# 45 β-Lactam Antibiotics

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## DRUG LIST

## INTRODUCTION

A number of antibiotics produced by fungi of the genus *Cephalosporium* have been identified. These antibiotics called cephalosporins contain, in common with the penicillins, a β-lactam ring. In addition to the numerous penicillins and cephalosporins in use, three other classes of β-lactam antibiotics are available for clinical use. These are the carbapenems, the carbacephems, and the monobactams. All β-lactam antibiotics have the same bactericidal mechanism of action. They block a critical step in bacterial cell wall synthesis.

## MECHANISM OF ACTION

The final reaction in bacterial cell wall synthesis is a cross-linking of adjacent peptidoglycan (murein) strands by a transpeptidation reaction. In this reaction, bacterial transpeptidases cleave the terminal D-alanine from a pentapeptide on one peptidoglycan strand and then cross-link it with the pentapeptide of another peptidoglycan strand. The cross-linked peptidoglycan (murein) strands give structural integrity to cell walls and permit bacteria to survive environments that do not match the organism's internal osmotic pressure.

The β-lactam antibiotics structurally resemble the terminal D-alanyl-D-alanine (D-Ala-D-Ala) in the pentapeptides on peptidoglycan (murein) (Fig. 45.1). Bacterial transpeptidases covalently bind the β-lactam antibiotics at the enzyme active site, and the resultant acyl enzyme molecule is stable and inactive. The intact β-lactam ring is required for antibiotic action. The β-lactam ring modifies the active serine site on transpeptidases and blocks further enzyme function.

In addition to transpeptidases, other penicillin-binding proteins (PBPs) function as transglycosylases and carboxypeptidases. All of the PBPs are involved with assembly, maintenance, or regulation of peptidoglycan cell wall synthesis. When β-lactam antibiotics inactivate PBPs, the consequence to the bacterium is a structurally weakened cell wall, aberrant morphological form, cell lysis, and death.

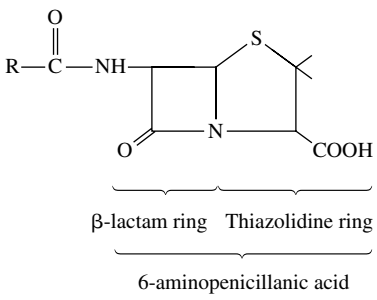


**FIGURE 45.1**
The structure of penicillins.

## MECHANISMS OF RESISTANCE

A number of microorganisms have evolved mechanisms to overcome the inhibitory actions of the β-lactam antibiotics. There are four major mechanisms of resistance: inactivation of the β-lactam ring, alteration of PBPs, reduction of antibiotic access to PBPs, and elaboration of antibiotic efflux mechanisms. Bacterial resistance may arise from one or more than one of these mechanisms.

The most important mechanism of resistance is hydrolysis of the β-lactam ring by β-lactamases (penicillinases and cephalosporinases). Many bacteria (*Staphylococcus aureus, Moraxella* [*Branhamella*] *catarrhalis, Neisseria gonorrhoeae,* Enterobacteriaceae, *Haemophilus influenzae,* and *Bacteroides* spp.) possess β-lactamases that hydrolyze penicillins and cephalosporins. The β-lactamases evolved from PBPs and acquired the capacity to bind β-lactam antibiotics, form an acyl enzyme molecule, then deacylate and hydrolyze the β-lactam ring. Some bacteria have chromosomal (inducible) genes for β-lactamases. Other bacteria acquire β-lactamase genes via plasmids or transposons. Transfer of β-lactamase genes between bacterial species has contributed to the proliferation of resistant organisms resulting in the appearance of clinically important adverse consequences.

Efforts to overcome the actions of the β-lactamases have led to the development of such β-lactamase inhibitors as clavulanic acid, sulbactam, and tazobactam. They are called suicide inhibitors because they permanently bind when they inactivate β-lactamases. Among the β-lactamase inhibitors, only clavulanic acid is available for oral use. Chemical inhibition of β-lactamases, however, is not a permanent solution to antibiotic resistance, since some β-lactamases are resistant to clavulanic acid, tazobactam, or sulbactam. Enzymes resistant to clavulanic acid include the cephalosporinases produced by *Citrobacter* spp., *Enterobacter* spp., and *Pseudomonas aeruginosa.*

An additional mechanism of antibiotic resistance involves an alteration of PBPs. Resistant bacteria, usually gram-positive organisms, produce PBPs with low affinity for β-lactam antibiotics. The development of mutations of bacterial PBPs is involved in the mechanism for β-lactam resistance in *Streptococcus pneumoniae, Enterococcus faecium,* and methicillin-resistant *S. aureus* (MRSA).

Some gram-negative bacteria employ a third mechanism of resistance, namely, one that reduces antibiotic access to PBPs. Gram-positive organisms have an exposed peptidoglycan layer easily accessible to β-lactam antibiotics (Fig. 45.2). In contrast, gram-negative organisms have an outer membrane surrounding the peptidoglycan layer. The gram-negative outer membrane hinders ingress of large molecules and helps bacteria resist the actions of antibiotics. In susceptible gram-negative

