the preferred ARB.
- Aldosterone blockade (eplerenone, spironolactone)

Table 26**ACEI, ARB, and Aldosterone Blocker Use Post-STEMI**

- Patients within the first 24 hours of a suspected MI or with clinical HF without contraindications should receive an ACEI.
- All other patients without contraindications should receive an ACEI within the first 24 hours.
- ACEIs remain the first choice for inhibition of the RAAS system in the long-term management of patients post-STEMI.
- IV ACEIs should not be given to patients within the first 24 hours of STEMI because of the risk of hypotension.
- ARBs should be given to those patients who are intolerant of an ACEI. Valsartan and candesartan are the only ARBs that have established efficacy for this indication.
- Long-term aldosterone blockade should be prescribed for post-STEMI patients without contraindications with an LVEF $\leq 40\%$, and having either symptomatic heart failure or diabetes.

- should be prescribed post-STEMI in those patients already on an ACEI with an LVEF $\leq 40\%$ and having either symptomatic heart failure or diabetes.
- Aldosterone blockers should be avoided in patients with renal dysfunction (SCr ≥ 2.5 mg/dL in men or ≥ 2.0 in women) or hyperkalemia (potassium > 5 mEq/L).
- Less is known about the combination of an aldosterone blocker and an ARB and the triple combination of an ACEI, ARB, and aldosterone blocker.
- Indications for therapy (Table 26)

Lipid lowering

- Indications for therapy (see Table 18 in UA/STEMI section)

Calcium channel blockers (CCBs)

- Indications for therapy (Table 27)

Warfarin

- Indications for therapy (Table 28)

Treatment of ventricular fibrillation (VF) post-MI

- The risk of VF is at highest during the first 4 hours post-MI and then declines sharply.
- Prophylactic antiarrhythmic use has been shown to increase all-cause mortality when used to prevent VF. The use of lidocaine for VF prophylaxis is not recommended.
- Amiodarone may be utilized if patients experience VF or hemodynamically compromising ventricular tachycardia following MI.

Table 27**Calcium Channel Blockers Post-STEMI**

- Verapamil or diltiazem only with continuing ischemia when BB use is either contraindicated or used at maximum dose with nitrates.
- Verapamil or diltiazem should not be used in patients with systolic dysfunction, AV block, or bradycardia.

Table 28**Warfarin Use Post-STEMI**

- The indications for long-term anticoagulation with warfarin are evolving yet remain controversial.
- Recommended in patients with indications for anticoagulation (ie, LV thrombus, atrial fibrillation, extensive wall motion abnormalities, etc)
- Patients over age 75 have not been adequately studied in secondary prevention trials post-STEMI. Warfarin is not recommended in these patients unless a clear indication for anticoagulation exists.
- Clopidogrel is preferred in patients who cannot tolerate aspirin for secondary prevention unless a clear indication for warfarin exists.

7. Revascularization**Percutaneous Coronary Intervention (PCI)****Procedures**

- Procedure types include: balloon angioplasty (PTCA), coronary stenting, and ablative technologies (laser, atherectomy).
- Primary PCI is a very effective method for re-establishing coronary perfusion and is suitable for at least 90% of patients.
- Primary PCI should be performed as quickly as possible with the goal of a medical contact-to-balloon or door-to-balloon time of 90 minutes or less.
- Primary PCI is favored over fibrinolytic therapy because PCI-treated patients experience lower short-term mortality rates, fewer nonfatal reinfarctions and hemorrhagic strokes than those treated with fibrinolytic therapy.
- Facilitated PCI refers to a strategy of planned immediate PCI after an initial pharmacologic regimen such as full-dose fibrinolytics, GPIs, or another pharmacologic regimen.
- Potential complications of invasive PCI include problems with arterial access site, technical complications, acute vessel closure, restenosis, and acute renal failure secondary to nephrotoxic dye.

Drug eluting stents (DES)

- Restenosis is the loss of 50% or more of the diameter of the in-stent lumen at the site of an initially successful intervention; it usually occurs within the first 3-6 months after PTCA.
- DES were introduced in 2003, and have the principal advantage of reducing in-stent thrombosis and restenosis over bare metal stents (BMS).
- Sirolimus and paclitaxel are two options of pharmacologic agents that are embedded in the steel stent with release modulated by a polymeric coating so the agent is released over a period of time.
- Clopidogrel in combination with aspirin is used to reduce in-stent thrombosis, and is used for at least 1 month with BMS, 3 months for sirolimus-coated, and 6 months for paclitaxel-coated stents.

Anticoagulation during PCI

- Mandatory, as the vessel manipulation during PCI is inherently thrombogenic.

Possible agents

- UFH is currently the mainstay of therapy.
- Bivalirudin: studies have shown that this direct thrombin inhibitor may be as effective as heparin but with less bleeding.

- LMWHs have been utilized in varying doses during PCI; however, there is no consensus on their use during PCI.

Glycoprotein inhibitors (GPIIb/IIIa inhibitors)

- Although similar effects have been noted with each of the GPIs, the timing of PCI should be determined before an agent is selected.
- Use abciximab or eptifibatide if PCI is anticipated soon after presentation (<4 hours), reserving tirofiban for patients treated medically during the first 48 hours.
- Abciximab should not be used for patients who are conservatively managed without plans for PCI.

Coronary artery bypass graft surgery (CABG)

- Indicated in patients with multivessel disease with LV dysfunction or significant disease of a major coronary vessel

8. Primary Prevention: Risk Factor Modification

Background

- The majority of the causes of cardiovascular disease are known and modifiable.
- Risk factor screening should begin at age 20 with the hope that all adults know the levels and significance of risk factors as routinely assessed by their primary care provider.

Nonmodifiable Risk Factors

Age

- Men >45; women >55 (or those who had an early hysterectomy regardless of age)

Race

- Higher risk in African-American males and females compared to Caucasian males and females

Family history

- Father or brother with a coronary event before age 55
- Mother or sister with a coronary event before age 65

Modifiable Risk Factors

- Smoking
- Hypertension
- Hyperlipidemia
- Hyperhomocysteinemia
- Diabetes
- Metabolic syndrome
- Obesity
- Physical inactivity
- Alcohol consumption

Pharmacologic Therapy

Aspirin

- The Seventh ACCP Consensus Conference on Antithrombotic Therapy (Chest Guidelines) recommends that ASA (80-325 mg/day) be considered for individuals >50 years old who have at least one major risk factor for CAD and who are free of contraindications.
- The ACC/AHA recommends doses of 75-162 mg/day in persons at higher risk of CVD (especially those with a 10-year risk of CHD >10%).
- The American Diabetes Association recommends ASA therapy to prevent CV events in most patients

with DM who are >40 years of age and have no contraindications to ASA.

- The recommendation for aspirin use for primary prevention is stronger in men than in women.

Angiotensin-converting enzyme inhibitors (ACEIs)

- In the HOPE trial, ramipril demonstrated effectiveness in reducing the risk of MI, stroke, and death from cardiovascular causes in patients at high risk of a major cardiovascular event. ACEIs may be used as protective agents.
- EUROPA similarly showed perindopril to be beneficial in patients with evidence of coronary heart disease but without heart failure, and has led to the increased use of ACEIs in patients with vascular disease but without heart failure or LV dysfunction.
- Results from PEACE suggest that low-risk patients with CAD, who are receiving maximal therapy with β -blockers, aspirin, and lipid-lowering therapies, do not gain additional benefit from the addition oftrandolapril 4 mg daily.
- Chronic ACEI therapy may be most beneficial in high-risk patients (uncontrolled hyperlipidemia, hypertension, smoking, proteinuria, vascular disease).

Lipid lowering

- Consider in all patients at risk for a coronary event.

Antioxidants

- There is no consistent evidence with vitamin E or other antioxidant therapy to recommend its use for primary prevention of heart disease.

Nonpharmacologic Therapy for IHD

Smoking cessation

- One of the most important risk-modifying behaviors
- Evidence suggests that the best adherence to a cessation program combines pharmacotherapy with behavioral modification.
- A wide range of smoking cessation aids (prescription and nonprescription) products are available.
- Nicotine replacement alone is not an effective management strategy for smoking cessation. Nicotine combined with bupropion has been the most successful.

Diet

- Diets low in saturated fat and high in fruits, vegetables, whole grains, and fiber are associated with a reduced risk of CVD.
- Omega-3 fatty acids: the AHA Dietary Guidelines recommends inclusion of at least two servings of fish per week (particularly fatty fish).
- Food sources high in alpha-linolenic acid (eg, soy-

bean, canola, walnut, and flaxseed oil and walnuts and flaxseeds) are also recommended.

Exercise

- Regular aerobic physical activity increases a person's capacity for exercise. Exercise plays a role in both primary and secondary prevention of cardiovascular disease.
- Current guidelines from the CDC and NIH recommend that Americans should accumulate at least 30 minutes of moderate-intensity physical activity on most, preferably all, days of the week to prevent risk of chronic disease in the future.
- The Institute of Medicine recommends 60 minutes of physical activity per day.

Weight loss

- Weight loss can reduce blood pressure, lower blood glucose levels, and improve blood lipid abnormalities.
- A goal of 5-10% of body weight loss is associated with decreased morbidity and mortality.
- Pharmacotherapy used for weight loss should be reserved for those with a BMI >30, or in those with BMI >25 with other risk factors for comorbid diseases.

Alcohol consumption

- Lowest CV mortality occurs in those who consume 1 or 2 drinks per day. People with no alcohol consumption have higher total mortality than those drinking 1 to 2 drinks per day.
- In the absence of alcohol-related illnesses, 1 to 2 drinks per day in males and 1 alcoholic drink per day in females may be considered for high-risk patients.
- A drink equivalent amounts to a 12-ounce bottle of beer, a 4-ounce glass of wine, or a 1.5-ounce shot of 80-proof spirits.
- A general increase in alcohol consumption at the population level is not recommended.

9. Pharmacology

Anti-Ischemic Drug Therapy

β-Blockers (see hypertension chapter)

Nitrates

Mechanism of action

- Organic nitrates are prodrugs that must be transformed to exert pharmacological effect.
- NTG leads to denitration of the nitrate, liberation of nitric oxide (NO), guanylyl cyclase stimulation, the conversion of guanosine triphosphate to cGMP, and vasodilation.
- NO also reduces platelet adhesion and aggregation and affects endothelial function and vascular growth.

Properties

- Oral: Isosorbide dinitrate (ISDN) and NTG undergo extensive first-pass metabolism when given orally. Mononitrate does not; it is completely bioavailable.
- IV: Achieves highest concentrations; usually used for only 24 hours to avoid developing tolerance
- SL tablet/spray for immediate-release
 - * Spray does not degrade when exposed to air like tablets.
 - * Half-life: 1-5 minutes regardless of route

Doses (Table 29)

Monitoring parameters

- Blood pressure, heart rate

Adverse drug reactions (Table 30)

Table 29

Pharmacologic Properties and Doses of Nitrates

Drug	Route	Onset (min)	Duration of action	Dose
Nitroglycerin sublingual tablet (Nitrostat [®] , Nitroquick [®])	Sublingual	1-3	30-60 min	0.2-0.6 mg every 5 minutes. Seek emergency treatment if chest pain is unrelieved after 1 dose
Nitroglycerin spray (Nitrolingual [®])	Translingual	2	30-60 min	0.4 mg every 5 minutes. Seek emergency treatment if chest pain unrelieved after 1 spray
Nitroglycerin transmucosal tablets (Nitroguard [®])	Buccal	1-2	3-5 h	Insert 1 tablet into cheek every 3-5 h
Nitroglycerin ointment (Nitrobid [®] , Nitrol [®])	Topical	30-60	2-12 h	1-2 inches every 8 h up to 4-5 inches every 4 h
Nitroglycerin transdermal patches (Nitro-dur [®] , Transderm Nitro [®] , Nitrek [®] , Nitrodisc [®] , Deponit [®] , Minitrans [®])	Topical	30-60	Up to 24 h	Starting dose: 0.2-0.4 mg/h. Apply and allow patch to stay in place for 12 h. Remove the patch after 12 h to allow for a nitrate-free interval
Nitroglycerin sustained-release tablets/capsules (Nitrong [®] , Nitroglyn [®] , Nitro-Time [®])	Oral	20-45	3-8 h	Starting dose: 2.5 mg tid-qid. Increase the dose by 2.5 mg two to four times daily to reach effective dose
Nitroglycerin intravenous (Tridil [®] , Nitro-Bid IV [®])	IV	1-2	3-5 min	Starting dose: 5 mcg/min. Titrate to response
Isosorbide mononitrate (Ismo [®] , Monoket [®])	Oral	30-60	No data	20 mg bid (given 7 hours apart). May need to start with 5 mg bid for low-weight patients
Isosorbide mononitrate, extended-release (Imdur [®] , Isolate ER [®])	Oral	30-60	No data	Starting dose: 30-60 mg qd. Maximum dose: 240 mg qd
Isosorbide dinitrate (Isordil Titradose [®] , Sorbitrate [®])	Oral	20-40	4-6 h	Starting dose: 5-20 mg q6h. Maintenance dose: 10-40 mg q6h
Isosorbide dinitrate, sustained-release tablets/capsules (Isordil Tembids [®] , Dilatrate-SR [®])	Oral	Up to 4 h	6-8 h	Initial dose: 40 mg q8h. Maintenance dose: 40-80 mg q8-12 h

Table 30**Nitrate Adverse Reactions**

Tolerance	Tolerance to the vasodilatory effects can develop if dosing does not allow for a nitrate-free interval (10-12 h)
CNS	Headache (up to 50%), dizziness, anxiety, nervousness
CV	Hypotension, tachycardia, palpitations, syncope
GI	Nausea, vomiting, dyspepsia
Dermatologic	Rash, dermatitis
Other	Blurred vision, muscle twitching, perspiration, edema, arthralgia

Drug-drug interactions (Table 31)**Drug-disease interactions**

- Glaucoma
 - * Intraocular pressure may increase.
 - * Use with caution in patients with glaucoma.
- Hypertrophic obstructive cardiomyopathy
- Severe aortic stenosis
 - * Can cause hypotension and syncope

Contraindications

- Sildenafil and vardenafil: use within 24 hours
- Tadalafil: use within 48 hours
- Hypersensitivity to nitrates

Table 31**Nitrate Drug-Drug Interactions**

Interacting medication	Effect
Sildenafil (Viagra®), vardenafil (Levitra®), tadalafil (Cialis®)	Significant reduction of systolic and diastolic blood pressure. Do not give sildenafil or vardenafil within 24 hours of nitrate use. Do not give tadalafil within 48 hours of nitrate use.
Calcium channel blockers	Marked symptomatic hypotension may occur
Alcohol	Severe hypotension may occur

Patient instructions/counseling

- Avoid alcohol consumption.
- May cause dizziness; use caution when driving or engaging in hazardous activities until drug effect is known.
- When standing from a sitting position, rise slowly to avoid an abrupt drop in blood pressure.
- Notify physician of acute headache, dizziness, or blurred vision.
- Sublingual tablets
 - * Keep tablets in their original container.
 - * Dissolve tablet under the tongue. Lack of tingling does not indicate a lack of potency.
 - * Take one tablet at the first sign of chest pain. If chest pain is unrelieved, seek emergency medical attention.
- Translingual spray
 - * Spray under tongue or onto tongue.
 - * Hold spray nozzle as close to the mouth as possible and spray medicine onto or under the tongue.
 - * Do not inhale the spray or use near heat, open flame, or while smoking.
 - * Close mouth immediately after spraying
 - * Avoid eating, drinking, or smoking for 5-10 minutes.
 - * If the pain does not go away after 1 spray, seek emergency medical attention.
- Transmucosal tablets
 - * Place between cheek and gum. Do not chew tablet; allow to dissolve over a 3- to 5-hour period.
 - * Touching the tablet with the tongue or hot liquids may increase release of the medication.
- Ointment
 - * Measure the correct amount using the papers provided with the product.
 - * Use papers for the application, not fingers.
 - * Apply to the chest or back.
- Transdermal patches
 - * Tear the wrapper open carefully. Never cut the wrapper or patch with scissors. Do not use any patch that has been cut by accident.
 - * Apply to a hairless area and rotate sites to avoid irritation. Be sure to remove the old patch before applying a new one.
 - * Do not put the patch over burns, cuts, or irritated skin.
 - * Remove the patch approximately 12-14 hours after placing it on every day. This prevents tolerance to the beneficial effects of NTG.
 - * Used patches may still contain residual medication; use caution when disposing around children and pets.

- * Store the patches at room temperature in a closed container, away from heat, moisture, and direct light. Do not refrigerate.
- Sustained-release tablets
 - * Take at the same time each day as directed.
 - * Do not chew or crush tablets/capsules.

Inhibition of the renin-angiotensin-aldosterone (RAA) system

Angiotensin-converting enzyme Inhibitors (see heart failure chapter)

Angiotensin receptor blockers (see heart failure chapter)

Aldosterone blockers (see heart failure chapter)

Calcium channel blockers (see hypertension chapter)

Antiplatelet Drug Therapy

Aspirin

Mechanism of action

- Blocks prostaglandin synthesis, which prevents the formation of thromboxane A_2

Dose

- At the onset of chest pain: 160-325 mg chewed and swallowed
- Maintenance dose: 75-325 mg for life
- Monitoring parameters: signs of bleeding, renal function, tinnitus

Adverse drug reactions (Table 32)

Table 32

Aspirin Adverse Reactions

CV	Hypotension, edema, tachycardia
CNS	Fatigue, nervousness, dizziness
Dermatologic	Rash, urticaria, angioedema
GI	Nausea, vomiting, dyspepsia, gastrointestinal ulceration, gastric erosion, duodenal ulcers
Hematologic	Bleeding, anemia
Otic	Hearing loss, tinnitus
Renal	Renal impairment, increased serum creatinine, proteinuria
Respiratory	Asthma, bronchospasm, dyspnea, tachypnea, respiratory alkalosis

Drug-drug interactions

- Clopidogrel, GPI, UFH, LMWH, NSAIDs, and warfarin may all increase the risk of bleeding if used in combination with ASA.

Drug-disease interactions

- PUD
- Other active bleeding
 - * May cause gastric ulceration
 - * Recommend enteric-coated tablet

Patient instructions/counseling

- Avoid additional over-the-counter (OTC) products containing ASA, NSAIDs, or salicylate ingredients without the direction of a physician.
 - * Patients who have received a stent will need the combination of clopidogrel and aspirin.
- Notify physician of dark, tarry stools, persistent stomach pain, difficulty breathing, unusual bruising or bleeding, or skin rash.
- Do not crush an enteric-coated product.

Thienopyridines

Mechanism of action

- Blocks adenosine diphosphate (ADP)-mediated activation of platelets by selectively and irreversibly blocking ADP activation of the glycoprotein IIb/IIIa complex

Dose

Clopidogrel

- Loading dose: 300-600 mg PO
- Maintenance dose
 - * 75 mg daily combined with aspirin for up to 9 months in patients who did not undergo cardiac cath
 - * 75 mg daily combined with aspirin for at least 1 month with BMS, 3 months for sirolimus-coated, and 6 months for paclitaxel-coated stents and possibly continued for up to one year.
 - * 75 mg daily for life in patients with aspirin allergy

Ticlopidine ticlid 250 mg

- Loading dose: 500 mg PO
- Maintenance dose: 250 mg bid
- Monitoring parameters
 - * Clopidogrel: signs of bleeding
 - * Ticlopidine: CBC with differential every 2 weeks for the first 3 months of therapy; liver function tests periodically; signs of bleeding
 - * Discontinue ticlopidine if the absolute neutrophil count drops to <1200 or platelet count drops to <80,000.

Adverse drug reactions (Table 33)

Table 33

Thienopyridine Adverse Reactions

Clopidogrel	Chest pain, headache, dizziness, abdominal pain, vomiting, diarrhea, arthralgia, back pain, upper respiratory infections, flu-like symptoms; <1% blood dyscrasias, bleeding, rash
Ticlopidine	Rash, nausea, dyspepsia, diarrhea; 2.4% neutropenia; <1% blood dyscrasias, thrombotic thrombocytopenic purpura (TTP), bleeding

Table 34

Thienopyridine Drug-Drug Interactions

Interacting medication	Effect
ASA, GPI, UFH, LMWH, NSAIDs, warfarin	Combination may increase the risk of bleeding
CYP450-2C9 substrates (phenytoin, fluvastatin, NSAIDs, losartan, irbesartan, valsartan)	May have increased serum levels

Drug-drug interactions (Table 34)**Drug-disease interactions**

- PUD or other active bleeding

Contraindications

- Hypersensitivity to an individual product
- Active bleeding (eg, PUD or intracranial hemorrhage)
- Severe liver disease
- **Ticlopidine: neutropenia, thrombocytopenia**

Patient instructions/counseling

- Combination with ASA is necessary in patients receiving stents
- Avoid additional ASA, salicylates, and NSAID products unless under the direction of a physician
- Notify physician for unusual bleeding or bruising, blood in the urine, stool, or emesis; skin rash or yellowing of the skin or eyes.
- Do not stop taking without discussing with physician.

Glycoprotein IIb/IIIa receptor inhibitors (GPI)**Mechanism of action**

- Blockade of the GP receptor prevents fibrinogen bind-

Table 35

Pharmacologic Properties of the Glycoprotein IIb/IIIa Receptor Inhibitors

Drug	Chemical nature	Duration of effect	Renal elimination	Renal dosing adjustment
Abciximab (ReoPro®)	Antibody	>12 h. Note: action can be reversed by a platelet infusion	No	No
Eptifibatide (Integrilin®)	Nonpeptide	4-8 h	Yes	Yes
Tirofiban (Aggrastat®)	Peptide fragment	4 h	Yes	Yes

ing, thus inhibiting platelet aggregation; the receptor is the final common pathway for platelet aggregation.

Properties of individual agents (Table 35)**Indications and dose (Table 36)****Monitoring parameters**

- Hematocrit/hemoglobin, platelet count, PT/aPTT, activated clotting time (ACT) with PCI

Adverse drug reactions

- Bleeding, thrombocytopenia, allergic reaction from repeated exposure (abciximab)

Drug-drug interactions

- ASA, clopidogrel, UFH, LMWH, NSAIDs and warfarin may increase the risk of bleeding if used in combination with GPI

Drug-disease interactions

- PUD or other active bleeding

Contraindications

- Active bleeding
- Platelet count <100,000
- History of intracranial hemorrhage, neoplasms, AV malformations, or aneurysm
- History of stroke within the past 30 days or any history of hemorrhage stroke
- Severe hypertension (BP >180/110 mm Hg)

Table 36

Indications and Doses of the Glycoprotein IIb/IIIa Receptor Inhibitors

Drug	Indication	Dose
Abciximab (ReoPro)	Adjunct to PCI or when PCI is planned within 24 hours	0.25 mg/kg IV bolus, 0.125 mg/kg infusion continued for 12 hours postprocedure; maximum length of infusion: 18-24 h
Eptifibatide (Integrilin)	Adjunct to PCI	180 mcg/kg IV bolus x 2, 10 minutes apart; 2 mcg/kg/min infusion (SCr >2 mg/dL or CrCl <50 mL/min; 1 mcg/kg/min) started after the 1st bolus and continued for 18-24 h postprocedure
	Patients with ACS managed with or without PCI	180 mcg/kg IV bolus, 2 mcg/kg/min infusion (SCr >2 mg/dL or CrCl <50 mL/kg; 1 mcg/kg/min) continued for 18-24 h postprocedure; maximum length of infusion: 96 hours
Tirofiban (Aggrastat)	Adjunct to PCI	0.4 mcg/kg IV bolus over 30 minutes, 0.1 mcg/kg/min infusion for 72 h; minimum infusion time: 48 h
		OR
	Patients with ACS managed with or without PCI	10 mcg/kg IV bolus over 3 minutes followed by 0.15 mcg/kg/min infusion for 36 h 0.4 mcg/kg IV bolus over 30 minutes, 0.1 mcg/kg/min infusion for 72 h
		Note: If CrCl <30 mL/min, bolus and infusion are reduced by 50%

- Major surgery within the past 6 weeks
- SCr >4 mg/dL or dialysis dependent (eptifibatide only)

Anticoagulants**Heparin**

Mechanism of action

- Enhances the action of antithrombin III, thereby inactivating thrombin and preventing the conversion of fibrinogen to fibrin

Dose

- UA/NSTEMI: 60-70 units/kg (maximum 5000 units) IV bolus, 12-15 units/kg/h (maximum 1000 units/h) infusion titrated to an aPTT 1.5-2 times control
- STEMI (in combination with tPA, rPA or tenecteplase):
 - * 60 units/kg (maximum 4000 units) IV bolus, 12 units/kg/h (maximum 1000 units/h) infusion
 - * Titrate to an aPTT of 1.5-2 times control for 48 hours.

Monitoring parameters

- aPTT, PT, platelet count, hemoglobin/hematocrit, signs of bleeding, ACT (w/PCI)

Adverse drug reactions

- Bleeding, thrombocytopenia, hemorrhage, epistaxis, allergic reactions, osteoporosis.
- Protamine can be used to reverse the effects of heparin. Dose: 1 mg of protamine neutralizes 100 units of heparin.

Drug-drug interactions

- ASA, clopidogrel, GPI, NSAIDs, and warfarin may increase the risk of bleeding if used in combination with UFH.
- LMWH: combination may increase the risk of bleeding and has been reported to cause death.

Drug-disease interaction

- PUD or other active bleeding

Contraindications

- History of heparin-induced thrombocytopenia (HIT)
- Severe thrombocytopenia
- Active bleeding
- Suspected intracranial hemorrhage

Low molecular weight heparin (LMWH)

Mechanism of action

- Same mechanism as heparin; stronger inhibitor of thrombin (factor Xa)

Properties (Table 37)

Dose

- Enoxaparin (Lovenox): 1 mg/kg SC q12h (CrCl <30 mL/min: 1 mg/kg SC q24h)
- Dalteparin (Fragmin): 120 IU/kg q12h (maximum 10,000 IU q12h)

Monitoring parameters

- Platelet count, hemoglobin/hematocrit, anti-Xa levels, signs of bleeding
- **Note:** It is not necessary to monitor aPTT, PT.

Table 37

Properties of Low Molecular Weight Heparin versus Unfractionated Heparin

Drug	Half-life	MW (daltons)	Anti-Xa: Anti-IIa	Renal elimination
Enoxaparin	4.5 h	4500	2.7:1	Yes
Dalteparin	3-5 h	5000	2.0:1	Yes
UFH	1 h	15,000	1:1	No

Adverse drug reactions

- Bleeding, thrombocytopenia, hemorrhage, epistaxis

Drug-drug interactions

- ASA, clopidogrel, GPI, NSAIDs, and warfarin may increase the risk of bleeding if used in combination with LMWH.
- UFH: combination may increase the risk of bleeding and has been reported to cause death.

Drug-disease interactions

- PUD or any active bleeding.

Warnings

- Patients with recent or anticipated epidural or spinal anesthesia are at risk of hematoma and subsequent paralysis.

Contraindications

- Severe thrombocytopenia
- Active bleeding
- Suspected intracranial hemorrhage

Thrombolytic Therapy**Mechanism of action**

- Acts either directly or indirectly to activate or convert plasminogen to plasmin to lyse a formed clot; the conversion of plasminogen to plasmin activates the body's natural thrombolytic/fibrinolytic system, which lyses the clot and releases fibrin degradation products.

Dose (Table 38)**Monitoring parameters**

- CBC, ECG, aPTT, signs of bleeding, signs of reperfusion

Adverse drug reactions

- Bleeding, intracranial hemorrhage (<1%), stroke (<2%), epistaxis

Drug-drug interactions

- ASA, clopidogrel, GPI, UFH, LMWH, NSAIDs and warfarin may increase the risk of bleeding if used in combination with thrombolytics.

Table 38

Thrombolytic Doses

Drug	Dose
Streptokinase (SK, Streptase®)	1.5 million units in 50 mL of normal saline or D ₅ W given over 60 minutes
Tissue plasminogen activator (tPA, Alteplase®)	15-mg IV bolus, followed by 0.75-mg/kg IV infusion over 30 minutes (not to exceed 50 mg); then 0.5-mg/kg IV infusion over 1 hour (not to exceed 35 mg)
Retepase (rPA, Retevase®)	10 U IVP over 2 minutes, followed in 30 minutes by a repeat 10-U IV bolus over 10 minutes
Tenecteplase (TNK, TNKase®)	<60 kg give 30-mg IV bolus; 60-69.9 kg give 35-mg IV bolus; 70-79.9 kg give 40-mg IV bolus; 80-89.9 kg give 45-mg IV bolus; >90 kg give 50-mg IV bolus;

Note: Each bolus is given over 5 seconds.

Contraindications (Table 39)

Table 39

Contraindications and Cautions for Fibrinolytic Use**Contraindications:**

1. Any prior intracranial hemorrhage.
2. Known structural cerebrovascular lesion.
3. Ischemic stroke within 3 months; except acute ischemic stroke within 3 hours
4. Known intracranial neoplasm (primary or metastatic)
5. Active internal bleeding or bleeding diathesis (does not include menses)
6. Suspected aortic dissection
7. Significant closed head or facial trauma within 3 months

Relative contraindications:

1. Severe uncontrolled hypertension (BP >180/110 mm Hg)
2. History of prior ischemic stroke greater than 3 months, dementia, or known intracerebral pathology not covered in contraindications
3. Current use of anticoagulants in therapeutic doses (INR >2-3)
4. Traumatic or prolonged (>10 min) CPR or major surgery (<3 wk)
5. Noncompressible vascular punctures
6. Recent (within 2-4 weeks) internal bleeding
7. For streptokinase: prior exposure (especially within 5 d-2 y) or prior allergic reaction
8. Pregnancy
9. Active peptic ulcer
10. History of chronic severe hypertension

10. Key Points

- Angina is a syndrome described as discomfort or pain in the chest, arm, shoulder, back, or jaw. Angina is frequently worsened by physical exertion or emotional stress and is usually relieved by sublingual nitroglycerin (NTG). Patients with angina usually have coronary artery disease (CAD).
- Anginal symptoms are caused by a decrease in O_2 supply due to reduced flow.
- The goals for treating stable angina are to prevent death, reduce symptoms, and improve quality of life.
- Aspirin has been shown to decrease the incidence of MI, adverse CV events, and sudden death in patients with coronary artery disease.
- β -Blockers are first-line therapy for treatment of angina in patients with or without a history of MI if there are no contraindications.
- Patients prescribed nitrates for treatment of angina need to be counseled on their appropriate use.
- Upon hospital presentation with UA/NSTEMI/STEMI, initial therapy for all patients is MONA (morphine, oxygen, nitroglycerin, and aspirin). If there are no contraindications, all patients should be given aspirin therapy for life.
- The first-line anti-ischemic therapy for the treatment of UA/NSTEMI is a β -blocker. If chest pain continues or a β -blocker is contraindicated, a calcium channel blocker or long-acting nitrate should be considered, in that order.
- In addition to aspirin therapy for life, clopidogrel should be administered to all patients who undergo stent replacement for at least 1 month after BMS, 3 months for sirolimus-coated, and 6 months for paclitaxel-coated stents and may be continued up to one year. Long-term treatment with clopidogrel may be beneficial in patients with established vascular disease. Clopidogrel should be withheld for 5-7 days prior to surgery to reduce the risk of major bleeding.
- Any of the available GP IIb/IIIa agents should be considered in patients undergoing a PCI procedure. In patients without a planned PCI, eptifibatide or tirofiban can be used for medical treatment.
- All patients presenting with UA/NSTEMI should receive anticoagulation with UFH or LMWH.
- STEMI differs from UA/NSTEMI in that there is a totally occlusive clot that causes damage across the entire thickness of the myocardial wall. The damage to the heart is more extensive with STEMI and ECG changes differ.
- Primary reperfusion (either percutaneous coronary intervention or fibrinolytic therapy) is the main treatment strategy for STEMI.
- Ventricular remodeling (post-MI) resulting after myocardial damage can be slowed and possibly reversed by using long-term ACE inhibition and β -blockade.
- Secondary prevention of MI should include aspirin, β -blockers, ACE inhibitors, and statin therapy (to achieve an LDL goal of <100 mg/dL; <70 mg/dL in high-risk patients) in all patients who have no contraindications.
- Aldosterone blockade should be considered post-STEMI in patients with an LVEF $\leq 40\%$ and either symptomatic heart failure or diabetes.

11. Questions and Answers

Mr. Smith is a 66-year-old white male who presented to his local physician with complaints of chest pain. He described the pain as sharp, aching, and non-radiating. The pain, which he has had for the past few weeks, has occurred mainly during his daily walk and is usually relieved when he stops to rest.

PMH: HTN, PUD, asthma, CAD

FH: Father died of a stroke at 86; mother age 82 with DM, HF; sister died of MI at 52

SH: Smokes 1 ppd x 40 years; drinks alcohol socially 1-2 times a week

Meds: Proventil MDI 2 puffs prn

Flovent 44 mcg 2 puffs bid

Prilosec 20 mg qd

Aspirin 75 mg qd

HCTZ 25 mg qd

VS: BP 148/92; HR 82; RR 18; Ht 72"; Wt 200 lbs

Labs: (fasting) total cholesterol 226 mg/dL, TG 110 mg/dL, HDL 38 mg/dL, LDL 166 mg/dL, Chem 12-WNL

ECG: Normal (patient currently pain-free)

Cath 6 years ago: Minimal two-vessel disease.

- How would you classify Mr. Smith's chest pain?
 - Unstable angina
 - Stable angina
 - Variant angina
 - Silent Ischemia
 - NSTEMI
- Considering Mr. Smith's situation, which of the following would be the most appropriate therapeutic intervention?
 - SL NTG prn
 - Propranolol
 - Tirofiban
 - Verapamil and SL NTG prn
 - Atenolol, amlodipine and SL NTG
- What additional medication should be considered for Mr. Smith?
 - Ticlopidine
 - Atorvastatin
 - Clopidogrel
 - Eptifibatide
 - Reteplase
- Which of the following effects on myocardial oxygen demand do β -blockers NOT cause?
 - Decrease HR
 - Decrease BP
 - Decrease contractility
 - Peripheral vasodilation
 - Decrease conduction through the AV node
- Which of the following statements is true regarding the use of calcium channel blockers in IHD?
 - Amlodipine and felodipine reduce MVO_2 by decreasing conduction through the AV node
 - They should be used as first-line therapy in patients with stable angina
 - Newer-generation dihydropyridines like nifedipine immediate-release are safe in the treatment of IHD
 - Can use in combination with β -blockers to attenuate the effect of increased sympathetic tone that some dihydropyridines may cause
 - The combination of verapamil and metoprolol in a patient with reduced LV systolic function is safe and well-tolerated by most patients
- Which of the following counseling points should be made to a patient being prescribed SL NTG?
 - Take at the same time each day as directed
 - Keep tablets in their original container
 - Take at the first sign of chest pain; if chest pain is unrelieved, seek emergency medical attention
 - III only
 - I, II, and III
 - I and III only
 - I and II only
 - II and III only
- Which of the following are not considered potential cardiovascular benefits of ACE inhibitors in IHD?
 - Reduce the incidence of MI
 - Reduce the incidence of CV death and stroke in patients at high risk for vascular disease
 - Agents with high tissue ACE inhibition have been proven to be superior and provide better protection
 - ACE inhibitors should be used in all stable angina patients with known CAD who also have diabetes
 - ACE inhibitors have shown greater benefit post-MI in higher-risk patients

8. Which of the following drugs do not appear to interact with an exercise tolerance test (ETT)?
- Nitrates
 - Digoxin
 - Atenolol
 - Flecainide
 - Clopidogrel
9. Ideal properties for a β -blocker in the treatment of UA/NSTEMI include all of the following, EXCEPT
- available in both IV and PO forms
 - low lipophilicity
 - has intrinsic sympathomimetic activity (ISA)
 - does not have ISA
 - cardioselectivity
10. Nitrates decrease oxygen demand via the following mechanism(s):
- Peripheral vasodilation
 - Arterial vasodilation
 - Decreasing contractility
- I only
 - II only
 - I and II only
 - II and III only
 - I, II, and III
11. The possible benefits of LMWH over UFH include all of the following EXCEPT
- predictable response
 - ease of administration
 - no recommended routine monitoring
 - stronger affinity for thrombin
 - no renal adjustment necessary
12. Which of the following β -blocker has ISA activity?
- Tenormin
 - Sectral
 - Inderal
 - Lopressor
 - Coreg
13. Which of the following medications is contraindicated within 24 hours of a nitrate?
- Metoprolol
 - Quinapril
 - Verapamil

- Sildenafil
- Felodipine

14. The preferred narcotic to relieve chest pain after the use of SL NTG is:
- meperidine
 - oxycodone
 - morphine
 - hydromorphone
 - fantanyl

Questions 15 and 16 refer to this case:

J.O. is a 54-year-old male who presents to the hospital with crushing substernal chest pain and radiation to his left arm. Past medical history is significant for HTN, COPD, and gout. J.O. has a history of smoking x 30 years and occasionally consumes alcohol. Vital signs on admission include BP 170/85; Pulse 72; RR 18; Temp 97. Before admission the patient was taking enteric coated aspirin 81 mg qd; Combivent inhaler two puffs qid; Tiazac 240 mg qd; allopurinol 300-mg qd.

Allergies: sulfa

Lab/diagnostic tests:

- ECG: ST-segment depression, T-wave changes
- Troponin: T-positive x 3
- Ejection fraction: <35%
- LDL: 135 mg/dL

Diagnosis:

- NSTEMI
- Heart Failure

15. What is the preferred β -blocker for this patient?
- Propranolol
 - Carvedilol
 - Labetalol
 - Atenolol
 - Nadolol
16. All of the following therapies should be considered in this patient, EXCEPT
- reteplase
 - clopidogrel
 - enalapril
 - simvastatin
 - eptifibatide

Questions #17-18 refer to this case:

S.D. is a 56-year-old female who presents to the local ER complaining of crushing, substernal CP x 3 hours, which has been unrelieved by SL NTG. PMH is pertinent for HTN, T2DM, hypercholesterolemia, and metabolic syndrome. Heart rate and rhythm are regular and no S₃ or S₄ sounds are present. Vital signs include BP 184/119, HR 100, and RR 32/min. S.D.'s ECG shows ST-segment elevation >1 mm in leads II, III, and aVF. She is immediately admitted to the chest pain center and started on oxygen.

17. Which of the following criteria for the diagnosis of MI are present in S.D.?
 - A. Chest pain symptoms relieved by SL NTG
 - B. ST-segment elevation >1 mm in two or more noncontiguous leads
 - C. Chest pain symptoms with ECG changes that are consistent with myocardial ischemia or necrosis
 - D. S.D. does not meet the criteria for MI based on the above presentation, because myocardial enzymes have not been evaluated
 - E. Since S.D. has negative enzymes, MI is ruled out
18. Which of the following agents should be administered to S.D.?
 - A. tPA 100 mg IV over 90 minutes
 - B. IV magnesium
 - C. Prophylactic lidocaine
 - D. Metoprolol 5 mg IV
 - E. Cardizem 240 mg
19. What medications should a patient who is post-MI with preserved LVEF receive as discharge therapy?
 - A. Aspirin, Plavix, Cardizem, and simvastatin
 - B. Aspirin, metoprolol, enalapril, atorvastatin, and SL NTG
 - C. Plavix, metoprolol, enalapril, and simvastatin
 - D. Morphine, aspirin, SL NTG, and Lovenox
 - E. Morphine, IV NTG, aspirin, and oxygen
20. The anticoagulant effect of unfractionated heparin requires the binding to which plasma co-factor?
 - A. Thrombospondin
 - B. Antithrombin III
 - C. Plasminogen
 - D. Factor XIIa
 - E. Factors II, VII, IX, and X

S.P. is a 45-year-old marathon runner. He presents to the emergency department with complaints of chest pain during his morning run. His father died of a myocardial infarction at age 48. His past medical history is positive for angina, hyperlipidemia, and hypertension. His current medications include aspirin, pravastatin, nifedipine, and clonidine. His electrocardiogram is consistent with acute ischemia. His HR is 52/min and BP is 170/100. CBC and Chem-7 are within normal limits.

21. All of the following interventions are appropriate for S.P. EXCEPT
 - A. enoxaparin 1 mg/kg SC bid
 - B. IV metoprolol followed by PO metoprolol
 - C. nitroglycerin SL prn and IV drip titrated to pain and blood pressure
 - D. continue aspirin
 - E. morphine if NTG does not control the pain
22. Which one of the following agents is not indicated in the setting of STEMI when pharmacologic reperfusion is the planned strategy?
 - A. Eptifibatide
 - B. LMWH
 - C. Aspirin
 - D. tPA
 - E. Metoprolol
23. Which of the following agents would not be administered at the same time as heparin?
 - A. tPA
 - B. Reteplase
 - C. Eptifibatide
 - D. TNKase
 - E. Streptokinase
24. Which of the following statements about the GPIs is NOT true?
 - A. Abciximab, eptifibatide, and tirofiban are all administered as a bolus followed by a continuous infusion
 - B. It is possible to experience an allergic reaction after repeat exposure of abciximab
 - C. Eptifibatide, tirofiban, and abciximab can all be reversed by a platelet infusion
 - D. Tirofiban and eptifibatide are renally eliminated; therefore, dosage adjustment is required for patients with renal dysfunction
 - E. Abciximab, eptifibatide, and tirofiban are all indicated as adjuncts to PCI

Answers

1. **B.** Angina is considered stable if symptoms have been occurring for several weeks without worsening, it lasts <30 minutes, and is relieved by rest or SL NTG.
2. **D.** This regimen will help control his angina without β_2 -blocking effects in this asthmatic patient, as well as lower his BP. SL NTG will be useful for acute attacks. **A** is not the best answer, as this patient also needs a medication to lower his BP. **B** is incorrect, as propranolol is not β_1 -selective and could worsen his asthma. **C** is incorrect, as GP IIb/IIIa inhibitors are not indicated in stable angina. **E** is incorrect; combination therapy is not recommended as first-line therapy and should only be considered when initial treatment with a β -blocker is not successful.
3. **B.** Mr. Smith has an elevated LDL with known heart disease and he needs to be treated to a goal LDL of <100 mg/dL (consider LDL <70 mg/dL). **A** and **C** are incorrect; these antiplatelet agents are not indicated for treating stable angina unless a patient cannot tolerate aspirin. **D** and **E** are incorrect, as glycoprotein IIb/IIIa inhibitors and thrombolytics are not indicated in stable angina.
4. **D.** β -Blockers do not cause peripheral vasodilation like nitrates or calcium channel blockers.
5. **D.** The increased sympathetic tone caused by some dihydropyridines can lead to a reflex tachycardia, which would be detrimental in an IHD patient. Therefore, using a β -blocker to block this effect would be desirable. **A** is incorrect; the dihydropyridines do not decrease conduction through the AV node like verapamil or diltiazem. **B** is incorrect; CCBs are not indicated as first-line therapy unless a patient has a contraindication to a β -blocker. **E** is incorrect, as both verapamil and metoprolol can lead to worsening systolic function, and used in combination would be unsafe.
6. **E.** SL NTG should be kept in the original amber bottle, as exposure to light or extreme temperatures will cause it to lose potency. **III** is correct and patients should be counseled to take 1 tablet and seek medical attention if chest pain is not relieved. **I** is incorrect; SL NTG is used on a prn basis and should not be taken at the same time each day.
7. **C.** It has not been proven that so-called "tissue" ACE inhibitors are better than other ACE inhibitors.
8. **E.** Clopidogrel, or Plavix, does not have any pharmacologic interaction with an ETT. Digoxin can cause an abnormal exercise-induced ST depression in ~30% of healthy patients. β -Blockers and vasodilators can alter hemodynamic response to BP and should be withdrawn gradually 4-5 half-lives before ETT. Nitrates can attenuate angina and flecainide may cause exercise-induced ventricular tachycardia.
9. **C.** It has ISA. β -Blockers with ISA reduce heart rate to a lesser degree than non-ISA β -blockers, thus producing a smaller decrease in oxygen demand. Ideally, a β -blocker used for the treatment of UA/NSTEMI would be available in IV and PO formulations. In addition, it would have β_1 -receptor selectivity, no ISA, and low lipophilicity.
10. **C.** Nitrates are vasodilators acting on both arteries and in the periphery, thereby decreasing preload and afterload. As far as anti-ischemic therapy, only β -blockers and nondihydropyridine calcium channel blockers reduce contractility.
11. **E.** Renal adjustment is necessary with LMWH. UFH does not require dosage adjustment in renal patients and is preferred to LMWH in patients with a CrCl <30 mL/min. LMWH does appear to have advantages over UFH in ease of administration, its affinity to thrombin (stronger than UFH), its more predictable response, and the fact that it does not require monitoring.
12. **B.** β -Blockers with ISA activity include Sectral (acebutolol), Cartrol (carteolol), Levatol (penbutolol), and Visken (pindolol). Tenormin (atenolol), Inderal (propranolol), Lopressor (metoprolol), and Coreg (carvedilol) do not have ISA activity.
13. **D.** Sildenafil. Viagra (sildenafil) use is contraindicated within 24 hours of a nitrate. Likewise, if sildenafil has been used within 24 hours, a nitrate cannot be used. β -Blockers (metoprolol), ACE inhibitors (quinapril), and calcium channel blockers (verapamil, felodipine) can be safely combined with nitrates.

14. **C. Morphine.** Morphine has vasodilator properties, thereby decreasing both preload and afterload, which decreases oxygen demand. In addition, morphine lowers heart rate by relieving pain and anxiety. If a true morphine allergy exists, meperidine may be used as an alternate agent. Oxycodone, hydromorphone, and fentanyl are not recommended for the treatment of anginal pain.
15. **D. Atenolol.** With the patient's history of COPD, a β_1 -blocker with β_1 -receptor selectivity is preferred. The only agent with β_1 -selectivity in this list is atenolol. All of the remaining agents are nonselective.
16. **A. Reteplase.** Reteplase is a thrombolytic agent, which does not have a role in the treatment of NSTEMI. Thrombolytic therapy is indicated for the treatment of STEMI. Clopidogrel and GPI (eptifibatide) should be considered in all patients with NSTEMI with or without PCI. Eptifibatide and tirofiban can be used in patients who are medically managed; abciximab is reserved for patients with a scheduled PCI procedure. Lipid-lowering therapy with an HMG-CoA reductase inhibitor (eg, simvastatin) should be initiated in this patient due to his LDL level of >130 mg/dL. This patient has a clear indication for an ACE inhibitor (enalapril) due to his EF of $<40\%$.
17. **C.** A is incorrect, as chest pain unrelieved by NTG is a diagnostic criterion for MI, but two criteria must be present before the diagnosis can be made. B is incorrect because ST-segment elevation >1 mm must be found in two or more contiguous leads. S.D. has both CP symptoms and ECG changes that are consistent with myocardial infarction. C is correct because she meets two of the three criteria for diagnosing MI. S.D. does not have positive enzymes, which would meet the third diagnostic criteria. D is incorrect because positive enzymes do not have to be present for the diagnosis of MI to be made (as in the case with S.D.).
18. **D.** One of the relative contraindications to fibrinolytic therapy is severe uncontrolled hypertension (BP $>180/110$ mm Hg). A is not appropriate in this patient with BP of 184/119 mm Hg. Routine use of magnesium post-MI is not recommended and should only be reserved for patients with hypomagnesemia. No labs were given for S.D., so answer B is not appropriate at this time. Prophylactic lidocaine has been shown to increase all-cause mortality, and is not recommended in the early management of STEMI for prevention of VF. Therefore, C is incorrect. β -Blockers reduce the incidence of ventricular arrhythmias, recurrent ischemia, reinfarction, infarct size, and mortality in patients with STEMI. Since S.D. does not have any contraindications to β -blockade, D is the correct choice. E, calcium channel blockers, do not have a role in STEMI when a β -blocker can be given.
19. **B.** ACE inhibitors, β -blockers, aspirin, statin therapy, and SL NTG should be given to all patients without contraindications post-MI. Plavix can be combined with aspirin, and can be continued for 1 to 9 months. All of the answers including Plavix are incorrect, however, because A omits β -blockade, and C omits aspirin therapy. Calcium channel blockers can be given if a patient has contraindications to β -blockade, but it is not recommended as first-line treatment. Answers D and E are incorrect because ACE inhibition and β -blockade are omitted. Answer E would be a correct choice for the immediate treatment of someone who presents with STEMI, but not as discharge medications.
20. **B.** Heparin's anticoagulant effect requires binding to antithrombin (previously antithrombin III), and that binding converts antithrombin from a slow, progressive thrombin inhibitor to a very rapid inhibitor of thrombin and factor Xa.
21. **B.** One of the contraindications to β -blockade is a HR <55 bpm. Since S.P. has a HR of 52 bpm at this time, the only inappropriate therapy out of the above choices would be B. Enoxaparin, NTG, morphine, and aspirin are all therapies that should be continued.
22. **A.** GP IIb/IIIa inhibition is still controversial in the setting of STEMI, especially when a fibrinolytic agent is administered. The role of platelet GPI in STEMI is rapidly evolving, and trials to date in combination with full- and half-dose fibrinolytic agents have shown a more complete reperfusion at the price of higher bleeding rates. At this point, there is no formal recommendation on using eptifibatide or another GPI in STEMI.

23. **E.** A GPI should be administered with heparin, and therefore **C** is not the correct answer. Combination of UFH with streptokinase (SK) is less desirable because it is a nonspecific fibrinolytic, and UFH may increase the risk of bleeding because of SK's long half-life. Therefore, answer **E** is the correct choice. Heparin should be administered for at least 48 hours with the other lytic choices to reduce risk of reocclusion.
24. **C.** The only GPI that is reversed by a platelet infusion is abciximab. All of the remaining selections are true statements. All of the available GPI agents are administered as a bolus and infusion. **A**, abciximab, is a monoclonal antibody; therefore it is possible to develop an allergic reaction upon rechallenge. There are only two GPIs that are renally eliminated: eptifibatide and tirofiban. All of the agents are indicated as adjunct to PCI, so **E** is true.

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12. Hyperlipidemia

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1. Hyperlipidemia
2. Drug Therapy
3. Nondrug Therapy
4. Key Points
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1. Hyperlipidemia

- **Hyperlipidemia** is an elevation in the blood concentration of a **lipid** such as cholesterol or triglyceride (in the form of lipoprotein).
- **Dyslipidemia** refers to any lipid disorder.
- **Lipids** include **cholesterol**, **triglycerides** (TG), and **phospholipids**.
- Lipoproteins: **apolipoproteins + cholesterol + triglyceride + phospholipids**
- Major lipoproteins are **chylomicrons**, **very-low density lipoproteins** (VLDL), **intermediate-density lipoproteins** (IDL), **low-density lipoproteins** (LDL), **high-density lipoproteins** (HDL), and **lipoprotein (a)**.
- Apolipoproteins: structural components of lipoproteins
- Friederwald equation: formula used to calculate LDL:

$$\text{LDL} = \text{total cholesterol} - (\text{HDL} + \text{TG}/5)$$

Classification of Lipids

- Total cholesterol, LDL, HDL, and triglycerides are measured in **mg/dL**.
- ATP III: Adult Treatment Panel III recommendations from the National Cholesterol Education Program [NCEP] are shown in Table 1.

Clinical Presentation

- Hyperlipidemia can cause **atherosclerosis**, **atheroma formation**, **atherothrombosis**, and the subsequent consequences of these disease processes:
 - * **Coronary artery disease** (angina and myocardial infarction)
 - * **Cerebrovascular disease** (TIA and/or stroke)
 - * **Peripheral arterial disease** (intermittent claudication)
 - * A state of elevated lipids alone generally promotes no symptoms except in some familial lipid disorders, in which there may be cutaneous manifestations of lipid **deposition** (eg, **tendon xanthomas**, **planar xanthomas**, **xanthelasmas**, and **eye manifestations** [**corneal arcus**]).

Pathophysiology of Atherosclerosis

- Progressive, systemic disease starting early in life
- * Atheroma lesions, called fatty streaks, develop in the arterial vascular walls and result from the accumulation of cholesterol within vessel walls.

Table 1

Classification of Lipids

LDL cholesterol: primary target of therapy

<100	Optimal
100-129	Near optimal/above optimal
130-159	Borderline high
160-189	High
≥190	Very high

Total cholesterol

<200	Desirable
200-239	Borderline high
≥240	High

HDL cholesterol

<40	Low
≥60	High

Triglycerides: secondary target of therapy after LDL

<150	Normal
150-199	Borderline high
200-499	High
>500	Very high

- * Atheroma lesions may lead to **occlusion** by thrombus or embolus formation.
- * LDL cholesterol accumulates below the **intimal** surface of the artery. General guideline: the higher the cholesterol elevation in the blood, the more **LDL** migrates into the artery.
- * Endothelial dysfunction occurs, and this increases **LDL** cholesterol's permeability.
- * LDL becomes oxidized and recruits monocytes.
- * Monocytes are transformed into **macrophages** and ingest the **oxidized LDL**.
- * This process results in **lipid-filled cells** called **foam cells**.
- * Foam cells are the initial lesion of atherosclerosis. Growth factors are produced by macrophages.
- * Other processes are also occurring (eg, additional endothelial cell injury and inflammatory responses that can further accelerate the development of plaque).
- * Elevated cholesterol and hyperlipidemia enhance this process.
- * **Plaque** may continue to develop, may become stable, or it may **rupture**.

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- * Plaque rupture exposes atherogenic materials in the lesion to blood.
- * Platelets are activated and a clot may form.
- * Partial occlusion or obstruction can result in angina; complete occlusion results in myocardial infarction.
- * Other vascular beds promote similar outcomes.

Diagnostic Criteria

- Lipid disorders (dyslipidemias) are classified as familial or secondary.
 - * Familial disorders usually are caused by a defect in lipid metabolism.
 - Categorized into the hypercholesterolemias and the combined hyperlipidemias
 - Assessment of fasting lipid panels provides diagnostic information and classification of lipid disorders.
 - Familial hypercholesterolemia (FH): LDL = 250-450 mg/dL
 - Familial defective apolipoprotein B-100
 - Polygenic hypercholesterolemia is the most common form (LDL = 160-250 mg/dL)
 - * Combined hyperlipidemias:
 - Familial combined hyperlipidemia (FCH): (LDL = 160-250 mg/dL and triglycerides = 200-800 mg/dL)
 - Familial hyperapobetalipoproteinemia
 - Hypoalphalipoproteinemia
 - Dysbetalipoproteinemia
 - Elevated Lp(a)
- These disorders are characterized by variations in the amounts of LDL, IDL, VLDL, and HDL.
- The most common secondary causes of lipid disorders:
 - * Diabetes mellitus
 - * Hypothyroidism
 - * Renal failure
 - * Obstructive liver disease
 - * Drugs such as β -blockers, thiazide diuretics, oral contraceptives, oral estrogens, glucocorticosteroids, and cyclosporine
- Risk factors are used to assess the potential for an individual to develop coronary heart disease (CHD) or another equivalent atherosclerotic process over the next 10 years. The Framingham Global Risk Score is calculated to provide this information. The major nonlipid risk factors for CHD are counted and used to assess the 10-year risk of developing CHD.
- Major nonlipid risk factors for CHD:
 - * Cigarette smoking
 - * Hypertension (BP $\geq 140/90$ mm Hg or on anti-hypertensive medication)
 - * Low HDL cholesterol (<40 mg/dL)

- * Family history of premature CHD (CHD in a male first-degree relative aged <55 years and CHD in a female first-degree relative aged <65 years)
- * Age (men ≥ 45 years; women ≥ 55 years)
- HDL ≥ 60 mg/dL counts as a negative risk factor and acts to remove one of the other risk factors from the total count.

Treatment Principles

- Treatment and target lipid goals are based on the estimation of risk for coronary heart disease using the Framingham Global Risk Score.
- If a patient has a form of clinical CHD, such as angina, myocardial infarction, stroke, or transient ischemic attack, he or she is considered to be at high risk for another ischemic event within the next 10 years.
- Those at highest risk require the most aggressive therapy (ie, drug therapy and achieving the lowest possible LDL level). The major nonlipid risk factors above are used in the risk analysis for those individuals who do not have CHD or a CHD risk equivalent. Table 2 identifies risk categories, lipid goals, and risk of event.
- Treatment consists of lifestyle changes, ie, therapeutic lifestyle changes (TLC), which are discussed in the nonpharmacologic and pharmacotherapy sections of this chapter.
- Algorithm for drug therapy in primary prevention ($<20\%$ risk):
 - * Initiate LDL-lowering drug therapy (statins, niacin, resin) for 6 weeks. If LDL goal is not met, intensify LDL-lowering therapy (higher dose or combination) for 6 weeks. If LDL goal is still not achieved, intensify drug therapy or

Table 2

Risk Categories, Lipid Goals, and Risk of Event

Risk category	LDL goal	Risk of event
CHD and CHD risk equivalent ¹	<100 mg/dL	$>20\%$ over 10 years
Multiple risk factors (2+)	<130 mg/dL	10-20% over 10 years
0-1 Risk factor	<160 mg/dL	$<10\%$ over 10 years

¹CHD risk equivalent = clinical CHD, symptomatic carotid artery disease, peripheral arterial disease, abdominal aortic aneurysm, and diabetes.

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refer to a lipid specialist for 4-6 months.

Monitor response and adherence. **استال**

- Drug therapy in secondary prevention (>20% risk):
 - * The most aggressive treatment is required.
 - * A large LDL reduction requires a statin and possibly a statin in combination with another agent. Follow the same algorithm as outlined in primary prevention above.

Monitoring (Clinical Evaluation)

- **Screening:** The National Cholesterol Education Program (NCEP) Adult Treatment Panel III (ATP III) recommends that starting at age 20, adults receive a fasting lipid profile (FLP). If this is normal, then repeat in 5 years.
- Children do not need to be screened without the presence of significant family history or other reasons to test the lipids.

Monitoring

- The main tool is fasting lipid profile (FLP).
 - * Baseline FLP is done before drug or dietary interventions.
 - * After therapeutic lifestyle changes and/or drug therapy is started, monitor every 6 weeks times two initially, again in 4-6 months, and then periodically thereafter (usually annually). Results of FLP will show the effects of lifestyle and drug therapy interventions and help direct changes in therapy.

2. Drug Therapy

- See Tables 3, 4, and 5 for details on dosing, efficacy, and drug combinations.

Lower LDL **أدوية د**

Statins

- Conduct baseline liver function tests (LFTs) and creatine kinase (CK) before therapy is initiated. LFTs should be repeated again in 4-6 weeks, at 3 months, and then periodically (usually annually).
- Creatine kinase needs to be monitored only if the patient has suspected muscle damage.
- Assess effectiveness at 6 weeks.

Resins

- Determine baseline FLP to screen for hypertriglyceridemia.
 - * If TG >200 mg/dL, use with caution.
 - * Contraindicated if TG >400 mg/dL
- Assess effectiveness at 6 weeks.

Nicotinic acid

- Determine baseline fasting glucose, LFTs, and serum uric acid levels before initiating therapy.
- Repeat these tests 4-6 weeks after each dose level is reached.
- Sustained-release niacin requires monthly LFT readings while dosage is titrated; subsequent LFT readings should occur every 12 weeks for the first year and then periodically.
- Diabetics require routine fasting glucose tests.
- Monitor serum uric acid after the highest dose level is achieved in those with a history of hyperuricemia or gout. **النقرص**
- Assess effectiveness at 6 weeks.

Fibric acids

- Determine baseline fasting lipid panel (total cholesterol, HDL, LDL, and TG) before therapy and again at 3 and 6 months.
- Monitor changes in triglycerides at 3 months and assess effectiveness.

Cholesterol inhibitors

- Determine baseline lipid panel.
- Assess effectiveness at 6 weeks.

Mechanism of Action

HMG-CoA reductase inhibitors (statins)

- Competitively inhibit HMG-CoA reductase, which is the enzyme responsible for conversion of HMG-CoA to mevalonate.
- Mevalonate is an early precursor and a rate-limiting step in cholesterol synthesis. This reduction in liver

Table 3

Drug Products and Dosage

Generic name (trade name)	Dosage range and schedule	Dosage form and strength
Statins		
Atorvastatin (Lipitor)	10-80 mg/d qhs	10-, 20-, 40-, 80-mg tablet
Fluvastatin (Lescol)	20-80 mg/d qhs	20- and 40-mg capsule; 80-mg XL tablet
Lovastatin (Mevacor)	20-80 mg/d qhs	10-, 20-, 40-mg tablet
Lovastatin extended-release (Altoprev)	10-60 mg/d qhs	10-, 20-, 40-, 60-mg tablet
Pravastatin (Pravachol)	20-80 mg/d qhs	10-, 20-, 40-, 80-mg tablet
Simvastatin (Zocor)	20-80 mg/d qhs	5-, 10-, 20-, 40-, 80-mg tablet
Rosuvastatin (Crestor)	5-40 mg/d hs	5-, 10-, 20-, 40-mg tablet
Bile acid sequestrants		
Cholestyramine (Questran)	4-16 g/d divided	Powder
Colestipol (Colestid)	5-20 g/d divided	Powder/tablet
Colesevelam (WelChol)	2.6-3.8 g/d (once or bid)	625-mg tablet
Nicotinic acid		
Immediate release (Niacor)	1.5-3 g/d (divided tid)	500-mg tablet
Sustained release (Slo-Niacin)	1-2 g/d qhs	250-, 500-, 750-mg tablet
Extended release (Niaspan)	1-2 g/d qhs	500-, 750-, 1000-mg tablet
Fibric acids		
Gemfibrozil (Lopid)	600 mg before meals bid	600-mg tablet
Fenofibrate (Tricor)	48-145 mg/d	48-, 145-mg tablet
Cholesterol inhibitors		
Ezetimibe (Zetia)	10 mg/d	10-mg tablet
Combinations		
Aspirin + pravastatin (Pravigard PAC)	81/20-325/80 mg qhs	81/20-, 81/40-, 81/80-mg tablets 325/20-, 325/40-, 325/80-mg tablets (Note: Aspirin tablets and pravastatin tablets are separate tablets within the PAC)
Ezetimibe + simvastatin (Vytorin)	10/10-10/80 mg qhs	10/10-, 10/20-, 10/40-, 10/80-mg tablet
Lovastatin + Niaspan (Advicor)	20/500-40/2000 mg/d	20/500-, 20/750-, 20/1000-mg tablets

cholesterol synthesis results in upregulation of liver **LDL** receptors and increased clearance of **LDL** and **VLDL** particles in the blood. These actions induce a decrease in total cholesterol and LDL cholesterol, promote a slight increase in HDL cholesterol, and affect a modest decrease in triglycerides.

Bile acid sequestrants (BAS or resins)

- Nonabsorbable anion exchange resins exchange chloride ions for bile acids and other anions in the intestine.

- This inhibits enterohepatic recycling, which results in bile excretion and a decrease in the cholesterol pool in the liver.
- LDL receptors are upregulated, increased LDL is cleared, and LDL is lowered.

Niacin

- Reduces LDL cholesterol and triglycerides, increases **HDL**.
- May decrease VLDL synthesis, thereby leading to decreased LDL cholesterol and triglycerides
- Niacin may inhibit metabolism of apolipoprotein A-I, which increases HDL cholesterol.

Table 4

Efficacy of Drugs Used to Treat Hyperlipidemia

Drug class	Lipid/lipoprotein effect
Statins	LDL ↓18-55% HDL ↑5-15% TG ↓7-30%
Resins	LDL ↓15-30% HDL ↑3-5% TG (no change)
Nicotinic acid	LDL ↓5-25% HDL ↑15-35% TG ↓20-50%
Fibric acids	LDL ↓5-20% HDL ↑10-20% TG ↓20-50%
Cholesterol inhibitors	LDL ↓17% HDL ↓1.3% TG ↓6%

Fibric acids (fibrates)

- Reduce triglycerides by reduction of apolipoproteins B, C-III, and E
- Increase HDL by increasing apolipoproteins A-I and A-II

Cholesterol inhibitors (ezetimibe)

- Selectively inhibit intestinal absorption of dietary and biliary cholesterol at the brush border of the small intestine, which results in a decrease in the

absorption of cholesterol and a decrease in cholesterol in the blood.

Patient Instructions and Counseling

Statins

- Usually administered in the evening because most hepatic cholesterol production occurs during the night.
- Lovastatin conventional tablets should be given with the evening meal since absorption is better with food; however, the extended-release lovastatin products should be taken at bedtime.
- The lovastatin + Niaspan combination product should be taken at bedtime with a low-fat snack.
- Non-extended release statins can be dosed once daily.
- Other regular dosage forms should be divided as the doses are raised above 40 mg/d.
- Atorvastatin may be given any time of the day because of its longer half-life.
- Rosuvastatin dosage adjustment is required in patients with severe renal impairment. Plasma concentrations of rosuvastatin increased to a clinically significant extent (about 3-fold) in patients with severe renal impairment ($CL_{CR} < 30 \text{ mL/min/1.73m}^2$) compared with healthy subjects ($CL_{CR} > 80 \text{ mL/min/1.73m}^2$). Dosage adjustment is also required in patients with liver disease.
- Monitor LFTs and muscle toxicity as described above.

Bile acid sequestrants (resins)

- Cholestyramine and colestipol: start with 1 dose daily with the largest meal. May be increased (after the patient adjusts to the resin) to two doses daily with the largest meals or divided between breakfast and dinner.
- Titrate doses slowly to avoid gastrointestinal side effects.
- Powdered doses can be mixed with food such as soup, oatmeal, nonfat yogurt, applesauce, etc. The mixture can also be chilled overnight to improve palatability.
- Do not use carbonated beverages to mix, as this promotes increased air swallowing.
- Drinking through a straw may also help.
- Patients who suffer constipation with the resins may mix them with psyllium; however, this mixture should be ingested immediately after mixing in order to prevent a gel from forming.
- Counsel the patient to rinse the glass to ensure ingestion of all resin.
- Colesevelam is a tablet formulation, which may be easier for some patients to self-administer. However, the tablets are large, and some patients may not be able to swallow them.
- Monitor for adherence and gastrointestinal side effects for all resins.

Table 5

Pharmacotherapeutic Options for Treatment of Hyperlipidemia

Lipid target	Pharmacotherapy
LDL	Statin most potent and effective for large LDL reductions Niacin and resins effective for moderate LDL reductions Combination of statin + niacin; statin + ezetimibe; statin + resin
LDL + TG	Statin + niacin or statin + fibric acid
TG	Fibric acid or niacin

Nicotinic acid (niacin)

- Immediate-release (IR) niacin should be started at a low dose and slowly titrated upward:
 - * Start with 100 mg tid and adjust upward the second week to 200 mg tid; the next week increase to 350 mg tid; the following week raise to 500 mg tid. When 1500 mg/d is reached and maintained for 4 weeks, assess effectiveness before increasing the dose.
 - * If further titration is needed, go to 750 mg tid and assess effectiveness after 4 weeks before increasing. Maximum dose is 1000 mg tid.
 - * Aspirin 325 mg or ibuprofen 200 mg must be given 30 minutes before the morning dose to minimize flushing and itching.
 - * Caution patients to avoid hot beverages and hot showers so as not to exacerbate the flushing effect.
- Extended-release formulation (ER) should be taken at bedtime (500 mg) and titrated weekly to a maximum of 1500 mg/d. Aspirin should be taken 30 minutes before the dose.
- Sustained-release formulations are started at 250 mg bid and increased at weekly intervals to a maximum of 2000 mg/d. Aspirin should be given 30 minutes before the dose.
- Monitor for adherence and side effects. The titration schedule for some patients may have to be gradual due to flushing and itching.

Fibric acids (fibrates)

- Gemfibrozil should be taken twice daily 30 minutes before meals.
- Tricor can be taken with or without food once daily.
- Reduce dose in renal insufficiency and monitor for muscle toxicity, especially when used in combination with statins and niacin.

Cholesterol inhibitors

- Dosed once daily without regard to food
- Can be taken simultaneously in combination with statins

Adverse Drug Events**HMG-CoA reductase inhibitors (statins)**

- Myopathy due to muscle damage
- Myalgia from muscle soreness or tenderness
- Myositis occurs in 0.2% of patients

myalgia + ↑creatinine kinase
(3-10 times upper limit of normal)

- Rhabdomyolysis occurs rarely, but can cause acute renal failure. Stop drug immediately.

severe myositis + creatine kinase

10 x upper limit of normal,

↑serum creatinine and urine myoglobin

- Elevated liver enzymes occur in 0.1-2.3% of patients. Obtain baseline LFTs, repeat at 4-6 weeks, again at 6 months, and yearly thereafter.
- Flu-like symptoms and headache
- Mild GI complaints
- Absolute contraindication in active or chronic liver disease
- Relative contraindication in combination with certain drugs (see drug interactions)

Bile acid sequestrants (resins)

- Gastrointestinal distress
- Palatability problems with the resin slurry
- Constipation that increases with dose and in the elderly
- Decreased absorption of other drugs:
 - * Dose other drugs 1 hour before or 4 hours after resin.
- An absolute contraindication is dysbetalipoproteinemia (highly elevated VLDL) and TG >400 mg/dL.
- Relative contraindication when TG >200 mg/dL

Nicotinic acid (niacin)

- Flushing is common. Pretreat with aspirin (325 mg) 30 minutes before the first niacin dose of the day.
- Hyperglycemia risk; use with caution in diabetics.
- Hyperuricemia (or gout)
 - * Upper GI distress
 - * Hepatotoxicity
 - * Absolute contraindication in chronic liver disease and severe gout
 - * Relative contraindication in diabetes, hyperuricemia, or severe gout

Fibric acids (fibrates)

- Dyspepsia
- Gallstones
- Myopathy increases when combined with statins.
- Absolutely contraindicated in severe renal or severe hepatic disease

Cholesterol inhibitors

- Elevated liver enzymes (same as placebo)
- GI distress (less than with resins)
- Absolutely contraindicated in moderate to severe hepatic disease

Drug-Drug and Drug-Disease Interactions

HMG-CoA reductase inhibitors (statins)

- CYP450 mixed function oxidase enzymes metabolize statins, and drugs that inhibit this process can cause increases in statin concentrations, thus predisposing to myopathy and liver toxicity.
 - Common CYP450 3A4 inhibitors include amiodarone, clarithromycin, cyclosporine, danazol, delavirdine, diltiazem, erythromycin, fluoxetine, fluvoxamine, grapefruit juice, indinavir, itraconazole, ketoconazole, miconazole, nefazodone, nelfinavir, nicardipine, nifedipine, pimozide, propoxyphene, quinidine, ritonavir, saquinavir, sildenafil, tacrolimus, tamoxifen, testosterone, troleandomycin, verapamil, and zafirlukast.
 - Pravastatin is not metabolized by the CYP450 system; therefore, these drug-drug interactions are avoided.
- Absolute contraindication in active or chronic liver disease

Bile acid sequestrants (resins)

- Avoid concomitant use with all other drugs, especially warfarin, digoxin, levothyroxine, tetracycline, fat-soluble vitamins, and minerals.
- Always separate other drugs by 1 hour before use and 4 hours after.
- Colesevelam does not appear to have these drug and nutrient interactions.
- Absolute contraindication in dysbetalipoproteinemia

Nicotinic acid (niacin)

- Use caution in combination with resins.
- Combination therapy with statins and gemfibrozil may cause an increased risk of myopathy.
- Absolute contraindications in chronic liver disease and severe gout

Fibric acids (fibrates)

- Highly protein-bound and metabolized by the CYP450 3A4 enzyme system.
- Increased warfarin effect
- Cyclosporine may increase gemfibrozil concentrations.
- Fenofibrate may have less interaction potential with warfarin and cyclosporine.
- BAS (resins) decrease fibrate absorption.
 - Combinations with statins and niacin may increase the risk of myopathy.
 - Absolute contraindications are severe renal disease and severe liver disease.

Cholesterol inhibitors

- Cyclosporine may increase ezetimibe concentrations.
- Combination with a resin may decrease absorption.

- Combination with a fibric acid may predispose to gallbladder disease.
- Absolute contraindication in moderate to severe hepatic disease

Landmark Clinical Trials with Statins

Primary prevention trials

West of Scotland Study (WOSCOPS)

- This trial with pravastatin showed decreased coronary morbidity and mortality in hypercholesterolemic men with no clinical evidence of coronary heart disease (CHD).

Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TexCAPS)

- This trial with lovastatin showed reduced incidence of first acute major coronary events in patients who did not have CHD but did have normal to mildly elevated total cholesterol and LDL with low HDL.

Secondary prevention trials

Scandinavian Simvastatin Survival Study (4S)

- This trial with simvastatin showed decreased cardiac morbidity and mortality in patients with CHD and elevated cholesterol.

Cholesterol and Current Events Study (CARE)

- This trial with pravastatin showed reduced incidence of myocardial infarction (MI), death from CHD, stroke, and need for revascularization procedures in patients with recent MI and normal cholesterol levels.

Long-term Intervention with Pravastatin in Ischemic Disease Study (LIPID)

- This trial with pravastatin showed reduced mortality and incidence of MI and stroke in patients with CHD and a broad range of cholesterol.

Heart Protection Study (HPS)

- This trial with simvastatin is the largest single cholesterol trial (as of 2002) in patients at high-risk of CHD (prior MI, diabetes, or hypertension) and LDL >135 mg/dL. Antioxidants studied included vitamins E and C and beta-carotene. Simvastatin therapy showed a reduced incidence of CHD regardless of age (also elderly) or pre-existing condition. There was not a threshold for LDL at 100 mg/dL (ie, benefits extended below this level). In addition, there was no cardiovascular protective effect from vitamins E and C and beta-carotene.

3. Nondrug Therapy

- Nonpharmacologic therapy focuses on therapeutic lifestyle changes (TLC), which incorporate dietary changes, physical activity, and weight reduction.
 - * "Heart healthy" nutrition is the foundation for any therapeutic interventions.

General Therapeutic Lifestyle Change (TLC) Recommendations

- Decrease the amount of high-fat foods consumed (especially foods high in saturated fat).
- Decrease intake of high-cholesterol foods.
- Replace saturated fats with monounsaturated fats and fish oils.
- Use foods high in complex carbohydrates (fiber, starch, fruits, vegetables).
- Strive for and maintain an acceptable weight.
- Patients should be instructed on how to read a nutrition label.
- Recommended nutrient makeup of the TLC diet is shown in Table 6.

Algorithm for Therapeutic Lifestyle Changes

- Begin lifestyle therapies and continue for 6 weeks. Evaluate LDL response, and if the LDL goal is not achieved, intensify LDL-lowering therapy (diet + weight management + physical activity) for 6 more weeks. Evaluate LDL response, and if LDL goal is

not achieved, consider adding drug therapy (if not already added). Monitor adherence to TLC every 4-6 months.

Other Nonpharmacologic Therapies

- Soluble fiber and plant sterols/stanols can help lower LDL.
- Viscous or soluble fiber such as psyllium or pectin in the amount of 5-10 g/d, or other sources of fiber such as vegetables, fruits, and whole grains can reduce LDL by up to 8%.
- Fish oils
 - * Active ingredient is omega-3 fatty acid
 - * Can reduce triglycerides as much as 30-60%
 - * Can be added when niacin or fibrates do not control triglycerides
- Antioxidant and vitamin therapy
 - * Recent clinical trials have shown that the antioxidants, vitamins A, C, E, and beta-carotene are not protective for cardiovascular disease.
- Alcohol
 - * Light to moderate alcohol use (1 drink per day for women, 2 drinks per day for men) has been associated with reductions in coronary heart disease rates. The benefit may be potentially due to a rise in HDL.
 - * Use of alcohol should not be encouraged as a means of lowering cholesterol.
 - * Excessive alcohol can cause elevations of triglycerides.
- Alternative therapies
 - * Herbal therapies have not been systematically studied in hyperlipidemia and should not be recommended for treatment of hyperlipidemia or other lipid disorders.

Table 6

Nutrient Makeup of the TLC Diet

Nutrient	Recommended Intake
Saturated fat	<7% of total calories
Polyunsaturated fat	Up to 10% of total calories
Monounsaturated fat	Up to 20% of total calories
Total fat	25-35% of total calories
Carbohydrate	50-60% of total calories
Fiber	20-30 g/d
Protein	About 15% of total calories
Cholesterol	<200 mg/d
Total calories	Individualize to balance energy intake and expenditure to maintain desirable weight and/or prevent weight gain

4. Key Points

- Hyperlipidemia is the elevation of the blood concentration of a lipid such as cholesterol or triglyceride (in the form of lipoprotein).
- There are four major classifications of lipids: total cholesterol, low-density lipoproteins (LDL), high-density lipoproteins (HDL), and triglycerides.
- The process of atherosclerosis begins with atheroma lesions in the arterial vascular walls resulting from the accumulation of cholesterol within vessel walls.
- Polygenic hypercholesterolemia (LDL = 160-250 mg/dL) is the most common form of familial dyslipidemia.
- Major nonlipid risk factors for coronary heart disease (CHD) are cigarette smoking, hypertension, family history of premature CHD, and age (men over 45 years, women over 55 years).
- Persons with a history of CHD such as angina, MI, stroke, or transient ischemic attack are considered at highest risk of having another ischemic event in the next 10 years and require the most aggressive therapy and the lowest target LDL goal (<100 mg/dL).
- Monitoring for drug therapy of hyperlipidemia includes laboratory monitoring for adverse effects (eg, liver function tests, uric acid, and creatine kinase) and fasting lipid profiles (FLPs) for effectiveness.
- The mechanism of action of statin agents to treat hyperlipidemia is to competitively inhibit HMG-CoA reductase, which is the enzyme responsible for conversion of HMG-CoA to mevalonate, which is an early precursor and a rate-limiting step in cholesterol synthesis.
- The statins are usually administered in the evening because most hepatic cholesterol production occurs during the night, except for atorvastatin, which has a longer half-life than the other agents in this class.
- The only class of agents to control hyperlipidemias that is not contraindicated in patients with active or chronic liver disease is the bile acid sequestrant (resin) type.
- Pravastatin is not metabolized by the CYP450 enzyme system and thus avoids most of the drug interactions with the other statin agents.
- Advicor should not be substituted for equivalent doses of immediate-release (crystalline) niacin. For patients switching from immediate-release niacin to extended-release niacin, therapy with the latter should be initiated with low doses (ie, 500 mg once daily at bedtime) and the dose should then be titrated to the desired therapeutic response.

- The bile acid sequestrants (resins) may decrease the absorption of warfarin, digoxin, levothyroxine, tetracycline, fat-soluble vitamins, and minerals.
- The new formulation of Tricor can be taken with or without food once daily.
- Therapeutic lifestyle changes (TLC) that incorporate dietary changes, increased physical activity, and weight reduction, are the first recommended therapy for hyperlipidemia for 6-12 weeks prior to addition of drug therapy.

5. Questions and Answers

Case Presentation: Medication Profile—Community

H.L. is a 50-year-old man who comes to your pharmacy for cholesterol and medication monitoring. His medical history is notable for stage 1 hypertension, recent-onset type 2 diabetes, and hypercholesterolemia. Family history is noncontributory. Social history indicates he neither smokes nor uses alcohol. He has no known allergies. His medication history reveals that he occasionally takes acetaminophen for headaches and no other OTC medications or herbal products. Current medications include hydrochlorothiazide 25 mg/d (for 4 years) and a new prescription today for atorvastatin 10 mg/d. Your physical assessment reveals the following:

BP 144/90 mm Hg, pulse 70 and regular, weight 185 lb, height 5'9"

FLP today reveals total cholesterol = 250 mg/dL, HDL = 40 mg/dL, and triglycerides = 145 mg/dL.

Answer Questions 1-5 using the above case.

- What is H.L.'s LDL cholesterol?
 - 130 mg/dL
 - 153 mg/dL
 - 162 mg/dL
 - 178 mg/dL
 - 181 mg/dL
- What is H.L.'s LDL goal?
 - <100 mg/dL
 - 130-160 mg/dL
 - 160-189 mg/dL
 - <200 mg/dL
 - >40 mg/dL
- H.L. is started on TLC and atorvastatin because of his high LDL. When should you assess the effectiveness of therapy?
 - 12 weeks
 - 6 months
 - 3 weeks
 - 6 weeks
 - Annually
- H.L. is most likely to have which of the following?
 - Familial hypercholesterolemia
 - Polygenic hypercholesterolemia
 - Familial combined hyperlipidemia
 - Elevated triglycerides
 - Isolated low HDL
- H.L. returns for reassessment at the appropriate time. His FLP shows that his LDL is now 100 mg/dL. What is your recommendation?
 - Stop the statin since you have achieved optimal LDL
 - Increase statin dose
 - Intensify TLC
 - Add gemfibrozil
 - Add cholestyramine
- The National Cholesterol Education Program (NCEP) Expert Panel identifies which of the following as a positive risk factor for coronary heart disease (CHD)?
 - Hypertension
 - Low HDL (<40 mg/dL)
 - Family history of premature CHD
 - Current cigarette smoking
 - All of the above
- Which of the following is NOT a secondary cause of hyperlipidemia?
 - High LDL
 - Hypothyroidism
 - Diabetes
 - Renal disease
 - β -Blockers
- Cholesterol biosynthesis can be decreased by which of the following?
 - Statins
 - Oat bran
 - Bile acid sequestrants (resins)
 - Ezetimibe
 - Aspirin
- Choose the medication with the greatest effect on raising HDL.
 - Lovastatin
 - Pravastatin

- C. Gemfibrozil
 - D. Niaspan
 - E. Colesevelam
10. Choose the drug class with the most potent lowering effect on LDL.
 - A. Nicotinic acid
 - B. Fibric acids
 - C. Bile acid sequestrants (resins)
 - D. Cholesterol inhibitors
 - E. HMG-CoA reductase inhibitors
 11. The initial lesion in the development of atherosclerosis is
 - A. development of foam cells
 - B. increase in HDL reverse transport
 - C. rupture of a vulnerable plaque
 - D. clot formation in the artery lumen
 - E. development of a thin cap over the lipid pool
 12. Choose the correct statement.
 - A. Diabetes is an absolute contraindication to the use of nicotinic acid.
 - B. Aspirin is dosed three times per day in order to prevent flushing from niacin.
 - C. Gemfibrozil may reduce triglycerides by as much as 50%.
 - D. Colesevelam has similar patient tolerability problems as cholestyramine.
 - E. Ezetimibe frequently causes muscle toxicity.
 13. Hyperlipidemia refers to
 - A. elevation of apolipoproteins
 - B. hypercholesterolemia
 - C. high levels of white blood cells
 - D. increased ingestion of protein
 - E. endothelial dysfunction
 14. Which of the following indicates an optimal LDL?
 - A. >190 mg/dL
 - B. <40 mg/dL
 - C. >60 mg/dL
 - D. <100 mg/dL
 - E. <150 mg/dL
 15. Polygenic hypercholesterolemia is characterized by which of the following?
 - A. LDL = 150-450 mg/dL
 - B. LDL = 160-250 mg/dL
 - C. Triglycerides >400 mg/dL
 - D. HDL = 50 mg/dL
 - E. LDL = 160-250 mg/dL + triglycerides >400 mg/dL
 16. Identify a baseline laboratory test required before statin treatment.
 - A. White blood cell count
 - B. Complete blood cell count
 - C. Liver function test
 - D. Serum creatinine
 - E. Creatinine clearance
 17. The major troublesome side effect in nicotinic acid therapy is:
 - A. Diarrhea
 - B. Vomiting
 - C. Hair growth
 - D. Flushing
 - E. Dizziness
 18. Which of the following medications has the following warning: "For patients switching from immediate-release niacin, therapy with this drug should be initiated with a low dose and then titrated to the desired therapeutic response"?
 - A. Pravigard
 - B. Vytorin
 - C. Advicor
 - D. Atorvastatin
 - E. Ezetimibe
 19. Identify the drug interaction that involves the CYP450 system.
 - A. Ezetimibe + niacin
 - B. Colestipol + simvastatin
 - C. Gemfibrozil + cholestyramine
 - D. Fenofibrate + ezetimibe
 - E. Lovastatin + itraconazole
 20. A TLC diet could include
 - A. antioxidant therapy such as vitamin E
 - B. <7% of total calories from saturated fat
 - C. 150-250 g/d of fiber
 - D. 2-4 drinks of alcohol per day
 - E. assessing the effectiveness of TLC at 12-week intervals

Answers

1. **E.** Use the Friederwald equation to calculate LDL.

$$\text{LDL} = \text{TC} - (\text{HDL} + \text{TG}/5)$$
2. **A.** H.L. has type 2 diabetes that is a CHD risk equivalent, therefore he is at highest risk for an event in the future and his LDL goal should be optimal or <100 mg/dL.
3. **D.** Both TLC and drug therapy measures should be assessed at 6-week intervals.
4. **B.** H.L.'s LDL is 181 mg/dL, which falls into the range for polygenic hypercholesterolemia (160-250 mg/dL) and he does not have elevated triglycerides or low HDL.
5. **C.** Since H.L.'s LDL is still slightly above optimal; intensify TLC. That is, continue to decrease saturated fat in the diet and to intensify weight reduction and physical activity. If after the next assessment in 6 weeks the LDL is still above 100 mg/dL, options would be to increase the statin dose (double it), or add another agent such as niacin or ezetimibe.
6. **E.** All of the answers are positive risk factors for CHD as defined by the NCEP ATP III. The remaining positive risk factors are gender and age (ie, males 45 and over and females 55 and over).
7. **A.** Causes of hyperlipidemia must be ruled out. The common secondary causes are renal failure, hypothyroidism, obstructive liver disease, diabetes, and drugs such as β -blockers, thiazide diuretics, oral contraceptives, oral estrogens, glucocorticoids, and cyclosporine.
8. **A.** Statins competitively inhibit HMG-CoA reductase, which is the enzyme responsible for converting HMG-CoA to mevalonate. Inhibition of mevalonate reduces cholesterol synthesis.
9. **D.** Nicotinic acid (Niaspan) has the most efficacy in raising HDL compared to other therapies. HDL may be raised 15-35%.
10. **E.** Statins (HMG-CoA reductase inhibitors) have the most efficacy in lowering LDL. LDL may be lowered 18-55%.
11. **A.** Foam cells represent the initial lesion of atherosclerosis and develop as a result of the ingestion of oxidized LDL by macrophages in the subintimal space of the artery.
12. **C.** Diabetes is a relative contraindication to the use of nicotinic acid. Aspirin is dosed once daily, before the first nicotinic acid dose of the day. Gemfibrozil can reduce TGs 20-50%. Colesevelam is a tablet and avoids most of the palatability problems of other resins. Ezetimibe does not cause muscle toxicity.
13. **B.** Hyperlipidemia is defined as an elevation of a lipid in the blood. The lipid can be cholesterol or triglyceride in the form of a lipoprotein.
14. **D.** Level <100 = optimal; 100-129 = near optimal/above optimal; 130-159 = borderline high; 160-189 = high; ≥ 190 = very high
15. **B.** Polygenic hypercholesterolemia is the most common cause of mild to moderately elevated LDL (LDL = 160-250 mg/dL).
16. **C.** Baseline tests before statin use include liver function tests (LFTs) and creatine kinase (CK).
17. **D.** The most common side effect is flushing, which may occur in many patients. To decrease flushing intensity, aspirin 325 mg should be taken 30 minutes prior to the first dose of nicotinic acid. Itching may also occur with flushing.
18. **C.** Advicor (Niaspan + lovastatin) contains Niaspan, which is not dose-equivalent to immediate-release niacin or modified-release (sustained-release or time-release) niacin preparations.
19. **E.** Lovastatin is metabolized by CYP450 3A4 enzymes, and itraconazole will inhibit this enzyme system. Inhibition causes lovastatin blood and tissue concentrations to rise, thus predisposing to potential muscle or liver toxicity.

20. **B.** TLC diet includes <7% saturated fat, 20-30 g/d fiber, avoidance of alcohol, and assessment at 6 weeks. Vitamin E is not recommended for cardiovascular risk reduction.

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13. Diabetes Mellitus

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1. Overview

Diabetes mellitus (DM) is a group of chronic metabolic diseases due to defects in insulin secretion and/or action, which result in hyperglycemia; abnormal metabolism of carbohydrates, fats, and proteins; and long-term macrovascular and microvascular complications.

- Affects 20.8 million people or ~7% of the population
 - * 14.6 million diagnosed
 - * 6.2 million undiagnosed
- Sixth leading cause of death
- Risk of death is two times that of people without diabetes of similar age

Classification

Type 1 diabetes

- Previously called insulin-dependent diabetes mellitus (IDDM) or juvenile-onset diabetes
- Requires exogenous insulin for survival
- 5%-10% of all diagnosed cases

Type 2 diabetes

- Previously called non-insulin dependent diabetes mellitus (NIDDM) or adult-onset diabetes
- 90%-95% of all diagnosed cases

Gestational diabetes mellitus (GDM)

- Glucose intolerance with onset or first recognition during pregnancy (second and third trimesters)
- Approximately 4%-7% of pregnancies in American women; >200,000 annually
- Up to 50% later develop type 2 diabetes; 5%-10% of those diagnosed in the postpartum period.
- Primary fetal complication of concern: macrosomia

Other types (secondary DM)

- Due to genetic defects of β -cell function (eg, maturity onset diabetes of youth [MODY]), surgery, drugs, malnutrition, infections, and other illnesses
- 1%-5% of all diagnosed cases

Prediabetes

- Plasma glucose levels are higher than normal but lower than those diagnostic for diabetes
- Formerly characterized as IFG (impaired fasting glucose) and IGT (impaired glucose tolerance)

- Risk factor for future diabetes and cardiovascular disease

Clinical Presentation

- Classic signs and symptoms include polydipsia, polyuria, and polyphagia
- Other common findings include fatigue, blurred vision, and frequent infections
- Type 1: rapid onset; unexplained weight loss; potentially ketonuric or in ketoacidosis
 - * May experience a "honeymoon" period, a phase of erratic insulin secretion lasting months to a year during destruction of β -cells
- Type 2: progressive onset; asymptomatic or mild classic signs and symptoms; 80% are obese or have history of obesity; may present with microvascular and macrovascular chronic complications

Pathophysiology and Etiology

Type 1 DM

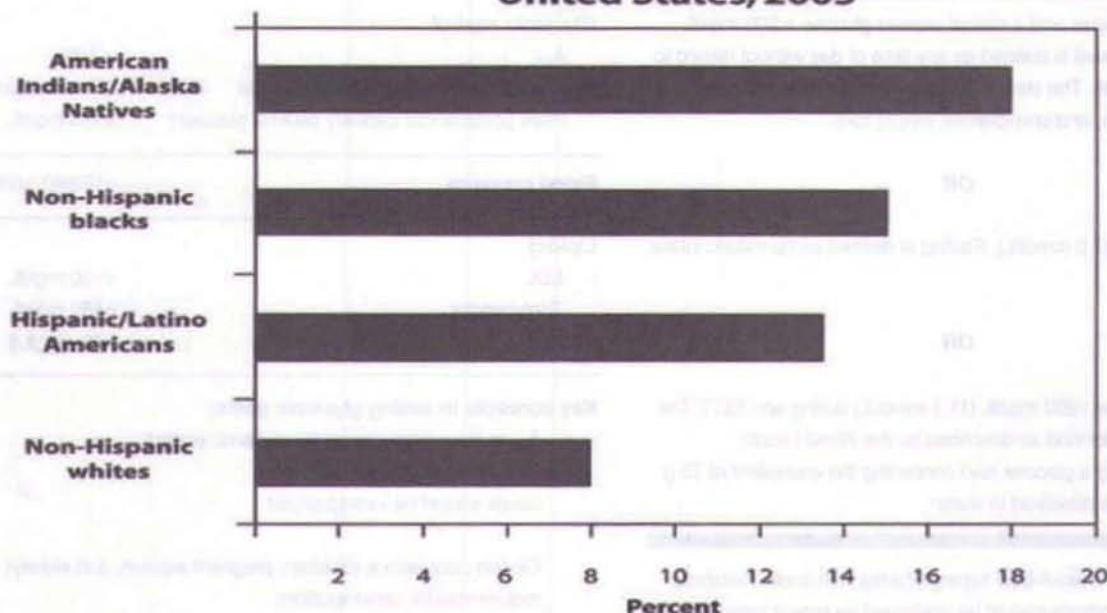
- β -Cell destruction leading to absolute insulin deficiency
- Subgroups:
 - * Immune mediated
- Strong HLA (human leukocyte antigen) association indicates genetic predisposition
- Related to environmental factors; stimulus (eg, virus) triggers immunologic process
 - * Idiopathic: no evidence of autoimmunity or other known etiology
- Prone to ketoacidosis
- Peak onset occurs at the time of puberty but may occur at any age

Type 2 DM

- Insulin resistance and progressive β -cell dysfunction
- Strong genetic predisposition
- Associated with environmental factors such as excessive calorie intake, decreased activity, weight gain and obesity
- Insulin resistance may be present years before the onset of diabetes
- Initially normal glucose levels are maintained by increased insulin secretion by β -cells
- Increasing insulin resistance or a failure of β -cells to maintain insulin secretion leads to glucose intolerance and development of diabetes
- Insulin resistance is influenced by age, ethnicity, physical activity, medications, and weight

Figure 1

**Estimated age-adjusted total prevalence of diabetes
in people aged 20 years or older, by race/ethnicity—
United States, 2005**



Source: For American Indians/Alaska Natives, the estimate of total prevalence was calculated using the estimate of diagnosed diabetes from the 2003 outpatient database of the Indian Health Service and the estimate of undiagnosed diabetes from the 1999-2002 National Health and Nutrition Examination Survey. For the other groups, 1999-2002 NHANES estimates of total prevalence (both diagnosed and undiagnosed) were projected to year 2006.

* Graph and information obtained from CDC (Center for Disease Control and Prevention) website at <http://www.cdc.gov/diabetes/pubs/estimates05.html#prev4> on December 1, 2006.

- Usually diagnosed in adulthood but can occur at any age
- The incidence of type 2 diabetes is higher among certain ethnic populations (Figure 1)

Diagnostic Criteria

Type 1 and type 2 DM (Table 1)

- Diagnosis can be made based on a fasting plasma glucose (FPG), a random plasma glucose, or an oral glucose tolerance test (OGTT)
- Diagnosis must be confirmed on a subsequent day using any of the three methods
- FPG is the test of choice due to simplicity, accuracy and reproducibility
- Abnormal results not meeting criteria outlined in Table 1 are classified as prediabetes
 - * impaired fasting glucose (IFG) = FPG ≥ 100 mg/dL and ≤ 126 mg/dL
 - * Impaired glucose tolerance (IGT) = 2-hour OGTT plasma glucose ≥ 140 mg/dL and < 200 mg/dL

- Serum C peptide level: diagnostic for functioning of β -cells and may be used for classification

Gestational diabetes mellitus

- OGTT is preferred screening test in pregnancy
- For average-risk patients test at 24-28 weeks of gestation
- For high-risk patients (marked obesity, personal history of GDM, glycosuria, or strong family history of DM) perform risk assessment at first prenatal visit and test as soon as possible; if negative at initial screenings, retest between 24 and 28 weeks of gestation
- In average- or high-risk patients use one of two approaches:
 - * One-step approach: diagnostic 75-g or 100-g OGTT
 - * Two-step approach: 1-hour 50-mg glucose challenge test followed by diagnostic OGTT if 1-hour level ≥ 140 mg/dL

Table 1**Criteria for the Diagnosis of Diabetes Mellitus¹**

Symptoms of diabetes and a casual plasma glucose ≥ 200 mg/dL (11.1 mmol/L). Casual is defined as any time of day without regard to time since last meal. The classic symptoms of diabetes include polyuria, polydipsia, and unexplained weight loss.

OR

FPG ≥ 126 mg/dL (7.0 mmol/L). Fasting is defined as no caloric intake for at least 8 h.

OR

2-h plasma glucose ≥ 200 mg/dL (11.1 mmol/L) during an OGTT. The test should be performed as described by the World Health Organization, using a glucose load containing the equivalent of 75 g anhydrous glucose dissolved in water.

¹In the absence of unequivocal hyperglycemia with acute metabolic decompensation, criteria should be confirmed by repeat testing on a different day.

Report of the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. Copyright 1997 American Diabetes Association from *Diabetes Care*, Vol. 20, 1997; 1183-1197. Reprinted with permission from The American Diabetes Association.

Table 2**Summary of Recommendations for Adults with Diabetes****Glycemic control**

A _{1c}	<7.0%
Preprandial capillary plasma glucose	90–130 mg/dL
Peak postprandial capillary plasma glucose†	<180 mg/dL

Blood pressure

<130/80 mmHg

Lipids‡

LDL	<100 mg/dL
Triglycerides	<150 mg/dL
HDL	>40 mg/dL§

Key concepts in setting glycemic goals:

A_{1c} is the primary target for glycemic control

Goals should be individualized

Certain populations (children, pregnant women, and elderly) require special considerations

More stringent glycemic goals (ie, a normal A_{1c}, <6%) may further reduce complications at the cost of increased risk of hypoglycemia

Less intensive glycemic goals may be indicated in patients with severe or frequent hypoglycemia

Postprandial glucose may be targeted if A_{1c} goals are not met despite reaching preprandial glucose goals

* Referenced to a nondiabetic range of 4.0–6.0% using a DCCT-based assay.

† Postprandial glucose measurements should be made 1–2 h after the beginning of the meal, generally peak levels in patients with diabetes.

‡ Current NCEP/ATP III guidelines suggest that in patients with triglycerides ≥ 200 mg/dL, the “non-HDL cholesterol” (total cholesterol minus HDL) be utilized. The goal is 130 mg/dL.

§ For women, it has been suggested that the HDL goal be increased by 10 mg/dL.

Adapted from *Standards of Medical Care in Diabetes – 2007*.

Source: American Diabetes Association

- Diagnostic criteria with 100-g glucose load—fasting: 95 mg/dL; 1-hour: 180 mg/dL; 2-hour: 155 mg/dL; 3-hour: 140 mg/dL
- Diagnostic criteria with 75-g glucose load—fasting: 95 mg/dL; 1-hour: 180 mg/dL; 2-hour: 155 mg/dL
- Diagnosis positive if two glucose values meet or exceed those listed for 100-mg or 75-g load
- FPG >126 mg/dL or casual PG >200 mg/dL confirmed on subsequent day precludes the need for glucose challenge
- At least 6 weeks postpartum re-evaluation and reclassification should be conducted

Treatment Principles and Goals

- Achieve and maintain glycemic control (Table 2)
- Attain recommended blood pressure and lipid goals (Table 2)
- Lifestyle modifications to promote general health and achieve weight management goals
- Prevent or slow progression of chronic complications
- Prevent or resolve acute complications
- Achieve an acceptable quality of life and satisfaction with care

Prevention of complications

- Smoking cessation
- Aspirin/antiplatelet therapy
 - * Use as secondary prevention with a history of CVD
 - * Use as primary prevention if >40 years of age or have additional risk factors (family history of CVD, hypertension, smoking, dyslipidemia, or albuminuria)
 - * Aspirin 75-162 mg/d
- Immunization
 - * Annual influenza vaccine if 6 months of age or older and no contraindications
 - * At least one lifetime pneumococcal vaccine for adults with no contraindications
 - * One-time pneumococcal revaccination if >64 years of age, previously immunized at <65 and vaccine administered >5 years ago
- Foot care: self-inspection daily; visual inspection at each office visit, and annual comprehensive exam
- Skin inspection and care daily
- Dental care: annual examination
- Eye care: annual dilated eye examination

Complications of diabetes

Chronic complications

- Coronary atherosclerosis: death rate is 2 to 4 times higher than adults without diabetes
- Cerebrovascular atherosclerosis: risk of stroke is 2 to 4 times higher among people with diabetes
- Peripheral vascular disease: pain due to intermittent claudication; insufficient circulation impairs healing, increases risk of gangrene and amputation

Microvascular disease

- Retinopathy
 - * Leading cause of new cases of blindness in adults 20-74
 - * May develop without symptoms; annual dilated eye examination recommended for detection
 - * Treatment includes glycemic and blood pressure control, laser photocoagulation
- Nephropathy
 - * Occurs in 20%-40% of diabetics and is the leading cause of end-stage renal disease (ESRD)
 - * May develop without symptoms; detection relies on laboratory screening which should be done annually
 - * Random spot collection of the albumin-to-creatinine ratio is the easiest screening to perform; a value of >30 mg/g is considered abnormal
 - * Serum creatinine should be measured at least annually for the estimation of glomerular filtration rate (GFR)
 - * Treatment includes glycemic and blood pressure control; ACE inhibitors or ARBs should be used except during pregnancy.
- Polyneuropathy
 - * Sensorimotor nervous system dysfunction; pain and diminished sensation with progression from lower to upper extremities; poor detection of trauma, which increases risk for ulcers and infection, particularly in lower extremities and feet
- Autonomic neuropathy
 - * Gastrointestinal: gastroparesis, constipation, diarrhea
 - * Genitourinary: neurogenic bladder and sexual dysfunction in men
 - * Cardiovascular: orthostatic hypotension, resting tachycardia

- Diabetic foot problems
 - * DM accounts for >60% of nontraumatic amputations in the U.S.
 - * Prevention, early detection with regular foot exams, and prompt treatment of lesions are essential to avoid complications

Acute complications

- Hypoglycemia
 - * Plasma glucose <70 mg/dL
 - * Glucose (15-20 g) is the preferred treatment
 - * Other forms of carbohydrate that contain glucose can be used
 - * Treatment effects should be seen in 15 minutes
 - * Symptoms can range from mild (tremor, palpitations, sweating) to severe (unresponsiveness, unconsciousness, or convulsions)
 - * Severe hypoglycemia may require assistance from another individual for treatment with glucagon or IV glucose
- Diabetic ketoacidosis (DKA)
 - * Medical emergency in type 1 diabetes due to absolute or relative insulin deficiency
 - * Omission of insulin, major stress, infection or trauma may precipitate DKA
 - * Characterized by glucose >250 mg/dL, elevated ketones, arterial pH <7.2, plasma bicarbonate <15 mEq/l
 - * Ketone bodies are formed in excess due to fatty acid metabolism in the liver, leading to ketonuria and ketonemia and ultimately diabetic ketoacidosis.
 - * Kussmaul respirations (deep and rapid); attempt to compensate for metabolic acidosis
 - * Requires prompt intervention with insulin, fluids and electrolytes to prevent coma and death
- Hyperosmolar hyperglycemic state (HHS)
 - * Also known as hyperglycemic hyperosmolar nonketotic coma (HHNC)
 - * Complication of type 2 diabetes
 - * Elevated plasma glucose (typically >500 mg/dL), dehydration, and hyperosmolality in the absence of significant ketoacidosis

- * May be triggered by infection or other stressors such as stroke or myocardial infarction
- * Treatment includes fluid and electrolyte replacement and treatment with insulin

2. Drug Therapy

Oral Medications for the Treatment of Diabetes Mellitus

SECRETAGOGUES

Mechanism of Action: Primary mechanism is to cause a reduction in blood glucose by stimulating the release of insulin from the pancreas. This may in turn cause a decrease in hepatic gluconeogenesis and a slight decrease in insulin resistance at the muscle level. Effectiveness is dependent on pancreatic beta-cell function.

Clinical/Counseling Considerations:

- Should be taken before meals (sulfonylureas [QD-BID], meglitinides [before each meal])
- Causes 1-2 kg weight gain
- + risk of hypoglycemia (sulfonylureas > meglitinides)
- Typically not indicated during pregnancy, breastfeeding, or in children
- Carry fast-acting oral carbohydrate for emergency use

- Wear medical identification
- Store drug in a cool, dry place (not the bathroom or kitchen)

A_{1c} Reduction: 1%-2% (sulfonylureas)
0.5%-2% (meglitinides)

Monthly Cost: generically available / ~\$75-\$200 (meglitinides)

Cautions / Contraindications:

- Caution in elderly (do NOT use chlorpropamide)
- Caution in renal and hepatic insufficiency (glipizide & glimepiride safer)
- Avoid in pts with significant alcohol use
- Drug interactions (worse with 1st generation sulfonylureas) may cause ↑ risk of hypoglycemia: anticoagulants, fluconazole, salicylates, gemfibrozil, sulfonamides, tricyclic antidepressants, digoxin
- Contraindicated in patients with DKA, severe infection, surgery, or trauma
- SIADH, disulfiram-like reaction with ETOH, and sun-sensitivity reactions more common in 1st vs. 2nd generation sulfonylureas

SULFONYLUREAS

FIRST-GENERATION

NAME (generic/brand/strength)	DAILY DOSE	DURATION OF ACTION	COMMENTS
Acetohexamide (<i>Dymelor</i> ®) 250, 500 mg	250 – 1500 mg	up to 16 hours	Active metabolite excreted by kidney
Chlorpropamide (<i>Diabinese</i> ®) 100, 250 mg	100 – 500 mg	up to 72 hours	Contraindicated in renal insufficiency
Tolazamide (<i>Tolinase</i> ®) 100, 250, 500 mg	100 – 1000 mg	up to 10 hours	
Tolbutamide (<i>Orinase</i> ®) 250, 500 mg	500 – 3000 mg QD - BID	up to 10 hours	

SECOND-GENERATION

NAME (generic/brand/strength)	DAILY DOSE	DURATION OF ACTION	COMMENTS
Glipizide (<i>Glucotrol</i> ®, <i>Glucotrol XL</i> ®) 5, 10 mg	5-40 mg QD-BID 5-20 mg QD (XL)	up to 20 hours	Given with or without meal; do not cut XL tab
Glyburide (<i>DiaBeta</i> ®, <i>Micronase</i> ®) 1.25, 2.5, 5 mg	1.25-20 mg QD-BID	up to 24 hours	3mg <i>Glynase</i> ® = 5mg Glyburide
Glyburide micronized (<i>Glynase</i> ®) 1.5, 3, 4.5, 6mg	1.5-12 mg QD	up to 24 hours	
Glimepiride (<i>Amaryl</i> ®) 1, 2, 4 mg	1-8 mg QD	24 hours	Begin with 1 mg in renal insufficiency

(Continued)

SULFONYLUREAS (cont.)**MEGLITINIDES / PHENYLALANINES**

NAME (generic/brand/strength)	DAILY DOSE	DURATION OF ACTION	COMMENTS
Repaglinide (<i>Prandin</i> ®) 0.5, 1, 2 mg	0.5-4 mg before each meal MAX DOSE = 16 mg/day	Peak effect: ~ 1 hour Duration: ~ 2-3 hours	skip dose if meal skipped; do not give in combination with sulfonylureas
Nateglinide (<i>Starlix</i> ®) 60, 120 mg	60-120 mg before each meal	Peak effect: ~ 1 hour Duration: ~ 4 hours	EFFICACY: <i>Prandin</i> ® > <i>Starlix</i> ®

BIGUANIDES

Mechanism of Action: Primary mechanism is seen through decreased hepatic gluconeogenesis, as well as improved glucose utilization and uptake in peripheral tissues and decreased intestinal absorption of glucose.

Clinical Considerations:

- Considered first choice to begin in newly diagnosed DM patients unless contraindicated
- Minimal risk of hypoglycemia unless combined with secretagogues or insulin
- May decrease weight up to 5 kg
- ↓ triglycerides, ↓ LDL, ↔/↑ HDL
- GI symptoms (nausea, vomiting, bloating, flatulence, anorexia, and diarrhea) are the most common adverse effects
 - Take doses with or after meals to reduce GI symptoms
 - GI symptoms are transient and improve in most patients over time
 - Titrate the dose up slowly to minimize GI symptoms
- 500 mg QD with the largest meal X 1 week, then ↑ to
- 500 mg BID with the 2 largest meals X 1 week, then ↑ to
- 1 gm [two 500 mg tabs] with largest meal & 500 mg with the 2nd largest meal X 1 week, then ↑ to
- 1 gm BID with the 2 largest meals of the day
 - Interferes with vitamin B₁₂ absorption
- May require as much as 8 weeks of therapy before assessing effectiveness
- Generally not indicated during pregnancy or

breastfeeding

- Indicated for the treatment of type 2 DM in children 10 years and older
- May decrease the progression to diabetes from IGT & IFG (prediabetes)
- +CV benefits when used in obese patients with DM

A_{1c} Reduction: 1%-2%

Monthly Cost: generically available

Cautions / Contraindications:

- Most cautions & contraindications are related to their ability to ↑ the risk of lactic acidosis with metformin

➤ CONTRAINDICATIONS:

- Renal Insufficiency (SCr ≥1.4 females; SCr ≥1.5 males)
- Hepatic dysfunction
- Excessive alcohol use (binge or chronic use >2 drinks per day or at one sitting)
- May be contraindicated in CHF (NYHA III & IV)

➤ CAUTIONS:

- Should be held in situations of increased risk for lactic acidosis, including acute MI, CHF exacerbation, severe respiratory disease, shock, septicemia
- Should be held X 48 hours after iodinated contrast media and major surgeries

NAME (generic/brand/strength)	DAILY DOSE	DURATION OF ACTION	COMMENTS
Metformin (<i>Glucophage</i> ®) 500, 850, 1000 mg	1000-2550 mg (adult) up to 2000 mg (10 yo +)	≥ 24 hours	
Metformin extended release (<i>Glucophage XR</i> ®) 500, 750 mg	2000 mg QPM; may take 1gm BID if QD dosing		DO NOT cut, crush, or chew
(<i>Glumetza</i> ®) 500, 1000 mg	causes GI symptoms		

NAME (generic/brand/strength)	DAILY DOSE	DURATION OF ACTION	COMMENTS
Rosiglitazone (Avandia®) 2, 4, 8 mg	4-8 mg QD OR 2-4 mg BID	24 hours	May be more effective when given BID
Pioglitazone (Actos®) 15, 30, 45 mg	30-45 mg QD	24 hours	

THIAZOLIDINEDIONES (GLITAZONES/TZDs)

Mechanism of Action:

- Agonists of the PPAR_γ (peroxisome proliferators-activated receptor-γ) receptor which, when stimulated, improves peripheral muscle and adipose tissue insulin sensitivity as well as suppresses hepatic glucose output.

Clinical Considerations:

- Minimal risk of hypoglycemia unless combined with secretagogues or insulin
- May cause a 5 kg weight gain, more if combined with secretagogues or insulin
- ↓ triglycerides (PIO > ROSI), ↑ HDL (PIO = ROSI), ↑ LDL (ROSI) / ↔ LDL (PIO)
- Dosed QD, though ROSI may be slightly more effective when dosed BID
- May require as much as 16 weeks of therapy before assessing effectiveness
- Generally not indicated during breastfeeding or pregnancy
- May decrease the progression to diabetes from IGT & IFG (prediabetes)
- Edema may best be treated by aldosterone antagonists
- Not FDA-indicated for treatment of type 2 DM in children, though has been used
- May be helpful in Non-Alcoholic Fatty Liver Disease (NAFLD)
- Generally not indicated during pregnancy or breastfeeding

A_{1c} Reduction: 1%-2%

Monthly Cost: ~ \$120-\$200

Cautions/Contraindications:

- Edema – with PO therapies (~5%), with insulin (~15%) – this may occur in patients with NO history of heart problems [may be dose related]. Recommendation: D/C therapy if significant problem of edema, decrease dose if minor problem of edema → consider further cardiac workup.
- Recent black box warning added for CHF (PIO & ROSI)
- Hepatotoxicity – incidence = ~ 0.2% of ALT > 3X ULN for both agents. Recommendation:

LFT's every other month for 1st 12 months, periodically thereafter. If ALT >2.5 ULN, don't start; if ALT = 1-2.5 ULN, monitor closely; if ALT 3X ULN, D/C medication.

- May cause resumption of ovulation in anovulatory women
- ↓ oral contraceptive effectiveness

NAME (generic/brand/strength)	DAILY DOSE	DURATION OF ACTION	COMMENTS
Acarbose (Precose®) 50, 100 mg	25-100 mg TID	1-3 hours	MAX DOSE: <60 kg = 50 mg TID >60 kg = 100 mg TID
Miglitol (Glyset®) 25, 50, 100 mg	25-100 mg TID	1-3 hours	

ALPHA-GLUCOSIDASE INHIBITORS

Mechanism of Action: Causes delay in the digestion of carbohydrates into simple sugars, and their subsequent absorption in the small intestine.

Clinical Considerations:

- Minimal risk of hypoglycemia unless combined with secretagogues or insulin
- Minimal effect on weight, possible ↓ weight secondary to side effects
- Main target of therapy should be post-prandial hyperglycemia
- GI symptoms (flatulence, GI upset, abdominal pain, diarrhea, bloating) are the most common side effects. These tend to dissipate over time with continued treatment. Dosing must be individualized and slowly titrated up as tolerated:
 - 25 mg QD X 1 week, then
 - 25 mg BID X 1 week, then
 - 25 mg TID X 1 week, then
 - continued increased dose as tolerated up to 50 mg TID
- Diet considerations: pt should be counseled to ↑ complex carbohydrate intake and ↓ intake of simple sugars
- Treatment of hypoglycemia:
 - should use milk (lactose) or fruit juice (fructose), NOT SUCROSE
 - any carbohydrate can be used if >2-3 hours since last dose of alpha-glucosidase inhibitor agent
- Generally not indicated during pregnancy, breastfeeding or in children
- Drug Interactions: ↓ bioavailability of digoxin, propranolol, and ranitidine.

A_{1c} Reduction: 0.5%-1%

Monthly Cost: ~ \$75-\$100

Cautions/Contraindications:

- Avoid use in patients with GI disorders: ulcerative colitis, Crohn's disease, possible bowel obstruction, short bowel syndrome.
- Avoid use in patients with SCr >2 mg/dL (acarbose) or CrCl of ≤ 25 mL/min (both agents)
- Possible increased LFTs (acarbose) – dose related (>300mg/day) and weight (of patient) related. [Avoid use in patients with cirrhosis.]

DIPEPTIDYL PEPTIDASE-4 (DPP-4) INHIBITORS

Mechanism of Action: Inhibits the degradation of endogenous glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP), which in turn causes: 1) increased insulin production in a glucose-dependent fashion, 2) decreased production of glucagon, and 3) improved beta-cell functioning.

Clinical Considerations:

- Minimal risk of hypoglycemia unless combined with secretagogues or insulin
- Minimal/no effect on weight
- Can be used either as monotherapy or in combination with metformin or thiazolidinediones, and possibly insulin

- Only drug class impacting the GLP-1 system dosed orally
- Generally, very well tolerated with the most common side effects including nasopharyngitis and upper respiratory tract infections
- Secondary to newness of the drug, no significant long-term outcome data is yet available

A_{1c} Reduction: 0.6%-1.2%

Monthly Cost: ~ \$150

Cautions / Contraindications:

- Dose should be adjusted for renal insufficiency
- May cause adverse immunologic reactions through T-cell inhibition
- Should not be used in patients with DKA or type 1 DM

COMBINATION ORAL AGENTS FOR DIABETES MELLITUS (See write-up of individual agents for details)

NAME (generic/brand/strength)	DAILY DOSE	DURATION OF ACTION	COMMENTS
Sitagliptin (Januvia [®]) 25, 50, 100 mg	100 mg QD	24 hours	CrCl 30-50: 50 mg QD CrCl <30: 25 mg QD

	Glipizide	Glyburide	Glimepiride	Metformin	Rosiglitazone	Pioglitazone	Januvia
Metaglip[®]	2.5 mg —————→			250 mg			
	2.5 mg —————→			500 mg			
	5 mg —————→			500 mg			
Glucovance[®]		1.25 mg —————→		250 mg			
		2.5 mg —————→		500 mg			
		5 mg —————→		500 mg			
Avandaryl[®]			1 mg —————→	4 mg			
			2 mg —————→	4 mg			
			4 mg —————→	4mg			
Duetact[®]			2 mg —————→			30 mg	
			4 mg —————→			30 mg	
Avandamet[®]				500 mg —————→			1 mg
				500 mg —————→			2 mg
				500 mg —————→			4 mg
				1000 mg —————→			2 mg
				1000 mg —————→			4 mg
ACTOplus met[®]				500 mg —————→			5 mg
				850 mg —————→			15 mg
Janumet[®]				500 mg —————→			50 mg
				1000 mg —————→			50 mg

Injectable Medications for the Treatment of Diabetes Mellitus

INSULIN PRODUCTS

Mechanism of Action: At low levels, insulin causes suppression of endogenous hepatic glucose production. At higher levels, insulin promotes glucose uptake by muscle tissue.

Clinical Considerations:

- + Risk of hypoglycemia
- ↑ weight
- Should be considered as initial agent if glucose is $>250\text{mg/dL}$ or A_{1c} is $>10\%$
- No dosage limit
- Dosing is often started with a basal insulin ($0.1\text{--}0.2\text{ u/kg/day}$) and added to an existing PO regimen of 2 or more agents
- Insulin regimen should be individualized to the patient accounting for:
 - glucose readings
 - patient preferences
 - patient schedule
 - patient education / intelligence level
 - level of intensity needed
 - cost to patient

- Consider for prandial insulin coverage when:
 - Patient with fasting blood glucose target (<100), but $A_{1c} \geq 7\%$
 - $A_{1c} \geq 7\%$ with evidence of frequent 2-hour post-prandial glucose values $>160\text{ mg/dL}$
 - Nighttime or daytime hypoglycemia with skipped/delayed meals

A_{1c} Reduction: 2.5% or more

Monthly Cost: variable depending insulin product prescribed and device (ie, pen) vs. vial/syringe used

Cautions/Contraindications:

- Dose cautiously in patients with renal and hepatic insufficiency
- Dose cautiously in elderly patients
- Do not mix the following insulins with any others: Lantus[®], Levemir[®], Lente[®], and Ultralente[®]
- Patients should be counseled on signs and symptoms of hypoglycemia and how to appropriately treat
- Most insulin products are stable at room temperature for 30 days, other than premixed-insulin products (14 days) and Levemir (45 days).

