# Lippincott's Illustrated Reviews:

# Pharmacology

You will have learned within, those are

Chapter no. **26** to **30**

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# Chapter 26

# Adrenal Hormones

## I. Overview

The adrenal gland consists of the cortex and the medulla. The latter secretes epinephrine, whereas the cortex, the subject of this chapter, synthesizes and secretes two major classes of steroid hormonesâ€"the adrenocorticosteroids (glucocorticoids and mineralocorticoids; Figure 26.1), and the adrenal androgens. The adrenal cortex is divided into three zones that synthesize various steroids from cholesterol and then secrete them (Figure 26.2). The outer zona glomerulosa produces mineralocorticoids (for example, aldosterone), which are responsible for regulating salt and water metabolism. Production of aldosterone is regulated primarily by the renin-angiotensin system (see p. 216). The middle zona fasciculata synthesizes glucocorticoids (for example, cortisol), which are involved with normal metabolism and resistance to stress. The inner zona reticularis secretes adrenal androgens (for example, *dehydroepiandrosterone*). Secretion by the two inner zones and, to some extent, the outer zone is controlled by pituitary *corticotropin adrenocorticotropic hormone* [*ACTH;* also called *cortictropin*], which is released in response to the hypothalamic corticotropin-releasing hormone (CRH; also called corticotropin-releasing factor). Glucocorticoids serve as feedback inhibitors of *corticotropin* and CRH secretion. Hormones of the adrenal cortex are used in replacement therapy; in the treatment and management of asthma as well as other inflammatory diseases, such as rheumatoid arthritis; in the treatment of severe allergic reactions; and in the treatment of some cancers.

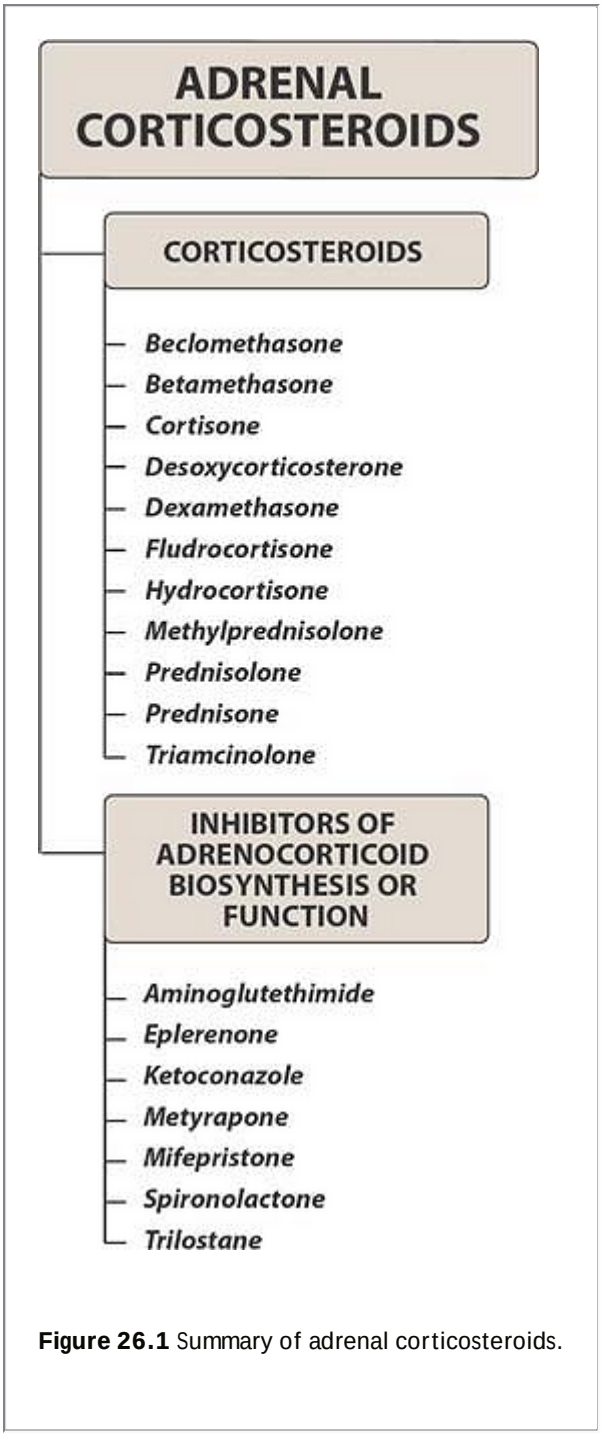



**Figure 26.1** Summary of adrenal corticosteroids.

## II. Adrenocorticosteroids

The adrenocorticoids bind to specific intracellular cytoplasmic receptors in target tissues. [Note: The glucocorticoid receptor is widely distributed throughout the body, whereas the mineralocorticoid receptor is confined mainly to excretory organs, such as the kidney, colon, and salivary and sweat glands.] After dimerizing, the receptor-hormone complex translocates into the nucleus, where it attaches to gene promoter elements, acting as a transcription factor to turn genes on or off, depending on the tissue (Figure 26.3)[1]. This mechanism requires time to produce an effect, but other glucocorticoid effects, such as their interaction with catecholamines to mediate relaxation of bronchial musculature or lipolysis, have effects that are immediate. Some normal actions and some selected mechanisms of adrenocorticoids are described in this section.

## *A. Glucocorticoids*

Cortisol is the principal human glucocorticoid. Normally, its production is diurnal, with a peak early in the morning followed by a decline and then a secondary, smaller peak in the late afternoon. Factors such as stress and levels of the circulating steroid influence secretion. The effects of cortisol are many and diverse. In general, all glucocorticoids:

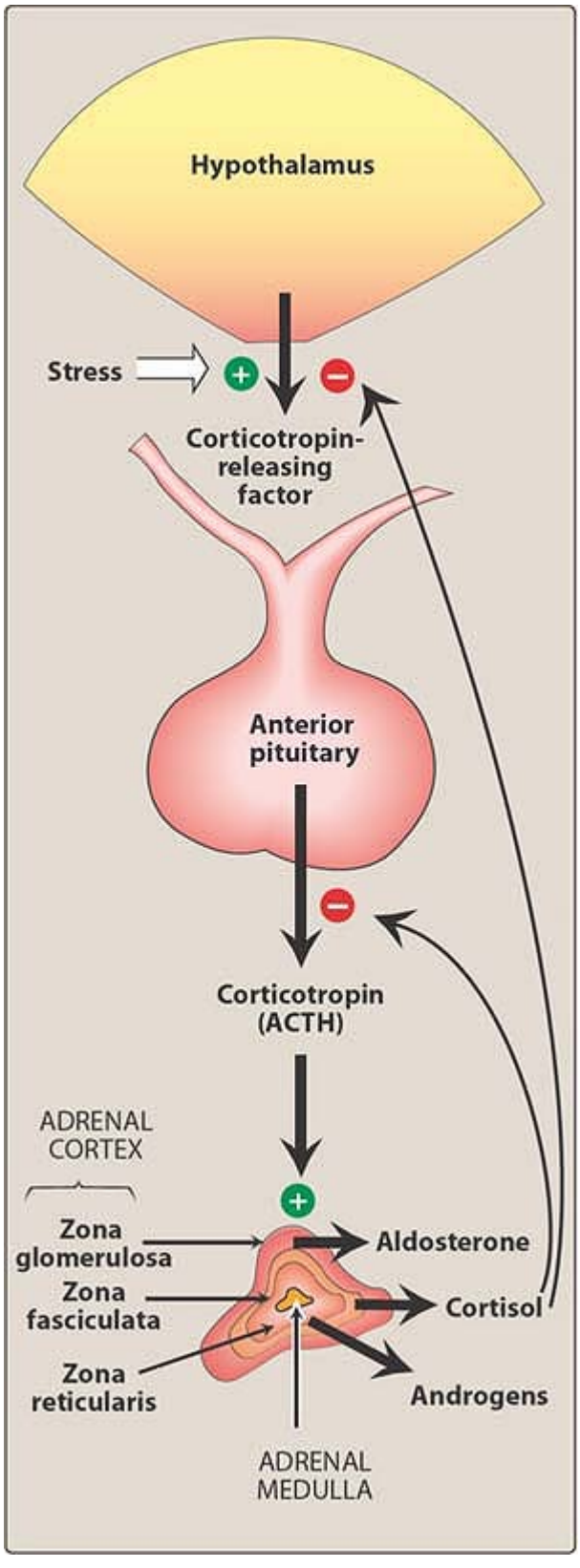



**Figure 26.2** Regulation of corticosteroid secretion.

1. **Promote normal intermediary metabolism:** Glucocorticoids favor gluconeogenesis through increasing amino acid uptake by the liver and kidney and elevating activities of gluconeogenic enzymes. They stimulate protein catabolism (except in the liver) and lipolysis, thereby providing the building blocks and energy that are needed for glucose synthesis. [Note: Glucocorticoid insufficiency may result in hypoglycemia (for example, during stressful periods or fasting).] Lipolysis results as a consequence of the glucocorticoid augmenting the action of growth hormone on adipocytes, causing an increase in the activity of hormone-sensitive lipase.

2. **Increase resistance to stress:** By raising plasma glucose levels, glucocorticoids provide the body with the energy it requires to combat stress caused, for example, by trauma, fright, infection, bleeding, or debilitating disease. Glucocorticoids can cause a modest rise in blood pressure, apparently by enhancing the vasoconstrictor action of adrenergic stimuli on small vessels. [Note: Individuals with adrenal insufficiency may respond to severe stress by becoming hypotensive.]

3. **Alter blood cell levels in plasma:** Glucocorticoids cause a decrease in eosinophils, basophils, monocytes, and lymphocytes by redistributing them from the circulation to lymphoid tissue. In contrast to this effect, they increase the blood levels of hemoglobin, erythrocytes, platelets, and polymorphonuclear leukocytes. [Note: The decrease in circulating lymphocytes and macrophages compromises the body's ability to fight infections. However, this property is important in the treatment of leukemia (see p. 478).]

4. **Have anti-inflammatory action:** The most important therapeutic property of the glucocorticoids is their ability to dramatically reduce the inflammatory response and to suppress immunity. The exact mechanism is complex and incompletely understood. However, the lowering and inhibition of peripheral lymphocytes and macrophages is known to play a role. Also involved is the indirect inhibition of phospholipase $A_2$ (due to the steroid-mediated elevation of lipocortin), which blocks the release of arachidonic acidâ€"the precursor of the prostaglandins and leukotrienesâ€"from membrane-bound phospholipid. Cyclooxygenase-2 synthesis in inflammatory cells is further reduced, lowering the availability of prostaglandins. In addition, interference in mast cell degranulation results in decreased histamine and capillary permeability.

5. **Affect other components of the endocrine system:** Feedback inhibition of *corticotropin* production by elevated glucocorticoids causes inhibition of further glucocorticoid synthesis as well as further production of thyroid-stimulating hormone. In contrast, growth hormone production is increased.



6. **Can have effects on other systems:** Adequate cortisol levels are essential for normal glomerular filtration. However, the effects of corticosteroids on other systems are mostly associated with the adverse effects of the hormones. High doses of glucocorticoids stimulate gastric acid and pepsin production and may exacerbate ulcers. Effects on the central nervous system that influence mental status have been identified. Chronic glucocorticoid therapy can cause severe bone loss. Myopathy leads patients to complain of weakness.

## *B. Mineralocorticoids*

Mineralocorticoids help to control the body's water volume and concentration of electrolytes, especially sodium and potassium. Aldosterone acts on kidney tubules and collecting ducts, causing a reabsorption of sodium, bicarbonate, and water. Conversely, aldosterone decreases reabsorption of potassium, which, with $H^+$, is then lost in the urine. Enhancement of sodium reabsorption by aldosterone also occurs in gastrointestinal mucosa and in sweat and salivary glands. [Note: Elevated aldosterone levels may cause alkalosis and hypokalemia, whereas retention of sodium and water leads to an increase in blood volume and blood pressure. Hyperaldosteronism is treated with *spironolactone*.] Target cells for aldosterone action contain mineralocorticoid receptors that interact with the hormones in a manner analogous to that of the glucocorticoid receptor (see above).

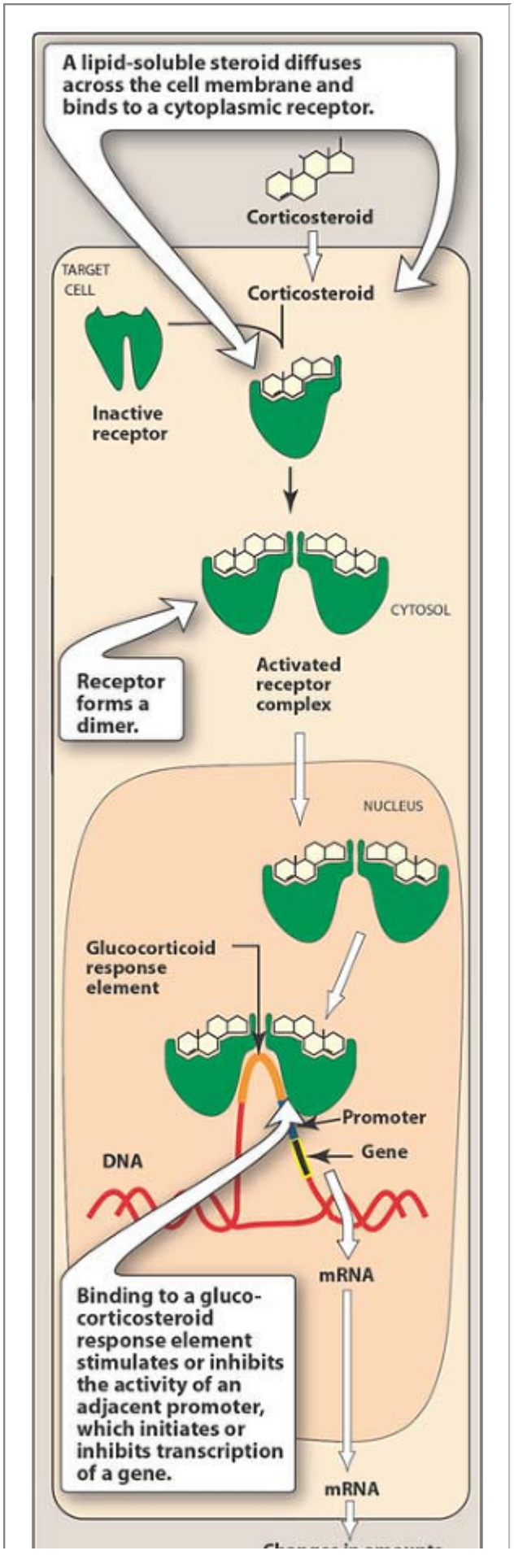

A lipid-soluble steroid diffuses across the cell membrane and binds to a cytoplasmic receptor.
Corticosteroid
TARGET CELL
Corticosteroid
Inactive receptor
CYTOSOL
Receptor forms a dimer.
Activated receptor complex
NUCLEUS
Glucocorticoid response element
Promoter
Gene
DNA
mRNA
Binding to a gluco-corticosteroid response element stimulates or inhibits the activity of an adjacent promoter, which initiates or inhibits transcription of a gene.
mRNA

**Figure 26.3** Gene regulation by glucocorticoids.

## *C. Therapeutic uses of the adrenal corticosteroids*

Several semisynthetic derivatives of the glucocorticoids have been developed that vary in their anti-inflammatory potency, degree to which they cause sodium retention, and duration of action. These are summarized in Figure 26.4.

1. **Replacement therapy for primary adrenocortical insufficiency (Addison's disease):** This disease is caused by adrenal cortex dysfunction (as diagnosed by the lack of patient response to *corticotropin* administration). *Hydrocortisone* [hye-droe-KOR-ti-sone], which is identical to natural cortisol, is given to correct the deficiency. Failure to do so results in death. The dosage of *hydrocortisone* is divided so that two-thirds of the normal daily dose is given in the morning and one-third is given in the afternoon. [Note: The goal of this regimen is to approximate the daily hormone levels resulting from the circadian rhythm exhibited by cortisol, which causes plasma levels to be maximal around 8 AM and then decrease throughout the day to their lowest level around 1 AM] Administration of *fludrocortisone* [floo-droe-KOR-tih-sone], a potent synthetic mineralocorticoid with some glucocorticoid activity, may also be necessary to raise the mineralocorticoid activity to normal levels.
2. **Replacement therapy for secondary or tertiary adrenocortical insufficiency:** These deficiencies are caused by a defect either in CRH production by the hypothalamus or in *corticotropin* production by the pituitary. [Note: Under these conditions, the synthesis of mineralocorticoids in the adrenal cortex is less impaired than that of glucocorticoids.] The adrenal cortex responds to *corticotropin* (*ACTH*) administration by synthesizing and releasing the adrenal corticosteroids. *Hydrocortisone* is also used for these deficiencies.



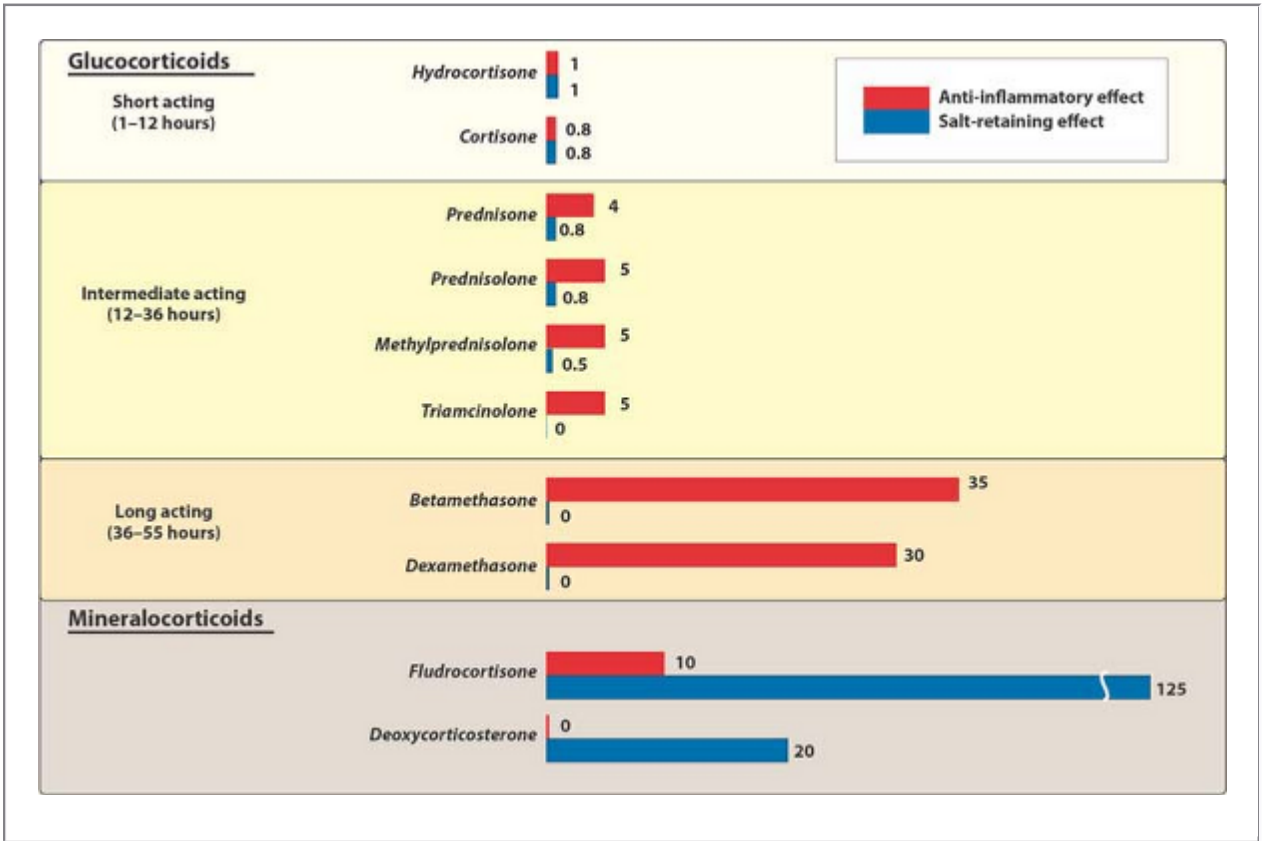


**Figure 26.4** Pharmacologic effects and duration of action of some commonly used natural and synthetic corticosteroids. Activities are all relative to that of *hydrocortisone*, which is considered to be 1.

3. **Diagnosis of Cushing's syndrome:** Cushing's syndrome is caused by a hypersecretion of glucocorticoids that results either from excessive release of corticotropin by the anterior pituitary or an adrenal tumor. The *dexamethasone* [dex-a-METH-a-sone] suppression test is used to diagnose the cause of an individual's case of Cushing's syndrome. This synthetic glucocorticoid suppresses cortisol release in individuals with pituitary-dependent Cushing's syndrome, but it does not suppress glucocorticoid release from adrenal tumors. [Note: Chronic treatment with high doses of glucocorticoid is a frequent cause of iatrogenic Cushing's syndrome.]

4. **Replacement therapy for congenital adrenal hyperplasia:** This is a group of diseases resulting from an enzyme defect in the synthesis of one or more of the adrenal steroid hormones. This condition may lead to virilization in females due to overproduction of adrenal androgens (see below). Treatment of this condition requires administration of sufficient corticosteroids to normalize the patient's hormone levels by suppressing release of CRH and ACTH. This decreases production of adrenal androgens. The choice of replacement hormone depends on the specific enzyme defect.

5. **Relief of inflammatory symptoms:** Glucocorticoids dramatically reduce the manifestations of inflammations (for example, rheumatoid and osteoarthritic inflammations, as well as inflammatory conditions of the skin), including the redness, swelling, heat, and tenderness



that are commonly present at the inflammatory site. The effect of glucocorticoids on the inflammatory process is the result of a number of actions, including the redistribution of leukocytes to other body compartments, thereby lowering their blood concentration (their function is also compromised). Other effects include an increase in the concentration of neutrophils; a decrease in the concentration of lymphocytes (T and B cells), basophils, eosinophils, and monocytes; and an inhibition of the ability of leukocytes and macrophages to respond to mitogens and antigens. The decreased production of prostaglandins and leukotrienes is believed to be central to the anti-inflammatory action. Glucocorticoids also influence the inflammatory response by their ability to reduce the amount of histamine that is released from basophils and mast cells, thus diminishing the activation of the kinin system [Note: The ability of glucocorticoids to inhibit the immune response is also a result of the other actions described above.]

6. **Treatment of allergies:** Glucocorticoids are beneficial in the treatment of the symptoms of bronchial asthma, allergic rhinitis, and drug, serum, and transfusion allergic reactions. These drugs are not, however, curative. [Note: *Beclomethasone dipropionate* [bek-loe-METH-ah-sone], *triamcinolone* [tri-am-SIN-o-lone], and others (see Figure 26.4) are applied topically to the respiratory tract through inhalation from a metered-dose dispenser. This minimizes systemic effects and allows the patient to significantly reduce or eliminate the use of oral steroids.]

7. **Acceleration of lung maturation:** Respiratory distress syndrome is a problem in premature infants. Fetal cortisol is a regulator of lung maturation. Consequently, a dose of *beclomethasone* is administered intramuscularly to the mother 48 hours prior to birth, followed by a second dose 24 hours before delivery.

## *D. Pharmacokinetics*

1. **Absorption and fate:** Synthetic glucocorticoid preparations with unique pharmacokinetic characteristics are used therapeutically. Those that are administered orally are readily absorbed from the gastrointestinal tract. Selected compounds can also be administered intravenously, intramuscularly, intra-articularly (for example, into arthritic joints), topically, or as an aerosol for inhalation (Figure 26.5). Greater than 90 percent of the absorbed glucocorticoids are bound to plasma proteinsâ€”most to corticosteroid-binding globulin, and the remainder to albumin. Corticosteroids are metabolized by the liver microsomal oxidizing enzymes. The metabolites are

conjugated to glucuronic acid or sulfate, and the products are excreted by the kidney. [Note: The half-life of adrenal steroids may increase dramatically in individuals with hepatic dysfunction.] The only glucocorticoid that has no effect on the fetus in pregnancy is *prednisone* [PRED-ni-sone]. It is a prodrug that is not converted to the active compound, *prednisolone* [pred-NIH-so-lene], in the fetal liver. Any *prednisolone* formed in the mother is biotransformed to *prednisone* by the fetus.

2. **Dosage:** In determining the dosage of adrenocortical steroids, many factors need to be considered, including glucocorticoid versus mineralocorticoid activity, duration of action, type of preparation, and



time of day when the steroid is administered. For example, when large doses of the hormone are required over an extended period of time (more than 2 weeks), suppression of the hypothalamic-pituitary-adrenal (HPA) axis occurs. To prevent this adverse effect, a regimen of alternate-day administration of the adrenocortical steroid may be useful. This schedule allows the HPA axis to recover/function on the days the hormone is not taken.

## *E. Adverse effects*

The common side effects of long-term corticosteroid therapy are summarized in Figure 26.6. Osteoporosis is the most common adverse effect due to the ability of glucocorticoids to suppress intestinal $Ca^{2+}$ absorption, inhibit bone formation, and decrease sex hormone synthesis. Alternate-day dosing does not prevent osteoporosis. Patients are advised to take calcium and vitamin D supplements. Drugs that are effective in treating osteoporosis may also be beneficial. [Note: Increased appetite is not necessarily an adverse effect. In fact, it is one of the reasons for the use of *prednisone* in cancer chemotherapy.] The classic Cushing-like syndromeâ€"redistribution of body fat, puffy face, increased body hair growth, acne, insomnia, and increased appetiteâ€"are observed when excess corticosteroids are present. Increased frequency of cataracts also occurs with long-term corticosteroid therapy. Hyperglycemia may develop and lead to diabetes mellitus. Diabetics should monitor their blood glucose and adjust their medications accordingly. Hypokalemia caused by corticosteroid therapy can be counteracted by potassium supplementation. Coadministration of medications that induce or inhibit the hepatic mixed-function oxidases may require adjustment of the glucocorticoid dose.