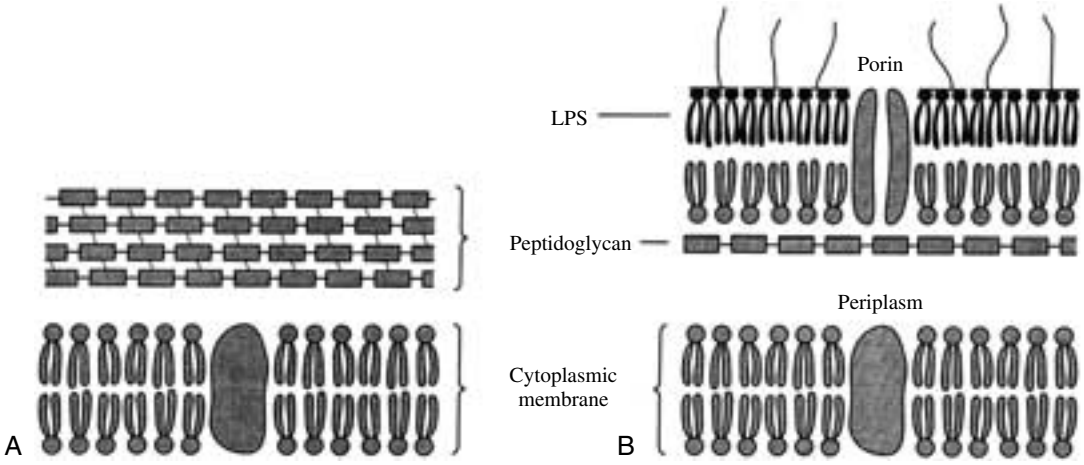


**FIGURE 45.2**
Differences between gram-positive and gram-negative bacteria that affect antibiotic access. **A.** The cell wall structure of a gram-positive organism. The exposed porous peptidoglycan (murein) layer allows easy antibiotic access. **B.** The cell wall structure of a gram-negative organism. The outer membrane contains lipopolysaccharides (LPS) and porins with narrow, restrictive channels that function as barriers to antibiotic permeability. (Modified with permission from Nikaido H. Prevention of drug access to bacterial targets: Permeability barriers and active efflux. Science 1994;264:382–388.)

bacteria, protein channels (porins) allow β-lactam antibiotics to traverse the outer membrane and interact with PBPs in the periplasmic space. In resistant bacteria like *P. aeruginosa,* porin mutants impede the β-lactam transfer across the outer membrane.

Finally, some gram-negative organisms demonstrate a fourth mechanism of resistance. For example, strains of *P. aeruginosa* produce xenobiotic efflux pumps to eject antibiotics. Drug efflux mechanisms are associated with multiple drug resistance, including resistance to β-lactam antibiotics.

Widespread use of β-lactam antibiotics exerts selective pressure on bacteria and permits the proliferation of resistant organisms. A comparison of current antibiograms with those from previous decades shows an alarming increase in bacterial resistance to β-lactam antibiotics.

## PENICILLINS

The penicillins are a large group of bactericidal compounds. They can be subdivided and classified by their chemical structure and spectrum of activity. The structure common to all penicillins is a β-lactam ring fused with a thiazolidine nucleus (Fig. 45.1). The antimicrobial activity of penicillin resides in the β-lactam ring. Splitting of the β-lactam ring by either acid hydrolysis or β-lactamases results in the formation of penicilloic acid, a product without antibiotic activity. Addition of various side chains (R) to the basic penicillin molecule creates classes of compounds with the same mechanism of action as penicillin but with different chemical and biological properties. For example, some analogues are resistant to hydrolysis by acid or β-lactamase; some have an extended the spectrum of antibacterial activity; and others show improved absorption from the intestinal tract.

Penicillins may be classified into four groups: natural penicillins (G and V), antistaphylococcal (penicillinase-resistant) penicillins, aminopenicillins, and antipseudomonal penicillins. Natural penicillins have therapeutic effects limited to streptococci and a few gram-negative organisms. The antistaphylococcal (penicillinase-resistant) penicillins treat infections caused by streptococci and staphylococci but do not affect MRSA. The aminopenicillins are effective against streptococci, enterococci, and some gram-negative organisms but have variable activity against staphylococci and are ineffective against *P. aeruginosa.* The antipseudomonal penicillins retain activity against streptococci and possess additional effects against gram-negative organisms, including various Enterobacteriaceae and *Pseudomonas.*

### Natural Penicillins

Penicillin G (benzylpenicillin) is an acid-labile compound having variable bioavailability after oral administration. Consequently, penicillin G is most appropriate for intramuscular or intravenous therapy. The drug distributes to most tissues and serosa-lined cavities, although low concentrations appear in breast milk and

cerebrospinal fluid. When the meninges are inflamed, cerebrospinal fluid concentrations of penicillin G approximate 5% of the serum concentration. In inflamed joints, concentrations of the drug approach serum levels.

Penicillin G is excreted by the kidneys, with 90% of renal elimination occurring via tubular secretion and 10% by glomerular filtration. Probenecid blocks tubular secretion and has been used to increase the serum concentration and prolong the half-life of penicillin G and other penicillins. Additional pharmacokinetic information can be found in Table 45.1.

The clinical uses of penicillin G include endocarditis caused by *S. viridans* (or *Streptococcus bovis*), pharyngitis (group A β-hemolytic streptococci), cat bite cellulitis (*Pasteurella multocida*), and syphilis (*Treponema pallidum*).

Depot intramuscular formulations of penicillin G, including procaine penicillin and benzathine penicillin, have decreased solubility, delayed absorption, and a prolonged half-life. Drug concentrations are detectable 24 hours after injection of procaine penicillin, and low levels of benzathine penicillin (0.003 units/mL) are detectable 4 weeks after injection.

When prescribing one of the penicillin G depot formulations, practitioners must individualize treatment to clinical and microbial conditions. Some long-acting formulations may not maintain adequate plasma and tissue concentrations to treat specific organisms or infections. For acute streptococcal meningitis, the goal is rapid achievement of high antibiotic concentrations in the cerebrospinal fluid. Consequently, depot formulations are inappropriate for meningitis. Intravenous penicillin G is among the antibiotics of first choice for therapy of meningitis caused by susceptible *S. pneumoniae*. In contrast, a depot formulation of benzathine penicillin G suffices for rheumatic fever prophylaxis.

Penicillin V is an orally administered phenoxymethyl congener of penicillin G having an antibacterial spectrum of activity that is similar to that of penicillin G. Penicillin V is used to treat streptococcal infections when oral therapy is appropriate and desirable.