Sample Titration Schedules for Basal & Prandial Insulin

Basal Insulin Titration		Prandial Insulin Titration	
Fasting Blood Glucose Levels for 3 Consecutive Days	Adjust Basal Insulin Dose (units)	Preprandial or Bedtime Glucose Levels for 3 Consecutive Days	Adjust Rapid-Acting Insulin Dose (units)
$\geq 180\text{ mg/dL}$	+8	$\geq 180\text{ mg/dL}$	+3
160-180 mg/dL	+6	140-180 mg/dL	+2
140-160 mg/dL	+4	140-180 mg/dL	+2
120-140 mg/dL	+2	120-140 mg/dL	+1
100-120 mg/dL	+1	100-120 mg/dL	NO CHANGE
80-100 mg/dL	NO CHANGE	80-100 mg/dL	-1
60-80 mg/dL	-2	60-80 mg/dL	-2
$< 60\text{ mg/dL}$	-4	$< 60\text{ mg/dL}$	-4

• For ↑ fasting glucose, adjust basal dose ONLY

- For ↑ preprandial / HS glucose levels:
- 1) if ↑ at lunchtime, adjust breakfast prandial insulin
 - 2) if ↑ at dinnertime, adjust lunchtime prandial insulin
 - 3) if ↑ at bedtime, adjust dinnertime prandial insulin

INSULIN TYPE	ONSET OF ACTION	TIME OF PEAK	DURATION OF ACTION
Rapid Acting Analogs			
glulisine (<i>Apidra</i> ®)*	15-30 min	30-90 min	1-3 hours
aspart (<i>Novolog</i> ®)**	10-15 min	30-90 min	3-5 hours
lispro (<i>Humalog</i> ®)***, +	10-15 min	30-90 min	
Intermediate Acting			
human NPH (<i>Novolin N</i> ®®, #, <i>Humulin N</i> ®®)	1-3 hours	4-12 hours	10-18 hours
human <i>Lente</i>	2-5 hours	7-15 hours	24 hours
Long Acting			
human <i>Ultralente</i>	4-8 hours	10-30 hours	18-30 hours
Basal			
glargine (<i>Lantus</i> ®)*, ^	1-2 hours	peakless	24 hours
detemir (<i>Levemir</i> ®)**	1-2 hours	6-8 hours	18-24 hours
Pre-Mixed Insulins			
NPH + Regular			
<i>Novolin 70/30</i> ®, #			
<i>Humulin 70/30</i> ®			
<i>Humulin 50/50</i> ®			
Insulin Protamine + Analogs			
<i>Novolog 70/30</i> ®			
<i>Humalog 75/25</i> ®			
<i>Humalog 50/50</i> ®			

DEVICE AVAILABILITY: * = OptiClick pen; ** = NovoPen®; *** = Lilly pen; # = InnoLet®; ^ = SoloSTAR®
 += HumaPen MEMOIR™ & Luxura™ HD pens

INSULIN AVAILABILITY: U-100 = 100 units per mL [most common available concentration]
 U-500 = 500 units per mL [used in severe insulin resistance]

INCRETIN MIMETICS

Mechanism of Action: A receptor agonist of endogenous glucagon-like peptide-1 (GLP-1) which causes: 1) increased insulin production in a glucose-dependent fashion, 2) decreased production of glucagon, 3) slowing of gastric emptying, 4) increased satiety and weight loss, and 5) improved beta-cell functioning.

Clinical Considerations:

- Minimal risk of hypoglycemia unless combined with secretagogues (consider initial reduction in secretagogue), minor increase in hypoglycemia risk if combined with TZDs
- Moderate weight loss of ~10 pounds seen after sustained use
- Dose limiting side effect is nausea – ~ 50% of patients report some degree of nausea, though ~3%-5% stop the drug secondary to the problem – this problem seems to lessen with time
- Patients should decrease meal size and carbohydrate content of meals prior to use of exenatide to lessen problem of nausea
- Dose should be given ~10-15 minutes prior to the 2 largest meals of the day that are at least 6 hours apart

- Can be stored at room temperature for 30 days after first dose is given
- Can be combined with sulfonylurea, metformin, sulfonylurea + metformin, TZDs, or metformin + TZD. Currently not indicated in combination with insulin.
- Begin with 5 mcg injected BID for 1 month, then increase to 10 mcg BID as tolerated secondary to GI toxicity
- Supplied as a pen device which contains 60 doses (1 month supply)
- Most effective to lower post-prandial glucose elevations

A_{1c} Reduction: 0.5%-1%

Monthly Cost: ~ \$150-\$200

Cautions / Contraindications:

- Should NOT be given to patients with GFR ≤30 mL/min
- Should NOT be given to patients with severe gastrointestinal disease including gastroparesis
- Should not be used in patients with DKA or type 1 DM

NAME (generic/brand/strength)	DAILY DOSE	DURATION OF ACTION	COMMENTS
Exenatide (Byetta [®]) 5, 10 mcg pen	5-10 mcg BID	~ 8-10 hours	

AMYLIN MIMETICS

Mechanism of Action: Is an analog of endogenous amylin which when dosed at therapeutic levels causes: 1) decreased production of glucagon, 2) slowing of gastric emptying, and 3) increased satiety and weight loss

Clinical Considerations:

- Can be used in combination with insulin therapy in both type 1 and type 2 DM patients who have failed to achieve desired glucose control
- Due to significant risk of severe hypoglycemia, prandial insulin dose should be decreased by 50% when starting pramlintide
- Dose limiting side effect is nausea which seems to lessen over time
- Type 2 DM—start with 60 mcg (10 units) before meals, increase to 120 mcg before meals when no significant nausea has occurred for 3-7 days
- Type 1 DM—start with 15 mcg (2.5 units) before meals, increase to 30 to 60 mcg before meals when no significant nausea has occurred for 3-7 days

- Opened vials may be stored at room temperature for 28 days

A_{1c} Reduction: 0.5%-1%

Monthly Cost: ~ \$100-\$300/month

Cautions / Contraindications:

- Should NOT be used in the following patients:
 - severe gastrointestinal disease including gastroparesis
 - poor adherence with current insulin regimen or self-monitoring of blood glucose
 - recurrent severe hypoglycemia requiring assistance in the past 6 months
 - having an A_{1c} ≥9%
 - presence of hypoglycemia unawareness

NAME (generic/brand/strength)	DAILY DOSE	DURATION OF ACTION	COMMENTS
Pramlintide (Symlinr®) 0.6 mg/mL – 5 mL vial	<u>TYPE 1 DM:</u> 15-60 mcg TID with meals <u>TYPE 2 DM:</u> 60-120 mcg TID with meals	4-6 hours	Dosed using an insulin syringe: 30 mcg = 5 units 60 mcg = 10 units 120 mcg = 20 units

Inhaled Medications for the Treatment of Diabetes Mellitus

A_{1c} Reduction: dose dependent (insulin product)
Monthly Cost: ~ \$150/month

Mechanism of Action: see discussion on insulin above

Clinical Considerations:

- Provides prandial insulin coverage without use of injection
- Patients should have baseline spirometry (FEV₁) prior to initiation, 6 months after beginning therapy, and yearly thereafter
- Dosing issues: 1 mg packet = 3 units
3 mg packet = 8 units
(3 X 1 mg packets DOES NOT = 1 X 3 mg packet)
- Significant education of the patient required before initially starting the medication
- Can be used in type 1 and type 2 DM patients, though long-term safety and effectiveness has not yet been established in pediatric patients
- If used in type 1 DM patients, should be used with a basal insulin product

Cautions / Contraindications:

- Should NOT be used in patients with chronic lung diseases (asthma or COPD)
- Should NOT be used in patients who are active smokers or those who have stopped smoking <6 months prior to beginning Exubera® (insulin exposure rates may ↑ 2 to 5 fold compared to non-smokers)
- Patients should be counseled on signs and symptoms of hypoglycemia and how to appropriately treat
- Dose cautiously in patients with renal and hepatic insufficiency

NAME (generic/brand/strength)	DAILY DOSE	DURATION OF ACTION	COMMENTS
Insulin inhaled (Exubera®) 1, 3 mg	Dosed for mealtime carbohydrate coverage (see chart on next page)	6-8 hours	Onset of action is similar to analog insulins; duration of action is similar to regular insulin

Guidelines for Initial, Pre-Meal Exubera® Dose

Pt wt (in kg)	Pt wt (in lb)	Initial dose per meal	Number of 1 mg blisters per dose	Number of 3 mg blisters per dose
30-39.9	60-87	1 mg per meal	1	-
40-59.9	88-132	2 mg per meal	2	-
60-79.9	133-176	3 mg per meal	-	1
80-99.9	177-220	4 mg per meal	1	1
100-119.9	221-264	5 mg per meal	2	1
120-139.9	265-308	6 mg per meal	-	2

Approximate Equivalent IU Dose of Regular Human Insulin for Exubera®

Dose (mg)	Regular insulin dose (units)	Number of 1 mg blisters per dose	Number of 3 mg blisters per dose
1	3	1	-
2	6	2	-
3	8	-	1
4	11	1	1
5	14	2	1
6	16	-	2

3. Nondrug Therapy

- Weight loss is recommended for all diabetics who are overweight or obese
- Modest weight loss (5%) has been shown to decrease insulin resistance in type 2 diabetes
- Lifestyle changes through diet and exercise should be emphasized
- Patient education is an essential component of successful diabetes management

Medical Nutrition Therapy (MNT)

- Individualized to achieve treatment goals with consideration of usual dietary habits, metabolic profile, and lifestyle
- Monitor carbohydrate by exchanges, carbohydrate counting or experience-based estimation
- Carbohydrate (CHO) 45%-60% of total daily caloric intake; if intensive insulin therapy used with pre-meal bolus dose of insulin, then insulin should be adjusted to cover the daily CHO intake; with basal insulin therapy (when the pre-meal bolus is not used) or oral antidiabetic medications, then CHO intake must be adjusted so it is consistent with the effects of therapy
- Protein 15%-20% of total daily caloric intake; should be modified if renal function is reduced
- Saturated fat <7% of total daily calories
- Cholesterol <200 mg/d
- Fiber intake should be encouraged, but there is no reason to recommend a greater amount than that recommended for persons without DM
- Limit daily alcohol intake (adult females: one drink or less; adult males: two drinks or less)

Physical Activity/Exercise

- Regular exercise improves blood glucose control, reduces cardiovascular risk factors, and contributes to weight loss. Regular exercise may prevent type 2 diabetes in high-risk individuals
- Individualized; pre-exercise program history and detailed medical examination are essential
- Recommended 150 min/week of moderate-intensity aerobic exercise and/or at least 90 min/week of vigorous aerobic exercise distributed over at least 3 days/week
- Program should be adjusted in the presence of macro- and microvascular complications that may be worsened

- * Retinopathy: Vigorous aerobic or resistance exercise may be contraindicated in the presence of proliferative diabetic retinopathy or severe non-proliferative diabetic retinopathy because of the risk of triggering vitreous hemorrhage or retinal detachment
- * Peripheral neuropathy: Non-weight bearing activities may be best because decreased pain sensation in the extremities increase the risk of skin breakdown and infection
- * Autonomic neuropathy: Should undergo cardiac investigation before increasing physical activity (may lead to decreased cardiac responsiveness to exercise, postural hypotension, etc.)
- SMBG necessary before and after exercise
- Fast-acting oral carbohydrates should be available during and after exercise

Diabetes Self-Management Education (DSME)

- Provides means for persons with DM to become empowered and assist with self-care
- Education content includes the disease process; acute and long-term complications; drug and nondrug treatment; monitoring; preventive measures; decision-making skills; specific self-care measures relative to foot, skin, dental and eye care; goal setting; and psychosocial adjustment

4. Key Points

- Diabetes mellitus (DM) is a group of chronic metabolic diseases exhibiting hyperglycemia resulting from defects in insulin secretion and/or action.
- The principal treatment goals include maintaining blood glucose levels in the normal or near normal range and preventing acute and chronic complications.
- Type 1 diabetes results from immune mediated β -cell destruction, which leads to absolute insulin deficiency.
- Type 2 diabetes is characterized by relative insulin deficiency and/or insulin resistance.

Comparison of Type 1 and Type 2 Diabetes Mellitus

	Type 1	Type 2
Previous names	Insulin-dependent diabetes mellitus (IDDM); juvenile-onset	Non-insulin dependent diabetes mellitus (NIDDM); adult-onset
Percentage of DM cases	5%-10%	90%-95%
Age of occurrence	<30 years of age (usually childhood or adolescence); at any age following autoimmune stimulus (eg, virus)	>30 years of age; increasing in childhood/adolescence in association with obesity and inactivity
Onset	Rapid	Gradual
Primary etiology	Autoimmune mediated mechanism with genetic predisposition	Genetic and environmental (eg, family history, ethnicity, obesity, inactivity)
Pathogenesis	Destruction of β -cells resulting in absolute insulin deficiency and abnormal glucose control	Increasing resistance of tissue (liver and skeletal muscle) to insulin; impaired insulin secretion resulting in relative deficiency of insulin; increased hepatic glucose production
Signs and symptoms	Polyuria, polydipsia, polyphagia, unexplained weight loss, fatigue, blurred vision; possibly ketoacidosis	Polyuria, polydipsia, polyphagia, obesity, fatigue, blurred vision; possibly asymptomatic
Diagnostic criteria	See Table 1	See Table 1
Ketoacidosis	Ketosis prone (diabetic ketoacidosis; DKA)	Not ketosis prone due to residual insulin (hyperglycemic hyperosmolar nonketotic syndrome [HHNS])
Treatment:		
Nondrug therapy	<ul style="list-style-type: none"> • Medical nutrition therapy (MNT) • Physical activity/exercise therapy approved by physician; type based on presence of factors such as retinopathy, neuropathy, and cardiovascular status 	Essential adjunct to oral antidiabetic therapy; may be sufficient as monotherapy to control blood glucose
Drug therapy	Insulin monotherapy OR rarely oral antidiabetic drugs as adjunct to insulin therapy (if accompanied by insulin resistance)	<ul style="list-style-type: none"> • MNT monotherapy OR • Oral antidiabetic drugs OR • Oral antidiabetic drugs in combination therapy OR • Insulin monotherapy OR • Insulin and oral antidiabetic drugs

- Goals of diabetes therapy include achieving and maintaining glycemic control, and reaching recommended blood pressure and lipid goals.
- Outcomes of uncontrolled BG include cardiovascular, kidney, eye, and nerve disease.
- Pharmacotherapy treatment of DM should be individualized to each patient considering such factors as glucose control goals, length of time with DM, concomitant diseases, psychosocial issues including available support for the patient, patient motivation, medication and DM supply costs, as well as level of risk for complications secondary to DM control.
- Multiple studies have shown improved glycemic control delays the onset of, slows the progression of, or lowers the risk of long-term microvascular complications
- Combination therapy of either 2 or more PO therapies, PO therapies PLUS insulin, PO products PLUS GLP-1 analogs, will be required in most patients to maintain continued DM control
- Metformin
 - * considered 1st-line therapy in newly diagnosed type 2 DM
 - * contraindicated in renal dysfunction patients
 - * low/minimal risk of hypoglycemia with monotherapy
 - * GI side effects (flatulence, GI upset, abdominal pain, diarrhea, bloating) are the dose-limiting problems
 - * no weight gain
 - * may decrease the progression to DM in high-risk patients
- Secretagogues
 - * are helpful in combination with other PO agents and injectable products
 - * increases risk of hypoglycemia (sulfonylureas > meglitinides)
 - * increases weight (sulfonylureas > meglitinides)
 - * high rate of failure over time
 - * use with caution in renally impaired and elderly patients
- Thiazolidinediones
 - * helps to improve peripheral insulin resistance
 - * increases weight and edema
 - * low/minimal risk of hypoglycemia with monotherapy
 - * contraindicated in patients with CHF
 - * delayed time to see full impact on DM control
 - * may decrease the progression to DM in high-risk patients
- Alpha-Glucosidase Inhibitors
 - * blocks absorption of carbohydrates in small intestine
 - * low/minimal risk of hypoglycemia with monotherapy
 - * GI side effects (flatulence, GI upset, abdominal pain, diarrhea, bloating) are the dose-limiting problems
 - * more effective for post-prandial hyperglycemia
 - * minimal effect on weight
- GLP-1 / Amylin based medications
 - * Byetta (GLP-1 analog)
- increases insulin production in a glucose-dependent fashion
- decreases production of glucagon
- improves beta-cell functioning
- slows gastric emptying
- increases satiety and possible weight loss
- dose-limiting side effect = nausea
- injectable product
- for use in type 2 DM
- high cost
 - * Januvia (DPP-IV inhibitor)
- increases insulin production in a glucose-dependent fashion
- decreases production of glucagon
- improves beta-cell functioning
- no effect on weight
- well tolerated with few side effects
- for use in type 2 DM
- high cost
 - * Symmlin (Amylin mimetic)
- decreases production of glucagons
- slows gastric emptying
- increases satiety and possible weight loss
- significant risk of hypoglycemia in combination with insulin in type 1 DM
- dose-limiting side effect = nausea
- for use in type 1 & 2 DM
- high cost
- Insulin
 - * essential for type 1 DM
 - * often used in type 2 DM in combination with other therapies
 - * should be considered initial agent if glucose is >250 mg/dL or A_{1c} >10%
 - * often stated as basal therapy (0.1–0.2 units/kg/day) added to an existing PO regimen
 - * should be individualized to the patient's goals and motivation
 - * intensive insulin therapy (>3 doses/day or use of CSII) is replacing conventional insulin therapy (split-mix dosing: two-thirds of total daily dose [TDD])

* Insulins vary principally by their source, appearance, time-activity profiles (onset, peak, and duration), dosing, and route of administration. The main adverse events are hypoglycemia, weight gain, and lipodystrophies. Mechanism of action is the same for all types.

- Patient education is essential for the management of DM, as it provides a means for persons with this chronic disease to become empowered, cope effectively, and engage in appropriate self-care.
- Recommend lifestyle modifications including weight management, increased physical activity, and smoking cessation.

Patient Profile #1—Institution or Nursing Home Care

Patient Name: Barbara Evens

Address: 413 Summit Street

Age: 68

Height: 5' 5"

Weight: 190 lb

Sex: Female

Race: African-American

Allergies: Penicillin, sulfa drugs

Diagnosis:

Primary 1) Type 2 DM

Secondary 1) Hypertension

2) Asthma

Lab/Diagnostic Tests:

	Date	Test
1)	2/1	LFTs
2)	2/1	Serum K
3)	5/1	LFTs
4)	5/1	Serum K
5)	6/1	A _{1c}

Medication Orders:

Date	RX No	Physician	Drug & strength	Qty	Sig	Refills
2/1	834924	Jones	Propranolol 20 mg	30	1 PO bid	3
2/1	834925	Jones	Albuterol inhaler	1	1-2 inhalations q4-6h	3
2/1	834926	Jones	Acarbose 25 mg	90	1 tab PO w/meals	2
5/1	834927	Jones	Acarbose 50 mg	90	1 tab PO w/meals	2
6/1	834928	Jones	Prednisone 10 mg	30	1 tab PO daily	0
6/1	834929	Jones	Propranolol 20 mg	30	1 tab PO bid	3
6/1	834930	Jones	Albuterol inhaler	1	1-2 inhalations q4-6h	3
6/1	834931	Jones	ASA 81 mg	30	1 tab PO daily	3

Date Test

6)	6/1	Serum creatinine
7)	6/1	BUN
8)	6/1	Serum K

Additional Orders:

- 1) Referral to dietitian for weight reduction diet
- 2) Low impact exercise 30 mins 3 days per week

Dietary Consideration:

- 1) Dietary changes per dietitian consult
- 2) Enteral and parenteral

Pharmacist Notes and Other Patient Information:

Date	Comment
1) 2/1	Advise patient to continue SMBG and to report any hypoglycemic episodes. Instruct patient to treat hypoglycemia with glucose or lactose products. Instruct patient to take acarbose with first bite of meal. Foot exam negative. Patient reports having 1-2 drinks of bourbon per day.
2)	Inform patient to report any changes in BG.

5. Questions and Answers

Use Patient Profile #1 to answer Questions 1-5.

1. Chlorpropamide would be problematic in this case for which of the following reasons?
 - I. Alcohol intake
 - II. Sulfa allergy
 - III. Asthma
 - IV. Hypertension
 - V. Drug-drug interaction

- A. I only
- B. III only
- C. I and II only
- D. II, III, and IV
- E. I, II, and V

2. Due to a renal protection mechanism, the drug class of choice for B.E.'s hypertension is:

- A. β -blocker
- B. Loop diuretic
- C. Thiazide diuretic
- D. α -adrenergic blocker
- E. Angiotensin-converting enzyme inhibitor

3. One of the most common adverse drug events caused by B.E.'s oral antidiabetic agent is:

- A. Flatulence
- B. Hypoglycemia
- C. Renal failure
- D. Hyperglycemia
- E. Weight gain

4. Which of the following medications on the medication list in this case can mask the symptoms of hypoglycemia?

- A. Propranolol
- B. Albuterol
- C. Acarbose
- D. Prednisone
- E. Aspirin

5. What change in the following laboratory tests might be observed with the addition of prednisone to B.E.'s drug regimen?

- A. Increase in liver function tests (LFTs)
- B. Decrease in BUN
- C. Decrease in serum creatinine
- D. Increase in serum creatinine
- E. Increase in blood glucose

Use Patient Profile #2 to answer Questions 6-10.

6. What is the principal drug-related problem in this patient's medication record?

- A. Insulin therapy is not indicated for persons with type 2 DM
- B. Therapeutic duplication of sulfonylurea therapy
- C. Potential decrease of BG due to drug-drug interaction between phenytoin and tolazamide
- D. Potential increase of BG due to drug-drug interaction between glimepiride and itraconazole
- E. Use of an ACE inhibitor for hypertension in type 2 DM

7. All of the following monitoring parameters are necessary for T.R. except:

- A. Periodic glycosylated hemoglobin A_{1c}
- B. SMBG levels
- C. Phenytoin levels
- D. Blood pressure readings
- E. Quarterly serum C-peptide level

8. Which of the following is inappropriate treatment for a mild hypoglycemic episode?

- A. $\frac{1}{2}$ cup of diet soda
- B. 6-7 hard candies containing sugar
- C. 3 glucose tablets
- D. $\frac{1}{2}$ cup of regular soda
- E. 5 small sugar cubes

9. Persons on insulin therapy should be advised to rotate their injection sites for the following reason:

- A. Reduces the risk of infection
- B. Reduces the risk of lipoatrophy
- C. Reduces the risk of lipohypertrophy
- D. Reduces the risk of generalized myalgia
- E. This advice is outdated due to the use of human insulin

Patient Profile #2—Community**Patient Name:** Tom Right**Address:** 20 Blue Ridge Drive**Age:** 48**Height:** 5' 6"**Weight:** 135 lb**Sex:** Male**Race:** Caucasian**Allergies:** NKDA**Diagnosis:**

Primary 1) Type 2 DM

2) Epilepsy

Secondary 1) Hypertension

2) Fungal infection under toenails

Pharmacist Notes and Other Patient Information:

	Date	Comment
1)	4/8	Patient should be monitored closely for hypoglycemia. Teach patient signs and symptoms of hypoglycemia and treatment measures.

Medication Orders:

Date	RX No	Physician	Drug & strength	Qty	Sig	Refills
1/6	765321	Smith	Tolazamide 250 mg	90	1 tab PO daily	0
4/8	765323	Smith	Glimepiride 2 mg	90	1 tab PO daily	0
8/6	765324	Smith	Lisinopril 5 mg	90	1 tab PO daily	0
8/6	765325	Thomas	Phenytoin extended	60	300 mg PO daily	0
8/6	765366	Smith	Itraconazole	14	50 mg PO daily	0
8/6	765367	Smith	Regular insulin	Trial	5 units SC before meals	0

10. Which of the following is the most appropriate treatment for a severe hypoglycemic episode?
 - A. $\frac{1}{2}$ cup of diet soda
 - B. 3 hard candies containing sugar
 - C. 1 glucose tablet
 - D. Glucagon injection
 - E. 2-3 small sugar cubes
11. Commercially available insulin (as of May 2005) may be administered by which of the following routes?
 - I. Intravenously
 - II. Subcutaneously
 - III. Via inhalation
 - IV. Transdermally
 - V. Sublingually
 - A. I only
 - B. II only
 - C. I and II only
 - D. II, III, and IV
 - E. I, II, and V
12. Insulin therapy is indicated in all of the following except:
 - A. Newly diagnosed type 1 DM
 - B. Gestational diabetes mellitus (GDM) not controlled by diet
 - C. Hyperglycemic hyperosmolar nonketotic syndrome (HHNS)
 - D. Newly diagnosed type 2 DM
 - E. Diabetic ketoacidosis (DKA)
13. Insulin dosing is adjusted based on the following parameters:
 - I. Liver function test results
 - II. Dietary intake
 - III. Physical activity/exercise
 - IV. Blood glucose levels
 - V. Ophthalmic examinations
 - A. I only
 - B. II only
 - C. I and II only
 - D. II, III, and IV
 - E. I, II, and V

14. Which of the following oral antidiabetic agents is a micronized formulation?
 - A. Micronase®
 - B. Glynase®
 - C. Glucotrol XL®
 - D. Amaryl®
 - E. Orinase®
15. Insulin that has been stored in a refrigerator should be allowed to reach room temperature prior to administration in order to:
 - A. Allow for proper mixing
 - B. Minimize painful injections
 - C. Prevent frosting or clumping
 - D. Delay systemic absorption
 - E. Prevent change in clarity
16. When mixing rapid- or short-acting insulin with intermediate- or long-acting insulin, which insulin in the list below should be drawn up first?
 - A. Regular
 - B. NPH
 - C. Lente
 - D. Ultralente
 - E. Glargine
17. Uniform dispersion of insulin suspensions can be obtained by:
 - A. Vigorously shaking the vial
 - B. Rolling the vial gently between the hands
 - C. Warming the vial in a microwave
 - D. Packing the vial in dry ice
 - E. Keeping the vial at room temperature (68-75°F)
18. Of the following types of insulin, which can be administered intravenously?
 - A. Glargine
 - B. Lente
 - C. Regular
 - D. Ultralente
 - E. NPH
19. Diabetes mellitus is the leading cause of which of the following complications?
 - A. Pancreatitis
 - B. Fatty liver
 - C. Blindness
 - D. Stroke
 - E. Deafness
20. Which of the following is an indication that a patient is developing a long-term complication from diabetes mellitus?
 - A. Tachycardia
 - B. Glucosuria
 - C. Leukocytosis
 - D. Proteinuria
 - E. Tinnitus
21. What sulfonylurea has been associated with the greatest incidence of prolonged hypoglycemia in the elderly?
 - A. Tolazamide
 - B. Tolbutamide
 - C. Chlorpropamide
 - D. Glimepiride
 - E. Glipizide
22. Which of the following drugs taken with alcohol is most likely to cause a disulfiram-like reaction?
 - A. Chlorpropamide
 - B. Acarbose
 - C. NPH insulin
 - D. Glucagon
 - E. Pioglitazone
23. Metformin should be withheld for 48 hours prior to any procedure requiring the use of parenteral iodinated contrast media due to the potential for this adverse drug event:
 - A. Optic neuritis
 - B. Metabolic alkalosis
 - C. Lactic acidosis
 - D. Purple toe syndrome
 - E. Tinnitus

24. The use of insulin in a woman with GDM helps reduce the incidence of which complication in the fetus?
- Macrosomia
 - Cystic fibrosis
 - Deafness
 - "Soft bones"
 - Eczema
25. Metformin would not be an option for a patient with the following diagnosis:
- Iron deficiency anemia
 - Impaired renal function
 - Hypertension
 - Type 2 diabetes
 - Frequent hypoglycemic episodes
26. Nocturnal hypoglycemia resulting in rebound hyperglycemia in type 1 DM is termed:
- Honeymoon period
 - Somogyi effect
 - Dawn phenomenon
 - Hyperglycemic phase
 - Insulin resistance syndrome
27. Which of the following is a potentially fatal adverse drug event of Glucophage®?
- Weight gain
 - Frequent urination
 - Diarrhea
 - Lactic acidosis
 - Angioedema
28. All of the following are true of acarbose therapy except:
- Contraindicated in inflammatory bowel disease
 - Should be taken with the first bite of each meal
 - Does not cause hypoglycemia or weight gain
 - Hypoglycemia due to combination therapy should be treated with sucrose
 - LFTs are monitored every 3 months during the first year and periodically thereafter (if the dose is >50 mg tid)
29. Prandin® is a nonsulfonylurea secretagogue. Adverse drug events include all of the following except:
- Upper respiratory infection (URI)
 - Arthropathy
 - Hypoglycemia
 - Back pain
 - Hyperglycemia
30. Patient counseling relative to meglitinides should include the following points:
- Must be taken 30 minutes before main meals
 - If a meal is omitted, do not take
 - Enhances preprandial glucose utilization
 - Hyperglycemia is a potential adverse drug event
 - Disulfiram-like reaction possible when ingested with ETOH
- I only
 - III only
 - I and II only
 - II, III, and IV
 - I, II, and V
31. Which one of the following antidiabetic agents does not require liver function tests for monitoring?
- Glargine
 - Miglitol
 - Rosiglitazone
 - Acarbose
 - Metformin
32. Adverse drug events reported for pioglitazone (Actos), a thiazolidinedione, include all of the following except:
- Exacerbation of CHF
 - Resumption of ovulation
 - Edema
 - Upper respiratory infection (URI)
 - Megaloblastic anemia

33. All of the following drugs have a direct glucogenic effect except:
- A. Thiazide diuretics
 - B. Corticosteroids
 - C. Nicotinic acid
 - D. Sympathomimetics
 - E. Acetohexamide
34. Which of the following is the mechanism of action (MOA) for the sulfonylureas?
- A. Stimulate pancreatic β -cells to secrete insulin
 - B. Delay carbohydrate metabolism and absorption (due to inhibition of intestinal and pancreatic enzymes)
 - C. Increases hepatic insulin sensitivity and decreases hepatic glucose production
 - D. Increases skeletal muscle and adipose tissue insulin sensitivity and decreases hepatic glucose production
 - E. Decrease blood glucose and assists with blood glucose control by increasing glucose uptake and utilization by peripheral tissues
35. All of the following are signs or symptoms of hypoglycemia except:
- A. Tachycardia
 - B. Diaphoresis
 - C. Shakiness
 - D. Polyuria
 - E. Pallor
36. Pramlintide (Symlin[®]):
- A. Is a basal insulin
 - B. Is an insulin analogue
 - C. Is an oral insulin
 - D. Is an inhaled insulin
 - E. Is an injectable synthetic version of the human hormone amylin
37. Which of the following statements correctly states the current thinking on insulin storage, according to a study in *Diabetes Care*, 2003;26:2655-9?
- A. Glargine insulin (Lantus[®]) can safely be prefilled in a syringe and stored for up to 28 days
 - B. Lispro insulin (Humalog[®]) should not be refrigerated since refrigeration causes crystallization
 - C. Unopened insulin vials kept under refrigeration are stable until their labeled expiration dates
 - D. Opened vials of any insulin product should be stored in the refrigerator and destroyed if left at room temperature for more than 3 days

Answers

1. **E.** Chlorpropamide is contraindicated in persons with a sulfa allergy. Alcohol (ETOH) ingestion with chlorpropamide could lead to a disulfiram-like reaction. Also, acute ingestion of ETOH (especially in the fasting state) includes the risk of severe hypoglycemia. Chlorpropamide and prednisone may produce a drug-drug interaction resulting in hyperglycemia. Items 3 and 4 are non-problematic in this case in relation to chlorpropamide.
2. **E.** Angiotensin-converting enzyme inhibitors (ACEIs) exhibit a renal protective mechanism in persons with DM. None of the remaining drugs exhibit such an effect.
3. **A.** The most common adverse drug events for acarbose are flatulence, abdominal pain, and diarrhea. These adverse effects may be decreased by titrating the dose gradually and taking the drug with the first bite of each meal. There may also be an increase in LFTs.
4. **A.** Propranolol (a nonselective β -blocker) can mask the symptoms of hypoglycemia (ie, tachycardia [palpitations], pallor, shakiness [tremor], paresthesia, hunger, diaphoresis [sweating], dizziness, and blurred vision). None of the remaining drugs listed have this effect.
5. **E.** The increase in LFTs may be due to acarbose, and the increase in serum creatinine may represent the development or progression of nephropathy, a long-term complication of DM. The decrease in the serum creatinine and BUN are incorrect answers. Prednisone, a corticosteroid, has a dose-dependent, direct glucogenic and glycosuric effect, and therefore an increase in BG might be observed.
6. **B.** Though tolazamide and glimepiride are first- and second-generation sulfonylureas, duplication of drug class is inappropriate. These agents are both intermediate-acting and therefore might potentiate the adverse drug event of hypoglycemia. Insulin may be indicated in the person with type 2 DM as the disease progresses. The potential drug-drug interaction between phenytoin and tolazamide could result in an increased BG level, and the potential drug-drug interaction between glimepiride and itraconazole could result in a decreased BG level. An ACEI for hypertension in type 2 DM is appropriate as this drug is renal protective.
7. **E.** The A_{1c} and SMBG tests are essential for monitoring the success of glucose control therapy. The SMBG gives an immediate determination of BG level and the A_{1c} gives an average reading over the previous 2-3 months (or 120 days, the lifespan of an RBC). Phenytoin levels are necessary for monitoring therapeutically appropriate levels, and BP readings are for monitoring the success of anti-hypertensive therapy. A serum C-peptide might be diagnostic for the determination of functioning β -cells; however, if performed, it is done very infrequently to reduce cost.
8. **A.** One-half cup of diet soda would be inappropriate, because a mild hypoglycemic episode requires a fast-acting oral carbohydrate for resolution and diet soda has none. The other options would all be appropriate for resolution of the event.
9. **C.** Lipohypertrophy (a bulging of the injection site) is due to nonrotation of injection sites. The risk of infection may be reduced by using aseptic injecting technique. Lipoatrophy (a pitting of the injection site) may be due to an antigenic response to insulin. The advice regarding rotation of injection site is not outdated.
10. **D.** Glucagon, a pancreatic hormone which is given parenterally, is the most appropriate treatment for a severe hypoglycemic episode (life-threatening), as the patient may be unconscious and not able to take a fast-acting carbohydrate by mouth. The other items represent inappropriate treatment for mild to moderate hypoglycemia (the amounts of items B, C, and E are inadequate, and the soda in item A should be regular soda).
11. **C.** Pharmaceutical research has developed an inhaled insulin product which is still being tested. Presently, the commercially available insulins may only be administered intravenously or subcutaneously.
12. **D.** Newly diagnosed type 2 DM should first have a trial with MNT and exercise, and if this nondrug therapy fails, then oral antidiabetic monotherapy should be added. Combination oral therapy would be indicated next with failure of monotherapy, and then following its failure, insulin monotherapy or in combination with oral agents is indicated. Insulin is indicated in all the other situations.

13. **D.** Dietary intake, physical activity/exercise, and blood glucose levels are the parameters used in adjusting insulin dosing (eg, if the parameters of dietary intake and blood glucose levels are decreased and physical activity/exercise is increased, then the insulin dosing would require reduction to avoid hypoglycemia). Monitoring of these parameters is critical to adjusting the insulin regimen. Items 1 and 5 are incorrect.
14. **B.** Glynase® is a micronized formulation of glyburide that is significantly absorbed (eg, a 3-mg tablet provides blood levels similar to a 5-mg conventional tablet). Micronase® is a trade name for non-micronized glyburide. Glucotrol XL® is the name of an extended formulation of glipizide. Orinase® is the trade name for tolbutamide (the only first-generation sulfonylurea listed here), and Amaryl® is the trade name for glimepiride.
15. **B.** Refrigerated insulin is allowed to reach room temperature prior to administration to minimize painful injections. Proper mixing, prevention of frosting or clumping, or maintenance of clarity have nothing to do with reaching room temperature. Systemic absorption would actually be enhanced by increasing to room temperature, not delayed.
16. **A.** Regular or clear insulin is always drawn up first (to assure that all persons mixing insulins will use the same procedure and no intermediate- or long-acting insulin will be placed in the regular insulin vial, potentially causing contamination and dose variance). Glargine is also a clear insulin; however, it is never to be mixed with other insulins due to the low pH (4.0) of its diluents.
17. **B.** Uniform dispersion of insulin suspensions can be obtained by gently rolling the vial between the hands. Insulin is a fragile molecule and all the other means listed could cause molecular degradation.
18. **C.** Of these insulins, regular is the only one that can be administered intravenously. Though glargine is clear like regular insulin, its pH is 4.0 and it should never be given intravenously. The remaining insulins are suspensions and also should never be given intravenously.
19. **C.** DM is the leading cause of new cases of blindness among adults 20-74 years of age in the U.S. There is also an increased incidence of stroke with DM, but DM is not the leading cause of this problem. The other items are incorrect.
20. **D.** Proteinuria is an indication that a patient is developing the long-term complication of nephropathy. Items A, B, and C could be related to acute complications such as DKA (glucosuria and leukocytosis) and hypoglycemia (tachycardia). Item E is incorrect.
21. **C.** Chlorpropamide has a $t_{1/2}$ of 35 hours and a duration of action of 60 hours, therefore it has been associated with prolonged hypoglycemia in the elderly (perhaps due to their declining renal function). The other sulfonylureas have reported less hypoglycemia.
22. **A.** Chlorpropamide has had the greatest reporting of this drug interaction relative to the first-generation sulfonylureas. The remaining drugs listed have not had reports of this adverse drug event.
23. **C.** Lactic acidosis can result if metformin (Glucophage) is given in this situation and it can be potentially fatal. Renal function must be evaluated following such a procedure, and it must be normal before metformin may be resumed. The other items are incorrect.
24. **A.** Macrosomia (abnormally large fetal body size) is one of the fetal complications of concern in GDM. The primary benefit of insulin therapy is reduction in the incidence of macrosomia. The other items are incorrect.
25. **B.** Contraindications for metformin are renal dysfunction for those predisposed to lactic acidosis. Metformin does not cause hypoglycemia and it is indicated in type 2 DM. Hypertension and iron deficiency anemia are incorrect answers. Metformin may cause megaloblastic anemia.

26. **B.** The Somogyi effect is rebound hyperglycemia or early morning hyperglycemia secondary to nocturnal hypoglycemia. The person with type 1 DM may experience a honeymoon period—a phase of erratic insulin secretion during destruction of β -cells by islet cell antibodies. This apparent short-lived remission lasts months to a year. The dawn phenomenon is fasting hyperglycemia (pre-breakfast) due to decreased plasma insulin during the night or the anti-insulin effect of nocturnal growth hormone. Items D and E are incorrect.
27. **D.** Lactic acidosis is a potentially fatal adverse drug event of Glucophage (metformin). It does not cause weight gain. Modest weight loss is possible and no hypoglycemia is reported when metformin is used as monotherapy. Diarrhea is an adverse drug event, but with gradual dose titration and administration with food, it decreases over time. Items B and E are incorrect.
28. **D.** Oral glucose instead of carbohydrate sources with sucrose (cane sugar) or fructose is used because absorption of these is inhibited. The remaining items are true of acarbose therapy.
29. **E.** Prandin may cause hypoglycemia like the sulfonylureas. Hyperglycemia is not one of the adverse drug events (ADEs) reported. All the other ADEs may be caused by Prandin.
30. **C.** Meglitinides should be taken 30 minutes before main meals and if a meal is omitted, the drug should not be taken. It enhances postprandial glucose utilization, hypoglycemia and not hyperglycemia may occur, and disulfiram-like reactions are not reported.
31. **A.** The α -glucosidase inhibitors (eg, acarbose), biguanides (eg, metformin), and thiazolidinediones (eg, rosiglitazone) all require LFTs for monitoring. Glargine, a long-acting insulin, does not require LFTs for monitoring; rather it requires blood glucose monitoring.
32. **E.** Megaloblastic anemia is a reported adverse drug effect for metformin but not for Actos. All the other items listed are reported ADEs. Since troglitazone (Rezulin®), a thiazolidinedione, was withdrawn from the market in 2000 due to severe liver toxicity, this ADE could potentially occur with Actos®; therefore LFTs should be performed periodically.
33. **E.** Acetohexamide has a hypoglycemic effect. All the other drugs listed have a direct glucogenic effect.
34. **A.** The sulfonylureas stimulate pancreatic β -cells to secrete insulin. Item B is the MOA for α -glucosidase inhibitors, item C is the MOA for the biguanide metformin, item D is the MOA for the glitizones, and item E is the MOA for insulin.
35. **D.** Polyuria (excessive urination) is one of the classic signs and symptoms of DM. All of the other answers listed are some of the signs and symptoms of hypoglycemia, which can be life threatening.
36. **E.** Pramlintide (Symlin®) was approved in March 2005 as the first new type 1 diabetes treatment in more than 80 years. It is an injectable synthetic version of the human hormone amylin.
37. **C.** Unopened insulin vials kept under refrigeration are stable until their labeled expiration dates. Glargine insulin (Lantus®) is stable in a prefilled syringe for only 2 to 3 days. Lispro insulin (Humalog®) should be refrigerated when not in use. Opened vials of any insulin product should be stored in the refrigerator and are stable for up to 28 days.

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19. Oncology

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1. Overview

2. Drug Therapy

3. Nondrug Therapy

4. Key Points

5. Questions and Answers

6. References

1. Overview

Definition

- Oncology can be defined as the science dealing with the etiology, pathogenesis, and treatment of cancers (synonymous with malignant neoplasms).
- It encompasses more than 100 different diseases that share characteristics of uncontrollable cell proliferation, invasion of local tissues, and metastases (eg, spread from original site).
- In the United States, men have roughly a 1 in 2 cumulative lifetime risk of developing cancer and women have a 1 in 3 risk. In 2007, approximately 1,444,920 new cases of cancer will develop and 559,650 cancer deaths will occur. The most common types of cancer are prostate, lung, and colorectal in men and breast, lung, and colorectal in women.

Classifications

- Neoplastic malignancies arise from four tissue types (epithelial, connective, lymphoid, and nerve) and are classified based on this origin. Table 1 lists the tis-

Table 1

Tissue Origin of Malignant Tumor Types

Origin	Tissue type	Malignant tumor
Epithelial	Surface epithelium	Carcinoma
	Glandular tissue	Adenocarcinoma
Connective	Fibrous	Fibrosarcoma
	Bone	Osteosarcoma
	Smooth/striated muscle	Leiomyosarcoma/ rhabdomyosarcoma
	Fat	Liposarcoma
Lymphoid	Bone marrow	Leukemia
	Lymphoid	Hodgkin, non-Hodgkin lymphoma
	Plasma	Multiple myeloma
Neural	Glial	Glioblastoma, astrocytoma
	Nerve sheath	Neurofibrosarcoma
	Melanocytes	Malignant melanoma
Mixed	Gonadal tissue	Teratocarcinoma

Adapted from Balmer et al, 2002.

Table 2

Warning Signs of Cancer in Adults

Change in bowel or bladder habits
 A sore that does not heal
 Unusual bleeding or discharge
 Thickening of lump in breast or elsewhere
 Indigestion or difficulty swallowing
 Obvious change in wart or mole
 Nagging cough or hoarseness

sue origin of each type of malignancy and the corresponding medical terminology.

Clinical Presentation

- The first signs and symptoms of cancer develop when the tumor has grown to approximately 10^9 cells (1 cm in diameter or 1 g mass).
- The type of cancer determines the presentation of signs and symptoms, which vary widely across tumor types.
- Positive screening tests (see section on nondrug therapy) or generalized signs of anorexia, fatigue, fever, weight loss, and anemia must also be evaluated.
- Tables 2 and 3 show the American Cancer Society's seven warning signs of cancer for adults and the warning signs for children.

Pathophysiology and Etiology

- Cancer promoting factors include:
 - * External factors: tobacco, chemicals, radiation, infectious organisms, diet

Table 3

Warning Signs of Cancer in Children

Continued, unexplained weight loss
 Headaches with vomiting in the morning
 Increased swelling or persistent pain in bones or joints
 Lump or mass in abdomen, neck, or elsewhere
 Development of a whitish appearance in the pupil of the eye
 Recurrent fevers not caused by infection
 Excessive bruising or bleeding
 Noticeable paleness or prolonged tiredness

- * Internal factors: genetics, hormones, immune conditions
- Development of cancer is genetically regulated and is a multistage process:
 - * Initiation: normal cells are exposed to chemical, physical, or biological carcinogens. This results in irreversible damage, genetic mutations, and selective growth advantages.
 - * Promotion: reversible environmental changes favor the growth of the mutated cells.
 - * Transformation: the cells become cancerous.
 - * Progression: additional genetic changes occur resulting in increased cancerous proliferation. Tumors invade local tissues and metastasis occurs.
- Genetic alterations are necessary for the development and growth of cancer. Some of the most common are:
 - * **Oncogenes promote growth advantages in mutated cells and** cause excessive proliferation (eg, ras, c-myc).
 - * **Inactivation of tumor suppressor genes (TSGs)** results in inappropriate cell growth, as TSGs normally regulate the cell cycle (eg, p53).
 - * **Activation of anti-apoptotic genes (eg, bcl-2).**
 - * **Reduced activity of DNA repair genes.**
- Malignant tumor cells do not resemble their tissue of origin (in contrast to benign tumors). They are unstable and are incapable of performing normal cell functions.

Diagnostic Criteria

- A sample of suspected malignant tissues or cells is needed for a definitive diagnosis. This can be done with a biopsy, fine-needle aspiration, or exfoliative cytology.
- Radiation or chemotherapy should not begin without pathological staging. Further pathological imaging may include:
 - * Chest x-ray: evaluates spread to bones or lungs
 - * Computed tomography (CT): assesses the size, shape, and position of tumor; detects masses in lymph nodes, brain, or adrenal glands via a three-dimensional view
 - * Magnetic resonance imaging (MRI): evaluates spread to the brain or spinal cord
 - * Positron emission tomography (PET): evaluates lymph and other metastatic involvement
 - * Bone scanning: assesses for the presence of bone metastasis
- Laboratory work may include: complete blood counts (CBCs), blood chemistries, and tumor markers (see section on nondrug therapy).
- If a diagnosis of cancer is made, the malignancy will need to be staged or categorized based on severity of

the disease and the results of the pathological staging tests. Staging guides the oncology practitioner in determining the prognosis and the treatment regimen for the patient.

- * The TNM staging system is the most commonly used tool for solid tumors. Tumors are scored numerically based on the size of the tumor (T), the extent of lymph node involvement (N), and presence or absence of metastases (M). This allows classification of tumors **by stage, from stage 0 to stage IV, with stage IV denoting the presence of metastasis** (eg, most severe disease). A **stage 0 tumor** is called a **carcinoma in situ**, where the **malignancy** has not yet invaded the **basement membrane** of the epithelial surface.
- * Lymphoid tumors are staged differently and are beyond the scope of this review. Refer to Balmer et al, 2002, Chaps. 129, 131, and 132, for more information.

Treatment Principles and Goals

- Treatment regimens are based on the type of cancer, stage, the age of the patient, and other prognostic factors (eg, presence of a tumor marker, poor performance status, and ethnicity, among others).
- Primary therapy is the initial and mainstay approach to treat cancer. It usually consists of removal of the tumor or debulking through surgery.
- **Neoadjuvant therapy** is therapy given prior to the primary therapy. The goal **is to shrink the tumor**, thereby increasing the efficacy of the primary treatment. Examples include **chemotherapy or radiation**.
- **Adjuvant therapy** is additional therapy given after the main treatment. The goal is to make sure that all residual disease has been eradicated.
- The four main cancer treatments include: surgery, radiation, chemotherapy, and biologic therapy. Most regimens are a combination of modalities.
 - * Surgery alone is reserved for solid localized tumors, where the entire cancer can be resected. It may also be combined with other modalities in later stages of disease. This is not an option for patients with lymphoid-based disease (eg, Hodgkin disease).
 - * Radiation alone is also reserved for curing localized tumors, as it treats a very focused area. It also can be combined with other treatments as neoadjuvant or adjuvant therapy to reduce disease-related symptoms or to reduce the incidence of disease recurrence.
 - * Chemotherapy is a means of systemic treatment, in contrast to the two types of local treatment just described. It can be used to treat the primary tumor as well as metastases. This is

generally not administered to patients with local disease that can be fully resected.

- * Biologic therapy is another systemic treatment and includes agents such as monoclonal antibodies, interferons, interleukins, and tumor vaccines. It is a new type of treatment and acts by stimulating the host immune system.
- The goals of cancer therapy are based on the type and stage of cancer, as well patient characteristics (eg, an older patient with a short life expectancy may not be offered intense treatment that may impair quality of life).
- * **Localized or regional disease** (ie, stages 0, I, II, and early III): curative intent, inhibit recurrence of disease
 - Stage 0 diseases are often not treated, but monitored until clinically apparent.
- * **Advanced or metastasized disease** (ie, advanced stage III and all stage IV): palliate symptoms, reduce tumor load, prolong survival, and increase quality of life

Survival and response to treatment

- In 2007, more than 1500 people a day will die of a cancer, which accounts for one in four deaths.
- Survival depends on patient characteristics, type of disease, stage of disease, and treatment regimen. Older patients with more severe disease, a poor performance status, and faster-growing tumors have a poor prognosis.
- Response to treatment modalities for solid tumors are classified as:
 - * Cure: 5 years of cancer-free survival for most tumor types
 - * Complete response (CR): absence of all neoplastic disease for a minimum of 1 month after cessation of treatment
 - * Partial response (PR): $\geq 50\%$ decrease in tumor size or other disease markers for a minimum of 1 month
 - * Stable disease: no change or criteria for PR or progression are not met
 - * Progression: $\geq 25\%$ increase in tumor size or new lesion
- Response to treatment for hematologic cancers are measured by the elimination of abnormal cells, a decrease in tumor markers to normal, and the improved function of affected cells.

2. Drug Therapy

Chemotherapy

- Chemotherapeutic agents have a very narrow therapeutic index and a toxic side-effect profile.
- They are generally more effective in combination due to synergism through biochemical interactions.
 - * It is important to choose drugs with different mechanisms of action, resistance, and toxicity profiles to get the full benefit of combination therapy.
- **Chemotherapy has the greatest effect on rapidly-dividing cells, as most of the potent chemotherapy drugs act by damaging DNA.**
 - * These agents are more active in different phases of the cell cycle. A therapeutic effect is seen on cancer cells, but adverse effects are also seen on human cells that rapidly divide (eg, hair follicles, gastrointestinal tract, blood cells).
 - * Agents can be phase-specific or phase-nonspecific. **Nonspecific agents are effective in all phases.**

Cell Cycle Phase

- G_0 = resting phase: no cell division occurs and cancer cells are generally not susceptible to chemotherapy. This is problematic for slow-growing tumors that exist primarily in this phase.
- G_1 = **postmitotic phase: enzymes for DNA synthesis are manufactured; lasts 10-24 hours.**
- **S = DNA synthesis phase: DNA separation and replication occurs; lasts 10-20 hours.**
- G_2 = **premitotic phase: specialized proteins and RNA are made; lasts 2-10 hours.**
- **M = mitosis: actual cell division occurs; lasts 30-60 minutes.**

Drug Classes

There are numerous chemotherapy agents. Drugs are grouped by class. Please refer to the corresponding table for each class of drugs.

Alkylating agents (Table 4)

Mechanism of action

- Covalent bond formation of drugs to nucleic acids and proteins; results in the **cross-linking of one or two DNA strands and inhibition of DNA replication.** These **are non-phase** specific agents. The most commonly used agents include: **cyclophosphamide (C)**, ifosfamide (I), **car**mustine, dacarbazine, and temozolomide.

Table 4

Alkylating Agents

Generic name (trade name)	Dosage range	Dosage forms	Frequency	Diseases ¹
Nitrogen mustard				
Mechlorethamine (Mustargen®)	6-10 mg/m ²	IV	Days 1, 8	HL, NHL
Cyclophosphamide (Cytoxan, Neosar®)	500-2000 mg/m ² , 40-500 mg/m ²	IV, PO	qd 2-5 days, qd	ALL, CLL, HL, NHL, myeloma, testis, neuroblastoma, breast, ovary, lung, cervix
Ifosfamide (Ifex®)	1.2 g/m ² , 4 g/m ²	IV	qd x 5 days q 3 wk, qd x 6 d	HL, NHL, lung, bladder, sarcoma
Melphalan (Alkeran®)	16 mg/m ² , 6 mg	IV, PO	q 2 wk x 4, 2-3 wk	Myeloma, breast, ovary
Chlorambucil (Leukeran®)	0.1-0.2 mg/kg	PO	qd x 3-6 wk	CLL, HL, NHL
Ethylenimines and methylmelamines				
Altretamine (Hexalen®)	260 mg/m ²	PO	qd x 14-21 d	Ovarian
Thiotepa (Thiopex®)	10-20 mg/m ²	IV	q 3-4 wk	Bladder, breast, ovarian, HL, NHL
Alkyl sulfonates				
Busulfan (Myleran, Busulfex®)	4-8 mg/kg	IV, PO	qd	CML, BMT
Nitrosureas				
Carmustine (BICNU)	150-200 mg/m ²	IV	q 6 wk	HL, NHL, brain, myeloma
Streptozocin (Zanosar)	500 mg/m ²	IV	qd 5 d	Islet cell carcinoma
Polifeprosan 20 with carmustine implant (Gliadel®)	7.7-mg implant	—	Implant	Glioblastoma multiforme

¹Does not indicate FDA approval.

ALL, acute lymphocytic leukemia; BMT, bone marrow transplant; CLL, chronic lymphocytic leukemia; CML, chronic myelogenous leukemia; HL, Hodgkin lymphoma; NHL, non-Hodgkin lymphoma.

Patient instructions and counseling

- All drugs are carcinogenic, teratogenic, and mutagenic. Medications may cause sterility. Let your dentist know you are on chemotherapy, due to an increased risk of bleeding and infections. Hydration and mesna therapy are recommended for C and I. Let your doctor know if you have burning upon urination.

Adverse drug events

- Myelosuppression, primarily leukopenia; mucosal ulceration; pulmonary fibrosis (carmustine) and interstitial pneumonitis; alopecia; nausea and vomiting; amenorrhea and azoospermia; hemorrhagic cystitis with C and I; encephalopathy with I; seizures (polifeprosan/carmustine).

Drug interactions

- Drugs with specific interactions of moderate to major severity include:

* Altretamine: tricyclic antidepressants, monoamine oxidase inhibitors

* Busulfan: itraconazole, phenytoin, acetaminophen

* Carmustine: cimetidine, ethyl alcohol, phenytoin, amphotericin B

* Cyclophosphamide: allopurinol, barbiturates, digoxin, phenytoin, warfarin

* Ifosfamide: allopurinol, phenytoin, warfarin

* Streptozocin: nephrotoxic agents

Monitoring parameters

- Pulmonary function tests; renal and hepatic tests; chest x-ray; CBC with differential (baseline and expected nadir prior to next cycle) and electrolytes; urinalysis for RBC detection from hemorrhagic cystitis; signs of bleeding (bruising, melena); infection (sore throat, fever); nausea or vomiting

Antimetabolites: S-phase-specific (Table 5)

Mechanism of action

- Structural analogues of natural metabolites. Act by falsely inserting themselves in place of a pyrimidine or purine ring, causing an interference in nucleic acid synthesis. Phase-specific agents are most active

Table 5

Antimetabolites

Generic name (trade name)	Dosage range	Dosage forms	Frequency	Disease ¹
Folic acid antagonists	500-600 mg/m ²	IV	q 21 d	Malignant mesothelioma,
Pemetrexed (Alimta®)	10-100 mg/m ² , 1-2,	IV, PO, IM, SC,	qd	NSCLC Breast, NHL,
Methotrexate (Rheumatrex®)	10-12 mg/m ²	intrathecal, intra-arterial		sarcoma, ALL
Pyrimidine analogs	75-100 mg/m ²	SC	qd x 7 d	Myelodysplastic syndrome
Azacitidine (Vidaza®)	450 mg/m ²	IV	qd x 5 d	Colorectal, breast, head,
Fluorouracil, 5-FU (Adrucil®)	100-300 mg/m ² , 50 mg	IV, intrathecal	qd x 7 d, q 14d	neck ALL, AML, CML
Cytarabine (Cytosar-U®, DepoCyt®)	2500 mg/m ² 1000-1250 mg/m ²	PO IV	qd x 14 d q 3 wk q wk	Breast, colorectal
Capecitabine (Xeloda®)	15 mg/m ²	IV	q8h x 3 d, q 6W	Pancreatic, NSCLC, bladder
Gemcitabine (Gemzar®)				Myelodysplastic syndrome
Decitabine (Dacogen®)	52 mg/m ² 1.5-2.5 mg/kg	IV PO	qd x 5 d qd	Acute lymphoblastic leukemia (pediatric)
Purine analogs				
Clofarabine (Clolar®)	2-3 mg/kg	PO	qd	ALL
Mercaptopurine (Purinethol®)	4 mg/m ² 0.09-0.1 mg/kg	IV IV	q 2 wk qd x 7 d	ALL, AML CLL, hairy cell leukemia, ALL
Thioguanine (Tabloid®)	25 mg/m ²	IV	qd x 5 d	NHL, hairy cell leukemia, CLL
Pentostatin (Nipent®)				CLL
Cladribine (Leustatin®)				CLL, NHL
Fludarabine (Fludara®)				
Guanosine Analogs	Children: 650 mg/m ² /day	IV	qd xd, q 21 d	T-cell ALL/NHL
Nelarabine (Arranon®)	Adults: 1500 mg/m ² /day	IV	d 1, 3, 5, q 21 d	

¹Does not indicate FDA approval.

ALL, acute lymphocytic leukemia; AML, acute myelogenous leukemia; CLL, chronic lymphocytic leukemia; CML, chronic myelogenous leukemia; NHL, non-Hodgkin lymphoma; NSCLC, non-small cell lung cancer.

in the S phase and in tumors with a high growth fraction. They are subdivided into three groups: folate, purine, and pyrimidine antagonists.

Patient instructions and counseling

- Avoid crowds and sick people. You may be asked to chew ice if receiving fluorouracil (5-FU). This is to reduce damage to the mucosal lining in your mouth. Contact your MD if you have uncontrollable nausea or vomiting, excessive diarrhea, or pain, swelling, or tingling in palms and soles of feet (hand-foot syndrome). Call your doctor if you feel dizzy, lightheaded, or have trouble urinating (clofarabine). You

should be receiving folic acid and vitamin B₁₂ injections if you are receiving pemetrexed.

- Nelarabine may cause sleepiness and dizziness.

Adverse drug events

- Hand-foot syndrome, stomatitis (5-FU, capecitabine); severe diarrhea, GI mucosal damage, nausea, vomiting, fatigue, myelosuppression, alopecia, neurotoxicity (nelarabine, cytarabine, fludarabine, methotrexate); rash and fever, flu-like symptoms (gemcitabine); renal toxicity, mucositis (5-FU, methotrexate); conjunctivitis (cytarabine); hemolytic uremic syndrome (gemcitabine); opportunistic infections (cladribine, fludarabine); tumor

lysis syndrome, systemic inflammatory response syndrome (SIRS), or capillary leak with clofarabine.

Interactions

- Specific interactions include:
 - * Capecitabine: warfarin, phenytoin
 - * Cytarabine: digoxin
 - * Fluorouracil: warfarin
 - * **Mercaptopurine: warfarin, allopurinol**
 - * Methotrexate: NSAIDs, amiodarone, amoxicillin, **sulfasalazine**, doxycycline, erythromycin, hydrochlorothiazide, mercaptopurine, omeprazole, phenytoin, folic acid
 - * Pentostatin: cyclophosphamide, fludarabine

Monitoring parameters

- Note any complaints of mucositis or mouth soreness, monitor for neurotoxicity (eg, ask the patient to write their name); CBC with differential prior to each dose of drug; hepatic and renal function; monitor for tingling or swelling of palms and soles of hands and feet; bruising or bleeding; INR (capecitabine); monitor weight and question patient

about diarrhea, jaundice, and hepatomegaly (mercaptopurine). Continuous IV fluids and allopurinol should be administered for clofarabine patients and prophylactic corticosteroids for SIRS and capillary leak. Plasma homocysteine with pemetrexed, and dexamethasone should be given to prevent cutaneous reactions.

Antitumor antibiotics: (Table 6)

Mechanism of action

- **Anthracyclines block DNA and RNA transcription** through the intercalation (insertion) of adjoining nucleic acid pairs in DNA, which results in **DNA strand breakage**. They also **inhibit the topoisomerase II enzyme**. Mitomycin is an alkylating-like agent that cross-links DNA. Dactinomycin blocks RNA synthesis. **Bleomycin inhibits DNA synthesis in mitosis and G₂ stages of growth**. Bleomycin is the **only cell cycle-specific agent**.

Patient instructions and counseling

- Contact doctor for fast, slow, or irregular heartbeats and/or breathing difficulties; anthracyclines may cause a **change of urine color** or whites of eyes to a

Table 6

Antitumor Antibiotics

Generic name (trade name)	Dosage range	Dosage forms	Frequency	Disease ¹
Anthracyclines				
Doxorubicin (Adriamycin®, Doxil® [liposomal])	60-75 mg/m ² , 20-50 mg/m ² (lipo)	IV	q 3 wk	ALL, AML, NHL, HL, solid tumors of every major organ
Daunorubicin (Cerubidine®, Daunoxome® [liposomal])	45 mg/m ² , 40-100 mg/m ² (lipo)	IV	qd x 3 d, q 2-3 wk	ALL, AML, NHL
Epirubicin (Ellence®, Phamarubicin®)	60-120 mg/m ²	IV	q 3 wk	Breast, bladder, lung, ovarian, gastric
Idarubicin (Idamycin®)	12 mg/m ²	IV	qd x 3 d	AML, ALL, breast
Mitoxantrone (Novantrone®)	12-14 mg/m ²	IV	qd x 3 d	Prostate, NHL, AML, breast
Valrubicin (Valstar®)	800 mg	Intravesically	q wk x 6 wk	Bladder
Alkylating-like				
Mitomycin (Mutamycin®)	10-20 mg/m ²	IV	q 6-8 wk	Bladder, breast, NSCLC, cervix, pancreatic, colon
Chromomycin				
Dactinomycin (Cosmegen®)	12-15 mcg/kg	IV	qd x 5 d	Wilms', testis, sarcoma
Miscellaneous				
Bleomycin (Blenoxane®)	10-20 USP U/m ² /wk	IV, IM, SC	q wk	HL, NHL, testis, head, neck, lung, skin

¹Does not indicate FDA approval.

ALL, acute lymphocytic leukemia; AML, acute myelogenous leukemia; HL, Hodgkin lymphoma; NHL, non-Hodgkin lymphoma; NSCLC, non-small cell lung cancer.

bluish-green or orangish-red. Bleomycin may cause a change in skin color or nail growth.

Adverse drug events

- Severe nausea and vomiting, alopecia, and stomatitis; anthracyclines: cardiac toxicity, acute or chronic (doxorubicin = daunorubicin > idarubicin > epirubicin > mitoxantrone). All anthracyclines have limits on cumulative lifetime dosing, are vesicants, and are associated with secondary acute myelogenous leukemia (AML); avoid in patients with a cardiac history. Myelosuppression risk with all agents, although mitomycin demonstrates a delayed effect. Dactinomycin: renal toxicity, leukopenia, increased pigmentation of previously radiated skin; bleomycin: pulmonary fibrosis and interstitial pneumonitis

Interactions

- Specific interactions include:
 - * Bleomycin: phenytoin, digoxin
 - * Doxorubicin: cisplatin, digoxin, paclitaxel, phenytoin, phenobarbital, trastuzumab, zidovudine
 - * Epirubicin: cimetidine, trastuzumab
 - * Idarubicin: probenecid, trastuzumab

Monitoring parameters

- Hepatic, renal, CBC with differential monitoring; pulmonary function tests pre- and post-treatment with bleomycin; cardiac monitoring via left ventricular ejection fraction (LVEF) measurements for anthracyclines as well as monitoring the cumulative lifetime dose; extravasation and necrosis with anthracyclines. Adjust anthracycline dosing based on elevated total bilirubin.

Pharmacokinetics

- Anthracyclines are extensively bound in the tissue, have large volumes of distribution and long half-lives, and are excreted in the bile. They need dosing adjustments in hepatic impairment. Bleomycin is renally excreted and needs dosing adjustments in impaired patients.

Other

- Lifetime doses of doxorubicin should not exceed 450-550 mg/m², taking into account other anthracycline agents received; lifetime maximum of epirubicin is 900 mg/m², idarubicin <150 mg/m².

Hormones and antagonists (Table 7)

Mechanism of action

- A diverse group of compounds that act on hormone-dependent tumors by inhibiting or decreasing the

production of the disease-causing hormone.

Patient instructions and counseling

- **Avoid use in pregnant women;** several agents may cause **weight gain** and menstrual irregularities in women. Be aware of leg swelling or tenderness (eg, signs of a deep vein thrombosis), breathing problems, and sweating. Transient muscle or bone pain, problems urinating, and spinal cord compression may occur initially in patients receiving LHRH agonists. Take exemestane after meals.

Adverse drug events

- Edema, menstrual disorders, hot flashes, transient muscle or bone pain, tumor flare, transient increase in serum testosterone (LHRH) thromboembolic events, gynecomastia, elevated liver enzymes, nausea and vomiting, diarrhea, erectile impotence, decreased libido, endometrial cancers with tamoxifen, bone loss (LHRH, aromatase inhibitors); black box warning for hypotension and syncope with abarelix; also risk of ventricular arrhythmias and QT prolongation

Interactions

- Specific interactions include:
 - * Abarelix: amiodarone, procainamide, quinidine, sotalol
 - * Aminoglutethimide: dexamethasone, warfarin, tamoxifen, theophylline
 - * Bicalutamide: warfarin
 - * Flutamide: warfarin
 - * Megestrol: dofetilide contraindication
 - * Medroxyprogesterone acetate: aminoglutethimide, rifampin
 - * Nilutamide: alcohol
 - * Tamoxifen: anticoagulants, cyclophosphamide
 - * Toremifene: cytochrome P450 (CYP450) 3A4 inducers (carbamazepine, phenytoin)
 - * Fluoxymesterone: cyclosporine, anticoagulants, valerian

Monitoring parameters

- Check WBCs with differential, platelets, liver function tests, thyroid function, and serum creatinine regularly. Note any weight changes, abnormal vaginal bleeding, body or bone pain, galactorrhea, or decreased libido. Monitor for embolic disorders and uterine cancer (in females). Check PSA and testosterone levels in males; bone mineral density for LHRH agonist and aromatase inhibitors.

Pharmacokinetics

- The majority of agents are available orally with longer half-lives, allowing once-daily dosing.

Table 7

Hormones and Antagonists

Generic name (trade name)	Dosage range	Dosage forms	Frequency	Disease ¹
Adrenocorticoids				
Aminoglutethimide (Cytadren®)	250 mg	PO	qd	Adrenal, breast, prostate
Progestins				
Megestrol acetate (Megace®)	40 mg, 40-320 mg	PO	qid, qd divided	Breast, endometrial
Medroxyprogesterone acetate (Provera, Depo-Provera®)	400-1000 mg	IM	qw	Endometrial
Estrogens				
Ethinyl estradiol (Estinyl®)	150 mcg-3 mg, 100 mcg to 1 mg	PO	qd	Prostate, breast
Antiestrogen				
Tamoxifen (Nolvadex®)	20-40 mg	PO	qd	Breast
Fulvestrant (Faslodex®)	250 mg	IM	q mo	Breast
Toremifene (Fareston®)	60 mg	PO	qd	Breast
Aromatase inhibitors				
Exemestane (Aromasin®)	25 mg	PO	qd	Breast
Anastrozole (Arimidex®)	1 mg	PO	qd	Breast
Letrozole (Femara®)	2.5 mg	PO	qd	Breast
Androgens				
Testosterone propionate (Delatestryl®)	200-400 mg	IM	qd	Breast
Fluoxymesterone (Halotestin®)	10-40 mg	PO	q 2-4 wk	Breast
Antandrogens				
Flutamide (Eulexin®)	750 mg	PO	tid	Prostate
Bicalutamide (Casodex®)	50 mg	PO	qd	Prostate
Nilutamide (Nilandron®)	300 mg	PO	qd	Prostate
LHRH agonists				
Triptorelin (Trelstar®)	3.75, 11.25 mg	IM	q 28 d, q 34 d	Prostate
Leuprolide (Lupron®, Eligard®)	7.5, 22.5, 30 mg	IM, SC	q mo, q 3 mo, q 4 mo	Prostate, breast
Goserelin (Zoladex®)	3.6, 10.8 mg	SC	q mo, q 3 mo	Prostate, breast
GNRH agonist				
Abarelix (Plenaxis®)	100 mg	IM	q 2 w	Prostate

¹Does not indicate FDA approval.

GNRH, gonadotropin-releasing hormone; LHRH, luteinizing hormone-releasing hormone.

Other

- Agents are often contraindicated if the patient has more than one hormone-dependent tumor. With the exception of tamoxifen and LHRH agonists, the majority of agents are not indicated for first-line therapy.

Plant alkaloids (Table 8)

Mechanism of action

- Inhibit the replication of cancerous cells; taxanes and vincas interfere with microtubule assembly in the M phase; camptothecins and epipodophyllotoxins inhibit topoisomerase I and II enzymes, respectively, causing DNA strand breaks. Topoisomerase I and II affect G₂ and S phases, respectively.

Table 8

Plant Alkaloids

Generic name (trade name)	Dosage range	Dosage forms	Frequency	Disease ¹
Taxanes				
Docetaxel (Taxotere®) gastric	60-100 mg/m ²	IV	q 3 wk	NSCLC, breast, ovarian, head, neck, gastric
Paclitaxel (Taxol®)	135-175 mg/m ²	IV	q 3 wk	NSCLC, breast, ovarian, head
Paclitaxel (Abraxane®)	260 mg/m ²	IV	q w wk	Breast
Epipodophyllotoxins				
Etoposide (VePesid®)	100 mg/m ² , 50 mg/m ²	IV, PO	qd x 4-5 d, qd x 21 d	SCLC, testis, NSCLC
Teniposide (Vumon®)	165 mg/m ²	IV	q wk x 4 doses	ALL, SCLC
Camptothecins				
Irinotecan (Camptosar®)	100-125 mg/m ²	IV	q wk x 4 doses	Colorectal, NSCLC, SCLC
Topotecan (Hycamtin®)	1.5 mg/m ²	IV	qd x 5 d q 21 d	Ovarian, lung, AML, cervical
Vinca alkaloids				
Vincristine (Oncovin®)	1.4 mg/m ²	IV	q wk	ALL, HL, NHL, CLL
Vinblastine (Velban®)	6 mg/m ²	IV	q wk	HL, NHL, testis
Vinorelbine (Navelbine®)	25-30 mg/m ²	IV	q wk	NSCLC, breast, ovarian

¹Does not indicate FDA approval.

ALL, acute lymphocytic leukemia; CLL, chronic lymphocytic leukemia; HL, Hodgkin lymphoma; NHL, non-Hodgkin lymphoma; NSCLC, non-small cell lung cancer; SCLC, small cell lung cancer.

Patient instructions and counseling

- Contact doctor for uncontrollable diarrhea (irinotecan), nausea or vomiting, or signs and symptoms of an infection; should receive prophylaxis for emesis, pretreatment for anaphylaxis or peripheral edema (taxanes); you should receive a prescription for loperamide and atropine with irinotecan therapy.

Adverse drug events

- Myelosuppression, mucositis, nausea and vomiting, alopecia, edema (docetaxel); hypotension/hypersensitivity upon administration (paclitaxel); neurotoxicity (vincristine); diarrhea, headache, secondary malignancies (topoisomerase II inhibitors); syndrome of inappropriate ADH secretion (SIADH) (vinca alkaloids)

Interactions

- Specific interactions include:
 - * Docetaxel: CYP450 3A4 inducers and inhibitors
 - * Etoposide: cyclosporine, St. John's wort, warfarin
 - * Irinotecan: St. John's wort
 - * Paclitaxel: CYP450 3A4 inducers and inhibitors

- * Teniposide: CYP450 3A4 inducers and inhibitors
- * Vincas: CYP450 3A4 inhibitors; itraconazole, voriconazole
- * Vincristine: phenytoin, l-asparaginase, carbamazepine, digoxin, filgrastim, nifedipine, zidovudine
- * Vinblastine: phenytoin, erythromycin, mitomycin, zidovudine

Monitoring parameters

- Monitor WBCs with differential for all agents; peripheral neuropathy, liver and renal function, painful mouth sores, blood pressure (taxanes and epipodophyllotoxins); acute and late-onset diarrhea or dyspnea on exertion (irinotecan); bilirubin elevations (taxanes and camptothecins); fluid retention (docetaxel); neuropathy, shortness of breath, bronchospasm, and SIADH (vincas)

Pharmacokinetics

- Taxanes and epipodophyllotoxins are extensively bound to plasma and tissues.

Other

- Drug resistance may occur via p-glycoprotein pumps for all agents; topotecan needs dose adjustments for

Table 9

Biologic Response Modifiers and Monoclonal Antibodies

Generic name (trade name)	Dosage range	Dosage forms	Frequency	Disease ²
Immune therapies				
Aldesleukin (Proleukin®)	600,000 U/kg	IV	q8h x 14 doses	Metastatic renal cell, metastatic melanoma
Interferon-alfa 2b (Intron A®)	10-20 x 10 ⁶ U, 2 x 10 ⁶ U (hairy)	IV and SC	qd x 5 d per wk, ¹ 3 x wk x 6 mo	Malignant melanoma, hairy cell leukemia
Thalidomide (Thalomid®)	200 mg	PO	qd	Multiple myeloma, erythema nodosum
Lenalidomide (Revlimid®)	10 mg	PO	qd	leprosum
	25 mg	PO	qd d 1-21 q 28 d	Myelodysplastic syndrome
				Multiple myeloma
Monoclonal antibodies				
Rituximab (Rituxan®)	375 mg/m ²	IV	q wk x 4-8 doses	NHL, CLL
Trastuzumab (Herceptin®)	2-4 mg/kg	IV and SC	q wk	Metastatic breast
Gemtuzumab (Mylotarg®)	9 mg/m ²	IV	q 2 wk	AML
Alemtuzumab (Campath®)	3-10 mg	IV	qd, then 30 mg/d 3 x wk	B-cell CLL
Bevacizumab (Avastin®)	5-10 mg/kg	IV	q 2 wk	Colorectal, NSCLC
Cetuximab (Erbix®)	250-500 mg/m ²	IV	qw x 7 wk	Colorectal, head and neck
Denileukin diftitox (Ontak®)	9 or 18 mcg/kg	IV	qd x 5 d	T cell lymphoma
Ibritumomab tiuxetan (Zevalin®) ³				NHL
Tositumomab (Bexxar®) ³				NHL

¹Induction dose.²Does not indicate FDA approval.³See package insert for dosing information.

AML, acute myelogenous leukemia; CLL, chronic lymphocytic leukemia; NHL, non-Hodgkin lymphoma.

patients with a CrCl <40 mL/min; vincas are vesicants and need close monitoring for extravasation; vincristine should not be administered intrathecally or in doses higher than 2 mg.

Biologic response modifiers and monoclonal antibodies (Table 9)**Mechanism of action**

- Biologic response modifiers activate the body's immune-mediated host defense mechanisms to malignant cells. In contrast to immunotherapy, these agents have direct biological effects on malignancies. Monoclonal antibodies bind to specific antigens and kill malignant cells through the activation of apoptosis, an antibody-mediated toxicity, or complement-mediated lysis.

Patient instructions and counseling

- Let your doctor know if you have severe fatigue, trouble breathing, or irregular heart rhythms. Chills, fever, depression, and flu-like symptoms are

common. Taste and smell alterations occur with levamisole. Monoclonal antibodies can cause infusion-related reactions such as fever and chills. If you receive bevacizumab, you should have your blood pressure checked regularly and have tests checking for protein in your urine. You should wear sunscreen and avoid excessive sunlight if receiving cetuximab. You should receive medication for your thyroid if you are going to receive tositumomab. Do not try to conceive until 12 months after finishing therapy for both men and women.

- With thalidomide and lenalidomide, do not get pregnant. Two forms of birth control must be used, including men on the drug that have sexual contact with women of childbearing age.

Adverse drug events

- Hypotension and hypersensitivity upon infusion, cardiac, pulmonary, and renal impairment; avoid in patients with autoimmune disorders. Mental status changes (eg, depression), fever, chills, nausea, and musculoskeletal pain with all agents; tumor lysis syndrome with rituximab; bleeding, hemorrhage, hypertension, proteinuria, skin rash with bevacizumab; cutaneous and severe infusion reactions, interstitial lung disease with cetuximab; hypothyroidism with tositumomab
- Neurotoxicity with thalidomide, neutropenia with thalidomide and lenalidomide, deep vein thrombosis and pulmonary embolism with thalidomide and lenalidomide

Interactions

- Specific drug interactions include:
 - * Aldesleukin: glucocorticoids, NSAIDs, antihypertensives
 - * Interferon- α 2b: zidovudine, theophylline, phenytoin, phenobarbital
 - * Ibritumomab: antiplatelets, anticoagulants
 - * Levamisole: warfarin, alcohol
 - * Tositumomab: antiplatelets, anticoagulants
 - * Trastuzumab: anthracyclines, cyclophosphamide, warfarin

Monitoring parameters

- Baseline and follow-up pulmonary, cardiac, and renal function tests; check CBCs with differential, LFTs, TSH, electrolytes, and glucose regularly. Premedicate with acetaminophen and diphenhydramine for monoclonal antibodies. Observe blood pressure during infusion (hypotension concerns) for all agents. Perform blood pressure monitoring (hypertensive concerns) and urine dipstick analysis for bevacizumab. Monitor for vital signs, itching, and swelling. Trouble breathing with cetuximab and ibritumomab.

Other

- Make sure correct form of interferon α is being used (four forms). Do not administer gemtuzumab and alemtuzumab as an IV push or bolus.

Miscellaneous (Table 10)

Platinum compounds

- Alkylating-like agents causing the inhibition of DNA synthesis. These include: cisplatin, carboplatin, and oxaliplatin. Adverse effects include: nephrotoxicity, peripheral neurotoxicity, myelosuppression, ototoxicity, nausea, and vomiting.
 - * Cisplatin: hydration therapy and premedications are needed. Interactions: doxorubicin,

Table 10

Miscellaneous Agents

Generic name (trade name)	Dosage range	Dosage forms	Frequency	Disease ¹
Platinum compounds				
Cisplatin (Platinol-AQ®)	50-100 mg/m ²	IV	q 3-4 wk	NSCLC, ovarian, testis, bladder, head, neck, lung
Carboplatin (Paraplatin®)	300-400 mg/m ²	IV	q 3-4 wk	Ovarian, testis, NSCLC, head, neck, lung
Oxaliplatin (Eloxatin®)	85-200 mg/m ²	IV	qd x 2 d q 2 wk	Colorectal
Enzymes				
Asparaginase (Elspar®)	6000-10,000 IU/kg	IV	q 3 d x 9 doses	ALL
Cell-specific				
Hydroxyurea (Hydrea®)	20-30 mg/kg	PO	qd	CML, AML, head, neck
Tyrosine kinase inhibitor				
Imatinib mesylate (Gleevec®)	400-600 mg	PO	qd	CML, gastrointestinal stromal tumors
Erlotinib (Tarceva®)	150 mg	PO	qd	NSCLC
Gefitinib (Iressa®)	250-500 mg	PO	qd	NSCLC
Sutinib (Sutent®)	50 mg	PO	qd x 28 d, 14 d off	Kidney, gastrointestinal stromal tumors
Dasatinib (Sprycel®)	70 mg	PO	bid	CML or AML resistant to or intolerant to imatinib
Sorafenib (Nexavar®)	400 mg	PO	bid	renal cell
26S Proteasome inhibitor				
Bortezomib (Velcade®)	1.3 mg/m ²	IV	Days 1, 4, 8, 11	Multiple myeloma

¹Does not indicate FDA approval.

AML, acute myelogenous leukemia; CML, chronic myelogenous leukemia; NSCLC, non-small cell lung cancer.

rituximab, tacrolimus, topotecan, amino-glycosides

- * Carboplatin: monitor for thrombocytopenia. Interactions: aminoglycosides
- * Oxaliplatin: unique neurotoxicities (eg, bronchial spasms)

Sorafenib

- Inhibits multiple tyrosine kinases. Used for treatment of advanced renal cell cancer. Take tablets on an empty stomach. Causes diarrhea, fatigue, rash, hand-foot syndrome, hypertension, nausea/vomiting, neutropenia, alopecia. Can decrease doxorubicin and irinotecan levels.

Sunitinib

Inhibits multiple tyrosine kinases. Used for treatment of advanced renal cell cancer and gastrointestinal stromal tumors. Take with or without food. Causes neutropenia, rash changes in skin color, fatigue, myalgia, headaches, hypertension, nausea/vomiting, diarrhea, increased liver enzymes. Extensively metabolized by CYP3A4; CYP3A4 inhibitors may increase levels, CYP3A4 inducers may decrease levels. Ketoconazole increases levels, rifampin reduces levels.

Table 11

Common Toxicities of Chemotherapeutic Agents

Toxicity	Causative drugs ¹	Recommended therapy
Alopecia	Cyclophosphamide, doxorubicin, paclitaxel, mechlorethamine	N/A
Cardiac toxicity	Anthracyclines	Limit cumulative doses
Diarrhea	Irinotecan, fluorouracil	Premedicate with atropine (irinotecan); treat with loperamide
Extravasation	Anthracyclines, mitomycin, vinca alkaloids, paclitaxel, mechlorethamine	Treat with heat packs for vincas, cold compresses for all other causes or instill normal saline to dilute drug
Hemorrhagic cystitis	Cyclophosphamide, ifosfamide	Premedicate with hydration therapy, mesna
Hepatotoxicity	Asparaginase, cytarabine, mercaptopurine, methotrexate	N/A
Hypersensitivity	Paclitaxel, asparaginase, cisplatin, carboplatin, etoposide, teniposide	Premedicate with ranitidine or cimetidine, diphenhydramine, dexamethasone or test dose; treat with emergency resuscitation
Infertility	Cyclophosphamide, chlorambucil, melphalan, mechlorethamine	N/A
Myelosuppression	Alkylating agents, fluorouracil, methotrexate, lomustine, cyclophosphamide, methotrexate	Treat with G-CSF, platelet transfusions, erythropoietin-stimulating agents
Nausea and vomiting	Cisplatin, cyclophosphamide, cytarabine, dacarbazine, ifosfamide, melphalan, mitomycin, mechlorethamine	Premedicate with dexamethasone, phenothiazines (eg, compazine), 5-HT ₃ -receptor antagonists (eg, granisetron), neurokinin-1 antagonists
Neurotoxicity	Paclitaxel, cisplatin, cytarabine, methotrexate, vincristine, asparaginase	N/A
Pulmonary toxicity	Bleomycin, busulfan, carmustine, mitomycin	Treat with corticosteroids
Renal toxicity	Cisplatin, ifosfamide, methotrexate, streptozocin	Premedicate with hydration therapy, mannitol
Stomatitis	Fluorouracil, methotrexate	Hold ice chips in mouth; palifermin ²
Edema	Docetaxel	Prophylactic dexamethasone

¹Adverse effects are not limited to the listed drugs.

²For hematologic malignancies requiring myelotoxic therapy requiring hematopoietic agents only.

Table 12

Pharmacologic Management for the Prevention of Acute Chemotherapy-Induced Nausea and Vomiting

Generic name (trade name)	Dosage range	Dosage forms	Frequency	Side effects
5-HT₃ receptor antagonists				
Dolasetron (Anzemet®)	100-200 mg	PO	30 min before treatment	Headache, dizziness, constipation, blurred vision,
Granisetron (Kytril®)	5-20 mg	PO	30 min before treatment	elevated liver enzymes
Ondansetron (Zofran®)	10-25 mg	PO	30 min before treatment	
Palonosetron (Aloxi®)	0.25 mg	IV	Day 1 (not to be repeated within 7 d)	Diarrhea, headache, fatigue, insomnia, arrhythmias
Phenothiazines				
Prochlorperazine (Compazine®)	10-25 mg	PO	q4h prn	Sedation, hypotension, extrapyramidal effects,
Chlorpromazine (Thorazine®)	1.25-5 mg	PO	q4-6h prn	lethargy
Promethazine (Phenergan®)	1-4 mg	PO	q4-6h prn	
Butyrophenones				
Droperidol (Inapsine®)	10-20 mg	IV	q4h prn	Sedation, tachycardia, hypotension
Haloperidol (Haldol®)	5-15 mg/m ²	IV, IM, PO	q4-6h prn	
Corticosteroids				
Dexamethasone (Decadron®)	0.5-2 mg	PO	Varies	Anxiety, insomnia, GI upset, psychosis
Cannabinoids				
Dronabinol (Marinol®)	10-20 mg	PO	q3-6h	Drowsiness, euphoria, dry mouth
Nabilone (Cesamet®)	1-2 mg	PO	bid	Drowsiness, euphoria, dry mouth
Benzodiazepines				
Lorazepam (Ativan®)	2 mg	PO	q6h	Sedation, amnesia
Benzamides				
Metoclopramide (Reglan®)	24 mg	PO	tid-qid	Diarrhea, sedation, agitation
Neurokinin-1 antagonist				
Aprepitant (Emend®)	80-125 mg	PO	Day 1 (125 mg) Days 2-3 (80 mg daily)	Somnolence, fatigue, diarrhea

¹**Note:** Most agents are available in more than one dosage form. Due to space limitations, oral dosing has been given preference.

Dasatinib

Specifically targets BCR-ABL mutations, including those resistant to imatinib, inhibiting leukemic cell growth. Used for treatment of CML and pH+ ALL. Causes rash neutropenia, thrombocytopenia, edema, diarrhea, nausea/vomiting, weight changes, arthralgia, myalgia, cough, shortness of breath, infection, electrolyte changes, arrhythmias. Significant drug interactions with CYP3A4 inhibitors, avoid concurrent use or reduce dose. Avoid acid reduction therapies as they will reduce absorption, avoid medications which prolong QT interval.

Asparaginase

- Removes exogenous asparagines from leukemic cells, which are required for their survival.
- Intradermal skin testing is needed due to severe anaphylactic reactions. Myelosuppression, hyperuricemia, hyperglycemia, and renal problems; interactions: methotrexate, prednisolone, prednisone, vincristine

Hydroxyurea

- Inhibits DNA synthesis without interfering with RNA and protein synthesis. Myelosuppression (leukopenia), development of secondary leukemias, nausea, vomiting, diarrhea, constipation, mucositis, and rare fatal hepatotoxicity and pancreatitis; interactions: didanosine, stavudine.

Imatinib mesylate

- Selective inhibitor of the Philadelphia chromosome (biomarker in CML); causes hepatotoxicity, fluid retention (pleural effusions, weight gain), neutropenia, GI effects, muscle cramps, nausea, and vomiting; interactions: CYP450 3A4 substrates (cyclosporine, simvastatin, erythromycin, itraconazole), CYP450 2C9 substrates (warfarin)

Erlotinib

- Human epidermal growth factor receptor type 1 (HER-1), epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor; oral therapy; take pills 1 hour before or 2 hours after meals. Causes rash, diarrhea, anorexia, stomatitis, interstitial lung disease; interactions: CYP450 3A4 inducers, inhibitors; monitor hepatic function.

Gefitinib

- EGFR tyrosine kinase inhibitor; third-line agent for NSCLC; causes diarrhea, rash, acne, dry skin; interactions: CYP450 3A4 inducers and inhibitors, warfarin

Bortezomib

- Inhibits the 26S proteasome; stabilizes regulatory proteins causing apoptosis and disrupting cell proliferation; causes nausea, vomiting, thrombocytopenia, neuropathy, hypotension, diarrhea

Common Toxicities and Treatments

- Common toxicities of chemotherapeutic agents are outlined in Table 11. These can be classified as acute or subacute, chronic and/or cumulative. Rapidly dividing cells, including mucous membranes, hair, skin, GI tract, and bone marrow are the most common acute toxicities. Examples of delayed or cumulative toxicities include: nephrotoxicity, neurotoxicity, cardiomyopathy, pulmonary fibrosis, and secondary malignancies.
- The prevention and treatment of chemotherapy-induced nausea and vomiting (CINV) is an important area in which pharmacists may play a role in drug selection in oncology patients. The selection of antiemetic agents should be based primarily on the emetogenic potential of the drug regimen. Other factors that increase the risk of CINV include: female gender, young age, prior chemotherapy exposure, lack of chronic alcohol use, combination chemotherapy, high dosage and numerous cycles, and short infusion times. It is important that patients also receive prescriptions to prevent delayed CINV.
- Table 12 summarizes the pertinent antiemetic drugs used in the prophylactic setting.
- For highly to moderately emetogenic drug regimens, dexamethasone and 5-HT₃ receptor antagonists are recommended at a minimum for the prevention of acute CINV. Aprepitant should also be considered.
- For low-risk to unlikely emetogenic drug regimens, dexamethasone and a phenothiazine are recommended.

Table 13**American Cancer Society Screening Recommendations**

Disease ¹	Sex	Age (y)	Procedure	Frequency
Colorectal	M and F	50+	Fecal occult blood test (FOBT)	Every year
	M and F	50+	Flexible sigmoidoscopy OR colonoscopy OR double contrast barium enema	Every 5 years OR every 10 years OR every 5 years
Breast	F	20+	Breast self-exam	Every month
	F	20-39 OR 40+	Clinical breast exam	Every 3 years OR every year
	F	40+	Mammography	Every year
Cervical	F	21+ ²	Pap smear and pelvic exam	Every 3 years
Prostate	M	50+	Digital rectal exam (DRE)	Every year
	M	50+	Prostate-specific antigen (PSA) test	Every year

¹No specific screening recommendations have been made for lung, skin, and testicular cancer in patients with average risk. However, after the age of 40, it is recommended that all men and women receive health counseling and a physical exam every year.

²Earlier if sexually active.

Adapted from the American Cancer Society.

Table 14

Common Tumor Markers and Associated Cancers

Tumor marker	Abnormal level	Cancer
Alpha-fetoprotein (AFP)	>20 ng/mL	Hepatocellular, ovarian
β -2 Microglobulin (β 2M)	>3 ng/mL	Multiple myeloma, lymphoma
CA 15-3	>25 U/mL	Breast
CA 125	>30 U/mL	Ovarian
CA 19-9	>37 U/mL	Pancreatic, colorectal
Calcitonin ¹	>70 pg/mL	Thyroid
Carcinoembryonic antigen (CEA)	>5 U/mL	Colorectal, breast, non-small cell lung
Chromogranin A	>76 ng/mL (men); >51 (women)	Neuroendocrine, lung, prostate
Gamma globulin	>2-3 g/100 mL	Multiple myeloma
Her-2/neu	>450 fmol/mL	Breast
Human chorionic gonadotropin (HCG)	>5 mIU/mL	Testicular
Prostate-specific antigen (PSA) ¹	>4-10 ng/mL	Prostate
Thyroglobulin	>10 ng/mL	Thyroid

¹Can be used to diagnose early disease.

- For delayed CINV (>24 hours after administration of chemotherapy), metoclopramide and dexamethasone are recommended, at a minimum.
- All patients receiving agents with emetogenic potential should receive prophylactic therapy for CINV with rescue medication readily available.

Miscellaneous Commonalities Across Chemotherapy Agents

- All patients should not receive live and rotavirus vaccines during chemotherapy due to their suppressed immune systems.
- The majority of agents are teratogenic and mutagenic.
- Patients should avoid becoming pregnant or breastfeeding during and immediately after chemotherapy.
- Patients should receive lab work on a regular basis to check for common toxicities, such as myelosuppression, renal and hepatic impairment, and electrolyte disturbances.

3. Nondrug Therapy

- As mentioned above, cancer treatment is generally a combination of modalities. Chemotherapy is an important component, as most patients present with advanced disease upon diagnosis.
- Surgery plays a role in resecting primary tumors or metastases. It can also be used diagnostically to biopsy tumors or for other exploratory purposes.
- Radiation is used to shrink primary tumors in local disease or metastases. It can be used in both neoadjuvant therapy to downsize tumors and in adjuvant therapy to eradicate residual disease.
- Screening is also an important part of cancer therapy, as it can allow the detection of disease in very early stages, when the survival rates are much more acceptable. Table 13 refers to American Cancer Society (ACS) screening recommendations for patients at average risk of developing cancer.
- Tumor markers are additional screening and monitoring tests. They are found in the plasma, serum, or other body fluids, and may be used to identify neoplastic growth.
 - * These markers are often not sensitive to diagnose cancer and may produce false-positive results (ie, falsely identify people with a disease that do not have the disease).
 - * They are helpful in identifying the recurrence of advanced disease in patients that had elevated levels upon diagnosis. Table 14 lists some commonly used tumor markers.

4. Key Points

- Oncology includes over 100 diverse diseases that share properties of abnormal and detrimental cell growth.
- Diseases are classified based on the tissue they originate in (eg, breast cancer metastasized to the brain is classified as breast cancer).
- Signs and symptoms of cancer do not follow a specific pattern. A health care provider should evaluate any unusual or persistent change in body appearance or function.
- Before a diagnosis of cancer can be made and systemic treatment can begin, a positive biopsy or blood examination must confirm the presence of the disease.
- Further imaging and lab work-up should be done to evaluate the extent of the disease (ie, determine the stage of disease).
- Cancer therapy must be individualized to each patient based on the type and severity of disease, patient characteristics, and patient and family preferences.
- Surgery, radiation, chemotherapy, and biologic therapy are all cancer treatment modalities that are often used in combination.
- Pharmacists can impact patients' chemotherapy and biologic therapy by counseling the patients and educating health care providers on details of the individual drug regimens.
- Chemotherapy is often employed in combinations to take advantage of different mechanisms of action, avoid resistance, and minimize toxicities.
- Most chemotherapy is aimed at rapidly proliferating cancerous cells. However, many chemotherapy-related side effects occur in normal highly proliferative cells of the body, such as hair follicles, the GI tract lining, and blood cells.
- Patients should be aware of expected toxicities of chemotherapy, which are not limited to alopecia, diarrhea, nausea and vomiting, infertility, myelosuppression, neurotoxicity, nephrotoxicity, hepatotoxicity, stomatitis, and pulmonary toxicity.
- Lab work and the importance of follow-up appointments to treatment should be stressed to the patient.
- All prophylactic and post-treatment medications for chemotherapy-related complications should be made available to the patient. Counsel the patient to keep a diary of events that occur prior to and after treatments. Use this record to make interventions and monitor the patient's quality of life.
- All pharmacists should be aware of the accepted cancer screening recommendations and discuss these with all pertinent patients. Many diseases can be cured if they are caught early enough.
- It is the pharmacist's responsibility to make sure that the patient and family are educated enough to participate in making decisions about their care.

5. Questions and Answers

Use Patient Profile #1 to answer Questions 1-5

1. Which of the following agents that Ms. Tiny is taking can be used to treat breast and prostate cancer?

- I. Zoladex®
- II. Tamoxifen
- III. Celebrex®

- A. I only
- B. III only
- C. I and II only
- D. II and III only
- E. I, II, and III

2. When the patient presents with the tamoxifen prescription, you notice that the directions are missing. You call the doctor to clarify what the instructions are. Which of the following is a CORRECT choice?

- A. 10 mL PO qd
- B. 20 mL PO qd
- C. 40 mg PO bid
- D. 20 mg PO qd
- E. 5 mg PO bid

3. Ms. Tiny presents to your pharmacy with complaints of lower leg calf pain that is tender to the touch and red. You suspect a deep vein thrombosis. Which of the following agents is MOST likely to be associated with this?

- I. Megace®
- II. Goserelin
- III. Tamoxifen

- A. I only
- B. III only
- C. I and II only
- D. II and III only
- E. I, II, and III

Patient Profile #1—Medication Profile: Community

Patient Name Tina Tiny
Address 234 Small St.
Age 33
Sex Female
Allergies Sulfa, penicillin

Height 5'8"
Weight 150 lb

DIAGNOSIS
1. Diagnosed on 12/03 with metastatic breast cancer
2. Mastectomy to right breast on 12/15/03
3. Weight loss of 20 lb
4. Allergies

MEDICATION RECORD

Date	Rx #	Physician	Drug/Strength	Quantity	Sig	Refills
12/03	12345	Buford	Percocet 325/5	30	1-2 q4h prn	0
03/04	12347	Buford	Tamoxifen 20 mg	30	1 PO qd	2
03/04	12349	Buford	Megace 40 mg/mL	80 mg/d	—	2
03/04	12350	Charles	Celebrex 10 mg	30	1 PO qd	2

PHARMACIST NOTES

Date	Note
01/04	Patient complained of soreness after mastectomy and swelling of right arm
03/04	Patient did not pick up birth control last month (2/01)
03/04	Patient is receiving Zoladex 3/6 mg SC q28d at oncology clinic. Received dose today.

4. Ms. Tiny calls you 2 days after her 03/04 visit to your pharmacy. She has been feeling a lot of bone pain and describes an "achy, creaky feeling all over." She is worried that her cancer has spread to her bones. What advice can you give her?

- I. She should call her oncology caretaker and be formally evaluated
- II. This could be a side effect of her Zoladex therapy and the pain should subside
- III. This could be a side effect of her Celebrex therapy and the pain should subside

- A. I only
- B. III only
- C. I and II only
- D. II and III only
- E. I, II, and III

5. Ms. Tiny's mother (age 59) is worried that she will develop breast cancer like her daughter. Which of the following is NOT an appropriate initial screening test for breast cancer?

- A. Monthly breast self-examination
- B. Clinical breast examination
- C. Mammography
- D. Biopsy
- E. Mammography and clinical breast examination

6. Which of the following classes of agents is best known for causing infusion-related reactions, such as fever and chills?

- I. Monoclonal antibodies
- II. Alkylating agents
- III. Vinca alkaloids

- A. I only
- B. III only
- C. I and II only
- D. II and III only
- E. I, II, and III

7. Your patient has just received 5-FU and irinotecan for the treatment of colorectal cancer. Before he leaves the clinic, you make sure that he has a prescription to prevent and/or treat which of the following side effects from irinotecan?

- A. Nausea with Aloxi®
- B. Diarrhea with loperamide
- C. Headache with aspirin
- D. Delayed allergic reaction with epinephrine
- E. Change in urine color: no treatment available

8. Which of the following drugs is an oral prodrug of 5-FU?

- A. Fluorouracil
- B. Xeloda®
- C. Fludara®
- D. Cytosan
- E. Alkeran®

9. An elderly male patient comes to your pharmacy and is worried that he might have prostate cancer. He just had some lab work done and his doctor told him that some level was abnormal, indicating potential prostate cancer. Which lab test might he be talking about?

- I. PSA
- II. Cortisol
- III. ESR

- A. I only
- B. III only
- C. I and II only
- D. II and III only
- E. I, II, and III

10. Stomatitis is the clinical term for which of the following chemotherapy-related adverse effects?

- I. Nausea and projectile vomiting
- II. Obstruction of the lower esophageal sphincter
- III. Inflammation of the mucosal lining of the mouth

- A. I only
- B. III only
- C. I and II only
- D. II and III only
- E. I, II, and III

11. Which of the following does not describe characteristics of most chemotherapy agents?

- A. A wide therapeutic index
- B. Interfere with DNA synthesis and replication
- C. More effective in combination
- D. Acute adverse effects occur primarily in rapidly dividing normal cells
- E. Phase-specific and non-phase specific actions

Use Patient Profile #2 to answer Questions 12-17.

12. A nurse would like to know if she can administer the diphenhydramine and the cimetidine in the same IV line simultaneously. Which of the following resources will provide you with this information?

- I. Facts and Comparisons™
- II. Trissel's
- III. Micromedex®

- A. I only
- B. III only
- C. I and II only
- D. II and III only
- E. I, II, and III

13. Which of the following agents that Mr. Migash is taking requires the premedication regimen of dexamethasone, diphenhydramine, and ranitidine or cimetidine to prevent an anaphylactic reaction?

- I. Taxotere
- II. Paraplatin
- III. Taxol

- A. I only
- B. III only
- C. I and II only
- D. II and III only
- E. I, II, and III

Patient Profile #2—Medication Profile: Institution

Patient Name	Cassimer Migash		
Address	579 Hunter's Ridge		
Age	60	Height	180 cm
Sex	Male	Weight	200 lb
Allergies	NKDA		

DIAGNOSIS	1. Diagnosed on 02/04 with metastatic non-small cell lung cancer
	2. Chronic obstructive pulmonary disease
	3. Asthma

LABS AND DIAGNOSTIC TESTS

Date	Test
05/04	WBC: 2500/microliter
05/04	RBC: $2.8 \times 10^6/\text{mm}^3$
05/04	PLT: $100 \times 10^3/\text{microliter}$
05/04	Theophylline: 10 mcg/mL
05/04	Hgb: 9 g/dL
05/04	Hct: 30%

MEDICATION RECORD

Date	Route	Drug	Sig
04/04	IV	Paclitaxel 135 mg/m ²	135 mg/m ² over 3 h q 3 wk
04/04	IV	Carboplatin AUC 6	AUC 6 over 2 h q 3 wk
04/04	PO	Theophylline SR 400 mg	1 tab PO bid
04/04	INH	Albuterol inhaler	2 puffs prn
04/04	INH	Cromolyn inhaler	1 puff qid
04/04	INH	Beclomethasone inhaler	2 puffs qid
04/04	PO	Dexamethasone 20 mg	1 tab 12 h and 6 h prior to chemo
4/03	IV	Diphenhydramine 50 mg	Infuse 30 min and 60 min prior to chemo
4/03	IV	Cimetidine 300 mg	Infuse 30 min and 60 min prior to chemo

14. Based on the patient's weight and height, you calculate Mr. Migash's body surface area to be 2.1 m². Paclitaxel is supplied as 6 mg/mL in 5-mL, 16.7-mL, and 50-mL vials. Your pharmacy has all quantities available. What is the best way to correctly dose this patient?
- One 50-mL vial
 - One 50-mL vial and one 5-mL vial
 - Two 16.7-mL vials
 - Two 16.7-mL vials and one 5-mL vial
 - Three 16.7-mL vials
15. You are concerned that Mr. Migash will develop nausea and vomiting from his chemotherapy regimen. Which of the following regimens would be suitable to prevent acute CINV?
- Dexamethasone, granisetron, and aprepitant
 - Granisetron and prochlorperazine
 - Metoclopramide, dexamethasone, and aprepitant
 - Palonosetron and granisetron
 - Lorazepam and droperidol
16. Based on the patient's lab values, which of the following adverse reactions appear to have occurred as a likely result of the chemotherapy?
- Thrombocytopenia
 - Leukopenia
 - Anemia
- I only
 - III only
 - I and II only
 - II and III only
 - I, II, and III
17. The goal of Mr. Migash's treatment regimen is:
- to cure his disease
 - to palliate his disease-related symptoms
 - to increase his quality of life
- I only
 - III only
 - I and II only
 - II and III only
 - I, II, and III
18. Doxorubicin is an antineoplastic agent that:
- is not related to epirubicin and daunorubicin
 - interacts with the microtubules of cells during mitosis
 - has an oral dosage form commercially available
 - causes cumulative cardiac toxicity
 - can also be used to treat tuberculosis
19. Which of the following agents is used in cancer regimens, but is not considered an antineoplastic agent?
- Methotrexate
 - Levamisole
 - Doxorubicin
 - Cyclophosphamide
 - Gemcitabine
20. Methotrexate (Rheumatrex®) is not available as which of the following dosage forms?
- An intravenous injection
 - An oral tablet or capsule
 - An intrathecal injection
 - An ointment
 - An intramuscular injection

Answers

- A. Zoladex** (goserelin) is an LHRH agonist that can be used to treat both breast and prostate cancer. LHRH agonists are FDA approved for premenopausal women, as they inhibit estrogen production from the ovaries.
- D.** 20 mg PO qd is the FDA approved dose for breast cancer therapy. The drug is not available in a liquid form.
- E.** All three agents are hormonal products and are associated with thromboembolic side effects. It is important that patients on these products are aware of the signs and symptoms of DVTs.
- C.** While the bone pain is most likely a side effect of her Zoladex therapy, she should notify her oncology practitioner so they can document this side effect. If other factors point to metastatic disease, this patient may need additional evaluation.

5. D. Biopsies should never be performed as initial screening tests. However, if results from the mammography and other tests point to disease, a biopsy is needed to make a diagnosis. There is some debate about the usefulness of clinical breast examinations (CBEs) for women that are reluctant to perform breast self-examinations; CBEs should be offered.
6. A. Monoclonal antibodies are commonly associated with infusion-related reactions. Patients should receive premedication, such as acetaminophen, to prevent this.
7. B. Diarrhea is a dose-limiting toxicity of irinotecan. Late diarrhea can be life threatening. All patients should receive a prescription for loperamide to treat delayed-onset diarrhea. Patients should be instructed to take 2 mg PO q2h while awake and 4 mg PO q4h during the night until the diarrhea has stopped for at least 12 hours. Acute-onset diarrhea can be treated with atropine.
8. B. Xeloda, generic name capecitabine, is an oral prodrug of 5-FU. Fluorouracil is another name for 5-FU. Fludara is the brand name for fludarabine and is used to treat CLL and NHL intravenously. Cytosan is the brand name for cyclophosphamide and is available in IV and PO dosage forms. Alkeran is the brand name for melphalan and is also available in IV and PO dosage forms.
9. A. PSA is a lab test that is commonly done in men over the age of 40. It should be tested annually in men over the age of 50 to check for prostate cancer. PSA stands for prostate-specific antigen.
10. B. Stomatitis is used to describe an irritation or ulceration of the mucosal lining. This side effect is common with fluorouracil and methotrexate. Having the patient hold ice chips in their mouth during treatment can prevent it. The cold is thought to cause vasoconstriction of the lining and prevent damage.
11. A. Chemotherapy agents have a very narrow therapeutic index. This is one of the main reasons why there are so many toxic effects with these drugs. They can be phase-specific or non-phase specific drugs and cause many adverse reactions to normal cells that undergo rapid proliferation.
12. D. Both Trissel's *Handbook of Injectable Drugs* and the Micromedex IV compatibility tool can be used to assess whether the diphenhydramine and cimetidine are compatible.
13. B. Taxol is the brand name of paclitaxel. This agent has been shown to cause hypersensitivity reactions in patients. It is unclear if these reactions are due to the drug itself or the drug's vehicle (Cremophor®). All patients receiving paclitaxel should receive a premedication regimen of dexamethasone, diphenhydramine, and ranitidine or cimetidine. Taxotere is the brand name of docetaxel. This agent also requires premedications with a minimum of a corticosteroid. However, this is to prevent peripheral edema, not an anaphylactic reaction.
14. A. The patient requires 283.5 mg of drug, which can be rounded up to 300 mg. Both choices A and E will provide 300 mg of drug; however, using one large vial is more economical than using three smaller vials.
15. A. This patient's regimen contains carboplatin and paclitaxel. Together these agents have a high likelihood of causing acute (and delayed) CINV. The patient should receive a corticosteroid, a 5-HT₃ antagonist, and a neurokinin-1 inhibitor. Aprepitant is approved in combination with a corticosteroid and a 5-HT₃ antagonist, making choices B and C incorrect. Choice D contains two 5-HT₃ antagonists. Therapy should include more than one class of agent. Choice E agents are not efficacious in moderate to severe CINV.
16. E. Myelosuppression is a common adverse reaction to most chemotherapy agents. Both paclitaxel and carboplatin can cause anemia, thrombocytopenia, and leukopenia. It is very important to monitor blood levels in these patients. If myelosuppression is too severe, the length of time between chemotherapy cycles may be increased so all or some of the blood cells can return to normal levels.
17. D. Mr. Migash has metastatic disease. Anytime a solid tumor is diagnosed as stage IV, this is representative of the fact that their disease is incurable. The treatment goals for these patients include relieving any disease-related symptoms, minimizing toxicity from treatments, and increasing the patient's quality of life through treatment or supportive care measures.

18. D. Doxorubicin is an antitumor antibiotic related to epirubicin and daunorubicin. These agents act by binding tightly to DNA via intercalation and by inhibiting the topoisomerase II enzyme. Doxorubicin does have a liposomal IV product, but it is not available orally. All anthracyclines are associated with cardiac toxicity and have cumulative dosing limits to prevent this.
19. B. Levamisole is an anthelmintic agent that is approved for combination therapy with 5-FU in the treatment of colorectal cancer.
20. D. Methotrexate is not commercially available for topical use. It is available in all of the other dosage forms.

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28. Asthma and Chronic Obstructive Pulmonary Disease

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Contents

1. Asthma
2. Chronic Obstructive Pulmonary Disease (COPD)
3. Key Points
4. Questions and Answers
5. References

1. Asthma

- Asthma is a chronic inflammatory disorder of the airways in which many cells and cellular elements play a role, in particular mast cells, eosinophils, T lymphocytes, neutrophils, and epithelial cells. In susceptible individuals, this inflammation causes recurrent episodes of wheezing, breathlessness, chest tightness, and cough, particularly at night and in the early morning. Asthma affects over 15 million Americans, and is the most common cause of missed school days for children. Mortality due to asthma is increasing; death rates are greatest in inner city African-Americans and Hispanics.

Types and Classifications

- Childhood-onset (atopic): positive family history of asthma, allergy to tree or grass pollen, house dust mites, household pets, and molds (extrinsic asthma)
- Adult-onset: usually a negative family history and negative skin tests to common aeroallergens (intrinsic asthma)
- Classification of severity is shown in Figure 1 (this classification is extremely important in defining treatment options; see Figure 2).

Clinical Presentation

- Episodic wheezing, coughing, chest tightness, shortness of breath; worse at night, early morning, and with exercise

Pathophysiology

- Inflammatory airway disease; also a disease with bronchospasm
- Common triggers of symptoms include aeroallergens, respiratory viral illness, exercise (especially in cold, dry air), environmental smoke, fumes, and cats.
- Drug-induced asthma includes that due to aspirin, NSAIDs, and β -blockers (low-dose β_1 -selective agents okay if concurrent post MI or CHF and do not have severe asthma; COX-2 inhibitors may be okay in aspirin-sensitive asthma)
- Complex interaction among inflammatory cells (eg, mast cells, eosinophils, lymphocytes), mediators (eg, leukotrienes), and cytokines (eg, IL-4, IL-5)
- The result is airway inflammation (mucus and swelling in the lining of the airways) and airway hyperreactivity.
- Early phase** response to inhaling an aeroallergen occurs immediately; **late phase** response occurs 4-12 hours later.

- Asthma is commonly worsened by poorly controlled concurrent allergic rhinitis, sinusitis, and GERD; it may also worsen in the premenstrual or perimenstrual period.

Diagnostic Criteria

- The main basis for diagnosis is a detailed history of episodic symptoms that are typically worse at nighttime/early morning and associated with common triggers.
- Reversible airway obstruction (improvement in pulmonary function tests [FEV₁] of >12% after inhaling a short-acting β_2 agonist)
- Exclude alternate diagnoses.

Treatment Principles and Goals

- Optimal long-term management of asthma includes four major areas, including objective assessment and monitoring, environmental control, pharmacologic therapy, and patient education as a partnership.
- Treatment goals are shown in Figure 1; a stepwise approach to managing asthma is shown in Figures 2 and 3. See Table 1 for long-term control medications.
- Inhaled corticosteroids are the most efficacious drugs for long-term management of persistent asthma. Addition of a long-acting inhaled β_2 agonist is recommended for patients with moderate or severe persistent asthma.
- Omalizumab (Xolair[®]) was released in the U.S. in 2003 after the NIH Asthma Guidelines were last updated. This anti-IgE therapy is primarily indicated for severe persistent asthma patients who have frequent emergency department visits and hospitalizations despite optimal therapy. It is given SC every 2-4 weeks.

Drug therapy for acute exacerbations of asthma

- See Table 2 for quick-relief medications, and Figure 4 for management of asthma exacerbations.

Monitoring

- Optimal management for the great majority of patients will result in a dramatic reduction in symptoms (including nocturnal and early morning symptoms), as well as reduced acute care visits, lost work or school days, and the need for quick-relief medications.
- Monitoring peak expiratory flow (PEF) using a peak flow meter at home is required ("green zone" is 80-100% of personal best value; "yellow zone" is 50-79% of personal best, and indicates consultation with a health care professional is advisable; and "red

Figure 1.

Classification of asthma severity.**Goals of Asthma Treatment**

- Prevent chronic and troublesome symptoms (e.g., coughing or breathlessness in the night, in the early morning, or after exertion)
- Maintain (near) "normal" pulmonary function
- Maintain normal activity levels (including exercise and other physical activity)
- Prevent recurrent exacerbations of asthma and minimize the need for emergency department visits or hospitalizations
- Provide optimal pharmacotherapy with minimal or no adverse effects
- Meet patients' and families' expectations of and satisfaction with asthma care

Classify Severity of Asthma			
Clinical Features Before Treatment*			
	Symptoms**	Nighttime Symptoms	Lung Function
STEP 4 Severe Persistent	<ul style="list-style-type: none"> ■ Continual symptoms ■ Limited physical activity ■ Frequent exacerbations 	Frequent	<ul style="list-style-type: none"> ■ FEV₁ or PEF $\leq 60\%$ predicted ■ PEF variability $> 30\%$
STEP 3 Moderate Persistent	<ul style="list-style-type: none"> ■ Daily symptoms ■ Daily use of inhaled short-acting beta₂-agonist ■ Exacerbations affect activity ■ Exacerbations ≥ 2 times a week; may last days 	> 1 time a week	<ul style="list-style-type: none"> ■ FEV₁ or PEF $> 60\% - < 80\%$ predicted ■ PEF variability $> 30\%$
STEP 2 Mild Persistent	<ul style="list-style-type: none"> ■ Symptoms > 2 times a week but < 1 time a day ■ Exacerbations may affect activity 	> 2 times a month	<ul style="list-style-type: none"> ■ FEV₁ or PEF $\geq 80\%$ predicted ■ PEF variability 20–30%
STEP 1 Mild Intermittent	<ul style="list-style-type: none"> ■ Symptoms ≤ 2 times a week ■ Asymptomatic and normal PEF between exacerbations ■ Exacerbations brief (from a few hours to a few days); intensity may vary 	≤ 2 times a month	<ul style="list-style-type: none"> ■ FEV₁ or PEF $\geq 80\%$ predicted ■ PEF variability $< 20\%$

* The presence of one of the features of severity is sufficient to place a patient in that category. An individual should be assigned to the most severe grade in which any feature occurs. The characteristics noted in this figure are general and may overlap because asthma is highly variable. Furthermore, an individual's classification may change over time.

** Patients at any level of severity can have mild, moderate, or severe exacerbations. Some patients with intermittent asthma experience severe and life-threatening exacerbations separated by long periods of normal lung function and no symptoms.

PEF, peak expiratory flow; FEV₁, forced expiratory volume in 1 second.

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Figure 2.

Stepwise approach for managing infants and young children (≤ 5 years of age) with acute or chronic asthma.

Classify Severity: Clinical Features Before Treatment or Adequate Control		Medications Required To Maintain Long-Term Control
	Symptoms/Day Symptoms/Night	Daily Medications
Step 4 Severe Persistent	Continual Frequent	<ul style="list-style-type: none"> ■ Preferred treatment: <ul style="list-style-type: none"> – High-dose inhaled corticosteroids AND – Long-acting inhaled β_2-agonists AND, if needed, – Corticosteroid tablets or syrup long term (2 mg/kg/day, generally do not exceed 60 mg per day). (Make repeat attempts to reduce systemic corticosteroids and maintain control with high-dose inhaled corticosteroids.)
Step 3 Moderate Persistent	Daily > 1 night/week	<ul style="list-style-type: none"> ■ Preferred treatments: <ul style="list-style-type: none"> – Low-dose inhaled corticosteroids and long-acting inhaled β_2-agonists OR – Medium-dose inhaled corticosteroids. ■ Alternative treatment: <ul style="list-style-type: none"> – Low-dose inhaled corticosteroids and either leukotriene receptor antagonist or theophylline. <p>If needed (particularly in patients with recurring severe exacerbations):</p> <ul style="list-style-type: none"> ■ Preferred treatment: <ul style="list-style-type: none"> – Medium-dose inhaled corticosteroids and long-acting β_2-agonists. ■ Alternative treatment: <ul style="list-style-type: none"> – Medium-dose inhaled corticosteroids and either leukotriene receptor antagonist or theophylline.
Step 2 Mild Persistent	> 2/week but < 1x/day > 2 nights/month	<ul style="list-style-type: none"> ■ Preferred treatment: <ul style="list-style-type: none"> – Low-dose inhaled corticosteroid (with nebulizer or MDI with holding chamber with or without face mask or DPI). ■ Alternative treatment (listed alphabetically): <ul style="list-style-type: none"> – Cromolyn (nebulizer is preferred or MDI with holding chamber) OR leukotriene receptor antagonist.
Step 1 Mild Intermittent	≤ 2 days/week ≤ 2 nights/month	<ul style="list-style-type: none"> ■ No daily medication needed.

Quick Relief**All Patients**

- Bronchodilator as needed for symptoms. Intensity of treatment will depend upon severity of exacerbation.
 - Preferred treatment: Short-acting inhaled β_2 -agonists by nebulizer or face mask and spacer/holding chamber
 - Alternative treatment: Oral β_2 -agonist
- With viral respiratory infection
 - Bronchodilator q 4–6 hours up to 24 hours (longer with physician consult); in general, repeat no more than once every 6 weeks
 - Consider systemic corticosteroid if exacerbation is severe or patient has history of previous severe exacerbations
- Use of short-acting β_2 -agonists > 2 times a week in intermittent asthma (daily, or increasing use in persistent asthma) may indicate the need to initiate (increase) long-term control therapy.

**Step down**

Review treatment every 1 to 6 months; a gradual stepwise reduction in treatment may be possible.

**Step up**

If control is not maintained, consider step up. First, review patient medication technique, adherence, and environmental control.

Goals of Therapy: Asthma Control

- Minimal or no chronic symptoms day or night
- Minimal or no exacerbations
- No limitations on activities; no school/parent's work missed
- Minimal use of short-acting inhaled β_2 -agonist (< 1x per day, < 1 canister/month)
- Minimal or no adverse effects from medications

Note

- The stepwise approach is intended to assist, not replace, the clinical decisionmaking required to meet individual patient needs.
- Classify severity: assign patient to most severe step in which any feature occurs.
- There are very few studies on asthma therapy for infants.
- Gain control as quickly as possible (a course of short systemic corticosteroids may be required); then step down to the least medication necessary to maintain control.
- Provide parent education on asthma management and controlling environmental factors that make asthma worse (e.g., allergies and irritants).
- Consultation with an asthma specialist is recommended for patients with moderate or severe persistent asthma. Consider consultation for patients with mild persistent asthma.

Figure 3.

Stepwise approach for managing asthma in adults and children >5 years of age: Treatment.

Classify Severity: Clinical Features Before Treatment or Adequate Control			Medications Required To Maintain Long-Term Control
	Symptoms/Day Symptoms/Night	PEF or FEV ₁ PEF Variability	Daily Medications
Step 4 Severe Persistent	Continual Frequent	≤ 60% > 30%	<ul style="list-style-type: none"> ■ Preferred treatment: <ul style="list-style-type: none"> – High-dose inhaled corticosteroids AND – Long-acting inhaled beta₂-agonists AND, if needed, – Corticosteroid tablets or syrup long term (2 mg/kg/day, generally do not exceed 60 mg per day). (Make repeat attempts to reduce systemic corticosteroids and maintain control with high-dose inhaled corticosteroids.)
Step 3 Moderate Persistent	Daily > 1 night/week	> 60% – < 80% > 30%	<ul style="list-style-type: none"> ■ Preferred treatment: <ul style="list-style-type: none"> – Low-to-medium dose inhaled corticosteroids and long-acting inhaled beta₂-agonists. ■ Alternative treatment (listed alphabetically): <ul style="list-style-type: none"> – Increase inhaled corticosteroids within medium-dose range OR – Low-to-medium dose inhaled corticosteroids and either leukotriene modifier or theophylline. <p>If needed (particularly in patients with recurring severe exacerbations):</p> <ul style="list-style-type: none"> ■ Preferred treatment: <ul style="list-style-type: none"> – Increase inhaled corticosteroids within medium-dose range and add long-acting inhaled beta₂-agonists. ■ Alternative treatment: <ul style="list-style-type: none"> – Increase inhaled corticosteroids within medium-dose range and add either leukotriene modifier or theophylline.
Step 2 Mild Persistent	> 2/week but < 1x/day > 2 nights/month	≥ 80% 20–30%	<ul style="list-style-type: none"> ■ Preferred treatment: <ul style="list-style-type: none"> – Low-dose inhaled corticosteroids. ■ Alternative treatment (listed alphabetically): cromolyn, leukotriene modifier, nedocromil, OR sustained release theophylline to serum concentration of 5–15 mcg/mL.
Step 1 Mild Intermittent	≤ 2 days/week ≤ 2 nights/month	≥ 80% < 20%	<ul style="list-style-type: none"> ■ No daily medication needed. ■ Severe exacerbations may occur, separated by long periods of normal lung function and no symptoms. A course of systemic corticosteroids is recommended.

