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Pancreatic Hormones & Antidiabetic Drugs

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C A S E S T U D Y

A 56-year-old Hispanic woman presents to her medical practitioner with symptoms of fatigue, increased thirst, frequent urination, and exercise intolerance with shortness of breath of many months' duration. She does not get regular medical care and is unaware of any medical problems. Her family history is significant for obesity, diabetes, high blood pressure, and coronary artery disease in both parents and several siblings. She is not taking any medications. Five of her six children had a birthweight of over 9 pounds. Physical examination reveals a BMI (body mass index) of 34, blood pressure of 150/90 mm Hg, and evidence of mild peripheral neuropathy. Laboratory tests reveal a random blood sugar of 261 mg/dL; this is confirmed with a fasting plasma glucose of 192 mg/dL. A fasting lipid panel reveals total cholesterol 264 mg/dL, triglycerides 255 mg/dL, high-density lipoproteins 43 mg/dL, and low-density lipoproteins 170 mg/dL. What type of diabetes does this woman have? What further evaluations should be obtained? How would you treat her diabetes?

■ THE ENDOCRINE PANCREAS

The endocrine pancreas in the adult human consists of approximately 1 million islets of Langerhans interspersed throughout the pancreatic gland. Within the islets, at least four hormone-producing cells are present (Table 41–1). Their hormone products include **insulin,** the storage and anabolic hormone of the body; **islet amyloid polypeptide (IAPP, or amylin),** which modulates appetite, gastric emptying, and glucagon and insulin secretion; **glucagon,** the hyperglycemic factor that mobilizes glycogen stores; **somatostatin,** a universal inhibitor of secretory cells; **gastrin,** which stimulates gastric acid secretion; and **pancreatic peptide,** a small protein that facilitates digestive processes by a mechanism not yet clarified.

Diabetes mellitus is defined as an elevated blood glucose associated with absent or inadequate pancreatic insulin secretion, with or without concurrent impairment of insulin action. The disease states underlying the diagnosis of diabetes mellitus are now classified into four categories: type 1, *insulin-dependent diabetes;* type 2, *non–insulin-dependent diabetes;* type 3, *other;* and type 4, *gestational diabetes mellitus* (Expert Committee, 2003).

Type 1 Diabetes Mellitus

The hallmark of type 1 diabetes is selective beta cell (B cell) destruction and *severe* or *absolute* insulin deficiency. Type 1 diabetes is further subdivided into immune and idiopathic causes. The immune form is the most common form of type 1 diabetes. Although most patients are younger than 30 years of age at the time of diagnosis, the onset can occur at any age. Type 1 diabetes is found in all ethnic groups, but the highest incidence is in people from northern Europe and from Sardinia. Susceptibility appears to involve a multifactorial genetic linkage, but only 10–15% of patients have a positive family history.

For persons with type 1 diabetes, insulin replacement therapy is necessary to sustain life. Pharmacologic insulin is administered by injection into the subcutaneous tissue using a manual injection device or an insulin pump that continuously infuses insulin under

TABLE 41–1 Pancreatic islet cells and their secretory products.

Cell Types	Approximate Percent of Islet Mass	Secretory Products
Alpha (A) cell	20	Glucagon, proglucagon
Beta (B) cell	75	Insulin, C-peptide, proinsulin, amylin
Delta (D) cell	3–5	Somatostatin
G cell	1	Gastrin
F cell (PP cell)[1]	1	Pancreatic polypeptide (PP)

[1]Within pancreatic polypeptide-rich lobules of adult islets, located only in the posterior portion of the head of the human pancreas, glucagon cells are scarce (< 0.5%) and F cells make up as much as 80% of the cells.

the skin. Interruption of the insulin replacement therapy can be life-threatening and can result in **diabetic ketoacidosis** or death. Diabetic ketoacidosis is caused by insufficient or absent insulin and results from excess release of fatty acids and subsequent formation of toxic levels of ketoacids.

Type 2 Diabetes Mellitus

Type 2 diabetes is characterized by tissue resistance to the action of insulin combined with a *relative* deficiency in insulin secretion. A given individual may have more resistance or more beta-cell deficiency, and the abnormalities may be mild or severe. Although insulin is produced by the beta cells in these patients, it is inadequate to overcome the resistance, and the blood glucose rises. The impaired insulin action also affects fat metabolism, resulting in increased free fatty acid flux and triglyceride levels and reciprocally low levels of high-density lipoprotein (HDL).

Individuals with type 2 diabetes may not require insulin to survive, but 30% or more will benefit from insulin therapy to control blood glucose. It is likely that 10–20% of individuals in whom type 2 diabetes was initially diagnosed actually have both type 1 and type 2 or a slowly progressing type 1 called latent autoimmune diabetes of adults (LADA), and they ultimately require full insulin replacement. Although persons with type 2 diabetes ordinarily do not

develop ketosis, ketoacidosis may occur as the result of stress such as infection or the use of medication that enhances resistance, eg, corticosteroids. Dehydration in individuals with untreated or poorly controlled type 2 diabetes can lead to a life-threatening condition called **nonketotic hyperosmolar coma**. In this condition, the blood glucose may rise to 6–20 times the normal range and an altered mental state develops or the person loses consciousness. Urgent medical care and rehydration are required.

Type 3 Diabetes Mellitus

The type 3 designation refers to multiple *other* specific causes of an elevated blood glucose: pancreatectomy, pancreatitis, nonpancreatic diseases, drug therapy, etc. For a detailed list the reader is referred to the reference Expert Committee, 2003.

Type 4 Diabetes Mellitus

Gestational diabetes (GDM) is defined as any abnormality in glucose levels noted for the first time during pregnancy. Gestational diabetes is diagnosed in approximately 7% of all pregnancies in the USA. During pregnancy, the placenta and placental hormones create an insulin resistance that is most pronounced in the last trimester. Risk assessment for diabetes is suggested starting at the first prenatal visit. High-risk women should be screened immediately. Screening may be deferred in lower-risk women until the 24th to 28th week of gestation.

■ INSULIN

Chemistry

Insulin is a small protein with a molecular weight in humans of 5808. It contains 51 amino acids arranged in two chains (A and B) linked by disulfide bridges; there are species differences in the amino acids of both chains. Proinsulin, a long single-chain protein molecule, is processed within the Golgi apparatus of beta cells and packaged into granules, where it is hydrolyzed into insulin and a residual connecting segment called C-peptide by removal of four amino acids (Figure 41–1).
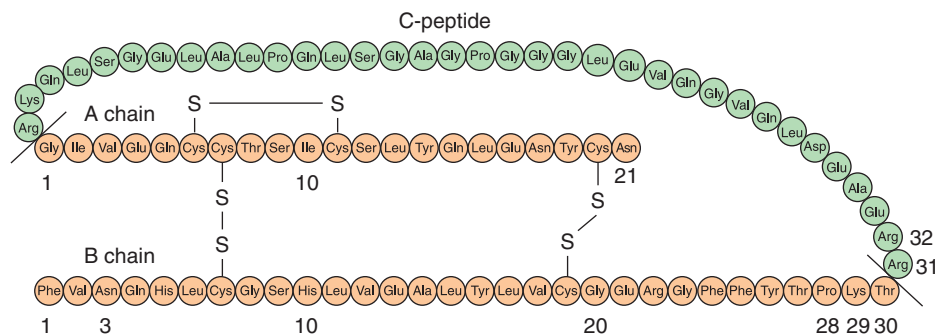

FIGURE 41–1 Structure of human proinsulin (C-peptide plus A and B chains) and insulin. Insulin is shown as the shaded (orange color) peptide chains, A and B. Differences in the A and B chains and amino acid modifications for the rapid-acting insulin analogs (aspart, lispro, and glulisine) and long-acting insulin analogs (glargine and detemir) are discussed in the text.

Insulin and C-peptide are secreted in equimolar amounts in response to all insulin secretagogues; a small quantity of unprocessed or partially hydrolyzed proinsulin is released as well. Although proinsulin may have some mild hypoglycemic action, C-peptide has no known physiologic function. Granules within the beta cells store the insulin in the form of crystals consisting of two atoms of zinc and six molecules of insulin. The entire human pancreas contains up to 8 mg of insulin, representing approximately 200 biologic units. Originally, the unit was defined on the basis of the hypoglycemic activity of insulin in rabbits. With improved purification techniques, the unit is presently defined on the basis of weight, and present insulin standards used for assay purposes contain 28 units per milligram.

Insulin Secretion

Insulin is released from pancreatic beta cells at a low basal rate and at a much higher stimulated rate in response to a variety of stimuli, especially glucose. Other stimulants such as other sugars (eg, mannose), amino acids (especially gluconeogenic amino acids, eg, leucine, arginine), hormones such as glucagon-like polypeptide-1 (GLP-1), glucose-dependent insulinotropic polypeptide (GIP), glucagon, cholecystokinin, high concentrations of fatty acids, and β-adrenergic sympathetic activity are recognized. Stimulatory drugs are sulfonylureas, meglitinide and nateglinide, isoproterenol, and acetylcholine. Inhibitory signals are hormones including insulin itself and leptin, α-adrenergic sympathetic activity, chronically elevated glucose, and low concentrations of fatty acids. Inhibitory drugs include diazoxide, phenytoin, vinblastine, and colchicine.

One mechanism of stimulated insulin release is diagrammed in Figure 41–2. As shown in the figure, hyperglycemia results in increased intracellular ATP levels, which close the ATP-dependent potassium channels. Decreased outward potassium efflux results in depolarization of the beta cell and opening of voltage-gated calcium channels. The resulting increased intracellular calcium triggers secretion of the hormone. The insulin secretagogue drug group (sulfonylureas, meglitinides, and D-phenylalanine) exploits parts of this mechanism.

Insulin Degradation

The liver and kidney are the two main organs that remove insulin from the circulation. The liver normally clears the blood of approximately 60% of the insulin released from the pancreas by virtue of its location as the terminal site of portal vein blood flow, with the kidney removing 35–40% of the endogenous hormone. However, in insulin-treated diabetics receiving subcutaneous insulin injections, this ratio is reversed, with as much as 60% of exogenous insulin being cleared by the kidney and the liver removing no more than 30–40%. The half-life of circulating insulin is 3–5 minutes.
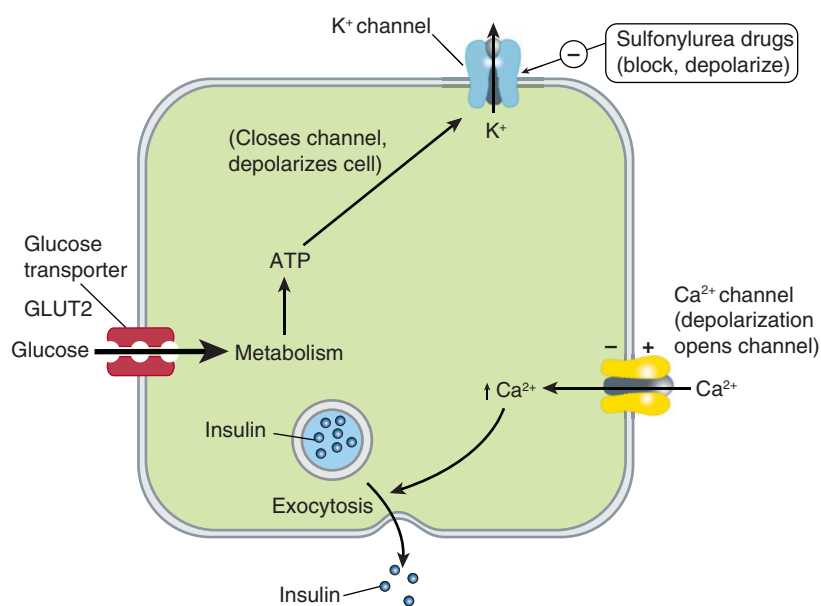

FIGURE 41–2 One model of control of insulin release from the pancreatic beta cell by glucose and by sulfonylurea drugs. In the resting cell with normal (low) ATP levels, potassium diffuses down its concentration gradient through ATP-gated potassium channels, maintaining the intracellular potential at a fully polarized, negative level. Insulin release is minimal. If glucose concentration rises, ATP production increases, potassium channels close, and depolarization of the cell results. As in muscle and nerve, voltage-gated calcium channels open in response to depolarization, allowing more calcium to enter the cell. Increased intracellular calcium results in increased insulin secretion. Insulin secretagogues close the ATP-dependent potassium channel, thereby depolarizing the membrane and causing increased insulin release by the same mechanism. (Modified and reproduced, with permission, from *Basic & Clinical Endocrinology*, 4th ed. Greenspan F, Baxter JD [editors]: Originally published by Appleton & Lange. Copyright © 1994 by The McGraw-Hill Companies, Inc.)

Circulating Insulin

Basal insulin values of 5–15 μU/mL (30–90 pmol/L) are found in normal humans, with a peak rise to 60–90 μU/mL (360–540 pmol/L) during meals.

The Insulin Receptor

After insulin has entered the circulation, it diffuses into tissues, where it is bound by specialized receptors that are found on the membranes of most tissues. The biologic responses promoted by these insulin-receptor complexes have been identified in the primary target tissues, ie, liver, muscle, and adipose tissue. The receptors bind insulin with high specificity and affinity in the picomolar range. The full insulin receptor consists of two covalently linked heterodimers, each containing an α subunit, which is entirely extracellular and constitutes the recognition site, and a β subunit that spans the membrane (Figure 41–3). The β subunit contains a tyrosine kinase. The binding of an insulin molecule to the α subunits at the outside surface of the cell activates the receptor and through a conformational change brings the catalytic loops of the opposing cytoplasmic β subunits into closer proximity. This facilitates mutual phosphorylation of tyrosine residues on the β subunits and tyrosine kinase activity directed at cytoplasmic proteins.

The first proteins to be phosphorylated by the activated receptor tyrosine kinases are the docking proteins, insulin receptor substrates (IRS). After tyrosine phosphorylation at several critical sites, the IRS molecules bind to and activate other kinases—most significantly phosphatidylinositol-3-kinase—which produce further phosphorylations. Alternatively, they may bind to an adaptor protein such as growth factor receptor-binding protein 2, which translates the insulin signal to a guanine nucleotide-releasing factor that ultimately activates the GTP binding protein, ras, and the mitogen-activated protein kinase (MAPK) system. The particular IRS-phosphorylated tyrosine kinases have binding specificity with downstream molecules based on their surrounding 4–5 amino acid sequences or motifs that recognize specific Src homology 2 (SH2) domains on the other protein. This network of phosphorylations within the cell represents insulin's second message and results in multiple effects, including translocation of glucose transporters (especially GLUT 4, Table 41–2) to the cell membrane with a resultant increase in glucose uptake; increased glycogen synthase activity and increased glycogen formation; multiple effects on protein synthesis, lipolysis, and lipogenesis; and activation of
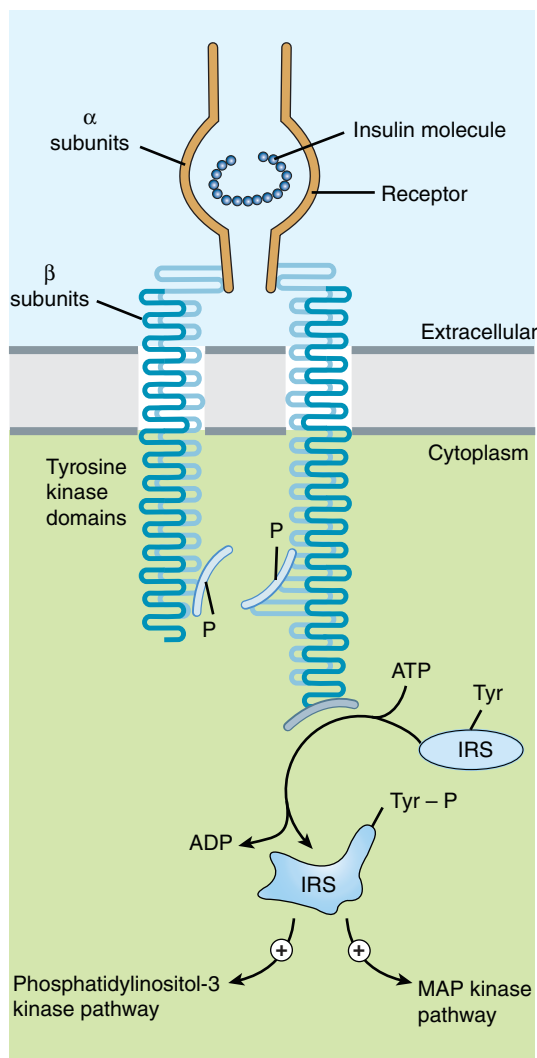

FIGURE 41–3 Schematic diagram of the insulin receptor heterodimer in the activated state. IRS, insulin receptor substrate; MAP, mitogen-activated protein; P, phosphate; Tyr, tyrosine.

transcription factors that enhance DNA synthesis and cell growth and division.

Various hormonal agents (eg, glucocorticoids) lower the affinity of insulin receptors for insulin; growth hormone in excess increases this affinity slightly. Aberrant serine and threonine phosphorylation

TABLE 41–2 Glucose transporters.

| Transporter	Tissues	Glucose K_m (mmol/L)	Function
GLUT 1	All tissues, especially red cells, brain	1–2	Basal uptake of glucose; transport across the blood-brain barrier
GLUT 2	Beta cells of pancreas; liver, kidney; gut	15–20	Regulation of insulin release, other aspects of glucose homeostasis
GLUT 3	Brain, placenta	< 1	Uptake into neurons, other tissues
GLUT 4	Muscle, adipose	≈ 5	Insulin-mediated uptake of glucose
GLUT 5	Gut, kidney	1–2	Absorption of fructose
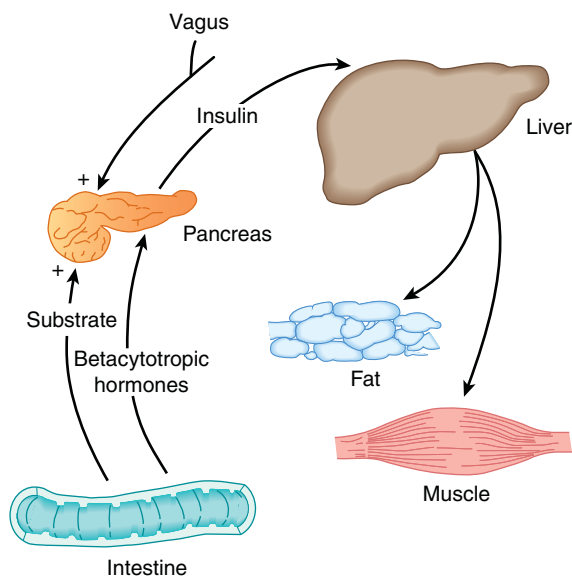
FIGURE 41–4 Insulin promotes synthesis (from circulating nutri-ents) and storage of glycogen, triglycerides, and protein in its major target tissues: liver, fat, and muscle. The release of insulin from the pancreas is stimulated by increased blood glucose, incretins, vagal nerve stimulation, and other factors (see text).

of the insulin receptor β subunits or IRS molecules may result in insulin resistance and functional receptor down-regulation.

Effects of Insulin on Its Targets

Insulin promotes the storage of fat as well as glucose (both sources of energy) within specialized target cells (Figure 41–4) and influences cell growth and the metabolic functions of a wide variety of tissues (Table 41–3).

Characteristics of Available Insulin Preparations

Commercial insulin preparations differ in a number of ways, such as differences in the recombinant DNA production techniques, amino acid sequence, concentration, solubility, and the time of onset and duration of their biologic action.

A. Principal Types and Duration of Action of Insulin Preparations

Four principal types of injected insulins are available: (1) rapid-acting, with very fast onset and short duration; (2) short-acting, with rapid onset of action; (3) intermediate-acting; and (4) long-acting, with slow onset of action (Figure 41–5, Table 41–4). Injected rapid-acting and short-acting insulins are dispensed as clear solutions at neutral pH and contain small amounts of zinc to improve their stability and shelf life. Injected intermediate-acting NPH insulins have been modified to provide prolonged action and are dispensed as a turbid suspension at neutral pH with protamine in phosphate buffer (neutral protamine Hagedorn [NPH] insulin). Insulin glargine and insulin detemir are clear, soluble long-acting insulins.

TABLE 41–3 Endocrine effects of insulin.

Effect on liver:
Reversal of catabolic features of insulin deficiency
Inhibits glycogenolysis
Inhibits conversion of fatty acids and amino acids to keto acids
Inhibits conversion of amino acids to glucose
Anabolic action
Promotes glucose storage as glycogen (induces glucokinase and glycogen synthase, inhibits phosphorylase)
Increases triglyceride synthesis and very-low-density lipoprotein formation
Effect on muscle:
Increased protein synthesis
Increases amino acid transport
Increases ribosomal protein synthesis
Increased glycogen synthesis
Increases glucose transport
Induces glycogen synthase and inhibits phosphorylase
Effect on adipose tissue:
Increased triglyceride storage
Lipoprotein lipase is induced and activated by insulin to hydro-lyze triglycerides from lipoproteins
Glucose transport into cell provides glycerol phosphate to permit esterification of fatty acids supplied by lipoprotein transport
Intracellular lipase is inhibited by insulin

The goal of subcutaneous insulin therapy is to replicate normal physiologic insulin secretion and replace the background or basal (overnight, fasting, and between-meal) as well as bolus or prandial (mealtime) insulin. An exact reproduction of the normal glycemic profile is not technically possible because of the limitations inher-ent in subcutaneous administration of insulin. Current regimens generally use insulin analogs because of their more predictable action. Intensive therapy ("tight control") attempts to restore near-normal glucose patterns throughout the day while minimizing the risk of hypoglycemia.

Intensive regimens involving multiple daily injections (MDI) use long-acting insulin analogs to provide basal or background coverage, and rapid-acting insulin analogs to meet the mealtime requirements. The latter insulins are given as supplemental doses to correct transient hyperglycemia. The most sophisticated insulin regimen delivers rapid-acting insulin analogs through a continu-ous subcutaneous insulin infusion device. Conventional therapy consists of split-dose injections of mixtures of rapid- or short-acting and intermediate-acting insulins.

1. Rapid-acting insulin—Three injected rapid-acting insulin analogs—**insulin lispro, insulin aspart,** and **insulin glulisine**—are commercially available. The rapid-acting insulins permit more physiologic prandial insulin replacement because their rapid onset
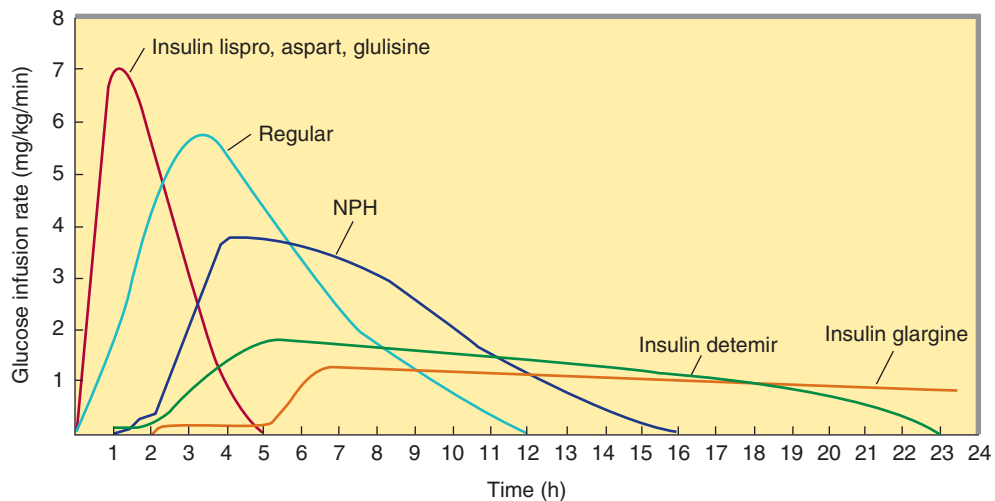
FIGURE 41–5 Extent and duration of action of various types of insulin as indicated by the glucose infusion rates (mg/kg/min) required to maintain a constant glucose concentration. The durations of action shown are typical of an average dose of 0.2–0.3 U/kg. The durations of regular and NPH insulin increase considerably when dosage is increased.

TABLE 41–4 Some insulin preparations available in the USA.[1]

Preparation	Species Source	Concentration
Rapid-acting insulins		
Insulin lispro, Humalog (Lilly)	Human analog	U100
Insulin aspart, Novolog (Novo Nordisk)	Human analog	U100
Insulin glulisine, Apidra (Aventis)	Human analog	U100
Short-acting insulins		
Regular Novolin R (Novo Nordisk)	Human	U100
Regular Humulin R (Lilly)	Human	U100, U500
Intermediate-acting insulins		
NPH Humulin N (Lilly)	Human	U100
NPH Novolin N (Novo Nordisk)	Human	U100
Premixed insulins		
Novolin 70 NPH/30 regular (Novo Nordisk)	Human	U100
Humulin 70 NPH/30 regular (Lilly)	Human	U100
75/25 NPL, Lispro (Lilly)	Human analog	U100
70/30 NPA, Aspart (Novo Nordisk)	Human analog	U100
Long-acting insulins		
Insulin detemir, Levemir (Novo Nordisk)	Human analog	U100
Insulin glargine, Lantus (Aventis/Hoechst Marion Roussel)	Human analog	U100

[1]These agents (except insulin lispro, insulin aspart, insulin detemir, insulin glargine, insulin glulisine, and U500 regular Humulin) are available without a prescription. All insulins should be refrigerated and brought to room temperature just before injection.

NPL, neutral protamine lispro; NPA, neutral protamine aspart.

and early peak action more closely mimic normal endogenous prandial insulin secretion than does regular insulin, and they have the additional benefit of allowing insulin to be taken immediately before the meal without sacrificing glucose control. Their duration of action is rarely more than 4–5 hours, which decreases the risk of late postmeal hypoglycemia. The injected rapid-acting insulins have the lowest variability of absorption (approximately 5%) of all available commercial insulins (compared with 25% for regular insulin and 25% to over 50% for long-acting analog formulations and intermediate insulin, respectively). They are the preferred insulins for use in continuous subcutaneous insulin infusion devices.

Insulin lispro, the first monomeric insulin analog to be marketed, is produced by recombinant technology wherein two amino acids near the carboxyl terminal of the B chain have been reversed in position: Proline at position B28 has been moved to B29, and lysine at position B29 has been moved to B28 (Figure 41–1). Reversing these two amino acids does not interfere in any way with insulin lispro's binding to the insulin receptor, its circulating half-life, or its immunogenicity, which are similar to those of human regular insulin. However, the advantage of this analog is its very low propensity—in contrast to human insulin—to self-associate in antiparallel fashion and form dimers. To enhance the shelf life of insulin in vials, insulin lispro is stabilized into hexamers by a cresol preservative. When injected subcutaneously, the drug quickly dissociates into monomers and is rapidly absorbed with onset of action within 5–15 minutes and peak activity as early as 1 hour. The time to peak action is relatively constant, regardless of the dose.

Insulin aspart is created by the substitution of the B28 proline with a negatively charged aspartic acid (Figure 41–1). This modification reduces the normal ProB28 and GlyB23 monomer-monomer interaction, thereby inhibiting insulin self-aggregation. Its absorption and activity profile are similar to those of insulin lispro, and it is more reproducible than regular insulin, but it has binding properties, activity, and mitogenicity characteristics similar to those of regular insulin in addition to equivalent immunogenicity.

Insulin glulisine is formulated by substituting a lysine for asparagine at B3 and glutamic acid for lysine at B29. Its absorption, action, and immunologic characteristics are similar to those of other injected rapid-acting insulins. After high-dose insulin glulisine interaction with the insulin receptor, there may be downstream differences in IRS-2 pathway activation relative to human insulin. The clinical significance of such differences is unclear.

2. Short-acting insulin—Regular insulin is a short-acting soluble crystalline zinc insulin that is now made by recombinant DNA techniques to produce a molecule identical to that of human insulin. Its effect appears within 30 minutes, peaks between 2 and 3 hours after subcutaneous injection, and generally lasts 5–8 hours. In high concentrations, eg, in the vial, regular insulin molecules self-aggregate in antiparallel fashion to form dimers that stabilize around zinc ions to create insulin hexamers. The hexameric nature of regular insulin causes a delayed onset and prolongs the time to peak action. After subcutaneous injection, the insulin hexamers are too large and bulky to be transported across the vascular endothelium into the bloodstream. As the insulin depot is diluted by interstitial fluid and the concentration begins to fall, the hexamers break down into dimers and finally monomers. This results in three rates of absorption of the injected insulin, with the final monomeric phase having the fastest uptake out of the injection site.

The clinical consequence is that when regular insulin is administered at mealtime, the blood glucose rises faster than the insulin with resultant early postprandial hyperglycemia and an increased risk of late postprandial hypoglycemia. Therefore, regular insulin should be injected 30–45 or more minutes before the meal to minimize the mismatching. As with all older insulin formulations, the duration of action as well as the time of onset and the intensity of peak action increase with the size of the dose. Clinically, this is a critical issue because the pharmacokinetics and pharmacodynamics of small doses of regular and NPH insulins differ greatly from those of large doses. The delayed absorption, dose-dependent duration of action, and variability of absorption (~ 25%) of regular human insulin frequently results in a mismatching of insulin availability with need, and its use is declining.

However, short-acting, regular soluble insulin is the only type that should be administered intravenously because the dilution causes the hexameric insulin to immediately dissociate into monomers. It is particularly useful for intravenous therapy in the management of diabetic ketoacidosis and when the insulin requirement is changing rapidly, such as after surgery or during acute infections.

3. Intermediate-acting and long-acting insulins

a. NPH (neutral protamine Hagedorn, or isophane) insulin—-NPH insulin is an intermediate-acting insulin whose absorption and onset of action are delayed by combining appropriate amounts of insulin and protamine so that neither is present in an uncomplexed form ("isophane"). After subcutaneous injection, proteolytic tissue enzymes degrade the protamine to permit absorption of insulin. NPH insulin has an onset of approximately 2–5 hours and duration of 4–12 hours (Figure 41–5); it is usually mixed with regular, lispro, aspart, or glulisine insulin and given two to four times daily for insulin replacement. The dose regulates the action profile; specifically, small doses have lower, earlier peaks and a short duration of action with the converse true for large doses. The action of NPH is highly unpredictable, and its variability of absorption is over 50%. The clinical use of NPH is waning because of its adverse pharmacokinetics combined with the availability of long-acting insulin analogs that have a more predictable and physiologic action.

b. Insulin glargine—Insulin glargine is a soluble, "peakless" (ie, having a broad plasma concentration plateau), long-acting insulin analog. This product was designed to provide reproducible, convenient, background insulin replacement. The attachment of two arginine molecules to the B-chain carboxyl terminal and substitution of a glycine for asparagine at the A21 position created an analog that is soluble in an acidic solution but precipitates in the more neutral body pH after subcutaneous injection. Individual

insulin molecules slowly dissolve away from the crystalline depot and provide a low, continuous level of circulating insulin. Insulin glargine has a slow onset of action (1–1.5 hours) and achieves a maximum effect after 4–6 hours. This maximum activity is maintained for 11–24 hours or longer. Glargine is usually given once daily, although some very insulin-sensitive or insulin-resistant individuals benefit from split (twice a day) dosing. To maintain solubility, the formulation is unusually acidic (pH 4.0), and insulin glargine should not be mixed with other insulins. Separate syringes must be used to minimize the risk of contamination and subsequent loss of efficacy. The absorption pattern of insulin glargine appears to be independent of the anatomic site of injection, and this drug is associated with less immunogenicity than human insulin in animal studies. Glargine's interaction with the insulin receptor is similar to that of native insulin and shows no increase in mitogenic activity in vitro. It has sixfold to sevenfold greater binding than native insulin to the insulin-like growth factor-1 (IGF-1) receptor, but the clinical significance of this is unclear.

c. Insulin detemir—This insulin is the most recently developed long-acting insulin analog. The terminal threonine is dropped from the B30 position and myristic acid (a C-14 fatty acid chain) is attached to the terminal B29 lysine. These modifications prolong the availability of the injected analog by increasing both self-aggregation in subcutaneous tissue and reversible albumin binding. Insulin detemir has the most reproducible effect of the intermediate- and long-acting insulins, and its use is associated with less hypoglycemia than NPH insulin. Insulin detemir has a dose-dependent onset of action of 1–2 hours and duration of action of more than 12 hours. It is given twice daily to obtain a smooth background insulin level.

4. Mixtures of insulins—Because intermediate-acting NPH insulins require several hours to reach adequate therapeutic levels, their use in diabetic patients usually requires supplements of rapid- or short-acting insulin before meals. For convenience, these are often mixed together in the same syringe before injection. Insulin lispro, aspart, and glulisine can be *acutely* mixed (ie, just before injection) with NPH insulin without affecting their rapid absorption. However, *premixed* preparations have thus far been unstable. To remedy this, intermediate insulins composed of isophane complexes of protamine with insulin lispro and insulin aspart have been developed. These intermediate insulins have been designated as "NPL" (neutral protamine lispro) and "NPA" (neutral protamine aspart) and have the same duration of action as NPH insulin. They have the advantage of permitting formulation as premixed combinations of NPL and insulin lispro, and as NPA and insulin aspart, and they have been shown to be safe and effective in clinical trials. The Food and Drug Administration (FDA) has approved 50%/50% and 75%/25% NPL/insulin lispro and 70%/30% NPA/insulin aspart premixed formulations. Additional ratios are available abroad. Insulin glargine and detemir must be given as separate injections. They are not miscible acutely or in a premixed preparation with any other insulin formulation.

Premixed formulations of 70%/30% NPH/regular continue to be available. These preparations have all the limitations of regular

insulin, namely, highly dose dependent pharmacokinetic and pharmacodynamic profiles, and variability in absorption.

B. Insulin Production

Mass production of human insulin and insulin analogs by recombinant DNA techniques is carried out by inserting the human or a modified human proinsulin gene into *Escherichia coli* or yeast and treating the extracted proinsulin to form the insulin or insulin analog molecules.

C. Concentration

All insulins in the USA and Canada are available in a concentration of 100 U/mL (U100). A limited supply of U500 regular human insulin is available for use in rare cases of severe insulin resistance in which larger doses of insulin are required.

Insulin Delivery Systems

A. Standard Delivery

The standard mode of insulin therapy is subcutaneous injection using conventional disposable needles and syringes.

B. Portable Pen Injectors

To facilitate multiple subcutaneous injections of insulin, particularly during intensive insulin therapy, portable pen-sized injectors have been developed. These contain cartridges of insulin and replaceable needles.

Disposable insulin pens are also available for selected formulations. These are regular insulin, insulin lispro, insulin aspart, insulin glulisine, insulin glargine, insulin detemir, and several mixtures of NPH with regular, lispro, or aspart insulin (Table 41–4). They have been well accepted by patients because they eliminate the need to carry syringes and bottles of insulin to the workplace and while traveling.

C. Continuous Subcutaneous Insulin Infusion Devices (CSII, Insulin Pumps)

Continuous subcutaneous insulin infusion devices are external open-loop pumps for insulin delivery. The devices have a user-programmable pump that delivers individualized basal and bolus insulin replacement doses based on blood glucose self-monitoring results.

Normally, the 24-hour background basal rates are preprogrammed and relatively constant from day to day, although temporarily altered rates can be superimposed to adjust for a short-term change in requirement. For example, the basal delivery rate might need to be decreased for several hours because of the increased insulin sensitivity associated with strenuous activity.

Boluses are used to correct high blood glucose levels and to cover mealtime insulin requirements based on the carbohydrate content of the food and concurrent activity. Bolus amounts are either dynamically programmed or use preprogrammed algorithms. When the boluses are dynamically programmed, the user calculates the dose based on the amount of carbohydrate consumed and the current blood glucose level. Alternatively, the meal

or snack dose algorithm (grams of carbohydrate covered by a unit of insulin) and insulin sensitivity or blood glucose correction factor (fall in blood glucose level in response to a unit of insulin) can be preprogrammed into the pump. If the user enters the carbohydrate content of the food and current blood glucose value, the insulin pump will calculate the most appropriate dose of insulin. Advanced insulin pumps also have an "insulin on board" feature that adjusts a high blood glucose correction dose to correct for residual activity of previous bolus doses.

The traditional pump—which contains an insulin reservoir, the program chip, the keypad, and the display screen—is about the size of a pager. It is usually placed on a belt or in a pocket, and the insulin is infused through thin plastic tubing that is connected to the subcutaneously inserted infusion set. The abdomen is the favored site for the infusion set, although flanks and thighs are also used. The insulin reservoir, tubing, and infusion set need to be changed using sterile techniques every 2 or 3 days. Currently, only one pump does not require tubing. In this model, the pump is attached directly to the infusion set. Programming is done through a hand-held unit that communicates wirelessly with the pump. CSII delivery is regarded as the most physiologic method of insulin replacement.

Use of these continuous infusion devices is encouraged for people who are unable to obtain target control while on multiple injection regimens and in circumstances in which excellent glycemic control is desired, such as during pregnancy. Optimal use of these devices requires responsible involvement and commitment by the patient. Insulin aspart, lispro, and glulisine all are specifically approved for pump use and are preferred pump insulins because their favorable pharmacokinetic attributes allow glycemic control without increasing the risk of hypoglycemia.

Treatment with Insulin

The current classification of diabetes mellitus identifies a group of patients who have virtually no insulin secretion and whose survival depends on administration of exogenous insulin. This insulin-dependent group (type 1) represents 5–10% of the diabetic population in the USA. Most type 2 diabetics do not require exogenous insulin for survival, but many need exogenous supplementation of their endogenous secretion to achieve optimum health.

Benefit of Glycemic Control in Diabetes Mellitus

The consensus of the American Diabetes Association is that intensive glycemic control and targeting normal or near-normal glucose control associated with comprehensive self-management training should become standard therapy in diabetic patients (see Box: Benefits of Tight Glycemic Control in Diabetes). Exceptions include patients with advanced renal disease and the elderly, because the risks of hypoglycemia may outweigh the benefit of normal or near-normal glycemic control in these groups. In children under 7 years, the extreme susceptibility of the developing brain to incur damage from hypoglycemia contraindicates attempts at intensive glycemic control.

Insulin Regimens

A. Intensive Insulin Therapy

Intensive insulin regimens are prescribed for almost everyone with type 1 diabetes—diabetes associated with a severe deficiency or absence of endogenous insulin production—as well as many with type 2 diabetes.

Generally, the total daily insulin requirement in units is equal to the weight in pounds divided by four, or 0.55 times the person's weight in kilograms. Approximately half the total daily insulin dose covers the background or basal insulin requirements, and the remainder covers meal and snack requirement and high blood sugar corrections. This is an approximate calculation and has to be individualized. Examples of reduced insulin requirement include newly diagnosed persons and those with ongoing endogenous insulin production, longstanding diabetes with insulin sensitivity, significant renal insufficiency, or other endocrine deficiencies. Increased insulin requirements typically occur with obesity, during adolescence, during the latter trimesters of pregnancy, and in individuals with type 2 diabetes.

In intensive insulin regimens, the meal or snack and high blood sugar correction boluses are prescribed by formulas. The patient uses the formulas to calculate the rapid-acting insulin bolus dose by considering how much carbohydrate is in the meal or snack, the current plasma glucose, and the target glucose. The formula for the meal or snack bolus is expressed as an insulin-to-carbohydrate ratio, which refers to how many grams of carbohydrate will be disposed of by 1 unit of rapid-acting insulin. The high blood sugar correction formula is expressed as the predicted fall in plasma glucose (in mg/dL) after 1 unit of rapid-acting insulin. Diurnal variations in insulin sensitivity can be accommodated by prescribing different basal rates and bolus insulin doses throughout the day. Continuous subcutaneous insulin infusion devices provide the most sophisticated and physiologic insulin replacement.

B. Conventional Insulin Therapy

Conventional insulin therapy is usually prescribed only for certain people with type 2 diabetes who are felt not to benefit from intensive glucose control. The insulin regimen ranges from one injection per day to many injections per day, using intermediate- or long-acting insulin alone or with short- or rapid-acting insulin or premixed insulins. Referred to as sliding-scale regimens, conventional insulin regimens customarily fix the dose of the intermediate- or long-acting insulin, but vary the short- or rapid-acting insulin based on the plasma glucose level before the injection.

Insulin Treatment of Special Circumstances

A. Diabetic Ketoacidosis

Diabetic ketoacidosis (DKA) is a life-threatening medical emergency caused by inadequate or absent insulin replacement, which occurs in people with type 1 diabetes and infrequently in those with type 2 diabetes. It typically occurs in newly diagnosed type 1 patients or in those who have experienced interrupted insulin replacement, and rarely in people with type 2 diabetes who have concurrent unusually stressful conditions such as sepsis or

Benefits of Tight Glycemic Control in Diabetes

A long-term randomized prospective study involving 1441 type 1 patients in 29 medical centers reported in 1993 that "near normalization" of blood glucose resulted in a delay in onset and a major slowing of progression of microvascular and neuropathic complications of diabetes during follow-up periods of up to 10 years (Diabetes Control and Complications Trial [DCCT] Research Group, 1993). In the intensively treated group, mean glycated hemoglobin HbA_{1c} of 7.2% (normal < 6%) and mean blood glucose of 155 mg/dL were achieved, whereas in the conventionally treated group, HbA_{1c} averaged 8.9% with mean blood glucose of 225 mg/dL. Over the study period, which averaged 7 years, a reduction of approximately 60% in risk of diabetic retinopathy, nephropathy, and neuropathy was noted in the tight control group compared with the standard control group.

The DCCT study, in addition, introduced the concept of *glycemic memory*, which comprises the long-term benefits of any significant period of glycemic control. During a 6-year follow-up period, both the intensively and the conventionally treated groups had similar levels of glycemic control, and both had progression of carotid intimal-medial thickness. However, the intensively treated cohort had significantly less progression of intimal thickness.

The United Kingdom Prospective Diabetes Study (UKPDS) was a very large randomized prospective study carried out to study the effects of intensive glycemic control with several types of therapies and the effects of blood pressure control in type 2 diabetic patients. A total of 3867 newly diagnosed type 2 diabetic patients were studied over 10 years. A significant fraction of these were overweight and hypertensive. Patients were given dietary treatment alone or intensive therapy with insulin, chlorpropamide, glyburide, or glipizide. Metformin was an option for patients with inadequate response to other therapies. Tight control of blood pressure was added as a variable, with an angiotensin-converting enzyme inhibitor, a β blocker, or in some cases, a calcium channel blocker available for this purpose.

Tight control of diabetes, with reduction of HbA_{1c} from 9.1% to 7%, was shown to reduce the risk of microvascular complications overall compared with that achieved with conventional therapy (mostly diet alone, which decreased HbA_{1c} to 7.9%). Cardiovascular complications were not noted for any particular therapy; metformin treatment alone reduced the risk of macrovascular disease (myocardial infarction, stroke). Epidemiologic analysis of the study suggested that every 1% decrease in the HbA_{1c} achieved an estimated risk reduction of 37% for microvascular complications, 21% for any diabetes-related end point and death related to diabetes, and 14% for myocardial infarction.

Tight control of hypertension also had a surprisingly significant effect on microvascular disease (as well as more conventional hypertension-related sequelae) in these diabetic patients. Epidemiologic analysis of the results suggested that every 10 mm Hg decrease in the systolic pressure achieved an estimated risk reduction of 13% for diabetic microvascular complications, and 12% for any diabetes-related complication, 15% for death related to diabetes, and 11% for myocardial infarction.

Post-study monitoring showed that 5 years after the closure of the UKPDS, the benefits of intensive management on diabetic end points was maintained and the risk reduction for a myocardial infarction became significant. The benefits of metformin therapy were maintained.

These studies show that tight glycemic control benefits both type 1 and type 2 patients.

The STOP-NIDDM trial followed 1429 patients with impaired glucose tolerance who were randomized to treatment with acarbose or placebo over 3 years. This trial demonstrated that normalization of glycemic control in subjects with impaired glucose tolerance significantly diminished cardiovascular risk. The acarbose-treated group had a significant reduction in the development of major cardiovascular events and hypertension. A prospective placebo-controlled subgroup analysis has shown a marked decrease in the progression of intimal-medial thickness.

pancreatitis or are on high-dose steroid therapy. Signs and symptoms include nausea, vomiting, abdominal pain, deep slow (Kussmaul) breathing, change in mental status, elevated blood and urinary ketones and glucose, an arterial blood pH lower than 7.3, and low bicarbonate (< 15 mmol/L).

The fundamental treatment for DKA includes aggressive intravenous hydration and insulin therapy and maintenance of potassium and other electrolyte levels. Fluid and insulin therapy is based on the patient's individual needs and requires frequent reevaluation and modification. Close attention has to be given to hydration and renal status, the sodium and potassium levels, and the rate of correction of plasma glucose and plasma osmolality. Fluid therapy generally begins with normal saline. Regular human insulin should be used for intravenous therapy with a usual starting dose of about 0.1 IU/kg/h.

B. Hyperosmolar Hyperglycemic Syndrome

Hyperosmolar hyperglycemic syndrome (HHS) is diagnosed in persons with type 2 diabetes and is characterized by profound hyperglycemia and dehydration. It is associated with inadequate oral hydration, especially in elderly patients, with other illnesses, the use of medication that elevates the blood sugar or causes dehydration, such as phenytoin, steroids, diuretics, and β blockers, and with peritoneal dialysis and hemodialysis. The diagnostic hallmarks are declining mental status and even seizures, a plasma glucose of over 600 mg/dL, and a calculated serum osmolality higher than 320 mmol/L. Persons with HHS are not acidotic unless DKA is also present.

The treatment of HHS centers around aggressive rehydration and restoration of glucose and electrolyte homeostasis; the rate of correction of these variables must be monitored closely. Low-dose insulin therapy may be required.

Complications of Insulin Therapy

A. Hypoglycemia

1. Mechanisms and diagnosis—Hypoglycemic reactions are the most common complication of insulin therapy. They usually result from inadequate carbohydrate consumption, unusual physical exertion, or too large a dose of insulin.

Rapid development of hypoglycemia in persons with intact hypoglycemic awareness causes signs of autonomic hyperactivity—both sympathetic (tachycardia, palpitations, sweating, tremulousness) and parasympathetic (nausea, hunger)—and may progress to convulsions and coma if untreated.

In persons exposed to frequent hypoglycemic episodes during tight glycemic control, autonomic warning signals of hypoglycemia are less common or even absent. This dangerous acquired condition is termed "hypoglycemic unawareness." When patients lack the early warning signs of low blood glucose, they may not take corrective measures in time. In patients with persistent, untreated hypoglycemia, the manifestations of insulin excess may develop—confusion, weakness, bizarre behavior, coma, seizures—at which point they may not be able to procure or safely swallow glucose-containing foods. Hypoglycemic awareness may be restored by preventing frequent hypoglycemic episodes. An identification bracelet, necklace, or card in the wallet or purse, as well as some form of rapidly absorbed glucose, should be carried by every diabetic person who is receiving hypoglycemic drug therapy.