## Antistaphylococcal (penicillinase-resistant) Penicillins

Nafcillin, oxacillin, cloxacillin, and dicloxacillin are more resistant to bacterial β-lactamases than is penicillin G. Consequently, these antibiotics are effective against streptococci and most community-acquired penicillinase-producing staphylococci. Methicillin, which is no longer marketed in the United States, is another penicillinase-resistant antibiotic similar to nafcillin and oxacillin. For historical reasons, staphylococci resistant to oxacillin or nafcillin are labeled methicillin resistant. Many hospitals are reservoirs for MRSA and methicillin-resistant *Staphylococcus epidermidis* (MRSE). These nosocomial pathogens are resistant in vitro to all β-lactam antibiotics.

**TABLE 45.1 Pharmacokinetic Parameters of Selected Penicillins**

| Drug | Route | Half-life (hr) | Renal Excretion (%) | Dose Adjustment in Renal Failure |
|---|---|---|---|---|
| **Natural penicillins** | | | | |
| Penicillin G | IM, IV | 0.5 | 79–85 | Yes |
| Penicillin V | Oral | 0.5 | 20–40 | Yes |
| **Antistaphylococcal penicillins (penicillinase resistant)** | | | | |
| Nafcillin | IM, IV | 0.8–1.2 | 31–38 | No |
| Oxacillin | IM, IV | 0.4–0.7 | 39–66 | No |
| Cloxacillin | Oral | 0.5–0.6 | 40–70 | No |
| Dicloxacillin | Oral | 0.6–0.8 | 35–90 | No |
| **Aminopenicillins** | | | | |
| Ampicillin | Oral, IM, IV | 1.1–1.5 | 40–92 | Yes |
| Amoxicillin | Oral | 1.4–2.0 | 86 | Yes |
| **Antipseudomonal penicillins** | | | | |
| Carbenicillin | Oral | 0.8–1.2 | 85 | Yes |
| Mezlocillin | IM, IV | 0.9–1.7 | 61–69 | Yes |
| Piperacillin | IM, IV | 0.8–1.1 | 74–89 | Yes |
| Ticarcillin | IM, IV | 1.0–1.4 | 95 | Yes |

IM, intramuscular; IV, intravenous.

For parenteral therapy, nafcillin and oxacillin offer comparable efficacy and antimicrobial spectra of activity. Although both drugs undergo hepatic metabolism, only nafcillin requires dose adjustment in patients with combined hepatic and renal insufficiency. Other pharmacokinetic data for nafcillin and oxacillin appear in Table 45.1. Indications for nafcillin or oxacillin include severe staphylococcal infections like cellulitis, empyema, endocarditis, osteomyelitis, pneumonia, septic arthritis, and toxic shock syndrome.

For oral therapy, cloxacillin and dicloxacillin are comparable alternatives. Both undergo hepatic metabolism, and neither drug requires dose adjustment in patients with hepatic insufficiency. Additional pharmacokinetic data are in Table 45.1. Indications for cloxacillin or dicloxacillin include clinically mild staphylococcal infections like impetigo.

## Aminopenicillins

The pharmacokinetics of ampicillin and amoxicillin are similar (Table 45.1). Both have good oral bioavailability; ampicillin is also bioavailable after intramuscular injection. Concomitant ingestion of food decreases the bioavailability of ampicillin but not amoxicillin. Consequently, oral doses of ampicillin should be given on an empty stomach. Ampicillin achieves therapeutic concentrations in the cerebrospinal fluid only during inflammation. Therefore, ampicillin is effective treatment for meningitis caused by *Listeria monocytogenes.* Amoxicillin does not reach adequate concentrations in the central nervous system and is not appropriate for meningitis therapy. Other indications for ampicillin include serious infections like enterococcal endocarditis and pneumonia caused by β-lactamase-negative *H. influenzae.* Amoxicillin oral therapy is appropriate for clinically acute nonserious bacterial infections like otitis media and sinusitis. Amoxicillin also has use in multidrug regimens for the eradication of *Helicobacter pylori* in duodenal and gastric ulcers.

## Antipseudomonal Penicillins

Mezlocillin, piperacillin, and ticarcillin are parenteral antibiotics formulated as sodium salts, so prescribers must consider the sodium content of these antibiotics when administering them to patients with congestive heart failure. During their distribution phase, antipseudomonal penicillins achieve only low concentrations in the cerebrospinal fluid. Consequently, antipseudomonal penicillins are not among the drugs of first choice for meningitis therapy.

The antipseudomonal penicillins undergo renal elimination (Table 45.1). Piperacillin and ticarcillin have minimal hepatic metabolism. In contrast, mezlocillin has significant hepatic metabolism and requires dose adjustment in patients with hepatic insufficiency.

The antipseudomonal penicillins have comparable spectra of activity against many gram-positive and gram-negative pathogens, including most anaerobes. Mezlocillin, piperacillin, and ticarcillin have similar clinical outcomes in patients with known or suspected *P. aeruginosa* infections. Antipseudomonal penicillins are used to treat pneumonias associated with cystic fibrosis or mechanical ventilation.

Carbenicillin indanyl sodium is an antipseudomonal penicillin formulated for oral administration. The drug achieves negligible carbenicillin concentrations in the urine of patients with renal failure. Consequently, carbenicillin is not appropriate for patients with renal failure. In patients with normal renal function, however, carbenicillin indanyl sodium is used to treat urinary tract infections caused by *P. aeruginosa, Proteus* spp., and *Escherichia coli.*

## β-Lactamase Inhibitor Combinations

Several formulations combine a β-lactam antibiotic with a β-lactamase inhibitor (ampicillin-sulbactam [*Unasyn*], ticarcillin-clavulanic acid [*Timentin*], piperacillin-tazobactam [*Zosyn*], and amoxicillin–clavulanic acid [*Augmentin*]). All of the β-lactamase inhibitor combinations except amoxicillin-clavulanic acid are parenteral formulations. Amoxicillin–clavulanic acid is the only combination drug with oral bioavailability. Elimination of the combination drugs occurs primarily by renal excretion. Therefore, all of the β-lactamase inhibitor combinations require dose adjustments in patients with renal insufficiency. The addition of the β-lactamase inhibitor significantly broadens the spectrum of antibacterial activity against β-lactamase-producing organisms. Consequently, these drugs have clinical use in treating infections with known or suspected mixed bacterial flora, such as biliary infections, diabetic foot ulcers, endomyometritis, and peritonitis.