Quick Relief

All Patients

- Short-acting bronchodilator: 2–4 puffs short-acting inhaled beta₂-agonists as needed for symptoms.
- Intensity of treatment will depend on severity of exacerbation; up to 3 treatments at 20-minute intervals or a single nebulizer treatment as needed. Course of systemic corticosteroids may be needed.
- Use of short-acting beta₂-agonists > 2 times a week in intermittent asthma (daily, or increasing use in persistent asthma) may indicate the need to initiate (increase) long-term control therapy.



Step down

Review treatment every 1 to 6 months; a gradual stepwise reduction in treatment may be possible.



Step up

If control is not maintained, consider step up. First, review patient medication technique, adherence, and environmental control.

Goals of Therapy: Asthma Control

- Minimal or no chronic symptoms day or night
- Minimal or no exacerbations
- No limitations on activities; no school/work missed
- Maintain (near) normal pulmonary function
- Minimal use of short-acting inhaled beta₂-agonist (< 1x per day, < 1 canister/month)
- Minimal or no adverse effects from medications

Note

- The stepwise approach is meant to assist, not replace, the clinical decisionmaking required to meet individual patient needs.
- Classify severity: assign patient to most severe step in which any feature occurs (PEF is % of personal best; FEV₁ is % predicted)
- Gain control as quickly as possible (consider a short course of systemic corticosteroids); then step down to the least medication necessary to maintain control.
- Provide education on self-management and controlling environmental factors that make asthma worse (e.g., allergens and irritants).
- Refer to an asthma specialist if there are difficulties controlling asthma or if step 4 care is required. Referral may be considered if step 3 care is required.

Table 1

Long-Term Asthma Control Medications

Generic name	Trade name	Usual dosage range	Dosage form	Schedule ¹
Inhaled corticosteroids				
Beclomethasone HFA 40 mcg/puff; 80 mcg/puff	QVAR [®]	80-480 mcg/day	MDI	bid
Budesonide 200 mcg/inhalation	Pulmicort [®]	1-3 inhalations/day	Turbuhaler	bid
Budesonide 0.25 & 0.5 mg	Respules [®]	0.5-2.0 mg/day	Nebulized	bid
Flunisolide 250 mcg/puff	Aerobid [®]	1-8 puffs/day	MDI	bid
Fluticasone 44, 110, 220 mcg/puff	Flovent [®]	88-660 mcg/day	MDI	bid
Fluticasone	Flovent Rotadisk [®]	100-500 mcg/day	DPI	bid
Fluticasone-salmeterol combination (each dose: 50 mcg salmeterol + 100, 250, or 500 mcg fluticasone)	Advair Diskus [®] (Advair 100, 250, 500)	1 inhalation	DPI	bid
Mometasone 220 mcg/inhalation	Asmanex [®] Twisthaler	1-2 inhalations/day	DPI	hs
Triamcinolone 100 mcg/puff	Azmacort [®]	4-20 puffs/day	MDI/spacer	bid
Leukotriene modifiers				
Montelukast	Singulair [®]	4 mg (12-23 months) 4 mg (age 2-5 y) 5 mg (age 6-14 y) 10 mg (adult) tablet	Oral granules Chewable tab Chewable tab Tablet	qhs qhs qhs qhs
Zafirlukast	Accolate [®]	20-40 mg/day tablet	Tablet	bid
Zileuton	Zyflo [®]	2400 mg/day tablet	Tablet	qid
Mast cell stabilizers				
Cromolyn	Intal [®]	1-4 puffs MDI	MDI	qid
	Intal [®]	20 mg	Nebulizer solution	qid
Nedocromil	Tilade [®]	1-4 puffs MDI	MDI	qid
Long-acting inhaled β_2 agonists				
Formoterol	Foradil Aerolizer [®]	1 inhalation DPI	DPI	bid
Salmeterol	Serevent Diskus [®]	1 inhalation DPI	DPI	bid
Methylxanthines				
Theophylline (numerous products)	Uniphyll [®]	10 mg/kg per day ² up to 300 mg max in adults to start; aim for 5-15 mcg/mL steady state	Tablet	Daily; 5 or 6 pm

MDI, metered dose inhaler; DPI, dry powder inhaler (breath-activated).

¹Usual schedule (some patients do well on once-daily dosing).²Complex, high-risk drug to dose; see references cited for details; do not use unless competent in dosing and monitoring serum theophylline concentrations.

zone," or <50% of personal best, indicates a written action plan should be implemented, and if there is no quick response, immediate medical attention should be sought).

- Spirometry in the physician's office

Mechanism of Action

(For more details, see the section on mechanism of action from the NIH Expert Panel Report 2.)

Long-term control medications

Corticosteroids

- Anti-inflammatory: block late reaction to allergen

Table 2

Quick-Relief Asthma Medications

Generic name	Trade name	Usual dosage ¹	Dosage form	Schedule
Short-acting inhaled β_2 agonists²				
Albuterol	Proventil [®] , Ventolin [®]	2 puffs 2.5 mg	MDI Nebulizer solution	q4h prn q4h prn
Pirbuterol	Maxair Autohaler [®]	2 puffs	MDI	q4h prn
Anticholinergics				
Ipratropium	Atrovent [®]	2 puffs 0.25 mg	MDI Nebulizer solution	q6h q6h
Ipratropium with albuterol	Combivent [®]	2 puffs 3 mL	MDI Nebulizer solution	q6h q6h
Systemic corticosteroids³				
Methylprednisolone	Medrol [®]	1 mg/kg per day	Tablets	Daily
Prednisone		1 mg/kg per day	Tablets/liquid	Daily
Prednisolone		1 mg/kg per day	Tablets	Daily

¹Usual dosage for routine home use (dose in emergency department is higher/more frequent).

²For prevention of exercise-induced asthma, inhale 2 puffs 5-15 minutes before exercise. Increasing use indicates poor asthma control; increase anti-inflammatory therapy and reassess environmental control (good asthma control is indicated by infrequent need for quick-relief therapy).

³Short courses are used for <2 weeks.

- and reduce airway hyperresponsiveness; inhibit cytokine production, adhesion protein activation, and inflammatory cell migration and activation
- Reverse β_2 -receptor downregulation: inhibit microvascular leakage

Cromolyn and nedocromil

- Anti-inflammatory: block early and late reaction to allergen; interfere with chloride channel function; stabilize mast cell membranes and inhibit activation and release of mediators from eosinophils and epithelial cells
- Inhibit acute response to exercise, cold dry air, and SO_2

Long-acting β_2 agonists

- Bronchodilation: smooth muscle relaxation following adenylate cyclase activation and increase in cyclic AMP, producing functional antagonism of bronchoconstriction
- In vitro, inhibit mast cell mediator release, decrease vascular permeability, and increase mucociliary clearance
- Compared to short-acting inhaled β_2 agonist, salmeterol (but not formoterol) has a slower onset of action (15-30 minutes) but longer duration (>12 hours).

Methylxanthines

- Bronchodilation: smooth muscle relaxation from phosphodiesterase inhibition and possibly adenosine antagonism
- May affect eosinophilic infiltration into bronchial mucosa as well as decrease T-lymphocyte numbers in epithelium
- Increases diaphragm contractility and mucociliary clearance

Leukotriene modifiers

- Leukotriene receptor antagonist; selective competitive inhibitor of LTD_4 and LTE_4 receptors
- 5-Lipoxygenase inhibitor

Anti-IgE therapy

- Omalizumab (Xolair) is a humanized monoclonal anti-IgE antibody that binds circulating IgE, thus inhibiting the allergic inflammatory cascade that results when aeroallergens bind to IgE on mast cells.

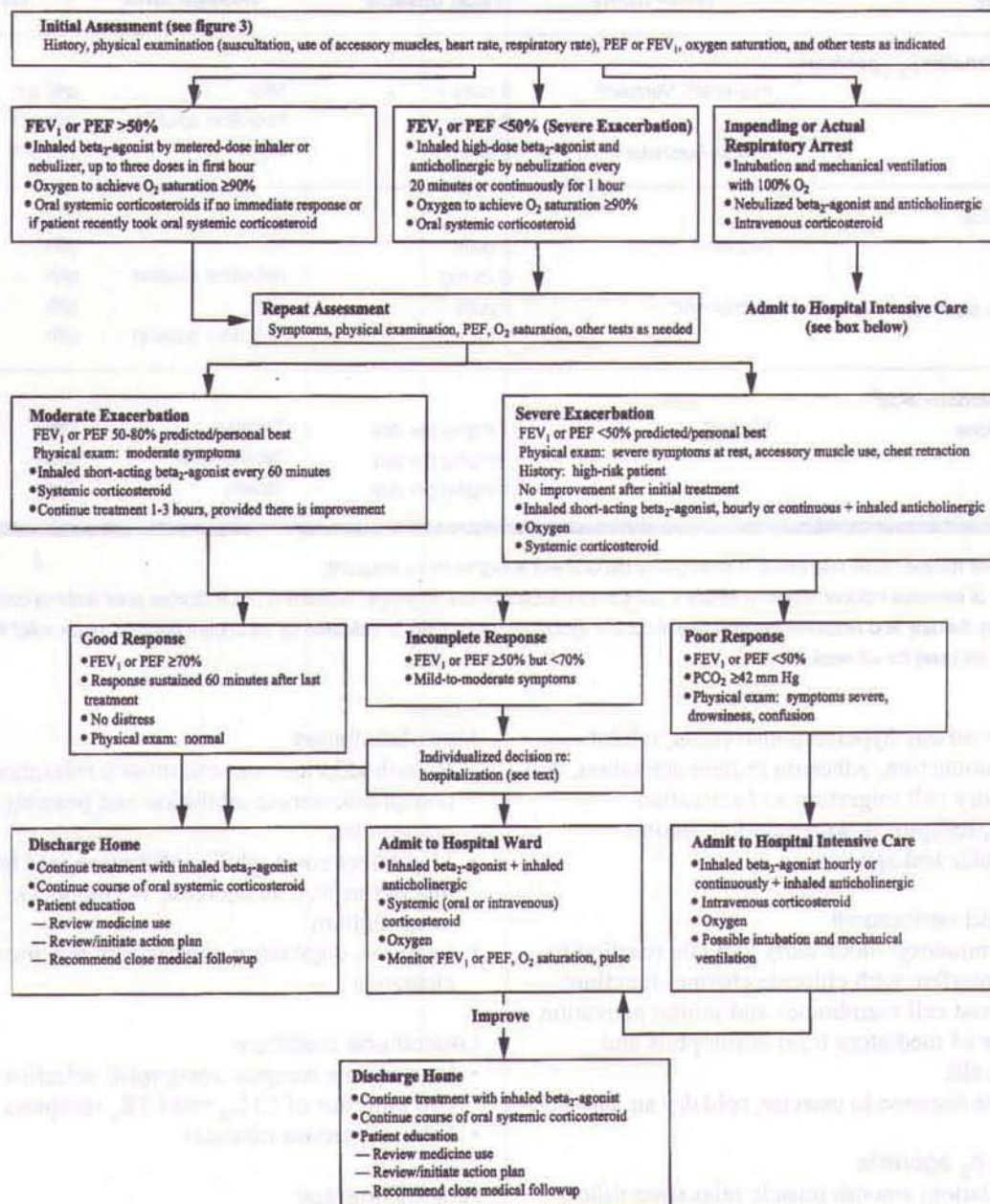
Quick-relief medications

Short-acting inhaled β_2 agonists

- Bronchodilation: smooth muscle relaxation following adenylate cyclase activation and increase in

Figure 4.

Management of asthma exacerbations: Emergency department and hospital-based care.



PCO₂, partial pressure of carbon dioxide; PEF, peak expiratory flow; FEV₁, forced expiratory volume in 1 second.
Reproduced from NIH Expert Panel Report 2.

cyclic AMP, producing functional antagonism of bronchoconstriction

Anticholinergics

- Bronchodilation: competitive inhibition of muscarinic cholinergic receptors
- Reduce intrinsic vagal tone to the airways; may block reflex bronchoconstriction secondary to irritants or to reflux esophagus
- May decrease mucus gland secretion

Patient Instructions and Counseling

- Patient education is absolutely essential for optimal asthma management.
- Emphasize the necessity to take controller/preventer medications **EVERYDAY**, even when the patient feels well and is having no breathing problems.
- Instruct the patient regarding the dangers of overuse of short-acting inhaled β_2 agonists (if inflammation is worsening, see a physician if the usual dose does not give quick relief).
- Demonstrate the correct use of the MDI, the MDI plus spacer, and dry powder inhalers (DPI), and then OBSERVE the patient using the devices (most patients do not perform well initially; the devices can be difficult to use at first; see Figure 5 for MDI or MDI spacer use). For DPIs, remember to stress that inhalation must be RAPID and deep.
- Demonstrate correct use of peak flow meters and OBSERVE the patient using them (Table 3); explain about the green, yellow, and red zones (including the written action plan).
- Teach how to prevent exercise-induced asthma.
- Be sure patients receive an influenza vaccination every fall.

Adverse Drug Effects

(For more details, see the section on adverse drug effects from NIH Expert Panel Report 2.)

Long-term control medications

Inhaled corticosteroids

- Cough, dysphonia, oral thrush (candidiasis)
- In high doses, systemic effects may occur, although studies are not conclusive, and the clinical significance of these effects (eg, adrenal suppression, osteoporosis, growth suppression, skin thinning, and easy bruising) has not been established.

Cromolyn and nedocromil

- Fifteen to twenty percent of patients complain of an unpleasant taste from nedocromil.

Table 3

Directions for Use of Peak Flow Meter¹

1. Stand while using the meter.
2. Position the indicator at the bottom of the scale.
3. Hold the peak flow meter so your fingers do not block the opening.
4. Inhale as deeply as possible, place mouthpiece well into your mouth, and make sure your lips form a tight seal around it.
5. Blow out as fast and as hard as possible!² BLAST! Emphasize to the patient that the maneuver is highly effort-dependent.
6. Repeat steps 2-5 two more times, and record the highest of the three readings along with the date and time.

¹If a short-acting inhaled β_2 agonist is required in the early morning, remember to check the peak expiratory flow before using the drug, and record the value; then repeat PEF testing 15 minutes later.

²Do not accelerate air with your tongue (ie, use a spitting motion). This incorrect maneuver will give false elevation in PEF.

Long-acting β_2 agonists

- Tachycardia, skeletal muscle tremor, hypokalemia, prolongation of QTc interval in overdose
- A diminished bronchoprotective effect may occur within 1 week of chronic therapy. Clinical significance has not been established.

Methylxanthines

- 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 males with prostatism.

Leukotriene modifiers

(updated from 1997 NIH Guidelines)

- Montelukast and zafirlukast are usually well tolerated.
- Zileuton can cause liver dysfunction.

Figure 5.

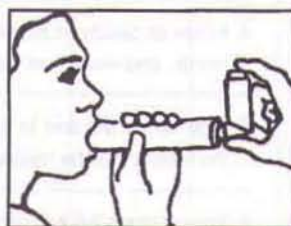
Steps for using an inhaler.

Please demonstrate your inhaler technique at every visit.

1. Remove the cap and hold inhaler upright.
2. Shake the inhaler.
3. Tilt your head back slightly and breathe out slowly.
4. Position the inhaler in one of the following ways (A or B is optimal, but C is acceptable for those who have difficulty with A or B. C is required for breath-activated inhalers):



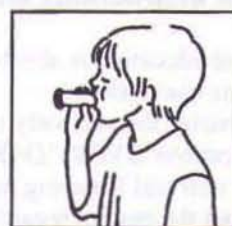
A. Open mouth with inhaler 1 to 2 inches away.



B. Use spacer/holding chamber (that is recommended especially for young children and for people using corticosteroids).



C. In the mouth. Do not use for corticosteroids.



D. NOTE: Inhaled dry powder capsules require a different inhalation technique. To use a dry powder inhaler, it is important to close the mouth tightly around the mouthpiece of the inhaler and to inhale rapidly.

5. Press down on the inhaler to release medication as you start to breathe in slowly.
6. Breathe in slowly (3 to 5 seconds).
7. Hold your breath for 10 seconds to allow the medicine to reach deeply into your lungs.
8. Repeat puff as directed. Waiting 1 minute between puffs may permit second puff to penetrate your lungs better.
9. Spacers/holding chambers are useful for all patients. They are particularly recommended for young children and older adults and for use with inhaled corticosteroids.

Avoid common inhaler mistakes. Follow these inhaler tips:

- Breathe out *before* pressing your inhaler.
- Inhale *slowly*.
- Breathe in through your mouth, not your nose.
- Press down on your inhaler at the *start* of inhalation (or within the first second of inhalation).
- Keep inhaling as you press down on inhaler.
- Press your inhaler only *once* while you are inhaling (one breath for each puff).
- Make sure you breathe in evenly and deeply.

NOTE: Other inhalers are becoming available in addition to those illustrated above. Different types of inhalers may require different techniques.

Quick-relief medications**Short-acting inhaled β_2 agonists**

- Tachycardia, skeletal muscle tremor, hypokalemia, increased lactic acid, headache, hyperglycemia; in general the inhaled route causes few systemic adverse effects; patients with preexisting cardiovascular disease, especially the elderly, may have adverse cardiovascular reactions with inhaled therapy

Anticholinergics

- Drying of mouth and respiratory secretions, increased wheezing in some individuals, blurred vision if sprayed in eyes

Systemic corticosteroids

- Short-term use: reversible abnormalities in glucose metabolism, increased appetite, fluid retention, weight gain, mood alteration, hypertension, peptic ulcer, and rarely aseptic necrosis of the femur
- Consideration should be given to coexisting conditions that could be worsened by systemic corticosteroids, such as herpes virus infections, varicella, tuberculosis, hypertension, peptic ulcer disease, and strongyloidiasis.

Drug-Drug and Drug-Disease Interactions

- For zafirlukast, administration with meals decreases bioavailability; take at least 1 hour before or 2 hours after meals.
- Zileuton and zafirlukast may increase the effect of warfarin and increase theophylline levels.
- Well known inducers of cytochrome P450 (carbamazepine, phenobarbital, phenytoin, and rifampin) are documented to decrease the effect of systemic corticosteroids.
- Examples of drugs that may increase the effect of systemic corticosteroids include erythromycin, clarithromycin, itraconazole, oral contraceptives, and conjugated estrogen.

Parameters to Monitor

- Refill record for daily controller/preventer meds and quick-relief meds
- Reduction in symptoms (including nocturnal and early morning symptoms)
- ED visits and hospitalizations; unscheduled office visits
- Need for "bursts" of systemic corticosteroids
- Lost work or school days, and the need for quick-relief medications
- Peak expiratory flow (PEF) using a peak flow meter at home

- If the patient also has rhinitis or GERD, monitor refills to ensure optimal control (if rhinitis and GERD are not well controlled, asthma control will likely suffer).

Kinetics

- Theophylline is no longer used extensively in asthma, but when it is used, knowledge of its kinetics is essential due to its high risk.
- Other drugs, disease states, smoking, age, and diet can all affect theophylline kinetics and dose requirements.
- Therapeutic serum theophylline concentrations are 5-15 mcg/mL (**NOT** the old recommendation of 10-20 mcg/mL; see latest NIH Guidelines [1997 and 2002]).
- Elimination half-life in an otherwise healthy non-smoking adult is about 8 hours, but in a smoker about 4 hours, and in a small child (>1 year) about 4 hours.
- Neonates have greatly prolonged elimination half-life.
- Elimination half-life in decompensated heart failure or cirrhosis is about 24 hours.
- Volume of distribution is about 0.5 L/kg.
- High-fat meals may cause "dose dumping" for some products (check product literature).

Other

- MDIs should be stored at room temperature, between 59 and 86°F; if left in a car in freezing or near-freezing temperatures, aerosol particles will be too large to inhale into the lungs.
- MDIs should be "primed" (release one dose) only with first use, or if it is a prn agent used only once every few weeks (frequent priming is unnecessary and wastes expensive medications).
- MDI dust cap should be left on inhaler when not in use! Check mouthpiece for foreign objects before inhaling!

Non-Drug Therapy

- An essential component of optimal asthma management is environmental control.
- Without good control of the environment at home, school, and work, drug therapy will often be inadequate.
- Have the patient identify known asthma triggers, and help the patient identify potential triggers not yet realized (do not forget someone smoking at home or work!).

Table 4.

Factors Affecting Serum Theophylline Levels

Factor	Decreases Theophylline Concentrations	Increases Theophylline Concentrations	Recommended Action
Food	↓ or delays absorption of some sustained-release theophylline (SRT) products	↑ rate of absorption (fatty foods) products	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 percent 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 to 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 H ₂ blocker (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. Circumvent with ofloxacin if quinolone therapy is required.
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.

* This list is not all-inclusive; for discussion of other factors, see package inserts.

Reproduced from NIH Expert Panel Report 2.

TAO, triacetyloleandomycin.

2. Chronic Obstructive Pulmonary Disease (COPD)

- COPD is characterized by airflow limitation that is not fully reversible. The airflow limitation is usually both progressive and associated with an abnormal inflammatory response of the lungs to noxious particles or gases. COPD is a major cause of death and suffering in the U.S. and around the world. It is the fourth leading cause of chronic morbidity and mortality in the U.S.

Types and Classifications (Table 5)

- Some clinicians still refer to chronic bronchitis and emphysema in characterizing different levels of COPD (eg, emphysema patients have destructive damage to the alveolar walls, whereas chronic bronchitis is associated with chronic productive cough).

Clinical Presentation

- Shortness of breath
- Cough and sputum production
- Usually a history of cigarette smoking for several years
- In the more severe form, respiratory failure and heart failure

Pathophysiology

- Usually caused by long-term smoking (may also be caused by exposure to other noxious particles and gases)
- Chronic inflammation throughout the airways but via different inflammatory cells and mediators than those that cause asthma (thus the response to inhaled corticosteroids is much less than that seen with asthma)
- Imbalance of proteinases and antiproteinases in the lung
- A rare hereditary cause of emphysema is α_1 -antitrypsin deficiency.
- Pathologic changes are found in the central and peripheral airways as well as the alveoli and pulmonary vasculature.
- Mucus hypersecretion
- Ciliary dysfunction
- Airflow limitation
- Lung hyperinflation
- Gas exchange abnormalities
- Secondary pulmonary hypertension
- Cor pulmonale

Diagnostic Criteria

- History of cigarette smoking or exposure to other noxious particles or fumes
- Chronic cough and sputum production
- Spirometry (reduced FEV_1 ; see Table 5 for classification of severity)
- Rule out other lung diseases.

Table 5

Classification of COPD by Severity

Stage	Characteristics
0: At Risk	<ul style="list-style-type: none"> • Normal spirometry • Chronic symptoms (cough, sputum, production)
I: Mild COPD	<ul style="list-style-type: none"> • $FEV_1/FVC < 70\%$ • $FEV_1 \geq 80\%$ predicted • With or without chronic symptoms (cough, sputum production)
II: Moderate COPD	<ul style="list-style-type: none"> • $FEV_1/FVC < 70\%$ • $50\% \leq FEV_1 < 80\%$ predicted (IIA: $50\% FEV_1 < 80\%$ predicted) (IIB: $30\% FEV_1 < 50\%$ predicted) • With or without chronic symptoms (cough, sputum production, dyspnea)
III: Severe COPD	<ul style="list-style-type: none"> • $FEV_1/FVC < 70\%$ • $30\% \leq FEV_1 < \text{predicted}$ or $FEV_1 < 50\%$ predicted plus respiratory failure or clinical signs of right heart failure
IV: Very severe COPD	<ul style="list-style-type: none"> • $FEV_1/FVC < 70\%$ • $FEV_1 < 30\%$ predicted or $FEV_1 < 50\%$ predicted plus chronic respiratory failure

FEV_1 , forced expiratory volume in 1 second; FVC, forced vital capacity.

Respiratory failure defined as arterial partial pressure of oxygen (PAO_2) less than 8.0 kPa (60 mm Hg) with or without arterial partial pressure of CO_2 ($PACO_2$) greater than 6.7 kPa (50 mm Hg) while breathing air at sea level.

From Pauwels et al, 2001.

Treatment Principles and Goals

- Prevent disease progression.
- Relieve symptoms.
- Improve exercise tolerance.
- Improve health status.
- Prevent and treat complications.
- Prevent and treat exacerbations.
- Reduce mortality.
- Bronchodilators are central to the symptomatic treatment of COPD; these agents will increase exercise capacity without necessarily improving the FEV₁.
- Inhaled bronchodilators are preferred to oral bronchodilators for initial therapy; the specific choice of agent depends on patient response.
- Long-acting inhaled bronchodilators are more effective and convenient but more expensive.
- One of the long-acting anticholinergic bronchodilators (tiotropium, Spiriva®) is a logical first choice for maintenance therapy of moderate to severe COPD.
- Short-acting inhaled β_2 agonists are preferred for prn use in patients already receiving long-acting β_2 agonists and anticholinergics.
- Theophylline is a logical step 3 agent for maintenance therapy in patients who are not optimally controlled with β_2 agonists and anticholinergics.

Therapy at each stage

(per Global Initiative for Chronic Obstructive Lung Disease [GOLD] Workshop Summary 2004 Update)

- For each stage, avoid risk factors (eg, smoking cessation) and receive influenza vaccine each autumn. Also, consider pneumococcal vaccine per current guidelines.

Stage 0: At risk

- No recommended drug treatment

Stage I: Mild COPD

- As-needed short-acting bronchodilator

Stage II: Moderate COPD

- Add regular treatment with one or more long-acting bronchodilators and rehabilitation

Stage III: Severe COPD

- Regular treatment with one or more long-acting bronchodilators
- Add inhaled corticosteroids if significant symptoms and lung function responses or if repeated exacerbations occur.

Stage IV: Very severe COPD

- Same treatments as for stage III and consider surgical treatment
- Long-term O₂ therapy if chronic respiratory failure

Drug therapy for acute exacerbations of COPD

- Inhaled albuterol and/or ipratropium
- Systemic corticosteroids (eg, prednisone 40 mg daily for 10 days)
- Oral antibiotics for purulent sputum (typically trimethoprim-sulfamethoxazole, amoxicillin, or doxycycline)
- O₂

Monitoring

- Spirometry: FEV₁
- Symptoms of dyspnea, cough, sputum production, change in sputum color and volume
- PaO₂
- Exercise tolerance/fatigue

Long-term drug therapy

- See content under asthma for specific drugs.
- Tiotropium is a once-daily anticholinergic bronchodilator that is arguably step one treatment of moderate to severe COPD. It is administered by a DPI (Handihaler®). Each dose must be loaded, and deep inhalation does not have to be forceful, but must be sufficient to hear the capsule vibrate.

Nondrug therapy

- The most important nondrug therapy is smoking cessation (ie, nicotine replacement therapy, bupropion, support groups, and counseling).
- Oxygen therapy
- Nutritional support
- Psychosocial support
- Pulmonary rehabilitation

3. Key Points

Asthma

- Asthma is primarily an inflammatory airway disease.
- It is undertreated, resulting in much unnecessary suffering and economic loss.
- Managing patients via the principles of the NIH Guidelines has been clearly shown to reduce ED visits and hospitalizations and improve patient quality of life.
- Optimal long-term management includes objective assessment, environmental control, drug therapy, and patient education working in a partnership.
- Patients with persistent asthma need daily controller therapy (anti-inflammatory agents).
- **Inhaled corticosteroids** are the **most efficacious agents to control asthma**.
- Inhaled long-acting inhaled β_2 agonists are indicated with inhaled corticosteroids for patients with moderate persistent or severe persistent asthma.
- **Short-acting inhaled β_2 agonists** are the agents of choice for **quick** relief of symptoms.
- Pharmacists should teach patients how to use inhalers (MDI, MDI-spacer, and DPI) by demonstration and **OBSERVATION** of the patient.
- Pharmacists should instruct patients on how to use peak flow meters, including color-coded zone management with a written action plan.
- Patients must clearly understand the purpose of daily controller/preventer meds vs. quick-relief meds.

Chronic obstructive pulmonary disease

(Taken from GOLD Workshop Summary 2004 Update)

- The overall approach to managing stable COPD should be characterized by a **stepwise increase in treatment, depending on the severity of the disease**.
- For patients with COPD, health education can play a role in improving skills, ability to cope with the illness, and health status. It is effective in accomplishing certain goals, including smoking cessation.
- None of the existing medications for COPD has been shown to modify the long-term decline in lung function that is the hallmark of this disease. Therefore, pharmacotherapy for COPD is used to improve symptoms and/or decrease complications.
- Bronchodilator medications are central to the symptomatic management of COPD.
- The principal bronchodilator treatments are β_2 agonists, anticholinergics, theophylline, and a **combination of one or more** of these drugs. Inhaled therapy with long-acting agents is preferred.
- Combining bronchodilators may improve efficacy and decrease the risk of side effects compared to increasing the dose of a single bronchodilator.
- Regular treatment with inhaled glucocorticosteroids should only be prescribed for symptomatic COPD

patients with a documented spirometric response to glucocorticosteroids or for those with an FEV_1 **<50% predicted** and repeated exacerbations requiring treatment with antibiotics and/or oral glucocorticosteroids.

- **Chronic treatment** with systemic glucocorticosteroids should be avoided because of an unfavorable benefit:risk ratio.
- All COPD patients benefit from exercise training programs, improving with respect to both exercise tolerance and symptoms of dyspnea and fatigue.
- The long-term administration of oxygen (>15 hours per day) to patients with chronic respiratory failure has been shown to increase survival.

4. Questions and Answers

1. Asthma is primarily due to which underlying problem?
 - A. Pulmonary fibrosis
 - B. Infection
 - C. Inflammation
 - D. Bronchospasm
 - E. Granulomas
2. Which objective measure for routine monitoring of asthma is available at home?
 - A. PEF
 - B. FEV₁
 - C. FVC
 - D. O₂ saturation
 - E. PD20
3. Which device requires slow inhalation?
 - A. Diskus
 - B. Turbuhaler
 - C. Aerolizer
 - D. MDI
 - E. Rotadisk
4. How many seconds is optimal for breath holding after inhaling from an MDI?
 - A. 4
 - B. 5
 - C. 15
 - D. 2
 - E. 10
5. When using a peak flow meter, what percentage of the personal best value is the yellow zone?
 - A. <50
 - B. <60
 - C. 50-79
 - D. 60-89
 - E. 40-60
6. What are the trade names for long-acting inhaled β_2 agonists?
 - A. Foradil and Serevent
 - B. Pulmicort and Flovent
 - C. Aerobid and Combivent
 - D. Maxair and Atrovent
 - E. Flovent and Ventolin
7. Which disease states decrease theophylline elimination and often result in reduced dosage requirements?
 - A. Hepatitis
 - B. Heart failure (decompensated)
 - C. Hypertension
 - D. A, B, and C
 - E. A and B
8. Which drug(s) are preferred for long-term treatment of moderate persistent asthma?
 - A. Budesonide + formoterol
 - B. Fluticasone + salmeterol
 - C. Beclomethasone + ipratropium
 - D. A or B
 - E. B or C
9. Which drug is a once-daily anticholinergic bronchodilator?
 - A. Atrovent
 - B. Serevent
 - C. Foradil
 - D. Spiriva
 - E. Proventil
10. For patients with asthma or COPD exacerbations not responding adequately to inhaled bronchodilators, what is the agent of choice to add to manage the acute exacerbation?
 - A. Fluticasone
 - B. Budesonide
 - C. Cromolyn
 - D. Theophylline
 - E. Prednisone
11. Which drug may increase serum theophylline concentrations?
 - A. Clarithromycin
 - B. Hydrochlorothiazide
 - C. Carbamazepine
 - D. Rifampin
 - E. Phenytoin
12. Which side effect of inhaled corticosteroids is reduced by spacer devices?
 - A. Hoarseness
 - B. Decreased bone density
 - C. Thinning of skin
 - D. Oropharyngeal candidiasis
 - E. Cataracts

Case Study 1: Medication Profile

Patient Name: Thomas Johnson
 Address: 5689 Washington St.
 DOB: 9-15-55
 Drug Allergies: aspirin sensitivity
 Height: 5'10" Weight: 75 kg
 Diagnosis: (1) asthma (childhood onset, moderate persistent)
 (2) allergic rhinitis
 (3) hypertension

Medications:

Date	Rx #	MD	Drug & Strength	Quantity	Sig	Refills
3/16	94385	Betts	Accolate 20 mg	60	1 bid	3
3/16	94386	Betts	albuterol MDI	1	2 puffs q4h	6
3/16	94387	Betts	Flonase	1	bid as dir.	3
3/25	95523	T. Jones	Lopressor 50 mg	60	1bid	6
3/27	95734	Betts	albuterol MDI	1	2 puffs q4h	5

Pharmacist Notes: 3/16—discussed proper use of MDI and observed patient use. Coached Mr. Johnson to inhale slowly (he was inhaling fast); he used the MDI correctly for the other steps.

13. The therapeutic range for theophylline per the NIH Guidelines for asthma management is:

A. 5-15 mcg/mL
 B. 8-12 mcg/mL
 C. 10-20 mcg/mL
 D. 15-25 mcg/mL
 E. 10-15 mcg/mL

14. Which asthma controller drug is given qhs?

A. Accolate
 B. Singulair
 C. Zflo
 D. Intal
 E. Tilade

15. When it is not well controlled, which disease state may worsen asthma?

A. Coronary artery disease
 B. GERD
 C. Diabetes
 D. Hypertension
 E. Arthritis

16. Which class of drugs is only indicated in COPD patients who have frequent exacerbations?

A. Long-acting inhaled β_2 agonists
 B. Anticholinergics
 C. Short-acting inhaled β_2 agonists
 D. Inhaled corticosteroids
 E. Methylxanthines

The next two questions relate to Case Study 1.

17. Which class of drugs is preferred in Mr. Johnson for optimal control of asthma?

A. Anticholinergics
 B. Inhaled corticosteroids
 C. Methylxanthines
 D. Mast cell stabilizers
 E. Oral corticosteroids

18. What is an appropriate alternative to Lopressor in Mr. Johnson?

A. An ACE inhibitor
 B. Propranolol 40 mg bid
 C. Clonidine
 D. Hydralazine
 E. Atenolol 200 mg daily

The next two questions relate to Case Study 2.

19. What concerns should the pharmacist have in this situation regarding theophylline?

A. Cirrhosis is well documented to decrease elimination of theophylline
 B. The milligrams per kilogram dose is too low
 C. Mrs. Adams should be on a q12h product
 D. Theophylline SR should be dosed in the morning, not evening
 E. Long-acting inhaled β_2 agonists increase theophylline clearance

Case Study 2: Medication Profile

Patient Name: Mrs. S.T. Adams

Address: 7129 James Ave.

DOB: 1-6-37

Drug Allergies: sulfonamides

Height: 5'3" Weight: 55 kg

Diagnosis: (1) COPD—53 pack-year Hx smoking
(quit 2 years ago)
(2) cirrhosis

Medications:

Date	Rx #	MD	Drug	Quantity	Sig	Refills
			& Strength			
2/18	84389	Jones	Serevent Diskus	1	1 bid	6
2/18	84390	Jones	albuterol MDI	1	2 puffs q4h prn	6
2/18	84391	Jones	Atrovent MDI	1	2 puffs q6h	6
2/18	84392	Jones	Uniphyl 600 mg	30	1 qd 6 PM	2

Pharmacist Notes: 2/18—discussed proper use of Diskus and observed patient use; taught Mrs. Adams to inhale deeply and rapidly (she was inhaling slowly for only <2 seconds). Also observed use of MDI (she forgot to exhale gently before pressing down on MDI).

- 20.** The patient has a friend who has COPD and has told her about Spiriva. Mrs. Adams wants to know the opinion of the pharmacist. You would say:
- I'll call your doctor and suggest a new prescription for Spiriva
 - Spiriva is a third-line drug for COPD; I would not use it now
 - Spiriva is a good drug, but I want to talk to your doctor about starting a medicine called Flovent
 - Since you have a prescription for Atrovent, I will call your doctor and suggest changing from Atrovent to Spiriva
 - I think Foradil Aerolizer would be better for you
- 21.** Which drug is best for long-term management of mild persistent asthma?
- Cromolyn
 - Montelukast
 - Nedocromil
 - Theophylline
 - Budesonide
- 22.** Which total daily dose of prednisone is best for home management of an acute exacerbation of asthma in a 60-kg adult?
- 5 mg
 - 60 mg
 - 10 mg
 - 20 mg
 - 7.5 mg
- 23.** Which drug is most likely to cause an asthma exacerbation in a patient sensitive to aspirin?
- Ibuprofen
 - Acetaminophen
 - Celecoxib
 - Salsalate
 - Sodium salicylate
- 24.** Which type of inhaler does not work well in very cold temperatures?
- Diskus
 - Turbuhaler
 - Aerolizer
 - MDI
 - Rotahaler

Answers

1. **C.** Although asthma certainly does have a bronchospastic component, it is primarily due to inflammation, so good control of inflammation dramatically reduces bronchospasm. A good indicator of disease control is the rare need for short-acting inhaled β_2 agonists.
2. **A.** Peak flow meters are inexpensive and relatively easy to use. Good measurement of peak expiratory flow (PEF) requires appropriate technique, and if good technique is used, patients have valuable objective evidence of asthma control (or exacerbation).
3. **D.** Dry powder inhalers currently available require rapid inhalation. MDIs require slow inhalation to minimize impaction of aerosol in the mouth and throat.
4. **E.** Ten seconds is best; there is no need to hold longer. Four to five seconds is okay if 10 seconds is uncomfortable.
5. **C.** The yellow zone is 50-79%, which indicates suboptimal control (the red zone is <50%, which indicates to start the crisis action plan and seek medical attention).
6. **A.** Foradil (formoterol) and Serevent (salmeterol).
7. **E.** Hepatitis and decompensated heart failure both can dramatically reduce theophylline clearance.
8. **D.** (A. budesonide + formoterol **or** B. fluticasone + salmeterol). See Figures 2 and 3.
9. **D.** Atrovent is also a quick-relief agent, but it is not as efficacious in asthma and has a slower onset than albuterol and other short-acting inhaled β_2 agonists.
10. **E.** Prednisone or other systemic corticosteroids (eg, methylprednisolone) are well documented to be efficacious in asthma and acute exacerbations of COPD.
11. **A.** Clarithromycin is documented to increase serum concentrations. Hydrochlorothiazide does not affect serum theophylline concentrations and the remaining choices are all documented to decrease serum theophylline concentrations.
12. **D.** Oropharyngeal candidiasis or thrush is correct. The other side effects are not reduced by spacers.
13. **A.** The currently accepted range for asthma is 5-15 mcg/mL (**NOT** the old range of 10-20 mcg/mL). There is no benefit in exceeding 15 mcg/mL, and many patients receive benefit at lower doses.
14. **B.** Since asthma is a disease of circadian rhythm and is worse between 2 AM and 6 AM, it is best to give this once-daily drug at bedtime.
15. **B.** GERD can worsen asthma if it is not properly treated. The exact mechanisms are debated, but there is excellent documentation that asthma improves if this condition is well managed.
16. **D.** This class of drugs should **NOT** be used routinely in COPD patients with mild disease. In moderate disease, inhaled corticosteroids are only indicated if there are frequent exacerbations. Remember: In asthma, inhaled corticosteroids are the best agents for long-term control, but in COPD their role is limited.
17. **B.** Inhaled corticosteroids is correct (see Figures 2 and 3 for treatment choices). The pharmacist should share the NIH Guidelines with Mr. Johnson's prescriber to help ensure optimal care. In addition, the pharmacist should educate the patient regarding the purpose of the meds and proper use of inhalers (eg, should observe the patient using the device).
18. **A.** An ACE inhibitor should be efficacious with few side effects (monitor for cough). β -Blockers should be avoided in Mr. Johnson unless he is post MI or had CHF (in which case use a low dose of a β_1 -selective blocker and monitor carefully).
19. **A.** Cirrhosis is well documented to decrease elimination of theophylline. Ensure a check of a steady-state theophylline level (peak) and anticipate dose reduction (usually 50% dose reduction in liver disease).
20. **D.** Since the patient has prescriptions for Atrovent and Serevent, a logical change here would be to discontinue the short-acting anticholinergic Atrovent, and add the long-acting once-daily anticholinergic tiotropium (Spiriva).

21. **E.** Budesonide is an inhaled corticosteroid, the class of drugs recommended to treat even mild persistent asthma.
22. **B.** Sixty milligrams is an appropriate dose. If it is started as soon as the patient is in the red zone and not responding quickly to short-acting inhaled β_2 agonists, usually only a few days of treatment will be required (usually <1 week).
23. **A.** Ibuprofen has the same mechanism of action as aspirin and will predictably trigger symptoms in an aspirin-sensitive patient (ie, increased production of leukotrienes). COX-2 inhibitors are likely to be safe (rofecoxib was proven safe in one excellent study). Acetaminophen is the choice agent for minor pain in these patients.
24. **D.** MDIs release large aerosol particles that do not penetrate deeply into the lungs in cold temperatures. Dry powder inhalers are okay.

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Asthma

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29. Infectious Disease

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Contents

1. General Principles of Infectious Disease
2. Common Bacterial, Fungal and Viral Infections
3. Key Points
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1. General Principles of Infectious Disease

Note: Several infectious disease topics are addressed in other chapters of this review. They are: HIV/AIDS in Chapter 31, common colds in Chapter 27, and otitis media in Chapter 33. For additional information about specific anti-infective agents, please see Chapter 30.

Diagnosis

- Diagnosis of most infectious diseases consists of: (1) isolation and identification of microorganisms; (2) assessment of patient signs and symptoms; and (3) analysis of other laboratory data.

Isolation of organisms

- To identify the causative agent of the disease, samples should be taken from appropriate body sites prior to the initiation of anti-infective therapy. Higher predictive value comes from organisms isolated from normally sterile body sites (blood, urine, and spinal fluid), than from normally bacteriologically colonized areas such as skin or fecal material.

Identification of organisms

- Organisms should be Gram stained as soon as it is practical to determine cell morphology and guide empiric therapy. After the species of organism is determined, standardized concentrations of antibiotics are exposed to the isolated organism to determine what concentrations inhibit growth. The lowest concentration that prevents microbial growth after 18-24 hours is called the minimum inhibitory concentration (MIC). Breakpoint concentrations of antibiotics are defined as susceptible, intermediate, or resistant. These concentrations are determined by considering tissue concentrations with normal dosing and population distribution of the organism and determine if the antibiotic can be used for therapy.
- Physical signs and symptoms of infection such as fever, redness, swelling, pain, and cough must be considered both for initial diagnosis and assessment of antibiotic effectiveness.

Laboratory tests

- White blood cell (WBC) count. In the initial stage of infection, the neutrophil count may increase above normal, and immature neutrophil forms (bands) may appear.
- Inflammatory markers such as C-reactive protein, erythrocyte sedimentation rate, and tumor necrosis factor may increase during infection.

- Laboratory tests may not be reliable in patients who are elderly, malnourished, neonatal, or severely infected.

Treatment Strategies

- Anti-infective agents should only be used when a significant infection has been diagnosed, is strongly suspected, or where indication for prophylactic therapy exists.

Prophylactic therapy

- Anti-infective therapy is directed to prevent infection. Common uses of prophylactic therapy are after exposure to infection, such as tuberculosis, or before surgical intervention in areas of high bacterial inoculum, such as bowel surgery.
- **Empiric therapy**, usually broad-spectrum in nature, is therapy that is directed toward all common pathogens associated with a disease state.
- **Culture-guided therapy** is characterized by a narrower spectrum than empiric therapy; therapy covers only the specific organism isolated that is sensitive to the therapy. This approach is preferred due to increased cost-effectiveness and decreased bacterial resistance from unnecessary antibiotic exposure.

Choice of Anti-Infective Agent

- The clinician must answer several questions to determine optimal anti-infective therapy, or to review the appropriateness of other decisions. These include:
 - * Is an antibiotic indicated on the basis of the clinical findings?
 - * Have appropriate specimens been obtained, examined, and sent for culture?
 - * What organisms are most likely to be causing the infection?
 - * If several antibiotics are available to treat this likely or known organism, which agent is best for the patient? Patient allergies and concurrent disease states will be of consideration.
 - * Is an antibiotic combination appropriate? A combination of drugs should be given only when clinical experience has shown such therapy to be more effective than single-agent therapy in a particular setting. Such multiple-agent regimens can increase the risk of toxic drug effects, and occasionally may result in drug antagonism and loss of effectiveness. However, some combinations of anti-infective agents have demonstrated increased effectiveness that is greater than their individual effectiveness combined, a phenomenon known as **synergy**. An example of this is the combination of aminoglycosides with cell wall inhibitors

such as penicillin in many gram-positive organisms.

- * What is the best route of administration? This will depend on the overall plan for the patient. Oral therapy is preferred for outpatient therapy, and many intravenous anti-infectives have oral forms with similar pharmacokinetic profiles.
- * What is the appropriate dose and dose interval? Regimen design should take into account patient size, renal/hepatic function, the disease state to be treated, and pharmacodynamic considerations of the agents used.
- * Will initial therapy need modification after culture data are returned?
- * What is the optimal duration of therapy, and is the development of resistance during prolonged therapy likely to occur?

Lack of Therapeutic Effectiveness

- When anti-infective therapy fails, careful analysis of possible causes should be made prior to changing the regimen. Factors associated with therapeutic failure include: misdiagnosis of the infection, improper drug regimen, inappropriate choice of antibiotic agent, microbial resistance, and situations in which antibiotic therapy may not be effective without additional interventions, such as surgical drainage.

2. Common Bacterial, Fungal, and Viral Infections

Meningitis

- Meningitis is defined as an inflammation of the meninges that is identified by an abnormal number of white blood cells in the cerebrospinal fluid.

Causative agents

- A wide variety of organisms are associated with this disease, including many gram-positives and gram-negatives.

Clinical presentation

- Patients may present with fever, headache, photophobia, neck rigidity, diarrhea, vomiting, and altered mental status. Infants may present with a bulging anterior fontanelle.

Diagnostic criteria

- Analysis of the cerebrospinal fluid may be diagnostic of the infective agent. Bacterial agents are associated with a large increase in WBCs, increased CSF protein, and decreased CSF glucose. Fungal and viral agents exhibit smaller increases in CSF WBCs, smaller increases in CSF protein, and limited decreases in CSF glucose.

Treatment

- Empiric treatment is usually determined by the age of the patient. Due to limited antibiotic penetration by many agents, the highest safe antibiotic doses are generally used. Table 1 summarizes empiric therapy for meningitis.

Endocarditis

- Endocarditis is an infection of the endocardium, the membrane lining the heart chamber and valves.

Causative agents

- Most patients have previous damage to the heart, such as artificial valve placement, prior to infection. The most common organisms are *Streptococcus* and *Staphylococcus* species.

Clinical presentation

- Patients present with low-grade fever, fatigue, and weakness. A diagnostic finding is the presence of splinter hemorrhages and petechiae.

Diagnostic criteria

- There are no specific laboratory tests for this infection; most present with elevated ESR or CRP.

Table 1

Empiric Treatment of Meningitis

Age of patient	Most likely organism(s)	Empiric treatment
Newborn to 1 month	Gram negative enterics (<i>E coli</i>) Group B streptococci <i>Listeria monocytogenes</i>	Ampicillin and aminoglycoside or Cefotaxime or Ceftriaxone
1 month to 4 years	<i>Haemophilus influenzae</i> <i>Neisseria meningitidis</i> <i>Streptococcus pneumoniae</i>	Cefotaxime or ceftriaxone and Vancomycin
5-29 years	<i>Neisseria meningitidis</i> <i>Streptococcus pneumoniae</i> <i>Haemophilus influenzae</i>	Cefotaxime or ceftriaxone and Vancomycin
30-60 years	<i>Streptococcus pneumoniae</i> <i>Neisseria meningitidis</i>	Cefotaxime or ceftriaxone and Vancomycin
>60 years	<i>Streptococcus pneumoniae</i> Gram-negative enterics (<i>E coli</i>) <i>Listeria monocytogenes</i>	Ampicillin and aminoglycoside/vancomycin or Cefotaxime or Ceftriaxone

Visualization of the vegetations on the surface of the heart is often diagnostic of the disease.

Treatment

- According to American Heart Association guidelines, treatment varies by causative organism and the presence of prosthetic devices (which requires longer therapy) (Table 2).

Acute/Chronic Bronchitis

- Bronchitis is an inflammation of the bronchioles, often associated with bronchopneumonia. Chronic bronchitis is largely associated with heavy smoking.

Causative agents

- Viral infections account for half of all cases. *Mycoplasma pneumoniae*, *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Moraxella catarrhalis*, and *Chlamydia pneumoniae* are common bacterial pathogens.

Clinical presentation

- Patients present with a history of acute productive cough, low-grade fever, and a clear chest x-ray.

Diagnostic criteria

- Sputum cultures are usually not useful in diagnosis due to multiple etiologies, and most physicians prescribe from physical findings.

Treatment

- Treatment is controversial for most acute illnesses due to the large percentage of viral cases. Chronic cases are treated, but due to multiple antibiotic treatments, bacterial resistance can easily develop (Table 3).

Pneumonia

- Pneumonia is an inflammation of the lung parenchyma characterized by consolidation of the affected part, filling of the alveolar air spaces with exudates, inflammatory cells, and fibrin. Distribution may be lobar, segmental, or lobular. If associated with bronchitis (see above), it is termed bronchopneumonia.

Causative agents

- Multiple bacterial etiologies are possible, depending on predisposing conditions (Table 4).

Table 2

Therapy for Endocarditis

Organism	Therapy	Duration (wk)
Penicillin-susceptible streptococci	Penicillin G alone or	4
	Penicillin G with gentamicin or	2
	Ceftriaxone alone or	4
	Vancomycin (if allergic to penicillin)	4
Streptococci relatively resistant to penicillin	Penicillin G alone or	4
	Penicillin G with gentamicin or	2
	Vancomycin (if allergic to penicillin)	4
Staphylococcus without prosthetic material (methicillin-sensitive)	Nafcillin or oxacillin	4-6
	(3-5 days of gentamicin may be added)	4-6
	Cefazolin (with or without gentamicin)	4-6
	Vancomycin (if allergic to penicillin)	4-6
Staphylococcus without prosthetic material (methicillin-resistant)	Vancomycin (if allergic to penicillin)	4-6

Clinical presentation

- Typically, the onset of illness is abrupt or subacute, with fever, chills, dyspnea, and productive cough predominating. On physical examination, the patient is tachypneic and tachycardic, frequently with chest wall retractions and grunting respirations. The complete blood count usually reflects a leukocytosis with a predominance of polymorphonuclear cells.

Diagnostic criteria

- Sputum culture may be useful in identification of some pathogens. However, difficulty in obtaining deep sputum cultures, and problems in culturing some organisms (such as *Legionella*) makes positive identification of the organism difficult.

Treatment

- Varies by age groups

Tuberculosis

- Tuberculosis is a communicable infectious disease caused by *Mycobacterium tuberculosis*. It can produce silent, latent infection as well as active infection. Although infection of any tissue or organ with *Mycobacterium tuberculosis* is possible, the usual site of infection is pulmonary.

Clinical presentation

- Tuberculosis can present with generalized symptoms of weight loss, fever, and night sweats with persistent cough productive of sputum. Latent disease is defined by a positive PPD test, in absence of other symptoms.

Diagnostic criteria

- Diagnosis is often made by a combination of chest x-ray, which often shows patchy or nodular infiltrates in the apical areas of the upper lobes or the superior segment of the lower lobes, and positive PPD skin test. Patients with severe HIV disease may not react to the standard PPD skin test. Sputum or lung biopsy may be acid-fast stained to reveal the organism. Due to the extended time period needed to grow the organism, sensitivities to anti-infective agents may take weeks to months to determine.

Treatment

- See Table 5.

Table 3

Treatment for Acute and Chronic Bronchitis

Illness	Treatment (7-10 days usual duration)
Acute (rare; for severe disease only)	Erythromycin, clarithromycin, azithromycin (drugs used for treatment of chronic disease may be used; see below)
Chronic	Amoxicillin, amoxicillin-clavulanate, trimethoprim-sulfamethoxazole (TMP-SMX), erythromycin, clarithromycin, azithromycin, doxycycline, cefuroxime, cefaclor, cefprozil

Table 4

Empiric Treatment for Pneumonia

Age or type	Usual organisms	Empiric treatment(s)
Neonatal	Group B streptococci, <i>Listeria monocytogenes</i> , <i>Escherichia coli</i>	Ampicillin and gentamicin or cefotaxime and gentamicin
1-3 months	<i>Chlamydia trachomatis</i> , <i>Bordetella</i>	Erythromycin, clarithromycin, cefuroxime
3 months to 5 years	<i>Streptococcus pneumoniae</i> , <i>C trachomatis</i>	Clarithromycin, cefuroxime, cefotaxime
5-18 years	<i>Mycoplasma pneumoniae</i> , <i>S pneumoniae</i> , <i>Chlamydia pneumoniae</i>	Clarithromycin, erythromycin, cefuroxime
Adult, community acquired	<i>S pneumoniae</i> , <i>Haemophilus influenzae</i> , <i>Klebsiella pneumoniae</i> , <i>M pneumoniae</i>	Ambulatory: oral macrolide (azithromycin, clarithromycin, erythromycin) or fluoroquinolone (levofloxacin, gatifloxacin or moxifloxacin) Hospitalized: cefotaxime or ceftriaxone with or without macrolide, or fluoroquinolone alone (levofloxacin, gatifloxacin or moxifloxacin)
Adult, hospitalized acquired	<i>K pneumoniae</i> , <i>Enterobacter aerogenes</i> , <i>Serratia</i> spp, <i>Acinetobacter</i> spp, <i>Pseudomonas aeruginosa</i> , <i>Staphylococcus aureus</i>	Aminoglycoside (tobramycin, amikacin or gentamicin) plus one of the following: cefotaxime, ceftriaxone, cefepime, ticarcillin-clavulanic acid, piperacillin-tazobactam, meropenem, or imipenem; vancomycin to be added if MRSA suspected
Adult, aspiration	Mouth anaerobes	Uncomplicated: penicillin G, clindamycin Hospital-acquired: ticarcillin-clavulanic acid, piperacillin-tazobactam

Infectious Diarrhea

- Diarrhea is defined as an increase in frequency and/or liquidity of stool compared with a patient's normal stool.

Causative agents

- Many disease states, drugs, and infectious organisms have been associated with diarrhea.

Clinical presentation

- The patient may present with several of the following symptoms: fever, chills, nausea, vomiting, and abdominal cramping.

Diagnostic criteria

- Etiology is often determined by patient history and physical examination. Due to the nature of the disease, cultures are not often diagnostic, except for determination of carrier states.

Table 5

Treatment of Tuberculosis

Disease stage	Treatment	Duration
Latent (probably isoniazid sensitive)	Isoniazid	9 months (6 months possible except for children and HIV+ persons)
Latent (probably isoniazid resistant)	Rifampin + pyrazinamide	2 months
Active disease	Isoniazid + rifampin + pyrazinamide	2-4 months

Treatment (Table 6)

- Supportive care (hydration, antipyretics, and antiemetics) is useful. Antimotility agents are discouraged due to the potential to cause toxic megacolon. Antibacterial therapy is reserved for severe presentations or patients with risk factors.

Skin and Soft Tissue Infections

- Bacterial infection of the skin can be classified as direct infection of the skin (cellulitis) or secondary infection of a wound or incision.

Causative agents

- Cellulitis is usually infection by a single organism. The most common organisms are *Streptococcus pyogenes* and *Staphylococcus aureus*. Secondary infections may be polymicrobial, including both anaerobic and aerobic organisms.

Clinical presentation

- These infections are characterized by erythema and edema of the skin.

Diagnostic criteria

- Diagnosis is usually made from physical examination. Cultures are not usually diagnostic.

Treatment

- Treatment is empiric, based on likely organisms (Table 7).

Urinary Tract Infections

- Infections of the urinary tract represent a wide variety of clinical syndromes, including urethritis, cystitis, prostatitis, and pyelonephritis.

Causative agents

- The most common agents are gram-negative facultatively anaerobic rods (coliforms). Hospitalized catheterized patients may also acquire *Pseudomonas* and *Staphylococcus* species.

Clinical presentation

- Lower urinary tract infections tend to present with dysuria, urgency, frequency, nocturia, and suprapu-

Table 6**Treatment of Infectious Diarrhea**

Symptoms	Organism	Treatment
Violent presentation 1-6 hours after eating high-protein foods (eggs)	<i>Staphylococcus aureus</i>	Supportive
Indolent presentation with mild fever after eating meat, vegetables, or eggs	<i>Bacillus cereus</i>	Supportive
Mild to severe presentation 8-16 hours after eating canned products	<i>Clostridium perfringens</i>	Supportive
Mild to severe presentation with mild fever; may be associated with meat/egg contamination or contamination of other foods with contaminated water	<i>Escherichia coli</i>	Supportive, if outpatient; if hospitalized, fluoroquinolones or trimethoprim-sulfamethoxazole (TMP-SMX)
Mild to severe presentation with mild fever, chills, and cramping; associated with contamination of other foods with contaminated water; carrier state possible	<i>Salmonella</i> spp	Treatment only if febrile (fluoroquinolones or TMP-SMX)
Bloody mucoid diarrhea with fever and cramps	<i>Shigella</i> spp	TMP-SMX
Mild indolent presentation, often thought to be "flu"; transmitted by contaminated water	<i>Campylobacter</i>	Macrolides or fluoroquinolones
Severe presentation with fever and abdominal pain associated with seafood ingestion	<i>Yersinia enterocolitica</i>	Fluoroquinolones
Mild presentation with fever and abdominal pain associated with seafood ingestion	<i>Vibrio parahaemolyticus</i>	Tetracycline or fluoroquinolones
Severe, explosive presentation associated with contaminated water	<i>Vibrio cholerae</i>	Tetracycline or fluoroquinolones
Mild to severe presentation associated with travel, 6-10 days after exposure, with cramping and low-grade fever	<i>Escherichia coli</i>	Mostly supportive; severe prophylactic regimens

Table 7

Treatment of Infections of the Skin and Soft Tissues

Infection	Organisms	Treatments
Cellulitis	Group A streptococcus; <i>Staphylococcus aureus</i>	Outpatient: dicloxacillin, cefadroxil, cephalixin, erythromycin Inpatient: cefazolin, erythromycin Severe cases: vancomycin
Diabetic foot infections	<i>Proteus</i> spp, <i>Escherichia coli</i> , <i>S aureus</i> , <i>Bacteroides fragilis</i> , anaerobic streptococci	Clindamycin or cephalixin Severe cases: ticarcillin-clavulanic acid or other beta-lactamase inhibitor; vancomycin may be needed if MRSA
Decubitus ulcers	Gram-negative bacilli, <i>Pseudomonas aeruginosa</i> , anaerobes	As for diabetic foot infections, above

bic heaviness or pain. Fever is rare. Upper urinary tract infections tend to present with flank pain and fever.

Diagnostic criteria

- Key to the diagnosis of urinary tract infections is the ability to demonstrate significant numbers of organisms present in an appropriately drawn urine sample. In general, higher numbers of organisms ($>10^5$ cells/mL) are needed to diagnose UTIs in females than males ($>10^3$ cells/mL), due to the fact that more organisms are able to ascend the shorter female urethra. In addition, the presence of WBCs in the urine sample may be a significant clue for infection.

Treatment

- A variety of antibacterials may be useful for the treatment of urinary tract infections (Table 8). These include: fluoroquinolones, cephalosporins, TMP-

SMX, and doxycycline. Fluoroquinolones are especially useful for treatment of prostatitis. Length of therapy varies according to the severity of disease.

Bacterial Venereal Diseases (Gonorrhea and Syphilis)

- Venereal diseases are diseases that can be transmitted via sexual intercourse. This section covers only the major bacterial venereal diseases, gonorrhea and syphilis. Additional viral venereal diseases will be covered in sections below (ie, herpes and hepatitis), or in other chapters (HIV, Chapter 31).

Causative agents

- Syphilis is caused by an infection with the spirochete *Treponema pallidum*, while gonorrhea is caused by the gram-negative coccus *Neisseria gonorrhoeae*.

Table 8

Treatment of Urinary Tract Infections

Diagnosis	Organisms	Treatments
Acute uncomplicated cystitis	<i>E coli</i> , <i>Staphylococcus saprophyticus</i>	TMP-SMX x 3 days or Quinolone x 3 days
Acute pyelonephritis	<i>E coli</i> , <i>Proteus mirabilis</i> , <i>Klebsiella pneumoniae</i> , <i>Enterococcus</i>	Quinolone x 14 days or TMP-SMX x 14 days; if severe, parenteral therapy with quinolone, extended-spectrum penicillin plus aminoglycoside should be used
Prostatitis	<i>E coli</i> , <i>Proteus</i> spp, <i>K pneumoniae</i>	Quinolone x 4-6 weeks or TMP-SMX x 4-6 weeks

Clinical presentation

- Primary syphilis presents as a painless lesion or chancre appearing at the site of infection around 21 days after exposure. These lesions persist for about 8 weeks before spontaneously disappearing.
- Secondary syphilis develops 2-6 weeks after the onset of the primary stage. It is characterized by a variety of rashes and flu-like symptoms. These symptoms disappear without treatment within 4-10 weeks. Untreated patients will develop symptoms of tertiary syphilis within 2-25 years after infection. These include general paresis, nerve deafness, progressive dementia, and aortic insufficiency.
- Gonorrhea, in contrast, presents as a urethritis within 2-3 days of exposure. Dysuria, urinary frequency, and purulent discharge are common. The majority of infected patients become asymptomatic without treatment within 6 months. About 15% of infected women will develop pelvic inflammatory disease, which can be an indirect cause of infertility.

Diagnostic criteria

- Since *T pallidum* cannot be grown in culture, dark-field or indirect fluorescent antibody microscopic examination is used in conjunction with serologic testing for diagnosis. The most common tests are the Venereal Disease Research Laboratory (VDRL) and the rapid plasma reagin (RPR) tests. Gonorrhea is diagnosed by Gram stain and culture of infected secretions. Alternative methods of diagnosis include enzyme immunoassay and DNA probes. Patients should be screened for the presence of other venereal diseases.

Treatment

- Due to the potential of both diseases to cause significant morbidity to infants born to infected mothers, diagnosis and treatment of pregnant women is of concern. The two organisms differ sharply in resist-

ance to anti-infective agents. *Treponema pallidum* is sensitive to penicillin and has not developed any significant resistance. *Neisseria gonorrhoeae* has not only developed significant resistance to penicillin, but fluoroquinolones as well, leaving third-generation cephalosporins as the major treatment modality (Table 9). Patients diagnosed with gonorrhea should also receive therapy against chlamydial infection (usually doxycycline 100 mg bid for 7 days or azithromycin 1 g once). All sexual partners must also be treated.

Sepsis

- Sepsis has been defined by the American College of Chest Physicians as the systemic inflammatory response syndrome (SIRS) produced in response to infection. SIRS has been defined as requiring two of the following criteria: $T > 38^{\circ}\text{C}$ or $< 36^{\circ}\text{C}$; $\text{HR} > 90$ bpm; $\text{RR} > 20$ breaths/min or $\text{PaCO}_2 < 32$ torr; $\text{WBC} > 12,000$ cells/mm³ or < 4000 cells/mm³, or $> 10\%$ immature (band) forms.

Causative agents

- Sepsis may be caused by a variety of organisms, including gram-negative and gram-positive organisms, as well as fungi. Most cases occur in the setting of hospitalized patients and reflect the organisms and resistance pattern of the institution.

Clinical presentation

- In the early phase, the patient may have fever or hypothermia, rigors, chills, tachycardia, tachypnea, hyperglycemia, and lethargy, progressing to hypotension, hypoglycemia, myocardial depression, oliguria, leukopenia, and pulmonary edema leading to multi-system organ failure.

Table 9

Treatment for Syphilis and Gonorrhea

Type	Syphilis	Gonorrhea
Uncomplicated adult presentation	Benzathine penicillin G 2.4 million units IM x 1	Ceftriaxone 125 mg IM x 1 or Spectinomycin 2 g IM q12h x 2
Infant born of untreated mother	Penicillin G 50,000-75,000 U/kg q12h x 10-21 days	Cefotaxime 25 mg/kg q12h x 7 days
Disseminated infections	Secondary/latent disease: benzathine penicillin G 2.4 million units IM q week x 3 Tertiary disease: penicillin G 2-4 million units q4h for 10-14 days	Ceftriaxone 1 g qd x 10 days

Diagnostic criteria

- In addition to physical signs and symptoms, cultures of blood, urine, and sputum may yield clues for antibacterial therapy.

Treatment

- Local organisms and sensitivities will determine anti-infective therapy. Initial therapy should be broad, covering all likely organisms, until culture results are obtained. The *Medical Letter* suggests the following regimens for life-threatening sepsis in adults: cefotaxime, ceftriaxone, cefepime, ticarcillin-clavulanic acid, piperacillin-tazobactam, meropenem, or imipenem with an aminoglycoside (tobramycin, gentamicin, or amikacin). If gram-positive organisms are suspected, vancomycin may be added to the regimen.

**Tick-Borne Systemic Febrile Syndromes
(Lyme Disease, Rocky Mountain Spotted
Fever, Ehrlichiosis, and Tularemia)**

- These diseases are similar in transmission and natural history. The organisms responsible for these infections are *Rickettsia*, known for their intracellular growth in host cells. As such, they cannot be grown in culture media, and serologic tests are used for diagnosis. Patients present with fever, rash, and flu-like symptoms, with a history of tick exposure.

Treatment

- See Table 10.

Systemic Fungal Infections

- Fungal infections fall into two categories: primary, able to cause infection in both healthy and immunocompromised patients; and opportunistic, able to cause infection only in immunocompromised patients. Many fungal infections have a pulmonary focus, due to the aerosol spread of mold spores. Due to increasing use of antibacterial agents and the

increase in immunocompromised patients, the incidence of fungal infection is rising.

Clinical presentation

- Patients present with a gradual onset of general malaise, fever, and weakness, unrelieved by antibacterial therapy. Pulmonary infection presents with pneumonia-like symptoms.

Diagnostic criteria

- Diagnosis is made from patient history, cultures (usually blood, sputum, and biopsy of lesions), and serologic tests.

Treatment

- Treatment is often empiric until the organism is isolated (Table 11). Due to the relatively slow culture of most fungi, and the lack of commercial testing against antifungal agents, patient response is used to determine resistance to therapy.

Viral Infections
**(Hepatitis, Influenza, and the Herpes
Simplex Family)**

Note: Antiviral therapy is not curative, but decreases the level of virus so that a patient's immune system can handle the infection.

Hepatitis

- Hepatitis is a general term referring to a generalized inflammation of the liver. Etiologies may be viral or chemical.

Causative agents

- Five viruses (hepatitis types A through E) have been identified as causative agents for hepatitis. Syndromes may be either acute or chronic.

Clinical presentation

- Patients present with a history of anorexia, nausea, fatigue, and malaise. This usually progresses to

Table 10**Treatment of Tick-Borne Diseases**

Disease	Causative agent	Primary treatment	Alternative treatment
Lyme disease	<i>Borrelia burgdorferi</i>	Doxycycline	Cefuroxime
Rocky Mountain spotted fever	<i>Rickettsia rickettsii</i>	Doxycycline	Chloramphenicol
Ehrlichiosis	<i>Ehrlichia phagocytophila</i>	Doxycycline	Tetracycline
Tularemia	<i>Francisella tularensis</i>	Gentamicin or tobramycin	Chloramphenicol; possibly ciprofloxacin

Table 11

Treatment of Systemic Fungal Infections

Disease	Organism	Treatment(s)
Invasive pulmonary disease	<i>Aspergillus</i> spp	Amphotericin B, itraconazole, caspofungin, voriconazole
Cutaneous, pulmonary or extrapulmonary	<i>Blastomyces dermatitidis</i>	Itraconazole, amphotericin B, fluconazole
Bloodstream infection	<i>Candida albicans</i>	Fluconazole, amphotericin B
Primary pulmonary disease	<i>Coccidioides immitis</i>	Itraconazole, fluconazole
Meningitis	<i>Cryptococcus neoformans</i>	Amphotericin B + flucytosine, fluconazole
Pulmonary, disseminated, or localized	<i>Histoplasma capsulatum</i>	Itraconazole (moderate disease); amphotericin B (severe disease)

fever, right upper quadrant pain, dark urine, light colored stools, and worsening of systemic symptoms. Some patients have no symptoms and little hepatic damage.

Diagnostic criteria

- In addition to physical signs, laboratory tests are remarkable for elevations in AST, ALT, and serum bilirubin.

Treatment

- Treatment is dependent upon the viral strain and type of presentation (Table 12). Standard therapies have not been established for hepatitis A, D, or E.

Influenza

- Influenza is an acute respiratory viral infection.

Causative agents

- Three viruses, influenza A, B, and C, are responsible for most infections.

Clinical presentation

- Patients present with sudden onset of chills, fever, severe prostration, headache, muscle aches, and a cough that usually is dry and may be followed by secondary bacterial infections.

Diagnostic criteria

- Diagnosis is from patient physical signs and symptoms.

Therapy

- Therapy may be either prophylactic or treatment and is determined by viral strain in the community (Table 13). Currently, no therapies exist for influenza C infections.

Herpes simplex family (herpes, cytomegalovirus [CMV], chickenpox/shingles)

- The herpes simplex family is responsible for three serious viral infections: herpes genital infections, cytomegalovirus infections in the immunocompromised, and varicella-zoster infections (chickenpox/shingles).

Table 12

Treatment for Hepatitis

Organism	Presentation	Therapy
Hepatitis B	Chronic	Lamivudine + interferon alfa-2b
Hepatitis C	Chronic	Interferon alfa-2b + ribavirin
Hepatitis C	Acute	Interferon alfa-2b

Table 13

Treatment for Influenza

Organism	Treatment type	Therapy
Influenza A	Prophylaxis	Oseltamivir, rimantadine, amantadine
Influenza A	Treatment	Zanamivir, oseltamivir, rimantadine, amantadine
Influenza B	Prophylaxis	Oseltamivir
Influenza B	Prophylaxis	Zanamivir, oseltamivir

Causative agents

- Each disease is caused by a slightly different herpes virus.

Clinical presentation

- Varies by disease:
 - * Genital herpes presents with flu-like symptoms of fever, headache, malaise, and myalgias, in addition to development of painful pustular or ulcerative lesions on the external genitalia.
 - * CMV usually presents as retinitis, colitis, or esophagitis.
 - * Varicella zoster presents with flu-like symptoms with a pustular rash located on body dermatomes.

Diagnostic criteria

- Mostly from signs and symptoms, although tissue samples may be examined for the presence of the virus by immunofluorescence.

Treatment

- Depends upon viral and disease state; treatment is summarized in Table 14.

3. Key Points

- The hallmark of initial anti-infective therapy is to target the specific organisms associated with the disease.
- Conversely, after the identification of the organism causing the disease, anti-infective therapy should be narrowed to cover that specific organism.
- Therapy should reflect not only the best anti-infective agent for the organism, but also should reflect aspects of the patient's condition (eg, renal function and concurrent disease states).
- Combination anti-infective therapy should be reserved for documented clinical efficacy, therapeutic failure of monotherapy, and polymicrobial infection.
- Clinical signs of infection should be followed to determine patient response to therapy.
- Empiric therapy of meningitis is age-specific, reflecting the age-specific nature of the common pathogens.
- Endocarditis therapy is specific to the organism isolated. The presence of a prosthetic valve increases the time of therapy.
- Many cases of bronchitis are viral in etiology, making routine antibiotic therapy controversial.
- Empiric pneumonia therapy reflects both coverage of age-related organisms and organisms associated with patient-specific risk factors.
- Diarrhea therapy should be mainly supportive, with careful use of anti-infectives and antimotility agents.
- Diagnosis of urinary tract infections varies by numbers of organisms found in the urine. Higher numbers ($>10^5$ cells/mL) are needed to diagnose UTIs in females than are needed in males ($>10^3$ cells/mL), due to the higher numbers of organisms able to ascend the shorter female urethra.

Table 14**Treatment of Herpes Virus Infections**

Organism	Disease	Treatment
Herpes simplex	Initial episode	Acyclovir
	Reoccurrence	Famciclovir
	Chronic suppression	Valacyclovir
	Immunocompromised	Acyclovir
	Resistant to acyclovir	Foscarnet
Cytomegalovirus	Retinitis, colitis, esophagitis	Ganciclovir, valganciclovir, foscarnet, cidofovir, fomivirsen
Varicella zoster	Chickenpox, shingles	Acyclovir
Varicella zoster	Immunocompromised, resistant to acyclovir	Foscarnet

- A frequently overlooked aspect of treatment of bacterial venereal disease is treatment of sexual partners.
- Initial therapy of sepsis should be broad in scope, covering all likely organisms, until results of cultures are obtained.
- Due to the long doubling time of most fungi, and the difficulty in obtaining sensitivity to specific antifungal agents, patient response is used to determine resistance to therapy.
- Antiviral therapy is not curative, but decreases the level of virus so that a patient's immune system can handle the infection.

4. Questions and Answers

- The lowest concentration of anti-infective that prevents microbial growth is called the
 - minimum bactericidal concentration
 - minimum bacteriostatic concentration
 - minimum inhibitory concentration
 - minimum inhibiting concentration
 - minimum Schillings concentration
- Laboratory markers of infections, such as C-reactive protein, white blood cell count, and erythrocyte sedimentation rate may not be accurate in which patient populations?
 - Elderly patients
 - Patients with chronic obstructive pulmonary disease
 - Malnourished patients
 - I only
 - II only
 - I and III only
 - II and III only
 - I, II, and III
- The hallmark of empiric therapy is
 - coverage of the most common pathogen associated with the infection
 - coverage of the common pathogens associated with the infection
 - coverage of all possible pathogens associated with the infection
 - coverage of polymicrobial pathogens associated with the infection
 - coverage of all viral organisms associated with the infection
- When two anti-infective therapies together produce a greater effect than the effects of each added together, this is termed
 - commensalism
 - synergy
 - antagonism
 - additive
 - interacting
- Analysis of the cerebrospinal fluid may give valuable clues to the identity of the pathogen in meningitis. Given the following results, what would be indicative of a fungal infection?
 - Gram stain shows many Gram-negative bacilli
 - Gram stain shows many Gram-positive cocci
 - Gram stain shows many Gram-negative cocci
 - Gram stain shows many Gram-positive bacilli
 - Gram stain shows many Gram-negative bacilli and Gram-positive cocci

- I. Increase in WBCs
 - II. Decreased glucose
 - III. Increased protein
- A. I only
 - B. II only
 - C. I and III only
 - D. II and III only
 - E. I, II, and III
6. Empiric therapy for meningitis for patients up to 1 month of age includes
 - A. vancomycin and ampicillin
 - B. aminoglycoside and ampicillin
 - C. ceftriaxone and vancomycin
 - D. vancomycin and aminoglycoside
 - E. ampicillin and ceftriaxone
 7. When treating penicillin-allergic patients for endocarditis, _____ may be used for therapy.
 - A. vancomycin
 - B. erythromycin
 - C. cefazolin
 - D. meropenem
 - E. nafcillin
 8. Patients presenting with acute bronchitis without risk factors should be treated empirically with
 - A. supportive care
 - B. clarithromycin
 - C. cefuroxime
 - D. ciprofloxacin
 - E. erythromycin
 9. The most common organism(s) associated with community-acquired pneumonia in adults are
 - A. *Chlamydia pneumoniae*, *Mycoplasma pneumoniae*, *Haemophilus influenzae*
 - B. *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Chlamydia pneumoniae*
 - C. *Mycoplasma pneumoniae*, *Chlamydia pneumoniae*, *Streptococcus pneumoniae*
 - D. *Mycoplasma pneumoniae*, *Streptococcus pneumoniae*, *Haemophilus influenzae*
 - E. *Chlamydia pneumoniae*, *Staphylococcus aureus*, *Haemophilus influenzae*
 10. Empiric therapy for patients with hospital-acquired pneumonia should include
 - A. tobramycin and gentamicin
 - B. cefotaxime and cefepime
 - C. vancomycin and gentamicin
 - D. gentamicin and cefepime
 - E. cefepime and vancomycin
 11. Treatment of latent tuberculosis infections where isoniazid-resistant strains of *Mycobacterium tuberculosis* are predominant should include
 - A. rifabutin and pyrazinamide
 - B. rifampin and pyrazinamide
 - C. isoniazid, rifampin, and pyrazinamide
 - D. isoniazid, rifabutin, and pyrazinamide
 - E. ethambutol and rifampin
 12. The use of antimotility agents in infectious diarrhea is
 - A. discouraged, due to the potential to cause toxic megacolon
 - B. encouraged, due to increased cure rates
 - C. discouraged, due to increased reinfections
 - D. encouraged, due to decreased reinfections
 - E. discouraged, due to lack of efficacy
 13. Cellulitis is usually associated with
 - A. *Staphylococcus aureus*
 - B. *Streptococcus bovis*
 - C. *Peptostreptococcus boydii*
 - D. *Escherichia coli*
 - E. *Klebsiella pneumoniae*
 14. The best empiric regimen to treat prostate infection is
 - A. ciprofloxacin for 10 days
 - B. TMP-SMX for 10 days
 - C. ciprofloxacin and TMP-SMX for 10 days
 - D. ciprofloxacin for 4-6 weeks
 - E. TMP-SMX for 4-6 weeks
 15. Tertiary syphilis in adults should be treated with
 - A. benzathine penicillin 2.4 million units x 1
 - B. penicillin 50,000 U/kg q12h x 10-21 days
 - C. penicillin 4 million units q4h x 10-14 days
 - D. benzathine penicillin 2.4 million units q week x 3
 - E. penicillin 150,000 U/kg q12h x 10-21 days
 16. *Candida albicans* infections may be treated with
 - A. itraconazole
 - B. amphotericin B

- C. voriconazole
D. caspofungin
E. ketoconazole
17. The antiviral agent with the widest spectrum of activity against influenza is
A. zanamivir
B. rimantadine
C. amantadine
D. oseltamivir
E. amantadine
18. Herpes infections resistant to acyclovir may be treated with
A. famciclovir
B. valacyclovir
C. foscarnet
D. ganciclovir
E. high-dose acyclovir
19. The only organism below that can be easily cultured is
A. *Treponema pallidum*
B. *Mycobacterium tuberculosis*
C. *Rickettsia rickettsii*
D. *Ehrlichia phagocytophila*
E. *Francisella tularensis*
20. Anti-infective therapy should always be used with infectious diarrhea caused by which organism?
A. *Escherichia coli*
B. *Vibrio cholerae*
C. *Staphylococcus aureus*
D. *Salmonella*
E. *Bacillus cereus*
21. J.B. is an 18-year-old white female who just gave birth to her first child. Since she presented without any prenatal care or history, a full prenatal panel of tests including a vaginal swab was taken. Two days after birth, she complained of a purulent vaginal discharge and low-grade fever. Blood cultures were negative, but the vaginal swab revealed the presence of gram-negative cocci. WBCs are elevated at 13,000 cells/mm³. What is the probable infection that J.B. has?
A. Herpes simplex
B. Gonorrhea
C. Syphilis
D. Urinary tract infection
E. Food poisoning
22. What should be done for J.B. and her baby?
A. Both mother and child should be treated
B. Neither mother nor child should be treated
C. The child should be treated, but the mother should not
D. The mother should be treated, but the child should not
E. Mother, child, and partner should be treated
23. L.B. is a 45-year-old white female presenting to the emergency department with a fever of 103°F, flank pain, dysuria, urgency, and frequency. Her laboratory tests are significant for an increased WBC of 18,000 cells/mm³ and 3% immature forms (bands). Her urinalysis revealed >105 cells/mL of gram-negative rods. What does L.B. have?
A. Herpes simplex
B. Gonorrhea
C. Syphilis
D. Urinary tract infection
E. Food poisoning
24. What therapy would be useful for L.B.?
A. Oral quinolone
B. IV quinolone
C. Oral penicillin
D. IV carbapenem
E. IV vancomycin

Answers

1. C. The minimum inhibitory concentration determines the level of anti-infective to which dosing regimens may be set.
2. C. Each of these groups of patients may not be able to respond with appropriate laboratory markers of infections, due to limited reserves or deletion of inflammatory factors.
3. B. Coverage of common pathogens associated with the infection increases the probability of curing the infection without increasing anti-infective exposure to other organisms, which increases the possibility of resistance.
4. B.

5. E. Although fungal CNS infections show relatively slight changes in WBCs, protein, and glucose compared to bacterial infections, the trend is similar.
6. B. This regimen covers the most likely organism(s) for meningitis in this age group: gram-negative enterics, such as *E coli*, group B streptococci, and *Listeria monocytogenes*.
7. A. Vancomycin covers all gram-positive organisms associated with endocarditis, with no cross-sensitivity to penicillin.
8. A. Since half of bronchitis infections are caused by a viral etiology, antibacterial therapy for low-risk patients should not be attempted, with the exception of severe presentation.
9. D. *Chlamydia pneumoniae* is not a pathogen associated with adult pneumonia.
10. D. Empiric therapy for hospital-acquired pneumonia should have an aminoglycoside and one other gram-negative agent, such as cefepime. Vancomycin can be added if MRSA is suspected.
11. B. Latent infections are usually treated with isoniazid alone. In the case of isoniazid-resistant TB, rifampin and pyrazinamide are effective at treating latent infections. The three-drug regimens are used to treat active disease.
12. A. Use of such agents increases the chance of intestinal perforation and increases the length of symptoms.
13. A. Most cellulitis infections are associated with *Staphylococcus aureus* and *Streptococcus pyogenes*.
14. D. Prostate infections are difficult to treat, requiring 4-6 weeks of therapy. Although TMP-SMX is a reasonable choice to treat most prostate infections, ciprofloxacin is preferred due to its ability to concentrate in prostatic fluid.
15. C. Due to the organism load of tertiary syphilis, high doses of penicillin G are needed for clinical cure. B and E are congenital syphilis doses for neonates.
16. B. Voriconazole and caspofungin have activity against *Candida*, but have not yet been tested in a variety of settings. Ketoconazole and itraconazole should not be used for serious *Candida* infections. Amphotericin B and fluconazole are currently recommended for *Candida*.
17. D. Oseltamivir may be used for either treatment or prophylaxis against both influenza A and B.
18. C. Foscarnet has activity against acyclovir-resistant herpes.
19. B. *Mycobacterium tuberculosis*, although very slow growing, can be grown on culture media. The remaining organisms cannot be grown without use of cell culture techniques, forcing the clinician to rely on serum testing and direct staining for identification of the organism.
20. B. *Staphylococcus* and *Bacillus* diarrhea is an intoxication, not caused by a living organism. Both *Salmonella* and *E coli* diarrheas should not be treated unless severe, or signs of systemic infection are present. *Vibrio cholerae* causes a severe diarrhea requiring anti-infective treatment.
21. B. Given the lack of prenatal care, physical signs and symptoms, and presence of gram-negative cocci, J.B. most likely has gonorrhea.
22. E. Mother, partner, and child should be treated. J.B. and her partner should receive ceftriaxone 125 mg IM x 1 and treatment for concurrent chlamydial infection (doxycycline 100 mg bid x 7 days). The child should receive cefotaxime 25 mg/kg q12h x 7 days. Both mother and child should be screened for additional sexually transmitted diseases.
23. D. Given the clinical presentation and laboratory test results, L.B. has a severe urinary tract infection. The presence of systemic symptoms (fever and chills) suggests an upper urinary tract infection or pyelonephritis.
24. B. Given the severity of disease, parenteral therapy would be reasonable for initial therapy. Since the Gram stain of the urine revealed gram-negative rods, either a quinolone or extended-spectrum penicillin in combination with an aminoglycoside would be reasonable empiric therapy until the organism was identified and sensitivities obtained.

5. References

Many general references will provide basic information concerning anti-infective therapy. A good brief yearly review of antibacterial and antiviral therapies is published by *The Medical Letter* (www.medletter.com). Listed here are recent practice guidelines in areas of infectious disease.

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30. Anti-Infective Agents

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1. Aminoglycosides

Aminoglycosides are antibiotics active against most aerobic gram-negative bacteria and select aerobic gram-positive bacteria, but they are not effective against most anaerobic bacteria. Aminoglycosides are primarily used in serious infections due to their significant toxicity. The most commonly used aminoglycosides include amikacin, kanamycin, gentamicin, neomycin, netilmicin, streptomycin, and tobramycin.

Mechanism of Action

- Aminoglycosides inhibit bacterial protein synthesis through binding to the 30S ribosomal subunit, thereby irreversibly inhibiting bacterial RNA synthesis. Aminoglycosides are bactericidal.

Spectrum of Activity

- Amikacin is a semisynthetic parenteral aminoglycoside with the broadest antimicrobial activity of the class, and it frequently possesses activity against bacteria resistant to other aminoglycosides.
- Kanamycin is a minimally absorbed oral aminoglycoside used to decrease bacterial content of the bowel. Kanamycin has been used for preoperative bowel preparation and as an adjunct in hepatic encephalopathy.
- Gentamicin is a parenteral aminoglycoside that is more active against *Acinetobacter*, *Serratia*, and enterococci than tobramycin.
- Neomycin: see kanamycin.
- Netilmicin is a parenteral aminoglycoside that may be the least ototoxic aminoglycoside.
- Streptomycin is a parenteral aminoglycoside active against enterococci, streptococci, mycobacteria, and some gram-negative anaerobes. Streptomycin is used as an adjunct agent only because many bacterial isolates are resistant to streptomycin monotherapy. Streptomycin should only be administered by IM injection.
- Tobramycin is a parenteral aminoglycoside that is more active against *Pseudomonas* than gentamicin.

Adverse Drug Events

- Nephrotoxicity is demonstrated by an increase in blood urea nitrogen (BUN) and serum creatinine. The nephrotoxicity is usually manifest as non-oliguric renal failure and may cause potassium, calcium, and magnesium wasting. Nephrotoxicity may occur in 10-25% of patients receiving aminoglycosides and is usually reversible upon discontinuation of the agent. Risk factors include:

- Pre-existing renal dysfunction
- Prolonged duration of therapy
- Concomitant use of other nephrotoxic agents
- Possibly elevated trough concentrations:
 - Gentamicin and tobramycin >2 mcg/mL
 - Amikacin >8 mcg/mL
- Neuromuscular blockade is an uncommon but potentially serious toxicity. Risk factors include:
 - Concomitant use of neuromuscular blocking agents
 - Myasthenia gravis
 - Hypocalcemia
 - Elevated peak serum concentrations
- Ototoxicity is due to eighth cranial nerve damage demonstrated by auditory and vestibular symptoms. Auditory symptoms include tinnitus and loss of high-frequency hearing. Vestibular toxicity is demonstrated by dizziness, nystagmus, vertigo, and ataxia. The incidence of ototoxicity is not clearly known since profound high-frequency hearing loss can occur prior to detection.

Pharmacokinetics

- Aminoglycosides are renally eliminated.
 - $t_{1/2}$ = 2.5-2.7 hours (normal renal function)
 - $t_{1/2}$ = ~69 hours (anephric clearance)
 - V_d = 0.27-0.3 L/kg (IBW)

Target serum concentrations (traditional dosing; Table 1)

- Amikacin peak = 15-30 mcg/mL
- Amikacin trough = <5 mcg/mL
- Gentamicin and tobramycin peak = 4-10 mcg/mL
- Gentamicin and tobramycin trough = <2 mcg/mL

Extended interval dosing

- Amikacin trough = <3 mcg/mL
- Gentamicin and tobramycin = <1 mcg/mL

Table 1

Aminoglycosides

Generic name	Trade name	Dosage forms	Normal dose	Elimination
Amikacin	Amikin®	IV, IM	15 mg/kg per day	Renal
Gentamicin	Garamycin®	IV, IM	3 mg/kg per day conventional dose, 7 mg/kg per day extended interval	Renal
Kanamycin		IV, PO	15 mg/kg per day	Renal
Neomycin		PO	50-100 mg/kg per day	Renal
Netilmicin		IV, IM	3-6 mg/kg per day	Renal
Streptomycin		IM	15 mg/kg per day	Renal
Tobramycin		IV, IM	3 mg/kg per day conventional dose, 7 mg/kg per day extended interval	Renal

Note: Use ideal body weight for all aminoglycoside dosing.

2. Penicillins**Mechanism of Action**

- Penicillin binding proteins (PBPs) make up the cell wall. When penicillin binds to these PBPs, it is able to inhibit cell wall synthesis in the bacteria, causing cell wall lysis and ultimately cell death.
- Bactericidal (they inhibit bacterial cell wall synthesis).
- They are known as β -lactam antibiotics because their chemical structure consists of a β -lactam ring adjoined to a thiazolidine ring.
- Penicillinase-resistant penicillins: substitutions to the β -lactam ring sterically inhibit penicillinase.

Spectrum of Activity and Dosing

- See Tables 2 and 3.

Adverse Drug Events

- Allergic/hypersensitivity reaction occurs in 3-10% of patients. Rash (4-8%) to anaphylaxis (0.01-0.05%) can occur within 10-20 minutes; IV > PO.
- GI: nausea and vomiting with PO use

- Neurologic reactions (seizures) are seen with high doses of penicillin given to patients with renal insufficiency.
- Hypokalemia, hyponatremia (carboxypenicillins; carbenicillin > ticarcillin)
- Increased transaminases: oxacillin, nafcillin, carbenicillin
- Cholestatic jaundice: ureidopenicillins
- Hematologic reactions (hemolytic anemia)
- Interstitial nephritis

Drug-Drug Interactions

- Probenecid increases blood levels of natural penicillins and may be given with them for this purpose.
- Aminoglycosides: either incompatible or synergistic
- Oral contraceptives: concomitant use may decrease the effectiveness of oral contraceptives and increase incidence of breakthrough bleeding.

Other Characteristics

- Nafcillin and oxacillin: primarily biliary excretion, therefore do not have to adjust for renal dysfunction
- Penicillin G benzathine: repository drug formulation; given IM, insoluble salt allows slow drug absorption from the injection site, and therefore it has a longer duration of action (12-24 h).

Table 2

Spectrum of Activity of the Penicillins

Category	Spectrum
Natural penicillins	Effective against all viridans streptococci, <i>S pyogenes</i> , and 60% of <i>S pneumoniae</i> , mouth anaerobes, and <i>Clostridium perfringens</i> (gas gangrene) Because natural penicillins are readily hydrolyzed by penicillinases (β -lactamases), they are ineffective against <i>S aureus</i> and other organisms that resist penicillin Penicillin G is 5-10 times more active than penicillin V against gram-negative organisms and some anaerobic organisms
Penicillinase-resistant penicillins	Methicillin-sensitive staphylococci, streptococci (not enterococci species)
Aminopenicillins	Greater penetration of outer membrane of gram-negative rods and higher affinity for PBPs Cover most enterococci, <i>Listeria</i> , <i>Proteus mirabilis</i> Cover 60% of <i>Streptococcus pneumoniae</i> , <i>Haemophilus influenzae</i> , <i>Escherichia coli</i> , some <i>Salmonella</i> and <i>Shigella</i>
Carboxypenicillins and ureidopenicillins	Spectrum like ampicillin, but less gram-positive coverage; covers <i>Proteus</i> (including <i>P vulgaris</i>), <i>Klebsiella</i> (not ticarcillin), <i>Enterobacter</i> , <i>Pseudomonas</i> (piperacillin > ticarcillin); add an aminoglycoside for synergy for serious gram-negative infections Ureidopenicillins possess better in vitro activity against <i>Pseudomonas</i> and other gram-negative organisms Ureidopenicillins have in vitro activity against streptococci, enterococci, most Enterobacteriaceae, <i>Pseudomonas</i> , and many anaerobes, including <i>Bacteroides fragilis</i> , <i>Fusobacterium</i> , <i>Clostridium</i> , and peptostreptococci; β -lactamase-producing staphylococci and <i>H influenzae</i> are resistant to the ureidopenicillins
β -Lactamase inhibitors (clavulanic acid, sulbactam, and tazobactam)	Active against some chromosomally produced β -lactamases of <i>S aureus</i> , <i>H influenzae</i> , <i>Moraxella catarrhalis</i> , <i>Bacteroides</i> , <i>E coli</i> , and other Enterobacteriaceae Not active against the chromosomally produced β -lactamases of <i>Enterobacter</i> , <i>Citrobacter</i> , <i>Serratia</i> , and <i>Pseudomonas</i>
Amoxicillin-clavulanic acid	<i>H influenzae</i> , <i>M catarrhalis</i> , <i>Klebsiella pneumoniae</i> , methicillin-sensitive <i>S aureus</i> (MSSA), anaerobes
Ticarcillin-clavulanic acid	More activity against <i>H influenzae</i> , <i>M catarrhalis</i> , <i>Klebsiella pneumoniae</i> , MSSA, anaerobes
Piperacillin-tazobactam	More gram-positive, gram-negative, and anaerobic coverage than ticarcillin-clavulanic acid; monotherapy treatment failures against <i>Pseudomonas</i>

3. Cephalosporins

Cephalosporins are β -lactam antibiotics that are structurally and pharmacologically similar to penicillins.

Mechanism of Action

- Cephalosporins are bactericidal agents. Antimicrobial activity is achieved via inhibition of mucopeptide synthesis in the bacterial cell wall, which results in the formation of defective cell walls and subsequent cell lysis and cell death.

Spectrum of Activity

- Cephalosporins are broad-spectrum antimicrobial agents; however, the spectrum of activity varies greatly among the individual agents. Thus, cephalosporins are grouped into four broad classes, or generations, according to their antimicrobial coverage (Table 4).

Table 3

Dosing of Penicillins

Type and generic name	Trade name	Elimination route	Administration route	Common doses
Natural penicillins				
Penicillin G	Pfizerpen®	Renal	IV, IM, PO	2-4 million units IV q4h
Penicillin G procaine	Wycillin®	Renal	IM	300,000-600,000 U/d
Penicillin G benzathine	Bicillin LA®	Renal	IM	Strep throat: 1.2 million units; syphilis: 2.4 million units
Penicillin V (phenoxymethyl penicillin)	Pen-Vee K®; Veetids®	Renal	PO	250-500 mg PO bid-qid (250 mg bid for prophylaxis)
Penicillinase-resistant penicillins				
Methicillin ¹	Staphcillin®	Renal	IV, IM	1-2 g IV q4-6h
Oxacillin	Prostaphilin®, Bactocill® ¹	Hepatic	PO, IV, IM	1-2 g IV q4-6h
Nafcillin	Nafcil®, Unipen®	Hepatic	IV, IM	1-2 g IV q4-6h
Cloxacillin	Cloxapen®	Renal	PO	200-500 mg q6h
Dicloxacillin	Dynapen®, Dycill®	Renal	PO	250-500 mg PO q6h
Aminopenicillins				
Ampicillin	Omnipen®, Principen®	Renal	PO, IM, IV	1-2 g IV q6h
Amoxicillin	Amoxil®, Trimox®	Renal	PO	250-500 mg PO q8h
Bacampicillin	Spectrobid®	Renal	PO	400-800 mg q12h
Carboxypenicillins				
Carbenicillin	Geopen®	Renal	IM, IV	1-5 g q4-6h
Ticarcillin	Ticar®	Renal	IV, IM	3-4 g IV q4-6h
Ureidopenicillins				
Azlocillin	Azlin®	Renal	IV, IM	2-4 g IV q4-6h
Mezlocillin	Mezlin®	Renal	IV, IM	1-3 g q4-6h
Piperacillin	Pipracil®	Renal	IV, IM	3-4 g IV q4-6h
Penicillin plus β-lactamase inhibitors				
Amoxicillin-clavulanic acid	Augmentin®	Renal	PO	250-500 mg PO tid, 500-875 mg PO bid
Ampicillin-sulbactam	Unasyn®	Renal	IV, IM	1.5 g or 3 g IV q6-8h
Piperacillin-tazobactam	Zosyn®	Renal	IV	3.375 g IV q6h
Ticarcillin-clavulanic acid	Timentin®	Renal	IV	3.1 g IV q4-6h

¹Discontinued in the United States.**First-generation agents (cefadroxil, cefazolin, cephalexin)**

- Gram-positive activity is extensive, including many strains of *Staphylococcus aureus* and *S. epidermidis* in addition to *Streptococcus pyogenes* (group A beta-hemolytic streptococci), *S. agalactiae* (group B strep-

tococci), and *S. pneumoniae*. First-generation agents are inactive against enterococci, methicillin-resistant staphylococci (MRSA/MRSE), and *Listeria monocytogenes*.

Table 4

Cephalosporins

Generic name	Trade name	Dosage forms	Dose	Elimination	Notes
First-generation (more gram-positive than gram-negative activity)					
Cefadroxil	Duricef®, Ultracef®	PO	1-2 g/d	Renal	
Cefazolin	Ancef®, Kefzol	IV	250-1000 mg q8h	Renal	
Cephalexin	Keflex®	PO	250-500 mg q6h	Renal	
Cephapirin	Cefadyl®	IV, IM	500-2000 mg q4-6h	Renal	
Cephadrine	Anspor®, Velosef®	PO, IV	250-500 mg q6h	Renal	
Second-generation (enhanced gram-negative activity vs. first-generation drugs)					
Cefaclor	Ceclor®	PO	250-500 mg q8h	Renal	
Cefmetazole	Zefazone®	IV	2 g q6-12h	Renal	NMTT side-chain
Cefonicid	Monocid®	IV	1-2 g/d	Renal	
Cefotetan	Cefotan®	IV, IM	1-2 g q12h	Renal	Anaerobic activity, NMTT side-chain
Cefoxitin	Mefoxin®	IV	1-2 g q6-8h	Renal	Anaerobic activity
Cefprozil	Cefzil®	PO	250-500 mg q12-24h	Renal	Anaerobic activity
Cefuroxime	Ceftin®, Zinacef®	IV, IM	750-1500 mg q8h	Renal	
Cefamandole	Mandole®	IV	500-1000 mg q4-8h	Renal	NMTT side-chain
Loracarbef	Lorabid®	PO	200 mg q12h	Renal	Anaerobic activity
Third-generation (more gram-negative than gram-positive activity; CSF penetration)					
Cefixime	Suprax®	PO	400 mg/d	Renal	
Cefdinir	Omnicef®	PO	300 mg q12h	Renal	
Cefoperazone	Cefobid®	IV	2-4 g q12h	Hepatic	NMTT side-chain
Cefotaxime	Claforan®	IV	1-2 g q6-8h	Renal	
Cefpodoxime	Vantin®	PO	100-400 mg q12h	Renal	Anaerobic activity
Ceftazidime	Fortaz®, Tazicef®	IV, IM	1-2 g q8-12h	Renal	Antipseudomonal activity
Ceftibuten	Cedax®	PO	400 mg/d	Renal	
Ceftizoxime	Cefizox®	IV	1-2 g q8-12h	Renal	
Ceftriaxone	Rocephin®	IV, IM	1-2 g/d	Renal	
Fourth-generation (gram-positive and gram-negative activity)					
Cefepime	Maxipime®	IV, IM	1-2 g q12h	Renal	Antipseudomonal activity

¹Discontinued in the United States.

- Gram-negative activity is limited, although some strains of *Escherichia coli*, *Klebsiella pneumoniae*, *Proteus mirabilis*, and *Shigella* may display susceptibility. First-generation agents are inactive against *Haemophilus influenzae*, *Pseudomonas*, *Entero-*

bacter, *Citrobacter*, *Serratia*, other *Proteus* spp, and anaerobes such as *Bacteroides fragilis*.

Second-generation agents (cefaclor, cefamandole, cefotetan, cefoxitin, cefprozil, cefuroxime, cefmetazole, loracarbef)

- Gram-positive activity is similar to that of first-generation agents.
- Gram-negative activity of second-generation agents is generally more extensive than that of first-generation agents, including some strains of *Acinetobacter*, *Citrobacter*, *Enterobacter*, *Neisseria*, *Proteus*, and *Serratia*, in addition to *E. coli* and *Klebsiella*. Second-generation agents are active against *Haemophilus influenzae*, and some (cefotetan, cefoxitin, cefamandole) also have anaerobic activity. Second-generation agents are inactive against *Pseudomonas*.

Third-generation agents (cefixime, cefoperazone, cefotaxime, ceftizoxime, ceftriaxone)

- Gram-positive activity is decreased versus first- and second-generation agents.
- Gram-negative activity is extensive, including *Enterobacter*, *Citrobacter*, *Serratia*, *Neisseria*, and *Haemophilus*. Some third-generation agents are active against *Pseudomonas* (ceftazidime, cefoperazone). Anaerobic coverage varies among individual agents.

Fourth-generation (cefepime)

- Gram-positive activity is increased versus third-generation agents. Cefepime is inactive against MRSA, enterococci, and *Listeria*.
- Gram-negative activity is extensive, including enhanced activity against *Pseudomonas* and Enterobacteriaceae that produce inducible β -lactamases.
- The extended spectrum of activity of cefepime is attributed to a more rapid penetration of the outer membrane of gram-negative bacteria. Cefepime is also more resistant to inactivation by β -lactamases.

Adverse Drug Events

- Hypersensitivity: fever, rash, pruritus, urticaria, anaphylaxis, hemolytic anemia
- Gastrointestinal effects: nausea, vomiting, diarrhea
- Nephrotoxicity (rare)
- Seizures: potential risk with high doses in patients with renal impairment
- *Clostridium difficile* colitis
- Bleeding/hypoprothrombinemia (cefoperazone, cefmetazole, cefotetan): this is due to the presence of an N-methylthiotetrazole (NMTT) side chain in the structure of these agents and can be prevented or reversed with administration of vitamin K.
- Blood dyscrasias (rare)

Drug-Drug Interactions

- Disulfiram-like reactions have been reported with ingestion of alcohol during treatment with cephalosporin antibiotics.
- Probenecid competitively inhibits tubular secretion of cephalosporins, resulting in higher serum concentrations.

Drug-Disease Interactions

- All cephalosporins (except cefoperazone) require dosage adjustments in patients with renal insufficiency.

Monitoring Parameters

- Serum concentration monitoring is not necessary.
- Patients should be monitored for clinical response and resolution of infection.

Patient Instructions and Counseling

- Verify that the patient is not allergic to penicillins. Cross-sensitivity with penicillins has been reported in up to 10% of patients receiving cephalosporins. A thorough history should be obtained in any patient with a previous hypersensitivity reaction to any β -lactam antibiotic. In general, cephalosporins should be avoided in these patients.

Other

- Bacterial resistance to cephalosporins may result via production of β -lactamases.

4. Gram-Positive Antibiotics

Linezolid

- Linezolid is a synthetic oxazolidine antibiotic (Table 5).

Mechanism of action

- Linezolid binds to the 23S ribosomal subunit of the 50S RNA subunit which inhibits bacterial translation.

Spectrum of activity

- Linezolid is bacteriostatic against enterococci and staphylococci and bactericidal against streptococci. Linezolid is active against *Enterococcus faecium* isolates, including VRE, while most *E faecalis* isolates are resistant.

Adverse drug effects

- Hematologic effects including myelosuppression (anemia, leukopenia, pancytopenia, and thrombocytopenia) have been reported. Hematologic effects appear to be reversible upon discontinuation of the agent.
- Monoamine oxidase inhibition: linezolid is a weak MAO inhibitor, but caution should be exercised in patients receiving vasopressors.

Quinupristin-Dalfopristin

- Quinupristin-dalfopristin is a semisynthetic streptogramin antibiotic. The combination acts synergistically against gram-positive bacteria.

Mechanism of action

- Quinupristin inhibits late phase protein synthesis, while dalfopristin inhibits early phase protein synthesis through binding to the 50S subunit of bacterial RNA.

Spectrum of activity

- Quinupristin-dalfopristin is bactericidal against staphylococci and streptococci and bacteriostatic against *Enterococcus faecium*, including VRE. Quinupristin-dalfopristin is not active against *E faecalis*.

Adverse drug effects

- Thrombophlebitis and severe injection site reactions are common, and some sources recommend administration via a central venous catheter only.
- Hyperbilirubinemia has been reported in up to 25% of patients receiving the agent.
- Arthralgias and myalgias are common, some requiring discontinuation of the agent.

Vancomycin

- Vancomycin is a glycopeptide antibiotic.

Mechanism of action

- Vancomycin binds to the bacterial cell wall, inhibiting peptidoglycan synthesis. This binding occurs at a site different from that of the penicillins. Vancomycin may also inhibit RNA synthesis.

Spectrum of activity

- Vancomycin is active against most gram-positive bacteria including staphylococci (including MRSA), streptococci, enterococci, *Corynebacterium*, and *Clostridium* (including *C difficile*). Vancomycin is bactericidal against all susceptible isolates except enterococci (bacteriostatic). Vancomycin acts synergistically with aminoglycosides against enterococci.

Adverse drug effects

- Nephrotoxicity is manifested by an increase in serum creatinine and BUN. The incidence of nephrotoxicity is not well described, but appears to be low in the absence of concomitant nephrotoxic agents. Renal dysfunction is normally reversible upon discontinuation of the agent, but may be irreversible.

Table 5

Gram-Positive Antibiotics

Generic name	Trade name	Dosage forms	Dose	Elimination	Notes
Linezolid	Zyvox®	IV, PO	600 mg q12h	Renal	
Quinupristin-dalfopristin	Synercid®	IV	7.5 mg/kg q8h	Hepatic	
Vancomycin	Vancocin®	IV, PO	500 mg q6h or 1 g q12h IV; 125-250 mg PO q6h	Renal	Adjust dose per serum concentrations

- Ototoxicity is induced by eighth cranial nerve damage and has been reported to cause permanent hearing loss. Vancomycin rarely causes vestibular toxicity. The incidence of ototoxicity appears to be low in the absence of concomitant ototoxic agents.
- Thrombophlebitis is common and requires frequent IV site rotation.
- Histamine release or "red-man syndrome" is a reaction most commonly associated with rapid IV infusion. Histamine reactions can be minimized by slow IV infusion, not to exceed 500 mg/30 min.

Monitoring

- Vancomycin trough concentrations should be monitored in patients with pre-existing renal dysfunction or patients with increased serum creatinine or BUN during therapy. Vancomycin peak concentrations are not routinely required, but may be monitored in patients with serious infections, central nervous system infections, or those patients not responding to therapy.

Pharmacokinetics

- Vancomycin is renally eliminated.
 - * $t_{1/2}$ = 6 hours (normal renal function)
 - * $t_{1/2}$ = 7-10 days (anephric patients)
 - * V_d = 0.7 L/kg (TBW)
 - * Peak concentration = 20-40 mcg/mL
 - * Trough concentration = 5-10 mcg/mL

5. Fluoroquinolones

- Quinolones are broad-spectrum antibacterial agents (Table 6).

Mechanism of Action

- Fluoroquinolones are bactericidal agents. The mechanism of action of these agents is not understood entirely, but antimicrobial activity is known to involve inhibition of bacterial DNA topoisomerase and subsequent disruption of bacterial DNA replication.

Spectrum of Activity

- Gram-positive activity includes many strains of staphylococci. Streptococcal activity is variable, and streptococcal resistance to quinolones is increasingly common. Newer fluoroquinolones (sparfloxacin, gatifloxacin, clinafloxacin, moxifloxacin) generally demonstrate superior gram-positive coverage versus older agents (ciprofloxacin, ofloxacin, levofloxacin). Fluoroquinolones have limited enterococcal activity and are inactive against MRSA.
- Gram-negative activity is extensive, including *Escherichia coli*, *Klebsiella*, *Enterobacter*, *Citrobacter*, *Proteus*, *Salmonella*, and *Shigella*, in addition to *Moraxella catarrhalis* and *Haemophilus influenzae*. Activity against *Pseudomonas aeruginosa* and *Stenotrophomonas maltophilia* varies among individual agents.
- Anaerobic coverage is poor.
- Atypical coverage varies among individual agents. All fluoroquinolones are highly active against *Legionella*. Newer agents have more reliable coverage of *Mycoplasma pneumoniae* and *Chlamydia pneumoniae*.

Adverse Drug Events

- GI: nausea, dyspepsia
- CNS: headache, dizziness, insomnia
- CV: QT prolongation (avoid use in patients with pre-existing QT prolongation)
- Endocrine: hypoglycemia or hyperglycemia
- GU: crystalluria (at high doses with alkaline pH)
- Other: arthropathy, tendinitis, photosensitivity
- Rare: rash, urticaria, leukopenia, hepatotoxicity (trovafloxacin)

Table 6

Fluoroquinolones and Nonfluorinated Quinolones

Generic name	Trade name	Dosage forms	Normal dose	Elimination	Notes
Fluoroquinolones					
Ciprofloxacin	Cipro®	IV	400 mg q12h	Renal	Less gram-positive activity, enhanced antipseudomonal activity versus other fluoroquinolones
		PO	500 mg q12h		
Enoxacin	Penetrex®	PO	200-400 mg q12h	Renal	
Gatifloxacin	Tequin®	IV, PO	400 mg q24h	Renal	
Levofloxacin	Levaquin®	IV, PO	500 mg q24h	Renal	
Lomefloxacin	Maxaquin®	PO	400 mg qd	Renal	
Moxifloxacin	Avelox®	PO	400 mg qd	Hepatic	
Norfloxacin	Noroxin®	PO	400 mg bid	Hepatic	
Ofloxacin	Floxin®	PO, IV	100-400 mg/d	Renal	
Sparfloxacin	Zagam®	PO	200 mg q24h	Renal	Enhanced anaerobic activity
Trovafoxacin	Trovan®	IV alatrofloxacin	300 mg q24h	Hepatic/fecal	Gram-negative, gram-positive, atypicals, anaerobes; rarely used due to hepatotoxicity
		PO	200 mg q24h		
Nonfluorinated quinolones					
					No gram-positive activity; effective only in GU and GI tracts
Cinoxacin	Cinoxacin®/Cinobac®	PO	500 mg bid	Renal	
Nalidixic acid	NegGram®	PO	1 g q6h	Renal	

Drug-Drug Interactions

- Ciprofloxacin increases theophylline levels. Concomitant use should be avoided, or theophylline levels should be monitored during treatment. The risk of theophylline toxicity is less with other fluoroquinolones.
- Antacids, sucralfate, and divalent or trivalent cations (Ca, Mg, Fe) significantly decrease the absorption of fluoroquinolones. These agents should not be administered for at least 2 hours after each dose of a fluoroquinolone.
- Fluoroquinolones may enhance the effects of oral anticoagulants. PT and INR should be monitored if concomitant therapy cannot be avoided.
- Agents that increase the QT interval (cisapride, class IA or III antiarrhythmics) increase the risk of torsades de pointes. Concomitant use of fluoroquinolones with these agents should be avoided.

Drug-Disease Interactions

- Dosage adjustments should be made for renally-cleared fluoroquinolones when CrCl is <40 mL/min.

Monitoring Parameters

- Serum concentrations are not monitored.
- The patient should be monitored for clinical response/resolution of infection.

Kinetics

- Quinolones display concentration-dependent activity and have a post-antibiotic effect against most susceptible organisms.
- Fluoroquinolones have a large volume of distribution and achieve high tissue concentrations in the lung, gallbladder, kidney, prostate, and genital tract.

Patient Instructions and Counseling

- Fluoroquinolones should be avoided in children or pregnant or nursing women due to the risk of cartilage erosion in growing bone tissue.
- Do **NOT** take antacids, multivitamins, or other calcium, magnesium, or iron supplements for at least 2 hours after each dose.

6. Macrolides

Mechanism of Action

- Macrolides are bacteriostatic against susceptible organisms (Table 7). The agents bind to the 50S RNA subunit, thereby inhibiting RNA synthesis.
- Ketolides are similar to the macrolides. Telithromycin is a derivative of 14-membered ring macrolides and is the first ketolide antibiotic.

Spectrum of Activity

- Macrolides, or erythromycins, are active principally against gram-positive organisms including penicillin-resistant streptococci. The macrolides are also effective against *Chlamydia*, *Mycoplasma*, *Ureaplasma*, spirochetes, and mycobacteria.
- Telithromycin possesses greater in vitro activity against multidrug-resistant gram-positive organisms and *Haemophilus influenzae* compared to the erythromycins.

Adverse Drug Events

- Gastrointestinal effects: erythromycins stimulate GI motility, leading to abdominal pain and cramping, nausea, vomiting, and diarrhea. Clarithromycin appears to be the least stimulating to the GI tract.
- Local effects: erythromycin lactobionate is reported to cause venous irritation and thrombophlebitis. The agent should be diluted in at least 250 mL and infused over 30-60 minutes to decrease the venous irritation.

- Cardiac effects: QT interval prolongation and torsades de pointes have been rarely reported with erythromycins. Adequate dilution and slow IV infusion appear to decrease this reaction.
- Ototoxicity: erythromycin has been rarely reported to be ototoxic in doses of 4 g/d or more.
- Telithromycin appears comparable to the macrolides.

Table 7

Macrolides and Ketolide

Generic name	Trade name	Dosage forms	Normal dose	Elimination	Notes
Macrolides					
Azithromycin	Zithromax®	PO, IV	250 mg/d	Hepatic	PO dose = IV dose
Clarithromycin	Biaxin®, Biaxin XL®	PO	250 mg bid	Renal	XL = qd dosing
Erythromycin	Various	PO	250-500 mg q6h	Hepatic	Erythromycin base, ethyl succinate, and stearate
		IV	500-1000 mg q6h	Hepatic	Erythromycin lactobionate
Ketolide					
Telithromycin	Ketek®	PO	800 mg/d	Hepatic	Treatment duration: 5 days for bronchitis, 7-10 days for community-acquired pneumonia

7. Tetracyclines

Mechanism of Action

- Bacteriostatic: they inhibit bacterial protein synthesis by reversible binding on the 30S ribosomal subunit and blocking the attachment of transfer RNA to an acceptor site on the messenger RNA ribosomal complex (Table 8).

Spectrum of Activity

- Tetracyclines are the drugs of choice for infections caused by the following organisms:
 - * Respiratory infections: atypical pneumonia (*Mycoplasma pneumoniae*, *Chlamydia pneumoniae*)
 - * Genital infections: *Chlamydia trachomatis*, granuloma inguinale
 - * Systemic infections: relapsing fever (*Borrelia recurrentis*), *Vibrio* (*V cholerae*, *V vulnificus*, and *V parahaemolyticus*)
 - * Other infections: methicillin-resistant *Staphylococcus aureus* and *S epidermidis* (minocycline) when vancomycin or other agents are not considered appropriate; *Pasteurella multocida*, *Mycobacterium marinum*, *Yersinia pestis*, *Helicobacter pylori* (in combination with bismuth subsalicylate and metronidazole or clarithromycin)
 - * Prophylaxis: mefloquine-resistant *Plasmodium falciparum* malaria
- Doxycycline:
 - * *Mycobacterium fortuitum* and *M chelonae*
 - * *Streptococcus pneumoniae*

- *Pseudomonas* and *Proteus* organisms are now resistant to tetracyclines.
- Used in the treatment of *Propionibacterium acnes*

Patient Instructions and Counseling

- Administering the drug with food can minimize GI distress.

Adverse Drug Events

- Photosensitivity reactions (may be less frequent with doxycycline and minocycline)
- Generally contraindicated during pregnancy, breastfeeding, and in children younger than 8 years old because of their association with tooth discoloration and interference with bone growth
- Hepatotoxicity, specifically acute fatty necrosis, may occur in pregnant women and in patients with renal impairment.
- Minocycline use:
 - * Vestibular side effects (dizziness, ataxia, nausea, and vertigo)
 - * Skin and mucous membrane pigmentation
 - * Lupus-like symptoms
- GI intolerance (diarrhea, nausea, anorexia)
- Cross-sensitivity within the tetracycline group is common.
- IV tetracyclines may cause phlebitis.

Drug-Drug and Drug-Disease Interactions

- Milk, antacids, iron supplements, and probably other substances with calcium, magnesium, aluminum, and iron decrease tetracycline GI absorption considerably and should be ingested at least several hours before or after administration of tetracycline.

Table 8

Tetracyclines

Generic name	Trade name	Dosage forms	Common doses	Primary mode of elimination
Demeclocycline	Declomycin®	PO	300-1000 mg/d	Renal
Doxycycline	Vibramycin® and others	PO	100-200 mg q12h	Renal
Methacycline		PO, IV	150 mg q6h to 300 mg q12h	Hepatic
Minocycline	Minocin®	PO, IV	100-200 mg q12h	Hepatic
Oxytetracycline	Terramycin®	PO, IM	250-500 mg q6h, 250-500 mg qid, or 300 mg/d in 1 or 2 divided doses	Renal
Tetracycline	Achromycin V®, Sumycin®, Tetracyn®, and others	PO, IV, IM	1-2 g/d	Renal

- Although doxycycline and minocycline absorption may be less affected by these divalent and trivalent cations, avoiding administration within 1 to 2 hours after ingestion of interfering foods is wise.
- Anticonvulsants (eg, barbiturates, carbamazepine, and phenytoin) induce hepatic microsomal metabolism of tetracyclines and therefore decrease tetracycline serum concentrations.
- If given with cholestyramine or colestipol, may bind tetracycline and reduce GI absorption.
- Oral contraceptive efficacy may be decreased with concurrent use of tetracyclines.
- May potentiate warfarin-induced anticoagulation; therefore monitor PT and INR.
- Demeclocycline antagonizes the action of antidiuretic hormone.

8. Sulfonamides

Sulfonamides are synthetic derivatives of sulfanilamide (Table 9). Sulfonamide utility has decreased over time due to the development of resistance.

Mechanism of Action

- Sulfonamides interfere with bacterial folic acid synthesis by competitively inhibiting p-aminobenzoic acid utilization. Sulfonamides are bacteriostatic.

Spectrum of Activity

Gram-positive bacteria

- Staphylococci (MSSA and MRSA); streptococci (not enterococci); *Bacillus anthracis*; *Clostridium perfringens*; *Nocardia*

Gram-negative bacteria

- *Enterobacter*; *E coli*; *Klebsiella*; *Proteus*; *Salmonella*; *Shigella*

Other organisms

- *Chlamydia trachomatis*; *Toxoplasma gondii*; *Plasmodium*

Adverse Drug Effects

- Hypersensitivity reactions appear to be cross-reactive with other sulfonamides, diuretics (including acetazolamide and thiazides), and sulfonylurea antidiabetic agents.
- Dermatologic reactions include rash, urticaria, and Stevens-Johnson syndrome.

