TABLE 20.7 Adverse Reactions to Penicillins

TYPE OF REACTION	OCCURS MOST FREQUENTLY WITH	FREQUENCY (%)
Allergic		
IgE antibody Anaphylaxis Early urticarial (<72 h)	Penicillin G	0.015–0.04
Cytotoxic antibody Hemolytic anemia	Penicillin G	Rare
Antigen-antibody complex disease	Penicillin G	Rare
Serum sickness		
Delayed hypersensitivity contact dermatitis	Ampicillin, amoxicillin	2–5
Idiopathic	Ampicillin, amoxicillin	2–5
Rash		
Fever		
Late-onset urticaria		
Gastrointestinal		
Diarrhea	Ampicillin, amoxicillin	3–11
Clostridioides difficile (formerly *Clostridium difficile*)–associated colitis	Ampicillin	Rare
Hematologic		
Hemolytic anemia	Penicillin G	Rare
Neutropenia	Penicillin G, nafcillin, oxacillin	10–17[a]
Platelet dysfunction	Piperacillin	43–73
Hepatic		
Elevated serum aspartate aminotransferase level	Oxacillin, flucloxacillin	0.01–22
Electrolyte Disturbance		
Hypokalemia	Nafcillin, oxacillin	Rare
Acute hyperkalemia	Penicillin G	Rare
Neurologic		
Seizures	Penicillin G	Rare
Bizarre sensations (Hoigné syndrome)	Procaine penicillin	Rare
Renal		
Interstitial nephritis	Any penicillin	Variable

[a]With prolonged therapy.
IgE, Immunoglobulin E.
Data from references ***49***, ***56***, *182–190.*

of the kidney show an interstitial infiltrate of mononuclear and eosinophilic cells with tubular damage but no glomerular lesions. Discontinuation of the penicillin results in the return of renal function to normal in most cases.

Administration of massive doses of any penicillin may result in hypokalemia, owing to the large dose of nonreabsorbable anion presented to the distal renal tubules, which alters hydrogen ion excretion and secondarily results in potassium loss. Among the penicillinase-resistant penicillins, nafcillin may carry higher risk of hypokalemia than oxacillin.[51]

Central nervous system (CNS) toxicity in the form of myoclonic seizures can follow the administration of massive doses of penicillin G (40–100 million units/day).[52] If there is reduced renal function, the drugs accumulate, and this form of toxicity becomes more likely, even with lower doses.[53] Direct instillation of small doses of oxacillin or nafcillin into the ventricles at the time of surgery for placement of atrioventricular shunts has not resulted in seizures, but direct application of penicillin to the cortex provokes seizure activity.

Gastrointestinal (GI) disturbances may follow the use of any of the oral forms but are most pronounced with the amoxicillin-clavulanate combination.[54] *Clostridioides difficile* (formerly *Clostridium difficile*)–associated diarrhea has followed the use of penicillins, but the risk appears to be lower than with cephalosporins.[55] All penicillins used at high doses for prolonged periods alter the normal microbiota, with resulting colonization with resistant gram-negative bacilli or with fungi such as *Candida.* Abnormalities in liver function test results, such as elevation of the alkaline phosphatase and aminotransferase levels, have been reported, most often after the use of oxacillin and flucloxacillin.[56] Human leukocyte antigen (HLA)-B*5701 genotype has been identified as a major determinant of this reaction by flucloxacillin.[57] Major hepatic injury is uncommon.

Clinical Use

Some uses of penicillins are shown in Table 20.8. Penicillin G remains the primary agent for treatment of infections due to *Streptococcus pyogenes,* penicillin-susceptible strains of *Streptococcus pneumoniae,* and penicillin-susceptible strains of *S. aureus.* IV penicillin G remains the treatment of choice for pneumococcal and meningococcal meningitis, streptococcal endocarditis, and neurosyphilis. None of the semisynthetic penicillins or agents in other classes has been shown to be more effective. For *Enterococcus faecalis,* the most potent activity is observed with ampicillin. Penicillin-susceptible strains of *S. pneumoniae* are inhibited at concentrations less than 0.1 μg of penicillin per milliliter. Other penicillins also are highly active, although minimal inhibitory concentrations (MICs) usually exceed that of penicillin G. This hierarchy of activity of the penicillins is maintained against penicillin-resistant strains of *S. pneumoniae,* albeit at higher MICs. Penicillin, ampicillin, and amoxicillin are the most active compounds, with MICs rarely exceeding 4 μg/mL.[58] Except in pneumococcal meningitis, for which clinical failures with penicillin are well documented, infections caused by pneumococci with MICs of up to 1 μg/mL appear to respond to penicillin G, provided a sufficiently high dose is used.[59] For serious pneumococcal infections caused by penicillin-resistant strains with MICs greater than 1 μg/mL, particularly in immunocompromised patients, vancomycin or another non–β-lactam antibiotic may be preferred over a penicillin or other β-lactam antibiotic based on susceptibility.[60] Penicillin should be used alone to treat pneumococcal meningitis only if the isolate is fully penicillin susceptible.[61]

Virtually all *Neisseria meningitidis* strains are susceptible to penicillin G. *Neisseria gonorrhoeae* strains frequently are resistant to penicillin, which is no longer recommended for treatment of gonorrhea. Penicillin G is the drug of choice for syphilis at all stages. Puerperal infections due to anaerobic streptococci or group B streptococci *(Streptococcus agalactiae),* as well as genital clostridial infections, are treated with penicillin G. Infections produced by anaerobic oral microbiota, including gram-positive and gram-negative cocci and actinomycetes, can be treated with penicillin G, although penicillin-resistant strains of *Prevotella melaninogenica* that produce β-lactamase are encountered.[62]

The penicillinase-resistant penicillins are indicated solely for the treatment of infections caused by methicillin-susceptible strains of staphylococci, for which they are the agents of choice. They also can be used to treat viridans streptococci, *S. pyogenes* and other hemolytic streptococci, penicillin-susceptible strains of *S. pneumoniae,* anaerobic gram-positive cocci, and anaerobic gram-positive bacilli, but penicillin is more active against these organisms and is the preferred drug. These compounds are inactive against *Listeria monocytogenes, Enterococcus* spp., and methicillin-resistant strains of staphylococci. The basis of methicillin resistance in staphylococci is the production of PBP2a, which has low affinity for binding methicillin. They are also active against gram-negative cocci, including *Neisseria* spp.

Aminopenicillins are indicated for treatment of upper respiratory tract infections, lower respiratory tract infections, bacterial gastroenteritis (ampicillin only), bacterial endocarditis, meningitis, and urinary tract infections (UTIs) caused by susceptible (i.e., non–β-lactamase–producing) organisms. Amoxicillin, because of its excellent bioavailability, is the preferred agent for oral administration in most situations; it is well tolerated even in high doses up to 4 g/day (80 to 90 mg/kg/day in

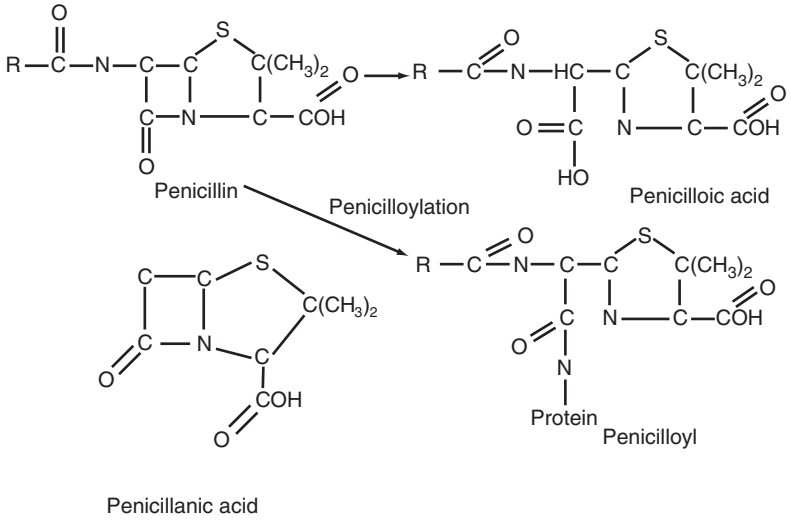


FIG. 20.3 **Mechanisms for formation of antigens from penicillins.**

children).[63] Amoxicillin is also recommended as one component of several triple-drug combination regimens for eradication of *Helicobacter pylori*.[64]

The antipseudomonal penicillins are indicated for the treatment of infections caused by resistant gram-negative bacilli, especially *P. aeruginosa*. The ureidopenicillins, particularly piperacillin, are active against many strains of *Klebsiella* spp., *Enterobacter* spp., *Serratia marcescens,* and *Providencia* spp. and can be used to treat infections caused by these organisms if their susceptibility is confirmed. Piperacillin is often given in combination with tazobactam because of the prevalence of β-lactamase–producing strains. However, the activity of piperacillin against many of the gram-negative species, such as *P. aeruginosa, Enterobacter* spp., *Citrobacter freundii, S. marcescens,* and *Providencia* spp., is usually not improved by tazobactam because these organisms typically produce a class C β-lactamase, which is not inhibited well by tazobactam, and piperacillin can be used without tazobactam for infections caused by these organisms.