## β-Lactam Antibiotics in Pregnancy

All of the penicillin antibiotics are classified by the U. S. Food and Drug Administration (FDA) in pregnancy category B, that is, as drugs having either no fetal risk in animal studies but human trials are inadequate, or animal studies show adverse fetal effects but well-controlled human trials reveal no fetal damage. Obstetricians frequently prescribe ampicillin, penicillin G, and penicillin V because they are effective against the infections most frequently encountered in caring for pregnant women (e.g., upper respiratory and lower urinary tract infections).

## Adverse Effects

While being associated with a low percentage of adverse reactions, the β-lactams are the most frequent

source of troublesome allergic reactions among the antibiotics. The overall frequency of adverse effects associated with penicillin use is less than 10%, including allergic and other reactions. Anaphylaxis is a serious, rare allergic response with an occurrence rate between 0.004% and 0.015% of penicillin courses. Allergic reactions to penicillin are immediate immunoglobulin (Ig) E–mediated type I immune responses. Symptoms and signs of IgE-mediated reactions may include urticaria, pruritus, bronchospasm, angioedema, laryngeal edema, and hypotension. Late onset immune-mediated reactions to β-lactam antibiotics may manifest as eosinophilia, hemolytic anemia, interstitial nephritis, or serum sickness. In contrast to the rare allergic reactions, nonallergic β-lactam rashes are common. For example, ampicillin is associated with nonurticarial rashes in 5 to 10% of recipients.

The incidence of nonallergic ampicillin eruptions is 40 to 100% in patients with concomitant Epstein-Barr virus (mononucleosis), cytomegalovirus, acute lymphocytic leukemia, lymphoma, or reticulosarcoma. Nonallergic penicillin-associated rashes are characteristically morbilliform (symmetrical, erythematous, confluent, maculopapular) eruptions on the extremities. The onset of typical nonallergic eruptions is more than 72 hours after β-lactam exposure. The mechanism for the nonurticarial ampicillin rash is not known and is not related to IgE or type I hypersensitivity. Penicillin skin tests are not useful in the evaluation of nonurticarial ampicillin rashes. Patients with a history of nonurticarial ampicillin rashes may receive other β-lactam antibiotics without greater risk of subsequent serious allergic reactions.

Allergic cross-reactivity between β-lactam antibiotics is significant. The frequency of allergic reactions to another β-lactam antibiotic is 5.6% among patients with a history of IgE-mediated hypersensitivity to one β-lactam antibiotic plus positive results from a penicillin skin test. In general, patients with a convincing history of type I reaction to one β-lactam antibiotic should avoid all other β-lactam antibiotics except aztreonam. However, most patients give unreliable histories of penicillin allergy because of confusion with nonallergic penicillin rashes. Among patients who report penicillin allergies, 80 to 90% have negative results from penicillin skin tests, and 98% tolerate subsequent β-lactam antibiotic treatments. A careful history may discriminate between nonallergic reactions and true penicillin allergy and permit safe β-lactam therapy.

## CEPHALOSPORINS

The cephalosporins are semisynthetic antibiotics derived from products of various microorganisms, including *Cephalosporium* and *Streptomyces*. All cephalosporins have a 7-aminocephalosporanic acid composed of a dihydrothiazine ring fused to a β-lactam ring (Fig. 45.3). As with the penicillins, the cephalosporin β-lactam ring is the chemical group associated with antibacterial activity. The different pharmacological, pharmacokinetic, and antibacterial properties of individual cephalosporins result from substitution of various groups on the basic molecule. Cephalosporins also vary in acid stability and β-lactamase susceptibility. Table 45.2 shows the large number of available cephalosporins.

The β-lactamases (penicillinases) inactivate some cephalosporins but are much less efficient than are the cephalosporinases (β-lactamases specific for the cephalosporins). Resistance to cephalosporins also results from modification of microbial PBPs.

### Antibacterial Spectrum

The cephalosporins are classified into generations (Table 45.2) according to their antibacterial spectrum and stability to β-lactamases. The first-generation cephalosporins have in vitro antimicrobial activity against streptococci, methicillin-sensitive *S. aureus,* and a few gram-negative bacilli. The second-generation cephalosporins have greater stability against β-lactamase inactivation and possess a broader spectrum of activity to include gram-positive cocci, gram-negative organisms, and anaerobes. Among the second-generation cephalosporins, the cephamycins (cefoxitin [Mefoxin], cefotetan [Cefotan], and cefmetazole [Zefazone]) have the most activity against *Bacteroides fragilis.* The extended-spectrum, or third-generation, cephalosporins possess a high degree of in vitro potency and β-lactamase stability and a broader spectrum of action against many common gram-negative bacteria and anaerobes while retaining good activity against streptococci. Third-generation cephalosporins are less active against staphylococci than the earlier generations. The agents with the greatest activity against *P. aeruginosa* are cefepime, cefoperazone, and ceftazidime. Cefepime has been called a fourth-generation cephalosporin because of its great in vitro activity against several gram-positive and gram-negative organisms. The distinction between third and fourth