2. Treatment of hypoglycemia—All the manifestations of hypoglycemia are relieved by glucose administration. To expedite absorption, simple sugar or glucose should be given, preferably in liquid form. To treat mild hypoglycemia in a patient who is conscious and able to swallow, dextrose tablets, glucose gel, or any sugar-containing beverage or food may be given. If more severe hypoglycemia has produced unconsciousness or stupor, the treatment of choice is to give 20–50 mL of 50% glucose solution by intravenous infusion over a period of 2–3 minutes. If intravenous therapy is not available, 1 mg of glucagon injected either subcutaneously or intramuscularly may restore consciousness within 15 minutes to permit ingestion of sugar. If the patient is stuporous and glucagon is not available, small amounts of honey or syrup can be inserted into the buccal pouch. In general, however, oral feeding is contraindicated in unconscious patients. Emergency medical services should be called immediately for all episodes of severely impaired consciousness.

B. Immunopathology of Insulin Therapy

At least five molecular classes of insulin antibodies may be produced in diabetics during the course of insulin therapy: IgA, IgD, IgE, IgG, and IgM. There are two major types of immune disorders in these patients:

1. Insulin allergy—Insulin allergy, an immediate type hypersensitivity, is a rare condition in which local or systemic urticaria results from histamine release from tissue mast cells sensitized by anti-insulin IgE antibodies. In severe cases, anaphylaxis results.

Because sensitivity is often to noninsulin protein contaminants, the human and analog insulins have markedly reduced the incidence of insulin allergy, especially local reactions.

2. Immune insulin resistance—A low titer of circulating IgG anti-insulin antibodies that neutralize the action of insulin to a negligible extent develops in most insulin-treated patients. Rarely, the titer of insulin antibodies leads to insulin resistance and may be associated with other systemic autoimmune processes such as lupus erythematosus.

C. Lipodystrophy at Injection Sites

Injection of animal insulin preparations sometimes led to atrophy of subcutaneous fatty tissue at the site of injection. Since the development of human and analog insulin preparations of neutral pH, this type of immune complication is almost never seen. Injection of these newer preparations directly into the atrophic area often results in restoration of normal contours.

Hypertrophy of subcutaneous fatty tissue remains a problem if injected repeatedly at the same site. However, this may be corrected by avoiding the specific injection site or by liposuction.

D. Increased Cancer Risk

An increased risk of cancer attributed to insulin resistance and hyperinsulinemia has been reported in individuals with insulin resistance, prediabetes, and type 2 diabetes. Treatment with insulin and sulfonylureas, which increase circulating insulin levels, but not metformin possibly exacerbates that risk. These epidemiologic observations are preliminary and have not changed prescribing guidelines.

■ ORAL ANTIDIABETIC AGENTS

Seven categories of oral antidiabetic agents are now available in the USA for the treatment of persons with type 2 diabetes: insulin secretagogues (sulfonylureas, meglitinides, D-phenylalanine derivatives), biguanides, thiazolidinediones, α-glucosidase inhibitors, incretin-based therapies, an amylin analog, and a bile acid-binding sequestrant. The sulfonylureas and biguanides have been available the longest and are the traditional treatment choice for type 2 diabetes. Novel classes of rapid-acting insulin secretagogues, the meglitinides and D-phenylalanine derivatives, are alternatives to the short-acting sulfonylureas. Insulin secretagogues increase insulin secretion from beta cells. Biguanides decrease hepatic glucose production. The thiazolidinediones reduce insulin resistance. The incretin-based therapies control post-meal glucose excursions by increasing insulin release and decreasing glucagon secretion. The amylin analog also decreases post-meal glucose levels and reduces appetite. Alpha-glucosidase inhibitors slow the digestion and absorption of starch and disaccharides. Although still speculative, the mechanism of bile acid sequestrant's glucose-lowering effect is presumed to be related to a decrease in hepatic glucose output.

TABLE 41–5 **Regulation of insulin release in humans.**

Stimulants of insulin release
Humoral: Glucose, mannose, leucine, arginine, other amino acids, fatty acids (high concentrations)
Hormonal: Glucagon, glucagon-like peptide 1(7–37), glucose-dependent insulinotropic polypeptide, cholecystokinin, gastrin
Neural: β-Adrenergic stimulation, vagal stimulation
Drugs: Sulfonylureas, meglitinide, nateglinide, isoproterenol, acetylcholine
Inhibitors of insulin release
Hormonal: Somatostatin, insulin, leptin
Neural: α-Sympathomimetic effect of catecholamines
Drugs: Diazoxide, phenytoin, vinblastine, colchicine

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INSULIN SECRETAGOGUES: SULFONYLUREAS

Mechanism of Action

The major action of sulfonylureas is to increase insulin release from the pancreas (Table 41–5). Two additional mechanisms of action have been proposed—a reduction of serum glucagon levels and closure of potassium channels in extrapancreatic tissue (which are of unknown but probably minimal significance).

A. Insulin Release from Pancreatic Beta Cells

Sulfonylureas bind to a 140-kDa high-affinity sulfonylurea receptor (Figure 41–2) that is associated with a beta-cell inward rectifier ATP-sensitive potassium channel. Binding of a sulfonylurea inhibits the efflux of potassium ions through the channel and results in depolarization. Depolarization opens a voltage-gated calcium channel and results in calcium influx and the release of preformed insulin.

B. Reduction of Serum Glucagon Concentrations

Long-term administration of sulfonylureas to type 2 diabetics reduces serum glucagon levels, which may contribute to the hypoglycemic effect of the drugs. The mechanism for this suppressive effect of sulfonylureas on glucagon levels is unclear but appears to involve indirect inhibition due to enhanced release of both insulin and somatostatin, which inhibit alpha-cell secretion.

Efficacy & Safety of the Sulfonylureas

In 1970, the University Group Diabetes Program (UGDP) in the USA reported that the number of deaths due to cardiovascular disease in diabetic patients treated with tolbutamide was excessive compared with either insulin-treated patients or those receiving placebos. Owing to design flaws, this study and its conclusions were not generally accepted. In the United Kingdom, the UKPDS did not find an untoward cardiovascular effect of sulfonylurea usage in their large, long-term study.

The sulfonylureas continue to be widely prescribed, and six are available in the USA (Table 41–6). They are conventionally divided into first-generation and second-generation agents, which differ primarily in their potency and adverse effects. The first-generation sulfonylureas are increasingly difficult to procure, and as the second-generation agents become generic and less expensive, the older compounds probably will be discontinued.

FIRST-GENERATION SULFONYLUREAS

Tolbutamide is well absorbed but rapidly metabolized in the liver. Its duration of effect is relatively short, with an elimination half-life of 4–5 hours, and it is best administered in divided doses. Because of its short half-life, it is the safest sulfonylurea for elderly diabetics. Prolonged hypoglycemia has been reported rarely, mostly in patients receiving certain drugs (eg, dicumarol, phenylbutazone, some sulfonamides) that inhibit the metabolism of tolbutamide.

Chlorpropamide has a half-life of 32 hours and is slowly metabolized in the liver to products that retain some biologic activity; approximately 20–30% is excreted unchanged in the urine. Chlorpropamide also interacts with the drugs mentioned above that depend on hepatic oxidative catabolism, and it is contraindicated in patients with hepatic or renal insufficiency. Dosages higher than 500 mg daily increase the risk of jaundice. The average maintenance dosage is 250 mg daily, given as a single dose in the morning. Prolonged hypoglycemic reactions are more common in elderly patients, and the drug is contraindicated in this group. Other adverse effects include a hyperemic flush after alcohol ingestion in genetically predisposed patients and dilutional hyponatremia. Hematologic toxicity (transient leukopenia, thrombocytopenia) occurs in less than 1% of patients.

Tolazamide is comparable to chlorpropamide in potency but has a shorter duration of action. Tolazamide is more slowly absorbed than the other sulfonylureas, and its effect on blood glucose does not appear for several hours. Its half-life is about 7 hours. Tolazamide is metabolized to several compounds that retain hypoglycemic effects. If more than 500 mg/d are required, the dose should be divided and given twice daily.

SECOND-GENERATION SULFONYLUREAS

The second-generation sulfonylureas are prescribed more frequently in the USA than are the first-generation agents because they have fewer adverse effects and drug interactions. These potent sulfonylurea compounds—glyburide, glipizide, and glimepiride—should be used with caution in patients with cardiovascular disease or in elderly patients, in whom hypoglycemia would be especially dangerous.

Glyburide is metabolized in the liver into products with very low hypoglycemic activity. The usual starting dosage is 2.5 mg/d

TABLE 41–6 Sulfonylureas.

Sulfonylureas	Chemical Structure	Daily Dose	Duration of Action (hours)
Tolbutamide (Orinase)		0.5–2 g in divided doses	6–12
Tolazamide (Tolinase)		0.1–1 g as single dose or in divided doses	10–14
Chlorpropamide (Diabinese)		0.1–0.5 g as single dose	Up to 60
Glyburide (glibenclamide[1]) (Diaβeta, Micronase, Glynase PresTab)		1.25–20 mg	10–24
Glipizide (glydiazinamide[1]) (Glucotrol, Glucotrol XL)		5–30 mg (20 mg in Glucotrol XL)	10–24[2]
Glimepiride (Amaryl)		1–4 mg	12–24

[1]Outside USA.

[2]Elimination half-life considerably shorter (see text).

or less, and the average maintenance dosage is 5–10 mg/d given as a single morning dose; maintenance dosages higher than 20 mg/d are not recommended. A formulation of "micronized" glyburide (Glynase PresTab) is available in a variety of tablet sizes. However, there is some question as to its bioequivalence with nonmicronized formulations, and the FDA recommends careful monitoring to re-titrate dosage when switching from standard glyburide doses or from other sulfonylurea drugs.

Glyburide has few adverse effects other than its potential for causing hypoglycemia. Flushing has rarely been reported after ethanol ingestion, and the compound slightly enhances free water clearance. Glyburide is contraindicated in the presence of hepatic impairment and in patients with renal insufficiency.

Glipizide has the shortest half-life (2–4 hours) of the more potent agents. For maximum effect in reducing postprandial hyperglycemia, this agent should be ingested 30 minutes before breakfast because absorption is delayed when the drug is taken with food. The recommended starting dosage is 5 mg/d, with up to 15 mg/d given as a single dose. When higher daily dosages are required, they should be divided and given before meals. The maximum total daily dosage recommended by the manufacturer is 40 mg/d, although some studies indicate that the maximum therapeutic effect is achieved by 15–20 mg of the drug. An extended-release preparation (Glucotrol XL) provides 24-hour action after a once-daily morning dose (maximum of 20 mg/d). However, this formulation appears to have sacrificed its lower propensity for severe hypoglycemia compared with longer-acting glyburide without showing any demonstrable therapeutic advantages over the latter (which can be obtained as a generic drug).

Because of its shorter half-life, the regular formulation of glipizide is much less likely than glyburide to produce serious hypoglycemia. At least 90% of glipizide is metabolized in the liver to inactive products, and 10% is excreted unchanged in the urine. Glipizide therapy is therefore contraindicated in patients with

significant hepatic or renal impairment, who would be at high risk for hypoglycemia.

Glimepiride is approved for once-daily use as monotherapy or in combination with insulin. Glimepiride achieves blood glucose lowering with the lowest dose of any sulfonylurea compound. A single daily dose of 1 mg has been shown to be effective, and the recommended maximal daily dose is 8 mg. Glimepiride has a long duration of effect with a half-life of 5 hours, allowing once-daily dosing and thereby improving compliance. It is completely metabolized by the liver to metabolites with weak or no activity.

INSULIN SECRETAGOGUE: MEGLITINIDE

Repaglinide is the first member of the meglitinide group of insulin secretagogues (Table 41–7). These drugs modulate beta-cell insulin release by regulating potassium efflux through the potassium channels previously discussed. There is overlap with the sulfonylureas in their molecular sites of action because the meglitinides have two binding sites in common with the sulfonylureas and one unique binding site.

Repaglinide has a very fast onset of action, with a peak concentration and peak effect within approximately 1 hour after ingestion, but the duration of action is 4–7 hours. It is hepatically cleared by CYP3A4 with a plasma half-life of 1 hour. Because of its rapid onset, repaglinide is indicated for use in controlling post-prandial glucose excursions. The drug should be taken just before each meal in doses of 0.25–4 mg (maximum 16 mg/d); hypoglycemia is a risk if the meal is delayed or skipped or contains inadequate carbohydrate. This drug should be used cautiously in individuals with renal and hepatic impairment. Repaglinide is approved as monotherapy or in combination with biguanides.
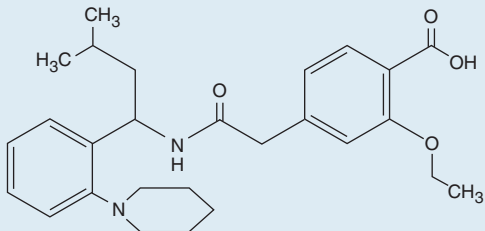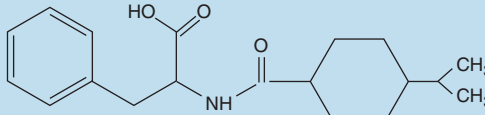
There is no sulfur in its structure, so repaglinide may be used in type 2 diabetics with sulfur or sulfonylurea allergy.

INSULIN SECRETAGOGUE: D-PHENYLALANINE DERIVATIVE

Nateglinide, a D-phenylalanine derivative, is the latest insulin secretagogue to become clinically available. Nateglinide stimulates very rapid and transient release of insulin from beta cells through closure of the ATP-sensitive K^+ channel. It also partially restores initial insulin release in response to an intravenous glucose tolerance test. This may be a significant advantage of the drug because type 2 diabetes is associated with loss of this initial insulin response. The restoration of more normal insulin secretion may suppress glucagon release early in the meal and result in less endogenous or hepatic glucose production. Nateglinide may have a special role in the treatment of individuals with isolated post-prandial hyperglycemia, but it has minimal effect on overnight or fasting glucose levels. Nateglinide is efficacious when given alone or in combination with nonsecretagogue oral agents (such as metformin). In contrast to other insulin secretagogues, dose titration is not required.

Nateglinide is ingested just before meals. It is absorbed within 20 minutes after oral administration with a time to peak concentration of less than 1 hour and is metabolized in the liver by CYP2C9 and CYP3A4 with a half-life of about 1 hour. The overall duration of action is about 4 hours. Nateglinide amplifies the insulin secretory response to a glucose load, but it has a markedly diminished effect in the presence of normoglycemia. The incidence of hypoglycemia with nateglinide may be the lowest of all the secretagogues, and nateglinide has the advantage of being safe in those with very reduced renal function.

TABLE 41–7 **Other insulin secretagogues.**

Drug	Chemical Structure	Oral Dose	$t_{1/2}$	Duration of Action (hours)
Repaglinide (Prandin)		0.25–4 mg before meals	1 hour	4–7
Nateglinide (Starlix)		60–120 mg before meals	1 hour	4

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BIGUANIDES

The structure of **metformin** is shown below. Phenformin (an older biguanide) was discontinued in the USA because of its association with lactic acidosis and because there was no documentation of any long-term benefit from its use.

$$H_2N-\underset{H_2N}{\overset{}{C}}=N-\underset{\overset{||}{NH}}{C}-N\overset{CH_3}{\underset{CH_3}{<}}$$

Metformin
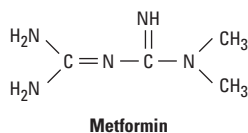
Mechanisms of Action

A full explanation of the mechanism of action of the biguanides remains elusive, but their primary effect is to reduce hepatic glucose production through activation of the enzyme AMP-activated protein kinase (AMPK). Possible minor mechanisms of action include impairment of renal gluconeogenesis, slowing of glucose absorption from the gastrointestinal tract, with increased glucose to lactate conversion by enterocytes, direct stimulation of glycolysis in tissues, increased glucose removal from blood, and reduction of plasma glucagon levels. The biguanide blood glucose-lowering action does not depend on functioning pancreatic beta cells. Patients with type 2 diabetes have considerably less fasting hyperglycemia as well as lower postprandial hyperglycemia after administration of biguanides; however, hypoglycemia during biguanide therapy is essentially unknown. These agents are therefore more appropriately termed "euglycemic" agents.

Metabolism & Excretion

Metformin has a half-life of 1.5–3 hours, is not bound to plasma proteins, is not metabolized, and is excreted by the kidneys as the active compound. As a consequence of metformin's blockade of gluconeogenesis, the drug may impair the hepatic metabolism of lactic acid. In patients with renal insufficiency, biguanides accumulate and thereby increase the risk of lactic acidosis, which appears to be a dose-related complication.

Clinical Use

Biguanides are recommended as first-line therapy for type 2 diabetes. Because metformin is an insulin-sparing agent and does not increase body weight or provoke hypoglycemia, it offers obvious advantages over insulin or sulfonylureas in treating hyperglycemia in such persons. The UKPDS reported that metformin therapy decreases the risk of macrovascular as well as microvascular disease; this is in contrast to the other therapies, which only modified microvascular morbidity. Biguanides are also indicated for use in combination with insulin secretagogues or thiazolidinediones in type 2 diabetics in whom oral monotherapy is inadequate. Metformin is useful in the prevention of type 2 diabetes; the landmark Diabetes Prevention Program concluded that metformin is efficacious in preventing the new onset of type 2 diabetes in middle-aged, obese persons with impaired glucose tolerance and fasting hyperglycemia. It is interesting that metformin did not prevent diabetes in older, leaner prediabetics.

The dosage of metformin is from 500 mg to a maximum of 2.55 g daily, with the lowest effective dose being recommended. Depending on whether the primary abnormality is fasting hyperglycemia or postprandial hyperglycemia, metformin therapy can be initiated as a once-daily dose at bedtime or before a meal. A common schedule for fasting hyperglycemia would be to begin with a single 500-mg tablet at bedtime for a week or more. If this is tolerated without gastrointestinal discomfort and if hyperglycemia persists, a second 500-mg tablet may be added with the evening meal. If further dose increases are required, an additional 500-mg tablet can be added to be taken with breakfast or the midday meal, or the larger (850-mg) tablet can be prescribed twice daily or even three times daily (the maximum recommended dosage) if needed. Dosage should always be divided because ingestion of more than 1000 mg at any one time usually provokes significant gastrointestinal adverse effects.

Epidemiologic studies suggest that metformin use may dramatically reduce the risk of some cancers. These data are still preliminary, and the speculative mechanism of action is a decrease in insulin (which also functions as a growth factor) levels as well as direct cellular effects mediated by AMPK.
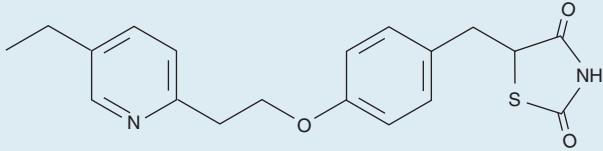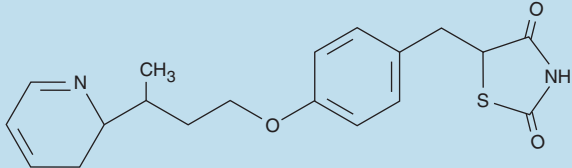
Toxicities

The most common toxic effects of metformin are gastrointestinal (anorexia, nausea, vomiting, abdominal discomfort, and diarrhea), which occur in up to 20% of patients. They are dose related, tend to occur at the onset of therapy, and are often transient. However, metformin may have to be discontinued in 3–5% of patients because of persistent diarrhea. Absorption of vitamin B_{12} appears to be reduced during long-term metformin therapy, and annual screening of serum vitamin B_{12} levels and red blood cell parameters has been encouraged by the manufacturer to determine the need for vitamin B_{12} injections. In the absence of hypoxia or renal or hepatic insufficiency, lactic acidosis is less common with metformin therapy than with phenformin therapy.

Biguanides are contraindicated in patients with renal disease, alcoholism, hepatic disease, or conditions predisposing to tissue anoxia (eg, chronic cardiopulmonary dysfunction) because of the increased risk of lactic acidosis induced by these drugs.

THIAZOLIDINEDIONES

Thiazolidinediones (Tzds) act to decrease insulin resistance. Tzds are ligands of **peroxisome proliferator-activated receptor-gamma (PPAR-γ),** part of the steroid and thyroid superfamily of nuclear receptors. These PPAR receptors are found in muscle, fat, and liver. PPAR-γ receptors modulate the expression of the genes involved in lipid and glucose metabolism, insulin signal transduction, and adipocyte and other tissue differentiation. The available Tzds do not have identical clinical effects, and new drug development will focus on defining PPAR effects and designing ligands that have selective action—much like the selective estrogen receptor modulators (see Chapter 40).

TABLE 41–8 Thiazolidinediones.

Thiazolidinedione	Chemical Structure	Oral Dose
Pioglitazone (Actos)		15–45 mg once daily
Rosiglitazone (Avandia)		2–8 mg once daily

In addition to targeting adipocytes, myocytes, and hepatocytes, Tzds also have significant effects on vascular endothelium, the immune system, the ovaries, and tumor cells. Some of these responses may be independent of the PPAR-γ pathway. The Tzd oncogenic effects are complex and may be both tumorigenic and antitumorigenic.

In persons with diabetes, a major site of Tzd action is adipose tissue, where the drug promotes glucose uptake and utilization and modulates synthesis of lipid hormones or cytokines and other proteins involved in energy regulation. Tzds also regulate adipocyte apoptosis and differentiation. Numerous other effects have been documented in animal studies, but applicability to human tissues has yet to be determined.

Two thiazolidinediones are currently available: pioglitazone and rosiglitazone (Table 41–8). Their distinct side chains create differences in therapeutic action, metabolism, metabolite profile, and adverse effects. An earlier compound, troglitazone, was withdrawn from the market because of hepatic toxicity thought to be related to its side chain.

Pioglitazone has PPAR-α as well as PPAR-γ activity. It is absorbed within 2 hours of ingestion; although food may delay uptake, total bioavailability is not affected. Absorption is decreased with concomitant use of bile acid sequestrants. Pioglitazone is metabolized by CYP2C8 and CYP3A4 to active metabolites. The bioavailability of numerous other drugs also degraded by these enzymes may be affected by pioglitazone therapy, including estrogen-containing oral contraceptives; additional methods of contraception are advised. Pioglitazone may be taken once daily; the usual starting dose is 15–30 mg/d, and the maximum is 45 mg/d. A triglyceride-lowering effect is observed with pioglitazone and is more significant than that of rosiglitazone, presumably because of its PPAR-α-binding characteristics. Pioglitazone is approved as a monotherapy and in combination with metformin, sulfonylureas, and insulin for the treatment of type 2 diabetes. The risk of bladder cancer appears to be cumulatively increased with high doses.

Rosiglitazone is rapidly absorbed and highly protein-bound. It is metabolized in the liver to minimally active metabolites, predominantly by CYP2C8 and to a lesser extent by CYP2C9. It is administered once or twice daily; 2–8 mg is the usual total dose.

Rosiglitazone shares the common Tzd adverse effects but appears to carry more cardiovascular risk than pioglitazone. Concurrent administration of nitrates and insulin putatively enhances the risk of myocardial infarction and is contraindicated; renin-angiotensin system blockers may have a similar risk but are not specifically prohibited. Because of toxicities, the FDA now limits rosiglitazone prescriptions to patients already on treatment with the medication, and to those whose blood sugar cannot be controlled with other antidiabetic medicines and who, after consultation with their provider, do not wish to be on pioglitazone or a pioglitazone-containing drug. *For those restricted populations, rosiglitazone is approved for use in type 2 diabetes as monotherapy, in double combination therapy with a biguanide or sulfonylurea, or in quadruple combination with a biguanide, sulfonylurea, and insulin.*

Tzds are considered euglycemics and are efficacious in about 70% of new users. The overall response is similar to that achieved with sulfonylurea and biguanide monotherapy. Individuals experiencing secondary failure with other oral agents should benefit from the addition (rather than substitution) of a Tzd. Because their mechanism of action involves gene regulation, the Tzds have a slow onset and offset of activity over weeks or even months. Combination therapy with sulfonylureas and insulin can lead to hypoglycemia and may require dosage adjustment.

An adverse effect common to both Tzds is fluid retention, which presents as a mild anemia and peripheral edema, especially when the drugs are used in combination with insulin or insulin secretagogues. Both drugs increase the risk of heart failure. Many users have a dose-related weight gain (average 1–3 kg), which may be fluid related. Rarely, new or worsening macular edema has been reported in association with treatment. Loss of bone mineral density and increased atypical extremity bone fractures in women are described for both compounds, which is postulated to be due to decreased osteoblast formation. Studies are ongoing to determine whether the demineralization and fracture risk is increased in men. Long-term therapy is associated with a drop in triglyceride levels and a slight rise in high-density lipoprotein (HDL) and low-density lipoprotein (LDL) cholesterol values. These agents should not be used during pregnancy or in the presence of significant liver disease (ALT more than 2.5 times upper limit of normal) or with

a concurrent diagnosis of heart failure. Because of the hepatotoxicity observed with troglitazone, a discontinued Tzd, the FDA continues to require monitoring of liver function tests before initiation of Tzd therapy and periodically afterward. To date, hepatotoxicity has not been associated with rosiglitazone or pioglitazone. Anovulatory women may resume ovulation and should be counseled on the increased risk of pregnancy.

Thiazolidinediones have benefit in the *prevention* of type 2 diabetes. The Diabetes Prevention Trial reported a 75% reduction in diabetes incidence rate when troglitazone was administered to patients with prediabetes. Another study reported that troglitazone therapy significantly decreased the recurrence of diabetes mellitus in high-risk Hispanic women with a history of gestational diabetes.

Although these medications are highly efficacious, the adverse effects of weight gain, congestive heart failure, demineralization and increased bone fracture in women; possible (for rosiglitazone) worsening of cardiovascular status; and unknown oncogenic risk potentially limit their popularity and future use.

ALPHA-GLUCOSIDASE INHIBITORS

Acarbose and **miglitol** are competitive inhibitors of the intestinal α-glucosidases and reduce postmeal glucose excursions by delaying the digestion and absorption of starch and disaccharides (Table 41–9). Only monosaccharides, such as glucose and fructose, can be transported out of the intestinal lumen and into the bloodstream. Complex starches, oligosaccharides, and disaccharides must be broken down into individual monosaccharides before being absorbed in the duodenum and upper jejunum. This digestion is facilitated by enteric enzymes, including pancreatic α-amylase and α-glucosidases that are attached to the brush border of the intestinal cells. Miglitol differs structurally from acarbose and is six times more potent in inhibiting sucrase. Although the binding affinity of the two compounds differs, acarbose and miglitol both target the α-glucosidases: sucrase, maltase, glucoamylase, and dextranase. Miglitol alone has effects on isomaltase and on β-glucosidases, which split β-linked sugars such as lactose. Acarbose alone has a small effect on α-amylase. The consequence of enz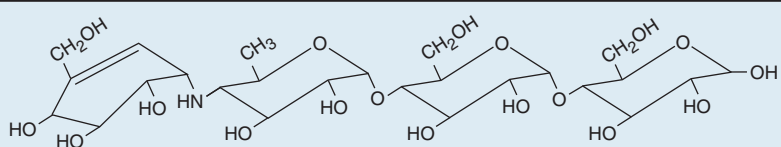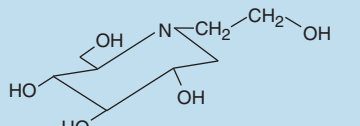yme inhibition is to minimize upper intestinal digestion and defer digestion (and thus absorption) of the ingested starch and disaccharides to the distal small intestine, thereby lowering postmeal glycemic excursions as much as 45–60 mg/dL and creating an insulin-sparing effect.

Monotherapy with these drugs is associated with a modest drop (0.5–1%) in glycohemoglobin levels and a 20–25 mg/dL fall in fasting glucose levels. They are FDA-approved for persons with type 2 diabetes as monotherapy and in combination with sulfonylureas, in which the glycemic effect is additive. Both acarbose and miglitol are taken in doses of 25–100 mg just before ingesting the first portion of each meal; therapy should be initiated with the lowest dose and slowly titrated upward, and a similar amount of starch and disaccharides should be ingested at each meal.

Prominent adverse effects include flatulence, diarrhea, and abdominal pain and result from the appearance of undigested carbohydrate in the colon that is then fermented into short-chain fatty acids, releasing gas. These adverse effects tend to diminish with ongoing use because chronic exposure to carbohydrate induces the expression of α-glucosidase in the jejunum and ileum, increasing distal small intestine glucose absorption and minimizing the passage of carbohydrate into the colon. Although not a problem with monotherapy or combination therapy with a biguanide, hypoglycemia may occur with concurrent sulfonylurea treatment. Hypoglycemia should be treated with glucose (dextrose) and not sucrose, whose breakdown may be blocked. These drugs are contraindicated in patients with inflammatory bowel disease or any intestinal condition that could be worsened by gas and distention. Because both miglitol and acarbose are excreted by the kidneys, these medications should not be prescribed in individuals with renal impairment. Acarbose has been associated with reversible hepatic enzyme elevation and should be used with caution in the presence of hepatic disease.

The STOP-NIDDM trial demonstrated that α-glucosidase therapy in prediabetic persons successfully prevented a significant number of new cases of type 2 diabetes and helped restore beta-cell function, in addition to reducing cardiovascular disease and hypertension. Intervention with acarbose also reduced cardiovascular events in persons with diabetes. Diabetes and cardiovascular disease prevention may become a further indication for this class of medications.

TABLE 41–9 Alpha-glucosidase inhibitors.

Alpha-Glucosidase Inhibitor	Chemical Structure	Oral Dose
Acarbose (Precose)		25–100 mg before meals
Miglitol (Glyset)		25–100 mg before meals

Alpha-glucosidase inhibitors are infrequently prescribed in the United States because of their prominent gastrointestinal adverse effects and relatively minor glucose-lowering benefit.

BILE ACID SEQUESTRANTS

Initially developed as a bile acid sequestrant and cholesterol-lowering drug, **colesevelam hydrochloride** is now approved as an antihyperglycemic therapy for persons with type 2 diabetes who are taking other medications or have not achieved adequate control with diet and exercise. The exact mechanism of action is unknown but presumed to involve an interruption of the enterohepatic circulation and a decrease in farnesoid X receptor (FXR) activation. FXR is a nuclear receptor with multiple effects on cholesterol, glucose, and bile acid metabolism. Bile acids are natural ligands of the FXR. Additionally, the drug may impair glucose absorption.

Colesevelam is administered as a pill or an oral suspension in a dosage of 1875 mg twice daily or 3750 mg once daily. It is not systemically absorbed or modified and is eliminated intact in the feces. In clinical trials, it lowered the hemoglobin A_{1c} (HbA_{1c}) concentration about 0.5%, and LDL cholesterol by 15% or more. Side effects include gastrointestinal complaints (constipation, indigestion, flatulence). The medication may impair absorption of multiple other medications including fat-soluble vitamins, glyburide, levothyroxine, and oral contraceptives, and should not be used in individuals with hypertriglyceridemia, a history of pancreatitis secondary to hypertriglyceridemia, or esophageal, gastric, or intestinal disorders.

AMYLIN ANALOG

Pramlintide, a synthetic analog of amylin, is an injectable antihyperglycemic agent that modulates postprandial glucose levels and is approved for preprandial use in persons with type 1 and type 2 diabetes. It is administered in addition to insulin in those who are unable to achieve their target postprandial blood sugar levels. Pramlintide suppresses glucagon release via undetermined mechanisms, delays gastric emptying, and has central nervous system-mediated anorectic effects. It is rapidly absorbed after subcutaneous administration; levels peak within 20 minutes, and the duration of action is not more than 150 minutes. Pramlintide is renally metabolized and excreted, but even at low creatinine clearance there is no significant change in bioavailability. It has not been evaluated in dialysis patients. The most reliable absorption is from the abdomen and thigh; arm administration is less reliable.

Pramlintide should be injected immediately before eating; doses range from 15 to 60 mcg subcutaneously for individuals with type 1 diabetes and from 60 to 120 mcg subcutaneously for individuals with type 2 diabetes. Therapy with this agent should be initiated with the lowest dose and titrated upward. Because of the risk of hypoglycemia, concurrent rapid- or short-acting mealtime insulin doses should be decreased by 50% or more. Concurrent insulin secretagogue doses also may need to be decreased in persons with type 2 diabetes. Pramlintide should always be injected by itself with a separate syringe; it cannot be mixed with insulin. The major adverse effects of pramlintide are hypoglycemia and gastrointestinal symptoms, including nausea, vomiting, and anorexia.

GLUCAGON-LIKE POLYPEPTIDE-1 (GLP-1) RECEPTOR AGONISTS

In type 2 diabetes, the release of glucagon-like polypeptide is diminished postprandially, which leads to inadequate glucagon suppression and excessive hepatic glucose output. Two synthetic analogs of glucagon-like polypeptide, **exenatide** and **liraglutide,** are commercially available to help restore GLP-1 activity. These therapies have multiple actions such as potentiation of glucose-mediated insulin secretion, suppression of postprandial glucagon release through as-yet unknown mechanisms, slowed gastric emptying, and a central loss of appetite. The increased insulin secretion is speculated to be due in part to an increase in beta-cell mass. The increased beta-cell mass may result from decreased beta-cell apoptosis, increased beta-cell formation, or both.

Exenatide, a derivative of the exendin-4 peptide in Gila monster venom, was the first incretin therapy to become available for the treatment of diabetes. It has a 53% homology with native GLP-1, and a glycine substitution to reduce degradation by dipeptidyl peptidase-4 (DPP-4). Exenatide is approved as an injectable, adjunctive therapy in persons with type 2 diabetes treated with metformin or metformin plus sulfonylureas who still have suboptimal glycemic control. Exenatide is absorbed equally from arm, abdomen, or thigh injection sites, reaching a peak concentration in approximately 2 hours with a duration of action of up to 10 hours. It undergoes glomerular filtration, and dosage adjustment is required only when the creatinine clearance is less than 30 mL/min.

Exenatide is injected subcutaneously within 60 minutes before a meal; therapy is initiated at 5 mcg twice daily, with a maximum dosage of 10 mcg twice daily. When exenatide is added to preexisting sulfonylurea therapy, the oral hypoglycemic dosage may need to be decreased to prevent hypoglycemia. The major adverse effects are nausea (about 44% of users) and vomiting and diarrhea. The nausea decreases with ongoing exenatide usage. Exenatide mono- and combination therapy results in HbA_{1c} reductions from 0.2% to 1.2%. Weight loss in the range of 2–3 kg is reported in some users, presumably because of the nausea and anorectic effects. A serious and, in some cases, fatal adverse effect of exenatide is necrotizing and hemorrhagic pancreatitis. Antibodies to exenatide are formed with chronic use, the clinical significance of which is unclear.

Liraglutide is a long-acting synthetic GLP-1 analog with 97% homology to native GLP-1 but has a prolonged half-life that permits once-daily dosing. Liraglutide interacts with the GLP-1 receptor and acts to increase insulin and decrease glucagon release.

Liraglutide is approved for the treatment of type 2 diabetes as an injectable therapy in patients who achieve inadequate control with diet and exercise, and are receiving concurrent treatment with metformin, sulfonylureas, or Tzds. It is not recommended as a first-line therapy or for use with insulin. Treatment is initiated at 0.6 mg and is titrated in weekly increments of 0.6 mg as needed, and as tolerated, to achieve glycemic goals. Peak levels are obtained in 8–12 hours, and the elimination half-life is about 13 hours.

Liraglutide therapy results in a reduction of HbA_{1c} from 0.8% to 1.5%; weight loss ranges from nominal to 3.2 kg.. Experience with liraglutide in patients with renal or hepatic impairment is limited and it should be used with caution in these populations.

Common side effects of liraglutide are headache, nausea, and diarrhea; antibody formation, urticaria, and other immune reactions also are observed Hypoglycemia can occur with concomitant sulfonylurea use and may require a dose reduction of the oral hypoglycemic agent. Pancreatitis is another serious adverse effect; liraglutide is contraindicated in individuals with a history of pancreatitis and should be permanently discontinued if pancreatitis develops. Because rodents exposed to liraglutide developed thyroid C-cell tumors, there is an FDA mandated "black box" warning that liraglutide is contraindicated in individuals with a personal or family history of medullary cancer or multiple endocrine neoplasia type 2.

Although they require injection, the GLP-1 receptor ligands have gained popularity because of the improved glucose control and associated anorexia and weight loss in some users. Safety issues, however, may deter future use.

DIPEPTIDYL PEPTIDASE-4 (DPP-4) INHIBITORS

Sitagliptin, saxagliptin, and **linagliptin** are inhibitors of DPP-4, the enzyme that degrades incretin hormones. These drugs increase circulating levels of native GLP-1 and glucose-dependent insulinotropic polypeptide (GIP), which ultimately decreases postprandial glucose excursions by increasing glucose-mediated insulin secretion and decreasing glucagon levels. They are approved as adjunctive therapy to diet and exercise in the treatment of individuals with type 2 diabetes who have failed to achieve glycemic goals.

Sitagliptin has an oral bioavailability of over 85%, achieves peak concentrations within 1–4 hours, and has a half-life of approximately 12 hours. It is primarily (87%) excreted in the urine in part by active tubular secretion of the drug. Hepatic metabolism is limited and mediated largely by the cytochrome CYP3A4 isoform and, to a lesser degree, by CYP2C8. The metabolites have insignificant activity. The usual dosage is 100 mg orally once daily. Sitagliptin has been studied as monotherapy and in combination with metformin, sulfonylureas, and Tzds. Therapy with sitagliptin has resulted in HbA_{1c} reductions of between 0.5% and 1.0%.

Common adverse effects include nasopharyngitis, upper respiratory infections, headaches, and hypoglycemia when the drug is combined with insulin secretagogues or insulin. There are postmarketing reports of acute pancreatitis (fatal and nonfatal) and severe allergic and hypersensitivity reactions. Sitagliptin should be immediately discontinued if pancreatitis or allergic and hypersensitivity reactions occur. Dosage should be reduced in patients with renal impairment and may need to be adjusted to prevent hypoglycemia if there is concurrent insulin secretagogue or insulin therapy.

Saxagliptin is given orally as 2.5–5 mg daily. The drug reaches maximal concentrations within 2 hours (4 hours for its active metabolite). It is minimally protein bound, and undergoes hepatic metabolism by CYP3A4/5. The major metabolite is active, and

excretion is by both renal and hepatic pathways. The terminal plasma half-life is 2.5 hours for saxagliptin and 3.1 hours for its active metabolite. Dosage adjustment is recommended for individuals with renal impairment and concurrent use of strong CYP3A4/5 inhibitors such as antiviral, antifungal, and certain antibacterial agents.

Saxagliptin is approved as monotherapy and in combination with biguanides, sulfonylureas, and Tzds. It has not been studied in combination with insulin. During clinical trials, mono- and combination therapy with sitagliptin resulted in an HbA_{1c} reduction in the range of 0.4–0.9%.

Adverse effects include an increased rate of infections (upper respiratory tract and urinary tract), headaches, peripheral edema (when combined with a Tzd), hypoglycemia (when combined with a sulfonylurea), and hypersensitivity reactions (urticaria, facial edema). The dose of a concurrently administered insulin secretagogue or insulin may need to be lowered to prevent hypoglycemia.

Linagliptin is the most recently introduced drug in this class and appears to have properties similar to sitagliptin and saxagliptin. It is approved for use as monotherapy and in combination with metformin, glimepiride, and pioglitazone.

COMBINATION THERAPY—ORAL ANTIDIABETIC AGENTS & INJECTABLE MEDICATION

Combination Therapy in Type 2 Diabetes Mellitus

Failure to maintain a good response to therapy over the long term owing to a progressive decrease in beta-cell mass, reduction in physical activity, decline in lean body mass, or increase in ectopic fat deposition remains a disconcerting problem in the management of type 2 diabetes. Multiple medications may be required to achieve glycemic control. Unless there is a contraindication, medical therapy should be initiated with a biguanide. If clinical failure occurs with metformin monotherapy, a second agent or insulin is added. The second-line drug can be an insulin secretagogue, Tzd, incretin-based therapy, amylin analog, or a glucosidase inhibitor; preference is given to sulfonylureas or insulin because of cost, adverse effects, and safety concerns. Third-line therapy can include metformin, multiple other oral medications, or a noninsulin injectable and metformin and intensified insulin therapy. Recommended fourth-line therapy is intensified insulin management with or without metformin or Tzd.

A. Combination Therapy with GLP-1 Receptor Agonists

Exenatide and liraglutide are approved for use in individuals who fail to achieve desired glycemic control on metformin, sulfonylureas, metformin plus sulfonylureas, or (for liraglutide) metformin plus sulfonylureas and Tzds. Hypoglycemia is a risk when the GLP-1 receptor agonists are used with an insulin secretagogue or with insulin. The doses of the latter drugs should be reduced at the initiation of therapy and subsequently titrated.

B. Combination Therapy with DPP-4 Inhibitors

Sitagliptin, saxagliptin, and linagliptin are approved for use in individuals who fail to achieve desired glycemic control on metformin, sulfonylureas, or Tzds. Hypoglycemia is a risk when the DPP-4 inhibitors are used with an insulin secretagogue or with insulin, and a dosage adjustment of the latter drugs may be required to prevent hypoglycemia.

C. Combination Therapy with Pramlintide

Pramlintide is approved for concurrent mealtime administration in individuals with type 2 diabetes treated with insulin, metformin, or a sulfonylurea who are unable to achieve their postprandial glucose targets. Combination therapy results in a significant reduction in early postprandial glucose excursions; mealtime insulin or sulfonylurea doses usually have to be reduced to prevent hypoglycemia.

D. Combination Therapy with Insulin

Bedtime insulin has been suggested as an adjunct to oral antidiabetic therapy in patients with type 2 diabetes who have not responded to maximal oral therapy. Although not formally FDA approved, clinical practice has evolved to include sulfonylureas, meglitinides, D-phenylalanine derivatives, biguanides, thiazolidinediones, α-glucosidase inhibitors, GLP-1 receptor agonists, DPP-4 inhibitors, and bile acid sequestrants given in conjunction with insulin. National and international committee practice guidelines, however, recommend avoiding polypharmacy, especially with more expensive agents, and urge early introduction of insulin when an individual is unable to achieve glycemic targets.

Persons unable to achieve glycemic control with bedtime insulin as described generally require full insulin replacement and multiple daily injections of insulin. Insulin secretagogues are redundant when a person is receiving multiple daily insulin injections, but persons with severe insulin resistance may benefit from the addition of metformin. When metformin is added to the regimen of a person already taking insulin, the blood glucose should be closely monitored and the insulin dosage decreased as needed to avoid hypoglycemia.

Combination Therapy in Type 1 Diabetes Mellitus

Insulin secretagogues (sulfonylureas, meglitinides, or D-phenylalanine derivatives), Tzds, metformin, α-glucosidase inhibitors, GLP-1 receptor agonists, DPP-4 inhibitors, or bile acid sequestrants are *not* approved for use in type 1 diabetes.

Combination Therapy with Pramlintide

Pramlintide is approved for concurrent mealtime administration in individuals with type 1 diabetes who have poor glucose control after eating despite optimal insulin therapy. The addition of pramlintide leads to a significant reduction in early postprandial glucose excursions; mealtime insulin doses usually should be reduced to prevent hypoglycemia.

■ GLUCAGON

Chemistry & Metabolism

Glucagon is synthesized in the alpha cells of the pancreatic islets of Langerhans (Table 41–1). Glucagon is a peptide—identical in all mammals—consisting of a single chain of 29 amino acids, with a molecular weight of 3485. Selective proteolytic cleavage converts a large precursor molecule of approximately 18,000 MW to glucagon. One of the precursor intermediates consists of a 69-amino-acid peptide called **glicentin,** which contains the glucagon sequence interposed between peptide extensions.

Glucagon is extensively degraded in the liver and kidney as well as in plasma and at its tissue receptor sites. Because of its rapid inactivation by plasma, chilling of the collecting tubes and addition of inhibitors of proteolytic enzymes are necessary when samples of blood are collected for immunoassay of circulating glucagon. Its half-life in plasma is between 3 and 6 minutes, which is similar to that of insulin.

"Gut Glucagon"

Glicentin immunoreactivity has been found in cells of the small intestine as well as in pancreatic alpha cells and in effluents of perfused pancreas. The intestinal cells secrete **enteroglucagon,** a family of glucagon-like peptides, of which glicentin is a member, along with glucagon-like peptides 1 and 2 (GLP-1 and GLP-2). Unlike the pancreatic alpha cell, these intestinal cells lack the enzymes to convert glucagon precursors to true glucagon by removing the carboxyl terminal extension from the molecule.

Glucagon-like Peptide 1 (GLP-1)

The function of the enteroglucagons has not been clarified, although smaller peptides can bind hepatic glucagon receptors where they exert partial activity. A derivative of the 37-amino-acid form of GLP-1 that lacks the first six amino acids (GLP-1[7–37]) is a potent stimulant of insulin synthesis and release and beta-cell mass. In addition, it inhibits glucagon secretion, slows gastric emptying, and has an anorectic effect. After oral glucose ingestion, GLP-1 along with another gut hormone, GIP, accounts for as much as 70% of the induced insulin secretion. GLP-1 represents the predominant form of GLP in the human intestine and has been termed *insulinotropin*. It has been considered as a potential therapeutic agent in type 2 diabetes. However, GLP-1 requires continuous subcutaneous infusion to produce a sustained lowering of both fasting and postprandial hyperglycemia in type 2 diabetic patients; therefore, its clinical usefulness is limited. Exenatide and liraglutide (see previous text) are GLP-1 receptor agonist analogs with more practical half-lives.

Pharmacologic Effects of Glucagon

A. Metabolic Effects

The first six amino acids at the amino terminal of the glucagon molecule bind to specific G_s protein-coupled receptors on liver

cells. This leads to an increase in cAMP, which facilitates catabolism of stored glycogen and increases gluconeogenesis and ketogenesis. The immediate pharmacologic result of glucagon infusion is to raise blood glucose at the expense of stored hepatic glycogen. There is no effect on skeletal muscle glycogen, presumably because of the lack of glucagon receptors on skeletal muscle. Pharmacologic amounts of glucagon cause release of insulin from normal pancreatic beta cells, catecholamines from pheochromocytoma, and calcitonin from medullary carcinoma cells.

B. Cardiac Effects

Glucagon has a potent inotropic and chronotropic effect on the heart, mediated by the cAMP mechanism described above. Thus, it produces an effect very similar to that of β-adrenoceptor agonists without requiring functioning β receptors.

C. Effects on Smooth Muscle

Large doses of glucagon produce profound relaxation of the intestine. In contrast to the above effects of the peptide, this action on the intestine may be due to mechanisms other than adenylyl cyclase activation.

Clinical Uses

A. Severe Hypoglycemia

The major use of glucagon is for emergency treatment of severe hypoglycemic reactions in patients with type 1 diabetes when unconsciousness precludes oral feedings and intravenous glucose treatment is not possible. Recombinant glucagon is currently available in 1-mg vials for parenteral use (Glucagon Emergency Kit). Nasal sprays have been developed for this purpose but have not yet received FDA approval.

B. Endocrine Diagnosis

Several tests use glucagon to diagnose endocrine disorders. In patients with type 1 diabetes mellitus, a classic research test of pancreatic beta-cell secretory reserve uses 1 mg of glucagon administered as an intravenous bolus. Because insulin-treated patients develop circulating anti-insulin antibodies that interfere with radioimmunoassays of insulin, measurements of C-peptide are used to indicate beta-cell secretion.

C. Beta-Adrenoceptor Blocker Overdose

Glucagon is sometimes useful for reversing the cardiac effects of an overdose of β-blocking agents because of its ability to increase cAMP production in the heart. However, it is not clinically useful in the treatment of cardiac failure.