Prophylactic Use

Penicillins have been used in a number of situations for prevention of infection. The oral administration of 250 mg of penicillin V every 12 hours or IM injections of 1.2 million units of penicillin G benzathine given once every 3 to 4 weeks are effective in prevention of recurrences of rheumatic fever. Outbreaks of streptococcal infection due to *S. pyogenes* have been aborted by the use of oral penicillin G or V given twice daily for 5 days, by single injections of procaine penicillin daily, or by administration of benzathine penicillin.

Intrapartum prophylaxis with penicillin is recommended at the time of labor or rupture of membranes to prevent early-onset *S. agalactiae* disease in the infant for pregnant women who are colonized with this organism. The recommended dosing regimen of penicillin G is 5 million units IV, followed by 2.5 to 3 million units IV every 4 hours.[65]

Ampicillin or amoxicillin has been administered orally to asplenic children or to children with agammaglobulinemia to prevent infections caused by *Haemophilus influenzae* and *S. pneumoniae*. Amoxicillin is recommended as a single 2-g (adults) or 50-mg/kg (children) oral dose for prophylaxis of bacterial endocarditis among those with the highest risk of adverse outcome.[66] A recent double-blind, randomized, controlled trial in the United Kingdom and Ireland showed that penicillin prophylaxis decreased the risk of recurrent lower extremity cellulitis in subjects with two or more prior episodes of cellulitis.[67] Penicillin prophylaxis has not been of benefit in the prevention of meningococcal infection, bacterial infection after viral respiratory tract infection, or pneumonia after coma, shock, or congestive heart failure.

PROPERTIES OF INDIVIDUAL PENICILLINS

Dosage guidelines for the penicillins are shown in Tables 20.9 and 20.10.

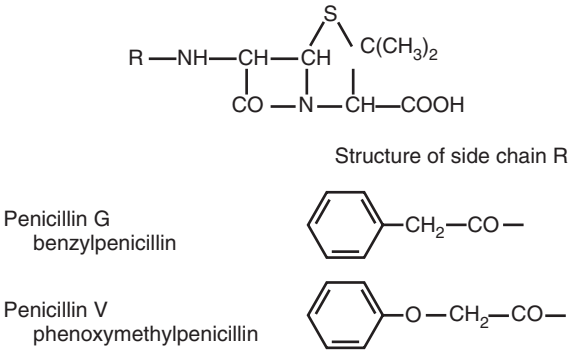


FIG. 20.4 **The structures of penicillin G and penicillin V.**

Natural Penicillins

Penicillin G

Penicillin G, or benzylpenicillin (Fig. 20.4), is available as salts for oral and parenteral administration and as repository salts for IM injection. Because penicillin G is unstable in acid, penicillin V or amoxicillin should be used for oral administration.

Crystalline penicillin G in aqueous solution has been used IM, subcutaneously, IV, and intrathecally. Given IM as an aqueous solution, penicillin G is very rapidly cleared from the body, and it may be preferable to use a repository form. It is available as sterile dry powder in vials containing 5 or 20 million units per vial. Each million unit of penicillin G contains 1.7 mEq of sodium or potassium.

Repository penicillins provide tissue depots from which the drug is absorbed over hours in the case of penicillin G procaine or over days in the case of benzathine penicillin G. Repository penicillins are only for IM use and cannot be used IV or subcutaneously. Penicillin G procaine is a mixture of equal-molar parts of procaine and penicillin G. The use of this suspension delays the peak of activity to 2 to 4 hours after injection and provides serum and tissue levels for 24 hours.[68] Doubling the dose of penicillin G procaine given at a single injection site does not double the serum level. To increase the peak level, it is necessary to use two body sites, as is done in the treatment of gonorrhea, for example, with 2.4 million units of penicillin G procaine given in each buttock.

Benzathine penicillin G is a repository form of penicillin G that combines penicillin G and dibenzylethylenediamine.[69] It provides detectable serum levels for 3 to 4 weeks, depending on the size of the dose.[68] Although benzathine penicillin G is the treatment of choice for syphilis, concentrations of penicillin G in the CSF after use of benzathine penicillin G may be inadequate to treat neurosyphilis, thus IV penicillin G is preferred.[70]

TABLE 20.8 Antimicrobial Spectrum of Penicillins

INFECTING ORGANISM	PENICILLIN OF CHOICE	ALTERNATIVE ACCEPTABLE PENICILLIN	FREQUENCY OF RESISTANCE TO PENICILLINS (%)
Gram-Positive Cocci			
Streptococcus pneumoniae	G	Amoxicillin	10–20
Streptococcus pyogenes	G	V	None
Streptococcus agalactiae	G	Ampicillin	None[a]
Viridans streptococci	G		5–15
Streptococcus bovis	G		Rare
Enterococcus faecalis	Ampicillin	Piperacillin	Rare
Staphylococcus aureus (non–penicillinase-producing)	G	Penicillin-resistant	Rare[b]
S. aureus (penicillinase-producing)	Penicillin-resistant		50–60[c]
S. aureus (methicillin-resistant)	None	None	100
S. epidermidis	Penicillin-resistant		80[c]
S. epidermidis (methicillin-resistant)	None	None	100
Gram-Negative Cocci			
Neisseria meningitidis	G	Ampicillin	Rare
Neisseria gonorrhoeae	G	Ampicillin	5–20
Gram-Positive Bacilli			
Bacillus anthracis	G		None
Corynebacterium diphtheriae	G		None
Listeria monocytogenes	Ampicillin	G	None
Anaerobic Species			
Peptostreptococcus spp.	G	Ampicillin	5
Actinomyces spp.	G	V	None
Prevotella spp.	G	Piperacillin	80
Fusobacterium spp.	G	Ampicillin	10
Bacteroides fragilis	None		100
Clostridium spp.	G	Ampicillin	Rare
Gram-Negative Bacilli			
Haemophilus influenzae	Ampicillin		30
Escherichia coli	Ampicillin		50–60
Proteus mirabilis	Ampicillin		25–30
Salmonella enterica serovar Typhi	Ampicillin		5–10
Salmonella enterica, non-Typhi	Ampicillin		10–20
Klebsiella spp.	Piperacillin		50
Enterobacter spp.	Piperacillin		50–60
Citrobacter spp.	Piperacillin		40
Proteus, indole-positive spp.	Piperacillin		25
Serratia marcescens	Piperacillin		40
Morganella morganii	Piperacillin		20
Pseudomonas aeruginosa	Piperacillin		15–30
Acinetobacter baumannii	Piperacillin		>70
Providencia spp.	Piperacillin		30
Stenotrophomonas maltophilia	None		85–90
Other Organisms Infrequently Encountered			
Erysipelothrix spp.	G	Ampicillin	None
Pasteurella multocida	G	Ampicillin	Rare
Streptobacillus moniliformis	G		None
Spirillum minus	G		None
Treponema pallidum	G	Ampicillin	None

[a]Reduced susceptibility has been observed on rare occasions.
[b]Most non–penicillinase-producing strains are methicillin susceptible.
[c]Approximate frequency of methicillin-resistant strains among penicillinase-producing strains.

TABLE 20.9 Dosage of Penicillins

COMPOUND	DOSAGE		
	Oral	Intramuscular	Intravenous[a]
Penicillin G			Adult: 2–4 million units q4h Pediatric: 300,000 units/kg/day, 6 divided doses
Procaine		Adult: 600,000–1 million units daily Pediatric: 50,000 units/kg daily	
Benzathine		Adult: 1.2–2.4 million units qwk Pediatric: 50,000 units/kg qwk	
Penicillin V	Adult: 125–500 mg qid Pediatric: 25–75 mg/kg/day, 3–4 divided doses		
Ampicillin	Adult: 500 mg qid Pediatric: 50–100 mg/kg/day, 4 divided doses	Adult: 2 g q4–6h Pediatric: 300 mg/kg/day, 4 divided doses	Adult: 2 g q4–6h Pediatric: 300 mg/kg/day, 4 divided doses
Amoxicillin	Adult: 0.5–1 g tid Pediatric: 25–90 mg/kg/day, 2–3 divided doses		
Cloxacillin	Adult: 250–500 mg qid Pediatric: 50–100 mg/kg/day, 4 divided doses		
Dicloxacillin	Adult: 125–500 mg qid Pediatric: 12.5–100 mg/kg/day, 4 divided doses		
Flucloxacillin	Adult: 250–500 mg qid Pediatric: 62.5–125 mg qid	Adult: 250 mg q6h Pediatric: 125 mg q6h	Adult: 2 g q6h Pediatric: 100–200 mg/kg/day, 4 divided doses
Nafcillin		Adult: 0.5–1 g q4–6h Pediatric: 50–100 mg/kg/day, 4 divided doses	Adult: 1–2 g q4h Pediatric: 200 mg/kg/day, 4 divided doses
Oxacillin		Adult: 1 g q4–6h Pediatric: 100 mg/kg/day, 4 divided doses	Adult: 1–2 g q4h Pediatric: 200 mg/kg/day, 4 divided doses
Piperacillin		Adult: 2 g q6–12h Pediatric: 100–125 mg/kg/day, 2–4 divided doses	Adult: 3–4 g q4–6h Pediatric: 200–300 mg/kg/day, 4–6 divided doses

[a]Intravenous doses used for more severe infections, including meningitis and endocarditis.
qid, Four times daily; *qwk,* once per week; *tid,* three times daily.