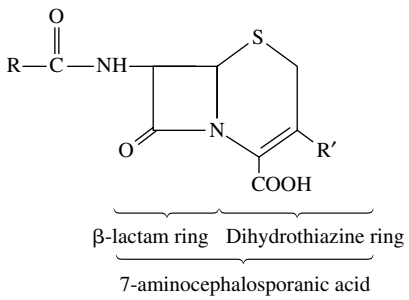


**FIGURE 45.3**
The structure of cephalosporins.

**TABLE 45.2 Pharmacokinetic Parameters of Selected Cephalosporins**

| Drug | Route | Half-life (hr) | Renal Excretion (%) | Dose Adjustment in Renal Failure |
|---|---|---|---|---|
| **First generation** | | | | |
| Cefadroxil | Oral | 1.2–2.5 | 70–90 | Yes |
| Cefazolin | IM, IV | 1.5–2.5 | 70–95 | Yes |
| Cephalexin | Oral | 1.0 | 95 | Yes |
| Cephapirin | IM, IV | 0.6 | 50–70 | Yes |
| Cephradine | Oral | 0.7 | 75–100 | Yes |
| **Second generation** | | | | |
| Cefaclor | Oral | 0.6–0.9 | 60–85 | Yes |
| Cefamandole | IM, IV | 0.5–1.2 | 100 | Yes |
| Cefmetazole | IV | 1.2–1.5 | 85 | Yes |
| Cefonicid | IM, IV | 3.5–4.5 | 95–99 | Yes |
| Cefotetan | IM, IV | 2.8–4.6 | 60–91 | Yes |
| Cefoxitin | IM, IV | 0.7–1.0 | 85 | Yes |
| Cefprozil | Oral | 1.2–1.4 | 64 | Yes |
| Cefuroxime | IM, IV | 1.1–1.3 | 95 | Yes |
| Cefuroxime axetil | Oral | 1.1–1.3 | 52 | Yes |
| Loracarbef[a] | Oral | 1.0 | 87–97 | Yes |
| **Third generation** | | | | |
| Cefdinir | Oral | 1.7 | 18 | Yes |
| Cefepime | IM, IV | 2.0 | 70–99 | Yes |
| Cefixime | Oral | 2.3–3.7 | 50 | Yes |
| Cefoperazone | IM, IV | 2.0 | 20–30 | No |
| Cefotaxime | IM, IV | 1.0 | 40–60 | Yes |
| Cefpodoxime proxetil | Oral | 1.9–3.7 | 40 | Yes |
| Ceftazidime | IM, IV | 1.9 | 80–90 | Yes |
| Ceftibuten | Oral | 1.5–2.8 | 57–75 | Yes |
| Ceftizoxime | IM, IV | 1.4–1.8 | 57–100 | Yes |
| Ceftriaxone | IM, IV | 5.8–8.7 | 33–67 | No |
| Carbapenems | | | | |
| Imipenem-cilastatin | IM, IV | 1.0 | 50–70 | Yes |
| Meropenem | IV | 1.0 | 79 | Yes |
| Monobactam | | | | |
| Aztreonam | IM, IV | 2.0 | 75 | Yes |

[a]Loracarbef is in the carbacephem class. IM, intramuscular; IV, intravenous.

generation may be irrelevant, however, since clinical outcomes are similar in human trials comparing cefepime and other third-generation cephalosporins. None of the cephalosporins adequately treats infections caused by *Enterococcus faecalis, E. faecium,* MRSA, or *L. monocytogenes.*

## Absorption, Distribution, Metabolism, and Excretion

Most parenteral cephalosporins have good bioavailability after intramuscular injection, and a few members of each cephalosporin generation have good oral bioavailability (Table 45.2). The ester prodrugs cefuroxime axetil (*Ceftin*) and cefpodoxime proxetil (*Vantin*) are oral formulations in which the ester is hydrolyzed during drug passage through the intestinal mucosa; the free cephalosporin enters the systemic circulation. Concomitant ingestion of food reduces the bioavailability of some cephalosporins, e.g., cefaclor (*Ceclor*), and therefore, these compounds should be administered on an empty stomach.

The cephalosporins distribute in satisfactory concentrations to most tissues except the central nervous system. Only cefepime, cefuroxime (*Zinacef*), cefotaxime (*Claforan*), ceftriaxone (*Rocephin*), and ceftazidime (*Fortaz*) achieve therapeutic concentrations in cerebrospinal fluid. Cefotaxime and ceftriaxone are antibiotics of first choice for the empirical treatment of brain abscess and meningitis.

There is considerable variation in the protein binding among the cephalosporins. Drugs like ceftriaxone that have extensive protein binding (85–95%) may displace bilirubin from serum albumin. Consequently, ceftriaxone may increase the risk of kernicterus in jaundiced neonates.

Urinary excretion is the major elimination path for most cephalosporins. When prescribing cephalosporins to patients with renal failure, practitioners must consider dose reduction or dose interval extension (Table 45.2). Renal tubular secretion contributes to the elimination of some cephalosporins, and an increase in cephalosporin plasma concentrations may occur when probenecid blocks renal tubular secretion of cephalosporins. Biliary elimination is important for some cephalosporins. Cefmetazole, cefoperazone (*Cefobid*), cefoxitin, and ceftriaxone achieve biliary concentrations greater than those in plasma. After parenteral administration of cefoperazone, 70% of the dose appears in the bile within 24 hours. Practitioners should decrease the dose of cefoperazone when prescribing for patients with hepatic failure or biliary obstruction. Metabolism is not a major elimination path for most cephalosporins. Cefotaxime is one of the few cephalosporins having an active metabolite, desacetyl cefotaxime.

### Clinical Uses

The first-generation cephalosporins have activity against most of the bacterial pathogens that colonize skin and infect wounds. Consequently, first-generation cephalosporins are useful in antimicrobial prophylaxis before surgery. Second-generation cephalosporins are used to treat infections caused by susceptible organisms. For example, cefoxitin and cefotetan have good anaerobic activity, and they have utility in the treatment and prophylaxis of lower abdominal and gynecological infection. A broad spectrum of antibacterial activity makes third-generation cephalosporins important in the treatment of a wide range of infections, including Lyme disease, pneumonia, peritonitis, and sepsis syndrome.

### Adverse Effects

The cephalosporins have good safety profiles. The overall incidence of adverse events attributed to cephalosporins is between 1 and 10%. The most common adverse drug reactions are rashes (1–5%), eosinophilia (3–10%), gastrointestinal symptoms (3%), hematological abnormalities (1–2%), phlebitis (2%), and fever (<1%). Anaphylactic reactions to cephalosporins are rare (<0.02%).