D. Radiology of the Bowel

Glucagon has been used extensively in radiology as an aid to X-ray visualization of the bowel because of its ability to relax the intestine.

Adverse Reactions

Transient nausea and occasional vomiting can result from glucagon administration. These are generally mild, and glucagon is relatively free of severe adverse reactions. It should not be used in a patient with pheochromocytoma.

■ ISLET AMYLOID POLYPEPTIDE (IAPP, AMYLIN)

Amylin is a 37-amino-acid peptide originally derived from islet amyloid deposits in pancreas material from patients with long-standing type 2 diabetes or insulinomas. It is produced by pancreatic beta cells, packaged within beta-cell granules in a concentration 1–2% that of insulin and co-secreted with insulin in a pulsatile manner and in response to physiologic secretory stimuli. Approximately 1 molecule of amylin is released for every 10 molecules of insulin. It circulates in a glycated (active) and nonglycated (inactive) form with physiologic concentrations ranging from 4 to 25 pmol/L and is primarily excreted by the kidney. Amylin appears to be a member of the superfamily of neuroregulatory peptides, with 46% homology with the calcitonin gene-related peptide CGRP (see Chapter 17). The physiologic effect of amylin may be to modulate insulin release by acting as a negative feedback on insulin secretion. At pharmacologic doses, amylin reduces glucagon secretion, slows gastric emptying by a vagally medicated mechanism, and centrally decreases appetite. An analog of amylin, **pramlintide** (see previous section), differs from amylin by the substitution of proline at positions 25, 28, and 29. These modifications make pramlintide soluble and non–self-aggregating, and suitable for pharmacologic use.

SUMMARY Drugs Used for Diabetes

Subclass	Mechanism of Action	Effects	Clinical Applications	Pharmacokinetics, Toxicities, Interactions
INSULINS				
• Rapid-acting: Lispro, aspart, glulisine • Short-acting: Regular • Intermediate-acting: NPH • Long-acting: Detemir, glargine	Activate insulin receptor	Reduce circulating glucose • promote glucose transport and oxidation; glycogen, lipid, protein synthesis; and regulation of gene expression	Type 1 and type 2 diabetes	Parenteral (SC or IV) • duration varies (see text) • *Toxicity:* Hypoglycemia, weight gain, lipodystrophy (rare)
SULFONYLUREAS				
• Glipizide • Glyburide • Glimepiride	Insulin secretagogues: Close K$^+$ channels in beta cells • increase insulin release	In patients with functioning beta cells, reduce circulating glucose • increase glycogen, fat, and protein formation • gene regulation	Type 2 diabetes	Orally active • duration 10–24 h • *Toxicity:* Hypoglycemia, weight gain
• *Tolazamide, tolbutamide, chlorpropamide: Older sulfonylureas, lower potency, greater toxicity; rarely used*				
GLITINIDES				
• Repaglinide	Insulin secretagogue: Similar to sulfonylureas with some overlap in binding sites	In patients with functioning beta cells, reduces circulating glucose • increases glycogen, fat, and protein formation • gene regulation	Type 2 diabetes	Oral • very fast onset of action • duration 5–8 h • *Toxicity:* Hypoglycemia
• Nateglinide	Insulin secretagogue: Similar to sulfonylureas with some overlap in binding sites	In patients with functioning beta cells, reduces circulating glucose • increases glycogen, fat, and protein formation • gene regulation	Type 2 diabetes	Oral • very fast onset and short duration (< 4 h) • *Toxicity:* Hypoglycemia
BIGUANIDES				
• Metformin	Obscure: Reduced hepatic and renal gluconeogenesis	Decreased endogenous glucose production	Type 2 diabetes	Oral • maximal plasma concentration in 2–3 h • *Toxicity:* Gastrointestinal symptoms, lactic acidosis (rare) • cannot use if impaired renal/hepatic function • congestive heart failure (CHF), hypoxic/acidotic states, alcoholism
ALPHA-GLUCOSIDASE INHIBITORS				
• Acarbose, miglitol	Inhibit intestinal α-glucosidases	Reduce conversion of starch and disaccharides to mono-saccharides • reduce post-prandial hyperglycemia	Type 2 diabetes	Oral • rapid onset • *Toxicity:* Gastrointestinal symptoms • cannot use if impaired renal/hepatic function, intestinal disorders

Subclass	Mechanism of Action	Effects	Clinical Applications	Pharmacokinetics, Toxicities, Interactions
THIAZOLIDINEDIONES				
• Pioglitazone	Regulates gene expression by binding to PPAR-γ and PPAR-α	Reduces insulin resistance	Type 2 diabetes	Oral • long-acting (> 24 h) • *Toxicity:* Fluid retention, edema, anemia, weight gain, macular edema, bone fractures in women • cannot use if CHF, hepatic disease
• Rosiglitazone	Regulates gene expression by binding to PPAR-γ	Reduces insulin resistance	Type 2 diabetes	Oral • long-acting (> 24 h) • *Toxicity:* Fluid retention, edema, anemia, weight gain, macular edema, bone fractures in women • cannot use if CHF, hepatic disease • may worsen heart disease
GLUCAGON-LIKE POLYPEPTIDE-1 (GLP-1) RECEPTOR AGONISTS				
• Exenatide	Analog of GLP-1: Binds to GLP-1 receptors	Reduces post-meal glucose excursions: Increases glucose-mediated insulin release, lowers glucagon levels, slows gastric emptying, decreases appetite	Type 2 diabetes	Parenteral (SC) • half-life ~2.4 h • *Toxicity:* Nausea, headache, vomiting, anorexia, mild weight loss, pancreatitis
• *Liraglutide: Similar to exenatide; duration up to 24 h; immune reactions, possible thyroid carcinoma risk*				
DIPEPTIDYL PEPTIDASE-4 (DPP-4) INHIBITORS				
• Sitagliptin	DPP-4 inhibitor: Blocks degradation of GLP-1, raises circulating GLP-1 levels	Reduces post-meal glucose excursions: Increases glucose-mediated insulin release, lowers glucagon levels, slows gastric emptying, decreases appetite	Type 2 diabetes	Oral • half-life ~12 h • 24-h duration of action • *Toxicity:* Rhinitis, upper respiratory infections, headaches, pancreatitis, rare allergic reactions
• *Saxagliptin, linagliptin: Similar to sitagliptin; longer duration of action*				
AMYLIN ANALOG				
• Pramlintide	Analog of amylin: Binds to amylin receptors	Reduces post-meal glucose excursions: Lowers glucagon levels, slows gastric emptying, decreases appetite	Type 1 and type 2 diabetes	Parenteral (SC) • rapid onset • half-life ~ 48 min • *Toxicity:* Nausea, anorexia, hypoglycemia, headache
BILE ACID SEQUESTRANT				
Colesevelam hydrochloride	Bile acid binder	Lowers glucose through unknown mechanisms	Type 2 diabetes	Oral • 24-h duration of action • *Toxicity:* Constipation, indigestion, flatulence

P R E P A R A T I O N S   A V A I L A B L E [1]

SULFONYLUREAS

Chlorpropamide (generic, Diabinese)
Oral: 100, 250 mg tablets

Glimepiride (generic, Amaryl)
Oral: 1, 2, 4 mg tablets

Glipizide (generic, Glucotrol, Glucotrol XL)
Oral: 5, 10 mg tablets; 2.5, 5, 10 mg extended-release tablets

Glyburide (generic, Diaβeta, Micronase, Glynase PresTab)
Oral: 1.25, 2.5, 5 mg tablets; 1.5, 3, 4.5, 6 mg Glynase PresTab, micronized tablets

Tolazamide (generic, Tolinase)
Oral: 100, 250, 500 mg tablets

Tolbutamide (generic, Orinase)
Oral: 500 mg tablets

MEGLITINIDE & RELATED DRUGS

Nateglinide (Starlix)
Oral: 60, 120 mg tablets

Repaglinide (Prandin)
Oral: 0.5, 1, 2 mg tablets

BIGUANIDE

Metformin (generic, Glucophage, Glucophage XR)
Oral: 500, 850, 1000 mg tablets; extended-release (XR): 500, 750, 1000 mg tablets; 500 mg/5 mL solution

METFORMIN COMBINATIONS[2]

Glipizide plus metformin (generic, Metaglip)
Oral: 2.5/250, 2.5/500, 5/500 mg tablets

Glyburide plus metformin (generic, Glucovance)
Oral: 1.25/250, 2.5/500, 5/500 mg tablets

Pioglitazone plus metformin
Oral: 15/500, 15/850 mg tablets

Repaglinide plus metformin
Oral: 1/500, 2/500 mg tablets

Rosiglitazone plus metformin (Avandamet)
Oral: 1/500, 2/500, 4/500, 2/1000, 4/1000 mg tablets

Saxagliptin plus metformin (Kombiglyze)
Oral: 5/500, 5/1000, 2.5/1000 mg tablets

Sitagliptin plus metformin (Janumet)
Oral: 50/500, 50/1000 mg tablets

THIAZOLIDINEDIONE DERIVATIVES

Pioglitazone (Actos)
Oral: 15, 30, 45 mg tablets

Rosiglitazone (Avandia)
Oral: 2, 4, 8 mg tablets

THIAZOLIDINEDIONE COMBINATION

Pioglitazone plus glimepiride (Duetact)
Oral: 30/2, 30/4 mg tablets

Rosiglitazone plus glimepiride (Avandaryl)
Oral: 4/1, 4/2, 4/4, 8/2, 8/4 mg rosiglitazone/mg glimepiride tablets

ALPHA-GLUCOSIDASE INHIBITORS

Acarbose (Precose)
Oral: 25, 50, 100 mg tablets

Miglitol (Glyset)
Oral: 25, 50, 100 mg tablets

AMYLIN ANALOGS

Pramlintide (Symlin)
Parenteral: vial: 0.6, 1 mg/mL

GLUCAGON-LIKE POLYPEPTIDE-1 RECEPTOR AGONISTS

Exenatide (Byetta)
Parenteral: 250 mcg/mL

Liraglutide (Victoza)
Parenteral: 0.6, 1.2, 1.8 mg

DIPEPTIDYL PEPTIDASE-4 INHIBITOR

Linagliptin (Tradjenta)
Oral: tablets [TK]

Saxagliptin (Onglyza)
Oral: 2.5, 5 mg tablets

Sitagliptin (Januvia)
Oral: 25, 50 100 mg tablets

BILE ACID SEQUESTRANT

Colesevelam hydrochloride
Oral: 625 mg tablets, 1.875, 3.75 g packages for oral suspension

GLUCAGON

Glucagon (generic)
Parenteral: 1 mg lyophilized powder to reconstitute for injection

[1]See Table 41–4 for insulin preparations.

[2]Other combinations are available.

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CASE STUDY ANSWER

This patient has multiple risk factors for type 2 diabetes. Although she does not have a prior history of fasting hyperglycemia, glucose intolerance, or gestational diabetes, other risk factors are present. Further evaluations that should be obtained include HbA_{1c} concentration, dilated retinal examination, baseline laboratory tests, spot urine test for microalbumin/creatinine ratio, plasma creatinine level, and neurologic examination. The patient should be taught how to use a glucose meter and monitor her fingerstick blood glucose level, referred to a nutritionist for dietary instruction, and given diabetes self-management education. Assuming she has no renal or hepatic impairment, hygienic interventions (diet and exercise) and metformin would be the first line of treatment. If she is unable to achieve adequate glycemic control on metformin, an additional agent such an insulin secretagogue (ie, sulfonylureas, meglitinide, or nateglinide), insulin, or another antidiabetic medication could be added.

Agents That Affect Bone Mineral Homeostasis

42

Daniel D. Bikle, MD, PhD

C A S E   S T U D Y

A 65-year-old man is referred to you from his primary care physician (PCP) for evaluation and management of possible osteoporosis. He saw his PCP for evaluation of low back pain. X-rays of the spine showed some degenerative changes in the lumbar spine plus several wedge deformities in the thoracic spine. The patient is a long-time smoker (up to two packs per day) and has two to four glasses of wine with dinner, more on the weekends. He has chronic bronchitis, presumably from smoking, and has been treated many times with oral prednisone for exacerbations of bronchitis. He is currently on 10 mg/d prednisone. Examination shows kyphosis of the thoracic spine, with some tenderness to fist percussion over the thoracic spine. The DEXA (dual-energy X-ray absorptiometry) measurement of the lumbar spine is "within the normal limits," but the radiologist noted that the reading may be misleading because of degenerative changes. The hip measurement shows a T score (number of standard deviations by which the patient's measured bone density differs from that of a normal young adult) in the femoral neck of –2.2. What further workup should be considered, and what therapy should be initiated?

■ BASIC PHARMACOLOGY

Calcium and phosphate, the major mineral constituents of bone, are also two of the most important minerals for general cellular function. Accordingly, the body has evolved complex mechanisms to carefully maintain calcium and phosphate homeostasis (Figure 42–1). Approximately 98% of the 1–2 kg of calcium and 85% of the 1 kg of phosphorus in the human adult are found in bone, the principal reservoir for these minerals. This reservoir is dynamic, with constant remodeling of bone and ready exchange of bone mineral with that in the extracellular fluid. Bone also serves as the principal structural support for the body and provides the space for hematopoiesis. This relationship is more than fortuitous as elements of the bone marrow affect skeletal processes just as skeletal elements affect hematopoeitic processes. Abnormalities in bone mineral homeostasis can lead to a wide variety of cellular dysfunctions (eg, tetany, coma, muscle weakness), and to disturbances in structural support of the body (eg, osteoporosis with fractures) and loss of hematopoietic capacity (eg, infantile osteopetrosis).

Calcium and phosphate enter the body from the intestine. The average American diet provides 600–1000 mg of calcium per day, of which approximately 100–250 mg is absorbed. This amount represents net absorption, because both absorption (principally in the duodenum and upper jejunum) and secretion (principally in the ileum) occur. The quantity of phosphorus in the American diet is about the same as that of calcium. However, the efficiency of absorption (principally in the jejunum) is greater, ranging from 70% to 90%, depending on intake. In the steady state, renal excretion of calcium and phosphate balances intestinal absorption. In general, over 98% of filtered calcium and 85% of filtered phosphate is reabsorbed by the kidney. The movement of calcium and phosphate across the intestinal and renal epithelia is closely regulated. Dysfunction of the intestine (eg, nontropical sprue) or kidney (eg, chronic renal failure) can disrupt bone mineral homeostasis.

Three hormones serve as the principal regulators of calcium and phosphate homeostasis: **parathyroid hormone (PTH), fibroblast growth factor 23 (FGF23),** and **vitamin D** (Figure 42–2). Vitamin D is a prohormone rather than a true
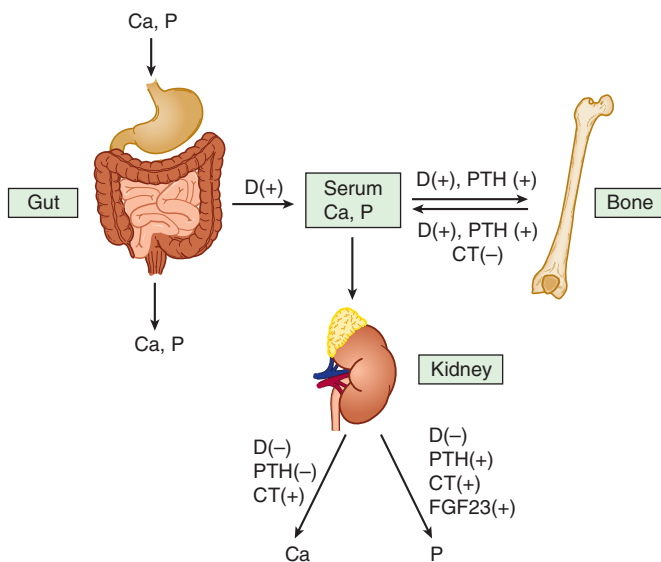
FIGURE 42–1 Mechanisms contributing to bone mineral homeostasis. Serum calcium (Ca) and phosphorus (P) concentrations are controlled principally by three hormones, 1,25-dihydroxyvitamin D (1,25[OH]$_2$D, D), fibroblast growth factor 23 (FGF23), and parathyroid hormone (PTH), through their action on absorption from the gut and from bone and on renal excretion. PTH and 1,25(OH)$_2$D increase the input of calcium and phosphorus from bone into the serum and stimulate bone formation. 1,25(OH)$_2$D also increases calcium and phosphate absorption from the gut. In the kidney, 1,25(OH)$_2$D decreases excretion of both calcium and phosphorus, whereas PTH reduces calcium but increases phosphorus excretion. FGF23 stimulates renal excretion of phosphate. Calcitonin (CT) is a less critical regulator of calcium homeostasis, but in pharmacologic concentrations can reduce serum calcium and phosphorus by inhibiting bone resorption and stimulating their renal excretion. Feedback may alter the effects shown; for example, 1,25(OH)$_2$D increases urinary calcium excretion indirectly through increased calcium absorption from the gut and inhibition of PTH secretion and may increase urinary phosphate excretion because of increased phosphate absorption from the gut and stimulation of FGF23 production.

hormone, because it must be further metabolized to gain biologic activity. PTH stimulates the production of the active metabolite of vitamin D, 1,25-dihydroxyvitamin D (1,25[OH]$_2$D), in the kidney. Other tissues also produce 1,25(OH)$_2$D; the control of this production differs from that in the kidney, as will be discussed subsequently. The complex interplay among PTH, FGF23, and 1,25(OH)$_2$D is discussed in detail later. To summarize briefly: 1,25(OH)$_2$D suppresses the production of PTH as does calcium, whereas phosphate stimulates PTH secretion. 1,25(OH)$_2$D stimulates the intestinal absorption of calcium and phosphate. 1,25(OH)$_2$D and PTH promote both bone formation and resorption in part by stimulating the proliferation and differentiation of osteoblasts and osteoclasts. Both PTH and 1,25(OH)$_2$D enhance renal retention of calcium, but PTH promotes renal phosphate excretion, whereas 1,25(OH)$_2$D promotes renal reabsorption of phosphate. FGF23 is a recently discovered hormone produced primarily by bone that stimulates renal phosphate excretion and

inhibits renal production of 1,25(OH)$_2$D. 1,25(OH)$_2$D and phosphate in turn stimulate the production of FGF23.

Other hormones—calcitonin, prolactin, growth hormone, insulin, thyroid hormone, glucocorticoids, and sex steroids—influence calcium and phosphate homeostasis under certain physiologic circumstances and can be considered secondary regulators. Deficiency or excess of these secondary regulators within a physiologic range does not produce the disturbance of calcium and phosphate homeostasis that is observed in situations of deficiency or excess of PTH, FGF23, and vitamin D. However, certain of these secondary regulators—especially calcitonin, glucocorticoids, and estrogens—are useful therapeutically and discussed in subsequent sections.

In addition to these hormonal regulators, calcium and phosphate themselves, other ions such as sodium and fluoride, and a variety of drugs (bisphosphonates, plicamycin, and diuretics) also alter calcium and phosphate homeostasis.

PRINCIPAL HORMONAL REGULATORS OF BONE MINERAL HOMEOSTASIS

PARATHYROID HORMONE

Parathyroid hormone (PTH) is a single-chain peptide hormone composed of 84 amino acids. It is produced in the parathyroid gland in a precursor form of 115 amino acids, the remaining 31 amino terminal amino acids being cleaved off before secretion. Within the gland is a calcium-sensitive protease capable of cleaving the intact hormone into fragments, thereby providing one mechanism by which calcium limits the production of PTH. A second mechanism involves the calcium-sensing receptor which, when stimulated by calcium, reduces PTH production and secretion. The parathyroid gland also contains the vitamin D receptor and the enzyme, CYP27B1, that produces the active metabolite of vitamin D, 1,25-dihydroxyvitamin D (1,25(OH)2D) thus enabling circulating or endogenously produced 1,25(OH)2D to suppress PTH production. Biologic activity resides in the amino terminal region such that synthetic PTH 1-34 (available as teriparatide) is fully active. Loss of the first two amino terminal amino acids eliminates most biologic activity.

The metabolic clearance of intact PTH is rapid, with a half-time of disappearance measured in minutes. Most of the clearance occurs in the liver and kidney. The inactive carboxyl terminal fragments produced by metabolism of the intact hormone have a much lower clearance, especially in renal failure. In the past, this accounted for the very high PTH values observed in patients with renal failure when the hormone was measured by radioimmunoassays directed against the carboxyl terminal region. Currently, most PTH assays differentiate between intact PTH 1-34 and large inactive fragments, so that it is possible to more accurately evaluate biologically active PTH status in patients with renal failure.

PTH regulates calcium and phosphate flux across cellular membranes in bone and kidney, resulting in increased serum calcium and decreased serum phosphate (Figure 42–1). In bone, PTH increases the activity and number of osteoclasts, the cells
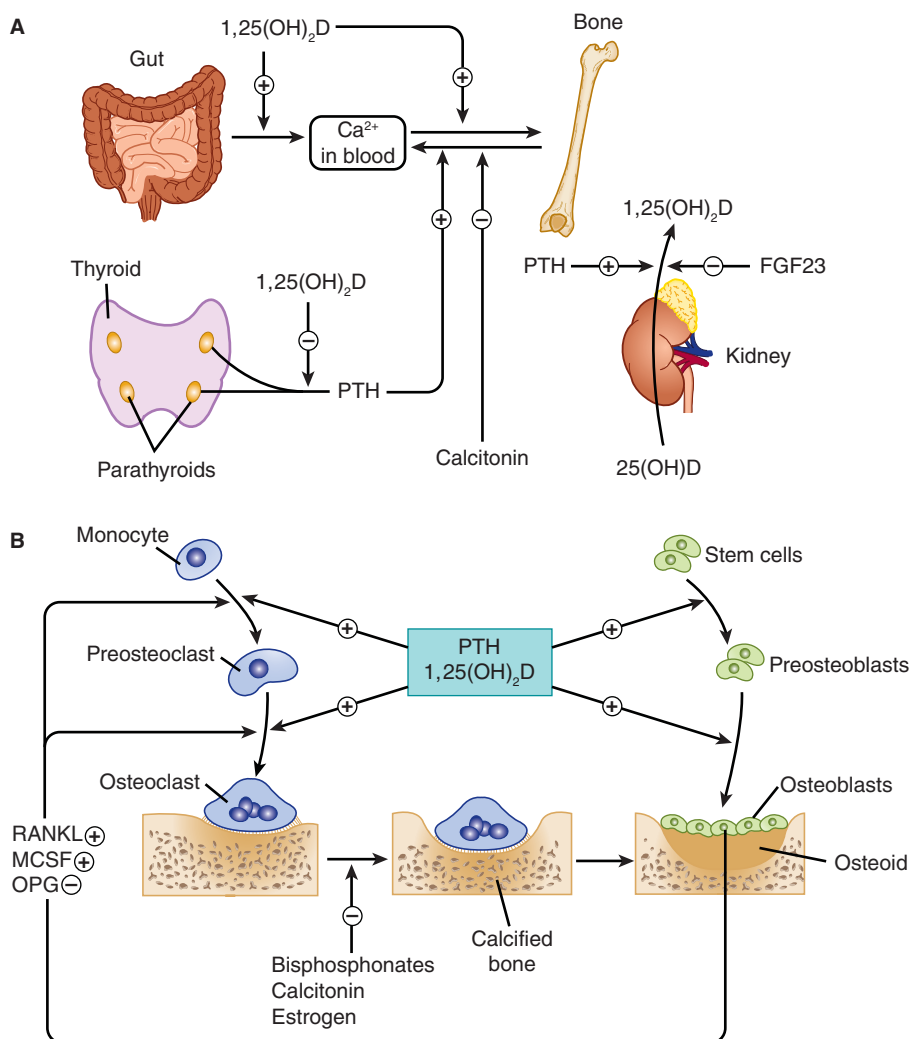
FIGURE 42–2 The hormonal interactions controlling bone mineral homeostasis. In the body **(A)**, 1,25-dihydroxyvitamin D (1,25[OH]$_2$D) is produced by the kidney under the control of parathyroid hormone (PTH), which stimulates its production, and fibroblast growth factor 23 (FGF23), which inhibits its production. 1,25(OH)$_2$D in turn inhibits the production of PTH by the parathyroid glands and stimulates FGF23 release from bone. 1,25(OH)$_2$D is the principal regulator of intestinal calcium and phosphate absorption. At the level of the bone **(B)**, both PTH and 1,25(OH)$_2$D regulate bone formation and resorption, with each capable of stimulating both processes. This is accomplished by their stimulation of preosteoblast proliferation and differentiation into osteoblasts, the bone-forming cell. PTH and 1,25(OH)$_2$D stimulate the expression of RANKL by the osteoblast, which, with MCSF, stimulates the differentiation and subsequent activation of osteoclasts, the bone-resorbing cell. FGF23 in excess leads to osteomalacia by inhibiting 1,25(OH)$_2$D production and lowering phosphate levels. MCSF, macrophage colony-stimulating factor; OPG, osteoprotegerin; RANKL, ligand for receptor for activation of nuclear factor-κB.

responsible for bone resorption (Figure 42–2). However, this stimulation of osteoclasts is not a direct effect. Rather, PTH acts on the osteoblast (the bone-forming cell) to induce membrane-bound and secreted soluble forms of a protein called **RANK ligand (RANKL)**. RANKL acts on osteoclasts and osteoclast precursors to increase both the numbers and activity of osteoclasts. This action increases bone remodeling, a specific sequence of cellular events initiated by osteoclastic bone resorption and followed by osteoblastic bone formation. An antibody that inhibits the action of RANKL has been developed (**denosumab**) for the treatment of excess bone resorption in patients with osteoporosis and certain cancers. Although both bone resorption and bone formation are enhanced by PTH, the net effect of excess endogenous PTH is to increase bone resorption. However, administration of exogenous PTH in low and intermittent doses increases bone formation without first stimulating bone resorption. This net anabolic action may be indirect, involving other growth factors such as insulin-like growth factor 1 (IGF-1). It has led to the approval of recombinant PTH 1-34 (**teriparatide**) for the treatment of osteoporosis. In the kidney, PTH increases tubular reabsorption of calcium and magnesium but reduces reabsorption of phosphate, amino acids, bicarbonate, sodium, chloride, and sulfate. Another important action of PTH on the kidney is stimulation of 1,25-dihydroxyvitamin D (1,25[OH]$_2$D) production.

VITAMIN D

Vitamin D is a secosteroid produced in the skin from 7-dehydrocholesterol under the influence of ultraviolet radiation. Vitamin D is also found in certain foods and is used to supplement dairy products. Both the natural form (vitamin D$_3$, cholecalciferol) and the plant-derived form (vitamin D$_2$, ergocalciferol) are present in the diet. These forms differ in that ergocalciferol contains a double bond (C$_{22-23}$) and an additional methyl group in the side chain (Figure 42–3). Ergocalciferol and its metabolites bind less well than cholecalciferol and its metabolites to vitamin D-binding protein, the major transport protein of these compounds in blood, and have a different path of catabolism. As a result their half-lives are shorter than those of the cholecalciferol metabolites. This influences treatment strategies, as will be discussed. However, the key steps in metabolism and biologic activities of the active metabolites are comparable, so with this exception the following comments apply equally well to both forms of vitamin D.

Vitamin D is a precursor to a number of biologically active metabolites (Figure 42–3). Vitamin D is first hydroxylated in the liver to form 25-hydroxyvitamin D (25[OH]D, calcifediol). This metabolite is further converted in the kidney to a number of other forms, the best studied of which are 1,25-dihydroxyvitamin D (1,25[OH]$_2$D, calcitriol) and 24,25-dihydroxyvitamin D (24,25[OH]$_2$D). The regulation of vitamin D metabolism is complex, involving calcium, phosphate, and a variety of hormones, the most important of which is PTH, which stimulates, and FGF23, which inhibits the production of 1,25(OH)$_2$D by the kidney. Of the natural metabolites, only vitamin D and 1,25(OH)$_2$D (as calcitriol) are available for clinical use (Table 42–1). A number of analogs of 1,25(OH)$_2$D have been synthesized to extend the usefulness of this metabolite to a variety of nonclassic conditions. Calcipotriene (calcipotriol), for example, is being used to treat psoriasis, a hyperproliferative skin disorder (Chapter 61). Doxercalciferol and paricalcitol are approved for the treatment of secondary hyperparathyroidism in patients with chronic kidney disease. Other analogs are being investigated for the treatment of various malignancies.

Vitamin D and its metabolites circulate in plasma tightly bound to the vitamin D-binding protein. This α-globulin binds 25(OH)D and 24,25(OH)$_2$D with comparable high affinity and vitamin D and 1,25(OH)$_2$D with lower affinity. As noted above the affinity for the D$_2$ metabolites is less than that for the D$_3$
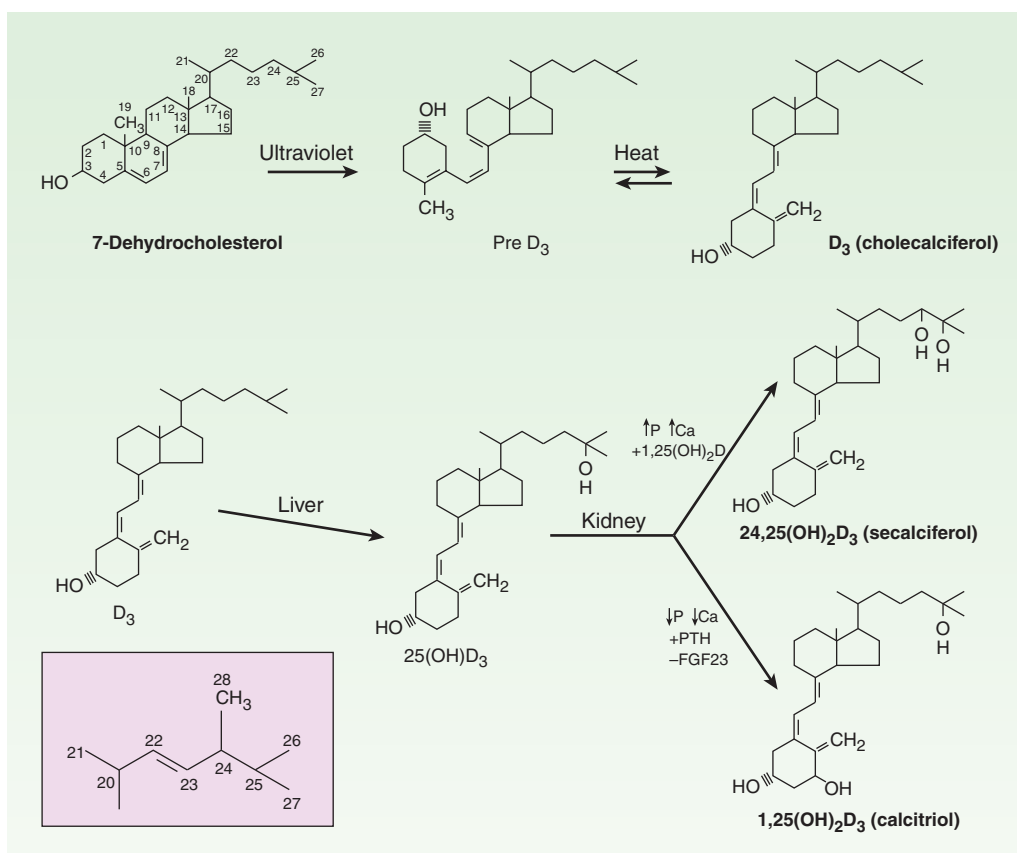

FIGURE 42–3 Conversion of 7-dehydrocholesterol to vitamin D$_3$ and metabolism of D$_3$ to 1,25-dihydroxyvitamin D$_3$ (1,25[OH]$_2$D$_3$) and 24,25-dihydroxyvitamin D$_3$ (24,25[OH]$_2$D$_3$). Control of the latter step is exerted primarily at the level of the kidney, where low serum phosphorus, low serum calcium, and high parathyroid hormone favor the production of 1,25(OH)$_2$D$_3$, whereas fibroblast growth factor 23 inhibits its production. The inset shows the side chain for ergosterol. Ergosterol undergoes similar transformation to vitamin D$_2$ (ergocalciferol), which, in turn, is metabolized to 25-hydroxyvitamin D$_2$, 1,25-dihydroxyvitamin D$_2$, and 24,25-dihydroxyvitamin D$_2$. In humans, corresponding D$_2$ and D$_3$ derivatives have equivalent effects although they differ in pharmacokinetics.

TABLE 42–1 Vitamin D and its major metabolites and analogs.

Chemical and Generic Names	Abbreviation
Vitamin D_3; cholecalciferol	D_3
Vitamin D_2; ergocalciferol	D_2
25-Hydroxyvitamin D_3; calcifediol	$25(OH)D_3$
1,25-Dihydroxyvitamin D_3; calcitriol	$1,25(OH)_2D_3$
24,25-Dihydroxyvitamin D_3; secalciferol	$24,25(OH)_2D_3$
Dihydrotachysterol	DHT
Calcipotriene (calcipotriol)	None
1α-Hydroxyvitamin D_2; doxercalciferol	$1\alpha(OH)D_2$
19-nor-1,25-Dihydroxyvitamin D_2; paricalcitol	$19\text{-nor-}1,25(OH)D_2$

metabolites. In normal subjects, the terminal half-life of injected calcifediol is 23 days, whereas in anephric subjects it is 42 days. The half-life of $24,25(OH)_2D$ is probably similar. Tracer studies with vitamin D have shown a rapid clearance from the blood. The liver appears to be the principal organ for clearance. Excess vitamin D is stored in adipose tissue. The metabolic clearance of calcitriol in humans indicates a rapid turnover, with a terminal half-life measured in hours. Several of the $1,25(OH)_2D$ analogs are bound poorly by the vitamin D-binding protein. As a result, their clearance is very rapid, with a terminal half-life of minutes. Such analogs have less of the hypercalcemic, hypercalciuric effects of calcitriol, an important aspect of their use for the management of conditions such as psoriasis and hyperparathyroidism.

The mechanism of action of the vitamin D metabolites remains under active investigation. However, $1,25(OH)_2D$ is well established as the most potent agent with respect to stimulation of intestinal calcium and phosphate transport and bone resorption. $1,25(OH)_2D$ appears to act on the intestine both by induction of new protein synthesis (eg, calcium-binding protein and TRPV6, an intestinal calcium channel) and by modulation of calcium flux across the brush border and basolateral membranes by a means that does not require new protein synthesis. The molecular action of $1,25(OH)_2D$ on bone has received less attention. However, like PTH, $1,25(OH)_2D$ can induce RANKL in osteoblasts and proteins such as osteocalcin, which may regulate the mineralization process. The metabolites $25(OH)D$ and $24,25(OH)_2D$ are far less potent stimulators of intestinal calcium and phosphate transport or bone resorption. However, $25(OH)D$ appears to be more potent than $1,25(OH)_2D$ in stimulating renal reabsorption of calcium and phosphate and may be the major metabolite regulating calcium flux and contractility in muscle. Specific receptors for $1,25(OH)_2D$ exist in target tissues. However, the role and even the existence of separate receptors for $25(OH)D$ and $24,25(OH)_2D$ remain controversial.

The receptor for $1,25(OH)_2D$ exists in many tissues—not just bone, gut, and kidney. In these "nonclassic" tissues, $1,25(OH)_2D$ exerts a number of actions including regulation of the secretion of PTH, insulin, and renin, dendritic cell as well as T-cell differentiation, and proliferation and differentiation of a number of cancer cells. Thus, the clinical utility of $1,25(OH)_2D$ and its analogs is expanding.

FIBROBLAST GROWTH FACTOR 23

Fibroblast growth factor 23 (FGF23) is a single-chain protein with 251 amino acids including a 24-amino-acid leader sequence. It inhibits $1,25(OH)_2D$ production and phosphate reabsorption (via the sodium phosphate co-transporters NaPi 2a and 2c) in the kidney, leading to both hypophosphatemia and inappropriately low levels of circulating $1,25(OH)_2D$. Whereas FGF23 was originally identified in certain mesenchymal tumors, osteoblasts and osteocytes in bone appear to be its primary site of production. Other tissues can also produce FGF23, though at lower levels. FGF23 requires *O*-glycosylation for its secretion, a glycosylation mediated by the glycosyl transferase GALNT3. Mutations in GALNT3 result in abnormal deposition of calcium phosphate in periarticular tissues (tumoral calcinosis) with elevated phosphate and $1,25(OH)_2D$. FGF23 is normally inactivated by cleavage at an RXXR site (amino acids 176–179). Mutations in this site lead to excess FGF23, the underlying problem in autosomal dominant hypophosphatemic rickets. A similar disease, X-linked hypophosphatemic rickets, is due to mutations in PHEX, an endopeptidase, which initially was thought to cleave FGF23. However, this concept has been shown to be invalid, and the mechanism by which PHEX mutations lead to increased FGF23 levels remains obscure. FGF23 binds to FGF receptors 1 and 3c in the presence of the accessory receptor Klotho. Both Klotho and the FGF receptor must be present for signaling. Mutations in Klotho disrupt FGF23 signaling, resulting in elevated phosphate and $1,25(OH)_2D$ levels with what has been characterized as premature aging. FGF23 production is stimulated by $1,25(OH)_2D$ and directly or indirectly inhibited by the dentin matrix protein DMP1 found in osteocytes. Mutations in DMP1 lead to increased FGF23 levels and osteomalacia.

INTERACTION OF PTH, FGF23, & VITAMIN D

A summary of the principal actions of PTH, FGF23, and vitamin D on the three main target tissues—intestine, kidney, and bone—is presented in Table 42–2. The net effect of PTH is to raise serum calcium and reduce serum phosphate; the net effect of FGF23 is to decrease serum phosphate; the net effect of vitamin D is to raise both. Regulation of calcium and phosphate homeostasis is achieved through important feedback loops. Calcium is one of two principal regulators of PTH secretion. It binds to a novel ion recognition site that is part of a G_q protein-coupled receptor called the calcium-sensing receptor (CaSR) that employs the phosphoinositide second messenger system to link changes in the extracellular calcium concentration to changes in the intracellular free calcium. As serum calcium levels rise and activate this receptor, intracellular calcium levels increase and inhibit PTH secretion. This inhibition by calcium of PTH secretion, along with inhibition of renin and atrial natriuretic factor secretion, is the opposite of the effect in other tissues such as the beta cell of the pancreas, in which calcium stimulates secretion. Phosphate regulates PTH secretion directly and indirectly by forming complexes with calcium in the serum. Because it is the ionized free concentration of extracellular calcium

TABLE 42–2 Actions of parathyroid hormone (PTH), vitamin D, and FGF23 on gut, bone, and kidney.

	PTH	Vitamin D	FGF23
Intestine	Increased calcium and phosphate absorption (by increased 1,25(OH)$_2$D production)	Increased calcium and phosphate absorption by 1,25(OH)$_2$D	Decreased calcium and phosphate absorption by decreased 1,25(OH)$_2$ production
Kidney	Decreased calcium excretion, increased phosphate excretion	Calcium and phosphate excretion may be decreased by 25(OH)D and 1,25(OH)$_2$D[1]	Increased phosphate excretion
Bone	Calcium and phosphate resorption increased by high doses. Low doses may increase bone formation.	Increased calcium and phosphate resorption by 1,25(OH)$_2$D; bone formation may be increased by 1,25(OH)$_2$D and 24,25(OH)$_2$D	Decreased mineralization due to hypophosphatemia and low 1,25(OH)2D levels, but may have a direct action on bone as well.
Net effect on serum levels	Serum calcium increased, serum phosphate decreased	Serum calcium and phosphate both increased	Decreased serum phosphate

[1]Direct effect. Vitamin D also indirectly increases urine calcium owing to increased calcium absorption from the intestine and decreased PTH.

that is detected by the parathyroid gland, increases in serum phosphate levels reduce the ionized calcium, leading to enhanced PTH secretion. Such feedback regulation is appropriate to the net effect of PTH to raise serum calcium and reduce serum phosphate levels. Likewise, both calcium and phosphate at high levels reduce the amount of 1,25(OH)$_2$D produced by the kidney and increase the amount of 24,25(OH)$_2$D produced.

High serum calcium works directly and indirectly by reducing PTH secretion. High serum phosphate works directly and indirectly by increasing FGF23 levels. Since 1,25(OH)$_2$D raises serum calcium and phosphate, whereas 24,25(OH)$_2$D has less effect, such feedback regulation is again appropriate. 1,25(OH)$_2$D directly inhibits PTH secretion (independent of its effect on serum calcium) by a direct inhibitory effect on PTH gene transcription. This provides yet another negative feedback loop. In patients with chronic renal failure who frequently are deficient in producing 1,25(OH)$_2$D, loss of this 1,25(OH)$_2$D-mediated feedback loop coupled with impaired phosphate excretion and intestinal calcium absorption often leads to secondary hyperparathyroidism. The ability of 1,25(OH)$_2$D to inhibit PTH secretion directly is being exploited with calcitriol analogs that have less effect on serum calcium because of their lesser effect on intestinal calcium absorption. Such drugs are proving useful in the management of secondary hyperparathyroidism accompanying chronic kidney disease and may be useful in selected cases of primary hyperparathyroidism. 1,25(OH)$_2$D also stimulates the production of FGF23. This completes the negative feedback loop in that FGF23 inhibits 1,25(OH)$_2$D production while promoting hypophosphatemia, which in turn inhibits FGF23 production and stimulates 1,25(OH)$_2$D production.

SECONDARY HORMONAL REGULATORS OF BONE MINERAL HOMEOSTASIS

A number of hormones modulate the actions of PTH, FGF23, and vitamin D in regulating bone mineral homeostasis. Compared with that of PTH, FGF23, and vitamin D, the physiologic impact of such secondary regulation on bone mineral homeostasis is minor. However, in pharmacologic amounts, several of these hormones, including cal-

citonin, glucocorticoids, and estrogens, have actions on bone mineral homeostatic mechanisms that can be exploited therapeutically.

CALCITONIN

The calcitonin secreted by the parafollicular cells of the mammalian thyroid is a single-chain peptide hormone with 32 amino acids and a molecular weight of 3600. A disulfide bond between positions 1 and 7 is essential for biologic activity. Calcitonin is produced from a precursor with MW 15,000. The circulating forms of calcitonin are multiple, ranging in size from the monomer (MW 3600) to forms with an apparent MW of 60,000. Whether such heterogeneity includes precursor forms or covalently linked oligomers is not known. Because of its chemical heterogeneity, calcitonin preparations are standardized by bioassay in rats. Activity is compared to a standard maintained by the British Medical Research Council (MRC) and expressed as MRC units.

Human calcitonin monomer has a half-life of about 10 minutes. Salmon calcitonin has a longer half-life, making it more attractive as a therapeutic agent. Much of the clearance occurs in the kidney by metabolism; little intact calcitonin appears in the urine.

The principal effects of calcitonin are to lower serum calcium and phosphate by actions on bone and kidney. Calcitonin inhibits osteoclastic bone resorption. Although bone formation is not impaired at first after calcitonin administration, with time both formation and resorption of bone are reduced. In the kidney, calcitonin reduces both calcium and phosphate reabsorption as well as reabsorption of other ions, including sodium, potassium, and magnesium. Tissues other than bone and kidney are also affected by calcitonin. Calcitonin in pharmacologic amounts decreases gastrin secretion and reduces gastric acid output while increasing secretion of sodium, potassium, chloride, and water in the gut. Pentagastrin is a potent stimulator of calcitonin secretion (as is hypercalcemia), suggesting a possible physiologic relationship between gastrin and calcitonin. In the adult human, no readily demonstrable problem develops in cases of calcitonin deficiency (thyroidectomy) or excess (medullary carcinoma of the thyroid). However, the ability of calcitonin to block bone resorption and lower serum calcium makes it a useful drug for the treatment of Paget's disease, hypercalcemia, and osteoporosis.

GLUCOCORTICOIDS

Glucocorticoid hormones alter bone mineral homeostasis by antagonizing vitamin D-stimulated intestinal calcium transport, stimulating renal calcium excretion, and blocking bone formation. Although these observations underscore the negative impact of glucocorticoids on bone mineral homeostasis, these hormones have proved useful in reversing the hypercalcemia associated with lymphomas and granulomatous diseases such as sarcoidosis (in which unregulated ectopic production of $1,25[OH]_2D$ occurs) or in cases of vitamin D intoxication. Prolonged administration of glucocorticoids is a common cause of osteoporosis in adults and can cause stunted skeletal development in children.

ESTROGENS

Estrogens can prevent accelerated bone loss during the immediate postmenopausal period and at least transiently increase bone in postmenopausal women.

The prevailing hypothesis advanced to explain these observations is that estrogens reduce the bone-resorbing action of PTH. Estrogen administration leads to an increased $1,25(OH)_2D$ level in blood, but estrogens have no direct effect on $1,25(OH)_2D$ production in vitro. The increased $1,25(OH)_2D$ levels in vivo following estrogen treatment may result from decreased serum calcium and phosphate and increased PTH. Estrogen receptors have been found in bone, and estrogen has direct effects on bone remodeling. Case reports of men who lack the estrogen receptor or who are unable to produce estrogen because of aromatase deficiency noted marked osteopenia and failure to close epiphyses. This further substantiates the role of estrogen in bone development, even in men. The principal therapeutic application for estrogen administration in disorders of bone mineral homeostasis is the treatment or prevention of postmenopausal osteoporosis. However, long-term use of estrogen has fallen out of favor due to concern about adverse effects. Selective estrogen receptor modulators (SERMs) have been developed to retain the beneficial effects on bone while minimizing deleterious effects on breast, uterus, and the cardiovascular system (see Box: Newer Therapies for Osteoporosis and Chapter 40).

Newer Therapies for Osteoporosis

Bone undergoes a continuous remodeling process involving resorption and formation. Any process that disrupts this balance by increasing bone resorption relative to formation results in osteoporosis. Inadequate gonadal hormone production is a major cause of osteoporosis in men and women. Estrogen replacement therapy at menopause is a well-established means of preventing osteoporosis in the female, but many women fear its adverse effects, particularly the increased risk of breast cancer from continued estrogen use (the well-demonstrated increased risk of endometrial cancer is prevented by combining the estrogen with a progestin) and do not like the persistence of menstrual bleeding that often accompanies this form of therapy. Medical enthusiasm for this treatment has waned with the demonstration that it does not protect against and may increase the risk of heart disease. Raloxifene is the first of the selective estrogen receptor modulators (SERMs; see Chapter 40) to be approved for the prevention of osteoporosis. Raloxifene shares some of the beneficial effects of estrogen on bone without increasing the risk of breast or endometrial cancer (it may actually reduce the risk of breast cancer). Although not as effective as estrogen in increasing bone density, raloxifene has been shown to reduce vertebral fractures.