TABLE 20.10 Dosage of Antibiotics in Neonates

AGENT	INFANTS <1 WK OLD		INFANTS 1 WK TO 1 MO OLD	
	Dosage (per kg/day)	Interval Between Doses (h)	Dosage (per kg/day)	Interval Between Doses (h)
Penicillin G	100,000 units	12	150,000 units	8
Ampicillin (intravenous)	150 mg	8	200 mg	6
Nafcillin	75 mg	8–12	100–150 mg	6–8
Oxacillin	75 mg	8–12	150–200 mg	6–8

Penicillin V

Phenoxymethyl penicillin, or penicillin V (see Fig. 20.4), is available only for oral use as a sodium or a potassium salt in suspension or tablets in doses of 125, 250, and 500 mg. The usual dosage for children is 25 to 50 mg/kg/day and for adults is 1 to 4 g/day in three or four divided doses. The potassium salt produces higher blood levels than the other salts. Serum levels are from two to five times those obtained with oral penicillin G. Blood levels after 500 mg administered to an adult are equivalent to the levels achieved with 600,000 units of penicillin G procaine administered IM. Penicillin V can be substituted for penicillin G in most situations in which it is reasonable to treat an infection by the oral route. However, penicillin V is less active than penicillin G against *Haemophilus* and *Neisseria* spp.

Penicillinase-Resistant Penicillins

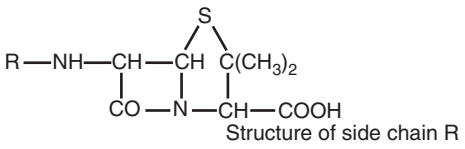
The antibacterial spectra of all penicillinase-resistant penicillins are identical (Fig. 20.5). They are active against methicillin-susceptible strains of staphylococci; penicillin-susceptible strains of streptococci, including *S. pneumoniae;* and most anaerobic gram-positive cocci. None are active against methicillin-resistant staphylococci, high-level penicillin-resistant streptococci, enterococci, *L. monocytogenes,* aerobic gram-negative cocci or bacilli, or anaerobic gram-negative bacteria.

Methicillin

Methicillin (2,6-dimethoxyphenylpenicillin) was the first of several penicillinase-resistant penicillins developed. Methicillin is the least active of the penicillinase-resistant penicillins by weight; it is acid labile and therefore can be administered only parenterally; and it is more likely to cause interstitial nephritis. For these reasons, methicillin is no longer available for clinical use.

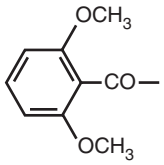
Nafcillin

Nafcillin (2-ethoxy-1-naphthylpenicillin) has more intrinsic activity than methicillin against susceptible organisms. It is highly protein bound. Oral absorption of nafcillin is erratic, and levels after IM injection are low; therefore the only practical route of administration is IV. The

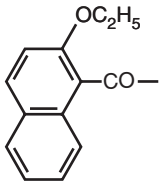


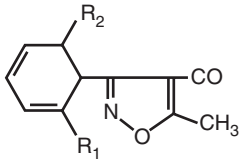
Structure of side chain R

Methicillin
2,6-dimethoxyphenylpenicillin



Nafcillin
2-ethoxy-1-naphthylpenicillin





	R_2	R_1
Oxacillin 3-phenyl-5-methyl-4-isoxazolylpenicillin	H	H
Cloxacillin 3-(2-chlorophenyl)-5-methyl-4-isoxazolylpenicillin	Cl	H
Dicloxacillin 3-(2,6-dichlorophenyl)-5-methyl-4-isoxazolylpenicillin	Cl	Cl
Flucloxacillin 3-(2-chloro-6-fluorophenyl)-5-methyl-4-isoxazolylpenicillin	Cl	F

FIG. 20.5 **Antistaphylococcal penicillins.**

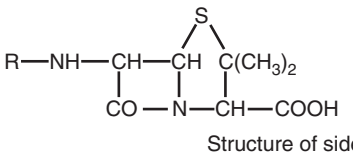
antibiotic is primarily excreted by the liver and to a lesser extent by the kidney. Serum levels are elevated, and the half-life is prolonged by probenecid. The usual dosage of nafcillin is 6 to 12 g/day, depending on the severity of the infection, and 100 to 200 mg/kg/day for children.

Isoxazolyl Penicillins

The isoxazolyl penicillins (oxacillin, cloxacillin, dicloxacillin, and flucloxacillin) are absorbed after oral administration, but absorption is adversely affected by food. Dicloxacillin and flucloxacillin yield the highest total drug serum concentrations, but because of differences in protein binding, free-drug concentrations are similar for all three compounds (see Table 20.5). After IV infusion of 1 g over 15 minutes, serum levels are approximately 25 μg/mL 1 hour later and less than 1 μg/mL at 6 hours. The isoxazolyl penicillins undergo some metabolism but are excreted primarily by the kidney, with slight biliary excretion. Oxacillin undergoes more rapid degradation in the body than does cloxacillin or dicloxacillin.

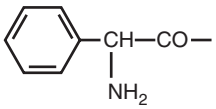
Oxacillin sodium for injection may be given IM or IV. The adult dosage is 6 to 12 g/day, and for children it is 100 to 200 mg/kg/day given every 4 to 6 hours. Oxacillin may be associated with a higher incidence of hepatotoxicity and rash than nafcillin or other antistaphylococcal agents.[56]

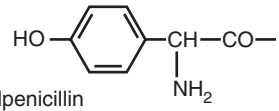
Cloxacillin sodium is available in the United States only as an oral solution (125 mg/5 mL) or capsules of 250 and 500 mg. The dosage for children is 50 to 100 mg/kg/day given as four equal doses, and the dosage for adults is 1 to 2 g/day given as four equal doses.



Structure of side chain R

Ampicillin
D(-) α-aminobenzylpenicillin





Amoxicillin
D(-) α-amino-p-hydroxybenzylpenicillin

FIG. 20.6 **Aminopenicillins.**

Dicloxacillin sodium is available as a suspension (62.5 mg/5 mL) and as capsules of 125 and 250 mg. The dosage for children weighing less than 40 kg is 12.5 to 100 mg/kg/day given as four doses. For adults a dosage of 125 to 500 mg every 6 hours can be given, depending on the severity of the infection.

Flucloxacillin and dicloxacillin are similar in pharmacokinetics, activity, and indications.[71] It is not available in the United States but is widely used in Europe and other countries. Flucloxacillin is available as a sodium salt in an oral suspension (125 mg/5 mL or 500 mg/5 mL), capsules (250 and 500 mg), and in powder form for reconstitution for parenteral administration.

Aminopenicillins

The antibacterial activities of all aminopenicillins are similar (Fig. 20.6). They are susceptible to β-lactamases. For practical purposes the activity of aminopenicillins is virtually identical to that of penicillin G against penicillin-susceptible organisms, except that aminopenicillins are slightly more active against enterococci. Non–β-lactamase–producing strains of *H. influenzae* and *Haemophilus parainfluenzae* are susceptible. Strains of *E. coli, Shigella sonnei,* and *Salmonella* spp., including many strains of *Salmonella enterica* serovar Typhi, once uniformly susceptible to aminopenicillins, often are resistant due to β-lactamase production. Species that intrinsically produce β-lactamase, such as *Enterobacter* spp., *Serratia* spp., *Acinetobacter* spp., *Pseudomonas* spp., and indole-positive *Proteus,* are resistant to aminopenicillins.

Ampicillin

Ampicillin is moderately well absorbed after oral administration, but peak levels are delayed and lowered if it is ingested with food. Peak blood levels of 3 μg/mL occur 1 to 2 hours after ingestion of 500 mg; levels peak later in diabetic patients with neurologic disease and in patients with renal failure. After IM injection of 0.5 g, peak levels of 10 μg are achieved at 1 hour. The elimination half-life is approximately 80 minutes. Probenecid increases the magnitude of peak levels and the area under the concentration-time curve (AUC). Ampicillin is well distributed to body compartments and after parenteral administration achieves therapeutic concentrations in cerebrospinal, pleural, joint, and peritoneal fluids in the presence of inflammation. The drug undergoes enterohepatic circulation, and significant levels appear in bile and stool. Urinary levels are high even in the presence of markedly reduced renal function. Peritoneal dialysis is ineffective in removing the drug, but hemodialysis removes approximately 35% in a 4-hour period. The half-life of ampicillin is about 3 hours during continuous venovenous hemofiltration.

Ampicillin is available for oral use as the sodium salt as 250-mg or 500-mg capsules and oral suspensions of 125 or 250 mg/5 mL. The sodium salt can be used for either IM or IV administration. For most indications, oral ampicillin has been abandoned in favor of oral amoxicillin because of the greater bioavailability of the latter. Ampicillin is effective for upper and lower respiratory tract infections caused by *S. pneumoniae,* β-hemolytic streptococci, and non–β-lactamase–producing

strains of *H. influenzae*. It is effective in the treatment of meningitis caused by group B streptococci, *L. monocytogenes, N. meningitidis,* and penicillin-susceptible strains of *S. pneumoniae*. Although formerly useful in treating UTIs caused by *E. coli* and gastroenteritis caused by *S. enterica* or *Shigella* spp., owing to the high prevalence of β-lactamase–producing strains, ampicillin should not be used until susceptibility has been documented.