Because of cross-reactions between cephalosporins and penicillins, caution should be used when prescribing cephalosporins to patients with penicillin allergy. If a patient had anaphylaxis, angioedema, or urticaria following penicillin use, cephalosporins should be avoided. Among patients with morbilliform rashes (resembling measles) after penicillin, the majority (95%) will tolerate cephalosporins without adverse effects and with no increased risk of anaphylaxis. When evaluating patients with histories of allergic penicillin reactions, practitioners may order penicillin skin tests to screen potential cephalosporin recipients. The frequency of allergic reactions to cephalosporins is 1.7% in patients with histories of type I penicillin reactions and negative penicillin skin tests. Most patients with negative penicillin skin tests may receive cephalosporins safely.

The cephalosporins are valuable because of their broad spectrum of antimicrobial activity. However, their bactericidal action alters gut flora and selects for overgrowth of resistant organisms. Cephalosporins have been associated with superinfections with *Clostridium difficile,* enterococci, MRSA, coagulase-negative staphylococci, *P. aeruginosa,* and *Candida albicans.* Overgrowth by toxigenic *C. difficile* occasionally causes pseudomembranous colitis in patients treated with cephalosporins. Some third-generation cephalosporins induce production of extended-spectrum β-lactamases (ESBLs) in *P. aeruginosa.* The ESBLs can transfer to various Enterobacteriaceae and produce organisms resistant to almost all β-lactam antibiotics.

Bleeding is an uncommon but serious side effect of some cephalosporins. The *N*-methylthiotetrazole (MTT) side chain on the R′substituent inhibits production of active vitamin K. Cephalosporins with the MTT side chain (cefamandole, cefmetazole, cefoperazone, cefotetan) are associated with hypoprothrombinemia, coagulation abnormalities, and bleeding. In addition, the MTT cephalosporins increase the effect of oral anticoagulants. Bleeding or coagulation abnormalities caused by MTT cephalosporins can be treated or prevented with supplemental vitamin K. Additional bleeding problems may result from antiplatelet effects. The MTT side chain confers a structure and activity similar to that of disulfiram, so patients taking MTT cephalosporins who also ingest alcohol may develop symptoms similar to the disulfiram reaction.

Children and adults receiving high doses of ceftriaxone may develop gallbladder sludge (pseudolithiasis). While most patients with sludge have no symptoms, occasionally the sludge identified by abdominal ultrasonography has led to laparotomy. Biliary sludge usually disappears after discontinuation of ceftriaxone.

## CARBAPENEMS AND CARBACEPHEMS

The newest classes of β-lactam antibiotics are the carbapenems and carbacephems. Their mechanism of action is the same as those of the other β-lactam antibiotics.

### Imipenem

The first carbapenem, imipenem–cilastatin (Primaxin), is a chemically stable analogue of thienamycin produced by *Streptomyces cattleya.* The antibacterial spectrum of imipenem is among the broadest of all of the β-lactam antibiotics. Imipenem is active against most gram-positive, gram-negative, and anaerobic bacteria. When compared with the in vitro activities of third-generation cephalosporins, imipenem is more potent against *E. faecalis, B. fragilis,* and *P. aeruginosa.* Imipenem's stability against β-lactamases is attributable to the trans position of the 6-hydroxyethyl side chain on the β-lactam ring. Organisms resistant to imipenem include *E. faecium, Stenotrophomonas maltophilia,* and MRSA.

Imipenem–cilastatin is only available for intramuscular or intravenous administration because oral bioavailability is poor. The enzyme, dehydropeptidase I, present in renal tubules, converts imipenem to an inactive metabolite. To decrease metabolic clearance, imipenem is combined with cilastatin, an inhibitor of dehydropeptidase I. Additional pharmacokinetic information appears in Table 45.2.

Imipenem–cilastatin is one of the drugs of first choice for the empirical therapy of many polymicrobial pulmonary, intraabdominal, and soft tissue infections. The notable adverse effect of imipenem–cilastatin is seizures affecting 1% of patients. Risk factors for seizures are old age, head trauma, previous seizure disorder, cerebrovascular accident, and renal failure. Among patients with a history of penicillin allergy, 10% are cross-sensitive to imipenem–cilastatin.

### Meropenem

Meropenem (*Merrem*) is another carbapenem antibiotic with a broad spectrum of activity comparable to that of imipenem. A methyl group attached at the one-position on the five-member ring confers stability to dehydropeptidase I. Consequently, meropenem does not require administration with cilastatin. When compared in human trials, imipenem–cilastatin and meropenem achieve similar clinical outcomes in patients with serious intraabdominal and soft tissue infections. Both imipenem–cilastatin and meropenem are used to treat infections caused by highly resistant *Klebsiella pneumoniae* producing ESBLs. The major clinically relevant distinction between imipenem–cilastatin and meropenem is the lower likelihood of seizures associated with meropenem.

### Loracarbef

Loracarbef (*Lorabid*) is a synthetic β-lactam antibiotic of the carbacephem class. The chemical structure of loracarbef is similar to that of cefaclor. Selected pharmacokinetic information appears in Table 45.2. Loracarbef's spectrum of antibacterial activity resembles those of the second-generation cephalosporins. Comparative clinical trials reveal similar outcomes in patients treated with cefaclor, cefprozil, and loracarbef.

## MONOBACTAMS

Another interesting group of compounds produced by several bacterial genera are the monocyclic β-lactams (monobactams). The natural monobactams have little antimicrobial activity. A synthetic derivative, aztreonam (*Azactam*), has excellent activity against gram-negative organisms, including *P. aeruginosa.* Aztreonam has low affinity for penicillin-binding proteins in streptococci, staphylococci, and anaerobes and therefore has no significant activity against gram-positive bacteria or anaerobes. Specific activity against gram-negative organisms relates to the aminothiazolyl oxime moiety on the acyl side chain. Addition of two methyl groups and a carboxylic acid group on the oxime side chain enhances activity against *P. aeruginosa.* Aztreonam is stable to most β-lactamases (chromosomal and plasmid).