Nonhormonal forms of therapy for osteoporosis with proven efficacy in reducing fracture risk have also been developed. Bisphosphonates such as alendronate, risedronate, and ibandronate have been conclusively shown to increase bone density and reduce fractures over at least 5 years when used continuously at a dosage of 10 mg/d or 70 mg/wk for alendronate; 5 mg/d or 35 mg/wk for risedronate; or 2.5 mg/d or 150 mg/month for ibandronate, and more recently intravenous zoledronate, 5 mg annually. Side-by-side trials between alendronate and calcitonin (another approved nonestrogen drug for osteoporosis) indicated a greater efficacy of alendronate. Bisphosphonates are poorly absorbed and must be given on an empty stomach or infused intravenously. At the higher oral doses used in the treatment of Paget's disease, alendronate causes gastric irritation, but this is not a significant problem at the doses recommended for osteoporosis when patients are instructed to take the drug with a glass of water and remain upright. Denosumab is a human monoclonal antibody directed against RANKL, and is very effective in inhibiting osteoclastogenesis and activity. Denosumab is given in 60 mg doses subcutaneously every 6 months. All of these drugs inhibit bone resorption with secondary effects to inhibit bone formation. On the other hand, teriparatide, the recombinant form of PTH 1-34, directly stimulates bone formation. However, teriparatide must be given daily by subcutaneous injection. Its efficacy in preventing fractures appears to be at least as great as that of the bisphosphonates. In all cases, adequate intake of calcium and vitamin D needs to be maintained.

Furthermore, there are several other forms of therapy in the pipeline. In Europe, strontium ranelate, a drug that appears to stimulate bone formation and inhibit bone resorption, has been used for several years with favorable results in large clinical trials; approval for use in the USA is expected. Additional promising new treatments undergoing clinical trials include an antibody against sclerostin (a protein produced by osteocytes that inhibits bone formation), that has been shown to stimulate bone formation, and inhibitors of cathepsin K, an enzyme in osteoclasts that facilitates bone resorption.

NONHORMONAL AGENTS AFFECTING BONE MINERAL HOMEOSTASIS

BISPHOSPHONATES

The bisphosphonates are analogs of pyrophosphate in which the P-O-P bond has been replaced with a nonhydrolyzable P-C-P bond (Figure 42–4). Currently available bisphosphonates include **etidronate, pamidronate**, **alendronate, risedronate, tiludronate**, **ibandronate**, and **zoledronate**. With the development of the more potent bisphosphonates, etidronate is seldom used.

Results from animal and clinical studies indicate that less than 10% of an oral dose of these drugs is absorbed. Food reduces absorption even further, necessitating their administration on an empty stomach. A major adverse effect of oral forms of the bis- phosphonates (risedronate, alendronate, ibandronate) is esopha- geal and gastric irritation, which limits the use of this route by patients with upper gastrointestinal disorders. This complication can be circumvented with infusions of pamidronate, zoledronate, and ibandronate. Intravenous dosing also allows a larger amount of drug to enter the body and markedly reduces the frequency of administration (eg, zoledronate is infused once per year). Nearly half of the absorbed drug accumulates in bone; the remainder is excreted unchanged in the urine. Decreased renal function dic- tates a reduction in dosage. The portion of drug retained in bone depends on the rate of bone turnover; drug in bone often is retained for months if not years.
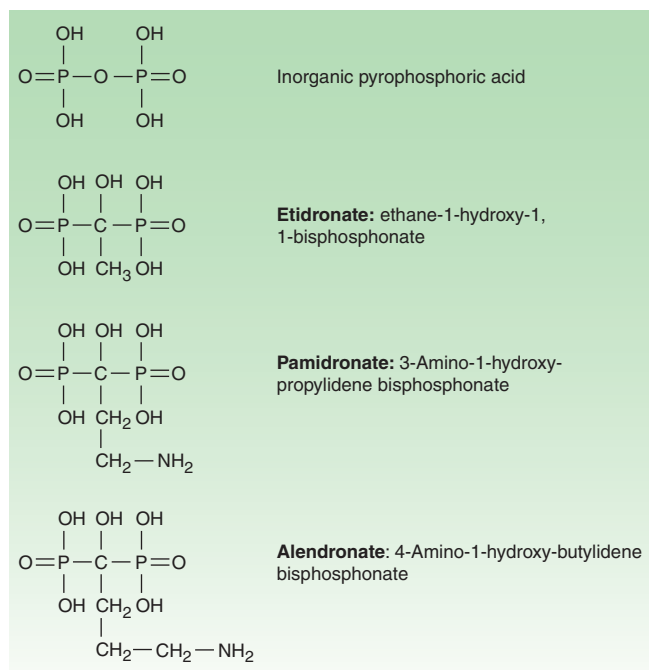

FIGURE 42–4 The structure of pyrophosphate and of the first three bisphosphonates—etidronate, pamidronate, and alendronate— that were approved for use in the USA.

The bisphosphonates exert multiple effects on bone mineral homeostasis, which make them useful for the treatment of hyper- calcemia associated with malignancy, for Paget's disease, and for osteoporosis (see Box: Newer Therapies for Osteoporosis). They owe at least part of their clinical usefulness and toxicity to their ability to retard formation and dissolution of hydroxyapatite crystals within and outside the skeletal system. Some of the newer bisphosphonates appear to increase bone mineral density well beyond the 2-year period predicted for a drug whose effects are limited to slowing bone resorption. This may be due to their other cellular effects, which include inhibition of $1,25(OH)_2D$ produc- tion, inhibition of intestinal calcium transport, metabolic changes in bone cells such as inhibition of glycolysis, inhibition of cell growth, and changes in acid and alkaline phosphatase activity.

Amino bisphosphonates such as alendronate and risedronate inhibit farnesyl pyrophosphate synthase, an enzyme in the mevalonate pathway that appears to be critical for osteoclast sur- vival. The cholesterol-lowering statin drugs (eg, lovastatin), which block mevalonate synthesis (see Chapter 35), stimulate bone for- mation, at least in animal studies. Thus, the mevalonate pathway appears to be important in bone cell function and provides new targets for drug development. The mevalonate pathway effects vary depending on the bisphosphonate (ie, only amino bisphos- phonates have this property), and may account for some of the clinical differences observed in the effects of the various bisphos- phonates on bone mineral homeostasis.

With the exception of the induction of a mineralization defect by higher than approved doses of etidronate and gastric and esophageal irritation by the oral bisphosphonates, these drugs have proved to be remarkably free of adverse effects when used at the doses recommended for the treatment of osteoporosis. Esophageal irritation can be minimized by taking the drug with a full glass of water and remaining upright for 30 minutes or by using the intra- venous forms of these compounds. Of the other complications, osteonecrosis of the jaw has received considerable attention but is rare in patients receiving usual doses of bisphosphonates (perhaps 1/100,000 patient-years). This complication is more frequent when high intravenous doses of zoledronate are used to control bone metastases and cancer-induced hypercalcemia. More recently, concern has been raised about over-suppressing bone turnover, and case reports have appeared describing unusual subtrochanteric (femur) fractures in patients on long-term bisphosphonate treat- ment. This complication appears to be rare, comparable to that of osteonecrosis of the jaw, but has led some authorities to recom- mend a "drug holiday" after 5 years of treatment if the clinical condition warrants it (ie, if the fracture risk of discontinuing the bisphosphonate is not deemed high).

DENOSUMAB

Denosumab is a fully human monoclonal antibody that binds to and prevents the action of RANKL. As described earlier, RANKL is produced by osteoblasts. It stimulates osteoclastogenesis via RANK, the receptor for RANKL that is present on osteoclasts and osteoclast precursors. By interfering with RANKL function,

denosumab inhibits osteoclast formation and activity. It is at least as effective as the potent bisphosphonates in inhibiting bone resorption and has recently been approved for treatment of post-menopausal osteoporosis and some cancers (prostate and breast). The latter application is to limit the development of bone metastases or bone loss resulting from the use of drugs suppressing gonadal function. Denosumab is administered subcutaneously every 6 months, which avoids gastrointestinal side effects. The drug appears to be well tolerated but two concerns remain. First, a number of cells in the immune system also express RANKL, suggesting that there could be an increased risk of infection associated with the use of denosumab. Second, because the suppression of bone turnover with denosumab is similar to that of the potent bisphosphonates, the risk of osteonecrosis of the jaw and subtrochanteric fractures may be increased, although this has not been reported in the clinical trials leading to its approval by the Food and Drug Administration (FDA).

CALCIMIMETICS

Cinacalcet is the first representative of a new class of drugs that activates the calcium-sensing receptor (CaSR). CaSR is widely distributed but has its greatest concentration in the parathyroid gland. By activating the parathyroid gland CaSR, cinacalcet inhibits PTH secretion. Cinacalcet is approved for the treatment of secondary hyperparathyroidism in chronic kidney disease and for the treatment of parathyroid carcinoma. CaSR antagonists are also being developed, and may be useful in conditions of hypoparathyroidism or as a means to stimulate intermittent PTH secretion in the treatment of osteoporosis.

PLICAMYCIN (MITHRAMYCIN)

Plicamycin is a cytotoxic antibiotic (see Chapter 54) that has been used clinically for two disorders of bone mineral metabolism: Paget's disease and hypercalcemia. The cytotoxic properties of the drug appear to involve binding to DNA and interruption of DNA-directed RNA synthesis. The reasons for its usefulness in the treatment of Paget's disease and hypercalcemia are unclear but may relate to the need for protein synthesis to sustain bone resorption. The doses required to treat Paget's disease and hypercalcemia are about one tenth the amount required to achieve cytotoxic effects. With the development of other less toxic drugs for these purposes, the clinical use of plicamycin is seldom indicated.

THIAZIDE DIURETICS

The chemistry and pharmacology of the thiazide family of drugs are discussed in Chapter 15. The principal application of thiazides in the treatment of bone mineral disorders is in reducing renal calcium excretion. Thiazides may increase the effectiveness of PTH in stimulating reabsorption of calcium by the renal tubules or may act on calcium reabsorption secondarily by increasing sodium reabsorption in the proximal tubule. In the distal tubule, thiazides block sodium reabsorption at the luminal surface,

increasing the calcium-sodium exchange at the basolateral membrane and thus enhancing calcium reabsorption into the blood at this site (see Figure 15–4). Thiazides have proved to be useful in reducing the hypercalciuria and incidence of urinary stone formation in subjects with idiopathic hypercalciuria. Part of their efficacy in reducing stone formation may lie in their ability to decrease urine oxalate excretion and increase urine magnesium and zinc levels, both of which inhibit calcium oxalate stone formation.

FLUORIDE

Fluoride is well established as effective for the prophylaxis of dental caries and has previously been investigated for the treatment of osteoporosis. Both therapeutic applications originated from epidemiologic observations that subjects living in areas with naturally fluoridated water (1–2 ppm) had less dental caries and fewer vertebral compression fractures than subjects living in nonfluoridated water areas. Fluoride accumulates in bones and teeth, where it may stabilize the hydroxyapatite crystal. Such a mechanism may explain the effectiveness of fluoride in increasing the resistance of teeth to dental caries, but it does not explain its ability to promote new bone growth.

Fluoride in drinking water appears to be most effective in preventing dental caries if consumed before the eruption of the permanent teeth. The optimum concentration in drinking water supplies is 0.5–1 ppm. Topical application is most effective if done just as the teeth erupt. There is little further benefit to giving fluoride after the permanent teeth are fully formed. Excess fluoride in drinking water leads to mottling of the enamel proportionate to the concentration above 1 ppm.

Because of the paucity of agents that stimulate new bone growth in patients with osteoporosis, fluoride for this disorder has been examined (see Osteoporosis, below). Results of earlier studies indicated that fluoride alone, without adequate calcium supplementation, produced osteomalacia. More recent studies, in which calcium supplementation has been adequate, have demonstrated an improvement in calcium balance, an increase in bone mineral, and an increase in trabecular bone volume. Despite these promising effects of fluoride on bone mass, clinical studies have failed to demonstrate a reliable reduction in fractures, and some studies showed an increase in fracture rate. At present, fluoride is not approved by the FDA for treatment or prevention of osteoporosis, and it is unlikely to be.

Adverse effects observed—at the doses used for testing fluoride's effect on bone—include nausea and vomiting, gastrointestinal blood loss, arthralgias, and arthritis in a substantial proportion of patients. Such effects are usually responsive to reduction of the dose or giving fluoride with meals (or both).

STRONTIUM RANELATE

Strontium ranelate is composed of two atoms of strontium bound to an organic ion, ranelic acid. Although not yet approved for use in the USA, this drug is used in Europe for the treatment of osteoporosis. Strontium ranelate appears to block differentiation of osteoclasts

while promoting their apoptosis, thus inhibiting bone resorption. At the same time, strontium ranelate appears to promote bone formation. Unlike bisphosphonates, denosumab, or teriparatide, this drug increases bone formation markers while inhibiting bone resorption markers. Large clinical trials have demonstrated its efficacy in increasing bone mineral density and decreasing fractures in the spine and hip. Toxicities reported thus far are similar to placebo.

■ CLINICAL PHARMACOLOGY

Individuals with disorders of bone mineral homeostasis usually present with abnormalities in serum or urine calcium levels (or both), often accompanied by abnormal serum phosphate levels. These abnormal mineral concentrations may themselves cause symptoms requiring immediate treatment (eg, coma in malignant hypercalcemia, tetany in hypocalcemia). More commonly, they serve as clues to an underlying disorder in hormonal regulators (eg, primary hyperparathyroidism), target tissue response (eg, chronic kidney disease), or drug misuse (eg, vitamin D intoxication). In such cases, treatment of the underlying disorder is of prime importance.

Since bone and kidney play central roles in bone mineral homeostasis, conditions that alter bone mineral homeostasis usually affect one or both of these tissues secondarily. Effects on bone can result in osteoporosis (abnormal loss of bone; remaining bone histologically normal), osteomalacia (abnormal bone formation due to inadequate mineralization), or osteitis fibrosa (excessive bone resorption with fibrotic replacement of resorption cavities and marrow). Biochemical markers of skeletal involvement include changes in serum levels of the skeletal isoenzyme of alkaline phosphatase, osteocalcin, and N- and C- terminal propeptides of type I collagen (reflecting osteoblastic activity), and serum and urine levels of tartrate-resistant acid phosphatase and collagen breakdown products (reflecting osteoclastic activity). The kidney becomes involved when the calcium × phosphate product in serum rises above the point at which ectopic calcification occurs (nephrocalcinosis) or when the calcium × oxalate (or phosphate) product in urine exceeds saturation, leading to nephrolithiasis. Subtle early indicators of such renal involvement include polyuria, nocturia, and hyposthenuria. Radiologic evidence of nephrocalcinosis and stones is not generally observed until later. The degree of the ensuing renal failure is best followed by monitoring the decline in creatinine clearance. On the other hand, chronic kidney disease can be a primary cause of bone disease because of altered handling of calcium and phosphate, decreased $1,25(OH)_2D$ production, and secondary hyperparathyroidism.

ABNORMAL SERUM CALCIUM & PHOSPHATE LEVELS

HYPERCALCEMIA

Hypercalcemia causes central nervous system depression, including coma, and is potentially lethal. Its major causes (other than thiazide therapy) are hyperparathyroidism and cancer, with or without bone metastases. Less common causes are hypervitaminosis D, sarcoidosis, thyrotoxicosis, milk-alkali syndrome, adrenal

insufficiency, and immobilization. With the possible exception of hypervitaminosis D, the latter disorders seldom require emergency lowering of serum calcium. A number of approaches are used to manage the hypercalcemic crisis.

Saline Diuresis

In hypercalcemia of sufficient severity to produce symptoms, rapid reduction of serum calcium is required. The first steps include rehydration with saline and diuresis with furosemide, although the efficacy of furosemide in this setting has not been proved and use of the drug for this purpose appears to be falling out of favor. Most patients presenting with severe hypercalcemia have a substantial component of prerenal azotemia owing to dehydration, which prevents the kidney from compensating for the rise in serum calcium by excreting more calcium in the urine. Therefore, the initial infusion of 500–1000 mL/h of saline to reverse the dehydration and restore urine flow can by itself substantially lower serum calcium. The addition of a loop diuretic such as furosemide following rehydration enhances urine flow and also inhibits calcium reabsorption in the ascending limb of the loop of Henle (see Chapter 15). Monitoring of central venous pressure is important to forestall the development of heart failure and pulmonary edema in predisposed subjects. In many subjects, saline diuresis suffices to reduce serum calcium to a point at which more definitive diagnosis and treatment of the underlying condition can be achieved. If this is not the case or if more prolonged medical treatment of hypercalcemia is required, the following agents are available (discussed in order of preference).

Bisphosphonates

Pamidronate, 60–90 mg, infused over 2–4 hours, and zoledronate, 4 mg, infused over at least 15 minutes, have been approved for the treatment of hypercalcemia of malignancy and have largely replaced the less effective etidronate for this indication. The bisphosphonate effects generally persist for weeks, but treatment can be repeated after a 7-day interval if necessary and if renal function is not impaired. Some patients experience a self-limited flu-like syndrome after the initial infusion, but subsequent infusions generally do not have this side effect. Repeated doses of these drugs have been linked to renal deterioration and osteonecrosis of the jaw, but this adverse effect is rare.

Calcitonin

Calcitonin has proved useful as ancillary treatment in some patients. Calcitonin by itself seldom restores serum calcium to normal, and refractoriness frequently develops. However, its lack of toxicity permits frequent administration at high doses (200 MRC units or more). An effect on serum calcium is observed within 4–6 hours and lasts for 6–10 hours. Calcimar (salmon calcitonin) is available for parenteral and nasal administration.

Gallium Nitrate

Gallium nitrate is approved by the FDA for the management of hypercalcemia of malignancy. This drug inhibits bone resorption.

At a dosage of 200 mg/m^2 body surface area per day given as a continuous intravenous infusion in 5% dextrose for 5 days, gallium nitrate proved superior to calcitonin in reducing serum calcium in cancer patients. Because of potential nephrotoxicity, patients should be well hydrated and have good renal output before starting the infusion.

Plicamycin (Mithramycin)

Because of its toxicity, plicamycin (mithramycin) is not the drug of first choice for the treatment of hypercalcemia. However, when other forms of therapy fail, 25–50 mcg/kg of plicamycin given intravenously usually lowers serum calcium substantially within 24–48 hours. This effect can last several days. This dose can be repeated as necessary. The most dangerous toxic effect is sudden thrombocytopenia followed by hemorrhage. Hepatic and renal toxicity can also occur. Hypocalcemia, nausea, and vomiting may limit therapy. Use of this drug must be accompanied by careful monitoring of platelet counts, liver and kidney function, and serum calcium levels.

Phosphate

Intravenous phosphate administration is probably the fastest and surest way to reduce serum calcium, but it is a hazardous procedure if not done properly. Intravenous phosphate should be used only after other methods of treatment (bisphosphonates, calcitonin, and saline diuresis) have failed to control symptomatic hypercalcemia. Phosphate must be given slowly (50 mmol or 1.5 g elemental phosphorus over 6–8 hours) and the patient switched to oral phosphate (1–2 g/d elemental phosphorus, as one of the salts indicated below) as soon as symptoms of hypercalcemia have cleared. The risks of intravenous phosphate therapy include sudden hypocalcemia, ectopic calcification, acute renal failure, and hypotension. Oral phosphate can also lead to ectopic calcification and renal failure if serum calcium and phosphate levels are not carefully monitored, but the risk is less and the time of onset much longer. Phosphate is available in oral and intravenous forms as sodium or potassium salts. Amounts required to provide 1 g of elemental phosphorus are as follows:

Intravenous:

In-Phos: 40 mL
Hyper-Phos-K: 15 mL

Oral:

Fleet Phospho-Soda: 6.2 mL
Neutra-Phos: 300 mL
K-Phos-Neutral: 4 tablets

Glucocorticoids

Glucocorticoids have no clear role in the immediate treatment of hypercalcemia. However, the chronic hypercalcemia of sarcoidosis, vitamin D intoxication, and certain cancers may respond within several days to glucocorticoid therapy. Prednisone in oral doses of 30–60 mg daily is generally used, although equivalent doses of other glucocorticoids are effective. The rationale for the use of glucocorticoids in these diseases differs, however. The hypercalcemia of sarcoidosis is secondary to increased production of 1,25(OH)$_2$D, possibly by the sarcoid tissue itself. Glucocorticoid therapy directed at the reduction of sarcoid tissue results in restoration of normal serum calcium and 1,25(OH)$_2$D levels. The treatment of hypervitaminosis D with glucocorticoids probably does not alter vitamin D metabolism significantly but is thought to reduce vitamin D-mediated intestinal calcium transport. An action of glucocorticoids to reduce vitamin D-mediated bone resorption has not been excluded, however. The effect of glucocorticoids on the hypercalcemia of cancer is probably twofold. The malignancies responding best to glucocorticoids (ie, multiple myeloma and related lymphoproliferative diseases) are sensitive to the lytic action of glucocorticoids. Therefore part of the effect may be related to decreased tumor mass and activity. Glucocorticoids have also been shown to inhibit the secretion or effectiveness of cytokines elaborated by multiple myeloma and related cancers that stimulate osteoclastic bone resorption. Other causes of hypercalcemia—particularly primary hyperparathyroidism—do not respond to glucocorticoid therapy.

HYPOCALCEMIA

The main features of hypocalcemia are neuromuscular—tetany, paresthesias, laryngospasm, muscle cramps, and seizures. The major causes of hypocalcemia in the adult are hypoparathyroidism, vitamin D deficiency, chronic kidney disease, and malabsorption. Hypocalcemia can also accompany the infusion of potent bisphosphonates and denosumab for the treatment of osteoporosis, but this is seldom of clinical significance unless the patient is already hypocalcemic at the onset of the infusion. Neonatal hypocalcemia is a common disorder that usually resolves without therapy. The roles of PTH, vitamin D, and calcitonin in the neonatal syndrome are under investigation. Large infusions of citrated blood can produce hypocalcemia secondary to the formation of citrate-calcium complexes. Calcium and vitamin D (or its metabolites) form the mainstay of treatment of hypocalcemia.

Calcium

A number of calcium preparations are available for intravenous, intramuscular, and oral use. Calcium gluceptate (0.9 mEq calcium/mL), calcium gluconate (0.45 mEq calcium/mL), and calcium chloride (0.68–1.36 mEq calcium/mL) are available for intravenous therapy. Calcium gluconate is preferred because it is less irritating to veins. Oral preparations include calcium carbonate (40% calcium), calcium lactate (13% calcium), calcium phosphate (25% calcium), and calcium citrate (21% calcium). Calcium carbonate is often the preparation of choice because of its high percentage of calcium, ready availability (eg, Tums), low cost, and antacid properties. In achlorhydric patients, calcium carbonate should be given with meals to increase absorption, or the patient should be switched to calcium citrate, which is somewhat better absorbed. Combinations of vitamin D and calcium are available, but treatment must be tailored to the individual patient and the individual disease, a flexibility lost by fixed-dosage combinations.

Treatment of severe symptomatic hypocalcemia can be accomplished with slow infusion of 5–20 mL of 10% calcium gluconate. Rapid infusion can lead to cardiac arrhythmias. Less severe hypocalcemia is best treated with oral forms sufficient to provide approximately 400–1200 mg of elemental calcium (1–3 g calcium carbonate) per day. Dosage must be adjusted to avoid hypercalcemia and hypercalciuria.

Vitamin D

When rapidity of action is required, $1,25(OH)_2D_3$ (calcitriol), 0.25–1 mcg daily, is the vitamin D metabolite of choice because it is capable of raising serum calcium within 24–48 hours. Calcitriol also raises serum phosphate, although this action is usually not observed early in treatment. The combined effects of calcitriol and all other vitamin D metabolites and analogs on both calcium and phosphate make careful monitoring of these mineral levels especially important to prevent ectopic calcification secondary to an abnormally high serum calcium × phosphate product. Since the choice of the appropriate vitamin D metabolite or analog for long-term treatment of hypocalcemia depends on the nature of the underlying disease, further discussion of vitamin D treatment is found under the headings of the specific diseases.

HYPERPHOSPHATEMIA

Hyperphosphatemia is a common complication of renal failure and is also found in all types of hypoparathyroidism (idiopathic, surgical, and pseudohypoparathyroidism), vitamin D intoxication, and the rare syndrome of tumoral calcinosis (usually due to insufficient bioactive FGF23). Emergency treatment of hyperphosphatemia is seldom necessary but can be achieved by dialysis or glucose and insulin infusions. In general, control of hyperphosphatemia involves restriction of dietary phosphate plus phosphate-binding gels such as **sevelamer** and calcium supplements. Because of their potential to induce aluminum-associated bone disease, aluminum-containing antacids should be used sparingly and only when other measures fail to control the hyperphosphatemia. In patients with chronic kidney disease enthusiasm for the use of large doses of calcium to control hyperphosphatemia has waned because of the risk of ectopic calcification.

HYPOPHOSPHATEMIA

Hypophosphatemia is associated with a variety of conditions, including primary hyperparathyroidism, vitamin D deficiency, idiopathic hypercalciuria, conditions associated with increased bioactive FGF23 (eg, X-linked and autosomal dominant hypophosphatemic rickets and tumor-induced osteomalacia), other forms of renal phosphate wasting (eg, Fanconi's syndrome), overzealous use of phosphate binders, and parenteral nutrition with inadequate phosphate content. Acute hypophosphatemia may cause a reduction in the intracellular levels of high-energy organic phosphates (eg, ATP), interfere with normal hemoglobin-to-tissue oxygen transfer by decreasing red cell 2,3-diphosphoglycerate levels, and lead to rhabdomyolysis. However, clinically significant acute effects of hypophosphatemia are seldom seen, and emergency treatment is generally not indicated. The long-term effects of hypophosphatemia include proximal muscle weakness and abnormal bone mineralization (osteomalacia). Therefore, hypophosphatemia should be avoided when using forms of therapy that can lead to hypophosphatemia (eg, phosphate binders, certain types of parenteral nutrition) and treated in conditions that cause hypophosphatemia, such as the various forms of hypophosphatemic rickets. Oral forms of phosphate are listed above.

SPECIFIC DISORDERS INVOLVING BONE MINERAL-REGULATING HORMONES

PRIMARY HYPERPARATHYROIDISM

This rather common disease, if associated with symptoms and significant hypercalcemia, is best treated surgically. Oral phosphate and bisphosphonates have been tried but cannot be recommended. Asymptomatic patients with mild disease often do not get worse and may be left untreated. The calcimimetic agent **cinacalcet**, discussed previously, has been approved for secondary hyperparathyroidism and is in clinical trials for the treatment of primary hyperparathyroidism. If such drugs prove efficacious and cost effective, medical management of this disease will need to be reconsidered.

HYPOPARATHYROIDISM

In PTH deficiency (idiopathic or surgical hypoparathyroidism) or an abnormal target tissue response to PTH (pseudohypoparathyroidism), serum calcium falls and serum phosphate rises. In such patients, $1,25(OH)_2D$ levels are usually low, presumably reflecting the lack of stimulation by PTH of $1,25(OH)_2D$ production. The skeletons of patients with idiopathic or surgical hypoparathyroidism are normal except for a slow turnover rate. A number of patients with pseudohypoparathyroidism appear to have osteitis fibrosa, suggesting that the normal or high PTH levels found in such patients are capable of acting on bone but not on the kidney. The distinction between pseudohypoparathyroidism and idiopathic hypoparathyroidism is made on the basis of normal or high PTH levels but deficient renal response (ie, diminished excretion of cAMP or phosphate) in patients with pseudohypoparathyroidism.

The principal therapeutic concern is to restore normocalcemia and normophosphatemia. Vitamin D (25,000–100,000 units three times per week) and dietary calcium supplements have been used in the past. More rapid increments in serum calcium can be achieved with calcitriol. Many patients treated with vitamin D experience episodes of hypercalcemia. This complication is more rapidly reversible with cessation of therapy using calcitriol than therapy with vitamin D. This would be of importance to the patient in whom such hypercalcemic crises are common. Although teriparatide (PTH 1-34) is not approved for the treatment of hypoparathyroidism, it can be quite effective in patients who

respond poorly to calcium and vitamin D and may become the drug of choice for this condition.

NUTRITIONAL VITAMIN D DEFICIENCY OR INSUFFICIENCY

The level of vitamin D thought to be necessary for good health is being reexamined with the appreciation that vitamin D acts on a large number of cell types beyond those responsible for bone and mineral metabolism. A level of 25(OH)D above 10 ng/mL is necessary for preventing rickets or osteomalacia. However, substantial epidemiologic and some prospective trial data indicate that a higher level, such as 30 ng/mL, is required to optimize intestinal calcium absorption, optimize the accrual and maintenance of bone mass, reduce falls and fractures, and prevent a wide variety of diseases including diabetes mellitus, hyperparathyroidism, autoimmune diseases, and cancer. However, an expert panel for the Institute of Medicine (IOM) has recently recommended that a level of 20 ng/mL (50 nM) was sufficient for 97.5% of the population, although up to 50 ng/mL (125 nM) was considered safe. For individuals between the ages of 1–70 yrs 600 iu vitamin was thought to be sufficient to meet these goals, although up to 4000 iu vitamin D was considered safe. These recommendations are based primarily on data from randomized placebo controlled clinical trials (RCT) that evaluated falls and fractures; data supporting the non skeletal effects of vitamin D were considered too preliminary to be used in their recommendations because of lack of RCT for these other actions. The lower end of these recommendations has been considered too low and the upper end too restrictive by a number of vitamin D experts, but the call for better clinical data especially for the non skeletal actions is well taken. These guidelines—at least with respect to the lower recommended levels of vitamin D supplementation—are unlikely to correct vitamin D deficiency in individuals with obesity, dark complexions, limited capacity for sunlight exposure, or malabsorption. Furthermore, a large body of data from animal and cell studies as well and epidemiologic associations support a large range of beneficial actions of vitamin D that with adequate RCT data may alter these IOM recommendations. Vitamin D deficiency or insufficiency can be treated by higher dosages (4000 units per day or 50,000 units per week for several weeks). No other vitamin D metabolite is indicated. Because the half-life of vitamin D_3 metabolites in blood is greater than that of vitamin D_2, there may be some advantage to using vitamin D_3 supplements, although when administered on a daily or weekly schedule these differences may be moot. The diet should also contain adequate amounts of calcium and phosphate.

CHRONIC KIDNEY DISEASE

The major sequelae of chronic kidney disease that impact bone mineral homeostasis are deficient 1,25(OH)$_2$D production, retention of phosphate with an associated reduction in ionized calcium levels, and the secondary hyperparathyroidism that results from the parathyroid gland response to lowered serum ionized calcium

and low 1,25(OH)$_2$D. FGF23 levels are also increased in this disorder in part due to the increased phosphate, and this can further reduce 1,25(OH)$_2$D production by the kidney. With impaired 1,25(OH)$_2$D production, less calcium is absorbed from the intestine and less bone is resorbed under the influence of PTH. As a result hypocalcemia usually develops, furthering the development of secondary hyperparathyroidism. The bones show a mixture of osteomalacia and osteitis fibrosa.

In contrast to the hypocalcemia that is more often associated with chronic kidney disease, some patients may become hypercalcemic from overzealous treatment with calcium. However, the most common cause of hypercalcemia is the development of severe secondary (sometimes referred to as tertiary) hyperparathyroidism. In such cases, the PTH level in blood is very high. Serum alkaline phosphatase levels also tend to be high. Treatment often requires parathyroidectomy. A less common circumstance leading to hypercalcemia is development of a form of bone disease characterized by a profound decrease in bone cell activity and loss of the calcium buffering action of bone (adynamic bone disease). In the absence of kidney function, any calcium absorbed from the intestine accumulates in the blood. Such patients are very sensitive to the hypercalcemic action of 1,25(OH)$_2$D. These individuals generally have a high serum calcium but nearly normal alkaline phosphatase and PTH levels. The bone in such patients may have a high aluminum content, especially in the mineralization front, which blocks normal bone mineralization. These patients do not respond favorably to parathyroidectomy. Deferoxamine, an agent used to chelate iron (see Chapter 57), also binds aluminum and is being used to treat this disorder. However, with the reduction in use of aluminum-containing phosphate binders, most cases of adynamic bone disease are not associated with aluminum deposition but are attributed to overzealous suppression of PTH secretion.

Vitamin D Preparations

The choice of vitamin D preparation to be used in the setting of chronic kidney disease depends on the type and extent of bone disease and hyperparathyroidism. Individuals with vitamin D deficiency or insufficiency should first have their 25(OH)D levels restored to normal (above 30 ng/mL) with vitamin D. 1,25(OH)$_2$D$_3$ (calcitriol) rapidly corrects hypocalcemia and at least partially reverses secondary hyperparathyroidism and osteitis fibrosa. Many patients with muscle weakness and bone pain gain an improved sense of well-being.

Two analogs of calcitriol—doxercalciferol and paricalcitol—are approved for the treatment of secondary hyperparathyroidism of chronic kidney disease. Their principal advantage is that they are less likely than calcitriol to induce hypercalcemia for any given reduction in PTH. Their greatest impact is in patients in whom the use of calcitriol may lead to unacceptably high serum calcium levels.

Regardless of the drug used, careful attention to serum calcium and phosphate levels is required. A calcium × phosphate product (in mg/dL units) less than 55 is desired with both calcium and phosphate in the normal range. Calcium adjustments in the diet and dialysis bath and phosphate restriction (dietary and with oral ingestion of phosphate binders) should be used along with vitamin D metabolites. Monitoring of serum PTH and alkaline phosphatase

levels is useful in determining whether therapy is correcting or preventing secondary hyperparathyroidism. In patients on dialysis, a PTH value of approximately twice the upper limits of normal is considered desirable to prevent adynamic bone disease. Although not generally available, percutaneous bone biopsies for quantitative histomorphometry may help in choosing appropriate therapy and following the effectiveness of such therapy, especially in cases suspected of adynamic bone disease. Unlike the rapid changes in serum values, changes in bone morphology require months to years. Monitoring of serum vitamin D metabolite levels is useful for determining adherence, absorption, and metabolism.

INTESTINAL OSTEODYSTROPHY

A number of gastrointestinal and hepatic diseases cause disordered calcium and phosphate homeostasis, which ultimately leads to bone disease. The bones in such patients show a combination of osteoporosis and osteomalacia. Osteitis fibrosa does not occur, in contrast to renal osteodystrophy. The important common feature in this group of diseases appears to be malabsorption of calcium and vitamin D. Liver disease may, in addition, reduce the production of 25(OH)D from vitamin D, although its importance in patients other than those with terminal liver failure remains in dispute. The malabsorption of vitamin D is probably not limited to exogenous vitamin D as the liver secretes into bile a substantial number of vitamin D metabolites and conjugates that are normally reabsorbed in (presumably) the distal jejunum and ileum. Interference with this process could deplete the body of endogenous vitamin D metabolites in addition to limiting absorption of dietary vitamin D.

In mild forms of malabsorption, high doses of vitamin D (25,000–50,000 units three times per week) should suffice to raise serum levels of 25(OH)D into the normal range. Many patients with severe disease do not respond to vitamin D. Clinical experience with the other metabolites is limited, but both calcitriol and calcifediol have been used successfully in doses similar to those recommended for treatment of renal osteodystrophy. Theoretically, calcifediol should be the drug of choice under these conditions, because no impairment of the renal metabolism of 25(OH)D to 1,25(OH)$_2$D and 24,25(OH)$_2$D exists in these patients. However, calcifediol is no longer available in the USA. Both calcitriol and 24,25(OH)$_2$D may be of importance in reversing the bone disease. Intramuscular injections of vitamin D would be an alternative form of therapy, but there are currently no FDA-approved intramuscular preparations available in the USA.

As in the other diseases discussed, treatment of intestinal osteodystrophy with vitamin D and its metabolites should be accompanied by appropriate dietary calcium supplementation and monitoring of serum calcium and phosphate levels.

OSTEOPOROSIS

Osteoporosis is defined as abnormal loss of bone predisposing to fractures. It is most common in postmenopausal women but also occurs in men. The annual direct medical cost of fractures in older women and men in the USA is estimated to be 17–20 billion dollars per year, and is increasing as our population ages. Osteoporosis is most commonly associated with loss of gonadal function as in menopause but may also occur as an adverse effect of long-term administration of glucocorticoids or other drugs, including those that inhibit sex steroid production; as a manifestation of endocrine disease such as thyrotoxicosis or hyperparathyroidism; as a feature of malabsorption syndrome; as a consequence of alcohol abuse and cigarette smoking; or without obvious cause (idiopathic). The ability of some agents to reverse the bone loss of osteoporosis is shown in Figure 42–5. The postmenopausal form of osteoporosis may be accompanied by lower 1,25(OH)$_2$D levels and reduced intestinal calcium transport. This form of osteoporosis is due to reduced estrogen production and can be treated
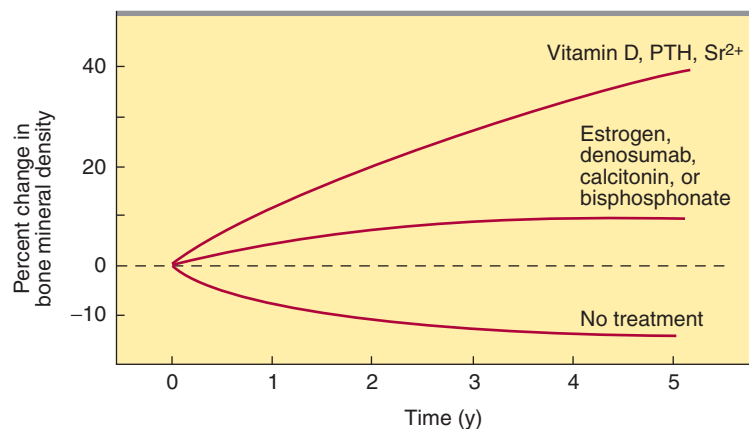

FIGURE 42–5 Typical changes in bone mineral density with time after the onset of menopause, with and without treatment. In the untreated condition, bone is lost during aging in both men and women. Strontium (Sr^{2+}), parathyroid hormone (PTH), and vitamin D promote bone formation and can increase bone mineral density in subjects who respond to them throughout the period of treatment, although PTH and vitamin D in high doses also activate bone resorption. In contrast, estrogen, calcitonin, denosumab, and bisphosphonates block bone resorption. This leads to a transient increase in bone mineral density because bone formation is not initially decreased. However, with time, both bone formation and bone resorption decrease with these pure antiresorptive agents, and bone mineral density reaches a new plateau.

with estrogen (combined with a progestin in women with a uterus to prevent endometrial carcinoma). However, concern that estrogen increases the risk of breast cancer and fails to reduce or may actually increase the development of heart disease has reduced enthusiasm for this form of therapy, at least in older individuals.

Bisphosphonates are potent inhibitors of bone resorption. They increase bone density and reduce the risk of fractures in the hip, spine, and other locations. **Alendronate, risedronate, ibandronate,** and **zoledronate** are approved for the treatment of osteoporosis, using daily dosing schedules of alendronate, 10 mg/d, risedronate, 5 mg/d, or ibandronate, 2.5 mg/d; or weekly schedules of alendronate, 70 mg/wk, or risedronate, 35 mg/wk; or monthly schedules of ibandronate, 150 mg/month; or quarterly (every 3 months) injections of ibandronate, 3 mg; or annual infusions of zoledronate, 5 mg. These drugs are effective in men as well as women and for various causes of osteoporosis.

As previously noted, estrogen-like SERMs (selective estrogen receptor modulators, Chapter 40) have been developed that prevent the increased risk of breast and uterine cancer associated with estrogen while maintaining the benefit to bone. The SERM **raloxifene** is approved for treatment of osteoporosis. Like tamoxifen, raloxifene reduces the risk of breast cancer. It protects against spine fractures but not hip fractures—unlike bisphosphonates, denosumab, and teriparatide, which protect against both. Raloxifene does not prevent hot flushes and imposes the same increased risk of venous thromboembolism as estrogen. To counter the reduced intestinal calcium transport associated with osteoporosis, vitamin D therapy is often used in combination with dietary calcium supplementation. There is no clear evidence that pharmacologic doses of vitamin D are of much additional benefit beyond cyclic estrogens and calcium supplementation. However, in several large studies, vitamin D supplementation (800 IU/d) with calcium has been shown to improve bone density, reduce falls, and prevent fractures. Calcitriol and its analog, $1\alpha(OH)D_3$, have also been shown to increase bone mass and reduce fractures. Use of these agents for osteoporosis is not FDA-approved, although they are used for this purpose in other countries.

Teriparatide, the recombinant form of PTH 1-34, is approved for treatment of osteoporosis. Teriparatide is given in a dosage of 20 mcg subcutaneously daily. Teriparatide stimulates new bone formation, but unlike fluoride, this new bone appears structurally normal and is associated with a substantial reduction in the incidence of fractures. Teriparatide is approved for only 2 years of use. Trials examining the sequential use of teriparatide followed by a bisphosphonate after 1 or 2 years are in progress and look promising. Use of teriparatide with a bisphosphonate has not shown greater efficacy than the bisphosphonate alone.

Calcitonin is approved for use in the treatment of postmenopausal osteoporosis. It has been shown to increase bone mass and reduce fractures, but only in the spine. It does not appear to be as effective as bisphosphonates or teriparatide.

Denosumab, the RANKL inhibitor, has recently been approved for treatment of postmenopausal osteoporosis. It is given subcutaneously every 6 months in 60 mg doses. Like the bisphosphonates it suppresses bone resorption and secondarily bone formation. Denosumab reduces the risk of both vertebral and nonvertebral fractures with comparable effectiveness to the potent bisphosphonates.

Strontium ranelate has not been approved in the USA for the treatment of osteoporosis but is being used in Europe, generally at a dose of 2 g/d.

X-LINKED & AUTOSOMAL DOMINANT HYPOPHOSPHATEMIA & RELATED DISEASES

These disorders usually manifest in childhood as rickets and hypophosphatemia, although they may first present in adults. In both X-linked and autosomal dominant hypophosphatemia, biologically active FGF23 accumulates, leading to phosphate wasting in the urine and hypophosphatemia. In autosomal dominant hypophosphatemia, mutations in the FGF23 gene replace an arginine required for hydrolysis and result in increased FGF23 stability. X-linked hypophosphatemia is caused by mutations in the gene encoding the PHEX protein, an endopeptidase. Initially, it was thought that FGF23 was a direct substrate for PHEX, but this no longer appears to be the case. Tumor-induced osteomalacia is a similar acquired syndrome in adults that results from overexpression of FGF23 in tumor cells. The current concept for all of these diseases is that FGF23 blocks the renal uptake of phosphate and blocks $1,25(OH)_2D$ production leading to rickets in children and osteomalacia in adults. Phosphate is critical to normal bone mineralization; when phosphate stores are deficient, a clinical and pathologic picture resembling vitamin D–dependent rickets develops. However, affected children fail to respond to the standard doses of vitamin D used in the treatment of nutritional rickets. A defect in $1,25(OH)_2D$ production by the kidney has also been noted, because the serum $1,25(OH)_2D$ levels tend to be low in comparison with the degree of hypophosphatemia observed. This combination of low serum phosphate and low or low-normal serum $1,25(OH)_2D$ provides the rationale for treating these patients with oral phosphate (1–3 g daily) and calcitriol (0.25–2 mcg daily). Reports of such combination therapy are encouraging in this otherwise debilitating disease, although prolonged treatment often leads to secondary hyperparathyroidism.

VITAMIN D–DEPENDENT RICKETS TYPES I & II (PSEUDOVITAMIN D DEFICIENCY RICKETS & HEREDITARY VITAMIN D–RESISTANT RICKETS)

These distinctly different autosomal recessive diseases present as childhood rickets that do not respond to conventional doses of vitamin D. Type I vitamin D–dependent rickets, now known as pseudovitamin D deficiency rickets, is due to an isolated deficiency of $1,25(OH)_2D$ production caused by mutations in 25(OH)-D-1α-hydroxylase (CYP27B1). This condition can be treated with vitamin D (4000 units daily) or calcitriol (0.25–0.5 mcg daily). Type II vitamin D–dependent rickets, now known as hereditary vitamin D resistant rickets, is caused by mutations in the gene for

the vitamin D receptor. The serum levels of $1,25(OH)_2D$ are very high in type II but inappropriately low for the level of calcium in type I vitamin D–dependent rickets. Treatment with large doses of calcitriol has been claimed to be effective in restoring normocalcemia in some patients, presumably those with a partially functional vitamin D receptor, although many patients are completely resistant to all forms of vitamin D. Calcium and phosphate infusions have been shown to correct the rickets in some children, similar to studies in mice in which the *VDR* gene has been deleted. These diseases are rare.

NEPHROTIC SYNDROME

Patients with nephrotic syndrome can lose vitamin D metabolites in the urine, presumably by loss of the vitamin D-binding protein. Such patients may have very low 25(OH)D levels. Some of them develop bone disease. It is not yet clear what value vitamin D therapy has in such patients, because therapeutic trials with vitamin D (or any vitamin D metabolite) have not yet been carried out. Because the problem is not related to vitamin D metabolism, one would not anticipate any advantage in using the more expensive vitamin D metabolites in place of vitamin D.

IDIOPATHIC HYPERCALCIURIA

Individuals with idiopathic hypercalciuria, characterized by hypercalciuria and nephrolithiasis with normal serum calcium and PTH levels, have been divided into three groups: (1) hyperabsorbers, patients with increased intestinal absorption of calcium, resulting in high-normal serum calcium, low-normal PTH, and a secondary increase in urine calcium; (2) renal calcium leakers, patients with a primary decrease in renal reabsorption of filtered calcium, leading to low-normal serum calcium and high-normal serum PTH; and (3) renal phosphate leakers, patients with a primary decrease in renal reabsorption of phosphate, leading to increased $1,25(OH)_2D$ production, increased intestinal calcium absorption, increased ionized serum calcium, low-normal PTH levels, and a secondary increase in urine calcium. There is some disagreement about this classification, and many patients are not readily categorized. Many such patients present with mild hypophosphatemia, and oral phosphate has been used with some success in reducing stone formation. However, a clear role for phosphate in the treatment of this disorder has not been established.

Therapy with hydrochlorothiazide, up to 50 mg twice daily, or chlorthalidone, 50–100 mg daily, is recommended. Loop diuretics such as furosemide and ethacrynic acid should not be used because they increase urinary calcium excretion. The major toxicity of thiazide diuretics, besides hypokalemia, hypomagnesemia, and hyperglycemia, is hypercalcemia. This is seldom more than a biochemical observation unless the patient has a disease such as hyperparathyroidism in which bone turnover is accelerated. Accordingly, one should screen patients for such disorders before starting thiazide therapy and monitor serum and urine calcium when therapy has begun.

An alternative to thiazides is allopurinol. Some studies indicate that hyperuricosuria is associated with idiopathic hypercalcemia

and that a small nidus of urate crystals could lead to the calcium oxalate stone formation characteristic of idiopathic hypercalcemia. Allopurinol, 100–300 mg daily, may reduce stone formation by reducing uric acid excretion.

OTHER DISORDERS OF BONE MINERAL HOMEOSTASIS

PAGET'S DISEASE OF BONE

Paget's disease is a localized bone disorder characterized by uncontrolled osteoclastic bone resorption with secondary increases in poorly organized bone formation. The cause of Paget's disease is obscure, although some studies suggest that a slow virus may be involved. The disease is fairly common, although symptomatic bone disease is less common. The biochemical parameters of elevated serum alkaline phosphatase and urinary hydroxyproline are useful for diagnosis. Along with the characteristic radiologic and bone scan findings, these biochemical determinations provide good markers by which to follow therapy.

The goal of treatment is to reduce bone pain and stabilize or prevent other problems such as progressive deformity, hearing loss, high-output cardiac failure, and immobilization hypercalcemia. Calcitonin and bisphosphonates are the first-line agents for this disease. Treatment failures may respond to plicamycin. Calcitonin is administered subcutaneously or intramuscularly in doses of 50–100 MRC (Medical Research Council) units every day or every other day. Nasal inhalation at 200–400 units per day is also effective. Higher or more frequent doses have been advocated when this initial regimen is ineffective. Improvement in bone pain and reduction in serum alkaline phosphatase and urine hydroxyproline levels require weeks to months. Often a patient who responds well initially loses the response to calcitonin. This refractoriness is not correlated with the development of antibodies.