Dosage varies with the age of the patient, the status of renal function, and the severity of the disease. For children older than 1 month the oral dosage is 50 to 100 mg/kg/day in four divided doses; the IM or IV dosage is 100 to 300 mg/kg/day in four or six doses. For adults the oral dosage is 2 to 4 g/day given in divided doses every 6 hours. For severe infection the parenteral dosage is 6 to 12 g/day given in divided doses every 4 hours.

Amoxicillin

Amoxicillin differs from ampicillin only in the presence of hydroxyl group in the *para* position of the benzene side chain. Its in vitro activity is identical to that of ampicillin. It is significantly better absorbed when given by mouth compared with ampicillin, and for this reason it is preferred for most indications. Peak blood levels are from 2 to 2.5 times those achieved with a similar dose of ampicillin, and food does not decrease absorption. Oral amoxicillin produces blood levels similar to those produced by IM administration. The elimination half-life averages 80 minutes in adults with normal renal function. Urinary excretion of amoxicillin is greater than that of ampicillin, and tissue distribution is similar to that of ampicillin. Parenteral amoxicillin, which is available in Europe but not in the United States, is pharmacologically identical to parenterally administered ampicillin.

Clinical studies with amoxicillin have been extensive; this antibiotic has been used in the treatment of otitis media, bronchitis, pneumonia, typhoid, gonorrhea, and UTIs. High-dose amoxicillin (80–90 mg/kg/day) is first-line therapy for otitis media in children because it covers penicillin-resistant pneumococci.[72] Amoxicillin 1 g three times daily is recommended in the oral therapy for community-acquired pneumonia.[60] Amoxicillin can achieve concentrations that exceed MICs effective for nonmeningeal infections caused by penicillin-resistant strains of *S. pneumoniae*.[73,74] Amoxicillin is less effective than ampicillin for the treatment of shigellosis.[75]

Side effects of amoxicillin are similar to those seen with ampicillin, although diarrhea may be less common than with ampicillin. The usual dosage for children is 20 to 40 mg/kg/day and as high as 90 mg/kg/day given in two or three divided doses every 8 hours; for adults the dosage is 0.5 to 1 g every 8 to 12 hours, although it has been used in doses up to 1 g every 4 hours.

Carboxypenicillins

Ticarcillin, carbenicillin, and indanyl carbenicillin (Fig. 20.7)—α-carboxy esters of carbenicillin used for oral administration—are no longer used because of the large doses required, the greater potential for toxicity, and the availability of more potent alternatives.

Ureidopenicillins

Ureidopenicillins (see Fig. 20.7) all have similar spectra of activity and pharmacologic properties. Azlocillin and mezlocillin are no longer on the market, having been replaced in clinical practice by piperacillin-tazobactam, and are not discussed further.

Piperacillin is similar to ampicillin in activity against gram-positive species. It has excellent activity against streptococcal species and against *Neisseria, Haemophilus,* and many members of the family Enterobacteriaceae. It also has excellent activity against anaerobic species of both cocci and bacilli. It inhibits 60% to 90% of *P. aeruginosa* strains at concentrations less than 16 μg/mL. Like ampicillin, it is hydrolyzed by class A β-lactamases. Although it is hydrolyzed by class C β-lactamases produced by *P. aeruginosa* and *Enterobacter* spp., it is not an inducer, which accounts for its activity against the majority of strains of these and related species. Emergence of resistance to piperacillin is often due to selection of mutants that constitutively express high levels of class C β-lactamase.[76] Piperacillin acts synergistically against most *P. aeruginosa* strains and against some of the Enterobacteriaceae species when it is combined with aminoglycosides[77,78]; the antibacterial activity is either synergistic or additive when combined with a fluoroquinolone.[79,80]

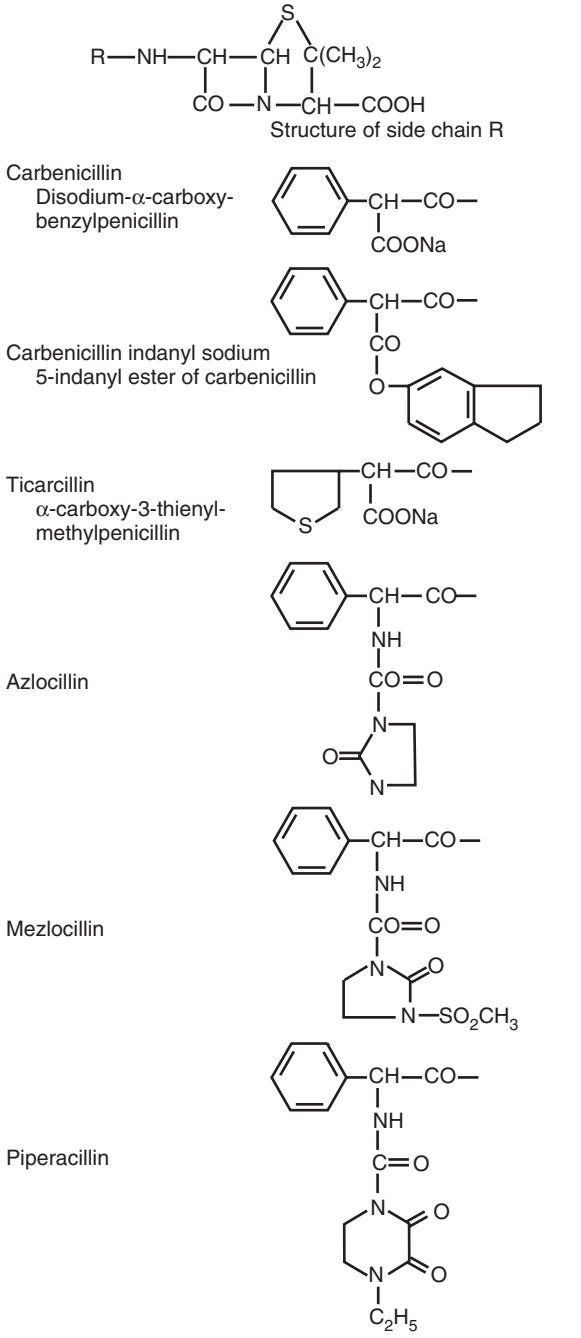


FIG. 20.7 **Penicillins active against gram-negative bacteria.**

IV bolus administration of 4 g produces peak serum drug levels above 300 μg/mL. Piperacillin's kinetics are dose dependent. It accumulates in renal failure to a lesser degree than does carbenicillin, and its half-life is only 4 to 6 hours at CrCls less than 10 mL/min. It is removed through hemodialysis and should be dosed after dialysis. The half-life with continuous venovenous hemofiltration is approximately 5 hours, and 4 g administered twice daily is recommended.[81]

Piperacillin has shown adverse reactions similar to those for the other penicillins noted earlier. After prolonged administration at high doses, neutropenia has been reported. Alteration of bleeding time and hypokalemia occur infrequently. Clinical studies have shown that it is a useful agent in the treatment of a variety of infections.[26] It is administered to adults in daily doses of 12 to 18 g. It is almost always used

as a piperacillin-tazobactam combination to extend its activity against class A β-lactamase–producing strains.

β-LACTAMASE INHIBITORS AND INHIBITOR COMBINATIONS

β-Lactamase inhibitors are grouped into β-lactam compounds (e.g., clavulanic acid, sulbactam, and tazobactam) and non–β-lactam compounds (e.g., avibactam, vaborbactam). Five β-lactamase inhibitors are currently in clinical use: clavulanic acid, sulbactam, tazobactam, and avibactam and vaborbactam. The former three are potent inhibitors of class A β-lactamases, with a notable exception of the *Klebsiella pneumoniae* carbapenemase (KPC) β-lactamase. The latter two are inhibitors of class A β-lactamases, including KPC β-lactamase, and also class C (AmpC) β-lactamase. When combined with β-lactam antibiotics that are substrates for these β-lactamases and therefore inactive against bacteria producing them, the inhibitors prevent hydrolysis of the antibiotics, thereby restoring their activity (Tables 20.11 and 20.12). Although competitive inhibition is seen, the β-lactam β-lactamase inhibitors—clavulanic acid, sulbactam, and tazobactam—primarily act as suicide inhibitors that form a stable intermediate, rendering the enzyme inactive. Avibactam and vaborbactam differ from β-lactam β-lactamase inhibitors in that they are reversible inhibitors with unique non-β-lactam structures.