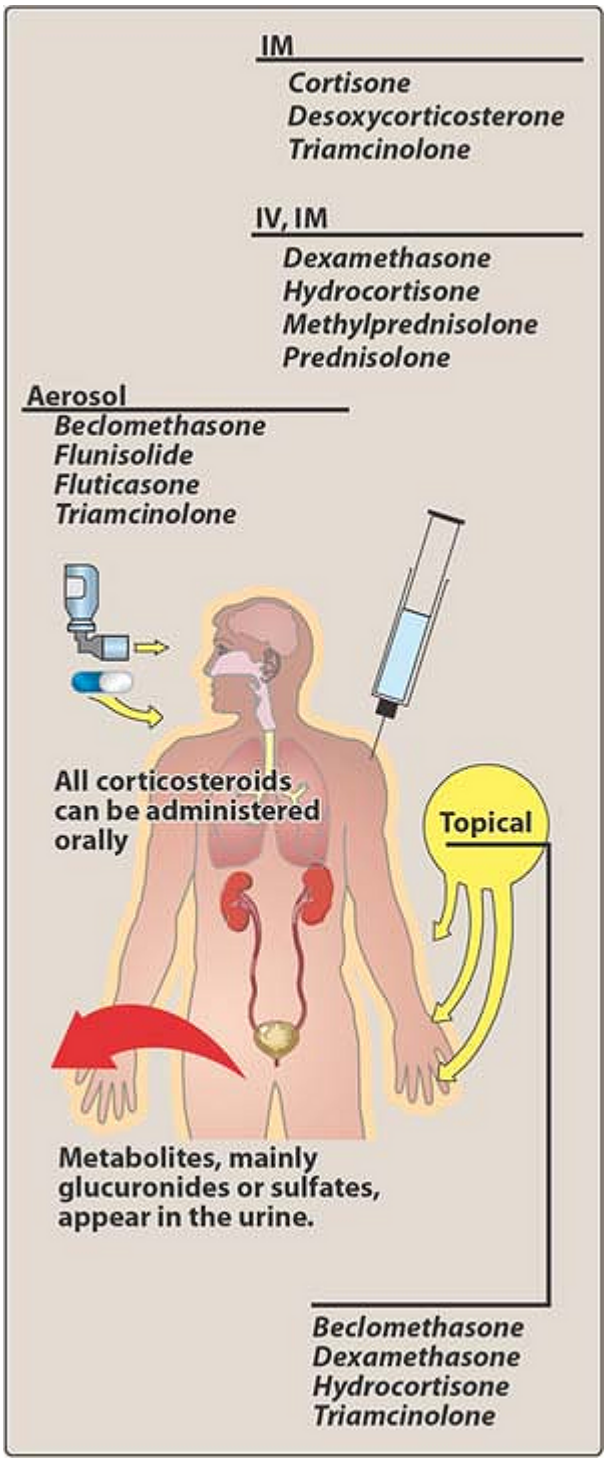



**Figure 26.5** Routes of administration and elimination of corticosteriods.

## *F. Withdrawal*

Withdrawal from these drugs can be a serious problem, because if the patient has experienced HPA suppression, abrupt removal of the corticosteroids causes an acute adrenal insufficiency syndrome that can be lethal. This, coupled with the possibility of psychologic dependence on the drug and the fact that withdrawal might cause an

exacerbation of the disease, means the dose must be tapered according to the individual, possibly through trial and error. The patient must be monitored carefully.

## *G. Inhibitors of adrenocorticoid biosynthesis*

Several substances have proven to be useful as inhibitors of the synthesis of adrenal steroids: *metyrapone, aminoglutethimide, ketoconazole, trilostane, spironolactone*, and *eplerenone*. *Mifepristone* competes with glucocorticoids for the receptor.

1. **Metyrapone:** *Metyrapone* [me-TEER-ah-pone] is used for tests of adrenal function and can be used for the treatment of pregnant women with Cushing's syndrome. [Note: *Dexamethasone* suppression is now used more commonly for diagnosis.] *Metyrapone* interferes with corticosteroid synthesis by blocking the final step (11-hydroxylation) in glucocorticoid synthesis, leading to an increase in 11-deoxycortisol as well as adrenal androgens and the potent mineralocorticoid 11-deoxycorticosterone. The adverse effects encountered with *metyrapone* include salt and water retention, hirsutism, transient dizziness, and gastrointestinal disturbances.



2. **Aminoglutethimide:** This drug acts by inhibiting the conversion of cholesterol to pregnenolone. As a result, the synthesis of all hormonally active steroids is reduced. *Aminoglutethimide* [ah-mee-noe-glu-TETH-ih-mide] has been used therapeutically in the treatment of breast cancer to reduce or eliminate androgen and estrogen production. [Note: *Tamoxifen* has largely replaced *aminoglutethimide* in the treatment of breast cancer.] In these cases, it is used in conjunction with *dexamethasone*. However, it increases the clearance of *dexamethasone*. *Aminoglutethimide* may also be useful in the treatment of malignancies of the adrenal cortex to reduce the secretion of steroids. Recent studies indicate it is an aromatase inhibitor.

Decreased growth in children

**Negative Calcium Balance**

Osteoporosis

**Impaired Wound Healing**


Increased risk of infection

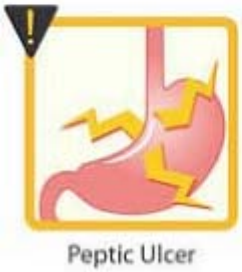
Increased appetite

**Euphoria Depression**

Emotional disturbances


Hypertension

Peripheral edema



Peptic Ulcer

Glaucoma


**Figure 26.6** Some commonly observed effects of long-term corticosteroid therapy.

3. **Ketoconazole:** *Ketoconazole* [kee-toe-KON-ah-zole] is an antifungal agent that strongly inhibits all gonadal and adrenal steroid hormone synthesis. It is used in the treatment of patients with Cushing's syndrome.
4. **Trilostane:** *Trilostane* [TRYE-loe-stane] reversibly inhibits 3Î²-hydroxysteroid dehydrogenase and, thus, affects aldosterone, cortisol, and gonadal hormone synthesis. Its side effects are gastrointestinal.
5. **Mifepristone:** At high doses, *mifepristone* [mih-feh-PRIH-stone] is a potent glucocorticoid antagonist as well as an antiprogestin. It forms a complex with the glucocorticoid receptor, but the rapid dissociation of the drug from the receptor leads to a faulty translocation into the nucleus. Its use is presently limited to the treatment of inoperable patients with ectopic ACTH syndrome.
6. **Spironolactone:** This antihypertensive drug competes for the mineralocorticoid receptor and, thus, inhibits sodium reabsorption in the kidney. It can also antagonize aldosterone and testosterone synthesis. It is effective against hyperaldosteronism. *Spironolactone* [speer-oh-no-LAK-tone] is also useful in the treatment of hirsutism in women, probably due to interference at the androgen receptor of the hair follicle. Adverse effects include hyperkalemia, gynecomastia, menstrual irregularities, and skin rashes.
7. **Eplerenone:** *Eplerenone* [e-PLER-en-one] specifically binds to the mineralocorticoid receptor, where it acts as an aldosterone antagonist. This specificity avoids the side effect of gynecomastia that is associated with the use of *spironolactone*. It is approved as an antihypertensive.



## Study Questions

Choose the ONE best answer.

**26.1 Measurements of cortisol precursors and plasma dehydroepiandrosterone sulfate confirm the diagnosis of congenital adrenal hyperplasia (CAH) in a child. This condition can be effectively treated by:**

A. Suppressing the release of ACTH.

B. Administering an androgen antagonist.

C. Administering metapyrone to decrease cortisol synthesis.

D. Removing the adrenal gland surgically.

View Answer

**26.2 Osteoporosis is a major adverse effect caused by the glucocorticoids. It is due to their ability to:**

A. Increase the excretion of calcium.

B. Inhibit absorption of calcium.

C. Stimulate the HPA axis.

D. Decrease production of prostaglandins.

View Answer

**26.3 A child with asthma is being treated effectively with an inhaled preparation of beclomethasone dipropionate. Which of the following adverse effects is of particular concern?**

A. Hypoglycemia.

B. Hirsutism.

C. Growth suppression.

D. Cushing's syndrome.

E. Cataract formation.

View Answer

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# Chapter 27

# Respiratory System

## I. Overview

Asthma, chronic obstructive pulmonary disease (COPD), and allergic rhinitis are commonly encountered respiratory diseases. Each of these conditions may be associated with a troublesome cough, which may be the patient's only presenting complaint. Asthma is a chronic disease characterized by hyperresponsive airways, affecting 10 million patients (four to five percent of the U.S. population), and resulting annually in 2 million emergency room visits, 500,000 hospitalizations, and 5,000 deaths. COPD, also called emphysema or chronic bronchitis, affects approximately 30 million Americans and is currently the fourth most common cause of preventable deaths in the United States. Allergic rhinitis, characterized by itchy, watery eyes, runny nose, and a nonproductive cough, is an extremely common condition that significantly decreases patient-reported quality of life. Allergic rhinitis affects approximately 20 percent of the population, or over 61 million Americans. Coughing is an important defensive respiratory response to irritants and has been cited as the number-one reason why patients seek medical care. A troublesome cough may represent several etiologies, such as the common cold, sinusitis, and/or an underlying chronic respiratory disease.

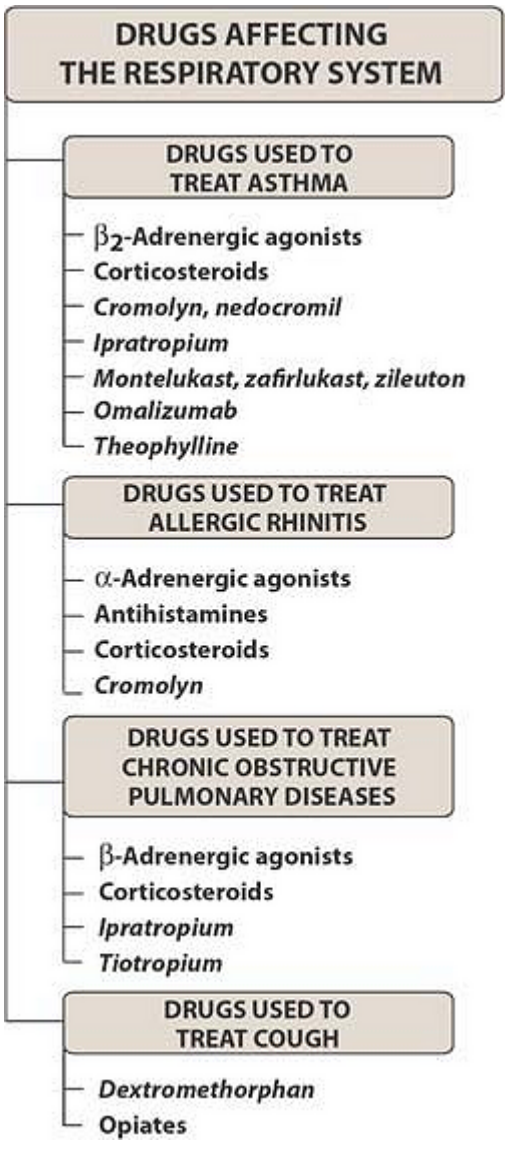


**Figure 27.1** Summary of drugs affecting the respiratory system.

Each of these respiratory conditions can be adequately controlled through a combined approach of appropriate lifestyle changes and medication management. Drugs used to treat respiratory conditions can be delivered topically to the nasal mucosa, inhaled into the lungs, or given orally or parenterally for systemic absorption. Topical delivery methods, such as nasal sprays or inhalers, are preferred so as to target affected tissues while minimizing systemic side effects. Clinically useful drugs mitigate the specific pathology, such as by relaxing bronchial smooth muscle or modulating the inflammatory response. Medications used to treat these commonly encountered respiratory disorders are summarized in Figure 27.1.



## II. First-Line Drugs Used to Treat Asthma

Asthma is an inflammatory disease of the airways characterized by episodes of acute bronchoconstriction causing shortness of breath, cough, chest tightness, wheezing, and rapid respiration. These acute symptoms may resolve spontaneously, with nonpharmacologic relaxation exercises, or with use of â€œquick reliefâ€ medications, such as

a short-acting Î²$_2$-adrenergic agonist (see p. 72). Unlike chronic bronchitis, cystic fibrosis, or bronchiectasis, asthma is usually not a progressive disease; that is, it does not inevitably lead to crippled airways. Asthma is a chronic disease with an underlying inflammatory pathophysiology that, if untreated, may incur airway remodeling, resulting in increased severity and incidence of exacerbations and/or death. Deaths due to asthma are relatively infrequent, but significant morbidity results in high outpatient costs, numerous hospitalizations, and decreased quality of life.

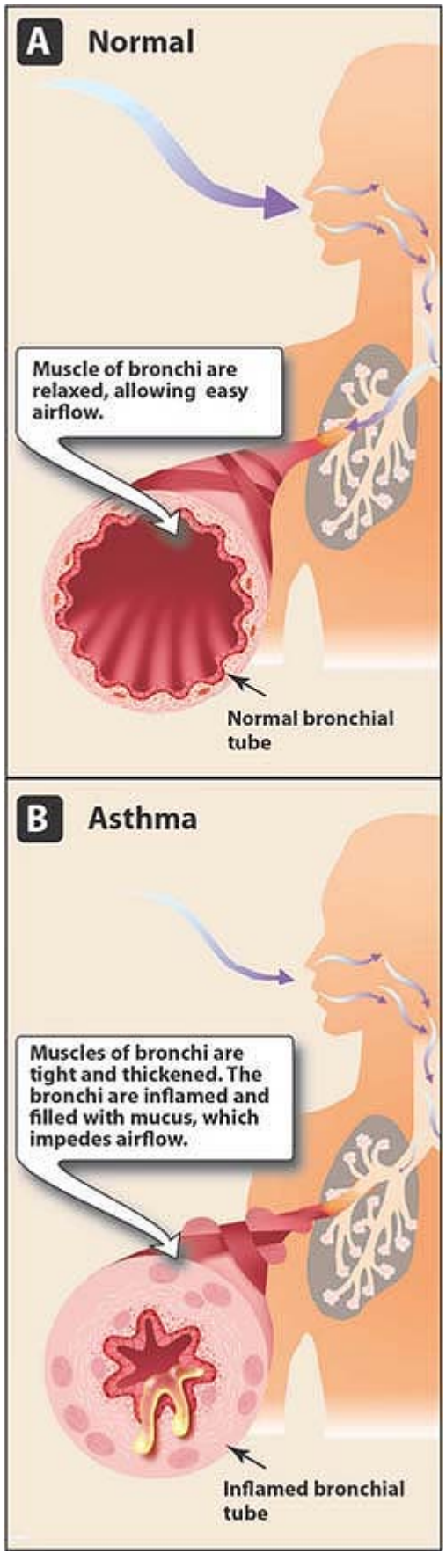
A
Normal
Muscle of bronchi are relaxed, allowing easy airflow.
Normal bronchial tube
B
Asthma
Muscles of bronchi are tight and thickened. The bronchi are inflamed and filled with mucus, which impedes airflow.
Inflamed bronchial tube

**Figure 27.2** Comparison of bronchi of normal and asthmatic individuals.

## *A. Goals of therapy*

1. Reducing impairment:
    a. Prevent chronic and troublesome symptoms.
    b. Require infrequent use (â‰¤2 days a week) of inhaled short-acting Î²$_2$ agonist for quick relief of symptoms.
    c. Maintain (near) â€œnormalâ€ pulmonary function.
    d. Maintain normal activity levels (including exercise and other physical activity and attendance at work or school).
    e. Meet patients' and family expectations of and satisfaction with asthma care.
2. **Reducing risk:**
    a. Prevent recurrent exacerbations of asthma, and minimize the need for emergency department visits or hospitalizations.
    b. Prevent progressive loss of lung function; for children, prevent reduced lung growth.
    c. Provide optimal pharmacotherapy with minimal or no adverse effects.

## *B. Role of inflammation in asthma*

Airflow obstruction in asthma is due to bronchoconstriction that results from contraction of bronchial smooth muscle, inflammation of the bronchial wall, and increased mucous secretion (Figure 27.2). Asthmatic attacks may be related to recent exposure to allergens or inhaled irritants, leading to bronchial hyperactivity and inflammation of the airway mucosa. The symptoms of asthma may be effectively treated by several drugs, but no agent provides a cure for this obstructive lung disease.

## *C. Role of phenotype in asthma*

Recent research demonstrates a link between Î²-receptor polymorphism (phenotype) and response to long-acting Î²$_2$ agonists for approximately 16 to 20 percent of the patient population affected by asthma. Three asthma phenotypes have been reported: homozygous glycine, heterozygous glycine/arginine, and homozygous arginine. Evidence from clinical trials and postmarketing analysis suggests patients with



the homozygous arginine polymorphism may be at risk for worsening symptoms with long-acting Î²$_2$ agonists therapy. Because population-based genotyping to determine Î²-receptor phenotype is not feasible at this time, clinicians prescribing any new long-acting Î²$_2$ agonists prescription should counsel patients to carefully monitor symptoms for any signs of worsening. If the patient reports worsening symptoms, the long-acting Î²$_2$ agonists therapy should be discontinued with a subsequent increase in corticosteroid dosing as clinically appropriate. Further research is underway examining the mechanism of the various asthma phenotypes and how to appropriately target therapy to each for improved control.

| CLASSIFICATION | BRONCHO-CONSTRICTIVE EPISODES | RESULTS OF PEAK FLOW OR SPIROMETRY | LONG-TERM CONTROL | QUICK RELIEF OF SYMPTOMS |
|---|---|---|---|---|
| Mild intermittent | Less than two per week | Near normal* | No daily medication | Short-acting $\beta_2$ agonist |
| Mild persistent | More than two per week | Near normal* | Low-dose inhaled corticosteroids | Short-acting $\beta_2$ agonist |
| Moderate persistent | Daily | 60 to 80 percent of normal | Low- to medium-dose inhaled corticosteroids and a long-acting $\beta_2$ agonist | Short-acting $\beta_2$ agonist |
| Severe persistent | Continual | Less than 60 percent of normal | High-dose inhaled corticosteroids and a long-acting $\beta_2$ agonist | Short-acting $\beta_2$ agonist |

**Figure 27.3** Treatment of asthma. In all asthmatic patients, quick relief is provided by a short-acting Î²$_2$ agonist as needed for symptoms. *Eighty percent or more of predicted function.

## *D. Adrenergic agonists*

Inhaled adrenergic agonists with Î²$_2$ activity are the drugs of choice for mild asthmaâ€"that is, in patients showing only occasional, intermittent symptoms (Figure 27.3). Direct-acting Î²$_2$ agonists are potent bronchodilators that relax airway smooth muscle.

1. **Quick relief:** Most clinically useful Î²$_2$ agonists have a rapid onset of action (5â€“30 minutes) and provide relief for 4 to 6 hours. They are used for symptomatic treatment of bronchospasm, providing quick relief of acute bronchoconstriction. [Note: *Epinephrine* is the drug of choice for treatment of acute anaphylaxis.] Î²$_2$ Agonists have no anti-inflammatory effects, and they should never be used as the sole therapeutic agents for patients with persistent asthma. Monotherapy with short-acting Î²$_2$ agonists may be appropriate only for patients identified as having mild intermittent asthma, such as exercise-induced asthma. The direct-acting Î²$_2$-selective agonists, such as *pirbuterol* [peer-BYOO-ter-ole], *terbutaline* [ter-BYOO-ta-leen], and *albuterol* [al-BYOO-teh-rall], offer the advantage of providing maximally attainable bronchodilation with little of the undesired effect of Î± or Î²$_1$ stimulation. (See p. 69 for the receptor-specific actions of adrenergic agonists.) The Î²$_2$ agonists are not catecholamines and, thus, are not inactivated by catechol-*O*-methyltransferase. Adverse effects, such as tachycardia, hyperglycemia, hypokalemia, and hypomagnesemia are minimized with dosing via inhalation versus systemic routes. Although tolerance to the effects of Î²$_2$ agonists on nonairway tissues occurs, it is uncommon with normal dosages. All



patients with asthma should be prescribed a quick-relief inhaler and regularly assessed for appropriate inhaler technique.

2. **Long-term control:** *Salmeterol* [sal-ME-te-rol] *xinafoate* and *formoterol* [for-MOH-ter-ol] are long-acting Î²$_2$ agonists bronchodilators. They are chemical analogs of *albuterol* but differ by having a lipophilic side chain, increasing the affinity of the drug for the Î²$_2$-adrenoceptor. *Salmeterol* and *formoterol* have a long duration of action, providing bronchodilation for at least 12 hours. Both s*almeterol* and *formoterol* have slower onsets of action and should not be used for quick relief of an acute asthma attack. long-acting Î²$_2$ agonists should be prescribed for routine administration. Whereas inhaled corticosteroids remain the long-term control drugs of choice in asthma, long-acting Î²$_2$ agonists are considered to be useful adjunctive therapy for attaining asthma control. Adverse effects of the long-acting Î²$_2$ agonists are similar to quick-relief Î²$_2$ agonists. Appropriate inhaler technique with long-acting Î²$_2$ agonists is critical to the success of therapy, may differ from the patient's other inhalers (metered-dose inhaler versus dry powder inhaler), and should be reassessed regularly.

## *E. Corticosteroids*

Inhaled corticosteroids (ICS) are the drugs of first choice in patients with any degree of persistent asthma (mild, moderate, or severe; see Figure 27.3). Severe persistent asthma may require the addition of a short course of oral glucocorticoid treatment. No other medications are as effective as ICS in the long-term control of asthma in children and adults. If appropriately prescribed and used, ICS therapy may reduce or eliminate the need for oral glucocorticoids in patients with severe asthma. To be effective in controlling inflammation, glucocorticoids must be taken continuously. (See p. 313 for a summary of the mechanism of action of corticosteroids.) Current guidelines recommend selecting ICS therapy for a newly diagnosed patient with asthma at dosing equivalent to the patient's asthma classification (National Heart, Lung, and Blood Institute [NHLBI] â€œStep Upâ€ therapy). Patients achieving 3 to 6 consecutive months of improved asthma control may be considered for a reduction in ICS dosing (NHLBI â€œStep Downâ€ therapy) as clinically indicated.

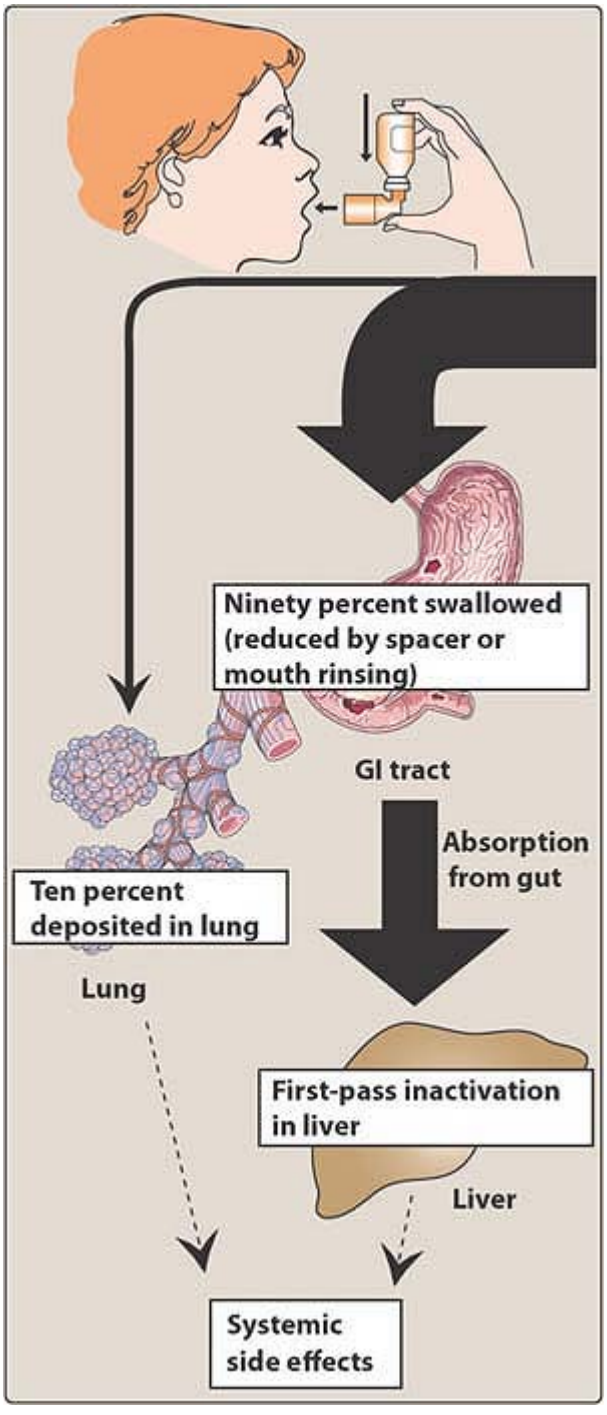


**Figure 27.4** Pharmacokinetics of inhaled glucocorticoids.

1. **Actions on lung:** ICS do not directly affect the airway smooth muscle. Instead, ICS therapy directly targets underlying airway inflammation by decreasing the inflammatory cascade (eosinophils, macrophages, and T lymphocytes), reversing mucosal edema, decreasing the permeability of capillaries, and inhibiting the release of leukotrienes. After several months of regular use, ICS reduce the hyperresponsiveness of the airway smooth muscle to a variety of bronchoconstrictor stimuli, such as allergens, irritants, cold air, and exercise.

2. **Route of administration**

a. **Inhalation:** The development of ICS has markedly reduced the need for systemic corticosteroid treatment to achieve asthma control. Appropriate inhalation technique is critical to the success of therapy. Metered-dose inhalers have propellants that eject the active medication from the canister. Patients should be instructed to SLOWLY and DEEPLY inhale upon activation of these inhalers to avoid impaction of the medication onto the laryngeal mucosa rather than the bronchial smooth muscle. Improper use



of a metered-dose inhaler can result in a large fraction (typically 80â€“90 percent) of inhaled glucocorticoids to be deposited in the mouth, pharynx, and/or swallowed (Figure 27.4). The 10 to 20 percent of the metered dose of inhaled glucocorticoids that is not swallowed is deposited in the airway. If ICS are inappropriately inhaled, systemic absorption and adverse effects are much more likely. ICS delivered by dry powder inhalers require a different inhaler technique. Patients should be instructed to inhale QUICKLY and DEEPLY to optimize drug delivery to the lungs. Even properly administered, corticosteroid deposition on the oral and laryngeal mucosa can cause adverse effects such as oropharyngeal candidiasis and hoarseness. Patient counseling incorporating a rinsing of these tissues via the â€œswish and spitâ€ method should avoid these adverse events.

b. **Oral/systemic:** Patients with severe exacerbation of asthma (status asthmaticus) may require intravenous administration of *methylprednisolone* or oral *prednisone*. Once the patient has improved, the dose of drug is gradually reduced, leading to discontinuance in 1 to 2 weeks. In most cases, suppression of the hypothalamic-pituitary axis will not occur during the short course of oral prednisone â€œburstâ€ typically prescribed for an asthma exacerbation; therefore, dose reduction is not necessary.