The pharmacokinetic properties of aztreonam are similar to those of the parenteral cephalosporins (Table 45.2). Aztreonam is not bioavailable after oral administration. During its distribution phase, the drug can achieve therapeutic concentrations in cerebrospinal fluid in the presence of inflamed meninges. Consequently, aztreonam is an alternative antibiotic to the cephalosporins for the therapy of meningitis caused by gram-negative bacilli.

Aztreonam may be used as a substitute for an aminoglycoside in the treatment of infections caused by susceptible gram-negative organisms. Most of the adverse effects of aztreonam are local reactions at the site of injection. Interestingly, aztreonam rarely causes allergic reactions in patients with a history of type I hypersensitivity to other β-lactam antibiotics.

## Study Questions

**1.** A 32-year-old man with quadriplegia and neurogenic bladder was admitted to the hospital from a long-term care facility. The patient had vomiting, fever, and cloudy urine. A year ago, the patient developed urticaria, wheezing, and hypotension within an hour after his first dose of nafcillin. Subsequently his penicillin skin test was positive. During the current admission, the physician examiner noted fever, quadriplegia, and chronic indwelling bladder catheter. Laboratory tests revealed leukocytosis in blood and urine. Urine stain showed gram-negative rods, and urine culture grew *P. aeruginosa.* Which of the following drugs would be most appropriate for this patient?
(A) Ampicillin–sulbactam
(B) Aztreonam
(C) Cefazolin
(D) Imipenem–cilastatin
(E) Piperacillin–tazobactam

**2.** A 22-year-old woman had her first prenatal visit. Her physical examination was normal for a woman at 12 weeks' gestation. Both the nontreponemal (Venereal Disease Research Laboratory) and fluorescent treponemal antibody tests were positive. She denied previous treatment for syphilis. She could not recall signs or symptoms of primary or secondary syphilis in the past year. She had no previous syphilis serology tests for purposes of comparison. Which of the following would be the best treatment for the patient?
(A) Benzathine penicillin G
(B) Doxycycline
(C) Spectinomycin
(D) Streptomycin
(E) Tetracycline

**3.** A 26-year-old woman, a kindergarten teacher, had pharyngitis last year treated with ampicillin for 3 days. She stopped the ampicillin when she learned her throat culture was negative. Three days after she stopped the ampicillin, she developed a rash. Her physician noted symmetrical erythematous confluent macular–papular eruptions on her extremities with no urticaria. The physician diagnosed non–IgE-mediated ampicillin eruption. Now the patient returns with new fever and sore throat. She has no cough or rash. Her physical examination is normal except for fever, tender anterior cervical lymphadenopathy, and tonsillar exudate. Her rapid streptococcal test of a pharyngeal specimen is positive. Which of the following would be the most appropriate treatment for this patient?
(A) Amikacin
(B) Lomefloxacin
(C) Metronidazole
(D) Netilmicin
(E) Penicillin V

**4.** A 24-year-old man came to the public health clinic because of a urethral discharge. He had had unprotected intercourse with multiple partners. Physical examination revealed a purulent urethral discharge with no penile ulcers or vesicles. There was no inguinal adenopathy. Gram stain of the discharge revealed gram-negative diplococci inside leukocytes. The antibiotic used to treat the patient's infection has which of the following mechanisms of action?
(A) Inhibits cell membrane integrity by binding to ergosterols to create pores
(B) Inhibits dihydrofolate reductase, thereby blocking formation of tetrahydrofolate required for purine synthesis
(C) Inhibits KasA, a β-ketoacyl carrier protein synthetase, thereby blocking mycolic acid synthesis
(D) Inhibits RNA synthesis by binding to the β-subunit of DNA-dependent RNA polymerase
(E) Inhibits transpeptidase, thereby blocking cross-linking of peptides in cell wall murein (peptidoglycan)

**5.** Parents brought their 3-year-old boy to the outpatient clinic because of a facial rash. Today the patient was one of several children sent home from day care because of similar rashes. Physical examination revealed a normal, healthy boy with discrete erythematous papular eruptions on his cheeks. There were no vesicles or bullae. The rash was covered with a honey crust, suggesting impetigo. Which of the following treatments would be most appropriate?
(A) Dapsone
(B) Dicloxacillin
(C) Doxycycline
(D) Ketoconazole
(E) Penciclovir

### ANSWERS

**1. B.** The patient has complicated urinary tract infection and nonsevere sepsis syndrome caused by *P. aeruginosa.* Effective antibiotics for *Pseudomonas* spp. include mezlocillin, piperacillin, piperacillin–tazobactam, ticarcillin, and ticarcillin–clavulanate. The carbapenems (imipenem and meropenem) and the monobactam (aztreonam) are also active against *P. aeruginosa.* Ampicillin–sulbactam and cefazolin are ineffective against *P.*

*aeruginosa.* The history defines a patient with type I allergic hypersensitivity to penicillin. The patient should avoid drugs in the penicillin class, including penicillin, nafcillin, oxacillin, cloxacillin, dicloxacillin, ampicillin, amoxicillin, ticarcillin, piperacillin, and mezlocillin. In addition, carbapenems (imipenem, meropenem) should not be administered to patients with a history of type I allergic response to penicillin or positive penicillin skin test. Cefazolin is a cephalosporin. Patients with type I allergy to penicillin and positive penicillin skin test have a 5.6% rate of allergic reactions to cephalosporins. Aztreonam may be used safely in patients with history of type I allergic response to penicillin.