Each inhibitor is available only as a fixed-combination preparation with an active β-lactam antibiotic as the companion agent. There are minor differences in potency, activity, and pharmacology among the β-lactam β-lactamase inhibitors, but it is the companion β-lactam antibiotic that primarily determines antibacterial spectrum of activity. β-Lactam β-lactamase inhibitors are effective only against Ambler class A β-lactamases (i.e., penicillinases), which often are plasmid encoded. Class A β-lactamases are produced by *S. aureus, H. influenzae, Moraxella catarrhalis, Bacteroides* spp. (the β-lactamases are chromosomal in the latter two species), and Enterobacteriaceae, which produce the Temoniera (TEM) and sulfhydryl-variable (SHV) β-lactamases. Clavulanic acid and piperacillin also have some inhibitory activity in vitro against extended-spectrum β-lactamases (ESBLs), including the emerging cefotaxime/ceftazidime-hydrolyzing (CTX-M) type, which are class A β-lactamases. However, reports of failure with β-lactam β-lactamase inhibitors in combination with a penicillin (i.e., amoxicillin, ampicillin, or piperacillin) for treatment of bacteremia and other systemic infections caused by ESBL-producing organisms suggest that activity in vivo may not be predictable. KPC-type β-lactamase, also belonging to class A, is only minimally inhibited by β-lactam β-lactamase inhibitors. Ambler class C β-lactamases (i.e., AmpC cephalosporinases) of *Serratia* spp., *C. freundii, Enterobacter* spp., *P. aeruginosa,* and some other Enterobacteriaceae species, which typically are chromosomally encoded, are not effectively inhibited by these β-lactam β-lactamase inhibitors either. In contrast, avibactam, a non–β-lactam diazabicyclo[3.2.1]octanone β-lactamase inhibitor, and vaborbactam, a non–β-lactam cyclic boronic acid β-lactamase inhibitor, inhibit both class A β-lactamases, including ESBLs and KPC-type β-lactamase, and class C β-lactamases. In addition, avibactam, but not vaborbactam, inhibits oxacillinase (OXA)-48, which is a class D β-lactamase capable of hydrolyzing carbapenems in Enterobacteriaceae. None of the currently approved β-lactamase inhibitors inhibits class B metallo-β-lactamases (MBLs), which are structurally unrelated to the other β-lactamase classes in that they are not PBPs but are derived from metalloproteases.

Clavulanic Acid

The β-lactamase inhibitor clavulanic acid (Fig. 20.8) was originally identified in cultures of *Streptomyces clavuligerus.*[82] Clavulanic acid is

TABLE 20.11 Usual Minimal Inhibitory Concentrations (μg/mL) of Penicillin–β-Lactamase Inhibitor Combinations

ORGANISM	AMOXICILLIN, AMPICILLIN	AMOXICILLIN-CLAVULANATE[a]	AMPICILLIN-SULBACTAM[b]	PIPERACILLIN	PIPERACILLIN-TAZOBACTAM[c]
Staphylococcus aureus (MSSA)	16	1	1	8	1
S. aureus (MRSA)	>16	16	8	>16	>16
Haemophilus influenzae[d]	>16	0.5	0.25	16	0.06
Moraxella catarrhalis	2	0.06	0.06	0.5	0.015
Escherichia coli	>16	4	2	2	2
Klebsiella pneumoniae	>16	2	4	8	4
Proteus mirabilis	1	1	1	0.5	0.5
Proteus vulgaris	>16	4	8	1	0.5
Bacteroides fragilis	>16	0.5	2	8	2
Enterobacter, Citrobacter, Serratia spp.	>16	8–>16	2–>16	2–8	1–8
Pseudomonas aeruginosa	>16	>16	>16	4	4

[a]Contains amoxicillin and clavulanic acid in a 2:1 to 16:1 ratio.
[b]Contains amoxicillin or ampicillin and clavulanic acid or sulbactam in a 2:1 ratio.
[c]Contains piperacillin and tazobactam in an 8:1 ratio.
[d]β-Lactamase–producing strains.
MRSA, Methicillin-resistant *S. aureus; MSSA,* methicillin-susceptible *S. aureus.*
Data from references 170 and 191–201.

TABLE 20.12 Properties of β-Lactamase Inhibitors

	CLAVULANIC ACID	SULBACTAM	TAZOBACTAM	AVIBACTAM	VABORBACTAM
Class	β-Lactam	β-Lactam	β-Lactam	Diazabicyclooctane	Boronic acid
Spectrum of inhibition	Class A, including some ESBLs	Class A	Class A, including some ESBLs	Class A, including KPC and ESBLs Class C Class D, including OXA-48	Class A, including KPC and ESBLs Class C
Partner β-lactams	Amoxicillin	Ampicillin, cefoperazone	Piperacillin, ceftolozane	Ceftazidime	Meropenem

ESBLs, Extended-spectrum β-lactams; *KPC, Klebsiella pneumoniae* carbapenemase; *OXA,* oxazolidinone.

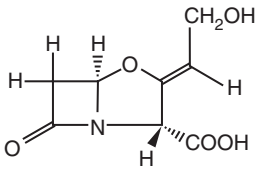


FIG. 20.8 Clavulanic acid.

formulated in combination with amoxicillin, which is available for oral administration only in the United States, and is available as a parenteral preparation in many other countries.

Pharmacology

Clavulanic acid is moderately well absorbed from the GI tract. Peak serum concentration of 3 μg/mL in adults occurs 40 to 120 minutes after ingestion of 125 mg.[83] Combining clavulanic acid with amoxicillin does not alter significantly the pharmacologic parameters of either drug. The absorption of clavulanic acid is largely unaffected by the simultaneous administration of food, milk, H2 receptor antagonists, or aluminum hydroxide–containing antacids.[84] After IV infusion of clavulanic acid combined with amoxicillin, the drug is distributed rapidly, producing peak serum concentrations of approximately 8 μg/mL after a 100-mg IV dose. The serum half-life of clavulanic acid is about 1 hour. No accumulation occurs until CrCl is less than 10 mL/min. Dose adjustment is made on the basis of the desired dose for amoxicillin. Clavulanic acid is degraded in vivo, with metabolites being excreted via lung, feces, and urine; only 20% to 60% appears unchanged in urine 6 hours after an oral dose. Urinary levels after a 125-mg dose of clavulanic acid are between 20 and 30 μg/mL 4 to 6 hours after dosing.[85]

Clavulanic acid produces therapeutic levels in bile, middle ear fluid, and tonsillar tissue. It crosses the placenta and may be found in the cord blood of neonates and in the amniotic fluid, but no clavulanic acid can be detected in breast milk.[86] Clavulanic acid does not penetrate noninflamed meninges. In patients with meningitis CSF levels are in the range of 0.25 μg/mL.[87] Clavulanic acid concentrations of less than 1 μg/mL are achieved in sputum after the oral administration of amoxicillin-clavulanate.[88] There is rapid penetration of clavulanic acid into peritoneal fluid, with an AUC ratio comparable to serum.[89]

Adverse Reactions

No major adverse reactions to the use of clavulanic acid combined with amoxicillin have been reported. Delayed hepatotoxicity may occur, which usually follows a benign course.[90] The incidence of skin reactions has been similar to that seen when penicillin is used alone. Diarrhea is the most common side effect.[54] Nausea also accompanies use of these doses. In accordance, the oral dose of clavulanic acid is recommended not to exceed 125 mg two or three times a day.

Amoxicillin-Clavulanate

Amoxicillin-clavulanate (Augmentin) has proved useful as therapy for acute otitis media in children.[91,92] It also has been used to treat sinusitis or pneumonia caused by susceptible β-lactamase–producing or non–β-lactamase–producing bacteria. It is particularly useful in treating polymicrobial infections in which β-lactamase–producing organisms may be present, including bite wounds of human or animal origin and diabetic foot infections.[93] Skin structure infections caused by streptococci and staphylococci have responded to amoxicillin-clavulanate with results comparable to those achieved with oral antistaphylococcal agents and oral cephalosporins.

The agent is formulated as tablets containing 250, 500, or 875 mg of amoxicillin combined with 125 mg of clavulanic acid and also as a sustained-release formulation of 1000 mg of amoxicillin combined with 62.5 mg of clavulanic acid. The usual dose is 250 mg of amoxicillin every 8 hours to 875 mg every 12 hours by mouth. The 500-/125-mg and 875-/125-mg dosage forms are effective as twice-daily regimens, which are associated with less diarrhea.[94] In children the dose is 20 to 45 mg/kg/day in two or three divided doses; a variety of oral suspensions and chewable tablets are available.

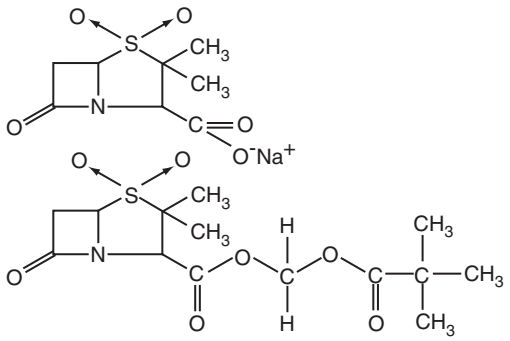


FIG. 20.9 Sulbactam *(top)* and sulbactam oral ester *(bottom)*.