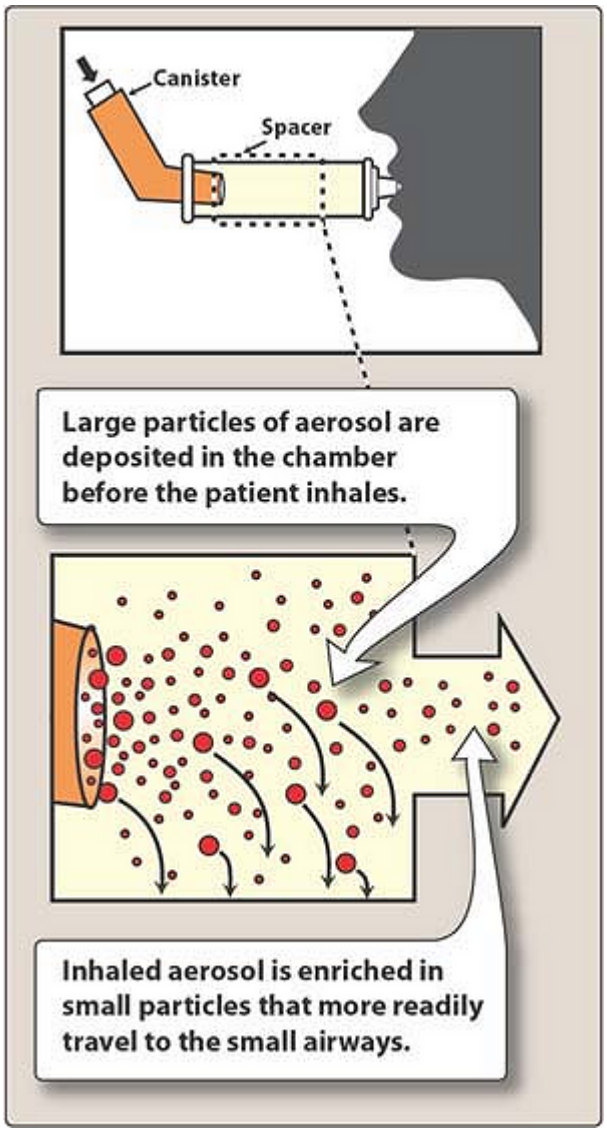


**Figure 27.5** Effect of a spacer on the delivery of an inhaled aerosol.

c. **Spacers:** A spacer is a large-volume chamber attached to a metered-dose inhaler. Spacers decrease the deposition of drug in the mouth caused by improper inhaler technique (Figure 27.5). The chamber reduces the velocity of the injected aerosol before entering the mouth, allowing large drug particles to be deposited in the device. The smaller, higher-velocity drug particles are less likely to be deposited in the mouth and more likely to reach the target airway tissue. Spacers minimize the problem of adrenal suppression by reducing the amount of glucocorticoid deposited in the oropharynx. Spacers improve delivery of inhaled glucocorticoids and are advised for virtually all patients, especially children less than 5 years old and elderly patients who may have difficulty coordinating actuation with inhalation. Patients should be counseled about regular washing and/or rinsing of spacers to reduce the risk of bacterial, mold, or mildew growth inducing an asthma attack.

3. **Adverse effects:** Oral or parenteral glucocorticoids have a variety of potentially serious side effects (see p. 317); inhaled glucocorticoids, particularly if used with a spacer, have few systemic effects. Studies have demonstrated the effect of ICS on vertical bone growth in children to be negligible, whereas the retardation of

vertical bone growth secondary to low oxygenated blood levels from uncontrolled asthma can occur in more severe cases.

## III. Alternative Drugs Used to Treat Asthma

These drugs are useful for treatment of moderate to severe allergic asthma in patients who are poorly controlled by conventional therapy or experience adverse effects secondary to high-dose or prolonged corticosteroid treatment. These drugs should be used in conjunction with ICS therapy, not as sole therapies.



### *A. Leukotriene antagonists*

Leukotriene (LT) $B_4$ and the cysteinyl leukotrienes, $LTC_4$, $LTD_4$, and $LTE_4$, are products of the 5-lipoxygenase pathway of arachidonic acid metabolism and part of the inflammatory cascade.[1] 5-Lipoxygenase is found in cells of myeloid origin, such as mast cells, basophils, eosinophils, and neutrophils. $LTB_4$ is a potent chemoattractant for neutrophils and eosinophils, whereas the cysteinyl leukotrienes constrict bronchiolar smooth muscle, increase endothelial permeability, and promote mucous secretion. *Zileuton* [zye-LOO-ton] is a selective and specific inhibitor of 5-lipoxygenase, preventing the formation of both $LTB_4$ and the cysteinyl leukotrienes. *Zafirlukast* [za-FIR-loo-kast] and *montelukast* [mon-tee-LOO-kast] are selective, reversible inhibitors of the cysteinyl leukotriene-1 receptor, thereby blocking the effects of cysteinyl leukotrienes (Figure 27.6). *Montelukast*, the market leader in this pharmacologic class, claims two primary advantages: dosing recommendations for children 1 year of age and older as well as being available in chewable tablets and granule formulations. All three drugs are approved for the prophylaxis of asthma but are not effective in situations where immediate bronchodilation is required. Modest reductions in the doses of $Î²_2$-adrenergic agonists and corticosteroids, as well as improved respiratory function, are among the therapeutic benefits.

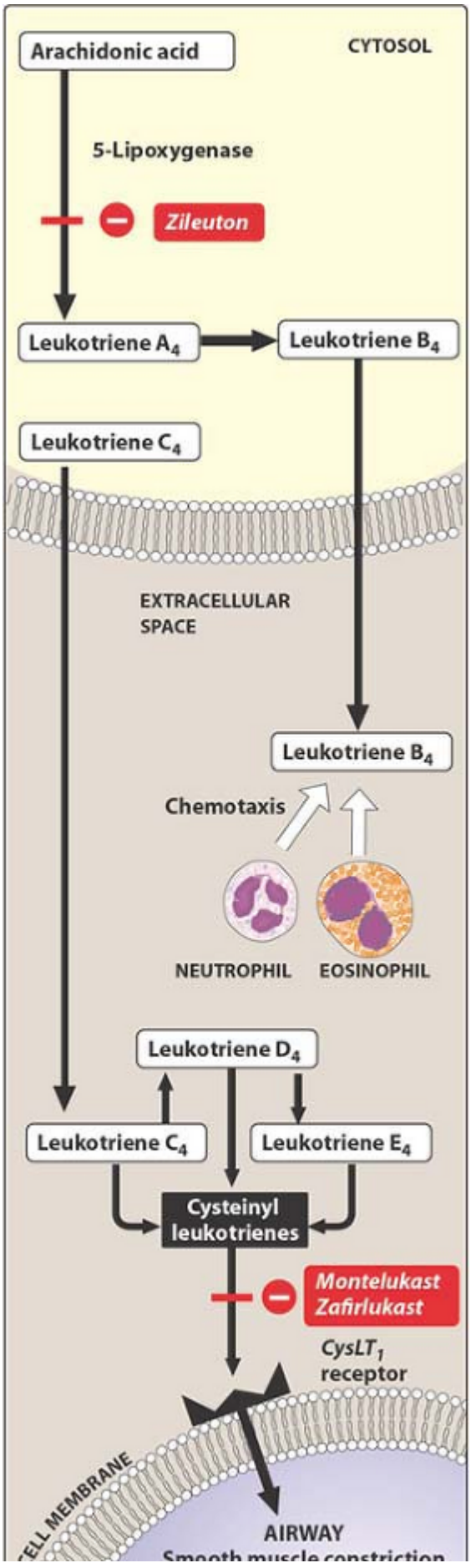
Arachidonic acid
CYTOSOL
5-Lipoxygenase
Zileuton
Leukotriene $A_4$
Leukotriene $B_4$
Leukotriene $C_4$
EXTRACELLULAR SPACE
Leukotriene $B_4$
Chemotaxis
NEUTROPHIL
EOSINOPHIL
Leukotriene $D_4$
Leukotriene $C_4$
Leukotriene $E_4$
Cysteinyl leukotrienes
Montelukast
Zafirlukast
$CysLT_1$ receptor
CELL MEMBRANE
AIRWAY
Smooth muscle constriction

**Figure 27.6** Sites of action of leukotrienemodifying drugs. $CysLT_1$ = cysteinyl leukotriene-1.

1. **Pharmacokinetics:** All three drugs are orally active, although food impairs the absorption of *zafirlukast*. Greater than 90 percent of each drug is bound to plasma protein. The drugs are extensively metabolized. *Zileuton* and its metabolites are excreted in the urine, whereas *zafirlukast* and *montelukast* and their metabolites undergo biliary excretion.
2. **Adverse effects:** Elevations in serum hepatic enzymes have occurred with all three agents, requiring periodic monitoring and discontinuation when enzymes exceed three to five times the upper limit of normal. Although rare, eosinophilic vasculitis (Churg-Strauss syndrome) has been reported with all agents, particularly when the dose of concurrent glucocorticoids is reduced. Other effects include headache and dyspepsia. Both *zafirlukast* and *zileuton* are inhibitors of cytochrome P450. Both drugs can increase serum levels of *warfarin*. Figure 27.6 summarizes the drugs that modify the action of leukotrienes.

## *B. Cromolyn and nedocromil*

*Cromoly*n [KROE-moe-lin] and *nedocromil* [ne-doe-KROE-mil] are effective prophylactic anti-inflammatory agents. However, they are not useful in managing an acute asthma attack, because they are not direct bronchodilators. These agents can block the initiation of immediate and delayed asthmatic reactions. For use in asthma, *cromolyn* is administered either by inhalation of a microfine powder or as an aerosolized solution. Because it is poorly absorbed, only minor adverse effects are associated with it. Pretreatment with *cromolyn* blocks allergen- and exercise-induced bronchoconstriction. *Cromolyn* is also useful in reducing the symptoms of allergic rhinitis. A 4 to 6-week trial is required to determine



efficacy. Given its safety, an initial trial of *cromolyn* is often recommended, particularly in children and pregnant women. Toxic reactions are mild and include a bitter taste and irritation of the pharynx and larynx. Due to short duration of action, these agents require frequent daily dosing, which has been shown to affect adherence and, therefore, therapeutic efficacy. Neither *cromolyn* nor *nedocromil* should replace ICS or quick-relief $Î²_2$ agonists as the mainstay of asthma therapy.

## *C. Cholinergic antagonists*

Anticholinergic agents are generally less effective than $Î²_2$-adrenergic agonists. They block the vagally mediated contraction of airway smooth muscle and mucus secretion. Inhaled *ipratropium* [i-pra-TROE-pee-um], a quaternary derivative of *atropine*, is useful in patients who are unable to tolerate adrenergic agonists. *Ipratropium* is slow in onset and nearly free of side effects. These agents are not traditionally effective for patients with asthma unless COPD is also present.

## *D. Theophylline*

*Theophylline* [thee-OFF-i-lin] is a bronchodilator that relieves airflow obstruction in chronic asthma and decreases its symptoms. *Theophylline* is well absorbed by the gastrointestinal tract, and several sustained-release preparations are available. Previously the mainstay of asthma therapy, *theophylline* has been largely replaced with $Î²_2$ agonists and corticosteroids due to a narrow therapeutic window, high side-effect profile, and potential for drug interactions. Overdose may cause seizures or potentially fatal arrhythmias. *Theophylline* is metabolized in the liver, is a CYP1A2 and 3A4 substrate, and interacts adversely with many drugs.

## *E. Omalizumab*

*Omalizumab* [oh-mah-lye-ZOO-mab] is a recombinant DNAâ€“derived monoclonal antibody that selectively binds to

human immunoglobulin E (IgE). This leads to decreased binding of IgE to the high-affinity IgE receptor on the surface of mast cells and basophils. Reduction in surface-bound IgE limits the degree of release of mediators of the allergic response. *Omalizumab* may be particularly useful for treatment of moderate to severe allergic asthma in patients who are poorly controlled with conventional therapy. Due to the high cost of the drug (approximately $600 for a 150-mg vial), limitations on dosage, and available clinical trial data, it is not presently used as first-line therapy.

## IV. Drugs Used to Treat Chronic Obstructive Pulmonary Disease

Chronic obstructive pulmonary disease is a chronic, irreversible obstruction of airflow. Smoking is the greatest risk factor for COPD and is directly linked to the progressive decline of lung function as demonstrated by forced expiratory volume (FEV). Smoking cessation and/or continued avoidance should be recommended regardless of stage/severity of COPD and age of patient. Inhaled bronchodilators, such as anticholinergic agents (*ipratropium* and *tiotropium*) and Î²$_2$-adrenergic agonists, are the foundation of therapy for COPD (Figure 27.7). These drugs increase airflow, alleviate symptoms, and decrease exacerbation of disease. Combinations of an anticholinergic plus a Î²$_2$ agonist may be helpful in patients for whom a single inhaled bronchodilator has failed to provide an adequate response. For example, the combination



of *albuterol* and *ipratropium* provides greater bronchodilation than with either drug alone. Longer-acting drugs, such as *salmeterol* and *tiotropium* [tee-oh-TROE-pee-um], have the advantage of less frequent dosing. ICS should be restricted to patients with an FEV in 1 second (FEV$_1$) of less than 50 percent of predicted and three or more exacerbations in the last 3 years (Stage III or IV). Whereas the addition of ICS may provide symptomatic relief, the progressive decline in FEV$_1$ is not impacted. Addition of a long-acting Î²$_2$ agonists such as *salmeterol*, improves lung function compared to either a short-acting Î²$_2$ agonist or steroid alone.

| STAGE | CHARACTERISTICS | LONG-TERM CONTROL |
|---|---|---|
| I: Mild COPD | FEV$_1$ greater than 80 percent predicted | Short-acting bronchodilator when needed |
| II: Moderate COPD | FEV$_1$ 50 to 80 percent predicted | Regular treatment with one or more bronchodilators<br>Inhaled glucocorticosteroid |
| III: Severe COPD | FEV$_1$ less than 30 percent predicted | Regular treatment with one or more bronchodilators<br>Inhaled glucocorticosteroid<br>Antibiotics for acute exacerbations of COPD characterized by increased volume and purulence of secretions<br>Long-term oxygen therapy |

**Figure 27.7** Treatment of stable chronic obstructive pulmonary disease (COPD). FEV$_1$ = forced expiratory volume in one second.

## V. Drugs Used to Treat Allergic Rhinitis

Rhinitis is an inflammation of the mucous membranes of the nose and is characterized by sneezing, itchy nose/eyes, watery rhinorrhea, and nasal congestion. An attack may be precipitated by inhalation of an allergen (such as dust, pollen, or animal dander). The foreign material interacts with mast cells coated with IgE generated in response to a previous allergen exposure (Figure 27.8). The mast cells release mediators, such as histamine, leukotrienes, and chemotactic factors, that promote bronchiolar spasm and mucosal thickening from edema and cellular infiltration. Combinations of oral antihistamines with decongestants are the first-line therapies for allergic rhinitis. Systemic

effects associated with these oral preparations (sedation, insomnia, and, rarely, cardiac arrhythmias) have prompted interest in topical intranasal delivery of drugs.

## *A. Antihistamines ($H_1$-receptor blockers)*

Antihistamines are the most frequently used agents in the treatment of sneezing and watery rhinorrhea associated with allergic rhinitis. $H_1$-histamine receptor blockers, such as *diphenhydramine, chlorpheniramine, loratadine,* and *fexofenadine*, are useful in treating the symptoms of allergic rhinitis caused by histamine release. Ocular and nasal antihistamine delivery devices are available over-the-counter for more targeted tissue delivery. Combinations of antihistamines with decongestants (see below) are effective when congestion is a feature of rhinitis. Antihistamines differ in their ability to cause sedation and in their duration of action. In general, anticholinergic side effects of the first-generation antihistamines (dry eyes/mouth, difficulty urinating and/or defecating) are transient and may resolve in 7 to 10 days. Constipation associated with chronic use of the first-generation antihistamines is not



transient and may require treatment with a stool softener, especially in more susceptible patients.

## *B. Î±-Adrenergic agonists*

Short-acting Î±-adrenergic agonists (â€œnasal decongestantsâ€), such as *phenylephrine*, constrict dilated arterioles in the nasal mucosa and reduce airway resistance. Longer-acting *oxymetazoline* [ok-see-met-AZ-oh-leen] is also available. When administered as an aerosol, these drugs have a rapid onset of action and show few systemic effects. Oral administration results in longer duration of action but also increased systemic effects. Combinations of these agents with antihistamines are frequently used. The Î±-adrenergic agonists should be used no longer than several days due to the risk of rebound nasal congestion (rhinitis medicamentosa). Î±-Adrenergic agents have no place in the long-term treatment of allergic rhinitis.

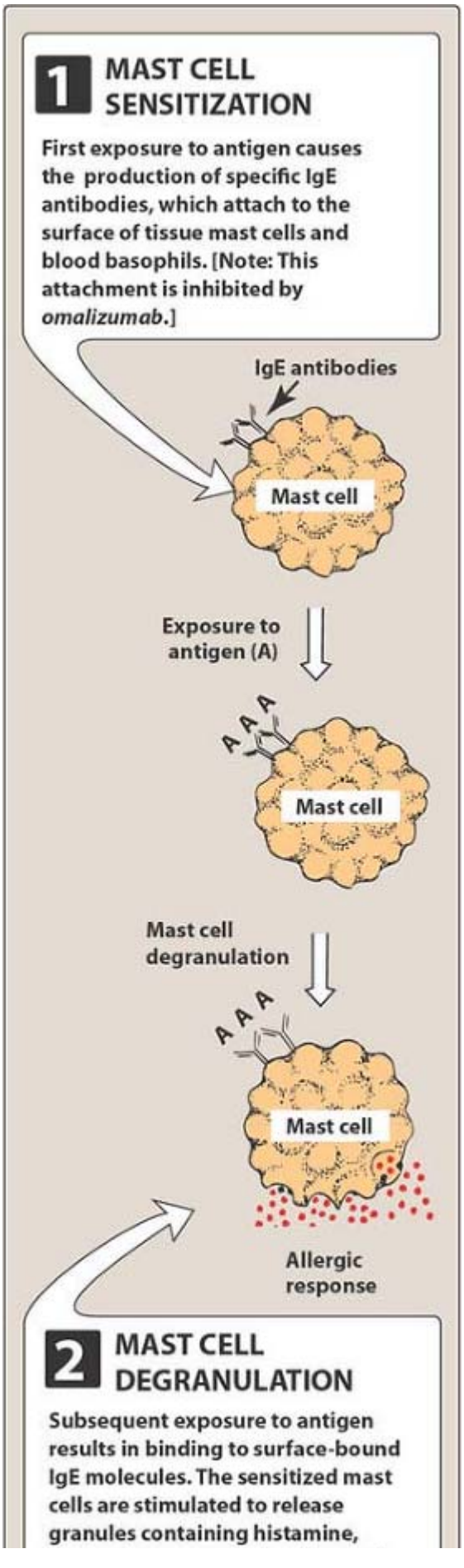
1
MAST CELL SENSITIZATION
First exposure to antigen causes the production of specific IgE antibodies, which attach to the surface of tissue mast cells and blood basophils. [Note: This attachment is inhibited by *omalizumab*.]
IgE antibodies
Mast cell
Exposure to antigen (A)
A A A
Mast cell
Mast cell degranulation
A A A
Mast cell
Allergic response
2
MAST CELL DEGRANULATION
Subsequent exposure to antigen results in binding to surface-bound IgE molecules. The sensitized mast cells are stimulated to release granules containing histamine,

**Figure 27.8** Hypersensitivity reactions mediated by immunoglobulin E (IgE) molecules can cause rhinitis.

### *C. Corticosteroids*

Corticosteroids, such as *beclomethasone, budesonide, fluticasone, flunisolide,* and *triamcinolone*, are effective when administered as nasal sprays. [Note: Systemic absorption is minimal, and side effects of intranasal corticosteroid treatment are localized. These include nasal irritation, nosebleed, sore throat, and rarely, candidiasis.] To avoid systemic absorption, patient counseling should emphasize the importance of topical deposition of the drug (tell patients NOT to deeply inhale while administering these drugs because the target tissue is in the nose, not in the lungs or the throat). Topical steroids may be more effective than systemic antihistamines in relieving the nasal symptoms of both allergic and nonallergic rhinitis. The effects of long-term usage are unknown, but these agents are considered to be generally safe. Periodic assessment of the patient is advised. Treatment of chronic rhinitis may not result in improvement until 1 to 2 weeks after starting therapy.

### *D. Cromolyn*

Intranasal *cromolyn* may be useful, particularly when administered before contact with an allergen. To optimize the therapeutic effect of cromolyn, dosing should occur at least 1 to 2 weeks prior to allergen exposure. Due to a short duration of action, *cromolyn* requires multiple daily dosing, which may deleteriously impact adherence and, therefore, therapeutic efficacy.

## VI. Drugs Used to Treat Cough

*Codeine* [KOE-deen] is the gold-standard treatment for cough suppression due to its long history of availability and use. *Codeine* decreases the sensitivity of cough centers in the central nervous system to peripheral stimuli and decreases mucosal secretion. These therapeutic effects occur at doses lower than those required for analgesia but still incur common sides effects like constipation, dysphoria, and fatigue, in addition to its addictive potential. (See p. 159 for a more complete discussion of the opiates.) *Dextromethorphan* [dek-stroe-METH-or-fan] is a synthetic derivative of *morphine* that suppresses the response of the central cough center. It has no analgesic effects, has a low addictive profile, but may cause dysphoria at high doses, which may explain its status as a potential drug of abuse. *Dextromethorphan* has a significantly better side effect profile than *codeine* and has been demonstrated to be equally effective for cough suppression.



## Study Questions

Choose the ONE best answer.

**27.1 A 12-year-old girl with a childhood history of asthma complained of cough, dyspnea, and wheezing after visiting a riding stable. Her symptoms became so severe that her parents brought her to the emergency room. Physical examination revealed diaphoresis, dyspnea, tachycardia, and tachypnea. Her respiratory rate was 42 breaths per minute, pulse rate 110 beats per minute, and blood pressure 132/65 mm Hg. Which of the following is the most appropriate drug to rapidly reverse her bronchoconstriction?**

A. Inhaled cromolyn.

B. Inhaled beclomethasone.

C. Inhaled albuterol.

D. Intravenous propranolol.

View Answer

**27.2 A 9-year-old girl has severe asthma, which required three hospitalizations in the last year. She is now receiving therapy that has greatly reduced the frequency of these severe attacks. Which of the following therapies is most likely responsible for this benefit?**

A. Albuterol by aerosol.

B. Cromolyn by inhaler.

C. Fluticasone by aerosol.

D. Theophylline orally.

E. Zafirlukast orally.

View Answer

**27.3 A 68-year-old male retired police officer who has smoked a 1/2 pack of cigarettes a day for the past 40 years is diagnosed with chronic obstructive pulmonary disease (COPD). He has a difficulty in expiration during breathing, but the symptms are mild and intermittent. Which one of the following agents would most appropratate initial therapy.**

A. Systemic corticosteroids

B. Albuterol

C. Salmeterol

D. Tiotropium plus salmeterol

E. Theophylline

View Answer

**Editors:** **Finkel, Richard; Clark, Michelle A.; Cubeddu, Luigi X.**
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# Chapter 28

# Gastrointestinal and Antiemetic Drugs

## I. Overview

This chapter describes drugs used to treat three common medical conditions involving the gastrointestinal tract: peptic ulcers and gastroesophageal reflux disease (GERD), chemotherapy-induced emesis, and diarrhea and constipation. Many drugs described in other chapters also find application in the treatment of gastrointestinal disorders. For example, the *meperidine* derivative *diphenoxylate*, which decreases peristaltic activity of the gut, is useful in the treatment of severe diarrhea, and the corticosteroid *dexamethasone* has excellent antiemetic properties. Other drugs, (for example, $H_2$-receptor antagonists and proton-pump inhibitors (PPIs), are employed to heal peptic ulcers; the selective inhibitors of the serotonin receptors, such as *ondansetron* or *granisetron*, which prevent vomiting, are used almost exclusively to treat gastrointestinal tract disorders.

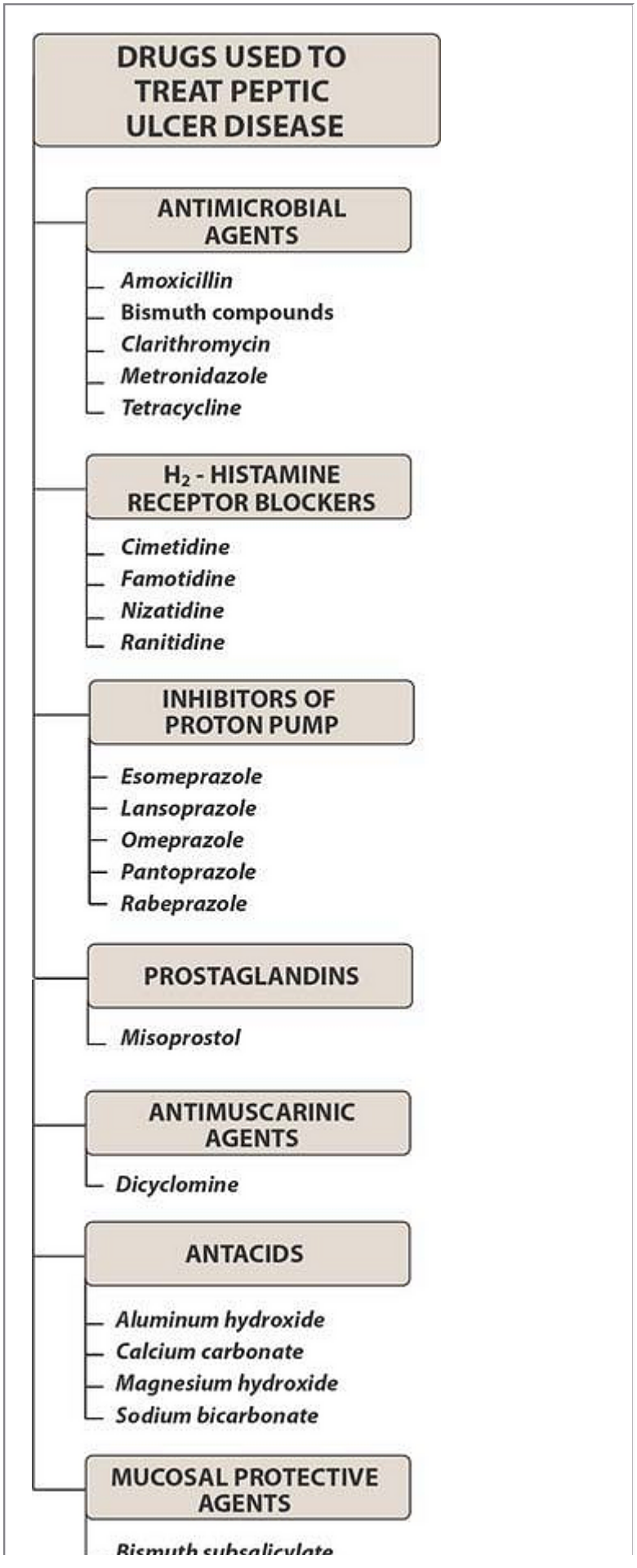

DRUGS USED TO TREAT PEPTIC ULCER DISEASE
ANTIMICROBIAL AGENTS
Amoxicillin
Bismuth compounds
Clarithromycin
Metronidazole
Tetracycline
H2 - HISTAMINE RECEPTOR BLOCKERS
Cimetidine
Famotidine
Nizatidine
Ranitidine
INHIBITORS OF PROTON PUMP
Esomeprazole
Lansoprazole
Omeprazole
Pantoprazole
Rabeprazole
PROSTAGLANDINS
Misoprostol
ANTIMUSCARINIC AGENTS
Dicyclomine
ANTACIDS
Aluminum hydroxide
Calcium carbonate
Magnesium hydroxide
Sodium bicarbonate
MUCOSAL PROTECTIVE AGENTS

**Figure 28.1** Summary of drugs used to treat peptic ulcer disease.

## II. Drugs Used to Treat Peptic Ulcer Disease

Although the pathogenesis of peptic ulcer disease is not fully understood, several major causative factors are recognized: nonsteroidal anti-inflammatory drug (NSAID) use, infection with gram-negative Helicobacter pylori, increased hydrochloric acid secretion, and inadequate mucosal defense against gastric acid. Treatment approaches include 1) eradicating the H. pylori infection, 2) reducing secretion of gastric acid with the use of $H_2$-receptor antagonists or PPIs, and/or 3) providing agents that protect the gastric mucosa from damage, such as *misoprostol* and *sucralfate.* (Note: If patients are unable to tolerate the above therapies, neutralizing gastric acid with nonabsorbable antacids is an option). Figure 28.1 summarizes agents that are effective in treating peptic ulcer disease.