2. **B.** The patient is pregnant and has latent syphilis of indeterminate duration. The pathogenic organism is *T. pallidum.* Benzathine penicillin G is the drug of first choice for treating latent syphilis. Doxycycline and tetracycline are alternatives treatments for nonpregnant patients with latent syphilis. Spectinomycin is not effective against syphilis; it is a treatment for disseminated gonorrhea in patients who are allergic to cephalosporins. Streptomycin is not effective against syphilis.
3. **E.** The patient has exudative pharyngitis, presumably secondary to group A streptococcus. Antibiotic treatment is indicated to reduce the duration and severity of symptoms and to prevent acute rheumatic fever. The antibiotic of first choice is penicillin V. Other reasonable alternatives are benzathine penicillin G, erythromycin, cephalosporin, clindamycin, azithromycin, and clarithromycin. Amikacin, lomefloxacin, metronidazole, and netilmicin are not active against group A streptococcus.
4. **E.** The patient has uncomplicated urethritis caused by *N. gonorrhoeae.* Effective antibiotics for gonorrhea include cephalosporins (ceftriaxone, cefixime, ceftizoxime, cefotaxime, cefotetan, cefoxitin), fluoroquinolones (ciprofloxacin, ofloxacin, enoxacin, lomefloxacin, gatifloxacin), and spectinomycin. Gonorrhea is resistant to trimethoprim and rifampin. Amphotericin B is an antifungal drug, and isoniazid is an antimycobacterial drug. Neither has antigonococcal activity. Cephalosporins and other β-lactam antibiotics act to inhibit bacterial transpeptidase and block cross-linking of peptides in cell wall murein (peptidoglycan). Fluoroquinolone antibiotics inhibit DNA gyrase (topoisomerase) and interfere with bacterial DNA transcription and replication. Spectinomycin and doxycycline inhibit bacterial protein synthesis and act at the 30S ribosome subunit. Azithromycin inhibits bacterial protein synthesis and acts at the 50S ribosome subunit. Trimethoprim inhibits dihydrofolate reductase and blocks formation of tetrahydrofolate required for purine synthesis. Rifampin inhibits RNA synthesis by binding to the βsubunit of DNA-dependent RNA polymerase. Amphotericin B inhibits fungal cell membrane integrity by binding to ergosterols to create pores. Isoniazid inhibits KasA, a β-ketoacyl carrier protein synthetase, and blocks mycolic acid synthesis.
5. **B.** The patient has impetigo. The causative organism is either *Streptococcus pyogenes* (group A) or *S. aureus.* Recommended antibiotic treatment is dicloxacillin or cloxacillin. Dapsone is used to treat skin infections with *Mycobacterium leprae* (leprosy) and to treat brown recluse spider (*Loxosceles*) bites. Doxycycline is used to treat skin infections with *Bacillus anthracis* (anthrax), *Bartonella henselae* (bacillary angiomatosis), *Borrelia burgdorferi* (Lyme disease, erythema migrans), *Propionibacterium acnes* (acne vulgaris), *Vibrio vulnificus* and *Vibrio damsela* (hemorrhagic bullous cellulitis). The question does not provide historical or epidemiological information to support these diagnoses. Ketoconazole is used to treat fungal infections of the skin (tinea capitis, tinea cruris, tinea corporis, tinea pedis, tinea versicolor). Dermatophyte infections are usually erythematous, with vesicles, fissures, and scaling. Penciclovir is a treatment for herpes simplex virus infections including herpes labialis fever blisters.

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## CASE Study Choosing an Antibiotic Therapy

A 65-year-old man came to the emergency department via ambulance after a generalized seizure. Relatives accompanied the patient and described a 1-day history of fever and intermittent confusion. The patient had a 10-year history of chronic lymphocytic leukemia; 2 months ago, he had a trial of oral chlorambucil because of progressive fatigue, anemia, thrombocytopenia, and splenomegaly. Then, 3 weeks ago, the patient attended a family reunion at a cousin's dairy farm. He enjoyed eating homemade soft cheese, sausage, and fresh vegetables from the garden. Several family members who attended the reunion reported transient febrile gastroenteritis. The patient's physical examination in the emergency department revealed a stuporous man with temperature 103.3°F (39.6°C), blood pressure 122/68 mm Hg, pulse 112 beats per minute, and respirations 26 per minute. He had nuchal rigidity, diffuse adenopathy, and hepatosplenomegaly. Passive flexion of the neck caused flexion at hips and knees (Brudzinski's sign). The patient resisted passive extension of the flexed knee and hip (Kernig's sign). Papilledema was absent. There were no focal neurological deficits. Skin examination revealed no eruption. Peripheral blood tests showed 36,000 leukocytes (66% lymphocytes), hemoglobin 9.0 g/dL, platelet count 99,000. A lumbar puncture was performed. The opening pressure of cerebrospinal fluid was 220 mm of water. Cerebrospinal fluid tests revealed no organisms on Gram stain, glucose 60 mg/dL, protein 200 mg/dL, lactate 50 mg/dL, leukocytes 2000 per $mm^3$ (10% neutrophils, 60% lymphocytes, 30% monocytes). Bacterial antigen tests on cerebrospinal fluid were negative for *H. influenzae* type B, *S. pneumoniae, Neisseria meningitidis, E. coli* K1, and group B streptococci. What is the best empirical antibiotic therapy for this patient?

**ANSWER:** The emergency department physician suspected acute bacterial meningitis in a patient with impaired immunity secondary to hematologic malignancy. The physician also noted the exposure to a food-borne pathogen associated with dairy products. The epidemiological risk assessment suggested the need for empirical antibiotic therapy to cover potential gram-negative enteric pathogens and *L. monocytogenes.* Immediately after obtaining blood and spinal fluid specimens, the emergency department personnel initiated therapy with ampicillin 2 g intravenously every 4 hours and ceftazidime 2 g intravenously every 8 hours. On the next day, the clinical microbiology laboratory reported diphtheroids growing in the patient's blood culture bottles. On the second hospital day, the laboratory identified *L. monocytogenes* growing in blood and spinal fluid specimens. Ceftazidime was discontinued. The patient completed a 21-day course of ampicillin and gentamicin 1.7 mg/kg intravenously every 8 hours.