The extended-release formulation is administered as a dose of 1000/62.5 mg twice daily. This dosage is effective for treatment of bacterial sinusitis and community-acquired pneumonia, including infections caused by penicillin-resistant strains of *S. pneumoniae*. Infectious Diseases Society of America guidelines include amoxicillin-clavulanate extended-release 2000 mg/125 mg twice daily in combination with a macrolide as an alternative to fluoroquinolones for empirical, outpatient therapy for community-acquired pneumonia in patients with medical comorbidities.[60]

Sulbactam

Sulbactam (Fig. 20.9) is a 6-desaminopenicillin sulfone. It is a somewhat broader spectrum β-lactamase inhibitor than clavulanic acid but less potent. Sulbactam is available in the United States only in combination with ampicillin (Unasyn), in a ratio of 0.5 g of sulbactam to 1 g of ampicillin as a parenteral formulation for IV administration. It is also available in combination with cefoperazone (Sulperazon) in a 1:1 ratio as a parenteral formulation in certain countries and used primarily for treatment of *Acinetobacter* infections.[95]

Pharmacology

Sulbactam has pharmacokinetics in humans similar to those of ampicillin.[96] The average peak serum level after IV infusion of 1 g is 60 μg/mL. The serum half-life is 1 hour. Sulbactam is excreted by the kidney and has a urinary recovery rate of 70% to 80% of a dose.[97] Biliary excretion is minimal, and metabolism is less than 25%. Renal excretion is blocked by probenecid. The half-life is not altered significantly until the CrCl decreases to less than 30 mL/min. The half-life is 9.2 hours at clearances of 5 to 15 mL/min and 20 hours in anuria. Dosage adjustment is required for CrCl less than 50 mL/min and is based on the ampicillin component. Concentrations of sulbactam in intestinal fluid and peritoneal secretions are comparable to levels in serum. Penetration of sulbactam into inflamed meninges is low and variable, with levels of less than 2% to 32% of the concentrations in the serum.[97]

Adverse Reactions

Clinical studies of the combination of sulbactam plus ampicillin have revealed no major hematologic, renal, hepatic, or CNS reactions.[98] Diarrhea has not been a major problem after IV use. Skin reactions are similar to those found for ampicillin, and there is occasional elevation of aminotransferase levels.

Clinical Use

Ampicillin-sulbactam has a spectrum of antibacterial activity that is similar to that of amoxicillin-clavulanate. It has been used in the treatment of mixed bacterial infections, such as intraabdominal infections, obstetric and gynecologic infections, and soft tissue and bone infections.[99] Sulbactam alone has modest activity in vitro against strains of *Acinetobacter baumannii*.[100] Because it is available only as a combination, its clinical utility independent of the companion β-lactam for treatment of infections caused by *A. baumannii* cannot be determined. One retrospective study

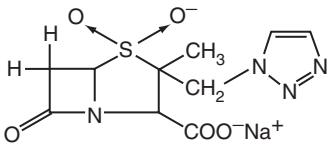


FIG. 20.10 Tazobactam.

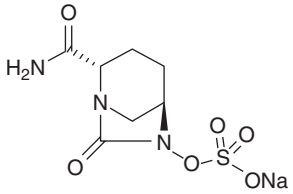


FIG. 20.11 Avibactam.

found that ampicillin-sulbactam was more efficacious than polymyxins for treatment of infections caused by carbapenem-resistant *A. baumannii* strains,[101] and its addition to a combination regimen may have a role in the treatment of pandrug-resistant *A. baumannii* infection.[102]

Tazobactam

Tazobactam is a penicillanic acid sulfone β-lactamase inhibitor with a structure similar to that of sulbactam (Fig. 20.10).[103] Its spectrum of β-lactamase inhibition is similar to that of sulbactam, but its potency is more like that of clavulanic acid. It is available for parenteral administration in combination with piperacillin in an 8:1 ratio (Zosyn) and in combination with ceftolozane in a 2:1 ratio (Zerbaxa).

Pharmacology

Mean peak serum concentration after a 30-minute IV infusion of 500 mg of tazobactam in combination with piperacillin is about 24 μg/mL in healthy subjects.[104] Plasma elimination half-life is approximately 1 hour. Tazobactam is cleared primarily renally, and dosage interval should be extended for CrCls of less than 40 mL/min. Combining tazobactam with piperacillin reduces clearance of tazobactam, but the clearance of piperacillin is not affected. Clearances of piperacillin and tazobactam are similar in subjects with normal renal function. Peak serum concentrations are approximately 50% higher in patients with end-stage renal disease.[105] The half-life of tazobactam is approximately 7 hours in patients with end-stage renal disease. These differences in pharmacokinetics of piperacillin and tazobactam do not require adjustment of the dose of tazobactam independent of piperacillin; the dose is adjusted based on the pharmacokinetics of piperacillin.

Tissue levels of tazobactam reflect a percentage penetration that is similar to that of piperacillin for each tissue type. Tazobactam penetrates inflamed meninges. CSF concentrations of piperacillin and tazobactam were 16% and 32% of simultaneous serum concentrations in a rabbit meningitis model.[106]

Adverse Reactions

Limited clinical data do not indicate any new or unusual toxicity unique to tazobactam. Diarrhea and skin reactions are common.[107]

Piperacillin-Tazobactam

Clinical Use

Clinical studies of piperacillin-tazobactam have been conducted mainly in adults; experience with this combination for treatment of serious infections in children indicates that it is safe and effective.[108] In clinical trials the efficacy of piperacillin-tazobactam has been equivalent and occasionally superior to similarly broad-spectrum comparator drugs (e.g., carbapenems, third-generation cephalosporins) for treatment of pneumonia, skin and soft tissue infections, intraabdominal infections, polymicrobial infections, and febrile neutropenia in combination with an aminoglycoside.[109] The usual adult dose is 12 g of piperacillin/1.5 g of tazobactam administered at a dose of 3.375 g (3 g piperacillin, 0.375 g of tazobactam) every 6 hours, or 4.5 g every 6 to 8 hours for CrCl greater than 40 mL/min.

ESBL-producing strains of *E. coli* and *Klebsiella* spp. often are susceptible to piperacillin-tazobactam in vitro, but there has been some reluctance to use this agent because of the possibility of treatment failure when β-lactam antibiotics other than carbapenems are used to treat infections caused by ESBL-producing strains. Whether bacteremia caused by ESBL-producing organisms can be treated as efficaciously with piperacillin-tazobactam as with carbapenems remains uncertain. However, a recently completed randomized trial comparing piperacillin-tazobactam and meropenem as definitive therapy for bacteremia due to ceftriaxone-resistant *Klebsiella* spp. and *E. coli* showed significantly higher mortality rates among patients randomized to receive piperacillin-tazobactam[110,111]; meropenem monotherapy performed better.

Ceftolozane-Tazobactam

Ceftolozane is an antipseudomonal cephalosporin with improved stability against AmpC compared with ceftazidime. Ceftolozane-tazobactam is active against the majority of *P. aeruginosa* strains, including multidrug-resistant ones. It is active against approximately 60% of carbapenem-nonsusceptible *P. aeruginosa* strains when using the US Food and Drug Administration (FDA)-approved susceptibility breakpoint of 4 μg/mL for this species.[112] The combination is also active against most Enterobacteriaceae clinical strains. It is active against about 90% of ESBL-producing *E. coli* when applying the approved susceptibility breakpoint of 2 μg/mL for this family. Ceftolozane-tazobactam is not active against carbapenem-resistant *K. pneumoniae*, including those producing KPC-type carbapenemase or MBL. Its activity against lactose-nonfermenting organisms other than *P. aeruginosa* is limited.[113]

Ceftolozane-tazobactam has been approved for clinical use based on two phase III randomized trials: one for complicated UTIs and the other for complicated intraabdominal infections. In the former trial, in which the majority of patients had pyelonephritis, the efficacy of ceftolozane-tazobactam was noninferior to levofloxacin.[114] In the latter trial the efficacy of ceftolozane-tazobactam in combination with metronidazole was found to be noninferior to meropenem.[115]

Postmarketing clinical experience suggests that ceftolozane-tazobactam may be a reasonable option for serious infections, such as pneumonia, due to multidrug-resistant *P. aeruginosa*, but detectable bacterial resistance at baseline may be associated with treatment failure, and treatment-emergent resistance also has been noted.[116,117] Susceptibility testing is therefore recommended when treatment with this agent is considered.

Avibactam

Avibactam (Fig. 20.11) is a bridged diazabicyclo[3.2.1]octanone non–β-lactam β-lactamase inhibitor with a structure that is distinct from the conventional β-lactam β-lactamase inhibitors.[118] Its spectrum of β-lactamase inhibition includes class A β-lactamases, including ESBLs and KPCs, class C β-lactamases, and some class D β-lactamases, notably OXA-48 carbapenemase. It does not inhibit MBLs.[119] It is available for parenteral administration in combination with ceftazidime in a 4:1 ratio of ceftazidime to avibactam (Avycaz, Zavicefta). The FDA-approved susceptibility breakpoint is 8/4 μg/mL for both Enterobacteriaceae and *P. aeruginosa*.

Pharmacology

At steady state, mean peak serum concentration after a 2-hour IV infusion of 500 mg of avibactam in combination with ceftazidime is about 15 μg/mL in healthy subjects.[120] Plasma elimination half-life is approximately 2.7 hours. Most avibactam is excreted unchanged in the urine, and dosage should be reduced for CrCls of less than 50 mL/min. About 55% of avibactam is removed during a 4-hour hemodialysis session, which suggests that a dose should be given after dialysis for patients on intermittent hemodialysis.

Adverse Reactions

The most common adverse reactions observed in the registrational clinical trials were vomiting, nausea, constipation, and anxiety, which were similar to those observed among the comparator patients.

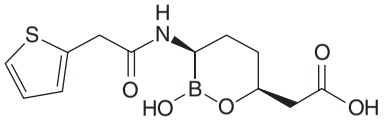


FIG. 20.12 Vaborbactam.