### *A. Antimicrobial agents*

Optimal therapy for patients with peptic ulcer disease (both duodenal and gastric ulcers) who are infected with H. pylori requires antimicrobial treatment. To document infection with H. pylori, endoscopic biopsy of the gastric mucosa or various noninvasive methods are utilized, including serologic tests and urea breath tests. Figure 28.2 shows a biopsy sample in which H. pylori is closely associated with the gastric mucosa. Eradication of H. pylori results in rapid healing of active peptic ulcers and low recurrence rates (less than 15 percent compared with 60 to 100 percent per year for patients with initial ulcers healed by traditional antisecretory therapy). Successful eradication of H. pylori (80â€“90 percent) is possible with various combinations



of antimicrobial drugs. Currently, either triple therapy consisting of a PPI with either *metronidazole* or *amoxicillin* plus *clarithromycin*, or quadruple therapy of *bismuth subsalicylate* and *metronidazole* plus *tetracycline* plus a PPI, are administered for a 2-week course. This usually results in a 90 percent or greater eradication rate. Bismuth salts do not neutralize stomach acid, but they inhibit pepsin and increase the secretion of mucus, thus helping to form a barrier against the diffusion of acid in the ulcer. Treatment with a single antimicrobial drug is less effective (20 to 40 percent eradication rates), results in antimicrobial resistance and is absolutely not recommended; switching of antibiotics is also not recommended (that is, do not substitute *amoxicillin* for *ampicillin* or *erythromycin* for *clarithromycin* or *doxycycline* for *tetracycline*). [Note: GERD (that is, a heartburn-like sensation) is not associated with H. pylori infection and does not respond to treatment with antibiotics.]

### *B. Regulation of gastric acid secretion*

Gastric acid secretion by parietal cells of the gastric mucosa is stimulated by acetylcholine, histamine, and gastrin (Figure 28.3). The receptor-mediated binding of acetylcholine, histamine, or gastrin results in the activation of protein kinases, which in turn stimulates the $H^+/K^+$â€“adenosine triphosphatase (ATPase) proton pump to secrete hydrogen ions in exchange for $K^+$ into the lumen of the stomach. A $Cl^-$ channel couples chloride efflux to the release of $H^+$. In contrast, receptor binding of prostaglandin $E_2$ and somatostatin diminish gastric acid production. [Note: Histamine binding causes activation of adenylyl cyclase, whereas binding of prostaglandin $E_2$ inhibits this enzyme. Gastrin and acetylcholine act by inducing an increase in intracellular calcium levels.]

### *C. H2-receptor antagonists*

Although antagonists of the histamine $H_2$ receptor block the actions of histamine at all $H_2$ receptors, their chief clinical use is to inhibit gastric acid secretion, being particularly effective against nocturnal acid secretion. By competitively blocking the binding of histamine to $H_2$ receptors, these agents reduce the intracellular concentrations of cyclic adenosine monophosphate and, thereby, secretion of gastric acid. The four drugs used in

the United Statesâ€"*cimetidine* [si-MET-ih-deen], *ranitidine* [ra-NI-tih-deen], *famotidine* [fa-MOE-ti-deen], and *nizatidine* [nye-ZA-ti-deen]â€"potently inhibit (greater than 90 percent) basal, food-stimulated, and nocturnal secretion of gastric acid after a single dose. *Cimetidine* is the prototype histamine $H_2$-receptor antagonist; however, its utility is limited by its adverse effect profile and drug interactions.

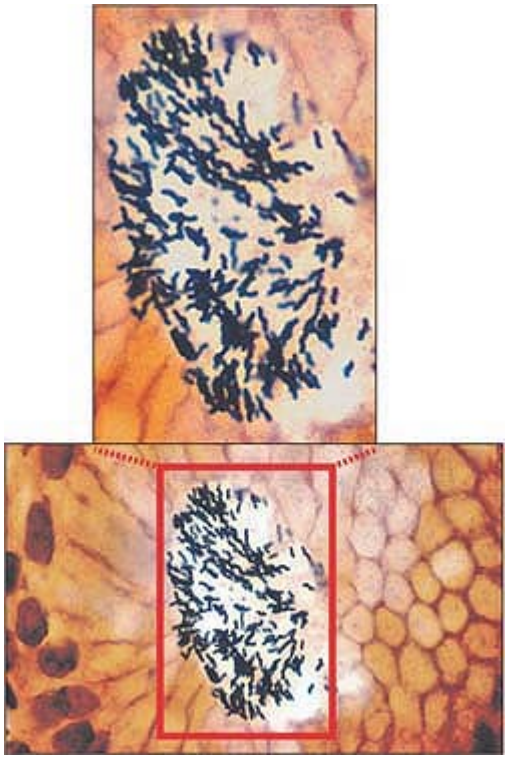


**Figure 28.2** Helicobacter pylori in association with gastric mucosa.

1. **Actions:** The histamine $H_2$-receptor antagonistsâ€"*cimetidine, ranitidine, famotidine*, and *nizatidine*â€"act selectively on $H_2$ receptors in the stomach, blood vessels, and other sites, but they have no effect on $H_1$ receptors. They are competitive antagonists of histamine and are fully reversible. These agents completely inhibit gastric acid secretion induced by histamine or gastrin. However, they only partially inhibit gastric acid secretion induced by acetylcholine or *bethanechol*.

2. **Therapeutic uses:** The use of these agents has decreased with the advent of the PPIs.

    a. **Peptic ulcers:** All four agents are equally effective in promoting healing of duodenal and gastric ulcers. However, recurrence is common after treatment with $H_2$ antagonists is stopped (60â€“100



    percent per year). Patients with NSAID-induced ulcers should be treated with PPIs, because these agents heal and prevent future ulcers better than $H_2$ antagonists.

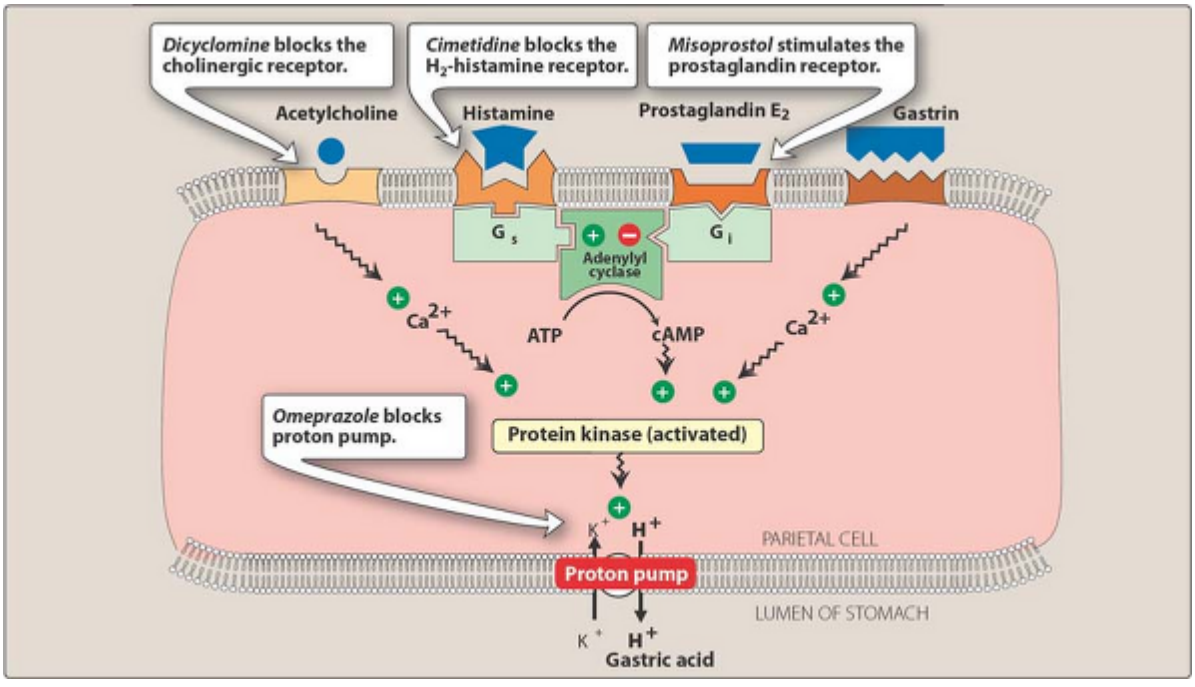



**Figure 28.3** Effects of acetylcholine, histamine, prostaglandin $E_2$, and gastrin on gastric acid secretion by the parietal cells of stomach. $G_s$ and $G_i$ are membrane proteins that mediate the stimulatory or inhibitory effect of receptor coupling to adenylyl cyclase.

b. **Acute stress ulcers:** These drugs are useful in managing acute stress ulcers associated with major physical trauma in high-risk patients in intensive care units. They are usually injected intravenously.

c. **Gastroesophageal reflux disease:** Low doses of $H_2$ antagonists, recently released for over-the-counter sale, appear to be effective for prevention and treatment of heartburn (gastroesophageal reflux). However, about 50 percent of patients do not find benefit, and PPIs are now used preferentially in the treatment of this disorder. Because $H_2$-receptor antagonists act by stopping acid secretion, they may not relieve symptoms for at least 45 minutes. Antacids more efficiently, but temporarily, neutralize secreted acid already in the stomach. Finally, tolerance to the effects of $H_2$ antagonists can be seen within 2 weeks of therapy.

3. **Pharmacokinetics:**

a. **Cimetidine:** *Cimetidine* and the other $H_2$ antagonists are given orally, distribute widely throughout the body (including into breast milk and across the placenta), and are excreted mainly in the urine (Figure 28.4). *Cimetidine* normally has a short serum half-life, which is increased in renal failure. Approximately 30 percent of a dose of *cimetidine* is slowly inactivated by the liver's



microsomal mixed-function oxygenase system (see p. 14) and can interfere in the metabolism of many other drugs; the other 70 percent is excreted unchanged in the urine. The dosage of all these drugs must be decreased in patients with hepatic or renal failure. *Cimetidine* inhibits cytochrome P450 and can slow metabolism (and, thus, potentiate the action) of several drugs (for example, *warfarin, diazepam, phenytoin, quinidine, carbamazepine, theophylline*, and *imipramine*; Figure 28.5), sometimes resulting in serious adverse clinical effects.

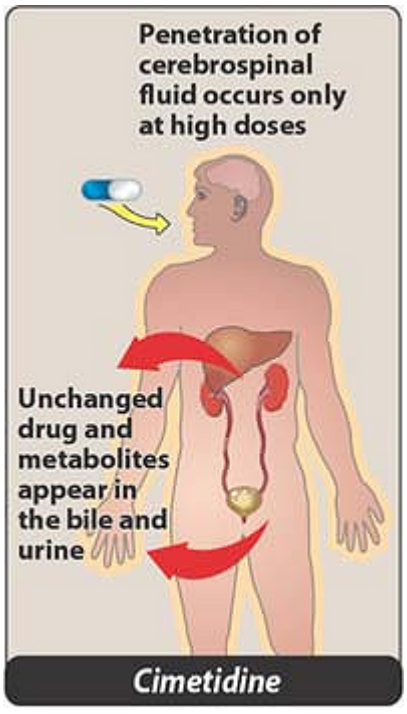



**Figure 28.4** Administration and fate of *cimetidine.*

b. **Ranitidine:** Compared to *cimetidine, ranitidine* is longer acting and is five- to ten-fold more potent. *Ranitidine* has minimal side effects and does not produce the antiandrogenic or prolactin-stimulating effects of *cimetidine*. Unlike *cimetidine*, it does not inhibit the mixed-function oxygenase system in the liver and, thus, does not affect the concentrations of other drugs.

c. **Famotidine:** *Famotidine* is similar to *ranitidine* in its pharmacologic action, but it is 20 to 50 times more potent than *cimetidine*, and 3 to 20 times more potent than *ranitidine*.

d. **Nizatidine:** *Nizatidine* is similar to *ranitidine* in its pharmacologic action and potency. In contrast to *cimetidine, ranitidine*, and *famotidine*, which are metabolized by the liver, *nizatidine* is eliminated principally by the kidney. Because little first-pass metabolism occurs with *nizatidine*, its bioavailability is nearly 100 percent. No intravenous preparation is available.

4. **Adverse effects:** The adverse effects of *cimetidine* are usually minor and are associated mainly with the major pharmacologic activity of the drugâ€”namely, reduced gastric acid production. Side effects occur only in a small number of patients and generally do not require discontinuation of the drug. The most common side effects are headache, dizziness, diarrhea, and muscular pain. Other central nervous system effects (confusion, hallucinations) occur primarily in elderly patients or after intravenous administration. *Cimetidine* can also have endocrine effects, because it acts as a nonsteroidal antiandrogen. These effects include gynecomastia, galactorrhea (continuous release/discharge of milk), and reduced sperm count. Except for *famotidine*, all these agents inhibit the gastric first-pass metabolism of ethanol. Drugs such as *ketoconazole*, which depend on an acidic medium for gastric absorption, may not be efficiently absorbed if taken with one of these antagonists.

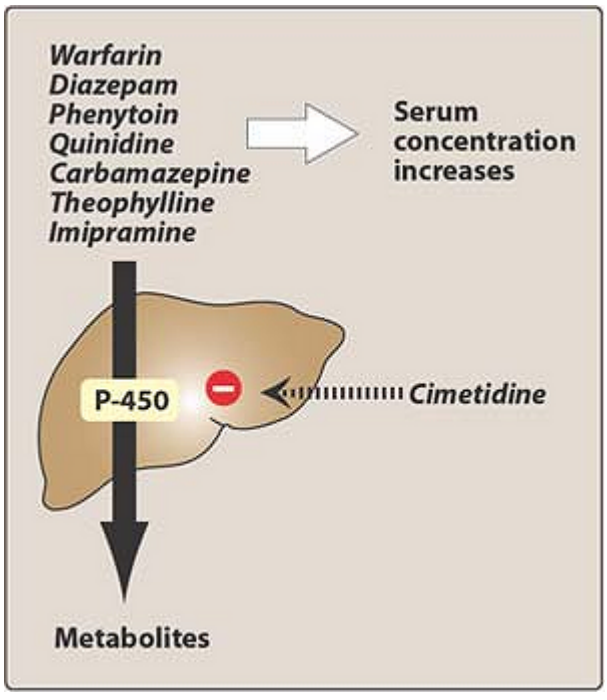



**Figure 28.5** Drug interactions with *cimetidine.*

## *D. Inhibitors of the H+/K+-ATPase proton pump*

*Omeprazole* [oh-MEH-pra-zole] is the first of a class of drugs that bind to the $H^+/K^+$-ATPase enzyme system (proton pump) of the parietal cell, thereby suppressing secretion of hydrogen ions into the gastric lumen. The membrane-bound proton pump is the final step in the secretion of gastric acid (see Figure 28.3). Four additional PPIs are now available: *lansoprazole* [lan-SO-pra-zole], *rabeprazole* [rah-BEH-pra-zole], *pantoprazole* [pan-TOE-pra-zole], and *esomeprazole* [es-oh-MEH-pra-zole].

1. **Actions:** These agents are prodrugs with an acid-resistant enteric coating to protect them from premature degradation by gastric acid. The coating is removed in the alkaline duodenum, and the prodrug, a weak base, is absorbed and transported to the parietal cell canaliculus.



   There, it is converted to the active form, which reacts with a cysteine residue of the $H^+/K^+$-ATPase, forming a stable covalent bond. It takes about 18 hours for the enzyme to be resynthesized. At standard doses, all PPIs inhibit both basal and stimulated gastric acid secretion by more than 90 percent. Acid suppression begins within 1 to 2 hours after the first dose of *lansoprazole* and slightly earlier with *omeprazole*. There is also an oral product containing *omeprazole* combined with *sodium bicarbonate* for faster absorption. It is available in powder to be dissolved in water and taken orally as well as in capsule form.

2. **Therapeutic uses:** The superiority of the PPIs over the $H_2$ antagonists for suppressing acid production and healing peptic ulcers has made them the preferred drugs for treating erosive esophagitis and active duodenal ulcer and for long-term treatment of pathologic hypersecretory conditions (for example, Zollinger-Ellison syndrome, in which a gastrin-producing tumor causes hypersecretion of HCl). They are approved for the treatment of GERD. Clinical studies have shown that PPIs reduce the risk of bleeding from an ulcer caused by *aspirin* and other NSAIDs. They are also successfully used with antimicrobial regimens to eradicate H. pylori. For maximum effect, PPIs should be taken 30 minutes before breakfast or the largest meal of the day. If an

$H_2$-receptor antagonist is also needed, it should be taken well after the PPI for best effect. The $H_2$ antagonists will reduce the activity of the proton pump, and PPIs require active pumps to be effective. In patients with GERD in whom once-daily PPI is partially effective, increasing to a twice-daily regimen or keeping the PPI in the morning and adding an $H_2$ antagonist in the evening may improve symptom control.

3. **Pharmacokinetics:** All these agents are delayed-release formulations and are effective orally. [Note: Some are also available for intravenous injection.] Metabolites of these agents are excreted in urine and feces.

4. **Adverse effects:** The PPIs are generally well tolerated, but concerns about long-term safety have been raised due to the increased secretion of gastrin. In animal studies, the incidence of gastric carcinoid tumors increased, possibly related to the effects of prolonged hypochlorhydria and secondary hypergastrinemia. However, this has not been found in humans. Increased concentrations of viable bacteria in the stomach have been reported with continued use of these drugs. *Omeprazole* inhibits the metabolism of *warfarin, phenytoin, diazepam*, and *cyclosporine*. However, drug interactions are not a problem with the other PPIs. Prolonged therapy with agents that suppress gastric acid, such as the PPIs and $H_2$ antagonists, may result in low vitamin $B_{12}$, because acid is required for its absorption. Another problem with prolonged elevation of gastric pH is that calcium carbonate products require low gastric pH to be absorbed in the upper intestine. Increasing gastric pH increases the potential for incomplete absorption of calcium carbonate products. An effective option would be to use calcium citrate as a source of calcium by patients taking prolonged acid-suppressing medications. The absorption of the citrate salt is not affected by gastric pH. There are increased reports of diarrhea and Clostridium difficile colitis in community patients receiving PPIs; therefore, patients must be counseled to discontinue PPI therapy if they have diarrhea for several days and to contact their physicians for further follow-up.



## *E. Prostaglandins*

Prostaglandin $E_2$, produced by the gastric mucosa, inhibits secretion of HCl and stimulates secretion of mucus and bicarbonate (cytoprotective effect). A deficiency of prostaglandins is thought to be involved in the pathogenesis of peptic ulcers. *Misoprostol* [mye-soe-PROST-ole], a stable analog of prostaglandin $E_1$, as well as some PPIs, are approved for prevention of gastric ulcers induced by NSAIDs (Figure 28.6). It is less effective than $H_2$ antagonists and the PPIs for acute treatment of peptic ulcers. Although *misoprostol* has cytoprotective actions, it is clinically effective only at higher doses that diminish gastric acid secretion. Routine prophylactic use of *misoprostol* may not be justified except in patients who are taking NSAIDs and are at high risk of NSAID-induced ulcers, such as the elderly or patients with ulcer complications. Like other prostaglandins, *misoprostol* produces uterine contractions and is contraindicated during pregnancy. Dose-related diarrhea and nausea are the most common adverse effects and limit the use of this agent.

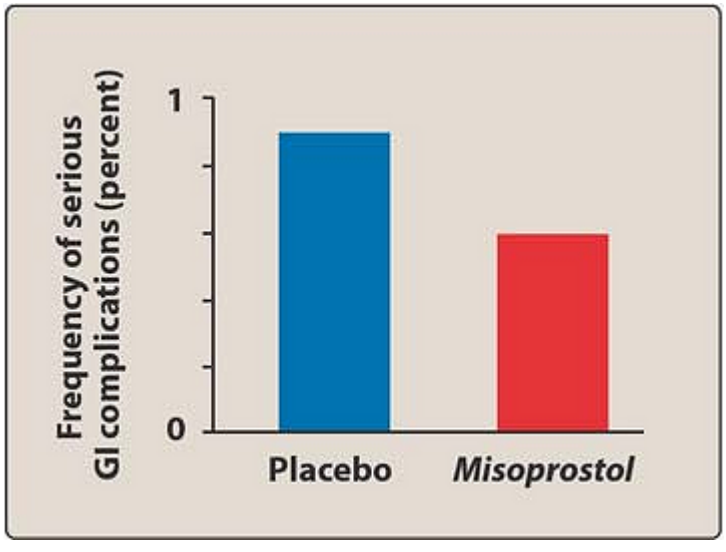


**Figure 28.6** *Misoprostol* reduces serious gastrointestinal (GI) complications in patients with rheumatoid arthritis receiving nonsteroidal antiinflammatory drugs.

## F. Antimuscarinic agents (anticholinergic agents)

Muscarinic receptor stimulation increases gastrointestinal motility and secretory activity. A cholinergic antagonist, such as *dicyclomine* [dye-SYE-kloe-meen], can be used as an adjunct in the management of peptic ulcer disease and Zollinger-Ellison syndrome, particularly in patients who are refractory to standard therapies. However, its many side effects (for example, cardiac arrhythmias, dry mouth, constipation, and urinary retention) limit its use.

## G. Antacids

Antacids are weak bases that react with gastric acid to form water and a salt, thereby diminishing gastric acidity. Because pepsin is inactive at a pH greater than 4, antacids also reduce pepsin activity.

1. **Chemistry of antacids:** Antacid products vary widely in their chemical composition, acid-neutralizing capacity, sodium content, palatability, and price. The acid-neutralizing ability of an antacid depends on its capacity to neutralize gastric HCl and on whether the stomach is full or empty (food delays stomach emptying, allowing more time for the antacid to react). Commonly used antacids are salts of aluminum and magnesium, such as *aluminum hydroxide* (usually a mixture of $Al(OH)_3$ and aluminum oxide hydrates) or *magnesium hydroxide* [$Mg(OH)_2$], either alone or in combination. *Calcium carbonate* [$CaCO_3$] reacts with HCl to form $CO_2$ and $CaCl_2$ and is a commonly used preparation. Systemic absorption of *sodium bicarbonate* [$NaHCO_3$] can produce transient metabolic alkalosis; therefore, this antacid is not recommended for long-term use.
2. **Therapeutic uses:** Aluminum- and magnesium-containing antacids are used for symptomatic relief of peptic ulcer disease and GERD; they may promote healing of duodenal ulcers, but the evidence for efficacy in the treatment of acute gastric ulcers is less compelling; therefore, these agents are used as last-line therapy. [Note: *Calcium carbonate* preparations are also used as calcium supplements for the treatment of osteoporosis.]
3. **Adverse effects:** *Aluminum hydroxide* tends to be constipating, and *magnesium hydroxide* tends to produce diarrhea. Preparations that combine these agents aid in normalizing bowel function. The



binding of phosphate by aluminum-containing antacids can lead to hypophosphatemia. In addition to the potential for systemic alkalosis, *sodium bicarbonate* liberates $CO_2$, causing belching and flatulence. Absorption of the cations from antacids ($Mg^{2+}$, $Al^{3+}$, $Ca^{2+}$) is usually not a problem in patients with normal renal function, but the sodium content of antacids can be an important consideration in patients with hypertension or congestive heart failure. Adverse effects may also occur in patients with renal impairment, caused by accumulation of magnesium, calcium, sodium, and other electrolytes. Excessive intake of *calcium carbonate* along with calcium foods can result in hypercalcemia.

## H. Mucosal protective agents

These compounds, known as cytoprotective compounds, have several actions that enhance mucosal protection mechanisms, thereby preventing mucosal injury, reducing inflammation, and healing existing ulcers.

1. **Sucralfate:** This complex of *aluminum hydroxide* and sulfated sucrose binds to positively charged groups in proteins of both normal and necrotic mucosa. By forming complex gels with epithelial cells, *sucralfate* [soo-KRAL-fate] creates a physical barrier that impairs diffusion of HCl and prevents degradation of mucus by pepsin and acid. It also stimulates prostaglandin release as well as mucus and bicarbonate output, and it inhibits peptic digestion. By these and other mechanisms, *sucralfate* effectively heals duodenal ulcers and is used in long-term maintenance therapy to prevent their recurrence. Because it requires an acidic pH for activation,

*sucralfate* should not be administered with $H_2$ antagonists or antacids. Little of the drug is absorbed systemically. It is very well tolerated, but it can interfere with the absorption of other drugs by binding to them. This agent does not prevent NSAID-induced ulcers, nor does it heal gastric ulcers.

2. **Bismuth subsalicylate:** Preparations of this compound effectively heal peptic ulcers. In addition to their antimicrobial actions, they inhibit the activity of pepsin, increase secretion of mucus, and interact with glycoproteins in necrotic mucosal tissue to coat and protect the ulcer crater.

## III. Drugs Used to Control Chemotherapy-Induced Emesis

Although nausea and vomiting may occur in a variety of conditions (for example, motion sickness, pregnancy, or hepatitis) and are always unpleasant for the patient, it is the nausea and vomiting produced by many chemotherapeutic agents that demand effective management. Nearly 70 to 80 percent of all patients who undergo chemotherapy experience nausea or vomiting. Several factors influence the incidence and severity of chemotherapy-induced emesis (Figure 28.7), including the specific chemotherapeutic drug, dose, route, schedule of administration, and patient variables. For example, the young and women are more susceptible than older patients and men, and 10 to 40 percent of patients experience nausea or vomiting in anticipation of their chemotherapy (anticipatory vomiting). Emesis not only affects the quality of life but can lead to rejection of potentially curative antineoplastic treatment. In addition, uncontrolled vomiting can produce dehydration, profound metabolic imbalances, and nutrient depletion.