Table 9

Sulfonamides

Generic name	Trade name	Dosage forms	Dose	Elimination	Notes
Sulfadiazine		IV, PO	2-4 g/d	Renal	
Sulfamethizole	Urobiotic®	PO	0.5-1 g q6h	Renal	
Sulfamethoxazole	Septra®	IV, PO	1-3 g/d	Hepatic	Combined with trimethoprim (Septra)
Sulfisoxazole	Gantrisin®	IV, PO	2-8 g/d	Renal	

9. Miscellaneous Antibiotics

Clindamycin

Clindamycin is a semisynthetic antibiotic derived from lincomycin (Table 10).

Mechanism of action

- Clindamycin inhibits the 50S subunit, thereby inhibiting RNA synthesis. Clindamycin is either bacteriostatic or bactericidal depending on the serum concentration of the agent and the MIC of the organism.

Spectrum of activity

- Clindamycin is active against most aerobic gram-positive and most anaerobic gram-negative bacteria. Clindamycin has no activity against aerobic gram-negative bacteria.

Adverse drug effects

- Adverse GI effects occur frequently with all forms of clindamycin, and include nausea, vomiting, diarrhea, abdominal pain, and tenesmus. Clindamycin has induced *C difficile* enterocolitis.
- IV administration can lead to thrombophlebitis, erythema, and pain and swelling at the IV site. IM administration has caused pain, induration, and sterile abscesses.
- Clindamycin has caused transient leukopenia, neutropenia, eosinophilia, thrombocytopenia, and agranulocytosis. These effects are usually reversible upon discontinuation of the drug.

Imipenem-Cilastatin

Imipenem is a semisynthetic carbapenem β -lactam antibiotic. Cilastatin prevents renal metabolism of imipenem by dehydropeptidases.

Mechanism of action

- Imipenem binds to penicillin-binding proteins similarly to β -lactams, thereby inhibiting peptidoglycan synthesis. Imipenem is bactericidal in susceptible isolates. Cilastatin competitively inhibits dehydropeptidase, an enzyme present on the brush border of the proximal renal tubule, which hydrolyzes imipenem. Cilastatin has no antibacterial activity.

Spectrum of activity

- Imipenem is a very broad-spectrum antibiotic with activity against most gram-positive and gram-negative aerobes and anaerobes, as well as activity against some *Mycobacterium* and *Chlamydia* spp.

Adverse drug effects

- GI adverse effects are the most common ADRs reported with imipenem. The effects include nausea, vomiting, diarrhea (including *C difficile* enterocolitis), gastroenteritis, abdominal pain, glossitis, papillary hypertrophy, staining of the teeth, heartburn, pharyngeal pain, and taste abnormalities.
- Eosinophilia, leukopenia, neutropenia, agranulocytosis, hemolytic anemia, and thrombocytopenia have been reported.
- Seizures have been reported in approximately 0.4% of patients receiving imipenem. Risk factors include:
 - * History of seizures or head trauma
 - * High doses
 - * Renal dysfunction

Meropenem

- Similar to imipenem with the following differences:
 - * Decreased CNS toxicity
 - * No hydrolysis by dehydropeptidases

Table 10

Miscellaneous Antibiotics

Generic name	Trade name	Dosage forms	Dose	Elimination	Notes
Clindamycin	Cleocin®	IV, PO	300 mg q6h PO; 600-900 mg q8h IV	Hepatic	PO only for <i>C difficile</i>
Imipenem-cilastatin	Primaxin®	IV, IM	250 mg q6h; 500 mg or 1 g q6h or q8h depending on whether the organism is fully or moderately susceptible	Renal	
Meropenem	Merrem®	IV	500-2000 mg q8h	Renal	

10. Antifungal Agents

Amphotericin B

Amphotericin B is a polyene antifungal agent used in the treatment of potentially life-threatening systemic fungal infections (Table 11).

Mechanism of action

- Amphotericin B binds to ergosterol in the fungal cell wall, leading to increased permeability and cell death. Amphotericin B is fungistatic.

Spectrum of activity

- *Aspergillus*, *Coccidioides*, *Cryptococcus*, *Histoplasma*, *Mucor*
- *Candida*, including *C. albicans*, *C. dubliniensis*, *C. glabrata*, *C. krusei*, *C. parapsilosis*, and *C. tropicalis*; *C. lusitanae* exhibits variable sensitivity

Adverse drug effects

- Infusion reactions: fever, chills, hypotension, rigors, pain, thrombophlebitis, anaphylaxis
- Renal and electrolyte effects: nephrotoxicity is the major dose-limiting toxicity.
 - * Hypokalemia, hypocalcemia, hypomagnesemia
 - * Usually reversible upon discontinuation of the agent
 - * Renal tubular acidosis and nephrocalcinosis are possible.
- Hematologic effects: normocytic, normochromic anemia secondary to decreased erythropoietin production

- Hepatic effects: increased AST, ALT, alkaline phosphatase, bilirubin

Amphotericin B lipid formulations

- Amphotericin B cholesterol sulfate complex (Amphotec®), amphotericin B lipid complex (Abelcet®), and amphotericin B liposomal (AmBisome®) formulations are available for the treatment of severe fungal infections in patients who fail or are intolerant of conventional amphotericin B. The lipid formulations may decrease toxicity ~20-30%.

Caspofungin

Caspofungin is approved for the treatment of aspergillosis in patients refractory to or intolerant of other therapies.

Adverse drug effects

- Hepatic effects: increased AST, ALT
- Sensitivity reactions: histamine-release reactions such as rash, pruritus, and anaphylaxis
- Infusion reactions: fever, thrombophlebitis, nausea, vomiting, myalgias

Fluconazole

Fluconazole is a synthetic triazole antifungal and is fungistatic.

Table 11

Antifungal Agents

Generic name	Trade name	Dosage forms	Normal dose	Elimination	Notes
Amphotericin B	Fungizone®	IV	0.5-1 mg/kg per day	Unknown	Dose should not exceed 1.5 mg/kg/d
Caspofungin	Cancidas®	IV	50 mg/d	Hepatic	
Fluconazole	Diflucan®	IV, PO	100-800 mg/d	Renal	
Flucytosine	Ancobon®	PO	50-150 mg/kg per day	Renal	
Griseofulvin	Fulvicin P/G®	PO	500 mg	Hepatic	
Itraconazole	Sporanox®	IV, PO	200-600 mg/d	Hepatic	
Ketoconazole	Nizoral®	PO, topical	200-400 mg bid	Hepatic	Requires acid environment for dissolution and absorption
Nystatin	Mycostatin®	Topical		Fecal	
Terbinafine	Lamisal®	PO	250 mg/d	Hepatic	Pulse therapy also effective
Voriconazole	Vfend®	IV, PO	200 mg q12h PO; 4-6 mg/kg q12h IV	Renal	

Mechanism of action

- The azole antifungals appear to inhibit fungal cytochrome P450 14- α -demethylase, thereby decreasing ergosterol concentrations in susceptible fungi.

Spectrum of activity

- *Candida krusei*, *C. glabrata*, *C. lusitanae*, and *C. tropicalis* are commonly resistant.

Adverse drug effects

- GI effects: nausea, vomiting, abdominal pain, and diarrhea
- Hepatic effects: cholestasis, increased AST, ALT, and GGTP, hepatic necrosis, and rarely severe hepatic dysfunction
- Hemolytic effects: eosinophilia, anemia, leukopenia, neutropenia, and thrombocytopenia
- Nervous system effects: dizziness, headache, somnolence, coma, and seizures are rare.

Flucytosine**Mechanism of action**

- Flucytosine appears to enter fungal cells, where it is converted to 5-fluorouracil. Flucytosine is either fungistatic or fungicidal depending on the concentration of the agent.

Spectrum of activity

- Active against most strains of *Candida* and *Cryptococcus*

Adverse drug effects

- GI effects: GI hemorrhage, ulcerative colitis due to the antiproliferative effects, anorexia, abdominal pain, nausea, vomiting, and diarrhea
- Hepatic effects: increased AST, ALT, and bilirubin
- Renal effects: increased serum creatinine, BUN, and crystalluria
- Nervous system effects: confusion, hallucinations, psychosis, headache, parkinsonism, paresthesias, peripheral neuropathy, hearing loss, and vertigo
- Sensitivity reactions: erythema, pruritus, urticaria, rash, and toxic epidermal necrolysis

Griseofulvin**Mechanism of action**

- Griseofulvin disrupts the fungal cell's mitotic spindle structure, thereby inhibiting the metaphase of cell division. Griseofulvin is fungistatic.

Spectrum of activity

- *Trichophyton*, *Microsporum*, and *Epidermophyton*

Adverse drug effects

- Nervous system effects: headache, fatigue, dizziness, paresthesias of the hands and feet after prolonged therapy
- GI effects: epigastric pain, nausea, vomiting, flatulence, and diarrhea
- Renal effects: proteinuria and nephrosis
- Sensitivity reactions: rash, urticaria, erythema multiforme, angioedema, serum sickness, photosensitivity, and lupus-like reactions

Itraconazole

Itraconazole is a synthetic triazole antifungal.

Spectrum of activity

- Effective in aspergillosis, blastomycosis, histoplasmosis, oropharyngeal and esophageal candidiasis, sporotrichosis, onychomycosis, coccidioidomycosis, and cryptococcosis

Adverse drug effects

- GI effects: nausea, vomiting, diarrhea, abdominal pain, dyspepsia, dysphagia, flatulence, gastritis, ulcerative stomatitis
- Dermatologic and sensitivity reactions: rash, pruritus, urticaria, angioedema, Stevens-Johnson syndrome
- Nervous system reactions: headache, dizziness, tremor, neuropathy
- Cardiovascular effects: congestive heart failure, peripheral edema, pulmonary edema, prolonged QT interval, ventricular dysrhythmias, and death
- Hepatic effects: increased AST, ALT
- Electrolyte and metabolic effects: hypokalemia, adrenal insufficiency, gynecomastia

Ketoconazole

Ketoconazole is a synthetic imidazole antifungal.

Spectrum of activity

- Blastomycosis, candidiasis, coccidioidomycosis, histoplasmosis, dermatophytosis

Adverse drug effects

- GI effects: nausea, vomiting, abdominal pain, GI bleeding
- Hepatic effects: increased AST, ALT, alkaline phosphatase
- Endocrine and metabolic effects: gynecomastia, decreased cortisol production
- Dermatologic and sensitivity reactions: pruritus, rash, dermatitis, purpura
- Nervous system effects: headache, dizziness, lethargy, photophobia, abnormal dreams

Nystatin

Mechanism of action

- Nystatin binds to fungal sterols. Nystatin is fungistatic.

Spectrum of activity

- Cutaneous and mucocutaneous candidiasis

Adverse drug effects

- Mild nausea and diarrhea

Terbinafine

Terbinafine is a synthetic allylamine antifungal.

Mechanism of action

- Interferes with sterol biosynthesis

Spectrum of activity

- *Trichophyton*, *Microsporum*, *Epidermophyton*, *Aspergillus*, blastomycosis, and yeasts

Adverse drug effects

- Hepatic effects: hepatitis, hepatic failure
- Dermatologic and sensitivity reactions: anaphylactoid reactions, Stevens-Johnson syndrome, and erythema multiforme

Voriconazole

Voriconazole is a synthetic triazole antifungal.

Spectrum of activity

- Aspergillosis

Adverse drug effects

- Hepatic effects: hepatitis, cholestasis, fulminant hepatic failure
- Dermatologic and sensitivity reactions: anaphylactoid reactions, pruritus, rash, Stevens-Johnson syndrome, and photosensitivity

11. Antitubercular Agents

Aminosalicylic Acid

Mechanism of action

- Aminosalicylic acid (PAS; para aminosalicylate) inhibits folic acid synthesis similarly to the sulfonamides and is bacteriostatic (Table 12).

Spectrum of activity

- Aminosalicylic acid is active against *Mycobacterium tuberculosis* only.

Adverse drug events

- Gastrointestinal effects: nausea, vomiting, abdominal pain, diarrhea, and anorexia
- Vitamin and mineral absorption: vitamin B₁₂, folic acid, and iron malabsorption have been rarely reported.
- Hypersensitivity reactions: fever, skin eruptions, joint pain, and leukopenia have been reported.

Capreomycin

Mechanism of action

- The exact mechanism of action of capreomycin is unknown. The agent is bacteriostatic against susceptible isolates.

Spectrum of activity

- Capreomycin is active against the following *Mycobacterium* species: *M. tuberculosis*, *M. bovis*, *M. kansasii*, and *M. avium*.

Adverse drug events

- Renal effects: Nephrotoxicity is exhibited in up to 30% of patients receiving the agent. It is manifest as acute tubular necrosis which is usually reversible upon discontinuation of the agent.
- Ototoxicity: experienced by up to 30% of patients; caused by eighth cranial nerve damage which can produce irreversible hearing loss
- Hepatic effects: elevated liver function tests have been noted when used in conjunction with other hepatotoxins
- Hypersensitivity reactions: fever, urticaria, and skin eruptions have been noted.

Cycloserine

Mechanism of action

- Cycloserine is structurally similar to d-alanine and inhibits cell wall synthesis by competing for incorporation into the bacterial cell wall.

Table 12

Antitubercular Agents

Generic name	Trade name	Dosage forms	Normal dose	Elimination	Notes
Aminosalicilic acid	Paser®	PO	150 mg/kg per day	Renal	Max dose 12 g/d
Capreomycin	Capastat®	IM	15 mg/kg per day	Renal	Max dose 1 g/d
Cycloserine	Seromycin®	PO	15-20 mg/kg per day	Renal	Max dose 1 g/d
Ethambutol	Myambutol®	PO	15-25 mg/kg per day	Hepatic	
Ethionamide	Trecator-SC®	PO	500-1000 mg per day	Hepatic	
Isoniazid	Various	PO	5-10 mg/kg per day	Hepatic	Max dose 300 mg/d
Pyrazinamide	Various	PO	15-30 mg/kg per day	Hepatic	Max dose 2 g/d
Rifampin	Various	PO, IV	10-20 mg/kg per day	Hepatic	Max dose 600 mg/d

Spectrum of activity

- Cycloserine is active against the following *Mycobacterium* species: *M tuberculosis*, *M bovis*, *M avium*, and some *M kansasii* isolates.

Adverse drug events

- CNS effects: headache, vertigo, confusion, psychosis, and seizures

Ethambutol**Mechanism of action**

- Ethambutol appears to inhibit bacterial cellular metabolism and is bacteriostatic.

Spectrum of activity

- Ethambutol is active against the following *Mycobacterium* species: *M tuberculosis*, *M bovis*, and some isolates of *M kansasii* and *M avium*.

Adverse drug events

- Ocular effects: optic neuritis with decreased visual acuity, central and peripheral scotomas, and loss of red-green color discrimination have been noted. These effects are usually reversible upon discontinuation of the agent.

Ethionamide**Mechanism of action**

- Ethionamide appears to inhibit cell wall synthesis by an unidentified mechanism. Ethionamide is bactericidal or bacteriostatic depending on tissue concentrations of the agent.

Spectrum of activity

- Ethionamide is active against the following *Mycobacterium* species: *M tuberculosis*, *M bovis*, *M kansasii*, and some *M avium* isolates.

Adverse drug events

- Hepatic effects: hepatitis is a rare complication.

Isoniazid (INH)**Mechanism of action**

- INH appears to inhibit the bacterial cell wall of susceptible isolates and is therefore active against actively dividing cells only. INH is bacteriocidal or bacteriostatic depending on tissue concentrations of the agent.

Spectrum of activity

- INH is active against the following *Mycobacterium* species: *M tuberculosis*, *M bovis*, and some strains of *M kansasii*.

Adverse drug events

- CNS effects: peripheral neuritis and rarely seizures, encephalopathy, and psychosis have been reported.
- Hepatic effects: increases in bilirubin, AST, and ALT are noted in up to 20% of patients receiving this agent. INH has lead to fulminant hepatitis and death.
- Hematologic effects: agranulocytosis, eosinophilia, thrombocytopenia, and hemolytic anemia have been reported.

Pyrazinamide (PZA)**Mechanism of action**

- Mycobacterium tuberculosis* converts PZA to pyrazinoic acid which possesses antitubercular activity.

Spectrum of activity

- PZA is active against *Mycobacterium tuberculosis* only.

Adverse drug events

- Hepatic effects: increased liver enzymes are common, and fulminant hepatitis has been reported.
- Gout: PZA inhibits renal excretion of uric acid and may induce or worsen gout.

Rifampin**Mechanism of action**

- Rifampin inhibits RNA synthesis in susceptible isolates.

Spectrum of activity

- Rifampin is active against the following *Mycobacterium* species: *M. tuberculosis*, *M. bovis*, *M. kansasii*, and some *M. avium* isolates.
- Rifampin also has activity against many gram-positive and gram-negative organisms.

Adverse drug events

- GI effects: nausea, vomiting, diarrhea, and abdominal pain may require discontinuation of the agent. *C. difficile* colitis has been reported with rifampin.
- CNS effects: headache, dizziness, mental confusion, and psychosis have been reported.
- Hepatic effects: increased bilirubin, AST, and ALT are common. Fulminant hepatitis has been reported.
- Hematologic effects: thrombocytopenia, leukopenia, and hemolytic anemia have been reported rarely.
- Renal effects: renal insufficiency and interstitial nephritis have been reported.

12. Key Points**Aminoglycosides**

- Aminoglycoside antibiotics exhibit concentration-dependent bacterial killing.
- Aminoglycoside antibiotics are reserved for severe infections or for use against multidrug-resistant bacteria.
- Aminoglycoside antibiotic dosing should be pharmacokinetically tailored for each patient to optimize the therapeutic effect and minimize toxicity.

Antifungal anti-infectives

- Amphotericin B, caspofungin, fluconazole, itraconazole, and voriconazole are effective against systemic fungal infections.
- Imidazole antifungal antibiotics are potent inhibitors of hepatic metabolism, thereby decreasing the elimination of numerous agents.

Gram-positive antibiotics

- Linezolid and quinupristin-dalfopristin are clinically effective against MRSA, MRSE, and VRE.
- Vancomycin is a broad-spectrum gram-positive antibiotic that should be pharmacokinetically tailored for each patient to maximize therapeutic benefit and minimize toxicity.

Miscellaneous antibiotics

- Clindamycin is an effective anaerobic antibiotic as well as an effective gram-positive aerobic antibiotic with activity against many MRSA isolates.
- The carbapenem antibiotics possess a very broad spectrum of activity and should be restricted to appropriate indications to minimize development of resistance.

Penicillins

- Penicillin antibiotics exhibit time-above-MIC-dependent bacterial killing.
- All penicillins, except nafcillin and oxacillin, are renally eliminated and require dosage adjustments in renal dysfunction.

Cephalosporins

- Cephalosporin antibiotics exhibit time-above-MIC-dependent bacterial killing.
- First-generation cephalosporins: gram-positive activity is extensive, but gram-negative activity is limited.
- Second-generation cephalosporins: gram-positive activity is similar to that of first-generation agents, but gram-negative activity is generally more extensive than that of first-generation agents.

- Third-generation cephalosporins: gram-positive activity is decreased versus first- and second-generation agents, but gram-negative activity is extensive.

Fluoroquinolones

- Quinolone antibiotics exhibit concentration-dependent bacterial killing similar to the aminoglycosides.
- The later-generation quinolones possess improved gram-positive activity, including resistant streptococci.

Sulfonamides

- Sulfonamides are primarily urinary anti-infectives whose utility has decreased due to the development of resistance.

Tetracyclines

- Tetracyclines are drugs of choice for atypical pneumonias.

Macrolides

- Erythromycins are primarily active against gram-positive bacteria including penicillin-resistant streptococci.
- Telithromycin possesses greater in vitro activity against multidrug-resistant gram-positive organisms and *Haemophilus influenzae* compared to the erythromycins.

Antitubercular agents

- Isoniazid, rifampin, and streptomycin exhibit the lowest incidence of resistance.
- Isoniazid, rifampin, and pyrazinamide are the agents of first choice.

13. Questions and Answers

- Which of the following statements regarding aminoglycoside antibiotics is/are true?
 - Aminoglycoside antibiotics are bactericidal against most susceptible isolates
 - Aminoglycoside antibiotics exhibit concentration-dependent bacterial killing
 - Aminoglycoside antibiotics should be reserved for serious infections
 - I only
 - I and II
 - I and III
 - II and III
 - I, II, and III
- Which of the following statements most accurately characterizes aminoglycoside toxicity?
 - Ototoxicity due to eighth cranial nerve damage
 - Nephrotoxicity exhibited as acute tubular necrosis
 - Bone marrow suppression
 - I only
 - II only
 - III only
 - I and II
 - II and III
- Which of the following statements best characterizes aminoglycoside antimicrobial activity?
 - Active against most aerobic gram-negative bacteria
 - Active against most anaerobic gram-negative bacteria
 - Active against most fungal isolates
 - I only
 - II only
 - II only
 - I and II
 - II and III
- Which of the following antifungals is/are effective against systemic infections?
 - Amphotericin B
 - Fluconazole
 - Nystatin

- A. I only
B. II only
C. III only
D. I and II
E. I and III
5. Which of the following statements is/are true about amphotericin B-induced nephrotoxicity?
- Nephrotoxicity is the major dose-limiting toxicity
 - Nephrotoxicity is usually reversible upon discontinuation of the drug
 - Amphotericin B lipid formulations decrease nephrotoxicity by 20-30%
- A. I only
B. II only
C. I and II
D. II and III
E. I, II, and III
6. Which of the following statements best describe the drug interactions noted with the imidazole antifungals?
- Increased elimination of warfarin
 - Decreased elimination of warfarin
 - Increased metabolism of the oral contraceptives
- A. I only
B. II only
C. III only
D. II and III
E. I, II, and II
7. Linezolid is best described by which of the following statements?
- Linezolid is bacteriostatic against staphylococci
 - Linezolid is bactericidal against staphylococci
 - Linezolid is a weak MAO inhibitor
- A. I only
B. II only
C. I and III
D. II and III
E. I, II, and III
8. Linezolid possesses activity against which of the following bacteria?
- MRSA
 - Enterococcus faecium*
 - Enterococcus faecalis*
- A. I only
B. II only
C. III only
D. I and II
E. I and III
9. Quinupristin-dalfopristin is best described by which of the following statements?
- Exhibits activity against MSSA
 - Exhibits activity against MRSA
 - Exhibits activity against streptococci
- A. I only
B. II only
C. III only
D. I and II
E. I, II, and III
10. Vancomycin is best described by which of the following statements?
- Exhibits activity against MRSA
 - Exhibits activity against *Enterobacter*
 - Exhibits activity against *Clostridium difficile*
- A. I only
B. II only
C. III only
D. I and II
E. I and III
11. Vancomycin toxicity is best described by which of the following statements?
- Nephrotoxicity exhibited as acute tubular necrosis that is seldom reversible
 - Ototoxicity that is commonly exhibited as vestibular toxicity
 - Histamine release or "red-man syndrome," which is associated with rapid IV infusion
- A. I only
B. II only
C. III only
D. I and II
E. II and III
12. Which of the following statements best describes appropriate vancomycin monitoring?
- Trough serum concentrations should be routinely monitored in patients with pre-existing renal dysfunction.

- II. Peak serum concentrations should be routinely monitored in patients with pre-existing renal dysfunction.
 - III. Serum concentration monitoring is of no benefit in vancomycin monitoring.
 - A. I only
 - B. II only
 - C. III only
 - D. I and II
 - E. II and III
13. Clindamycin exhibits antibacterial activity against which of the following microorganisms?
- I. Aerobic gram-positive bacteria
 - II. Anaerobic gram-negative bacteria
 - III. Aerobic gram-negative bacteria
- A. I only
 - B. II only
 - C. III only
 - D. I and II
 - E. I and III
14. Which statements best describes the carbapenem antibiotics?
- I. Exhibit activity against most gram-positive and gram-negative aerobes and anaerobes
 - II. Meropenem induces seizures more commonly than imipenem
 - III. Cilastatin exhibits activity against most gram-positive aerobes
- A. I only
 - B. II only
 - C. III only
 - D. I and II
 - E. II and III
15. Which of the following statements best describes the penicillins?
- I. Exhibit concentration-dependent bacterial killing
 - II. Exhibit time-above-MIC-dependent bacterial killing
 - III. Exhibit excellent MRSA activity
- A. I only
 - B. II only
 - C. III only
 - D. I and II
 - E. II and III
16. Which of the following penicillins require dosage adjustment in renal dysfunction?
- I. Ampicillin
 - II. Nafcillin
 - III. Oxacillin
- A. I only
 - B. II only
 - C. III only
 - D. I and II
 - E. II and III
17. Which of the following statements best describes the cephalosporins?
- I. Exhibit concentration-dependent bacterial killing
 - II. Exhibit time-above-MIC-dependent bacterial killing
 - III. Exhibit excellent MRSA activity
- A. I only
 - B. II only
 - C. III only
 - D. I and II
 - E. II and III
18. Which of the following statements best describes the antibacterial activity of the cephalosporins?
- I. First-generation cephalosporins: gram-positive activity is extensive, but gram-negative activity is limited
 - II. Second-generation cephalosporins: gram-positive activity is similar to that of first-generation agents, but gram-negative activity is generally more extensive than that of first-generation agents
 - III. Third-generation cephalosporins: gram-positive activity is decreased versus first- and second-generation agents, but gram-negative activity is extensive
- A. I only
 - B. II only
 - C. III only
 - D. All of the above
 - E. None of the above
19. Which of the following statements best describes the antibacterial activity of the quinolones?
- I. Exhibit concentration-dependent bacterial killing
 - II. Exhibit time-above-MIC-dependent bacterial killing
 - III. Exhibit extensive anaerobic activity

- A. I only
B. II only
C. III only
D. I and II
E. II and III
20. Which of the following statements best describes the important patient counseling points for the quinolones?
- Avoid use in children and pregnant or nursing women due to the risk of cartilage erosion in growing bone tissue
 - Do not take within 2 hours of antacids, multivitamins, calcium, magnesium, or iron supplements
 - Take with a full glass of water and remain sitting or upright for 2 hours to avoid esophageal irritation
- A. I only
B. II only
C. III only
D. I and II
E. II and III
21. Which of the following statements best describes the sulfonamides?
- Interfere with vitamin B₁₂ synthesis by competitively inhibiting PABA utilization
 - Drugs of choice for *C difficile* colitis
 - Primarily urinary anti-infectives whose utility has decreased due to the development of resistance
- A. I only
B. II only
C. III only
D. I and II
E. I, II, and III
22. Which of the following statements best describes the tetracyclines?
- Exhibit bacteriostatic activity
 - Are the drugs of choice for atypical pneumonia
 - Tetracycline is contraindicated in children less than 8 years old
- A. I only
B. II only
C. III only
D. I and II
E. I, II, and III
23. Which of the following statements best describes the macrolides?
- Primarily effective against gram-positive aerobic bacteria
 - Effective against penicillin-resistant streptococci
 - Ineffective against penicillin-resistant streptococci
- A. I only
B. II only
C. III only
D. I and II
E. I and III
24. Which antitubercular agent(s) exhibits the lowest incidence of resistance?
- Isoniazid
 - Rifampin
 - Streptomycin
- A. I only
B. II only
C. III only
D. I and II
E. I, II, and III
25. Which of the following drug combination regimens are considered the agents of first choice for empiric treatment of TB?
- Isoniazid, rifampin, and streptomycin
 - Isoniazid, rifampin, and pyrazinamide
 - Isoniazid, ethambutol, and cycloserine
- A. I only
B. II only
C. III only
D. All of the above
E. None of the above

Answers

- E. Aminoglycoside antibiotics are bacteriocidal against most susceptible isolates, exhibit concentration-dependent bacterial killing, and are usually reserved for serious infections due to toxicity.
- D. Ototoxicity is due to eighth cranial nerve damage and may be irreversible. Nephrotoxicity is exhibited as an acute tubular necrosis that is usually reversible and seldom requires dialysis. Neuromuscular blockade is the third most

common toxicity noted with the aminoglycosides.

3. **A.** Aminoglycosides are active against most aerobic gram-negative and selected aerobic gram-positive bacteria. They have no activity against anaerobic bacteria or fungi.
4. **D.** Amphotericin B, caspofungin, fluconazole, itraconazole, and voriconazole are effective against systemic fungal infections.
5. **E.** Acute renal dysfunction is the most common dose-limiting amphotericin B toxicity, the renal dysfunction is usually reversible and seldom requires dialysis, and lipid formulations decrease toxicity by ~20-30%.
6. **B.** The imidazole antifungals decrease hepatic clearance of numerous hepatically metabolized medications, thereby increasing their activity and risk for toxicity.
7. **C.** Linezolid is bacteriostatic against staphylococci and enterococci. It is bactericidal against *Streptococcus* species only. The agent is a weak MAO inhibitor.
8. **D.** Linezolid is active against MSSA, MRSA, and *Enterococcus faecium* (VRE). *Enterococcus faecalis* isolates are resistant.
9. **E.** Quinupristin-dalfopristin is active against MSSA, MRSA, streptococci, and *Enterococcus faecium* (VRE). *Enterococcus faecalis* isolates are commonly resistant.
10. **E.** Vancomycin is active against aerobic gram-positive bacteria only; it has no clinically significant gram-negative activity. Vancomycin is the second-line drug of choice for *C. difficile* colitis.
11. **C.** Vancomycin nephrotoxicity is uncommon and is exhibited as acute tubular necrosis, which is commonly reversible and seldom requires dialysis. Ototoxicity is due to eighth cranial nerve damage which is manifest as high-frequency hearing loss, seldom affecting the vestibular system. The histamine or "red-man syndrome" reaction is most commonly infusion rate-related.
12. **A.** Vancomycin serum concentration monitoring is not required in patients responding well to therapy and with normal renal function. Vancomycin trough concentrations should be assessed in patients with pre-existing renal dysfunction, worsening renal function, or those not responding to therapy.
13. **D.** Clindamycin exhibits activity against aerobic gram-positive bacteria and anaerobic gram-positive and gram-negative bacteria. It has no clinically significant aerobic gram-negative activity.
14. **A.** Carbapenems are active against most aerobic and anaerobic gram-positive and gram-negative bacteria. Imipenem is more likely to induce seizures, and cilastatin inhibits the metabolism of imipenem but has no antibacterial activity.
15. **B.** Penicillins exhibit time-dependent bacterial killing and have no activity against MRSA.
16. **A.** All penicillins with the exception of nafcillin and oxacillin require dosage adjustment in renal dysfunction.
17. **B.** Cephalosporins exhibit time-dependent bacterial killing and have no activity against MRSA.
18. **D.** First-generation cephalosporins exhibit extensive gram-positive activity but limited gram-negative activity. Second-generation cephalosporins maintain gram-positive activity similar to the first-generation agents, but their gram-negative activity is generally improved. Third-generation cephalosporins exhibit decreased gram-positive activity, but gram-negative activity is significantly improved.
19. **A.** Quinolones exhibit concentration-dependent bacterial killing similar to the aminoglycosides. They possess good aerobic gram-positive and gram-negative activity, but have limited anaerobic activity.
20. **D.** Quinolones have been shown to decrease cartilage formation in beagle pups, but this effect in humans is somewhat controversial. Their use in children should be reserved for serious infections to avoid the risk. Quinolones are bound to divalent cations and should not be coadministered. They do not cause significant esophageal irritation.

21. **C.** Sulfonamides interfere with folic acid metabolism by inhibiting PABA utilization. They have no activity against *C difficile* colitis, and are primarily relegated to urinary anti-infectives due to resistance.
22. **E.** Tetracyclines are bacteriostatic. They are drugs of choice for atypical pulmonary pathogens, and should not be administered to children less than 8 years old to avoid permanent tooth staining and potential deposition into bone.
23. **D.** Erythromycins are primarily gram-positive aerobic antibiotics with good activity against most penicillin-resistant *Streptococcus* isolates.
24. **E.** Isoniazid, rifampin, and streptomycin exhibit the lowest incidence of MTB resistance.
25. **B.** Isoniazid, rifampin, and pyrazinamide are considered agents of first choice for empiric treatment of TB due to a low incidence of resistance and acceptable tolerability profile. Ethambutol is commonly added to the regimen in areas of increased resistance.

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31. Human Immunodeficiency Virus and the Acquired Immunodeficiency Syndrome

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1. Overview
2. Drug Therapy
3. Prevention
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1. Overview

- Human immunodeficiency virus (HIV) is a retrovirus that depletes the helper T lymphocytes (CD4 cells), resulting in continued destruction of the immune system and subsequent gradual development of opportunistic infections and malignancies.
- Acquired immunodeficiency syndrome (AIDS) is HIV with a CD4 count less than 200 cells/mm³ or a history of opportunistic infection (eg, unexplained fever for more than 2 weeks, thrush, *Pneumocystis carinii* pneumonia, toxoplasmosis, cryptococcal meningitis, histoplasmosis, and *Mycobacterium avium*).

Epidemiology

- At the end of 2004, these were the global estimates of children and adults with HIV/AIDS:
 - * People living with HIV/AIDS: 39.4 million
 - * New HIV infections in 2004: 2.9 million
 - * Deaths due to HIV/AIDS in 2004: 3.1 million
 - * Cumulative number of deaths due to HIV/AIDS: 31 million
- Complete current world epidemiology can be found at www.unaids.org.
- At the end of 2003, these were the estimates of children and adults with HIV/AIDS in the U.S.:
 - * People living with HIV/AIDS: 850,000-950,000
 - * New HIV infections in 2003: 43,171
 - * Deaths due to HIV/AIDS in 2003: 18,017
 - * Cumulative number of deaths due to HIV/AIDS: 524,060
 - * 180,000-280,000 don't know they are infected with HIV
- Complete current United States epidemiology can be found at: www.cdc.gov/hiv/stats/hasrlink.htm.

Subtypes

- HIV-1: most commonly found in the U.S.
- HIV-2: most commonly found in Africa

Clinical Presentation

- Opportunistic infection
- Patient not ill but has tested as HIV-positive
- Acute retroviral syndrome:
 - * 50-90% of patients acutely infected with HIV experience some of the symptoms.
 - * Symptoms generally appear 2-4 weeks after virus exposure.
 - * Duration of the clinical syndrome is ~14 days (the range is a few days to >10 weeks).

- * The disease is not readily recognized in the primary care setting because its symptoms are similar to those of the flu, mononucleosis, and other common illnesses.

Pathophysiology

- A retrovirus that replicates in and destroys CD4 cells
- The result is a chronically deteriorating immune system leading to opportunistic infections and eventual death.
- Seroconversion typically occurs ~3 weeks after the acute infection (the range is from 2 weeks to 6 months).
- Antibodies generally appear within 3 months of infection (the range is from 2 weeks to 6 months).
- Transmission is via infected blood or hazardous body fluids:
 - * Unprotected sexual contact with an infected person
 - Multiple partners increase risk.
 - Ongoing or past medical history of sexually transmitted disease increases risk.
 - * Sharing needles and/or syringes with an infected person
 - * Transfusions of infected blood or blood clotting factors (the U.S. began screening the blood supply in 1985).
 - * Vertical transmission (infected mother to infant)
 - * Breastfeeding
 - * Occupational exposure is rare.
 - * Household contact is rare.

Diagnostic Criteria

- Enzyme-linked immunosorbent assay (ELISA):
 - * Initial screening test for detection of anti-HIV antibodies
 - * False-positive results can occur in patients with:
 - Collagen vascular diseases
 - Chronic hepatitis
 - Other chronic diseases
- Western blot:
 - * All positive ELISA tests must be confirmed by a Western blot.
 - * Specificity and sensitivity of the Western blot is >99%.
 - * Western blot tests for anti-HIV antibodies.
- Other diagnostic tests are available (all should be confirmed by Western blot).
 - * Rapid tests can give results from a fingerstick or swab of oral fluid in 20 minutes.

Monitoring Tools

Viral load

- Measures amount of virus in blood
- Can assess disease progression and evaluate the efficacy of antiretroviral therapy
- Lower limit of detection is less than 50 copies/mL for ultrasensitive assays (less than 400 copies/mL for non-ultrasensitive assays).
- A minimally significant change in viral load is considered to be a threefold or 0.5 log₁₀ increase or decrease.
- Acute illness and immunizations can cause increases in viral load for 2-4 weeks; testing should not be performed during this time.
- Baseline viral loads are established by averaging two viral loads (that do not differ by >0.5 log₁₀) taken 2-4 weeks apart.
- Monitoring of viral load in patients not on antiretroviral therapy should occur every 3-4 months.
- Monitoring of viral load in patients starting a new regimen should occur 2-8 weeks after treatment initiation and then every 3-4 months.

CD4 cell count

- Indicates extent of immune system damage and risk of developing opportunistic infections
- Normal CD4⁺ cell counts are 800-1200 cell/mm³.
- CD4⁺ cell counts should be measured every 3-4 months in patients on or off antiretroviral therapy.
- A significant change in CD4⁺ cells is considered to be a 30% increase or decrease from baseline.

Treatment Principles and Goals

Goals of therapy

- Maximal and durable suppression of viral load
- Restoration and/or preservation of immunologic function
- Improvement in quality of life
- Reduction of HIV-related morbidity and mortality
- Factors involved in achieving goals of therapy:
 - * Adherence to the antiretroviral regimen
 - * Rational sequencing of drugs
 - * Preservation of future treatment options
 - * Use of resistance testing in selected clinical settings
- See Table 1 for indications for the initiation of antiretroviral therapy in the chronically HIV-1 infected patient.
- See Table 2 for antiretroviral agents recommended by DHHS for initial treatment of established HIV infection.

Indications for Consideration of Changing Antiretroviral Therapy

- Failure to suppress plasma HIV RNA to undetectable levels (<50 copies/mL) within 4-6 months of initiating a therapy
- Repeated detection of virus in plasma following initial suppression to undetectable levels
- Consider genotyping and/or phenotyping to assist in identifying drugs for the next regimen if:
 - * Adherent to failing regimen for at least the previous 4-6 weeks or within 4 weeks after regimen discontinuation

Table 1

Indications for the Initiation of Antiretroviral Therapy in the Chronically HIV-1 Infected Patient

Clinical category	CD4 ⁺ cell count	Plasma HIV RNA	Recommendation
Symptomatic (AIDS, severe symptoms)	Any value	Any value	Treat
Asymptomatic, AIDS	<200/mm ³	Any value	Treat
Asymptomatic	>200/mm ³ but <350/mm ³	Any value	Treatment should generally be offered though controversy exists
Asymptomatic	>350/mm ³	Viral load >100,000 copies/mL	Some experts would recommend initiating therapy, recognizing that the 3-year risk of developing AIDS in untreated patients is >30%, and some would defer therapy and monitor CD4 ⁺ cell counts more frequently
Asymptomatic	>350/mm ³	Viral load <100,000 copies/mL	Many experts would defer therapy and observe, recognizing that the 3-year risk of developing AIDS in untreated patients is <15%

Table 2

Antiretroviral Regimens for Treatment of HIV Infection in Antiretroviral-Naïve Patients**NNRTI-based regimens**

Preferred regimens	Efavirenz ¹ + (lamivudine <i>or</i> emtricitabine) + (zidovudine <i>or</i> tenofovir)
Alternative regimens	Efavirenz ¹ + (lamivudine <i>or</i> emtricitabine) + (didanosine <i>or</i> abacavir <i>or</i> stavudine)
	Nevirapine ² + (lamivudine <i>or</i> emtricitabine) + (zidovudine + <i>or</i> stavudine <i>or</i> didanosine <i>or</i> abacavir <i>or</i> tenofovir)

PI-based regimens

Preferred regimens Lopinavir + ritonavir (co-formulation) + (lamivudine *or* emtricitabine) + zidovudine

Alternative regimens (use one medication from each column)	Column A	Column B	Column C
	Atazanavir ³	Lamivudine	Zidovudine
	Fosamprenavir	Emtricitabine	Stavudine
	Fosamprenavir/r ⁴		Abacavir
	Indinavir/r ⁴		Tenofovir
	Lopinavir/r ⁴		Didanosine
	Nelfinavir		
	Saquinavir ⁵ /r ⁴		

3 NRTI-based

Abacavir + zidovudine + lamivudine: only when a preferred or an alternative NNRTI- or PI-based regimen cannot or should not be used

NNRTI, non-nucleoside reverse transcriptase inhibitor; NRTI, nucleoside reverse transcriptase inhibitor; PI, protease inhibitor.

¹Efavirenz is not recommended for use in first-trimester pregnancy or in women with a high pregnancy potential.

²Use caution in women with CD4 cell counts >250 cells/mm³ and men with CD4 cell counts >400 cells/mm³ due to increased risk of nevirapine-associated toxicity.

³Must boost atazanavir with low-dose ritonavir if used with tenofovir.

⁴Low-dose 100-400 mg ritonavir.

⁵Saquinavir is currently available in 3 formulations: soft gel caps, hard gel caps, and the mesylate tablet formulation, which is preferred.

IAS-USA guidelines differ slightly from DHHS guidelines above. Preferred PI regimens include atazanavir/r, saquinavir/r, and indinavir/r as well as lopinavir/r. Nucleoside reverse transcriptase inhibitor (NRTI) pairs are (zidovudine or tenofovir) plus (lamivudine or emtricitabine) for both PI- and NNRTI-based regimens.

* Viral load above 1000 copies/mL

- Persistently declining CD4⁺ T cell numbers as measured on at least two separate occasions
- Clinical deterioration
- Never change just one medication in a failing regimen (ie, use at least two new drugs, and preferably an entirely new regimen).
- Changing one medication in a successful regimen can be done if a patient is experiencing intolerable side effects or if there is overlapping toxicity with other medications (Table 3).
- Use the treatment history and past and current resistance test results to identify active agents (preferably two or more) to design a new regimen.

2. Drug Therapy**Nucleoside Reverse Transcriptase Inhibitors (NRTIs) (Table 4)****Mechanism of action**

- Interfere with HIV viral RNA-dependent DNA polymerase, resulting in chain termination and inhibition of viral replication

Class toxicities (monitor for signs and symptoms)

- Lactic acidosis
- Severe hepatomegaly with steatosis
- Most patients should be dose-adjusted for renal impairment (exception: abacavir).

Table 3

HIV-Related Drugs with Overlapping Toxicities

Bone marrow suppression	Peripheral neuropathy	Pancreatitis	Nephrotoxicity	Hepatotoxicity	Rash	Diarrhea	Ocular effects
Amphotericin B	Didanosine	Cotrimoxazole	Acyclovir	Azithromycin	Abacavir	Atovaquone	Cidofovir
Cidofovir	Isoniazid	Didanosine	(IV, high-dose)	Clarithromycin	Amprenavir	Clindamycin	Didanosine
Cotrimoxazole	Linezolid	Lamivudine	Adefovir	Delavirdine	Atazanavir	Darunavir	Ethambutol
Cytotoxic chemotherapy	Stavudine	(children)	Aminoglycosides	Efavirenz	Atovaquone	Didanosine	Linezolid
	Zalcitabine	Pentamidine	Amphotericin B	Fluconazole	Cotrimoxazole	(buffered formulations)	Rifabutin
Dapsone		Ritonavir	Cidofovir	Isoniazid	Dapsone		Voriconazole
Flucytosine		Stavudine	Foscarnet	Itraconazole	Darunavir	Fosamprenavir	
Ganciclovir		Zalcitabine	Indinavir	Ketoconazole	Delavirdine	Lopinavir/ritonavir	
Hydroxyurea			Pentamidine	Nevirapine	Efavirenz		
Interferon alfa			Tenofovir	NRTIs	Fosamprenavir	Nelfinavir	
Linezolid				PIs – especially tipranavir	Nevirapine	Ritonavir	
Peginterferon alfa				Rifabutin	Sulfadiazine	Tipranavir	
Primaquine				Rifampin	Voriconazole		
Pyrimethamine				Voriconazole			
Ribavirin							
Rifabutin							
Sulfadiazine							
Trimetrexate							
Valganciclovir							
Zidovudine							

- Didanosine, stavudine, and lamivudine are dosed based on weight.
- Lamivudine and emtricitabine are chemically similar and should not be used in the same regimen.
- Most are not affected by food (except didanosine).
- Low pill burden as a class; few drug interactions.
- All are prodrugs requiring 2-3 phosphorylations for activation.
- Do not use zidovudine with stavudine due to antagonism (both require thymidine for activation).
- Do not use didanosine with stavudine during pregnancy due to increased risk of lactic acidosis and liver damage.
- Tenofovir increases didanosine levels and decreases atazanavir levels; dosage adjustments are required.
- Four combination products are available:
 - * Combivir® (zidovudine 300 mg + lamivudine 150 mg) every 12 hours
 - * Trizivir® (zidovudine 300 mg + lamivudine 150 mg + abacavir 300 mg) every 12 hours
 - * Truvada® (tenofovir 300 mg + emtricitabine 200 mg) every 24 hours
 - * Epzicom® (lamivudine 300 mg + abacavir 600 mg) every 24 hours
- No special storage requirements are necessary for drugs in this class.
- The “D” drugs (ddI [didanosine], d4T [stavudine], and ddC [zalcitabine]) can cause pancreatitis and peripheral neuropathy; when used together, this effect can be additive.
- The “D” drugs are more closely associated with lactic acidosis.
- Therapy with zalcitabine has the highest incidence of peripheral neuropathy and is contraindicated with didanosine, stavudine, and lamivudine.
- Usually use two NRTIs in combination with 1 NNRTI or 1 PI

Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs) (Table 5)

Mechanism of action

- Bind to reverse transcriptase at a different site than the NRTIs, resulting in inhibition of HIV replication
- Class toxicities include rash and hepatic toxicity.
- One-step mutation confers class resistance.
- All should be dose-adjusted for hepatic impairment.
- Most are not affected by food (except efavirenz).

Table 4

Characteristics of Nucleoside Reverse Transcriptase Inhibitors (NRTIs)

Generic name [trade name]	Zidovudine (AZT, ZDV) [Retrovir®]	Lamivudine (3TC) [Epivir®]	Abacavir (ABC) [Ziagen®]	Didanosine (ddI) [Videx EC®, Videx®]
Form	100 mg caps; 300 mg tabs; also available in combination products ¹ ; available as generic	150, 300 mg tabs; 10 mg/mL oral solution; also available in combination products ¹	300 mg tabs; 20 mg/mL oral solution; also available in combination products ¹	Videx EC® caps: 125, 200, 250, 400 mg; Videx® buffered tabs: 25, 50, 100, 150, 200 mg; Videx® buffered powders: 100, 167, 250 mg; available as generic: Didanosine DR
Dosing recommendations	300 mg q12h; 200 mg q8h	150 mg q12h; 300 mg q24h (dosage based on weight for pediatrics)	300 mg q12h; 600 mg q24h	>60 kg: 400 mg q24h; with TDF ↓ddI to 250 mg; <60 kg: 250 mg q24h; with TDF: appropriate ddI dose not known
Food effect	Take without regard to meals	Take without regard to meals	Take without regard to meals	Take 1/2 h before or 2 h after meals
Adverse events	Bone marrow suppression (macrocytic anemia or neutropenia); GI intoler- erance, headache, insomnia, asthenia	Minimal toxicity	Hypersensitivity reaction can be fatal; symptoms include rash, fever, nausea/vomiting, malaise or fatigue, loss of appetite; respiratory symptoms include sore throat, cough, shortness of breath	Pancreatitis, peripheral neuropathy, nausea, diarrhea
Drug interactions	Ribavirin, stavudine, methadone; with high dose: ganciclovir, TMP- SMX, other medications that can cause bone marrow suppression	No clinically significant drug interactions	Alcohol increases abacavir levels by 41%	Methadone, ribavirin, tenofovir, ganciclovir, alcohol; medications that need acidic environment for absorption—buffered forms; use caution with other meds that can cause peripheral neuropathy
Monitoring*	CBC, LFTs	None necessary	Signs and symptoms of hypersensitivity reaction	CBC, LFTs, amylase, uric acid; signs and symptoms of above side effects

(continued)

Bold type highlights the most common dosing and important side effects.

1 Combivir: zidovudine 300 mg + lamivudine 150 mg; 1 tablet q12h

Trizivir: zidovudine 300 mg + lamivudine 150 mg + abacavir 300 mg; 1 tablet q12h

Epzicom: abacavir 600 mg + lamivudine 300 mg; 1 tablet q24h

2 Monitor all for signs and symptoms of NRTI class toxicities, lactic acidosis, and hepatic steatosis.

- Efavirenz is contraindicated in pregnancy.
- Usually use one NNRTI in combination with two NRTIs.
- No special storage requirements are necessary for drugs in this class.
- Drug interactions: all are cytochrome P450 (CYP450)-3A4 inducers and/or inhibitors; see Tables 6 and 7.

Protease Inhibitors (PIs) (Table 8)

Mechanism of action

- PIs inhibit protease, which then prevents the cleavage of HIV polyproteins and subsequently induces the formation of immature noninfectious viral particles.
- All should be dose-adjusted for hepatic impairment.
- Most should be taken with food (except amprenavir and indinavir).

Table 4

Characteristics of Nucleoside Reverse Transcriptase Inhibitors (NRTIs) (continued)

Generic name [trade name]	Stavudine (d4T) [Zerit®]	Zalcitabine (ddC) [Hivid®]	Tenofovir (TDF) [Viread®]	Emtricitabine (FTC) [Emtriva®]
Form	15, 20, 30, 40 mg caps	0.375, 0.75 mg tabs; will no longer be manufactured by the end of 2006	300 mg tabs; also available in combination products ¹	200 mg tabs; also available in combination products ¹
Dosing recommendations	>60 kg: 40 mg q12h ; <60 kg: 30 mg q12h	0.75 mg q8h	300 mg q24h	200 mg q24h
Food effect	Take without regard to meals	Take without regard to meals	Take without regard to meals	Take without regard to meals
Adverse events	Pancreatitis; peripheral neuropathy; lipodystrophy, hyper- lipidemia; rapidly progressive ascending neurosomuscular weakness (rare)	Pancreatitis, peripheral neuropathy, stomatitis	Renal insufficiency, asthenia, headache, diarrhea, nausea/vomiting, flatulence	Minimal toxicity; hyperpigmentation of palms of hands and soles of feet (rare)
Drug interactions	Use with caution with other medications that can cause peripheral neuropathy	Use with caution with other medications that can cause peripheral neuropathy Signs and symptoms of above side effects	Didanosine, atazanavir, cidofovir, ganciclovir, valganciclovir	No clinically significant drug interactions
Monitoring	Signs and symptoms of above side effects	Signs and symptoms of above side effects	Renal function	None necessary

Bold type highlights the most common dosing and important side effects.

1 Truvada: tenofovir 300 mg + emtricitabine 200 mg; 1 tablet q24h

Atripla – Tenofovir 300 mg + emtricitabine 200 mg + efavirenz 600 mg; 1 tablet q24h at bedtime

2 Monitor all for signs and symptoms of NRTI class toxicities, lactic acidosis, and hepatic steatosis; higher incidence with stavudine than with other NRTIs.

- Amprenavir and fosamprenavir are chemically similar and should not be used in the same regimen
- Atazanavir and indinavir require normal acid levels in the stomach for absorption.
- Ritonavir is the most potent inhibitor in the class and is primarily used for intensification of other PIs.
- Lopinavir/ritonavir, ritonavir, and saquinavir soft gel caps require refrigeration.
- Goals of intensification:
 - * Decrease pill burden
 - * Decrease frequency of doses (ie, decrease from q8h to q12h)
- Class toxicities:
 - * Lipodystrophy
 - * Hyperglycemia
 - * Hyperlipidemia
 - * Hypertriglyceridemia
 - * Bleeding in hemophiliacs
 - * Osteonecrosis and avascular necrosis of the hips
 - * Osteopenia and osteoporosis
- PI monitoring (baseline is 4-6 weeks after starting PI and every 3-6 months thereafter):
 - * Glucose
 - * LFTs
 - * Total cholesterol panel (particularly triglycerides)
 - * GI side effects
 - * Signs and symptoms of bone pain (particularly hip pain)
 - * Signs and symptoms of fat redistribution
- Usually use one PI in combination with two NRTIs
- All are CYP450-3A4 inhibitors (ie, drug interactions are typical of CYP450-3A4 inhibitors); see Tables 9 and 10.

Table 5

Characteristics of Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs)

Generic name [trade name]	Efavirenz (EFV) [Sustiva [®]]	Nevirapine (NVP) [Viramune [®]]	Delavirdine (DLV) [Rescriptor [®]]
Form	50, 100, 200 mg caps; 600 mg tabs; Also available in combination product ¹	200 mg tab; 10 mg/mL oral suspension	100, 200 mg tabs
Dosing recommendations	600 mg q24hs at bedtime	200 mg q24h x 14 d, then 200 mg q12h (note CD4 cell count) ²	400 mg q8h
Food effect	Take on an empty stomach	Take without regard to meals	Take without regard to meals
Adverse events	CNS side effects³; rash⁴, ↑LFTs, false-positive cannabinoid test, teratogenic in monkeys	Rash⁴, symptomatic hepatitis, including fatal hepatic necrosis have been reported	Rash⁴, ↑ LFTs, headaches
Drug interactions	CYP450-3A4, -2C19 inhibitor and -3A4 inducer (see Tables 6 and 7)	CYP450-3A4 inducer (see Tables 6 and 7)	CYP450-3A4 and -2D6 inhibitor (see Tables 6 and 7); separate dosing with buffered ddi or antacids by 1 hour
Monitoring⁵	CNS side effects, LFTs, rash	LFTs 2, 4, and 6 weeks, and then monthly for the first 18 weeks	LFTs, rash

Bold type highlights the most common dosing and important side effects.

¹ Atripla - tenofovir 300 mg + emtricitabine 200 mg + efavirenz 600 mg - one tablet q24h at bedtime

² Due to the increased risk of symptomatic hepatic events, nevirapine should not be started in women with baseline CD4 cell counts of greater than 250 cells/mm³ or men with baseline CD4 cell counts greater than 400 cells/mm³

³ CNS side effects include: dizziness, somnolence, insomnia, abnormal dreams, confusion, abnormal thinking, impaired concentration, amnesia, agitation, depersonalization, hallucinations and euphoria. Use caution in patients with a psychiatric history or previous addictions.

⁴ Rare cases of Stevens-Johnson syndrome have been reported with the use of NNRTIs, the highest incidence seen with nevirapine use.

⁵ Monitor all for signs and symptoms of NNRTI class toxicities, rash and hepatic toxicity

Table 6

Drugs That Should Not Be Used with NNRTIs

Drug category	Nevirapine	Delavirdine	Efavirenz
Calcium channel blockers	None	None	None
Cardiac	None	None	None
Lipid-lowering agents	None	Simvastatin, lovastatin	None
Antimycobacterial	Rifampin, rifapentine	Rifampin, rifapentine, rifabutin	Rifapentine
Antihistamine	None	Astemizole, terfenadine	Astemizole, terfenadine
Gastrointestinal drugs	None	Cisapride, H ₂ -blockers, proton pump inhibitors	Cisapride
Psychotropics	None	Alprazolam, midazolam, triazolam	Midazolam, triazolam
Ergot alkaloids (vasoconstrictor)	None	Ergotamine derivatives	Ergotamine derivatives
Herbs	St. John's wort	St. John's wort	St. John's wort
Other		Amprenavir, fosamprenavir, carbamazepine, phenobarbital, phenytoin	Voriconazole

Table 7

Drug Interactions with NNRTIs Requiring Dose Modifications or Cautious Use

Drugs affected	Nevirapine (NVP)	Delavirdine (DLV)	Efavirenz (EFV)
Antifungals			
Ketoconazole (keto)	Levels: keto ↓63%; NVP ↑15-30%; dose: not recommended	DLV C _{min} ↑50%; keto levels: no data; dose: standard	No data
Voriconazole (vori)	Metabolism of vori may be induced by NVP; vori may inhibit NNRTI metabolism; frequently monitor for NNRTI toxicity and antifungal outcome	Metabolism of vori may be inhibited by DLV; vori may inhibit NNRTI metabolism; frequently monitor for NNRTI toxicity and antifungal outcome	Levels: EFV ↑44%; vori: ↓77%; dose: not recommended
Fluconazole (flu)	Levels: NVP ↑100%; flu: no change; risk of hepatotoxicity may increase with this combination; if concomitant use is necessary, recommend monitoring of NVP toxicity	No clinically significant changes in DLV or flu concentrations	No clinically significant changes in DLV or flu concentrations
Antimycobacterials			
Rifampin	Levels: NVP ↓20-58%; virologic consequences are uncertain; the potential for additive hepatotoxicity exists; use of this combination is not recommended; however, if used, coadministration should be done with careful monitoring	Levels: DLV ↓96%; contraindicated	Levels: EFV ↓25%; dose: consider ↑EFV to 800 mg q24h
Rifabutin	Levels: NVP ↓16%; no dose adjustments ¹	Levels: DLV ↓80%; rifabutin ↑100%; dose: not recommended	Levels: EFV unchanged; rifabutin ↓35%; dose: ↑ rifabutin dose to 450-600 mg qd or 600 mg 3 x per wk; EFV dose standard
Clarithromycin (clarithro)	Levels: NVP ↑26%; clarithro ↓30%; monitor for efficacy or use alternative agent	Levels: DLV ↓44% clarithro ↑100%; dose adjust for renal failure	Levels: clarithro ↓39%; monitor for efficacy or use alternative agent
Oral contraceptives			
	Levels: ethinyl estradiol (EE) ↓20%; use alternative or additional birth control methods	Levels: EE may increase; clinical significance unknown	Levels: EE ↑37%; no data on other component; use alternative or additional birth control methods
Lipid-lowering agents			
Simvastatin (simva), lovastatin	No data	Potential for large increase in statin levels; avoid concomitant use	Levels: simva AUC ↓58%; EFV unchanged; dose: adjust simva dose according to lipid responses, not to exceed the maximum simva dose
Atorvastatin (atorva)	No data	Potential for inhibition of atorva metabolism; use lowest dose and monitor for toxicity	Levels: atorva AUC ↓58%; EFV unchanged; adjust atorva dose according to lipid responses, not to exceed the maximum atorva dose

(continued)

¹These recommendations apply to regimens that do not include PIs, which can substantially increase rifabutin levels.

Table 7

Drug Interactions with NNRTIs Requiring Dose Modifications or Cautious Use (continued)

Drugs affected	Nevirapine (NVP)	Delavirdine (DLV)	Efavirenz (EFV)
Anticonvulsants			
Phenobarbital, phenytoin, carbamazepine	Unknown; use with caution; monitor anticonvulsant levels	Levels: DLV C_{min} ↓90%; contraindicated	Use with caution; monitor anticonvulsant levels
Methadone	Levels: NVP unchanged, methadone ↓ significantly; ↑ methadone dose often necessary	Levels: DLV unchanged; methadone: no data; potential for ↑ methadone levels; monitor for toxicity; may require dose reduction	Levels: methadone ↓60%; ↑ methadone dose often necessary; titrate methadone dose to effect
Miscellaneous	No data	May ↑ levels of dapsone, warfarin, quinidine; sildenafil; vardenafil, tadalafil	Monitor warfarin when used concomitantly

Table 8

Characteristics of Protease Inhibitors (PIs)

Generic name [trade name]	Lopinavir + ritonavir (LPV/r) [Kaletra®]	Nelfinavir (NFV) [Viracept®]	Atazanavir (ATV) [Reyataz®]
Form	200 mg lopinavir + 100 mg ritonavir tabs; 400 mg lopinavir + 100 mg ritonavir per 5 mL oral solution 500 mg q 12h with ritonavir 200 mg q 12h	250, 625 mg tabs; 50 mg/g oral powder	100, 150, 200 mg caps
Dosing recommendations	400 mg lopinavir + 100 mg ritonavir q 12h; 800 mg lopinavir + 200 mg ritonavir q 24h	1250 mg q 12h; 750 mg q 8h	400 mg q day; ATV 300 mg + RTV 100 mg q 24h
Food effect	Tab – No food effect Liquid – Take with food	Take with food	Take with food
Adverse events¹	GI intolerance, asthenia, ↑ LFTs	Diarrhea	Increased indirect hyperbilirubinemia, prolonged PR interval-some patients experienced asymptomatic 1st degree AV block, use with caution in patients with underlying conduction defects or on concomitant medications that can cause PR prolongation
Drug interactions	CYP450 3A4 inhibitor and substrate, see tables 10 and 11	CYP450 3A4 inhibitor and substrate, see tables 10 and 11	CYP450 3A4 inhibitor and substrate, see tables 10 and 11
Storage	Tabs – Room temperature Refrigerated liquid stable until date on label; stable for 2 months at room temperature	Room temperature	Room temperature
Additional information	Oral solution contains 42% alcohol	Needs 500 kcal of food for absorption; take after eating; boosting with RTV not effective	Reduced incidence of hyperlipidemia, must use boosted regimen with tenofovir or efavirenz, needs normal GI acid concentrations for absorption

Bold type highlights the most common dosing and important side effects.

¹ PI class side effects: lipodystrophy, hyperglycemia, hyperlipidemia, hypertriglyceridemia, bleeding in hemophiliacs, osteonecrosis and avascular necrosis of the hips, osteopenia and osteoporosis

Table 8

Characteristics of Protease Inhibitors (PIs)

Generic name [trade name]	Fosamprenavir (f-APV) [Lexiva®]	Amprenavir (APV) [Agenerase®]	Saquinavir (SQV) SQV-hard gel cap (HGC) [Invirase®]	Darunavir (TMC-114) [Prezista®]
Form	700 mg tab	50 mg cap, 15 mg/mL oral solution	200 mg cap, 500 mg tab	300 mg tabs
Dosing recommendations	ART naïve patients: f-APV 1,400 mg q 12h; or f-APV 1,400 mg + RTV 200 mg q day; or f- APV 700 mg + RTV 100 mg q 12h PI experienced patients: f-APV 700 mg + RTV 100 mg q 12h	1,400 mg q 12h (oral solution) – Do not take with RTV oral solution	SQV 1,000 mg + RTV 100 mg q 12 h – Invirase is not recommended as a single PI	600 mg q 12h with ritonavir 100 mg q 12h
Food effect	With or without food	With or without food, avoid high fat meal	Take with food	Take with food
Adverse events¹	Skin rash, GI intolerance, headache	GI intolerance, skin rash, oral paresthesias, ↑LFTs	GI intolerance, headache, ↑LFTs	Diarrhea, nausea, headache nasopharyngitis, rash, ↑pancreatic amylase (significance unknown)
Drug interactions	CYP450 3A4 inhibitor, inducer and substrate, see Tables 10 and 11	CYP450 3A4 inhibitor, inducer and substrate, see Tables 10 and 11	CYP450 3A4 inhibitor, and substrate, see Tables 10 and 11	CYP 450 3A4 inhibitor and substrate
Storage	Room temperature	Room temperature	Room temperature	Room temperature
Additional information	Sulfonamide, caution in patients with history of sulfa allergy, caps and solution are not equivalent, oral solution contains propylene glycol ²	Sulfonamide, caution in patients with history of sulfa allergy	Invirase is not recommended as a single PI, always boost Fortovase will no longer be manufactured by the end of 2006.	TMC-114 has a sulfonamide moiety, use with caution in patients with known sulfonamide allergy

Bold type highlights the most common dosing and important side effects.

¹ PI class side effects: lipodystrophy, hyperglycemia, hyperlipidemia, hypertriglyceridemia, bleeding in hemophiliacs, osteonecrosis and avascular necrosis of the hips, osteopenia and osteoporosis. ² Contraindicated in pregnant women, children <4 years old, patients with hepatic or renal failure, and patients treated with disulfiram or metronidazole.

(continued)

Table 8

Characteristics of Protease Inhibitors (PIs) (continued)

Generic name [trade name]	Tipranavir (TPV) [Aptivus®]	Ritonavir (RTV) [Norvir®]	Indinavir (IDV) [Crixivan®]
Form	250 mg caps	100 mg caps; 600 mg/7.5 mL oral solution	200, 333, 400 mg caps
Dosing recommendations	500 mg q 12h with ritonavir 200 mg q 12h	100-400 mg with other PIs for intensification; 600 mg q 12h as single PI	800 mg q 8h or 800 mg IDV + 100-200 mg RTV q 12h
Food effect	Take with food	Take with food	Take 1 h before or 2 h after meals; may take with skim milk or low fat meal, when boosting can take with or without food
Adverse events¹	Hepatotoxicity, skin rash, intracranial hemorrhage (rare), inhibits human platelet aggregation, ↑PT and pTT in rodents	GI intolerance, paresthesias, hepatitis, pancreatitis, asthenia, taste perversion	Nephrolithiasis, GI intolerance, ↑bilirubinemia, headache, asthenia, blurred vision, dizziness, rash, metallic taste, thrombocytopenia, alopecia, hemolytic anemia
Drug interactions	CYP450 3A4 inducer and substrate Net effect when combined with RTV – CYP 3A4 and 2D6 inhibitor	CYP450 3A4, 2D6 inhibitor	CYP450 3A4 inhibitor
Storage	Refrigerated caps stable until date on label; stable for 60 days at room temperature	Refrigerated caps stable until date on label; stable for 1 month at room temperature	Room temperature
Additional information	Clinical hepatitis including hepatic decompensation has been reported, monitor closely, esp. in patients with underlying liver diseases. TPV has a sulfonamide moiety, use with caution in patients with known sulfonamide allergy Fourteen intracranial hemorrhage (ICH) events including 8 fatalities have been reported. Many ICH patients had other medical conditions increasing risk.	Primary role is in intensification of other PIs, most potent CYP450 inhibitor in the class, when used as a single PI dose should be titrated to above target dose	Patients should drink ≥ 48 oz of H ₂ O daily to reduce incidence of kidney stones; boosted indinavir increases incidence of kidney stones, requires additional monitoring for signs and symptoms of kidney stones, indirect bilirubin and platelets

Bold type highlights the most common dosing and important side effects.

¹PI class side effects: lipodystrophy, hyperglycemia, hyperlipidemia, hypertriglyceridemia, bleeding in hemophiliacs, osteonecrosis and avascular necrosis of the hips, osteopenia and osteoporosis

- Entry inhibitors include enfuvirtide (T20), Fuzeon®
 - * Mechanism of action: binds to gp41 on HIV surface, which inhibits HIV binding to CD4 cell
 - * Dose: 90 mg SC q12h
 - * Side effects: injection-site reactions, increased rate of bacterial pneumonia, hypersensitivity
- Generally reserved for deep salvage regimens
- Preferably should be used with at least two other active drugs
- Resistance develops quickly with less potent regimens and in cases of poor adherence.

- No known significant drug interactions seen to date.
- Take without regard to meals.
- Store at room temperature; reconstituted form should be stored in the refrigerator, where it will be stable for 24 hours.

Counseling

- All patients should be counseled on the importance of adherence.
 - * >95% adherence is necessary to decrease the incidence of resistance.

Table 9

Drugs That Should Not Be Used with PIs

Drug category	Indinavir	Ritonavir	Saquinavir	Darunavir	Tipranavir
Calcium channel blockers	None	Bepridil	None	None	Bepridil
Cardiac	Amiodarone	Amiodarone, flecainide, propafenone, quinidine	None	None	Amiodarone, flecainide, propafenone, quinidine
Lipid-lowering agents	Simvastatin, lovastatin	Simvastatin, lovastatin	Simvastatin, lovastatin	Simvastatin, lovastatin	Simvastatin, lovastatin
Antimycobacterial	Rifampin, rifapentine	Rifapentine	Rifampin, rifabutin, rifapentine	Rifampin	Rifampin, rifapentine
Antihistamine	Astemizole, terfenadine	Astemizole, terfenadine	Astemizole, terfenadine	Astemizole, terfenadine	Astemizole, terfenadine
Gastrointestinal drugs	Cisapride	Cisapride	Cisapride	Cisapride	Cisapride
Neuroleptic	Pimozide	Pimozide	Pimozide	Pimozide	Pimozide
Psychotropic	Midazolam, triazolam	Midazolam, triazolam	Midazolam, triazolam	Midazolam, triazolam	Midazolam, triazolam
Ergot alkaloids (vasoconstrictor)	Ergot derivatives	Ergot derivatives	Ergot derivatives	Ergot derivatives	Ergot derivatives
Herbs	St. John's wort	St. John's wort	St. John's wort	St. John's wort	St. John's wort
Other	Atazanavir	Voriconazole (with RTV ≥ 400 mg bid), fluticasone, alfuzosin		Carbamazepine, phenobarbital, phenytoin	Fluticasone

(continued)

- Patients should be given tools to facilitate adherence to complicated regimens (eg, pill boxes, calendars, pagers, etc).
- Patients should be counseled on class side effects, especially any that are unique or potentially serious.

Antiretroviral Therapy in the HIV-Infected Pregnant Woman

- Highly active antiretroviral therapy (HAART) should be offered if the patient is not already receiving treatment.
 - * Efavirenz should be avoided.
 - * Avoid combining stavudine and didanosine.
 - * Consider starting treatment after the first trimester.
- Continue current combination regimens (preferably with zidovudine) if the patient is already receiving therapy (decreases the risk of transmission from 30 to 2.5%).
- Zidovudine alone can decrease risk of transmission when taken during pregnancy. The mother should also receive IV zidovudine during labor; the infant should receive 6 weeks of zidovudine (Table 11).
- Single-dose nevirapine at onset of labor in women who have had no prior antiretroviral therapy and given once to the infant between 48 and 72 hours of

age, has been shown to decrease the transmission rate. This can also result in resistance to nevirapine if used in future regimens.

Postexposure Prophylaxis (PEP) (Table 12)

- Use universal precautions.
- The most common infectious exposure is needle-sticks or cuts (1 in 300 risk).
- The risk with mucous membrane exposure is much lower (1 in 1000 risk).
- There have been 52 documented cases of occupationally-acquired HIV infection.
- Postexposure prophylaxis can reduce HIV infection by about 80%.
- Start therapy within 1-2 hours of exposure.
- Length of therapy is 4 weeks.

Postexposure Prophylaxis After Sexual, Injection-Drug Use, or Other Nonoccupational Exposure to HIV (nPEP)

- Patients with exposure to HIV from a known positive source should receive nPEP.
- nPEP should be started within 72 hours of the exposure.

Table 9

Drugs That Should Not Be Used with PIs (continued)

Drug category	Nelfinavir	Amprenavir Fosamprenavir	Lopinavir/ ritonavir	Atazanavir
Calcium channel blockers	None	Bepridil	None	Bepridil
Cardiac	None	None	Flecainide, propafenone	None
Lipid-lowering agents	Simvastatin, lovastatin	Simvastatin, lovastatin	Simvastatin, lovastatin	Simvastatin, lovastatin
Antimycobacterial	Rifampin, rifapentine	Rifampin, rifapentine	Rifampin, rifapentine	Rifampin, rifapentine
Antihistamine	Astemizole, terfenadine	Astemizole, terfenadine	Astemizole, terfenadine	Astemizole, terfenadine
Gastrointestinal drugs	Cisapride	Cisapride	Cisapride	Cisapride, proton pump inhibitors
Neuroleptic	Pimozide	Pimozide	Pimozide	Pimozide
Psychotropic	Midazolam, triazolam	Midazolam, triazolam	Midazolam, triazolam	Midazolam, triazolam
Ergot alkaloids (vasoconstrictor)	Ergot derivatives	Ergot derivatives	Ergot derivatives	Ergot derivatives
Herbs	St. John's Wort	St. John's Wort	St. John's Wort	St. John's Wort
Other		Delavirdine, oral contraceptives	Fluticasone	Indinavir, Irinotecan

- The length of therapy is 28 days.
- Treatment options are the same as those listed on the DHHS guidelines for initial regimens (see Table 2).

Opportunistic Infections

- Only two opportunistic infections require primary prophylaxis:
 - * *Pneumocystis carinii* pneumonia (PCP)
 - When CD4⁺ cells fall below 200/mm³
 - The treatment of choice is trimethoprim-sulfamethoxazole (TMP-SMX) DS PO qd (see Table 13 for alternatives).
 - * *Mycobacterium avium* complex bacteremia (MAC)
 - When CD4⁺ cells fall below 50/mm³
 - Treatment of choice is azithromycin 1200 mg PO every week
- All other primary prophylaxis occurs only if the patient is antigen-positive and at high risk of exposure to the causative factor.
- All other opportunistic infections are treated when the patient is diagnosed.
- After treatment, patients receive suppressive therapy.
- Some primary and secondary prophylaxis could possibly be discontinued with immune reconstitution (undetectable viral load and an increase in CD4 cells in response to HAART therapy; see Table 13).

3. Prevention

- Abstain from sex with an infected person.
- Ask about the sexual history of current and future sex partners.
- Reduce the number of sex partners to minimize the risk of HIV infection.
- Always use a latex condom from start to finish during any type of sex (vaginal, anal, or oral).
- Use only water-based lubricants.
- Avoid alcohol, illicit drugs, and sharing of needles (or syringes, cookers, or other drug paraphernalia).
- Do not share personal items such as toothbrushes, razors, or any devices used during sex. Such items may be contaminated by blood, semen, or vaginal secretions.
- Do not donate blood, plasma, sperm, body organs, or tissues if you are infected with HIV or have engaged in sex or needle-sharing behaviors that are risk factors for infection with HIV.

Table 10

Drug Interactions with PIs Requiring Dose Modifications or Cautious Use

Drugs affected	Indinavir (IDV)	Ritonavir (RTV)	Saquinavir (SQV)
Antifungals			
Itraconazole (itra)	Levels: IDV ↑	No data, but potential for bi-directional inhibition between itra and RTV; monitor for toxicities	Bi-directional interaction between itra and SQV has been observed
Ketoconazole (keto)	Levels: IDV ↑ 68%	Levels: keto ↓ 3x	Levels: SQV ↑ 3x
Voriconazole (vori)	No changes in levels of either drug	Levels: vori AUC ↓ 82% when coadministered with 400 mg bid of RTV; concomitant therapy contraindicated	No data, but potential for bi-directional inhibition between vori and PIs; monitor for toxicities
Antimycobacterials			
Rifampin	Contraindicated	Levels: RTV ↓ 35%; dose: no change; ↑ liver toxicity possible	Levels: SQV ↓ 84%; contraindicated
Rifabutin	Levels: IDV ↓ 32%; rifabutin ↑ 2x; dose: ↓ rifabutin to 150 mg qd or 300 mg 3 x per week; IDV 1000 mg q8h	Levels: rifabutin ↑ 4x; dose: ↓ rifabutin to 150 mg qd or 300 mg 3x/week	Levels: SQV ↓ 40%; contraindicated unless using SQV/RTV; dose: ↓ rifabutin to 150 mg qd or 300 mg 3x/week
Clarithromycin (clarithro)	Levels: clarithro ↑ 53%; no dose adjustment	Levels: clarithro ↑ 77%; dose: adjust dose for moderate and severe renal impairment	Levels: clarithro ↑ 45%; SQV ↑ 177%; no dose adjustment
Oral contraceptives			
	Levels: norethindrone ↑ 26%, ethinyl estradiol ↑ 24%; no dose adjustment	Levels: ethinyl estradiol ↓ 40%; use alternative or additional method	No data
Lipid-lowering agents			
Simvastatin, lovastatin	Levels: potential for large increase in statin levels; avoid concomitant use	Levels: potential for large increase in statin levels; avoid concomitant use	Levels: potential for large increase in statin levels; avoid concomitant use
Atorvastatin (atorva)	Use lowest possible starting dose of atorva with careful monitoring	Use lowest possible starting dose of atorva with careful monitoring	Use lowest possible starting dose of atorva with careful monitoring
Pravastatin (prava)	No data	Adjust prava dose based on lipid response	Levels: ↓ 50% when administered with SQV/RTV
Anticonvulsants			
Phenobarbital, phenytoin, carbamazepine	Carbamazepine ↓ IDV	↑ Carbamazepine levels	All may ↓ SQV levels
Methadone	No change in methadone levels	↓ Methadone levels	↓ Methadone levels
Erectile dysfunction agents			
Sildenafil	Sildenafil AUC ↑ 3-fold; use with caution and lowest dose	Sildenafil AUC ↑ 11-fold; use with caution and lowest dose	Sildenafil AUC ↑ 2-fold; use with caution and lowest dose
Vardenafil	Vardenafil AUC ↑ 16-fold; use with caution and lowest dose	Vardenafil AUC ↑ 49-fold; use with caution and lowest dose	No data but same interaction as with other PIs is suspected; use with caution and lowest dose
Tadalafil	Tadalafil AUC ↑ substantially; use with caution and lowest dose	Tadalafil AUC ↑ 124%; use with caution and lowest dose	Tadalafil AUC ↑ substantially; use with caution and lowest dose
Miscellaneous			
	Grapefruit juice ↓ IDV levels 26%; vitamin C ≥ 1 g/d ↓ IDV levels; amlodipine AUC ↑ 90%	Many possible interactions; desipramine ↑ 145%; trazodone AUC ↑ 2.4-fold; theophylline ↓ 47%; ↑ oral or nasal fluticasone	Grapefruit juice ↑ SQV levels; dexamethasone ↓ SQV levels

(continued)

Table 10

Drug Interactions with PIs Requiring Dose Modifications or Cautious Use (continued)

Drugs affected	Nelfinavir (NFV)	Amprenavir (APV)	Fosamprenavir (f-APV)
Antifungals			
Itraconazole (itra)	No data, but potential for bi-directional inhibition between itra and PIs; monitor for toxicities	No data, but potential for bi-directional inhibition between itra and PIs; monitor for toxicities	No data, but potential for bi-directional inhibition between itra and PIs; monitor for toxicities
Ketoconazole (keto)	No dose adjustment necessary	Levels: keto ↑44%; APV ↑31%	Presumably similar interactions as with APV
Voriconazole (vori)	No data, but potential for bi-directional inhibition between vora and PIs; monitor for toxicities	No data, but potential for bi-directional inhibition between vora and PIs; monitor for toxicities	No data, but potential for bi-directional inhibition between vora and PIs; monitor for toxicities
Antimycobacterials			
Rifampin	Contraindicated	Contraindicated	Contraindicated
Rifabutin	Rifabutin ↑ 2x; dose: ↓ rifabutin to 150 mg qd or 300 mg 3x/week; NFV 1250 mg q12h	Levels: rifabutin ↑193%; dose: ↓ rifabutin to 150 mg qd or 300 mg 3x/week	Presumably similar interactions as with APV
Clarithromycin (clarithro)	No data	No dose adjustment	Presumably similar interactions as with APV
Oral contraceptives			
	Levels: norethindrone ↓18%, ethinyl estradiol ↓47%; use alternative or additional method	Levels: ↑ levels of ethinyl estradiol and norethindrone; APV levels ↓20%; use alternative method	Presumably similar interactions as with APV
Lipid-lowering agents			
Simvastatin, lovastatin	Levels: potential for large increase in statin level; avoid concomitant use	Levels: potential for large increase in statin level; avoid concomitant use	Levels: potential for large increase in statin level; avoid concomitant use
Atorvastatin (atorva)	Use lowest possible starting dose of atorva with careful monitoring	Use lowest possible starting dose of atorva with careful monitoring	Use lowest possible starting dose of atorva with careful monitoring
Pravastatin (prava)	No data	No data	No data
Anticonvulsants			
Phenobarbital, phenytoin, carbamazepine	Unknown, but may ↓ NFV levels substantially	Unknown, but may ↓ APV levels substantially	Unknown, but may ↓ f-APV levels substantially
Methadone	↓ Methadone levels	↓ Methadone levels	↓ Methadone levels
Erectile dysfunction agents			
Sildenafil	Sildenafil AUC ↑ 2- to 11-fold; use with caution and lowest dose	Sildenafil AUC ↑ 2- to 11-fold; use with caution and lowest dose	Presumably similar interactions as with APV
Vardenafil	No data, but vardenafil AUC may be substantially ↑; use with caution and lowest dose	No data, but vardenafil AUC may be substantially ↑; use with caution and lowest dose	Presumably similar interactions as with APV
Tadalafil	Tadalafil AUC ↑ substantially; use with caution and lowest dose	Tadalafil AUC ↑ substantially; use with caution and lowest dose	Presumably similar interactions as with APV

(continued)

Table 10

Drug Interactions with PIs Requiring Dose Modifications or Cautious Use (continued)

Drugs affected	Atazanavir (ATV)	Lopinavir (LPV)
Antifungals		
Itraconazole (itra)	No data, but potential for bi-directional inhibition between itra and PIs; monitor for toxicities	Levels: ↑ itra
Ketoconazole (keto)	No dose adjustment necessary	Levels: keto ↑ 3-fold; LPV AUC ↓ 13%
Voriconazole (vori)	No data, but potential for bi-directional inhibition between vori and PIs; monitor for toxicities	No data, but potential for bi-directional inhibition between vora and PIs; monitor for toxicities
Antimycobacterials		
Rifampin	Contraindicated	Contraindicated
Rifabutin	Rifabutin AUC ↑ 2.5-fold; dose: ↓ rifabutin to 150 mg qd or 300 mg 3x/week; NFV 1250 mg q12h	Levels: rifabutin AUC ↑ 3-fold; dose: ↓ rifabutin to 150 mg qd or 300 mg 3x/week
Clarithromycin (clarithro)	Clarithro AUC ↑ 94%; may cause QT prolongation; ↓ dose 50%	Clarithro AUC ↑ 77%; adjust clarithro dose for moderate to severe renal impairment
Oral contraceptives		
	Levels: norethindrone AUC ↑ 110%, ethinyl estradiol ↑ 48%; use alternative or additional method	Levels: ↑ ethinyl estradiol 42%; use alternative or additional method
Lipid-lowering agents		
Simvastatin, lovastatin	Levels: potential for large increase in statin level; avoid concomitant use	Levels: potential for large increase in statin level; avoid concomitant use
Atorvastatin (atorva)	Use lowest possible starting dose of atorva with careful monitoring	Use lowest possible starting dose of atorva with careful monitoring
Pravastatin (prava)	No data	No dosage adjustment necessary
Anticonvulsants		
Phenobarbital, phenytoin, carbamazepine	Unknown, but may ↓ ATV levels substantially	Avoid concomitant use or monitor LPV level
Methadone	No change in methadone levels	↓ Methadone levels
Erectile dysfunction agents		
Sildenafil	Sildenafil levels ↑; use with caution and lowest dose	Sildenafil AUC ↑ 11-fold; use with caution and lowest dose
Vardenafil	No data, but vardenafil AUC may be substantially ↑; use with caution and lowest dose	No data, but vardenafil AUC may be substantially ↑; use with caution and lowest dose
Tadalafil	Tadalafil AUC ↑ substantially; use with caution and lowest dose	Tadalafil AUC ↑ substantially; use with caution and lowest dose
Miscellaneous		
	Diltiazem AUC ↑ 125%; caution with other calcium channel blockers; contraindicated with irinotecan; separate from H ₂ -blockers by 12 hours; separate from antacids (give ATV 2 hours before or 1 hour after antacids)	

(continued)

Table 10

Drug Interactions with PIs Requiring Dose Modifications or Cautious Use (continued)

Drugs affected	Tipranavir (TPV)
Antifungals	
Itraconazole (itra)	No data. Use with caution; do not exceed 200 mg itraconazole daily.
Ketoconazole (keto)	No data. Use with caution; do not exceed 200 mg ketoconazole daily.
Voriconazole (vori)	Potential for bi-directional inhibition between voriconazole and PIs exists. Voriconazole AUC ↓ 39% with RTV 100 mg BID; interaction between TPV and voriconazole unknown. Co-administration is not recommended unless the benefit outweighs the risk.
Antimycobacterials	
Rifampin	No data; should not be coadministered
Rifabutin	Levels: Rifabutin AUC ↑ 2.9 fold Dose: ↓ rifabutin to 150 mg qod or 3x/week
Clarithromycin (clarithro)	Levels: TPV ↑ 66%, clarithromycin ↑ 19%, 14-hydroxy-clarithromycin metabolite ↓ 97%. Dose: No adjustment for patients with normal renal function; reduce clarithromycin dose by 50% for CrCl 30-60 mL/min; reduce clarithromycin dose by 75% for CrCl < 30 mL/min.
Oral contraceptives	
	Levels: ↓ ethinyl estradiol C _{max} and ↓ AUC 50%. Use alternative or additional method. Women on estrogen may have ↑ risk of non-serious rash.
Lipid-lowering agents	
Simvastatin, lovastatin	Levels: Potential for large increase in statin level. Avoid concomitant use.
Atorvastatin (atorva)	Levels: atorvastatin AUC ↑ 9 fold. Use lowest possible starting dose of atorvastatin with careful monitoring.
Pravastatin (prava)	No data
Anticonvulsants	
Phenobarbital, phenytoin, carbamazepine	No data. Consider alternative anticonvulsant. Monitor anticonvulsant levels and consider obtaining TPV levels.
Methadone	No data. Dosage of methadone may need to be increased when co-administered with TPV/r.
Erectile dysfunction agents	
Sildenafil	No data. Starting dose should not exceed 25 mg sildenafil within 48 hours.
Vardenafil	No data. Starting dose should not exceed 2.5 mg vardenafil every 72 hours.
Tadalafil	No data. Starting dose should not exceed 10 mg tadalafil every 72 hours.
Miscellaneous	
	Abacavir ↓ 35-44%. Appropriate doses for combination of ABC and TPV/r have not been established.
	Zidovudine ↓ 31-43%. Appropriate doses for the combination of ZDV and TPV/r have not been established.
	Loperamide ↓ 51%. TPV C _{min} ↓ 26% with loperamide
	Antacids ↓ TPV ~30%, TPV should be administered 2 hrs before or 1 hour after antacids.
	Fluconazole: Doses > 200 mg/day are not recommended to be given with TPV.
	TPV capsules contain alcohol. Avoid use of disulfiram and metronidazole.

(continued)

Table 10

Drug Interactions with PIs Requiring Dose Modifications or Cautious Use (continued)

Drugs affected	Darunavir (TMC-114)
Antifungals	
Itraconazole (itra)	No data. Use with caution; do not exceed 200 mg itraconazole daily.
Ketoconazole (keto)	Use with caution; do not exceed 200 mg ketoconazole daily.
Voriconazole (vori)	Potential for bi-directional inhibition between voriconazole and PIs exists. Voriconazole AUC ↓ 39% with RTV 100 mg BID; interaction between TMC-114 and voriconazole unknown. Co-administration is not recommended unless the benefit outweighs the risk.
Antimycobacterials	
Rifampin	
Rifabutin	Levels: ↑ rifabutin; ↓ TMC-114 Dose: ↓ rifabutin to 150 mg qod or 3x/week
Clarithromycin (clarithro)	↑ Clarithromycin – no dose adjustment of TMC-114 or clarithromycin is required for patients with normal renal function. Reduce clarithromycin dose by 50% for CrCl 30-60 mL/min; reduce clarithromycin dose by 75% for CrCl <30 mL/min.
Oral contraceptives	
	↓ ethinyl estradiol; ↓ norethindrone Use alternative or additional method.
Lipid-lowering agents	
Simvastatin, lovastatin	Levels: Potential for large increase in statin level. Avoid concomitant use.
Atorvastatin (atorva)	Levels: ↑ atorvastatin. Use lowest possible starting dose of atorvastatin with careful monitoring.
Pravastatin (prava)	Levels: ↑ pravastatin AUC 81% - 5 fold. Use lowest possible starting dose of pravastatin with careful monitoring.
Anticonvulsants	
Phenobarbital, phenytoin, carbamazepine	Contraindicated
Methadone	↓ methadone
Erectile dysfunction agents	
Sildenafil	↑ sildenafil. Starting dose should not exceed 25 mg sildenafil within 48 hours.
Vardenafil	↑ vardenafil. Starting dose should not exceed 2.5 mg vardenafil every 72 hours.
Tadalafil	↑ tadalafil. Starting dose should not exceed 10 mg tadalafil every 72 hours.
Miscellaneous	
	Concentrations of bepridil, lidocaine, quinidine and amiodarone may be ↑ when co-administered with TMC-114. Caution is warranted and therapeutic monitoring is recommended.
	↑ levels of trazadone – use with caution
	Concentrations of felodipine, nifedipine, and nifedipine may be ↑ when co-administered with TMC-114. Caution is warranted and therapeutic monitoring is recommended.
	↓ TMC-114; ↑ fluticasone, dexamethasone (theoretical) – consider alternatives
	↓ sertraline, ↓ paroxetine – monitor carefully

Table 11

ACTG 076 Guidelines: Dosing of AZT for Prevention of Vertical Transmission

Antepartum	Initiation at 14-34 weeks' gestation and continued throughout pregnancy A. PACTG 076 regimen: AZT 100 mg 5 times daily B. Acceptable alternative regimens: AZT 200 mg 3 times daily <i>or</i> AZT 300 mg 2 times daily
Intrapartum	During labor, AZT 2 mg/kg IV over 1 hour, followed by a continuous infusion of 1 mg/kg/h IV until delivery
Postpartum	Oral administration of AZT to the newborn: AZT syrup 2 mg/kg every 6 hours for the first 6 weeks of life, beginning 8-12 hours after birth

Table 12

Prevention or Postexposure Prophylaxis Treatment Options

Small volume, short duration <i>and</i> high HIV titer exposure <i>or</i>	AZT 200 mg PO q8h or 300 mg PO q12h <i>plus</i>
Large volume or less severe percutaneous <i>and</i> low HIV titer exposure	3TC (lamivudine) 150 mg PO q12h
Large volume or less severe percutaneous <i>and</i> high HIV titer exposure <i>or</i>	AZT 200 mg PO q8h or 300 mg PO q12h + 3TC (lamivudine) 150 mg PO q12h + Indinavir 800 mg q8h <i>or</i>
More severe percutaneous <i>and</i> low or high HIV titer exposure	Nelfinavir 750 mg PO q8h or 1250 mg q12h

4. Hematologic Complications**Anemia****Causes**

- HIV infection of marrow progenitor cells
- Drug-induced marrow suppression (AZT, ganciclovir, amphotericin, ribavirin, pyrimethamine, interferon, TMP-SMX)

Treatment

- See Figure 1.

5. Key Points

- Human immunodeficiency virus (HIV) is a virus that destroys the immune system.
- Acquired immunodeficiency syndrome (AIDS) is caused by HIV and is defined as a CD4⁺ cell count less than 200/mm³ or the presence of an opportunistic infection.
- Acute retroviral syndrome occurs in 50%-90% of patients within the first 2-4 weeks of infection with HIV.
- The viral load indicates the amount of virus in the body and is an indication of how well antiretroviral medications are working.
- The CD4⁺ cell count refers to the status of the immune system and how at-risk a patient is for developing an opportunistic infection.
- Nucleoside reverse transcriptase inhibitors (NRTIs),

Table 13

Opportunistic Infections

Pathogen	Indication	First choice	Alternative regimens	Comments
<i>Pneumocystis jiroveci</i> pneumonia (PCP)	Prophylaxis: CD4 ⁺ <200/mm ³ ; thrush; unexplained fever ≥2 weeks; history of PCP	TMP-SMX DS qd; TMP-SMX SS PO qd	Dapsone 100 mg PO qd; atovaquone 1500 mg qd; aerosolized pentamidine 300 mg q mo; TMP-SMX DS q MWF; others	Primary and secondary prophylaxis can possibly be stopped for PCP upon immune reconstitution (patients on HAART with CD4 ⁺ greater than 200/mm ³ for >3 mo)
<i>Pneumocystis jiroveci</i> pneumonia (PCP)	Acute infection	TMP 15-20 mg/kg/d + SMX 75-100 mg/kg/d PO or IV x 21 d in 3-4 divided doses (typical oral dosage is TMP-SMX DS 2 tabs q8h)	TMP 15 mg/kg/d PO + dapsone 100 mg PO qd x 21 d; atovaquone 750 mg suspension PO with meal bid 21 days; pentamidine 4 mg/kg/d IV x 21 d (severe cases); clindamycin 600-900 mg IV q8h or 300-450 mg PO q6h + primaquine 15-30 mg base PO/d x 21 d; trimethoprim 45 mg/m ² IV/d + folinic acid 20 mg/m ² PO or IV q6h	Patients with Po ₂ <70 mm Hg or A-a gradient >35 mm Hg should receive a corticosteroid taper; treatment is for 21 d
<i>Candida</i>	Treatment	Oropharyngeal (thrush): fluconazole 100 mg qd x 7-14 days; itraconazole solution 200 mg qd x 7-14 days; clotrimazole oral troches 10 mg 5 x/d for 7-14 d; nystatin 500,000 U gargled qid for 7-14 d; esophagitis: fluconazole 100-400 mg qd x 2-3 wk; itraconazole solution 200 mg qd x 2-3 wk; voriconazole 200 mg bid x 2-3 wk; caspofungin 50 mg IV qd x 2-3 wk	Thrush: fluconazole 100 mg qd; amphotericin B 0.3-0.5 mg/kg/d IV; itraconazole solution 7200 mg PO qd; esophagitis: ketoconazole 200 mg qd; itraconazole 200 mg qd (caps) or 100 mg qd (susp)	Thrush: treat for 10-14 d; CD4 ⁺ <500/mm ³ increases risk; esophagitis: treat for 2-3 wk; CD4 ⁺ <500/mm ³ increases risk

(continued)

non-nucleoside reverse transcriptase inhibitors (NNRTIs), protease inhibitors (PIs), and entry inhibitors are the currently available classes of medications used to treat HIV.

- Prevention of vertical transmission occurs by treating the mother with highly active antiretroviral therapy (HAART; preferred) or zidovudine alone.

- *Pneumocystis carinii* pneumonia (PCP) requires primary prophylaxis at CD4⁺ cell counts <200/mm³. TMP-SMX is the preferred treatment.
- *Mycobacterium avium* complex (MAC) requires primary prophylaxis at CD4⁺ cell counts <50/mm³. Azithromycin is the preferred drug.
- All other opportunistic infections require treatment followed by secondary prophylaxis.

Table 13

Opportunistic Infections (continued)

Pathogen	Indication	First choice	Alternative regimens	Comments
<i>Candida</i>	Maintenance	Thrush: fluconazole 100 mg qd; esophagitis : fluconazole 100-200 mg qd	Thrush: itraconazole solution 200 mg qd; esophagitis : itraconazole solution 200 mg qd	Thrush: most patients relapse within 3 mo in absence of immune reconstitution; options are treatment of each episode or maintenance: esophagitis : maintenance therapy is generally needed to prevent relapse
<i>Candida</i>	Primary prophylaxis	Not recommended; efficacy of fluconazole is established for AIDS patients with CD4 counts $<100/\text{mm}^3$; not done because no survival benefit was found, the cost was high, and there is risk of azole-resistant infections		
Cryptococcal meningitis	Treatment	Amphotericin B 0.7 mg/kg/d IV with or w/o flucytosine 100 mg/kg/d x 14 d, then fluconazole 400 mg/d for 8-10 wk; liposomal amphotericin B 4 mg/kg IV qd +/- flucytosine	Fluconazole 400-800 mg/d PO with or w/o flucytosine 100 mg/kg/d PO x 4-6 wk	CD4 ⁺ $<100/\text{mm}^3$ increases risk; spread through inhalation of soil contaminated with bird droppings; fluconazole is superior to itraconazole
Cryptococcal meningitis	Maintenance	Fluconazole 200 mg qd	Amphotericin B 0.6-1 mg/kg 1-3x/wk; fluconazole 400 mg qd; itraconazole 400 mg qd (caps) or 200 mg oral susp qd	Primary and secondary prophylaxis can possibly be stopped for cryptococcosis upon immune reconstitution (patients on HAART with CD4 ⁺ >100 - $200/\text{mm}^3$ for >6 mo)
Cryptococcal meningitis	Primary prophylaxis	Not generally recommended	Fluconazole 200 mg qd; itraconazole 200 mg PO or 100 mg oral susp qd	Indications for primary prophylaxis : antigen-positive high-risk patients (CD4 ⁺ $<100/\text{mm}^3$ and work with soil)
Toxoplasmosis	Treatment	Pyrimethamine PO 200 mg loading dose then 50-75 mg + folinic acid PO 10-20 mg/d + sulfadiazine PO 1-2 g q6h for at least 6 wk	Pyrimethamine + folinic acid + clindamycin 650 mg IV or PO q6h or q6h; pyrimethamine + folinic acid + azithromycin 900-1200 mg/d or atovaquone 1500 mg with food bid	Spread through raw or undercooked meat (lamb, beef, and pork) and by contact with infected cat feces; may require dexamethasone if significant cerebral edema is present
Toxoplasmosis	Suppressive therapy	Pyrimethamine PO 25-50 mg/d + folinic acid PO 10-25 mg/d + sulfadiazine PO 0.5-1 g q6h	Pyrimethamine + folinic acid + clindamycin or atovaquone	May be able to discontinue when CD4 $>200/\text{mm}^3$ for >6 mo and free of signs and symptoms
Toxoplasmosis	Primary prophylaxis	Not generally recommended	TMP-SMX DS qd	Indications for primary prophylaxis : positive IgG serology plus CD4 ⁺ $<100/\text{mm}^3$

(continued)

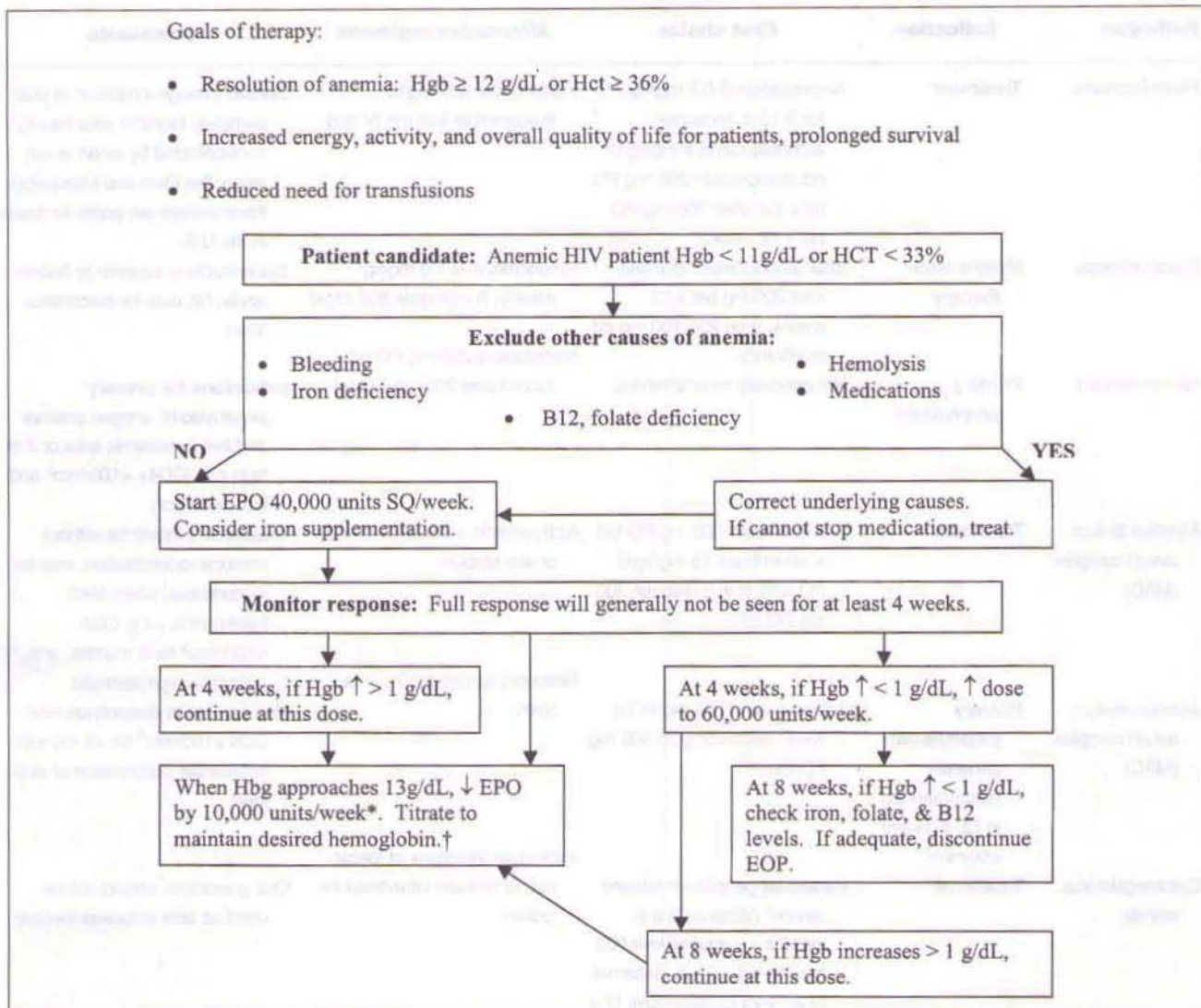
Table 13

Opportunistic Infections (continued)

Pathogen	Indication	First choice	Alternative regimens	Comments
Histoplasmosis	Treatment	Amphotericin B 0.7 mg/kg/d IV for 3-10 d; liposomal amphotericin B 4 mg/kg IV qd; itraconazole 200 mg PO tid x 3 d, then 200 mg PO bid x 12 weeks	Fluconazole 800 mg/d; itraconazole 400 mg IV qod	Spread through inhalation of dust particles; found in soils heavily contaminated by avian or bat feces; the Ohio and Mississippi River valleys are endemic areas in the U.S.
Histoplasmosis	Maintenance therapy	After amphotericin: itraconazole 200 mg bid x 12 weeks, then 200-400 mg qd indefinitely	Amphotericin B 1.0 mg/kg weekly; fluconazole 800 mg/d	Itraconazole is superior to fluconazole; No data for discontinuation
Histoplasmosis	Primary prophylaxis	Not generally recommended	Itraconazole 200 mg PO qd; fluconazole 200 mg PO qd	Indications for primary prophylaxis: antigen positive and live in endemic area or if at high risk (CD4+ <100/mm ³ and work with soil)
<i>Mycobacterium avium</i> complex (MAC)	Treatment	Clarithromycin 500 mg PO bid + ethambutol 15 mg/kg/d PO with or w/o rifabutin 300 mg PO qd	Azithromycin + ethambutol with or w/o rifabutin	Treatment is indefinite without immune reconstitution; may be discontinued when MAC treatment is >1 y, CD4 >100/mm ³ for 6 months, and patient is asymptomatic
<i>Mycobacterium avium</i> complex (MAC)	Primary prophylaxis: generally recommended at CD4 counts <50/mm ³	Azithromycin 1200 mg PO q week; clarithromycin 500 mg PO bid	Rifabutin; azithromycin + rifabutin	May be able to discontinue when CD4 >100/mm ³ for >6 mo with substantial suppression of viral load
Cytomegalovirus retinitis	Treatment	Intraocular ganciclovir release device ¹ (Vitrasert®) q 6 months + valganciclovir 900 mg PO bid x 21 d; foscarnet IV x 14-21 d; ganciclovir IV x 14-21 d; cidofovir IV q wk x 2 wk	Intraocular injections of foscarnet; fomivirsen intravitreal injection	Oral ganciclovir should not be used as sole induction therapy
Cytomegalovirus retinitis	Maintenance	Valganciclovir 900 mg PO qd; ganciclovir IV q 5-7 d/wk; foscarnet IV/d; cidofovir IV q 2 wk; intraocular ganciclovir release device (Vitrasert) q 6 mo + oral ganciclovir 1.0-1.5 g PO tid	Ganciclovir PO 1 g tid	Lifelong maintenance therapy is required for retinitis in patients without immune recovery (CD4 >100-150/mm ³ for greater than 6 mo)
Cytomegalovirus retinitis	Primary prophylaxis	Not generally recommended unless positive serology and CD4 count <50/mm ³		

¹Intraocular device does not protect contralateral eye and does not protect against systemic infection with cytomegalovirus.

Figure 1.

Guidelines for the treatment of anemia in the HIV patient.

EPO, erythropoietin.

*If Hgb >15 g/dL at any point, hold EPO and restart when Hgb <12 g/dL, using dose reduced by 10,000 U/week.

†During the dose adjustment phase, Hgb should be monitored every 2-4 weeks. Allow at least 4 weeks to assess response to dose changes.

6. Questions and Answers

1. C.T. is a 23-year-old HIV-positive female who presents to the emergency department with shortness of breath and a fever. Physical exam reveals a temperature of 102°F, HR of 100 bpm, and decreased breath sounds in the left lower lobe of lungs. Chest x-ray is positive for infiltrates in the left lung. She is diagnosed with PCP pneumonia. She has no previous history of

opportunistic infections and is not on any medications at this time (she has not been seen by a health care provider in over a year). Her CD4⁺ count is 13 cells/mm³ and viral load is 170,198 copies/mL. What is the treatment of choice for C.T.'s PCP?

- A. TMP-SMX DS 2 tabs PO q8h for 21 days, then 1 tab PO qd
- B. Azithromycin 500 mg PO on day one, then 250 mg PO qd indefinitely

- C. Doxycycline 100 mg PO bid for 7 days, then 100 mg PO qd
 D. Clarithromycin 500 mg PO bid for 10 days, then 250 mg PO qd
 E. Vancomycin 1 g IV q12h for 10 days, then TMP-SMX DS PO qd
2. Should C.T. receive any other prophylaxis against opportunistic infections?
- A. Yes, against MAC: Zithromax® 1200 mg PO q week
 B. Yes, against thrush: Diflucan® 100 mg PO qd
 C. Yes, against toxoplasmosis: Bactrim DS® 1 tab PO q M, W, and F
 D. Yes, against CMV: Valcyte® 450 mg PO q M, W, and F
 E. No
3. Six weeks later C.T. presents to the HIV clinic for follow-up. Her CD4⁺ count is 12 cells/mm³ and viral load is 140,202 copies/mL. Should C.T. be started on HIV therapy?
- A. Yes; her CD4⁺ cell count is <200 cells/mm³ and she has had an opportunistic infection
 B. Yes; her viral load is greater than 100,000 copies/mL
 C. Yes; her Western blot was positive for HIV
 D. Yes; all patients with HIV should be treated as soon as the diagnosis is made
 E. No
4. C.T. wishes to be started on HIV therapy. Which of the following would be an appropriate regimen?
- A. Zidovudine + efavirenz + nelfinavir
 B. Zidovudine + stavudine + indinavir
 C. Zalcitabine + didanosine + amprenavir
 D. Zidovudine + lamivudine + lopinavir/ritonavir
 E. Nelfinavir + indinavir + amprenavir
5. HIV can be transmitted by:
- A. Unprotected sexual contact with an infected person
 B. Sharing needles or syringes with an infected person
 C. Infected mother to infant (vertical transmission)
 D. Transfusion of blood (before 1985)
 E. All of the above
6. M.J. is 13 weeks pregnant and just tested positive for HIV. Her viral load is 22,434 copies/mL and her CD4⁺ cell count is 425 cells/mm³. M.J. wishes to receive treatment for her HIV. Which of the following would be an appropriate regimen for M.J.?
- A. Zidovudine + stavudine + indinavir
 B. Zidovudine + lamivudine + nelfinavir
 C. Zidovudine + lamivudine + efavirenz
 D. Stavudine + didanosine + nevirapine
 E. No treatment is necessary
7. Which of the following antiretroviral medications has shown efficacy as monotherapy in decreasing the vertical transmission of HIV?
- A. Efavirenz
 B. Nelfinavir
 C. Zidovudine
 D. Zalcitabine
 E. Stavudine
8. R.C. is a nurse in the emergency department. She has just been stuck with a needle that was used for an HIV-positive patient with a known high viral load. Which of the following is true concerning postexposure prophylaxis?
- I. The regimen should be started within 2 hours of exposure
 II. R.C. will only need to be treated with zidovudine
 III. R.C. will need to be treated with a combination of zidovudine + lamivudine + nelfinavir
 IV. Treatment will continue for 4 weeks
- A. I, III, and IV
 B. II only
 C. II, III, and IV
 D. I, IV
 E. I, II, and IV
9. The CD4⁺ cell count relates to
- I. the activity of the virus
 II. the status of the immune system
 III. how at-risk a patient is for acquiring an opportunistic infection
 IV. when the patient was infected
 V. time to death in treated patients
- A. IV, V
 B. I, II, and III
 C. II, III

- D. II, III, and IV
E. I, II, V
10. The viral load relates to
- the activity of the virus and efficacy of antiretroviral therapy
 - the status of the immune system
 - when the patient was infected
 - how at-risk a patient is for acquiring an opportunistic infection
 - time to death in a treated patient
11. S.J. presents to the emergency department with extreme flank pain with nausea and vomiting. He is diagnosed with a kidney stone. His past medical history is positive for HIV and diabetes. His medications include indinavir, stavudine, didanosine, dapsone, and metformin. Which of his medications might have caused his kidney stone?
- Indinavir
 - Stavudine
 - Didanosine
 - Metformin
 - Dapsone
12. L.L. comes to the clinic today with a chief complaint of burning and tingling in his feet that started about 1 month ago. His current medications include nelfinavir, stavudine, lamivudine, sertraline, and gemfibrozil. Which medication(s) might be causing this problem?
- Nelfinavir
 - Stavudine
 - Lamivudine
 - Sertraline
 - Gemfibrozil
13. S.E. presents to the emergency department with a 2-day history of extreme nausea, vomiting, and abdominal pain. Labs reveal elevations in amylase and lipase and a diagnosis of pancreatitis is made. His medications include nevirapine, tenofovir, didanosine, and amitriptyline. Which of his medications could have caused his pancreatitis?
- Nevirapine
 - Tenofovir
 - Didanosine
 - Amitriptyline
 - All of the above
14. Which of the following HIV medications has a 5% incidence of a hypersensitivity reaction?
- Efavirenz
 - Ritonavir
 - Zidovudine
 - Abacavir
 - Lamivudine
15. C.J. is starting efavirenz, zidovudine, lamivudine, and TMP-SMX today. What should C.J. be counseled about concerning efavirenz?
- Anemia
 - CNS side effects
 - Neutropenia
 - Renal toxicity
 - Kidney stones
16. Which of the following can cause hepatotoxicity and requires monitoring of liver enzymes at baseline, 2 weeks, 4 weeks, 6 weeks, and then monthly for the first 18 weeks of therapy?
- Zidovudine
 - Zalcitabine
 - Lopinavir
 - Amprenavir
 - Nevirapine
17. Which of the following can cause hyperglycemia, hyperlipidemia (particularly elevations in triglycerides), and lipodystrophy?
- Amprenavir
 - Delavirdine
 - Didanosine
 - Abacavir
 - Lamivudine
18. Lactic acidosis and hepatic steatosis have been reported with which of these antiretroviral medications?
- Nevirapine
 - Efavirenz
 - Stavudine
 - Saquinavir
 - Nelfinavir
19. The mechanism of action of nucleoside reverse transcriptase inhibitors is to
- directly inhibit reverse transcriptase
 - prevent entry of the proviral DNA into the nucleus of the CD4⁺ cell

- C. cause chain termination, resulting in a defective copy of proviral DNA
 D. prevent entry of HIV into the CD4⁺ cell
 E. prevent cleavage of the newly formed polypeptide chains into a viable HIV
20. The mechanism of action of non-nucleoside reverse transcriptase inhibitors is to
- A. prevent cleavage of the newly formed polypeptide chains into viable HIV
 B. prevent entry of HIV into the CD4⁺ cell
 C. prevent entry of the proviral DNA into the nucleus of the CD4⁺ cell
 D. directly inhibit reverse transcriptase
 E. cause chain termination, resulting in a defective copy of proviral DNA
21. The mechanism of action of protease inhibitors is to
- A. cause a defective copy of proviral DNA to be made
 B. prevent entry of the proviral DNA into the nucleus of the CD4⁺ cell
 C. prevent cleavage of the newly formed polypeptide chains into a viable HIV
 D. prevent entry of HIV into the CD4⁺ cell
 E. directly inhibit reverse transcriptase
22. Which of the following nucleoside reverse transcriptase inhibitor combinations is acceptable?
- A. Stavudine + zidovudine
 B. Zalcitabine + stavudine
 C. Tenofovir + emtricitabine
 D. Zalcitabine + didanosine
 E. Zalcitabine + delavirdine
23. Which of the following opportunistic infections are the only ones requiring primary prophylaxis?
- A. PCP and MAC
 B. PCP and toxoplasmosis
 C. MAC and histoplasmosis
 D. MAC and CMV
 E. PCP and thrush
24. The antifungal of first choice for maintenance therapy after treatment of cryptococcal meningitis is
- A. itraconazole
 B. fluconazole
 C. ketoconazole

- D. amphotericin B
 E. terbinafine

25. The first-choice antifungal for treatment of histoplasmosis is

- A. itraconazole
 B. fluconazole
 C. ketoconazole
 D. caspofungin
 E. terbinafine

Answers

1. A. The treatment of choice for PCP is TMP-SMX in patients who are not allergic to sulfa medications. Duration of treatment is for 21 days. Since this patient's CD4⁺ cell count is below 200 cells/mm³ and she has had PCP, she will require secondary prophylaxis once treatment is completed. Preferred prophylaxis is once-daily TMP-SMX DS.
2. A. This patient's CD4⁺ cell count is below 50 cells/mm³; therefore she requires primary prophylaxis against MAC. Zithromax is the drug of choice. Prophylaxis against other opportunistic infections is generally not required.
3. A. Current guidelines state that any patient who has had an opportunistic infection or a CD4⁺ cell count less than 200 cells/mm³ should start treatment for HIV. This patient has had both.
4. D. Most regimens contain two NRTIs and either one PI or one NNRTI. A includes one NRTI, one NNRTI and one PI. E includes three PIs. Zidovudine and stavudine competitively inhibit each other and would not be used in the same regimen (thus B is incorrect). Zalcitabine is contraindicated with didanosine, stavudine, and lamivudine, due to increased toxicity (which makes C incorrect).
5. E. All items are important risk factors for transmission of HIV. Breastfeeding, history of STDs, occupational exposure to HIV-infected fluids (rare), and household exposure to HIV-infected fluids (rare) are also risk factors.
6. B. All HIV-positive pregnant women should receive treatment for HIV to decrease the risk of transmission to their offspring. Zidovudine and stavudine competitively inhibit each other and should not be used together. Efavirenz is

teratogenic and should not be used in pregnancy. Stavudine and didanosine together are contraindicated in pregnancy due to increased risk of lactic acidosis and liver damage.

7. **C.** Zidovudine and nevirapine are the only HIV medications that can reduce vertical transmission when used as monotherapy. Most practitioners treat with combination therapy due to the increased risk of resistance with monotherapy, which has an impact on future choices of drug regimen.
8. **A.** The approved regimens for postexposure prophylaxis are zidovudine and lamivudine with or without nelfinavir or indinavir. Treatment should continue for 4 weeks and should start within 2 hours of exposure.
9. **C.** CD4⁺ cell count describes the status of the immune system (ie, how at-risk a patient is for acquiring an opportunistic infection).
10. **A.** Viral load relates to the activity of the virus and efficacy of antiretroviral therapy. The goal of therapy is an undetectable viral load (<50 copies/mL).
11. **A.** Indinavir can cause kidney stones. Patients should drink at least 48 ounces of water a day to decrease the risk of developing a kidney stone.
12. **B.** All the "D" drugs, d4T (stavudine), ddI (didanosine), and ddC (zalcitabine), can cause peripheral neuropathy and pancreatitis.
13. **C.** All the "D" drugs, d4T (stavudine), ddI (didanosine), and ddC (zalcitabine), can cause peripheral neuropathy and pancreatitis.
14. **D.** Abacavir has a 5% incidence of hypersensitivity. Symptoms can include rash, fever, stomach symptoms, throat symptoms, or flu-like symptoms.
15. **B.** Efavirenz can cause CNS side effects such as dizziness, trouble sleeping, drowsiness, trouble concentrating, and/or unusual dreams during the first 2-4 weeks of treatment.
16. **E.** All NNRTIs can cause hepatotoxicity. There have been rare reports of hepatotoxicity after just one dose of nevirapine. Liver enzymes should be monitored at baseline, 2 weeks, 4 weeks, 6 weeks, and monthly for the first 18 weeks of therapy.
17. **A.** Class side effects of PIs include hyperglycemia, hyperlipidemia, lipodystrophy, increased bleeding in hemophiliacs, and possibly osteoporosis or osteopenia.
18. **C.** Class side effects of NRTIs include lactic acidosis and hepatic steatosis.
19. **C.** NRTIs affect reverse transcriptase by causing chain termination, resulting in a defective copy of proviral DNA.
20. **D.** NNRTIs affect reverse transcriptase by directly inhibiting reverse transcriptase, resulting in less proviral DNA being made.
21. **C.** PIs prevent cleavage of the newly formed polypeptide chains into viable HIV, resulting in an immature virus that is unable to infect other CD4⁺ cells.
22. **C.** Stavudine is contraindicated with zidovudine due to competitive inhibition. Zalcitabine is contraindicated with other NRTIs that may cause peripheral neuropathy (eg, stavudine and didanosine). Delavirdine is an NNRTI.
23. **A.** PCP requires primary prophylaxis when the CD4⁺ cell count falls below 200 cells/mm³. The preferred medication is TMP-SMX. MAC requires primary prophylaxis when the CD4⁺ cell count falls below 50 cells/mm³. The preferred medication is azithromycin.
24. **B.** Generally, cryptococcal meningitis is initially treated with amphotericin B during the induction phase, and then fluconazole for the consolidation phase and maintenance therapy.
25. **A.** Histoplasmosis is generally initially treated with amphotericin B or itraconazole for induction therapy, and then itraconazole for maintenance therapy.

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- Guidelines for postexposure prophylaxis can be located as a living document on the web at www.aidsinfo.nih.gov, which is updated 3-4 times a year.
- Guidelines for prevention and treatment and medications used for the treatment of HIV can be located as a living document at www.aidsinfo.nih.gov, which is updated 3-4 times a year.
- Guidelines for prophylaxis and treatment of opportunistic infections can be located as a living document at www.aidsinfo.nih.gov, which is updated 3-4 times a year.
- Guidelines for prevention of vertical transmission can be located as a living document at www.aidsinfo.nih.gov, which is updated 3-4 times a year.
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32. Immunization

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1. Introduction

Definitions

Immunity: a naturally or artificially acquired state resulting in an individual being resistant or relatively resistant to the occurrence or effects of a foreign substance; this is the mechanism the body develops for protection from infectious disease. This is usually very specific to a single organism or to a group of closely related organisms.

Antigen: a live or inactivated substance capable of evoking antibody production; antigens can be a live organism, such as bacteria or viruses, or an inactivated or killed organism or portion of an organism. A live organism generally evokes the most effective immune response.

Antibody: a protein evoked by an antigen which acts to eliminate that antigen

Mechanisms for Acquiring Immunity

Active immunity: protection produced by an individual's own immune system; immunity acquired in this manner has a delayed onset and is usually permanent. Active immunity may be acquired by having an active disease or by vaccination. B lymphocytes (B cells) circulate in the blood and bone marrow for many years. Re-exposure to the antigen causes the cells to replicate and to produce antibody. These cells are also called memory B cells.