Sodium etidronate, alendronate, risedronate, and tiludronate are the bisphosphonates currently approved for clinical use in Paget's disease of bone in the USA. Other bisphosphonates, including pamidronate, are being used in other countries. The recommended dosages of bisphosphonates are etidronate, 5 mg/kg/d; alendronate, 40 mg/d; risedronate, 30 mg/d; and tiludronate, 400 mg/d. Long-term (months to years) remission may be expected in patients who respond to a bisphosphonate. Treatment should not exceed 6 months per course but can be repeated after 6 months if necessary. The principal toxicity of etidronate is the development of osteomalacia and an increased incidence of fractures when the dosage is raised substantially above 5 mg/kg/d. The newer bisphosphonates such as risedronate and alendronate do not share this adverse effect. Some patients treated with etidronate develop bone pain similar in nature to the bone pain of osteomalacia. This subsides after stopping the drug. The principal adverse effect of alendronate and the newer bisphosphonates is gastric irritation when used at these high doses. This is reversible on cessation of the drug.

The use of a potentially lethal cytotoxic drug such as plicamycin in a generally benign disorder such as Paget's disease is recommended only when other less toxic agents (calcitonin, alendronate) have failed and the symptoms are debilitating. Clinical data on

long-term use of plicamycin are insufficient to determine its useful-ness for extended therapy. However, short courses involving 15–25 mcg/kg/d intravenously for 5–10 days followed by 15 mcg/kg intravenously each week have been used to control the disease.

ENTERIC OXALURIA

Patients with short bowel syndromes and associated fat malabsorp-tion can present with renal stones composed of calcium and oxalate. Such patients characteristically have normal or low urine calcium levels but elevated urine oxalate levels. The reasons for the

development of oxaluria in such patients are thought to be twofold: first, in the intestinal lumen, calcium (which is now bound to fat) fails to bind oxalate and no longer prevents its absorption; second, enteric flora, acting on the increased supply of nutrients reaching the colon, produce larger amounts of oxalate. Although one would ordinarily avoid treating a patient with calcium oxalate stones with calcium supplementation, this is precisely what is done in patients with enteric oxaluria. The increased intestinal calcium binds the excess oxalate and prevents its absorption. One to 2 g of calcium carbonate can be given daily in divided doses, with careful moni-toring of urinary calcium and oxalate to be certain that urinary oxalate falls without a dangerous increase in urinary calcium.

SUMMARY Major Drugs Used in Diseases of Bone Mineral Homeostasis

Subclass	Mechanism of Action	Effects	Clinical Applications	Toxicities
VITAMIN D, METABOLITES, ANALOGS • Cholecalciferol • Ergocalciferol • Calcitriol • Doxercalciferol • Paricalcitol • Calcipotriene	Regulate gene transcrip-tion via the vitamin D receptor	Stimulate intestinal calcium absorption, bone resorption, renal calcium and phosphate reabsorption • decrease para-thyroid hormone (PTH) • promote innate immunity • inhibit adaptive immunity	Osteoporosis, osteomalacia, renal failure, malabsorption, psoriasis	Hypercalcemia, hypercalciuria • the vitamin D preparations have much longer half-life than the metabolites and analogs
BISPHOSPHONATES • Alendronate • Risedronate • Ibandronate • Pamidronate • Zoledronate	Suppress the activity of osteoclasts in part via inhibition of farnesyl pyrophosphate synthesis	Inhibit bone resorption and secondarily bone formation	Osteoporosis, bone metastases, hypercal-cemia	Adynamic bone, possible renal failure, rare osteonecrosis of the jaw, rare subtrochanteric (femur) fractures
HORMONES • Teriparatide • Calcitonin	These hormones act via their cognate G protein-coupled receptors	Teriparatide stimulates bone turnover • calcitonin sup-presses bone resorption	Both are used in osteo-porosis • calcitonin is used for hypercalcemia	Teriparatide may cause hyper-calcemia and hypercalciuria
SELECTIVE ESTROGEN RECEPTOR MODULATORS (SERMs) • Raloxifene	Interacts selectively with estrogen receptors	Inhibits bone resorption with-out stimulating breast or endometrial hyperplasia	Osteoporosis	Does not prevent hot flashes • increased risk of venous thromboembolism
RANK LIGAND (RANKL) INHIBITOR • Denosumab	Monoclonal antibody • binds to RANKL and pre-vents it from stimulating osteoclast differentiation and function	Blocks bone resorption	Osteoporosis	May increase risk of infections
CALCIUM RECEPTOR AGONIST • Cinacalcet	Activates the calcium-sensing receptor	Inhibits PTH secretion	Hyperparathyroidism	Nausea
MINERALS • Calcium • Phosphate • Strontium	Multiple physiologic actions through regulation of multiple enzymatic pathways	Strontium suppresses bone resorption and increases bone formation • calcium and phosphate required for bone mineralization	Osteoporosis • osteomalacia • deficiencies in calcium or phosphate	Ectopic calcification

PREPARATIONS AVAILABLE

VITAMIN D, METABOLITES, AND ANALOGS

Calcitriol
Oral (generic, Rocaltrol): 0.25, 0.5 mcg capsules, 1 mcg/mL solution
Parenteral (generic, Calcijex): 1, 2 mcg/mL for injection

Cholecalciferol [D_3] (vitamin D_3, Delta-D)
Oral: numerous forms containing 400–50,000 IU per unit

Doxercalciferol (Hectorol)
Oral: 0.5, 1, 2.5 mcg capsules
Parenteral: 2 mcg/mL

Ergocalciferol [D_2] (vitamin D_2, Calciferol, Drisdol)
Oral: 50,000 IU capsules; 8000 IU/mL drops

Paricalcitol (Zemplar)
Oral: 1, 2, 4 mcg capsules
Parenteral: 2, 5 mcg/mL for injection

CALCIUM

Calcium acetate [25% calcium] (generic, PhosLo)
Oral: 668 mg (169 mg calcium) tablets or capsules

Calcium carbonate [40% calcium] (generic, Tums, Cal-Sup, Os-Cal 500, others)
Oral: Numerous forms available containing 260–600 mg calcium per unit

Calcium chloride [27% calcium] (generic)
Parenteral: 10% solution for IV injection

Calcium citrate [21% calcium] (generic, Citracal)
Oral: 950 mg (200 mg calcium), 2376 mg (500 mg calcium)

Calcium glubionate [6.5% calcium] (Calcionate, Calciquid)
Oral: 1.8 g (115 mg calcium)/5 mL syrup

Calcium gluceptate [8% calcium] (Calcium Gluceptate)
Parenteral: 1.1 g/5 mL solution for IM or IV injection

Calcium gluconate [9% calcium] (generic)
Oral: 500 mg (45 mg calcium), 650 mg (58.5 mg calcium), 975 mg (87.75 mg calcium), 1 g (90 mg calcium) tablets
Parenteral: 10% solution for IV or IM injection

Calcium lactate [13% calcium] (generic)
Oral: 650 mg (84.5 mg calcium), 770 mg (100 mg calcium) tablets

Tricalcium phosphate [39% calcium] (Posture)
Oral: 1565 mg (600 mg calcium) tablets (as phosphate)

PHOSPHATE AND PHOSPHATE BINDER

Phosphate
Oral (Fleet Phospho-soda): solution containing 2.5 g phosphate/5 mL (816 mg phosphorus/5 mL; 751 mg sodium/5 mL)

Oral (K-Phos-Neutral): tablets containing 250 mg phosphorus, 298 mg sodium, 45 mg phosphorus
Oral (Neutra-Phos): For reconstitution in 75 mL water, packet containing 250 mg phosphorus; 164 mg sodium; 278 mg potassium
Oral (Neutra-Phos-K): For reconstitution in 75 mL water, packet containing 250 mg phosphorus; 556 mg potassium; 0 mg sodium
Parenteral (potassium or sodium phosphate): 3 mmol/mL

Sevelamer carbonate or HCl (Renagel, Renvela)
Oral: 400, 800 mg capsules

BISPHOSPHONATES

Alendronate sodium (generic, Fosamax)
Oral: 5, 10, 35, 40, 70 mg tablets; 70 mg/75 mL oral solution

Etidronate disodium (generic, Didronel)
Oral: 200, 400 mg tablets

Ibandronate sodium (Boniva)
Oral: 2.5, 150 mg tablets
Parenteral: 1 mg/mL for IV injection

Pamidronate disodium (generic, Aredia)
Parenteral: 30, 60, 90 mg/vial for IV injection

Risedronate sodium (Actonel)
Oral: 5, 30, 35, 75, 150 mg tablets

Tiludronate disodium (Skelid)
Oral: 200 mg tablets (as tiludronic acid)

Zoledronic acid (Zometa)
Parenteral: 4 mg/vial for IV injection

OTHER DRUGS

Calcitonin-Salmon
Nasal spray (Miacalcin): 200 IU/puff
Parenteral (Calcimar, Miacalcin, Salmonine): 200 IU/mL for injection

Cinacalcet (Sensipar)
Oral: 30, 60, 90 mg tablets

Denosumab (Prolia)
Parenteral: 60 mg/mL solution for SC injection

Gallium nitrate (Ganite)
Parenteral: 25 mg/mL solution for IV injection

Plicamycin (mithramycin) (Mithracin)
Parenteral: 2.5 mg per vial powder to reconstitute for injection

Sodium fluoride (generic)
Oral: 0.55 mg (0.25 mg F), 1.1 mg (0.5 mg F), 2.2 mg (1.0 mg F) tablets; drops

Teriparatide (Forteo)
Subcutaneous: 250 mcg/mL in prefilled pen for SC injectiont

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CASE STUDY ANSWER

There are multiple reasons for this patient's osteoporosis, including a heavy smoking history, possible alcoholism, and chronic inflammatory disease treated with glucocorticoids. High levels of cytokines from the chronic inflammation activate osteoclasts. Glucocorticoids increase urinary losses of calcium, suppress bone formation, and inhibit intestinal calcium absorption as well as decreasing gonadotropin production, leading to hypogonadism. Management should include measurement of serum testosterone, serum calcium, and the 24-hour urine calcium level, with treatment as appropriate for these secondary causes, plus initiation of bisphosphonate or denosumab therapy as primary treatment.

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SECTION VIII CHEMOTHERAPEUTIC DRUGS

INTRODUCTION TO ANTIMICROBIAL AGENTS

Antimicrobial agents provide some of the most dramatic examples of the advances of modern medicine. Many infectious diseases once considered incurable and lethal are now amenable to treatment with a few pills. The remarkably powerful and specific activity of antimicrobial drugs is due to their selectivity for targets that are either unique to prokaryote and fungal microorganisms or much more important in these organisms than in humans. Among these targets are bacterial and fungal cell wall-synthesizing enzymes (Chapters 43 and 48), the bacterial ribosome (Chapters 44 and 45), the enzymes required for nucleotide synthesis and DNA replication (Chapter 46), and the machinery of viral replication (Chapter 49). The special group of drugs used in mycobacterial infections is discussed in Chapter 47. The much older and less selective cytotoxic antiseptics and disinfectants are discussed in Chapter 50. The clinical uses of all these agents are summarized in Chapter 51.

The major problem threatening the continued success of antimicrobial drugs is the development of resistant organisms. Microorganisms can adapt to environmental pressures in a variety of effective ways, and their response to antibiotic pressure is no exception. An inevitable consequence of antimicrobial usage is the selection of resistant microorganisms, perhaps the most obvious example of evolution in action. Overuse and inappropriate use of antibiotics in patients has fueled a major increase in prevalence of multidrug-resistant pathogens. Antibacterial antibiotics are misused by providers in a variety of ways, including use in patients who are unlikely to have bacterial infections, use over unnecessarily prolonged periods, and use of multiple agents or broad-spectrum agents when not needed.

As a result of antibiotic pressure, highly resistant gram-negative organisms with novel mechanisms of resistance are increasingly reported. Some of these strains have spread over vast geographic areas as a result of patients seeking medical care in different countries. Much larger quantities of antibiotics have been used in agriculture to stimulate growth and prevent infection in farm animals and this has added to the selection pressure that results in resistant organisms.

Unfortunately, as the need has grown in recent years, development of novel drugs has slowed. The most vulnerable molecular targets of antimicrobial drugs have been identified and, in many cases, crystallized and characterized. Pending the identification of new targets and compounds, it seems likely that over the next decade we will have to rely on currently available families of drugs. In the face of continuing development of resistance, considerable effort will be required to maintain the effectiveness of these drug groups.

Beta-Lactam & Other Cell Wall- & Membrane-Active Antibiotics

**Daniel H. Deck, PharmD &
Lisa G. Winston, MD**[*]

CASE STUDY

A 55-year-old man is brought to the local hospital emergency department by ambulance. His wife reports that he had been in his normal state of health until 3 days ago when he developed a fever and a productive cough. During the last 24 hours he has complained of a headache and is increasingly confused. His wife reports that his medical history is significant only for hypertension, for which he takes hydrochlorothiazide and lisinopril, and that he is allergic to amoxicillin. She says that he developed a rash many years ago when prescribed amoxicillin for bronchitis. In the emergency department, the man is febrile (38.7°C [101.7°F]), hypotensive (90/54 mm Hg), tachypneic (36/min), and tachycardic (110/min). He has no signs of meningismus but is oriented only to person. A stat chest x-ray shows a left lower lung consolidation consistent with pneumonia. The plan is to start empiric antibiotics and perform a lumbar puncture to rule out bacterial meningitis. What antibiotic regimen should be started to treat both pneumonia and meningitis? Does the history of amoxicillin rash affect the antibiotic choice? Why or why not?

■ BETA-LACTAM COMPOUNDS

PENICILLINS

The penicillins share features of chemistry, mechanism of action, pharmacology, and immunologic characteristics with cephalosporins, monobactams, carbapenems, and β-lactamase inhibitors. All are β-lactam compounds, so named because of their four-membered lactam ring.

Chemistry

All penicillins have the basic structure shown in Figure 43–1. A thiazolidine ring (A) is attached to a β-lactam ring (B) that carries a secondary amino group (RNH–). Substituents (R; examples shown in Figure 43–2) can be attached to the amino group. Structural integrity of the 6-aminopenicillanic acid nucleus (rings A plus B) is essential for the biologic activity of these compounds.

Hydrolysis of the β-lactam ring by bacterial β-lactamases yields penicilloic acid, which lacks antibacterial activity.

A. Classification

Substituents of the 6-aminopenicillanic acid moiety determine the essential pharmacologic and antibacterial properties of the resulting molecules. Penicillins can be assigned to one of three groups (below). Within each of these groups are compounds that are relatively stable to gastric acid and suitable for oral administration, eg, penicillin V, dicloxacillin, and amoxicillin. The side chains of some representatives of each group are shown in Figure 43–2, with a few distinguishing characteristics.

1. Penicillins (eg, penicillin G)—These have greatest activity against gram-positive organisms, gram-negative cocci, and non-β-lactamase producing anaerobes. However, they have little activity against gram-negative rods, and they are susceptible to hydrolysis by β-lactamases.

2. Antistaphylococcal penicillins (eg, nafcillin)—These penicillins are resistant to staphylococcal β-lactamases. They are
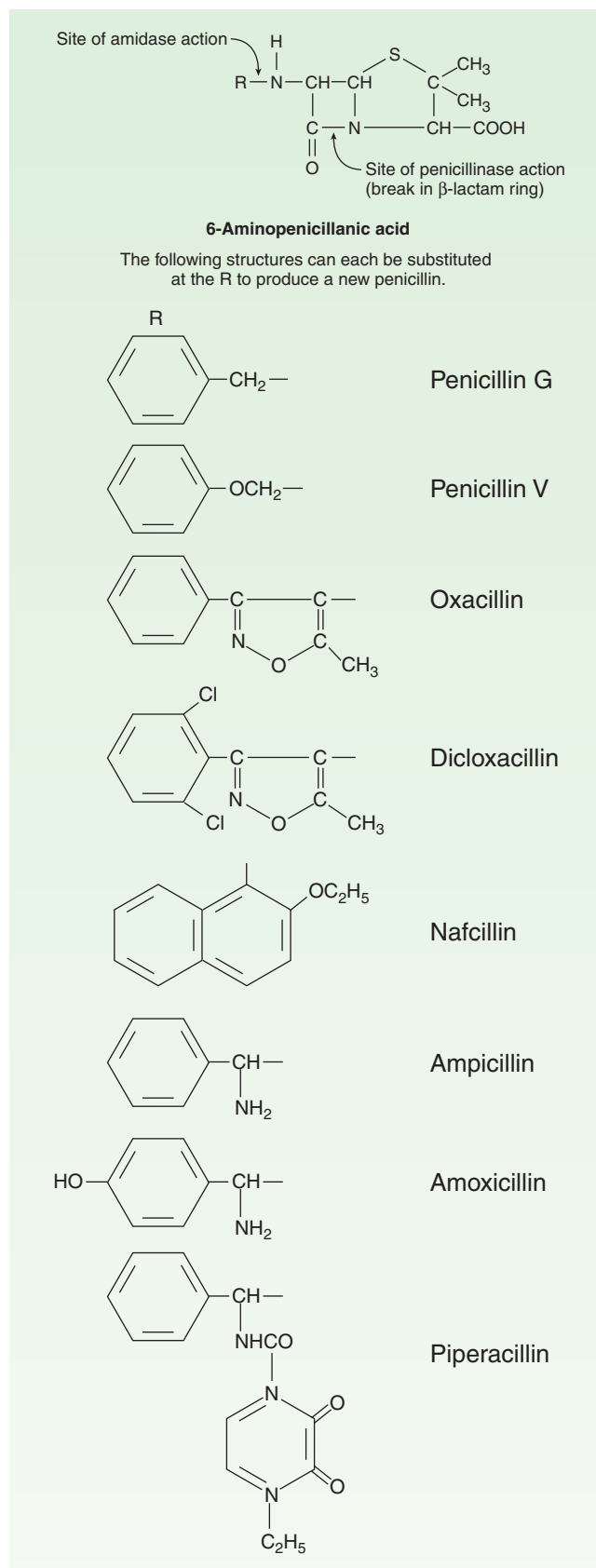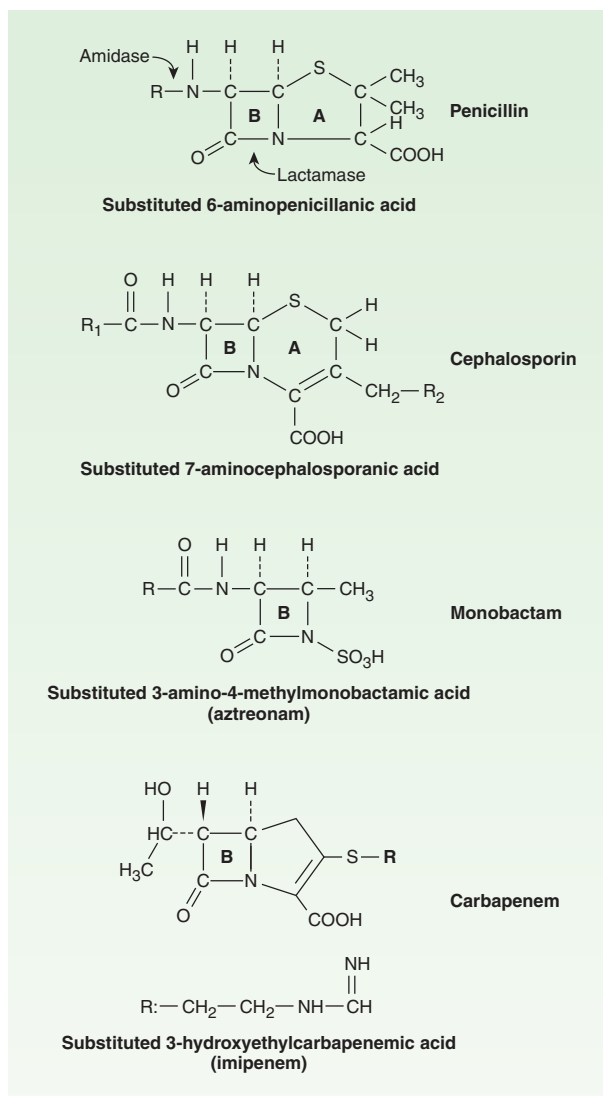

FIGURE 43–1 Core structures of four β-lactam antibiotic families. The ring marked B in each structure is the β-lactam ring. The penicillins are susceptible to bacterial metabolism and inactivation by amidases and lactamases at the points shown. Note that the carbapenems have a different stereochemical configuration in the lactam ring that imparts resistance to most common β lactamases. Substituents for the penicillin and cephalosporin families are shown in Figures 43–2 and 43–6, respectively.

active against staphylococci and streptococci but not against enterococci, anaerobic bacteria, and gram-negative cocci and rods.

3. Extended-spectrum penicillins (ampicillin and the antipseudomonal penicillins)—These drugs retain the antibacterial spectrum of penicillin and have improved activity against gram-negative organisms. Like penicillin, however, they are relatively susceptible to hydrolysis by β-lactamases.

B. Penicillin Units and Formulations

The activity of penicillin G was originally defined in units. Crystalline sodium penicillin G contains approximately

FIGURE 43–2 Side chains of some penicillins (R groups of Figure 43–1).

1600 units per mg (1 unit = 0.6 mcg; 1 million units of penicillin = 0.6 g). Semisynthetic penicillins are prescribed by weight rather than units. The **minimum inhibitory concentration (MIC)** of any penicillin (or other antimicrobial) is usually given in mcg/mL. Most penicillins are formulated as the sodium or potassium salt of the free acid. Potassium penicillin G contains about 1.7 mEq of K^+ per million units of penicillin (2.8 mEq/g). Nafcillin contains Na^+, 2.8 mEq/g. Procaine salts and benzathine salts of penicillin G provide repository forms for intramuscular injection. In dry crystalline form, penicillin salts are stable for years at 4°C. Solutions lose their activity rapidly (eg, 24 hours at 20°C) and must be prepared fresh for administration.

Mechanism of Action

Penicillins, like all β-lactam antibiotics, inhibit bacterial growth by interfering with the transpeptidation reaction of **bacterial cell wall synthesis.** The cell wall is a rigid outer layer unique to bacterial species. It completely surrounds the cytoplasmic membrane (Figure 43–3), maintains cell shape and integrity, and prevents cell lysis from high osmotic pressure. The cell wall is composed of a complex, cross-linked polymer of polysaccharides and polypeptides, peptidoglycan (also known as murein or mucopeptide). The polysaccharide contains alternating amino sugars,

N-acetylglucosamine and *N*-acetylmuramic acid (Figure 43–4). A five-amino-acid peptide is linked to the *N*-acetylmuramic acid sugar. This peptide terminates in D-alanyl-D-alanine. Penicillin-binding protein (PBP, an enzyme) removes the terminal alanine in the process of forming a cross-link with a nearby peptide. Cross-links give the cell wall its structural rigidity. Beta-lactam antibiotics, structural analogs of the natural D-Ala-D-Ala substrate, covalently bind to the active site of PBPs. This inhibits the transpeptidation reaction (Figure 43–5), halting peptidoglycan synthesis, and the cell dies. The exact mechanism of cell death is not completely understood, but autolysins and disruption of cell wall morphogenesis are involved. Beta-lactam antibiotics kill bacterial cells only when they are actively growing and synthesizing cell wall.

Resistance

Resistance to penicillins and other β-lactams is due to one of four general mechanisms: (1) inactivation of antibiotic by β-lactamase, (2) modification of target PBPs, (3) impaired penetration of drug to target PBPs, and (4) efflux. Beta-lactamase production is the most common mechanism of resistance. Hundreds of different β-lactamases have been identified. Some, such as those produced by *Staphylococcus aureus, Haemophilus influenzae*, and *Escherichia coli*,
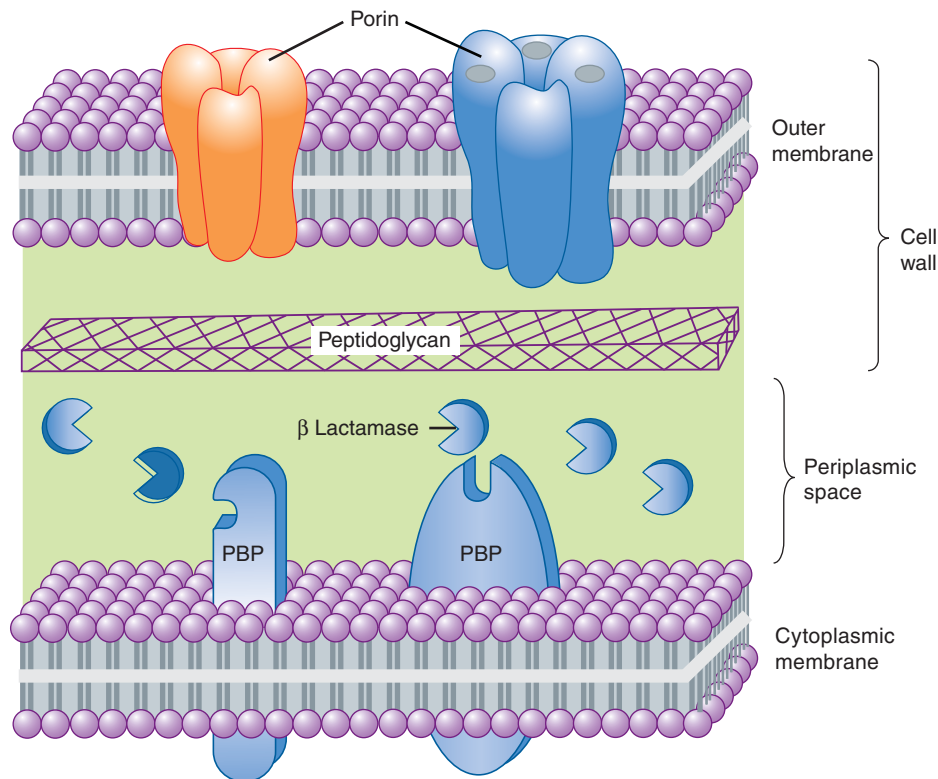

FIGURE 43–3 A highly simplified diagram of the cell envelope of a gram-negative bacterium. The outer membrane, a lipid bilayer, is present in gram-negative but not gram-positive organisms. It is penetrated by porins, proteins that form channels providing hydrophilic access to the cytoplasmic membrane. The peptidoglycan layer is unique to bacteria and is much thicker in gram-positive organisms than in gram-negative ones. Together, the outer membrane and the peptidoglycan layer constitute the cell wall. Penicillin-binding proteins (PBPs) are membrane proteins that cross-link peptidoglycan. Beta lactamases, if present, reside in the periplasmic space or on the outer surface of the cytoplasmic membrane, where they may destroy β-lactam antibiotics that penetrate the outer membrane.
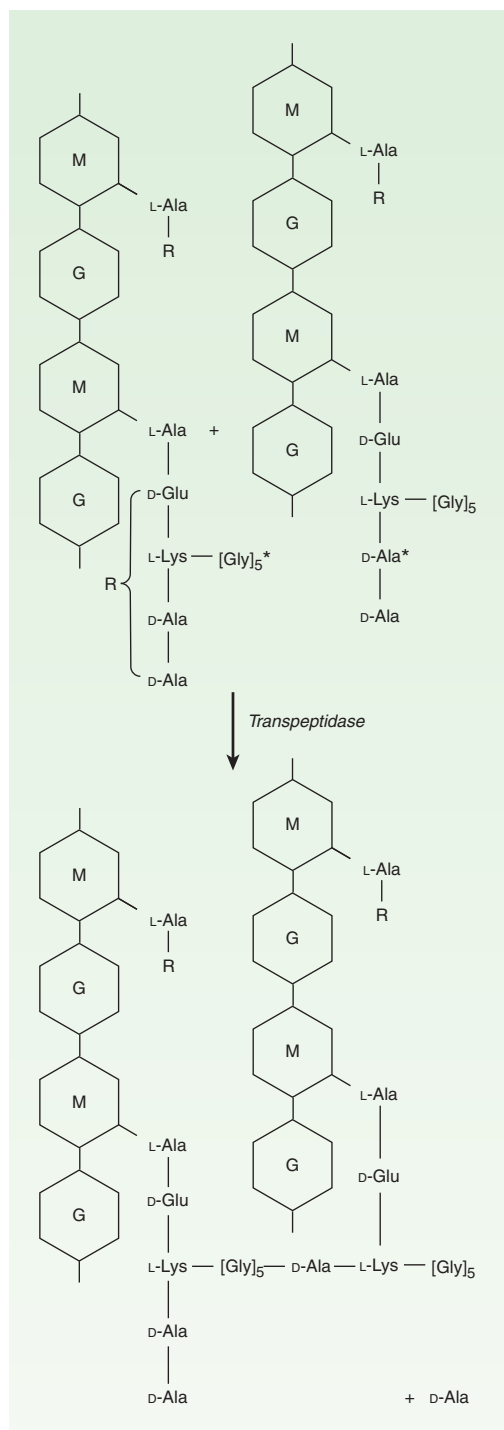
are relatively narrow in substrate specificity, preferring penicillins to cephalosporins. Other β-lactamases, eg, AmpC β-lactamase produced by *Pseudomonas aeruginosa* and *Enterobacter* sp, and extended-spectrum β-lactamases (ESBLs), hydrolyze both cephalosporins and penicillins. Carbapenems are highly resistant to hydrolysis by penicillinases and cephalosporinases, but they are hydrolyzed by metallo-β lactamase and carbapenemases.

Altered target PBPs are the basis of methicillin resistance in staphylococci and of penicillin resistance in pneumococci and enterococci. These resistant organisms produce PBPs that have low affinity for binding β-lactam antibiotics, and consequently, they are not inhibited except at relatively high, often clinically unachievable, drug concentrations.

Resistance due to impaired penetration of antibiotic to target PBPs occurs only in gram-negative species because of their impermeable outer cell wall membrane, which is absent in gram-positive bacteria. Beta-lactam antibiotics cross the outer membrane and enter gram-negative organisms via outer membrane protein channels called porins. Absence of the proper channel or down-regulation of its production can greatly impair drug entry into the cell. Poor penetration alone is usually not sufficient to confer resistance because enough antibiotic eventually enters the cell to inhibit growth. However, this barrier can become important in the presence of a β-lactamase, even a relatively inactive one, as long as it can hydrolyze drug faster than it enters the cell. Gram-negative organisms also may produce an efflux pump, which consists of cytoplasmic and periplasmic protein components that efficiently transport some β-lactam antibiotics from the periplasm back across the outer membrane.

Pharmacokinetics

Absorption of orally administered drug differs greatly for different penicillins, depending in part on their acid stability and protein binding. Gastrointestinal absorption of nafcillin is erratic, so it is not suitable for oral administration. Dicloxacillin, ampicillin, and amoxicillin are acid-stable and relatively well absorbed, producing serum concentrations in the range of 4–8 mcg/mL after a 500-mg oral dose. Absorption of most oral penicillins (amoxicillin being an exception) is impaired by food, and the drugs should be administered at least 1–2 hours before or after a meal.

Intravenous administration of penicillin G is preferred to the intramuscular route because of irritation and local pain from intramuscular injection of large doses. Serum concentrations 30 minutes after an intravenous injection of 1 g of a penicillin (equivalent to approximately 1.6 million units of penicillin G) are 20–50 mcg/mL. Only a small amount of the total drug in serum is present as free drug, the concentration of which is determined by protein binding. Highly protein-bound penicillins (eg, nafcillin) generally achieve lower free-drug concentrations in serum than less protein-bound penicillins (eg, penicillin G or ampicillin). Protein binding becomes clinically relevant when the protein-bound percentage is approximately 95% or more. Penicillins are widely distributed in body fluids and tissues with a few exceptions. They are polar molecules, so intracellular concentrations are well below those found in extracellular fluids.

FIGURE 43–4 The transpeptidation reaction in *Staphylococcus aureus* that is inhibited by β-lactam antibiotics. The cell wall of gram-positive bacteria is made up of long peptidoglycan polymer chains consisting of the alternating aminohexoses N-acetylglucosamine (G) and N-acetylmuramic acid (M) with pentapeptide side chains linked (in S aureus) by pentaglycine bridges. The exact composition of the side chains varies among species. The diagram illustrates small segments of two such polymer chains and their amino acid side chains. These linear polymers must be cross-linked by transpeptidation of the side chains at the points indicated by the asterisk to achieve the strength necessary for cell viability.
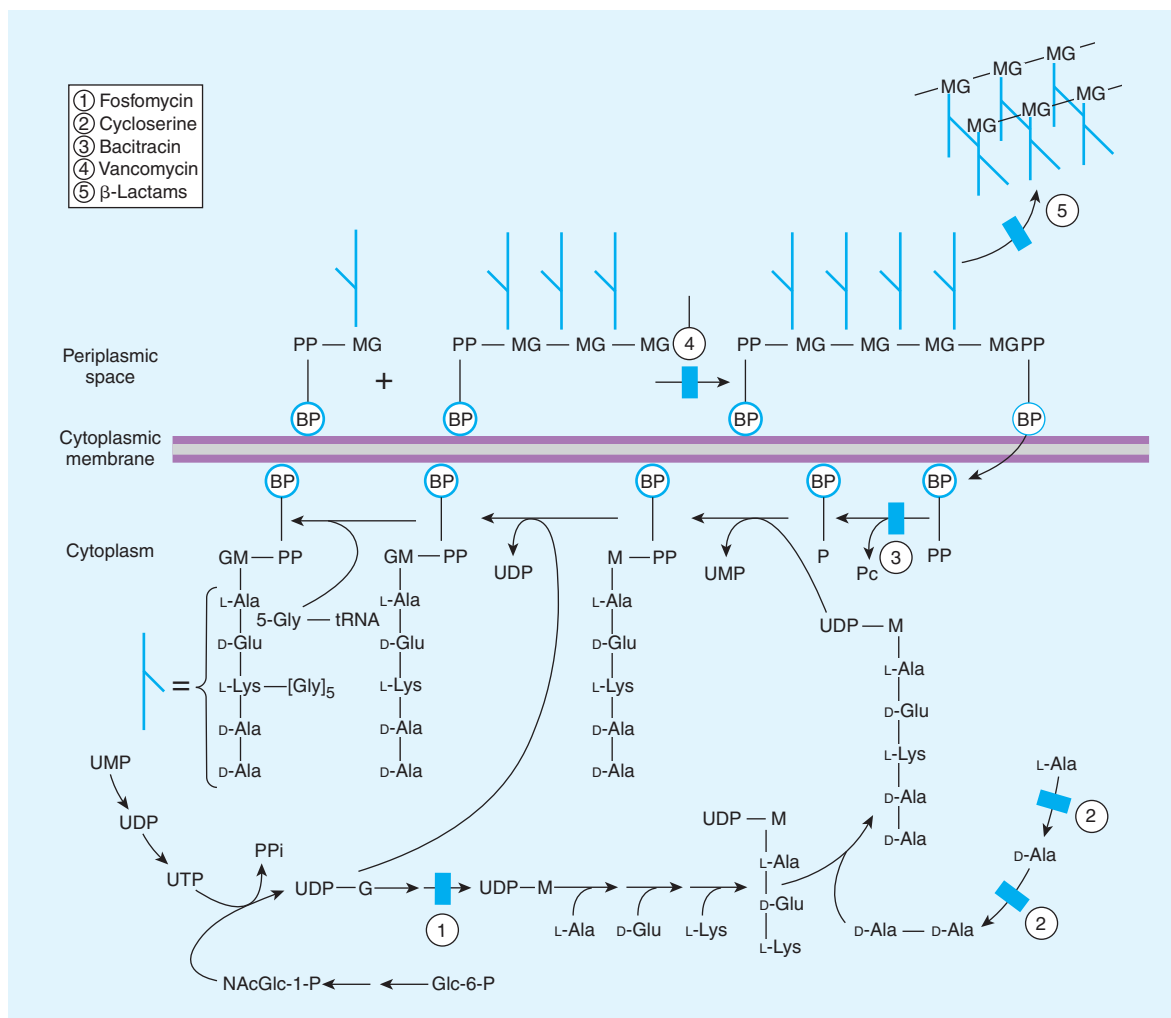
FIGURE 43−5 The biosynthesis of cell wall peptidoglycan, showing the sites of action of five antibiotics (shaded bars; 1 = fosfomycin, 2 = cycloserine, 3 = bacitracin, 4 = vancomycin, 5 = β-lactam antibiotics). Bactoprenol (BP) is the lipid membrane carrier that transports building blocks across the cytoplasmic membrane; M, *N*-acetylmuramic acid; Glc, glucose; NAcGlc or G, *N*-acetylglucosamine.

Benzathine and procaine penicillins are formulated to delay absorption, resulting in prolonged blood and tissue concentrations. A single intramuscular injection of 1.2 million units of benzathine penicillin maintains serum levels above 0.02 mcg/mL for 10 days, sufficient to treat β-hemolytic streptococcal infection. After 3 weeks, levels still exceed 0.003 mcg/mL, which is enough to prevent β-hemolytic streptococcal infection. A 600,000 unit dose of procaine penicillin yields peak concentrations of 1–2 mcg/mL and clinically useful concentrations for 12–24 hours after a single intramuscular injection.

Penicillin concentrations in most tissues are equal to those in serum. Penicillin is also excreted into sputum and milk to levels 3–15% of those in the serum. Penetration into the eye, the prostate, and the central nervous system is poor. However, with active inflammation of the meninges, as in bacterial meningitis, penicillin concentrations of 1–5 mcg/mL can be achieved with a daily parenteral dose of 18–24 million units. These concentrations are sufficient to kill susceptible strains of pneumococci and meningococci.

Penicillin is rapidly excreted by the kidneys; small amounts are excreted by other routes. About 10% of renal excretion is by glomerular filtration and 90% by tubular secretion. The normal half-life of penicillin G is approximately 30 minutes; in renal failure, it may be as long as 10 hours. Ampicillin and the extended-spectrum penicillins are secreted more slowly than penicillin G and have half-lives of 1 hour. For penicillins that are cleared by the kidney, the dose must be adjusted according to renal function, with approximately one fourth to one third the normal dose being administered if creatinine clearance is 10 mL/min or less (Table 43–1).

Nafcillin is primarily cleared by biliary excretion. Oxacillin, dicloxacillin, and cloxacillin are eliminated by both the kidney and biliary excretion; no dosage adjustment is required for these drugs in renal failure. Because clearance of penicillins is less efficient in

TABLE 43–1 Guidelines for dosing of some commonly used penicillins.

Antibiotic (Route of Administration)	Adult Dose	Pediatric Dose[1]	Neonatal Dose[2]	Adjusted Dose as a Percentage of Normal Dose for Renal Failure Based on Creatinine Clearance (Cl$_{cr}$)	
				Cl$_{cr}$ Approx 50 mL/min	Cl$_{cr}$ Approx 10 mL/min
Penicillins					
Penicillin G (IV)	$1–4 \times 10^6$ units q4–6h	25,000–400,000 units/kg/d in 4–6 doses	75,000–150,000 units/kg/d in 2 or 3 doses	50–75%	25%
Penicillin V (PO)	0.25–0.5 g qid	25–50 mg/kg/d in 4 doses		None	None
Antistaphylococcal penicillins					
Cloxacillin, dicloxacillin (PO)	0.25–0.5 g qid	25–50 mg/kg/d in 4 doses		100%	100%
Nafcillin (IV)	1–2 g q4–6h	50–100 mg/kg/d in 4–6 doses	50–75 mg/kg/d in 2 or 3 doses	100%	100%
Oxacillin (IV)	1–2 g q4–6h	50–100 mg/kg/d in 4–6 doses	50–75 mg/kg/d in 2 or 3 doses	100%	100%
Extended-spectrum penicillins					
Amoxicillin (PO)	0.25–0.5 g tid	20–40 mg/kg/d in 3 doses		66%	33%
Amoxicillin/potassium clavulanate (PO)	500/125 tid–875/125 mg bid	20–40 mg/kg/d in 3 doses		66%	33%
Piperacillin (IV)	3–4 g q4–6h	300 mg/kg/d in 4–6 doses	150 mg/kg/d in 2 doses	50–75%	25–33%
Ticarcillin (IV)	3 g q4–6h	200–300 mg/kg/d in 4–6 doses	150–200 mg/kg/d in 2 or 3 doses	50–75%	25–33%

[1]The total dose should not exceed the adult dose.
[2]The dose shown is during the first week of life. The daily dose should be increased by approximately 33–50% after the first week of life. The lower dosage range should be used for neonates weighing less than 2 kg. After the first month of life, pediatric doses may be used.

the newborn, doses adjusted for weight alone result in higher systemic concentrations for longer periods than in the adult.

Clinical Uses

Except for oral amoxicillin, penicillins should be given 1–2 hours before or after a meal; they should not be given with food to minimize binding to food proteins and acid inactivation. Blood levels of all penicillins can be raised by simultaneous administration of probenecid, 0.5 g (10 mg/kg in children) every 6 hours orally, which impairs renal tubular secretion of weak acids such as β-lactam compounds. Penicillins should never be used for viral infections and should be prescribed only when there is reasonable suspicion of, or documented infection with, susceptible organisms.

A. Penicillin

Penicillin G is a drug of choice for infections caused by streptococci, meningococci, some enterococci, penicillin-susceptible pneumococci, non-β-lactamase-producing staphylococci, *Treponema pallidum* and certain other spirochetes, *Clostridium* species,

Actinomyces and certain other gram-positive rods, and non-β-lactamase-producing gram-negative anaerobic organisms. Depending on the organism, the site, and the severity of infection, effective doses range between 4 and 24 million units per day administered intravenously in four to six divided doses. High-dose penicillin G can also be given as a continuous intravenous infusion.

Penicillin V, the oral form of penicillin, is indicated only in minor infections because of its relatively poor bioavailability, the need for dosing four times a day, and its narrow antibacterial spectrum. Amoxicillin (see below) is often used instead.

Benzathine penicillin and procaine penicillin G for intramuscular injection yield low but prolonged drug levels. A single intramuscular injection of benzathine penicillin, 1.2 million units, is effective treatment for β-hemolytic streptococcal pharyngitis; given intramuscularly once every 3–4 weeks, it prevents reinfection. Benzathine penicillin G, 2.4 million units intramuscularly once a week for 1–3 weeks, is effective in the treatment of syphilis. Procaine penicillin G, formerly a work horse for treating uncomplicated pneumococcal pneumonia or gonorrhea, is rarely used now because many strains are penicillin-resistant.

B. Penicillins Resistant to Staphylococcal Beta Lactamase (Methicillin, Nafcillin, and Isoxazolyl Penicillins)

These semisynthetic penicillins are indicated for infection by β-lactamase-producing staphylococci, although penicillin-susceptible strains of streptococci and pneumococci are also susceptible to these agents. *Listeria monocytogenes*, enterococci, and methicillin-resistant strains of staphylococci are resistant. In recent years the empirical use of these drugs has decreased substantially because of increasing rates of methicillin-resistance in staphylococci. However, for infections caused by methicillin-susceptible and penicillin-resistant strains of staphylococci, these are considered the drugs of choice.

An isoxazolyl penicillin such as oxacillin, cloxacillin, or dicloxacillin, 0.25–0.5 g orally every 4–6 hours (15–25 mg/kg/d for children), is suitable for treatment of mild to moderate localized staphylococcal infections. All are relatively acid-stable and have reasonable bioavailability. However, food interferes with absorption, and the drugs should be administered 1 hour before or after meals.

For serious systemic staphylococcal infections, oxacillin or nafcillin, 8–12 g/d, is given by intermittent intravenous infusion of 1–2 g every 4–6 hours (50–100 mg/kg/d for children).

C. Extended-Spectrum Penicillins (Aminopenicillins, Carboxypenicillins, and Ureidopenicillins)

These drugs have greater activity than penicillin against gram-negative bacteria because of their enhanced ability to penetrate the gram-negative outer membrane. Like penicillin G, they are inactivated by many β lactamases.

The aminopenicillins, ampicillin and amoxicillin, have nearly identical spectrums of activity, but amoxicillin is better absorbed orally. Amoxicillin, 250–500 mg three times daily, is equivalent to the same amount of ampicillin given four times daily. Amoxacillin is given orally to treat urinary tract infections, sinusitis, otitis, and lower respiratory tract infections. Ampicillin and amoxicillin are the most active of the oral β-lactam antibiotics against pneumococci with elevated MICs to penicillin and are the preferred β-lactam antibiotics for treating infections suspected to be caused by these strains. Ampicillin (but not amoxicillin) is effective for shigellosis. Its use to treat uncomplicated salmonella gastroenteritis is controversial because it may prolong the carrier state.

Ampicillin, at dosages of 4–12 g/d intravenously, is useful for treating serious infections caused by susceptible organisms, including anaerobes, enterococci, *L monocytogenes*, and β-lactamase-negative strains of gram-negative cocci and bacilli such as *E coli*, and *Salmonella* sp. Non-β-lactamase producing strains of *H influenzae* are generally susceptible, but strains that are resistant because of altered PBPs are emerging. Many gram-negative species produce β lactamases and are resistant, precluding use of ampicillin for empirical therapy of urinary tract infections, meningitis, and typhoid fever. Ampicillin is not active against *Klebsiella* sp, *Enterobacter* sp, *P aeruginosa*, *Citrobacter* sp, *Serratia marcescens*, indole-positive proteus species, and other gram-negative aerobes that are commonly encountered in hospital-acquired infections. These organisms produce β lactamase that inactivates ampicillin.

Carbenicillin, the first antipseudomonal carboxypenicillin, is no longer used in the USA, as there are more active, better tolerated alternatives. A carboxypenicillin with activity similar to that of carbenicillin is ticarcillin. It is less active than ampicillin against enterococci. The ureidopenicillins, piperacillin, mezlocillin, and azlocillin, are also active against selected gram-negative bacilli, such as *Klebsiella pneumoniae*. Although supportive clinical data are lacking for superiority of combination therapy over single-drug therapy, because of the propensity of *P aeruginosa* to develop resistance during treatment, an antipseudomonal penicillin is frequently used in combination with an aminoglycoside or fluoroquinolone for pseudomonal infections outside the urinary tract.

Ampicillin, amoxicillin, ticarcillin, and piperacillin are also available in combination with one of several β-lactamase inhibitors: clavulanic acid, sulbactam, or tazobactam. The addition of a β-lactamase inhibitor extends the activity of these penicillins to include β-lactamase-producing strains of *S aureus* as well as some β-lactamase-producing gram-negative bacteria (see Beta-Lactamase Inhibitors).

Adverse Reactions

The penicillins are generally well tolerated, and unfortunately, this encourages their misuse and inappropriate use. Most of the serious adverse effects are due to hypersensitivity. All penicillins are cross-sensitizing and cross-reacting. The antigenic determinants are degradation products of penicillins, particularly penicilloic acid and products of alkaline hydrolysis bound to host protein. A history of a penicillin reaction is not reliable; about 5–8% of people claim such a history, but only a small number of these will have an allergic reaction when given penicillin. Less than 1% of persons who previously received penicillin without incident will have an allergic reaction when given penicillin. Because of the potential for anaphylaxis, however, penicillin should be administered with caution or a substitute drug given if the person has a history of serious penicillin allergy. The incidence of allergic reactions in young children is negligible.