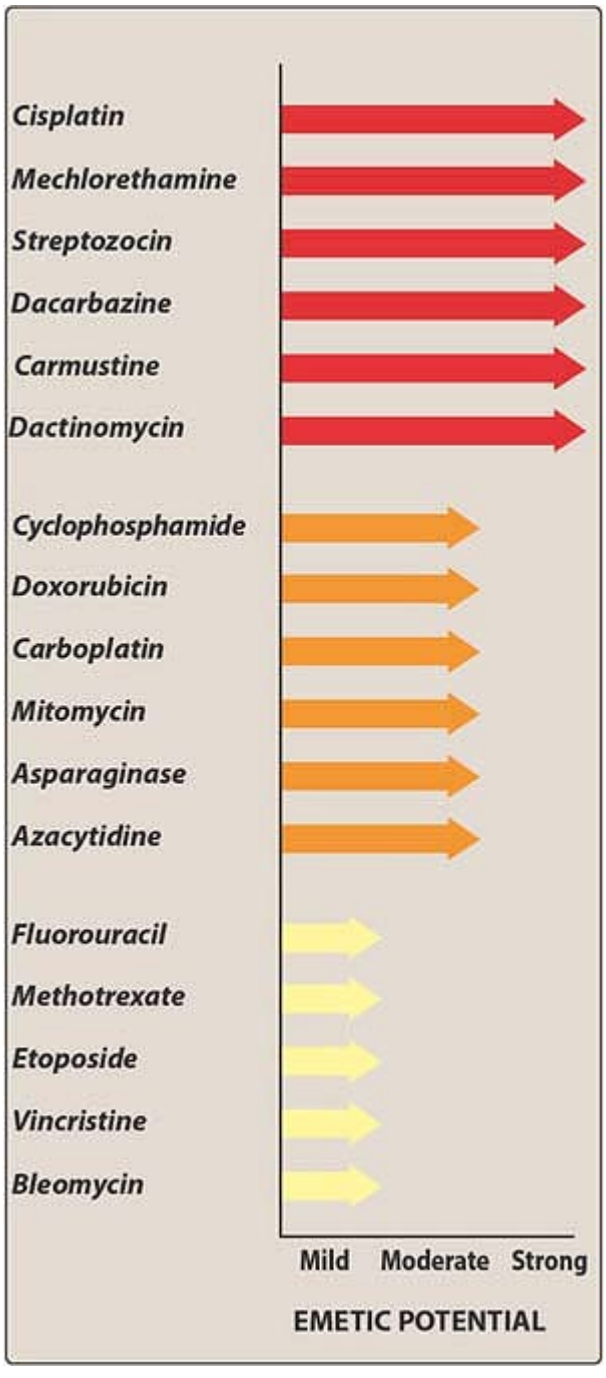



**Figure 28.7** Comparison of emetic potential of anticancer drugs.



## *A. Mechanisms that trigger vomiting*

Two brainstem sites have key roles in the vomiting reflex pathway. The chemoreceptor trigger zone, which is located in the area postrema (a circumventricular structure at the caudal end of the fourth ventricle) is outside the blood-brain barrier. Thus, it can respond directly to chemical stimuli in the blood or cerebrospinal fluid. The second important site, the vomiting center, which is located in the lateral reticular formation of the medulla, coordinates

the motor mechanisms of vomiting. The vomiting center also responds to afferent input from the vestibular system, the periphery (pharynx and gastrointestinal tract), and higher brainstem and cortical structures. The vestibular system functions mainly in motion sickness.

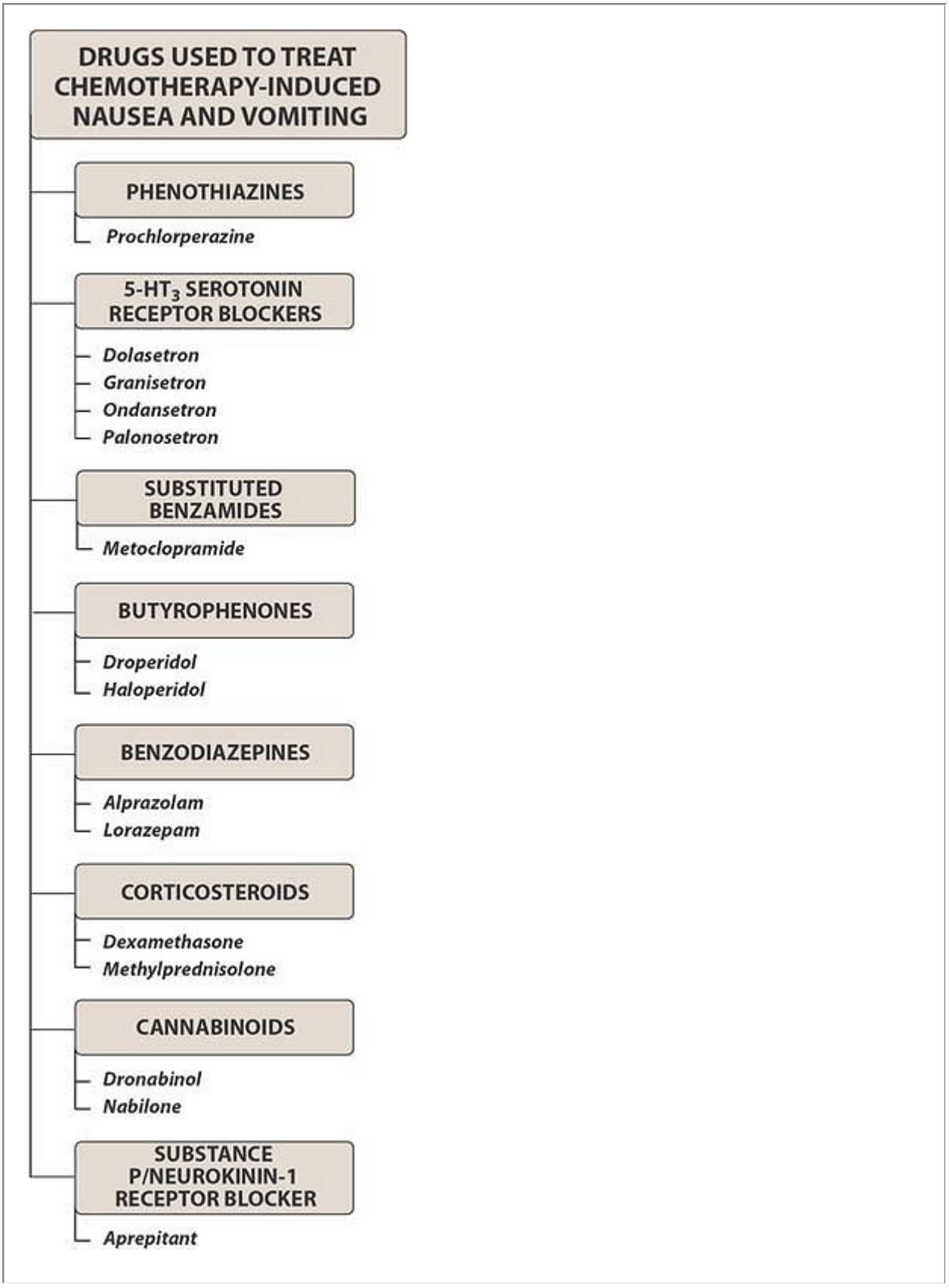


**Figure 28.8** Summary of drugs used to treat chemotherapy-induced nausea and vomiting. 5-$HT_3$ = serotonin Type 3.

## *B. Emetic actions of chemotherapeutic agents*

Chemotherapeutic agents (or their metabolites) can directly activate the medullary chemoreceptor trigger zone or vomiting center; several neuroreceptors, including dopamine receptor Type 2 and serotonin Type 3 (5-$HT_3$), play critical roles. Often, the color or smell of chemotherapeutic drugs (and even stimuli associated with chemotherapy, such as cues in the treatment room or the physician or nurse who administers the therapy) can activate higher brain centers and trigger emesis. Chemotherapeutic drugs can also act peripherally by causing cell damage in the gastrointestinal tract and releasing serotonin from the enterochromaffin cells of the small intestinal mucosa. The released serotonin activates 5-$HT_3$ receptors on vagal and splanchnic afferent fibers, which then carry sensory signals to the medulla, leading to the emetic response.

## *C. Antiemetic drugs*

Considering the complexity of the mechanisms involved in emesis, it is not surprising that antiemetics represent a variety of classes (Figure 28.8) and offer a range of efficacies (Figures 28.9). Anticholinergic drugs, especially the muscarinic receptor antagonist, *scopolamine*, and $H_1$-receptor antagonists, such as *dimenhydrinate, meclizine*, and *cyclizine*, are very useful in motion sickness but are ineffective against substances that act directly on the chemoreceptor trigger zone. The major categories of drugs used to control chemotherapy-induced nausea and vomiting include the following:

1. **Phenothiazines:** The first group of drugs shown to be effective antiemetic agents, phenothiazines, such as *prochlorperazine* [proe-klor-PER-ah-zeen], acts by blocking dopamine receptors. It is effective against low or moderately emetogenic chemotherapeutic agents (for example, *fluorouracil* and *doxorubicin*; see Figure 28.7). Although increasing the dose improves antiemetic activity, side effects, including hypotension and restlessness, are dose limiting. Other adverse reactions include extrapyramidal symptoms and sedation.

2. **5-$HT_3$ receptor blockers:** This class of agents commands an important place in treating emesis linked with chemotherapy. They have the advantage of a long duration of action. The specific antagonists of the 5-$HT_3$ receptorâ€"*ondansetron* [on-DAN-seh-tron], *granisetron* [gra-NI-seh-tron], *palonosetron* [pa-low-NO-seh-tron] and *dolasetron* [dol-A-se-tron]â€"selectively block 5-$HT_3$ receptors in the periphery (visceral vagal afferent fibers) and in the brain (chemoreceptor trigger zone). These drugs can be administered as a single dose prior to chemotherapy (intravenously or orally) and are efficacious against



all grades of emetogenic therapy. One trial reported *ondansetron* and *granisetron* prevented emesis in 50 to 60 percent of *cisplatin*-treated patients. These agents are extensively metabolized by the liver, with hydroxydolasetron being an active metabolite of *dolasetron*. Thus, doses of these agents should be adjusted in patients with hepatic insufficiency. Elimination is through the urine. Headache is a common side effect. Electrocardiographic changes, such as prolongation of the QT interval, can occur with *dolasetron*; therefore, patients who may be at risk should receive this medication with caution. These drugs are costly.

3. **Substituted benzamides:** One of several substituted benzamides with antiemetic activity, *metoclopramide* [met-oh-kloe-PRAH-mide], is highly effective at high doses against the highly emetogenic *cisplatin*, preventing emesis in 30 to 40 percent of patients and reducing emesis in the majority. Antidopaminergic side effects, including sedation, diarrhea, and extrapyramidal symptoms, limit its high-dose use.

4. **Butyrophenones:** *Droperidol* [droe-PER-i-doll] and *haloperidol* [hal-oh-PER-i-doll] act by blocking dopamine receptors. The butyrophenones are moderately effective antiemetics. *Droperidol* had been used most often for sedation in endoscopy and surgery, usually in combination with opiates or benzodiazepines. However, it may

prolong the QT interval, and current practice reserves it for patients whose response to other agents is inadequate. High-dose *haloperidol* was found to be nearly as effective as high-dose *metoclopramide* in preventing *cisplatin*-induced emesis.

5. **Benzodiazepines:** The antiemetic potency of *lorazepam* [lor-A-ze-pam] and *alprazolam* [al-PRAH-o-lam] is low. Their beneficial effects may be due to their sedative, anxiolytic, and amnesic properties. These same properties make benzodiazepines useful in treating anticipatory vomiting.

6. **Corticosteroids:** *Dexamethasone* [dex-a-MEH-tha-sone] and *methylprednisolone* [meth-ill-pred-NIH-so-lone], used alone, are effective against mildly to moderately emetogenic chemotherapy. Most frequently, however, they are used in combination with other agents. Their antiemetic mechanism is not known, but it may involve blockade of prostaglandins. These drugs can cause insomnia as well as hyperglycemia in patients with diabetes mellitus.

7. **Cannabinoids:** Marijuana derivatives, including *dronabinol* [droe-NAB-i-nol] and *nabilone* [NAB-il-own], are effective against moderately emetogenic chemotherapy. However, they are seldom first-line antiemetics because of their serious side effects, including dysphoria, hallucinations, sedation, vertigo, and disorientation. In spite of their psychotropic properties, the antiemetic action of cannabinoids may not involve the brain, because synthetic cannabinoids, which have no psychotropic activity, nevertheless are antiemetic.

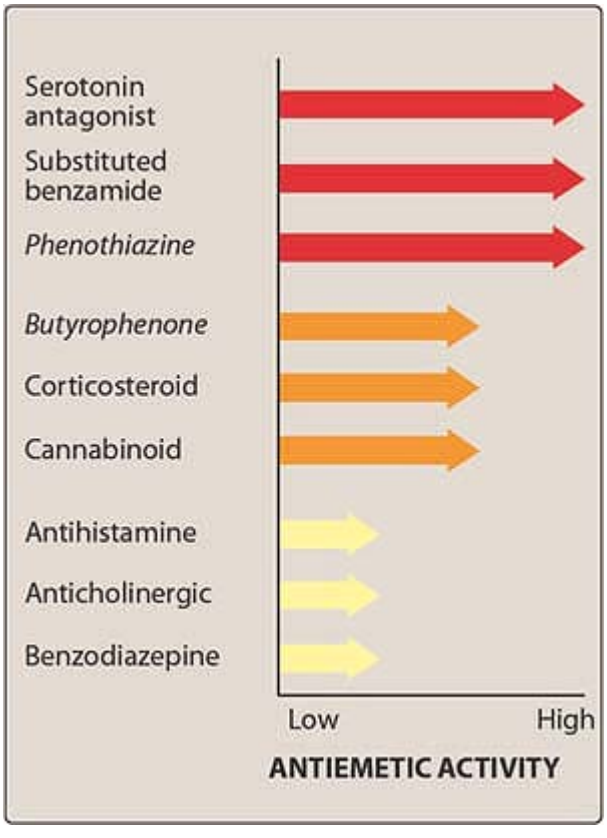



**Figure 28.9** Potencies of of antiemetic drugs.

8. **Substance P/neurokinin-1 receptor blocker:** *Aprepitant* [ah-PRE-pih-tant] belongs to a new family of antiemetic agents. It targets the neurokinin receptor in the brain and blocks the actions of the natural substance. *Aprepitant* is usually administered orally with *dexamethasone* and *palonosetron*. It undergoes extensive metabolism, primarily by CYP3A4. Thus, as would be expected, it can affect the metabolism of other

drugs that are metabolized by this enzyme. *Aprepitant* can also induce this enzyme and, thus, affect responses



to other agents; for example, concomitant use with *warfarin* can shorten the half-life of the anticoagulant. Constipation and fatigue appear to be the major side effects.

9. **Combination regimens:** Antiemetic drugs are often combined to increase antiemetic activity or decrease toxicity (Figure 28.10). Corticosteroids, most commonly *dexamethasone*, increase antiemetic activity when given with high-dose *metoclopramide*, a 5-$HT_3$ antagonist, *phenothiazine, butyrophenone*, a cannabinoid, or a benzodiazepine. Antihistamines, such as *diphenhydramine*, are often administered in combination with high-dose *metoclopramide* to reduce extrapyramidal reactions or with corticosteroids to counter *metoclopramide*-induced diarrhea.

## IV. Antidiarrheals

Increased motility of the gastrointestinal tract and decreased absorption of fluid are major factors in diarrhea. Antidiarrheal drugs include antimotility agents, adsorbents, and drugs that modify fluid and electrolyte transport (Figure 28.11).

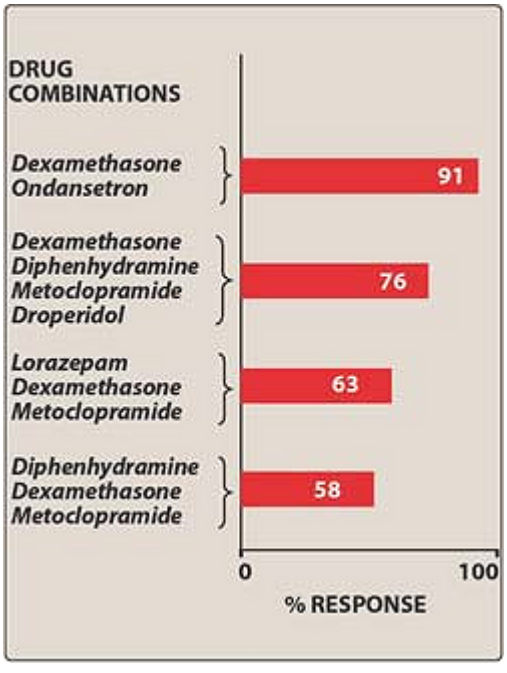



**Figure 28.10** Effectiveness of antiemetic activity of some drug combinations against emetic episodes in the first 24 hours after *cisplatin* chemotherapy.

### *A. Antimotility agents*

Two drugs that are widely used to control diarrhea are *diphenoxylate* [dye-fen-OX-see-late] and *loperamide* [loe-PER-ah-mide]. Both are analogs of *meperidine* and have opioid-like actions on the gut, activating presynaptic opioid receptors in the enteric nervous system to inhibit acetylcholine release and decrease peristalsis. At the usual doses, they lack analgesic effects. Side effects include drowsiness, abdominal cramps, and dizziness. Because these drugs can contribute to toxic megacolon, they should not be used in young children or in patients with severe colitis.

## *B. Adsorbents*

Adsorbent agents, such as *bismuth subsalicylate, methylcellulose* [meth-ill-CELL-you-lowse], and *aluminum hydroxide* are used to control diarrhea. Presumably, these agents act by adsorbing intestinal toxins or microorganisms and/or by coating or protecting the intestinal mucosa. They are much less effective than antimotility agents. They can interfere with the absorption of other drugs.

## *C. Agents that modify fluid and electrolyte transport*

*Bismuth subsalicylate*, used for traveler's diarrhea, decreases fluid secretion in the bowel. Its action may be due to its salicylate component as well as its coating action.

# V. Laxatives

Laxatives are commonly used to accelerate the movement of food through the gastrointestinal tract. These drugs can be classified on the basis of their mechanism of action as irritants or stimulants of the gut, bulking agents, and stool softeners. They all have a risk of being habit-forming. Laxatives also increase the potential of loss of pharmacologic effect of poorly absorbed, delayed-acting, and extended-release oral preparations by accelerating their transit through the intestines. They may cause electrolyte imbalances when used chronically.



## *A. Irritants and stimulants*

*Senna* is a widely used stimulant laxative. Its active ingredient is a group of sennosides, a natural complex of anthraquinone glycosides. Taken orally, it causes evacuation of the bowels within 8 to 10 hours. It also causes water and electrolyte secretion into the bowel. In combination products with a *docusate*-containing stool softener, it is useful in treating opioid-induced constipation. *Bisacodyl,* available as suppositories and enteric-coated tablets, is a potent stimulant of the colon. It acts directly on nerve fibers in the mucosa of the colon. Adverse effects include abdominal cramps and the potential for atonic colon with prolonged use. Antacids should not be taken at the same time as the enteric-coated tablets. The antacid would cause the enteric coating to dissolve prematurely in the stomach, resulting in stomach irritation and pain. The same adverse effects could be expected with milk, $H_2$-receptor antagonists, and PPIs. *Castor oil* is broken down in the small intestine to ricinoleic acid, which is very irritating to the gut, and promptly increases peristalsis. It should be avoided by pregnant patients, because it may stimulate uterine contractions.

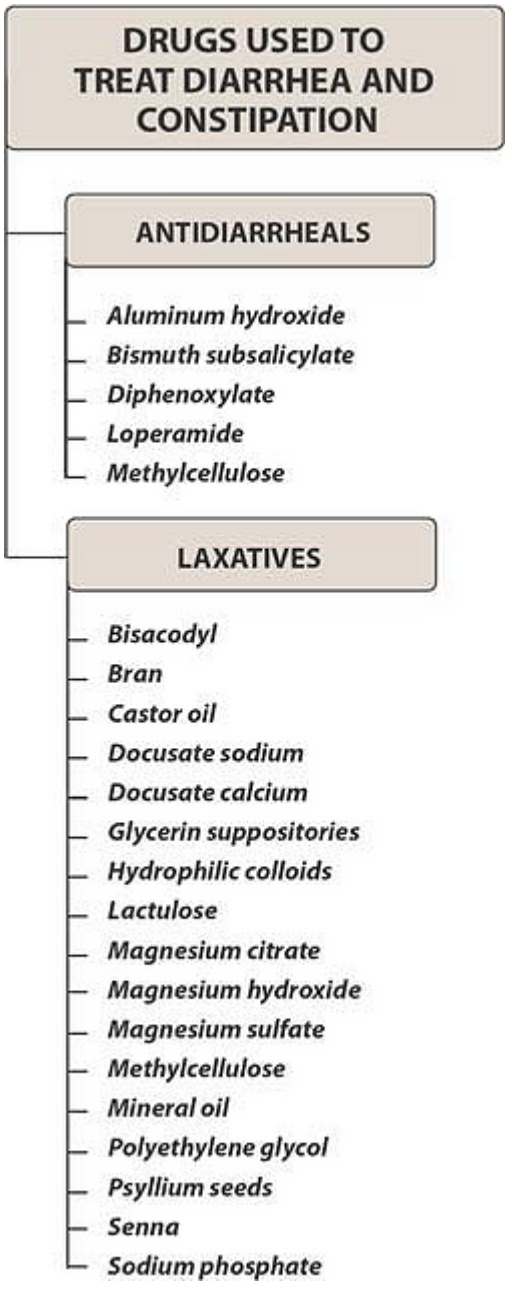



**Figure 28.11** Summary of drugs used to treat diarrhea and constipation.

## *B. Bulk laxatives*

The bulk laxatives include hydrophilic colloids (from indigestible parts of fruits and vegetables). They form gels in the large intestine, causing water retention and intestinal distension, thereby increasing peristaltic activity. Similar actions are produced by *methylcellulose, psyllium seeds*, and *bran*. They should be used cautiously in patients who are bed-bound, due to the potential for intestinal obstruction.

## *C. Saline and osmotic laxatives*

Saline cathartics, such as *magnesium citrate, magnesium sulfate, sodium phosphate*, and *magnesium hydroxide*,

are nonabsorbable salts (anions and cations) that hold water in the intestine by osmosis and distend the bowel, increasing intestinal activity and producing defecation in a few hours. Electrolyte solutions containing *polyethylene glycol* (PEG) are used as colonic lavage solutions to prepare the gut for radiologic or endoscopic procedures. PEG powder for solution is available as a prescription and also an over-the-counter laxative. *Lactulose* is a semisynthetic disaccharide sugar that also acts as an osmotic laxative. It is a product that cannot be hydrolyzed by intestinal enzymes. Oral doses are degraded in the colon by colonic bacteria into lactic, formic, and acetic acids. This increases osmotic pressure, thereby accumulating fluid, distending the colon, creating a soft stool, and causing defecation.

## *D. Stool softeners (emollient laxatives or surfactants)*

Surface-active agents that become emulsified with the stool produce softer feces and ease passage. These include *docusate sodium, docusate calcium*, and *docusate potassium*. They may take days to become effective. They should not be taken together with mineral oil because of the potential for absorption of the mineral oil.

## *E. Lubricant laxatives*

*Mineral oil* and *glycerin suppositories* are considered to be lubricants. They facilitate the passage of hard stools. Mineral oil should be taken orally in an upright position to avoid its aspiration and potential for lipid or lipoid pneumonia.



## Study Questions

Choose the ONE best answer.

**28.1 A 68-year-old patient with cardiac failure is diagnosed with ovarian cancer. She is started on cisplatin but becomes nauseous and suffers from severe vomiting. Which of the following medications would be most effective to counteract the emesis in this patient without exacerbating her cardiac problem?**

A. Droperidol.

B. Dolasetron.

C. Prochlorperazine.

D. Dronabinol.

E. Ondansetron.

View Answer

**28.2 A 45-year-old woman is distressed by the dissolution of her marriage. She has been drinking heavily and overeating. She complains of persistent heartburn and an unpleasant, acid-like taste in her mouth. The clinician suspects gastrointestinal reflux disease and advises her to raise the head of her bed 6 to 8 inches, not to eat for several hours before retiring, to avoid alcohol, and to eat smaller meals. Two weeks later, she returns and says the symptoms have subsided slightly but still are a concern. The clinician prescribes:**

A. An antacid such as aluminum hydroxide.

B. Dicyclomine.

C. An antianxiety agent such as alprazolam.

D. Esomeprazole.

View Answer

**28.3 Which of the following agents interferes with most of the cytochrome P450 enzymes and, thus, leads to**

**many drug-drug interactions?**

A. Famotidine.

B. Omeprazole.

C. Cimetidine.

D. Sucralfate.

E. Ondansetron.

View Answer

**28.4 A couple celebrating their fortieth wedding anniversary is given a trip to Peru to visit Machu Picchu. Due to past experiences while traveling, they ask their doctor to prescribe an agent for diarrhea. Which of the following would be effective?**

A. Omeprazole.

B. Loperamide.

C. Famotidine.

D. Lorazepam.

View Answer

**Editors:** **Finkel, Richard; Clark, Michelle A.; Cubeddu, Luigi X.**
**Title:** *Lippincott's Illustrated Reviews: Pharmacology, 4th Edition*





# Chapter 29

# Other Therapies

## I. Drugs Used to Treat Erectile Dysfunction

Erectile dysfunction (ED)â€”that is, the inability to maintain penile erection for the successful performance of sexual activityâ€”has many physical and psychological causes, including vascular disease, diabetes, medications, depression, and sequelae to prostatic surgery. ED is estimated to affect more than 30 million men in the United States. Previous therapies have included penile implants, intrapenile injections of *alprostadil*, and intraurethral suppositories of *alprostadil*. However, because of their efficacy, ease of use, and safety, oral phosphodiesterase (PDE) inhibitors are now considered to be first-line therapy for men with ED. Three PDE-5 inhibitors, *sildenafil* [sil-DEN-a-fil], *vardenafil* [var-DEN-na-fil], and *tadalafil* [ta-DAL-a-fil], are approved for the treatment of ED (Figure 29.1).


**Figure 29.1** Summary of drugs used in the treatment of erectile dysfunction, osteoporosis, and obesity.

## *A. PDE-5 inhibitors*

All three PDE-5 inhibitors are equally effective in treating ED, and the adverse effect profiles of the drugs are similar. However, the duration of action of PDE-5 inhibitors differ, as do the effects of food on the rates of drug absorption.