Passive immunity: protection produced by an animal or human and transferred to another; immunity acquired in this manner has a rapid onset and usually has a brief duration. This is the type of immunity an infant receives from his or her mother. All types of blood products contain varying amounts of antibody. Immune globulins and hyperimmune globulins are also used to induce passive immunity. One source of passive immunity is antitoxins, which contain antibodies against a known toxin.

2. Vaccines

Vaccination is the process of producing active immunity via use of vaccines. The immunological response is similar to natural infection, with a lower risk than that of the disease itself.

Classification of Vaccines

Live, attenuated vaccines: These are vaccines produced by modifying a virus or bacteria to produce immunity. These vaccines usually do not produce disease, however they may. When this occurs the disease is usually much milder than the natural disease. These vaccines must replicate to be effective. These vaccines also require special handling, such as protection from heat and light, to keep them alive. Circulating antibody from another source may destroy the vaccine virus and cause vaccine failure (Table 1).

Inactivated vaccines: These are vaccines composed of all or a fraction of a virus or bacterium. These fractions include subunits (subvirions), bacterial cell-wall polysaccharides, conjugated (attached to a protein carrier) bacteria cell-wall polysaccharides, or inactivated toxins (toxoids). The bacteria or virus is inactivated using heat and/or chemicals. Inactivated vaccines are not alive and cannot replicate, therefore they are unable to induce disease. Inactivated antigens are not affected by circulating antibody (Table 2).

Table 1

Live Vaccines Available in the United States, 2005

Herpes zoster

Influenza (live-attenuated)

Measles

Mumps

Rotavirus

Rubella

Typhoid oral

Varicella

Vaccinia (smallpox)

Yellow fever

Table 2

Inactivated Vaccines Available in the United States, 2005

Anthrax

Diphtheria

Haemophilus influenzae type b

Hepatitis A

Hepatitis B

Human papillomavirus

Influenza

Japanese encephalitis

Meningococcal A, C, Y, W-135 polysaccharide

Meningococcal A, C, Y, W-135 conjugate

Pertussis, acellular

Pneumococcal polysaccharide

Pneumococcal conjugate

Polio

Rabies

Tetanus toxoid

Typhoid injectable

Administration of Multiple Vaccines

- There are no contraindications to the simultaneous administration of any vaccines. Inactivated and live vaccines may be given in any combination at the same time.
- Live vaccines must be separated from the administration of antibodies, such as blood products and immune globulins. Inactivated vaccines are not affected by circulating antibody.
- If two live vaccines are not given at the same time, a 4-week minimal interval must be observed. This is not true for two inactivated vaccines or an inactivated plus a live vaccine.

Vaccine Adverse Reactions

- Vaccine adverse reactions are any untoward side effects caused by a vaccine.
- Local reactions are the most common type of adverse reaction. These include pain, swelling, and redness at the site of injection. These usually occur within minutes to hours of the injection and are usually mild and self-limiting. Occasionally, severe local reactions occur and are known as hypersensitivity reactions.
- Systemic adverse reactions include fever, malaise, myalgias, and headache. Systemic adverse reactions are more common following live vaccines, and are similar to a mild case of the disease.
- Allergic reactions are reactions to the vaccine antigens or some component of the vaccine. While rare, these reactions may be life threatening.
- Vaccine Adverse Events Reporting System (VAERS) is a CDC-monitored surveillance system, which should be notified within 30 days of an adverse event that requires medical attention.

Vaccination Schedules

- Vaccination schedules are available for children, adolescents, and adults (Figures 1 and 2). The schedules indicate the most ideal times to administer vaccines. Additional catch-up schedules are available for children and adolescents who are behind in their vaccinations.
- Intervals between doses of the same vaccine in a series are described in the tables.
- The minimum interval in a series for most vaccines is 4 weeks. Decreasing the interval may interfere with antibody response and protection.
- Usually the last dose in a series is separated from the previous dose by 4-6 months.
- Increasing the interval does not affect vaccine effectiveness. You never need to restart a series except for oral typhoid vaccine.

Contraindications and Precautions

- A contraindication is a condition that increases the risk of an adverse reaction or decreases the effect of a vaccine.
- A precaution is a condition that might possibly increase the risk of an adverse event or decrease the effect of a vaccine.

Contraindications include:

- An anaphylactic reaction to any previous dose of vaccine or to any of its components
- Pregnancy for live vaccines and selected inactivated vaccines
- Immunosuppression for live vaccines and selected inactivated vaccines
- Active, untreated tuberculosis and live vaccines

Figure 1.

Recommended adult immunization schedule by vaccine and age group—United States, October 2005–September 2006.

Vaccine ▼	Age group ►	19–49 years	50–64 years	≥ 65 years
Tetanus, diphtheria (Td) ^{1*}		1-dose booster every 10 yrs		
Measles, mumps, rubella (MMR) ^{2*}		1 or 2 doses	1 dose	
Varicella ^{3*}		2 doses (0, 4–8 wks)	2 doses (0, 4–8 wks)	
— Vaccines below broken line are for selected populations				
Influenza ^{4*}		1 dose annually	1 dose annually	
Pneumococcal (polysaccharide) ^{5,6}		1–2 doses	1 dose	
Hepatitis A ^{7*}		2 doses (0, 6–12 mos, or 0, 6–18 mos)		
Hepatitis B ^{8*}		3 doses (0, 1–2, 4–6 mos)		
Meningococcal ⁹		1 or more doses		

NOTE: These recommendations must be read along with the footnotes.

*Covered by the Vaccine Injury Compensation Program.

For all persons in this category who meet the age requirements and who lack evidence of immunity (e.g., lack documentation of vaccination or have no evidence of prior infection)

Recommended if some other risk factor is present (e.g., based on medical, occupational, lifestyle, or other indications)

Footnotes to Figure 1.

1. Tetanus and Diphtheria (Td) vaccination. Adults with uncertain histories of a complete primary vaccination series with diphtheria and tetanus toxoid-containing vaccines should receive a primary series using combined Td toxoid. A primary series for adults is 3 doses; administer the first 2 doses at least 4 weeks apart and the third dose 6–12 months after the second. Administer 1 dose if the person received the primary series and if the last vaccination was received ≥10 years previously. Consult ACIP statement for recommendations for administering Td as prophylaxis in wound management (www.cdc.gov/mmwr/preview/mmwrhtml/0041645.htm). The American College of Physicians Task Force on Adult Immunization supports a second option for Td use in adults: a single Td booster at age 50 years for persons who have completed the full pediatric series, including the teenage/young adult booster. A newly licensed tetanus-diphtheria-acellular pertussis vaccine is available for adults. ACIP recommendations for its use will be published.

2. Measles, Mumps, Rubella (MMR) vaccination. *Measles component:* adults born before 1957 can be considered immune to measles. Adults born during or after 1957 should receive ≥1 dose of MMR unless they have a medical contraindication, documentation of ≥1 dose, history of measles based on health care provider diagnosis, or laboratory evidence of immunity. A second dose of MMR is recommended for adults who (1) were recently exposed to measles or in an outbreak setting, (2) were previously vaccinated with killed measles vaccine, (3) were vaccinated with an unknown type of measles vaccine during 1963–1967, (4) are students in post-secondary educational institutions, (5) work in a health care facility, or (6) plan to travel internationally. Withhold MMR or other measles-containing vaccines from HIV-infected persons with severe immunosuppression. *Mumps component:* 1 dose of MMR vaccine should be adequate for protection for those born during or after 1957 who lack a history of mumps based on health care provider diagnosis or who lack laboratory evidence of immunity. *Rubella component:* administer 1 dose of MMR vaccine to women whose rubella vaccination history is unreliable or who lack laboratory evidence of immunity. For women of childbearing age, regardless of birth year, routinely determine rubella immunity and counsel women regarding congenital rubella syndrome. Do not vaccinate women who are pregnant or might become pregnant within 4 weeks of receiving the vaccine. Women who do not have evidence of immunity should receive MMR vaccine upon completion or termination of pregnancy and before discharge from the health care facility.

3. Varicella vaccination. Varicella vaccination is recommended for all adults without evidence of immunity to varicella. Special consideration should be given to those who (1) have close contact with persons at high risk for severe disease (health care workers and family contacts of immunocompromised persons) or (2) are at high risk for exposure or transmission (eg, teachers of young children; child care employees; residents and staff members of institutional settings, including correctional institutions; college students; military personnel; adolescents and adults living in households with children; nonpregnant women of childbearing age; and international travelers). Evidence of immunity to varicella in adults includes any of the following: (1) documented age-appropriate varicella vaccination (ie, receipt of 1 dose before age 13 years or receipt of 2 doses [administered at least 4 weeks apart] after age 13 years); (2) born in the United States before 1966; (3) history of varicella disease based on health care provider diagnosis or self- or parental-report of typical varicella disease for non-U.S.-born persons born before 1966 and all persons born during 1966–1997 (for a patient reporting a history of an atypical, mild case, health care providers should seek either an epidemiologic link with a typical varicella case or evidence of laboratory confirmation, if it was performed at the time of acute disease); (4) history

of herpes zoster based on health care provider diagnosis; or (5) laboratory evidence of immunity. Do not vaccinate women who are pregnant or might become pregnant within 4 weeks of receiving the vaccine. Assess pregnant women for evidence of varicella immunity. Women who do not have evidence of immunity should receive dose 1 of varicella vaccine upon completion or termination of pregnancy and before discharge from the health care facility. Dose 2 should be given 4-8 weeks after dose 1.

4. Influenza vaccination. *Medical indications:* chronic disorders of the cardiovascular or pulmonary systems, including asthma; chronic metabolic diseases, including diabetes mellitus, renal dysfunction, hemoglobinopathies, or immunosuppression (including immunosuppression caused by medications or by HIV); any condition (eg, cognitive dysfunction, spinal cord injury, seizure disorder or other neuromuscular disorder) that compromises respiratory function or the handling of respiratory secretions or that can increase the risk of aspiration; and pregnancy during the influenza season. No data exist on the risk for severe or complicated influenza disease among persons with asplenia; however, influenza is a risk factor for secondary bacterial infections that can cause severe disease among persons with asplenia. *Occupational indications:* health care workers and employees of long-term care and assisted living facilities. *Other indications:* residents of nursing homes and other long-term care and assisted living facilities; persons likely to transmit influenza to persons at high risk (ie, in-home household contacts and caregivers of children birth through 23 months of age, or persons of all ages with high-risk conditions); and anyone who wishes to be vaccinated.

For healthy nonpregnant persons aged 5-49 years without high-risk conditions who are not contacts of severely immunocompromised persons in special care units, intranasally administered influenza vaccine (FluMist) may be administered in lieu of inactivated vaccine.

5. Pneumococcal polysaccharide vaccination. *Medical indications:* chronic disorders of the pulmonary system (excluding asthma); cardiovascular diseases; diabetes mellitus; chronic liver diseases, including liver disease as a result of alcohol abuse (eg, cirrhosis); chronic renal failure or nephrotic syndrome; functional or anatomic asplenia (eg, sickle cell disease or splenectomy [if elective splenectomy is planned, vaccinate at least 2 weeks before surgery]); immunosuppressive conditions (eg, congenital immunodeficiency, HIV infection [vaccinate as close to diagnosis as possible when CD4 cell counts are highest], leukemia, lymphoma, multiple myeloma, Hodgkin's disease, generalized malignancy, organ or bone marrow transplantation); chemotherapy with alkylating agents, antimetabolites, or high-dose, long-term corticosteroids; and cochlear implants. *Other indications:* Alaska Natives and certain American Indian populations; residents of nursing homes and other long-term care facilities.

6. Revaccination with pneumococcal polysaccharide vaccine. One-time revaccination after 5 years for persons with chronic renal failure or nephrotic syndrome; functional or anatomic asplenia (eg, sickle cell disease or splenectomy); immunosuppressive conditions (eg, congenital immunodeficiency, HIV infection, leukemia, lymphoma, multiple myeloma, Hodgkin's disease, generalized malignancy, organ or bone marrow transplantation); or chemotherapy with alkylating agents, antimetabolites, or high-dose, long-term corticosteroids. For persons aged ≥ 65 years, one-time revaccination if they were vaccinated ≥ 5 years previously and were aged < 65 years at the time of primary vaccination.

7. Hepatitis A vaccination. *Medical indications:* persons with clotting factor disorders or chronic liver disease. *Behavioral indications:* men who have sex with men or users of illegal drugs. *Occupational indications:* persons working with hepatitis A virus (HAV)-infected primates or with HAV in a research laboratory setting. *Other indications:* persons traveling to or working in countries that have high or intermediate endemicity of hepatitis A (for list of countries, visit www.cdc.gov/travel/diseases.htm#hepa) as well as any person wishing to obtain immunity. Current vaccines should be given in a 2-dose series at either 0 and 6-12 months, or 0 and 6-18 months. If the combined hepatitis A and hepatitis B vaccine is used, administer 3 doses at 0, 1, and 6 months.

8. Hepatitis B vaccination. *Medical indications:* hemodialysis patients (use special formulation [40 mcg/mL] or two 20-mcg/mL doses) or patients who receive clotting factor concentrates. *Occupational indications:* health care workers and public safety workers who have exposure to blood in the workplace; and persons in training in schools of medicine, dentistry, nursing, laboratory technology, and other allied health professions. *Behavioral indications:* injection-drug users; persons with more than one sex partner in the previous 6 months; persons with a recently acquired sexually transmitted disease (STD); and men who have sex with men. *Other indications:* household contacts and sex partners of persons with chronic hepatitis B virus (HBV) infection; clients and staff of institutions for the developmentally disabled; all clients of STD clinics; inmates of correctional facilities; or international travelers who will be in countries with high or intermediate prevalence of chronic HBV infection for > 6 months (for list of countries, visit www.cdc.gov/travel/diseases.htm#hepa).

9. Meningococcal vaccination. *Medical indications:* adults with anatomic or functional asplenia, or terminal complement component deficiencies; first-year college students living in dormitories; microbiologists who are routinely exposed to isolates of *Neisseria meningitidis*; military recruits; and persons who travel to or reside in countries in which meningococcal disease is hyperendemic or epidemic (eg, the "meningitis belt" of sub-Saharan Africa during the dry season [Dec-June]), particularly if contact with the local populations will be prolonged. Vaccination is required by the government of Saudi Arabia for all travelers to Mecca during the annual Hajj. Meningococcal conjugate vaccine is preferred for adults meeting any of the above indications who are aged ≤ 55 years, although meningococcal polysaccharide vaccine (MPSV4) is an acceptable alternative. Revaccination after 5 years may be indicated for adults previously vaccinated with MPSV4 who remain at high risk for infection (eg, persons residing in areas in which disease is epidemic).

Figure 2.

Recommended childhood and adolescent immunization schedule—United States, 2006.

Vaccine ▼	Age ►	Birth	1 month	2 months	4 months	6 months	12 months	15 months	18 months	24 months	4–6 years	11–12 years	13–14 years	15 years	16–18 years
Hepatitis B ¹		HepB	HepB	HepB ¹			HepB					HepB Series			
Diphtheria, Tetanus, Pertussis ²			DTaP	DTaP	DTaP			DTaP			DTaP	Tdap		Tdap	
<i>Haemophilus influenzae</i> type b ¹			Hib	Hib	Hib ²		Hib								
Inactivated Poliovirus			IPV	IPV			IPV				IPV				
Measles, Mumps, Rubella ⁴							MMR				MMR			MMR	
Varicella ⁵							Varicella					Varicella			
Meningococcal ⁶								Vaccines within broken line are for selected populations			MPSV4	MCV4		MCV4	
Pneumococcal ⁷			PCV	PCV	PCV		PCV			PCV		PPV			
Influenza ⁸							Influenza (Yearly)					Influenza (Yearly)			
Hepatitis A ⁹											HepA Series				

This schedule indicates the recommended ages for routine administration of currently licensed childhood vaccines, as of December 1, 2005, for children through age 18 years. Any dose not administered at the recommended age should be administered at any subsequent visit when indicated and feasible. ■ Indicates age groups that warrant special effort to administer those vaccines not previously administered. Additional vaccines may be licensed and recommended during the year. Licensed combination vaccines may be used whenever

any components of the combination are indicated and other components of the vaccine are not contraindicated and if approved by the Food and Drug Administration for that dose of the series. Providers should consult the respective ACIP statement for detailed recommendations. Clinically significant adverse events that follow immunization should be reported to the Vaccine Adverse Event Reporting System (VAERS). Guidance about how to obtain and complete a VAERS form is available at www.vaers.hhs.gov or by telephone, 800-822-7967.

■ Range of recommended ages ■ Catch-up immunization ■ 11–12 year old assessment

- Hepatitis B vaccine (HepB).** AT BIRTH: All newborns should receive monovalent HepB soon after birth and before hospital discharge. Infants born to mothers who are HBsAg-positive should receive HepB and 0.5 mL of hepatitis B immune globulin (HBIG) within 12 hours of birth. Infants born to mothers whose HBsAg status is unknown should receive HepB within 12 hours of birth. The mother should have blood drawn as soon as possible to determine her HBsAg status; if HBsAg-positive, the infant should receive HBIG as soon as possible (no later than age 1 week). For infants born to HBsAg-negative mothers, the birth dose can be delayed in rare circumstances but only if a physician's order to withhold the vaccine and a copy of the mother's original HBsAg-negative laboratory report are documented in the infant's medical record. FOLLOWING THE BIRTHDOSE: The HepB series should be completed with either monovalent HepB or a combination vaccine containing HepB. The second dose should be administered at age 1–2 months. The final dose should be administered at age ≥ 24 weeks. It is permissible to administer 4 doses of HepB (e.g., when combination vaccines are given after the birth dose); however, if monovalent HepB is used, a dose at age 4 months is not needed. Infants born to HBsAg-positive mothers should be tested for HBsAg and antibody to HBsAg after completion of the HepB series, at age 9–18 months (generally at the next well-child visit after completion of the vaccine series).
- Diphtheria and tetanus toxoids and acellular pertussis vaccine (DTaP).** The fourth dose of DTaP may be administered as early as age 12 months, provided 6 months have elapsed since the third dose and the child is unlikely to return at age 15–18 months. The final dose in the series should be given at age ≥ 4 years. **Tetanus and diphtheria toxoids and acellular pertussis vaccine (Tdap – adolescent preparation)** is recommended at age 11–12 years for those who have completed the recommended childhood DTP/DTaP vaccination series and have not received a Td booster dose. Adolescents 13–18 years who missed the 11–12 year Td/Tdap booster dose should also receive a single dose of Tdap if they have completed the recommended childhood DTP/DTaP vaccination series. Subsequent tetanus and diphtheria toxoids (Td) are recommended every 10 years.
- Haemophilus influenzae* type b conjugate vaccine (Hib).** Three Hib conjugate vaccines are licensed for infant use. If PRP-OMP (PedvaxHIB® or ComVax® [Merck]) is administered at ages 2 and 4 months, a dose at age 6 months is not required. DTaP/Hib combination products should not be used for primary immunization in infants at ages 2, 4 or 6 months but can be used as boosters after any Hib vaccine. The final dose in the series should be administered at age ≥ 12 months.
- Measles, mumps, and rubella vaccine (MMR).** The second dose of MMR is recommended routinely at age 4–6 years but may be administered during any visit, provided at least 4 weeks have elapsed since the first dose and both doses are administered beginning at or after age 12 months. Those who have not previously received the second dose should complete the schedule by age 11–12 years.

- Varicella vaccine.** Varicella vaccine is recommended at any visit at or after age 12 months for susceptible children (i.e., those who lack a reliable history of chickenpox). Susceptible persons aged ≥ 13 years should receive 2 doses administered at least 4 weeks apart.
- Meningococcal vaccine (MCV4).** Meningococcal conjugate vaccine (MCV4) should be given to all children at the 11–12 year old visit as well as to unvaccinated adolescents at high school entry (15 years of age). Other adolescents who wish to decrease their risk for meningococcal disease may also be vaccinated. All college freshmen living in dormitories should also be vaccinated, preferably with MCV4, although meningococcal polysaccharide vaccine (MPSV4) is an acceptable alternative. Vaccination against invasive meningococcal disease is recommended for children and adolescents aged ≥ 2 years with terminal complement deficiencies or anatomic or functional asplenia and certain other high risk groups (see *MMWR* 2005;54 [RR-7]:1–21); use MPSV4 for children aged 2–10 years and MCV4 for older children, although MPSV4 is an acceptable alternative.
- Pneumococcal vaccine.** The heptavalent pneumococcal conjugate vaccine (PCV) is recommended for all children aged 2–23 months and for certain children aged 24–59 months. The final dose in the series should be given at age ≥ 12 months. **Pneumococcal polysaccharide vaccine (PPV)** is recommended in addition to PCV for certain high-risk groups. See *MMWR* 2000; 49(RR-9):1–35.
- Influenza vaccine.** Influenza vaccine is recommended annually for children aged ≥ 6 months with certain risk factors (including, but not limited to, asthma, cardiac disease, sickle cell disease, human immunodeficiency virus [HIV], diabetes, and conditions that can compromise respiratory function or handling of respiratory secretions or that can increase the risk for aspiration), healthcare workers, and other persons (including household members) in close contact with persons in groups at high risk (see *MMWR* 2005;54[RR-8]:1–55). In addition, healthy children aged 6–23 months and close contacts of healthy children aged 0–5 months are recommended to receive influenza vaccine because children in this age group are at substantially increased risk for influenza-related hospitalizations. For healthy persons aged 5–49 years, the intranasally administered, live, attenuated influenza vaccine (LAIV) is an acceptable alternative to the intramuscular trivalent inactivated influenza vaccine (TIV). See *MMWR* 2005;54(RR-8):1–55. Children receiving TIV should be administered a dosage appropriate for their age (0.25 mL if aged 6–35 months or 0.5 mL if aged ≥ 3 years). Children aged ≤ 8 years who are receiving influenza vaccine for the first time should receive 2 doses (separated by at least 4 weeks for TIV and at least 6 weeks for LAIV).
- Hepatitis A vaccine (HepA).** HepA is recommended for all children at 1 year of age (i.e., 12–23 months). The 2 doses in the series should be administered at least 6 months apart. States, counties, and communities with existing HepA vaccination programs for children 2–18 years of age are encouraged to maintain these programs. In these areas, new efforts focused on routine vaccination of 1-year-old children should enhance, not replace, ongoing programs directed at a broader population of children. HepA is also recommended for certain high risk groups (see *MMWR* 1999; 48(RR-12):1–37).

- DTaP or Tdap: Encephalopathy within 7 days of previous DTaP or DTP

Precautions include:

- Acute moderate to severe illness
- Recent administration of an antibody-containing blood products and live vaccines
- DTP or DTaP: unstable or evolving neurological disorder
- MMR: history of thrombocytopenia or thrombocytopenic purpura
- High fever, shock, persistent crying, seizure, or Guillain-Barré syndrome due to previous dose of DTP or DTaP

Vaccine Management

- Maintain cold-chain during shipping.
- Follow manufacturers' recommendation for shipping.
- Nonfrozen vaccines must not freeze during transport.
- Refrigerate or freeze depending upon vaccine immediately upon arrival
- Utilize proper refrigerators.
 - * Monitor temperatures daily.
 - * Do not store vaccines in refrigerator door.
 - * Store in the middle of the refrigerator.
 - * Keep temperature log.

- Inventory management
 - * Maintain inventory log.
 - * Rotate stock.
 - * Follow manufacturers' guidelines for shelf life.
 - * Check expiration dates.
 - * Designate a person to be responsible for vaccines.
 - * Train all staff to recognize vaccine shipment arrivals.
- Follow manufacturers' directions for reconstitution.

3. Diseases and Vaccines

Pneumococcal Disease

- ***Streptococcal pneumonia***: 90 known serotypes of gram-positive bacteria with a polysaccharide capsule
- Primary serious diseases include pneumonia, sepsis, and meningitis.

Rates of disease

- Highest rates seen in children less than 2 years of age
- Other children at high risk include those with asplenia, patients with HIV, American Indian-Alaskan Natives, African Americans, and day-care attendees.
- The elderly have fatality rates of 30-60% (those over the age of 50).
- Pneumococcal disease is one of the leading causes of vaccine-preventable diseases, with 20,000 to 40,000 cases of invasive disease every year.
- Pneumococcal bacteria are common respiratory tract inhabitants, with estimated asymptomatic carriage rates varying from 5-70%.
- Transmission is through direct person-to-person droplet contamination or autoinoculation by carriers.
- Clinical features include abrupt onset, fever, otitis media, shaking chills, productive cough, pleuritic chest pain, dyspnea, hypoxia, tachypnea, headaches, lethargy, vomiting, irritability, nuchal rigidity, seizures, coma, and death.
- Resistance to antibiotics is up to 35% in certain areas of the country and rising.

23-Valent polysaccharide vaccine (Pneumovax-23® by Merck)

- Ineffective in children less than 2 years old
- Effective against 88% of serotypes causing bacteremic disease

Indications

- Adults over the age of 65
- Everyone over age 2 years with chronic disease

Dose

- 0.5 mL IM or SC
- Revaccination (2-dose maximum)
 - * Patients at high risk of disease if >5 years since previous dose
 - * Everyone 65 years and older who received initial dose under the age of 65 and if >5 years since previous dose

Adverse reactions

- Adverse reactions include pain, swelling, and redness at the injection site and slight to moderate systemic reactions such as fever and myalgias.

7-Valent conjugated polysaccharide vaccine (Prevnar® by Wyeth)

- Effective against 86% of serotypes causing bacteremic disease, 83% of serotypes against meningitis, and 65% of serotypes causing otitis media

Indications

- Routine vaccination for all children less than 2 years of age
- Children 24-59 months of age with high-risk medical conditions

Dose

- 0.5 mL IM at 2, 4, 6, and 12-15 months of age (see schedules for catch-up recommendations)
- Revaccination not recommended but high-risk children should receive 23-valent polysaccharide vaccine after 2 years of age.

Adverse reactions

- Adverse reactions include pain, swelling, and redness at injection site, difficulty in moving the limb (rare), and slight to moderate systemic reactions such as fever and myalgias.

Influenza

- RNA virus of orthomyxovirus family
- Antigenic drift: frequent minor changes in the antigenic structure of the virus; this can reach epidemic proportions, but not every year. This is why yearly adjustments in vaccine formulations are required. All three types (A, B, and C) can undergo drifts.
- Antigenic shift: major changes in one or both of the major antigens in influenza A, resulting in a different subtype; this can result in major pandemics in all ages.

Influenza A

- Subtypes are based upon two surface antigens: hemagglutinin and neuraminidase.
- Six types of hemagglutinin (H1, H2, H3, H5, H7, and H9) cause disease in humans and cause virus attachment to cells.
- Two types of neuraminidase cause disease in humans (N1 and N2) and have a role in viral penetration of cells.
- Causes moderate to severe disease in all ages and can be transmitted in other animals

Influenza B

- No subgroups
- Causes milder disease and affects primarily children
- Only affects humans

Influenza C

- Rarely reported and many cases are subclinical

Influenza disease

- Major serious complications in all types include pneumonia, Reye's syndrome (progressive neurological symptoms associated with aspirin use in children), myocarditis, worsening of chronic bronchitis, and death.
- Rates of disease are highest in the elderly (>65), children less than 2 years of age, and persons of any age with medical conditions.
- Influenza is one of the leading causes of vaccine-preventable disease, with 20,000–40,000 deaths during epidemics. Pandemics could result in the deaths of over 400,000 people.
- Influenza virus penetrates the respiratory epithelial cells and destroys the host.
- Virus is shed in respiratory secretions for 5–10 days and transmission is through direct person-to-person droplet contamination or contact. The incubation period is approximately 2 days (range 1–5 days).
- Clinical features include abrupt onset, fever, myalgias, sore throat, nonproductive cough, and headache.
- Disease peaks between December and March in the Northern Hemisphere, but may occur earlier or later. Year-round cases may be seen in tropical climates.

Influenza vaccine (Fluvirin® by Novartis, Fluzone® by sanofi pasteur, Fluorix® by GSK)

- Inactivated, split-virus vaccine
- Contains 3 vaccine components (2 type A viruses and 1 type B virus)
- Vaccines are named according to the virus' type/geographic origin/strain sequence number/year of isolation (hemagglutinin neuraminidase for type A only): for example, A/Panama/2007/99(H3N2) or B/Hong Kong/330/2001.
- Effective in up to 90% of healthy adults, 50–60% of the elderly, and 30–40% of the frail elderly

Indications

- All children 6–59 months of age
- Close contacts of children 6–59 months of age
- Adults over the age of 50
- Adults and children over age 23 months with certain chronic diseases
- Residents of nursing homes or long-term care facilities
- People who may infect others, including contacts of patients with diseases, and health care workers

- Pregnancy in all trimesters or women who will become pregnant during the influenza season
- Patients 6 months to 18 years of age on chronic aspirin therapy
- Patients with neurological or neuromuscular disorders
- Anyone who wishes to decrease the likelihood of influenza disease

Dose

- 6–35 months: 0.25 mL IM (repeat in 1 month if first time); 3–8 years: 0.5 mL (repeat in 1 month if first time); >8 years: 0.5 mL
- Fluvirin by Novartis is indicated for those ≥4 years of age
- Fluorix is indicated for those ≥18 years of age
- Revaccination yearly

Contraindications

- Contraindications include severe allergic reactions to previous dose and egg allergy.

Adverse reactions

- Adverse reactions include pain, swelling, and redness at injection site and slight to moderate systemic reactions such as fever, myalgias, chills, and malaise. Severe neurologic reactions are rare.

Live attenuated influenza vaccine (LAIV)**(FluMist® by MedImmune)**

- Attenuated, cold-adapted live influenza vaccine
- Same vaccine antigens as in inactivated influenza vaccine
- Efficacy 86–93%
- Must be frozen (15°C or lower)

Indications

- Similar to inactivated vaccine unless contraindications exist
- Healthy persons age 5–49 years
- Contacts with high-risk patients, except the severely immunocompromised.

Contraindications (use inactivated influenza vaccine)

- Persons with chronic medical diseases
- Close contacts of severely immunocompromised persons
- Pregnancy
- Children receiving aspirin therapy
- Persons with a history of Guillain-Barré syndrome

Dose

- 0.25 mL sprayed in each nostril (0.5 mL total)
- Children age 5–8 who receive influenza vaccine for the first time need 2 doses 6–8 weeks apart.

Adverse reactions

- Similar to inactivated vaccine
- Nasal congestion
- Headache
- Vomiting

Tetanus

- Exotoxin produced by *Clostridium tetani*, a gram-positive anaerobic rod that may develop a highly resistant spore; these spores are widely spread in soil, animal intestines and feces, skin surfaces, and infected plants.
- The disease is characterized by generalized rigidity and convulsive spasms of skeletal muscles; usually involves muscles of the face (lockjaw) and neck. Spasms may last 3-4 weeks and complete recovery may take months.
- Enters the body through contamination of a wound. Spores germinate in an anaerobic environment. Toxins are released and transported through the body.
- Incubation period is usually 8 days (range, 3-21 days).
- Transmission risk factors include puncture wounds, surgery, burns, minor wounds, dental infections, animal bites, injection drug use, diabetes, and approximately 10% of cases are due to an unknown cause.
- Tetanus is not contagious person to person.
- Tetanus occurs in the U.S. at a rate of 0.02-0.05 per 100,000 per year. The case fatality rate is approximately 10%.
- Complications include: laryngospasm, fractures, hypertension, nosocomial infections, pulmonary embolism, aspiration, and death.
- Wound management recommendations may include tetanus immune globulin (Table 3).

Table 3**CDC Guidelines for Tetanus Wound Management**

	Clean minor wounds		All other wounds	
	Td ¹ or Tdap ²	TIG ³	Td ¹ or Tdap ²	TIG
Vaccination history				
Unknown or <3	Yes	No	Yes	Yes
Three or more	No ⁴	No	No ⁵	No

¹Td, tetanus-diphtheria vaccine.²Tdap, tetanus-diphtheria-pertussis vaccine.³TIG, tetanus immune globulin.⁴Yes, if >10 years since last dose.⁵Yes, if >5 years since last dose.**Tetanus toxoid vaccine**

- Usually combined with diphtheria toxoid pertussis vaccine
- Toxoid is formaldehyde-inactivated toxin adsorbed to aluminum.

Dose

- Pediatric dose: 0.5 mL IM of DT or DTaP given at 2, 4, 6, and 15-18 months of age; booster dose should be given at 4-6 years.
- Adolescent dose: 0.5 mL Tdap at 11-12 years
- Adult dose: 0.5 mL of Tdap if tetanus-containing vaccine is indicated
- Revaccination with Td every 10 years

Adverse reactions

- Adverse reactions include pain, swelling (nodule may form), and redness at injection site and systemic reactions are uncommon. An exaggerated (Arthus-type) reaction with extensive painful swelling from shoulder to elbow can occur at injection site and is thought to be caused by too-frequent injections.

Diphtheria

- Toxin produced by *Corynebacterium diphtheriae*, an aerobic gram-positive bacterium; this bacterium must be infected by a virus that carries a genetic code for toxin production.
- The most common presentation of diphtheria is characterized by early, nonspecific URI symptoms that develop into pharyngitis. Two to three days later, a bluish-white membrane starts to form that can cover the entire soft palate. The membrane can turn dark if bleeding occurs and manipulation of the membrane can result in bleeding. Airway obstruction may occur.
- Other sites of infection may include the larynx or the skin.
- Other complications may include myocarditis, neuritis with paralysis, respiratory failure, and death (overall case fatality rate of 5-10%).
- Asymptomatic human carriers are the source of most infections.
- The incubation period is usually 2-5 days (range, 1-10 days).
- Treatment of acute disease is with antitoxin and antibiotics.

Diphtheria toxoid vaccine

- Combined with tetanus toxoid pertussis vaccine; single toxoid antigen is not available.
- Toxoid is formaldehyde-inactivated toxin adsorbed to aluminum.
- Pediatric version of the combination (DT or DTaP)

contains 3-4 times as much antigen as the adult version (Td).

Dose

- Pediatric dose: 0.5 mL IM of DT or DTaP given at 2, 4, 6, and 15-18 months of age; booster dose should be given at 4-6 years.
- Adolescent dose: 0.5 mL Tdap at 11-12 years
- Adult dose: 0.5 mL of Tdap if tetanus-containing vaccine is indicated
- Revaccination with Td every 10 years

Adverse reactions

- Adverse reactions include pain, swelling (nodule may form), and redness at injection site; systemic reactions are uncommon. An exaggerated (Arthus-type) reaction with extensive painful swelling from shoulder to elbow can occur at the injection site and is thought to be caused by too-frequent injections of the tetanus antigen component of the combination vaccines.

Pertussis

- Pertussis, or whooping cough, is caused by *Bordetella pertussis*, an aerobic, gram-negative rod. The bacteria produces multiple antigenic products that are responsible for the clinical disease. The bacteria produces toxin that paralyzes the respiratory cilia and causes inflammation of the respiratory tract.
- The presentation of pertussis is in three stages. The first stage is a catarrhal stage with nonspecific URI symptoms. After 1-2 weeks the paroxysmal stage with the characteristic cough and inspiratory whoop begins and lasts up to 6 weeks. Recovery is gradual and the cough usually resolves in 2-3 weeks.
- The presentation in older children and adults may be much milder and present with a persistent mild cough that lasts up to 7 days and may appear to be similar to other upper respiratory infections.
- Complications may include pneumonia, encephalopathy, seizures, and death (overall case fatality rate of 0.2%).
- Asymptomatic human carriers are the source of most infections.
- The incubation period is usually 7-10 days (range, 14-21 days).
- Treatment of acute disease includes supportive care, antibiotics, and prophylaxis of contacts.
- Transmission is human-to-human by the respiratory route. Pertussis is highly contagious with attack rates of 80% in susceptible contacts.

Pertussis vaccine

- Combined with tetanus toxoid and diphtheria toxoid for children; single toxoid antigen is not available.
- Whole cell vaccine was developed in the 1930s, but is no longer available in the United States.
- Acellular pertussis vaccine was first licensed in 1991 and has fewer side effects than the whole cell vaccine.

Dose

- Pediatric dose: 0.5 mL IM of DTaP given at 2, 4, 6, and 15-18 months of age; booster dose should be given at 4-6 years.
- Adolescent dose: 0.5 mL of Tdap
- Adult dose: 0.5 mL of Tdap (one-time dose only)

Adverse reactions

- Adverse reactions include pain, swelling (nodule may form), and redness at the injection site and systemic reactions are uncommon. An exaggerated (Arthus-type) reaction with extensive painful swelling from shoulder to elbow can occur at the injection site and is thought to be caused by too-frequent injections of the tetanus antigen component of the combination vaccines.

Hepatitis B

- Hepatitis B is caused by a DNA virus and causes one of the most common infections worldwide. There are an estimated 200-300 million chronic carriers of hepatitis B worldwide.
- The clinical course is similar to that of all other types of viral hepatitis, with symptoms of malaise, weakness, anorexia, nausea, jaundice, abdominal pain, headache, and dark urine. Malaise and fatigue may last for weeks to months after all other symptoms disappear.
- Fulminant hepatitis occurs in 1-2% of all cases, with mortality rates of 60-90%.
- Complications are usually related to chronic infections with hepatitis B virus, and include chronic hepatitis, cirrhosis, liver failure, and hepatocellular carcinoma. Twenty-five percent of all carriers develop chronic, active hepatitis.
- The risk of becoming a carrier following infection ranges from 6-50%.
- The incubation period is usually 7-10 days (range, 14-21 days).
- Transmission is human-to-human by exposure of body fluids by parenteral or mucosal contact. Hepatitis B is a common sexually transmitted disease. Perinatal transmission is a significant mode of infection.

Hepatitis B vaccine

- The first vaccine was a plasma-derived vaccine released in 1981 and removed from the market in 1992.
- The current vaccine is hepatitis B surface antigen (HBsAg) produced using recombinant DNA technology; it was first released in 1986. Two products are currently marketed: Recombivax HB® (Merck) and Engerix-B® (GlaxoSmithKline). Although the antigen contents are different, the two vaccines are interchangeable.

Dose

- Pediatric dose: the usual dose is 0.5 mL IM given at birth, 2 months, and 6 months.
- Indications include all infants, all adolescents, and high-risk adults (eg, multiple sex partners, STDs, injection drug use, dialysis, hemophilia, others).
- The usual adult dose is 1.0 mL given at 0, 2, and 6 months.
- Adolescents aged 11-15 years may be given a two-dose series separated by 4 months. This is only approved for Recombivax HB.
- Booster doses should not be given.

Adverse reactions

- Adverse reactions include pain, swelling (nodule may form), and redness at the injection site; systemic reactions are uncommon.

Haemophilus influenzae Type b (Hib)

- *Haemophilus influenzae* is a gram-negative coccobacillus, whose outer shell consists of a polyribosyl-ribitol phosphate (PRP) polysaccharide capsule. There are six distinctly different types of *H influenzae*, labeled a-f; however, type b is responsible for 95% of human disease.
- The organism enters through the nasopharynx and

may cause disease or may colonize the nasopharynx, creating an asymptomatic carrier.

- The most common clinical infections caused by Hib are meningitis, epiglottitis, pneumonia, arthritis, and cellulitis. Meningitis accounts for 50-65% of all clinical disease and results in a mortality of 2-5% and neurological sequelae in 15-30% of cases. Other diseases caused by *Haemophilus influenzae* include otitis, sinusitis, and bronchitis; however, these are usually due to nontypable (unencapsulated) strains.
- Hib is primarily a disease of children, with a peak at age 6-7 months and rarely attacks after the age of 5 years.
- Treatment of acute disease includes hospitalization, intravenous antibiotics, and prophylaxis of contacts.
- Transmission is human-to-human by respiratory droplet spread to susceptible individuals.

Haemophilus influenzae vaccine

- The incidence of Hib disease has decreased by more than 99% since the introduction of vaccine.
- The first vaccine licensed (1985-1988) was a pure polysaccharide vaccine that was ineffective in children less than 18 months of age.
- Current vaccines are polysaccharide vaccine conjugated to protein carriers. The specific carriers vary by manufacturer (Table 4).
- HbOC (HibTITER), PRP-T (ActHIB or OmniHIB), and PRP-OMB (PedvaxHIB) are indicated for infants ≥ 6 weeks of age.
- Doses given before 6 weeks of age may inhibit the production of antibodies to subsequent doses; therefore the vaccines are contraindicated in children less than 6 weeks of age.

Dose

- The usual dose for the vaccines approved for infants is 0.5 mL IM given at 2 months, 4 months, and 6 months. A booster dose is recommended for children

Table 4.

Haemophilus influenzae Type B Vaccines

Vaccine	Protein carrier	Manufacturer	Age indications
HbOC (HibTITER®)	Mutant diphtheria toxoid	Lederle-Praxis	≥ 6 weeks
PRP-T (ActHIB® or OmniHIB®)	Tetanus toxoid	Aventis Pasteur	≥ 6 weeks
PRP-OMB (PedvaxHIB®)	Meningococcal group B outer membrane protein	Merck & Co	≥ 6 weeks

12-15 months of age. If PRP-OMB (PedvaxHIB) is used for the pediatric series, the 6-month dose should be omitted.

- The catch-up series for Hib vaccine varies by age and manufacturer. Consult the package insert for complete dosing information.
- Vaccination of children >59 months of age is not indicated unless there are certain medical indications. These include persons with asplenia, immunodeficiency conditions, and those undergoing immunosuppressive therapy.
- Combination vaccines of Hib vaccine and hepatitis B vaccine (COMVAX[®] by Merck) and Hib vaccine and DTaP (TriHIBit[®] by sanofi pasteur) are available. TriHIBit is not approved for the initial pediatric series (2, 4, and 6 months) and can only be used for a dose at ≥12 months of age when a previous dose of Hib was given ≥2 months earlier, and TriHIBit will be the last dose in the Hib series. COMVAX must not be administered before 6 weeks of age.

Adverse reactions

- Adverse reactions include pain, swelling, and redness at the injection site; systemic reactions are uncommon.

Hepatitis A

- Hepatitis A is caused by an RNA virus and is the most common hepatitis infection in the United States.
- The clinical course is similar to that of all other types of viral hepatitis, with symptoms of malaise, weakness, anorexia, nausea, jaundice, abdominal pain, headache, and dark urine. Malaise and fatigue usually lasts for 2 weeks; however, symptoms may last or recur for up to 6 months.
- Fulminant hepatitis A is rare, but can occur. The incidence increases with age >40 years. Not indicated for children <1 year of age.
- While serious complications are not as common as with hepatitis B, morbidity and its associated costs (health care costs and lost work days) are significant.
- There is no risk of becoming a chronic carrier.
- The incubation period averages 28 days (range, 15-50 days).
- Treatment of acute disease is supportive.
- Transmission is human-to-human by the fecal-oral route of exposure.
- Exposure of an unimmunized person to hepatitis A requires the administration of immune globulin intramuscular (IGIM) as well as beginning the hepatitis A vaccine series.

Hepatitis A vaccine: Havrix[®] by GlaxoSmithKline and VAQTA[®] by Merck and Co.)

- Inactivated whole virus vaccines
- Both vaccines are available in pediatric and adult formulations.
- Hepatitis A vaccine is not indicated for children <1 year of age.
- The two vaccines use different potency measurements, but the volume and schedule of the dose is the same.

Dose

- Children and adolescents over 1 year of age are given 0.5 mL and repeated in 6-12 months (Havrix) or 6-18 months (VAQTA), for a total of 2 doses.
- Adults over 18 years old are given 1.0 mL and repeated in 6-12 months, for a total of 2 doses.

Combination vaccine (Twinrix[®] by GlaxoSmithKline)

- A combination product with hepatitis B (adult dose) and hepatitis A (pediatric dose)
- Given at 0, 1, and 6-12 months
- Indicated for persons ≥18 years of age

Adverse reactions

- Adverse reactions include pain, redness, and swelling at the injection site. Mild systemic reactions are rare.

Meningococcal

- Meningococcal disease is caused by *Neisseria meningitidis*, a gram-negative bacteria with a polysaccharide capsule.
- The clinical diseases caused by *Neisseria meningitidis* include meningitis, sepsis, pneumonia, myocarditis, and urethritis. It is one of the leading causes of meningitis in the United States.
- The types of *Neisseria meningitidis* that cause over 95% of disease are serogroups A, B, C, W-135, and Y.
- There are approximately 2500-3000 cases per year with an incidence rate of 2 cases per 100,000 people. The incidence in college freshmen that live in dormitories is approximately 4 cases/100,000.
- There is a carrier state that increases in incidence during epidemics.
- Parts of the world, including parts of Africa and Asia, have a high rate of disease.
- Treatment of acute disease is with antibiotics.

Polysaccharide meningococcal vaccine (Menomune[®] by Sanofi Pasteur)

- This is a polysaccharide vaccine effective against serogroups A, C, W-135, and Y. The vaccine does

not protect against serogroup B, a common cause of infection.

- Indicated for persons over the age of 2 years.
- Those who should be vaccinated include military personnel, freshmen college students living in dormitories, those with anatomic or functional asplenia, and travelers to the "meningitis belt" of sub-Saharan Africa. Evidence of immunization is required for religious pilgrimages to Saudi Arabia for the Islamic Hajj. Vaccine may also be useful during an outbreak.

Dose

- The dose is 0.5 mL given subcutaneously.
- A booster dose after 3-5 years may be needed.

Adverse reactions

- Adverse reactions include pain, swelling (nodule may form), and redness at the injection site and mild systemic reactions, such as fever, headaches, and malaise.

Conjugated polysaccharide meningococcal vaccine (Menactra® by sanofi pasteur)

- This is a polysaccharide vaccine that is conjugated to diphtheria toxoid.
- It is effective against serogroups A, C, W-135, and Y. The vaccine does not protect against serogroup B, a common cause of infection.
- Approved for ages 11-55
- The Advisory Committee on Immunization Practices (ACIP) recommends vaccination for those aged 11-12 and college freshmen living in dormitories.
- Indications are the same as for the polysaccharide vaccine.

Dose

- The dose is 0.5 mL given intramuscularly.
- It is unknown if a booster dose will be needed.

Polio

- There are three poliovirus types identified as P1, P2, and P3.
- The virus enters the mouth and replicates in the gastrointestinal tract. From the GI tract, the virus enters the bloodstream and infects the cells of the central nervous system.
- Up to 95% of all infections are asymptomatic; however, these persons may transmit the infection to others.
- Approximately 4-8% of infections are mild with nonspecific symptoms of upper respiratory infection, gastroenteritis, and influenza-like symptoms.
- One to two percent of infections present as nonparalytic aseptic meningitis, which typically resolves in 2-10 days.

- Flaccid paralysis occurs in less than 1% of those infected.
- The incubation period is usually 6-20 days (range, 3-35 days).
- Treatment of acute disease includes supportive care.
- Transmission is person to person by the fecal-oral route.

Polio vaccine (IPOL® by sanofi pasteur)

- The current vaccine available in the United States is an inactivated, trivalent injectable vaccine (IPV).
- Use of oral polio vaccine (OPV) was discontinued in the United States due to the elimination of wild-type polio disease and because yearly cases of vaccine-associated paralytic poliomyelitis (VAPP) were reported.

Dose

- Pediatric dose: 0.5 mL IM given at 2, 4, 6-18 months, and 4-6 years of age
- Routine vaccine or booster doses for adults are not recommended.

Adverse reactions

- Adverse reactions include minor pain, swelling, and redness at the injection site; systemic reactions are uncommon.

Measles, Mumps, and Rubella

Measles

- Measles is a viral infection whose main presentation is a maculopapular rash.
- The virus is shed through the nasopharynx.
- Ten to twelve days after exposure, the prodrome phase begins, with progressive fever, cough, coryza, and conjunctivitis.
- Two to four days after the prodrome begins, a maculopapular rash begins on the face and head and gradually spreads throughout the body.
- The rash lasts 3-5 days then gradually fades.
- The incubation period is 10-12 days.
- Transmission is person to person through large respiratory droplets.
- Measles is highly contagious.
- Complications may include pneumonia, otitis, encephalitis, and death.

Mumps

- Mumps is a viral infection with a presentation of parotitis in 30-40% of cases.
- The virus is shed through the nasopharynx.
- Fourteen to eighteen days after exposure, the prodrome phase begins, with headache, malaise, myalgias, and low-grade fever.

- Two days after the prodrome begins is when the parotitis begins.
- Symptoms start to decrease after 1 week and disappear after 10 days.
- The incubation period is 14-18 days (range, 14-25 days).
- Transmission is person to person through large respiratory droplets.
- Complications can include orchitis, oophoritis, pancreatitis, and deafness.

Rubella

- Rubella is a viral infection with up to 20-50% of cases subclinical and inapparent.
- The virus is shed through the nasopharynx.
- A 1-5 day prodrome phase begins after incubation, with headache, malaise, myalgias, lymphadenopathy, low-grade fever, and URI symptoms. This phase is rare in children.
- Fourteen to seventeen days after exposure, a maculopapular rash appears, first on the face, and then descending to cover the rest of the body.
- The rash disappears after about 3 days.
- The incubation period is 14 days (range, 12-23 days).
- Transmission is person to person through large respiratory droplets.
- Complications may include arthritis, arthralgias, encephalitis, and hemorrhaging.
- The major complication is congenital rubella syndrome, which occurs in the offspring of a woman who had rubella during pregnancy. Babies born with CRS have major birth defects that can affect many organs.

Measles-mumps-rubella vaccine (MMRII® by Merck)

- The current vaccine available in the United States is a live, attenuated vaccine against all three diseases.

Dose

- Pediatric dose: 0.5 mL IM given at 12 months of age
- A second dose is recommended at 4-6 years of age to produce immunity in those who did not respond to the first dose.
- This vaccine is contraindicated in pregnancy. Pregnancy should be avoided for 4 weeks following vaccination.
- Serologic testing may be necessary to document immunity to rubella.
- Vaccination with the combination product should be used when one or more of the vaccines are needed unless a contraindication exists for an antigen component of the vaccine.

Adverse reactions

- Adverse reactions include minor pain, swelling, and redness at the injection site, and systemic reactions that mimic a mild case of the diseases.

Varicella (Chickenpox)

- Chickenpox is a viral infection caused by the herpes zoster virus.
- The primary infection is called chickenpox and the recurrent disease is herpes zoster (called shingles).
- The virus enters through the respiratory tract and replicates in the nasopharynx and regional lymph glands.
- The incubation period is 14-16 days (range, 10-21 days).
- A prodromal phase may precede the rash with a slight fever and malaise.
- The rash progresses from a macule to a papule to a vesicle before it crusts over.
- The rash appears in several waves that last 2-3 days each.
- The rash first appears on the face and then the trunk (where most of the rash occurs), and the extremities.
- Recurrent disease (herpes zoster) appears to be related to aging and immunosuppression.
- Recurrent disease usually presents as an outbreak of lesions along a dermatome and is usually unilateral. Neuralgia and intense pain may be present.
- Transmission is person to person by infected respiratory secretions.
- Complications may include pneumonia, secondary bacterial infections, CNS infections and symptoms, and Reye's syndrome if a child is taking aspirin.

Varicella vaccine (Varivax® by Merck)

- The current vaccine available in the United States is a live, attenuated vaccine.

Dose

- Pediatric dose: 0.5 mL IM given at 12-18 months of age
- A second dose is recommended at 4-6 years of age
- The adult dose (age >13 years) is 2 doses of 0.5 mL each separated by 4-8 weeks.
- This vaccine is contraindicated in pregnancy and pregnancy should be avoided for 4 weeks following vaccination.
- Other contraindications include immunosuppressive disease or patients receiving immunosuppressive therapy, and those receiving antibody-containing blood products.
- Adverse reactions include minor pain, swelling and redness at the injection site, and systemic reactions that mimic a mild case of the disease, including a mild generalized rash.

- The vaccine must be stored frozen at +5°F (−15°C). The diluent used to reconstitute the vaccine should be stored at room temperature.

Combination Vaccines

- As mentioned in several sections previously, there are several vaccination combinations on the market.
- Tetanus, diphtheria, and pertussis combinations (various manufacturers): DTaP, DT, Td, Tdap
- Twinrix by GlaxoSmithKline: a combination product with hepatitis B (adult dose) and hepatitis A (pediatric dose)
- Hib vaccine and hepatitis B vaccine: COMVAX by Merck
- Hib vaccine and DTaP: TriHIBit by sanofi pasteur
- Pediarix® (GlaxoSmithKline)
 - * DTaP + hepatitis B + inactivated polio
 - * Indicated when all vaccine components are indicated
 - * Not approved for <6 weeks or >7 years of age
 - * Efficacy, contraindications, and adverse reactions are similar to those of the vaccine components given separately.
 - * Dose: 0.5 mL IM given at 2, 4, and 6 months of age
 - * Must be shaken vigorously prior to drawing up in syringe
 - * Can be given even if infant receives birth dose of hepatitis B vaccine
- ProQuad® by Merck: a combination vaccine of measles, mumps, rubella, and varicella vaccine

4. Key Points

- The two types of vaccine antigens include live viruses and inactivated viruses or bacterial components.
- There are two types of immunity: active and passive.
- Adverse effects of inactivated vaccines include pain at the injection site and mild systemic symptoms (mild fever). Adverse effects of live vaccines mimic a mild case of the disease.
- Live vaccines should be avoided during pregnancy.
- Influenza viruses undergo shifts and drifts, which accounts for the need for yearly vaccine changes.
- Wound management must include evaluation for the need for tetanus toxoid and tetanus immune globulin.
- Diphtheria toxoid and tetanus toxoid should always be given together, unless there is a contraindication to one of the components. If there is a need for one, then there is a need for both.
- A new combination vaccine of tetanus, diphtheria, and pertussis is available for use in adolescents and adults (Tdap). It is recommended one time for persons 11-64 years of age. Children under the age of 7 years receive DTaP or DT (if unable to tolerate pertussis vaccine). All other ages should receive Td if vaccination is indicated.
- Hepatitis B vaccine is now recommended for all infants, starting at birth, as well as all adolescents. Other indications include adults with high-risk occupations or behaviors.
- Hepatitis A vaccine is recommended for travel to most parts of the world.
- Inactivated polio vaccine (IPV) is the only polio vaccine recommended for use in the U.S. Oral polio vaccine (OPV) is not recommended due to the high incidence of vaccine-associated paralytic poliomyelitis (VAPP).
- A second dose of MMR vaccine and varicella vaccine is recommended at 4-6 years of age.
- Combination vaccines are available to decrease the number of injections.

5. Questions and Answers

1. A 62-year-old patient presents to your pharmacy for a refill of his insulin. It is October and he asks you to review his immunization status with him. About which adult vaccine do you need to ask his status?
 - I. Influenza vaccine
 - II. Pneumococcal vaccine
 - III. Meningococcal vaccine
 - IV. Hepatitis A vaccine
 - V. Diphtheria-tetanus (Td) vaccine
 - A. I only
 - B. I and II only
 - C. III and IV only
 - D. I, III, and V only
 - E. I, II, and V only
2. The patient in question 1 states that he received his pneumococcal vaccine 2 years ago. When should he receive another?
 - A. Never
 - B. Every year
 - C. In 5 years
 - D. When he reaches the age of 67
 - E. When he reaches the age of 65
3. Which of the following describes the current injectable influenza vaccine used in the United States?
 - A. Inactivated virus
 - B. Live attenuated virus
 - C. Conjugated vaccine
 - D. Toxoid
 - E. Toxin
4. Indications for meningococcal conjugate vaccine include
 - I. all adolescents aged 11-12
 - II. travel to the "meningitis belt" of sub-Saharan Africa
 - III. asplenia
 - IV. pilgrimage to Saudi Arabia for the Islamic Hajj
 - V. college freshmen living in dormitories
 - A. I only
 - B. II, III, and V only
 - C. I, II, and III only
 - D. II, III, IV, and V only
 - E. All of the above
5. At what age does one switch from DTaP to Td?
 - A. 2 years
 - B. 5 years
 - C. 7 years
 - D. 10 years
 - E. DTaP can be used in all age groups
6. Which of the following vaccines has BOTH a polysaccharide and a conjugated vaccine on the U.S. market?
 - I. Influenza
 - II. Meningococcal vaccine
 - III. *Haemophilus influenzae* type B vaccine
 - IV. Hepatitis vaccine
 - V. Pneumococcal vaccine
 - A. IV only
 - B. II and V only
 - C. I, II, and III only
 - D. II, III, and V only
 - E. All of the above
7. Which polio vaccine schedule is recommended in the United States?
 - A. Four doses of IPV
 - B. Four doses of OPV
 - C. Four doses of IPV plus a booster at 18 years of age
 - D. Two doses of OPV and 2 doses of IPV
 - E. Polio vaccine is no longer recommended in the United States.
8. Hepatitis B vaccine is a
 - A. polysaccharide vaccine
 - B. recombinant hepatitis B surface antigen vaccine
 - C. live vaccine
 - D. conjugate vaccine
 - E. a toxoid
9. An 18-year-old, healthy student is told that she needs to come to the pharmacy for her routine vaccinations prior to starting college. She will be living in the dormitory at school. She has not received any vaccines since grade school. Which of the following vaccines are indicated?
 - I. MMR if she has not received a second dose
 - II. Varicella if she has not had previous vaccination or varicella vaccination
 - III. Meningococcal vaccine
 - IV. Pneumococcal vaccine

- V. Tdap if she has not received one for 10 years
- All of the above
 - I and II only
 - I, II, III, and IV only
 - I, III, and V only
 - I, II, III, and V only
10. The patient in question 9 is exposed to a patient with hepatitis A 1 month later. She should receive the following vaccines.
- Hepatitis A vaccine series only
 - Hepatitis B vaccine series only
 - Hepatitis A vaccine series plus IGIM
 - Hepatitis A vaccine plus hepatitis B vaccine series
 - IGIM only
11. Which of the following are high-risk groups that should be targeted for annual influenza vaccination?
- Persons aged 5-49 years
 - Persons with diabetes
 - Patients aged 21-49 with hypertension
 - Construction workers
 - Healthy teenagers
12. Which complication of rubella infection is the most significant health problem?
- Congenital rubella syndrome
 - Secondary infection
 - Patent ductus arteriosus
 - Diarrhea
 - Arthritis
13. Which of the following is a valid contraindication to the receipt of a live-virus vaccine?
- Taking antibiotics
 - Recent administration of antibody-containing blood products
 - Age over 12 months
 - Allergies to penicillin
 - A parent or sibling with a cold who is living in the same household
14. The most common adverse reaction to an inactivated vaccine is
- Rash
 - Severe headache
 - Injection site reactions
 - Rhinorrhea
 - Stomach pain
15. The only vaccine recommended at birth is
- DTaP
 - IPV
 - Hib
 - pneumococcal conjugate vaccine
 - hepatitis B
16. A 32-year-old female is injured in an automobile accident and her spleen is removed. Which of the following vaccines is NOT routinely recommended for asplenic adult patients?
- Pneumococcal vaccine
 - Meningococcal vaccine
 - IPV
 - Haemophilus influenzae* type B vaccine
 - Yearly influenza vaccines
17. If a second dose of a vaccine were given too soon (before the minimal interval time period has passed), the correct course of action would be
- Restarting the entire series
 - Do not count that dose and repeat it after the minimal time period has passed since the incorrect dose
 - Do not worry about it and continue with the next dose as scheduled
 - Draw antibody titers to confirm immunity
 - Double the next dose
18. Which of the following groups of children are NOT at increased risk for pneumococcal disease?
- Children with mild asthma
 - Children of Native Alaskan descent
 - Children of African-American descent
 - Children with sickle cell disease
 - Children infected with HIV
19. Which of the following statements are true concerning *Haemophilus influenzae* type b vaccine (Hib)?
- Hib is recommended for all infants without contraindications
 - Standard dosing for Hib vaccine is 2, 4, 6, and 12-18 months of age
 - The 6-month dose is omitted if PedvaxHIB is used for the first 2 doses

- IV. Hib vaccine is not routinely recommended for children aged 5 years and older
- A. Only I is correct
 - B. Only I, II, and III are correct
 - C. Only II, III, and IV are correct
 - D. Only II and III are correct
 - E. All are correct
20. Which of the following vaccines available in the United States is a live, attenuated virus vaccine?
- A. Polio (IPV)
 - B. *Haemophilus influenzae* vaccine (Hib)
 - C. DTaP
 - D. Varicella vaccine
 - E. Pneumococcal vaccine

Answers

1. E. Routine vaccinations in the adult are a yearly influenza vaccine, Td vaccine every 10 years, and a single pneumococcal vaccine for patients with select chronic illnesses (such as diabetes). Meningococcal and hepatitis vaccines are recommended only for certain indications.
2. D. Routine revaccination with pneumococcal vaccine is not recommended. Revaccination is recommended for select high-risk groups and everyone 65 years and older who received an initial dose under the age of 65 and if >5 years have elapsed since the previous dose.
3. A. Influenza vaccine is an attenuated, split virus vaccine. The LAIV is administered intranasally.
4. E. With the recent availability of a conjugate meningococcal vaccine, the ACIP recommended including all adolescents aged 11-12 among the other recommendations.
5. C. DTaP is indicated for children under the age of 7. Due to adverse effects of DTaP in children aged 7 and older, Td is used.
6. B. Polysaccharide pneumococcal vaccine (23-valent) is indicated for those over the age of 2 years and conjugated polysaccharide vaccine (7-valent) is approved for ages 2 months to 7 years. There is a recently approved meningococcal conjugate vaccine; however, the polysaccharide vaccine will be removed from the market once supplies of the conjugate vaccine are adequate.
7. A. OPV is no longer recommended in the United States and vaccination with IPV will continue until poliovirus is eradicated worldwide.
8. B.
9. E. Pneumococcal vaccine is not recommended for a healthy individual until the age of 65.
10. C. The hepatitis A vaccine will not protect an individual who has previously been exposed to the virus. IGIM, a source of antibodies (short-term protection), will help to protect immediately, and the vaccine will protect against future exposures (long-term protection).
11. B. High-risk groups targeted for influenza vaccination beginning in October include persons aged 6-23 months, persons >50 years old, persons at increased risk (age >24 months with chronic pulmonary disease [eg, emphysema, COPD], cardiovascular disease [eg, CHF, post-MI, heart anomalies], metabolic disease [eg, diabetes], renal dysfunction, hemoglobinopathies [eg, sickle cell], and immunosuppression [eg, HIV infection, chemotherapy]), residents of long-term care facilities, people 24 months to 18 years old on aspirin chronically, pregnant women in all trimesters, hospital and outpatient employees, nursing home employees with patient contact, home health care providers working with high-risk persons, household members of high-risk persons, and persons desiring to avoid influenza infection.
12. A. Complications of rubella may include arthritis, arthralgias, encephalitis, and hemorrhaging; however, the major complication is congenital rubella syndrome, which occurs in the offspring of a woman who had rubella during pregnancy. Babies born with CRS have major birth defects that can affect many organs.
13. B. Live virus vaccines will be killed if there has been recent administration of antibodies. The length of time that must separate these two products depends on the dose and type of antibody-containing blood product being used.
14. C. Local reactions are the most common type of adverse reaction, and include pain, swelling, and redness at the site of injection. These usually occur within minutes to hours of the injection and are usually mild and self-limiting. Systemic adverse reactions include fever, malaise,

myalgias, and headache, and are more common following live vaccines.

15. **E.** All of the other listed vaccines are first given at 2 months of age. Hepatitis B vaccine is recommended at birth to decrease the incidence of hepatitis B in infants of hepatitis B-infected mothers.
16. **C.** Asplenic patients require protection against the encapsulated bacteria (pneumococcus, meningococcus, and *Haemophilus*), as well as common viral infections. Previous series completions of routine vaccines, such as measles, varicella, and polio, are adequate for protection. Td vaccines should be repeated every 10 years.
17. **B.** The minimal interval in a series for most vaccines is 4 weeks. Decreasing the interval may interfere with antibody response and protection. Usually the last dose in a series is separated from the previous dose by 4-6 months. Increasing the interval does not affect vaccine effectiveness. You never need to restart a series except for oral typhoid vaccine.
18. **A.** Rates of pneumococcal disease are highest in children <2 years of age, those with asplenia, patients with HIV, American Indian-Alaskan Natives, African-Americans, and day care attendees. Mild asthma is not considered a high-risk disease for pneumococcal infection.
19. **E.** While all of the answers are correct, Hib vaccine may be indicated for children over the age of 5 with certain chronic conditions. This vaccine is relatively complicated to use since recommendations vary among manufacturers. Please consult package inserts before administering.
20. **D.** Varicella, live attenuated influenza vaccine (LAIV), and measles-mumps-rubella vaccines are the only routinely administered live vaccines in the U.S. Other non-routinely administered live vaccines include oral typhoid vaccine, vaccinia (smallpox) vaccine, and yellow fever vaccine. The majority of vaccines are inactivated or killed vaccines.

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33. Pediatrics

1. Special Drug Therapy Considerations in Pediatric Patients

Pediatric Age Definitions

Age Group	Definition
Neonate	0 to 28 days
Infant	29 days to 1 year
Child	1 to 11 years
Adolescent	12 to 18 years

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1. Special Drug Therapy Considerations in Pediatric Patients

Pediatric Age Definitions

Preterm:	<36 weeks gestation
Term:	≥36 weeks gestation
Neonate:	<1 month
Infant:	1 month to 1 year
Child:	1 to 11 years
Adolescent:	12 to 16 years

Absorption

Gastric pH

- Infants may be considered to be in a relative state of achlorhydria (due to decreased basal acid secretion and total volume of secretions); however, they are capable of producing sufficient gastric acid with stimuli (eg, in response to histamine or pentagastrin challenge, enteral feeding, or stress).
- Gastric acid production reaches adult values by approximately 3 years of age.

Implications for drug therapy

- * Increased bioavailability of basic drugs
- * Decreased bioavailability of acidic drugs
- * Increased bioavailability of acid-labile drugs (eg, penicillin G)

Gastric emptying time in pediatric patients

- Gastric emptying time (GET) is longer than it is for adults.
 - * GET is inversely related to postconceptional age.
- Irregular and unpredictable peristalsis
- Decreased motility
- Premature neonates have longer GET than term neonates and have a greater incidence of gastroesophageal reflux (GER)
- Related to type of feeding (formula-fed infants exhibit longer transit time than breast-fed infants)
- Approaches adult function by 7 to 9 months
 - * Stomach muscles are mature at 7 months.
 - * Stomach muscles are completely innervated at 9 months.

Implications for drug therapy

- * Erratic absorption of sustained-release products (eg, theophylline)
- * The rate of absorption in small intestine, where most drugs are absorbed, is slower; peak drug concentrations are lower than for adults.

Pancreatic enzymes and bile salts

- Low levels of amylase and lipase
- Low intraluminal bile acid concentrations and synthesis
- Decreased proteolytic ability

Implications for drug therapy

- Erratic absorption of drugs requiring pancreatic enzymes for hydrolysis (eg, chloramphenicol)
- Decreased absorption of lipid-soluble drugs
- Decreased fat absorption from enteral feedings
- Decreased absorption of fat-soluble vitamins

GI mucosa

- Decreased functional integrity of intestinal mucosa
- The surface area of the gastric mucosa is small compared to that of intestinal mucosa (most drugs are absorbed from the small intestine).
- Changes in splanchnic blood flow in the neonatal period may alter the concentration gradient across the intestinal mucosa.

Other absorption routes

Skin

- * Absorption via skin is inversely related to the thickness of the stratum corneum and directly related to hydration of the skin.
- * Neonates (particularly premature) have increased skin hydration.
- * The stratum corneum of preterm infants is immature and ineffective as an epidermal barrier.
- * Premature neonates may develop drug toxicity if a drug is administered via the dermal route.

Buccal route

- Not typically used in pediatric patients

Intramuscular route

- * Drug delivery is restricted by volume of medication and the pain associated with administration. Results are variable in premature neonates due to (1) blood flow and vasomotor instabilities; and (2) insufficient muscle mass and tone, contraction, and oxygenation.

Rectal administration

- Effective for drug delivery in older infants and children

Administration via intraosseous route (IO route)

- * This vessel-rich marrow (up to 5 years of age) is a great site for drug delivery to the systemic circulation. It may be an acceptable route in emergency situations for children over 5 years

of age (vessel-rich marrow is then replaced by yellow marrow).

Distribution

Protein binding

- Decreased albumin and α_1 -acid glycoprotein concentrations
- Lower binding capacity
- Qualitative differences in neonatal plasma proteins
- Competitive binding by endogenous substances (unconjugated bilirubin, free fatty acids)
- Risk of kernicterus (hypoalbuminemia, unconjugated hyperbilirubinemia, displacement by highly protein-bound drugs or free fatty acids)
- Exhibit adult-like binding by 3 to 6 months of age; adult concentrations of albumin and α_1 -acid glycoprotein are achieved at 10 to 12 months.

Differences in body composition

- Altered vascular and tissue perfusion
- The brain and liver are the largest organs in children.
- Total body water is greater in neonates and infants.
- Extracellular fluid volume is greater in neonates and infants.
- Relative lack of adipose tissue in neonates and infants (adipose level increases into adulthood)

Implications for drug therapy in neonates and infants

- Increased free fraction of drugs
- Increased potential of drug displacement by endogenous substances
- Potential risk of kernicterus with physiologic jaundice (unconjugated hyperbilirubinemia)
- Hydrophilic drugs, which parallel water in the body (eg, aminoglycosides), exhibit greater volume of distribution.
- Lipophilic drugs (eg, diazepam) parallel body fat and will exhibit a smaller volume of distribution.

Liver Metabolism

Phase I reactions (nonsynthetic): Oxidation, reduction, hydrolysis, and hydroxylation

- * The hepatic cytochrome P450 (CYP450) enzyme system is responsible for most phase I reactions.
- * The capacity of isoenzymes in the CYP450 system at birth is 20-70% of adult capacity and increases with postnatal age.
- * Full capacity for reduction at birth
- * Hydrolysis is most developed at birth, followed by the processes of oxidation and hydroxylation.

- * Benzyl alcohol, a preservative present in certain medications, can accumulate in neonates due to underdeveloped alcohol dehydrogenase. Gasping syndrome (ie, metabolic acidosis, respiratory failure, seizures, neurologic deterioration and CV collapse) can result.

Phase II reactions (synthetic): Conjugation with glycine or glutathione, glucuronidation, sulfation, methylation, and acetylation

- * The sulfation pathway is the most developed pathway at birth.
- * Glucuronidation begins around 2 months of age (it reaches adult capacity by 3 years of age).
- * Assumptions about substances primarily metabolized by glucuronidation (ie, morphine, bilirubin, chloramphenicol):
 - Potentially toxic in neonates
 - May exhibit long half-lives (eg, toxicity with chloramphenicol)
 - May require greater dosing in infants (eg, morphine conjugated to its more active metabolite)
 - May be metabolized by another pathway in infants (eg, acetaminophen is primarily metabolized via sulfation in infants).
- * Methylation is functional in infants but not significantly expressed in adults. (Methylation is responsible for the conversion of theophylline to caffeine.)

Implications for drug therapy

- For drugs undergoing phase I and II reactions, metabolism is reduced and half-life prolonged in infants and neonates.
- Insufficiency of one pathway may lead to metabolism via another.
- Drug metabolism, slower in the neonate, increases between 1 and 5 years of age and is similar to drug metabolism in adults after puberty.

Renal Elimination

- Renal blood flow is only 5-6% of cardiac output at birth, compared to 15-25% in adults (12 mL/min versus 140 mL/min).
- Glomerular filtration rate is lower at birth and reaches adult values by 1 to 5 months of age in term infants.
- Tubular secretion is low at birth and reaches adult values by 7 months of age in term infants.
- Renal elimination is affected by prematurity and postconceptional age; it increases with maturity.

Estimation of creatinine clearance in pediatric patients

- Altered by differences in renal blood flow, glomerular filtration, tubular secretion, and muscle mass
- May be affected by the presence of maternal serum creatinine over the first week of life (ie, false underestimation of creatinine clearance)
- The Schwartz equation may be used for calculation of creatinine clearance:

$$\text{CrCl (mL/min/1.73 m}^2\text{)} = k \times (\text{length in cm})/\text{SCr}$$

k = proportionality constant that changes with age and sex (Table 1)

Other Pediatric Drug Issues

- Digoxin-like immunoreactive substance (DLIS) is produced in infants and may interfere with digoxin assays and falsely elevate concentrations.
- Di(2-ethylhexyl)phthalate (DEHP), a plasticizer contained in IV bags, is shown to have an effect on the male reproductive system. Pediatric patients at highest risk of DEHP exposure are neonates on ECMO, those receiving parenteral and enteral nutrition, and those receiving plasma exchange transfusions.
- Polyethylene glycol (PEG), an additive used to promote stability in certain IV medications, can cause hyperosmolarity in infants.

Table 1

Proportionality Constant for Calculation of Creatinine Clearance Using the Schwartz Equation¹

Age	k
Low birth weight ≤1 year	0.33
Full term ≤1 year	0.45
1-12 years	0.55
14-21 years (female)	0.55
14-21 years (male)	0.70

¹From Schwartz et al, 1987.

2. Specific Infections and Disease States in the Pediatric Population

Otitis Media

Otitis media is an inflammatory process of the middle ear.

Classification

- Acute otitis media is an inflammation of the area behind the eardrum (tympanic membrane) in the chamber called the middle ear. It is accompanied by the presence of fluid in the middle ear (effusion) and by the rapid onset of signs or symptoms of ear infection (also see AAP/AAFP definition in section on diagnostic criteria).
- Recurrent otitis media is the diagnosis of three episodes of acute otitis media within a 6-month period or four episodes within a year.
- Otitis media with effusion is fluid in the middle ear (effusion) without the associated signs or symptoms of acute infection.

Clinical presentation

- Signs and symptoms include fever, otalgia (often manifested as ear tugging or pulling), otorrhea (discharge from the ear), changes in balance or hearing, irritability, difficulty sleeping, lethargy, anorexia, vomiting, and diarrhea.
- Associated findings may be runny nose, congestion, and/or cough.

Pathophysiology

Eustachian tube dysfunction

- * The infant's eustachian tube is shorter and more horizontal than that of the adult.
- * This prevents drainage of middle ear secretions into the nasopharynx and promotes pooling of secretions in the middle ear.
- Anatomic abnormalities increase risk (eg, cleft palate, adenoid hypertrophy).
- Immature immune system or altered host defenses increase risk.
- Viral infections and allergies increase risk.
- Risk factors include male gender; Native American, Canadian Eskimo, or Alaskan descent; family history of acute otitis media or respiratory tract infection; early age of first episode (earlier age is associated with greater severity and recurrence); day care environment; parental smoking; children not breast-fed; and pacifier use.
- Complications include mastoiditis, meningitis, subdural empyema, hearing loss, and delayed speech and language development.

Microbial pathogens

Viral

- Up to 50% of cases of acute otitis media may be viral in origin.

Bacterial

- *Streptococcus pneumoniae* is responsible for 40-50% of bacterial otitis media. Resistance is becoming an increasing problem; bacterial resistance occurs primarily through alteration in penicillin-binding protein (decreased affinity for binding sites).
- *Haemophilus influenzae* (primarily nonencapsulated/nontypable strains) is responsible for 20-30% of bacterial otitis media cases. Bacterial resistance occurs via β -lactamase production.
- *Moraxella catarrhalis* is responsible for 10-15% of bacterial otitis media; almost all strains are β -lactamase-producing.

Diagnostic criteria

- Clinical presentation (ie, signs and symptoms consistent with infection)
- The American Academy of Pediatrics (AAP) and American Academy of Family Physicians (AAFP) Clinical Practice Guideline on the Diagnosis and Management of Acute Otitis Media was published in 2004 and presented a revised definition of acute otitis media as follows:
 - * Diagnosis requires: (1) a history of acute onset of signs and symptoms, (2) the presence of middle ear fluid (by a bulging tympanic membrane, limited/absent mobility of or air-fluid level behind the tympanic membrane, or otorrhea), and (3) signs and symptoms of middle ear inflammation (distinct erythema of the tympanic membrane or distinct otalgia referable to the middle ear that interferes with normal sleep/activity).
- The presence of middle ear disease:
 - * Otoloscopic examination determines color, translucency, and position.
 - Redness or opacity of membrane, absence of light reflection, or bulging membrane
 - * Pneumatic otoscopic examination determines mobility of tympanic membrane (ie, presence or absence of effusion).
 - Membrane will not move briskly with positive and negative pressure if effusion is present.
 - * Tympanocentesis (ie, a needle is inserted through the tympanic membrane to withdraw fluid) allows for culture and identification of the pathogen.

Treatment principles and goals

- Assess and control pain.

- Eradicate infection.
- Prevent complications.
- Avoid unnecessary antibiotic therapy.
- Improve compliance.
- Eliminate presence of effusion.
- Prevent recurrence.

Drug therapy

- Many episodes of otitis media will have spontaneous resolution; however, since there is a risk of developing complications from untreated otitis media, antimicrobials remain the mainstay of therapy. Observation therapy may be appropriate in certain patients based on age, diagnostic certainty, and severity of illness, and when follow-up can be ensured.

First-line therapy

- Amoxicillin is the drug of choice for uncomplicated acute otitis media.
 - * Excellent in vitro activity against *S pneumoniae* and most *H influenzae*
 - * Optimal pharmacodynamic profile of available agents; reaches good concentrations in middle ear fluid
 - * Excellent safety and efficacy profile with narrow spectrum of activity
 - * Palatable and inexpensive
 - * May overcome drug-resistant *S pneumoniae* with higher doses (ie, achieves greater concentrations in middle ear fluid)
 - * Does not eradicate β -lactamase-producing organisms
- For penicillin-allergic patients (non-type I hypersensitivity, ie, urticaria or anaphylaxis), cefdinir, cefpodoxime, or cefuroxime may be used. In patients with type I reactions, azithromycin, clarithromycin, trimethoprim-sulfamethoxazole (6-10 mg/kg/day of trimethoprim), or erythromycin-sulfisoxazole (50 mg/kg/day of erythromycin) may be substituted; however, resistance appears to be increasing with these agents. Based on severity of illness, ceftriaxone therapy may be initiated. Clindamycin may be used when drug-resistant *S pneumoniae* is suspected.
- Amoxicillin-clavulanate may be used as first-line therapy based on severity of illness.
- Other effective antimicrobial agents include other cephalosporins (cefprozil, cefaclor, loracarbef, cefibuten). Fluoroquinolones (ciprofloxacin, ofloxacin, levofloxacin) are thought to be effective, but they are not approved for use in pediatric patients.

Dosing issues and drug resistance (Table 2)

- Amoxicillin
 - * Standard dose: 40-45 mg/kg per day (no longer recommended)
 - * High dose: 80-90 mg/kg per day (recommended)
- Amoxicillin-clavulanate
 - * Standard dose (no longer recommended) versus high dose (recommended) while maintaining clavulanate dose of <10 mg/kg/day (to prevent diarrhea)
 - * If using a high dose, use a formulation with higher ratio of amoxicillin to clavulanate (7:1 formulation). Alternatively, additional amoxicillin may be added to standard amoxicillin-clavulanate (4:1 formulation); however, this approach complicates therapy.
- IM ceftriaxone
 - * Single dose versus three daily doses

Duration of therapy

- Standard 10-day course
- Shorter course (1-7 days)
 - * Advantages are improved compliance, decreased adverse effects of drug therapy, decreased risk of bacterial resistance, and lower costs.
 - * Disadvantages are delayed or no cure, increased risk of complications from untreated acute otitis media, and greater risk of recurrence.
 - * Not appropriate for:
 - Children <2 years of age (AAP/AAFP states <6 years of age)
 - Children with severe disease
 - Those in day care
 - Those with underlying diseases
 - Those with a history of recurrent otitis media

Table 2

Treatment Options for Otitis Media

	First line	Penicillin allergy
Non-severe illness: At diagnosis (initial antibiotic therapy)	Amoxicillin (80-90 mg/kg/day)	Non type I: Cefdinir (14 mg/kg/day in 1 or 2 doses) OR cefuroxime (30 mg/kg/day in 2 doses) OR cefpodoxime (10 mg/kg/day once daily) Type I: Azithromycin (10 mg/kg day 1, 5 mg/kg days 2-5) OR clarithromycin (15 mg/kg/day in 2 doses) Ceftriaxone (50 mg/kg daily for 1 or 3 days)
Severe illness: At diagnosis (initial antibiotic therapy)	Amoxicillin-clavulanate (90 mg/kg/day amoxicillin, 6.4 mg/kg/day clavulanate)	
Non-severe illness: Treatment failure at 48-72 hours (initial observation option)	Amoxicillin (80-90 mg/kg/day)	Non type I: Cefdinir (14 mg/kg/day in 1 or 2 doses) OR cefuroxime (30 mg/kg/day in 2 doses) OR cefpodoxime (10 mg/kg/day once daily) Type I: Azithromycin (10 mg/kg day 1, 5 mg/kg days on 2-5) OR clarithromycin (15 mg/kg/day in 2 doses) Ceftriaxone (50 mg/kg daily for 1 or 3 days)
Severe illness: Treatment failure at 48-72 hours (initial observation option)	Amoxicillin-clavulanate (90 mg/kg/day amoxicillin, 6.4 mg/kg/day clavulanate)	
Non-severe illness: Treatment failure at 48-72 hours (initial antibiotic therapy)	Amoxicillin-clavulanate (90 mg/kg/day amoxicillin, 6.4 mg/kg/day clavulanate)	Non-type I: Ceftriaxone (50 mg/kg daily for 3 days) Type I: Clindamycin (30-40 mg/kg/day in 3 doses)
Severe illness: Treatment failure at 48-72 hours (initial antibiotic therapy)	Ceftriaxone (50 mg/kg daily for 3 days)	Tympanocentesis; clindamycin (30-40 mg/kg/day in 3 doses)

Observation option: must have follow-up at 48-72 hours; access to antibiotics if symptoms persist or worsen.

Non-severe illness: mild otalgia and fever <39°C.

Severe illness: moderate to severe otalgia or fever of 39°C.

From AAP/AAFP Clinical Practice Guideline, 2004.

Other therapy

- Antipyretics (**acetaminophen, ibuprofen**)/analgesics
 - * Use acetaminophen with caution in high doses (hepatotoxicity).
 - * Use ibuprofen with caution in patients with vomiting, diarrhea, and poor fluid intake (dehydration predisposes to ibuprofen-induced renal insufficiency).
 - * Avoid alternating antipyretic therapy. Encourage parents to choose one agent, inform them of any adverse effects, and educate them about symptoms of these effects (ie, hepatotoxicity or renal insufficiency).
- Narcotic analgesics may be used for moderate to severe pain not controlled with acetaminophen or ibuprofen.
- Topical analgesics include otic solutions, such as antipyrine-benzocaine (Auralgan[®], Americaine Otic[®]) and naturopathic agents (Otikon Otic Solution[®]).
- Topical antimicrobials may have a place in therapy, particularly with ruptured membranes (fluoroquinolone or fluoroquinolone/steroid combination otic suspensions [Floxin[®], Cipro HC[®], Ciprodex[®]]).
- Antihistamines/decongestants are ineffective at eliminating effusion or relieving symptoms. Use them only if indicated for other signs or symptoms.

Patient instructions and counseling

- Complete the entire course of prescribed antibiotics.
- Shake bottle well before administering dose. Follow labeling regarding temperature for storage of medication.
- Contact the physician if patient develops a rash, has difficulty breathing, or if symptoms persist after 72 hours of initiating therapy.

Adverse drug events

- Gastrointestinal: nausea and diarrhea
- Hypersensitivity: rash, anaphylaxis

Drug interactions

- Macrolides, particularly erythromycin and clarithromycin

Nondrug therapy

- Local heat or cold therapy may be used (counsel the caregiver on appropriate use and technique to prevent burn injury).
- Tympanostomy tubes decrease recurrent episodes, restore hearing, and relieve discomfort. Risks include anesthesia and permanent tympanic membrane scarring.

Observation therapy

- Appropriate only when follow-up at 48-72 hours can be ensured and antimicrobials initiated if symptoms persist or worsen
- Not appropriate for:
 - * Infants <6 months of age
 - * Infants and children between 6 months and 2 years old with a certain diagnosis (nonsevere or severe illness) or an uncertain diagnosis (severe illness)
 - * Children ≥ 2 years of age with a certain diagnosis and severe illness
- Nonsevere illness: mild otalgia and fever $<39.0^{\circ}\text{C}$
- Severe illness: moderate to severe otalgia or fever $\geq 39.0^{\circ}\text{C}$

Immunization and immunoprophylaxis

- Pneumococcal conjugate vaccination should provide some protection against strains responsible for a majority of bacterial otitis media.
- ***Haemophilus influenzae* type B vaccination is of no benefit in otitis media** (note that most strains causing otitis media are nontypable and not prevented by vaccination).
- Killed and live-attenuated intranasal influenza vaccine may decrease episodes of acute otitis media during the respiratory season (most children studied were >2 years of age).

Risk reduction

- Alter day care attendance (when possible).
- Exclusive breastfeeding for 6 months
- Avoid supine bottle feeding.
- Reduce or eliminate pacifier use after 6 months of age.
- Eliminate passive exposure to tobacco smoke.

Recurrent otitis media

- Prophylaxis with half therapeutic dosing of amoxicillin or sulfisoxazole has been initiated in high-risk patients; however, this practice is no longer recommended due to concerns over emergence of drug-resistant organisms

Otitis media with effusion

- The AAP, AAFP, and the American Academy of Otolaryngology-Head and Neck Surgery published a clinical practice guideline on otitis media with effusion in 2004.
- It applies to infants and children (2 months to 12 years of age) with or without developmental disabilities or underlying conditions that predispose patients to otitis media with effusion.
- Recommendations include:
 - * Pneumatic otoscopy as the primary diagnostic method

- * Distinguish otitis media with effusion from acute otitis media.
- * Determine the risk of speech, language, and learning problems.
 - At-risk children: more rapid evaluation and intervention
 - Children not at risk: watchful waiting for 3 months from date of onset or diagnosis
- * No role for antihistamines, decongestants, antimicrobials or corticosteroids
- * Hearing testing: recommended with effusion ≥ 3 months or when language delay, learning problems, or hearing loss exists
- * Persistent otitis media with effusion (not at risk): perform evaluations every 3 to 6 months until resolution of effusion, hearing loss is identified, structural abnormalities are suspected, or when the child becomes a surgical candidate (tympanostomy tube insertion preferred).

Otitis Externa

Otitis externa is an inflammation of the outer ear canal, also referred to as swimmer's ear.

Clinical presentation

- Itching, pain, otic exudate, and hearing impairment

Pathophysiology

- Presence of moisture in the ear canal
- Disruption of the integrity of the ear canal
- Most common organisms are *Pseudomonas aeruginosa* and *Staphylococcus aureus*.
- Other pathogens include fungi and *Bacillus* and *Proteus* species.
- Therapy consists of antibiotic/steroid otic preparations: neomycin/polymyxin/hydrocortisone (Cortisporin Otic[®]), neomycin/colistin/hydrocortisone (Coly-Mycin S Otic[®]), fluoroquinolone otic preparations (ciprofloxacin; Cipro HC; ofloxacin; Floxin), acetic acid and hydrocortisone otic preparations (VoSol HC Otic[®]), or oral analgesics.
- Preventive measures include drying ears after exposure to moisture, using drops containing isopropyl alcohol with or without acetic acid to reduce pH, and avoiding cotton swabs.
- Application of otic drops (see APhA Special Report, 1994):
 1. Wash hands before and after administration.
 2. Warm otic drops to room temperature by holding bottle in hands for several minutes. Avoid instilling cold or hot drops into the ear canal.
 3. Shake the bottle if indicated on the label.
 4. Tilt the child's head to the side or have the child lie down.

5. Pull the child's ear backward and upward and instill the drops in the ear canal. Do not put the dropper bottle inside the ear canal (to remain free from contamination it should not come into contact with the ear).
6. Press gently on the small flap over the ear to push the drops into the canal.
7. Have the child remain in the same position for the period of time indicated in the labeling. If this is not possible, place a cotton ball gently into the ear to prevent the drops from draining out of the ear canal.
8. Wipe excess medication from the outside of the ear.

Cystic Fibrosis

Cystic fibrosis is an autosomal recessive disease of exocrine gland function resulting in abnormal mucus production.

Genetic classification

- Cystic fibrosis is the result of a gene mutation on the long arm of chromosome 7. The protein encoded by this gene, the cystic fibrosis transmembrane regulator (CFTR), is a channel involved in the transport of water and electrolytes.

Defects in processing

- The most common genetic mutation involves a 3-base-pair deletion at position 508 ($\Delta F508$).
- Patients homozygous for $\Delta F508$ are pancreatic insufficient.
- Prognosis is not as good as for those who are pancreatic sufficient.
- Defects in protein production, regulation, and conduction

Clinical presentation

Pulmonary complications

- Initial manifestations include chronic cough, wheezing, hyperinflation of lungs, or lower respiratory tract infections.
- Patients present with hypoxia, clubbing, labored breathing, acute respiratory exacerbations (fever, sputum production, and increased oxygen requirements, and dyspnea); changes in forced vital capacity (FVC), forced expiratory volume in 1 second (FEV_1), and residual volume; and the development of a chronic obstructive picture as the disease progresses.

Gastrointestinal complications

- Poor digestion of proteins and fats, resulting in foul-smelling steatorrhea; distal intestinal obstruction

(commonly manifested as vomiting of bilious material, abdominal distension, and pain)

- Infants may have meconium ileus and gastroesophageal reflux.

Other

- Cirrhosis and cholelithiasis
- Pancreatic function
- Insulin insufficiency, diabetes mellitus
- Malnutrition
- Nasal polyps and sinusitis, anemia, arthritis, osteopenia, and osteoporosis

Pathophysiology

- Defect in the chloride transport channel in secretory epithelial cells

Normal physiology

- Chloride is transported out of blood followed by sodium and water.

Cystic fibrosis

- Decreased chloride and water secretion and increased sodium absorption leads to thick, dehydrated secretions and mucus.
- Exocrine gland involvement: pancreas, hepatobiliary ducts, gastrointestinal tract, and the lungs (secretions build up and block airways and pancreatic and hepatobiliary exocrine flow)

Pulmonary system

- Initial obstruction of small airways with mucus plugging results in bronchiolitis and persistence of bacteria.
- Early bacterial pathogens: *Staphylococcus aureus* and *Haemophilus influenzae* present in younger patients.
- Later bacterial pathogens: *Pseudomonas aeruginosa* is the primary pathogen in late childhood.
- Other bacterial pathogens: *Proteus* and *Klebsiella* species, *Stenotrophomonas maltophilia*, and *Burkholderia cepacia*
- Possible viral pathogens
- Chronic pulmonary infection and inflammation progress to large airway and eventual chronic obstructive disease

Pancreatic system

- Pancreatic enzyme insufficiency (trypsin, chymotrypsin, lipases, and amylase) and decreased bicarbonate secretion (necessary for optimal pancreatic enzyme activity)
 - * Maldigestion of fats and proteins and fat-soluble vitamin deficiency
- Insulin insufficiency (resistance and decreased secretion) leads to glucose intolerance and the devel-

opment of diabetes mellitus (occurs later in the disease process and may be associated with increased morbidity and mortality).

Biliary system

- Biliary cirrhosis or fatty infiltration may lead to portal hypertension, development of bleeding varices, hypersplenism, and cholelithiasis.

Sweat glands

- High concentration of sodium and chloride in sweat (representing the failure of sweat glands to reabsorb sodium and chloride)

Reproductive system

- Male infertility is common due to bilateral absence of vas deferens.
- Female infertility due to abnormal cervical mucus

Diagnostic criteria

- Laboratory confirmation of CFTR dysfunction via sweat chloride analysis (ie, administration of pilocarpine)
 1. Sweat is collected and electrolytes are measured.
 2. Chloride of 60 mEq/L or more is diagnostic (values of up to 80 mEq/L have been seen in non-CF patients)
 3. Levels of 50-60 mEq/L are indeterminate and tests may need to be repeated.
- Presence of clinical characteristics of cystic fibrosis

Treatment goals

- Halt or decrease disease progression.
- Maintain normal growth and development and nutrition status.
- Maintain pulmonary function.
- Optimize drug therapy for pharmacokinetic differences in cystic fibrosis patients.

Drug therapy (Table 3)

Antibiotic therapy in acute exacerbations

Antibiotic selection

- Empiric therapy initially and then treat based on sputum culture and sensitivity
- IV administration of two antibiotics for 14-21 days in combination with aggressive therapy for clearance of secretions
- Coverage for *Staphylococcus aureus*, *Haemophilus influenzae*, and *Pseudomonas aeruginosa*
- Double coverage of antibiotics when *Pseudomonas* species are suspected, with antipseudomonal penicillin (piperacillin, mezlocillin, piperacillin-tazobactam, ticarcillin-clavulanate, ticarcillin, aztreonam, meropenem, or imipenem) or a cephalosporin (cef-tazidime) and an aminoglycoside

* Tobramycin plus ticarcillin or piperacillin (*P aeruginosa*)

Table 3

Drug Therapy for Cystic Fibrosis

Therapeutic category	Indication and mechanism of action	Comments
Pancreatic enzymes		
Capsule (Cotazym [®] , Ku-Zyme [®])	Supplementation or replacement of pancreatic enzymes (treatment of malabsorption syndrome)	Products differ by enzyme content (units of lipase, protease, amylase) and dosage form
Microencapsulated (Cotazym-S [®] , Creon [®] , Pancrease [®] , Pancrélipase [®] , Protillase [®] , Ultrase [®] , Zymase [®])	Aids in digestion of proteins, carbohydrates, and fats	Primary enzyme component is lipase Dose is typically whole dose with meals; half dose with snacks
Tablet (Ilozyme [®] , Viokase [®])		Adequate replacement decreases bowel movements and improves stool consistency
Powder (Viokase [®])		
Fat-soluble vitamins		
	Supplementation of fat-soluble vitamins A, D, E, and K	May be dosed individually, through the use of 1 or 2 multivitamins daily, or with a water-miscible combination preparation
Nebulization therapy		
	Liquefaction of pulmonary secretions	Can be accomplished with normal saline or sterile water with or without other therapies ¹
N-acetylcysteine (Mucomyst[®])		
	Lowers mucus viscosity through sulfhydryl group, which opens the disulfide bond in mucoproteins	Bad taste and odor; significant efficacy has not been documented
Recombinant human DNase (dornase alfa, Pulmozyme[®])		
	DNA in mucus contributes to viscosity; mechanism of action is through cleavage of DNA (thereby decreasing mucus viscosity)	Expensive; reduces viscosity, improves pulmonary function; may decrease respiratory exacerbations
Ursodeoxycholic acid (ursodiol, Actigal[®])		
	Bile acid that suppresses hepatic synthesis and secretion of cholesterol; inhibits intestinal cholesterol absorption; solubilizes cholesterol	Aids in dissolution of stones with cholelithiasis
Bronchodilators (β_2-agonists, theophylline)		
	Bronchodilator in reversible or obstructive airway disease	May be of benefit for patients with component of reactive airway disease; should use β_2 -agonist before theophylline because of pharmacokinetic issues Response (improvement in FEV ₁) should be documented before initiating long-term therapy
Antibiotics		
	Treat infection	Altered pharmacokinetics may affect and complicate therapy
Ibuprofen		
	Nonsteroidal anti-inflammatory; controls airway inflammation	Not used routinely; may have an effect on slowing pulmonary disease High dosages needed to achieve good concentrations (requires therapeutic drug monitoring)
Corticosteroids		
	Anti-inflammatory	Not used routinely; positive effects on pulmonary function but negative effects on growth and development, glucose sensitivity, and bone health

¹Other therapies include N-acetylcysteine and recombinant human DNase.

- * Tobramycin plus ceftazidime (*P aeruginosa*)
- * Oxacillin or nafcillin (methicillin-sensitive *S aureus*)
- * Vancomycin (methicillin-resistant *S aureus*)
- *Burkholderia* and *Stenotrophomonas* species are commonly resistant. Follow culture and sensitivity results. Antibiotics that may be effective include trimethoprim-sulfamethoxazole, chloramphenicol, ceftazidime (*B cepacia*), doxycycline, and piperacillin (*S maltophilia*)
- Other agents: ciprofloxacin

Antibiotic therapy and chronic suppression

Chronic inhaled antibiotic therapy with tobramycin (TOB)

- Significant improvement in FEV₁, decreased hospitalizations, and decreased need for IV antibiotics
- Decreased systemic concentrations (ie, less resistance) and high pulmonary concentrations
- Therapy is expensive.

Oral antibiotic therapy

- Fluoroquinolones are the only oral antibiotics with good coverage against *Pseudomonas*.

Patient instructions and counseling

- Compliance with therapeutic regimens

Pancreatic enzyme supplementation

- Give immediately before or during snacks and meals.
- Capsule may be opened and contents sprinkled on applesauce or other acidic carrier; contents should not be crushed or chewed.

Aminoglycosides

- Monitor urine output.
- Use ibuprofen with caution if dehydration, diarrhea, and/or decreased oral intake is present.

Adverse drug events

Aminoglycosides

- Nephrotoxicity and ototoxicity

Ibuprofen

- Renal insufficiency

Fluoroquinolones

- Arthropathy

Drug interactions

- Pancreatic enzymes and acid suppression therapy may decrease inactivation of enzymes by gastric acid, thereby reducing dose requirement.

Parameters to monitor

Clinical status

- Fever, activity level
- Pulmonary function (as indicated by FEV₁, FVC, residual volume, and chest radiography)

Pharmacokinetic considerations

Aminoglycosides

- Increased clearance and larger Vd (necessitating greater dosing); concentration-dependent killing and postantibiotic effect against gram-negative organisms
- Higher doses (10 mg/kg per day)
- Peak concentrations from 8-12 mcg/mL
- Trough concentrations of less than 2 mcg/mL

β-Lactams

- No change or increased clearance
- No change or increased Vd
- No postantibiotic effect or concentration-dependent killing

Fluoroquinolones

- Concentration-dependent killing
- Postantibiotic effect against gram-negative organisms

Nondrug therapy

Pulmonary percussion therapy and postural drainage

- The purpose is to clear mucus and secretions from the pulmonary system.
- Conducted once or twice per day and up to five times daily or more
- Percussion usually conducted after nebulization therapy with or without bronchodilator or mucolytic
- Therapy with hand-held devices or oscillatory vests

Transplantation

- Lung transplantation
- Liver-lung transplantation if there is liver involvement

Attention-Deficit/Hyperactivity Disorder

According to *DSM-IV*, ADHD is a behavioral disorder of childhood onset (by the age of 7 years) characterized by symptoms of inattentiveness and impulsive or hyperactive behavior.

Classification (*DSM-IV*)

- Combined type: criteria for inattention, hyperactivity, and impulsivity are met.
- Predominantly inattentive type: criteria for inattention are met, but not for hyperactivity and impulsivity

Table 4

Drug Therapy for Attention-Deficit/Hyperactivity Disorder

Therapeutic category	Mechanism of action	Comments
Stimulants (first-line therapy)		
Short-acting: Methylphenidate (Ritalin®, Methylin®),	Reuptake blockade of catecholamines	Due to concern of sudden death and stroke, methylphenidate should not be used in children or adults with structural cardiac abnormalities
Intermediate-acting: Methylphenidate (Ritalin SR®, Metadate ER®, Methylin ER®)	(norepinephrine and dopamine) in presynaptic nerve endings	Do not give after 4 PM; may cause insomnia
Long-acting methylphenidate (Concerta®, Metadate CD®, Ritalin LA®, Daytrana®)		Spansules may be opened and contents sprinkled on applesauce
Short-acting amphetamine (Dexedrine®, Dextrostat®)		Methylphenidate is not labeled for use in children <6 years of age
Intermediate-acting amphetamine (Adderall®, Dexedrine® Spansule)		Daytrana is a transdermal patch and should be applied every morning to alternating hips and worn for 9 hours
Long-acting amphetamine (Adderall-XR®)		Amphetamines are not labeled for use in children <3 years of age
		Adderall can be crushed
		Drug holidays (eg, summer is a good time to see if patient is outgrowing disease)
		Not addictive in children with ADHD, but some parents or siblings may abuse child's medications
Antidepressants (second-line therapy)		
Tricyclics (imipramine, desipramine)	Reuptake blockade of norepinephrine and serotonin presynaptically	May use tricyclics in patients who fail to respond or are intolerant to stimulants
		Drug of choice in ADHD with depression
		Longer duration of action
		No rebound or wearing off effect
		Rapid onset in ADHD; effect can be noticed in 3-4 days
		Taper patient off over 2 to 3 weeks
		Baseline and follow-up ECGs
Bupropion (Wellbutrin®, Wellbutrin SR®, Wellbutrin XL®)	Indirect dopamine agonist and noradrenergic effects	May induce seizures
Other agents (not currently supported by most recent AAP Guidelines, 2001)		
D-threo-enantiomer of racemic methylphenidate, dexamethylphenidate (Focalin®)	Blockade of dopamine and norepinephrine in presynaptic nerve endings	D-enantiomer thought to be the more active enantiomer
Atomoxetine (Strattera®)	Noradrenergic-specific reuptake inhibitor	New nonstimulant agent; discontinue in patients who develop jaundice or laboratory evidence of liver injury
Clonidine	α_2 Noradrenergic agonist	Good drug to use with ADHD and coexisting conditions such as sleep disturbances
Pemoline (Cylert®)	Blockade of dopamine and norepinephrine in presynaptic nerve endings	Recently withdrawn by manufacturer; previously, was rarely used secondary to association with fatal hepatic failure (not dose- or time-related)

Recommendations for therapy and monitoring

Efficacy of therapy

- Assess behavior changes and evaluate feedback from teachers and parents.

Stimulants

- Begin with a low dose and titrate upward to optimal functioning ability.
- May need to decrease dose due to side effects or if no further improvement is seen with larger dose
- No therapeutic drug monitoring or ECG monitoring
- If one stimulant fails, the patient should be tried on another stimulant; children who fail two stimulants can be tried on a third type of stimulant.

Tricyclics

- Initial and periodic ECGs

Pharmacokinetic considerations

- Methylphenidate does not distribute well into adipose tissue (dose on milligram basis instead of milligrams per kilogram).

Nondrug therapy

- Behavioral techniques (ie, positive reinforcement, time-out, response cost, token economy)
- Environmental modifications
- Classroom management

Conjunctivitis

Conjunctivitis is an inflammation of the conjunctiva of the eye.

Classification

- Bacterial, viral, or allergic

Clinical presentation

- Conjunctivitis is characterized by redness of the eye, itching, ocular discharge, foreign body sensation, and crusting of the eye and eyelid. Patient may have alteration in vision due to the presence of discharge.

Pathophysiology

Conjunctivitis of the newborn

- Inflammation of the conjunctiva within the first month of life (causative agents include topical antimicrobial agents; bacteria, primarily *Neisseria gonorrhoeae*, *Chlamydia trachomatis*, *Staphylococcus aureus*, *S epidermidis*, *Streptococcus pneumoniae*, *Escherichia coli* and other gram-negative bacteria; viruses, primarily herpes simplex)

Bacterial (outside of first month of life)

- Most commonly *S aureus*, *S epidermidis*, *S pneumoniae*, and *Haemophilus influenzae* (also gonococcal and chlamydial)
- Treated with antibiotic therapy

Viral

- "Pink eye" is contagious. Adenovirus is the most common causative agent.
- Commonly preceded by a cold or sore throat or exposure to another person with viral conjunctivitis
- May also see herpes simplex (corneal involvement may yield permanent visual damage)

Allergic

- Caused by exposure to dander, pollen, or topical eye preparation
- Most patients will exhibit itching of the eye.

Diagnostic criteria

- Based on patient's symptoms

Treatment goals

- Eliminate or avoid the allergen (allergic conjunctivitis).
- Treat the underlying infection (bacterial conjunctivitis).
- Decrease severity and provide symptomatic relief (all forms).

Drug therapy

Neonatal

- Preventive medicine includes prophylaxis after delivery with antibacterial ophthalmic ointment (erythromycin, tetracycline, silver nitrate, povidone-iodine)
- Onset day 1: no treatment (secondary to prophylaxis after delivery)
- Onset days 2-4 (*N gonorrhoeae*): penicillin G or ceftriaxone for 7 days
- Onset days 3-10 (*C trachomatis*): oral + erythromycin ointment for 14 days
- Onset days 2-16 (herpes simplex): consider IV acyclovir.

Bacterial (outside of first month of life)

- Topical antibiotic therapy (bacitracin-polymyxin B, trimethoprim-polymyxin B, erythromycin, fluoroquinolone [ciprofloxacin, gentamicin, tobramycin]) in combination with antibiotic ointment [erythromycin or bacitracin] at bedtime for 5-7 days

Gonococcal

- Ceftriaxone for one dose (with corneal ulceration, systemic IV ceftriaxone therapy); also treat for *Chlamydia* species as below.

Chlamydial

- Oral tetracycline or doxycycline for 2-3 weeks (adults); azithromycin single dose (children)

Viral

- Ocular lubricant (artificial tears) every 3-4 hours while awake

Allergic

- Remove allergen; use ocular lubricant (artificial tears), ocular decongestants (phenylephrine, naphazoline, tetrahydrozoline, oxymetazoline: α -adrenergic activity), antihistamines (levocabastine [Livostin[®]], olopatadine [Patanol[®]], pheniramine maleate), antihistamine/decongestant combination products, topical mast cell stabilizer (cromolyn sodium), combination mast cell stabilizer and antihistamine, or oral antihistamine therapy.

Adverse drug effects

- Ocular decongestants can cause rebound congestion of the conjunctiva (this is less common with naphazoline and tetrahydrozoline).

Instilling eye drops and ointment

- Wash hands before and after administration. Tilt head back, grasp lower eyelid and pull away from eye, place dropper or ointment tube over eye and have the child look up immediately before instilling the drop. For ointment, use a sweeping motion and instill $\frac{1}{4}$ to $\frac{1}{2}$ inch of ointment inside eyelid. Close eye after instillation and wait 1-2 minutes. Blot excess ointment or solution away from around the eye. Vision may be temporarily blurred with ointment administration. Wait 5 minutes between drops for multiple drop therapy. If using suspension, place that drop in eye last. If using both ointment and drops, instill drops first and wait 10 minutes before applying ointment.

Patient instructions and counseling

- Stress the importance of handwashing and not sharing towels or linens.
- Store products according to labeling instructions.

Nondrug therapy

- Cold compresses

Recent Pediatric Medication Issues and Labeling Changes

- In October 2004, the FDA mandated "black box" warnings for all antidepressants regarding the potential for increased suicidal behavior in children.
- In January 2005, the FDA sent out a letter warning health care professionals that the use of promethazine is contraindicated in children <2 years of age due to the risk of respiratory depression and death.
- In January 2006, the FDA requested the addition of boxed warnings to the labeling for Elidel[®] Cream (pimecrolimus) and Protopic[®] Ointment (tacrolimus) to warn about the possible risk of cancer. Use of these drugs in children under 2 years of age is not recommended.
- In May 2006, the FDA requested labeling changes for Serevent Diskus[®] (salmeterol xinafoate inhalation powder), Advair Diskus[®] (fluticasone propionate and salmeterol inhalation powder), and Foradil Aerolizer[®] (formoterol fumarate inhalation powder) to include a warning that these medicines may increase the risk of severe asthma attacks and death when these attacks occur.

3. Key Points

- The pharmacokinetics and pharmacodynamics of medications are altered by developmental differences in absorption, distribution, metabolism, and elimination in pediatric patients.
- Pharmacotherapy should be adjusted according to the developmental differences in order to optimize therapeutic efficacy while minimizing the risk of toxicity.
- Although spontaneous resolution does occur in many cases of acute otitis media, antibiotic therapy is initiated to prevent complications such as meningitis and mastoiditis. The observation option is an acceptable initial treatment for select patients based on age, certainty of diagnosis, and disease severity.
- The incidence of drug-resistant *S pneumoniae* is increasing. Due to its safety profile, cost, and excellent pharmacodynamic profile against sensitive and drug-resistant *S pneumoniae*, amoxicillin remains the drug of choice for uncomplicated acute otitis media. Higher doses should routinely be used.
- Therapy for cystic fibrosis should focus on halting the progression of the disease and maintaining pulmonary function. Appropriate therapies decrease mucus viscosity and increase clearance of secretions, manage acute infectious exacerbations, and by using appropriate pancreatic enzyme supplementation, maintain normal growth and development.
- Pharmacokinetics of medications in cystic fibrosis patients may be altered; therapeutic drug monitoring and dose alterations should be conducted to ensure efficacy and decrease toxicity.
- An accurate diagnosis of attention-deficit/hyperactivity disorder, a behavioral disorder of childhood onset characterized by inattentiveness, hyperactivity, and impulsivity, should be obtained prior to initiating drug therapy.
- Pharmacotherapy for attention-deficit/hyperactivity disorder is with stimulants (first-line) and antidepressants (second-line).
- ADHD pharmacotherapy should be titrated to the desired functional effect without increasing the risk of side effects.
- ADHD therapy should include behavioral modification. Monitoring of drug and nondrug therapy should include input from different environments (ie, parents and teachers).
- Bacterial and viral conjunctivitis may occur in the first month of life; antimicrobial ointment administration should be instituted after delivery for prophylaxis.
- Bacterial, viral, and allergic conjunctivitis should be treated with antimicrobial therapy (bacterial), symptomatic therapy (bacterial, viral, and allergic), and ocular antihistamines, decongestants, mast cell stabilizers, or combination products (allergic).

4. Questions and Answers

1. J.S., a 4-day-old infant (37 weeks' gestation, birth weight 3.2 kg, length 52 cm), has been admitted to the hospital secondary to spiking temperatures. J.S. has demonstrated decreased oral intake and irritability since being discharged home from the newborn nursery 2 days ago. J.S. is started on IV fluid at maintenance volume and antimicrobial therapy with ampicillin 165 mg IV q6h and gentamicin 8 mg IV q8h. Cultures have been obtained and are pending from blood, urine, and CSF. Laboratory assessment includes the following: Na 142 mEq/L, K 3.5 mEq/L, Cl 108 mEq/L, HCO₃ 22 mEq/L, BUN 15 mg/dL, SCr 0.9 mg/dL, and Glc 88 mg/dL. What is J.S.'s estimated creatinine clearance (in milliliters per minute)?
 - A. 100
 - B. 80
 - C. 60
 - D. 50
 - E. 25
2. Which of the following may affect the creatinine clearance estimate in this patient?
 - I. The presence of maternal serum creatinine
 - II. Decreased glomerular filtration rate
 - III. Increased tubular secretion rate
 - A. I only
 - B. III only
 - C. I and II only
 - D. II and III only
 - E. I, II, and III
3. Aminoglycosides are hydrophilic compounds. Which of the following statements regarding aminoglycoside pharmacokinetic parameters in premature neonates compared to adults is true?
 - A. Increased clearance
 - B. Increased Vd
 - C. Decreased half-life
 - D. Unchanged elimination
 - E. Increased liver metabolism
4. Which of the following may complicate phenytoin therapy in a 2-day-old infant with new-onset seizures?
 - I. Hypoalbuminemia
 - II. Physiologic jaundice

III. IV lipid therapy

- A. I only
- B. III only
- C. I and II only
- D. II and III only
- E. I, II, and III

5. A drug metabolized via which of the following reactions is a concern in the neonatal population?

- A. Hydrolysis
- B. Reduction
- C. Sulfation
- D. Glucuronidation
- E. Methylation

6. M.J., a 7-month-old female, is brought to your pharmacy by her mother who describes the infant as having new onset of fever (102.5°F) and increased irritability in the last 24 hours. The mother states that she stayed home with M.J. today instead of sending her to day care. M.J. has been bottle-fed since birth. Family history is significant for an older sibling with a recent upper respiratory tract infection. Examination of her ear canal using a pneumatic otoscope reveals a bulging, red tympanic membrane with no mobility upon negative or positive pressure. Computer records reveal she has been treated for acute otitis media twice since birth (at 3 and 5 months of age). Decisions for antimicrobial therapy in this patient should be based on coverage for which of the following pathogens?

- A. *S epidermidis*, *S pneumoniae*, *P aeruginosa*
- B. *S pneumoniae*, *H influenzae*, *M catarrhalis*
- C. *H influenzae*, *S pyogenes*, *P aeruginosa*
- D. *S pneumoniae*, *S aureus*, *M catarrhalis*
- E. *S epidermidis*, *P aeruginosa*, *B cepacia*

7. The drug of choice for M.J.'s current episode of acute otitis media is

- A. amoxicillin
- B. amoxicillin-clavulanate
- C. IM ceftriaxone
- D. cefixime
- E. trimethoprim-sulfamethoxazole

8. When counseling M.J.'s mother about the antibiotic suspension prescribed by M.J.'s physician, which of the following should be discussed?

- I. Risks factors for otitis media
- II. Whether or not the suspension should be refrigerated
- III. The need to shake the suspension vigorously prior to administration

- A. I only
- B. III only
- C. I and II only
- D. II and III only
- E. I, II, and III

9. Which of the following is a common side effect of amoxicillin-clavulanate therapy?

- A. Hemolytic anemia
- B. Liver function test abnormalities
- C. Pancreatitis
- D. Diarrhea
- E. Headache

10. Which of the following is a side effect that should be a concern in a child with acute otitis media and nausea and vomiting who is receiving ibuprofen for fever?

- A. Stevens-Johnson syndrome
- B. Renal insufficiency
- C. Hyponatremia
- D. Oral candidiasis
- E. Liver failure

11. Otitis externa or "swimmer's ear" may be treated with

- A. application of an antimicrobial and steroid solution into the ear canal
- B. application of antimicrobial ointment into the ear canal with a cotton swab
- C. application of an antihistamine solution into the ear canal
- D. increase pH of the ear canal with administration of Burow's solution
- E. decrease pH of ear canal with administration of dilute HCl solution

12. R.E., age 15, weighs 40 kg and has cystic fibrosis. R.E. is admitted to the hospital secondary to an acute pulmonary exacerbation. Home medications include Ultrase as directed, TOBI nebulization, ADEK qd, and dornase alfa (qd nebulization). She is started on ceftazidime 2 g IV q8h and tobramycin 130 mg IV q8h. Which of the following should be ordered in this patient?

- A. Serum tobramycin peak concentration
 - B. Serum tobramycin trough concentration
 - C. Serum tobramycin peak and trough concentrations
 - D. Sputum ceftazidime concentration
 - E. Sputum ceftazidime and tobramycin concentrations
13. Sputum cultures taken from R.E. shortly after hospital admission are positive for *S aureus* (non-methicillin sensitive). Which of the following agents should be initiated at this time?
 - A. Oxacillin
 - B. Ticarcillin
 - C. Piperacillin
 - D. Vancomycin
 - E. Amikacin
14. Which of the following is a pancreatic enzyme supplement?
 - A. Actigall
 - B. Beractant
 - C. Creon®
 - D. Diabinese®
 - E. Pulmozyme
15. Which of the following products can be used to decrease the viscosity of pulmonary secretions?
 - A. Exosurf®
 - B. Mucomyst
 - C. Protilase
 - D. Liqueamin
 - E. Serevent®
16. Counseling a patient on the use of pancreatic enzyme supplementation should include which of the following statements?
 - A. Capsules may be opened and sprinkled over any food
 - B. Capsule contents should not be crushed or chewed
 - C. The total daily dose may be given at one time in the evening
 - D. Adequate supplementation will increase bowel movement frequency
 - E. The supplementation dose should not change with diet changes
17. N.G., age 8, has newly diagnosed attention-deficit/hyperactivity disorder. Which of the following is not considered first-line therapy for N.G.?
 - A. Ritalin
 - B. Dexedrine
 - C. Wellbutrin
 - D. Adderall
 - E. Methylin
18. Atomoxetine is associated with which of the following serious adverse effects?
 - A. Hepatic injury
 - B. Renal failure
 - C. Cardiovascular collapse
 - D. Anaphylaxis
 - E. Toxic epidermal necrolysis
19. T.S., age 9, is being started on imipramine therapy after failing therapy for attention-deficit/hyperactivity disorder with several different stimulants. T.S. has two other siblings, a 15-year-old brother and a 3-year-old sister. The pharmacist instructs T.S.'s parents to keep the medicine away and in a safe place. What is the most likely reason for the pharmacist's concern?
 - I. Toxicity of imipramine with overdose
 - II. Abuse potential of imipramine
 - III. Stability of imipramine product
 - A. I only
 - B. III only
 - C. I and II only
 - D. II and III only
 - E. I, II, and III
20. A decrease in seizure threshold is a side effect of which of the following agents used for ADHD?
 - I. Methylphenidate
 - II. Bupropion
 - III. Clonidine
 - A. I only
 - B. III only
 - C. I and II only
 - D. II and III only
 - E. I, II, and III
21. Every spring, M.S. develops itchy, red eyes that are often swollen and draining. Which of the following is the most likely cause of this ocular disorder?
 - A. Viral conjunctivitis
 - B. Bacterial conjunctivitis
 - C. Allergic conjunctivitis

- D. Blepharitis
- E. Episcleritis

22. Which of the following therapies is not an appropriate recommendation for M.S.'s symptoms?
- A. Ocular lubricant
 - B. Ocular decongestant
 - C. Ocular antihistamine
 - D. Ocular mast cell stabilizer
 - E. Ocular antimicrobial
23. Which of the following is not commonly associated with conjunctivitis?
- A. *Chlamydia*
 - B. *Neisseria*
 - C. *Staphylococcus*
 - D. *Streptococcus*
 - E. *Clostridium*
24. Which of the following is a side effect of the prolonged use of ocular decongestants?
- A. Peripheral vasodilation
 - B. Rebound conjunctival congestion
 - C. Development of arrhythmias
 - D. Development of tolerance
 - E. Development of allergy to product

Answers

1. E. Using the Schwartz equation, J.S.'s estimated creatinine clearance is 26 mL/min ($\text{CrCl} = 0.45 \times 52/0.9$).
2. C. The presence of maternal serum creatinine that decreases in neonates over the first week of life may falsely underestimate a creatinine clearance estimate calculated during this time. Assuming that by the end of the first week of life, J.S.'s SCr has decreased to within the normal infant range to 0.4 mg/dL, the estimated creatinine clearance would be 59 mL/min ($\text{CrCl} = 0.45 \times 52/0.4$). Other factors that affect creatinine clearance in the neonate and infant include a decreased glomerular filtration rate and a decreased tubular secretion rate. Therefore, only I and II are correct answers.
3. B. Aminoglycosides are hydrophilic compounds; they will exhibit larger volumes of distribution in patients with greater total body water. Neonates and infants have greater total body

water, greater extracellular fluid volume, and a relative lack of adipose tissue.