Allergic reactions include anaphylactic shock (very rare—0.05% of recipients); serum sickness-type reactions (now rare—urticaria, fever, joint swelling, angioneurotic edema, intense pruritus, and respiratory compromise occurring 7–12 days after exposure); and a variety of skin rashes. Oral lesions, fever, interstitial nephritis (an autoimmune reaction to a penicillin-protein complex), eosinophilia, hemolytic anemia and other hematologic disturbances, and vasculitis may also occur. Most patients allergic to penicillins can be treated with alternative drugs. However, if necessary (eg, treatment of enterococcal endocarditis or neurosyphilis in a patient with serious penicillin allergy), desensitization can be accomplished with gradually increasing doses of penicillin.

In patients with renal failure, penicillin in high doses can cause seizures. Nafcillin is associated with neutropenia; oxacillin can cause hepatitis; and methicillin causes interstitial nephritis (and is no longer used for this reason). Large doses of penicillins given orally may lead to gastrointestinal upset, particularly nausea, vomiting, and diarrhea. Ampicillin has been associated with pseudomembranous colitis. Secondary infections such as vaginal

candidiasis may occur. Ampicillin and amoxicillin can cause skin rashes that are not allergic in nature. These rashes frequently occur when aminopenicillins are inappropriately prescribed for a viral illness.

■ CEPHALOSPORINS & CEPHAMYCINS

Cephalosporins are similar to penicillins, but more stable to many bacterial β lactamases and therefore have a broader spectrum of activity. However, strains of *E coli* and *Klebsiella* sp expressing extended-spectrum β lactamases that can hydrolyze most cephalosporins are a growing clinical concern. Cephalosporins are not active against enterococci and *L monocytogenes.*

Chemistry

The nucleus of the cephalosporins, 7-aminocephalosporanic acid (Figure 43–6), bears a close resemblance to 6-aminopenicillanic acid (Figure 43–1). The intrinsic antimicrobial activity of natural cephalosporins is low, but the attachment of various R_1 and R_2 groups has yielded hundreds of potent compounds of low toxicity. Cephalosporins can be classified into four major groups or generations, depending mainly on the spectrum of antimicrobial activity.

FIRST-GENERATION CEPHALOSPORINS

First-generation cephalosporins include **cefazolin, cefadroxil, cephalexin, cephalothin, cephapirin,** and **cephradine.** These drugs are very active against gram-positive cocci, such as pneumococci, streptococci, and staphylococci. Traditional cephalosporins are not active against methicillin-resistant strains of staphylococci; however, new compounds have been developed that have activity against methicillin-resistant strains (see below). *E coli, K pneumoniae,* and *Proteus mirabilis* are often sensitive, but activity against *P aeruginosa,* indole-positive proteus species, *Enterobacter* sp, *S marcescens, Citrobacter* sp, and *Acinetobacter* sp is poor. Anaerobic cocci (eg, peptococci, peptostreptococci) are usually sensitive, but *Bacteroides fragilis* is not.

Pharmacokinetics & Dosage

A. Oral

Cephalexin, cephradine, and cefadroxil are absorbed from the gut to a variable extent. After oral doses of 500 mg, serum levels are 15–20 mcg/mL. Urine concentration is usually very high, but in most tissues levels are variable and generally lower than in serum. Cephalexin and cephradine are given orally in dosages of 0.25–0.5 g four times daily (15–30 mg/kg/d) and cefadroxil in dosages of 0.5–1 g twice daily. Excretion is mainly by glomerular filtration and tubular secretion into the urine. Drugs that block tubular secretion, eg, probenecid, may increase serum levels substantially. In patients with impaired renal function, dosage must be reduced (Table 43–2).
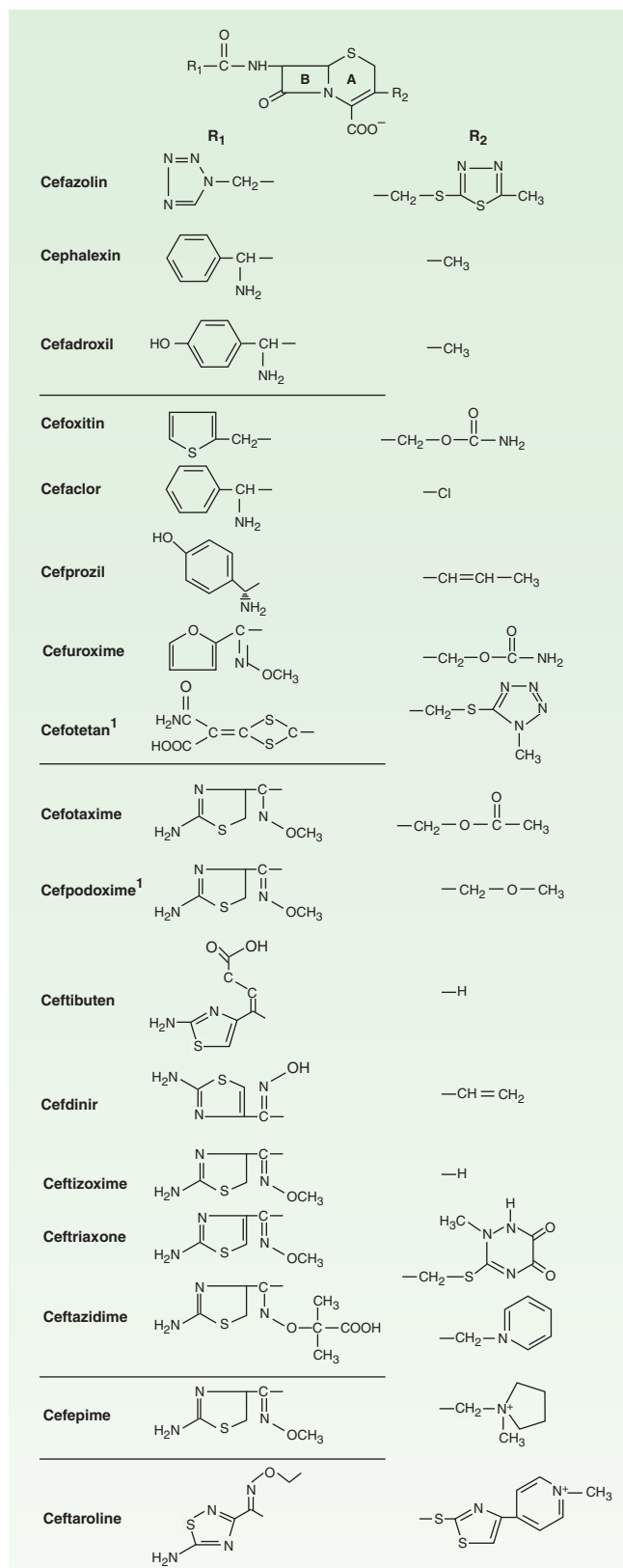

FIGURE 43–6 Structures of some cephalosporins. R_1 and R_2 structures are substituents on the 7-aminocephalosporanic acid nucleus pictured at the top. Other structures (cefoxitin and below) are complete in themselves. [1] Additional substituents not shown.

TABLE 43–2 Guidelines for dosing of some commonly used cephalosporins and other cell-wall inhibitor antibiotics.

Antibiotic (Route of Administration)	Adult Dose	Pediatric Dose[1]	Neonatal Dose[2]	Adjusted Dose as a Percentage of Normal Dose for Renal Failure Based on Creatinine Clearance (Cl_{cr})	
				Cl_{cr} Approx 50 mL/min	Cl_{cr} Approx 10 mL/min
First-generation cephalosporins					
Cefadroxil (PO)	0.5–1 g qd–bid	30 mg/kg/d in 2 doses		50%	25%
Cephalexin, cephradine (PO)	0.25–0.5 g qid	25–50 mg/kg/d in 4 doses		50%	25%
Cefazolin (IV)	0.5–2 g q8h	25–100 mg/kg/d in 3 or 4 doses		50%	25%
Second-generation cephalosporins					
Cefoxitin (IV)	1–2 g q6–8h	75–150 mg/kg/d in 3 or 4 doses		50–75%	25%
Cefotetan (IV)	1–2 g q12h			50%	25%
Cefuroxime (IV)	0.75–1.5 g q8h	50–100 mg/kg/d in 3 or 4 doses		66%	25–33%
Third- and fourth-generation cephalosporins including ceftaroline fosamil					
Cefotaxime (IV)	1–2 g q6–12h	50–200 mg/kg/d in 4–6 doses	100 mg/kg/d in 2 doses	50%	25%
Ceftazidime (IV)	1–2 g q8–12h	75–150 mg/kg/d in 3 doses	100–150 mg/kg/d in 2 or 3 doses	50%	25%
Ceftriaxone (IV)	1–4 g q24h	50–100 mg/kg/d in 1 or 2 doses	50 mg/kg/d qd	None	None
Cefepime (IV)	0.5–2 g q12h	75–120 mg/kg/d in 2 or 3 divided doses		50%	25%
Ceftaroline fosamil (IV)	600 mg q12h			50–66%	33%
Carbapenems					
Ertapenem (IM or IV)	1 g q24h			100%[3]	50%
Doripenem	500 mg q8h			50%	33%
Imipenem (IV)	0.25–0.5 g q6–8h			75%	50%
Meropenem (IV)	1 g q8h (2 g q8h for meningitis)	60–120 mg/kg/d in 3 doses (maximum of 2 g q8h)		66%	50%
Glycopeptides					
Vancomycin (IV)	30–60 mg/kg/d in 2–3 doses	40 mg/kg/d in 3 or 4 doses	15 mg/kg load, then 20 mg/kg/d in 2 doses	40%	10%
Lipopeptides (IV)					
Daptomycin	4-6 mg/kg IV daily			None	50%
Telavancin	10 mg/kg IV daily			75%	50%

[1]The total dose should not exceed the adult dose.
[2]The dose shown is during the first week of life. The daily dose should be increased by approximately 33–50% after the first week of life. The lower dosage range should be used for neonates weighing less than 2 kg. After the first month of life, pediatric doses may be used.
[3]50% of dose for Cl_{cr}< 30 mL/min.

B. Parenteral

Cefazolin is the only first-generation parenteral cephalosporin still in general use. After an intravenous infusion of 1 g, the peak level of cefazolin is 90–120 mcg/mL. The usual intravenous dosage of cefazolin for adults is 0.5–2 g intravenously every 8 hours. Cefazolin can also be administered intramuscularly. Excretion is via the kidney, and dose adjustments must be made for impaired renal function.

Clinical Uses

Oral drugs may be used for the treatment of urinary tract infections and staphylococcal or streptococcal infections, including cellulitis or soft tissue abscess. However, oral cephalosporins should not be relied on in serious systemic infections.

Cefazolin penetrates well into most tissues. It is a drug of choice for surgical prophylaxis. Cefazolin may also be a choice in infections for which it is the least toxic drug (eg, penicillinase-producing *E coli* or *K pneumoniae*) and in individuals with staphylococcal or streptococcal infections who have a history of penicillin allergy other than immediate hypersensitivity. Cefazolin does not penetrate the central nervous system and cannot be used to treat meningitis. Cefazolin is an alternative to an antistaphylococcal penicillin for patients who are allergic to penicillin.

SECOND-GENERATION CEPHALOSPORINS

Members of the second-generation cephalosporins include **cefaclor, cefamandole, cefonicid, cefuroxime, cefprozil, loracarbef,** and **ceforanide;** and the structurally related cephamycins **cefoxitin, cefmetazole,** and **cefotetan,** which have activity against anaerobes. This is a heterogeneous group with marked individual differences in activity, pharmacokinetics, and toxicity. In general, they are active against organisms inhibited by first-generation drugs, but in addition they have extended gram-negative coverage. *Klebsiella* sp (including those resistant to cephalothin) are usually sensitive. Cefamandole, cefuroxime, cefonicid, ceforanide, and cefaclor are active against *H influenzae* but not against serratia or *B fragilis*. In contrast, cefoxitin, cefmetazole, and cefotetan are active against *B fragilis* and some serratia strains but are less active against *H influenzae*. As with first-generation agents, none is active against enterococci or *P aeruginosa*. Second-generation cephalosporins may exhibit in vitro activity against *Enterobacter* sp., but resistant mutants that constitutively express a chromosomal β lactamase that hydrolyzes these compounds (and third-generation cephalosporins) are readily selected, and they should not be used to treat enterobacter infections.

Pharmacokinetics & Dosage

A. Oral

Cefaclor, cefuroxime axetil, cefprozil, and loracarbef can be given orally. The usual dosage for adults is 10–15 mg/kg/d in two to four divided doses; children should be given 20–40 mg/kg/d up to a maximum of 1 g/d. Except for cefuroxime axetil, these drugs are not predictably active against penicillin-non-susceptible pneumococci and should be used cautiously, if at all, to treat suspected or proved pneumococcal infections. Cefaclor is more susceptible to β-lactamase hydrolysis compared with the other agents, and its usefulness is correspondingly diminished.

B. Parenteral

After a 1-g intravenous infusion, serum levels are 75–125 mcg/mL for most second-generation cephalosporins. Intramuscular administration is painful and should be avoided. Doses and dosing intervals vary depending on the specific agent (Table 43–2). There are marked differences in half-life, protein binding, and interval between doses. All are renally cleared and require dosage adjustment in renal failure.

Clinical Uses

The oral second-generation cephalosporins are active against β-lactamase-producing *H influenzae* or *Moraxella catarrhalis* and have been primarily used to treat sinusitis, otitis, and lower respiratory tract infections, in which these organisms have an important role. Because of their activity against anaerobes (including many *B fragilis* strains), cefoxitin, cefotetan, or cefmetazole can be used to treat mixed anaerobic infections such as peritonitis, diverticulitis, and pelvic inflammatory disease. Cefuroxime is used to treat community-acquired pneumonia because it is active against β-lactamase-producing *H influenzae* or *K pneumoniae* and some penicillin-non-susceptible pneumococci. Although cefuroxime crosses the blood-brain barrier, it is less effective in treatment of meningitis than ceftriaxone or cefotaxime and should not be used.

THIRD-GENERATION CEPHALOSPORINS

Third-generation agents include **cefoperazone, cefotaxime, ceftazidime, ceftizoxime, ceftriaxone, cefixime, cefpodoxime proxetil, cefdinir, cefditoren pivoxil, ceftibuten,** and **moxalactam**.

Antimicrobial Activity

Compared with second-generation agents, these drugs have expanded gram-negative coverage, and some are able to cross the blood-brain barrier. Third-generation drugs are active against *Citrobacter*, *S marcescens*, and *Providencia* (although resistance can emerge during treatment of infections caused by these species due to selection of mutants that constitutively produce cephalosporinase). They are also effective against β-lactamase-producing strains of haemophilus and neisseria. Ceftazidime and cefoperazone are the only two drugs with useful activity against *P aeruginosa*. Like the second-generation drugs, third-generation cephalosporins are hydrolyzed by constitutively produced AmpC β lactamase, and they are not reliably active against *Enterobacter* species. *Serratia*, *Providencia*, and *Citrobacter* also produce a chromosomally encoded cephalosporinase that, when constitutively expressed, can confer resistance to third-generation cephalosporins. Ceftizoxime and moxalactam are active against *B fragilis*. Cefixime, cefdinir,

ceftibuten, and cefpodoxime proxetil are oral agents possessing similar activity except that cefixime and ceftibuten are much less active against pneumococci and have poor activity against *S aureus*.

Pharmacokinetics & Dosage

Intravenous infusion of 1 g of a parenteral cephalosporin produces serum levels of 60–140 mcg/mL. Third-generation cephalosporins penetrate body fluids and tissues well and, with the exception of cefoperazone and all oral cephalosporins, achieve levels in the cerebrospinal fluid sufficient to inhibit most susceptible pathogens.

The half-lives of these drugs and the necessary dosing intervals vary greatly: Ceftriaxone (half-life 7–8 hours) can be injected once every 24 hours at a dosage of 15–50 mg/kg/d. A single daily 1-g dose is sufficient for most serious infections, with 2 g every 12 hours recommended for treatment of meningitis. Cefoperazone (half-life 2 hours) can be infused every 8–12 hours in a dosage of 25–100 mg/kg/d. The remaining drugs in the group (half-life 1–1.7 hours) can be infused every 6–8 hours in dosages between 2 and 12 g/d, depending on the severity of infection. Cefixime can be given orally (200 mg twice daily or 400 mg once daily) for urinary tract infections and as a single 400 mg dose for uncomplicated gonococcal urethritis and cervicitis. The adult dose for cefpodoxime proxetil or cefditoren pivoxil is 200–400 mg twice daily; for ceftibuten, 400 mg once daily; and for cefdinir, 300 mg/12 h. The excretion of cefoperazone and ceftriaxone is mainly through the biliary tract, and no dosage adjustment is required in renal insufficiency. The others are excreted by the kidney and therefore require dosage adjustment in renal insufficiency.

Clinical Uses

Third-generation cephalosporins are used to treat a wide variety of serious infections caused by organisms that are resistant to most other drugs. Strains expressing extended-spectrum β lactamases, however, are not susceptible. Third-generation cephalosporins should be avoided in treatment of enterobacter infections—even if the clinical isolate appears susceptible in vitro—because of emergence of resistance. Ceftriaxone and cefotaxime are approved for treatment of meningitis, including meningitis caused by pneumococci, meningococci, *H influenzae*, and susceptible enteric gram-negative rods, but not by *L monocytogenes*. Ceftriaxone and cefotaxime are the most active cephalosporins against penicillin-non-susceptible strains of pneumococci and are recommended for empirical therapy of serious infections that may be caused by these strains. Meningitis caused by strains of pneumococci with penicillin MICs > 1 mcg/mL may not respond even to these agents, and addition of vancomycin is recommended. Other potential indications include empirical therapy of sepsis of unknown cause in both the immunocompetent and the immunocompromised patient and treatment of infections for which a cephalosporin is the least toxic drug available. In neutropenic, febrile immunocompromised patients, ceftazidime is often used in combination with other antibiotics.

FOURTH-GENERATION CEPHALOSPORINS

Cefepime is an example of a so-called fourth-generation cephalosporin. It is more resistant to hydrolysis by chromosomal β lactamases (eg, those produced by *Enterobacter*). However, like the third-generation compounds, it is hydrolyzed by extended-spectrum β lactamases. Cefepime has good activity against *P aeruginosa*, Enterobacteriaceae, *S aureus*, and *S pneumoniae*. It is highly active against *Haemophilus* and *Neisseria* sp. It penetrates well into cerebrospinal fluid. It is cleared by the kidneys and has a half-life of 2 hours, and its pharmacokinetic properties are very similar to those of ceftazidime. Unlike ceftazidime, however, cefepime has good activity against most penicillin-non-susceptible strains of streptococci, and it is useful in treatment of enterobacter infections.

Cephalosporins Active against Methicillin-Resistant Staphylococci

Beta-lactam antibiotics with activity against methicillin-resistant staphylococci are currently under development. **Ceftaroline** fosamil, the prodrug of the active metabolite ceftaroline, is the first such drug to be approved for clinical use in the USA. Ceftaroline has increased binding to penicillin-binding protein 2a, which mediates methicillin resistance in staphylococci, resulting in bactericidal activity against these strains. It has some activity against enterococci and a broad gram-negative spectrum, although it is not active against extended-spectrum β-lactamase-producing strains. Since clinical experience with this and similar investigational drugs is limited, their role in therapy is not yet defined.

ADVERSE EFFECTS OF CEPHALOSPORINS

A. Allergy

Cephalosporins are sensitizing and may elicit a variety of hypersensitivity reactions that are identical to those of penicillins, including anaphylaxis, fever, skin rashes, nephritis, granulocytopenia, and hemolytic anemia. However, the chemical nucleus of cephalosporins is sufficiently different from that of penicillins so that some individuals with a history of penicillin allergy may tolerate cephalosporins. The frequency of cross-allergenicity between the two groups of drugs is uncertain but is probably around 5–10%. Cross-allergenicity appears to be more common with penicillins and early generation cephalosporins compared with later generation cephalosporins. However, patients with a history of anaphylaxis to penicillins should not receive cephalosporins.

B. Toxicity

Local irritation can produce pain after intramuscular injection and thrombophlebitis after intravenous injection. Renal toxicity, including interstitial nephritis and tubular necrosis, has been demonstrated with several cephalosporins and caused the withdrawal of cephaloridine from clinical use.

Cephalosporins that contain a methylthiotetrazole group (cefamandole, cefmetazole, cefotetan, and cefoperazone) may cause hypoprothrombinemia and bleeding disorders. Oral administration of vitamin K$_1$, 10 mg twice weekly, can prevent this. Drugs with the methylthiotetrazole ring can also cause severe disulfiram-like reactions; consequently, alcohol and alcohol-containing medications must be avoided.

■ OTHER BETA-LACTAM DRUGS

MONOBACTAMS

Monobactams are drugs with a monocyclic β-lactam ring (Figure 43–1). Their spectrum of activity is limited to aerobic gram-negative rods (including *P aeruginosa*). Unlike other β-lactam antibiotics, they have no activity against gram-positive bacteria or anaerobes. **Aztreonam** is the only monobactam available in the USA. It has structural similarities to ceftazidime; hence, its gram-negative spectrum is similar to that of the third-generation cephalosporins. It is stable to many β lactamases with the notable exceptions being AmpC β lactamases and extended-spectrum β lactamases. It penetrates well into the cerebrospinal fluid. Aztreonam is given intravenously every 8 hours in a dose of 1–2 g, providing peak serum levels of 100 mcg/mL. The half-life is 1–2 hours and is greatly prolonged in renal failure.

Penicillin-allergic patients tolerate aztreonam without reaction. Occasional skin rashes and elevations of serum aminotransferases occur during administration of aztreonam, but major toxicity is uncommon. In patients with a history of penicillin anaphylaxis, aztreonam may be used to treat serious infections such as pneumonia, meningitis, and sepsis caused by susceptible gram-negative pathogens.

BETA-LACTAMASE INHIBITORS (CLAVULANIC ACID, SULBACTAM, & TAZOBACTAM)

These substances resemble β-lactam molecules (Figure 43–7), but they have very weak antibacterial action. They are potent inhibitors of many but not all bacterial β lactamases and can protect hydrolyzable penicillins from inactivation by these enzymes. Beta-lactamase inhibitors are most active against Ambler class A β lactamases (plasmid-encoded transposable element [TEM] β lactamases in particular), such as those produced by staphylococci, *H influenzae, N gonorrhoeae,* salmonella, shigella, *E coli,* and *K pneumoniae.* They are not good inhibitors of class C β lactamases, which typically are chromosomally encoded and inducible, produced by *Enterobacter* sp, *Citrobacter* sp, *S marcescens,* and *P aeruginosa,* but they do inhibit chromosomal β lactamases of *B fragilis* and *M catarrhalis.*

The three inhibitors differ slightly with respect to pharmacology, stability, potency, and activity, but these differences usually are of little therapeutic significance. Beta-lactamase inhibitors are available only in fixed combinations with specific penicillins. The antibacterial spectrum of the combination is determined by the companion penicillin, not the β-lactamase inhibitor. (The fixed combinations available in the USA are listed in Preparations Available.) An inhibitor extends the spectrum of a penicillin provided that the inactivity of the penicillin is due to destruction by β lactamase and that the inhibitor is active against the β lactamase that is produced. Thus, ampicillin-sulbactam is active against β-lactamase-producing *S aureus* and *H influenzae* but not against serratia, which produces a β lactamase that is not inhibited by sulbactam. Similarly, if a strain of *P aeruginosa* is resistant to piperacillin, it is also resistant to piperacillin-tazobactam because tazobactam does not inhibit the chromosomal β lactamase produced by *P aeruginosa.*

The indications for penicillin-β-lactamase inhibitor combinations are empirical therapy for infections caused by a wide range of potential pathogens in both immunocompromised and immunocompetent patients and treatment of mixed aerobic and anaerobic infections, such as intra-abdominal infections. Doses are the same as those used for the single agents except that the recommended dosage of piperacillin in the piperacillin-tazobactam combination is 3–4 g every 6 hours. Adjustments for renal insufficiency are made based on the penicillin component.

CARBAPENEMS

The carbapenems are structurally related to β-lactam antibiotics (Figure 43–1). **Doripenem, ertapenem, imipenem,** and **meropenem** are licensed for use in the USA. Imipenem, the first drug of this class, has a wide spectrum with good activity against many gram-negative rods, including *P aeruginosa,* gram-positive
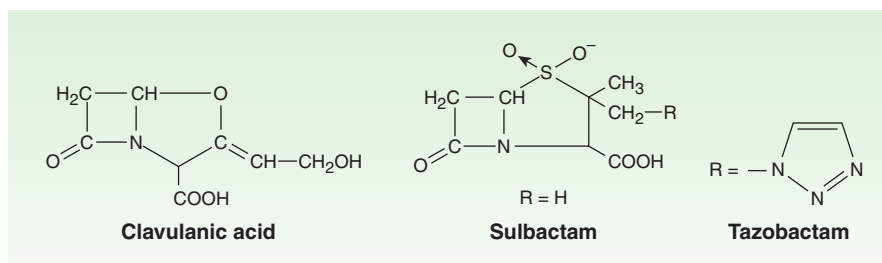

FIGURE 43–7 Beta-lactamase inhibitors.

organisms, and anaerobes. It is resistant to most β lactamases but not carbapenemases or metallo-β lactamases. *Enterococcus faecium*, methicillin-resistant strains of staphylococci, *Clostridium difficile*, *Burkholderia cepacia*, and *Stenotrophomonas maltophilia* are resistant. Imipenem is inactivated by dehydropeptidases in renal tubules, resulting in low urinary concentrations. Consequently, it is administered together with an inhibitor of renal dehydropeptidase, **cilastatin,** for clinical use. Doripenem and meropenem are similar to imipenem but have slightly greater activity against gram-negative aerobes and slightly less activity against gram-positives. They are not significantly degraded by renal dehydropeptidase and do not require an inhibitor. Ertapenem is less active than the other carbapenems against *P aeruginosa* and *Acinetobacter* species. It is not degraded by renal dehydropeptidase.

Carbapenems penetrate body tissues and fluids well, including the cerebrospinal fluid. All are cleared renally, and the dose must be reduced in patients with renal insufficiency. The usual dosage of imipenem is 0.25–0.5 g given intravenously every 6–8 hours (half-life 1 hour). The usual adult dosage of meropenem is 0.5–1 g intravenously every 8 hours. The usual adult dosage of doripenem is 0.5 g administered as a 1- or 4-hour infusion every 8 hours. Ertapenem has the longest half-life (4 hours) and is administered as a once-daily dose of 1 g intravenously or intramuscularly. Intramuscular ertapenem is irritating, and for that reason the drug is formulated with 1% lidocaine for administration by this route.

A carbapenem is indicated for infections caused by susceptible organisms that are resistant to other available drugs, eg, *P aeruginosa*, and for treatment of mixed aerobic and anaerobic infections. Carbapenems are active against many penicillin-non-susceptible strains of pneumococci. Carbapenems are highly active in the treatment of enterobacter infections because they are resistant to destruction by the β lactamase produced by these organisms. Clinical experience suggests that carbapenems are also the treatment of choice for infections caused by extended-spectrum β-lactamase-producing gram-negative bacteria. Ertapenem is insufficiently active against *P aeruginosa* and should not be used to treat infections caused by that organism. Imipenem, meropenem, or doripenem, with or without an aminoglycoside, may be effective treatment for febrile neutropenic patients.

The most common adverse effects of carbapenems—which tend to be more common with imipenem—are nausea, vomiting, diarrhea, skin rashes, and reactions at the infusion sites. Excessive levels of imipenem in patients with renal failure may lead to seizures. Meropenem, doripenem, and ertapenem are much less likely to cause seizures than imipenem. Patients allergic to penicillins may be allergic to carbapenems as well.

■ GLYCOPEPTIDE ANTIBIOTICS

VANCOMYCIN

Vancomycin is an antibiotic produced by *Streptococcus orientalis* and *Amycolatopsis orientalis*. With the exception of *Flavobacterium*, it is active only against gram-positive bacteria. Vancomycin is a glycopeptide of molecular weight 1500. It is water soluble and quite stable.

Mechanisms of Action & Basis of Resistance

Vancomycin inhibits cell wall synthesis by binding firmly to the D-Ala-D-Ala terminus of nascent peptidoglycan pentapeptide (Figure 43–5). This inhibits the transglycosylase, preventing further elongation of peptidoglycan and cross-linking. The peptidoglycan is thus weakened, and the cell becomes susceptible to lysis. The cell membrane is also damaged, which contributes to the antibacterial effect.

Resistance to vancomycin in enterococci is due to modification of the D-Ala-D-Ala binding site of the peptidoglycan building block in which the terminal D-Ala is replaced by D-lactate. This results in the loss of a critical hydrogen bond that facilitates high-affinity binding of vancomycin to its target and loss of activity. This mechanism is also present in vancomycin-resistant *S aureus* strains (MIC ≥ 16 mcg/mL), which have acquired the enterococcal resistance determinants. The underlying mechanism for reduced vancomycin susceptibility in vancomycin-intermediate strains (MICs = 4–8 mcg/mL) of *S aureus* is not fully known. However these strains have altered cell wall metabolism that results in a thickened cell wall with increased numbers of D-Ala-D-Ala residues, which serve as dead-end binding sites for vancomycin. Vancomycin is sequestered within the cell wall by these false targets and may be unable to reach its site of action.

Antibacterial Activity

Vancomycin is bactericidal for gram-positive bacteria in concentrations of 0.5–10 mcg/mL. Most pathogenic staphylococci, including those producing β lactamase and those resistant to nafcillin and methicillin, are killed by 2 mcg/mL or less. Vancomycin kills staphylococci relatively slowly and only if cells are actively dividing; the rate is less than that of the penicillins both in vitro and in vivo. Vancomycin is synergistic in vitro with gentamicin and streptomycin against *Enterococcus faecium* and *Enterococcus faecalis* strains that do not exhibit high levels of aminoglycoside resistance.

Pharmacokinetics

Vancomycin is poorly absorbed from the intestinal tract and is administered orally only for the treatment of antibiotic-associated colitis caused by *C difficile*. Parenteral doses must be administered intravenously. A 1-hour intravenous infusion of 1 g produces blood levels of 15–30 mcg/mL for 1–2 hours. The drug is widely distributed in the body. Cerebrospinal fluid levels 7–30% of simultaneous serum concentrations are achieved if there is meningeal inflammation. Ninety percent of the drug is excreted by glomerular filtration. In the presence of renal insufficiency, striking accumulation may occur (Table 43–2). In functionally anephric patients, the half-life of vancomycin is 6–10 days. A significant amount (roughly 50%) of vancomycin is removed during a standard hemodialysis run when a modern, high-flux membrane is used.

Clinical Uses

Important indications for parenteral vancomycin are bloodstream infections and endocarditis caused by methicillin-resistant staphylococci. However, vancomycin is not as effective as an antistaphylococcal penicillin for treatment of serious infections such as endocarditis caused by methicillin-susceptible strains. Vancomycin in combination with gentamicin is an alternative regimen for treatment of enterococcal endocarditis in a patient with serious penicillin allergy. Vancomycin (in combination with cefotaxime, ceftriaxone, or rifampin) is also recommended for treatment of meningitis suspected or known to be caused by a penicillin-resistant strain of pneumococcus (ie, penicillin MIC > 1 mcg/mL). The recommended dosage in a patient with normal renal function is 30–60 mg/kg/d in two or three divided doses. The traditional dosing regimen in adults with normal renal function is 1 g every 12 hours (~ 30 mg/kg/d); however, this dose will not typically achieve the trough concentrations (15–20 mcg/mL) recommended for serious infections. For serious infections (see below), a starting dose of 45–60 mg/kg/d should be given with titration of the dose to achieve trough levels of 15–20 mcg/mL. The dosage in children is 40 mg/kg/d in three or four divided doses. Clearance of vancomycin is directly proportional to creatinine clearance, and the dosage is reduced accordingly in patients with renal insufficiency. For functionally anephric adult patients, a 1-g dose administered once a week may be sufficient. For patients receiving hemodialysis, a common dosing regimen is a 1-g loading dose followed by 500 mg after each dialysis session. Patients receiving a prolonged course of therapy should have serum concentrations checked. Recommended trough concentrations are 10–15 mcg/mL for mild to moderate infections such as cellulitis and 15–20 mcg/mL for more serious infections such as endocarditis, meningitis, and necrotizing pneumonia.

Oral vancomycin, 0.125–0.25 g every 6 hours, is used to treat antibiotic-associated colitis caused by *C difficile*. Because of the emergence of vancomycin-resistant enterococci and the potential selective pressure of oral vancomycin for these resistant organisms, metronidazole had been preferred as initial therapy over the last two decades. However, receipt of oral vancomycin does not appear to be a significant risk factor for acquisition of vancomycin-resistant enterococci. Additionally, recent clinical data suggest that vancomycin is associated with a better clinical response than metronidazole for more severe cases of *C difficile* colitis. Therefore, oral vancomycin may be used as a first line treatment for severe cases or for cases that fail to respond to metronidazole.

Adverse Reactions

Adverse reactions are encountered in about 10% of cases. Most reactions are minor. Vancomycin is irritating to tissue, resulting in phlebitis at the site of injection. Chills and fever may occur. Ototoxicity is rare and nephrotoxicity uncommon with current preparations. However, administration with another ototoxic or nephrotoxic drug, such as an aminoglycoside, increases the risk of these toxicities. Ototoxicity can be minimized by maintaining peak serum concentrations below 60 mcg/mL. Among the more common reactions is the so-called "red man" or "red neck" syndrome. This infusion-related flushing is caused by release of histamine. It can be largely prevented by prolonging the infusion period to 1–2 hours or pretreatment with an antihistamine such as diphenhydramine.

TEICOPLANIN

Teicoplanin is a glycopeptide antibiotic that is very similar to vancomycin in mechanism of action and antibacterial spectrum. Unlike vancomycin, it can be given intramuscularly as well as intravenously. Teicoplanin has a long half-life (45–70 hours), permitting once-daily dosing. This drug is available in Europe but has not been approved for use in the United States.

TELAVANCIN

Telavancin is a semisynthetic lipoglycopeptide derived from vancomycin. Telavancin is active versus gram-positive bacteria, including strains with reduced susceptibility to vancomycin. Telavancin has two mechanisms of action. Like vancomycin, telavancin inhibits cell wall synthesis by binding to the D-Ala-D-Ala terminus of peptidoglycan in the growing cell wall. In addition, it disrupts the bacterial cell membrane potential and increases membrane permeability. The half-life of telavancin is approximately 8 hours, which supports once-daily intravenous dosing. Telavancin is approved for treatment of complicated skin and soft tissue infections at a dose of 10 mg/kg IV daily. Unlike vancomycin therapy, monitoring of serum telavancin levels is not required. Telavancin is potentially teratogenic, so administration to pregnant women must be avoided.

DALBAVANCIN

Dalbavancin is a semisynthetic lipoglycopeptide derived from teicoplanin. Dalbavancin shares the same mechanism of action as vancomycin and teicoplanin but has improved activity against many gram-positive bacteria including methicillin-resistant and vancomycin-intermediate *S aureus*. It is not active against most strains of vancomycin-resistant enterococci. Dalbavancin has an extremely long half-life of 6–11 days, which allows for once-weekly intravenous administration. Development of dalbavancin has been put on hold pending additional clinical trials.

■ OTHER CELL WALL- OR MEMBRANE-ACTIVE AGENTS

DAPTOMYCIN

Daptomycin is a novel cyclic lipopeptide fermentation product of *Streptomyces roseosporus* (Figure 43–8). It was discovered decades ago but has only recently been developed as the need for drugs
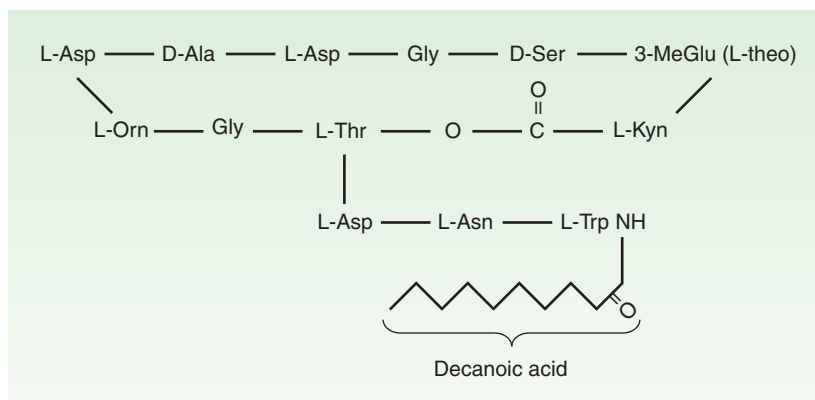
FIGURE 43–8 Structure of daptomycin. (Kyn, deaminated tryptophan.)

active against resistant organisms has become more acute. Its spectrum of activity is similar to that of vancomycin except that it is more rapidly bactericidal in vitro and may be active against vancomycin-resistant strains of enterococci and *S aureus*. The precise mechanism of action is not fully understood, but it is known to bind to the cell membrane via calcium-dependent insertion of its lipid tail. This results in depolarization of the cell membrane with potassium efflux and rapid cell death (Figure 43–9). Daptomycin is cleared renally. The approved doses are 4 mg/kg/dose for treatment of skin and soft tissue infections and 6 mg/kg/dose for treatment of bacteremia and endocarditis once daily in patients with normal renal function and every other day in patients with creatinine clearance of less than 30 mL/min. For

serious infections, many experts recommend using doses of daptomycin higher than 6 mg/kg/dose. In clinical trials powered for noninferiority, daptomycin was equivalent in efficacy to vancomycin. It can cause myopathy, and creatine phosphokinase levels should be monitored weekly. Pulmonary surfactant antagonizes daptomycin, and it should not be used to treat pneumonia. Daptomycin can also cause an allergic pneumonitis in patients receiving prolonged therapy (> 2 weeks). Treatment failures have been reported in association with an increase in daptomycin MIC for clinical isolates obtained during therapy, but the relation between the increase in MIC and treatment failure is unclear at this point. Daptomycin is an effective alternative to vancomycin, and its ultimate role continues to unfold.
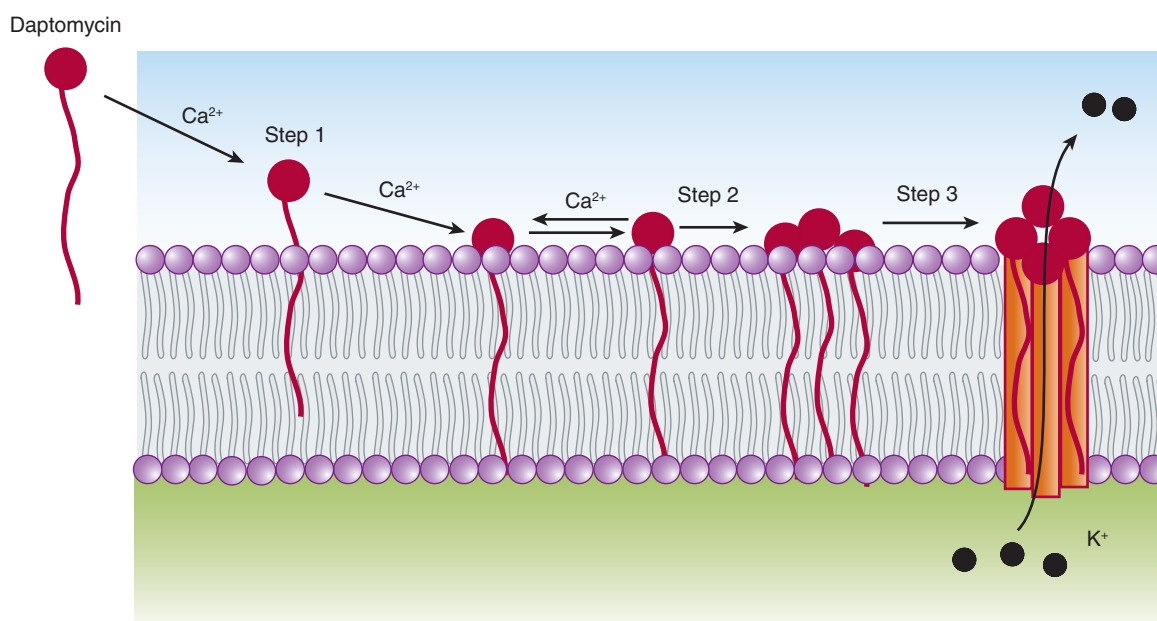

FIGURE 43–9 Proposed mechanism of action of daptomycin. Daptomycin first binds to the cytoplasmic membrane (step 1) and then forms complexes in a calcium-dependent manner (steps 2 and 3). Complex formation causes a rapid loss of cellular potassium, possibly by pore formation, and membrane depolarization. This is followed by arrest of DNA, RNA, and protein synthesis resulting in cell death. Cell lysis does not occur.

FOSFOMYCIN

Fosfomycin trometamol, a stable salt of fosfomycin (phosphonomycin), inhibits a very early stage of bacterial cell wall synthesis (Figure 43–5). An analog of phosphoenolpyruvate, it is structurally unrelated to any other antimicrobial agent. It inhibits the cytoplasmic enzyme enolpyruvate transferase by covalently binding to the cysteine residue of the active site and blocking the addition of phosphoenolpyruvate to UDP-*N*-acetylglucosamine. This reaction is the first step in the formation of UDP-*N*-acetylmuramic acid, the precursor of *N*-acetylmuramic acid, which is found only in bacterial cell walls. The drug is transported into the bacterial cell by glycerophosphate or glucose 6-phosphate transport systems. Resistance is due to inadequate transport of drug into the cell.

Fosfomycin is active against both gram-positive and gram-negative organisms at concentrations ≥ 125 mcg/mL. Susceptibility tests should be performed in growth medium supplemented with glucose 6-phosphate to minimize false-positive indications of resistance. In vitro synergism occurs when fosfomycin is combined with β-lactam antibiotics, aminoglycosides, or fluoroquinolones.

Fosfomycin trometamol is available in both oral and parenteral formulations, although only the oral preparation is approved for use in the USA. Oral bioavailability is approximately 40%. Peak serum concentrations are 10 mcg/mL and 30 mcg/mL following a 2-g or 4-g oral dose, respectively. The half-life is approximately 4 hours. The active drug is excreted by the kidney, with urinary concentrations exceeding MICs for most urinary tract pathogens.

Fosfomycin is approved for use as a single 3-g dose for treatment of uncomplicated lower urinary tract infections in women. The drug appears to be safe for use in pregnancy.

BACITRACIN

Bacitracin is a cyclic peptide mixture first obtained from the Tracy strain of *Bacillus subtilis* in 1943. It is active against gram-positive microorganisms. Bacitracin inhibits cell wall formation by interfering with dephosphorylation in cycling of the lipid carrier that transfers peptidoglycan subunits to the growing cell wall (Figure 43–5). There is no cross-resistance between bacitracin and other antimicrobial drugs.

Bacitracin is highly nephrotoxic when administered systemically and is only used topically (Chapter 61). Bacitracin is poorly absorbed. Topical application results in local antibacterial activity without systemic toxicity. Bacitracin, 500 units/g in an ointment base (often combined with polymyxin or neomycin), is indicated for the suppression of mixed bacterial flora in surface lesions of the skin, in wounds, or on mucous membranes. Solutions of bacitracin containing 100–200 units/mL in saline can be used for irrigation of joints, wounds, or the pleural cavity.

CYCLOSERINE

Cycloserine is an antibiotic produced by *Streptomyces orchidaceous.* It is water soluble and very unstable at acid pH. Cycloserine inhibits many gram-positive and gram-negative organisms, but it is used almost exclusively to treat tuberculosis caused by strains of *Mycobacterium tuberculosis* resistant to first-line agents. Cycloserine is a structural analog of D-alanine and inhibits the incorporation of D-alanine into peptidoglycan pentapeptide by inhibiting alanine racemase, which converts L-alanine to D-alanine, and D-alanyl- D-alanine ligase (Figure 43–5). After ingestion of 0.25 g of cycloserine blood levels reach 20–30 mcg/mL—sufficient to inhibit many strains of mycobacteria and gram-negative bacteria. The drug is widely distributed in tissues. Most of the drug is excreted in active form into the urine. The dosage for treating tuberculosis is 0.5 to 1 g/d in two or three divided doses.

Cycloserine causes serious dose-related central nervous system toxicity with headaches, tremors, acute psychosis, and convulsions. If oral dosages are maintained below 0.75 g/d, such effects can usually be avoided.