1. **Mechanism of penile erection:** Sexual stimulation results in smooth muscle relaxation of the corpus cavernosum, increasing the inflow of blood (Figure 29.2). The mediator of this response is nitric oxide (NO). NO activates guanylyl cyclase, which forms cyclic guanosine monophosphate (cGMP) from guanosine triphosphate. cGMP produces smooth muscle relaxation through a reduction in the intracellular $Ca^{2+}$ concentration. The duration of action of cyclic nucleotides is controlled by the action of PDE. At least 11 isozymes of PDE have been characterized. *Sildenafil, vardenafil*, and *tadalafil* inhibit PDE-5, the isozyme responsible for

degradation of cGMP in the corpus cavernosum. The action of PDE-5 inhibitors is to increase the flow of blood into the corpus cavernosum at any given level of sexual stimulation (Figure 29.3). At recommended doses, PDE-5 inhibitors have no effect in the absence of sexual stimulation. PDE-5 inhibitors are indicated for the treatment of ED due to organic or psychogenic causes.

2. **Pharmacokinetics:** *Sildenafil* and *vardenafil* have similar pharmacokinetic properties. Both drugs should be taken approximately 1 hour prior to anticipated sexual activity, with erectile enhancement observed up to 4 hours after administration. Thus, administration of *sildenafil* and *vardenafil* must be timed so that sexual activity occurs within 1 to 4 hours. The absorption of both drugs



is delayed by consumption of food, particularly high-fat meals. By contrast, *tadalafil* has a slower onset of action (Figure 29.4) but a significantly longer half-life of approximately 18 hours, resulting in enhanced erectile function for at least 36 hours. Furthermore, the absorption of *tadalafil* is not clinically influenced by food. The timing of sexual activity is less critical for *tadalafil* because of its prolonged duration of effect. All three PDE-5 inhibitors are metabolized by the cytochrome P450 3A4 (CYP3A4) enzyme. Dosage adjustments are recommended in patients with hepatic dysfunction.

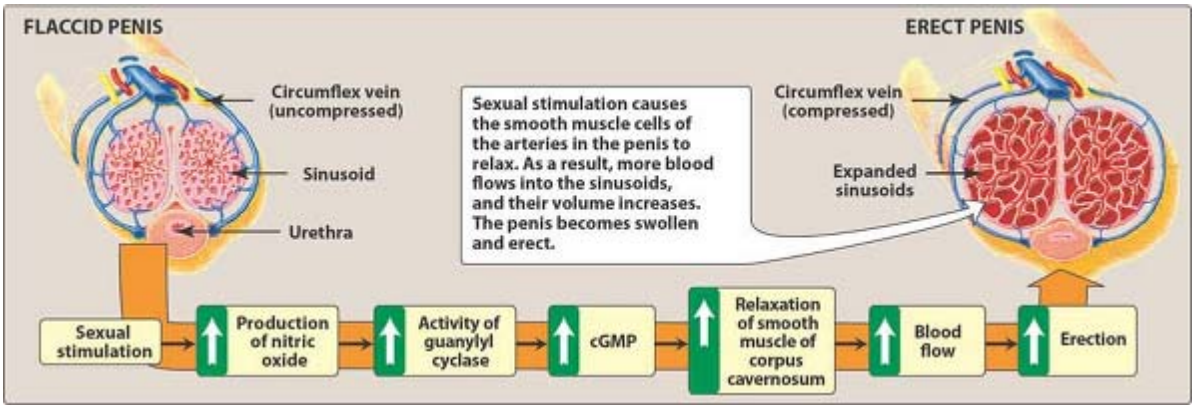



**Figure 29.2** Mechanism of penile erection. cGMP = cyclic guanosine monophosphate.

3. **Adverse effects:** The most frequent adverse effects reported for PDE inhibitors are headache, flushing, dyspepsia, and nasal congestion. These effects are generally mild, and men with ED rarely discontinue treatment because of side effects. Disturbances in color vision (loss of blue/green discrimination) occur with *sildenafil*, probably because of inhibition of PDE-6 (a PDE found in the retina that is important in color vision). *Tadalafil* does not appear to disrupt PDE-6, and reports of changes in color vision have been rare with this medication. The incidence of these reactions appears to be dose dependent. Because there is an inherent cardiac risk associated with sexual activity, PDE-5 inhibitors should be used with caution in patients with a history of cardiovascular disease (CVD) or those with strong risk factors for CVD. PDE-5 inhibitors should not be used more than once per day.

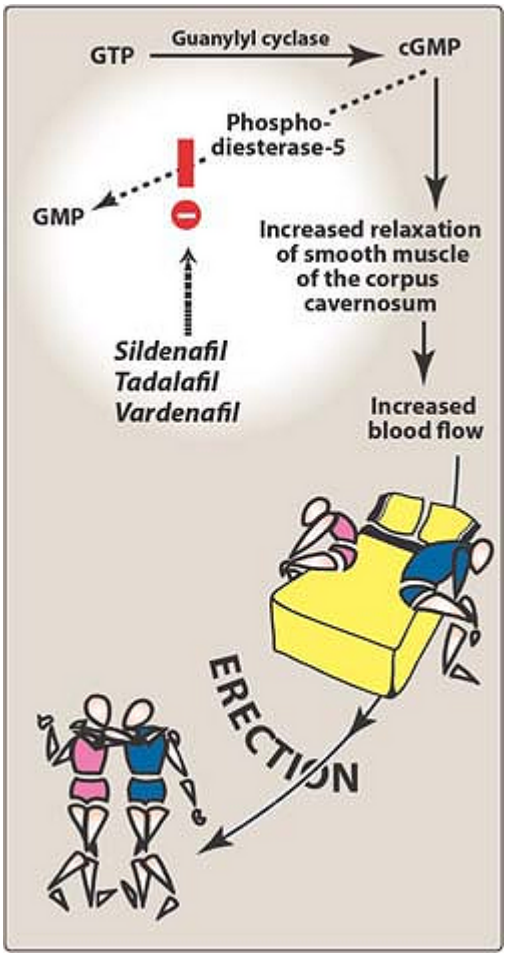



**Figure 29.3** Effect of phosphodiesterase inhibitors on cyclic guanosine monophosphate (cGMP) levels in the smooth muscle of the corpus cavernosum. GTP = guanosine triphosphate.

4. **Drug interactions:** Because of the ability of PDE inhibitors to potentiate the activity of NO, administration of these agents in patients taking any form of organic nitrates is contraindicated. PDE-5 inhibitors may produce additive blood pressureâ€"lowering effects when used in patients taking Î±-adrenergic antagonists (used to alleviate symptoms associated with benign prostatic hyperplasia). The combination of PDE-5 inhibitors and Î±-adrenergic antagonists should be used with caution. Patients should be on a stable dose of the Î±-adrenergic antagonist prior to the initiation of the PDE-5 inhibitor, and the PDE-5 inhibitor should be started at a low dose if this combination is to be used. Doses of PDE-5 inhibitors may need to be reduced in the presence of potent inhibitors of CYP3A4, such as protease inhibitors, *clarithromycin*, and *erythromycin.*



## II. Drugs Used to Treat Osteoporosis

Osteoporosis is a condition of skeletal fragility due to progressive loss of bone mass. It occurs in the elderly of both sexes but is most pronounced in postmenopausal women. Osteoporosis is characterized by frequent bone fractures, which are a major cause of disability among the elderly. Nondrug strategies to reduce bone loss in postmenopausal women include a diet adequate in calcium and vitamin D, weight-bearing exercise, and cessation of smoking. In addition, patients at risk for osteoporosis should avoid drugs that increase bone loss, such as glucocorticoids. Figure 29.5 shows the changes in bone morphology seen in osteoporosis.

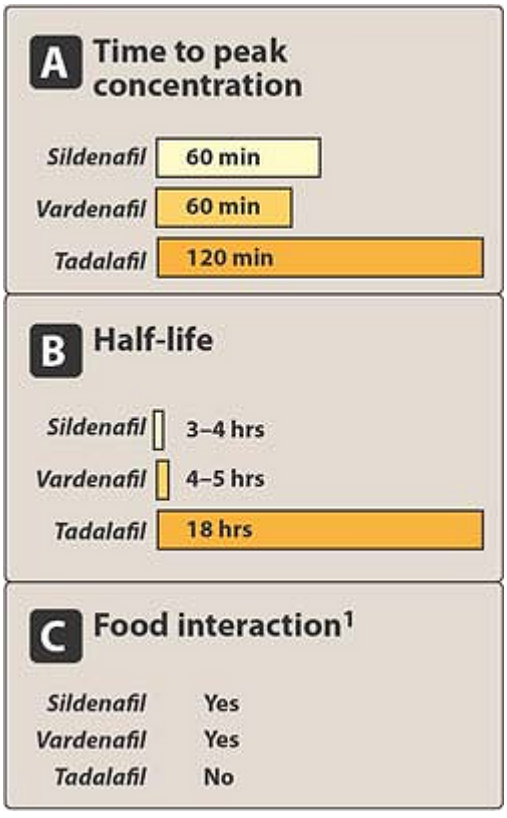



**Figure 29.4** Some properties of phosphodiesterase inhibitors. [1]Delay in time to reach peak drug concentration when taken with high-fat foods.

## *A. Bisphosphonates*

These analogs of pyrophosphate, including *etidronate* [e-TID-row-nate], *risedronate* [rih-SED-row-nate], *alendronate* [a-LEND-row-nate], *ibandronate* [eye-BAN-dro-nate], *pamidronate* [pah-MID-row-nate], *tiludronate* [till-UH-droe-nate], and *zoledronic* [zole-DROE-nick] *acid*, comprise an important drug group used for the treatment of disorders of bone remodeling, such as osteoporosis and Paget's disease, as well as for treatment of bone metastases and hypercalcemia of malignancy. In addition, *alendronate, risedronate,* and *ibandronate* have been approved for the prevention and treatment of osteoporosis. *Zoledronic acid* is also approved for the treatment of postmenopausal osteoporosis. The bisphosphonates decrease osteoclastic bone resorption via several mechanisms, including 1) inhibition of the osteoclastic proton pump necessary for dissolution of hydroxyapatite, 2) decrease in osteoclastic formation/activation, 3) increase in osteoclastic apoptosis (programmed cell death), and 4) inhibition of the cholesterol biosynthetic pathway important for osteoclast function. The relative importance of the mechanisms may differ among the individual bisphosphonates. The decrease in osteoclastic bone resorption results in a small but significant net gain in bone mass in osteoporotic patients, because the bone-forming osteoblasts are not inhibited. The beneficial effects of *alendronate* persist over several years of therapy (Figure 29.6), but discontinuation results in a gradual loss of its effects. Treatment with bisphosphonates decreases the risk of bone fracture in patients with osteoporosis. Bisphosphonates are preferred agents for the prevention and treatment of postmenopausal osteoporosis.

1. **Pharmacokinetics:** *Alendronate, risedronate*, and *ibandronate* are orally active agents for osteoporosis, although less than one percent of the administered dose is absorbed. *Alendronate* and *risedronate* may be dosed once daily or once weekly, whereas *ibandronate* is administered once monthly. Food significantly

interferes with absorption. Bisphosphonates should be administered with 6 to 8 ounces of plain water at least 30 minutes (60 minutes for *ibandronate*) before eating breakfast or taking other medications. The bisphosphonates are rapidly cleared from the plasma, primarily because they avidly bind to the hydroxyapatite mineral of bone. Once bound to bone, they are cleared over a period of hours to years. Elimination from the body is primarily through renal clearance, and the bisphosphonates should not be given to individuals with severe renal impairment. For patients unable to tolerate oral bisphosphonates, intravenous *ibandronate* and *zoledronic acid* are alternative treatments for osteoporosis. Intravenous *ibandronate* is administered once every 3 months, and *zoledronic acid* is administered once yearly.

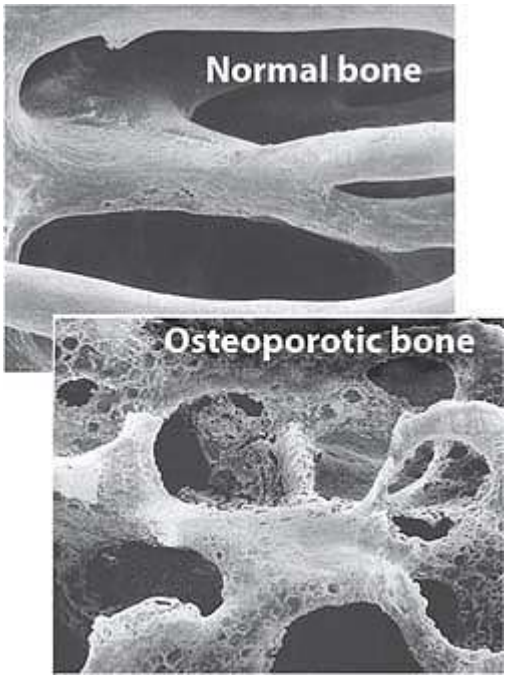



**Figure 29.5** Changes in bone morphology seen in osteoporosis.



2. **Adverse effects:** These include diarrhea, abdominal pain, and musculoskeletal pain. *Alendronate, risedronate, and ibandronate* are associated with esophagitis and esophageal ulcers. To minimize the risk of esophageal irritation, patients should remain upright for at least 30 minutes (60 minutes for *ibandronate*) after taking a bisphosphonate. Osteonecrosis of the jaw has been reported with bisphosphonates. *Etidronate* is the only member of the class that causes osteomalacia following long-term, continuous administration. Figure 29.7 shows the relative potencies of the bisphosphonates.

## *B. Selective estrogen-receptor modulators*

Estrogen replacement is an effective therapy for the prevention of postmenopausal bone loss. When initiated in the immediate postmenopausal period, estrogen therapy prevents osteoporosis and reduces the risk of hip fracture. [Note: Estrogen-progestogen therapy is no longer the therapy of choice for the treatment of osteoporosis in postmenopausal women because of increased risk of breast cancer, stroke, venous thromboembolism, and coronary disease.] *Raloxifene* [rah-LOX-ih-feen]is a selective estrogen-receptor modulator approved for the prevention and treatment of osteoporosis. It increases bone density without increasing the risk of endometrial cancer. In addition, *raloxifene* may reduce the risk of invasive breast cancer. *Raloxifene* is a first-line alternative for postmenopausal osteoporosis in women who are intolerant to bisphosphonates. *Raloxifene* reduces serum total and low-density

lipoprotein cholesterol concentrations. The risk of venous thromboembolism appears to be comparable to that with estrogen. Other adverse effects include hot flashes and leg cramps.

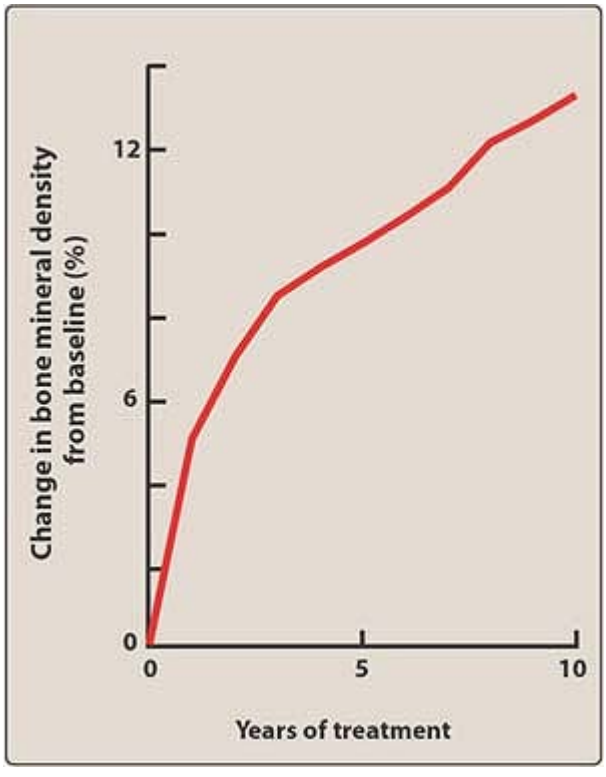



**Figure 29.6** Effect of *alendronate* therapy on the bone mineral density of the lumbar spine.

## *C. Calcitonin*

Salmon *calcitonin* [cal-SIH-toe-nin], administered intranasally, is effective and well tolerated in the treatment of postmenopausal osteoporosis. The drug reduces bone resorption, but it is less effective than the bisphosphonates. A unique property of calcitonin is the relief of pain associated with osteoporotic fracture. Therefore, calcitonin may be beneficial in patients who have recently suffered a vertebral fracture. Common adverse effects of the intranasal formulation include rhinitis and other nasal symptoms. A parenteral formulation of *calcitonin* is available for intramuscular or subcutaneous injection, but it is infrequently used in the treatment of osteoporosis. Resistance to the effects of *calcitonin* has been observed with long-term use in patients with Paget's disease .

| Bisphosphonate | Antiresorptive activity |
|---|---|
| *Etidronate* | 1 |
| *Pamidronate* | 100 |
| *Alendronate* | 1000 |
| *Risedronate* | 5,000 |
| *Ibandronate* | 10,000 |
| *Zoledronic acid* | 10,000 |

**Figure 29.7** Antiresorptive activity of some bisphosphonates.

### *D. Teriparatide*

*Teriparatide* [ter-ih-PAR-a-tide] is a recombinant segment of human parathyroid hormone that is administered subcutaneously for the treatment of osteoporosis. Parathyroid hormone given continuously leads to dissolution of bone, but when it is given subcutaneously once daily, bone formation is the predominant effect. It increases spinal bone density and decreases the risk of vertebral fracture. *Teriparatide* is the first approved treatment for osteoporosis that stimulates bone formation. Other drugs approved for this indication inhibit bone resorption. It is also effective in the treatment of glucocorticoid-induced osteoporosis. *Teriparatide* has been associated with an increased risk of osteosarcoma in rats. The safety and efficacy of this agent have not been evaluated beyond 24 months. *Teriparatide* should be reserved for patients at high risk of fractures or who cannot tolerate other osteoporosis therapies.



## III. Drugs Used to Treat Obesity

Two classes of drugs are used in treating obesity: the anorexiants (appetite suppressants) *phentermine, diethylpropion*, and *sibutramine*, and a lipase inhibitor, *orlistat*. *Phentermine* and *diethylpropion* are indicated for short-term management of obesity. *Sibutramine* and *orlistat* have been approved for up to 2 and 4 years of use, respectively.

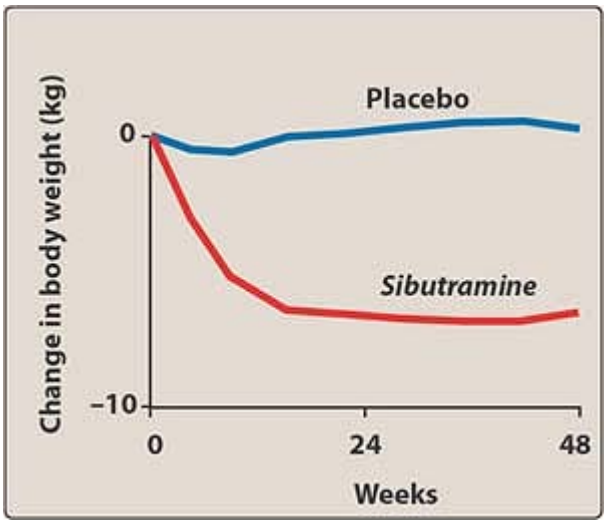



**Figure 29.8** Effect of *sibutramine* treatment on body weight.

## *A. Phentermine, diethylpropion, and sibutramine*

*Phentermine* [FEN-ter-meen] exerts its pharmacologic action by increasing release of norepinephrine and dopamine from the nerve terminals and by inhibiting reuptake of these neurotransmitters, thereby increasing levels of neurotransmitters in the brain. *Diethylpropion* [dye-eth-ill-PROE-pee-on] has similar effects on norepinephrine. S*ibutramine* [si-BYOO-tra-meen] inhibits central reuptake of serotonin, norepinephrine, and to a lesser extent, dopamine. Unlike the other agents, *sibutramine* does not cause the release of neurotransmitters. Figure 29.8 shows the effect of s*ibutramine* treatment.

1. **Pharmacokinetics:** Limited information is available regarding the pharmacokinetics of *phentermine.* The duration of activity is dependent on the formulation, and the primary route of excretion is via the kidney. *Diethylpropion* is rapidly absorbed and undergoes extensive first-pass metabolism. Many of the metabolites are active. *Diethylpropion* and its metabolites are excreted mainly via the kidney. The half-life of the metabolites is 4 to 8 hours. *Sibutramine* undergoes first-pass demethylation to active metabolites, which are primarily responsible for its pharmacologic effects. The active metabolites are biotransformed further in the liver and excreted primarily in the urine. The half-life of the active metabolites is about 15 hours.

2. **Adverse effects and contraindications:** All of the appetite suppressants are Schedule IV controlled agents due to potential for dependence or abuse. Dry mouth, headache, insomnia, and constipation are common problems. Heart rate and blood pressure may be increased with these agents, and they should be avoided in patients with a history of hypertension, CVD, arrhythmias, congestive heart failure, or stroke. In addition, *phentermine* has been associated with heart valve disorders and pulmonary hypertension. Concomitant use of appetite suppressants and monoamine oxidase inhibitors should be avoided. *Sibutramine* should also be avoided in patients who are taking selective serotonin inhibitors such as *fluoxetine*, serotonin agonists for migraine such as *sumatriptan*, as well as *lithium, dextromethorphan*, or *pentazocine*. Drug interactions can occur when *sibutramine* is administered with drugs that inhibit CYP3A4, such as *ketoconazole, erythromycin*, and *cimetidine*. The clinical relevance of these interactions is not known.

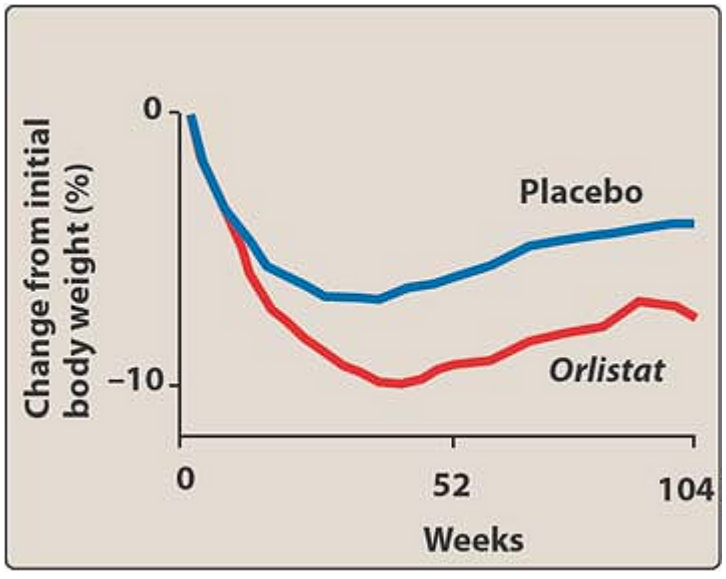



**Figure 29.9** Effect of *orlistat* treatment on body weight.

## *B. Orlistat*

*Orlistat* [OR-lih-stat] is the first drug in a class of antiobesity drugs known as lipase inhibitors. *Orlistat* is a pentanoic acid ester that inhibits gastric and pancreatic lipases, thus decreasing the breakdown of dietary fat into smaller molecules that can be absorbed. Fat absorption is decreased by about 30 percent. The loss of calories is the main cause of weight loss, but adverse gastrointestinal effects associated with the drug may also contribute to a decreased intake of food. *Orlistat* is administered



three times daily with meals. Figure 29.9 shows the effects of *orlistat* treatment. The most common adverse effects associated with *orlistat* are gastrointestinal symptoms, such as oily spotting, flatulence with discharge, fecal urgency, and increased defecation. It interferes with the absorption of fat-soluble vitamins and Î²-carotene. Thus, patients should be advised to take a multivitamin supplement that contains vitamins A, D, E, and K and also Î²-carotene. The vitamin supplement should not be taken within 2 hours of orlistat. *Orlistat* is contraindicated in patients with chronic malabsorption syndrome or cholestasis.

## Study Questions

Choose the ONE best answer.

**29.1 A 66-year-old man complained of decreased libido and difficulty maintaining an erection. He is concerned about the use of drugs to restore sexual function, particularly about the need to time therapy with anticipated sexual activity. Which one of the following therapeutic options is indicated for this patient?**

A. Sildenafil is indicated because of its long duration of action.

B. Vardenafil is indicated because its absorption is not affected by food.

C. Tadalafil is indicated because of its long duration of action

D. Tadalafil is not indicated because of its short duration of action.

View Answer

**29.2 Which of the following drugs causes osteomalacia and bone pain when administered chronically?**

A. Risedronate.

B. Calcitonin.

C. Teriparatide.

D. Calcitriol.

E. Etidronate.

View Answer

**29.3 A 58-year-old male has been effectively treated for Paget's disease for approximately 6 months. He is now beginning to experience renewed bone pain and radiologic evidence of advancing disease. Which of the following drugs is most likely to have resulted in this failure of therapy?**

A. Alendronate.

B. Calcitonin.

C. Dihydrotachysterol.

D. Ergocalciferol.

E. Raloxifene.

View Answer

**Editors:** **Finkel, Richard; Clark, Michelle A.; Cubeddu, Luigi X.**
**Title:** *Lippincott's Illustrated Reviews: Pharmacology, 4th Edition*





# Chapter 30

# Principles of Anti-microbial Therapy

## I. Overview

Antimicrobial therapy takes advantage of the biochemical differences that exist between microorganisms and human beings. Antimicrobial drugs are effective in the treatment of infections because of their selective toxicity; that is, they have the ability to injure or kill an invading microorganism without harming the cells of the host. In most instances, the selective toxicity is relative rather than absolute, requiring that the concentration of the drug be carefully controlled to attack the microorganism while still being tolerated by the host.