4. E. Phenytoin is highly plasma protein-bound. The total and free concentrations of highly protein-bound drugs may be altered due to developmental differences in protein binding (decreased protein concentrations and altered binding capacity) and displacement by endogenous substances (eg, free fatty acids and unconjugated bilirubin). Physiologic jaundice, as exhibited by increasing total and unconjugated bilirubin concentrations, may occur in the neonatal period. Unconjugated bilirubin may displace drugs from albumin binding sites. Additionally, one of the by-products of lipid metabolism, free fatty acids, may also displace drug from albumin binding sites (thereby increasing the free drug concentration). Kernicterus ("yellow brain") may occur when unconjugated bilirubin displaced by drugs or other endogenous substances (ie, free fatty acids) crosses the blood-brain barrier, where it can deposit in the brain and cause neurologic complications. Therefore, albumin concentration, physiologic jaundice, and the use of IV lipid therapy may complicate therapy with highly protein-bound agents.
5. D. UDPG-glucuronyl transferase is responsible for conjugation of endogenous substances (bilirubin) and medications (morphine, chloramphenicol). The capacity for glucuronidation metabolism does not begin until around 2 months of age and reaches adult capacity by 3 years of age. Medications metabolized through this system are potential toxins in the neonatal population. An example would be the use of chloramphenicol in neonates and the development of "gray-baby syndrome" due to drug accumulation. Hydrolysis, reduction, sulfation, and methylation are functional in the neonatal period and should not pose drug therapy complications in this population.
6. B. The most common pathogens in acute otitis media are *S pneumoniae* (40-50%), *H influenzae* (20-30%), and *M catarrhalis* (10-15%).
7. A. Despite the emergence of drug resistant *S pneumoniae*, amoxicillin, due to its excellent pharmacodynamic profile, side-effect profile, and cost, remains the drug of choice in uncomplicated acute otitis media. This patient is considered to be in the high-risk group (age <2

years, attending day care, recurrent otitis media). High-dose therapy (80-90 mg/kg per day) is now the accepted dosing regimen for acute otitis media.

8. **E.** Counseling should include specific information about the antibiotic, its side-effect profile, storage information, how to administer the medicine, dosage instructions, importance of taking the full course, and the need to shake the bottle prior to administering the dose. In addition, a discussion of risk factors for acute otitis media and preventive measures (pneumococcal and flu immunization) is appropriate in a counseling session.
9. **D.** The most common side effects with amoxicillin-clavulanate therapy include rash, urticaria, nausea, vomiting, and diarrhea. Although the other listed side effects may be seen with other antibiotic therapies, they do not typically occur with amoxicillin-clavulanate therapy.
10. **B.** Dehydration, which may develop in a vomiting child, is a risk factor for ibuprofen-induced renal insufficiency. If ibuprofen is used as an antipyretic or analgesic in pediatric patients, the parents and/or caregivers should be counseled regarding this risk and the need to follow intakes and outputs during the period of acute illness (ie, gastroenteritis) when the child may be receiving ibuprofen therapy.
11. **A.** The treatment of otitis externa includes the instillation of an antibiotic and steroid otic solution into the ear canal. Cotton swabs should be avoided to prevent otitis externa. Antihistamine solutions are not indicated in the treatment of otitis externa. Otic solutions containing acetic acid may also be of benefit in otitis externa by decreasing (not increasing) the pH of the ear canal and lowering its bacteria-harboring potential. Hydrochloric acid in any form should not be used in the ear canal.
12. **C.** Therapeutic drug monitoring is a critical part of the overall therapeutic plan in patients with cystic fibrosis. Patients with cystic fibrosis exhibit altered pharmacokinetic parameters of aminoglycosides, primarily increased clearance and greater volumes of distribution. Tobramycin peak concentrations should be obtained to make sure the dose being given is sufficient to reach concentrations of 8-12 mcg/mL and trough concentrations should be obtained to ensure adequate renal clearance (CF patients receive higher milligram per kilogram doses).
13. **D.** *S aureus* is a common pathogen in cystic fibrosis patients. Methicillin-sensitive *S aureus* may be treated with a number of agents (eg, oxacillin); however, methicillin-resistant *S aureus* (MRSA) should be treated with vancomycin.
14. **C.** Creon is the brand name for a pancreatic enzyme supplement. Creon is available as a microencapsulated formulation.
15. **B.** Mucomyst is the brand name for N-acetylcysteine, which lowers mucus viscosity (the sulfhydryl group opens the disulfide bond in mucoproteins).
16. **B.** Pancreatic enzyme products are available in powder, capsule, tablet, and microencapsulated formulations. The microencapsulated formulations may be opened and the contents sprinkled over acidic foods (ie, applesauce). Contents should not be crushed or chewed. Additionally, the dose should be based on the amount and type of food (ie, full doses with meals, half-doses with snacks and light meals). Adequate replacement will actually decrease bowel movements and improve stool consistency (ie, decrease steatorrhea).
17. **C.** All of the listed products are stimulants, with the exception of Wellbutrin. Stimulants are considered first-line therapy for attention-deficit/hyperactivity disorder; antidepressants may be considered second-line agents.
18. **A.** Atomoxetine's labeling has most recently been updated with a bolded warning about the potential for severe liver injury. Atomoxetine should be discontinued in any patient who develops jaundice or laboratory evidence of liver injury.
19. **A.** Overdose of tricyclic antidepressants may be fatal due to the development of arrhythmias. Since T.S. has a younger sibling in the house, there is a potential for the child to get into her older brother's medicine. Stimulants may have the potential for abuse in patients that do not have ADHD (ie, the 15-year-old brother), but tricyclic antidepressants are not associated with a high abuse potential. There are no stability issues with imipramine.

20. C. Both bupropion and methylphenidate may lower the seizure threshold. Clonidine is not associated with seizure occurrence.
21. C. Allergic conjunctivitis occurs after exposure to allergens, primarily dander or pollen. Patients suffering from allergic conjunctivitis will typically complain of eye itching.
22. E. Antimicrobial therapy has no place in therapy for allergic conjunctivitis. Ocular lubricants, decongestants, antihistamines, mast cell stabilizers, or combinations of these products are appropriate options for allergic conjunctivitis.
23. E. The most common pathogens in neonatal bacterial conjunctivitis are *N gonorrhoeae*, *C trachomatis*, *S aureus*, *S epidermidis*, *S pneumoniae*, and *E coli*. Bacterial conjunctivitis outside of the first month of life is most commonly caused by *S aureus*, *S epidermidis*, *S pneumoniae*, and *H influenzae*. *Clostridium*, an anaerobe, is not a common bacterial pathogen in conjunctivitis.
24. B. Not unlike reactions from prolonged use of nasal decongestants, prolonged use of ocular decongestants may cause rebound congestion of the conjunctiva. This effect is less pronounced with naphazoline and tetrahydrozoline.

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34. Geriatrics and Gerontology

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1. Overview

- Gerontology is the study of the problems of aging and all its aspects. Geriatrics focuses on the diseases associated with aging and the treatments for those conditions. Geriatrics is of particular concern for pharmacists.
- Over 12% of the United States population is older than 65 years of age. By the year 2050, it is expected that the percentage will increase to over 20%.
- Persons over 65 years of age have more chronic illnesses and take more prescription and nonprescription drugs than persons in younger age groups.
- Age-related physiologic changes and increased medication use contribute to a greater risk of adverse drug events.
- Changes in vision, hearing, and mental functioning can result in increased problems with medication compliance.

Changes in Pharmacokinetics Associated with Aging

- Decreased absorption of various drugs secondary to decreased stomach acidity and changes in blood flow to the stomach (the least altered by aging)
- Altered drug distribution caused by a decrease in total body water, increased lipid storage, and decreased serum albumin in malnourished elderly persons; these factors can contribute to increased serum levels of drugs
- Decreased hepatic blood flow and reduced hepatic enzyme activity cause slower drug metabolism. Increased levels of drugs require increased metabolism by the liver.
- Elimination of drugs by the kidneys is slowed due to decreased renal blood flow and lowered glomerular filtration; thus, drug accumulation develops.
- By using the Cockcroft-Gault formula for estimation of creatinine clearance, renal function can be predicted in the elderly:

$$\text{CrCl (mL/min)} = \frac{(140 - \text{age}) \times \text{weight in kg}}{72 \times \text{Cr}}$$

Note: Use ideal body weight. The equation above is for males. For females, multiply the result by .85.

- In dosing the elderly the general rule is to start with lower doses than used in younger patients and increase doses at a slower rate.

2. Drugs of Concern

- Drugs that can cause psychiatric symptoms:
 - * Anticholinergics
 - * Narcotics
 - * Tricyclic antidepressants
 - * CNS stimulants
 - * Antiparkinson drugs
- Drugs that can produce anxiety symptoms:
 - * Theophylline
 - * Nasal decongestants
 - * β -Agonists
 - * Antiparkinson drugs
 - * Appetite suppressants
- Drugs that can contribute to nutritional deficiencies:
 - * Diuretics
 - * Digoxin, digitalis
 - * Laxatives (overuse)
 - * Sedatives (overuse)
- Specific drugs with risk to geriatric patients:
 - * Long-acting benzodiazepines (eg, chlor-diazepoxide [Librium®] and diazepam [Valium®]) should be avoided due to the risk of prolonged sedation and increased risks of falls and fractures.
 - * Amitriptyline (Elavil®) has potent anticholinergic and sedating effects with risk to older patients.
 - * Digoxin (Lanoxin®) at higher doses (>0.125 mg daily) has an increased risk of toxicity without greater benefits.
 - * Meperidine (Demerol®) taken orally has an increased risk of respiratory and circulatory depression.
 - * Antipsychotic use may result in the increased risk of heart events and infections.

3. Medication Compliance and the Older Adult

- Types of noncompliant behavior in the elderly:
 - * Failure to take medications
 - * Premature discontinuation of a medication
 - * Excessive consumption of a medication
 - * Use of medications not currently prescribed
- Strategies to improve patient medication compliance:
 - * Limit the number of different medications and decrease dose frequency.
 - * Simplify dosage instructions.
 - * Tailor the regimen to the patient's schedule.
 - * Use compliance aids and telephone reminders.
 - * Enlist the assistance of family members and friends.

4. Basic Components of Evaluating Drug Therapy in Older Adults

- Questions to be answered:
 - * Why is the drug being used? (diagnosis or reason)
 - * Is the drug being given correctly? (dosage, form, and schedule of administration)
 - * Are any symptoms or complaints related to drug therapy?
 - * Is there ongoing monitoring of treatment?
 - * What is the endpoint of therapy?

5. Alzheimer's Disease and Related Dementias

- Dementia is the decline in intellectual abilities (eg, impairment of memory, judgment, and abstract thinking) coupled with changes in personality.
- Dementia patients tend to be described as cognitively impaired.
- Cognition is the mental process by which we become aware of objects of thought and perception, including all aspects of thinking and remembering.
- Impairment of cognition has a significant impact on the life of the dementia patient, his or her family members, and the community in general.

Types of Dementia

- Alzheimer's disease accounts for approximately 70% of dementias.
- Vascular dementias account for approximately 15% of dementias.
- Patients may have both Alzheimer's disease and vascular dementia.

Other Causes of Dementia

- Vascular disease, cerebrovascular accidents (strokes)
- Neurologic disorders such as Parkinson's disease, frontotemporal dementia, dementia with Lewy bodies, and Huntington's chorea
- Metabolic disorders such as hypothyroidism, alcoholism, and anemia
- Infectious diseases (eg, meningitis, syphilis, AIDS)

Clinical Presentation

- Alzheimer's disease is a progressive neurologic disease that results in impaired memory and intellectual functioning and altered behavior.
- Alzheimer's disease is characterized by the slow onset of symptoms leading to loss of ability to function independently.
- Symptoms may include psychoses with hallucinations, illusions, and delusional thinking.
- As Alzheimer's disease progresses, the brain continues to deteriorate.
- Depression can cause cognitive impairment similar to that of Alzheimer's disease and should be identified and treated.

Pathophysiology

- Hallmark pathologic changes in the brain are linked to Alzheimer's disease (ie, neuritic plaques and neurofibrillary tangles increase).

- Neuritic plaques are composed of amyloid proteins deposited on neurons; neurofibrillary tangles exist within neurons and disrupt normal function.
- Neurotransmitters are also altered in Alzheimer's disease; acetylcholine concentrations decrease significantly.

Diagnostic Criteria

- Diagnosis of Alzheimer's disease requires the presence of memory impairment and one or more of the following:
 - * Aphasia (language disturbance)
 - * Apraxia (impaired motor abilities)
 - * Agnosia (failure to recognize objects)
 - * Disturbance of executive function (eg, planning, organizing)

Treatment Principles

- When evaluating a patient for treatment of dementia and Alzheimer's disease, review the patient's medications and consider any that might cause mental confusion or worsen underlying disease states.
- Drugs that block activity of acetylcholine can worsen dementia and decrease the effectiveness of medications used to treat Alzheimer's disease.
- Anticholinergic drugs are used for a variety of conditions ranging from depression to incontinence; indications should be identified before treating Alzheimer's disease.
- Anticholinergic effects can be additive (ie, a combination of anticholinergic drugs can result in toxicity even when each is given at low doses; see Table 1).
- Provide support to caregivers and treat the patient's behavioral and mood symptoms.
- Consider a trial of a cholinesterase inhibitor and monitor for benefits to memory and cognitive functioning.

Monitoring

- Monitor memory and cognitive functions every 6-12 months.
- Routinely assess behaviors and ability to perform activities of daily living (eg, bathing, feeding, toileting, dressing).
- Monitor for focal neurologic signs and symptoms that may suggest other causes of changes in cognitive function.

Drug Therapy

- The pharmacologic approach to treatment falls into two categories:

Table 1

Anticholinergic Drugs That Can Worsen Alzheimer's Disease

Class	Drugs
Antidepressants	Highest effects: amitriptyline, amoxapine, clomipramine, protriptyline Moderate effects: bupropion, doxepin, imipramine, maprotiline, trimipramine
Antiparkinsonian agents	Benzotropine, trihexyphenidyl
Antipsychotics	Highest effects: clozapine, mesoridazine, olanzapine, promazine, triflupromazine, thioridazine Moderate effects: chlorpromazine, chlorprothixene, pimozide
Antispasmodics	Atropine, belladonna alkaloids, dicyclomine, glycopyrrolate, hyoscyamine, methscopolamine, oxyphenycyclimine, propantheline, oxybutynin, flavoxate, terodiline
Antihistamines	Highest effects: carbinoxamine, clemastine, diphenhydramine, promethazine Moderate effects: azatadine, brompheniramine, chlorpheniramine, cyproheptadine, dexchlorpheniramine, triprolidine, hydroxyzine
Antiemetic/antivertigo agents	Meclizine, scopolamine, dimenhydrinate, trimethobenzamide, prochlorperazine
Other agents with some anticholinergic activity	Paroxetine

* Medications used to control behavioral and emotional symptoms

* Medications used to slow or reverse the disease process

Symptomatic therapy

- Medications used to control behavioral and emotional symptoms are used to provide symptomatic improvement and do not affect the outcome of the disease.
- Anxiolytics are used to decrease anxiety and possibly agitation, motor restlessness, and insomnia; eg, lorazepam (Ativan®), oxazepam (Serax®), and buspirone (Buspar®). The benzodiazepines can increase the risk of falls and injury.

- Antidepressants improve depression that can worsen the cognitive functioning of a patient with Alzheimer's disease; eg, sertraline (Zoloft®), citalopram (Celexa®).
- Antipsychotics are used to decrease psychotic symptoms such as hallucinations and delusions. Antipsychotics may reduce agitation and aggressiveness; eg, haloperidol (Haldol®), risperidone (Risperdal®), and aripiprazole (Abilify®). There is an increased risk of cardiac events and infections associated with the use of antipsychotics in demented elderly patients.
- Sedative-hypnotics are used for short-term treatment of insomnia, but can increase confusion and memory impairment; eg, trazodone (Desyrel®), zolpidem (Ambien®), and temazepam (Restoril®).

Cholinesterase inhibitors

- Medications used to slow or reverse the symptoms of Alzheimer's disease have an impact on acetylcholine activity in the brain.
- Acetylcholine levels may be decreased by as much as 90% in Alzheimer's disease; these levels can be increased by inhibiting the enzyme acetylcholinesterase.
- Acetylcholinesterase inhibitors increase acetylcholine but do not replace lost cholinergic neurons or change the underlying pathology. This class of medications is used to prevent or slow deterioration in cognitive functioning.
- The first cholinesterase inhibitor approved to treat Alzheimer's disease was tacrine (Cognex®), which proved beneficial but may cause the following (Table 2):
 - * Potential hepatotoxicity (damage to the liver); requires regular liver function testing
 - * Tacrine is rarely prescribed.
- Safer cholinesterase inhibitors include:
 - * Donepezil (Aricept®) is selective for acetylcholinesterase in the brain (ie, not in peripheral tissues).
 - * Rivastigmine (Exelon®), a nonselective cholinesterase inhibitor, decreases both acetylcholinesterase and butyrylcholinesterase.
 - * Galantamine (Razadyne®) is a selective acetylcholinesterase inhibitor that activates nicotinic receptors, which may increase acetylcholine.

Patient instructions and counseling

- Donepezil: given orally, 5 mg daily for 4-6 weeks; increase to 10 mg daily at bedtime; take with or without food.
- Rivastigmine: given with gradual dosage increase; beginning at 1.5 mg twice daily, then 3 mg twice daily, 4.5 mg twice daily, and 6 mg twice daily, with a minimum of 2 weeks between dose increases; if

Table 2

Drugs Used to Treat Alzheimer's Disease

Generic name	Trade name	Usual dosage	Dosage forms	Adverse effects
Tacrine	Cognex®	10-20 mg bid	Capsules	Nausea/vomiting, hepatotoxicity
Donepezil	Aricept®	5-10 mg at bedtime	Tablets	Nausea/vomiting
Rivastigmine	Exelon®	1.5-6 mg bid	Capsules	Nausea/vomiting, anorexia, weight loss
Galantamine	Razadyne®	4-12 mg bid	Capsules, oral solution	Nausea/vomiting

rivastigmine is discontinued because of adverse effects, restart at beginning dose; take with meals in divided doses.

- Galantamine: doses begin with 4 mg twice daily for 4 weeks, 8 mg twice daily for 4 weeks, 12 mg twice daily for 4 weeks, then 16 mg twice daily. If discontinued for more than a few days, restart at beginning dose. In hepatic or renal dysfunction doses should not exceed 16 mg/day. Do not use in instances of severe dysfunction. Take with meals in divided doses.

Adverse drug events

- Donepezil: side effects include nausea/vomiting, GI symptoms; these may be minimized by increasing the dose at 6 weeks
- Rivastigmine: side effects include nausea, vomiting, GI upset, and possible significant weight loss. Adverse effects are dose related and may be lessened by increasing the dose at a slower rate.
- Galantamine: adverse effects include nausea, vomiting, and GI upset. Slow dose titration will decrease side effects.

NMDA-receptor antagonists

- Blocking the excitotoxicity effects of the neurotransmitter glutamate at NMDA receptors has been reported to be beneficial in Alzheimer's disease.
- Memantine (Namenda®) is an NMDA-receptor antagonist used for moderate to severe dementia. Doses begin with 5 mg daily for 1 week, increasing to 5 mg twice daily with weekly increases to 10 mg twice daily.
- Reduce dose to 5 mg twice daily in patients with renal impairment (Cr.Cl less than 30mL/min)
- Side effects include drowsiness, dizziness, headache, blood pressure elevations and motor restlessness.

Drug-drug interactions (Table 1)

- Anticholinergic drugs will reduce the effectiveness of cholinesterase inhibitors and cause dry mouth, blurred vision, constipation, and mental confusion (ie, conditions that are more problematic in the elderly).

- Cytochrome P450 enzyme inhibitors of 2D6 and 3A4 increase levels of galantamine and donepezil by inhibiting their metabolism.
- The use of dextromethorphan (Robitussin DM®), a potent NMDA-receptor antagonist, with memantine should be done with caution. Smoking and nicotine products may alter levels of memantine.

Parameters to monitor

- Cognitive function (eg, poor results on mini-mental state exam, decline in performance of activities of daily living, incidence of behaviors that indicate cognitive decline)
- Signs and symptoms of toxicity
- Active peptic ulcer disease, severe bradycardia, and acute medical illness are reasons to discontinue treatment.
- Periodic complete blood cell count and basic chemistries
- Expected benefits with the use of cholinesterase inhibitors and NMDA-receptor antagonists include improvement in memory, some stabilization of behaviors/mood, and possible slowing of the progression of the disease.

Non-prescription agents

- High-dose vitamin E (2000 U daily) has been recommended as an antioxidant to slow progression of Alzheimer's disease. Vitamin E may interfere with vitamin K absorption and result in increased risk of bleeding. Increased mortality has been reported with high-dose vitamin E. The potential toxicity of high-dose vitamin E may outweigh the benefits.
- Ginkgo biloba, an herb, has been used to treat symptoms of Alzheimer's disease with reports of modest benefits. Ginkgo biloba is associated with increased risk of bleeding and hemorrhage, especially when combined with daily aspirin use.

Nondrug Therapy

- The treatment of Alzheimer's disease includes non-pharmacologic and pharmacologic therapy.

- Patients need to live in an environment that permits safe activities while minimizing risk.
- Caregivers need training and support to deal with the behavioral and functional issues associated with this disease.
- Caregivers are at risk for depression and stress-related medical illnesses. Caregivers may also neglect their own health care needs and should be encouraged to maintain a healthy lifestyle.

6. Parkinson's Disease

- Parkinson's disease (PD) is a chronic progressive neurologic disorder with symptoms that present as a variable combination of rigidity, tremor, bradykinesia, and changes in posture and ambulation.
- An estimated 1 million persons in the U.S. suffer from PD. There are approximately 60,000 new cases diagnosed each year.
- The risk of developing PD increases with age, and there is predicted to be a substantial increase in the U.S. population of persons over 60 years of age.
- Since medications are the primary treatment for PD, pharmacists play an important role in the care of these patients.

Classification

- Primary parkinsonism has no identified cause.
- Secondary parkinsonism can be the result of drug use (eg, reserpine, metoclopramide, antipsychotics), infections, trauma, or toxins.

Clinical Presentation

- Clinical signs and symptoms of PD develop insidiously, progress slowly, may fluctuate, and worsen with time despite pharmacologic therapy.

Symptoms

- Tremors at rest may begin unilaterally and are present in 70% of PD patients.
- Tremors (not during sleep) may worsen with stress.
- Rigidity of limbs, trunk, and face with mask-like expression and difficulty with dressing or standing from a seated position
- Akinesia (the absence of movement) and bradykinesia (slowed movements)
- Postural instability with abnormal gait and an increased risk of falls
- Depression and possible dementia
- Other symptoms include micrographia (small writing), drooling, decreased blinking, constipation, and incontinence.

Pathophysiology

- PD involves a progressive degeneration of the substantia nigra in the brain with a decrease in dopaminergic cells (more than the typical decrease that accompanies normal aging).
- The most significant neurotransmitter in PD is dopamine, but other neurotransmitters may play a

role (eg, acetylcholine, glutamate, GABA, serotonin, norepinephrine).

- The etiology is unknown, but there is a possibility of genetic susceptibility.
- Environmental toxins combined with aging may also be responsible for the development of PD.

Diagnostic Criteria

- Clinical diagnosis based on the presence of bradykinesia and either rest tremor or rigidity.
- The stages of disease (Table 3)

Treatment Principles and Goals

- The goal for treating PD is to relieve symptoms and maintain or improve quality of life for the patient.
- Treatment should be initiated when there is functional impairment and discomfort for the patient and/or caregiver.
- A safe environment and caregiver support programs in addition to medications will often allow patients to remain in the community.

Drug Therapy

Mechanism of action

- Medications increase dopamine or dopamine activity by directly stimulating dopamine receptors or by blocking acetylcholine activity, which results in increased dopamine effects (Table 4).
- Selection of an initial medication to treat PD may vary with the prescriber. Some choose to begin therapy with selegiline (Eldepryl®), which offers possible neuroprotection; others prescribe carbidopa-levodopa (Sinemet®), which has proven benefits.

Table 3

The Stages of Parkinson's Disease

Stage 1	Unilateral involvement only with minimal or no functional impairment
Stage 2	Bilateral involvement without impairment of balance
Stage 3	Mild to moderate bilateral disease, some postural instability, can maintain independence
Stage 4	Severe disability, unable to live alone independently
Stage 5	Unable to walk or stand without assistance

Levodopa

- Levodopa is the most effective drug in the treatment of PD and is converted to dopamine in the body.
- Levodopa is given with carbidopa, a decarboxylase inhibitor that prevents the peripheral conversion of levodopa to dopamine, thereby reducing nausea and vomiting while allowing more drug to pass through the blood-brain barrier.
- Generally, doses are increased gradually to minimize the risk of side effects. Doses are given before meals to facilitate absorption.
- Levodopa provides benefits to all stages of PD, but chronic use is associated with adverse effects.
- Patients may have periods of good mobility alternating with periods of impaired motor function.

Treatment complications and strategies for improving patient response

- No initial response to levodopa (carbidopa-levodopa combination)
 - * Gradually increase dose to at least 1000-1500 mg of levodopa.
- Suboptimal response
 - * After increasing levodopa, add another drug, eg, a dopamine agonist, selegiline, or a COMT inhibitor.
- The "on and off" phenomenon (associated with advancing disease and loss of benefits from a dose of medication)
 - * Remedied by more frequent doses and/or use of sustained-release levodopa
- End of dose or "wearing off," ie, decreased duration of benefit after a dose
 - * Levodopa wanes after less than 4 hours; therefore, use combination therapy (two or more drugs), give levodopa more frequently, or use sustained-release levodopa (Sinemet CR®).

Patient instructions and counseling

- Usually take medications on an empty stomach; eat shortly afterward to avoid upset stomach.
- Take a missed dose as soon as possible; skip the missed dose if the next scheduled dose is within 2 hours.
- Dizziness, drowsiness, and stomach upset may occur and make operating equipment dangerous.
- Confusion, mood changes, and uncontrolled movements can result and should be reported to the prescriber as soon as possible.
- If taking a sustained-release product, do not crush.

Adverse effects (see Table 5)

Drug-drug interactions (see Table 6)

Table 4

Drugs for Treating Parkinson's Disease

Generic name (trade name)	Mechanism of action	Dosage and available strengths and forms
Carbidopa-levodopa (Sinemet®)	Levodopa increases DA; carbidopa prevents metabolism	25/100 mg/d at breakfast; increase to 25/100 mg tid; may increase to 25/250 mg qid; available in sustained-release 25/100- and 50/200-mg tablets
Bromocriptine (Parlodel®)	Directly stimulates DA receptors	1.25 mg bid with meals; increase by 2.5 mg/d every day, up to 100 mg/d; 2.5- and 5-mg tablets
Pergolide (Permax®)	Directly stimulates DA receptors	0.05 mg/d for 2 days; increase gradually to 2-3.5 mg/d (divided doses); maximum of 5 mg/d; 0.05-, 0.25-, and 1-mg tablets
Pramipexole (Mirapex®)	Directly stimulates DA receptors	0.125 mg tid increase weekly to 0.5-1.5 mg tid; 0.125-, 0.25-, 1-, and 1.5-mg tablets
Ropinirole (Requip®)	Directly stimulates DA receptors	0.25 mg tid; increased gradually to a maximum of 24 mg/d; 0.25-, 0.5-, 1-, 2-, 4-, 5-mg tablets
Selegiline (Eldepryl®, Carbex®, Atapryl®, Selpak®)	Inhibits MAOB, increases DA and serotonin	Initially 5 mg at breakfast; increase to 5 mg at breakfast and lunch; 5-mg capsules, 5-mg tablets
Entacapone (Comtan®)	Inhibits COMT, increasing DA	200 mg with each dose of carbidopa-levodopa; maximum 1600 mg/d; 200-mg tablets
Tolcapone (Tasmar®)	Inhibits COMT, increasing DA	100 mg tid; discontinue if no benefits in 3 weeks; 100-, 200-mg tablets
Amantadine (Symmetrel®)	May increase presynaptic release of DA, blocks reuptake	100 mg bid; maximum dose 400 mg/d; 100-mg tablets, 100-mg capsules, 50 mg/5 mL syrup
Benzotropine (Cogentin®)	Blocks acetylcholine, may balance DA	1-2 mg PO or IM or IV at bedtime or 0.5-6 mg/d in divided doses; 0.5-, 1-, 2-mg tablets, 1 mg/mL injection
Trihexyphenidyl (Artane®)	Blocks acetylcholine, may balance DA	1 mg/d up to 5 mg/d (divided doses); 2-, 5-mg tablets, 2 mg/5 mL elixir
Carbidopa/entacapone/ levodopa (Stalevo®)	Combined effects of all three agents	Dosage individualized, up to 8 tablets per day; available in 3 dosage combinations

COMT, catecholamine O-methyl transferase; DA, dopamine; MAOB, monoamine oxidase B.

Parameters to monitor

- Liver function, complete blood count, basic chemistries (periodically)
- Blood pressure, pulse, ECG (periodically)
- Reduction of rigidity, tremor, slowed movements
- Examination for mental confusion, mood changes, psychotic thinking

Nondrug Therapy for Parkinson's Disease

- Educate patient and caregiver about the benefits and side effects of PD medications.
- Aids for compliance should be provided to enable the patient to participate in medication use as long as physically possible.

- Physical therapy or occupational therapy may be important in maintaining physical activity and improving safety of work and living quarters.
- As PD progresses, speech therapy may be necessary to maintain communication ability.
- Dietary consultation may assist the patient in nutritional concerns related to swallowing difficulties and food selections.

Table 6

Drug-Drug Interactions with Medications Used to Treat Parkinson's Disease

Medication	Interacting drug	Outcome
Dopamine agonists (eg, bromocriptine, pergolide)	Dopamine antagonists (eg, haloperidol, metoclopramide)	Inhibition of benefits with worsening parkinsonism
Levodopa	Dopamine antagonists	Inhibition of benefits with worsening parkinsonism
Selegiline	Serotonergics, SSRIs, buspirone, mirtazapine	Serotonin syndrome may occur (confusion, agitation, tremor, seizures, coma)
COMT Inhibitors	Nonselective MAO inhibitors: phenelzine	Serotonin syndrome; hypertensive crisis secondary to increased catecholamines

COMT, catecholamine *O*-methyl transferase; MAO, monoamine oxidase; SSRI, selective serotonin reuptake inhibitor.

Table 5

Adverse Effects of Medications Used to Treat Parkinson's Disease

Drug	Adverse effects
Dopaminergics: levodopa, pergolide, bromocriptine, ropinirole, amantadine	Nausea/vomiting, agitation, confusion, depression, psychoses, orthostatic hypotension, dyskinetic movements
Selegiline	Nausea/vomiting, insomnia, dizziness, agitation, confusion, dyskinetic movements, anorexia
Amantadine	Confusion, dizziness, depression, anxiety, psychoses, insomnia
COMT inhibitors: tolcapone, entacapone	Nausea/vomiting, diarrhea, dyskinesia, urine coloration, liver toxicity (tolcapone)
Anticholinergics: benztropine, trihexyphenidyl	Dry mouth, blurred vision, constipation, urinary retention, confusion, agitation, psychoses

COMT, catecholamine *O*-methyl transferase.

7. Glaucoma

- Glaucoma is a group of eye diseases characterized by an increase in intraocular pressure, which causes pathologic changes in the optic nerve and typical visual field defects.
- Glaucoma affects over 4 million Americans; there may be as many as 15 million more persons with increased intraocular pressure but without clinical signs and symptoms of glaucoma.
- The prevalence of glaucoma increases with age and it is most often seen in those 65 years of age or older.
- The number of persons with glaucoma is expected to increase with the aging of the American population. With improved screening programs to identify those with increased intraocular pressure (IOP), an increase in the number of those diagnosed with glaucoma is expected.

Classification

- Open-angle glaucoma is a form of primary glaucoma. The angle of the anterior chamber remains open in an eye, but filtration of aqueous humor is gradually diminished because of the tissues of the angle. This accounts for approximately 80-90% of cases of glaucoma.
- Angle-closure (narrow angle) glaucoma is a form of primary glaucoma in an eye characterized by a shallow anterior chamber and a narrow angle. The filtration of aqueous humor is compromised as a result of the iris blocking the angle.
- Congenital glaucoma results from defective development of the structures in and around the anterior

chamber of the eye and results in impairment of aqueous humor.

Clinical Presentation

- Clinical signs and symptoms of glaucoma develop slowly and may present with only minor symptoms such as headache and mild eye pain.
- Optic nerve damage results from chronic elevations in IOP and this emphasizes the importance of early and consistent treatment to avoid loss of vision.
- Acute angle-closure glaucoma presents with blurred vision, severe ocular pain, and possible nausea and vomiting. This should be considered a medical emergency and immediate care should be recommended.
- Chronic angle-closure glaucoma may have symptoms similar to those of open-angle glaucoma.
- Tonometry is used to screen for IOP but direct ophthalmoscopy (slit-lamp examination) is necessary to accurately evaluate the eye for changes in the optic nerve.

Pathophysiology

- The pathogenesis of glaucoma results from changes in aqueous humor (the fluid filling the eye and in front of the lens) outflow that results in increased IOP. This increase in pressure leads to optic nerve atrophy and progressive loss of vision.
- Increased IOP can result from decreased elimination or increased production of aqueous humor.
- Aqueous humor is secreted by the ciliary processes into the posterior chamber of the eye. It then flows through the trabecular meshwork and the canal of Schlemm.
- Open-angle glaucoma is the result of decreased elimination of aqueous humor as it passes through the trabecular meshwork, thereby resulting in elevated IOP.
- Angle-closure glaucoma is caused by papillary blockage of aqueous humor outflow.
 - * This can result when a patient has a narrow anterior chamber in the eye or a dilated pupil where the iris comes into greater contact with the lens.
 - * With the blocking of outflow, aqueous humor accumulates in the posterior chamber, presses the lens forward, and further decreases drainage with possible complete blockage as the outcome.

Diagnostic Criteria

- Elevated IOP as determined by tonometry
- Fundusoscopic assessment to identify characteristic changes in the optic disc and retina

Treatment Principles (Figure 1)

- Reduce IOP to prevent optic nerve damage and visual field loss.
- Use topical medications as first-line treatment.
- Consider acute angle-closure glaucoma as a medical emergency.

Monitoring

- Periodic screening for increased IOP, with yearly examinations for those over 65 years of age and as part of routine eye examination

Drug Therapy

Mechanism of action

- Medications are considered the mainstay of therapy for the treatment of glaucoma (Table 7).
- β -Adrenergic blocking drugs (β -blockers) are considered first-line treatment for open-angle glaucoma.

Figure 1.

Algorithm for the treatment of open-angle glaucoma.

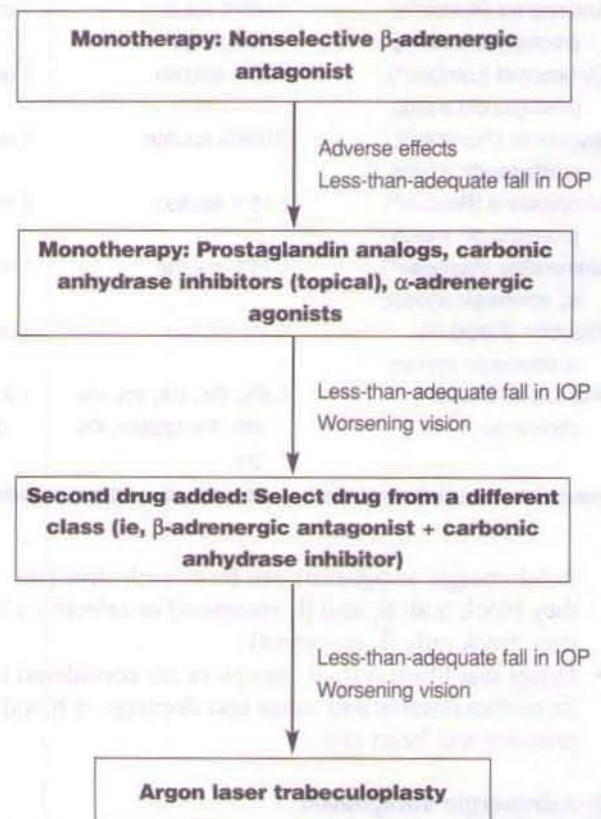


Table 7

Medications for the Treatment of Glaucoma

Generic name (trade name) and type	Form	Usual dosage	Comments
Timolol (Timoptic®), nonselective β antagonist (NSBA)	0.25% and 0.50% solution and gel- forming solution	1 drop twice daily; gel solution used once daily	Nonselective β antagonists are often first choice for open-angle glaucoma
Carteolol (Ocupress®), NSBA	1% ophthalmic solution	1 drop twice daily	
Levobunolol (Betagen®), NSBA	0.25% and 0.50% solution	1-2 drops 1-4 times daily	
Metipranolol (OptiPranolol®), NSBA	0.3% solution	1 drop twice daily	
Betaxolol (Betoptic®), selective β_1 antagonist	0.25% and 0.50% solution	1-2 drops twice daily	Cardioselective; less effect on heart rate and blood pressure
Levobetaxolol (Betaxon®), selective β_1 antagonist	0.50% solution	1 drop twice daily	Cardioselective
Acetazolamide (Diamox®), carbonic anhydrase inhibitor	125-, 250-mg tablets, 500-mg ER capsules	250 mg 1-4 times daily; extended- release 1-2 times daily	Do not use with sulfa allergy
Dorzolamide (Trusopt®) carbonic anhydrase inhibitor	2.0% solution	1 drop three times daily	Do not use with sulfa allergy
Brinzolamide (Azopt®), carbonic anhydrase inhibitor	1.0% solution	1 drop three times daily	Do not use with sulfa allergy
Methazolamide (Neptazane®), carbonic anhydrase inhibitor	25- and 50-mg tablets	15-50 mg 1-3 times daily	Do not use with sulfa allergy
Latanoprost (Xalatan®), prostaglandin analog	0.005% solution; refrigerate	1 drop at bedtime	Can change blue eyes to brown
Bimatoprost (Lumigan®), prostaglandin analog	0.03% solution	1 drop at bedtime	Can cause darkening of eyelids and eyelashes
Travoprost (Travatan®), prostaglandin analog	0.004% solution	1 drop at bedtime	Frequent ocular hyperemia
Unoprostone (Rescula®), prostaglandin analog	0.15% solution	1 drop twice daily	If used with another drop, wait 5 minutes
Brimonidine (Alphagan®), α_2 adrenergic agonist	0.15% solution	1 drop three times daily	Wait at least 15 minutes after using before placing soft contacts
Dipivefrin (Propine®); α -adrenergic agonist	0.1% solution	1 drop twice daily	Prodrug of epinephrine
Pilocarpine (Pilocar®), cholinergic, miotic	0.5%, 1%, 2%, 3%, 4%, 6%, 8% solution, 4% gel	1-2 drops 3-4 times daily; 1/2 inch gel at bedtime	Once weekly dose form called Ocuserts®

β -Adrenergic antagonists can be nonselective (ie, they block both β_1 and β_2 receptors) or selective (ie, they block only β_1 receptors).

- Drugs that block only β_1 receptors are considered to be cardioselective and cause less decrease in blood pressure and heart rate.

 β -Adrenergic antagonists

* Nonselective β antagonists: timolol, carteolol, levobunolol, metipranolol

* β_1 -Selective antagonists: betaxolol, levobetaxolol

- Therapy is initiated with a single topical ophthalmic solution, and additional agents are added if there is a less-than-acceptable decrease in IOP.
- The effects of therapy on IOP should be apparent after a week of treatment.
- Prostaglandin analogs are also used as first-line treatment (or in combination with β -blockers).

- Topical carbonic anhydrase inhibitors and α_2 agonists may be used in treatment.
- Medications such as epinephrine, pilocarpine, and oral carbonic anhydrase inhibitors are prescribed less often, but are considered to be effective adjunctive drugs.

Patient instructions and counseling

- Multiple factors present obstacles that can interfere with good compliance.
- Patients are often asymptomatic and do not feel treatment is necessary.
- Since decreased vision is associated with glaucoma, patients may have difficulty with written instructions.
- Adequate glaucoma therapy often requires two or more types of eye drops that may have to be given more than once daily.
- Correct administration of eye drops requires coordination and reasonable cognitive functioning.
- Glaucoma is more common in the elderly, who may have more difficulty complying with prescribed medications.
- Patient guidelines concerning the use of eye drops to treat glaucoma:
 - * Wash hands before administering eye drops and avoid touching the dropper tip.
 - * Confirm that the medication is not outdated and has been stored properly.
 - * Looking upward, pull the lower lid down and instill the correct number of drops.
 - * Close the eye to allow the medication to have maximal effect.

- * In most cases wait five or more minutes between different medications.

Adverse drug events (see Table 8)

Drug-drug interactions

- Drug interactions between topical medications and systemic drugs are unlikely.
- Acetazolamide interacts with the following:
 - * Aspirin to cause increased aspirin levels and possible toxicity
 - * Cyclosporine to cause increased cyclosporine levels
 - * Lithium to cause either increased or decreased lithium levels
 - * Phenytoin to cause an increased risk of osteomalacia

Parameters to monitor

- Medication use is critical to the successful treatment of glaucoma and should be monitored by the health professional.

Other

- A combination of timolol 0.5% and dorzolamide 2% (Cosopt[®]) is available. This combination effectively lowers IOP and only requires twice-daily doses. This simplified dosing should improve compliance with treatment. This combination (ie, using two drugs from different categories) represents a sound treatment approach. Poor response to therapy may result in the prescribing of multiple medications, which

Table 8

Classification, Mechanism of Action, and Adverse Effects of Glaucoma Medications

Medication class	Mechanism of action	Adverse effects
β -Adrenergic antagonists: timolol, metipranolol, carteolol, levobunolol, etc.	Decrease in aqueous humor formation with slight increase in outflow (β selective)	Adverse cardiac effects, worsening pulmonary disease, depression, dizziness
Miotics (cholinergics): pilocarpine, carbachol	Increase in aqueous humor outflow	Miosis, brow ache, dizziness, nausea, flushing, itching, sweating, confusion
Carbonic anhydrase inhibitors: dorzolamide, brinzolamide	Decrease in aqueous humor formation	Lethargy, decreased appetite, GI upset, urinary frequency
Prostaglandin analogs: latanoprost, travoprost, bimatoprost	Increased uveoscleral outflow without effect on aqueous humor formation	Iris pigmentation, eyelid darkening, macular edema
α_2 -Adrenergic agonists: apraclonidine, brimonidine	Decrease in aqueous humor formation	Tachycardia, dry mouth, eyelid elevation, CNS effects in the old and very young
Other α -adrenergic agonists: epinephrine, dipivefrin	Increase in aqueous humor outflow	Tachycardia, increased blood pressure, allergic responses

may negatively impact the patient's ability to successfully use the more complex regimen.

Nondrug Therapy

Laser surgery

- Argon laser trabeculoplasty (ALT) has proven effective as adjunctive therapy that increases the flow of aqueous humor.

Surgery

- The procedure involves creating new means of drainage for aqueous humor to leave the anterior chamber.

8. Key Points

Alzheimer's disease

- Alzheimer's disease is a progressive neurologic disease that results in impaired memory, intellectual functioning, and behavior.
- There is no known cure for Alzheimer's disease, but there are therapies to decrease memory impairment as well as improve behavior and patient functioning.
- Other forms of dementia that are potentially reversible should be identified and treated accordingly.
- New drug therapies may slow the progression of Alzheimer's disease and allow patients to remain in the least restrictive environment possible.
- Caregiver support and education is an important measure to assure patient safety and well-being.

Parkinson's disease

- Parkinson's disease is a chronic, progressive neurologic disease for which there is no cure; medications are available to slow the progression of symptoms.
- The etiology of Parkinson's disease is unknown, but may involve genetic susceptibility combined with environmental toxins and age-related changes in the brain.
- Dopamine, the central neurotransmitter, is decreased in Parkinson's disease and current drug therapy is primarily directed at increasing dopamine levels.
- Drug therapy monitoring in Parkinson's disease requires an understanding of a variety of different medications that may cause significant adverse effects.
- Physical therapy, occupational therapy, dietary considerations, and support counseling for caregivers are necessary components of treating Parkinson's disease.

Glaucoma

- Glaucoma, a group of eye diseases, is characterized by increased intraocular pressure resulting in damage to the optic nerve and possible blindness.
- Open-angle glaucoma is the most common form of this disease; angle-closure glaucoma can be a medical emergency.
- The goal of therapy is to reduce intraocular pressure with the simplest medication regimen possible.
- Drug therapy for glaucoma usually begins with a topical β -adrenergic antagonist; patients often require combination therapy.
- Medication compliance is essential in the control of glaucoma. Education of the patient and caregiver is required to overcome treatment barriers.

9. Questions and Answers

1. Of the following pharmacokinetic processes which is the least altered by aging?
 - A. Absorption
 - B. Distribution
 - C. Metabolism
 - D. Elimination
 - E. Excretion
2. Which of the following is given as a once-daily dose?
 - A. Buspirone
 - B. Donepezil
 - C. Galantamine
 - D. Rivastigmine
 - E. Tacrine
3. Galantamine increases levels of which neurotransmitter?
 - A. Acetylcholine
 - B. Dopamine
 - C. Melatonin
 - D. Norepinephrine
 - E. Serotonin
4. Weight loss is most often associated with which of the following?
 - A. Donepezil
 - B. Galantamine
 - C. Mirtazapine
 - D. Rivastigmine
 - E. Tacrine
5. What is the correct answer concerning donepezil?
 - I. Inhibits acetylcholinesterase but not butyrylcholinesterase
 - II. It should be taken with meals in divided doses
 - III. Side effects include tachycardia and blood pressure alterations
 - A. I only
 - B. III only
 - C. I and II only
 - D. II and III only
 - E. I, II, and III
6. All of the following medications are used to treat behavioral and emotional symptoms in Alzheimer's patients EXCEPT
 - A. benztropine
 - B. buspirone
 - C. citalopram
 - D. lorazepam
 - E. risperidone
7. The maximum daily dose of galantamine in patients with renal impairment is
 - A. 8 mg/d
 - B. 12 mg/d
 - C. 16 mg/d
 - D. 24 mg/d
 - E. 32 mg/d
8. All of the following could worsen cognition in AD patients EXCEPT
 - A. dicyclomine
 - B. dimenhydrinate
 - C. meclizine
 - D. trazodone
 - E. trihexyphenidyl
9. Memantine's reported benefits in treating the symptoms of Alzheimer's disease is thought to be the result of
 - A. increasing serotonin receptor activity
 - B. blocking the effect of glutamate on receptors
 - C. direct blocking of acetylcholine receptors
 - D. decreasing intracellular dopamine activity
 - E. decreasing amyloid deposits in the brain
10. Which works by direct stimulation of dopamine receptors?
 - A. Amantadine
 - B. Benztropine
 - C. Entacapone
 - D. Ropinirole
 - E. Selegiline
11. In treating parkinsonism the "on and off" phenomenon is most often associated with
 - A. benztropine
 - B. bromocriptine
 - C. carbidopa-levodopa
 - D. selegiline
 - E. tolcapone

12. What would be the most likely outcome if a Parkinson's patient on levodopa were also prescribed haloperidol?
 - A. Excessive nausea and vomiting
 - B. Hypertensive crisis
 - C. Tachycardia and possible chest pain
 - D. Worsening symptoms of Parkinson's disease
 - E. Excessive somnolence
13. Which inhibits monoamine oxidase (MAO)?
 - A. Benztropine
 - B. Bromocriptine
 - C. Pramipexole
 - D. Selegiline
 - E. Tolcapone
14. How does carbidopa affect levodopa?
 - A. Slows the release from presynaptic neurons
 - B. Prevents the excretion of dopamine
 - C. Increases stimulation of dopamine receptors
 - D. Decreases tolerance to normal doses
 - E. Inhibits the peripheral conversion to dopamine
15. A patient with Parkinson's disease currently taking selegiline has been prescribed mirtazapine (Remeron®). What would be the most likely outcome of this combination?
 - A. Inhibition of benefits with worsening parkinsonism
 - B. No significant drug interaction
 - C. Risk of serotonin syndrome
 - D. Increased benefits with improved parkinsonism
 - E. Hypertensive episode
16. Which of the following statements are true concerning the treatment of the "on and off" phenomenon that can be associated with PD?
 - I. Combine two or more medications with different mechanisms of action
 - II. Give more frequent doses of carbidopa-levodopa
 - III. Give a sustained-release carbidopa-levodopa product
 - A. I only
 - B. III only
 - C. I and II only
 - D. II and III only
 - E. I, II, and III
17. Timolol ophthalmic drops would be more likely to cause which adverse effect as compared to levobetaxolol ophthalmic drops?
 - A. Agitation and restlessness
 - B. Nausea and vomiting
 - C. Confusion
 - D. Change in heart rate and blood pressure
 - E. Altered intraocular pressure
18. Which of the following would not be considered for monotherapy of glaucoma?
 - A. Latanoprost
 - B. Dorzolamide
 - C. Carteolol
 - D. Methazolamide
 - E. Brimonidine
19. Which of the following can cause iris pigmentation changes?
 - A. Acetazolamide
 - B. Betaxolol
 - C. Brimonidine
 - D. Latanoprost
 - E. Pilocarpine
20. Which of the following is available as a fixed combination product?
 - A. Dorzolamide and timolol
 - B. Betaxolol and bimatoprost
 - C. Bimatoprost and levobunolol
 - D. Latanoprost and timolol
 - E. Methazolamide and latanoprost
21. All of the following are available as an ophthalmic solution EXCEPT
 - A. Brimonidine
 - B. Dipivefrin
 - C. Dorzolamide
 - D. Methazolamide
 - E. Metipranolol
22. Which should not be used if a patient has a sulfa allergy?
 - A. Betaxolol
 - B. Bimatoprost
 - C. Brimonidine
 - D. Brinzolamide
 - E. Unoprostone

23. α_2 -Adrenergic agonists cause a(n)
- A. Increase in aqueous humor synthesis
 - B. Decrease in aqueous humor formation
 - C. Increase in uveoscleral outflow
 - D. Increase in aqueous humor outflow
 - E. Decreased uveoscleral outflow
24. Which of the following statements concerning glaucoma therapy are correct?
- I. Carteolol is available as an ophthalmic solution and as a gel-forming solution
 - II. Latanoprost and metipranolol ophthalmic solutions should be stored in the refrigerator
 - III. Prostaglandin analogs, β -adrenergic antagonists, and α -adrenergic agonists can be used as monotherapy
- A. I only
 - B. III only
 - C. I and II only
 - D. II and III only
 - E. I, II, and III

Answers

1. A. Of all the age-related changes of the pharmacokinetic process, absorption is the least altered. This may relate to the fact that most drugs are passively absorbed.
2. B. All cholinesterase inhibitors except donepezil require at least twice-daily dosing. Donepezil has a long half-life, which allows for once-daily doses. None of these agents is available in sustained-release forms. Buspirone is an anxiolytic drug that is dosed twice or three times daily.
3. A. Galantamine is a cholinesterase inhibitor and all cholinesterase inhibitors increase levels of acetylcholine, the neurotransmitter that appears to be involved with memory function.
4. D. Weight loss, probably due to nausea and vomiting, is a warning for rivastigmine. In controlled trials, approximately 26% of women on doses of 9 mg/d or greater had weight loss of equal to or greater than 7% of their baseline weight.
5. A. Donepezil is selective for acetylcholinesterase and does not inhibit butyrylcholinesterase. Donepezil does not have to be taken with meals and is given once daily.
6. A. Benztropine is an anticholinergic used to treat side effects from antipsychotic medications and is also used to treat incontinence. All other drugs listed can be used to treat specific symptoms associated with AD.
7. C. With renal or hepatic dysfunction, galantamine doses should not exceed 16 mg/d. With severe renal or hepatic dysfunction, galantamine should not be used.
8. D. All of the drugs listed with the exception of trazodone have anticholinergic activity. Decreasing the activity of acetylcholine could worsen dementia and block benefits of cholinesterase inhibitors. Trazodone is an antidepressant with sedating properties but little anticholinergic activity. It may be given at bedtime to help with sleep. Trazodone does have a side effect of orthostatic hypotension.
9. B. Glutamate is the main excitatory neurotransmitter in the CNS and one theory states that blocking the effects of glutamate on NMDA receptors will decrease symptoms of Alzheimer's disease.
10. D. Ropinirole directly stimulates dopamine receptors; the other drugs increase dopamine activity by different mechanisms.
11. C. The "on and off" phenomenon is associated with advancing disease and loss of benefits from levodopa. It is treated by giving more frequent doses and/or using sustained-release levodopa.
12. D. Haloperidol and other antipsychotics block dopamine activity and can worsen PD. They can also block the benefits of PD medications, which increase dopamine activity.
13. D. Selegiline is an MAOI that is selective for MAOB, which decreases the potential for drug-drug and drug-food interactions. At doses higher than 10 mg/d this selectivity becomes less.
14. E. Carbidopa inhibits the peripheral conversion of levodopa to dopamine, thus allowing more levodopa to cross the blood-brain barrier and decreases adverse effects from dopamine.

15. **C.** The combination of two drugs that increase serotonin levels can result in serotonin syndrome which can cause confusion, agitation, tremor, seizures and coma.
16. **D.** Increasing frequency of drug or using a sustained-release form decreases blood level fluctuations and should improve symptoms.
17. **D.** Timolol is a nonselective β -adrenergic antagonist that causes a reduction in heart rate and blood pressure. There is enough absorption from eye drops to produce these cardiac effects.
18. **D.** All of the other choices could be considered as monotherapy for glaucoma. Methazolamide is an oral carbonic anhydrase inhibitor and is used in conjunction with ophthalmic drops.
19. **D.** Latanoprost, a prostaglandin analog, is known to change iris pigmentation and to darken eyelashes.
20. **A.** Dorzolamide plus timolol (Cosopt) is the only combination ophthalmic solution for treating glaucoma. An advantage for using a combination product would be increased compliance.
21. **D.** Methazolamide and acetazolamide are both available only as oral tablets or capsules. Topical carbonic anhydrase inhibitors are brinzolamide and dorzolamide.
22. **D.** Patients with sulfa allergy should not be given a carbonic anhydrase inhibitor.
23. **B.** α_2 -Adrenergic agonists such as brimonidine cause a decrease in aqueous humor formation.
24. **B.** All of these drugs can be used as monotherapy in glaucoma. Timolol and pilocarpine are available as gel forms. Latanoprost (but not metipranolol) should be stored in a refrigerator before dispensing.

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35. Toxicology and Chem-Bioterrorism

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1. Overview of Poisoning and Toxicology

Poisoning in America

- Poisoning exposures and overdoses affect over 2.5 million people annually, and there are over 26,000 deaths yearly (<1% of deaths are in preschool-aged children).
- A great number of poisonings occur in young children, but most fatalities occur in adults.
- Any chemical can become toxic if the exposure is too great in relation to body weight and tolerance.
- Medications are the most common cause of poisoning morbidity and mortality.
- Most poisonings in preschool-aged children are unintentional or accidental.
- Unintentional poisonings can also occur in adolescents and adults; however, intentional (suicide, drug abuse) poisonings and overdoses are common (Table 1).

Table 1

Ranking of Most Frequent Poisonings from U.S. Poison Centers and Emergency Departments During 2004

Cases from poison centers ¹	Cases from emergency departments ²
Analgesics	Alcohol, alone or in combination
Cleaning substances	Cocaine
Cosmetics and personal care products	Marijuana
Sedative drugs	Opioid analgesic drugs
Foreign bodies	Heroin
Topical drugs	Nonopioid analgesic drugs
Cough and cold drugs	Benzodiazepines
Antidepressant drugs	Amphetamines
Pesticides	Antidepressant drugs
Bites and envenomations	Antipsychotic drugs
Plants	Sedative drugs
Alcohols	Cardiovascular drugs

¹In decreasing order of frequency and based on 2,438,644 poison exposures. From: Watson WA, Litovitz TL, Rogers GC, et al. 2004 Annual Report of the American Association of Poison Control Centers Toxic Exposure Surveillance System. *Am J Emerg Med*. 2005;23:590-665.

²In decreasing order of frequency based on 1,997,993 cases of substance abuse, poisoning, overmedication and attempted suicide. From: Substance Abuse and Mental Health Services Administration, Drug Abuse Warning Network, 2004 national estimates of drug-related emergency department visits. Rockville, MD. Publ. SMA 06-4143.

Poison Prevention Approaches and Pharmacy

Poison Prevention Packaging Act of 1970: "Safety Caps"

- This act was issued to prevent preschool-aged children from opening and ingesting harmful substances or to delay the opening of packaging containing such substances (to limit the amount of harmful substance that may be ingested within a reasonable amount of time).
- Drugs requiring safety caps include aspirin, ibuprofen, acetaminophen, and oral prescription drugs with certain exceptions (eg, birth control pills, nitroglycerin).

Utilization of poison control centers

- Nationwide access is available at 1-800-222-1222 for 24-hour poison center services for the area from which the call is placed in the U.S.

Poison prevention tips for consumers

- Store all drugs and chemicals out of the reach of children.
- Never put chemicals in food containers.
- Choose products with safety caps when there is a choice and use them properly.
- Read and follow all label directions carefully.
- Never call medicine "candy."
- Use safety latches.

Pharmacy Requirements for the Joint Commission on Accreditation of Healthcare Organizations

- Maintain and keep available (for the medical staff) an approved stock of antidotes and other emergency drugs both in the pharmacy and patient care areas.
- Maintain authoritative, current antidote information.
- The phone number of the poison control center should also be readily available in areas outside of the pharmacy where drugs are stored.

Emergency Actions

- First aid, if applicable (Table 2)

Other considerations:

- Avoid wasting time to find an "antidote" at home.
- Do not use home remedies such as saltwater, mustard powder, raw eggs, hydrogen peroxide, cooking grease, or gagging.
- Call 911 or an ambulance if the person is not breathing, has had a seizure, or is unresponsive.
- Contact a poison center immediately to determine first aid or whether a poisoning emergency exists.

Table 2**First Aid for Poisoning Emergencies****Inhaled poison**

Immediately get the person to fresh air. Avoid breathing fumes. Open doors and windows wide.

Poison on the skin

Remove any contaminated clothing and flood skin with water for at least 15 minutes.

Poison in the eye

Flood the eye with water. Pour it from a large glass 2-3 inches from the eye. Repeat for a total of 15-30 minutes. Do not force the eyelid open. Remove contact lenses.

Swallowed poison

Unless the victim is unconscious, having convulsions, or cannot swallow, give a small glassful (2-4 ounces) of water immediately. Call a poison center for advice about whether other actions are needed.

Decontamination of the Gastrointestinal Tract

- The practice of using drugs to decrease the absorption of other drugs from the gastrointestinal tract is in a state of change. Drugs such as ipecac syrup are being abandoned by many as a home- or hospital-based therapy. Its use is primarily at the preference of the consulting poison center or health care professional. Current recommendations are described below as well as basic information about the drugs in case they are encountered.

Current recommendations

- Ipecac syrup has questionable effectiveness and its use is generally avoided.
- Gastric lavage involves placing a tube into the stomach through a nostril or the mouth and repetitively washing out the stomach contents with water or a saline solution. This method of gastric decontamination is of questionable effectiveness, particularly if it is performed more than 1 hour after ingestion.
- Cathartics such as magnesium citrate are not routinely used.
- Activated charcoal is often the only treatment necessary if the toxin is adsorbed and it is used within 1-2 hours of ingestion.
- Whole bowel irrigation can be considered if the toxin is poorly or slowly adsorbed and its presence in the gastrointestinal tract is likely.

Ipecac syrup**Indications and dosage**

- It was previously used for general prophylaxis of selected poisonings of expected minor or moderate severity in alert patients.
- It has been abandoned by many clinicians as a pre-hospital or hospital treatment. In November 2003 the American Academy of Pediatrics recommended that ipecac syrup no longer be used routinely as a home treatment for poisoning.

Contraindications

- The patient is experiencing pronounced sleepiness, coma, or seizures.
- Ingestion of caustics, aliphatic hydrocarbons, and fast-acting agents that produce coma or seizures (eg, tricyclic antidepressants, clonidine, calcium channel blockers, beta blockers, and hypoglycemic agents)
- Time since ingestion is believed to be 1 hour or more

Adverse effects

- Common: diarrhea, sleepiness, protracted vomiting
- Uncommon: Mallory-Weiss tears, tracheal aspiration into the lungs
- Disadvantages: relative lack of efficacy and emesis complicate administration of other oral therapies

Activated charcoal**Indications and dosage**

- Occasionally used to adsorb poisons in an alert or comatose patient
- Administer as a slurry by mouth or through a lavage tube:
 - * Children: 25-50 g
 - * Adults: 25-100 g

Contraindications

- Ingestions of aliphatic hydrocarbons and caustics
- If patient's bowel sounds are absent
- Ingestions of heavy metals (sodium, lithium, iron, or lead) or simple alcohols

Adverse effects

- Uncommon: tracheal aspiration, pneumonitis
- Common: emesis, soiling of clothes and furnishings

Advantages and disadvantages

- Advantages: rapid onset of action, nonspecific action for a wide variety of chemicals, and reasonable effectiveness within 1 hour of ingestion
- Disadvantages: messy and difficult to administer, may also remove beneficial drugs along with the toxin

Cathartics

- Previously used as an adjunct to activated charcoal administration to decrease gastrointestinal transit time
- Efficacy unproved
- Fluid and electrolyte disturbances are possible with repeated doses.
- May contribute to emesis following activated charcoal use
- Agents previously used include magnesium citrate, magnesium sulfate, sodium sulfate, and sorbitol.
- **Note:** Some activated charcoal products contain sorbitol mixed in the preparation. The sorbitol concentration varies from brand to brand.

Whole bowel irrigation

Indications and technique

- Generally used when charcoal may be inappropriate (eg, if iron or lithium was ingested) and the toxin is suspected to be present in the gastrointestinal tract (eg, when drugs are sustained-release formulations or ingested illicit drugs packed in condoms)
- Use larger volumes of polyethylene glycol electrolyte solutions (eg, CoLyte®, GoLYTELY®) than amounts conventionally used for bowel preparation.
- Administer by mouth or through a gastric or duodenal tube for treatment of poisoning:
 - * Children: 25 mL/kg per hour (approximately 500 mL/h) up to 2-5 L
 - * Adults: 2 L/h up to 5-10 L

Contraindications

- Ingestion of caustics or aliphatic hydrocarbons
- Patients with absent bowel sounds or gastrointestinal tract obstruction

Adverse effects

- Few adverse effects have been reported, but there are limited results available from which to draw conclusions. Some nausea and vomiting has been reported.

Advantages and disadvantages

- Advantages: prompt whole bowel evacuation within 2 hours
- Disadvantages: messy procedure due to rectal effluent

Other hospital-based therapies

- These include supportive and symptomatic care, multiple doses of activated charcoal (to enhance systemic elimination when appropriate), hemodialysis (to enhance systemic elimination when appropriate), and use of antidotes (to antagonize or reverse toxic effects when indicated).

2. Substance Abuse and Toxicology

- Substance abuse often leads to acute and chronic toxicity (Table 3).
- Management of the acute condition generally follows the same guidelines as managing poisonings and overdoses.
- A challenge in treating patients during acute drug overdose is determining the possible agents taken and possible adulterants (eg, talc, strychnine, other drugs) or contaminants.
- Chronic abuse can foster dependence, which often leads to withdrawal symptoms upon stopping use.

3. Antidotes

Role of Antidotes

- An antidote counteracts or changes the nature of a poison.
- There are few antidotes available relative to the large number of potential poisons. Table 4 lists commonly used antidotes for the treatment of a patient with a poisoning or an overdose.
- Many hospitals have an insufficient stock of antidotes; the pharmacy and therapeutics committee of the hospital should regularly review the inventory of antidotes.

Selected Antidotes

Acetylcysteine (Mucomyst® 10%, 20% oral solution; Acetadote® 20% for injection)

Uses

- Treatment of acute acetaminophen overdose
- Unapproved indication: to treat adverse reactions to drugs that may produce free radicals as part of the adverse reaction; the dosage regimen is unique to the application.

Mechanism of action

- It protects the liver from the toxic effects of an acetaminophen metabolite by supplying glutathione to aid in metabolism of the reactive metabolite.
- Other mechanisms are also proposed that include providing sulfate for acetaminophen metabolism and minimizing the formation of free radicals.

Table 3

Selected Drugs of Abuse and Addictive Substances

Substance (slang names)	Methods of abuse	Major or unique health effects
Androgenic anabolic steroids (Roids)	Anabolic steroids are taken orally or injected, typically in cycles of weeks or months ("cycling"); users often combine several different types of steroids ("stacking")	<ul style="list-style-type: none"> • Synthetic derivatives of testosterone; abuse can lead to serious health problems, some irreversible • Men: shrinking of the testicles, reduced sperm count, infertility, baldness, gynecomastia, increased risk for prostate cancer • Women: growth of facial hair, male-pattern baldness, changes in or cessation of the menstrual cycle, enlargement of the clitoris, deepened voice • Adolescents: stunted growth by premature skeletal maturation and accelerated puberty changes • Other major side effects can include jaundice, fluid retention, high blood pressure, severe acne; extreme mood swings can occur, including manic-like symptoms leading to violence and depression often experienced when drugs are stopped, and such symptoms may contribute to dependence
Barbiturates (barbs, downers)	Ingestion, injection	<ul style="list-style-type: none"> • CNS depressants that at high doses can become general anesthetics • With high doses, coma, ataxia, depressed reflexes, hypotension, respiratory depression • CNS depressants should not be combined with any medication or substance that causes sedation, including prescription pain medicines, certain over-the-counter cold and allergy medications, or alcoholic drinks. The effects of the drugs can combine to slow breathing, or slow both the heart and respiration, which can be fatal • Discontinuing prolonged use of high doses of barbiturates can lead to withdrawal
Cocaine (snow, crack, rock); crack is the street name given to cocaine that has been processed from cocaine hydrochloride to the free base for smoking	Sniffing or snorting, injecting; smoking of free-base and crack cocaine; poorly absorbed orally	<ul style="list-style-type: none"> • CNS stimulant that produces euphoric effects and hyperstimulation such as dilated pupils, increased temperature, tachycardia, and hypertension • Prolonged cocaine snorting can result in ulceration of the mucous membranes of the nose and can damage the nasal septum enough to cause it to collapse • Cocaine-related deaths are often a result of cardiac arrest or seizures followed by respiratory arrest • Tolerance to the euphoric effects develops • When addicted individuals stop using cocaine, they often become depressed

(continued)

Table 3

Selected Drugs of Abuse and Addictive Substances (continued)

Substance (slang names)	Methods of abuse	Major or unique health effects
Dextromethorphan (DXM, DM, Robo, Velvet, Rojo)	Orally by drinking dextromethorphan-containing cough syrups; availability of the powdered form has led to repackaging as capsules or tablets and to nasal insufflation (snorting)	<ul style="list-style-type: none"> Dextromethorphan (d-3-methoxy-N-methylmorphinan) is the dextro isomer of levomethorphan. It has no analgesic opiate-like dependence-producing properties. A behaviorally-active metabolite, dextrorphan, is structurally related to PCP and ketamine and may contribute to its abuse potential The typical clinical presentation of intoxication involves hyperexcitability, lethargy, ataxia, slurred speech, sweating, hypertension, and/or nystagmus. The abusers report a heightened sense of perceptual awareness, altered time perception, and visual hallucinations The majority of abuse occurs among teenagers and young adults who use dextromethorphan alone, or mixed with other drugs. It has been sold as "ecstasy." It has been identified as a filler in confiscated samples of bogus heroin and bogus ketamine. Procedures are described to extract dextromethorphan from cough syrups on the Internet, which has led to the availability of powdered forms
Ethanol (various names and alcoholic drinks)	Ingestion	<ul style="list-style-type: none"> CNS depressant at high doses can lead to hypotension, hypoglycemia, respiratory depression, and death Acute intoxication leads to ataxia, sedation, emesis, and slurred speech Chronic abuse leads to many medical complications such as esophageal varices, hepatic failure with ascites, and malnutrition Tolerance, dependence, and withdrawal develop with chronic abuse
GHB or gamma hydroxybutyrate (liquid ecstasy, soap, easy lay, Georgia home boy, somatomax, scoop, grievous bodily harm)	Ingestion	<ul style="list-style-type: none"> CNS depressant abused for euphoric, sedative, and anabolic (body building) effects Coma and seizures are likely; increased risk of seizures when combined with methamphetamine Use with alcohol causes nausea and difficulty breathing GHB and two of its precursors, gamma butyrolactone (GBL) and 1,4 butanediol (BD) have been involved in poisonings, overdoses, date rapes, and deaths; they are produced by illicit laboratories May produce withdrawal effects
Heroin (smack, H, skag, junk)	Injection, snorting, or smoking	<ul style="list-style-type: none"> Abuse associated with fatal overdose, spontaneous abortion, collapsed veins, and infectious diseases, including HIV/AIDS and hepatitis Euphoria ("rush") followed by an alternately wakeful and drowsy state ("on the nod") CNS depression, respiratory depression, miosis (pinpoint pupils), pulmonary edema Street heroin may have additives With regular use tolerance develops and withdrawal is possible
Inhalants	Inhaled by sniffing and huffing	<ul style="list-style-type: none"> A variety of breathable chemical vapors that produce psychoactive effects Found in industrial or household solvents or solvent-containing products, including paint thinners or solvents, degreasers, dry-cleaning fluids, gasoline, and glues Nearly all abused inhalants produce short-term intoxicating and CNS depressant effects similar to anesthetics Intoxication usually lasts only a few minutes; successive inhalations lead to loss of inhibition and control; continued use can lead to coma In some cases heart failure and death within minutes of a session of prolonged use, called "sudden sniffing death" is seen
Injected drugs (shooting up, mainlining)	Injection	<ul style="list-style-type: none"> The injecting drug user is at risk for transmitting or acquiring HIV/AIDS, hepatitis, bacterial infections, and fungal infections if needles or other injection equipment are shared Chronic users may develop collapsed veins, infection of the heart lining and valves, skin abscesses, cellulitis, and liver disease Since some abusers dissolve the tablets in water and inject the mixture, emboli can form from the insoluble materials in the tablets

(continued)

Table 3

Selected Drugs of Abuse and Addictive Substances (continued)

Substance (slang names)	Methods of abuse	Major or unique health effects
Ketamine (K, special K, cat Valium, vitamin K)	Injected, snorted	<ul style="list-style-type: none"> An anesthetic that has been approved for human and veterinary use Certain doses can cause dream-like states and hallucinations At high doses, can cause delirium, amnesia, impaired motor function, hypertension, depression, and potentially fatal respiratory depression
LSD, lysergic acid diethylamide (acid, L, blotter, cubes, sugar, dots)	Ingested; often added to absorbent paper, such as blotter paper, and divided into small decorated squares ("blotter acid") or placed on dot-like candy ("dots") or sugar cubes ("cubes," "sugar")	<ul style="list-style-type: none"> A hallucinogen sold on the street in tablets, capsules, and liquid form Effects are unpredictable; physical effects include mydriasis (dilated pupils), elevated temperature, tachycardia, hypertension, sweating, loss of appetite, sleeplessness, dry mouth, and tremors Sensations and feelings change more dramatically than the physical signs. In sufficient doses, the drug produces delusions and visual hallucinations Some users experience severe, terrifying thoughts and feelings, fear of losing control, fear of insanity and death, and despair Fatal accidents have occurred during intoxication Many users experience flashbacks
Marijuana (pot, herb, weed, grass, widow, ganja, hash, and trademarked varieties of cannabis, such as Bubble Gum, Northern Lights, Juicy Fruit, Afghani #1, and a number of Skunk varieties)	Smoked as a cigarette (joint, nail), in a pipe (bong) or in blunts (cigars that have been emptied of tobacco and refilled with marijuana, often in combination with another drug); also ingested when mixed in food or brewed as a tea	<ul style="list-style-type: none"> Main active chemical in marijuana is THC (delta-9-tetrahydrocannabinol) Delirium, conjunctivitis, food craving are typical Short-term effects include problems with memory and learning, distorted perception, difficulty in thinking and problem solving, loss of coordination, and tachycardia Risk of heart attack more than quadruples in the first hour after smoking marijuana Same respiratory problems as cigarette smokers (see nicotine); burning and stinging of the mouth and throat, often accompanied by a heavy cough Drug craving and withdrawal
MDMA, 3-4 methylenedioxymethamphetamine (Ecstasy, Adam, XTC, hug, beans, love drug)	Ingestion; some snort or inject it, or use it in suppository form	<ul style="list-style-type: none"> A synthetic, psychoactive drug with both stimulant and hallucinogenic properties Increases pulse and blood pressure In high doses it can cause malignant hyperthermia leading to rhabdomyolysis (muscle breakdown with kidney and cardiovascular system failure) Psychological difficulties: confusion, depression, sleep problems, drug craving, severe anxiety, and paranoia, during and sometimes weeks after use Physical symptoms: muscle tension, involuntary teeth clenching, nausea, blurred vision, nystagmus, faintness, chills, or sweating Content of the MDMA pills also varies widely, and may include caffeine, dextromethorphan, heroin, and mescaline. In some areas, the MDMA-like substance paramethoxyamphetamine (PMA) has led to death when mistaken for true MDMA; deaths were due to complications from hyperthermia
Methamphetamine (crank, meth, speed, chalk; the clear chunky crystals resembling ice can be smoked and are referred to as ice, crystal, and glass)	Ingestion, snorting the powder, injection, smoking	<ul style="list-style-type: none"> An addictive stimulant chemically related to amphetamine Produces euphoria, irritability, insomnia, confusion, tremors, convulsions, anxiety, paranoia, and aggressiveness; higher doses lead to hypertension, tachycardia, stroke, arrhythmias, cardiovascular collapse, and death Hyperthermia and convulsions can result in death Prolonged use leads to extreme anorexia; associated with tooth decay and skin lesions Made in illegal laboratories and may contain contaminants and by-products High potential for abuse and dependence
Nicotine (various names and products)	Smoked as cigarettes and other forms of tobacco, such as cigars, pipe tobacco, and chewing tobacco	<ul style="list-style-type: none"> Highly addictive CNS stimulant and sedative; stimulation is followed by depression and fatigue leading the user to seek more nicotine Women who take oral contraceptives are more prone to cardiovascular and cerebrovascular diseases, especially those older than 30 Pregnant women have an increased risk of having stillborn or premature infants or infants with low birthweight

(continued)

Table 3**Selected Drugs of Abuse and Addictive Substances (continued)**

Substance (slang names)	Methods of abuse	Major or unique health effects
Nicotine (various names and products) (cont'd)		<ul style="list-style-type: none"> • Respiratory problems: daily cough and phlegm production, more frequent acute respiratory illness, a heightened risk of lung infections, and a greater tendency toward obstructed airways, cancer of the respiratory tract and lungs • Tar in cigarettes associated with a higher rate of lung cancer, emphysema, and bronchial disorders • Carbon monoxide in the smoke increases the chance of cardiovascular diseases • Nicotine tolerance, dependence, and withdrawal symptoms occur
Opioids	Ingested, injection	<ul style="list-style-type: none"> • Includes morphine, codeine, oxycodone (Oxycontin[®], MS Contin[®]), propoxyphene (Darvon[®]), hydrocodone (Vicodin[®]), hydromorphone (Dilaudid[®]), and meperidine (Demerol[®]) • Cause drowsiness, constipation; large single doses cause coma, hypotension, respiratory depression, and in some cases seizures and death • Mixing with alcohol and other CNS depressants increases the risk of coma and death • Chronic use of opioids produces tolerance, physical dependence, and withdrawal symptoms
Phencyclidine (PCP, angel dust, ozone, wack, rocket fuel; killer joints or crystal supergrass when combined with marijuana)	Snorted, smoked, or eaten; for smoking, often applied to a leafy material such as mint, parsley, oregano, or marijuana	<ul style="list-style-type: none"> • An addictive hallucinogen and sedative that often leads to psychological dependence, craving, and compulsive PCP-seeking behavior • Users often become violent or suicidal and are very dangerous to themselves and to others • At low to moderate doses, slight tachypnea, more pronounced tachycardia and hypertension, shallow respirations, and profuse sweating; generalized numbness of the extremities and muscular incoordination also may occur • Psychological effects include distinct changes in body awareness, similar to those associated with alcohol intoxication • At high doses, decreased blood pressure, pulse, and respirations; nausea, vomiting; blurred vision, nystagmus; drooling; ataxia; seizures, coma, and death (though death more often results from accidental injury or suicide during PCP intoxication) • Psychological effects at high doses include illusions, hallucinations, and effects that mimic the full range of symptoms of schizophrenia • Interactions with other CNS depressants, such as alcohol and benzodiazepines, can lead to coma • Illegally manufactured in illicit laboratories
Rohypnol (rophia, roofies, roche, roach, rope, the date rape drug, forget-me)	Ingestion	<ul style="list-style-type: none"> • Rohypnol, a trade name for flunitrazepam, is a benzodiazepine that is not sold in the U.S.; it is smuggled into the U.S. • Produces sedative-hypnotic effects including muscle relaxation and amnesia; it can also produce physical and psychological dependence • When mixed with alcohol, rohypnol can incapacitate victims, prevent them from resisting sexual assault, and can produce anterograde amnesia • May be lethal when mixed with alcohol or other CNS depressants • Abuse of two other similar drugs, clonazepam (Klonopin[®]) and alprazolam (Xanax[®]), appears to be replacing rohypnol
Stimulants, amphetamines and related compounds (speed, dexies, uppers)	Ingestion, tablets crushed and snorted	<ul style="list-style-type: none"> • CNS stimulants increase alertness, attention, and energy as well as increase in blood pressure, pulse, and respiration • High doses: arrhythmias, hypertension, hyperthermia, potential for cardiovascular failure, stroke or lethal seizures; taking high doses of some stimulants repeatedly over a short period of time can lead to hostility or feelings of paranoia in some individuals • Stimulants such as dextroamphetamine (Dexedrine[®]) and methylphenidate (Ritalin[®]) when misused can be addictive

Sources: InfoFacts. National Institute on Drug Abuse, National Institutes of Health, Washington, DC.

Available at: <http://www.nida.nih.gov/Infofax/Infofaxindex.html>. Web page accessed July 21, 2006.

Drugs and Chemicals of Concern. Diversion Control Program, Drug Enforcement Administration, U.S. Department of Justice, Washington, DC.

Available at: http://www.deadiversion.usdoj.gov/drugs_concern. Web page accessed July 21, 2006.

Table 4**Commonly Used Antidotes**

Listed below are common antidotes that may need to be used emergently for patients presenting with acute toxic ingestion or dermal or inhalation exposure. Dosages are derived from standard texts and references and are given as convenience references. These should not be considered specific treatment guidelines; consult appropriate resources.

Toxin	Antidote (trade name)	Adult dose	Pediatric dose
Acetaminophen	Acetylcysteine (Mucomyst®)	Oral loading dose: 140 mg/kg; maintenance doses: 70 mg/kg every 4 hours for 17 doses	Same as adult dose regimen
	Acetylcysteine (Acetadote®)	IV infusion: 150 mg/kg in 200 mL D ₅ W infused over 15 min, then 50 mg/kg in 500 mL D ₅ W over 4 hours, followed by 100 mg/kg in 1000 mL D ₅ W over 16 hours	Same as adult dose regimen
Anticholinergic compounds	Physostigmine salicylate (Antilirium®)	1-2 mg slow IV infusion over 3-5 minutes titrated to effect	0.02 mg/kg slow IV infusion over 3-5 minutes titrated to effect
Arsenic	Succimer (Chemet®)	10 mg/kg orally 3 times a day	10 mg/kg orally 3 times a day
	Dimercaprol, also called British anti-lewisite (BAL in Oil®), only if unable to tolerate oral succimer	3-5 mg/kg intramuscular every 4-6 hours	3-5 mg/kg intramuscular every 4-6 hours
Benzodiazepines	Flumazenil ¹ (Romazicon®)	0.2 mg IV bolus titrated to effect or total dose of 3 mg	0.01 mg/kg IV bolus titrated to effect or total dose of 1-3 mg
β-Blocker	Glucagon (GlucaGen®)	5-10 mg IV bolus followed by 5-10 mg/h IV infusion titrated to effect	0.15 mg/kg mg IV bolus followed by 0.1 mg/h IV infusion titrated to effect
Calcium channel blockers	Calcium chloride 10%	10-20 mL IV bolus, repeat doses and IV infusions are common	0.1-0.2 mL/kg IV bolus, repeat doses and IV infusions are common
	Glucagon (GlucaGen)	5-10 mg/ IV bolus followed by 5-10 mg/h IV infusion titrated to effect	0.15 mg/ IV bolus followed by 0.1 mg/h IV infusion titrated to effect
Carbamates	Atropine	2-4 mg IV bolus, repeat doses titrated to effect	1 mg/kg IV bolus, repeat doses titrated to effect
Cyanide	<i>Cyanide antidote kit:</i> Sodium nitrite 3%	300 mg slow IV infusion	0.15-0.33 mL/kg to maximum of 300 mg slow IV infusion
	Sodium thiosulfate	12.5 g IV infusion	400 mg/kg up to 12.5 g IV infusion
Digoxin	Digoxin immune antibody fragment (Digibind®, DigiFab®)	Empiric dosing: 10-20 vials IV bolus for life- threatening toxicity; see package insert for other dosing regimens	Empiric dosing: 10-20 vials IV bolus for life-threatening toxicity; see package insert for other dosing regimens
Ethylene glycol, methanol	Ethanol 10%	Loading dose 10 mL/kg IV or orally followed by maintenance dose 1-2 mL/kg/h IV infusion maintenance dose or orally	Loading dose 10 mL/kg IV or orally followed by 1-2 mL/kg/h IV infusion or orally
	Fomepizole, also called 4- methylpyrazole (Antizol®)	15 mg/kg IV bolus, smaller repeat doses may be necessary	15 mg/kg IV bolus, smaller repeat doses may be necessary
Iron	Deferoxamine (Desferal®)	5-15 mg/kg/h IV infusion titrated to effect	5-15 mg/kg/h IV infusion titrated to effect
Isoniazid	Pyridoxine, also called vitamin B ₆	1 g per gram ingested or empiric dosing 5 g IV bolus	1 g per gram ingested or empiric dosing 75 mg/kg IV bolus up to 5 g
Lead	Succimer (Chemet®)	10 mg/kg orally 3 times a day, repeat doses are common	10 mg/kg orally 3 times a day, repeat doses are common

(continued)

Table 4

Commonly Used Antidotes (continued)

Toxin	Antidote (trade name)	Adult dose	Pediatric dose
Lead (continued)	Dimercaprol, also called British anti-lewisite [BAL], only for lead encephalopathy (BAL in Oil)	3-5 mg/kg intramuscularly or 50-75 mg/m ² intramuscularly	3-5 mg/kg intramuscularly or 50-75 mg/m ² intramuscularly
	Calcium disodium EDTA (Calcium Disodium Versenate®)	20-30 mg/kg diluted in 250 mL IV infusion over 12-24 hours (start 4 hours after BAL administration)	20-30 mg/kg diluted in 250 mL IV infusion over 12-24 hours (start 4 hours after BAL administration)
Methemoglobinemia	Methylene blue	1-2 mg/kg slow IV infusion, repeat doses are common	1-2 mg/kg slow IV infusion, repeat doses are common
Opioids	Naloxone hydrochloride (Narcan®)	0.4-2 mg IV titrated to effect	0.4-2 mg IV titrated to effect
Organophosphates	Atropine	2-4 mg IV bolus, repeat doses titrated to effect	0.1 mg/kg IV bolus, repeat doses titrated to effect
	Pralidoxime hydrochloride (Protopam®)	1-2 g slow IV infusion followed by 500 mg/h continuous infusion or 1 g every 4 hours	20-40 mg/kg slow IV infusion followed by 5-10 mg/kg/h continuous infusion or 20 mg/kg every 4 hours
Salicylate	Sodium bicarbonate	150 mEq with 40 mEq KCl in 1 L of D ₅ W infused to maintain urine output at 1-2 mL/kg/h and a urine pH approximately 7.5	150 mEq with 40 mEq KCl in 1 L of D ₅ W infused to maintain urine output at 1-2 mL/kg/h and a urine pH approximately 7.5
Tricyclic antidepressants, agents with type 1a antiarrhythmic effects	Sodium bicarbonate	1-2 mEq/kg IV bolus, titrate repeat boluses to QRS duration (do not exceed arterial pH of 7.55)	1-2 mEq/kg IV bolus, titrate boluses to QRS duration (do not exceed arterial pH of 7.55)
Warfarin, superwarfarins	Fresh frozen plasma	Fresh frozen plasma for life-threatening hemorrhage	Fresh frozen plasma for life-threatening hemorrhage
	Vitamin K ₁ (Mephyton®, AquaMEPHYTON®)	10-50 mg slow IV infusion, subcutaneous or orally	0.6 mg/kg slow IV infusion, subcutaneous or orally

¹Potential risks may exceed the benefits due to precipitation of intractable seizures.

Excerpt from: American College of Emergency Physicians: Clinical policy for the initial approach to patients presenting with acute toxic ingestion or dermal or inhalation exposure. *Ann Emerg Med*, 1999;33:735-761.

- It may also be useful to minimize hepatotoxic injury once it has begun and with fulminant hepatic failure.

Indications

- Acute overdoses of acetaminophen produce a reactive metabolite that leads to hepatotoxicity (jaundice, coagulopathy, hypoglycemia, hepatic failure, hepatic encephalopathy, and hepatorenal failure). Symptoms become evident 1-2 days after ingestion.
- N-acetylcysteine can prevent or minimize hepatic injury if given early. For best results, administer within 10 hours of ingestion of acetaminophen overdose. It is minimally effective when started 24 hours after ingestion.

- The need for therapy is determined by a serum concentration of acetaminophen obtained at least 4 hours after ingestion (and within 24 hours) and plotting it on the acetaminophen nomogram to determine whether there is a risk for hepatotoxicity.

Contraindications

- Known hypersensitivity to N-acetylcysteine

Adverse effects

- With oral administration, nausea and vomiting are common.
- With intravenous administration, anaphylactoid reactions (rash, hypotension, wheezing, dyspnea) have

been reported. Acute flushing and erythema may occur during the first hour of infusion and typically resolve spontaneously.

Dosage

- Drug products for oral or intravenous administration are available in the U.S. (Table 4).

Atropine

Indications

- Organophosphate (including chem-bioterrorism nerve agents) and carbamate anticholinesterase insecticide poisoning
- Bradycardia
- Nontoxicologic indications include atropine use for premedication to anesthesia induction (for antisecretory effects) and ophthalmic mydriasis and cycloplegia.

Mechanism of action

- Anticholinergic agent that competitively inhibits acetylcholine at muscarinic receptors. Atropine has little effect on nicotinic receptors.

Indications for use in the treatment of organophosphate or carbamate poisoning

- For control of pulmonary hypersecretion, atropine is given in repeated doses intravenously until secretions have dried. Atropinization may have to be maintained for hours to days.
- For control of bradycardia, atropine is given until the heart rate increases or until a need for alternatives is indicated.

Contraindications

- None for insecticide poisoning

Contraindications for other indications

- Hypersensitivity to atropine or anticholinergics
- Narrow-angle glaucoma
- Reflux esophagitis
- Obstructive gastrointestinal disease
- Ulcerative colitis or toxic megacolon
- Obstructive uropathy
- Unstable cardiovascular status in acute hemorrhage or thyrotoxicosis
- Paralytic ileus or intestinal atony
- Myasthenia gravis

Adverse effects

- Exaggeration of anticholinergic effects (eg, tachycardia, hypertension, sedation, hallucinations, mydriasis, changes in intraocular pressure, warm red skin, dry mouth, urinary retention, ileus, dysrhythmias, and seizures)

- For the use of large doses of atropine, the agent should be preservative-free since agents like benzyl alcohol or chlorobutanol can produce their own toxicity.

Dosage

- For bronchorrhea and bronchospasm from organophosphates or carbamates, the adult dose is 2-5 mg (pediatric dose is 0.05 mg/kg) administered slowly by IV. Dose is repeated at 10- to 30-minute intervals until bronchial hypersecretion is resolved. Severe poisonings may require up to 100 mg over a few hours to several grams over several weeks. If atropinization is required for several days, continuous atropine infusion may be used (rates of 0.02-0.08 mg/kg per hour are recommended).
- For symptomatic bradycardia (for mild poisonings) the adult dose is 1 mg (the pediatric dose is 0.01 mg/kg) intravenously. For moderate to severe poisonings, adult doses increase to 2-5 mg (pediatric doses are 0.02-0.05 mg/kg) and should be repeated every few minutes until heart rate increases.

Digoxin immune Fab (Digibind®, DigiFab®)

Uses

- Treatment of life-threatening acute or chronic digoxin poisoning
- Some cross-reactivity with digitoxin and other digoxin-like compounds (digitalis, foxglove, lily of the valley, bufadienolide from cane frogs)

Mechanism of action

- Digoxin immune Fab binds digoxin in plasma, promotes redistribution from tissues, and enhances elimination in the urine. The digoxin bound to digoxin immune Fab is inactive. Each 40 mg (1 vial) binds 0.6 mg of digoxin.
- Digoxin immune Fab is a monovalent, digoxin-specific, antigen-binding fragment (Fab) that is produced in healthy sheep.

Indications

- Chronic digoxin toxicity typically begins with nausea, vomiting, diarrhea, fatigue, confusion, blurred vision, diplopia, and seeing white borders or halos around dark objects. Deterioration of renal function, hypokalemia, or drug interactions often lead to toxicity.
- Acute digoxin poisoning has early symptoms similar to those of chronic poisoning, but the onset is more abrupt, nausea and vomiting are common, and the serum potassium concentration is typically normal or elevated.
- A wide variety of arrhythmias occur with acute or chronic digoxin poisoning.

- Digoxin immune Fab is reserved for life-threatening symptoms such as bradycardia, second-degree and third-degree heart block unresponsive to atropine, ventricular arrhythmias, and hyperkalemia (typically in excess of 5 mEq/L).

Contraindications

- Hypersensitivity to sheep

Adverse effects

- Common adverse effects include hypokalemia, allergic reactions (1%), and hypotension.
- For patients on maintenance digoxin therapy, the abrupt binding of digoxin will lead to loss of therapeutic effect and a prompt decrease in potassium concentrations.

Dosage

- It is administered by intravenous infusion or rapid intravenous bolus (Table 4).
- Dosage is determined by one of several approaches, depending upon available information, as follows: empiric dosage of 10-20 vials (Table 4), dosing based on the dose of digoxin ingested, or dosing based on the serum digoxin concentration.

Flumazenil (Romazicon®)

Uses

- Benzodiazepine overdose
- Reversal of conscious sedation and general anesthesia from benzodiazepines

Mechanism of action

- Flumazenil is a competitive antagonist of the benzodiazepine receptor in the central nervous system.

Indications

- Flumazenil should be used adjunctively with supportive care. Sedation can reoccur following ingestion of a benzodiazepine with a long half-life, requiring additional doses of flumazenil. In a suicidal overdose, it is rarely used due to the risk of potential co-ingestants. If no response occurs to a 5-mg cumulative dose, it is doubtful if the sedation is related to a benzodiazepine.

Contraindications

- Known hypersensitivity to flumazenil
- Co-ingestion of tricyclic antidepressants may precipitate ventricular dysrhythmias or seizures.
- Other mixed overdoses that can decrease the seizure threshold (ie, haloperidol, bupropion, lithium)
- Abrupt withdrawal in patients on maintenance therapy, such as for treatment of epilepsy, can precipitate seizures.
- Patients with increased intracranial pressure, because

the antidote may potentially alter cerebral blood flow

- It can produce withdrawal in the physically dependent patient.

Adverse effects

- Flumazenil has a wide margin of safety when not contraindicated.
- Side effects include agitation, sweating, headache, abnormal vision, dizziness, and pain at the administration site.
- Rarely reported: bradycardia, tachycardia, hypotension, or hypertension

Dosage

- IV administration (see Table 4)

Naloxone (Narcan)

Uses

- Reversal of opioid anesthesia
- Respiratory or central nervous system depression related to opioid toxicity
- Empiric administration in patients with altered mental status due to unknown etiology

Mechanism of action

- Naloxone is an opioid antagonist. Naloxone competes at three CNS opioid receptors (μ , κ , and δ) and leads to reversal of the depressive opioid effects.

Indications

- Opioids cause sedation, respiratory depression, hypotension, miosis, and analgesia. Because it has no agonist activity, naloxone will not worsen respiratory depression. The goal of therapy is to restore adequate spontaneous respirations. When administered, a patient should be monitored for respiratory rate changes and for opiate withdrawal symptoms (anxiety, hypertension, tachycardia, diarrhea, and seizure). To avoid withdrawal, use the lowest possible dose that maintains proper ventilation. The patient should be observed for respiratory depression once naloxone therapy is discontinued because the half-life of naloxone may be shorter than that of the opioid. If a patient is not responsive to 10 mg of naloxone, it is doubtful that an opioid is causing the respiratory depression.

Contraindications

- Known hypersensitivity
- Use with caution in the physically-dependent opioid patient.
- Use with caution in patients with preexisting cardiovascular disease or those receiving cardiotoxic drugs.

Adverse effects

- Use in an opiate-dependent patient can precipitate withdrawal.
- Withdrawal convulsions in a neonate can be life threatening.
- Hypertension and dysrhythmias occur more often with opioid reversal in postoperative patients with underlying cardiac and pulmonary complications.

Dosage

- The IV route is preferred in the emergency situation due to rapid onset of action within 1-2 minutes (Table 4).
- Naloxone has poor oral bioavailability.
- The intramuscular and subcutaneous routes have erratic absorption.

Pralidoxime or 2-PAM (Protopam)

Uses

- Severe organophosphate anticholinesterase insecticide or chem-bioterrorism nerve agent poisoning

Mechanism of action

- Pralidoxime dephosphorylates acetylcholinesterase and regenerates acetylcholinesterase activity.

Indications

- Severe organophosphate or nerve agent poisoning, in combination with atropine to resolve nicotinic (muscle and diaphragmatic weakness, fasciculations, muscle cramps) and central (coma, seizures) cholinergic manifestations; it is ineffective for organophosphates without anticholinesterase activity.
- Carbamate poisoning; use is controversial but recommended by some sources for severe cases.

Contraindications

- Hypersensitivity to pralidoxime

Adverse effects

- Tachycardia, dizziness, hyperventilation, and laryngospasm associated with rapid IV infusion
- Nausea, vomiting, diarrhea, bitter aftertaste, and rash after oral doses
- Blurred vision, diplopia
- Possible neuromuscular blockade (weakness) with high levels or in patients with myasthenia gravis

Dosage

- See Table 4 for intravenous doses.

4. Overview of Chem-Bioterrorism

- The world faces the growing threat of attacks with biological, chemical, explosive, and radiological weapons.
- Bioterrorism is the deliberate use of infectious biological agents to cause illness, and is categorized for risk by the Centers for Disease Control and Prevention (CDC).

* **Category A** agents are high priority agents that can be easily transmitted, result in high mortality rates, and have the potential for major public health impact. They include smallpox, anthrax, plague (*Yersinia pestis*), botulism, tularemia, and viral hemorrhagic fevers (filoviruses [eg, Ebola and Marburg] and arenaviruses [eg, Lassa and Machupo]).

* **Category B** agents include brucellosis, epsilon toxin of *Clostridium perfringens*, food safety threats (eg, *Salmonella* species, *Escherichia coli* O157:H7, *Shigella*), glanders (*Burkholderia mallei*), melioidosis (*Burkholderia pseudomallei*), psittacosis (*Chlamydia psittaci*), Q fever (*Coxiella burnetii*), ricin, staphylococcal enterotoxin B, typhus fever, viral encephalitis (alphaviruses [eg, Venezuelan equine encephalitis, eastern equine encephalitis, western equine encephalitis]), and water safety threats (eg, *Vibrio cholerae*, *Cryptosporidium parvum*).

* **Category C** agents include emerging infectious disease threats such as Nipah virus and hantavirus.

- See Table 5 for clinical features and suggested treatment for the most likely forms of category A diseases, and ricin, a previously weaponized and used category B agent.

- The mode of transmission for biological agents is essentially the same as with all other infectious diseases:

- * Aerosol (most common form for biological weapons)
- * Dermal contact
- * Injection
- * Food-borne
- * Water-borne

- Toxic chemicals that are used in warfare include nerve, blister/vesicant, blood, choking/lung/pulmonary, incapacitating, and riot control/tear- and vomit-inducing agents.

- See Table 6 for descriptions, symptoms, and treatment of the agents most likely to be used.
- Normally they are liquids or solids, often dispersed in the air in aerosols.

Table 5

Biological Agents That May Be Used in a Bioterrorism Attack

Biological agent	Clinical features	Treatment
Smallpox is caused by the variola virus; may be spread by aerosol or direct contact with infected persons/fluids	Early symptoms resemble a mild viral illness, with a 2- to 4-day nonspecific prodrome of fever and myalgias before rash onset. Pustules form, then scabs form and fall off, leaving pitted scars. When all the scabs have fallen off (in about 3 weeks), patients are no longer contagious. Smallpox rash is typically most prominent on the face and extremities, and lesions form at the same time. (By contrast, chickenpox rash is most prominent on the trunk and develops in successive groups of lesions over several days.)	No specific treatment. Vaccine is only preventive. The currently available vaccine (Dryvax® from Wyeth) is a live-virus preparation of vaccinia virus.
Anthrax is caused by <i>Bacillus anthracis</i> , a gram-positive spore-forming rod, and has three major forms: cutaneous, inhalation, and gastrointestinal; none are contagious	<p>Cutaneous: Begins as a small papule, progresses to a vesicle in 1-2 days, followed by a necrotic, normally painless ulcer. May have fever, malaise, headache, and regional lymphadenopathy.</p> <p>Inhalation: Initially resembles a viral illness with sore throat, mild fever, muscle aches, and malaise. Often has minimally productive cough, nausea or vomiting, and chest discomfort that may progress to respiratory failure and shock with meningitis frequently developing. In contrast to influenza, patients rarely have a runny nose and usually have an abnormal chest x-ray and high white blood cell count.</p> <p>Gastrointestinal: Causes severe abdominal or oropharyngeal distress followed by fever and signs of septicemia, bloody vomit, and diarrhea.</p>	Ciprofloxacin and doxycycline are FDA-approved for postexposure prophylaxis (PEP). Ciprofloxacin and doxycycline are FDA-approved for treatment. Amoxicillin may be considered if found to be sensitive to its action. Persons at risk for inhalation anthrax need 60 days of prophylactic antibiotics. The CDC recommends anthrax vaccine only for the military and similar high-risk personnel.

(continued)

- The CDC has recently added commonly available agents such as hydrofluoric acid, benzene, ethylene glycol (antifreeze), and metals like arsenic, mercury, and thallium to the threat list, although these are not listed as chemical warfare agents in other sources and are not detailed in Table 6.
- Radiological weapons involve nuclear radiation or radioactive materials with various radionuclides.
- Radionuclides can produce topical and systemic effects that may be immediate or delayed, depending upon the agent, route of exposure, and extent of exposure.
- Medical management of radiological emergencies and terrorist attacks is specific for the radionuclide. Guidance on treatment is available from the Radiation Emergency Assistance Center/Training Site (REAC/TS) at the Oak Ridge Institute for Science and Education. The emergency response phone number is 865-576-1005; ask for REAC/TS.

Program information is available at www.orau.gov/reacts.

- For example, the early use of stable iodine, taken as potassium iodide or sodium iodide tablets, can reduce the uptake of radioiodine by the thyroid. Many individuals near nuclear reactors will maintain a stock of stable iodine tablets in the event of a radioactive accident. Ingestion of stable iodine is of little value for other radionuclide exposures unless the radioactive constituents are unknown, as in a "dirty bomb."
- Prussian blue 500-mg capsules are approved for the treatment of patients with exposures to radioactive cesium (Cs-137) and thallium (Tl-201). It absorbs the radioactivity that is recirculated in the intestines and thereby enhances its elimination in the stool. The drug is available from the CDC.
- Calcium and zinc salts of diethylene triamine pentaacetic acid for intravenous infusion and aerosol neb-

Table 5

Biological Agents That May Be Used in a Bioterrorism Attack (continued)

Biological agent	Clinical features	Treatment
Plague , caused by <i>Yersinia pestis</i> , has several forms, with pneumonic plague being the most virulent	Clinical features of aerosolized pneumonic plague include fever, cough with mucopurulent sputum, hemoptysis, and chest pain with signs consistent with severe pneumonia 1-6 days after exposure. Septic shock and high mortality can occur within 2-4 days of symptom onset without early treatment. <i>Y. pestis</i> -caused bubonic plague is less likely to be weaponized.	Early treatment and PEP with streptomycin, gentamicin, doxycycline, ciprofloxacin, or chloramphenicol is advised. (Vaccine is ineffective for pneumonic plague.)
Botulism , caused by <i>Clostridium botulinum</i> , may be food-borne or air-borne	Clinical features include acute symmetric descending paralysis in a proximal to distal pattern, with prominent bulbar palsies such as diplopia, dysarthria, dysphonia, and dysphagia that typically present 12-72 hours postexposure, and respiratory dysfunction from respiratory muscle paralysis or upper airway obstruction without sensory deficits.	A supply of antitoxin is maintained and dispensed by the CDC. Most patients recover after supportive care, often with mechanical ventilation for weeks to months.
Tularemia , caused by <i>Francisella tularensis</i> , is one of the most infectious bacteria known	Inhalation exposure causes an abrupt onset of a nonspecific febrile illness beginning 3-5 days postexposure, with incipient pneumonia, pleuritis, and hilar lymphadenopathy. Without treatment, respiratory failure, shock, and death are possible. Like botulism and anthrax, tularemia is not contagious, so patients who have tularemia do not need to be isolated.	Prompt treatment with streptomycin, gentamicin, chloramphenicol, doxycycline, or ciprofloxacin advised, as is early PEP use of doxycycline or ciprofloxacin.
Viral hemorrhagic fevers (VHF): filoviruses and arenaviruses are most virulent, but all listed here are considered serious biological threats; exposure is via all routes, including direct and aerosol	<p>With filoviruses (Ebola and Marburg types), an abrupt onset of an undifferentiated febrile illness with high fever occurs 2-21 days after exposure. A maculopapular rash, prominent on the trunk, develops around 5 days later, with progressive bleeding symptoms such as petechiae, ecchymosis, disseminated intravascular coagulation, and hemorrhages.</p> <p>With arenaviruses (Lassa and multiple New World arenaviruses, including Machupo that causes Bolivian hemorrhagic fever) symptoms and onset are similar to filoviruses, but with a gradual onset of rash, hemorrhagic diathesis, and shock.</p> <p>Bunyaviruses cause Rift Valley fever (<1% develop hemorrhagic fever).</p> <p>Flaviviruses cause Yellow fever, Omsk hemorrhagic fever, and Kyasabur Forest disease. (Other VHFs exist, but they are not considered a serious bioterrorism risk.)</p>	The mainstay of treatment is supportive to maintain fluid and electrolyte balance, circulatory volume, and blood pressure. There are no FDA-approved antiviral drugs or vaccines.
Ricin , from castor beans, is cytotoxic via inhibition of protein synthesis; abrin is a similar toxalbumin agent	Within a few hours of inhalation, cough and dyspnea develop, with the lungs rapidly becoming severely inflamed and filled with fluid. Skin might turn blue from cyanosis or flush red. Ingestion causes internal bleeding of the stomach and intestines. Injection kills the closest muscles and lymph nodes before spreading to other organs. Death can occur within 36-48 hours of all types of exposure from multiple organ failure.	No antidote is available. The mainstay of treatment is supportive, varying with the route of exposure. If victims survive more than 5 days, survival is likely.

Table 6

Chemical Agents That May Be Used in a Chem-Bioterrorism Attack

Chemical agents (military name)	Clinical features	Treatment
Nerve agents. G agents: sarin (GB), soman (GD), tabun (GA), cyclohexyl sarin (GF); V agents: VX	These nerve agents are organophosphates that attach to and inhibit acetylcholinesterase at muscarinic and nicotinic receptors, causing cholinergic crisis with miosis, vomiting, diarrhea, excessive secretions (bronchial, lacrimal, dermal, nasal, and salivary), brady- or tachycardia, skeletal muscle fasciculations, paralysis, seizures, and respiratory failure. They are well absorbed through all routes of exposure. Symptoms occur within minutes after significant exposure, and up to 18 hours after liquid exposure.	Rapid, thorough decontamination. Antidotes include atropine to reverse muscarinic symptoms and pralidoxime early to restore acetylcholinesterase before permanent deactivation (aging) of the enzyme. Also give diazepam or lorazepam for seizures.
Blister agents. Mustards: sulfur gas (H), distilled (HD); mustard/T. nitrogen mustards: (HN-1, HN-2, HN-3); sesqui mustard; lewisites: (L, L-1, L-2, L-3); chloroarsines: (ED, MD, PD); mustard/lewisite combination: (HL); phosgene oxime: (CX)	Mustards are vesicants that cause blistering of the skin and mucous membranes on contact, damaging skin, eyes, and lungs. Damage is immediate but symptoms can be delayed 2-24 hours. Liquid forms are more likely to cause burns and scarring than gas. All forms are absorbed through the skin and distributed systemically. Nitrogen mustards cause bone marrow suppression in 3-5 days. Sulfur mustards have garlic, onion, mustard, or no odor. Nitrogen mustards can smell fishy, musty, soapy or fruity. <i>Lewisites and chloroarsines</i> are arsenical vesicants that cause immediate pain and damage to the eyes, skin, and respiratory tract, although lesions may take hours to form. After absorption, they cause increased capillary permeability leading to hypovolemia, shock, and organ damage. Lewisite smells like geraniums. Mustard/lewisite is lewisite combined with distilled mustard. <i>Phosgene oxime</i> is a readily absorbed urticant or nettle agent, causing immediate, painful corrosive and necrotic tissue damage. Does not cause blisters (but normally classified here). Disagreeable odor.	Sulfur and nitrogen mustards (thought to be alkylating agents that crosslink DNA strands) have no antidote. Avoiding contact or rapid thorough decontamination is only prevention. Treatment is supportive. Not usually fatal (sulfur type <5% fatal in World War I). No mustard in tissue or blister fluids. British anti-lewisite (BAL) is specific antidote for lewisite, used IM for systemic effects or topically as skin or eye ointment. Chloroarsine treatment is similar, except atropine sulfate ointment is used for eyes. No antidote exists for phosgene oxime. Rapid decontamination and supportive treatment used as for any corrosive agent.

(continued)

- ulization (Ca-DTPA and Zn-DTPA) are approved to treat patients who have been exposed to radionuclides that may be found in a "dirty bomb" such as plutonium, americium, and curium. The drugs form chelates with the radionuclides that are excreted in the urine. The drugs are available from the CDC.
- Health care professionals should have an awareness of the potential for biological terrorism, an appreciation for epidemiologic clues of a chem-bioterrorist event, and a basic understanding of the classes of agents that can be weaponized and their effects.
 - Pharmacists are in a unique position to quickly recognize community-wide patterns of symptoms, illness, and mortality in humans and animals that can be important clues to terrorist events.
 - The CDC advises that if citizens believe that they have been exposed to a biological or chemical agent, or if they believe an intentional biological threat will occur or is occurring, they should contact their local health department and/or local police or other law enforcement agency (eg, FBI). These agencies will notify the state health department and other response partners, per a pre-established notification list that channels to the CDC.

Table 6

Chemical Agents That May Be Used in a Chem-Bioterrorism Attack (continued)

Chemical agents (military name)	Clinical features	Treatment
Blood agents. Arsine: (SA); cyanide gases: hydrogen cyanide (AC), cyanogen chloride (CK); cyanide solids: potassium (KCN), and sodium (NaCN) cyanide	<i>Arsine</i> is a gas that causes nausea, vomiting, hemolysis, and secondary renal failure in 1-2 hours to 11 days. Garlic-like odor. Inhalation of highly concentrated <i>cyanide</i> causes increased rate and depth of breathing in 15 seconds, convulsions within 30 seconds, cessation of respiration in 2-4 minutes, and cessation of heartbeat in 4-8 minutes. Progress and severity of symptoms after ingestion or inhaling lower gas concentrations are slower and dose dependent. May have odor of bitter almonds or peach kernels (AC), with no odor or irritating, lacrimating properties like riot control agents (CK).	Arsines: symptomatic management of hemolysis, normally without chelation. Cyanides bind to cytochrome oxidase. Cyanide antidotes: (1) methemoglobin-forming agents like inhaled amyl nitrite (in civilian kits) and/or IV sodium nitrite free bound cyanide, restoring cellular ATP; (2) IV sodium thiosulfate (sulfur donor to convert cyanide to sodium thiocyanate). Fresh air, oxygen, supportive treatment.
Choking and pulmonary agents. Phosgene (CG), diphosgene (DP); also ammonia, chlorine (CL), hydrogen chloride, nitrogen oxide (NO), Teflon®, perfluoroisobutylene (PHIB), others	<i>Phosgene</i> gas causes eye, nose, throat, and pulmonary irritation, with serious pulmonary injury and edema delayed up to 48 hours, as it hydrolyzes to hydrochloric acid in moist conditions. New-mown-hay odor. <i>Phosgene</i> is the prototype agent in the group. Other agents cause immediate irritation with potential for more severe delayed effects. <i>Ammonia</i> hydrolyzes to caustic ammonium hydroxide. <i>Chlorine</i> (pungent, greenish gas) hydrolyzes to hydrochloric acid. <i>Perfluoroisobutylene</i> is a toxic pyrolysis product of <i>Teflon</i> . Nitrogen oxides are components of blast weapons or fire. Others include <i>red</i> (RP) and <i>white</i> phosphorus, <i>sulfur trioxide-chlorosulfonic acid</i> (FS), <i>titanium tetrachloride</i> (FM), and <i>zinc oxide</i> (HC).	<i>Phosgene</i> has no antidote. Good decontamination and symptomatic treatment needed. Treatment of other agents is similar as all agents in this class are gases with no antidotes (thorough, rapid decontamination with fresh air is best initial management, with thorough flushing of exposed eyes and skin and symptomatic treatment).
Incapacitating agents	Contains a variety of fast-acting central nervous system and respiratory depressants, often with hallucinogenic properties. CDC list includes <i>BZ/agent 15</i> (glycolate anticholinergic), <i>cannabinoids</i> , <i>fentanyl</i> s and other opioids, <i>LSD</i> , and <i>phenothiazines</i> .	Management is decontamination with supportive treatment and antidotes should be used when they exist (physostigmine for anticholinergics, naloxone for opioids).
Riot control and tear gases	Lacrimators include <i>chloroacetophenone</i> (CN) in several solvents, <i>chloropicrin</i> (PS), <i>bromobenzylcyanide</i> (CA), CR, and CS gases.	Treatment is symptomatic after decontamination. No antidotes are available.
Vomiting agents	Includes <i>adamsite</i> (DM), <i>diphenylchloroarsine</i> (DA) and <i>diphenylcyanoarsine</i> (DC). Rapidly incapacitating, irritant gases.	Symptomatic measures for sneezing, coughing, and vomiting (eg, antiemetics).

- The CDC maintains the Strategic National Stockpile to ensure the availability and rapid deployment of life-saving pharmaceuticals, antidotes, other medical supplies, and equipment necessary to counter nerve agents, biological pathogens, and chemical agents. The SNS program stands ready for immediate deployment to any U.S. location in the event of a terrorist attack using a biological toxin or chemical agent directed against a civilian population. A limited stock of drugs to treat nerve agents (ChemPack) has been deployed to EMS and hospital sites throughout the U.S. and is maintained by the CDC. Further information is available at the CDC website (www.cdc.gov).
- Pharmacists should consider volunteering in their communities to assist with emergency preparedness. Roles in mass dispensing and vaccination clinics, strategic national stockpile deployment, and general disaster medical relief are possible opportunities. Contact the local health department or emergency medical services agency.
- Essential steps to volunteering for emergency preparedness include reaching an understanding with family and employer, registering as a volunteer and identifying skills to contribute, obtaining security credentials, participating in training, and doing whatever it takes when needed.

5. Key Points

- Medications are the most common cause of poisoning morbidity and mortality. Any chemical can become toxic if too much is taken in relation to body weight and tolerance. A great number of poisonings occur in young children, but most fatalities occur in adults.
- Several approaches can minimize the risk of unintentional childhood poisonings (eg, safety latches, proper storage, following label instructions), but the proper use of child-resistant containers ("safety caps") is one of the most effective means. As part of the Poison Prevention Packaging Act of 1970, pharmacists are required to dispense oral prescription drugs (with certain exceptions such as nitroglycerin and oral contraceptives) in child-resistant containers unless the patient or prescriber indicates the desire for a non-safety cap.
- Immediate first aid for a poison exposure can minimize potential toxic effects, and involves water and fresh air, depending on the route of exposure. Contact a poison center immediately through the nationwide access number (1-800-222-1222) to determine first aid or whether a poisoning emergency exists.
- The use of drugs to decrease the absorption of drugs from the gastrointestinal tract after a poisoning or overdose is in a state of change. Ipecac syrup, an orally administered emetic, has questionable effectiveness and its use is generally now avoided. It should not be used (1) when the person exhibits sleepiness, coma, or seizures; (2) when agents such as caustics, aliphatic hydrocarbons, fast-acting agents that produce coma or seizures (eg, tricyclic antidepressants, clonidine, strychnine, and hypoglycemic agents) have been ingested; (3) when the ingestion was greater than 1 hour ago; or (4) there is an obvious need for hospital referral. Cathartics such as magnesium citrate are not routinely used. Activated charcoal, an orally administered adsorbent, is often the only treatment necessary if the toxin can be adsorbed and it is used within 1-2 hours of ingestion. It should be avoided in ingestions of aliphatic hydrocarbons and caustics and in patients with absent bowel sounds, and it is not useful with heavy metals (sodium, lithium, iron, or lead) or simple alcohols. Whole-bowel irrigation, with products such as CoLyte and GoLYTELY, can be considered if the toxin is poorly adsorbed and its presence in the gastrointestinal tract is likely. Other hospital-based therapies include supportive and symptomatic care, multiple doses of activated charcoal (to enhance systemic elimination when appropriate), hemodialysis (to enhance systemic elimination when appropriate),

and use of antidotes (to antagonize or reverse toxic effects when indicated).

- Substance abuse often leads to acute and chronic toxicity from a variety of medications, commercial products, and illicit agents. The management of acute toxicity from substance abuse typically follows the same general approaches as those for poisoning and overdose. A challenge faced in many acute drug overdose episodes is determining the agents taken and possible adulterants or contaminants. Chronic abuse can lead to dependence and withdrawal symptoms upon stopping use.
- There are few antidotes available relative to the large number of potential poisons. The use of an antidote is usually an adjunct to conventional and supportive therapies. Many hospitals have an insufficient stock of antidotes.
- Acetylcysteine (Mucomyst, Acetadote) is a glutathione substitute in the metabolism of the acetaminophen toxic reactive metabolite. It is most effective if given orally within 10 hours of an acetaminophen overdose in preventing hepatotoxicity, and may also help later to minimize hepatic injury once it has begun. Oral (Mucomyst) and intravenous (Acetadote) preparations are available.
- Atropine is used to treat the muscarinic effects (bronchorrhea, bradycardia, etc.) produced by organophosphate and carbamate insecticides and anticholinesterase nerve gas agents by competing with acetylcholine for binding at muscarinic receptors in the nervous system.
- Pralidoxime (Protopam) reactivates the enzyme acetylcholinesterase by dephosphorylation and allows metabolism of accumulated amounts of acetylcholine produced by enzyme inhibition from exposures to anticholinesterase nerve gas agents and organophosphate and carbamate insecticides.
- Digoxin immune Fab (DigiBind, DigiFab) is a specific antibody for digoxin, but it exhibits some cross reactivity with other digoxin-like compounds. It is an ovine derived antigen-binding fragment reserved for the treatment of life-threatening symptoms of digoxin overdose (eg, bradycardia, ventricular arrhythmias, second- and third-degree heart block, and hyperkalemia).
- Flumazenil (Romazicon) is a competitive antagonist of benzodiazepines at the benzodiazepine receptor in the central nervous system (CNS). It is used in the treatment of severe CNS and respiratory depression that may occur with benzodiazepines when they are used as an anesthetic or taken as an overdose. Seizures may occur when flumazenil is administered to patients with co-ingestants of tricyclic antidepressants, drugs that lower the seizure threshold, and in patients requiring benzodiazepines for seizure control.
- Administration of naloxone (Narcan), a competitive antagonist of opiate binding at the opioid receptors in the CNS, reverses the CNS and respiratory depression of opiate toxicity. Naloxone may precipitate withdrawal symptoms in opiate-dependent patients.
- Bioterrorism is the deliberate use of infectious biological agents to cause illness. High-priority agents can be easily transmitted, result in high mortality rates, and have the potential for major public health impact. They include smallpox, anthrax, plague (*Yersinia pestis*), botulism, tularemia, and viral hemorrhagic fevers (eg, Ebola, Marburg, Lassa, and Machupo).
- These toxic chemicals are used in warfare and may be used in an attack:
 - * Substances that act on nerves (eg, anticholinesterase agents such as sarin)
 - * Substances that are blistering/vesicants (eg, mustard agents and lewisites)
 - * Substances that act on blood (eg, arsine and cyanide)
 - * Substances that act on the pulmonary system (eg, phosgene, chlorine, and ammonia)
 - * Substances that are incapacitating (eg, fast-acting CNS depressants or hallucinogens)
 - * Substances that can also be used in riot control (eg, various lacrimating agents such as chloroacetophenone [CN]) and vomiting agents (eg, adamsite).
- Health care providers need to have an awareness of the potential for terrorism, an appreciation for epidemiologic clues of a chem-bioterrorist event, and a basic understanding of the classes of agents that can be weaponized and their effects. The Centers for Disease Control and Prevention (CDC) maintains the Strategic National Stockpile that can be rapidly deployed to communities to ensure the availability and rapid deployment of life-saving pharmaceuticals, antidotes, other medical supplies, and equipment necessary to counter nerve agents, biological pathogens, and chemical agents.