Clinical Use

The addition of avibactam to ceftazidime extends the spectrum to include Enterobacteriaceae that produce ESBL, AmpC, and KPC by reducing the ceftazidime MICs by 16- to greater than 1024-fold. MIC_{90} values for ESBL-producing *E. coli* and KPC-producing *K. pneumoniae* are 0.25 and 1 μg/mL, respectively.[120] Potentiation of ceftazidime activity toward *P. aeruginosa* is more modest, with MIC_{90} values for meropenem and ceftazidime nonsusceptible strains at 16 μg/mL.

Phase III randomized clinical trials have been conducted for adult patients with complicated UTIs, including acute pyelonephritis; complicated intraabdominal infections; and hospital-acquired bacterial pneumonia/ventilator-associated bacterial pneumonia in which ceftazidime-avibactam (in combination with metronidazole for complicated intraabdominal infections) showed comparable safety and efficacy with doripenem, meropenem, and meropenem, respectively.[121,122] Another phase III study comparing it with best available therapy for these types of infections caused by ceftazidime-resistant gram-negative bacteria has shown comparable overall favorable clinical outcome.[123] Since its approval for these indications, ceftazidime-avibactam has been mostly used for the treatment of infections caused by KPC-producing Enterobacteriaceae. Emergent postmarketing observation data suggest that the use of ceftazidime-avibactam–based therapy is associated with lower mortality than the use of colistin-based therapy in the treatment of infections due to carbapenem-resistant Enterobacteriaceae.[124] However, treatment-emergent resistance to avibactam has also been reported.[125]

Vaborbactam

Vaborbactam (Fig. 20.12) is a cyclic boronic acid non–β-lactam β-lactamase inhibitor with activity against class A β-lactamases, including ESBLs, KPC carbapenemase, and class C β-lactamases.[126] It does not inhibit MBLs or class D carbapenemases, including OXA-48. It is available for parenteral administration in combination with meropenem in a 1:1 ratio (2 g each) of meropenem to vaborbactam (Vabomere). The FDA-approved susceptibility breakpoint is 4/8 μg/mL using a fixed concentration of vaborbactam (8 μg/mL).

Pharmacology

The steady-state maximum plasma concentration after a 3-hour infusion of a 2-g dose of vaborbactam is about 40 μg/mL with AUC_{0-t} of 145 μg·h/mL in healthy individuals.[127] Plasma elimination half-life is approximately 1.7 hours. Renal clearance constitutes 80% to 90% of the total clearance of vaborbactam. In accordance, dosage is reduced for CrCls of less than 50 mL/min. A dose should be given after dialysis for patients on intermittent hemodialysis as 53% of vaborbactam is removed during hemodialysis.[128]

Adverse Reactions

The most common adverse reactions occurring in ≥3% of patients in the clinical trials were headache, phlebitis or infusion-site reactions, and diarrhea (https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/209776lbl.pdf).

Clinical Use

Meropenem-vaborbactam exhibits excellent activity against KPC-producing Enterobacteriaceae with MIC_{50} and MIC_{90} of 0.12 μg/mL and 0.5 μg/mL, respectively, compared with >32 μg/mL for both with meropenem alone.[129] On the other hand, its activity against OXA-48–producing Enterobacteriaceae and MBL-producing Enterobacteriaceae is similar to that of meropenem alone, with $MIC_{50/90}$ of 16/>32 μg/mL for OXA-48 producers and 32/>32 μg/mL for MBL producers. Likewise, there is no appreciable potentiation of meropenem activity against *P. aeruginosa*, *A. baumannii*, and *S. maltophilia*.

A phase III clinical trial has been completed for complicated UTIs and acute pyelonephritis, where patients were randomized to receive meropenem-vaborbactam or piperacillin-tazobactam.[130] The overall treatment success rate at the end of IV therapy was higher with meropenem-vaborbactam, and therapy was well tolerated. Another phase III trial was conducted for infections due to carbapenem-resistant Enterobacteriaceae, where the comparator was best available therapy at the enrolling sites. This trial was suspended early when monotherapy with meropenem-vaborbactam was shown to be associated with statistically higher clinical cure rates and lower treatment-emergent adverse event rates.[131]

Given the spectrum of vaborbactam, most clinical use of meropenem-vaborbactam will likely be in the treatment of infection confirmed as due to KPC-producing Enterobacteriaceae, with better results than have been obtained in the past for colistin- or tigecycline-based regimens.

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The complete reference list is available online at Expert Consult.

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21 Cephalosporins

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Although the discovery of the cephalosporin antibiotic class was reported in 1945, it took almost 2 decades for this class to achieve clinical utility. Giuseppe Brotzu is widely credited for discovery of the broad-spectrum inhibitory effects of sewage outflow in Sardinia, Italy.[1] Professor Brotzu subsequently isolated the mold *Cephalosporin acremonium* (now *Acremonium chrysogenum*) and demonstrated antimicrobial activity of culture filtrates against both gram-positive and gram-negative bacteria. He also demonstrated the in vivo activity of these culture filtrates in animal infection models and in several patients.

A decade after the initial discovery, the cephalosporin substances were isolated and identified as fermentation products of the mold.[2] Investigators at Oxford, including Florey and Abraham, systematically studied the physical, chemical, and structural characteristics of cephalosporins, as they had for the penicillin class a decade earlier. Three substances—cephalosporin P, N, and C—were identified. Each of the products possessed antimicrobial activity, but only cephalosporin C demonstrated activity against both gram-negative and gram-positive bacteria. In addition, it had advantageous stability in the presence of acid and penicillinases.[2] Cephalosporin C became the foundation of subsequent drug development.

The first cephalosporin pharmaceutical, cephalothin, was introduced for clinical use in 1964. There are more than 20 cephalosporin antibiotics in use today. The cephalosporin class is among the most widely prescribed antimicrobial classes because of its broad spectrum of activity, low toxicity, ease of administration, and favorable pharmacokinetic profile.

CHEMISTRY

Most of the available cephalosporins are semisynthetic derivatives of cephalosporin C. The basic structure of the cephem nucleus includes a β-lactam ring fused to a six-member sulfur-containing dihydrothiazine ring (Fig. 21.1). The cephem nucleus is chemically distinct from the penicillin nucleus, which contains a five-member thiazolidine ring. Basic structure numbering of the cephalosporin ring system begins within the dihydrothiazine ring at the sulfur moiety. The starting material used as the nucleus for current cephalosporin development is 7-aminocephalosporanic acid (7-ACA). Attempts to alter the physiochemical and biologic properties of the cephalosporins by chemical side chain modifications were based on successes with similar structural changes at the 6-aminopenicillanic acid side chain of penicillin.[3] Chemical modifications of the basic cephem structure by substitution of constituents at positions C1, C3, and C7 led to the various cephalosporin compounds in use today.[4,5] Alterations in positions C7 and C3 are also commonly referred to as R1 and R2, respectively. In general, changes at R1 affect the microbial spectrum of activity. These modifications often have an impact on the stability of the compound to enzymatic destruction by β-lactamases or on its affinity for the drug target (i.e., penicillin-binding proteins [PBPs]). Modifications at R2 often alter the pharmacology of the compound. For example, changes in the R2 constituent may influence the ability of the compound to reach certain infection sites, such as the central nervous system, or may prolong the elimination half-life of the drug. An exception to this rule is enhancement of oral absorption by the substitution of an aminobenzyl group in the C7 (R1) position.[5] Cephalexin, cephradine, cefaclor, cefprozil, and loracarbef all have this structure or a closely related one (Figs. 21.2 and 21.3). However, absorption of later-generation cephalosporins is enhanced by the production of ester formulations. Axetil, proxetil, or pivoxil esters of cefuroxime, cefpodoxime, and cefditoren are examples.

The predominant changes at R1 (position C7) include the substitution of the hydrogen with a methoxy group or the addition of an acyl side chain.[5] The R1 methoxy substitution led to the development of the cephamycin group of compounds, including cefoxitin, cefmetazole, and cefotetan (see Fig. 21.3). This alteration enhanced resistance to β-lactamase produced by gram-negative anaerobic and aerobic bacteria.[5,6] However, these compounds have lower affinity for the PBP target in gram-positive bacteria.[7]

Most of the chemical modifications in cephalosporin development that have resulted in changes in microbiologic spectrum are alterations at the α-carbon of the acyl side chain.[5] Many modifications of the acyl side chain have been undertaken. These changes have ranged from the relatively simple addition of a hydroxyl group to the addition of large synthetic moieties. Each of the acyl side chain alterations has led to enhanced gram-negative potency because of improved β-lactamase stability. The first compounds resulting from addition of a thienyl ring or a tetrazole structure at R1 included the first-generation cephalosporins—cephalothin, cephaloridine, and cefazolin (see Fig. 21.2). The addition of a hydroxyl group at the α-carbon led to the second-generation cephalosporin cefamandole. The second-generation cephalosporin cefuroxime resulted from the addition of a methoxyimino group in the α-position, along with a furyl ring at the β-acyl side chain. Addition of a 2-aminothiazol group to the C7 β-acyl side chain and a methoxyimino group to the α-carbon led to many of the third- and fourth-generation cephalosporins (Figs. 21.4 and 21.5).[8,9] Cefotaxime, ceftizoxime, ceftriaxone, cefepime, cefpirome, and cefpodoxime all have a similar structure at the C7 position. Ceftazidime and ceftolozane differ from these drugs in that the methoxyimino group is replaced with a dimethylacetic acid moiety attached to the imino group.[8,10] This alteration enhances activity against *Pseudomonas aeruginosa* but reduces activity against staphylococci. Two other modifications that have resulted in compounds with increased activity against *P. aeruginosa* are the addition of a ureido-2,3-dioxopiperazine group or a carboxyl group on the α-carbon, producing cefoperazone and moxalactam, respectively.[5] These changes are similar to those of piperacillin and carbenicillin.