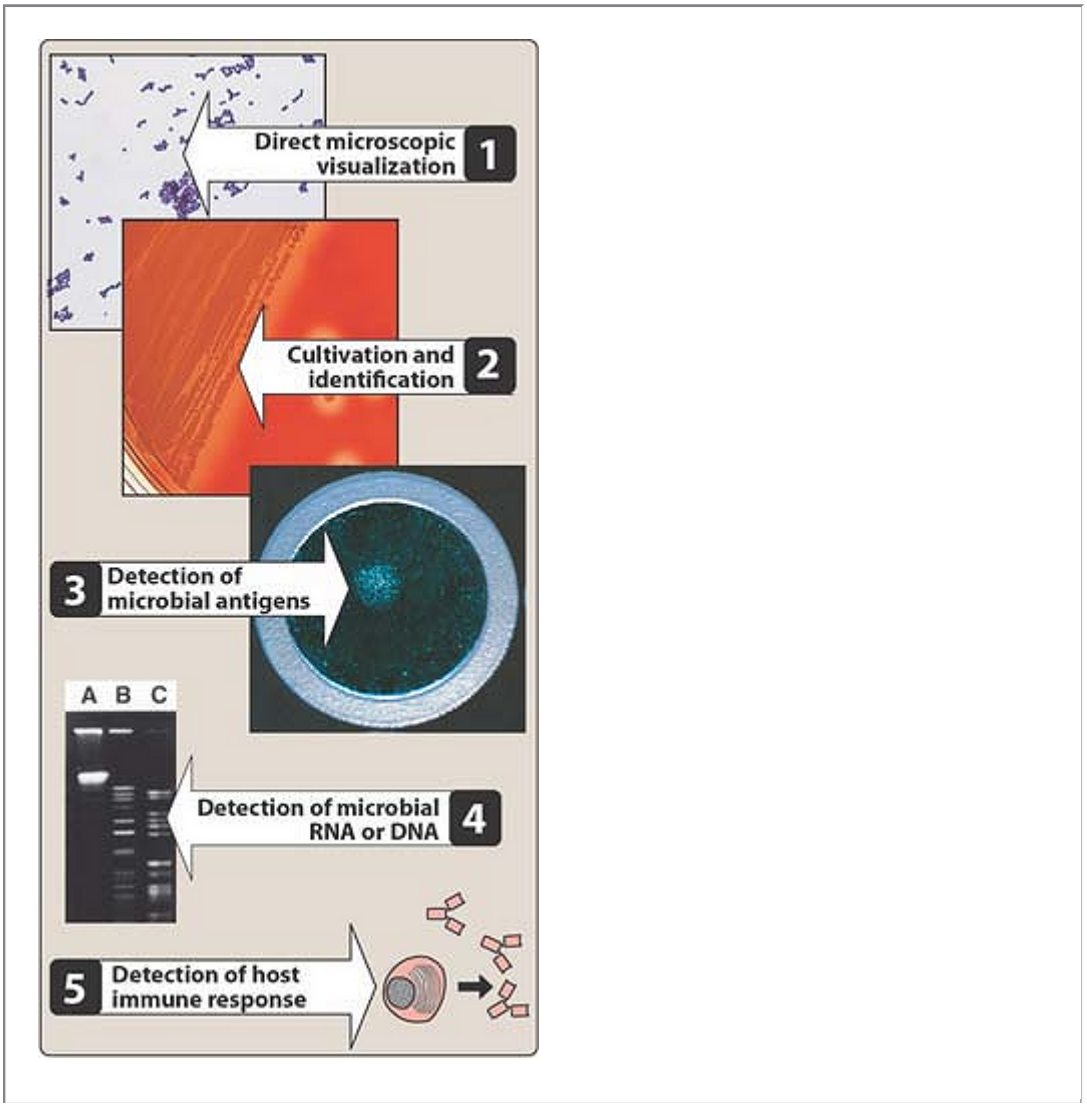


**Figure 30.1** Some laboratory techniques that are useful in the diagnosis of microbial diseases.

## II. Selection of Antimicrobial Agents

Selection of the most appropriate antimicrobial agent requires knowledge of 1) the organism's identity, 2) the organism's susceptibility to a particular agent, 3) the site of the infection, 4) patient factors, 5) the safety of the agent, and 6) the cost of therapy. However, some critically ill patients require empiric therapyâ€"that is, immediate administration of drug(s) prior to bacterial identification and susceptibility testing.

### *A. Identification of the infecting organism*

Characterization of the organism is central to selection of the proper drug. A rapid assessment of the nature of the pathogen can sometimes be made on the basis of the Gram stain, which is particularly useful in identifying the presence and morphologic features of microorganisms in body fluids that are normally sterile (cerebrospinal fluid [CSF], pleural fluid, synovial fluid, peritoneal fluid, and urine). However, it is generally necessary to culture the infective organism to arrive at a conclusive diagnosis and to determine the susceptibility of the bacteria to antimicrobial agents. Thus, it is essential to obtain a sample culture of the organism prior to initiating treatment. Definitive identification of the infecting organism may require other laboratory techniques, such as detection of microbial antigens, microbial DNA



or RNA, or detection of an inflammatory or host immune response to the microorganism (Figure 30.1).[1]

### *B. Empiric therapy prior to identification of the organism*

Ideally, the antimicrobial agent used to treat an infection is selected after the organism has been identified and its drug susceptibility established. However, in the critically ill patient, such a delay could prove fatal, and immediate empiric therapy is indicated.

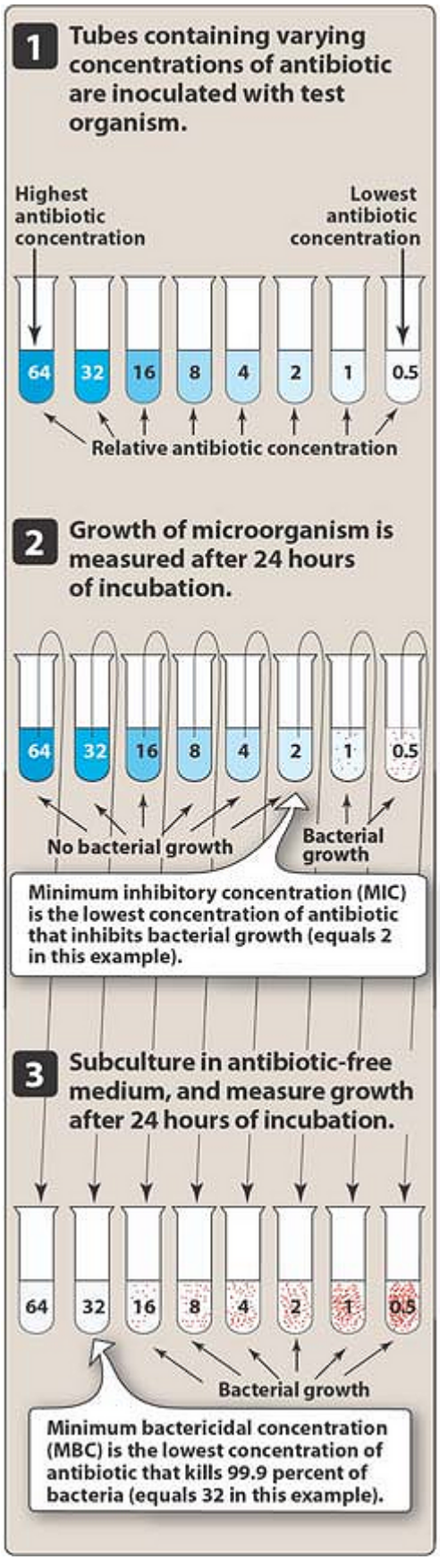

1
Tubes containing varying concentrations of antibiotic are inoculated with test organism.
Highest antibiotic concentration
Lowest antibiotic concentration
64
32
16
8
4
2
1
0.5
Relative antibiotic concentration
2
Growth of microorganism is measured after 24 hours of incubation.
64
32
16
8
4
2
1
0.5
No bacterial growth
Bacterial growth
Minimum inhibitory concentration (MIC) is the lowest concentration of antibiotic that inhibits bacterial growth (equals 2 in this example).
3
Subculture in antibiotic-free medium, and measure growth after 24 hours of incubation.
64
32
16
8
4
2
1
0.5
Bacterial growth
Minimum bactericidal concentration (MBC) is the lowest concentration of antibiotic that kills 99.9 percent of bacteria (equals 32 in this example).

**Figure 30.2** Determination of minimum inhibitory concentration (MIC) and minimum bactericidal concentration (MBC) of an antibiotic.

1. **Timing:** Acutely ill patients with infections of unknown originâ€"for example, a neutropenic patient (one who has a reduction in neutrophils, predisposing the patient to infections), or a patient with severe headache, a rigid neck, and sensitivity to bright lights (symptoms characteristic of meningitis)â€"require immediate treatment. Therapy is initiated after specimens for laboratory analysis have been obtained but before the results of the culture are available.
2. **Selecting a drug:** The choice of drug in the absence of susceptibility data is influenced by the site of infection and the patient's history (for example, whether the infection was hospital- or community-acquired, whether the patient is immunocompromised, as well as the patient's travel record and age). Broad-spectrum therapy may be needed initially for serious infections when the identity of the organism is unknown or the site makes a polymicrobial infection likely. The choice of agents may also be guided by known association of particular organisms with infection in a given clinical setting. For example, a gram-positive coccus in the spinal fluid of a newborn infant is unlikely to be Streptococcus pneumoniae (pneumococcus) and most likely to be Streptococcus agalactiae (Group B), which is sensitive to *penicillin G*. By contrast, a gram-positive coccus in the spinal fluid of a 40-year-old patient is most likely to be S. pneumoniae. This organism is frequently resistant to *penicillin G* and often requires treatment with a third-generation cephalosporin (such as *cefotaxime* or *ceftriaxone*) or *vancomycin*.

## *C. Determination of antimicrobial susceptibility of infective organisms*

After a pathogen is cultured, its susceptibility to specific antibiotics serves as a guide in choosing antimicrobial therapy. Some pathogens, such as Streptococcus pyogenes and Neisseria meningitidis, usually have predictable susceptibility patterns to certain antibiotics. In contrast, most gram-negative bacilli, enterococci, and staphylococcal species often show unpredictable susceptibility patterns to various antibiotics and require susceptibility testing to determine appropriate antimicrobial therapy. The minimum inhibitory and bactericidal concentrations of a drug can be experimentally determined (Figure 30.2).

1. **Bacteriostatic vs. bactericidal drugs:** Antimicrobial drugs are classified as either bacteriostatic or bactericidal. Bacteriostatic drugs arrest the growth and replication of bacteria at serum levels achievable in the patient, thus limiting the spread of infection while the body's immune system attacks, immobilizes, and eliminates the pathogens. If the drug is removed before the immune system has



scavenged the organisms, enough viable organisms may remain to begin a second cycle of infection. Bactericidal drugs kill bacteria at drug serum levels achievable in the patient. Because of their more aggressive antimicrobial action, these agents are often the drugs of choice in seriously ill patients. Figure 30.3 shows a laboratory experiment in which the growth of bacteria is arrested by the addition of a bacteriostatic agent. Note that viable organisms remain even in the presence of the bacteriostatic drug. By contrast, addition of a bactericidal agent kills bacteria, and the total number of viable organisms decreases. Although practical, this classification may be too simplistic, because it is possible for an antibiotic to be bacteriostatic for one organism and bactericidal for another. For example, *chloramphenicol* is bacteriostatic against gram-negative rods and is bactericidal against other organisms, such as S. pneumoniae.

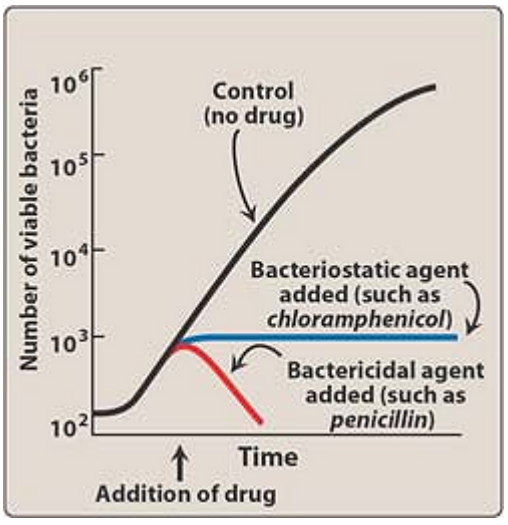



**Figure 30.3** Effects of bactericidal and bacteriostatic drugs on the growth of bacteria in vitro.

2. **Minimum inhibitory concentration:** To determine the minimum inhibitory concentration (MIC), tubes containing serial dilutions of an antibiotic are inoculated with the organism whose susceptibility is to be tested (see Figure 30.2). The tubes are incubated and later observed to determine the MICâ€"that is, the lowest concentration of antibiotic that inhibits bacterial growth. To provide effective antimicrobial therapy, the clinically obtainable antibiotic concentration in body fluids should be greater than the MIC. [Note: This assay is now done automatically using microtiter plates.]

3. **Minimum bactericidal concentration:** This quantitative assay determines the minimum concentration of antibiotic that kills the bacteria under investigation. The tubes that show no growth in the MIC assay are subcultured into antibiotic-free media. The minimum bactericidal concentration is the lowest concentration of antimicrobial agent that results in a 99.9 percent decline in colony count after overnight broth dilution incubations (see Figure 30.2).

## *D. Effect of the site of infection on therapy: The blood-brain barrier*

Adequate levels of an antibiotic must reach the site of infection for the invading microorganisms to be effectively eradicated. Capillaries with varying degrees of permeability carry drugs to the body tissues. For example, the endothelial cells comprising the walls of capillaries of many tissues have fenestrations (openings that act like windows) that allow most drugs not bound by plasma proteins to penetrate. However, natural barriers to drug delivery are created by the structures of the capillaries of some tissues, such as the prostate, the vitreous body of the eye, and the central nervous system (CNS). Of particular significance are the capillaries in the brain, which help to create and maintain the blood-brain barrier. This barrier is formed by the single layer of tile-like endothelial cells fused by tight junctions that impede entry from the blood to the brain of virtually all molecules, except those that are small and lipophilic (Figure 30.4). This barrier can be demonstrated by injecting dyes into laboratory animals. Dyes injected into the circulation stain all tissues except brain. However, the same dyes injected into the CSF stain only the cells of the CNS (Figure 30.5). The blood-brain barrier prevents the dye from escaping from the blood vessels in the brain, although they readily leak from the vessels throughout the rest of the body. The penetration and concentration of an antibacterial agent in the CSF is particularly influenced by the following:

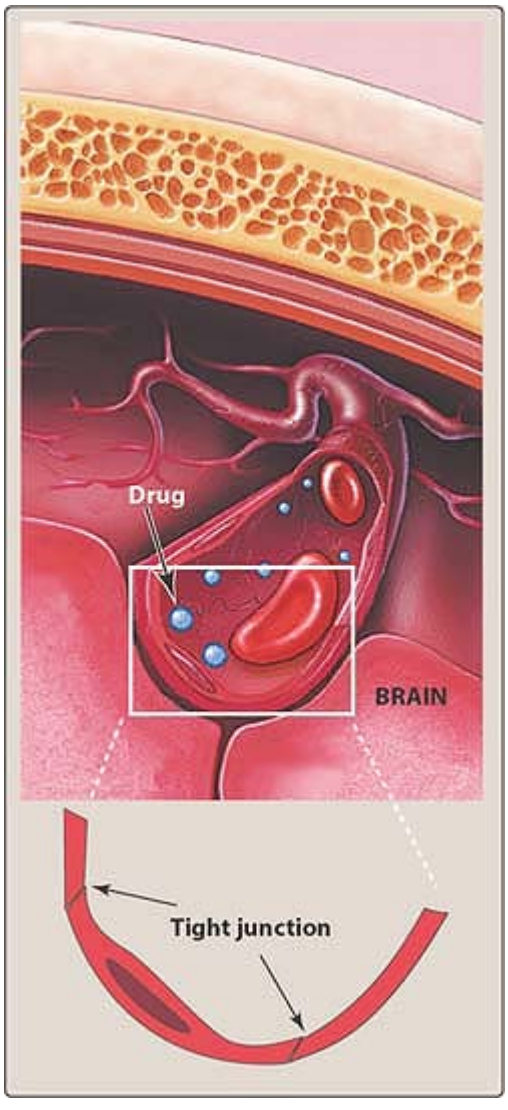



**Figure 30.4** Essential features of the blood-brain barrier.



1. **Lipid solubility of the drug:** All compounds without a specific transporter must pass intracellularly from the blood to the CSF (through two endothelial cell membranes; see Figure 30.5). The lipid solubility of a drug is therefore a major determinant of its ability to penetrate into the brain. For example, lipid-soluble drugs, such as the quinolones and *metronidazole*, have significant penetration into the CNS. In contrast, Î²-lactam antibiotics, such as *penicillin*, are ionized at physiologic pH and have low solubility in lipids. They therefore have limited penetration through the intact blood-brain barrier under normal circumstances. In infections such as meningitis, in which the brain becomes inflamed, the barrier does not function effectively, and local permeability is increased. Some Î²-lactam antibiotics can then enter the CSF in therapeutic amounts.
2. **Molecular weight of the drug:** A compound with a low molecular weight has an enhanced ability to cross the blood-brain barrier, whereas compounds with a high molecular weight (for example, *vancomycin*) penetrate poorly, even in the presence of meningeal inflammation.
3. **Protein binding of the drug:** A high degree of protein binding of a drug in the serum restricts its entry into the

CSF. Therefore, the amount of free (unbound) drug in serum, rather than the total amount of drug present, is important for CSF penetration.

## *E. Patient factors*

In selecting an antibiotic, attention must be paid to the condition of the patient. For example, the status of the patient's immune system, kidneys, liver, circulation, and age must be considered. In women, pregnancy or breast-feeding also affects selection of the antimicrobial agent.

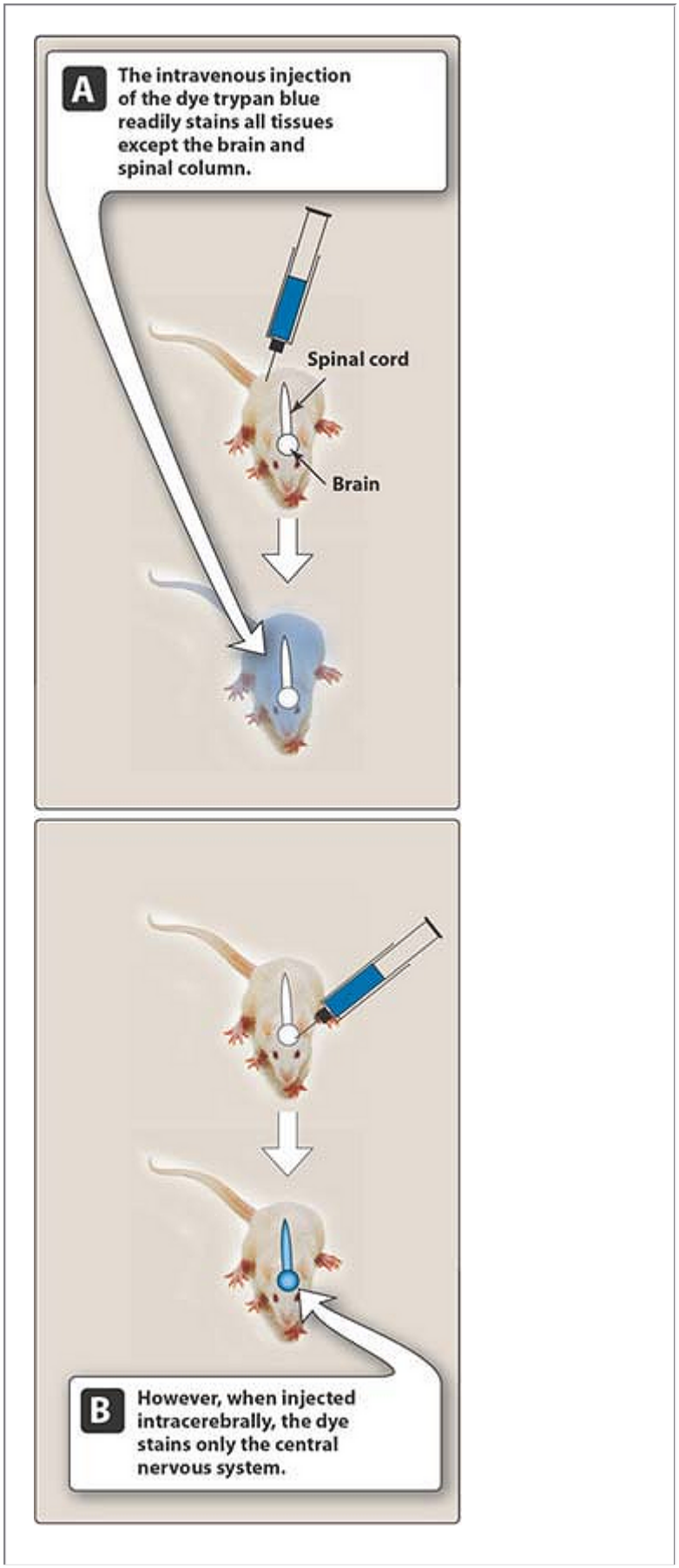

A
The intravenous injection of the dye trypan blue readily stains all tissues except the brain and spinal column.
Spinal cord
Brain
B
However, when injected intracerebrally, the dye stains only the central nervous system.

**Figure 30.5** Schematic representation of the blood-brain barrier.

1. **Immune system:** Elimination of infecting organisms from the body depends on an intact immune system. Antibacterial drugs decrease the microbial population (bactericidal) or inhibit further bacterial growth (bacteriostatic), but the host defense system must ultimately eliminate the invading organisms. Alcoholism, diabetes, infection with the human immunodeficiency virus, malnutrition, or advanced age can affect a patient's immunocompetence, as can therapy with immunosuppressive drugs. Higher-than-usual doses of bactericidal agents or longer courses of treatment are required to eliminate infective organisms in these individuals.

2. **Renal dysfunction:** Poor kidney function (10 percent or less of normal) causes accumulation in the body of antibiotics that ordinarily are eliminated by this route. This may lead to serious adverse effects unless drug accumulation is controlled by adjusting the dose or the dosage schedule of the antibiotic. Serum creatinine levels are frequently used as an index of renal function for adjustment of drug regimens.[2] However, direct monitoring of serum levels of some antibiotics (for example, aminoglycosides) is preferred to identify maximum and minimum values. Rising minimum values alert the physician to potential toxicity. [Note: The number of functioning nephrons



decreases with age. Thus, elderly patients are particularly vulnerable to accumulation of drugs eliminated by the kidneys. Antibiotics that undergo extensive metabolism or are excreted via the biliary route may be favored in such patients.]

3. **Hepatic dysfunction:** Antibiotics that are concentrated or eliminated by the liver (for example, *erythromycin* and *tetracycline*) are contraindicated in treating patients with liver disease.

4. **Poor perfusion:** Decreased circulation to an anatomic area, such as the lower limbs of a diabetic, reduces the amount of antibiotic that reaches that area, making infections notoriously difficult to treat.

5. **Age:** Renal or hepatic elimination processes are often poorly developed in newborns, making neonates particularly vulnerable to the toxic effects of *chloramphenicol* and sulfonamides. Young children should not be treated with tetracyclines, which affect bone growth.

6. **Pregnancy:** All antibiotics cross the placenta. Adverse effects to the fetus are rare, except the for tooth dysplasia and inhibition of bone growth encountered with the tetracyclines. However, some anthelmintics are embryotoxic and teratogenic. Aminoglycosides should be avoided in pregnancy because of their ototoxic effect on the fetus. Figure 30.6 summarizes the U.S. Food and Drug Administration (FDA) categories of antibiotic use during pregnancy. The drug examples listed in Figure 30.6 are not all inclusive; they merely represent an example from each category. This current U.S. Food and Drug Administration category system can be difficult to apply to combination medications with many active ingredients and does not take into consideration the potential for any drug interactions. Of course, all drugs should be used only during pregnancy under the supervision of a patient's physician. Moreover, clinicians should reference the most current literature before prescribing medications for pregnant patients, to stay up-to-date for risk assessment reasons.

7. **Lactation:** Drugs administered to a lactating mother may enter the nursing infant via the breast milk. Although the concentration of an antibiotic in breast milk is usually low, the total dose to the infant may be enough to cause problems.

| CATE-GORY | DESCRIPTION | DRUG |
|---|---|---|
| A | No human fetal risk or remote possibility of fetal harm | |
| B | No controlled studies show human risk; animal studies suggest potential toxicity | β-Lactams<br>β-Lactams with inhibitors<br>Cephalosporins<br>*Aztreonam*<br>*Clindamycin*<br>*Erythromycin*<br>*Azithromycin*<br>*Metronidazole*<br>*Nitrofurantoin*<br>Sulfonamides |
| C | Animal fetal toxicity demonstrated; human risk undefined | *Chloramphenicol*<br>Fluoroquinolones<br>*Clarithromycin*<br>*Trimethoprim*<br>*Vancomycin*<br>*Gentamicin*<br>*Trimethoprim-sulfa-methoxazole* |
| D | Human fetal risk present, but benefits outweigh risks | Tetracyclines<br>Aminoglycosides (except *gentamicin*) |
| X | Human fetal risk present but does not outweigh benefits; contraindicated in pregnancy | |

**Figure 30.6** United States Food and Drug Administration categories of antimicrobials and fetal risk.

## *F. Safety of the agent*

Many of the antibiotics, such as the penicillins, are among the least toxic of all drugs, because they interfere with a site unique to the growth of microorganisms. Other antimicrobial agents (for example, *chloramphenicol*) are less microorganism specific and are reserved for life-threatening infections because of the drug's potential for serious toxicity to the patient. [Note: As discussed above, safety is related not only to the inherent nature of the drug but also to patient factors that can predispose to toxicity.]

## *G. Cost of therapy*

Often, several drugs may show similar efficacy in treating an infection but vary widely in cost. Figure 30.7 illustrates the cost of some antibacterial agents showing similar efficacy in eradicating the gram-negative bacillus Helicobacter pylori from the gastric mucosa. None of these agents shows a clear therapeutic superiority; thus, a combination of



*metronidazole* with *bismuth subsalicylate* plus one other antibiotic is usually employed in the treatment of H.

pyloriâ€“induced peptic ulcers. Selecting *clarithromycin* instead as the drug of choice would clearly make a considerable cost impact.

## III. Route of Administration

The oral route of administration is chosen for infections that are mild and can be treated on an outpatient basis. In addition, economic pressures have prompted the use of oral antibiotic therapy in all but the most serious infectious diseases. In patients requiring a course of intravenous therapy initially, the switch to oral agents occurs as soon as possible. However, some antibiotics, such as *vancomycin*, the aminoglycosides, and *amphotericin B,* are so poorly absorbed from the gastrointestinal tract that adequate serum levels cannot be obtained by oral administration. Parenteral administration is used for drugs that are poorly absorbed from the gastrointestinal tract and for treatment of patients with serious infections, for whom it is necessary to maintain higher serum concentrations of antimicrobial agents than can be reliably obtained by the oral route.

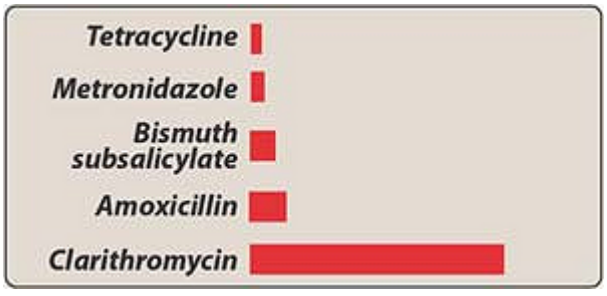



**Figure 30.7** Relative cost of some drugs used for the treatment of peptic ulcers causedby Helicobacter pylori.

## IV. Determinants of Rational Dosing

Rational dosing of antimicrobial agents is based on their pharmacodynamics (the relationship of drug concentrations to antimicrobial effects) as well as their pharmacokinetic properties (the absorption, distribution, and elimination of the drug by the body). Three important properties that have a significant influence on the frequency of dosing are concentration-dependent killing, time-dependent killing, and postantibiotic effect. Utilizing these properties to optimize antibiotic dosing regimens will improve clinical outcomes and possibly decrease the development of resistance.