6. Questions and Answers

1. Flumazenil is contraindicated in which case?
 - A. A patient with QRS widening with a known ingestion of Elavil®
 - B. A patient who was previously given flumazenil who complains of abnormal vision and dizziness
 - C. A patient with known use of cocaine
 - D. A and C
 - E. A and B
2. A patient is brought to the emergency department. She is experiencing CNS and respiratory depression due to a suspected ingestion of her sister's MS Contin®. You recommend supportive care and the administration of
 - A. flumazenil
 - B. naloxone
 - C. lorazepam
 - D. flumazenil and Narcan
 - E. pyridoxine
3. A policeman presents to the emergency room with a rash, fearing he was exposed to a biological weapon several days before the rash appeared. You notice the rash is forming pustules and is most prominent on the face and extremities. The patient says the rash developed all at once. He has possibly contracted
 - A. smallpox
 - B. chickenpox
 - C. anthrax
 - D. tularemia
 - E. none of the above
4. What is the recommended treatment for the likely disease?
 - I. Supportive; there is no specific treatment
 - II. Ciprofloxacin
 - III. Doxycycline
 - A. II or III
 - B. II and III
 - C. I only
 - D. II only
 - E. III only
5. The currently available prevention for smallpox is
 - I. Dryvax® from Wyeth
 - II. a live-virus preparation of the vaccinia virus
 - III. avoidance of direct contact with infected persons and their body fluids
 - A. I only
 - B. I and II only
 - C. II and III only
 - D. I, II, and III
 - E. No vaccine is currently available
6. A patient presents with a black, necrotic, painless skin lesion on her arm. She also complains of fever, malaise, headache, and swelling of her underarm lymph nodes. The possible biological agent responsible for these symptoms is
 - A. hemorrhagic fever virus
 - B. anthrax
 - C. botulism
 - D. tularemia
 - E. arsine
7. The recommended antibiotic treatment of the infection in Question 6 may include
 - A. ciprofloxacin
 - B. doxycycline
 - C. amoxicillin
 - D. all of the above
 - E. supportive; there is no specific treatment
8. Inhalation exposure to the agent in Question 6 requires:
 - A. postexposure prophylaxis with ciprofloxacin, doxycycline, or penicillin G procaine for 60 days
 - B. immediate vaccination of civilian personnel
 - C. early treatment with streptomycin or gentamicin
 - D. early treatment with ribavirin
 - E. none of the above
9. A cab driver presents to the emergency department with vomiting, diarrhea, sweating, salivation, moist rales, bradycardia, muscle tremor, and weakness. He reports inhaling a mist dropped from a low-flying plane several hours earlier. You also note that he has miosis and his respiratory difficulty is increasing rapidly. The likely mechanism of toxicity of the poison is
 - A. inhibition of protein synthesis
 - B. binding of the agent to cytochrome oxidase

- C. inhibition of acetylcholinesterase
 - D. an alkylating agent cross-linking DNA strands
 - E. none of the above
10. The recommended initial management of the symptoms in Question 9 includes all EXCEPT
- A. immediate decontamination of skin and eyes
 - B. disposal of contaminated clothes
 - C. British anti-lewisite
 - D. atropine
 - E. pralidoxime
11. The patient in Question 9 deteriorates and develops seizures. You recommend:
- A. phenytoin
 - B. diazepam
 - C. lithium
 - D. Dryvax
 - E. all of the above
12. Which one of the following conditions or situations is not a contraindication to the use of ipecac syrup?
- A. High blood pressure controlled with drug therapy
 - B. Seizures shortly before administration
 - C. Unresponsive to verbal commands
 - D. A corrosive agent has been ingested
 - E. A and C
13. Which one of the following is an effect of activated charcoal?
- A. Promotes dissolution of tablets
 - B. Minimizes drug absorption from the gastrointestinal tract
 - C. Increases urinary flow
 - D. Enhances systemic elimination of certain drugs
 - E. B and D
14. Which one of the following drugs is useful in the treatment of acetaminophen poisoning?
- A. Acetylcysteine
 - B. Dimercaprol
 - C. Pralidoxime
 - D. Atropine
 - E. Dryvax
15. Digoxin immune Fab is used to treat which one of the following signs or symptoms of digoxin poisoning?
- A. Hypokalemia
 - B. Diplopia
 - C. Ventricular tachycardia
 - D. Second-degree heart block unresponsive to atropine
 - E. C and D
16. How does crack cocaine differ from pharmaceutical cocaine?
- A. Crack is more stable under heat and can be smoked
 - B. Pharmaceutical cocaine is the hydrochloride salt
 - C. Crack is the free-base form of cocaine
 - D. Crack may be contaminated with other substances
 - E. All of the above

Answers

1. D. Flumazenil is contraindicated in all patients who have ingested a tricyclic antidepressant and have cardiac symptoms, as its use could cause ventricular dysrhythmias. It is not recommended in mixed overdose where the co-ingested drug can cause a seizure (ie, cocaine). Answer B is a list of associated adverse effects with its administration; they are not contraindications.
2. B. Naloxone is an opioid antagonist.
3. A. See Table 5. Smallpox is the most likely agent. The agent causes a pustular rash to form that is typically most prominent on the face and extremities, and lesions form at the same time. Chickenpox rash is most prominent on the trunk and develops in successive groups of lesions over several days. Anthrax forms painless necrotic lesions. Tularemia causes a nonspecific febrile illness that rapidly develops into pneumonia.
4. C. See Table 5. Smallpox has no specific treatment. Ciprofloxacin and doxycycline are used in the management of anthrax, plague, and tularemia.
5. D. See Table 5. All characteristics are correct.
6. B. See Tables 5 and 6. Anthrax forms a painless, necrotic ulcer. Hemorrhagic fever viruses cause

a rash that develops into petechiae, ecchymosis, hemorrhages, and other bleeding symptoms. Botulism causes a symmetric descending paralysis. Tularemia causes a nonspecific febrile illness that rapidly develops into pneumonia. Arsine is a chemical agent that causes nausea, vomiting, hemolysis, and secondary renal failure. Arsine is produced when water comes into contact with metallic arsenide or when acids come into contact with metallic arsenic or arsenical compounds. The mechanism of hemolysis is not specifically known, but the most recent mechanism postulated involves a direct arsine-hemoglobin interaction that forms arsenic metabolites, causing direct alteration of the erythrocyte cell membrane.

7. **D.** All of the above. See Table 5. Ciprofloxacin, doxycycline, and amoxicillin are FDA-approved for treatment of anthrax. These agents can be used separately or in combination, depending on symptoms and the patient's sensitivity to the agents. Antimicrobial resistance to ciprofloxacin has been growing rapidly due to widespread overuse after the anthrax mail episodes in 2002. At the time of this review, doxycycline is recommended by the CDC (but not by all sources) as the preferred initial treatment unless the patient is intolerant to the agent.
8. **A.** See Table 5. Persons at risk for inhalational anthrax need 60 days of prophylactic antibiotics. Ciprofloxacin, doxycycline, and penicillin G procaine are FDA-approved for postexposure prophylaxis (PEP). Anthrax vaccine adsorbed (AVA) is currently recommended by the CDC only for high-risk personnel (such as lab personnel working with the agent) and the military, not the civilian population. Streptomycin and gentamicin are among the suggested treatments for pneumonic plague. Ribavirin is a potential treatment for some hemorrhagic fever viruses.
9. **C.** See Table 6. The symptoms exhibited are classically cholinergic and the likely chemical agents causing these symptoms are organophosphates like the nerve agents or possibly organophosphate pesticides. Both can be spread by low-flying planes. Inhibition of protein synthesis is the mechanism of toxicity of ricin or abrin. Cyanides bind to cytochrome oxidase, interrupting normal cellular respiration and causing rapid convulsions. Blister agents like the sulfur and nitrogen mustards are thought to be alkylating agents that cross-link DNA strands, separating dermal layers in the skin and causing fluid-filled blisters to form.
10. **C.** British anti-lewisite is a specific antidote for lewisite. See Table 6. It also is used as a chelator for treatment of acute arsenic, inorganic or elemental mercury, gold, and other heavy metal poisonings. See Table 4. The other measures are treatments for organophosphate agents. Good decontamination and disposal of contaminated clothes (especially leather) are needed, because organophosphates are well absorbed across the skin, through the lungs, and via ingestion, essentially all possible routes of exposure. Atropine is used for muscarinic symptoms (miosis, nausea, vomiting, diarrhea, urination, bradycardia, and excessive bronchial, lacrimal, dermal, nasal, and salivary secretions), and pralidoxime is used with atropine to resolve severe organophosphate symptoms (such as those from nerve agents), including nicotinic symptoms of muscle weakness and cramps, fasciculations, tachycardia, and CNS symptoms such as coma and seizures.
11. **B.** See Table 6. Recommended treatment for seizures due to organophosphate agents is either diazepam or lorazepam. Phenytoin is a seizure medication, but benzodiazepines (then barbiturates if benzodiazepines fail) are generally preferred over phenytoin for the control of overdose- or withdrawal-related seizures. Lithium is not a seizure medicine, and in fact may cause seizures with elevated blood concentrations. Dryvax is a vaccine for smallpox.
12. **A.** Controlled high blood pressure is not a problem with the use of ipecac syrup, but the other situations are clear contraindications due to potential aspiration (seizures, unresponsiveness) and additional esophageal burns upon vomiting up gastric contents (corrosive).
13. **E.** Activated charcoal adsorbs chemicals on contact and prevents their absorption into the bloodstream. For certain drugs (eg, phenobarbital, theophylline), multiple doses of activated charcoal can promote the back diffusion of drugs across the intestinal capillary bed into the lumen of the gut, trap it there, and promote its elimination. The elimination half-life can be decreased by as much as one-half.
14. **A.** Acetylcysteine prevents the development of liver injury from acetaminophen if given early

after ingestion and it may help minimize the effects of hepatotoxicity after it has occurred in some cases.

15. E. Digoxin immune Fab is reserved for life-threatening symptoms due to its profound effects, scarcity, and high cost. Most serious cases of digoxin poisoning have normal or high potassium concentrations due to the digoxin's interference with the sodium-potassium ATPase pump.
16. E. All are differences between the two forms of cocaine.

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36. Anemias

1. Disease Overview

Anemia is a reduction in the number of red blood cells (RBCs) or the hemoglobin content of the blood. The clinical consequences of anemia are related to the degree of hemoglobin reduction and the rate of onset.

Etiology

Anemia can be classified by the degree of hemoglobin reduction and the rate of onset. The clinical consequences of anemia are related to the degree of hemoglobin reduction and the rate of onset. The clinical consequences of anemia are related to the degree of hemoglobin reduction and the rate of onset.

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Pathophysiology

The clinical consequences of anemia are related to the degree of hemoglobin reduction and the rate of onset. The clinical consequences of anemia are related to the degree of hemoglobin reduction and the rate of onset.

1. Disease Overview

- Anemia is a reduction in red cell mass that decreases the oxygen-carrying capacity of the blood. The focus of this chapter will be on iron deficiency anemia, megaloblastic anemias, and anemia of renal failure.

Epidemiology

- Approximately 3.4 million Americans have anemia.
- Anemia is more common in women than men.
- 75% of anemias are a result of iron deficiency, anemia of chronic disease, and acute bleeding. Iron deficiency anemia is the most common anemia, accounting for 25% of all cases.
- The remaining 25% of anemias are a result of bone marrow damage, decreased erythropoiesis, and hemolysis.

Classification

- The most common way to classify anemias is by the morphology (shape/structure) of the red blood cells.

Macrocytic (large cell)

- Megaloblastic anemia
- Vitamin B₁₂ deficiency
- Pernicious anemia
- Folic acid deficiency

Normochromic, normocytic

- Acute blood loss
- Bone marrow failure
 - * **Aplastic anemia:** marrow fails to produce all three types of blood cells, which results in anemia, neutropenia (decreased white blood cells), and thrombocytopenia (decreased platelets). About half of these cases are thought to be caused by drugs or chemicals. Examples of drugs causing aplastic anemia include chloramphenicol, felbamate, and phenytoin.
- Hemolysis
 - * Genetically inherited: enzyme deficiencies such as glucose-6-phosphate dehydrogenase (G6PD) deficiency. Red blood cells deficient in G6PD are susceptible to hemolysis when exposed to certain oxidant drugs. Examples of such drugs are dapson, sulfamethoxazole, and nitrofurantoin.
 - * Membrane abnormalities of RBCs such as in hereditary spherocytosis
- Immunologic destruction, such as in autoimmune diseases
 - * Anemia of chronic disease

- * Renal failure
- * Endocrine disorders
- * Autoimmune diseases

Hypochromic (low hemoglobin content), microcytic (small cell)

- Iron deficiency anemia
- Genetic anomalies
 - * Sickle cell anemia
 - * Thalassemia

Clinical Presentation

- The signs and symptoms of anemia depend on the time course over which the anemia developed, and the severity of RBC depletion.
- An anemia developed over a long period of time may be asymptomatic in beginning stages, and then progress to fatigue, malaise, headache, slight exertional dyspnea, angina, pallor, or loss of skin tone.
- A patient with acute anemia, such as from recent blood loss, may present with tachycardia, shortness of breath, or lightheadedness.
- Many of the signs and symptoms of anemia are secondary to tissue hypoxia. In the case of hypoxia, blood supply is shunted to life-sustaining organs (brain, heart, and kidney) and away from non-vital organs, such as extremities or nail beds, which results in pallor of the skin.
- The various types of anemia have additional signs and symptoms which will be discussed in further detail in the diagnosis section.

Pathophysiology

Iron deficiency anemia (IDA)

- IDA is the most common anemia, accounting for a quarter of all anemia cases.
- IDA is caused by iron store depletion resulting from:
 - * Inadequate oral intake of iron (especially animal protein)
 - * Increased iron demands
 - Pregnancy/lactation
 - Rapid growth: infancy/adolescence
 - Elderly
 - * Blood loss
 - Menstruation or postpartum blood loss
 - Trauma
 - GI ulcers
 - * Inadequate absorption
 - Medication (eg, tetracyclines)
 - Gastrectomy
 - Enteritis
 - Persistent diarrhea
 - * Disease states
 - Carcinomas

- Rheumatoid arthritis
- Hemoglobin is composed of iron (heme) and proteins (globin).
- Lack of iron results in reduced hemoglobin synthesis. The RBCs produced in these conditions are:
 - * Hypochromic
 - Decreased concentration of hemoglobin
 - * Microcytic
 - RBCs spend longer in marrow awaiting proper hemoglobin synthesis. This results in more cell divisions, which produces a smaller cell.

Megaloblastic anemias

- These anemias are caused by either a deficiency in or an inability to use vitamin B₁₂ (cobalamin) or folic acid.
- Vitamin B₁₂ deficiency:
 - * Decreased intake (strict vegetarians)
 - * Decreased absorption
 - Vitamin B₁₂ requires gastric intrinsic factor to be absorbed. The lack of intrinsic factor results in **pernicious anemia**. This can be inherited or acquired by gastrectomy.
 - Achlorhydria
 - * Inadequate utilization of vitamin B₁₂ due to protein deficiencies
- Folic acid deficiency
 - * Decreased intake (especially in alcoholics, indigent, elderly)
 - * Decreased absorption (Crohn's disease, celiac disease, drugs)
 - * Increased demands (pregnancy, growth spurts, malignancy, long-term hemodialysis)
 - * Drug induced (methotrexate, phenytoin)
- Vitamin B₁₂ and folic acid are both necessary for the RNA and DNA required for cell division during the development of RBCs. Since the RNA and DNA synthesis is impeded, cell divisions are skipped, resulting in an abnormally large cell (macrocytic anemia).

Anemia of renal failure

- The primary reason that patients with renal failure are anemic is due to the lack of production of erythropoietin (EPO). EPO is a hormone produced primarily (90%) in the kidneys that stimulates the synthesis and differentiation of erythroid progenitor cells (precursors to RBCs).
- The uremic environment of chronic renal failure decreases the lifespan of RBCs.
- Folic acid deficiency can also develop due to the increased demands of folic acid during synthesis of RBCs. Additionally, folic acid can be removed during hemodialysis.

- Patients with chronic renal failure can become iron deficient due to loss of iron and blood during dialysis.

Diagnostic Criteria

If anemia is suspected, the following blood tests should be performed:

- Complete blood cell count (CBC) which includes:
 - * Hemoglobin (Hgb)
 - * Hematocrit (Hct)
 - * RBC
 - * Red cell indices:
 - Mean corpuscular volume (MCV) is a measure of size of RBCs.
 - Mean corpuscular hemoglobin (MCH) is a measure of weight of hemoglobin in a RBC. MCH will be low in the case of microcytosis or hypochromia.
 - Mean corpuscular hemoglobin concentration (MCHC) is a measure of weight of hemoglobin, but is more useful than MCH because it can distinguish between low hemoglobin and a small cell. MCHC will only be low in the case of hypochromia.
 - Platelets
 - Reticulocyte count (pre-RBCs)
- * Red cell morphology
- * Serum iron, total iron binding capacity (TIBC), transferrin saturation, ferritin
- * Bilirubin (by-product of RBC destruction)

Other tests:

- Test stool for blood
- Peripheral blood smear
- Thorough history and physical examination

Iron deficiency anemia

Blood work

- The first level to decrease will be ferritin (storage form of iron).
- The iron level will be low.
- TIBC increases. This is a measure of the amount of binding space left on transferrin (transport protein of iron). Less iron in the blood translates to more space available on the transferrin molecule.
- As the iron deficiency progresses, there will be a decrease in hemoglobin (iron is a component of hemoglobin). Therefore, this is a hypochromic anemia.
- The hematocrit will also eventually fall.
- MCV will be decreased, which indicates microcytosis.
- MCH and MCHC will be decreased, which indicates decreased hemoglobin.

- Blood smear will show a microcytic, hypochromic cell.

Specific signs and symptoms

- In addition to the general signs and symptoms listed previously for anemia, these additional symptoms may be present in severe IDA:
 - * Koilonychia (spoon-shaped nails)
 - * Angular stomatitis or glossitis
 - * Pica (craving for substances low in iron, such as ice, clay, and cornstarch)

Megaloblastic anemias

Blood work

- Decreased Hct and Hgb
- Decreased RBC
- Elevated MCH, which indicates a macrocytosis
- The iron level, TIBC, and reticulocyte count will be normal.

Vitamin B₁₂ deficiency

- The serum B₁₂ level will be decreased.
- Positive Schilling test indicates pernicious anemia. (The Schilling test determines absorption of vitamin B₁₂ by measuring the amount of radioactive B₁₂ excreted in urine.)
- Additional signs and symptoms:
 - * Loss of vibratory sensation in lower extremities
 - * Ataxia or vertigo
 - * Glossitis
 - * Muscle weakness
 - * Neuropsychiatric abnormalities
 - Irritability or emotional instability
 - Dementia
 - Psychosis

Folic acid deficiency

- Folate level will be decreased.
- Overall, this is very similar to vitamin B₁₂ deficiency anemia, except with the absence of neurological symptoms.

Anemia of renal failure

- As the name implies, this anemia occurs in patients with chronic renal failure (CRF).
- Before diagnosis, other causes must be ruled out (eg, blood loss).
- CBC will reveal a normochromic, normocytic anemia.

Treatment Principles and Goals

Iron deficiency anemia

Goals

- To normalize Hgb and Hct
 - * 2-g/dL increase in Hgb in 3 weeks
 - * 6% increase in Hct in 3 weeks
 - * Reticulocytosis will usually occur within 1 week.
 - * If these indices do not improve within these time frames, the diagnosis should be re-evaluated.
- Replete iron stores
 - * Although Hgb and Hct will return to normal within 1-2 months, iron therapy should continue for 3-6 months after Hgb is normalized to replete total body iron stores.

Megaloblastic anemias

Goals of vitamin B₁₂ replacement

- Hgb should rise within 1 week.
- If neurologic symptoms were present, they should improve within 24 hours. However, if vitamin B₁₂ deficiency is long-standing, symptoms may not be completely relieved for several months.

Goals of folic acid replacement

- RBC morphology will correct within 1-2 days.
- Hgb starts to normalize within 10 days.
- Hct will return to normal levels within 2 months.
- Maintenance administration of folic acid should continue for as long as nutritional intake of folic acid is a problem.

Anemia of Renal Failure

Goal

- Initial therapy goal is to reach a target Hct of 36% through a slow, steady increase (usually within 2-4 months).
- Medication doses of epoetin should be titrated to maintain Hct in the range of 30%-36%.

2. Drug Therapy

Iron Deficiency Anemia

- Treatment consists of iron supplementation through therapeutic iron preparations (200 mg of elemental iron per day in 2-3 divided doses) (Table 1). Iron is best absorbed in the reduced (ferrous) form. Ferrous sulfate salt is the most common, which is 20% elemental iron. Therefore ferrous sulfate 325 mg tid will adequately treat iron deficiency.
- IV iron preparations should be used only in cases of:
 - * Iron malabsorption
 - * Oral noncompliance
 - * Refusal of blood transfusion
 - * IV iron formulations are often used in patients with chronic renal failure who require dialysis along with human recombinant erythropoietin therapy. There are three types of IV products available in the U.S.:
 - Iron dextran (InFeD[®])
 - Sodium ferric gluconate (Ferrlecit[®])
 - Iron sucrose (Venofer[®])
- A fourth IV iron product, ferumoxytol, is currently in phase III clinical trials

Mechanism of action

- Iron supplementation corrects the iron deficiency, and enables Hgb to be synthesized at normal levels.

Patient instructions

- Take 1-2 hours prior to a meal (on an empty stomach)
- If you are not able to tolerate iron on an empty stomach, you may administer with a small snack

Table 1

Drugs Used to Treat Iron Deficiency Anemia

Generic name (trade name)	Elemental		Fe content (mg)
	Fe (%)	Dose (mg)	
Ferrous sulfate (Feosol [®] , Fer-in-Sol [®])	20	325	65
Ferrous gluconate (Fergon [®])	12	300	35
Ferrous fumarate (Femiron [®] , Fumerin [®] , Feostat [®])	33	300	99

(crackers), but try to avoid dairy products or tea. (Food can decrease the absorption of iron by 50%.) Take with orange juice if possible (can double absorption).

- Keep out of reach of children. Iron is a major cause of ingestion deaths in children.
- Take iron 1 hour before or 3 hours after any antacids.
- There are medications that interact with iron. Please ask your physician or pharmacist before taking any new medications in combination with iron.
- You may take OTC docusate if constipation occurs.

Adverse drug effects

- The oral formulation has primarily GI effects:
 - * Dark colored stools
 - * Constipation or diarrhea
 - * Nausea and/or vomiting
- IV formulations:
 - * Injection site reactions
 - * GI: diarrhea, nausea
 - * Hypotension
 - * Allergic reactions, including anaphylaxis
 - The risk of anaphylaxis is greatest with iron dextran. The patient must be administered a test dose before using this agent.

Drug interactions

- Antibiotics (tetracycline, quinolones): iron binds to these antibiotics, preventing their absorption.
- Antacids: iron needs an acidic environment for optimal absorption.

Monitoring parameters

- Is there an increase in reticulocytes, Hgb, and Hct?
- Tolerability of iron (will influence compliance)
- Is patient symptomatically improving?

Kinetics

- Bioavailability is increased in acidic environment and decreased by food.

Megaloblastic Anemias

- Vitamin B₁₂ should be administered orally if absorption is not an issue.
 - * Recommended Daily Intake = 2 mcg daily
- Vitamin B₁₂ deficiency is usually corrected through IM vitamin B₁₂ (cyanocobalamin) supplementation as follows (pernicious anemia):
 - * 1000 mcg IM every day for 1 week, then
 - * 100-1000 mcg IM every week for 4 weeks, then
 - * 100-1000 mcg IM every month thereafter for prevention
 - * Although IM B₁₂ is still more frequently used, patients with deficiency states may be supple-

mented orally in very high doses, such as 1000-2000 mcg per day.

- * People choosing vegan diets should be supplemented with 1000 mcg (1 mg) B₁₂ daily.

Mechanism of action

- Vitamin B₁₂ supplementation allows for normal synthesis of the RNA/DNA involved in the synthesis of RBCs.

Patient instructions

- Counsel patient or family member(s) on sterile injection techniques and needle disposal if injections are given at home.

Adverse drug effects

- Increased synthesis of reticulocytes can cause hyperuricemia or hypokalemia.
- Sodium retention
- Increased synthesis of RBCs can produce an expansion of the intravascular volume, which can increase cardiac output causing angina or dyspnea.
- Itching: 1%-10%
- Diarrhea: 1%-10%
- Anaphylaxis: <1%

Monitoring parameters

- Monitor CBC. Is there an increase in Hgb?
- Is the patient symptomatically improving (especially neurologic symptoms, if present)?
- Potassium level

Kinetics

- Absorption: intrinsic factor must be present for vitamin B₁₂ to be transported across the GI mucosa.
- Vitamin B₁₂ is bound in blood to transcobalamin II and converted in tissues to active coenzymes methylcobalamin and deoxyadenosylcobalamin.

Folic Acid Deficiency Anemia

- Folic acid deficiency anemia is corrected by supplementing folic acid 1 mg daily for 4 months. Once the underlying cause of deficiency is corrected, folic acid may be discontinued. Long-term folate administration is necessary if the cause is not corrected, such as in hemodialysis or alcoholism.

Mechanism of action

- Folic acid supplementation allows for normal synthesis of the RNA and DNA involved in the synthesis of RBCs.

Patient instructions

- Stress compliance with regimen.

- Women of childbearing age should be counseled to take a multivitamin containing folic acid regardless if an anemia is present or not (to prevent neural tube birth defects).

Adverse drug effects

- Less than 1% of patients have allergic reactions to folic acid.

Drug interactions

- Folic acid may increase phenytoin metabolism.
- Phenytoin, primidone, sulfasalazine, para-aminosalicylic acid, and oral contraceptives may decrease folic acid concentrations.
- Chloramphenicol may blunt response to folic acid.

Monitoring parameters

- Is the RBC morphology normalizing?
- Are the Hgb and Hct normalizing?
- Monitor patient compliance.

Kinetics

- Folic acid is a water-soluble B vitamin absorbed in the small intestine with C_{max} at 1/2-1 hour.

Anemia of Renal Failure

Recombinant human erythropoietin

- Since the primary cause of anemia in renal failure is decreased (EPO) synthesis, the drug of choice for this type of anemia is recombinant human EPO (epoetin alfa, trade names Procrit® or Epogen®).
- Epoetin is indicated in the treatment of anemia associated with chronic renal failure, including dialysis and non-dialysis patients. It is indicated to elevate or maintain the RBCs and to decrease the need for transfusions in these patients. (Non-dialysis patients with symptomatic anemia considered for therapy should have a hematocrit <30%.) The National Kidney Foundation-Kidney Disease Outcomes Quality Initiative Guidelines (NKF-K/DOQI guidelines) recommend that epoetin be administered SC, since this route of administration is as effective (or more effective) than IV. However, epoetin is often administered IV in patients on dialysis, since there is easy access through the dialysis port.

Mechanism of action

- Human recombinant erythropoietin stimulates erythropoiesis (increased RBC production).

Patient instructions

- Do not shake the vial because the epoetin may break down, decreasing effectiveness.
- Store in refrigerator, but do not freeze. Keep out of direct sunlight.

- Make sure that the solution in the vial is clear and free of particulate matter. Do not use if the solution is cloudy or frothy.
- Monitor your blood pressure at home and alert your physician of any significant increases in blood pressure.
- Single-use vials are intended to be used only once. Discard any remaining solution and vial. If the label is marked with an M, it is a multi-dose vial, and it may be stored in the refrigerator for 21 days.
- It is very important that you take your blood pressure medications exactly as prescribed while on this medication, and maintain a sodium-restricted diet.
- Avoid hazardous activity in the first 90 days of therapy (eg, operating heavy machinery).
- Educate the patient about the possibility of allergic reactions:
 - * Local reaction (swelling, itching, redness); inform MD if any of these occur.
 - * Anaphylactic reaction (shortness of breath, wheezing, low blood pressure, rapid heart rate, sweating). If any of these occur, discontinue use immediately and call 911.
- Patient should be instructed on correct sterile injection technique and needle disposal as described in Figure 1.

Adverse drug effects (Table 2)

- Immunogenicity: pure red cell aplasia (PRCA), in association with neutralizing antibodies to native erythropoietin, has been reported rarely in the literature. If this is suspected, epoetin should be discontinued immediately.
- The most common adverse effect is elevated blood pressure. Epoetin is contraindicated in patients with uncontrolled hypertension.

Drug interactions

- No drug interactions have been reported.

Monitoring parameters

- Prior to initiation of therapy, the patient's iron stores should be evaluated. Transferrin saturation should be at least 20% and ferritin at least 100 ng/mL.
- Monitor Hct very closely. Once Hct approaches 36% or Hct increases more than 4 points in a 2-week period, the dose of epoetin should be decreased. The dose should be increased if Hct has not increased 5-6 points in 8 weeks, and is not in target Hct range of 30%-36%.
- Blood pressure should be adequately controlled prior to initiation of epoetin alfa therapy, and must be closely monitored and controlled during therapy.
- Serum chemistries

Kinetics

- Half life: ~4-13 hours
- There is no apparent difference in half-life between patients not on dialysis with SCr >3 and patients requiring dialysis.

Other

- Initial starting dose IV or SQ is 50-100 U/kg three times weekly. (Use IV in hemodialysis). Thereafter, the maintenance dose is titrated to maintain a Hct of 30%-36% or a Hgb of 10-12 g/dL.

Darbepoetin

Mechanism of action

- Darbepoetin has the same MOA as epoetin.

Patient instructions

- Counseling points are very similar with darbepoetin and epoetin, except that all vials are for single-use only, so dispose of the vial as instructed after each dose.

Adverse drug effects

- The most common adverse effects are:
 - * CV: hypertension, hypotension, edema, arrhythmia
 - * GI: nausea, vomiting, diarrhea, constipation
 - * CNS: fatigue, fever, headache
 - * Neuromuscular/skeletal: myalgia, arthralgia, limb pain
 - * Respiratory: infection, dyspnea, cough

Drug interactions

- No drug interactions have been reported.

Monitoring parameters

- Iron stores prior to and during therapy
- Blood pressure
- Dose is adjusted by closely monitoring Hgb every week until maintenance dose is established. Target Hgb is 12g/dL.
 - * Increase dose if Hgb increase is <1 g/dL over 4 weeks.
 - * Decrease dose by 25% if Hgb increase is >1 g/dL over 2 weeks.

Kinetics

- Half-life: IV, 21 hours; SC, 49 hours
- Half-life is approximately three times longer than that of epoetin.

Other

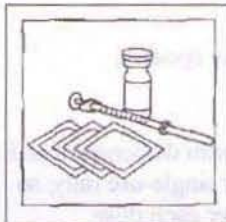
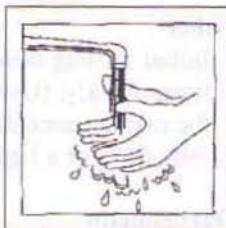
- Initial dose: 0.45 mcg/kg once weekly (IV recommended in hemodialysis patients); thereafter, dose is titrated to maintain Hgb of 12 g/dL. Some patients will require <0.45 mcg/kg, so in these patients, dosing will be only once every 2 weeks. Less frequent dosing is the advantage of darbepoetin over epoetin.

Figure 1.

Instructions for self-administering epoetin alfa.**Preparing the dose**

1. Wash your hands thoroughly with soap and water before preparing the medication.

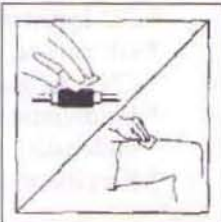
2. Check the date on the epoetin alfa vial to be sure that the drug has not expired.



3. Remove the vial of epoetin alfa from the refrigerator and allow it to reach room temperature. **Each epoetin alfa vial is designed to be used only once; do not re-enter the vial.** It is not necessary to shake epoetin alfa. Prolonged vigorous shaking may damage the product. Assemble the other supplies

you will need for your injection.

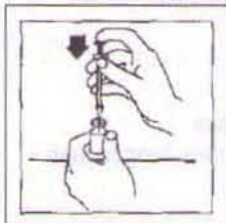
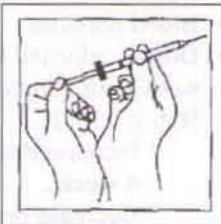
4. Hemodialysis patients should wipe off the venous port of the hemodialysis tubing with an antiseptic swab. Peritoneal dialysis patients should cleanse the skin with an antiseptic swab where the injection is to be made.



5. Flip off the red protective cap but do not remove the gray rubber stopper. Wipe the top of the gray rubber stopper with an antiseptic swab.

6. Using a syringe and needle designed

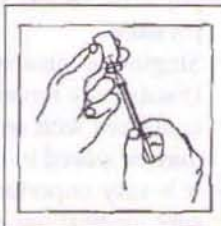
for subcutaneous injection, draw air into the syringe by pulling back on the plunger. The amount of air should be equal to your epoetin alfa dose.



7. Carefully remove the needle cover. Put the needle through the gray rubber stopper of the epoetin alfa vial.

8. Push the plunger in to discharge air into the vial. The air injected into the vial will allow epoetin alfa to be easily withdrawn into the syringe.

9. Turn the vial and syringe upside down in one hand. Be sure the tip of the needle is in the epoetin alfa solution. Your other hand will be free to move the plunger. Draw back on the plunger slowly to draw the correct dose of epoetin alfa into the syringe.

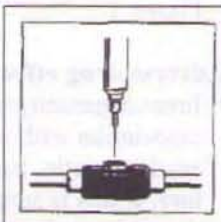


10. Check for air bubbles. The air is harmless, but too large an air bubble will reduce the epoetin alfa dose. To remove air bubbles, gently tap the syringe to move the air bubbles to the top of the syringe, then use the plunger to push the solution and the air back into the vial. Then re-measure your correct dose of epoetin alfa.

11. Double-check your dose. Remove the needle from the vial. Do not lay the syringe down or allow the needle to touch anything.

Injecting the dose**Patients on home hemodialysis using the intravenous injection route:**

1. Insert the needle of the syringe into the previously cleansed venous port and inject the epoetin alfa.



2. Remove the syringe and dispose of the whole unit. Use the disposable syringe only once. Dispose of syringes and needles as directed by your doctor, by following these simple steps:

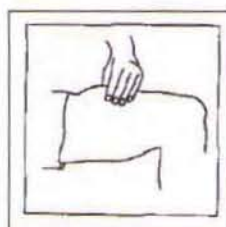
- Place all used needles and syringes in a hard plastic container with a screw-on cap, or a metal container with a plastic lid, such as a coffee can properly labeled as to contents. If a metal container is used, cut a small hole in the plastic lid and tape the lid to the metal container. If a hard plastic container is used, always screw the cap on tightly after each use. When the container is full, tape around the cap or lid, and dispose of it according to your doctor's instructions.
- Do not use glass or clear plastic containers, or any container that will be recycled or returned to a store.
- Always store the container out of the reach of children.
- Please check with your doctor, nurse, or pharmacist for other suggestions. There may be special state and local laws that they will discuss with you.

(continued)

Figure 1. (continued)

Instructions for self-administering epoetin alfa.

Patients on home peritoneal dialysis or home hemodialysis using the subcutaneous route:

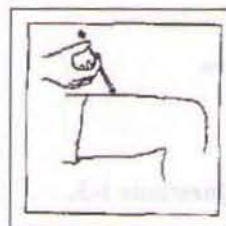
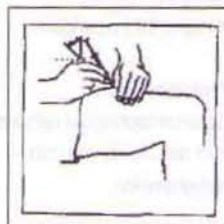


1. With one hand, stabilize the previously cleansed skin by spreading it or by pinching up a large area with your free hand.

2. Hold the syringe with the other hand, as you would a

pencil. Double check that the correct amount of epoetin alfa is in the syringe.

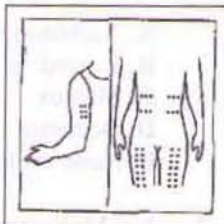
Insert the needle straight into the skin at a 90° angle. Pull the plunger back slightly. If blood comes into the syringe, do not inject epoetin alfa, as the needle has entered a blood vessel; withdraw the syringe and inject at a different site. Inject the epoetin alfa by pushing the plunger all the way down.



3. Hold an antiseptic swab near the needle and pull the needle straight out of the skin. Press the antiseptic swab over the injection site for several seconds. Use the disposable syringe only once.

4. Use the disposable syringe only once. Dispose of syringes and needles as directed in the instructions at left, under step 2.

5. Always change the site for each injection as directed. Occasionally a problem may develop at the injection site. If you notice a lump, swelling, or bruising that does not go away, contact your doctor. You may wish to record the site you just used so you can keep track.



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3. Nondrug Therapy**Iron Deficiency Anemia****Dietary supplementation**

- Increase intake of iron-rich foods, such as meat, fish, and poultry.
- Drink orange juice with meals when possible.

Table 2

Percentage of Patients Reporting Adverse Effects of Epoetin Alfa

Event	Patients treated with epoetin alfa (n = 200)	Patients on placebo (n = 135)
Hypertension	24%	19%
Headache	16%	12%
Arthralgias	11%	6%
Nausea	11%	9%
Edema	9%	10%
Fatigue	9%	14%
Vomiting	8%	5%
Chest pain	7%	9%
Skin reaction at site of administration	7%	12%
Asthenia		
Dizziness	7%	13%
Clotted access	7%	2%

Significant adverse events of concern in patients with CRF treated in double-blind, placebo-controlled trials occurred in the percentages of patients shown below during the blinded phase of the studies.

Seizure	1.1%	1.1%
CVA/TIA	0.4%	0.6%
MI	0.4%	1.1%
Death	0	1.7%

CRF, chronic renal failure; CVA/TIA, cerebrovascular accident/transient ischemic attack; MI, myocardial infarction.

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- Limit tea or milk with meals. Only use in moderation between meals.

Megaloblastic Anemias**Folic acid deficiency**

- In order to get as much dietary folate as possible, do not overcook vegetables. Eat them raw or steamed. Eat a wide variety of properly prepared vegetables, fruits, and mushrooms.

4. Key Points

- Anemia is a reduction in red cell mass, which decreases the oxygen-carrying capacity of the blood.
- Iron deficiency anemia is the most common anemia, accounting for 25% of all cases. IDA presents as a microcytic, hypochromic anemia.
- Iron preparations are best absorbed on an empty stomach.
- Iron preparations are hard to tolerate due to numerous GI effects, and this may necessitate administration with a small snack.
- Megaloblastic anemias are macrocytic and are the result of a folic acid or vitamin B₁₂ deficiency.
- Vitamin B₁₂ requires intrinsic factor to be absorbed. Patients deficient in intrinsic factor develop pernicious anemia.
- Due to the difficulties with the absorption of vitamin B₁₂ in many patients, it is often administered via an IM injection.
- The primary reason that patients with renal failure are anemic is due to the lack of production of erythropoietin (EPO).
- Anemia of renal failure is treated with SC or IV epoetin.
- Patients receiving epoetin must have their hematocrit and blood pressures routinely monitored.
- Darbepoetin has the same mechanism of action as epoetin, but is longer acting, and so can be administered less frequently.

5. Questions and Answers

Patient Profile #1: SuperPrice Drug Store Profile

G.M. McBeavy
1040 Dauberson Avenue
Jesup, IA 50648
319-555-6248

DOB: 7/11/52
Allergies: NKDA
Weight: 193 pounds

Problem List:

Gastroesophageal reflux disease
Iron deficiency anemia
Hypertension

Medication Record:

Ferrous sulfate 325 mg tid
Hydrochlorothiazide 25 mg daily

OTCs Recommended:

Maalox® 1 tbsq q2h prn for "indigestion"
Acetaminophen 325 mg q4-6h prn for headache
Ranitidine 75 mg daily prn for "heartburn"
Docusate 100 mg daily for constipation

Use Patient Profile #1 to answer Questions 1-5.

- Which OTC medication could present a problem with Mr. McBeavy's iron supplement?
 - Acetaminophen
 - Ranitidine
 - Maalox
 - Docusate
 - None of the above
- Mr. McBeavy admits to you that he is not able to take his iron tablet because it makes him nauseated. What advice can you give him?
 - Take your iron with some crackers and milk.
 - Take your iron with some crackers and water.
 - Don't worry about it. It's only a vitamin.
 - Start taking your iron with the largest meal of the day.
 - Take your iron after breakfast.
- If Mr. McBeavy's IDA progresses to severe stages, what effects may he experience?
 - Koilonychia (spooning of the nails)
 - Pica (eg, craving ice, clay, chalk)

- C. Glossitis (Sore, beefy red tongue)
 - D. Extreme fatigue
 - E. All of the above
4. If you were to examine Mr. McBeevy's blood smear, you would find cells that are:
 - A. Microcytic and hypochromic
 - B. Macrocytic and hypochromic
 - C. Macrocytic and normochromic
 - D. Microcytic and normochromic
 - E. Any of the above are possible
5. When examining Mr. McBeevy's iron study results, which of the following would be consistent with IDA?
 - A. Elevated TIBC
 - B. Elevated ferritin
 - C. Elevated MCV
 - D. Elevated hemoglobin
 - E. Elevated hematocrit
6. Which iron preparation is the most likely to cause an anaphylactic reaction?
 - A. IV iron dextran
 - B. IV iron sucrose
 - C. IV sodium ferric gluconate
 - D. PO extended-release ferrous sulfate
 - E. PO immediate-release ferrous sulfate
7. Why would the sustained-release (SR) preparations of iron not be the ideal formulation?
 - A. The incidence of nausea is higher with the SR formulations
 - B. They are only dosed once daily, and goal Hct levels are not attained
 - C. Since SR preparations are dissolved in the small intestines, the alkaline environment would result in a lower bioavailability than would the acidic environment of the stomach
 - D. Dissolution in the small intestines would not be bioavailable, because intrinsic factor is not present in the small intestines
 - E. They require dosing with food
8. To optimize iron absorption from meals, which would you advise a patient to drink with his meals?
 - A. Orange juice
 - B. Coffee
 - C. Tea
 - D. Milk
 - E. Soft drinks
9. The most likely regimen to replace vitamin B₁₂ would be:
 - A. 1000 mcg PO every month
 - B. 1000 mcg IV every month
 - C. 1000 mcg IM every month
 - D. 1000 mcg IM every day
 - E. Any of the above are reasonable regimens
10. Vitamin B₁₂ requires the following to be absorbed
 - A. Pernicious factor
 - B. Transcobalamin II
 - C. Intrinsic factor
 - D. Vitamin B₁₂ absorption factor
 - E. All of the above
11. Folic acid deficiency could be found in all of the following EXCEPT
 - A. strict vegetarians
 - B. alcoholics
 - C. the indigent
 - D. people who routinely overcook their vegetables
 - E. a college student whose diet consists of only burgers and potato chips
12. Folic acid may interact with the following medication:
 - A. Propranolol
 - B. Propoxyphene
 - C. Piroxicam
 - D. Phenytoin
 - E. Prednisone
13. The two macrocytic anemias are
 - A. vitamin B₁₂ deficiency and iron deficiency anemias
 - B. vitamin B₁₂ deficiency and folic acid deficiency anemias
 - C. iron deficiency and folic acid deficiency anemias
 - D. sickle cell anemia and anemia of renal failure
 - E. iron deficiency and pernicious anemias
14. The best regimen to replace folic acid would be
 - A. folic acid 1 mg PO every day for 3-4 months

- B. folic acid 10 mg PO every day for 3-4 months
 C. folic acid 10 mg IV for 2 weeks, then 1 mg PO every day for 2 months
 D. folic acid 1 mg PO three times weekly for 3-4 months
 E. folic acid 1 mg IM once monthly for 6 months
15. The most common medication given to treat anemia of renal failure is
- A. vitamin B₁₂
 B. solution of citric acid in combination with sodium acetate
 C. epoetin
 D. PO ferrous sulfate
 E. PO folic acid
16. What advantage does darbepoetin have over epoetin?
- A. Lower incidence of hypertension
 B. Fewer drug interactions
 C. Lower cost
 D. Longer half-life and less frequent administration
 E. Improved tolerability
17. The most common side effect of epoetin is
- A. anaphylaxis
 B. hypertension
 C. pure red cell aplasia
 D. injection site reaction
 E. weight gain
18. The initial dose of epoetin is
- A. 50-100 U/kg three times weekly SC or IV
 B. 50-100 U/kg once weekly SC or IV
 C. 100 U/kg once weekly SC or IV
 D. 50-100 U/kg three times weekly IV
 E. 100 U/kg once monthly IV
19. Prior to beginning epoetin therapy, which of the following should be evaluated?
- A. Folic acid and vitamin B₁₂ levels
 B. Transferrin and ferritin levels
 C. Erythropoietin receptor level
 D. Presence or absence of intrinsic factor
 E. All of the above

20. In which of the following patients would it be possible to teach self-administration of epoetin at home?
- I. A patient on home hemodialysis taking epoetin via the IV route
 II. A patient on home peritoneal dialysis taking epoetin via the SC route
 III. A patient on home hemodialysis taking epoetin via the SC route
- A. II only
 B. II and III only
 C. III only
 D. I, II, and III
 E. I only

Patient Profile #2: Central Dialysis Center

R.S. Wiley
 1460 Sawyer Brown Rd
 Reidsville, NC 27320
 336-555-0001

Allergies: Penicillin (rash)

Weight: 148 pounds

Dialysis schedule: Monday, Wednesday, Friday

Diagnosis:

Hypertension

Diabetes mellitus

End-stage renal disease

Hyperlipidemia

Medications:

Insulin NPH 30 U bid

Simvastatin 20 mg qhs

Atenolol 25 mg after dialysis

Nephrocaps 1 capsule daily

Labs:

ferritin 80ng/ml

transferrin 15%

HCT31

Hemoglobin 11

Use Patient Profile #2 to answer Questions 21-24.

21. Which of the following will be monitored upon starting epoetin therapy in Mrs. Wiley?
- A. Blood pressure
 B. Hematocrit
 C. Serum chemistries
 D. Iron profile
 E. All of the above

22. The target hematocrit range for Mrs. Wiley is
 - A. 30%-36%
 - B. 29%-38%
 - C. 30%-32%
 - D. 26%-34%
 - E. 40%-45%
23. Which of Mrs. Wiley's medications will interact with epoetin?
 - A. Insulin
 - B. Simvastatin
 - C. Atenolol
 - D. None of the above
 - E. All of the above
24. What medication should be added to Mrs. Wiley's regimen?
 - A. Oral propranolol
 - B. IV iron
 - C. Oral levothyroxine
 - D. IM vitamin B₁₂
 - E. No additional medications are required at this time
6. A. IV iron dextran has the highest incidence of anaphylaxis among the three IV iron preparations available.
7. C. SR preparations are left intact in the stomach, and are dissolved in the small intestine. The alkaline environment of the small intestine tends to form insoluble iron complexes that cannot be absorbed.
8. A. Tea and milk can decrease the absorption of iron from a meal by over 50%. Orange juice, however, can double the absorption of iron from food.
9. C. The most common IM dose of vitamin B₁₂ is 1000 mcg per month. However, vitamin B₁₂ may be supplemented by the oral route if absorption is not impaired. Additionally, it may be supplemented in very high doses, such as 1000-2000 mcg per day in pernicious anemia.
10. C. Vitamin B₁₂ requires intrinsic factor to be absorbed.

Answers

1. C. Iron is best absorbed in an acidic environment. Therefore antacids dramatically decrease the absorption of iron. They should be taken 1 hour before or 3 hours after antacids.
2. B. Many patients are not able to tolerate iron on an empty stomach. Tell those patients to take iron with a small snack. Milk would not be acceptable in this case, because dairy products decrease the absorption of iron.
3. E. Koilonychia, pica, extreme fatigue, and glossitis are all symptoms of severe iron deficiency anemia.
4. A. Iron deficiency produces a hypochromic (low-hemoglobin) anemia, given iron is a component of the hemoglobin molecule. The cells are also microcytic (meaning "small cell") because they spend longer in the marrow awaiting proper hemoglobin synthesis, and are therefore smaller.
5. A. Total iron-binding capacity, TIBC, is elevated in IDA. TIBC is a measure of the amount of binding space left on transferrin (the transport protein of iron). Less iron in the blood translates into more space available on the transferrin molecule.
11. A. Folic acid deficiency is found in alcoholics, the indigent, and rarely in people who routinely overcook their vegetables. Strict vegetarians do not develop folic acid deficiency because a folate-rich diet includes various types of vegetables.
12. D. Phenytoin increases the metabolism of folate, thereby decreasing its effectiveness.
13. B. Vitamin B₁₂ deficiency and folic acid anemias are both macrocytic (large cell) anemias. Iron deficiency anemia and sickle cell anemia are both microcytic and hypochromic anemias.
14. A. Folic acid is administered PO because there is no problem with absorption. The dose of folic acid is 1 mg PO every day, and the deficiency should be corrected in 3-4 months.
15. C. Epoetin is the most common medication used to treat anemia of renal failure, because it stimulates erythropoiesis. The lack of erythropoietin production is the primary cause of anemia of renal failure.
16. D. Darbepoetin is very similar to epoetin, having the same mechanism of action and similar side effects. It does have a longer half-life and can be administered less frequently.

17. **B.** Hypertension is the most common adverse drug effect from epoetin.
18. **A.** The initial dose of epoetin is 50-100 U/kg three times weekly. This can be given via either the SC or IV route.
19. **B.** Transferrin and ferritin levels should be evaluated prior to epoetin therapy. IDA is a common problem in patients with end-stage renal disease. The transferrin should be at least 20% and ferritin should be at least 100 ng/mL prior to beginning epoetin therapy.
20. **D.** Patients on home peritoneal dialysis or hemodialysis can be taught to self-administer SC injections. Additionally, if patients are receiving home hemodialysis, they can be taught to give their epoetin IV through the dialysis venous port.
21. **E.** Iron profiles need to be monitored prior to epoetin and periodically during therapy, since IDA is very common in dialysis patients. Blood pressure needs to be monitored, given this is the most common adverse effect of epoetin. The hematocrit needs to be checked as a measure of response to epoetin, and needs to be maintained at a level of 30%-36%. Serum chemistries need to be monitored regularly in any patient with end-stage renal disease, since most electrolytes are regulated by the kidney.
22. **A.** The target range of hematocrit for patients receiving epoetin is 30%-36%.
23. **D.** There are no known drug interactions with epoetin.
24. **B.** Mrs. Wiley's ferritin is below 100 ng/mL and her transferrin is below 20%. Most hemodialysis patients receiving epoetin will need iron therapy during their treatment at some point in time.

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39. Appendices

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Appendix 1

Normal Laboratory Values

Test	Conventional units	SI units
Albumin	3.5-5 g/dL	35-50 g/L
Alkaline phosphatase		
Adult	4.5-13 King-Armstrong U/dL	32-92 U/L
Infant	10-30 King-Armstrong U/dL	71-213 U/L
Amylase	60-160 Somogyi U/dL	25-125 U/L
Anion Gap	7-16 mEq/L	7-16 mmol/L
Arterial blood gases (ABG)		
HCO ₃	21-28 mEq/L	21-28 mEq/L
O ₂ saturation	94-100%	0.94-1
pH	7.35-7.45	7.35-7.45
PO ₂	83-108 mmHg	11.04-14.36 kPa
PCO ₂	35-45 mmHg	4.7-6 kPa
Basal metabolic panel (BMP)		
Bicarbonate	22-29 mEq/L	22-29 mmol/L
Blood urea nitrogen (BUN)	6-20 mg/dL	2.1-7.1 mmol/L
Chloride	98-107 mEq/L	98-107 mmol/L
Creatinine	0.6-1.3 mg/dL	53-115 micromol/L
Glucose	60-110 mg/dL	3.3-6.1 mmol/L
Potassium	3.5-5.1 mEq/L	3.5-5.1 mmol/L
Sodium	136-145 mEq/L	136-145 mmol/L
Blood pressure (mm Hg)		
Optimal	<120/<80	<120/<80
Normal	<130/<85	<130/<85
High normal	130-139/85-89	130-139/85-89
Hypertension		
Stage 1	140-159/90-99	140-159/90-99
Stage 2	160-179/100-109	160-179/100-109
Stage 3	>180/>110	>180/>110
Isolated systolic	>140/<90	>140/<90
Calcitonin	<150 pg/mL	<150 ng/L
Calcium	8.6-10 mg/dL	2.15-2.50 mmol/L
Carbon dioxide	22-29 mEq/L	22-29 mmol/L
Coagulation screen		
Activated partial thromboplastin time (aPTT)	<35 seconds	<35 seconds
Antithrombin III	21-30 mg/dL	210-300 mg/L
Bleeding time	1-<10 min	1-<10 min
Partial thromboplastin time (PTT)	22-37 seconds	22-37 seconds
Protein C	70-140%	0.70-1.40
Protein S	67-140%	0.67-1.40
Prothrombin time (PT)	11-15 seconds	11-15 seconds
Complete blood count (CBC)		
Hemoglobin (Hb)		
Male	13.1-18 g/dL	131-180 g/L
Female	11.7-16 g/dL	117-160 g/L
Hematocrit (Hct)		
Male	40-54%	0.40-0.54
Female	34-47%	0.34-0.47
Mean corpuscular volume (MCV)	80-96 micrometer ³	80-96 fL

(continued)

Appendix 1

Normal Laboratory Values (continued)

Test	Conventional units	SI units
CBC (continued)		
Mean corpuscular hemoglobin (MCH)	27-33 pg	27-33 pg
Mean corpuscular hemoglobin concentration (MCHC)	32-36%	0.32-0.36
Platelets	150-400 x 10 ³ /microliter	150-400 x 10 ⁹ /microliter
Red blood cells (RBC):		
Male	4.1-5.8 x 10 ⁶ cells/microliter	4.1-5.8 x 10 ¹² cells/L
Female	3.8-5.4 x 10 ⁶ cells/microliter	3.8-5.4 x 10 ¹² cells/L
White blood cells (WBC)	4.5-11 x 10 ³ cells/microliter	4.5-11 x 10 ⁹ cells/L
White blood cell differential:		
Band neutrophils	0.0-2.1 10 ³ cells/microliter	0.0-2.1 10 ⁹ cells/L
Basophils	0.0-0.19 10 ³ cells/microliter	0.0-0.19 10 ⁹ cells/L
Eosinophils	0.0-0.7 10 ³ cells/microliter	0.0-0.7 10 ⁹ cells/L
Lymphocytes	1.2-4.0 10 ³ cells/microliter	1.2-4.0 10 ⁹ cells/L
Monocytes	0.1-0.95 10 ³ cells/microliter	0.1-0.95 10 ⁹ cells/L
Segmented neutrophils	1.1-6.9 10 ³ cells/microliter	1.1-6.9 10 ⁹ cells/L
Corticotropin (ACTH) 08:00h	<120 pg/mL	<26 pmol/L
Cortisol 08:00h	5-23 mcg/dL	138-635 nmol/L
Creatinine kinase:		
Male	38-174 U/L	0.65-2.96 microKat/L
Female	26-140 U/L	0.46-2.38 microKat/L
Glucose tolerance test		
Baseline fasting blood glucose	70-105 mg/dL	3.9-5.8 mmol/L
30-Minute fasting blood glucose	110-170 mg/dL	6.1-9.4 mmol/L
60-Minute fasting blood glucose	120-170 mg/dL	6.7-9.4 mmol/L
90-Minute fasting blood glucose	100-140 mg/dL	5.6-7.8 mmol/L
120-minute fasting blood glucose	70-120 mg/dL	3.9-6.7 mmol/L
Hematologic tests		
Erythrocyte sedimentation rate (ESR)		
≥50 year old male	0-15 mm/h	0-15 mm/h
≥50 year old female	0-20 mm/h	0-20 mm/h
<50 year old male	0-20 mm/h	0-20 mm/h
<50 year old female	0-30 mm/h	0-30 mm/h
Ferritin		
Male	20-250 ng/mL	20-250 mcg/L
Female	10-120 ng/mL	10-120 mcg/L
Fibrinogen	200-400 mg/dL	2.00-4.00 g/L
Hemoglobin A _{1c}	4-6%	0.040-0.060
Reticulocytes	0.5-1.5%	0.005-0.015
Vitamin B ₁₂	200-835 pg/mL	148-616 pmol/L
Iron		
Male	65-175 (g/dL)	11.6-31.3 (mol/L)
Female	50-170 (g/dL)	9.0-30.4 (mol/L)
Total iron binding capacity (TIBC)	250-425 (g/dL)	44.8-76.1 (mol/L)
Transferrin saturation	20-50%	0.20-0.50

(continued)

Appendix 1

Normal Laboratory Values (continued)

Test	Conventional units	SI units
Isoenzymes		
Creatine phosphokinase (MM)	5-70 U/L	5-70 U/L
Creatine phosphokinase (MB)	0-7 U/L	0-7 U/L
Creatine phosphokinase (BB)	0-3 U/L	0-3 U/L
Lipase	<200 U/L	<3.4 microKat/L
Lipids		
Total cholesterol		
Desirable	<200 mg/dL	<5.2 mmol/L
Borderline-high	200-239 mg/dL	<5.2-6.2 mmol/L
High	>239 mg/dL	>6.2 mmol/L
LDL		
Desirable	<130 mg/dL	<3.36 mmol/L
Borderline-high	130-159 mg/dL	3.36-4.11 mmol/L
High	>159 mg/dL	>4.11 mmol/L
HDL		
Low	<40 mg/dL	<1.04 mmol/L
High	>60 mg/dL	>1.55 mmol/L
Triglycerides		
Desirable	<150 mg/dL	<1.7 mmol/L
Borderline-high	150-199 mg/dL	1.7-2.25 mmol/L
High	200-499 mg/dL	2.26-5.64 mmol/L
Very high	>500 mg/dL	>5.65 mmol/L
Liver function tests (LFTs)		
Aspartate aminotransferase (AST, SGOT)	8-20 U/L	0.14-0.34 microKat/L
Alanine aminotransferase (ALT, SGPT)	10-40 U/L	0.17-0.68 microKat/L
Ammonia (NH ₄ ⁺)	15-45 mcg/dL	11-32 micromol/L
Bilirubin		
Conjugated	<2 mg/dL	<3.4 microMol/L
Total	0.2-1 mg/dL	3-19 microMol/L
Lactate dehydrogenase (LDH)	90-280 U/L	1.50-4.67 microKat/L
Magnesium	1.3-2.6 mg/dL	0.65-1.07 mmol/L
Phosphate	2.5-4.5 mg/dL	0.81-1.45 mmol/L
Prolactin		
Male	3-15 ng/mL	3-15 mcg/L
Female	3-23 ng/mL	3-23 mcg/L
Protein, total	6.4-8.3 g/dL	64-83 g/L
Thyroid hormone function tests		
Free thyroxine (Free T ₄)	0.8-2.7 ng/dL	10-35 pmol/L
Thyroid-stimulating hormone (TSH)	0.4-8.9 microU/mL	0.4-8.9 mU/L
Thyroxine-binding globulin capacity	16-24 mcg/dL	206-309 nmol/L
Total triiodothyronine (T ₃)	70-204 ng/dL	1.08-3.14 nmol/L
Total thyroxine by RIA (T ₄)	4.6-11.0 mcg/dL	59-142 nmol/L
Uric acid	2.3-8.0 ng/dL	137-476 micromol/L

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Appendix 2

Drugs in Renal Failure

Generic name (trade name)	Normal dose	CrCl 30-50 mL/min	CrCl 10-30 mL/min	CrCl <10 mL/min	Hemodialysis
Analgesics					
Acetaminophen	650 mg PO q4h	650 mg PO q6h	650 mg PO q6h	650 mg PO q6h	No supplementation required
Aspirin	650 mg PO q4h	650 mg PO q 4h	650 mg PO q6h	Avoid	Dose after HD
Codeine	30-60 mg PO q4-6h	20-45 mg PO q4-6h	20-45 mg PO q4-6h	15-30 mg PO q4-6h	No data
Fentanyl (Sublimaze®)	0.5 mcg/kg IV q1-2h	Same	0.375 mcg/kg IV q1-2h	0.25 mcg/kg IV q1-2h	0.25 mcg/kg IV q1-2h
Hydromorphone (Dilaudid®)	1-2 mg IV q4-6h	Same	Same	Same	Same
Meperidine (Demerol®)	50-100 mg IV or PO q3-4h	37.5-75 mg IV or PO q3-4h	37.5-75 mg IV or PO q3-4h	25-50 mg IV or PO q3-4h	Avoid
Morphine	20-25 mg PO q4h; 2-15 mg IV q2-4h	15-20 mg PO q4h; 1.5-12 mg IV q2-4h	15-20 mg PO q4h; 1.5-12 mg IV q2-4h	10 pg PO q4h; 1-8 mg IV q2-4h	No supplemental PO dose required; 1-8 mg IV q2-4
Propoxyphene (Darvon®)	65 mg PO q6-8h	Same	Same	Avoid	Avoid
Antiarrhythmics					
Adenosine (Adenocard®)	6 mg IV push over 1-2 s, may repeat second dose at 12 mg IV if necessary, may repeat 12 mg dose x 1	Same	Same	Same	Same
Atropine	0.5-1 mg IV push q 3-5 min, max 0.04 mg/kg	Same	Same	Same	Same
Class I					
Moricizine (Ethmozine®)	200-300 mg PO q8h	Same	Same	Same	Same
Propafenone (Rythmol®)	150-300 mg PO q8h	Same	Same	Same	Same
Class Ia					
Disopyramide (Norpace®)	300 mg IR LD, then 150-300 mg PO q6h	100 mg PO q6h	100 mg PO q12h	100 mg PO q24h	100 mg post-HD
Procainamide (Procan®, Pronestyl®)	500-1000 mg PO q4-6h; 50-100 mg/min IV until arrhythmia is suppressed or reach 500-1000 mg, then 2-6 mg/min	500 mg PO q6h	500 mg PO q12h	500 mg PO q12-24h	500 mg PO q24h post-HD
Quinidine (Quinidex®, Quinaglute®)	Sulfate: 200-400 mg PO q4-6h; gluconate: 324-648 mg PO q8-12h; 200-300 mg IM q2-6h	Same	Same	Sulfate: 150-300 mg PO q4-6h	Sulfate: 100-200 mg post-HD

(continued)

Appendix 2

Drugs in Renal Failure (continued)

Generic name (trade name)	Normal dose	CrCl 30-50 mL/min	CrCl 10-30 mL/min	CrCl <10 mL/min	Hemodialysis
Antiarrhythmics (cont)					
<i>Class Ib</i>					
Lidocaine (Xylocaine®)	50-100 mg IV over 1- 2 min bolus, then 1-4 mg/min IV	Same	Same	Same	Same
Mexilitine (Mexitil®)	200-400 mg PO q8h	Same	Same	Same	Same
Tocainide (Tonocard®)	200-400 mg PO q8h	Same	Same	Same	Same
<i>Class Ic</i>					
Encainide (Enkaid®)	25-50 mg PO q12h	25-50 mg PO q8h	25 mg PO q8h	25 mg PO q12-24h	Same
Flecainide (Tambocor®)	100-200 mg PO q12h	No change	50-100 mg PO q12h	50 mg PO q12h	Same
<i>Class II (see β- blockers in antihyper- tensives)</i>					
<i>Class III</i>					
Amiodarone (Cordarone®)	800-1600 mg/d in divided doses for 1- 2 weeks LD, then 100-600 mg/d	Same	Same	Same	Same
Bretylium (Bretyol®)	5 mg/kg IV bolus, may repeat at 10 mg/kg to max of 30 mg/kg	Same	Same	Same	Same
<i>Class IV (see calcium channel blockers in antihypertensives)</i>					
Antibiotics					
<i>Aminoglycosides</i>					
Amikacin (Amikin®)	7.5 mg/kg IV q12h	7.5 mg/kg IV q18- 24h	7.5 mg/kg IV q24- 48h	7.5 mg/kg IV q48h	7.5 mg/kg IV based on serum levels; redose if level <5 mcg/mL
Gentamicin (Garamycin®)	1.7 mg/kg q8h	0.5-1 mg/kg IV q12h or 1.7 mg/kg q24-48h	0.5-1 mg/kg IV q12h or 1.7 mg/kg q24- 48h	0.35-0.5 mg/kg IV q24-48h or 1.7 mg/kg IV q48-72h	50% of dose post-HD
Tobramycin (Nebcin®)	1/7 mg/kg q8h	0.5-1 mg/kg IV q12h or 1.7 mg/kg q24-48h	0.5-1 mg/kg IV q12h or 1.7 mg/kg q24- 48h	0.35-0.5 mg/kg IV q24-48h or 1.7 mg/kg IV q48-72h	50% of dose post-HD
<i>Cephalosporins</i>					
Cefaclor (Ceclor®)	250-500 mg PO tid	125-500 mg PO tid	125-500 mg PO tid	125-250 mg PO tid	250 mg PO post-HD
Cefadroxil (Duricef®)	0.5-1 g PO q12h	0.5-1 g PO q12-24h	0.5-1 g po q12-24h	0.5-1 g PO q24-48h	0.5-1 g PO post-HD
Cefazolin (Ancef®, Kexol®)	1-2 g IV q8h	1-2 g PO q8h	1-2 g IV q12h	1-2 g IV q24h	1-2 g IV q24h given post-HD
Cefepime (Maxipime®)	1-2 g IV q8-12h	1-2 g IV q12-24h	1-2 g IV q24h	0.5-1 g IV q24h	0.5-1 g IV q24h given post-HD

(continued)

Appendix 2

Drugs in Renal Failure (continued)

Generic name (trade name)	Normal dose	CrCl 30-50 mL/min	CrCl 10-30 mL/min	CrCl <10 mL/min	Hemodialysis
<i>Cephalosporins (cont)</i>					
Cefixime (Suprax®)	200 mg PO q12h	150-200 mg PO q12h	150 mg PO q12h	100 mg PO q12h	300 mg PO post-HD
Cefotaxime (Claforan®)	1-2 g IV q8h	1-2 g IV q8h	1-2 g IV q12h	1-2 g IV q24h	1-2 g IV q24h given post-HD
Cefotetan (Cefotan®)	1-2 g IV q12h	1-2 g IV q12h	1-2 g IV q24h	1-2 g IV q48h	1-2 g IV q48h given post-HD
Cefoxitin (Mefoxin®)	1-2 g IV q6-8h	1-2 g IV q8h	1-2 g IV q12h	1-2 g IV q24h	1-2 g IV q24h given post-HD
Cefpodoxime (Vantin®)	200 mg PO q12h	200 mg PO q16h	200 mg PO q16h	200 mg PO q24-48h	200 mg PO post-HD only
Cefprozil (Cefzil®)	500 mg PO q12h	250 mg PO q12-16h	250 mg PO q12-16h	250 mg PO q24h	250 mg PO post-HD
Ceftazidime (Ceptaz®, Fortaz®, Tazicef®, Tazidime®)	2 g IV q8h	2 g IV q12h	2 g IV, then 0.5-1 g IV q24h	2 g IV, then 1 g IV q48h	2 g IV, then 1 g IV q48h given post-HD
Ceftizoxime (Cefizox®)	1-2 g IV q8h	1-2 g IV q12h	1-2 g IV q12h	1-2 g IV q24h	1 g IV q48h given post-HD
Ceftriaxone (Rocephin®)	1-2 g IV q24h	Same	Same	Same	Same
Cefuroxime (Ceftin®, Kefurox®, Zinacef®)	0.75-1.5 g IV q8h	0.75-1.5 g IV q8h	0.75-1.4 g IV q12h	0.75-1.5 g IV q24h	0.75-1.5 g IV q24h given post-HD
Cephalexin (Keflex®)	250-500 mg PO q6h	250-500 mg PO q8-12h	240-500 mg PO q12h	250-500 mg PO q12h	Dose post-HD
<i>Fluoroquinolones</i>					
Ciprofloxacin (Cipro®)	500-750 mg PO; 400 mg IV q12h	250-500 mg PO; 400 mg IV q12h	250-500 mg PO q18h; 400 mg IV q24h	250-500 mg PO q18h; 400 mg IV q24h	250-500 mg PO q24h; 400 mg IV q24h given post-HD
Gatifloxacin (Tequin®)	400 mg PO or IV q24h	400 mg PO or IV x 1, then 200 mg PO or IV q24h	400 mg PO or IV x1, then 200 mg PO or IV q24h	400 mg IV or PO x 1, then 200 mg PO or IV q24h	400 mg PO or IV x 1, then 200 mg PO or IV q24h given post-HD
Levofloxacin (Levaquin®)	250-500 mg PO or IV q24h	500 mg PO or IV x 1, then 250 mg PO or IV q24h	500 mg PO or IV x 1, then 250 mg PO or IV q48h	500 mg PO or IV, x 1, then 250 mg PO or IV q48h	500 mg PO or IV x1, then 250 mg PO or IV q48h given post-HD
<i>Miscellaneous</i>					
Aztreonam (Azactam®)	1-2 g IV q6-8h	1-2 g IV q6-8h	1-2 g IV LD, then 1 g IV q6-8h	1-2 g IV LD, then 0.5 g IV q6-8h	1-2 g IV LD, then 0.5 g IV q6-8h given post-HD
Erythromycin (E-Mycin®)	250 mg PO q8h	Same	Same	Same	Same
Imipenem (Primaxin®)	500 mg IV q6h	500 mg IV q8h	500 mg IV q12h	250 mg IV q12h	250 mg IV q12h given post-HD
Linezolid (Zyvox®)	600 mg IV q12h	No data	No data	No data	Give post-HD

(continued)

Appendix 2

Drugs in Renal Failure (continued)

Generic name (trade name)	Normal dose	CrCl 30-50 mL/min	CrCl 10-30 mL/min	CrCl <10 mL/min	Hemodialysis
<i>Misc. antibiotics (cont)</i>					
Meropenem (Merrem®)	1 g IV q8h	1 g IV q12h	500 mg IV q12h	500 mg IV q24h	500 mg IV q24h given post-HD
Quinupristin-dalfopristin (Synercid®)	7.5 mg/kg IV q8h	Same	Same	Same	Same
Rifampin (Rifadin®)	600 mg PO q24h	300-600 mg PO q24-48h	300-600 mg PO q24-48h	300-600 mg PO q48h	300-600 mg PO q48h given post-HF
Trimethoprim-sulfamethoxazole (Bactrim®, Septra®)	8-20 mg/kg/d PO 6-12h; IV q12h	4-10 mg/kg/d PO or IV q12h	4-10 mg/kg/d PPO or IV q12h	2-5 mg/kg/d PO or IV q24h	2-5 mg/kg/d PO or IV q24h given post-HD
Vancomycin (Vancocin®)	500 mg IV q6h or 1 g q12h	1 g IV q24-96h	1 g IV q24-96g	1 g IV q4-7d	1 g IV q4-7d
<i>Penicillins</i>					
Amoxicillin-clavulanic acid (Augmentin®)	250-500 mg PO q8h 875 mg PO bid	Same	250-500 mg PO q12h; 875 mg PO bid	250-500 mg PO q24h; 875 mg PO q24h	Give post-HD
Ampicillin (Principen®, Omnipen®)	1-2 g IV q4-6g	1-2 g IV q6-8h	1-2 g IV q8-12h	1-2 g IV q12h	1-2 g IV q12h
Ampicillin-sulbactam (Unasyn®)	1.5-3 g IV q6h	1.5-3 g IV q8h	1.5-3 g IV q12h	1.5-3 g IV q24h	1.5-3 g IV q24h given post-HD
Methicillin (Staphcillin®)	1-2 g IV q4-6h	1-2 g IV q8h	1-2 g IV q6-8h	1-2 g IV q8-12h	1-2 g IV q8-12h
Nafcillin (Nafcin®, Unipen®)	1-2 g IV q4-6h	Same	Same	Same	Same
Oxacillin (Bactocil®)	1-2 g IV q4-6h	Same	Same	Same	Same
Penicillin G	1-4 MU IV q4-6h	1-4 MU IV q6-8h	1-4 MU IV q8-12h	1-4 MU IV q12-18h	1-4 MU IV q12-18h
Piperacillin (Pipracil®)	3 g IV q4-6h	3 g IV q6h	3 g IV q8h	3 g IV q12h	2 g IV q8h given post-HD
Piperacillin-tazobactam (Zosyn®)	3.375 g IV q4-6h	3.375 g IV q6h	3.375 g IV q8h	3.375 g IV q12h	2.25 g IV q8h given post-HD
Ticarcillin (Ticar®)	3 g IV q4h	1-2 g IV q4-8h	1-2 g IV 8h	1-2 g IV q12h	3 g IV post-HD
Ticarcillin-clavulanic acid (Timentin®)	3.1 g IV q4-6h	2 g IV q4h	2 g IV q12h	2 g IV q12h	2 g IV q12h given post-HD
<i>Anticoagulants</i>					
Enoxaparin (Lovenox®)	30 mg SC q12h	Same	30 mg SC qd	30 mg SC qd	No data
	40 mg SC qd	Same	30 mg SC qd	30 mg SC qd	
	1 mg/kg SC q12h	Same	1 mg/kg SC qd	1 mg/kg SC qd	
<i>Anticonvulsants</i>					
Carbamazepine (Tegretol®)	200 mg PO bid to 1200 mg PO q24h	Same	Same	Same	Same
Diazepam (Valium®)	2-10 mg PO q6-12h prn; 2-10 mg IV or IM q2-4h prn	Same	Same	Same	Same

(continued)

Appendix 2

Drugs in Renal Failure (continued)

Generic name (trade name)	Normal dose	CrCl 30-50 mL/min	CrCl 10-30 mL/min	CrCl <10 mL/min	Hemodialysis
Anticonvulsants (cont)					
Ethosuximide (Zarontin®)	500-1500 mg PO q24h	Same	Same	Same	Same
Gabapentin (Neurontin®)	300-600 mg PO tid	200-700 mg PO bid	300 mg PO q12-24h	300 mg PO qod	300 mg load, then 200- 300 mg post-HD
Lamotrigine (Lamictal®)	15 mg PO q12-24h initially, then 100- 500 mg PO q24h	Same	Same	Same	No data
Lorazepam (Ativan®)	0.5-10 mg PO q4-6h prn; 1-10 mg IV or IM q2-4h prn	Same	Same	Same	Same
Oxcarbazepine (Trileptal®)	200-400 mg PO tid	Same	Same	Same	No data
Phenobarbital (Luminal®, Solfoton®)	60-250 mg PO q24h; 10-20 mg/kg IV	Same	Same	60-100 mg PO q24h	Give dose post-HD
Phenytoin (Dilantin®)	15 mg/kg LD, then 200-400 mg/d PO or IV divided q8- 12h	Same	Same	Same	Same
Primidone (Mysoline®)	250-500 mg PO qid	250-500 mg PO q8-12h	250-500 mg PO q8-12h	250-500 mg PO q12-24h	80-160 mg PO q12- 24h
Sodium valproate (Depakene®, Depakote®)	15-60 mg/kg q24h	Same	Same	Same	Same
Topiramate (Topamax®)	100-400 mg PO q12-24h	50-400 mg PO q12-24h	50-200 mg PO q12-24h	25-100 mg PO q12-24h	No data
Antiemetics					
Metoclopramide (Reglan®)	10-20 mg IV q6h	7.5-15 mg IV q6h	7.5-15 mg IV 6h	5-10 mg IV q6h	7.5-15 mg IV q6h
Antifungals					
Amphotericin B nonlipid (Fungizone®)	0.4-1 mg/kg IV q24h	0.4-1 mg/kg IV q24h	0.4-1 mg/kg IV q24h	0.4-1 mg/kg IV q48h	0.4-1 mg/kg IV q48h
Am B lipid complex (Abelcet®)	5 mg/kg IV q24h	5 mg/kg IV q24h	5 mg/kg IV q24h	5 mg/kg IV q48h	5 mg/kg IV q48h
Am B cholesteryl sulfate complex (Amphotec®)	3-6 mg/kg/d IV q24h	3-6 mg/kg/d IV q24h	3-6 mg/kg/d IV q24h	3-6 mg/kg/d IV q48h	3-6 mg/kg/d IV q 48h
Am B liposome (Ambisome®)	3-5 mg/kg IV q24h	3-5 mg/kg IV q24h	3-5 mg/kg IV q24h	3-5 mg/kg IV q48h	3-5 mg/kg IV q48h
Fluconazole (Diflucan®)	100-400 mg PO or IV q24h	LD: 100-400 mg PO or IV, then 50-200 mg PO or IV q24h	LD: 100-400 mg PO or IV, then 50-200 mg PO IV q24h	LD: 100-400 mg PO or IV, then 50-200 mg PO or IV q24h	100-400 mg PO or IV only after HD
Itraconazole (Sporanox®)	100-200 mg PO or IV q12h	100-200 mg PO or IV q12h	100-200 mg PO IV q12h	100-200 mg PO or IV q24h	100 mg PO q12-24h; 200 mg IV q24h post-HD
Ketoconazole (Nizoral®)	20 mg PO q24h	Same	Same	Same	Same

(continued)

Appendix 2

Drugs in Renal Failure (continued)

Generic name (trade name)	Normal dose	CrCl 30-50 mL/min	CrCl 10-30 mL/min	CrCl <10 mL/min	Hemodialysis
Antihistamines (cont)					
Cimetidine (Tagamet®)	400 mg PO bid; 300 mg IV q6h; 37.5-50 mg/h continuous infusion	200 mg PO bid; 300 mg IV q8h; 25-37.5 mg/h continuous infusion	200 mg PO bid; 200 mg IV q8h; 25-37.5 mg/h continuous infusion	100 mg PO bid; 300 mg IV q12h; 18-25 mg/h continuous infusion	No PO supplementation required; 300 mg IV q12h given post-HD
Famotidine (Pepcid®)	20-40 mg PO qhs; 20-40 mg IV q12h	5-20 mg PO qhs; 20 mg IV q12h	5-10 mg PO qhs; 20 mg IV q12h	2-4 mg PO qhs; 20 mg IV q24h, or 40 mg IV q48h	No PO supplementation required; 20 mg IV q24h given post-HD
Nizatidine (Axiid®)	150 mg PO q12h or 300 mg PO hs	150 mg PO q24h	150 mg PO q24h	150 mg PO q48h	150 mg PO q48h
Ranitidine (Zantac®)	150-300 mg PO qhs; 50 mg IV q8h; 6.25 mg/h continuous infusion	75-150 mg PO qhs; 50 mg IV a12h	75-150 mg PO qhs; 50 mg IV q12h	75 mg PO qhs; 50 mg IV q24h	50% of PO dose post-HD; 50 mg IV q24h given post-HD
Antihypertensives					
<i>ACE inhibitors</i>					
Benazepril (Lotensin®)	10-40 mg PO q24h	5-20 PO q24h	5-20 mg PO q24h	5-20 mg PO q24h	5-20 PO q24h
Captopril (Capoten®)	25-200 mg PO q8h	18.75-75 mg PO q12-18h	18.75-75 mg PO q12-18h	12.5-50 mg PO q24h	Supplement 25-30% of dose after HD
Enalapril (Vasotec®)	5-10 mg PO q12h	2.5-7.5 mg PO q12h	2.5 mg PO q24h	2.5 mg PO q24h	2.5-7.5 PO q12h
Enalaprilat (Vasotec®)	1.25-5 mg IV q6h	1.25-2.5 mg IV q6h	0.625 mg IV x 1, then up to 1.25 mg q6h if inadequate response	0.625 mg IV x 1, then up to 1.25 mg q6h if inadequate response	0.625 mg IV q6h
Fosinopril (Monopril®)	10-40 mg PO q24h	10-40 mg q24h	10-40 mg PO q24h	7.5-30 mg PO q24h	Same
Lisinopril (Zestril®)	10-40 mg PO q24h	5-30 mg PO q24h	5-30 mg PO q24h	2.5-20 mg PO q24h	2.5 mg initially, then 20% of patient's dose after HD if on a dosing regimen
Quinapril (Accupril®)	10-80 mg PO q24h	7.5-60 mg PO q24h	7.5-60 mg PO q24h	7.5-60 mg PO q24h	2.5 mg initially, then 25-35% of patient's dose after HD if on a dosing regimen
Ramipril (Altace®)	2.5-20 mg PO q24h	1.25-15 mg PO q24h	1.25-15 mg PO q24h	1.25-10 mg PO q24h	Supplement 20% of the patient's dose after HD
<i>α-Blockers</i>					
Doxazosin (Cardura®)	1-16 mg PO q24h	Same	Same	Same	Same
Prazosin (Minipress®)	1-15 mg PO q12h	Same	Same	Same	Same
Terazosin (Hytrin®)	1-20 mg/d PO	Same	Same	Same	Same

(continued)

Appendix 2

Drugs in Renal Failure (continued)

Generic name (trade name)	Normal dose	CrCl 30-50 mL/min	CrCl 10-30 mL/min	CrCl <10 mL/min	Hemodialysis
<i>Angiotensin-receptor blockers</i>					
Candesartan (Atacand®)	8-32 PO q24h	Same	Same	No data	Same
Losartan (Cozaar®)	25-100 mg PO q12-24h	Same	Same	Same	No data
<i>Angiotensin-receptor blockers (cont)</i>					
Irbesartan (Avapro®)	150-300 mg PO q24h	Same	Same		Same
Valsartan (Diovan®)	80-320 mg PO q24h	Same	Same	No data	No data
<i>β-Blockers</i>					
Atenolol (Ternormin®)	50-100 mg PO q24h	25-50 mg q48h	25-50 mg PO q24h	25-50 mg PO q96h	25-50 mg PO q96h; supplement 12.5-25 mg post-HD
Carvedilol (Coreg®)	6.25-50 mg PO q12h	Same	Same	Same	No data
Metoprolol (Lopressor®)	50-450 mg/d PO in 2-3 divided doses	Same	Same	Same	Supplement 50 mg PO post-HD
Labetalol (Normodyne®)	200-600 mg PO bid	Same	Same	Same	Same
Nadolol (Corgard®)	40-320 mg/d PO single or divided doses	20-160 mg/d PO q24-36h	20-160 mg/d PO q24-48h	10-80 mg/d PO q48h	Supplement 40 mg PO post-HD
Pindolol (Visken®)	10-40 mg PO q12h	Same	Same	Same	Same
Propranolol (Inderal®)	80-320 mg PO q6-12h	Same	Same	Same	Same
Sotalol (Betapace®)	80-320 mg PO q12h	80-320 mg PO q24h	80-320 mg PO q36-48h	10-100 mg PO according to clinical response	Same Supplement 80 mg post-HD
<i>Calcium channel blockers</i>					
Amlodipine (Norvasc®)	2.5-10 mg PO q24h	Same	Same	Same	Same
Diltiazem (Dilacor®, Cardizem®, Tiazac®)	30-90 mg PO q6-8h	Same	Same	Same	Same
Felodipine (Plendil®)	5-15 mg PO q 8-24 h	Same	Same	Same	Same
Isradipine (Dynacirc®)	1.25-10 mg/d PO bid	Same	Same	Same	Same
Nicardipine (Cardene®)	20-40 mg PO tid	Same	Same	Same	Same
Nifedipine (Adalat®, Procardia®)	10-30 mg/d PO tid	Same	Same	Same	Same
Nimodipine (Nimotop®)	60 mg PO q4h	Same	Same	Same	Same
Verapamil (Calan®, Isoptin®, Verelan®)	40-120 mg PO q8h	Same	Same	20-60 mg PO q8h	20-60 mg PO q8h

(continued)

Appendix 2

Drugs in Renal Failure (continued)

Generic name (trade name)	Normal dose	CrCl 30-50 mL/min	CrCl 10-30 mL/min	CrCl <10 mL/min	Hemodialysis
<i>Diuretics</i>					
Bumetanide (Bumex®)	1-2 mg IV q8-12h	Same	Same	8-10 mg PO or IV single dose, or 12 mg infusion over 12h	Same
Furosemide (Lasix®)	40-80 mg IV q12h	Same	Same	Same	Not effective
Hydrochlorothiazide (Hydrodiuril®)	25-200 mg PO qd-tid	Same	Same	Not effective	Not effective
Spironolactone (Aldactone®)	25-200 mg/d PO in 2- 4 divided doses	12.5-100 mg PO q12-24h	12.5-100 mg PO q24h	Not effective	Not effective
Triamterene (Dyrenium®)	50-100 mg PO bid	Same	Same	Not effective	Not effective
<i>Antivirals</i>					
Acyclovir (Zovirax®)	5-10 mg/kg PO or IV q8h	5-10 mg/kg PO or IV q12h	5-10 mg/kg PO or IV q24h	2.5 mg/kg PO or IV q24h	2.5-5 mg/kg PO or IV q24h given post-HD
Amantadine (Symmetrel®)	100 mg PO q12h	100 mg PO q24h	100 mg PO q48h	200 mg PO q7d	200 mg PO q7d
Didanosine (Videx®)	200 mg PO q12h	200 mg PO q12- 24h	200 mg PO q24h	100 mg PO q24h	Dose after HD
Entecavir (Baraclude®)	0.5-1 mg qd	0.25-0.5 mg qd	0.15-0.3 mg qd	0.05-0.1 mg qd	Dose after HD
Famciclovir (Famvir®)	125 mg PO q12h, or 500 mg PO q8h	125 mg PO q12h, 500 mg PO q12h	125 mg PO q12-48h, 500 mg PO 12- 48h	62.5 mg PO q48h, or 250 mg PO q48h	Dose after HD
Ganciclovir (Cytovene®)	1000 mg PO q8h, 5 mg/kg IV q12h, then 5 mg IV q24h	No data: 500-1000 mg PO q24h, 2.5 mg/kg IV q24h, then 1.24 mg/kg IV q24h	No data: 500-1000 mg PO q24h. 1.25 mg/kg IV q24h, then 0.625 mg/kg IV q24h	No data: 500 mg PO q48-96 h, 1.25 mg IV three times a week, then 0.625 mg/kg IV three times a week	No data: Dose PO after dialysis, 1.25 mg IV three times a week, then 0.625 mg/kg IV three times a week
Indinavir (Crixan®)	800 mg PO q8h	No data	No data	No data	No data
Lamivudine (EpiVir®)	150 mg PO q12h	50-150 mg PO q24h	50-150 mg PO q24h	25-50 mg PO q25h	Dose after HD
Nelfinavir (Viracept®)	750 mg PO q8h	No data	No data	No data	No data
Nevirapine (Viramune®)	200 mg PO q24 h x 14 d, then q12h	No data	No data	No data	No data
Ribavirin (Rebetrol®)	200 mg PO 8h	200 mg PO q8h	200 mg PO q8h	100 mg PO q8h	Dose after HD
Ritonavir (Norvir®)	600 mg PO q12h	No data	No data	No data	No data
Saquinavir (Fortovase®, Invirase®)	600 mg PO q8h	No data	No data	No data	No data
Stavudine (Zerit®)	30-40 mg PO q12h	15-20 mg PO q12- 24h	15-20 mg PO q12- 24h	15-20 mg PO q24h	15-20 mg PO q24h
Valaciclovir (Valtrex®)	500 mg PO q12h to 1000 mg PO q8h	500-1000 mg PO q12-24h	500-1000 mg PO q12-24h	500 mg q24h	Dose after HD
Zalcitabine (Hivid®)	0.75 mg PO q8h	0.75 mg PO q8-12h	0.75 mg PO q12h	0.75 mg PO q24h	No data; dose after HD
Zidovudine (Retrovir®)	200 mg PO q8h; 300 mg PO q12h	200 mg PO q8h; 300 mg PO q12h	200 mg PO q8h; 300 mg PO q12h	100 mg PO q8h	100 mg PO q8h
<i>Bisphosphonates</i>					
Zoledronic acid (Zometa®)	4 mg IV	3-3.5 mg IV	No data	No data	No data

(continued)

Drugs in Renal Failure (continued)

Generic name (trade name)	Normal dose	CrCl 30-50 mL/min	CrCl 10-30 mL/min	CrCl <10 mL/min	Hemodialysis
Gout agents					
Allopurinol (Zyloprim®)	300 mg PO q24h	150-200 mg PO q24h	150 mg PO q24h	100 mg PO q48h	150 mg supplemental dose
Colchicine (Acetycol®, Colsalide®)	Acute: 2 mg, then 0.5 mg PO q6h; Chronic: 0.5-1 mg PO q24h	Decrease dose by 50% to no change	Decrease dose by 50%	Decrease dose by 25%	Same
Probenecid (Benemid®)	500 mg PO bid	Not effective	Not effective	Not effective	Not effective
Hypoglycemic agents					
Acarbose (Precose®)	50-200 mg PO tid	Avoid	Avoid	Avoid	No data
Acetohexamide (Dymelor®)	250-1500 mg PO q24h	Avoid	Avoid	Avoid	No data
Chlorpropamide (Diabinese®)	100-500 mg PO q24h	Avoid	Avoid	Avoid	Avoid
Exenatide (Byetta®)	5-10 mcg SC q bid	Same	Avoid	Avoid	Avoid
Glipizide (Glucotrol®)	2.5-15 mg PO q24h	1.25-7.5 mg Po q24h	1.25-7.5 mg PO q24h	1.24-7.5 mg PO q24h	No data
Glyburide (Diabeta®, Glynase®, PresTab®, Micronase®)	1.25-20 mg PO q24h	Avoid	Avoid	Avoid	No supplement necessary
Insulin	Variable	75% of usual dose	75% of usual dose	50% of usual dose	No supplement necessary
Metformin (Glucophage®)	500-850 mg PO bid	125-425 mg PO bid	125-212 mg PO bid	Avoid	No data
Tolazamide (Tolinase®)	100-250 mg PO q24h	Same	Same	Same	No data
Tolbutamide (Orinase®)	1-2 g q24h	Same	Same	Same	No supplement necessary
Nonsteroidal anti-inflammatory agents					
Diclofenac (Voltaren®)	25-75 mg PO bid	12.5-37.5 mg PO bid	6.25-37.5 mg PO bid	6.25-18.75 mg PO bid	No supplement necessary
Etodolac (Lodine®)	200 mg bid	Same	Same	Same	Same
Ibuprofen (Advil®, Motrin®)	200-800 mg PO q6h	Same	Same	Same	Same
Indomethacin (Indocin®)	25-50 mg PO q6-12h	Same	Same	Same	Same
Ketorolac (Toradol®)	60 mg IM LD, then 15-30 mg q6h; 30 mg IV LD, then 15 mg q6h	Same	Same	15 mg IM or IV q6h (no bolus dose)	15 mg IM or IV q6h (no bolus dose)
Nabumetone (Relafen®)	1-2 g PO q24h	Same	0.5-1 g PO q24h	0.5-1 g PO q24h	No supplement necessary
Naproxen (Naprosyn®)	250-500 mg PO 8-12h	Same	Same	Same	Same
Oxaprozin (Daypro®)	1200 mg PO q24h	Same	Same	Same	Same
Tolmetin (Tolectin®)	400 mg PO tid	Same	Same	Same	Same
Proton pump inhibitors					
Esomeprazole (Nexium®)	20-40 mg PO q24h	Same	Same	Same	Same
Lansoprazole (Prevacid®)	15-30 mg PO q12-24h	Same	Same	Same	Same
Omeprazole (Prilosec®)	20-40 mg PO q12-24h	Same	Same	Same	Same
Pantoprazole (Protonix®)	20-80 mg PO q24h; 80 mg IV q12h	Same	Same	Same	Same

Reference: Micromedex® Healthcare Series, (electronic version). Thomson Micromedex, Greenwood Village, CO.
Available at: <http://www.thomsonhc.com> (cited 8/3/2006)

Appendix 3

Drugs in Hepatic Failure

Drug	Dose
Amiodarone (Cordarone [®] , Pacerone [®])	Dose adjustment may be necessary in patients with hepatic dysfunction
Amitriptyline (Elavil [®])	Decrease dose in patients with cirrhosis
Aspirin	Avoid in severe hepatic dysfunction
Atomoxetine (Strattera [®])	Decrease dose by 50% in moderate hepatic dysfunction; give 25% of normal dose in severe hepatic dysfunction
Azole antifungals	Consider decreased doses in patients with severe hepatic dysfunction
Azathioprine (Imuran [®])	Monitor hepatic transaminases every 2 weeks for 4 weeks, then monthly thereafter
Benzodiazepines	No dose adjustments are necessary with oxazepam (Serax [®]), lorazepam (Ativan [®]), or temazepam (Restoril [®]) Alprazolam (Xanax [®]): dose 0.25 mg bid-tid in patients with hepatic dysfunction Chlordiazepoxide (Librium [®]): avoid or decrease dose in patients with cirrhosis or hepatitis Diazepam (Valium [®]): decrease dose by 50% in patients with cirrhosis Midazolam (Versed [®]): doses may need to be decreased by 50% Triazolam (Halcion [®]): doses may need to be decreased by 50%
Bicalutamide (Casodex [®])	Use with caution in patients with moderate to severe hepatic dysfunction
Bisoprolol (Zebeta [®])	Decrease initial dose to 2.5 mg in patients with hepatic insufficiency; do not exceed a dose of 10 mg daily
Bosentan (Tracleer [®])	Liver function should be tested monthly
Buspirone (Buspar [®])	Avoid in patients with severe hepatic dysfunction
Carbamazepine (Tegreto [®])	Avoid in patients with hepatic disease
Celecoxib (Celebrex [®])	Decrease dose by 50% in patients with moderate hepatic dysfunction; avoid in patients with severe hepatic dysfunction
Clindamycin (Cleocin [®])	Decrease dose in patients with hepatic dysfunction
Cimetidine (Tagamet [®])	Decrease dose (50%) in patients with severe hepatic dysfunction
Darunavir (Prezista [®])	Monitor liver function tests at baseline, then periodically thereafter
Delavirdine (Rescriptor [®])	Decrease dose in patients with moderate hepatic disease
Diazepam (Valium [®])	Decrease dose by 50% in patients with cirrhosis
Diltiazem (Cardizem [®] , Cartia [®] , Dilacor [®] , Tiazac [®])	Doses should not exceed 90 mg/d in patients with cirrhosis
Disulfiram (Antabuse [®])	Use with caution in patients with hepatic cirrhosis or hepatic insufficiency; avoid in patients with advanced or severe hepatic disease
Erythromycin (E-Mycin [®])	Dose may need to be decreased in patients with severe hepatic dysfunction
Esomeprazole (Nexium [®])	Do not exceed a dose of 20 mg in patients with severe hepatic dysfunction
Estrogens	Use with caution in patients with impaired liver function
HMG-CoA reductase inhibitors	Avoid in patients with elevated serum transaminases
Indinavir (Crixivan [®])	Decrease dose to 600 mg q8h in patients with mild to moderate hepatic dysfunction
Interferon beta-1a (Avonex [®])	Consider a dose reduction
Interferon beta-1b (Betaseron [®])	Liver function should be tested at months 1, 3, and 6, then periodically thereafter
Isoniazid (Laniazid [®] , Nydrazid [®])	Defer therapy for prevention of tuberculosis in patients with acute hepatic disease
Isotretinoin (Accutane [®])	Monitor liver function tests at baseline, then at weekly or biweekly intervals until a response to the treatment is established
Lamivudine-zidovudine (Combivir [®])	Decrease zidovudine dose by 50% in hepatic insufficiency
Lamotrigine (Lamictal [®])	Reduce initial, escalation, and maintenance doses by 50% in patients with moderate hepatic dysfunction; decrease doses by 75% in patients with severe hepatic dysfunction
Lansoprazole (Prevacid [®])	Decrease dose in patients with hepatic dysfunction
Leflunomide (Arava [®])	Avoid in patients with moderate to severe hepatic dysfunction; decrease dose to 10 mg/d if liver enzymes are elevated to 2 times the upper limit of normal; discontinue if liver enzymes are elevated to 3 times the upper limit of normal
Losartan (Cozaar [®])	Decrease initial dose to 25 mg; total daily dose should not exceed 100 mg
Methotrexate (Folex [®] , Rheumatrex [®])	Decrease dose by 25% when the bilirubin is 3.1-5 mg% and the AST is >180 IU; avoid if the bilirubin is >5 mg%
Metoprolol (Lopressor [®])	Dose adjustment may be necessary in patients with hepatic insufficiency
Nabumetone (Relafen [®])	Use with caution in patients with severe hepatic insufficiency
Nefazodone (Serzone [®])	Avoid in patients with elevated transaminases
Nelfinavir (Viracept [®])	Use with caution in patients with hepatic impairment
Ofloxacin (Floxin [®])	Do not exceed 400 mg/d in patients with severe liver dysfunction
Omeprazole (Prilosec [®])	Decrease dose in patients with hepatic dysfunction
Ondansetron (Zofran [®])	Do not exceed 8 mg/d in patients with severe hepatic insufficiency
Oxycodone (Oxycontin [®])	Initiate dose at one third to one half the usual dose in patients with hepatic dysfunction; increase dose conservatively

(continued)

Appendix 3

Drugs in Hepatic Failure (continued)

Drug	Dose
Pantoprazole (Protonix®)	Consider every-other-day dosing in patients with severe hepatic dysfunction
Pioglitazone (Actos®)	Avoid in patients with hepatic disease or serum transaminases >2.5 times the upper limit of normal
Phenobarbital (Barbita®, Luminal®, Solfoton®)	Dose may need to be decreased in patients with hepatic dysfunction
Phenytoin (Dilantin®)	Monitor levels frequently as the dose may need to be decreased in hepatic failure
Procainamide (Procanbid®, Promine®, Pronestyl®, Rhythmin®)	Lower doses or longer dosing intervals may be required in patients with hepatic failure
Propranolol (Betachron®, Inderal®)	Monitor more frequently in patients with hepatic dysfunction
Quinidine (Cardioquin®, Quinaglute®, Quinalan®, Quinidex, Quinora®)	Maintenance doses may need to be decreased by 50% in patients with chronic hepatitis
Risperidone (Risperdal®)	Decrease dose in patients with hepatic dysfunction
Rofecoxib (Vioxx®)	Use the lowest dose possible in patients with moderate hepatic impairment
Rifampin (Rifadin®, Rimactane®)	Decrease dose in patients with a serum bilirubin >50 micromol/L; doses should not exceed 6-8 mg/kg biweekly in patients with severe hepatic dysfunction
Ritonavir (Norvir®)	Use with caution in patients with moderate to severe hepatic dysfunction
Saquinavir (Invirase®, Fortovase®)	Avoid in severe hepatic dysfunction
Selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors	The dose should be decreased or the dosing interval increased in patients with hepatic insufficiency Citalopram (Celexa®): a dose of 20 mg is recommended for patients with decreased hepatic function Fluoxetine (Prozac®): a 50% dose reduction is recommended in patients with cirrhosis Fluvoxamine (Luvox®): decrease the dose and titrate slowly in patients with hepatic insufficiency Paroxetine (Paxil®): dose initially at 10 mg daily or 12.5 mg daily of the controlled-release product; doses should not exceed 40 mg daily or 50 mg daily of the controlled-release product Sertraline (Zoloft®): decrease the dose or increase the interval Venlafaxine (Effexor®): decrease the dose by 50% in patients with moderate hepatic impairment
Sulfonylureas	Dose may need to be decreased in hepatic disease
Tacrolimus (Prograf®)	Dose at the low end of the dosing range in patients with hepatic insufficiency
Tetracyclines	Avoid in patients with hepatic dysfunction
Theophylline (Aerolate®, Aminophyllin®, Aqua-phyllin®, Asmalix®, Bronkodyl®, Choledyl®, Duraphyl®, Respbid®, Slo-bid®, Slo-Phyllin®, Sustaire®, Theo-24®, Theo-bid®, Theochron®, Theo-clear®, Theo-Dur®, Theolair®, Theon®, Theospan®, Theovent®, Truphylline®)	Dose may need to be decreased and serum levels should be monitored frequently in patients with hepatic insufficiency
Tipranavir (Aptivus®)	Contraindicated in patients with moderate to severe hepatotoxicity; monitor liver functions at baseline then periodically thereafter
Tramadol (Ultram®)	Dose 50 mg PO q12h in patients with cirrhosis
Tricyclic antidepressants: amitriptyline (Elavil®), clomipramine (Anafranil®), desipramine (Norpramin®), doxepin (Sinequan®), imipramine (Tofranil®), nortriptyline (Pamelor®), protriptyline (Vivactil®)	Dose should be decreased in patients with cirrhosis
Valdecoxib (Bextra®)	Do not exceed 10 mg/d in patients with moderate hepatic impairment; avoid in severe hepatic dysfunction
Valproic acid (Depakote®, Depakene®)	Avoid in patients with hepatic disease or significant hepatic insufficiency
Warfarin (Coumadin®)	Monitor INR more frequently
Zafirlukast (Accolate®)	Consider a decreased dose in patients with cirrhosis
Zalcitabine (Hivid®)	Avoid in patients with liver function tests >5 times the upper limit of normal
Zidovudine (Retrovir®)	Decrease dose by 50% in patients with cirrhosis

References: Micromedex® Healthcare Series (electronic version). Thomson Micromedex, Greenwood Village, CO.

Available at: <http://www.thomsonhc.com> (cited 8/3/2006).

Appendix 4

Top 200 Prescription Drugs

The following is a list of the top 200 prescriptions for 2005 by the number of U.S. prescriptions dispensed; obtained with permission from rxlist.com with data furnished by NDC Health.

Brand name	Generic name	Brand name	Generic name
1. Hydrocodone w/ APAP	hydrocodone w/ APAP	51. Levaquin	levofloxacin
2. Lipitor	atorvastatin	52. Tramadol	tramadol
3. Amoxicillin	amoxicillin	53. Ciprofloxacin	ciprofloxacin
4. Lisinopril	lisinopril	54. Lotrel	amlodipine/benazepril
5. Hydrochlorothiazide	hydrochlorothiazide	55. Ranitidine	ranitidine
6. Atenolol	atenolol	56. Allegra	fexofenadine
7. Zithromax	azithromycin	57. Levoxyl	levothyroxine
8. Furosemide	furosemide	58. Diovan	valsartan
9. Alprazolam	alprazolam	59. Enalapril	enalapril
10. Toprol XL	metoprolol XL	60. Diazepam	diazepam
11. Albuterol Aerosol	albuterol	61. Naproxen	naproxen
12. Norvasc	amlodipine	62. Fluconazole	fluconazole
13. Levothyroxine	levothyroxine	63. Lisinopril/hydrochlorothiazide	lisinopril/hydrochlorothiazide
14. Synthroid	levothyroxine	64. Klor-Con	potassium chloride
15. Metformin	metformin	65. Altace	ramipril
16. Zoloft	sertraline	66. Wellbutrin XL	bupropion
17. Lexapro	escitalopram	67. Celebrex	Celecoxib
18. Ibuprofen	ibuprofen	68. Viagra	sildenafil citrate
19. Cephalexin	cephalexin	69. Doxycycline	doxycycline
20. Ambien	zolpidem	70. Zetia	ezetimibe
21. Prednisone	prednisone	71. Avandia	rosiglitazone maleate
22. Nexium	esomeprazole	72. Lovastatin	lovastatin
23. Triamterene/ hydrochlorothiazide	triamterene/hydrochlorothiazide	73. Diovan HCT	valsartan/hydrochlorothiazide
24. Propoxyphene N/APAP	propoxyphene N/APAP	74. Carisoprodol	carisoprodol
25. Zocor	simvastatin	75. Yasmin 28	drospirenone/ethinyl estradiol
26. Singulair	montelukast	76. Allopurinol	allopurinol
27. Prevacid	lansoprazole	77. Clonidine	clonidine
28. Metoprolol tartrate	metoprolol	78. Methylprednisolone	methylprednisolone
29. Fluoxetine	fluoxetine	79. Actos	pioglitazone
30. Lorazepam	lorazepam	80. Pravachol	pravastatin
31. Plavix	clopidogrel	81. Actonel	risedronate
32. Oxycodone/APAP	oxycodone/APAP	82. Ortho Evra	norelgestromin/ethinyl estradiol
33. Amoxicillin/clavulanate	amoxicillin/clavulanate	83. Citalopram	citalopram
34. Advair Diskus	salmeterol/fluticasone	84. Verapamil SR	verapamil
35. Fosamax	alendronate	85. Isosorbide	isosorbide
36. Effexor XR	venlafaxine	86. Penicillin VK	penicillin VK
37. Warfarin	warfarin	87. Glyburide	glyburide
38. Paroxetine	paroxetine	88. Adderall XR	amphetamine mixed salts
39. Clonazepam	clonazepam	89. Nasonex	mometasone
40. Zyrtec	cetirizine	90. Folic acid	folic acid
41. Protonix	pantoprazole	91. Seroquel	quetiapine
42. Potassium chloride	potassium chloride	92. Cozaar	losartan
43. Acetaminophen/codeine	acetaminophen/codeine	93. Tricor	fenofibrate
44. Trimethoprim/ sulfamethoxazole	trimethoprim/sulfamethoxazole	94. Coreg	carvedilol
45. Gabapentin	gabapentin	95. Concerta	methylphenidate XR
46. Premarin	conjugated estrogens	96. Vytorin	ezetimibe/simvastatin
47. Flonase	fluticasone	97. Lantus	insulin glargine
48. Trazodone	trazodone	98. Promethazine	promethazine
49. Cyclobenzaprine	cyclobenzaprine	99. Mobic	meloxicam
50. Amitriptyline	amitriptyline	100. Flomax	tamsulosin
		101. Crestor	rosuvastatin
		102. Glipizide ER	glipizide ER

(continued)

Appendix 4

Top 200 Prescription Drugs (continued)

Brand name	Generic name	Brand name	Generic name
103. Ortho Tri-Cyclen Lo	norgestimate/ethinyl estradiol	152. Zyprexa	olanzapine
104. Temazepam	temazepam	153. Lamictal	lamotrigine
105. Omeprazole	omeprazole	154. Zyrtec Syrup	cetirizine
106. Omnicef	cefdinir	155. Glycolax	polyethylene glycol 3350
107. Albuterol Nebulizer Solution	albuterol nebulizer solution	156. Acyclovir	acyclovir
108. Risperidal	risperidone	157. Propranolol	propranolol
109. Aciphex	rabeprazole	158. Nasacort AQ	triamcinolone acetonide
110. Digitek	digoxin	159. Aricept	donepezil
111. Spironolactone	spironolactone	160. Butalbital/ acetaminophen/caffeine	butalbital/acetaminophen/caffeine
112. Valtrex	valacyclovir	161. Niaspan	niacin
113. Xalatan	latanoprost	162. Azithromycin	azithromycin
114. Metformin ER	metformin ER	163. Depakote	divalproex
115. Hyzaar	losartan/hydrochlorothiazide	164. Buspirone	buspirone
116. Quinapril	quinapril	165. Tri-Sprintec	norgestimate/ethinyl estradiol
117. Clindamycin	clindamycin	166. Methotrexate	methotrexate
118. Metronidazole Tabs	metronidazole	167. OxyContin	oxycodone
119. Triamcinolone	triamcinolone	168. Rhinocort Aqua	budesonide
120. Topamax	topiramate	169. Benicar HCT	olmesartan/hydrochlorothiazide
121. Combivent	ipratropium/albuterol	170. Terazosin	terazosin
122. Benazepril	benazepril	171. Skelaxin	metaxalone
123. Gemfibrozil	gemfibrozil	172. Clotrimazole/betamethasone	clotrimazole/betamethasone
124. Avapro	irbesartan	173. Cialis	tadalafil
125. Amaryl	glimepiride	174. Avalide	irbesartan/hydrochlorothiazide
126. Trinessa	norgestimate/ethinyl estradiol	175. Fexofenadine	fexofenadine
127. Estradiol	estradiol	176. Ortho Tri-Cyclen	norgestimate/ethinyl estradiol
128. Hydroxyzine	hydroxyzine	177. Bupropion SR	bupropion
129. Metoclopramide	metoclopramide	178. Benzonate	benzonate
130. Allegra-D 12 Hour	fexofenadine/pseudoephedrine	179. Patanol	olopatadine
131. Doxazosin	doxazosin	180. Quinine	quinine
132. Coumadin	warfarin	181. Cartia XT	diltiazem
133. Glipizide	glipizide	182. Humalog	insulin lispro
134. Diclofenac	diclofenac	183. Paxil CR	paroxetine
135. Evista	raloxifene	184. Aviane	levonorgestrel/ethinyl estradiol
136. Diltiazem CD	diltiazem	185. Lanoxin	digoxin
137. Detrol LA	tolterodine	186. Amphetamine mixed salts	amphetamine mixed salts
138. Meclizine	meclizine	187. Famotidine	famotidine
139. Glyburide/metformin	glyburide/metformin	188. Digoxin	digoxin
140. Stratterra	atomoxetine	189. Levothroid	levothyroxine
141. Cymbalta	duloxetine	190. Nifedipine ER	nifedipine
142. Nitrofurantoin	nitrofurantoin	191. Nortriptyline	nortriptyline
143. Promethazine/codeine	promethazine/codeine	192. Tussionex	hydrocodone/chlorpheniramine
144. Benicar	olmesartan	193. Nitroquick	nitroglycerin
145. Mirtazapine	mirtazapine	194. Phenytoin	phenytoin
146. Bisoprolol/ hydrochlorothiazide	bisoprolol/hydrochlorothiazide	195. Endocet	oxycodone/acetaminophen
147. Clarinex	desloratadine	196. Etodolac	etodolac
148. Oxycodone	oxycodone	197. Atenolol/chlorthalidone	atenolol/chlorthalidone
149. Minocycline	minocycline	198. Phentermine	phentermine
150. Imitrex	sumatriptan	199. Tramadol/acetaminophen	tramadol/acetaminophen
151. Nabumetone	Nabumetone	200. Tizanidine	tizanidine

The Top 200 Prescriptions for 2005 by Number of U.S. Prescriptions Dispensed. RxList the internet drug index web site.

Available at: www.rxlist.com/top200.htm. Accessed on: August 4, 2006.

Appendix 5

Top 200 Over-the-Counter Products

The following is a list of over-the-counter (OTC) and health and beauty care brands based on dollar amount in 2004.

Rank	Product	Rank	Product
1.	Private-label internal analgesic tablets	51.	Trojan male contraceptives
2.	Private-label cold/allergy/sinus tablets/packets	52.	Metamucil laxative/stimulant liq/pwdr/oil
3.	Private-label mineral supplements	53.	Osteo Bi Flex mineral supplements
4.	Advil internal analgesic tablets	54.	Boost weight control/nutritionals liq/pwd
5.	Tylenol internal analgesic tablets	55.	Private-label weight control/nutritionals liq/pwd
6.	Prilosec OTC antacid tablets	56.	Private-label cough syrup
7.	Depend adult incontinence products	57.	Tums EX antacid tablets
8.	Nicorette anti-smoking gum	58.	Ensure Plus weight control/nutritionals liq/pwd
9.	Private-label one- and two-letter vitamins	59.	Private-label nasal spray/drops/inhaler
10.	Private-label adult incontinence products	60.	Atkins Advantage weight control/nutritionals liq/pwd
11.	Private-label multivitamins	61.	Tylenol Arthritis internal analgesic tablets
12.	Aleve internal analgesic tablets	62.	Alavert cold/allergy/sinus tablets/packets
13.	Private-label first aid ointments/antiseptics	63.	Mucinex cold/allergy/sinus tablets/packets
14.	Ensure weight control/nutritionals liq/pwd	64.	Tylenol Sinus cold/allergy/sinus tablets/packets
15.	Private-label laxative tablets	65.	Sudafed cold/allergy/sinus tablets/packets
16.	Private-label antacid tablets	66.	Abreva lip balm/cold sore medication
17.	Slim Fast meal options weight control/nutritionals liq/pwd	67.	Imodium A-D diarrhea tablets
18.	Depend Poise adult incontinence products	68.	Private-label vaginal treatments
19.	Claritin D cold/allergy/sinus tablets/packets	69.	Private-label pregnancy test kits
20.	Private-label cold/allergy/sinus liquid/powder	70.	Commit anti-smoking tablets
21.	Benadryl cold/allergy/sinus tablets/packets	71.	Tylenol internal analgesic liquids
22.	Claritin cold/allergy/sinus tablets/packets	72.	Imodium Advanced diarrhea tablets
23.	Bayer internal analgesic tablets	73.	Children's Motrin internal analgesic liquids
24.	Tylenol PM internal analgesic tablets	74.	Neosporin Plus first aid ointments/antiseptics
25.	Nature Made one- and two-letter vitamins	75.	Tylenol Cold cold/allergy/sinus tablets/packets
26.	Centrum Silver multivitamins	76.	Private-label laxative/stimulant liq/pwdr/oil
27.	PediaSure weight control/nutritionals liq/pwd	77.	Futuro muscle/body support devices
28.	Private-label anti-smoking gum	78.	Monistat 3 vaginal treatments
29.	Private-label first aid – tape/bandage/gauze/cotton	79.	E P T pregnancy test kits
30.	Halls cough/sore throat drop	80.	Icy Hot external analgesics rubs
31.	Private-label eye/lens care solutions	81.	Tylenol Plus cold/allergy/sinus liquid/powder
32.	Pepcid AC antacid tablets	82.	Dulcolax laxative tablets
33.	Nicoderm CQ anti-smoking patch	83.	Theraflu cold/allergy/sinus tablets/packets
34.	Band-Aid first aid – tape/bandage/gauze cotton	84.	Private-label anti-smoking patch
35.	Dr. Scholl's foot care devices	85.	Alka-Seltzer plus cold/allergy/sinus tablets/packets
36.	Centrum multivitamins	86.	Breathe Right nasal strips
37.	Vicks Nyquil cold/allergy/sinus liquid/powder	87.	Bengay external analgesics rubs
38.	Nature Made mineral supplements	88.	Primatene Mist nasal spray/drops/inhaler
39.	Motrin IB internal analgesic tablets	89.	Pepcid Complete antacid tablets
40.	Bausch & Lomb ReNu Multiplus eye/lens care solutions	90.	Preparation H hemorrhoidal cream/ointment/spray
41.	Alcon Opti Free Express eye/lens care solutions	91.	Ensure Glucerna weight control/nutritionals liq/pwd
42.	Johnson & Johnson first aid – tape/bandage/gauze/cotton	92.	Private-label cough/sore throat drop
43.	Zantac 75 antacid tablets	93.	Zicam nasal spray/drops/inhaler
44.	Nature's Bounty mineral supplements	94.	Trim Spa weight control candy/tablets
45.	Ace muscle/body support devices	95.	First Response pregnancy test kits
46.	Robitussin DM cough syrup	96.	Excedrin Migraine internal analgesic tablets
47.	ThermaCare heat/ice packs	97.	Neosporin first aid ointments/antiseptics
48.	Private-label anti-itch treatments (inc. calamine)	98.	Advil cold & sinus cold/allergy/sinus tablets/packets
49.	Pepto-Bismol stomach remedy liquid/powder	99.	St. Joseph internal analgesic tablets
50.	Excedrin internal analgesic tablets	100.	Sundown mineral supplements

(continued)

Appendix 5

Top 200 Over-the-Counter Products (continued)

Rank	Product	Rank	Product
101.	Gas X antacid tablets	151.	Mylanta antacid liquid/powder
102.	Tylenol 8 Hour internal analgesic tablets	152.	Monistat 7 vaginal treatments
103.	Rolaids antacid tablets	153.	Rid lice treatments
104.	One-A-Day multivitamins	154.	Nature's Bounty one- and two-letter vitamins
105.	Monistat 1 vaginal treatments	155.	Cortizone 10 anti-itch treatments (inc. calamine)
106.	Trojan Enz male contraceptives	156.	Private-label hair growth products
107.	Tylenol allergy sinus cold/allergy/sinus tablets/packets	157.	Private-label Epsom salts
108.	Vicks Dayquil cold/allergy/sinus tablets/packets	158.	Flintstones multivitamins
109.	Private-label internal analgesic liquids	159.	Halls Fruit Breezers cough/sore throat drop
110.	Afrin nasal spray/drops/inhaler	160.	Tums Ultra antacid tablets
111.	Lamisil AT foot care/athletes foot medication	161.	Citrucel laxative/stimulant liq/pwdr/oil
112.	Vicks VapoRub chest rubs	162.	3M Nexcare first aid – tape/bandage/gauze/cotton
113.	Alka-Seltzer antacid/analgesic combo	163.	Infants' Motrin internal analgesic liquids
114.	Phillips stomach remedy liquid/powder	164.	Allergan Refresh Tears eye/lens care solutions
115.	ChapStick lip balm/cold sore medication	165.	Blistex lip balm/cold sore medication
116.	Serenity adult incontinence products	166.	Centrum Performance multivitamins
117.	Ricola cough/sore throat drop	167.	Ultra Slim-Fast weight control/nutritionals liq/pwd
118.	Metamucil laxative tablets	168.	Zantrex 3 weight control candy/tablets
119.	Private-label sleeping aid tablets	169.	Pepto-Bismol stomach remedy tablets
120.	Triaminic cold/allergy/sinus liquid/powder	170.	Natrol mineral supplements
121.	Rogaine hair growth products	171.	Estroven mineral supplements
122.	Nature's Resource mineral supplements	172.	Tylenol Flu cold/allergy/sinus tablets/packets
123.	Delsym cough syrup	173.	Excedrin Tension Headache internal analgesic tablets
124.	Robitussin cough syrup	174.	Clearblue Easy pregnancy test kits
125.	Private-label foot care/athletes foot medication	175.	Vicks Dayquil cold/allergy/sinus liquid/powder
126.	Ex-Lax laxative tablets	176.	Robitussin cold/allergy/sinus liquid/powder
127.	Private-label diarrhea tablets	177.	Xenadrine EFX weight control candy/tablets
128.	Benadryl cold/allergy/sinus liquid/powder	178.	Lifestyles male contraceptives
129.	Viactiv mineral supplements	179.	Hydroxycut weight control candy/tablets
130.	Lotrimin A F foot care/athletes foot medication	180.	Halls Defense cough/sore throat drop
131.	Midol feminine pain relievers	181.	Private-label lice treatments
132.	Vicks Nyquil cold/allergy/sinus tablets/packets	182.	Boost Plus weight control candy/tablets
133.	Ecotrin internal analgesic tablets	183.	Ludens cough/sore throat drop
134.	Claritin Reditabs cold/allergy/sinus tablets/packets	184.	Tums antacid tablets
135.	Dimetapp cold/allergy/sinus liquid/powder	185.	Excedrin PM internal analgesic tablets
136.	Robitussin CF cold/allergy/sinus liquid/powder	186.	Sudafed Sinus cold/allergy/sinus tablets/packets
137.	Sundown one- and two-letter vitamins	187.	Maalox Max antacid liquid/powder
138.	Preparation H hemorrhoidal remedies	188.	Summers Eve all other fem. Hygiene/med. treatments
139.	Private-label foot care devices	189.	K-Y Warming Liquid personal lubricants
140.	Tinactin foot care/athletes foot medication	190.	Motrin cold/allergy/sinus liquid/powder
141.	Caltrate 600 mineral supplements	191.	Visine eye/lens care solutions
142.	Citracal mineral supplements	192.	Chloraseptic sore throat remedy liquids
143.	Benadryl anti-itch treatments (inc. calamine)	193.	EAS Carb Control weight control/nutritionals liq/pwd
144.	Os Cal mineral supplements	194.	Mederma first aid ointments/antiseptics
145.	Private-label stomach remedy liquid/powder	195.	Metabolife Ultra weight control candy/tablets
146.	Bausch & Lomb ReNu eye/lens care solutions	196.	Vicks Sinex nasal spray/drops/inhaler
147.	Coricidin HBP cold/allergy/sinus tablets/packets	197.	Benefiber laxative/stimulant liq/pwdr/oil
148.	Pediacare cold/allergy/sinus liquid/powder	198.	AMO Complete Moisture Plus eye/lens care solutions
149.	One-A-Day Weight Smart multivitamins	199.	Slim Fast Optima weight control/nutritionals liq/pwd
150.	Cold Eeze cough/sore throat drop	200.	Bausch & Lomb Ocuvite Presr Vision multivitamins

Appendix 6

Drugs Excreted in Breast Milk

The following is not comprehensive; generics and alternate brands of some products may exist. When recommending drugs to pregnant or nursing patients, always check product labeling for specific precautions.