SUMMARY Beta-Lactam & Other Cell Wall- & Membrane-Active Antibiotics

Subclass	Mechanism of Action	Effects	Clinical Applications	Pharmacokinetics, Toxicities, Interactions
PENICILLINS				
• Penicillin G	Prevents bacterial cell wall synthesis by binding to and inhibiting cell wall transpeptidases	Rapid bactericidal activity against susceptible bacteria	Streptococcal infections, meningococcal infections, neurosyphilis	IV administration • rapid renal clearance (half-life 30 min, so requires frequent dosing (every 4 h) • *Toxicity:* Immediate hypersensitivity, rash, seizures
• *Penicillin V: Oral, low systemic levels limit widespread use*				
• *Benzathine penicillin, procaine penicillin: Intramuscular, long-acting formulations*				
• *Nafcillin, oxacillin: Intravenous, added stability to staphylococcal β lactamase, biliary clearance*				
• *Ampicillin, amoxicillin, ticarcillin, piperacillin: Greater activity versus gram-negative bacteria; addition of β-lactamase inhibitor restores activity against many β-lactamase-producing bacteria*				

Subclass	Mechanism of Action	Effects	Clinical Applications	Pharmacokinetics, Toxicities, Interactions
CEPHALOSPORINS				
• Cefazolin	Prevents bacterial cell wall synthesis by binding to and inhibiting cell wall transpeptidases	Rapid bactericidal activity against susceptible bacteria	Skin and soft tissue infections, urinary tract infections, surgical prophylaxis	IV administration • renal clearance (half-life 1.5 h) • dosed every 8 h • poor penetration into the central nervous system (CNS) • *Toxicity:* Rash, drug fever
• *Cephalexin: Oral, first-generation drug, used for treating skin and soft tissue infections and urinary tract infections*				
• *Cefuroxime: Oral and intravenous, second-generation drug, improved activity versus pneumococcus and* Haemophilus influenzae				
• *Cefotetan, cefoxitin: Intravenous, second-generation drugs, activity versus* Bacteroides fragilis *allows for use in abdominal/pelvic infections*				
• *Ceftriaxone: Intravenous, third-generation drug, mixed clearance with long half-life (6 hours), good CNS penetration, many uses including pneumonia, meningitis, pyelonephritis, and gonorrhea*				
• *Cefotaxime: Intravenous, third-generation, similar to ceftriaxone; however, clearance is renal and half-life is 1 hour*				
• *Ceftazidime: Intravenous, third-generation drug, poor gram-positive activity, good activity versus* Pseudomonas				
• *Cefepime: Intravenous, fourth-generation drug, broad activity with improved stability to chromosomal β lactamase*				
• *Ceftaroline: Intravenous, active against methicillin-resistant staphylococci, broad gram-negative activity*				
CARBAPENEMS				
• Imipenem-cilastatin	Prevents bacterial cell wall synthesis by binding to and inhibiting cell wall transpeptidases	Rapid bactericidal activity against susceptible bacteria	Serious infections such as pneumonia and sepsis	IV administration • renal clearance (half-life 1 h), dosed every 6–8 h, cilastatin added to prevent hydrolysis by renal dehydropeptidase • *Toxicity:* Seizures especially in renal failure or with high doses (> 2 g/d)
• *Meropenem, doripenem: Intravenous, similar activity to imipenem; stable to renal dehydropeptidase, lower incidence of seizures*				
• *Ertapenem: Intravenous, longer half-life allows for once-daily dosing, lacks activity versus* Pseudomonas *and* Acinetobacter				
MONOBACTAMS				
• Aztreonam	Prevents bacterial cell wall synthesis by binding to and inhibiting cell wall transpeptidases	Rapid bactericidal activity against susceptible bacteria	Infections caused by aerobic, gram-negative bacteria in patients with immediate hypersensitivity to penicillins	IV administration • renal clearance half-life 1.5 h • dosed every 8 h • *Toxicity:* No cross-allergenicity with penicillins
GLYCOPEPTIDE				
• Vancomycin	Inhibits cell wall synthesis by binding to the D-Ala-D-Ala terminus of nascent peptidoglycan	Bactericidal activity against susceptible bacteria, slower kill than β-lactam antibiotics	Infections caused by gram-positive bacteria including sepsis, endocarditis, and meningitis • *C difficile* colitis (oral formulation)	Oral, IV administration • renal clearance (half-life 6 h) • starting dose of 30 mg/kg/d in two or three divided doses in patients with normal renal function • trough concentrations of 10–15 mcg/mL sufficient for most infections • *Toxicity:* "Red man" syndrome • nephrotoxicity uncommon
• *Teicoplanin: Intravenous, similar to vancomycin except that long half-life (45–75 h) permits once-daily dosing*				
• *Dalbavancin: Intravenous, very long half-life (6–11 days) permits once-weekly dosing, more active than vancomycin*				
• *Telavancin: Intravenous, dual mechanism of action results in improved activity against bacteria with reduced susceptibility to vancomycin, once-daily dosing*				
LIPOPEPTIDE				
• Daptomycin	Binds to cell membrane, causing depolarization and rapid cell death	Bactericidal activity against susceptible bacteria • more rapidly bactericidal than vancomycin	Infections caused by gram-positive bacteria including sepsis and endocarditis	IV administration • renal clearance (half-life 8 h) • dosed once daily • inactivated by pulmonary surfactant so cannot be used to treat pneumonia • *Toxicity:* Myopathy • monitoring of weekly creatine phosphokinase levels recommended

P R E P A R A T I O N S   A V A I L A B L E

PENICILLINS

Amoxicillin (generic, Amoxil, others)
Oral: 125, 200, 250, 400 mg chewable tablets; 500, 875 mg tablets; 250, 500 mg capsules; powder to reconstitute for 50, 125, 200, 250, 400 mg/mL solution

Amoxicillin/potassium clavulanate (generic, Augmentin)[1]
Oral: 250, 500, 875 mg tablets; 125, 200, 250, 400 mg chewable tablets; 1000 mg extended-release tablet; powder to reconstitute for 125, 200, 250 mg/5 mL suspension

Ampicillin (generic)
Oral: 250, 500 mg capsules; powder to reconstitute for 125, 250 mg suspensions
Parenteral: powder to reconstitute for injection (125, 250, 500 mg, 1, 2 g per vial)

Ampicillin/sulbactam sodium (generic, Unasyn)[2]
Parenteral: 1, 2 g ampicillin powder to reconstitute for IV or IM injection

Carbenicillin (Geocillin)
Oral: 382 mg tablets

Dicloxacillin (generic)
Oral: 250, 500 mg capsules

Nafcillin (generic)
Parenteral: 1, 2 g per IV piggyback units

Oxacillin (generic)
Parenteral: powder to reconstitute for injection (0.5, 1, 2, 10 g per vial)

Penicillin G (generic, Pentids, Pfizerpen)
Parenteral: powder to reconstitute for injection (1, 2, 3, 5, 10, 20 million units)

Penicillin G benzathine (Permapen, Bicillin)
Parenteral: 0.6, 1.2, 2.4 million units per dose

Penicillin G procaine (generic)
Parenteral: 0.6, 1.2 million units/mL for IM injection only

Penicillin V (generic, V-Cillin, Pen-Vee K, others)
Oral: 250, 500 mg tablets; powder to reconstitute for 125, 250 mg/5 mL solution

Piperacillin (Pipracil)
Parenteral: powder to reconstitute for injection (2, 3, 4 g per vial)

Piperacillin and tazobactam sodium (Zosyn)[3]
Parenteral: 2, 3, 4 g powder to reconstitute for IV injection

Ticarcillin (Ticar)
Parenteral: powder to reconstitute for injection (1, 3, 6 g per vial)

Ticarcillin/clavulanate potassium (Timentin)[4]
Parenteral: 3 g powder to reconstitute for injection

CEPHALOSPORINS & OTHER BETA-LACTAM DRUGS

Narrow-Spectrum (First-Generation) Cephalosporins
Cefadroxil (generic, Duricef)
Oral: 500 mg capsules; 1 g tablets; 125, 250, 500 mg/5 mL suspension

Cefazolin (generic, Ancef, Kefzol)
Parenteral: powder to reconstitute for injection (0.25, 0.5, 1 g per vial or IV piggyback unit)

Cephalexin (generic, Keflex, others)
Oral: 250, 500 mg capsules and tablets; 1 g tablets; 125, 250 mg/5 mL suspension

Intermediate-Spectrum (Second-Generation) Cephalosporins
Cefaclor (generic, Ceclor)
Oral: 250, 500 mg capsules; 375, 500 mg extended-release tablets; powder to reconstitute for 125, 187, 250, 375 mg/5 mL suspension

Cefmetazole (Zefazone)
Parenteral: 1, 2 g powder for IV injection

Cefotetan (Cefotan)
Parenteral: powder to reconstitute for injection (1, 2, 10 g per vial)

Cefoxitin (Mefoxin)
Parenteral: powder to reconstitute for injection (1, 2, 10 g per vial)

Cefprozil (Cefzil)
Oral: 250, 500 mg tablets; powder to reconstitute 125, 250 mg/5 mL suspension

Cefuroxime (generic, Ceftin, Kefurox, Zinacef)
Oral: 125, 250, 500 mg tablets; 125, 250 mg/5 mL suspension
Parenteral: powder to reconstitute for injection (0.75, 1.5, 7.5 g per vial or infusion pack)

Loracarbef (Lorabid)
Oral: 200, 400 mg capsules; powder for 100, 200 mg/5 mL suspension

Broad-Spectrum (Third- & Fourth-Generation) Cephalosporins
Cefdinir (Omnicef)
Oral: 300 mg capsules; 125 mg/5 mL suspension

Cefditoren (Spectracef)
Oral: 200 mg tablets

Cefepime (Maxipime)
Parenteral: powder for injection 0.5, 1, 2 g

Cefixime (Suprax)
Oral: 200, 400 mg tablets; powder for oral suspension, 100 mg/5 mL

Cefotaxime (Claforan)
Parenteral: powder to reconstitute for injection (0.5, 1, 2 g per vial)

Cefpodoxime proxetil (Vantin)
Oral: 100, 200 mg tablets; 50, 100 mg granules for suspension in 5 mL

Ceftaroline fosamil (Teflaro)
Parenteral: powder to reconstitute for injection (0.6 g per vial)

Ceftazidime (generic, Fortaz, Tazidime)
Parenteral: powder to reconstitute for injection (0.5, 1, 2 g per vial)

Ceftibuten (Cedax)
Oral: 400 mg capsules; 90, 180 mg/5 mL powder for oral suspension

Ceftizoxime (Cefizox)
Parenteral: powder to reconstitute for injection and solution for injection (0.5, 1, 2 g per vial)

Ceftriaxone (Rocephin)
Parenteral: powder to reconstitute for injection (0.25, 0.5, 1, 2, 10 g per vial)

Carbapenems & Monobactam
Aztreonam (Azactam)
Parenteral: powder to reconstitute for injection (0.5, 1, 2 g)

Doripenem (Doribax)
Parenteral: powder to reconstitute for injection (500 mg per vial)

Ertapenem (Invanz)
Parenteral: 1 g powder to reconstitute for IV (0.9% diluent) or IM (1% lidocaine diluent) injection

Imipenem/cilastatin (Primaxin)
Parenteral: powder to reconstitute for injection (250, 500, 750 mg imipenem per vial)

Meropenem (Merrem IV)
Parenteral: powder for injection (0.5, 1 g per vial)

OTHER DRUGS DISCUSSED IN THIS CHAPTER

Cycloserine (Seromycin Pulvules)
Oral: 250 mg capsules

Daptomycin (Cubicin)
Parenteral: 0.25 or 0.5 g lyophilized powder to reconstitute for IV injection

Fosfomycin (Monurol)
Oral: 3 g packet

Telavancin (Vibativ)
Parenteral: 0.25 and 0.75 g powder to reconstitute for IV injection

Vancomycin (generic, Vancocin, Vancoled)
Oral: 125, 250 mg pulvules; powder to reconstitute for 250 mg/5 mL, 500 mg/6 mL solution
Parenteral: 0.5, 1, 5, 10 g powder to reconstitute for IV injection

[1]Clavulanate content varies with the formulation; see package insert.
[2]Sulbactam content is half the ampicillin content.
[3]Tazobactam content is 12.5% of the piperacillin content.
[4]Clavulanate content 0.1 g.

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CASE STUDY ANSWER

An intravenous third-generation cephalosporin (ceftriaxone or cefotaxime) with adequate penetration into inflamed meninges that is active against the common bacteria that cause community-acquired pneumonia and meningitis (pneumococcus, meningococcus, *Haemophilus*) should be ordered. Vancomycin should also be administered until culture and sensitivity results are available in case the patient is infected with a resistant pneumococcus. Although the patient has a history of rash to amoxicillin, the presentation is not consistent with an anaphylactic reaction. The aminopenicillins are frequently associated with rashes that are not allergic in nature. In this instance, cross-reactivity with a cephalosporin is unlikely.

Tetracyclines, Macrolides, Clindamycin, Chloramphenicol, Streptogramins, & Oxazolidinones

44

**Daniel H. Deck, PharmD
& Lisa G. Winston, MD**

C A S E   S T U D Y

A 19-year-old woman with no significant past medical history presents to her college medical clinic complaining of a 2-week history of foul-smelling vaginal discharge. She denies any fever or abdominal pain but does report vaginal bleeding after sexual intercourse. When questioned about her sexual activity, she reports having vaginal intercourse, at times unprotected, with two men in the last 6 months. A pelvic examination is performed and is positive for mucopurulent discharge from the endocervical canal. No cervical motion tenderness is present. A first-catch urine specimen is obtained to be tested for chlamydia and gonococcus. A pregnancy test is also ordered as the patient reports she "missed her last period." Pending these results, the decision is made to treat her empirically for gonococcal and chlamydial cervicitis. What are two potential treatment options for her possible chlamydial infection? How does her potential pregnancy affect the treatment decision?

The drugs described in this chapter inhibit bacterial protein synthesis by binding to and interfering with ribosomes. Most are bacteriostatic, but a few are bactericidal against certain organisms.

Because of overuse, tetracycline and macrolide resistance is common. Except for tigecycline and the streptogramins, these antibiotics are usually administered orally.
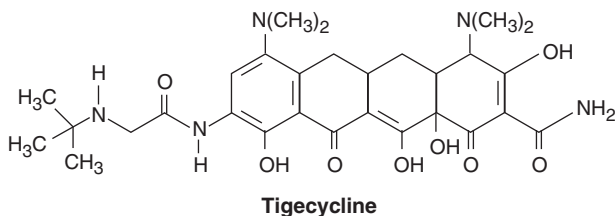
■ TETRACYCLINES

All of the tetracyclines have the basic structure shown below:
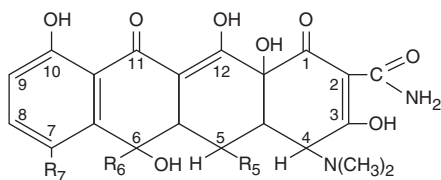
	R$_7$	**R$_6$**	**R$_5$**	Renal Clearance (mL/min)
Chlortetracycline	—Cl	—CH$_3$	—H	35
Oxytetracycline	—H	—CH$_3$	—OH	90
Tetracycline	—H	—CH3	—H	65
Demeclocycline	—Cl	—H	—H	35
Methacycline	—H	=CH$_2$*	—OH	31
Doxycycline	—H	—CH$_3$*	—OH	16
Minocycline	—N(CH$_3$)$_2$	—H	—H	10

*There is no — OH at position 6 on methacycline and doxycycline.

Free tetracyclines are crystalline amphoteric substances of low solubility. They are available as hydrochlorides, which are more soluble. Such solutions are acid and, with the exception of chlortetracycline, fairly stable. Tetracyclines chelate divalent metal ions, which can interfere with their absorption and activity. A newly approved tetracycline analog, tigecycline, is a glycylcycline and a semisynthetic derivative of minocycline.

Tigecycline

Mechanism of Action & Antimicrobial Activity

Tetracyclines are broad-spectrum bacteriostatic antibiotics that inhibit protein synthesis. Tetracyclines enter microorganisms in part by passive diffusion and in part by an energy-dependent process of active transport. Susceptible organisms concentrate the drug intracellularly. Once inside the cell, tetracyclines bind reversibly to the 30S subunit of the bacterial ribosome, blocking the binding of aminoacyl-tRNA to the acceptor site on the mRNA-ribosome complex (Figure 44–1). This prevents addition of amino acids to the growing peptide.

Tetracyclines are active against many gram-positive and gram-negative bacteria, including certain anaerobes, rickettsiae, chlamydiae, and mycoplasmas. The antibacterial activities of most tetracyclines are similar except that tetracycline-resistant strains may be susceptible to doxycycline, minocycline, and tigecycline, all of which are poor substrates for the efflux pump that mediates resistance. Differences in clinical efficacy for susceptible organisms are minor and attributable largely to features of absorption, distribution, and excretion of individual drugs.

Resistance

Three mechanisms of resistance to tetracycline analogs have been described: (1) impaired influx or increased efflux by an active transport protein pump; (2) ribosome protection due to production of proteins that interfere with tetracycline binding to the ribosome; and (3) enzymatic inactivation. The most important of these are production of an efflux pump and ribosomal protection. Tet(AE) efflux pump-expressing gram-negative species are resistant to the older tetracyclines, doxycycline, and minocycline. They are susceptible, however, to tigecycline, which is not a substrate of these pumps. Similarly, the Tet(K) efflux pump of staphylococci confers resistance to tetracycline, but not to doxycycline, minocycline, or tigecycline, none of which are pump substrates. The Tet(M) ribosomal protection protein expressed by gram-positives produces resistance to tetracycline, doxycycline, and minocycline, but not to tigecycline, which because of its bulky *t*-butylglycylamido substituent, has a steric hindrance effect on Tet(M) binding to the ribosome. Tigecycline is a substrate of the chromosomally encoded multidrug efflux pumps of *Proteus* sp and *Pseudomonas aeruginosa*, accounting for their intrinsic resistance to all tetracyclines including tigecycline.

Pharmacokinetics

Tetracyclines differ in their absorption after oral administration and in their elimination. Absorption after oral administration is approximately 30% for chlortetracycline; 60–70% for tetracycline, oxytetracycline, demeclocycline, and methacycline; and 95–100% for doxycycline and minocycline. Tigecycline is poorly absorbed orally and must be administered intravenously. A portion of an orally administered dose of tetracycline remains in the gut lumen, alters intestinal flora, and is excreted in the feces. Absorption occurs mainly in the upper small intestine and is impaired by food (except doxycycline and minocycline); by divalent cations (Ca^{2+}, Mg^{2+}, Fe^{2+}) or Al^{3+}; by dairy products and antacids, which contain multivalent cations; and by alkaline pH. Specially buffered tetracycline solutions are formulated for intravenous administration.

Tetracyclines are 40–80% bound by serum proteins. Oral dosages of 500 mg every 6 hours of tetracycline hydrochloride or oxytetracycline produce peak blood levels of 4–6 mcg/mL. Intravenously injected tetracyclines give somewhat higher levels, but only temporarily. Peak levels of 2–4 mcg/mL are achieved with a 200-mg dose of doxycycline or minocycline. Steady-state peak serum concentrations of tigecycline are 0.6 mcg/mL at the standard dosage. Tetracyclines are distributed widely to tissues and body fluids except for cerebrospinal fluid, where concentrations are 10–25% of those in serum. Minocycline reaches very high concentrations in tears and saliva, which makes it useful for eradication of the meningococcal carrier state. Tetracyclines cross the placenta to reach the fetus and are also excreted in milk. As a result of chelation with calcium, tetracyclines are bound to—and damage—growing bones and teeth. Carbamazepine, phenytoin, barbiturates, and chronic alcohol ingestion may shorten the half-life of doxycycline 50% by induction of hepatic enzymes that metabolize the drug.

Tetracyclines are excreted mainly in bile and urine. Concentrations in bile exceed those in serum tenfold. Some of the drug excreted in
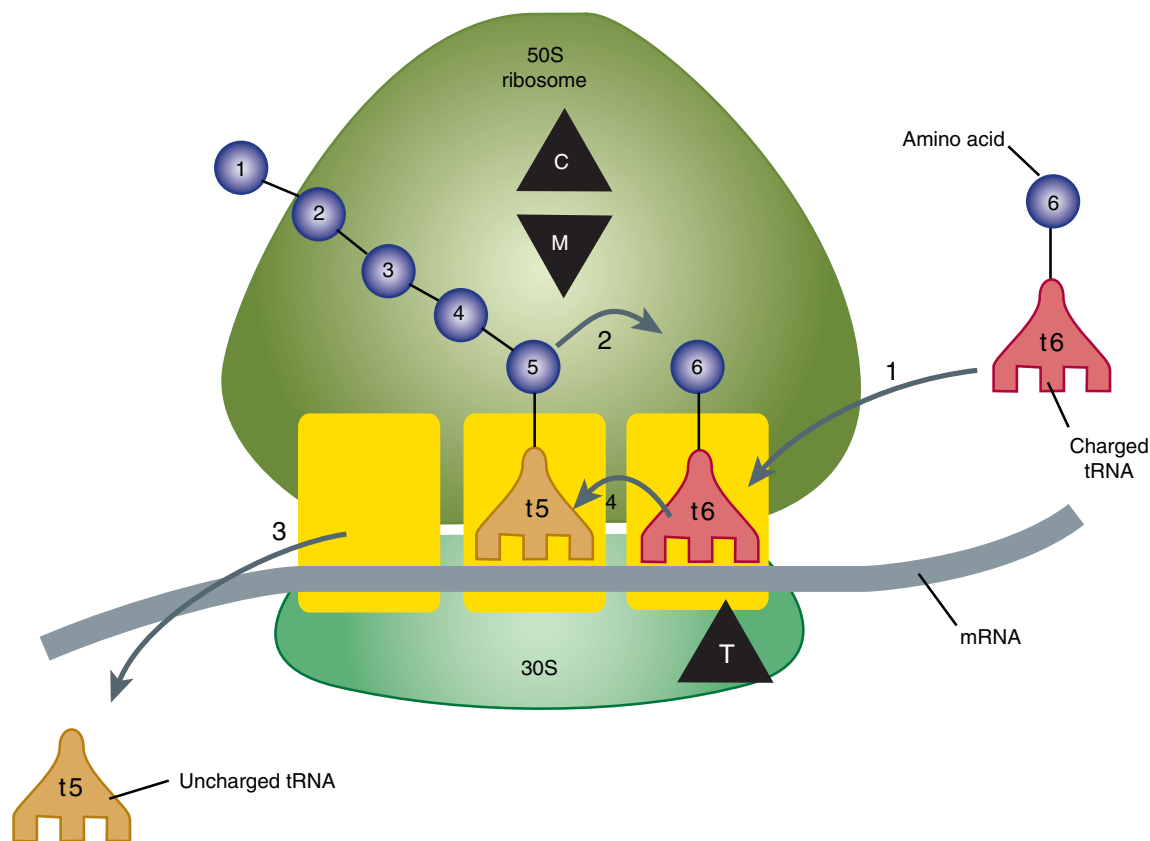
FIGURE 44–1 Steps in bacterial protein synthesis and targets of several antibiotics. Amino acids are shown as numbered circles. The 70S ribosomal mRNA complex is shown with its 50S and 30S subunits. In step 1, the charged tRNA unit carrying amino acid 6 binds to the acceptor site on the 70S ribosome. The peptidyl tRNA at the donor site, with amino acids 1 through 5, then binds the growing amino acid chain to amino acid 6 (peptide bond formation, step 2). The uncharged tRNA left at the donor site is released (step 3), and the new 6-amino acid chain with its tRNA shifts to the peptidyl site (translocation, step 4). The antibiotic binding sites are shown schematically as triangles. Chloramphenicol (C) and macrolides (M) bind to the 50S subunit and block peptide bond formation (step 2). The tetracyclines (T) bind to the 30S subunit and prevent binding of the incoming charged tRNA unit (step 1).

bile is reabsorbed from the intestine (enterohepatic circulation) and may contribute to maintenance of serum levels. Ten to fifty percent of various tetracyclines is excreted into the urine, mainly by glomerular filtration. Ten to forty percent of the drug is excreted in feces. Doxycycline and tigecycline, in contrast to other tetracyclines, are eliminated by nonrenal mechanisms, do not accumulate significantly, and require no dosage adjustment in renal failure.

Tetracyclines are classified as short-acting (chlortetracycline, tetracycline, oxytetracycline), intermediate-acting (demeclocycline and methacycline), or long-acting (doxycycline and minocycline) based on serum half-lives of 6–8 hours, 12 hours, and 16–18 hours, respectively. Tigecycline has a half-life of 36 hours. The almost complete absorption and slow excretion of doxycycline and minocycline allow for once-daily dosing for certain indications, but by convention these two drugs are usually dosed twice daily.

Clinical Uses

A tetracycline is the drug of choice in the treatment of infections caused by rickettsiae. Tetracyclines are also excellent drugs for the treatment of *Mycoplasma pneumonia*, chlamydiae, and some spirochetes. They are used in combination regimens to treat gastric and duodenal ulcer disease caused by *Helicobacter pylori*. They may be used in various gram-positive and gram-negative bacterial infections, including vibrio infections, provided the organism is not resistant. In cholera, tetracyclines rapidly stop the shedding of vibrios, but tetracycline resistance has appeared during epidemics. Tetracyclines remain effective in most chlamydial infections, including sexually transmitted infections. Tetracyclines are no longer recommended for treatment of gonococcal disease because of resistance. A tetracycline—in combination with other antibiotics—is indicated for plague, tularemia, and brucellosis. Tetracyclines are sometimes used in the treatment or prophylaxis of protozoal infections, eg, those due to *Plasmodium falciparum* (see Chapter 52). Other uses include treatment of acne, exacerbations of bronchitis, community-acquired pneumonia, Lyme disease, relapsing fever, leptospirosis, and some nontuberculous mycobacterial infections (eg, *Mycobacterium marinum*). Tetracyclines formerly were used for a variety of common infections, including bacterial gastroenteritis and urinary tract infections. However, many strains of bacteria causing these infections are now resistant, and other agents have largely supplanted tetracyclines.

Minocycline, 200 mg orally daily for 5 days, can eradicate the meningococcal carrier state, but because of side effects and resistance of many meningococcal strains, rifampin is preferred. **Demeclocycline** inhibits the action of antidiuretic hormone in the renal tubule and has been used in the treatment of inappropriate secretion of antidiuretic hormone or similar peptides by certain tumors (see Chapter 15).

Tigecycline, the first glycylcycline to reach clinical practice, has several unique features that warrant its consideration apart from the older tetracyclines. Many tetracycline-resistant strains are susceptible to tigecycline because the common resistance determinants have no activity against it. Its spectrum is very broad. Coagulase-negative staphylococci and *Staphylococcus aureus,* including methicillin-resistant, vancomycin-intermediate, and vancomycin-resistant strains; streptococci, penicillin-susceptible and resistant; enterococci, including vancomycin-resistant strains; gram-positive rods; Enterobacteriaceae; multidrug-resistant strains of *Acinetobacter* sp; anaerobes, both gram-positive and gram-negative; rickettsiae, *Chlamydia* sp, and *Legionella pneumophila;* and rapidly growing mycobacteria all are susceptible. *Proteus* sp and *P aeruginosa,* however, are intrinsically resistant.

Tigecycline, formulated for intravenous administration only, is given as a 100-mg loading dose, then 50 mg every 12 hours. As with all tetracyclines, tissue and intracellular penetration is excellent; consequently, the volume of distribution is quite large and peak serum concentrations are low. Elimination is primarily biliary, and no dosage adjustment is needed for patients with renal insufficiency. In addition to the tetracycline class effects, the chief adverse effect of tigecycline is nausea, which occurs in up to one third of patients, and occasionally vomiting. Neither nausea nor vomiting usually requires discontinuation of the drug.

Tigecycline is Food and Drug Administration (FDA)-approved for treatment of skin and skin-structure infection, intra-abdominal infections, and community-acquired pneumonia. Because active drug concentrations in the urine are relatively low, tigecycline may not be effective for urinary tract infections and has no indication for this use. Because it is active against a wide variety of multidrug-resistant nosocomial pathogens (eg, methicillin-resistant *S aureus,* extended-spectrum β-lactamase-producing gram-negatives, and *Acinetobacter* sp, tigecycline is a welcome addition to the antimicrobial drug group. However, its clinical efficacy in infections with multidrug-resistant organisms, compared with other agents, is largely unknown.

A. Oral Dosage

The oral dosage for rapidly excreted tetracyclines, equivalent to tetracycline hydrochloride, is 0.25–0.5 g four times daily for adults and 20–40 mg/kg/d for children (8 years of age and older). For severe systemic infections, the higher dosage is indicated, at least for the first few days. The daily dose is 600 mg for demeclocycline or methacycline, 100 mg once or twice daily for doxycycline, and 100 mg twice daily for minocycline. Doxycycline is the oral tetracycline of choice because it can be given twice daily, and its absorption is not significantly affected by food. All tetracyclines chelate with metals, and none should be orally administered with milk, antacids, or ferrous sulfate. To avoid deposition in growing bones or teeth, tetracyclines should be avoided in pregnant women and children younger than 8 years.

B. Parenteral Dosage

Several tetracyclines are available for intravenous injection in doses of 0.1–0.5 g every 6–12 hours (similar to oral doses) but doxycycline is the usual preferred agent, at a dosage of 100 mg every 12–24 hours. Intramuscular injection is not recommended because of pain and inflammation at the injection site.

Adverse Reactions

Hypersensitivity reactions (drug fever, skin rashes) to tetracyclines are uncommon. Most adverse effects are due to direct toxicity of the drug or to alteration of microbial flora.

A. Gastrointestinal Adverse Effects

Nausea, vomiting, and diarrhea are the most common reasons for discontinuing tetracycline medication. These effects are attributable to direct local irritation of the intestinal tract. Nausea, anorexia, and diarrhea can usually be controlled by administering the drug with food or carboxymethylcellulose, reducing drug dosage, or discontinuing the drug.

Tetracyclines alter the normal gastrointestinal flora, with suppression of susceptible coliform organisms and overgrowth of pseudomonas, proteus, staphylococci, resistant coliforms, clostridia, and candida. This can result in intestinal functional disturbances, anal pruritus, vaginal or oral candidiasis, or *Clostridium difficile*-associated colitis.

B. Bony Structures and Teeth

Tetracyclines are readily bound to calcium deposited in newly formed bone or teeth in young children. When a tetracycline is given during pregnancy, it can be deposited in the fetal teeth, leading to fluorescence, discoloration, and enamel dysplasia; it can also be deposited in bone, where it may cause deformity or growth inhibition. Because of these effects, tetracyclines are generally avoided in pregnancy. If the drug is given for long periods to children younger than 8 years, similar changes can result.

C. Other Toxicities

Tetracyclines can impair hepatic function, especially during pregnancy, in patients with preexisting hepatic insufficiency and when high doses are given intravenously. Hepatic necrosis has been reported with daily doses of 4 g or more intravenously.

Renal tubular acidosis and other renal injury resulting in nitrogen retention have been attributed to the administration of outdated tetracycline preparations. Tetracyclines given along with diuretics may produce nitrogen retention. Tetracyclines other than doxycycline may accumulate to toxic levels in patients with impaired kidney function.

Intravenous injection can lead to venous thrombosis. Intramuscular injection produces painful local irritation and should be avoided.

Systemically administered tetracycline, especially demeclocycline, can induce sensitivity to sunlight or ultraviolet light, particularly in fair-skinned persons.

Dizziness, vertigo, nausea, and vomiting have been noted particularly with doxycycline at doses above 100 mg. With dosages of 200–400 mg/d of minocycline, 35–70% of patients will have these reactions.

■ MACROLIDES

The macrolides are a group of closely related compounds characterized by a macrocyclic lactone ring (usually containing 14 or 16 atoms) to which deoxy sugars are attached. The prototype drug, erythromycin, which consists of two sugar moieties attached to a 14-atom lactone ring, was obtained in 1952 from *Streptomyces erythreus*. Clarithromycin and azithromycin are semisynthetic derivatives of erythromycin.

Erythromycin (R_1 = CH$_3$, R_2 = H)
Clarithromycin (R_1, R_2 = CH$_3$)
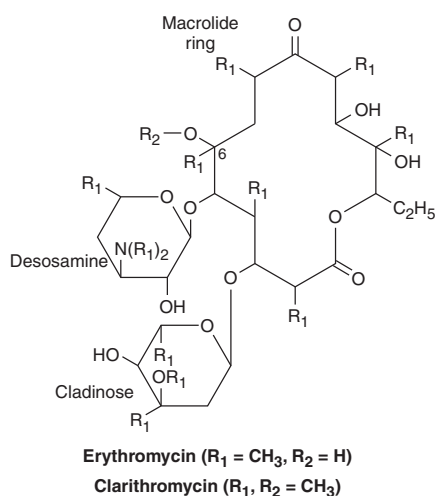
ERYTHROMYCIN

Chemistry

The general structure of erythromycin is shown with the macrolide ring and the sugars desosamine and cladinose. It is poorly soluble in water (0.1%) but dissolves readily in organic solvents. Solutions are fairly stable at 4°C but lose activity rapidly at 20°C and at acid pH. Erythromycins are usually dispensed as various esters and salts.

Mechanism of Action & Antimicrobial Activity

The antibacterial action of erythromycin and other macrolides may be inhibitory or bactericidal, particularly at higher concentrations, for susceptible organisms. Activity is enhanced at alkaline pH. Inhibition of protein synthesis occurs via binding to the 50S ribosomal RNA. The binding site is near the peptidyltransferase center, and peptide chain elongation (ie, transpeptidation) is prevented by blocking of the polypeptide exit tunnel. As a result, peptidyl-tRNA is dissociated from the ribosome. Erythromycin also inhibits the formation of the 50S ribosomal subunit (Figure 44–1).

Erythromycin is active against susceptible strains of gram-positive organisms, especially pneumococci, streptococci, staphylococci, and corynebacteria. *Mycoplasma pneumoniae, L pneumophila, Chlamydia trachomatis, Chlamydia psittaci, Chlamydia pneumoniae, H pylori, Listeria monocytogenes,* and certain mycobacteria *(Mycobacterium kansasii, Mycobacterium scrofulaceum)* are also susceptible. Gram-negative organisms such as *Neisseria* sp, *Bordetella pertussis, Bartonella henselae,* and *Bartonella quintana* as well as some *Rickettsia* species, *Treponema pallidum,* and *Campylobacter* species are susceptible. *Haemophilus influenzae* is somewhat less susceptible.

Resistance to erythromycin is usually plasmid-encoded. Three mechanisms have been identified: (1) reduced permeability of the cell membrane or active efflux; (2) production (by Enterobacteriaceae) of esterases that hydrolyze macrolides; and (3) modification of the ribosomal binding site (so-called ribosomal protection) by chromosomal mutation or by a macrolide-inducible or constitutive methylase. Efflux and methylase production are the most important resistance mechanisms in gram-positive organisms. Cross-resistance is complete between erythromycin and the other macrolides. Constitutive methylase production also confers resistance to structurally unrelated but mechanistically similar compounds such as clindamycin and streptogramin B (so-called macrolide-lincosamide-streptogramin, or MLS-type B, resistance), which share the same ribosomal binding site. Because nonmacrolides are poor inducers of the methylase, strains expressing an inducible methylase will appear susceptible in vitro. However, constitutive mutants that are resistant can be selected out and emerge during therapy with clindamycin.

Pharmacokinetics

Erythromycin base is destroyed by stomach acid and must be administered with enteric coating. Food interferes with absorption. Stearates and esters are fairly acid-resistant and somewhat better absorbed. The lauryl salt of the propionyl ester of erythromycin (erythromycin estolate) is the best-absorbed oral preparation. Oral dosage of 2 g/d results in serum erythromycin base and ester concentrations of approximately 2 mcg/mL. However, only the base is microbiologically active, and its concentration tends to be similar regardless of the formulation. A 500-mg intravenous dose of erythromycin lactobionate produces serum concentrations of 10 mcg/mL 1 hour after dosing. The serum half-life is approximately 1.5 hours normally and 5 hours in patients with anuria. Adjustment for renal failure is not necessary. Erythromycin is not removed by dialysis. Large amounts of an administered dose are excreted in the bile and lost in feces, and only 5% is excreted in the urine. Absorbed drug is distributed widely except to the brain and cerebrospinal fluid. Erythromycin is taken up by polymorphonuclear leukocytes and macrophages. It traverses the placenta and reaches the fetus.

Clinical Uses

Erythromycin is a drug of choice in corynebacterial infections (diphtheria, corynebacterial sepsis, erythrasma); in respiratory,

neonatal, ocular, or genital chlamydial infections; and in treatment of community-acquired pneumonia because its spectrum of activity includes pneumococcus, *M pneumoniae,* and *L pneumophila.* Erythromycin is also useful as a penicillin substitute in penicillin-allergic individuals with infections caused by staphylococci (assuming that the isolate is susceptible), streptococci, or pneumococci. Emergence of erythromycin resistance in strains of group A streptococci and pneumococci (penicillin-non-susceptible pneumococci in particular) has made macrolides less attractive as first-line agents for treatment of pharyngitis, skin and soft tissue infections, and pneumonia. Erythromycin has been recommended as prophylaxis against endocarditis during dental procedures in individuals with valvular heart disease, although clindamycin, which is better tolerated, has largely replaced it. Although erythromycin estolate is the best-absorbed salt, it imposes the greatest risk of adverse reactions. Therefore, the stearate or succinate salt may be preferred.

The oral dosage of erythromycin base, stearate, or estolate is 0.25–0.5 g every 6 hours (for children, 40 mg/kg/d). The dosage of erythromycin ethylsuccinate is 0.4–0.6 g every 6 hours. Oral erythromycin base (1 g) is sometimes combined with oral neomycin or kanamycin for preoperative preparation of the colon. The intravenous dosage of erythromycin gluceptate or lactobionate is 0.5–1.0 g every 6 hours for adults and 20–40 mg/kg/d for children. The higher dosage is recommended when treating pneumonia caused by *L pneumophila.*

Adverse Reactions

Anorexia, nausea, vomiting, and diarrhea are common. Gastrointestinal intolerance, which is due to a direct stimulation of gut motility, is the most common reason for discontinuing erythromycin and substituting another antibiotic.

Erythromycins, particularly the estolate, can produce acute cholestatic hepatitis (fever, jaundice, impaired liver function), probably as a hypersensitivity reaction. Most patients recover from this, but hepatitis recurs if the drug is readministered. Other allergic reactions include fever, eosinophilia, and rashes.

Erythromycin metabolites inhibit cytochrome P450 enzymes and, thus, increase the serum concentrations of numerous drugs, including theophylline, warfarin, cyclosporine, and methylprednisolone. Erythromycin increases serum concentrations of oral digoxin by increasing its bioavailability.

CLARITHROMYCIN

Clarithromycin is derived from erythromycin by addition of a methyl group and has improved acid stability and oral absorption compared with erythromycin. Its mechanism of action is the same as that of erythromycin. Clarithromycin and erythromycin are similar with respect to antibacterial activity except that clarithromycin is more active against *Mycobacterium avium* complex (see Chapter 47). Clarithromycin also has activity against *Mycobacterium leprae, Toxoplasma gondii,* and *H influenzae.* Erythromycin-resistant streptococci and staphylococci are also resistant to clarithromycin.

A 500-mg dose of clarithromycin produces serum concentrations of 2–3 mcg/mL. The longer half-life of clarithromycin (6 hours) compared with erythromycin permits twice-daily dosing. The recommended dosage is 250–500 mg twice daily or 1000 mg of the extended-release formulation once daily. Clarithromycin penetrates most tissues well, with concentrations equal to or exceeding serum concentrations.

Clarithromycin is metabolized in the liver. The major metabolite is 14-hydroxyclarithromycin, which also has antibacterial activity. Portions of active drug and this major metabolite are eliminated in the urine, and dosage reduction (eg, a 500-mg loading dose, then 250 mg once or twice daily) is recommended for patients with creatinine clearances less than 30 mL/min. Clarithromycin has drug interactions similar to those described for erythromycin.

The advantages of clarithromycin compared with erythromycin are lower incidence of gastrointestinal intolerance and less frequent dosing.

AZITHROMYCIN

Azithromycin, a 15-atom lactone macrolide ring compound, is derived from erythromycin by addition of a methylated nitrogen into the lactone ring. Its spectrum of activity, mechanism of action, and clinical uses are similar to those of clarithromycin. Azithromycin is active against *M avium* complex and *T gondii*. Azithromycin is slightly less active than erythromycin and clarithromycin against staphylococci and streptococci and slightly more active against *H influenzae.* Azithromycin is highly active against *Chlamydia* sp.

Azithromycin differs from erythromycin and clarithromycin mainly in pharmacokinetic properties. A 500-mg dose of azithromycin produces relatively low serum concentrations of approximately 0.4 mcg/mL. However, azithromycin penetrates into most tissues (except cerebrospinal fluid) and phagocytic cells extremely well, with tissue concentrations exceeding serum concentrations by 10- to 100-fold. The drug is slowly released from tissues (tissue half-life of 2–4 days) to produce an elimination half-life approaching 3 days. These unique properties permit once-daily dosing and shortening of the duration of treatment in many cases. For example, a single 1-g dose of azithromycin is as effective as a 7-day course of doxycycline for chlamydial cervicitis and urethritis. Community-acquired pneumonia can be treated with azithromycin given as a 500-mg loading dose, followed by a 250-mg single daily dose for the next 4 days.

Azithromycin is rapidly absorbed and well tolerated orally. It should be administered 1 hour before or 2 hours after meals. Aluminum and magnesium antacids do not alter bioavailability but delay absorption and reduce peak serum concentrations. Because it has a 15-member (not 14-member) lactone ring, azithromycin does not inactivate cytochrome P450 enzymes and, therefore, is free of the drug interactions that occur with erythromycin and clarithromycin.

KETOLIDES

Ketolides are semisynthetic 14-membered-ring macrolides, differing from erythromycin by substitution of a 3-keto group for the neutral sugar l-cladinose. **Telithromycin** is approved for limited

clinical use. It is active in vitro against *Streptococcus pyogenes, S pneumoniae, S aureus, H influenzae, Moraxella catarrhalis, Mycoplasma* sp, *L pneumophila, Chlamydia* sp, *H pylori, Neisseria gonorrhoeae, B fragilis, T gondii,* and certain nontuberculosis mycobacteria. Many macrolide-resistant strains are susceptible to ketolides because the structural modification of these compounds renders them poor substrates for efflux pump-mediated resistance, and they bind to ribosomes of some bacterial species with higher affinity than macrolides.

Oral bioavailability of telithromycin is 57%, and tissue and intracellular penetration is generally good. Telithromycin is metabolized in the liver and eliminated by a combination of biliary and urinary routes of excretion. It is administered as a once-daily dose of 800 mg, which results in peak serum concentrations of approximately 2 mcg/mL. It is a reversible inhibitor of the CYP3A4 enzyme system and may slightly prolong the QT_c interval. In the USA, telithromycin is now indicated only for treatment of community-acquired bacterial pneumonia. Other respiratory tract infections were removed as indications when it was recognized that use of telithromycin can result in hepatitis and liver failure.

■ CLINDAMYCIN

Clindamycin is a chlorine-substituted derivative of **lincomycin,** an antibiotic that is elaborated by *Streptomyces lincolnensis.*
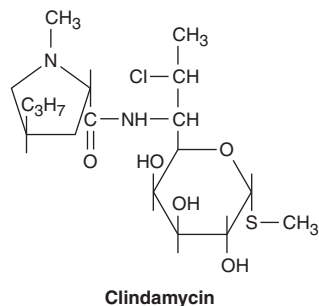
Clindamycin

Mechanism of Action & Antibacterial Activity

Clindamycin, like erythromycin, inhibits protein synthesis by interfering with the formation of initiation complexes and with aminoacyl translocation reactions. The binding site for clindamycin on the 50S subunit of the bacterial ribosome is identical with that for erythromycin. Streptococci, staphylococci, and pneumococci are inhibited by clindamycin, 0.5–5 mcg/mL. Enterococci and gram-negative aerobic organisms are resistant. *Bacteroides* sp and other anaerobes, both gram-positive and gram-negative, are usually susceptible. Resistance to clindamycin, which generally confers cross-resistance to macrolides, is due to (1) mutation of the ribosomal receptor site; (2) modification of the receptor by a constitutively expressed methylase (see section on erythromycin resistance, above); and (3) enzymatic inactivation of clindamycin. Gram-negative aerobic species are intrinsically resistant because of poor permeability of the outer membrane.

Pharmacokinetics

Oral dosages of clindamycin, 0.15–0.3 g every 8 hours (10–20 mg/kg/d for children), yield serum levels of 2–3 mcg/mL. When administered intravenously, 600 mg of clindamycin every 8 hours gives levels of 5–15 mcg/mL. The drug is about 90% protein-bound. Clindamycin penetrates well into most tissues, with brain and cerebrospinal fluid being important exceptions. It penetrates well into abscesses and is actively taken up and concentrated by phagocytic cells. Clindamycin is metabolized by the liver, and both active drug and active metabolites are excreted in bile and urine. The half-life is about 2.5 hours in normal individuals, increasing to 6 hours in patients with anuria. No dosage adjustment is required for renal failure.

Clinical Uses

Clindamycin is indicated for the treatment of skin and soft-tissue infections caused by streptococci and staphylococci. It is often active against community-acquired strains of methicillin-resistant *S aureus*, an increasingly common cause of skin and soft tissue infections. Clindamycin is also indicated for treatment of anaerobic infections caused by *Bacteroides* sp and other anaerobes that often participate in mixed infections. Clindamycin, sometimes in combination with an aminoglycoside or cephalosporin, is used to treat penetrating wounds of the abdomen and the gut; infections originating in the female genital tract, eg, septic abortion, pelvic abscesses, or pelvic inflammatory disease; and lung abscesses. Clindamycin is now recommended rather than erythromycin for prophylaxis of endocarditis in patients with valvular heart disease who are undergoing certain dental procedures and have significant penicillin allergies. Clindamycin plus primaquine is an effective alternative to trimethoprim-sulfamethoxazole for moderate to moderately severe *Pneumocystis jiroveci* pneumonia in AIDS patients. It is also used in combination with pyrimethamine for AIDS-related toxoplasmosis of the brain.

Adverse Effects

Common adverse effects are diarrhea, nausea, and skin rashes. Impaired liver function (with or without jaundice) and neutropenia sometimes occur. Administration of clindamycin is a risk factor for diarrhea and colitis due to *C difficile*.

■ STREPTOGRAMINS

Mechanism of Action & Antibacterial Activity

Quinupristin-dalfopristin is a combination of two streptogramins—quinupristin, a streptogramin B, and dalfopristin, a streptogramin A—in a 30:70 ratio. The streptogramins share the same ribosomal binding site as the macrolides and clindamycin and thus inhibit protein synthesis in an identical manner. It is rapidly bactericidal for most susceptible organisms except *Enterococcus faecium*, which is killed slowly. Quinupristin-dalfopristin is active against

gram-positive cocci, including multidrug-resistant strains of streptococci, penicillin-resistant strains of *S pneumoniae*, methicillin-susceptible and -resistant strains of staphylococci, and *E faecium* (but not *Enterococcus faecalis*). Resistance is due to modification of the quinupristin binding site (MLS-B type resistance), enzymatic inactivation of dalfopristin, or efflux.

Pharmacokinetics

Quinupristin-dalfopristin is administered intravenously at a dosage of 7.5 mg/kg every 8–12 hours. Peak serum concentrations following an infusion of 7.5 mg/kg over 60 minutes are 3 mcg/mL for quinupristin and 7 mcg/mL for dalfopristin. Quinupristin and dalfopristin are rapidly metabolized, with half-lives of 0.85 and 0.7 hours, respectively. Elimination is principally by the fecal route. Dose adjustment is not necessary for renal failure, peritoneal dialysis, or hemodialysis. Patients with hepatic insufficiency may not tolerate the drug at usual doses, however, because of increased area under the concentration curve of both parent drugs and metabolites. This may necessitate a dose reduction to 7.5 mg/kg every 12 hours or 5 mg/kg every 8 hours. Quinupristin and dalfopristin significantly inhibit CYP3A4, which metabolizes warfarin, diazepam, astemizole, terfenadine, cisapride, nonnucleoside reverse transcriptase inhibitors, and cyclosporine, among others. Dosage reduction of cyclosporine may be necessary.

Clinical Uses & Adverse Effects

Quinupristin-dalfopristin is approved for treatment of infections caused by staphylococci or by vancomycin-resistant strains of *E faecium*, but not *E faecalis*, which is intrinsically resistant, probably because of an efflux-type resistance mechanism. The principal toxicities are infusion-related events, such as pain at the infusion site, and an arthralgia-myalgia syndrome.

■ CHLORAMPHENICOL

Crystalline chloramphenicol is a neutral, stable compound with the following structure:
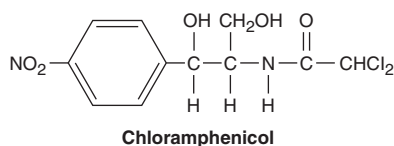
Chloramphenicol

It is soluble in alcohol but poorly soluble in water. Chloramphenicol succinate, which is used for parenteral administration, is highly water-soluble. It is hydrolyzed in vivo with liberation of free chloramphenicol.

Mechanism of Action & Antimicrobial Activity

Chloramphenicol is a potent inhibitor of microbial protein synthesis. It binds reversibly to the 50S subunit of the bacterial ribosome

(Figure 44–1) and inhibits peptide bond formation (step 2). Chloramphenicol is a bacteriostatic broad-spectrum antibiotic that is active against both aerobic and anaerobic gram-positive and gram-negative organisms. It is active also against *Rickettsiae* but not *Chlamydiae*. Most gram-positive bacteria are inhibited at concentrations of 1–10 mcg/mL, and many gram-negative bacteria are inhibited by concentrations of 0.2–5 mcg/mL. *H influenzae, Neisseria meningitidis*, and some strains of bacteroides are highly susceptible, and for these organisms, chloramphenicol may be bactericidal.