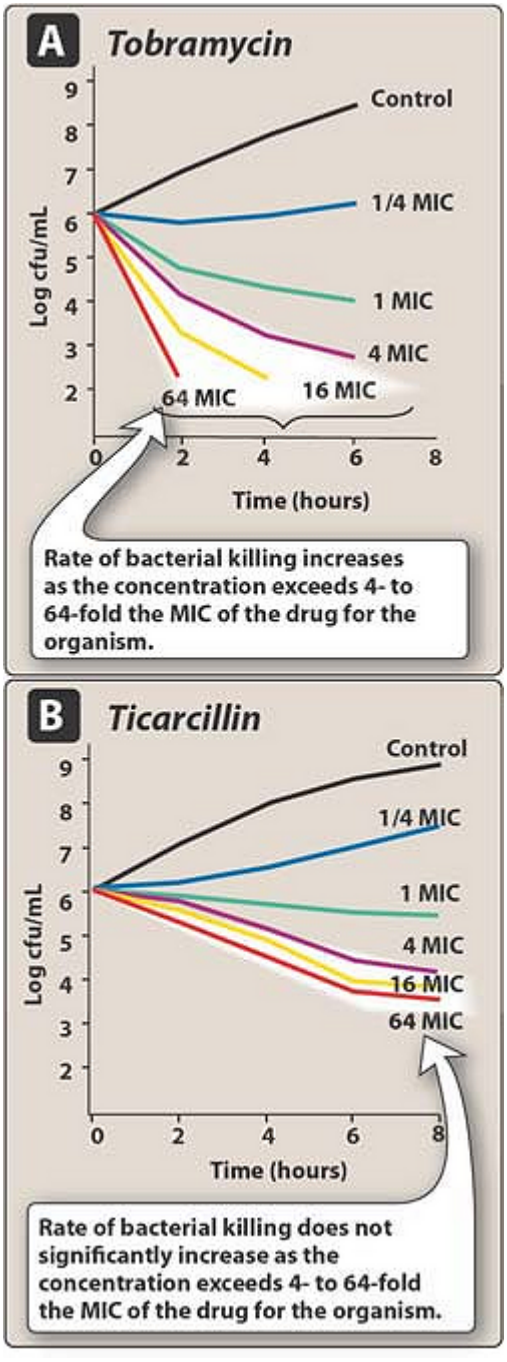



**Figure 30.8** A. Significant dose-dependent killing effect shown by tobramycin. B. Nonsignificant dose-dependent killing effect shown by ticarcillin. cfu = colony forming units; MIC = minimum inhibitory concentration.

## *A. Concentration-dependent killing*

Certain antimicrobial agents, including aminoglycosides, fluoroquinolones, and carbapenems show a significant increase in the rate of bacterial killing as the concentration of antibiotic increases from 4- to 64-fold the MIC of the drug for the infecting organism (Figure 30.8A). Giving drugs that exhibit this concentration-dependent killing by a

once-a-day bolus infusion achieves high peak levels, favoring rapid killing of the infecting pathogen.

### *B. Time-dependent (concentration-independent) killing*

By contrast, Î²-lactams, glycopeptides, macrolides, *clindamycin,* and *linezolid* do not exhibit this property; that is, increasing the concentration of antibiotic to higher multiples of the MIC does not significantly increase the rate of kill (Figure 30.8B). The clinical efficacy of antimicrobials that have a nonsignificant, dose-dependent killing effect is best predicted by the percentage of time that blood concentrations of a drug remain above the MIC. This effect is sometimes called concentration-independent or time-dependent killing. For example, for the penicillins and cephalosporins, dosing schedules that ensure blood levels greater than the MIC 60 to 70 percent of the time have been demonstrated to be clinically effective. Some experts therefore suggest that some severe infections are best treated by continuous infusion of these agents rather than by intermittent dosing.



### *C. Postantibiotic effect*

The postantibiotic effect (PAE) is a persistent suppression of microbial growth that occurs after levels of antibiotic have fallen below the MIC. To measure the PAE of an antibiotic, a test culture is first incubated in antibiotic-containing medium and then transferred to antibiotic-free medium. The PAE is defined as the length of time it takes (after the transfer) for the culture to achieve log-phase growth.[3] Antimicrobial drugs exhibiting a long PAE (several hours) often require only one dose per day. For example, antimicrobials, such as aminoglycosides and fluoroquinolones, exhibit a long PAE, particularly against gram-negative bacteria.

## V. Agents Used in Bacterial Infections

In this book, the clinically useful antibacterial drugs are organized into six familiesâ€”penicillins, cephalosporins, tetracyclines, aminoglycosides, macrolides, and fluoroquinolonesâ€”plus a seventh group labeled â€œOtherâ€ that is used to represent any drug not included in one of the other six drug families (Figure 30.9A). Here and throughout this book, these seven groups are graphically presented as a bar chart (as a â€œdrug stackâ€). The drug(s) of choice within each family that is/are used for treating a specific bacterial infection are shown in bold print, as illustrated for Staphylococcus aureus in Figure 30.9B. A key to additional antibiotic symbols used in this book is shown in Figure 30.9C.

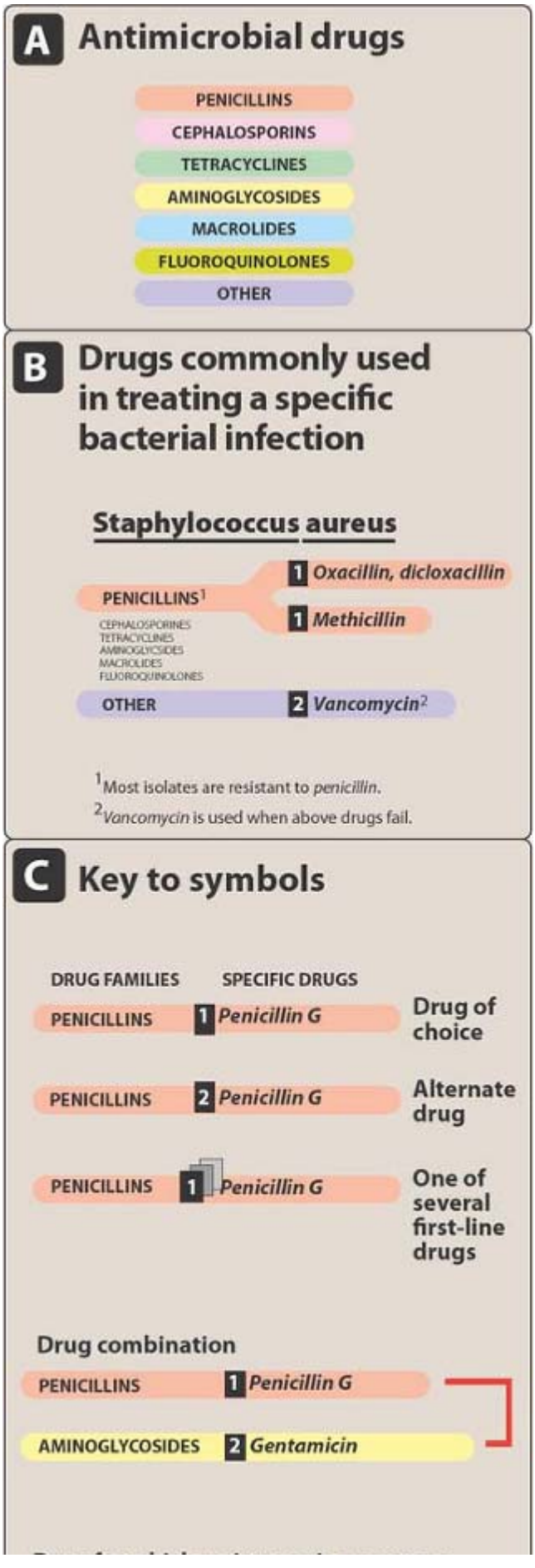

A Antimicrobial drugs
PENICILLINS
CEPHALOSPORINS
TETRACYCLINES
AMINOGLYCOSIDES
MACROLIDES
FLUOROQUINOLONES
OTHER
B Drugs commonly used in treating a specific bacterial infection
Staphylococcus aureus
PENICILLINS[1]
CEPHALOSPORINES
TETRACYCLINES
AMINOGLYCOSIDES
MACROLIDES
FLUOROQUINOLONES
1 Oxacillin, dicloxacillin
1 Methicillin
OTHER
2 Vancomycin[2]
[1]Most isolates are resistant to penicillin.
[2]Vancomycin is used when above drugs fail.
C Key to symbols
DRUG FAMILIES
SPECIFIC DRUGS
PENICILLINS 1 Penicillin G
Drug of choice
PENICILLINS 2 Penicillin G
Alternate drug
PENICILLINS 1 Penicillin G
One of several first-line drugs
Drug combination
PENICILLINS 1 Penicillin G
AMINOGLYCOSIDES 2 Gentamicin

**Figure 30.9** A. Bar chart showing the six most commonly used drug families. B. An example of the bar chart with the drugs of choice for the treatment of Staphylococcus aureus shown in bold print. C. Key to symbols used in this book.

## VI. Chemotherapeutic Spectra

In this book, the clinically important bacteria have been organized into eight groups based on Gram stain, morphology, and biochemical or other characteristics, and they are represented as wedges of a â€œpie chartâ€ (Figure 30.10A). The ninth section of the bacterial pie chart is labeled â€œOther,â€ and it is used to represent any organism not included in one of the other eight categories. In this chapter, the pie chart is used to illustrate the spectra of bacteria for which a particular class of antibiotics is therapeutically effective.

### *A. Narrow-spectrum antibiotics*

Chemotherapeutic agents acting only on a single or a limited group of microorganisms are said to have a narrow spectrum. For example, *isoniazid* is active only against mycobacteria (Figure 30.10B).

### *B. Extended-spectrum antibiotics*

Extended spectrum is the term applied to antibiotics that are effective against gram-positive organisms and also against a significant number of gram-negative bacteria. For example, *ampicillin* is considered to have an extended spectrum, because it acts against gram-positive and some gram-negative bacteria (Figure 30.10C).

### *C. Broad-spectrum antibiotics*

Drugs such as *tetracycline* and *chloramphenicol* affect a wide variety of microbial species and are referred to as broad-spectrum antibiotics



(Figure 30.10D). Administration of broad-spectrum antibiotics can drastically alter the nature of the normal bacterial flora and precipitate a superinfection of an organism such as Candida albicans, the growth of which is normally kept in check by the presence of other microorganisms.[4]

## VII. Combinations of Antimicrobial Drugs

It is therapeutically advisable to treat patients with the single agent that is most specific for the infecting organism. This strategy reduces the possibility of superinfection, decreases the emergence of resistant organisms (see below), and minimizes toxicity. However, situations in which combinations of drugs are employed do exist. For example, the treatment of tuberculosis benefits from drug combinations.

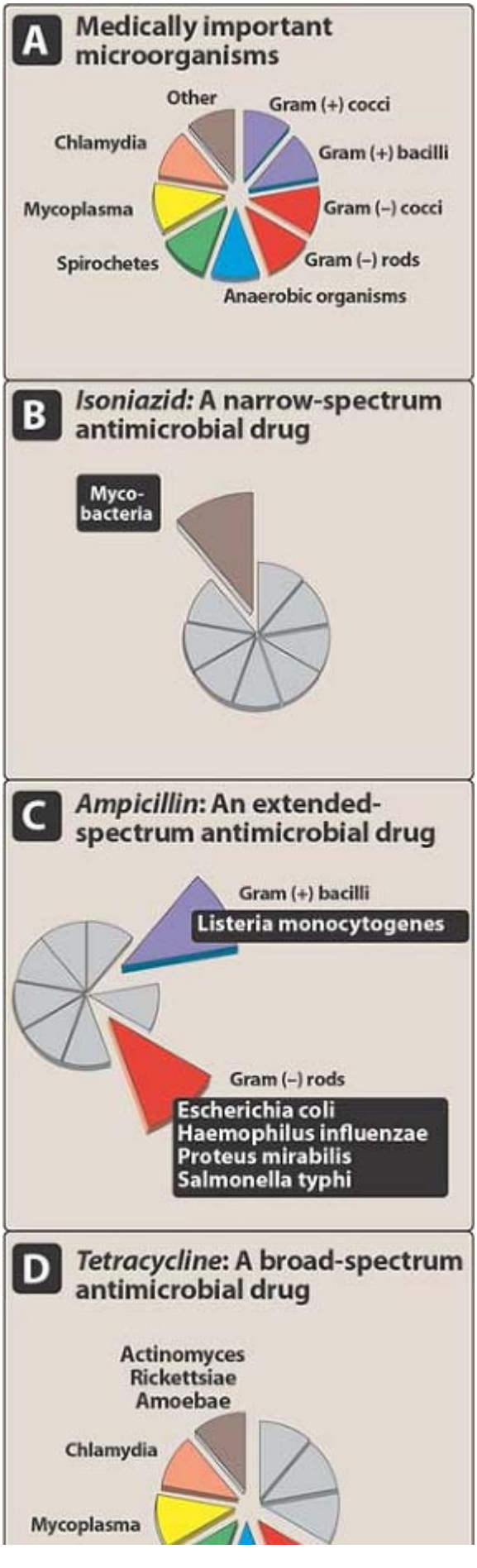

A
Medically important microorganisms
Other
Gram (+) cocci
Chlamydia
Gram (+) bacilli
Mycoplasma
Gram (–) cocci
Spirochetes
Gram (–) rods
Anaerobic organisms
B
Isoniazid: A narrow-spectrum antimicrobial drug
Myco-bacteria
C
Ampicillin: An extended-spectrum antimicrobial drug
Gram (+) bacilli
Listeria monocytogenes
Gram (–) rods
Escherichia coli
Haemophilus influenzae
Proteus mirabilis
Salmonella typhi
D
Tetracycline: A broad-spectrum antimicrobial drug
Actinomyces
Rickettsiae
Amoebae
Chlamydia
Mycoplasma

**Figure 30.10** A. Color-coded representation of medically important microorganisms. B. *Isoniazid*, a narrow-spectrum antimicrobial agent. C. *Ampicillin*, an extended-spectrum antimicrobial agent. D. *Tetracycline*, a broadspectrum antimicrobial agent.

## *A. Advantages of drug combinations*

Certain combinations of antibiotics, such as Î²-lactams and aminoglycosides, show synergism; that is, the combination is more effective than either of the drugs used separately. Because such synergism among antimicrobial agents is rare, multiple drugs used in combination are only indicated in special situationsâ€"for example, when an infection is of unknown origin.

## *B. Disadvantages of drug combinations*

A number of antibiotics act only when organisms are multiplying. Thus, coadministration of an agent that causes bacteriostasis plus a second agent that is bactericidal may result in the first drug interfering with the action of the second. For example, bacteriostatic tetracycline drugs may interfere with the bactericidal effect of penicillins and cephalosporins.

# VIII. Drug Resistance

Bacteria are said to be resistant to an antibiotic if the maximal level of that antibiotic that can be tolerated by the host does not halt their growth. Some organisms are inherently resistant to an antibiotic. For example, gram-negative organisms are inherently resistant to *vancomycin.* However, microbial species that are normally responsive to a particular drug may develop more virulent, resistant strains through spontaneous mutation or acquired resistance and selection. Some of these strains may even become resistant to more than one antibiotic.

## *A. Genetic alterations leading to drug resistance*

Acquired antibiotic resistance requires the temporary or permanent gain or alteration of bacterial genetic information. Resistance develops due to the ability of DNA to undergo spontaneous mutation or to move from one organism to another (Figure 30.11).

1. **Spontaneous mutations of DNA:** Chromosomal alteration may occur by insertion, deletion, or substitution of one or more nucleotides within the genome.[5] The resulting mutation may persist, be corrected by the organism, or be lethal to the cell. If the cell survives, it can replicate and transmit its mutated properties to progeny cells.



   Some spontaneous mutations have little or no effect on the susceptibility of the organism to antimicrobial agents. However, mutations that produce antibiotic-resistant strains can result in organisms that may proliferate under certain selective pressures. An example is the emergence of *rifampin*-resistant Mycobacterium tuberculosis when *rifampin* is used as a single antibiotic.

2. **DNA transfer of drug resistance:** Of particular clinical concern is resistance acquired due to DNA transfer from one bacterium to another. Resistance properties are usually encoded in extrachromosomal R factors (resistance plasmids). In fact, most resistance genes are plasmid mediated, although plasmid-mediated traits can become incorporated into host bacterial DNA. Plasmids may enter cells by processes such as transduction (phage mediated), transformation, or bacterial conjugation.[6]

## *B. Altered expression of proteins in drug-resistant organisms*

Drug resistance may be mediated by a variety of mechanisms, such as a lack of or an alteration in an antibiotic

target site, lowered penetrability of the drug due to decreased permeability, increased efflux of the drug, or presence of antibiotic-inactivating enzymes (see Figure 30.11).

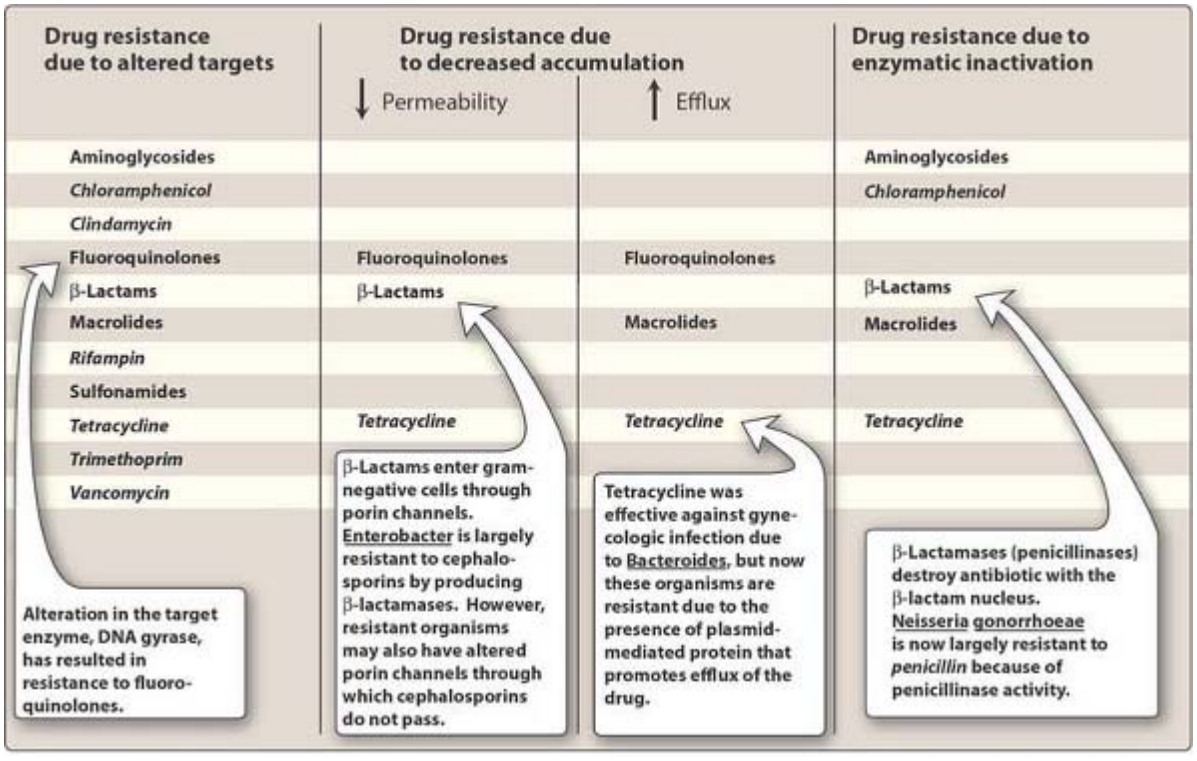



**Figure 30.11** Some mechanisms of resistance to antibiotics.



1. **Modification of target sites:** Alteration of an antibiotic's target site through mutation can confer organismal resistance to one or more related antibiotics. For example, S. pneumoniae resistance to Î²-lactam antibiotics involves alterations in one or more of the major bacterial *penicillin*-binding proteins, resulting in decreased binding of the antibiotic to its target.

**1**

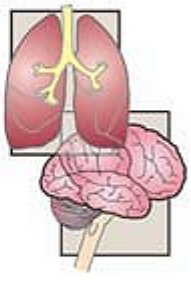
Prevention of streptococcal infections in patients with a history of rheumatic heart disease. Patients may require years of treatment.

**2**

Pretreatment of patients undergoing dental extractions who have implanted prosthetic devices, such as artificial heart valves, to prevent seeding of the prosthesis.

**3**

Prevention of tuberculosis or meningitis among individuals who are in close contact with infected patients.



**4**

Treatment prior to certain surgical procedures (such as bowel surgery, joint replacement, and some gynecologic interventions) to prevent infection.

**5**

Treatment of the mother with *zidovudine* to protect the fetus in the case of an HIV-infected, pregnant woman.

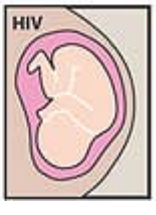



**Figure 30.12** Some clinical situations in which prophylactic antibiotics are indicated.

2. **Decreased accumulation:** Decreased uptake or increased efflux of an antibiotic can confer resistance, because the drug is unable to attain access to the site of its action in sufficient concentrations to injure or kill the organism. For example, gram-negative organisms can limit the penetration of certain agents, including Î²-lactam antibiotics, tetracyclines, and *chloramphenicol*, as a result of an alteration in the number and structure of porins (channels) in the outer membrane. Also, the presence of an efflux pump can limit levels of a drug in an organism.

3. **Enzymic inactivation:** The ability to destroy or inactivate the antimicrobial agent can also confer resistance on microorganisms. Examples of antibiotic-inactivating enzymes include 1) Î²-lactamases (â€œpenicillinasesâ€) that hydrolytically inactivate the Î²-lactam ring of penicillins, cephalosporins, and related drugs; 2) acetyltransferases that transfer an acetyl group to the antibiotic, inactivating chloramphenicol or aminoglycosides; and 3) esterases that hydrolyze the lactone ring of macrolides.

## IX. Prophylactic Antibiotics

Certain clinical situations require the use of antibiotics for the prevention rather than the treatment of infections (Figure 30.12). Because the indiscriminate use of antimicrobial agents can result in bacterial resistance and superinfection, prophylactic use is restricted to clinical situations in which the benefits outweigh the potential risks. The duration of prophylaxis is dictated by the duration of the risk of infection.

## X. Complications of Antibiotic Therapy

Because the mechanism of action of a particular antibiotic is selectively toxic to an invading organism does not insure the host against adverse effects. For example, the drug may produce an allergic response or be toxic in ways unrelated to the drug's antimicrobial activity.

### *A. Hypersensitivity*

Hypersensitivity reactions to antimicrobial drugs or their metabolic products frequently occur. For example, the penicillins, despite their almost absolute selective microbial toxicity, can cause serious hypersensitivity problems, ranging from urticaria (hives) to anaphylactic shock.

### *B. Direct toxicity*

High serum levels of certain antibiotics may cause toxicity by directly affecting cellular processes in the host. For example, aminoglycosides can cause ototoxicity by interfering with membrane function in the hair cells of the organ of Corti.



### *C. Superinfections*

Drug therapy, particularly with broad-spectrum antimicrobials or combinations of agents, can lead to alterations of the normal microbial flora of the upper respiratory, intestinal, and genitourinary tracts, permitting the overgrowth of opportunistic organisms, especially fungi or resistant bacteria. These infections are often difficult to treat.

## XI. Sites of Antimicrobial Actions

Antimicrobial drugs can be classified in a number of ways. These include 1) by their chemical structure (for example, Î²-lactams or aminoglycosides), 2) by their mechanism of action (for example, cell wall synthesis inhibitors), or 3) by their activity against particular types of organisms (for example, bacteria, fungi, or viruses). Chapters 31 through 33 are organized by the mechanisms of action of the drug, and Chapters 34 through 38 are organized according to the type of organisms affected by the drug (Figure 30.13).

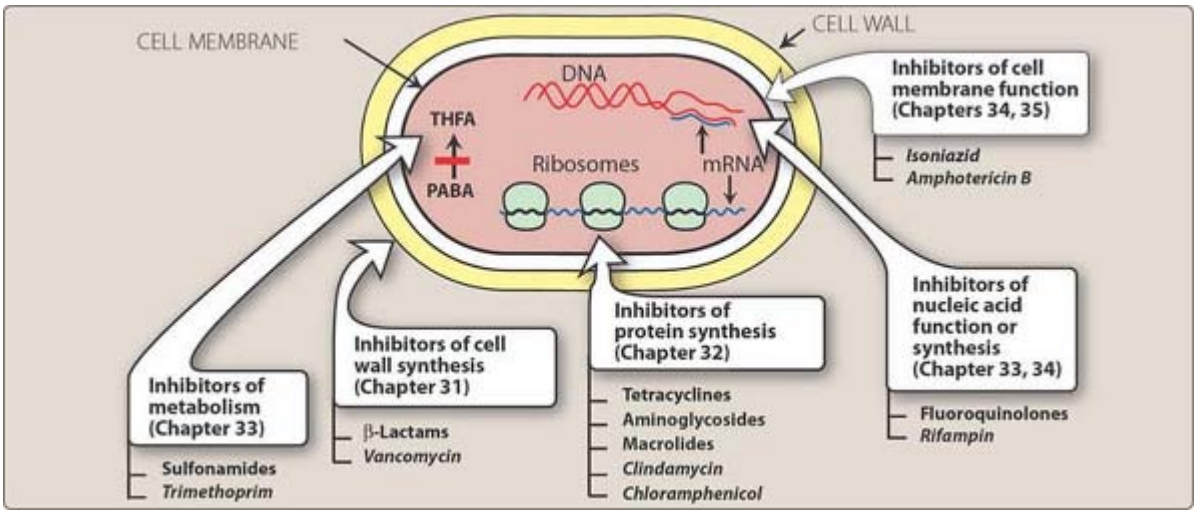



**Figure 30.13** Classification of some antibacterial agents by their sites of action. (THFA = tetrahydrofolic acid; PABA = *p*-aminobenzoic acid)



## Study Questions

Choose the ONE best answer.

**30.1 Which one of the following patients is least likely to require antimicrobial treatment tailored to the individual's condition?**

A. Patient undergoing cancer chemotherapy.

B. Patient with kidney disease.

C. Elderly patient.

D. Patient with hypertension.

E. Patient with liver disease.

View Answer

**30.2 In which one of the following clinical situations is the prophylactic use of antibiotics not warranted?**

A. Prevention of meningitis among individuals in close contact with infected patients.

B. Patient with a hip prosthesis who is having a tooth removed.

C. Presurgical treatment for implantation of a hip prosthesis.

D. Patient who complains of frequent respiratory illness.

E. Presurgical treatment in gastrointestinal procedures.

View Answer

**30.3 Which one of the following is the best route of administration/dosing schedule for treatment with aminoglycosides based on the drug's concentration-dependent killing property?**

A. Oral every 8 hours.

B. Oral every 24 hours.

C. Parenterally by continuous intravenous infusion.

D. Parenterally every 8 hours.

E. Parenterally every 24 hours.

View Answer