Accolate	Compazine	Floxin	Meruvax II	Phenergan	Tegretol
Accutec	Cordarone	Fluorescite	Methergine	Phenobarbital	Tenoretic
Achromycin	Corgard	Fortaz	Methotrexate	Phenilin	Tenormin
Actiq	Cortisporin	Furosemide	MetroCream/Gel/Lotion	Pipracil	Tenuate
Activella	Corzide	Gabitril	Mexitil	Plan B	Testoderm
Adalat	Cosopt	Galzin	Mezlin	Platinol-AQ	Thalitone
Adderall	Coumadin	Garamycin	Micronor	Ponstel	Theo-24
Advicor	Covera-HS	Glucophage	Microzide	Pravachol	Theo-Dur
Aggrenox	Crinone	Glyset	Midamor	Premphase	Thorazine
Aldactazide	Cyclessa	Guaifed	Migranal	Prempro	Tiazac
Aldactone	Cystospaz	Halcion	Miltown	Prevacid	Timolide
Aldoclor	Cytomel	Haldol	Minizide	Preven	Timoptic
Aldomet	Cytotec	Helidac	Minocin	PREVPAC	Tobi
Aldoril	Cytoxan	Hydrocet	Mirapex	Prinzide	Tofranil
Alesse	Dapsone	Hydrocortone	Mircette	Procanbid	Tolectin
Allegra-D	Daraprim	HydroDIURIL	M-M-R II	Prograf	Tol-Tab
Alfenta	Darvon	Iberet-Folic	Modicon	Proloprim	Toprol-XL
Aloprim	Darvon-N	Ifex	Moduretic	Prometrium	Toradol
Altace	Decadron	Imitrex	Monodox	Pronestyl	Trandate
Ambien	Deconsal II	Imuran	Mono-Gesic	Propofol	Tranxene
Anaprox	Demerol	Inderal	Monopril	Prosed/DS	Trental
Ancef	Demulen	Inderide	Morphine	Provera	Triafon
Androderm	Depacon	Indocin	MS Contin	Prozac	Trileptal
Apresoline	Depakene	INFeD	MSIR	Pseudoephedrine	Tri-Leven
Aralen	Depakote	Invanz	Myambutol	Pulmicort	Tri-Norinyl
Arthrotec	Depo-Provera	Inversine	Mykrox	Pyrzainamide	Triostat
Asacol	Desogen	Isoptin	Mysoline	Quibron	Triphasil
Astramorph/PF	Desoxyn	Kadian	Naprelan	Quibron-T	Trivora
Ativan	Desyrel	Keflex	Naprosyn	Quinidex	Trizivir
A/T/S	Dexedrine	Keftab	Nascobal	Quinine	Trovan
Augmentin	DextroStat	Kefurox	Necon	Reglan	Tylenol
Avalide	D.H.E. 45	Kefzol	NegGram	Relpax	Tylenol with Codeine
AVC	Diabinese	Keppra	Nembutal	Renese	Ultram
Axid	Diastat	Kerlone	Neoral	Requip	Unasyn
Acocet	Diflucan	Klonopin	Niaspan	Reserpine	Uniphyl
Azactam	Digitek	Kronofed-A	Nicotrol	Restoril	Uniretic
Azathioprine	Dilacor	Kutrase	Nizoral	Retrovir	Unithroid
Azulfidine	Dilantin	Lamictal	Norco	Ridaura	Urimax
Bactrim	Dilaudid	Lamisil	Nor-QD	Rifadin	Uroqid-Acid
Benadryl	Diovan	Lamprone	Nordette	Rifamate	Valium
Bentyl	Diprivan	Lanoxicaps	Norinyl	Rifater	Valtrex
Betapace	Disalcid	Lanoxin	Noritate	Rimactane	Vanceril
Bexxar	Diuril	Lariam	Normodyne	Risperdal	Vancocin
Bicillin	Dolobid	Lescol	Norpace	RMS	Vantin
Blocadren	Dolophine	Levbid	Norplant	Robaxisal	Vasor
Brethine	Doral	Levlen	Novantrone	Rocaltrol	Vaseretic
Brevicon	Doryx	Levlite	Nubain	Rocephin	Vasotec
Brontex	Droxia	Levora	Nucofed	Roferon A	Verelan
Cafergot	Duraclon	Levothroid	Nydrazid	Roxanol	Vermox
Calan	Duragesic	Levoxyl	Oramorph	Salflex	Versed
Capoten	Duramorph	Levsin	Oretic	Sandimmune	Vibramycin
Capozide	Duratuss	Levsinex	Ortho-Cept	Sansert	Vibra-Tabs
Captopril	Duricef	Lexapro	Ortho-Cyclen	Sarafem	Vicodin
Carbatrol	Dyazide	Lexxel	Ortho-Novum	Seconal	Viramune
Cardizem	Dyrenium	Lindane	Ortho Tri-Cyclen	Sectral	Voltaren
Cataflam	E.E.S.	Lioresal	Orudis	Sedapap	Wellbutrin
Catapres	EC-Naprosyn	Lithium	Ovcon	Semprex-D	Xanax
Cecilor	Ecotrin	Lithobid	Ovral	Sepra	Zagam
Cefizox	Effexor	Lo/Ovral	Ovrette	Sinequan	Zantac
Cefobid	EMLA	Loestrin	Oxistat	Slo-bid	Zarontin
Cefotan	Enduron	Lomitol	OxyContin	Solganal	Zaroxolyn
Ceftin	ERYC	Loniten	OxyFast	Soma	Zestoretic
Celexa	EryPed	Lopressor	OxyIR	Sonata	Ziac
Ceptaz	Ery-Tab	Lortab	Pacerone	Sporanox	Zinacef
Cerebyx	Erythrocin	Lotensin	Pamelor	Stadol	Zithromax
Ceredase	Erythromycin	Lotrel	Pancrease	Streptomycin	Zoloft
Cipro	Esgic-plus	Lufyllin	Panlor SS	Stromectol	Zonalon
Claforan	Eskalith	Lufyllin-GG	Paxil	Symmetrel	Zonegran
Clarinet	Estrostep	Luminal	PCE	Syn-Rx	Tagamet
Claritin	Ethmozine	Luvox	Pediapred	Synthroid	Zovia
Claritin-D	Felbatol	Macrobid	Pediazole	Tagamet	Zovirax
Cleocin	Feldene	Macroclantin	Pediotic	Tambocor	Zyban
Clozaril	fermhrt	Mandol	Pentasa	Tapazole	Zydone
Codeine	Fero-Folic	Marinol	Pepcid	Tarka	Zyloprim
CombiPatch	Floralin	Maxipime	Periostat	Tavist	Zyrtec
Combipres	Flagyl	Maxzide	Persantine	Tazicef	
Combivir	Florinef	Mefoxin	Pfizerpen	Tazidime	

Appendix 7

Drugs That May Cause Photosensitivity

The drugs in this table are known to cause photosensitivity in some individuals. Effects can range from itching, scaling, rash, and swelling to skin cancer, premature skin aging, skin and eye burns, cataracts, reduced immunity, blood vessel damage, and allergic reactions.

The list is not all-inclusive, and shows only representative brands of each generic. When in doubt, always check specific product labeling. Individuals should be advised to wear protective clothing and to apply sunscreens while taking the medications listed below.

Generic	Brand	Generic	Brand	Generic	Brand
Acetazolamide	Diamox	Cidofovir	Vistide	Haloperidol	Haldol
Acitretin	Soriatane	Ciprofloxacin	Cipro	Hexachlorophene	pHisoHex
Alatrofloxacin	Trovan I.V.	Citalopram	Celexa	Hydralazine/ hydrochlorothiazide	Apresazide
Alendronate	Fosamax	Clemastine	Tavist	Hydrochlorothiazide	HydroDIURIL, Microzide, Oretic
Alitretinoin	Panretin	Clozapine	Clozaril	Hydrochlorothiazide/fosinopril	Monopril HCT
Almotriptan	Axert	Cromolyn sodium	Gastrocrom	Hydrochlorothiazide/irbesartan	Avalide
Amiloride/hydrochlorothiazide	Moduretic	Cyclobenzaprine	Flexeril	Hydrochlorothiazide/lisinopril	Prinzide, Zestoretic
Aminolevulinic acid	Levulan Kerastick	Cyproheptadine	Periactin	Hydrochlorothiazide/ losartan potassium	Hyzaar
Amiodarone	Cardarone, Pacerone	Dacarbazine	DTIC-Dome	Hydrochlorothiazide/ methyldopa	Aldoril
Amitriptyline	Elavil	Dantrolene	Dantrium	Hydrochlorothiazide/ moexipril	Uniretic
Amitriptyline/chlordiazepoxide	Limbital	Demeclocycline	Declomycin	Hydrochlorothiazide/ propranolol	Inderide
Amitriptyline/perphenazine	Triavil	Desipramine	Norpramin	Hydrochlorothiazide/ quinapril	Accuretic
Amoxapine		Diclofenac potassium	Cataflam	Hydrochlorothiazide/ spironolactone	Aldactazide
Anagrelide	Agrylin	Diclofenac sodium	Voltaren	Hydrochlorothiazide/telmisartan	Micardis HCT
Apripiprazole	Abilify	Diclofenac sodium/ misoprostol	Arthrotec	Hydrochlorothiazide/timolol	Timolide
Atazanavir	Reyataz	Diffunisal	Dolobid	Hydrochlorothiazide/triamterene	Dyazide, Maxzide
Atenolol/chlorthalidone	Tenoretic	Dihydroergotamine	D.H.E. 45	Hydrochlorothiazide/valsartan	Diovan HCT
Atorvastatin	Lipitor	Diltiazem	Cardizem, Tiazac	Hydroflumethiazide	Diucardin
Aurothioglucose	Solganal	Diphenhydramine	Benadryl	Hydroxychloroquine	Plaquenil
Azatadine/pseudoephedrine	Rynatan, Trinalin	Divalproex	Depakote	Hypericum	Kira, St. John's Wort
Azithromycin	Zithromax	Doxepin	Sinequan	Hypericum/vitamin B/ vitamin C/kava-kava & Mood	One-A-Day Tension
Benazepril	Lotensin	Doxycycline hyclate	Doryx, Periostat, Vibra-Tabs, Vibramycin	Ibuprofen	Motrin
Benazepril/hydrochlorothiazide	Lotensin HCT	Doxycycline monohydrate	Monodox	Imatinib Mesylate	Gleevec
Bendroflumethiazide/nadolol	Corzide	Enalapril	Vasotec	Imipramine	Tofranil
Bexarotene	Targretin	Enalapril/felodipine	Lexxel	Indapamide	Lozol
Bismuth/metronidazole/ tetracycline	Helidac	Enalapril/hydrochlorothiazide	Vaseretic	Interferon alfa-2b, recombinant	Intron A
Bisoprolol/hydrochlorothiazide	Ziac	Enalaprilat	Vasotec I.V.	Interferon alfa-n3 (human leukocyte derived)	Alferon-N
Brompheniramine/ dextromethorphan/ phenylephrine	Alacol DM	Epirubicin	Ellence	Interferon beta-1a	Avonex
Brompheniramine/ dextromethorphan/ pseudoephedrine	Bromfed-DM	Eprosartan mesylate/ hydrochlorothiazide	Teveten HCT	Interferon beta-1b	Betaseron
Buffered aspirin/ pravastatin	Pravigard PAC	Erythromycin/sulfisoxazole	Pediazole	Irbesartan/ hydrochlorothiazide	Avalide
Bupropion		Estazolam	ProSom	Isoniazid/pyrazinamide/ rifampin	Rifater
Candesartan/ hydrochlorothiazide	Wellbutrin, Zyban	Estradiol	Gynodiol	Isotretinoin	Accutane, Amnesteem
Capecitabine	Atacand HCT	Ethionamide	Trecator-SC	Ketoprofen	Orudis, Oruvail
Captopril		Etodolac	Lodine	Lamotrigine	Lamictal
Captopril/hydrochlorothiazide		Felbamate	Felbatol	Leuprolide	Lupron
Carbamazepine		Fenofibrate	Tricor, Lofibra	Levamisole	Ergamisol
Carbinoxamine/ pseudoephedrine		Floxuridine	Sterile FUDR	Lisinopril	Prinivil, Zestril
Carvedilol		Flucytosine	Ancobon	Lomefloxacin	Maxaquin
Celecoxib		Fluorouracil	Efudex	Loratadine	Claritin
Cetirizine		Fluoxetine	Prozac, Sarafem	Loratadine/pseudoephedrine	Claritin-D
Cetirizine/pseudoephedrine		Fluphenazine	Prolixin	Losartan	Cozaar
Cevimeline		Flutamide	Eulexin	Lovastatin	Mevacor, Altocor
Chlorhexidine gluconate		Fluvastatin	Lescol	Lovastatin/niacin	Advicor
Chloroquine		Fluvoxamine	Luvox	Maprotiline	Ludiomil
Chlorothiazide		Fosinopril	Monopril	Mefenamic acid	Ponstel
Chlorpheniramine/ hydrocodone/ pseudoephedrine		Fosphenytoin	Cerebyx	Meloxicam	Mobic
Chlorpheniramine/ phenylephrine/pyrilamine		Furosemide	Lasix	Meperidine/promethazine	Mepergan
Chlorpromazine		Gabapentin	Neurontin	Mesalamine	Pentasa
Chlorpropamide		Glafloxacin	Tequin		
Chlorthalidone		Gemfibrozil	Lopid		
Chlorthalidone/clonidine		Gemifloxacin mesylate	Factive		
		Gentamicin	Garamycin		
		Glatiramer	Copaxone		
		Glimepiride	Amaryl		
		Glipizide	Glucotrol		
		Glyburide	DiaBeta, Glynase, Micronase		
		Glyburide/metformin HCl	Glucovance		
		Griseofulvin	Fulvicin P/G, Grifulvin, Gris-PEG		

(continued)

Appendix 7

Drugs That May Cause Photosensitivity (continued)

Generic	Brand	Generic	Brand	Generic	Brand
Methazolamide		Pentosan polysulfate	Elmiron	Somatropin	Serostim
Methotrexate	Trexall	Pentostatin	Nipent	Sotalol	Betapace, Betapace AF
Methoxsalen	Uvader, Oxsoalene, 8-MOP	Perphenazine	Trilafon	Sparfloxacin	Zagam
Methyclothiazide	Enduron	Phenazopyridine/sulfamethizole	Urobiotic-250	Sulfamethoxazole/trimethoprim	Bactrim, Septra
Methylidopa/Chlorothiazide	Aldoclor	Pilocarpine	Salagen	Sulfasalazine	Azulfidine
Metolazone	Mykrox, Zaroxolyn	Pimipinella major	Burnet	Sulfisoxazole	Gantrisin Pediatric
Minocycline	Dynacin, Minocin	Piroxicam	Feldene	Sulindac	Clinoril
Mirtazapine	Remeron	Polythiazide	Renese	Sumatriptan	Imitrex
Moexipril	Univasc	Polythiazide/prazosin	Minizide	Tacrolimus	Prograf, Protopic
Moxifloxacin	Avelox	Porfimer sodium	Photofrin	Tazarotene	Tazorac
Nabumetone	Relafen	Pravastatin	Pravachol	Tetracycline	Sumycin
Nalidixic acid	NegGram	Prochlorperazine	Compazine, Compro	Thalidomide	Thalomid
Naproxen	Naprosyn, EC-Naprosyn	Promethazine	Phenergan	Thioridazine hydrochloride	Mellaril
Naproxen sodium	Anaprox, Naprelan	Protriptyline	Vivactil	Thiothixene	Navane
Naratriptan	Amerge	Pyrazinamide	Pyrazinamide	Tiagabine	Gabitril
Nefazodone	Serzone	Quetiapine	Seroquel	Topiramate	Topamax
Nifedipine	Procardia	Quinapril	Accupril	Triamcinolone	Azmacort
Nisoldipine	Sular	Quinidine gluconate	Quinidine	Triamterene	Dyrenium
Norfloracin	Noroxin	Quinidine sulfate	Quinidex	Trifluoperazine	Stelazine
Nortriptyline	Pamelor	Rabeprazole sodium	Aciphex	Trimipramine	Surmontil
Ofloxacin	Floxin	Ramipril	Altace	Trovafloxacin	Trovan Tablets
Olanzapine	Zyprexa	Riluzole	Rilutek	Valacyclovir	Valtrex
Olmesartan medoxomil/hydrochlorothiazide	Benicar HCT	Risperidone	Risperdal	Valdecoxib	Bextra
Olsalazine	Dipentum	Ritonavir	Norvir	Valproate	Depacon
Oxaprozin	Daypro	Rizatriptan	Maxalt	Valproic acid	Depakene
Oxcarbazepine	Trileptal	Ropinirole	Requip	Venlafaxine	Effexor
Oxycodone	Roxicodone	Ruta graveolens	Rue	Verteporfin	Visudyne
Oxytetracycline	Terramycin	Saquinavir	Fortovase	Vinblastine	Vfend
Pantoprazole	Protonix	Saquinavir mesylate	Invirase	Voriconazole	Hivid
Paroxetine	Paxil	Selegiline	Eldepryl	Zalcitabine	Sonata
Pastinaca sativa	Parsnip	Sertraline	Zoloft	Zaleplon	Geodon
		Sibutramine	Meridia	Ziprasidone	Zomig
		Sildenafil	Viagra	Zolmitriptan	Ambien
		Simvastatin	Zocor	Zolpidem	

From Fleming T., ed. *Drug Topics Red Book*. Montvale, NJ: Thompson PDR, 2004.

Appendix 8

Drug Information Resources by Category

Adverse drug reactions/side effects

AHFS Drug Information
 Drug Facts & Comparisons
 Drug Information Handbook
 Martindale: The Complete Drug Reference
 Meyler's Side Effects of Drugs
 Micromedex DRUGDEX
 Physician's Desk Reference
 Side Effects of Drugs Annual
 Textbook of Adverse Drug Reactions
 EMBASE
 International Pharmaceutical Abstracts
 Medline
 TOXLINE (NLM Database)
 ClinAlert (www.nlm.nih.gov/databases/alerts/clinical_alerts.html)
 FDA Medwatch Program
 (<http://www.fda.gov/medwatch/safety.htm>)
 Institute for Safe Medication Practices
 (<http://www.ismp.org/>)
 Vaccine Adverse Event Reporting System
 (<http://www.vaers.org/>)

Alternative medicine/herbals/natural products

Herbs of Choice
 Honest Herbal
 Natural Medicines Comprehensive Database
 PDR for Nonprescription Drugs and Dietary Supplements
 Review of Natural Products
 The Complete German Commission E Monographs
 FDA CFSAN Dietary Supplements
 (<http://vm.cfsan.fda.gov>)
 National Center for Alternative and Complimentary Medicine
 (<http://nccam.nih.gov>)
 NIH Office of Dietary Supplements
 (<http://dietary-supplements.info.nih.gov>)

Drug dosing in renal dysfunction

AHFS Drug Information
 Drug Facts & Comparisons
 Drug Information Handbook
 Drug Prescribing in Renal Failure
 Handbook of Dialysis
 Physician's Desk Reference
 Sanford Guide to Antimicrobial Therapy
 (Antimicrobials Only)

EMBASE
 International Pharmaceutical Abstracts
 Medline
 Global Pharmacist Renal Dosing
 (<http://www.globalrph.com/renaldosing.htm> &
<http://www.globalrph.com/crcl.htm>)
 John Hopkins Aids Service
 (http://www.hopkins-aids.edu/publications/book/ch4_agents_tab0428.html#tab0428)
 Nephrology Pharmacy Associates (http://www.nephrologypharmacy.com/pub_dialysis.html)
 University of Louisville, Kidney Disease Program
 (<http://www.kdp-baptist.louisville.edu/renal/failure/>)

Drug interactions

AHFS Drug Information
 Drug Facts & Comparisons
 Drug Interaction Facts
 Drug Therapy Screening System (DTSS)
 Evaluation of Drug Interactions
 Hansten & Horn's Analysis and Management of Drug Interactions
 Micromedex DRUG-REAX
 EMBASE
 International Pharmaceutical Abstracts
 Medline
 Drug Store (<http://www.drugstore.com/pharmacy/drugchecker/>)
 Facts & Comparisons (www.factsandcomparisons.com/NewsArticle.asp?ID=91)
 Liverpool Pharmacology HIV group (<http://www.hiv-druginteractions.org/>)
 University of Indiana (<http://medicine.iupui.edu/flockhart/>)

Drug therapy/therapeutics

Applied Therapeutics: The Clinical Use of Drugs
 Cecil Textbook of Medicine
 Harrison's Principles of Internal Medicine
 Medical Letter
 Pharmacist's Letter
 Pharmacotherapy: A Pathophysiologic Approach
 Textbook of Therapeutics: Drug and Disease Management
 Washington Manual of Medical Therapeutics
 EMBASE

International Pharmaceutical Abstracts (IPA)
 Medline
 Global Pharmacist (<http://www.globalrph.com>)
 Merck Manual Diagnosis and Therapy Text
 (http://www.merck.com/pubs/mmanual_home/contents.htm)
 Mdchoice (<http://www.mdchoice.com/calculators.asp>)
 Excipient/Inactive Ingredient Information
 Drug Manufacturer/Company
 Handbook of Pharmaceutical Additives
 Micromedex POISINDEX
 Physician's Desk Reference/ Package Insert/Product Label

Legal and regulatory

Guide to Federal Pharmacy Law
 Pharmacy Law Digest
 USPD Volume III: Approved Drugs and Legal Requirements
 USP/NF
 Code of Federal Regulations (Title 21)
 (www.gpo.gov)
 FDA website (www.fda.gov)
 Joint Commission on Accreditation of Healthcare Organizations
 (www.jcaho.org)
 National Association of Boards of Pharmacy
 (<http://www.nabp.net>)
 US Drug Enforcement Administration
 (<http://www.usdoj.gov/dea/>)
 World Health Organization
 (<http://www.who.int/en/>)

Monographs/medication use evaluation (MUE, DUE)

AHFS Drug Information
 Drug Usage Evaluations (ASHP)
 Formulary Monograph Service (F & C)
 International Pharmaceutical Abstracts (IPA)
 ASHP Practices (<http://www.ashp.org/bestpractices/index.cfm>)
 The FIX System (www.theformulary.com)

News/new drug approvals

FAXStat
 Medical Letter
 Pharmacist's Letter
 The Pink Sheet
 CenterWatch (<http://www.centerwatch.com/patient/drugs/druglist.html>)

(continued)

Appendix 8**Drug Information Resources by Category (continued)**

FDA Website (<http://www.fda.gov/cder/approval/index.htm>)

Lexi-Comp (<http://www.lexi.com/web/newdrugs.jsp>)

Reuters News Service (www.reutershealth.com)

Nonprescription drugs/ OTC information

American Drug Index

Drug Facts & Comparisons

Drug Topics Redbook

Handbook of Nonprescription Drugs

Micromedex DRUGDEX, POISINDEX

PDR for Nonprescription Drugs and Dietary Supplements

DrugStore.com (www.drugstore.com)

Off-label/unlabeled/non-FDA approved uses

AHFS Drug Information

Drug Fact and Comparisons

Martindale

Micromedex DRUGDEX

Mosby's GenRX

USPDI Volume I

EMBASE

International Pharmaceutical Abstracts

Medline

Patient counseling/education

AHFS Drug Information

Drug Facts and Comparisons

Handbook of Nonprescription Drugs

Medication Teaching Manual (ASHP)

Micromedex DRUGDEX

Patient counseling handbook

Patient Drug Facts

USPDI Volume II: Advice for the Patient

Pediatric dosing and therapeutics

AHFS Drug Information

Drug Facts & Comparisons

Harriet Lane Handbook

Micromedex DRUGDEX

Nelson Textbook of Pediatrics

Neofax

Pediatric Dosage Handbook

Physician's Desk Reference

Principles and Practice of Pediatrics

EMBASE

International Pharmaceutical Abstracts
Medline

Pharmaceutics/compounding/manufacturing

Allen's Compounded Formulations

Extemporaneous Ophthalmic Preparations

Handbook on Extemporaneous Formulations

International Journal of Pharmaceutical

Compounding

Stability of Compounded Formulations

US Pharmacist Contemporary Compounding

Compendium

EMBASE

International Pharmaceutical Abstracts

Medline

Center for Drug Evaluation and Research

(<http://www.fda.gov/cder/pharmcomp/>)

International Journal of Pharmaceutical

Compounding (www.ijpc.com)

Pharmacokinetics

AHFS Drug Information

Applied Pharmacokinetics

Basic Clinical Pharmacokinetics

Clinical Pharmacokinetics

Drug Facts & Comparisons

Martindale

Micromedex DRUGDEX

Physician's Desk Reference

Principles of Therapeutic Drug Monitoring

USPDI Volume 1

EMBASE

International Pharmaceutical Abstracts

Medline

Foreign drug identification

Drugs Available Abroad

Drug Facts & Comparisons (Canadian Trade
Name Index)

European Drug Index

Martindale

Merck Index

Diccionario de Especialidades

Micromedex Index Nominum

Mosby's GenRX (International Drug Name
Index)

The British Pharmacopoeia

USP Dictionary

World Pharmaceuticals Directory

EMBASE

International Pharmaceutical Abstracts

Medline

British National Formulary

(<http://bnf.vhn.net/home/>)

Electronics Medicines Compendium

(<http://emc.vhn.net/>)

Royal Pharmaceutical Society of Great

Britain <http://www.pharmj.com/>

noticeboard/info/pip/foreignmedicines.
html

General drug information resources (compendia)

AHFS Drug Information

Drug Facts & Comparisons

Martindale's

Micromedex DRUGDEX

Mosby's GenRX

Physician's Desk Reference

USPDI Volume I: Drug Information for

Health Care Provider

Geriatrics

AHFS Drug Information

Consultant Pharmacist Journal

Drug Facts & Comparisons

Drug Therapy and the Elderly

Geriatric Dosage Handbook

Geriatric Pharmacology

Micromedex DRUGDEX

Physician's Desk Reference

Therapeutics in the Elderly

USPDI Volume I

EMBASE

International Pharmaceutical Abstracts

Medline

American Society of Consultant

Pharmacists (<http://www.ascp.com/>)

Geriatrics and Aging (http://www.geriatricsandaging.com/ga_links.htm)

Immunology/biotechnology/vaccines

Concepts in Immunology and

Immunotherapeutics

ImmunoFacts

Center for Disease Control (CDC) website

(www.cdc.gov/nip)

Immunize Action Coalition (<http://www.immunize.org/>)

(continued)

Appendix 8

Drug Information Resources by Category (continued)

US Health and Human Services

(<http://www.hrsa.gov/osp/vicp/>)

Vaccine Adverse Event Reporting System

(<http://www.vaers.org/>)

Intravenous stability/compatibility

AHFS Drug Information

Guide to Parenteral Admixtures

Handbook on Injectable Drugs

Micromedex DRUGDEX

Trissel's Tables of Physical Compatibility

EMBASE

International Pharmaceutical Abstracts

Medline

Handbook of Parenteral Drug Administration

(<http://members.ozemail.com.au/~jamesbc/frames.htm>)

Investigational drug identification

Drug Facts & Comparisons

Index Nominum

Martindale

Merck Index

Micromedex DRUGDEX, POISINDEX

NDA Pipeline

Unlisted Drugs

World Pharmaceuticals Directory

EMBASE

International Pharmaceutical Abstracts

Medline

Aids Clinical Trials (<http://www.actis.org/>)

CenterWatch (<http://www.centerwatch.com/patient/trials.html>)

NIH Clinical Trials Database (www.clinicaltrials.gov)

Pharmaceutical Research and Manufacturers of America (<http://www.newmedicines.org/>)

Reuters News Service

(www.reutershealth.com)

Laboratory Tests and Microbiology

Basic Skills in Interpreting Laboratory Data

Clinical Guide to Laboratory Tests

Laboratory Tests and Diagnostic Procedures

Laboratory Test Handbook

Pregnancy and lactation information

Breastfeeding: A Guide for the Medical Profession

Drugs in Pregnancy and Lactation

Micromedex REPRORISK

Focus Information Technology (<http://www.perinatology.com/exposures/druglist.htm>)

Safety of Drugs in Pregnancy and Lactation

(<http://www.accp.com/pod/p3b11pre01.pdf>)

UK's Drugs in Lactation Advisory Service

(<http://www.ukmicentral.nhs.uk/drugpreg/guide.htm>)

Pharmacology

AHFS Drug Information

Basic Concepts & Clinical Applications

Clinical Pharmacology

Drug Facts & Comparisons

Goodman & Gilman's Pharmacological Basic of Therapeutics

Principles of Pharmacology

Textbook of Pharmacology

Phone numbers and addresses

American Drug Index

Drug Facts & Comparisons

Drug Topics Redbook

Martindale

Micromedex DRUGDEX, POISINDEX

Mosby's GenRX

NDA Pipeline

PDR

Manufacturer websites (various)

Chemical/physical properties

CRC Handbook of Chemistry and Physics

Merck Index

Textbook of Organic, Medicinal, and Pharmaceutical Chemistry

USP-Dictionary

USP/NF

Product availability/shortages

American Drug Index

Drug Topics Red Book

Handbook of Nonprescription Drugs

ASHP Drug Shortage Center (<http://www.ashp.org/shortage/>)

Drug Wholesaler websites (various)

FDA Drug Shortage site (<http://www.fda.gov/cder/drug/shortages/default.htm>)

Product identification

American Drug Index

AHFS Drug Information

Diccionario de Especialidades Farmaceuticas

Drug Facts & Comparisons

Drug Topics Redbook

Drugs Available Abroad

European Drug Index

Index Nominum

Martindale

Merck Index

Micromedex POISINDEX

NDA Pipeline

Pharmacist's Letter

Unlisted Drugs

USP Dictionary

World Pharmaceuticals Directory

EMBASE

International Pharmaceutical Abstracts

Medline

FDA website (www.fda.gov)

Internet (various search engines, websites)

Reuters News Service (www.reutershealth.com)

Tablet/capsule identification

Drug Facts & Comparisons

Ident-A-Drug

Micromedex IDENTIDEX

Mosby's GenRX

Physician's Desk Reference (PDR)

RX-List website (www.rxlist.com)

Toxicology/poisoning

Clinical Management of Poisoning and Drug Overdose

Clinical Toxicology of Drugs

Handbook of Poisoning

Micromedex DRUGDEX, POISINDEX

Poisoning and Toxicology Compendium

Principles of Clinical Toxicology

Toxicologic Emergencies

EMBASE

International Pharmaceutical Abstracts

Medline

ToxNet

American Association of Poison Control Centers (<http://www.aapcc.org/>)

Environmental Protection Agency (<http://www.epa.gov/iris/>)

Merck Manual (<http://www.merck.com/pubs/mmanual/section23/chapter307/307a.htm>)

Oxford University

(<http://physchem.ox.ac.uk/MSDS/>)

Appendix 9

Drugs That Should Not Be Crushed

Pharmacists may sometimes encounter patients who cannot swallow tablets or capsules. When an alternative liquid formulation is not available, pulverizing the solid dosage form before administration can serve as a quick, safe solution to the problem.

However, not all pharmaceutical products may be crushed before administration. A variety of slow-release formulations can deliver dangerous immediate doses of their active ingredients if the integrity of the delivery system is destroyed, and enteric-coated products must remain intact in order to prevent their dissolution in the stomach.

Listed below are various slow-release as well as enteric-coated products that should not be crushed or chewed. Slow-release (sr) represents products that are controlled-release, extended-release, long-acting, or

timed-release. Enteric-coated (ec) represents products that are delayed-release.

In general, capsules containing slow-release or enteric-coated particles may be opened and their contents administered on a spoonful of soft food. Instruct patients not to chew the particles, though. (Patients should, in fact, be discouraged from chewing any medication unless it is specifically formulated for that purpose.)

This list should not be considered all-inclusive. Generic and alternate brands of some products may exist. Tablets intended for sublingual or buccal administration (not included in this list) should also be administered only as intended, in an intact form.

Drug	Manufacturer	Form	Drug	Manufacturer	Form
Accuhist LA	Pedimed	sr	Bromfenex	Ethex	sr
Aciphex	Janssen	ec	Bromfenex PD	Ethex	sr
Adalat CC	Bayer	sr	Bromfenex PE	Ethex	sr
Adderall XR	Shire US	sr	Bromfenex PE Pediatric	Ethex	sr
Advicor	KOS	sr	Caffedrine	Blairer	sr
Aerohist	Aero	sr	Calan SR	Pharmacia	sr
Aerohist Plus	Aero	sr	Carbatrol	Shire US	sr
Afedtab CR	Watson	sr	Cardene SR	Roche	sr
Aggrenox	Boehringer Ingelheim	sr	Cardizem CD	Biovail	sr
Aldex	Zyber	sr	Cardizem LA	Biovail	sr
Aleve Cold & Sinus	Bayer Consumer	sr	Cardizem SR	Biovail	sr
Aleve Sinus & Headache	Bayer Consumer	sr	Carox Plus	Seneca	sr
Allegra-D	Aventis	sr	Cartia XT	Andrx	sr
Allerx	Adams	sr	Catamine	Tyson Neutraceuticals	ec
Allerx-D	Adams	sr	Cemill 1000	Miller	sr
Allfen	MCR American	sr	Cemill 500	Miller	sr
Allfen-DM	MCR American	sr	Certuss-D	Capellon	sr
Allophen	Numark	ec	Cevi-Bid	Lee	sr
Altex-PSE	Alphagen	sr	Chlorex-A	Cypress	sr
Altacor	Andrx	sr	Chlor-Phen	Truxton	sr
Ambifed-G	MCR American	sr	Chlor-Trimeton Allergy	Schering Plough	sr
Ambifed-G DM	MCR American	sr	Chlor-Trimeton Allergy Decongestant	Schering Plough	sr
Amdry-C	PrasCo	sr	Cipro XR	Bayer	sr
Amdry-D	PrasCo	sr	Claritin-D	Schering Plough	sr
Amibid DM	Amide	sr	Claritin-D 24-Hour	Schering Plough	sr
Amibid LA	Amide	sr	Coldamine	Breckenridge	sr
Amidal	Amide	sr	Coldec D	Breckenridge	sr
Aminoxin	Tyson Neutraceuticals	ec	Coldec TR	Breckenridge	sr
Ami-Tex PSE	Amide	sr	Coldex-A	United Research	sr
Aquabid-DM	Alphagen	sr	Coldmist DM	Breckenridge	sr
Aquatab C	Adams	sr	Coldmist Jr.	Breckenridge	sr
Aquatab D	Adams	sr	Coldmist LA	Breckenridge	sr
Aquatab DM	Adams	sr	Colfed-A	Breckenridge	sr
Arthrotec	Pharmacia	ec	Concerta	McNeil Consumer	sr
Asacol	Procter & Gamble	ec	Contac 12-hour	GlaxoSmithKline Consumer	sr
Ascocid-1000	Key	sr	Correctol	Schering Plough	ec
Ascocid-500-D	Key	sr	Cotazym-S	Organon	ec
Ascriptin Enteric	Novartis Consumer	ec	Covera-HS	Pharmacia	sr
ATP	Tyson Neutraceuticals	ec	Crantex ER	Breckenridge	sr
Atrohist Pediatric	Celltech	sr	Crantex LA	Breckenridge	sr
Augmentin XR	GlaxoSmithKline	sr	Creon 10	Solvay	ec
Avinza	Ligand	sr	Creon 20	Solvay	ec
Azulfidine Entabs	Pharmacia	ec	Creon 5	Solvay	ec
Bayer Aspirin Regimen	Bayer Consumer	ec	C-Tym	Emrex/Economed	sr
Bellahist-D LA	Cypress	sr	Dairycare	Plainview	ec
Biaxin XL	Abbott	sr	Dallergy	Laser	sr
Bidex-DM	Stewart-Jackson	sr	Dallergy- Jr.	Laser	sr
Biohist LA	Ivax	sr	D-amine-SR	Alphagen	sr
Bisac-Evac	G & W	ec	Deconamine SR	Kenwood	sr
Biscolax	Global Source	ec	Deconex	Poly	sr
Bontril Slow-Release	Amarin	sr	Decongest II	Qualitest	sr
Bromfed	Muro	sr			
Bromfed-PD	Muro	sr			

Enteric-coated = ec

Slow-release = sr

(continued)

Appendix 9

Drugs That Should Not Be Crushed (continued)

Drug	Manufacturer	Form	Drug	Manufacturer	Form
De-Congestine	Qualitest	sr	Fero-Folic 500	Abbott	sr
Deconal II	Carolina	sr	Fero-Grad-500	Abbott	sr
Depakote	Abbott	ec	Ferro-Sequels	Inverness	sr
Depakote ER	Abbott	sr	Ferro-Time	Time-Cap	sr
Depakote Sprinkles	Abbott	ec	Ferrous Fumarate DS	Vita-Rx	sr
Despec SR	Int'l Ethical Labs	sr	Fetrin	LunsCo	sr
Detrol LA	Pharmacia	sr	Flagyl ER	Pharmacia	sr
Dex GG TR	Boca	sr	Fleet Bisacodyl	C.B. Fleet	ec
Dexaphen SA	Major	sr	Folitab 500	Rising	sr
Dexedrine Spansules	GlaxoSmithKline	sr	Fumatinic	Laser	sr
D-Feda II	WE Pharm	sr	G/P 1200/75	Cypress	sr
Diamox Sequels	Duramed	sr	Genacote	Ivax	ec
Dilacor XR	Watson	sr	Gentlax	Purdue Frederick	ec
Dilantin Kapseals	Pfizer	sr	GFN 1000/DM 50	Cypress	sr
Dilatrate-SR	Schwarz	sr	GFN 1200/DM 20/PE 40	Cypress	sr
Diltia XT	Andrx	sr	GFN 1200/DM 60/PSE 60	Cypress	sr
Dimetane Extentabs	Wyeth Consumer	sr	GFN 1200/Phenylephrine 40	Cypress	sr
Disophrol Chronotab	Schering Plough	sr	GFN 1200/PSE 50	Cypress	sr
Ditropan XL	Ortho-McNeil	sr	GFN 500/DM 30	Cypress	sr
Donnatal Extentabs	PBM	sr	GFN 550/PSE 60	Cypress	sr
Doryx	Warner Chilcott	ec	GFN 550/PSE 60/DM 30	Cypress	sr
Drexophed SR	Qualitest	sr	GFN 595/PSE 48	Cypress	sr
Drihist SR	PrasCo	sr	GFN 595-PSE 48-DM 32	Cypress	sr
Drituss GP	Qualitest	sr	GFN 795-PSE 85	Cypress	sr
Drixomed	loPharm	sr	GFN 800/DM 30	Cypress	sr
Drixoral	Schering Plough	sr	GFN 800/PSE 60	Cypress	sr
Drixoral Plus	Schering Plough	sr	Giltuss TR	Gil	sr
Drixoral Sinus	Schering Plough	sr	Glucophage XR	Bristol-Myers Squibb	sr
Drize-R	Monarch	sr	Glucotrol XL	Pfizer	sr
Drysec	A.G. Marin	sr	GP-1200	loPharm	sr
Dulcolax	Boehringer Ingelheim	ec	G-Phed	Alphagen	sr
	Consumer		Guaifed	Verum	sr
Duradryl Jr.	Breckenridge	sr	Guaifed-PD	Verum	sr
Durahist	Proethic	sr	Guaifenex DM	Ethex	sr
Durahist PE	Proethic	sr	Guaifenex G	Ethex	sr
Duraphen DM	Proethic	sr	Guaifenex GP	Ethex	sr
Duraphen II	Proethic	sr	Guaifenex LA	Ethex	sr
Durasal II	PrasCo	sr	Guaifenex PSE 120	Ethex	sr
Dynabac	Muro	ec	Guaifenex PSE 60	Ethex	sr
Dynabac D5-Pak	Muro	ec	Guaifenex PSE 80	Ethex	sr
Dynacirc CR	Reliant	sr	Guaifenex-Rx	Ethex	sr
Dynahist-ER Pediatric	Breckenridge	sr	Guaifenex-Rx DM	Ethex	sr
Dynex	Athlon	sr	Guaimax-D	Schwarz	sr
Easprin	New River	ec	Gua-SR	Seatrache	sr
EC Naprosyn	Roche	ec	Guiadex D	Breckenridge	sr
Ecotrin	GlaxoSmithKline	ec	Guiadex PD	Breckenridge	sr
	Consumer		Guiadrine DM	Breckenridge	sr
Ecotrin Adult, Low-Strength	GlaxoSmithKline	ec	Guiadrine G-1200	Breckenridge	sr
	Consumer		Guiadrine GP	Breckenridge	sr
Ecotrin Maximum-Strength	GlaxoSmithKline	ec	Guiadrine PSE	Breckenridge	sr
	Consumer		H 9600 SR	Hawthorn	sr
Ecpirin	Prime Marketing	ec	Halfprin	Kramer	ec
Ed-A-Hist	Edwards	sr	Hematron-AF	Seyer Pharmatec	sr
Effexor-XR	Wyeth-Ayerst	sr	Hemax	Pronova	sr
Efidac 24 Chlorpheniramine	Novartis Consumer	sr	Histaclear D	Ethex	sr
Efidac 24 Pseudoephedrine	Novartis Consumer	sr	Histade	Breckenridge	sr
Endal	Pediamed	sr	Histade MX	Breckenridge	sr
Entab-DM	Rising	sr	Hista-Vent DA	Ethex	sr
Entercole	Global Source	ec	Hista-Vent PSE	Ethex	sr
Entex ER	Andrx	sr	Histex CT	TEAMM	sr
Entex LA	Andrx	sr	Histex I/E	TEAMM	sr
Entex PSE	Andrx	sr	Histex SR	TEAMM	sr
Entocort EC	Astra Zeneca	ec	Humavent LA	WE Pharm	sr
Eryc	Warner Chilcott	ec	Humibid DM	Carolina	sr
Ery-Tab	Abbott	ec	Humibid LA	Carolina	sr
Eskalith-CR	GlaxoSmithKline	sr	Hydro Pro DM SR	Breckenridge	sr
Eudal SR	Forest	sr	Hyoscyamine TR	Breckenridge	sr
Extendryl Jr.	Fleming	sr	Iberet-500	Abbott	sr
Extendryl SR	Fleming	sr	Iberet-Folic-500	Abbott	sr
Feen-A-Mint	Schering Plough	ec	Icaps TR	AICon	sr
Femilax	G & W	ec	Icar-C Plus SR	Hawthorn	sr

Enteric-coated = ec

Slow-release = sr

(continued)

Appendix 9

Drugs That Should Not Be Crushed (continued)

Drug	Manufacturer	Form	Drug	Manufacturer	Form
Imdur	Key	sr	Mintab D	Breckenridge	sr
Inderal LA	Wyeth-Ayerst	sr	Mintab DM	Breckenridge	sr
Indocin SR	Forte	sr	Miraphen PSE	CaraCo	sr
Innopran XL	Reliant	sr	Modane	Savage	ec
Iobid DM	IoPharm	sr	MS Contin	Purdue Frederick	sr
Ionamin	Celltech	sr	MSP-BLU	Cypress	ec
Iosal II	IoPharm	sr	Mucinex	Adams	sr
Iotex PSE	IoPharm	sr	Muco-Fen DM	Ivax	sr
Isochron	Forest	sr	Multi-Ferrous Folic	United Research	sr
Isoptin SR	Abbott	sr	Multitret Folic-500	Amide	sr
K-10	Alra	sr	Nalex-A	Blansett	sr
K-8	Alra	sr	Naprelan	Elan	sr
Kadian	Faulding	sr	Nasatab LA	ECR	sr
Kaon-CL 10	Savage	sr	ND Clear	Seatrice	sr
K-Dur 10	Key	sr	New Ami-Tex LA	Amide	sr
K-Dur 20	Key	sr	Nexium	Astra Zeneca	ec
Klor-Con 10	Upsher-Smith	sr	Niaspan	KOS	sr
Klor-Con 8	Upsher-Smith	sr	Nicomide	Sirius	sr
Klor-Con M10	Upsher-Smith	sr	Nifedical XL	Teva	sr
Klor-Con M15	Upsher-Smith	sr	Nitrocol	Truxton	sr
Klor-Con M20	Upsher-Smith	sr	Nitro-Time	Time-Cap	sr
Klotrix	Bristol-Myers Squibb	sr	Norflex	3M	sr
Kronofed-A	Ferndale	sr	Norpace CR	Pharmacia	sr
Kronofed-A-Jr.	Ferndale	sr	Omnihist LA	WE Pharm.	sr
K-Tab	Abbott	sr	Oramorph SR	AAI Pharma	sr
Lescol XL	Novartis	sr	Oruvail	Wyeth-Ayerst	sr
Levall G	Athlon	sr	Oxycontin	Purdue	sr
Levbid	Schwarz	sr	Palgic-D	Pamlab	sr
Levsinex	Schwarz	sr	Pancrease	Ortho-McNeil	ec
Lexxel	Astra Zeneca	sr	Pancrease MT 10	Ortho-McNeil	ec
Lipram 4500	Global	ec	Pancrease MT 16	Ortho-McNeil	ec
Lipram-CR10	Global	ec	Pancrease MT 20	Ortho-McNeil	ec
Lipram-CR20	Global	ec	Pancrecarb MS-4	Digestive Care	ec
Lipram-CR5	Global	ec	Pancrecarb MS-8	Digestive Care	ec
Lipram-PN10	Global	ec	Pancrelipase 20,000	United Research	ec
Lipram-PN16	Global	ec	Pangestyme CN-10	Ethex	ec
Lipram-PN20	Global	ec	Pangestyme CN-20	Ethex	ec
Lipram-UL12	Global	ec	Pangestyme EC	Ethex	ec
Lipram-UL18	Global	ec	Pangestyme MT16	Ethex	ec
Lipram-UL20	Global	ec	Pangestyme UL12	Ethex	ec
Liquibid-D	Capellon	sr	Pangestyme UL18	Ethex	ec
Liquibid-D 1200	Capellon	sr	Pangestyme UL20	Ethex	ec
Liquibid-PD	Capellon	sr	Panmist DM	Pamlab	sr
Lithobid	Solvay	sr	Panmist Jr.	Pamlab	sr
Lodine XL	Wyeth-Ayerst	sr	Panmist LA	Pamlab	sr
Lodrane 12D	ECR	sr	Pannaz	Pamlab	sr
Lodrane 12-hour	ECR	sr	Papacon	Consolidated Midland	sr
Lodrane LD	ECR	sr	Para-Time SR	Time-Cap	sr
Lusonex	Wraser	sr	Paser	Jacobus	sr
Mag Delay	Major	ec	Pavacot	Truxton	sr
Mag64	Rising	ec	Paxil CR	GlaxoSmithKline	sr
Mag-SR	Cypress	sr	PCE Dispartab	Abbott	ec
Mag-SR Plus Calcium	Cypress	sr	PCM Allergy	Boca	sr
Mag-Tab SR	Niche	sr	PCM LA	Cypress	sr
Maxifed	MCR American	sr	Pentasa	Shire US	sr
Maxifed DM	MCR American	sr	Pentopak	Zoetica	sr
Maxifed-G	MCR American	sr	Pentoxil	Upsher-Smith	sr
Maxovite	Tyson Neutraceuticals	sr	Pharmadrine	Breckenridge	sr
Medent DM	Stewart-Jackson	sr	Phendiet-105	Truxton	sr
Medent LD	Stewart-Jackson	sr	Phenyleph 20/CPM 8/ Methscop 2.5 LA	United Research	sr
Mega-C	Merit	sr	Phenyleph 20/CPM 8/ Methscop 2.5 LA	United Research	sr
Melfiat	Numark	sr	Phenyleph 20/CPM 8/ Methscop 2.5 LA	United Research	sr
Mescolor	First Horizon	sr	Phenyleph 20/CPM 8/ Methscop 2.5 LA	United Research	sr
Mestinon Timespan	ICN	sr	Phenyleph 20/CPM 8/ Methscop 2.5 LA	United Research	sr
Metadate CD	Celltech	sr	Phenyleph 20/CPM 8/ Methscop 2.5 LA	United Research	sr
Metadate ER	Celltech	sr	Phenyleph 20/CPM 8/ Methscop 2.5 LA	United Research	sr
Methylin ER	Mallinckrodt	sr	Phenyleph 20/CPM 8/ Methscop 2.5 LA	United Research	sr
Micro-K	Ther-Rx	sr	Phenyleph 20/CPM 8/ Methscop 2.5 LA	United Research	sr
Micro-K 10	Ther-Rx	sr	Phenyleph 20/CPM 8/ Methscop 2.5 LA	United Research	sr
Mindal	Breckenridge	sr	Phenyleph 20/CPM 8/ Methscop 2.5 LA	United Research	sr
Mindal DM	Breckenridge	sr	Phenyleph 20/CPM 8/ Methscop 2.5 LA	United Research	sr
Mintab C	Breckenridge	sr	Phenyleph 20/CPM 8/ Methscop 2.5 LA	United Research	sr

Enteric-coated = ec

Slow-release = sr

(continued)

Appendix 9

Drugs That Should Not Be Crushed (continued)

Drug	Manufacturer	Form	Drug	Manufacturer	Form
Procardia XL	Pfizer	sr	Sular	First Horizon	sr
Profen Forte	Ivax	sr	Sulfazine EC	Qualitest	ec
Profen Forte DM	Ivax	sr	Symax-SR	Capellon	sr
Profen II	Ivax	sr	Tarka	Abbott	sr
Profen II DM	Ivax	sr	Taztia XT	Andrx	sr
Prohist-8	Emrex/Economed	sr	Tegretol-XR	Novartis	sr
Prolex PD	Blansett	sr	Tenuate Dospan	Aventis	sr
Prolex-D	Blansett	sr	Theo-24	UCB	sr
Pronestyl-SR	Bristol-Myers Squibb	sr	Theocap	Forest	sr
Protid	LunsCo	sr	Theochron	Forest	sr
Protonix	Wyeth-Ayerst	ec	Theo-Time	Major	sr
Prozac Weekly	Eli Lilly	ec	Thiamilate	Tyson Neutraceuticals	ec
Pseubrom	Alphagen	sr	Tiazac	Forest	sr
Pseubrom-PD	Alphagen	sr	Time-Hist	MCR American	sr
Pseudo CM TR	Boca	sr	Toprol XL	Astra Zeneca	sr
Pseudo GG TR	Boca	sr	TotalDay	National Vitamin	sr
Pseudocot-C	Truxton	sr	Touro Allergy	Dartmouth	sr
Pseudocot-G	Truxton	sr	Touro CC	Dartmouth	sr
Pseudovent	Ethex	sr	Touro DM	Dartmouth	sr
Pseudovent DM	Ethex	sr	Touro EX	Dartmouth	sr
Pseudovent PED	Ethex	sr	Touro LA	Dartmouth	sr
P-tuss DM	PrasCo	sr	Tranxene SD	Ovation	sr
Q-bid DM	Qualitest	sr	Tranxene-SD	Ovation	sr
Qdall	Atley	sr	Trental	Aventis	sr
Quadra-Hist D	Ethex	sr	Trikof-D	Respa	sr
Quadra-Hist D Ped	Ethex	sr	Trinalin Repetabs	Key	sr
Quibron-T/SR	Monarch	sr	Trituss-ER	Everett	sr
Quindal	Qualitest	sr	Tussafed-LA	Everett	sr
Reliable Gentle Laxative	Ivax	ec	Tussall-ER	Everett	sr
Rescon Jr.	Capellon	sr	Tussi-BID	Capellon	sr
Rescon MX	Capellon	sr	Tylenol Arthritis	McNeil Consumer	sr
Respa-1st	Respa	sr	Ultrabrom	WE Pharm	sr
Respa-AR	Respa	sr	Ultrabrom PD	WE Pharm	sr
Respa-DM	Respa	sr	Ultrase	Axcan ScandiPharm	ec
Respa-GF	Respa	sr	Ultrase MT12	Axcan ScandiPharm	ec
Respa-PE	Respa	sr	Ultrase MT18	Axcan ScandiPharm	ec
Respahist	Respa	sr	Ultrase MT20	Axcan ScandiPharm	ec
Respaire-120 SR	Laser	sr	Uniphyt	Purdue Frederick	sr
Respaire-60 SR	Laser	sr	Urimax	Integrity	ec
Rhinacon A	Breckenridge	sr	Urocit-K 10	Mission	sr
Ribo-2	Tyson Neutraceuticals	ec	Urocit-K 5	Mission	sr
Rinade-BID	Emrex/Economed	sr	Uroxatral	Sanofi-Synthelabo	sr
Risperdal Consta	Janssen	sr	Vanex Forte-D	Monarch	sr
Ritalin LA	Novartis	sr	V-Dec-M	Seatrice	sr
Ritalin SR	Novartis	sr	Veracolate	Numark	ec
Rodex Forte	Legere	sr	Verelan	Schwarz	sr
Rondamine	Major	sr	Verelan PM	Schwarz	sr
Rondec-TR	Biovail	sr	Versacaps	Seatrice	sr
Ru-Tuss 800	Sage	sr	Videx EC	Bristol-Myers Squibb	ec
Ru-Tuss 800 DM	Sage	sr	Vitamin C/Rose Hips	ADH Health	sr
Ru-Tuss Jr.	Sage	sr	Vivotif Berna	Berna	ec
Sam-E	Pharmavite	ec	Voltaren	Novartis	ec
Sinemet CR	Bristol-Myers Squibb	sr	Voltaren-XR	Novartis	sr
Sinutuss DM	WE Pharm	sr	Vospire ER	Odyssey	sr
Sinuvent PE	WE Pharm	sr	WE Mist II LA	WE Pharm	sr
Slo-Niacin	Upsher-Smith	sr	WE Mist LA	WE Pharm	sr
Slow FE	Novartis Consumer	sr	Wellbutrin SR	GlaxoSmithKline	sr
Slow FE With Folic Acid	Novartis Consumer	sr	Wellbutrin XL	GlaxoSmithKline	sr
Slow-Mag	Purdue	ec	Wobenzym N	Marlyn	ec
Spacol T/S	Dayton	sr	Xanax XR	Pharmacia	sr
St. Joseph Pain Reliever	McNeil Consumer	ec	Xiral	Hawthorn	sr
Sta-D	Magna	sr	Zaptec PSE	American Generics	sr
Stahist	Magna	sr	Z-Cof LA	Zyber	sr
Stamoist E	Magna	sr	Zephrex LA	Sanofi-Synthelabo	sr
Sudafed 12-Hour	Pfizer Consumer	sr	Zorprin	Par	sr
Sudafed 24-Hour	Pfizer Consumer	sr	Zyban	GlaxoSmithKline	sr
Sudal 60/500	Atley	sr	Zymase	Organon	ec
Sudal DM	Atley	sr	Zyrtec-D	Pfizer	sr
Sudal SR	Atley	sr			

Enteric-coated = ec

Slow-release = sr

Appendix 10

Use-in-Pregnancy Ratings

The U.S. Food and Drug Administration's Use-in-Pregnancy rating system weighs the degree to which available information has ruled out risk to the fetus against the drug's potential benefit to the patient. Below is a listing of drugs (by generic name) for which ratings are available.

X

CONTRAINDICATED IN PREGNANCY

Studies in animals or humans, or investigational or post-marketing reports, have demonstrated fetal risk which clearly outweighs any possible benefit to the patient.

Acitretin
Anisindione
Atorvastatin Calcium
Bicalutamide
Clomiphene Citrate
Danzol
Demecarium Bromide
Desogestrel/Ethinyl Estradiol
Diclofenac Sodium/Misoprostol
Dienestrol
Dihydroergotamine Mesylate
Estazolam
Estradiol
Estrogens, Conjugated
Estrogens, Conjugated/
Medroxyprogesterone
Acetate
Estrogens, Esterified
Estrogens, Esterified/
Methyltestosterone
Estropipate
Ethinyl Estradiol
Ethinyl Estradiol/Ethinodiol
Diacetate
Ethinyl Estradiol/Levonorgestrel
Ethinyl Estradiol/Norethindrone
Ethinyl Estradiol/Norethindrone
Acetate
Ethinyl Estradiol/Norgestimate
Ethinyl Estradiol/Norgestrel
Finasteride
Fluorouracil
Fluvastatin Sodium
Follitropin Alpha
Follitropin Beta
Gonadotropin, Chorionic
(Profasi)
Goserelin Acetate
Interferon Alfa-2B/Ribavirin
Isotretinoin
Leflunomide
Leuprolide Acetate
Levonorgestrel
Lovastatin
Medroxyprogesterone Acetate

Megestrol Acetate
(Megace Suspension)
Menotropins
Mestranol/Norethindrone
Methyltestosterone
Misoprostol
Nafarelin Acetate
Norethindrone
Norethindrone Acetate
Norgestrel
Oxandrolone
Oxymetholone
Plicamycin
Pravastatin Sodium
Raloxifene Hydrochloride
Ribavirin
Rosuvastatin Calcium
Simvastatin
Stanazolol
Tazarotene
Testosterone
Testosterone Enanthate
Thalidomide
Tositumomab/Iodine I 131
Tositumomab
Triazolam
Urofollitropin
Warfarin Sodium
Yohimbine Hydrochloride

D

POSITIVE EVIDENCE OF RISK

Investigational or postmarketing data show risk to the fetus. Nevertheless, potential benefits may outweigh the potential risk.

Alitretinoin
Alprazolam
Altretamine
Amiodarone Hydrochloride
Amlodipine Besylate/Benazepril
Hydrochloride*
Anastrozole
Atenolol
Atenolol/Chlorthalidone
Azathioprine
Azathioprine Sodium
Benazepril Hydrochloride*
Benazepril Hydrochloride/
Hydrochlorothiazide*
Bortezomib
Busulfan
Candesartan Cilexetil*

Capecitabine
Captopril*
Carbamazepine
Carboplatin
Carmustine
Chlorambucil
Cladribine
Clonazepam
Cytarabine Liposome
Dactinomycin
Daunorubicin Citrate Liposome
Daunorubicin Hydrochloride
Demeclocycline Hydrochloride
Divalproex Sodium
Docetaxel
Doxorubicin Hydrochloride
Doxorubicin Hydrochloride
Liposome
Doxycycline Calcium
Doxycycline Hyclate
Doxycycline Monohydrate
Enalapril Maleate*
Enalapril Maleate/Felodipine*
Enalapril Maleate/
Hydrochlorothiazide*
Enalaprilat*
Floxuridine
Fludarabine Phosphate
Flutamide
Fosinopril Sodium*
Fosphenytoin Sodium
Gemcitabine Hydrochloride
Gentamicin Sulfate
Goserelin Acetate
Hydrochlorothiazide/Irbesartan*
Hydrochlorothiazide/Lisinopril*
Hydrochlorothiazide/Losartan
Potassium*
Hydrochlorothiazide/Moexipril
Hydrochloride*
Hydrochlorothiazide/Valsartan*
Idarubicin Hydrochloride
Ifosfamide
Imatinib Mesylate
Irbesartan*
Letrozole
Lisinopril*
Lithium Carbonate
Lithium Citrate
Lorazepam
Losartan Potassium*
Methchloramine Hydrochloride
Megestrol Acetate
(Megace Tablets)
Melfalan
Mephobarbital
Mercaptopurine
Methimazole

Midazolam Hydrochloride
Minocycline Hydrochloride
Mitoxantrone Hydrochloride
Moexipril Hydrochloride*
Neomycin Sulfate/Polymyxin B
Sulfate
Nicotine
Paclitaxel
Pamidronate Disodium
Pentobarbital Sodium
Pentostatin
Perindopril Erbumine*
Potassium Iodide
Procarbazine Hydrochloride
Quinapril Hydrochloride*
Ramipril*
Streptomycin Sulfate
Tamoxifen Citrate
Telmisartan
Thioguanine
Thiotepa
Tobramycin (Inhalation)
Tobramycin Sulfate
Topotecan Hydrochloride
Toremifene Citrate
Trandolapril*
Trandolapril/Verapamil
Hydrochloride*
Tretinoin (Oral)
Valproate Sodium
Valproic Acid
Valsartan*
Vinblastine Sulfate
Vincristine Sulfate
Vinorelbine Tartrate
Voriconazole

C

RISK CANNOT BE RULED OUT

Human studies are lacking, and animal studies are either positive for risk or are lacking as well. However, potential benefits may outweigh the potential risk.

Abacavir Sulfate
Abciximab
Acetaminophen/Butalbital
Acetaminophen/Butalbital/
Caffeine
Acetaminophen/Caffeine/
Chlorpheniramine
Maleate/Hydrocodone
Bitartrate/Phenylephrine
Hydrochloride
Acetaminophen/Codeine

Phosphate
Acetaminophen/Hydrocodone
Bitartrate
Acetaminophen/Oxycodone
Hydrochloride
Acetaminophen/Pentazocine
Hydrochloride
Acetazolamide
Acetic Acid/Oxyquinoline
Sulfate/Ricinoleic Acid
Adapalene
Adenosine
Alatrofloxacin Mesylate
Albendazole
Albumin, Human
Albuterol
Albuterol Sulfate
Albuterol Sulfate/Ipratropium
Bromide
Alclometasone Dipropionate
Aldesleukin
Alendronate Sodium
Allopurinol Sodium
Alprostadil
Alteplase, Recombinant
Amantadine Hydrochloride
Amifostine
Aminhippurate Sodium
Aminosalicylic Acid
Amlodipine Besylate
Amlodipine Besylate/Benazepril
Hydrochloride*
Amoxicillin/Clarithromycin/
Lansoprazole
Amphetamine &
Dextroamphetamine Mixture
Amprenavir
Amylase/Cellulase/Hyoscyamine
Sulfate/Lipase/Phenyl-
toloxamine Citrate/Protease
Amylase/Cellulase/Lipase/
Protease
Amylase/Lipase/Protease
Anagrelide Hydrochloride
Antihemophilic Factor IX
Complex (Human)
Antihemophilic Factor IX
Complex (Recombinant)
Antihemophilic Factor VIIa
(Recombinant)
Antihemophilic Factor VIII
(Human)
Antihemophilic Factor VIII
(Human)/Von Willebrand
Factor Complex (Human)
Antihemophilic Factor VIII
(Recombinant)
Antihemophilic Factor VIII:C

* Category C or D depending on the trimester the drug is given.

Appendix 10

Use-in-Pregnancy Ratings (continued)

(Human)	Calcium Acetate	Cytomegalovirus Immune	Erythromycin Ethylsuccinate/	Vaccine/Hepatitis B,
Anti-Inhibitor Coagulant	Candesartan Cilexetil*	Globulin Intravenous, Human	Sulfisoxazole Acetyl	Recombinant Vaccine
Complex	Captopril*	Dacarbazine	Escitalopram Oxalate	Halcinonide
Antipyrine/Benzocaine	Carbachol	Daclizumab	Esmolol Hydrochloride	Haloperidol Decanoate
Anti-Thymocyte Globulin	Carbetapentane	Dantrolene Sodium	Ethiodized Oil	Halothane
Antivenin (Latrodectus	Tannate/Chlorpheniramine	Dapsone	Ethionamide	Hemin
Mactans)	Tannate/Ephedrine	Deferoxamine Mesylate	Etidronate Disodium	Heparin Sodium
Apraclonidine Hydrochloride	Tannate/Phenylephrine	Delavirdine Mesylate	Etodolac	Hepatitis A Vaccine, Inactivated
Aripiprazole	Tannate	Denileukin Diftitox	Etomidate	Hepatitis B Immune Globulin
Asparaginase	Carbetapentane	Desonide	Felbamate	Hepatitis B Vaccine-
Aspirin/Carisoprodol	Tannate/Chlorpheniramine	Desoximetason	Felodipine	Recombinant
Aspirin/Carisoprodol/Codeine	Tannate/Phenylephrine	Dexamethasone Sodium	Fenofibrate	Hexachlorophene
Phosphate	Tannate	Phosphate	Fentanyl	Homatropine Methylbromide/
Aspirin/Methocarbamol	Carbidopa/Levodopa	Dexamethasone Sodium	Fentanyl Citrate	Hydrocodone Bitartrate
Atovaquone	Carbinoxamine Maleate	Phosphate/Neomycin Sulfate	Ferrous Fumarate/Folic Acid/	Hydrochlorothiazide/Irbesartan*
Atropine Sulfate/Benzocic	Carvedilol	Dexamethasone/Neomycin	Intrinsic Factor/Vitamin B12/	Hydrochlorothiazide/Lisinopril*
Acid/Hyoscyamine	Celecoxib	Sulfate/Polymyxin B Sulfate	Vitamin C	Hydrochlorothiazide/Losartan
Sulfate/Methenamine/Methyl-	Chloramphenicol	Dexamethasone/Tobramycin	Ferrous Fumarate/Folic Acid/	Potassium*
ene Blue/Phenyl Salicylate	Chloroprocaine Hydrochloride	Dextrazoxane	Vitamins, Multi	Hydrochlorothiazide/
Atropine Sulfate/Difenoxin	Chlorothiazide	Dextroamphetamine Sulfate	Fexofenadine Hydrochloride	Methyldopa
Hydrochloride	Chlorothiazide Sodium	Dextromethorphan	Fexofenadine Hydrochloride/	Hydrochlorothiazide/Metoprolol
Atropine Sulfate/Diphenoxylate	Chlorothiazide/Methyldopa	Hydrobromide/Guaifenesin	Pseudoephedrine	Tartrate
Hydrochloride	Chloroxine	Dextromethorphan	Hydrochloride	Hydrochlorothiazide/Moexipril
Atropine Sulfate/Hyoscyamine	Chlorpheniramine	Hydrobromide/Promethazine	Filgrastim (G-CSF)	Hydrochloride*
Sulfate/Phenobarbital/	Maleate/Methscopolamine	Hydrochloride	Flecainide Acetate	Hydrochlorothiazide/
Scopolamine Hydrobromide	Nitrate/Phenylephrine	Dichlorphenamide	Fluconazole	Propranolol Hydrochloride
Azelastine Hydrochloride	Hydrochloride	Diflurasone Diacetate	Flucytosine	Hydrochlorothiazide/
Bacillus of Calmette & Guérin,	Chlorpheniramine	Diflunisal	Flumazenil	Spirolactone
Live (BCG Live)	Maleate/Pseudoephedrine	Digoxin	Flunisolide	Hydrochlorothiazide/Timolol
Becaplermin	Hydrochloride	Digoxin Immune Fab (Ovine)	Fluocinolone Acetonide	Maleate
Beclomethasone Dipropionate	Chlorpheniramine	Diltiazem Hydrochloride	Fluocinonide	Hydrochlorothiazide/Triamterene
Beclomethasone Dipropionate	Polistirex/Hydrocodone	Dinoprostone	Fluorometholone	Hydrochlorothiazide/Valsartan*
Monohydrate	Polistirex	Diphtheria Toxoid/Haemophilus	Fluorometholone Acetate	Hydrocodone Bitartrate/
Benazepril Hydrochloride*	Chlorpheniramine	B Conjugate Vaccine/	Fluorometholone/Sulfacetamide	Ibuprofen
Benazepril Hydrochloride/	Tannate/Phenylephrine	Pertussis Vaccine/Tetanus	Sodium	Hydrocortisone
Hydrochlorothiazide*	Tannate/Pyrimamine Tannate	Toxoid	Flurandrenolide	Hydrocortisone Acetate
Bendroflumethiazide/Nadolol	Chlorpropamide	Diphtheria Toxoid/Pertussis	Fluticasone Propionate	Hydrocortisone Acetate/
Benoxinate Hydrochloride/	Chlorthalidone/Clonidine	Vaccine, Acellular/Tetanus	Fluvoxamine Maleate	Neomycin Sulfate/
Fluorescein Sodium	Hydrochloride	Toxoid	Formoterol Fumarate	Polymyxin B Sulfate
Benzocaine	Choline Magnesium Trisilicate	Diphtheria Toxoid/Tetanus	Fosamprenavir Calcium	Hydrocortisone Acetate/
Benzonate	Cidofovir	Toxoid	Foscarnet Sodium	Pramoxine Hydrochloride
Benzoyl Peroxide	Cilastatin Sodium/Imipenem	Diphtheria Toxoid/Tetanus	Fosinopril Sodium*	Hydrocortisone Butyrate
Benzoyl Peroxide/Erythromycin	Cilostazol	Toxoid	Furosemide	Hydrocortisone Probutate
Bepridil Hydrochloride	Ciprofloxacin	Dirithromycin	Gabapentin	Hydrocortisone Valerate
Betamethasone Dipropionate,	Ciprofloxacin Hydrochloride	Disopyramide Phosphate	Gallium Nitrate	Hydrocortisone/Iodoquinol
Augmented	Ciprofloxacin Hydrochloride/	Donepezil Hydrochloride	Ganciclovir	Hydrocortisone/Neomycin
Betamethasone	Hydrocortisone	Dopamine Hydrochloride	Ganciclovir Sodium	Sulfate/Polymyxin B Sulfate
Dipropionate/Clotrimazole	Citalopram Hydrobromide	Dorzolamide Hydrochloride	Gemfibrozil	Hydromorphone Hydrochloride
Betaxolol Hydrochloride	Clarithromycin	Dorzolamide Hydrochloride/	Gentamicin Sulfate	Hydroquinone
Bethanechol Chloride	Clobetasol Propionate	Timolol Maleate	Glimepiride	Hyoscyamine
Bisoprolol Fumarate	Clofibrate	Doxazosin Mesylate	Glipizide	Hyoscyamine Sulfate
Bisoprolol Fumarate/	Clonidine	Dronabinol	Globulin, Immune	Ibutilide Fumarate
Hydrochlorothiazide	Clonidine Hydrochloride	Dyphylline	Glyburide	Imiglucerase
Botulinum Toxin Type A	Clotrimazole (Oral)	Dyphylline/Guaifenesin	Gonadotropin, Chorionic	Indinavir Sulfate
Brinzolamide	Codeine Phosphate/Guaifenesin	Echothiophate Iodide	(Novarel)	Indocyanine Green
Budesonide	Codeine Phosphate/	Efalizumab	Guaifenesin	Influenza Virus Vaccine
Bupivacaine Hydrochloride	Phenylephrine Hydrochloride/	Etavirenz	Guaifenesin/Hydrocodone	(Subvirion)
Bupivacaine Hydrochloride/	Promethazine Hydrochloride	Enalapril Maleate*	Bitartrate	Influenza Virus Vaccine
Epinephrine Bitartrate	Codeine Phosphate/	Enalapril Maleate/Felodipine*	Guaifenesin/Hydrocodone	(Whole-Virus)
Buprenorphine Hydrochloride	Promethazine Hydrochloride	Enalapril Maleate/	Bitartrate/Pseudoephedrine	Interferon Alfa-2A
Butabarbital/Hyoscyamine	Colistimethate Sodium	Hydrochlorothiazide*	Hydrochloride	Interferon Alfa-2B
Hydrobromide/	Corticorelin Ovine Trifluate	Enalaprilat*	Guaifenesin/Pseudoephedrine	Interferon Alfacon-1
Phenazopyridine	Corticotropin, Repository	Epinephrine	Hydrochloride (Duratuss,	Interferon Alfa-N3
Hydrochloride	Cosyntropin	Epinephrine Hydrochloride	Zephrex)	Interferon Beta-1A
Butorphanol Tartrate	Crotamiton	Epoetin Alfa	Haemophilus B Conjugate	Interferon Beta-1B
Calcitonin, Salmon	Cyanocobalamin (Nascobal)	Ergocalciferol	Vaccine	Interferon Gamma-1B
Calcitriol	Cyclosporine	Erythromycin, Solution (A/T/S)	Haemophilus B Conjugate	Irbesartan*

* Category C or D depending on the trimester the drug is given.

(continued)

Appendix 10

Use-in-Pregnancy Ratings (continued)

Iron Dextran	Naratriptan Hydrochloride	Sodium Phosphate/ Monobasic Sodium Phosphate	Succimer	B
Isoniazid/Pyrazinamide/ Rifampin	Natamycin	Nateglinide	Succinylcholine Chloride	
Isosorbide Dinitrate	Nateglinide	Potassium Phosphate/Sodium Phosphate	Sulconazole Nitrate	NO EVIDENCE OF RISK IN HUMANS <i>Either animal findings show risk while human findings do not, or, if no adequate human studies have been done, ani- mal findings are negative.</i>
Isosorbide Mononitrate (Ismo)	Nefazodone Hydrochloride	Pralidoxime Chloride	Sulfabenzamide/Sulfacetamide/ Sulfathiazole	
Isradipine	Neostigmine Methylsulfate	Pramipexole Dihydrochloride	Sulfacetamide Sodium	
Itraconazole	Niacin	Prazosin Hydrochloride	Sulfacetamide Sodium/Sulfur	
Ivermectin	Nicardipine Hydrochloride	Prednicarbate	Sulfamethoxazole/Trimethoprim	
Japanese Encephalitis Virus Vaccine	Nifedipine	Prednisolone Acetate	Sulfanilamide	
Ketoconazole	Nilutamide	Prednisolone Acetate/ Sulfacetamide Sodium	Sumatriptan	
Ketorolac Tromethamine	Nimodipine	Prednisolone Sodium	Sumatriptan Succinate	
Labetalol Hydrochloride	Nisoldipine	Proteinase Inhibitor (Human), Alpha 1	Tacrine Hydrochloride	
Lamivudine	Nitroglycerin	Protirelin	Tacrolimus	
Lamivudine/Zidovudine	Nortefloxacin	Procainamide Hydrochloride	Telmisartan*	Acarbose Acebutolol Hydrochloride Acetylcysteine Acrivastine/Pseudoephedrine Hydrochloride Acyclovir Acyclovir Sodium Alfuzosin Hydrochloride Amiloride Hydrochloride Amiloride Hydrochloride/ Hydrochlorothiazide Amlexanox Amoxicillin Amoxicillin/Clavulanate Potassium Amphotericin B Lipid Complex Amphotericin B Liposome Ampicillin Sodium/Sulbactam Sodium Amylase/Lipase/Protease (Pancrease) Antithrombin III (Human) Aprotinin Atazanavir Sulfate Azelaic Acid Azithromycin Dihydrate Aztreonam Basiliximab Brimonidine Tartrate Budesonide (Pulmicort Turbuhaler) Bupropion Hydrochloride Butenafine Hydrochloride Cabergoline Carbenicillin Indanyl Sodium Cefaclor Cefadroxil Cefamandole Nafate Cefazolin Sodium Cefdinir Cefepime Hydrochloride Cefixime Cefoperazone Sodium Cefotaxime Sodium Cefotetan Disodium Cefoxitin Sodium Cefpodoxime Proxetil Cefprozil Ceftazidime Ceftazidime Sodium Ceftibuten Ceftizoxime Sodium Ceftriaxone Sodium Cefuroxime Axetil
Levofloxacin	Nystatin	Proparacaine Hydrochloride	Terazosin Hydrochloride	
Levorphanol Tartrate	Ofloxacin	Proparacaine Hydrochloride	Terconazole	
Linezolid	Olanzapine	Proparacaine Hydrochloride	Testolactone	
Lisinopril*	Olopatadine Hydrochloride	Proparacaine Hydrochloride	Tetanus Immune Globulin	
Losartan Potassium*	Olisalazine Sodium	Proparacaine Hydrochloride	Tetanus Toxoid	
Mafenide Acetate	Omeprazole	Proparacaine Hydrochloride	Theophylline	
Measles/Mumps/Rubella Vaccine	Oprelvekin	Proparacaine Hydrochloride	Thiabendazole	
Mebendazole	Orphenadrine Citrate	Proteinase Inhibitor (Human), Alpha 1	Thrombin	
Mefenamic Acid	Oxaprozin	Pyrimethamine	Thyrotropin Alfa	
Mefloquine Hydrochloride	Oxcarbazepine	Quetiapine Fumarate	Tiagabine Hydrochloride	
Meningitis Vaccine	Oxymorphone Hydrochloride	Quinidine Gluconate	Tiludronate Disodium	
Mepivacaine Hydrochloride	Palivizumab	Quinidine Sulfate	Timolol Maleate	
Metaproterenol Sulfate	Pancratiolase	Rabies Immune Globulin	Tizanidine Hydrochloride	
Metaraminol Bitartrate	Paricalcitol	Rabies Vaccine	Tocainide Hydrochloride	
Methamphetamine Hydrochloride	Paroxetine Hydrochloride	Ramipril*	Tolcapone	
Methenamine	Pegademase Bovine	Repaglinide	Tolmetin Sodium	
Mandelate/Sodium Acid Phosphate	Pegaspargase	Retepase, Recombinant	Tolterodine Tartrate	
Methocarbamol	Peginterferon Alpha-2A	Rho (D) Immune Globulin	Topiramate	
Methoxsalen	Penbutolol Sulfate	Rifampin	Tramadol Hydrochloride	
Metoprolol Succinate	Pentoxifylline	Rifapentine	Trandolapril*	
Metoprolol Tartrate	Perindopril Erbumine*	Riluzole	Trandolapril/Verapamil Hydrochloride*	
Metirosine	Phentermine Hydrochloride	Rimantadine Hydrochloride	Tretinoin (Topical)	
Mexiletine Hydrochloride	Phenylephrine Hydrochloride	Risperidone	Triamcinolone Acetonide	
Midodrine Hydrochloride	Phenylephrine Hydrochloride/ Promethazine Hydrochloride	Rituximab	Triamterene	
Milrinone Lactate	Phytonadione	Rizatriptan Benzoate	Trientine Hydrochloride	
Mirtazapine	Pilocarpine Hydrochloride	Rocuronium Bromide	Triethanolamine Polypeptide Oleate	
Modafinil	Pimozide	Rofecoxib	Trifluoride	
Moexipril Hydrochloride*	Plasminogen Fraction	Ropinivole Hydrochloride	Trimethoprim	
Mometasone Furoate	Pneumococcal Vaccine	Rosiglitazone Maleate	Trimipramine Maleate	
Monobenzene	Podofilox	Rubella Virus Vaccine	Trovafoxacin Mesylate	
Morphine Sulfate	Polio Vaccine, Inactivated	Rubeola Virus Vaccine	Tuberculin	
Moxifloxacin Hydrochloride	Polyethylene Glycol	Salicylic Acid	Typhoid Vaccine	
Mumps Virus Vaccine	Polyethylene Glycol/Potassium Chloride/Sodium	Salicylic Acid	Typhoid Vi Polysaccharide Vaccine	
Murmonab-Cd3	Polyethylene Glycol/Potassium Chloride/Sodium	Salmeterol Xinafoate	Valrubicin	
Mycophenolate Mofetil	Polyethylene Glycol/Potassium Chloride/Sodium Sulfate	Sargramostim	Valsartan*	
Mycophenolate Mofetil Hydrochloride	Polymyxin B Sulfate/Trimethoprim Sulfate	Scopolamine	Vancomycin Hydrochloride (Injection, Suspension)	
Nabumetone	Polythiazide/Prazosin Hydrochloride	Selegiline Hydrochloride	Varicella Virus Vaccine	
Nadolol	Potassium Acid Phosphate	Sermorelin Acetate	Vecuronium Bromide	
Nalidixic Acid	Potassium Chloride	Sertraline Hydrochloride	Venlafaxine Hydrochloride	
Naloxone Hydrochloride/ Pentazocine Hydrochloride	Potassium Citrate	Sevelamer Hydrochloride	Verapamil Hydrochloride	
Naphazoline Hydrochloride	Potassium Phosphate/Dibasic	Sibutramine Hydrochloride	Vitamin B12 (Injection)	
		Sodium Polystyrene Sulfonate	Yellow Fever Vaccine	
		Somatrem	Zalcitabine	
		Somatropin, E-Coli Derived	Zaleplon	
		Spiriva	Zidovudine	
		Spironolactone	Zileuton	
		Stavudine	Zolmitriptan	
		Streptokinase	Zonisamide	

* Category C or D depending on the trimester the drug is given.

(continued)

Appendix 10

Use-in-Pregnancy Ratings (continued)

Cefuroxime Sodium	Enoxaparin Sodium	Lidocaine	Ondansetron	Sulfasalazine
Cephalexin	Epinephrine/Lidocaine Hydrochloride	Lidocaine Hydrochloride	Ondansetron Hydrochloride	Tadalafil
Cetirizine Hydrochloride	Hydrochloride	Lidocaine/Prilocaine	Orlistat	Tamsulosin Hydrochloride
Chlorhexidine Gluconate	Epoprostenol Sodium	Lindane	Oxiconazole Nitrate	Terbutaline Hydrochloride
Ciclopirox Olamine	Eptifibatide	Lodoxamide Tromethamine	Oxybutynin Chloride	Terbutaline Sulfate
Cimetidine	Erythromycin	Loracarbef	Oxycodone Hydrochloride	Ticlopidine Hydrochloride
Cimetidine Hydrochloride	Erythromycin Ethylsuccinate	Loratadine	Palonosetron Hydrochloride	Tirofiban Hydrochloride
Clavulanate	Erythromycin Stearate	Loratadine/Pseudoephedrine Sulfate	Pemoline	Tobramycin (Ophthalmic)
Potassium/Ticarcillin Disodium	Etanercept	Malathion	Penicillin G Benzathine	Torsemide
Clindamycin Hydrochloride	Ethacrynate Sodium	Meclizine Hydrochloride	Penicillin G Benzathine/Procaine	Trastuzumab
Clindamycin Phosphate	Ethacrynic Acid	Memantine Hydrochloride	Penicillin G Potassium	Urokinase
Clopidogrel Bisulfate	Famotidine	Meropenem	Pentosan Polysulfate Sodium	Ursodiol
Clotrimazole (Topical)	Fenoldopam Mesylate	Mesalamine	Pergolide Mesylate	Valacyclovir Hydrochloride
Clozapine	Ferric Sodium Gluconate	Metformin Hydrochloride	Permethrin	Vancomycin Hydrochloride (Capsules)
Cromolyn Sodium	Flavoxate Hydrochloride	Methohexital Sodium	Piperacillin Sodium	Vardenafil Hydrochloride
Cyclobenzaprine Hydrochloride	Fondaparinux Sodium	Methyldopa	Piperacillin Sodium/Tazobactam Sodium	Zafirlukast
Cyproheptadine Hydrochloride	Fosfomycin Tromethamine	Metoclopramide Hydrochloride	Praziquantel	Zolpidem Tartrate
Dalteparin Sodium	Glatiramer Acetate	Metolazone	Progesterone	
Danaparoid Sodium	Glucagon Hydrochloride	Metronidazole	Propofol	
Daptomycin	Glycopyrrolate	Metronidazole Hydrochloride	Psyllium	
Desflurane	Gonadorelin Hydrochloride	Miglitol	Quinupristin/Dalfopristin	
Desmopressin Acetate	Guaifenesin/Pseudoephedrine Hydrochloride (Guaifed)	Montelukast Sodium	Ranitidine Hydrochloride	
Diclofenac Potassium	Hydrochlorothiazide	Mupirocin	Rifabutin	
Diclofenac Sodium	Ibuprofen	Mupirocin Calcium	Ritonavir	
Didanosine	Imiquimod	Naftifine Hydrochloride	Ropivacaine Hydrochloride	
Diphenhydramine Hydrochloride	Indapamide	Nalbuphine Hydrochloride	Saquinavir	
Dipyridamole	Infliximab	Nalmefene Hydrochloride	Saquinavir Mesylate	
Dobutamine Hydrochloride	Insulin Lispro, Human	Naloxone Hydrochloride	Sildenafil Citrate	
Dolasetron Mesylate	Ipratropium Bromide	Naproxen	Silver Sulfadiazine	
Dornase Alpha	Iso sorbide Mononitrate (Monoket, Imdur)	Naproxen Sodium	Sodium Fluoride	
Doxapram Hydrochloride	Ketoprofen	Nelfinavir Mesylate	Somatropin, E-Coli Derived (Genotropin)	
Doxepin Hydrochloride (Zonalon)	Lactulose	Nitrofurantoin, Macrocrystals/Nitrofurantoin Monohydrate	Somatropin, Mammalian Derived (Serostim)	
Edetate Calcium Disodium	Lansoprazole	Nizatidine	Sotalol Hydrochloride	
Emedastine Difumarate	Lepirudin	Octreotide Acetate	Sucralfate	
Emtricitabine	Levocarnitine	Omalizumab		

A

CONTROLLED STUDIES SHOW NO RISK

Adequate, well-controlled studies in pregnant women have failed to demonstrate risk to the fetus.

Levothyroxine Sodium
Liothyronine Sodium

* Category C or D depending on the trimester the drug is given.

Appendix 11

Sugar-Free Products

Listed below, by therapeutic category, is a selection of drug products that contain no sugar. When recommending these products to diabetic patients, keep in mind that many may contain sorbitol, alcohol, or other sources of carbohydrates. This list should not be considered all-inclusive. Generics and alternate brands of some products may be available. Check product labeling for a current listing of inactive ingredients.

Analgesics

Actamin Maximum Strength Liquid	Cypress
Addaprin Tablet	Dover
Aminofen Tablet	Dover
Aminofen Max Tablet	Dover
Aspirin Tablet	Dover
Back Pain-Off Tablet	Textilease Medique
Backpain Tablet	Hart Health and Safety
Buffasal Tablet	Dover
Dyspel Tablet	Dover
Febrol Liquid	Scot-Tussin
I-Prin Tablet	Textilease Medique
Medi-Seltzer Effervescent Tablet	Textilease Medique
Ms.-Aid Tablet	Textilease Medique
PMS Relief Tablet	Textilease Medique
Silapap Children's Elixir	Silarx

Antacids/Antiflatulents

Almag Chewable Tablet	Textilease Medique
Alcalak Chewable Tablet	Textilease Medique
Aldroxicon I Suspension	Textilease Medique
Aldroxicon II Suspension	Textilease Medique
Baby Gasz Drops	Lee
Dimacid Chewable Tablet	Otis Clapp & Son
Diotame Chewable Tablet	Textilease Medique
Diotame Suspension	Textilease Medique
Gas-Ban Chewable Tablet	Textilease Medique
Mallamint Chewable Tablet	Textilease Medique

Mylanta Gelcaplet	Johnson & Johnson/Merck
Neutrin Tablet	Dover
Tums E-X Chewable Tablet	GlaxoSmithKline Consumer

Antiasthmatic/Respiratory Agents

Jay-Phyl Syrup	Pharmakon
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Antidiarrheals

Diarrest Tablet	Dover
Di-Gon II Tablet	Textilease Medique
Imogen Liquid	Pharmaceutical Generic

Blood Modifiers/Iron Preparations

I.L.X. B-12 Elixir	Kenwood
Irofel Liquid	Dayton
Nephro-Fer Tablet	R & D

Corticosteroids

Pediapred Solution	Celltech
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Cough/Cold/Allergy Preparations

Accuhist DM Pediatric Drops	Pediamed
Accuhist LA Tablets	Pediamed
Accuhist Pediatric Drops	Pediamed
Alacol DM Syrup	Ballay
Anaplex DM Syrup	ECR
Anaplex HD Syrup	ECR
Atuss EX Liquid	Atley
Benadryl Allergy/Sinus Children's Solution	Warner-Lambert Consumer
Biodec DM Drops	Bio-Pharm
Biodec DM Syrup	Bio-Pharm
Bromdec Solution	Scientific Laboratories
Bromdec DM Solution	Scientific Laboratories
Bromhist-DM Solution	Cypress
Bromhist Pediatric Solution	Cypress
Bromophed DX Syrup	Qualitest
B-Tuss Liquid	Blansett
Carbofed DM Syrup	Hi-Tech

Carbofed DM Drops	Hi-Tech
Cardec Syrup	Qualitest
Cardec DM Syrup	Qualitest
Cetafen Cold Tablet	Hart Health and Safety
Cheratussin DAC Liquid	Qualitest
Codal-DM Syrup	Cypress
Coldmist DM Syrup	Breckenridge
Coldonyl Tablet	Dover
Co-Tussin Liquid	American Generics
Cotuss-V Syrup	Alphagen
Cytuss HC Syrup	Cypress
Decorel Forte Tablet	Textilease Medique
Despec Liquid	International Ethical
Despec-SF Liquid	International Ethical
Diabetic Tussin Allergy Relief Liquid	Health Care Products
Diabetic Tussin Allergy Relief Gelcaplet	Health Care Products
Diabetic Tussin C Expectorant Liquid	Health Care Products
Diabetic Tussin Cold & Flu Gelcaplet	Health Care Products
Diabetic Tussin DM Liquid	Health Care Products
Diabetic Tussin DM Maximum Strength Liquid	Health Care Products
Diabetic Tussin EX Liquid	Health Care Products
Dimetapp Allergy Children's Elixir	Wyeth Consumer
Diphen Capsule	Textilease Medique
Double-Tussin DM Liquid	Reese
Dynatuss Syrup	Breckenridge
Dynatuss HC Solution	Breckenridge
Dynatuss HCG Solution	Breckenridge
Echotuss-HC Syrup	Superior
Endal HD Liquid	Pediamed

(continued)

Appendix 11

Sugar-Free Products (continued)

Endal HD Plus Liquid	Pediamed	Hydro-Tussin HD Liquid	Ethex	Phanasin Syrup	Pharmakon
Endotuss-HD Syrup	American Generics	Hyphen-HD Syrup	Alphagen	Phanasin Diabetic Choice Syrup	Pharmakon
Enplus-HD Syrup	Alphagen	Hytuss Tablet	Hyrex	Phanatuss Syrup	Pharmakon
Entex Syrup	Andrx	Hytuss 2X Capsule	Hyrex	Phenydryl Solution	Scientific Laboratories
Entex HC Syrup	Andrx	Iofen-C NF Liquid	Superior	Pneumotussin 2.5 Syrup	ECR
Exo-Tuss Syrup	American Generics	Iofen-DM NF Liquid	Superior	Poly-Tussin Syrup	Poly
Gani-Tuss NR Liquid	Cypress	Iofen-NF Liquid	Pharmakon	Poly-Tussin DM Syrup	Poly
Gani-Tuss-DM NR Liquid	Cypress	Jaycof Expectorant Syrup	Pharmakon	Poly-Tussin HD Syrup	Poly
Genecof-HC Liquid	Pharmaceutical Generic	Jaycof-HC Liquid	Pharmakon	Poly-Tussin XP Syrup	Poly
Genecof-XP Liquid	Pharmaceutical Generic	Jaycof-XP Liquid	R.I.D.	Pro-Cof Liquid	Qualitest
Genedel Syrup	Pharmaceutical Generic	Kita LA Tos Liquid	Athlon	Pro-Cof D Liquid	Qualitest
Genedotuss-DM Liquid	Pharmaceutical Generic	Levall 5.0 Liquid	ECR	Prolex DH Liquid	Blansett
Genexpect DM Liquid	Pharmaceutical Generic	Lodrane Liquid	Proethic Laboratories	Prolex DM Liquid	Blansett
Genexpect-PE Liquid	Pharmaceutical Generic	Lortuss DM Solution	Proethic Laboratories	Protex Solution	Scientific Laboratories
Genexpect-SF Liquid	Pharmaceutical Generic	Lortuss HC Solution	Marnel	Protex D Solution	Scientific Laboratories
Giltuss Liquid	Gil	Marcof Expectorant Syrup		Protuss Liquid	First Horizon
Giltuss HC Syrup	Gil	Maxi-Tuss HCX Solution	MCR American	Protuss-D Liquid	First Horizon
Giltuss Pediatric Liquid	Gil	M-Clear Syrup	McNeil, R.A.	Quintex Syrup	Qualitest
Giltuss TR Tablet	Gil	Mytussin AC Cough Syrup	Morton Grove	Quintex HC Syrup	Qualitest
Guai-Co Liquid	Alphagen	Mytussin DAC Syrup	Morton Grove	Romilar AC Liquid	Scot-Tussin
Guaicon DMS Liquid	Textilease Medique	Nalex DH Liquid	Blansett	Romilar DM Liquid	Scot-Tussin
Guai-DEX Liquid	Alphagen	Nalex-A Liquid	Blansett	Rondec Syrup	Biovail
Guaitussin AC Solution	Scientific Laboratories	Nalspan Senior DX Liquid	Morton Grove	Rondec DM Syrup	Biovail
Guaitussin DAC Solution	Scientific Laboratories	Neotuss S/F Liquid	A.G. Marin	Rondec DM Drops	Biovail
Guiatuss AC Syrup	Alpharma	Neotuss-D Liquid	A.G. Marin	Scot-Tussin Allergy Relief Formula Liquid	Scot-Tussin
Guiatuss AC Syrup	Ivax	Norel DM Liquid	U.S. Corp	Scot-Tussin DM Liquid	Scot-Tussin
Guiatuss DAC Syrup	Alpharma	Norel SD Solution	U.S. Corp	Scot-Tussin DM Cough Chasers Lozenge	Scot-Tussin
Halotussin AC Liquid	Watson	Nycoff Tablet	Dover	Scot-Tussin Expectorant Liquid	Scot-Tussin
Halotussin DAC Liquid	Watson	Onset Forte Tablet	Textilease Medique	Scot-Tussin Original Liquid	Scot-Tussin
Hayfebrof Liquid	Scot-Tussin	Orgadin Liquid	American Generics	Scot-Tussin Senior Liquid	Scot-Tussin
H-C Tussive Syrup	Vintage	Orgadin-Tuss Liquid	American Generics	Siladryl Allergy Liquid	Silarx
Histex PD Liquid	TEAMM	Orgadin-Tuss DM Liquid	American Generics	Siladryl DAS Liquid	Silarx
Histinex HC Syrup	Ethex	Organidin NR Liquid	Wallace	Sildec Syrup	Silarx
Histinex PV Syrup	Ethex	Organidin NR Tablet	Wallace	Sildec Drops	Silarx
Histuss HC Solution	Scientific Laboratories	Palgic-DS Syrup	Pamlab	Sildec-DM Syrup	Silarx
Hydro PC Syrup	Cypress	Pancof Syrup	Pamlab	Sildec-DM Liquid	Silarx
Hydron KGS Liquid	Cypress	Pancof EXP Syrup	Pamlab	Silexin Syrup	Otis Clapp & Son
Hydro-Tussin DM Elixir	Ethex	Pancof HC Liquid	Pamlab	Silexin Tablet	Otis Clapp & Son
Hydro-Tussin HC Syrup	Ethex	Pancof XP Liquid	Pamlab	Siltussin DAS Liquid	Silarx
		Pediatex DM Liquid	Zyber	Siltussin DM DAS Cough Syrup Formula	Silarx
		Pediatex D	Zyber	Siltussin SA Syrup	Silarx

(continued)

Appendix 11

Sugar-Free Products (continued)

S-T Forte 2 Liquid	Scot-Tussin	Metamucil Smooth Texture Powder	Procter & Gamble	Vademecum Mouthwash & Gargle Concentrate	Dermatone
Sudorin Tablet	Textilease Medique	Reguloid Powder	Rugby	Potassium Supplements	
Supress DX Pediatric Drops	Kramer-Novis	Miscellaneous		Cena K Liquid	Century
Suttar-SF Syrup	Gil	Acidoll Capsule	Key	Kaon Elixir	Savage
Tricodene Syrup	Pfeiffer	Alka-Gest Tablet	Key	Kaon-Cl 20% Liquid	Savage
Trispec-PE Liquid	Deliz	Bicitra Solution	Ortho-McNeil	Rum-K Liquid	Fleming
Tussafed Syrup	Everett	Colidrops Pediatric Drops	A.G. Marin	Vitamins/Minerals/Supplements	
Tussafed-EX Pediatric Drops	Everett	Cytra-2 Solution	Cypress	Action-Tabs Made For Men	Action Labs
Tussafed-HC Syrup	Everett	Cytra-K Solution	Cypress	Adaptosode For Stress Liquid	HVS
Tuss-DM Liquid	Seatrace	Cytra-K Crystals	Cypress	Adaptosode R+R For Acute Stress Liquid	HVS
Tuss-ES Syrup	Seatrace	Melatin Tablet	Mason Vitamins	Aminoplex Powder	Tyson
Tussi-Organidin DM NR Liquid	Wallace	Methadose Solution	Mallinckrodt	Aminostasis Powder	Tyson
Tussi-Organidin DM-S NR Liquid	Wallace	Neutra-Phos Powder	Ortho-McNeil	Aminotate Powder	Tyson
Tussi-Organidin NR Liquid	Wallace	Neutra-Phos-K Powder	Ortho-McNeil	Apetigen Elixir	Kramer-Novis
Tussi-Organidin-S NR Liquid	Wallace	Polycitra-K Solution	Ortho-McNeil	Apptrim Capsules	Physician Therapeutics
Tussi-Organidin-S NR Liquid	Wallace	Polycitra-LC Solution	Ortho-McNeil	B-C-Bid Caplet	Lee
Tussi-Organidin-S NR Liquid	Wallace	Questran Light Powder	Par	Bevitamel Tablet	Westlake
Tussi-Pres Liquid	Kramer-Novis	Mouth/Throat Preparations		Biosode Liquid	HVS
Tussirex Liquid	Scot-Tussin	Aquafresh Triple Protection Gum	Consumer	Biotect Plus Caplet	Gil
Vi-Q-Tuss Syrup	Vintage	GlaxoSmithKline	J.B. Williams	C & M Caps-375 Capsule	Key
Vitussin Expectorant Syrup	Cypress	Cepacol Maximum Strength Spray	J.B. Williams	Calbon Tablet	Emrex/Economed
Vortex Syrup	Superior	Cepacol Sore Throat Lozenges	Lee	Cal-Cee Tablet	Key
Z-Cof DM Syrup	Zyber	Cheracol Sore Throat Spray	Pharmakon	Calcimin-300 Tablet	Key
Z-Cof HC Syrup	Zyber	Cylex Lozenges	Health Care Products	Cal-Mint Chewable Tablet	Freedra Vitamins
Zyrtec Syrup	Pfizer	Diabetic Tussin Cough Drops	Mentholatum	Carox Plus Tablet	Seneca
Fluoride Preparations		Fisherman's Friend Lozenges	Geritrex	Cerefolin Tablet	Pamlab
Ethedent Chewable Tablet	Ethex	Fresh N Free Liquid	GlaxoSmithKline Consumer	Cevi-Bid Tablet	Lee
Fluor-A-Day Tablet	Pharmascience	Isodettes Sore Throat Spray	Dover	Cholestratin Tablet	Key
Fluor-A-Day Lozenge	Pharmascience	Larynx Lozenges	Pfizer Consumer	Chromacaps Tablet	Key
Flura-Loz Tablet	Kirkman	Listerine Pocketpaks Film	Textilease Medique	Chromium K6 Tablet	Rexall Consumer
Lozi-Flur Lozenge	Dreir	Medikoff Drops	Heritage Brand/Insight	Combi-Cart Tablet	Atrium Bio-Tech
Sensodyne w/Fluoride Gel	GlaxoSmithKline Consumer	N'Ice Lozenges	Parnell	Daily Herbs Formulas	Mason Vitamins
Sensodyne w/Fluoride Tartar Control Toothpaste	GlaxoSmithKline Consumer	Oragesic Solution	Pharmakon	Delta D3 Tablet	Freedra Vitamins
Sensodyne w/Fluoride Toothpaste	GlaxoSmithKline Consumer	Orasept Mouthwash/Gargle Liquid	Wyeth Consumer	Detoxosode Liquids	HVS
Laxatives		Robitussin Lozenges	Textilease Medique	DHEA Capsule	ADH Health Products
Citrucel Powder	GlaxoSmithKline Consumer	Sepasoothe Lozenges	Otis Clapp & Son	Diabeze Tablet	Key
Fiber Ease Liquid	Plainview	Thorets Maximum Strength Lozenges	S.S.S.	Diatx Tablet	Pamlab
Fibro-XL Capsule	Key	Throto-Ceptic Spray		Diet System 6 Gum	Applied Nutrition
Genfiber Powder	Ivax			Diucaps Capsule	Legere
Konsyl Easy Mix Formula Powder	Konsyl			DI-Phen-500 Capsule	Key
Konsyl-Orange Powder	Konsyl				

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Appendix 11

Sugar-Free Products (continued)

ElectroTab Tablet	Hart Health And Safety	Lynae Ginse-Cool Chewable Tablet	Boscogen	Sea Omega 30 Softgel	Rugby
Endorphenyl Capsule	Tyson	Mag-Caps Capsule	Rising	Sea Omega 50 Softgel	Rugby
Ensure Nutra Shake Pudding	Ross Products	Mag-Ox 400 Tablet	Blaine	Soy Care for Bone Health	Inverness Medical Tablet
Enterex Diabetic Liquid	Victus	Mag-SR Tablet	Cypress	Soy Care for Menopause	Inverness Medical Capsule
Essential Nutrients Plus Silica Tablet	Action Labs	Medi-Lyte Tablet	Textilease Medique	Strovite Forte Syrup	Everett
Evening Primrose Oil Capsule	National Vitamin	New Life Hair Tablet	Rexall Consumer	Sunnite Tablet	Green Turtle Bay Vitamin
Evolve Softgel	Bionutrics Health Products	Nutrisure OTC Tablet	Westlake	Sunvite Tablet	Rexall Consumer
Ex-L Tablet	Key	O-Cal Fa Tablet	Pharmics	Sunvite Platinum Tablet	Rexall Consumer
Extress Tablet	Key	Plenamins Plus Tablet	Rexall Consumer	Supervite Liquid	Seyer Pharmatec
Eyetamins Tablet	Rexall Consumer	Powermate Tablet	Green Turtle Bay Vitamin	Suplevit Liquid	Gil
Fem-Cal Tablet	Freeda Vitamins	Prostaplex Herbal Complex Capsule	ADH Health Products	Triamin Tablet	Key
Fem-Cal Plus Tablet	Freeda Vitamins	Prostatonin Capsule	Pharmaton Natural Health	Triamino Tablet	Freeda Vitamins
Folacin-800 Tablet	Key	Protect Plus Liquid	Gil	Ultramino Powder	Freeda Vitamins
Foltx Tablet	Pamlab	Protect Plus NR Softgel	Gil	Uro-Mag Capsule	Blaine
Gram-O-Leci Tablet	Freeda Vitamins	Quintabs-M Tablet	Freeda Vitamins	Vitalize Liquid	Scot-Tussin
Hemovit Tablet	Dayton	Re/Neph Liquid	Ross Products	Vitamin C/Rose Hips Tablet	ADH Health Products
Herbal Slim Complex Capsule	ADH Health Products	Replace Capsule	Key	Vitrum Jr Chewable Tablet	Mason Vitamins
Legatrin GCM Formula Tablet	Columbia	Replace w/o Iron Capsule	Key	Xtramins Tablet	Key
Lynae Calcium/Vitamin C Chewable Tablet	Boscogen	Resource Arginaid Powder	Novartis Nutrition	Yohimbe Power Max 1500 For Women Tablet	Action Labs
Lynae Chondroitin/ Glucosamine Capsule	Boscogen	Ribo-100 T.D. Capsule	Key	Yohimbized 1000 Capsule	Action Labs
		Samolinic Softgel	Key	Ze-Plus Softgel	Everett

Appendix 12

Alcohol-Free Products (continued)

PediaCare Decongestant Plus Cough Drops	Pharmacia	Tussi-Organidin DM NR Liquid	Wallace	Kaopectate Children's Liquid Suspension	Pharmacia Consumer
PediaCare Multi-Symptom Liquid	Pharmacia	Tussi-Organidin DM-S NR Liquid	Wallace	Liqui-Doss Liquid	Ferndale
PediaCare Nightrest Liquid	Pharmacia	Tussi-Organidin NR Liquid	Wallace	Mylicon Infants' Suspension	J&J-Merck
Pediahist DM Syrup	Boca	Tussi-Organidin-S NR Liquid	Wallace	Neoloid Liquid	Kenwood Therapeutics
Pedia-Relief Liquid	Major	Tussi-Pres Liquid	Kramer-Novis	Neutralin Tablet	Dover
Pediatex Liquid	Zyber	Tussirex Liquid	Scot-Tussin	Senokot Children's Syrup	Purdue Frederick
Pediatex-D Liquid	Zyber	Tussirex Syrup	Scot-Tussin		
Pediox Liquid	Atley	Tylenol Allergy-D Children's Liquid	McNeil Consumer	Hematinics	
Phanasin Syrup	Pharmakon	Tylenol Cold Children's Liquid	McNeil Consumer	Irofol Liquid	Dayton
Phanatuss Syrup	Pharmakon	Tylenol Cold Children's Suspension	McNeil Consumer		
Phena-S Liquid	GM	Tylenol Cold Infants' Drops	McNeil Consumer	Miscellaneous	
Pneumotussin 2.5 Syrup	ECR	Tylenol Cold Plus Cough Children's Liquid	McNeil Consumer	Cytra-2 Solution	Cypress
Poly-Tussin Syrup	Poly	Tylenol Cold Plus Cough Infants' Suspension	McNeil Consumer	Cytra-K Solution	Cypress
Poly-Tussin DM Syrup	Poly	Tylenol Flu Children's Suspension	McNeil Consumer	Emetrol Solution	Pharmacia Consumer
Poly-Tussin HD Syrup	Poly	Tylenol Flu Night Time Max Strength Liquid	McNeil Consumer	Fluorinse Solution	Oral B
Poly-Tussin XP Syrup	Poly	Tylenol Sinus Children's Liquid	McNeil Consumer	Rum-K Liquid	Fleming
Primsol Solution	Medicis	Vanex-HD Syrup	Monarch		
Pro-Col Liquid	Qualitest	Vicks 44E Pediatric Liquid	Procter & Gamble	Psychotropics	
Prolex DH Liquid	Blansett Pharmacal	Vicks 44M Pediatric Liquid	Procter & Gamble	Thorazine Syrup	GlaxoSmithKline
Prolex DM Liquid	Blansett Pharmacal	Vicks Dayquil Multi-Symptom Liquidcap	Procter & Gamble		
Protuss Liquid	First Horizon	Vicks Dayquil Multi-Symptom Liquid	Procter & Gamble	Topical Products	
Protuss-D Liquid	First Horizon	Vicks Nyquil Children's Liquid	Procter & Gamble	Aloe Vesta 2-N-1 Antifungal Ointment	Convatec
Q-Tussin PE Liquid	Qualitest	Vi-Q-Tuss Syrup	Vintage	Fleet Pain Relief Pads	Fleet
Quintex Syrup	Qualitest	Vitussin Expectoant Syrup	Cypress	Fresh & Pure Douche Solution	Unico
Robitussin Cough & Congestion Liquid	Wyeth Consumer	Vortex Syrup	Superior	Handclens Solution	Woodward
Robitussin DM Syrup	Wyeth Consumer	Z-Cof DM Syrup	Zyber	Joint-Ritis Maximum Strength Ointment	Naturopathic
Robitussin PE Syrup	Wyeth Consumer	Z-Cof HC Syrup	Zyber	Klenz Cloth Pads	Geritrex
Robitussin Pediatric Drops	Wyeth Consumer			Neutrogena Acne Wash Liquid	Neutrogena
Robitussin Pediatric Cough Syrup	Wyeth Consumer			Neutrogena Antiseptic Liquid	Neutrogena
Robitussin Pediatric Night Relief Liquid	Wyeth Consumer			Neutrogena Clear Pore Gel	Neutrogena
Romilar AC Liquid	Scot-Tussin			Neutrogena T/Derm Liquid	Neutrogena
Romilar DM Liquid	Scot-Tussin			Neutrogena Toner Liquid	Neutrogena
Rondec Syrup	Biovail			Podiclens Spray	Woodward
Rondec DM Drops	Biovail			Propa pH Foaming Face Wash Liquid	Del
Rondec DM Syrup	Biovail			Sea Breeze Foaming Face Wash Gel	Clairol
Scot-Tussin Allergy Relief Formula Liquid	Scot-Tussin			Stri-Dex Pad	Blistex
Scot-Tussin DM Liquid	Scot-Tussin			Stri-Dex Maximum Strength Pad	Blistex
Scot-Tussin Expectoant Liquid	Scot-Tussin			Stri-Dex Sensitive Skin Pad	Blistex
Scot-Tussin Original Syrup	Scot-Tussin			Stri-Dex Super Scrub Pad	Blistex
Scot-Tussin Senior Liquid	Scot-Tussin			Therasoft Anti-Acne Cream	SFC/Solvent Free
Siladryl Allergy Liquid	Silarx			Therasoft Skin Protectant Cream	SFC/Solvent Free
Siladryl DAS Liquid	Silarx				
Sildec Liquid	Silarx			Vitamins/Minerals/Supplements	
Sildec Syrup	Silarx			Adaptosode For Stress Liquid	HVS
Sildec-DM Drops	Silarx			Adaptosode R+R For Acute Stress Liquid	HVS
Sildec-DM Syrup	Silarx			Apetigen Elixir	Kramer-Novis
Siltussin DAS Liquid	Silarx			Biosode Liquid	HVS
Siltussin DM Syrup	Silarx			Detoxosode Products Liquid	HVS
Siltussin DM DAS Cough Formula Syrup	Silarx			Genesupp-500 Liquid	Pharmaceutical Generic
Siltussin SA Syrup	Silarx			Genetect Plus Liquid	Pharmaceutical Generic
Simply Cough Liquid	McNeil Consumer			Multi-Delyn w/Iron Liquid	Silarx
Simply Stuffy Liquid	McNeil Consumer			Poly-Vi-Sol Drops	Mead Johnson
S-T Forte 2 Liquid	Scot-Tussin			Poly-Vi-Sol w/Iron Drops	Mead Johnson
Sudatuss DM Syrup	Pharmaceutical Generic			Protect Plus Liquid	Gil
				Solvivite-F Drops	Pharmics
Sudatuss-2 Liquid	Pharmaceutical Generic			Strovite Forte Syrup	Everett
Sudatuss-SF Liquid	Pharmaceutical Generic			Supervite Liquid	Seyer Pharmatec
				Suplevit Liquid	Gil
Triaminic Infant Decongestant Drops	Novartis Consumer			Tri-Vi-Sol Drops	Mead Johnson
Trispec-PE Liquid	Deliz			Tri-Vi-Sol w/Iron Drops	Mead Johnson
Tussafed Syrup	Everett			Vitafof Syrup	Everett
Tussafed-EX Syrup	Everett			Vitalize Liquid	Scot-Tussin
Tussafed-EX Pediatric Liquid	Everett			Vitamin C/Rose Hips Tablet, Extended Release	ADH Health Products
Tussafed-HC Syrup	Everett				
Tuss-DM Liquid	Seatrace				
Tuss-ES Syrup	Seatrace				
		Gastrointestinal Agents			
		Baby Gasz Drops	Lee		
		Colidrops Pediatric Drops	A.G. Marin		
		Diarrest Tablet	Dover		
		Imogen Liquid	Pharmaceutical Generic		
		Kaodene NN Suspension	Pfleiffer		
		Kaopectate Advanced Formula Suspension	Pharmacia Consumer		

Appendix 13

Common Drug Interactions

Pharmacodynamic interactions

Object drug (trade name)	Precipitant drug (trade name)	Mechanism of Interaction
Antiarrhythmics	Antipsychotics, cisapride (Propulsid®), erythromycin (E-Mycin®), fluoroquinolones, fluoxetine (Prozac®), 5HT-3 antagonists, tricyclic antidepressants	Additive effects cause prolonged QT interval
Anticholinergic agents	Antihistamines, phenothiazine derivatives	Increased anticholinergic side effects
Aspirin, clopidogrel (Plavix®), heparin, low molecular weight heparins, ticlopidine (Ticlid®), warfarin (Coumadin®)	Garlic, ginkgo	Increased bleeding due to displacement of platelet-activating factor from its binding site
Clopidogrel (Plavix®), heparin, low molecular weight heparins, ticlopidine (Ticlid®), warfarin (Coumadin®)	Aspirin, NSAIDs	Increased bleeding due to inhibition of platelet aggregation
Benzodiazepines	Flumazenil (Romazicon®)	Antagonistic activity
β-Blockers	β-Agonists	Antagonistic activity
Naloxone (Narcan®)	Opiates	Antagonistic activity

Pharmacokinetic interactions

Digoxin (Lanoxin®), phenytoin (Dilantin®), quinolones, tetracyclines, warfarin (Coumadin®)	Antacids, cholestyramine (Questran®), Prevalite®, LoCHOLEST®, didanosine (Videx®), divalent cations (Ca ²⁺ , Co ²⁺ , Cu ²⁺ , Fe ²⁺ , Mg ²⁺ , Mn ²⁺), sucralfate (Carafate®)	Decreased efficacy of object drug due to complexation and chelation
Dapsone, itraconazole (Sporanox®), ketoconazole (Nizoral®)	Antacids, H ₂ -receptor antagonists, proton pump inhibitors	Decreased efficacy of object drug due to increased pH of GI fluids
Oral contraceptives, warfarin (Coumadin®)	Antibiotics	Decreased efficacy of object drug due to change in bacterial flora of GI tract
Phenytoin (Dilantin®), valproic acid (Depakene®, Depakote®), warfarin (Coumadin®)	Chloral hydrate, (Aquachloral®, Supprettes®), salicylates, valproic acid (Depakene®, Depakote®)	Increased fraction of object drug due to drug displacement with multiple highly protein-bound drugs
Digoxin (Lanoxin®)	Aminoglycosides, amphotericin B (Amphotec®, Amphocin®, Fungizone®, Abelcet®, Ambisome®)	Nephrotoxicity due to decreased glomerular filtration rate
Lithium (Eskalith®, Lithobid®)	NSAIDs, thiazides	Decreased clearance of lithium
Cephalosporins, penicillins, quinolones	Probenecid (Benemid®)	Decreased antibiotic excretion due to competition for renal tubular secretion
Aspirin	Acetazolamide (Diamox®), sodium bicarbonate	Increased elimination of aspirin due to increased urinary pH

Cytochrome P450 interactions

CYP1A2

Substrates (trade name)	Inhibitors (trade name)	Inducers (trade name)
Amitriptyline (Elavil®)	Cimetidine (Tagamet®)	Cigarette smoke
Clomipramine (Anafranil®)	Ciprofloxacin (Cipro®)	Phenobarbital (Luminal sodium®)
Clozapine (Clozaril®)	Clarithromycin (Biaxin®)	Phenytoin (Dilantin®)
Cyclobenzaprine (Flexeril®)	Erythromycin (E-Mycin®)	Rifampin (Rifadin®, Rimactane®)
Desipramine (Norpramin®)	Fluvoxamine (Luvox®)	Ritonavir (Norvir®)
Diazepam (Valium®)	Grapefruit juice	
Fluvoxamine (Luvox®)	Isoniazid (Nydrazid®)	
Ginkgo	Ketoconazole (Nizoral®)	

(continued)

Appendix 13

Common Drug Interactions (continued)

CYP2D6 (cont)

Substrates (trade name)	Inhibitors (trade name)	Inducers (trade name)
Clomipramine (Anafranil®)	Cimetidine (Tagamet®)	Rifampin (Rifadin®, Rimactane®)
Clozapine (Clozaril®)	Clomipramine (Anafranil®)	Ritonavir (Norvir®)
Codeine	Desipramine (Norpramin®)	
Cyclobenzaprine (Flexeril®)	Fluoxetine (Prozac®)	
Desipramine (Norpramin®)	Haloperidol (Haldol®)	
Dextromethorphan	Indinavir (Crixivan®)	
Doxepin (Sinequan®)	Paroxetine (Paxil®)	
Fluoxetine (Prozac®)	Propafenone (Rhythmol®)	
Ginkgo	Quinidine (Cardioquin®, Quinaglute®, Dura-Tabs®, Quinidex®)	
Haloperidol (Haldol®)		
Hydrocodone		
Imipramine (Tofranil®)	Ritonavir (Norvir®)	
Metoprolol (Lopressor®)	Sertraline (Zoloft®)	
Nortriptyline (Aventyl®, Pamelor®)	Thioridazine (Mellaril®)	
Oxycodone (Endocodone®, OxyContin®, OxyIR®, Percolone®, Roxicodone®)		
Paroxetine (Paxil®)		
Perfenazine (Trilafon®)		
Propafenone (Rhythmol®)		
Propranolol (Inderal®)		
Risperidone (Risperdal®)		
Thioridazine (Mellaril®)		
Timolol (Betimol®, Blocadrin®, Timoptic®)		
Tramadol (Ultram®)		
Trazodone (Desyre®)		
Venlafaxine (Effexor®)		

CYP2E1

Acetaminophen (Tylenol®)	Disulfam (Antabuse®)	Chronic ethanol
Chlorzoxazone (Parafon Forte®)		Isoniazid (Nydrazid®)
Ethanol, enflurane, halothane, isoflurane		

CYP3A

Alprazolam (Xanax®)	Amiodarone (Cordarone®, Pacerone®)	Carbamazepine (Tegretol®)
Astemizole (Hismanal®)	Cimetidine (Tagamet®)	Glucocorticoids
Atorvastatin (Lipitor®)	Clarithromycin (Biaxin®)	Phenobarbital (Luminal sodium®)
Buspirone (Buspar®)	Erythromycin (E-Mycin®)	Phenytoin (Dilantin®)
Calcium channel blockers	Fluconazole (Diflucan®)	Primidone (Mysoline®)
Carbamazepine (Tegretol®)	Fluoxetine (Prozac®)	Rifampin (Rifadin®, Rimactane®)
Cilostazol (Pletal®)	Fluvoxamine (Luvox®)	Ritonavir (Norvir®)
Cisapride (Propulsid®)	Grapefruit juice	St. John's wort
Citalopram (Celexa®)	Indinavir (Crixivan®)	
Clindamycin (Cleocin®)	Itraconazole (Sporanox®)	
Clomipramine (Anafranil®)	Ketoconazole (Nizoral®)	
Clonazepam (Klonopin®)	Metronidazole (Flagyl®)	
Cyclosporine (Gengraf®, Neoral®, Sandimmune®)	Miconazole (Monistat®)	

(continued)

Appendix 13**Common Drug Interactions (continued)**

CYP3A (cont)

Substrates (trade name)	Inhibitors (trade name)	Inducers (trade name)
Dapsone	Nefazodone (Serzone®)	
Erythromycin (E-Mycin®)	Nelfinavir (Viracept®)	
Estrogens	Norfloxacin (Chibroxin®, Noroxin®)	
Garlic	Ritonavir (Norvir®)	
Ginkgo	Saquinavir (Fortovase®, Invirase®)	
Imipramine (Tofranil®)	Sertraline (Zoloft®)	
Protease inhibitors	Valerian	
Ketoconazole (Nizoral®)	Zafirlukast (Accolate®)	
Losartan (Cozaar®)		
Lovastatin (Mevacor®)		
Miconazole (Monistat®)		
Midazolam (Versed®)		
Montelukast (Singulair®)		
Nefazodone (Serzone®)		
Ondansetron (Zofran®)		
Prednisone (Deltasone®, Meticorten®, Orasone®)		
Quinidine (Cardioquin®, Quinaglute®, Quinidex®)		
Rifampin (Rifadin®, Rimactane®)		
Sertraline (Zoloft®)		
Simvastatin (Zocor®)		
Tacrolimus (Prograf®)		
Tamoxifen (Nolvadex®)		
Temazepam (Restoril®)		
Triazolam (Halcion®)		
R-Warfarin (Coumadin®)		

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