Low-level resistance to chloramphenicol may emerge from large populations of chloramphenicol-susceptible cells by selection of mutants that are less permeable to the drug. Clinically significant resistance is due to production of chloramphenicol acetyltransferase, a plasmid-encoded enzyme that inactivates the drug.

Pharmacokinetics

The usual dosage of chloramphenicol is 50–100 mg/kg/d. After oral administration, crystalline chloramphenicol is rapidly and completely absorbed. A 1-g oral dose produces blood levels between 10 and 15 mcg/mL. Chloramphenicol palmitate is a prodrug that is hydrolyzed in the intestine to yield free chloramphenicol. The parenteral formulation is a prodrug, chloramphenicol succinate, which hydrolyzes to yield free chloramphenicol, giving blood levels somewhat lower than those achieved with orally administered drug. Chloramphenicol is widely distributed to virtually all tissues and body fluids, including the central nervous system and cerebrospinal fluid, such that the concentration of chloramphenicol in brain tissue may be equal to that in serum. The drug penetrates cell membranes readily.

Most of the drug is inactivated either by conjugation with glucuronic acid (principally in the liver) or by reduction to inactive aryl amines. Active chloramphenicol (about 10% of the total dose administered) and its inactive degradation products (about 90% of the total) are eliminated in the urine. A small amount of active drug is excreted into bile and feces. The systemic dosage of chloramphenicol need not be altered in renal insufficiency, but it must be reduced markedly in hepatic failure. Newborns less than a week old and premature infants also clear chloramphenicol less well, and the dosage should be reduced to 25 mg/kg/d.

Clinical Uses

Because of potential toxicity, bacterial resistance, and the availability of many other effective alternatives, chloramphenicol is rarely used in the United States. It may be considered for treatment of serious rickettsial infections such as typhus and Rocky Mountain spotted fever. It is an alternative to a β-lactam antibiotic for treatment of bacterial meningitis occurring in patients who have major hypersensitivity reactions to penicillin. The dosage is 50–100 mg/kg/d in four divided doses.

Chloramphenicol is used topically in the treatment of eye infections because of its broad spectrum and its penetration of ocular tissues and the aqueous humor. It is ineffective for chlamydial infections.

Adverse Reactions

Adults occasionally develop gastrointestinal disturbances, including nausea, vomiting, and diarrhea. This is rare in children. Oral or vaginal candidiasis may occur as a result of alteration of normal microbial flora.

Chloramphenicol commonly causes a dose-related reversible suppression of red cell production at dosages exceeding 50 mg/kg/d after 1–2 weeks. Aplastic anemia, a rare consequence (1 in 24,000 to 40,000 courses of therapy) of chloramphenicol administration by any route, is an idiosyncratic reaction unrelated to dose, although it occurs more frequently with prolonged use. It tends to be irreversible and can be fatal.

Newborn infants lack an effective glucuronic acid conjugation mechanism for the degradation and detoxification of chloramphenicol. Consequently, when infants are given dosages above 50 mg/kg/d, the drug may accumulate, resulting in the **gray baby syndrome,** with vomiting, flaccidity, hypothermia, gray color, shock, and vascular collapse. To avoid this toxic effect, chloramphenicol should be used with caution in infants and the dosage limited to 50 mg/kg/d (or less during the first week of life) in full-term infants more than 1 week old and 25 mg/kg/d in premature infants.

Chloramphenicol inhibits hepatic microsomal enzymes that metabolize several drugs. Half-lives of these drugs are prolonged, and the serum concentrations of phenytoin, tolbutamide, chlorpropamide, and warfarin are increased. Like other bacteriostatic inhibitors of microbial protein synthesis, chloramphenicol can antagonize bactericidal drugs such as penicillins or aminoglycosides.

■ OXAZOLIDINONES

Mechanism of Action & Antimicrobial Activity

Linezolid is a member of the oxazolidinones, a new class of synthetic antimicrobials. It is active against gram-positive organisms including staphylococci, streptococci, enterococci, gram-positive anaerobic cocci, and gram-positive rods such as corynebacteria, *Nocardia* sp, and *L monocytogenes*. It is primarily a bacteriostatic agent but is bactericidal against streptococci. It is also active against *Mycobacterium tuberculosis.*

Linezolid inhibits protein synthesis by preventing formation of the ribosome complex that initiates protein synthesis. Its unique binding site, located on 23S ribosomal RNA of the 50S subunit, results in no cross-resistance with other drug classes. Resistance is caused by mutation of the linezolid binding site on 23S ribosomal RNA.

Pharmacokinetics

Linezolid is 100% bioavailable after oral administration and has a half-life of 4–6 hours. It is metabolized by oxidative metabolism, yielding two inactive metabolites. It is neither an inducer nor an inhibitor of cytochrome P450 enzymes. Peak serum concentrations average 18 mcg/mL following a 600-mg oral dose. The recommended dosage for most indications is 600 mg twice daily, either orally or intravenously.

Clinical Uses

Linezolid is approved for vancomycin-resistant *E faecium* infections; nosocomial pneumonia; community-acquired pneumonia; and both complicated and uncomplicated skin and soft tissue infections caused by susceptible gram-positive bacteria. Off-label uses of linezolid include treatment of multidrug-resistant tuberculosis and *Nocardia* infections.

Adverse Effects

The principal toxicity of linezolid is hematologic; the effects are reversible and generally mild. Thrombocytopenia is the most common manifestation (seen in approximately 3% of treatment courses), particularly when the drug is administered for longer than 2 weeks. Anemia and neutropenia may also occur, most commonly in patients with a predisposition to or underlying bone marrow suppression. Cases of optic and peripheral neuropathy and lactic acidosis have been reported with prolonged courses of linezolid. These side effects are thought to be related to linezolid-induced inhibition of mitochondrial protein synthesis. There are case reports of serotonin syndrome occurring when linezolid is co-administered with serotonergic drugs, most frequently selective serotonin reuptake inhibitor antidepressants. The FDA issued a warning regarding the use of the drug with serotonergic agents in 2011.

SUMMARY Tetracyclines, Macrolides, Clindamycin, Chloramphenicol, Streptogramins, & Oxazolidinones

Subclass	Mechanism of Action	Effects	Clinical Applications	Pharmacokinetics, Toxicities, Interactions
TETRACYCLINES				
• Tetracycline	Prevents bacterial protein synthesis by binding to the 30S ribosomal subunit	Bacteriostatic activity against susceptible bacteria	Infections caused by mycoplasma, chlamydiae, rickettsiae, some spirochetes • malaria • *H pylori* • acne	Oral • mixed clearance (half-life 8 h) • dosed every 6 h • divalent cations impair oral absorption • *Toxicity:* Gastrointestinal upset, hepatotoxicity, photosensitivity, deposition in bone and teeth

- *Doxycycline: Oral and IV; longer half-life (18 h) so dosed twice daily; nonrenal elimination; absorption is minimally affected by divalent cations; used to treat community-acquired pneumonia and exacerbations of bronchitis*
- *Minocycline: Oral; longer half-life (16 h) so dosed twice daily; frequently causes reversible vestibular toxicity*
- *Tigecycline: IV; unaffected by common tetracycline resistance mechanisms; very broad spectrum of activity against gram-positive, gram-negative, and anaerobic bacteria; nausea and vomiting are the primary toxicities*

MACROLIDES				
• Erythromycin	Prevents bacterial protein synthesis by binding to the 50S ribosomal subunit	Bacteriostatic activity against susceptible bacteria	Community-acquired pneumonia • pertussis • corynebacterial and chlamydial infections	Oral, IV • hepatic clearance (half-life 1.5 h) • dosed every 6 h • cytochrome P450 inhibitor • *Toxicity:* Gastrointestinal upset, hepatotoxicity, QT$_c$ prolongation

- *Clarithromycin: Oral; longer half-life (4 h) so dosed twice daily; added activity versus M avium complex, toxoplasma, and M leprae*
- *Azithromycin: Oral, IV; very long half-life (68 h) allows for once-daily dosing and 5-day course of therapy of community-acquired pneumonia; does not inhibit cytochrome P450 enzymes*
- *Telithromycin: Oral; unaffected by efflux-mediated resistance so is active versus many erythromycin-resistant strains of pneumococci; rare cases of fulminant hepatic failure*

LINCOSAMIDE				
• Clindamycin	Prevents bacterial protein synthesis by binding to the 50S ribosomal subunit	Bacteriostatic activity against susceptible bacteria	Skin and soft tissue infections • anaerobic infections	Oral, IV • hepatic clearance (half-life 2.5 h) • dosed every 6–8 hours • *Toxicity:* Gastrointestinal upset, *C difficile* colitis
STREPTOGRAMINS				
• Quinupristin-dalfopristin	Prevents bacterial protein synthesis by binding to the 50S ribosomal subunit	Rapid bactericidal activity against most susceptible bacteria	Infections caused by staphylococci or vancomycin-resistant strains of *E faecium*	IV • hepatic clearance • dosed every 8–12 h • cytochrome P450 inhibitor • *Toxicity:* Severe infusion-related myalgias and arthralgias
CHLORAMPHENICOL	Prevents bacterial protein synthesis by binding to the 50S ribosomal subunit	Bacteriostatic activity against susceptible bacteria	Use is rare in the developed world because of serious toxicities	Oral, IV • hepatic clearance (half-life 2.5 h) • dosage is 50–100 mg/kg/d in four divided doses • *Toxicity:* Dose-related anemia, idiosyncratic aplastic anemia, gray baby syndrome
OXAZOLIDINONES				
• Linezolid	Prevents bacterial protein synthesis by binding to the 23S ribosomal RNA of 50S subunit	Bacteriostatic activity against susceptible bacteria	Infections caused by methicillin-resistant staphylococci and vancomycin-resistant enterococci	Oral, IV • hepatic clearance (half-life 6 h) • dosed twice-daily • *Toxicity:* Duration-dependent bone marrow suppression, neuropathy, and optic neuritis • serotonin syndrome may occur when coadministered with other serotonergic drugs (eg, selective serotonin reuptake inhibitors)

PREPARATIONS AVAILABLE

CHLORAMPHENICOL

Chloramphenicol (generic, Chloromycetin)
    Parenteral: 100 mg powder to reconstitute for injection

TETRACYCLINES

Demeclocycline (Declomycin)
    Oral: 150, 300 mg tablets

Doxycycline (generic, Vibramycin, others)
    Oral: 20, 50, 75, 100 mg tablets and capsules; powder to reconstitute
        for 25 mg/5 mL suspension; 50 mg/5 mL syrup
    Parenteral: 100, 200 mg powder to reconstitute for injection

Minocycline (generic, Minocin, various)
    Oral: 20, 50, 75, 100 mg tablets and capsules; 50 mg/5 mL
        suspension

Tetracycline (generic, others)
    Oral: 250, 500 mg capsules; 125 mg/5 mL suspension

Tigecycline (Tygacil)
    Parenteral: 50 mg powder to reconstitute for IV administration

MACROLIDES

Azithromycin (Zithromax)
    Oral: 250, 500, 600 mg capsules; powder for 100, 200 mg/5 mL oral
        suspension
    Parenteral: 500 mg powder for injection

Clarithromycin (generic, Biaxin)
    Oral: 250, 500 mg tablets, 500, 1000 mg extended-release tablets;
        granules for 125, 250 mg/5 mL oral suspension

Erythromycin (generic, others)
    Oral (base): 250, 333, 500 mg enteric-coated tablets
    Oral (base) delayed-release: 250 mg capsules, 500 mg tablets
    Oral (estolate): 125, 250 mg/5 mL suspension
    Oral (ethylsuccinate): 400 mg tablets; 200, 400 mg/5 mL suspension
    Oral (stearate): 250, 500 mg film-coated tablets
    Parenteral: lactobionate, 0.5, 1 g powder to reconstitute for
        IV injection

KETOLIDES

Telithromycin (Ketek)
    Oral: 300, 400 mg tablets

LINCOMYCIN

Clindamycin (generic, Cleocin)
    Oral: 75, 150, 300 mg capsules; 75 mg/5 mL granules to reconstitute
        for solution
    Parenteral: 150 mg/mL in 2, 4, 6, 60 mL vials for injection

STREPTOGRAMINS

Quinupristin and dalfopristin (Synercid)
    Parenteral: 30:70 formulation in 500 mg vial for reconstitution for
        IV injection

OXAZOLIDINONE

Linezolid (Zyvox)
    Oral: 600 mg tablets; 100 mg powder for 5 mL suspension
    Parenteral: 2 mg/mL for IV infusion

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CASE STUDY ANSWER

A tetracycline or a macrolide is effective in the treatment of chlamydial cervicitis. Doxycycline at a dose of 100 mg PO bid for 7 days is the preferred tetracycline, while azithromycin as a single 1 g dose is the preferred macrolide. If the patient is pregnant, then tetracyclines would be contraindicated and she should receive azithromycin, which is safe in pregnancy.

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Aminoglycosides & Spectinomycin

45

Daniel H. Deck, PharmD & Lisa G. Winston, MD[*]

A 45-year-old man with no medical history was admitted to the intensive care unit (ICU) 10 days ago after suffering third-degree burns over 40% of his body. He had been relatively stable until the last 24 hours. Now he is febrile (39.5°C [103.1°F]), and his white blood cell count has risen from 8,500 to 20,000/mm^3. He has also had an episode of hypotension (86/50 mm Hg) that responded to a fluid bolus. Blood cultures were obtained at the time of his fever and results are

pending. The ICU attending physician is concerned about sepsis and decides to treat with empiric combination therapy directed against *Pseudomonas*. The combination therapy includes tobramycin. The patient weighs 70 kg (154 lb) and has an estimated creatinine clearance of 90 mL/min. How should tobramycin be dosed using once-daily and conventional dosing strategies? How should each regimen be monitored for efficacy and toxicity?

The drugs described in this chapter are bactericidal inhibitors of protein synthesis that interfere with ribosomal function. These agents are useful mainly against aerobic gram-negative microorganisms.

■ AMINOGLYCOSIDES

The aminoglycosides include **streptomycin, neomycin, kanamycin, amikacin, gentamicin, tobramycin, sisomicin, netilmicin,** and others. They are used most widely in combination with a β-lactam antibiotic in serious infections with gram-negative bacteria, in combination with vancomycin or a β-lactam antibiotic for gram-positive endocarditis, and for treatment of tuberculosis.

General Properties of Aminoglycosides

A. Physical and Chemical Properties

Aminoglycosides have a hexose ring, either streptidine (in streptomycin) or 2-deoxystreptamine (in other aminoglycosides), to which

various amino sugars are attached by glycosidic linkages (Figures 45–1 and 45–2). They are water-soluble, stable in solution, and more active at alkaline than at acid pH.

B. Mechanism of Action

The mode of action of streptomycin has been studied far more closely than that of other aminoglycosides, but they probably all act similarly. Aminoglycosides are irreversible inhibitors of protein synthesis, but the precise mechanism for bactericidal activity is not known. The initial event is passive diffusion via porin channels across the outer membrane (see Figure 43–3). Drug is then actively transported across the cell membrane into the cytoplasm by an oxygen-dependent process. The transmembrane electrochemical gradient supplies the energy for this process, and transport is coupled to a proton pump. Low extracellular pH and anaerobic conditions inhibit transport by reducing the gradient. Transport may be enhanced by cell wall-active drugs such as penicillin or vancomycin; this enhancement may be the basis of the synergism of these antibiotics with aminoglycosides.

Inside the cell, aminoglycosides bind to specific 30S-subunit ribosomal proteins (S12 in the case of streptomycin). Protein synthesis is inhibited by aminoglycosides in at least three ways (Figure 45–3): (1) interference with the initiation complex of peptide
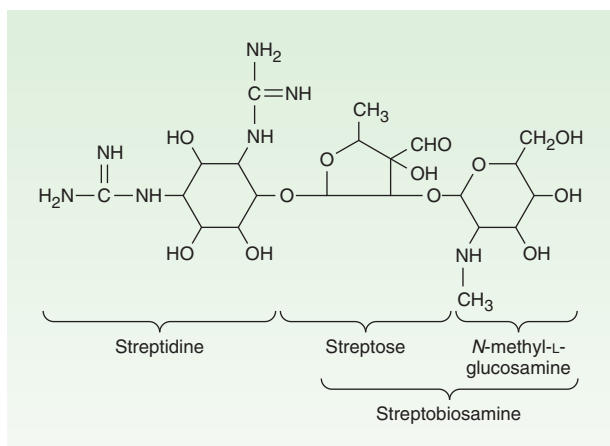
FIGURE 45–1 Structure of streptomycin.

formation; (2) misreading of mRNA, which causes incorporation of incorrect amino acids into the peptide and results in a nonfunctional or toxic protein; and (3) breakup of polysomes into nonfunctional monosomes. These activities occur more or less simultaneously, and the overall effect is irreversible and lethal for the cell.

C. Mechanisms of Resistance

Three principal mechanisms have been established: (1) production of a transferase enzyme or enzymes inactivates the aminoglycoside by adenylylation, acetylation, or phosphorylation. This is the principal type of resistance encountered clinically. (Specific transferase enzymes are discussed below.) (2) There is impaired entry of aminoglycoside into the cell. This may be genotypic, resulting from mutation or deletion of a porin protein or proteins involved in transport and maintenance of the electrochemical gradient; or phenotypic, eg, resulting from growth conditions under which the oxygen-dependent transport process described above is not functional. (3) The receptor protein on the 30S ribosomal subunit may be deleted or altered as a result of a mutation.

D. Pharmacokinetics and Once-Daily Dosing

Aminoglycosides are absorbed very poorly from the intact gastrointestinal tract, and almost the entire oral dose is excreted in feces after oral administration. However, the drugs may be absorbed if ulcerations are present. After intramuscular injection, aminoglycosides are well absorbed, giving peak concentrations in blood within 30–90 minutes. Aminoglycosides are usually administered intravenously as a 30- to 60-minute infusion; after a brief distribution phase, this results in serum concentrations that are identical with those following intramuscular injection. The normal half-life of aminoglycosides in serum is 2–3 hours, increasing to 24–48 hours in patients with significant impairment of renal function. Aminoglycosides are only partially and irregularly removed by hemodialysis—eg, 40–60% for gentamicin—and even less effectively by peritoneal dialysis. Aminoglycosides are highly polar compounds that do not enter cells readily. They are largely excluded from the central nervous system and the eye. In the
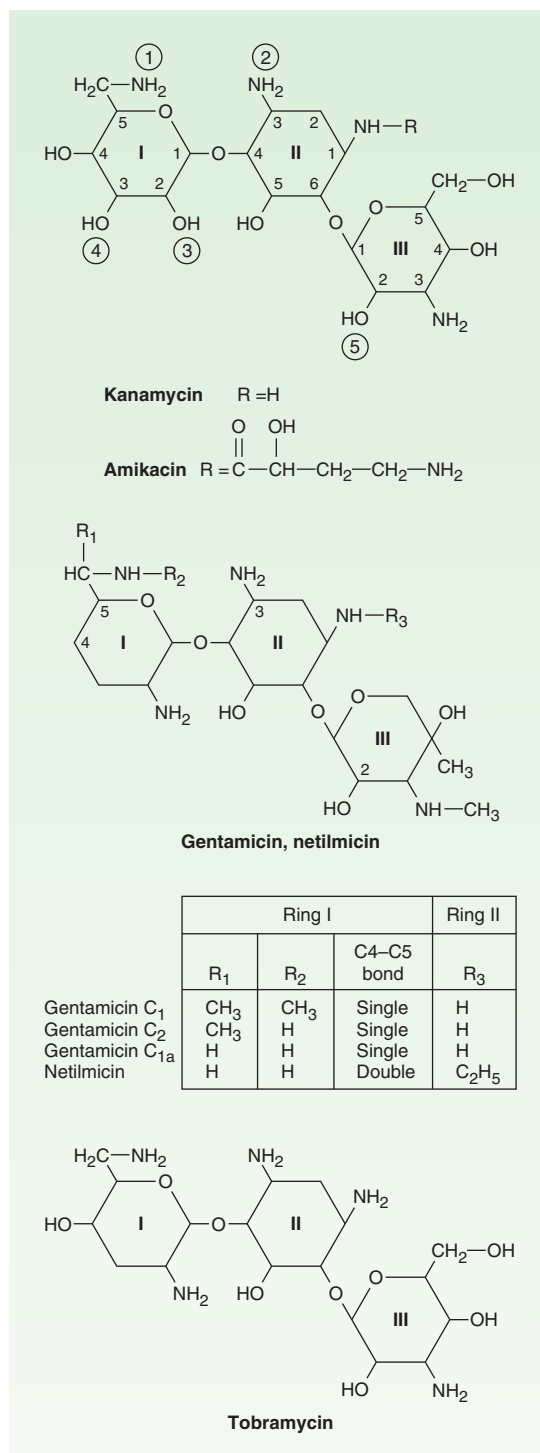

FIGURE 45–2 Structures of several important aminoglycoside antibiotics. Ring II is 2-deoxystreptamine. The resemblance between kanamycin and amikacin and between gentamicin, netilmicin, and tobramycin can be seen. The circled numerals on the kanamycin molecule indicate points of attack of plasmid-mediated bacterial transferase enzymes that can inactivate this drug. ①, ②, and ③, acetyltransferase; ④, phosphotransferase; ⑤, adenylyltransferase. Amikacin is resistant to modification at ②, ③, ④, and ⑤.
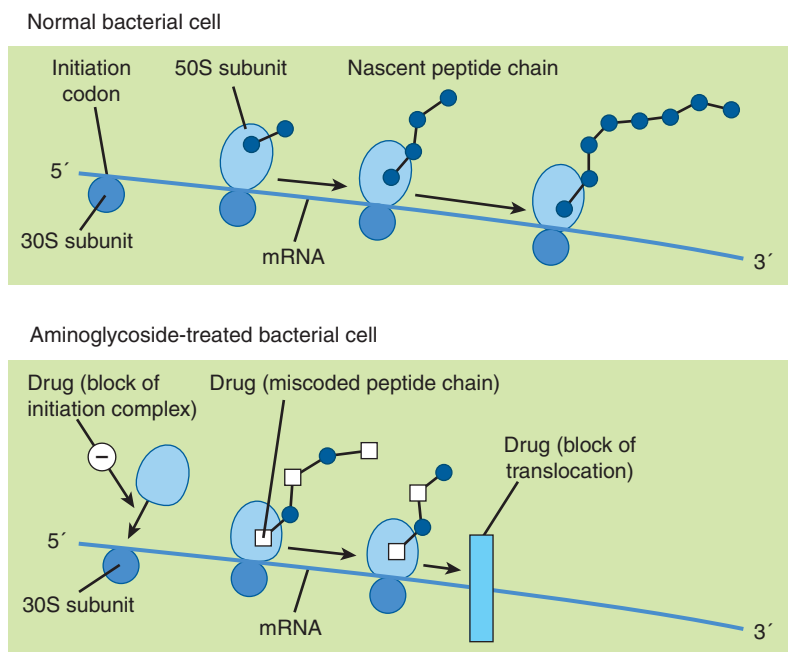
FIGURE 45–3 Putative mechanisms of action of the aminoglycosides in bacteria. Normal protein synthesis is shown in the top panel. At least three aminoglycoside effects have been described, as shown in the bottom panel: block of formation of the initiation complex; miscoding of amino acids in the emerging peptide chain due to misreading of the mRNA; and block of translocation on mRNA. Block of movement of the ribosome may occur after the formation of a single initiation complex, resulting in an mRNA chain with only a single ribosome on it, a so-called monosome. (Reproduced, with permission, from Trevor AT, Katzung BG, Masters SB: *Pharmacology: Examination & Board Review,* 6th ed. McGraw-Hill, 2002.)

presence of active inflammation, however, cerebrospinal fluid levels reach 20% of plasma levels, and in neonatal meningitis, the levels may be higher. Intrathecal or intraventricular injection is required for high levels in cerebrospinal fluid. Even after parenteral administration, concentrations of aminoglycosides are not high in most tissues except the renal cortex. Concentration in most secretions is also modest; in the bile, it may reach 30% of the blood level. With prolonged therapy, diffusion into pleural or synovial fluid may result in concentrations 50–90% of that of plasma.

Traditionally, aminoglycosides have been administered in two or three equally divided doses per day in patients with normal renal function. However, administration of the entire daily dose in a single injection may be preferred in many clinical situations. Aminoglycosides have **concentration-dependent killing;** that is, increasing concentrations kill an increasing proportion of bacteria and at a more rapid rate. They also have a significant **postantibiotic effect,** such that the antibacterial activity persists beyond the time during which measurable drug is present. The postantibiotic effect of aminoglycosides can last several hours. Because of these properties, a given total amount of aminoglycoside may have better efficacy when administered as a single large dose than when administered as multiple smaller doses. When administered with a cell wall-active antibiotic (a β lactam or vancomycin), aminoglycosides exhibit **synergistic killing** against certain bacteria. The effect of the drugs in combination is greater than the anticipated effect of each individual drug, ie, the killing effect of the combination is more than additive.

Adverse effects from aminoglycosides are both time- and concentration-dependent. Toxicity is unlikely to occur until a certain threshold concentration is reached, but once that concentration is achieved, the time beyond this threshold becomes critical. This threshold is not precisely defined, but a trough concentration above 2 mcg/mL is predictive of toxicity. At clinically relevant doses, the total time above this threshold is greater with multiple smaller doses of drug than with a single large dose.

Numerous clinical studies demonstrate that a single daily dose of aminoglycoside is just as effective—and probably less toxic—than multiple smaller doses. Therefore, many authorities now recommend that aminoglycosides be administered as a single daily dose in many clinical situations. However, the efficacy of once-daily aminoglycoside dosing in combination therapy of enterococcal and staphylococcal endocarditis remains to be defined, and the standard low-dose, thrice-daily administration is still recommended. In contrast, there are limited data supporting once-daily dosing in streptococcal endocarditis. The role of once-daily dosing in pregnancy and in neonates also is not well defined.

Once-daily dosing has potential practical advantages. For example, repeated determinations of serum concentrations are probably unnecessary unless aminoglycoside is given for more than 3 days. A drug administered once a day rather than three times a day is less labor intensive. And once-a-day dosing is more feasible for outpatient therapy.

Aminoglycosides are cleared by the kidney, and excretion is directly proportional to creatinine clearance. To avoid accumulation

and toxic levels, once-daily dosing of aminoglycosides is generally avoided if renal function is impaired. Rapidly changing renal function, which may occur with acute kidney injury, must also be monitored to avoid overdosing or underdosing. Provided these pitfalls are avoided, once-daily aminoglycoside dosing is safe and effective. If the creatinine clearance is > 60 mL/min, then a single daily dose of 5–7 mg/kg of gentamicin or tobramycin is recommended (15 mg/kg for amikacin). For patients with creatinine clearance < 60 mL/min, traditional dosing as described below is recommended. With once-daily dosing, serum concentrations need not be routinely checked until the second or third day of therapy, depending on the stability of renal function and the anticipated duration of therapy. It is unnecessary to check peak concentrations because they will be high. The goal is to administer drug so that concentrations of less than 1 mcg/mL are present between 18 and 24 hours after dosing. This provides a sufficient period of time for washout of drug to occur before the next dose is given. Appropriate trough levels can be accurately determined by measuring serum concentrations in samples obtained 2 hours and 12 hours after dosing and then adjusting the dose based on the actual clearance of drug or by measuring the concentration in a sample obtained 8 hours after a dose. If the 8-hour concentration is between 1.5 mcg/mL and 6 mcg/mL, the target trough can be achieved at 18 hours.

With traditional dosing, adjustments must be made to prevent accumulation of drug and toxicity in patients with renal insufficiency. Either the dose of drug is kept constant and the interval between doses is increased, or the interval is kept constant and the dose is reduced. Nomograms and formulas have been constructed relating serum creatinine levels to adjustments in treatment regimens. Because aminoglycoside clearance is directly proportional to the creatinine clearance, a method for determining the aminoglycoside dose is to estimate creatinine clearance using the Cockcroft-Gault formula described in Chapter 60. For a traditional twice- or thrice-daily dosing regimen, peak serum concentrations should be determined from a blood sample obtained 30–60 minutes after a dose, and trough concentrations from a sample obtained just before the next dose. Doses of gentamicin and tobramycin should be adjusted to maintain peak levels between 5 and 10 mcg/mL and trough levels < 2 mcg/mL (< 1 mcg/mL is optimal).

E. Adverse Effects

All aminoglycosides are ototoxic and nephrotoxic. Ototoxicity and nephrotoxicity are more likely to be encountered when therapy is continued for more than 5 days, at higher doses, in the elderly, and in the setting of renal insufficiency. Concurrent use with loop diuretics (eg, furosemide, ethacrynic acid) or other nephrotoxic antimicrobial agents (eg, vancomycin or amphotericin) can potentiate nephrotoxicity and should be avoided if possible. Ototoxicity can manifest either as auditory damage, resulting in tinnitus and high-frequency hearing loss initially, or as vestibular damage, evident by vertigo, ataxia, and loss of balance. Nephrotoxicity results in rising serum creatinine levels or reduced creatinine clearance, although the earliest indication often is an increase in trough serum aminoglycoside concentrations. Neomycin, kanamycin, and amikacin

are the most ototoxic agents. Streptomycin and gentamicin are the most vestibulotoxic. Neomycin, tobramycin, and gentamicin are the most nephrotoxic.

In very high doses, aminoglycosides can produce a curare-like effect with neuromuscular blockade that results in respiratory paralysis. This paralysis is usually reversible by calcium gluconate (given promptly) or neostigmine. Hypersensitivity occurs infrequently.

F. Clinical Uses

Aminoglycosides are mostly used against gram-negative enteric bacteria, especially when the isolate may be drug-resistant and when there is suspicion of sepsis. They are almost always used in combination with a β-lactam antibiotic to extend coverage to include potential gram-positive pathogens and to take advantage of the synergism between these two classes of drugs. Penicillin-aminoglycoside combinations also are used to achieve bactericidal activity in treatment of enterococcal endocarditis and to shorten duration of therapy for viridans streptococcal and some patients with staphylococcal endocarditis. Which aminoglycoside and what dose should be used depend on the infection being treated and the susceptibility of the isolate.

STREPTOMYCIN

Streptomycin (Figure 45–1) was isolated from a strain of *Streptomyces griseus*. The antimicrobial activity of streptomycin is typical of that of other aminoglycosides, as are the mechanisms of resistance. Resistance has emerged in most species, severely limiting the current usefulness of streptomycin, with the exceptions listed below. Ribosomal resistance to streptomycin develops readily, limiting its role as a single agent.

Clinical Uses

A. Mycobacterial Infections

Streptomycin is mainly used as a second-line agent for treatment of tuberculosis. The dosage is 0.5–1 g/d (7.5–15 mg/kg/d for children), which is given intramuscularly or intravenously. It should be used only in combination with other agents to prevent emergence of resistance. See Chapter 47 for additional information regarding the use of streptomycin in mycobacterial infections.

B. Nontuberculous Infections

In plague, tularemia, and sometimes brucellosis, streptomycin, 1 g/d (15 mg/kg/d for children), is given intramuscularly in combination with an oral tetracycline.

Penicillin plus streptomycin is effective for enterococcal endocarditis and 2-week therapy of viridans streptococcal endocarditis. Gentamicin has largely replaced streptomycin for these indications. Streptomycin remains a useful agent for treating enterococcal infections, however, because approximately 15% of enterococcal isolates that are resistant to gentamicin (and therefore resistant to netilmicin, tobramycin, and amikacin) will be susceptible to streptomycin.

Adverse Reactions

Fever, skin rashes, and other allergic manifestations may result from hypersensitivity to streptomycin. This occurs most frequently with prolonged contact with the drug either in patients who receive a prolonged course of treatment (eg, for tuberculosis) or in medical personnel who handle the drug. Desensitization is occasionally successful.

Pain at the injection site is common but usually not severe. The most serious toxic effect with streptomycin is disturbance of vestibular function—vertigo and loss of balance. The frequency and severity of this disturbance are in proportion to the age of the patient, the blood levels of the drug, and the duration of administration. Vestibular dysfunction may follow a few weeks of unusually high blood levels (eg, in individuals with impaired renal function) or months of relatively low blood levels. Vestibular toxicity tends to be irreversible. Streptomycin given during pregnancy can cause deafness in the newborn and, therefore, is relatively contraindicated.

GENTAMICIN

Gentamicin is an aminoglycoside (Figure 45–2) isolated from *Micromonospora purpurea*. It is effective against both gram-positive and gram-negative organisms, and many of its properties resemble those of other aminoglycosides. **Sisomicin** is very similar to the C_{1a} component of gentamicin.

Antimicrobial Activity

Gentamicin sulfate, 2–10 mcg/mL, inhibits in vitro many strains of staphylococci and coliforms and other gram-negative bacteria. It is active alone, but also as a synergistic companion with β-lactam antibiotics, against *Escherichia coli, Proteus, Klebsiella pneumoniae, Enterobacter, Serratia, Stenotrophomonas*, and other gram-negative rods that may be resistant to multiple other antibiotics. Like all aminoglycosides, it has no activity against anaerobes.

Resistance

Streptococci and enterococci are relatively resistant to gentamicin owing to failure of the drug to penetrate into the cell. However, gentamicin in combination with vancomycin or a penicillin produces a potent bactericidal effect, which in part is due to enhanced uptake of drug that occurs with inhibition of cell wall synthesis. Resistance to gentamicin rapidly emerges in staphylococci during monotherapy owing to selection of permeability mutants. Ribosomal resistance is rare. Among gram-negative bacteria, resistance is most commonly due to plasmid-encoded aminoglycoside-modifying enzymes. Gram-negative bacteria that are gentamicin-resistant usually are susceptible to amikacin, which is much more resistant to modifying enzyme activity. The enterococcal enzyme that modifies gentamicin is a bifunctional enzyme that also inactivates amikacin, netilmicin, and tobramycin, but not streptomycin; the latter is modified by a different enzyme. This is why some gentamicin-resistant enterococci are susceptible to streptomycin.

Clinical Uses

A. Intramuscular or Intravenous Administration

Gentamicin is used mainly in severe infections (eg, sepsis and pneumonia) caused by gram-negative bacteria that are likely to be resistant to other drugs, especially *P aeruginosa, Enterobacter* sp, *Serratia marcescens, Proteus* sp, *Acinetobacter* sp, and *Klebsiella* sp. It usually is used in combination with a second agent because an aminoglycoside alone may not be effective for infections outside the urinary tract. For example, gentamicin should not be used as a single agent to treat staphylococcal infections because resistance develops rapidly. Aminoglycosides also should not be used for single-agent therapy of pneumonia because penetration of infected lung tissue is poor and local conditions of low pH and low oxygen tension contribute to poor activity. Gentamicin 5–6 mg/kg/d traditionally is given intravenously in three equal doses, but once-daily administration is just as effective for some organisms and less toxic (see above).

Gentamicin, in combination with a cell wall-active antibiotic, is also indicated in the treatment of endocarditis caused by gram-positive bacteria (streptococci, staphylococci, and enterococci). The synergistic killing achieved by combination therapy may achieve bactericidal activity necessary for cure or allow for the shortening of the duration of therapy. The doses of gentamicin used for synergy against gram-positive bacteria are lower than traditional doses. Typically the drug is administered at a dose of 3 mg/kg/day in three divided doses. Peak levels should be approximately 3 mcg/mL, while trough levels should be < 1 mcg/mL. There are limited data to support administering the 3-mg/kg dose as a single daily injection in the treatment of streptococcal endocarditis.

B. Topical and Ocular Administration

Creams, ointments, and solutions containing 0.1–0.3% gentamicin sulfate have been used for the treatment of infected burns, wounds, or skin lesions and in attempts to prevent intravenous catheter infections. The effectiveness of topical preparations for these indications is unclear. Topical gentamicin is partly inactivated by purulent exudates. Ten mg can be injected subconjunctivally for treatment of ocular infections.

C. Intrathecal Administration

Meningitis caused by gram-negative bacteria has been treated by the intrathecal injection of gentamicin sulfate, 1–10 mg/d. However, neither intrathecal nor intraventricular gentamicin was beneficial in neonates with meningitis, and intraventricular gentamicin was toxic, raising questions about the usefulness of this form of therapy. Moreover, the availability of third-generation cephalosporins for gram-negative meningitis has rendered this therapy obsolete in most cases.

Adverse Reactions

Nephrotoxicity is usually reversible and mild. It occurs in 5–25% of patients receiving gentamicin for longer than 3–5 days. Such toxicity requires, at the very least, adjustment of the dosing regimen and should prompt reconsideration of the need for the drug,

particularly if there is a less toxic alternative agent. Measurement of gentamicin serum levels is essential. Ototoxicity, which tends to be irreversible, manifests itself mainly as vestibular dysfunction. Loss of hearing can also occur. The incidence of ototoxicity is in part genetically determined, having been linked to point mutations in mitochondrial DNA, and occurs in 1–5% for patients receiving gentamicin for more than 5 days. Hypersensitivity reactions to gentamicin are uncommon.

TOBRAMYCIN

This aminoglycoside (Figure 45–2) has an antibacterial spectrum similar to that of gentamicin. Although there is some cross-resistance between gentamicin and tobramycin, it is unpredictable in individual strains. Separate laboratory susceptibility tests are therefore necessary.

The pharmacokinetic properties of tobramycin are virtually identical with those of gentamicin. The daily dose of tobramycin is 5–6 mg/kg intramuscularly or intravenously, traditionally divided into three equal amounts and given every 8 hours. Monitoring blood levels in renal insufficiency is an essential guide to proper dosing.

Tobramycin has almost the same antibacterial spectrum as gentamicin with a few exceptions. Gentamicin is slightly more active against *S marcescens*, whereas tobramycin is slightly more active against *P aeruginosa*; *Enterococcus faecalis* is susceptible to both gentamicin and tobramycin, but *E faecium* is resistant to tobramycin. Gentamicin and tobramycin are otherwise interchangeable clinically.

Like other aminoglycosides, tobramycin is ototoxic and nephrotoxic. Nephrotoxicity of tobramycin may be slightly less than that of gentamicin, but the difference is clinically inconsequential.

Tobramycin is also formulated in solution (300 mg in 5 mL) for inhalation for treatment of *P aeruginosa* lower respiratory tract infections complicating cystic fibrosis. The drug is recommended as a 300-mg dose regardless of the patient's age or weight for administration twice daily in repeated cycles of 28 days on therapy, followed by 28 days off therapy. Serum concentrations 1 hour after inhalation average 1 mcg/mL; consequently, nephrotoxicity and ototoxicity rarely occur. Caution should be used when administering tobramycin to patients with preexisting renal, vestibular, or hearing disorders.

AMIKACIN

Amikacin is a semisynthetic derivative of kanamycin; it is less toxic than the parent molecule (Figure 45–2). It is resistant to many enzymes that inactivate gentamicin and tobramycin, and it therefore can be used against some microorganisms resistant to the latter drugs. Many gram-negative bacteria, including many strains of *Proteus*, *Pseudomonas*, *Enterobacter*, and *Serratia*, are inhibited by 1–20 mcg/mL amikacin in vitro. After injection of 500 mg of amikacin every 12 hours (15 mg/kg/d) intramuscularly, peak levels in serum are 10–30 mcg/mL.

Strains of multidrug-resistant *Mycobacterium tuberculosis*, including streptomycin-resistant strains, are usually susceptible to amikacin. Kanamycin-resistant strains may be cross-resistant to amikacin. The dosage of amikacin for tuberculosis is 7.5–15 mg/kg/d as a once-daily or two to three times weekly injection and always in combination with other drugs to which the isolate is susceptible.

Like all aminoglycosides, amikacin is nephrotoxic and ototoxic (particularly for the auditory portion of the eighth nerve). Serum concentrations should be monitored. Target peak serum concentrations for an every-12-hours dosing regimen are 20–40 mcg/mL, and troughs should be maintained between 4 and 8 mcg/mL.

NETILMICIN

Netilmicin shares many characteristics with gentamicin and tobramycin. However, the addition of an ethyl group to the 1-amino position of the 2-deoxystreptamine ring (ring II, Figure 45–2) sterically protects the netilmicin molecule from enzymatic degradation at the 3-amino (ring II) and 2-hydroxyl (ring III) positions. Consequently, netilmicin may be active against some gentamicin-resistant and tobramycin-resistant bacteria.

The dosage (5–7 mg/kg/d) and the routes of administration are the same as for gentamicin. Netilmicin is largely interchangeable with gentamicin or tobramycin but is no longer available in the United States.

NEOMYCIN & KANAMYCIN

Neomycin and kanamycin are closely related. **Paromomycin** is also a member of this group. All have similar properties.

Antimicrobial Activity & Resistance

Drugs of the neomycin group are active against gram-positive and gram-negative bacteria and some mycobacteria. *P aeruginosa* and streptococci are generally resistant. Mechanisms of antibacterial action and resistance are the same as with other aminoglycosides. The widespread use of these drugs in bowel preparation for elective surgery has resulted in the selection of resistant organisms and some outbreaks of enterocolitis in hospitals. Cross-resistance between kanamycin and neomycin is complete.

Pharmacokinetics

Drugs of the neomycin group are poorly absorbed from the gastrointestinal tract. After oral administration, the intestinal flora is suppressed or modified, and the drug is excreted in the feces. Excretion of any absorbed drug is mainly through glomerular filtration into the urine.

Clinical Uses

Neomycin and kanamycin are now limited to topical and oral use. Neomycin is too toxic for parenteral use. With the advent of more

potent and less toxic aminoglycosides, parenteral administration of kanamycin has also been largely abandoned. Paromomycin has recently been shown to be effective against visceral leishmaniasis when given parenterally (see Chapter 52), and this serious infection may represent an important new use for this drug.

A. Topical Administration

Solutions containing 1–5 mg/mL are used on infected surfaces or injected into joints, the pleural cavity, tissue spaces, or abscess cavities where infection is present. The total amount of drug given in this fashion must be limited to 15 mg/kg/d because at higher doses enough drug may be absorbed to produce systemic toxicity. Whether topical application for active infection adds anything to appropriate systemic therapy is questionable. Ointments, often formulated as a neomycin-polymyxin-bacitracin combination, can be applied to infected skin lesions or in the nares for suppression of staphylococci but they are largely ineffective.

B. Oral Administration

In preparation for elective bowel surgery, 1 g of neomycin is given orally every 6–8 hours for 1–2 days, often combined with 1 g of erythromycin base. This reduces the aerobic bowel flora with little effect on anaerobes. In hepatic encephalopathy, coliform flora can be suppressed by giving 1 g every 6–8 hours together with reduced protein intake, thus reducing ammonia production. Use of neomycin for hepatic encephalopathy has been largely supplanted by lactulose and other medications that are less toxic. Use of paromomycin in the treatment of protozoal infections is discussed in Chapter 52.

Adverse Reactions

All members of the neomycin group have significant nephrotoxicity and ototoxicity. Auditory function is affected more than vestibular function. Deafness has occurred, especially in adults with impaired renal function and prolonged elevation of drug levels.

The sudden absorption of postoperatively instilled kanamycin from the peritoneal cavity (3–5 g) has resulted in curare-like neuromuscular blockade and respiratory arrest. Calcium gluconate and neostigmine can act as antidotes.

Although hypersensitivity is not common, prolonged application of neomycin-containing ointments to skin and eyes has resulted in severe allergic reactions.

■ SPECTINOMYCIN

Spectinomycin is an aminocyclitol antibiotic that is structurally related to aminoglycosides. It lacks amino sugars and glycosidic bonds.
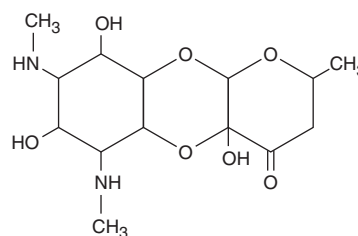
Spectinomycin

Spectinomycin is active in vitro against many gram-positive and gram-negative organisms, but it is used almost solely as an alternative treatment for drug-resistant gonorrhea or gonorrhea in penicillin-allergic patients. The majority of gonococcal isolates are inhibited by 6 mcg/mL of spectinomycin. Strains of gonococci may be resistant to spectinomycin, but there is no cross-resistance with other drugs used in gonorrhea. Spectinomycin is rapidly absorbed after intramuscular injection. A single dose of 40 mg/kg up to a maximum of 2 g is given. There is pain at the injection site and, occasionally, fever and nausea. Nephrotoxicity and anemia have been observed rarely. Spectinomycin is no longer available for use in the United States but may be available elsewhere.

SUMMARY   Aminoglycosides

Subclass	Mechanism of Action	Effects	Clinical Applications	Pharmacokinetics, Toxicities, Interactions
AMINOGLYCOSIDES & SPECTINOMYCIN				
• Gentamicin	Prevents bacterial protein synthesis by binding to the 30S ribosomal subunit	Bactericidal activity against susceptible bacteria • synergistic effects against gram-positive bacteria when combined with β lactams or vancomycin • concentration-dependent killing and a significant post-antibiotic effect	Sepsis caused by aerobic gram-negative bacteria • synergistic activity in endocarditis caused by streptococci, staphylococci, and enterococci	IV • renal clearance (half-life 2.5 h) • conventional dosing 1.3–1.7 mg/kg q8h with goal peak levels 5–8 mcg/mL • trough levels < 2 mcg/mL • once-daily dosing at 5–7 mg/kg as effective and may have less toxicity than conventional dosing • *Toxicity:* Nephrotoxicity (reversible), ototoxicity (irreversible), neuromuscular blockade

- *Tobramycin: Intravenous; more active than gentamicin versus* Pseudomonas; *may also have less nephrotoxicity*
- *Amikacin: Intravenous; resistant to many enzymes that inactivate gentamicin and tobramycin; higher doses and target peaks and troughs than gentamicin and tobramycin*
- *Streptomycin: Intramuscular, widespread resistance limits use to specific indications such as tuberculosis and enterococcal endocarditis*
- *Neomycin: Oral or topical, poor bioavailability; used before bowel surgery to decrease aerobic flora; also used to treat hepatic encephalopathy*
- *Spectinomycin: Intramuscular; sole use is for treatment of antibiotic-resistant gonococcal infections or gonococcal infections in penicillin-allergic patients*

P R E P A R A T I O N S   A V A I L A B L E

Amikacin (generic, Amikin)
Parenteral: 50, 250 mg (in vials) for IM, IV injection

Gentamicin (generic, Garamycin)
Parenteral: 10, 40 mg/mL vials for IM, IV injection

Kanamycin (Kantrex)
Parenteral: 500, 1000 mg for IM, IV injection; 75 mg for pediatric injection

Neomycin (generic, Mycifradin)
Oral: 500 mg tablets

Paromomycin (Humatin)
Oral: 250 mg capsules

Streptomycin (generic)
Parenteral: 400 mg/mL for IM injection

Tobramycin (generic, Nebcin)
Parenteral: 10, 40 mg/mL for IM, IV injection; powder to reconstitute for injection
Solution for inhalation (TOBI): 300 mg in 5 mL sodium chloride solution

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CASE STUDY ANSWER

The patient has normal renal function and thus qualifies for once-daily dosing. Tobramycin could be administered as a single once-daily injection at a dose of 350–490 mg (5–7 mg/kg). A serum level between 1.5 and 6 mcg/mL measured 8 hours after infusion correlates with an appropriate trough level. Alternatively, the same total daily dose could be divided and administered every 8 hours, as a conventional dosing strategy. With conventional dosing, peak and trough concentrations should be monitored with the target peak concentration of 5–10 mcg/mL and the target trough concentration of < 2 mcg/mL.