Numerous modifications at R2 (the C3 position) have also played a significant role in the development of the current cephalosporins. An acetoxy side chain is present in cephalothin, cephapirin, and cefotaxime.[5] Cephalosporins with this structure can be metabolized in both serum and liver to a less active desacetyl derivative. Such drugs also tend to have a short half-life. A chloride substitution at R2 enhanced the gram-negative spectrum of activity and led to the development of cefaclor, an early second-generation cephalosporin. The unique pharmacology of ceftriaxone results from an R2 modification. Substitution of a heterocyclic thiomethyl group at the C3 position increases biliary secretion and remarkably prolongs the elimination half-life of the compound because of high protein binding.[5,11] The addition of a positively charged quaternary ammonium moiety in the C3 position contributed to the development of the fourth-generation cephalosporins cefepime and cefpirome.[9] The chemical modification produces a zwitterion, which enhances the ability of the compound to penetrate the outer membrane of gram-negative organisms. The inclusion of additional amino groups to this ammonium moiety further enhances activity against *P. aeruginosa*.[10]

More recently, cephalosporins with enhanced activity against methicillin-resistant *Staphylococcus aureus* (MRSA) have been developed (Fig. 21.6). A variety of structural alterations at the C3 and C7 positions have increased the drug's stability to β-lactamase inactivation and enhanced tight binding to the altered PBP2A'.[12,13] Because some of these compounds require more lipophilicity at the C3 position for activity, prodrugs have been required to enhance aqueous solubility.[14,15]

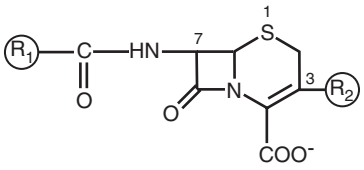

FIG. 21.1 Basic cephalosporin nucleus.

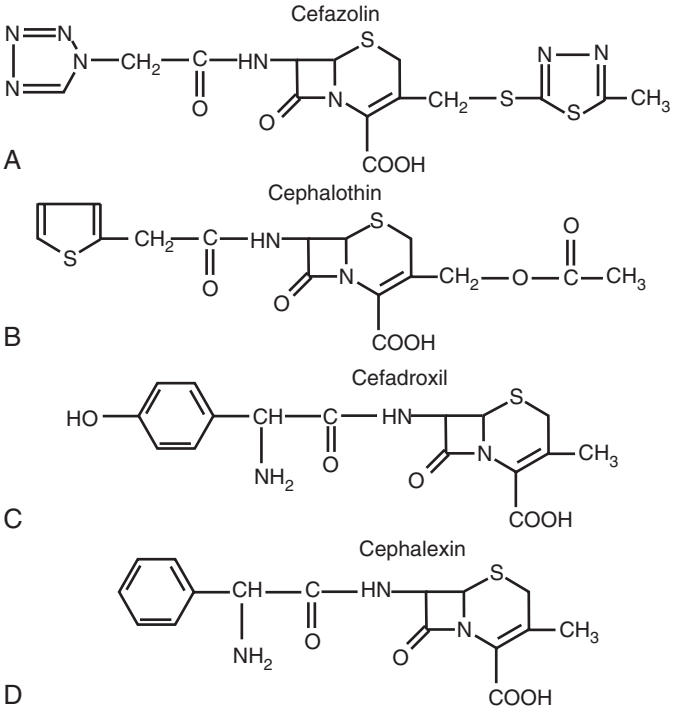

FIG. 21.2 First-generation cephalosporins. (A) Cefazolin. (B) Cephalothin. (C) Cefadroxil. (D) Cephalexin.

Ceftolozane (Fig. 21.7) is a 7-aminothiadiazole structure that is structurally similar to ceftazidime but contains a large pyrazole constituent at R2. This larger R2 moiety particularly inhibits AmpC β-lactamases, but also ensures that ceftolozane activity is unaffected by porin (OprD) loss and efflux pump activity.[16,17] These combined effects and high affinity for PBP1B, PBP1C, and PBP3 result in enhanced in vitro potency, especially against *P. aeruginosa,* compared with other agents.[18,19]

The newest members of the cephalosporin class are the siderophore cephalosporins; however, they have yet to be available for clinical use. Iron is a critical element for bacterial survival but is limited because it is tightly bound to mammalian proteins. In response, bacteria upregulate production of siderophores, which scavenge iron from the environment for bacterial use. Structurally, siderophore cephalosporins contain the traditional cephalosporin structure with the addition of a cathecol moiety at R2 that binds iron, after which it is taken up by the bacterial cell by iron transport systems in a manner that has been described as the "Trojan horse" effect.[20] The delivery of the cephalosporin into the cell allows its cellular action to take place. Important to note, siderophore cephalosporins have demonstrated in vitro activity against drug-resistant gram-negative rods.[21-25] Cefiderocol is the furthest siderophore cephalosporin in the developmental pipeline, which contains the same R1 sidechain as ceftazidime and an R2 catechol moiety (Fig. 21.8).

Not all modifications have led to desired effects. The placement of a thiomethyl tetrazole ring (methylthiotetrazole [MTT]) at the R2 position enhanced antibacterial activity but also resulted in two important adverse effects that have limited use of these compounds.[26,27] Cefamandole, cefotetan, cefoperazone, and moxalactam (an oxycephem) contain this MTT side chain, which is responsible for coagulation abnormalities related to antagonism of vitamin K action. This side chain is also responsible for the disulfiram-like properties of these compounds.

CLASSIFICATION

There are several microbiologic and pharmacologic differences that could serve as a basis for classification among the drugs in the cephalosporin class. The most widely accepted classification includes five divisions, or generations, based loosely on the microbial spectrum of activity (Table 21.1). The first-generation cephalosporins exhibit activity focused primarily on gram-positive bacteria. The second-generation drugs have enhanced activity against gram-negative bacilli but maintain varying degrees of activity against gram-positive cocci. The cephamycin group is included in the second-generation classification. The cephamycins are noted for their additional activity against gram-negative anaerobic bacteria, such as *Bacteroides* spp. The third-generation cephalosporins have markedly increased potency against gram-negative bacilli; however, for some compounds in this group, activity against gram-positive cocci is reduced. Among the third-generation group, a few compounds, such as ceftazidime and ceftolozane, are considered separately for activity against *P. aeruginosa.* The fourth-generation drugs have the widest

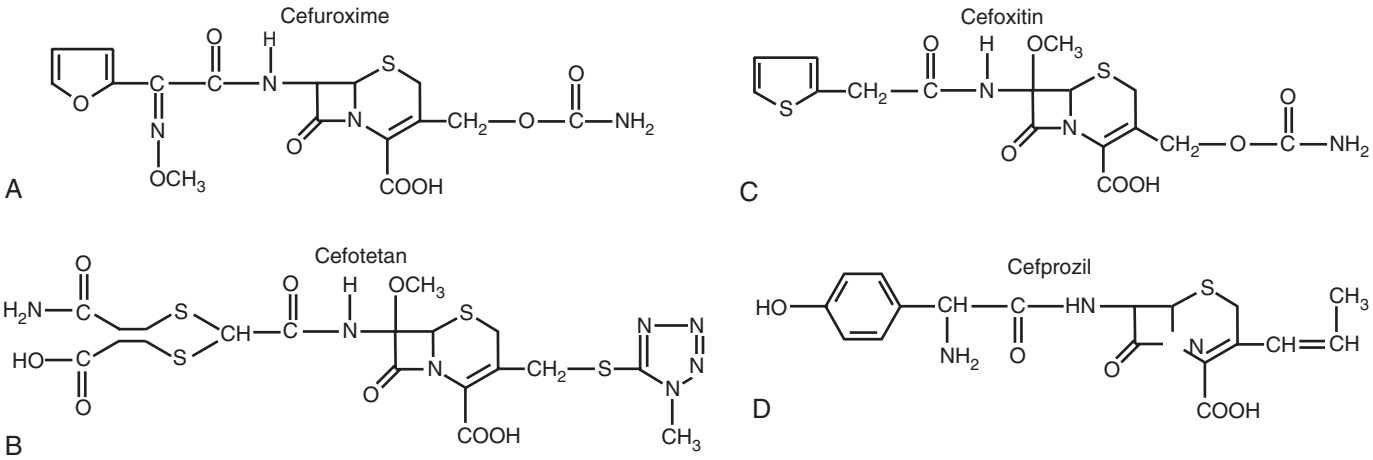

FIG. 21.3 Second-generation cephalosporins. (A) Cefuroxime. (B) Cefotetan. (C) Cefoxitin. (D) Cefprozil.

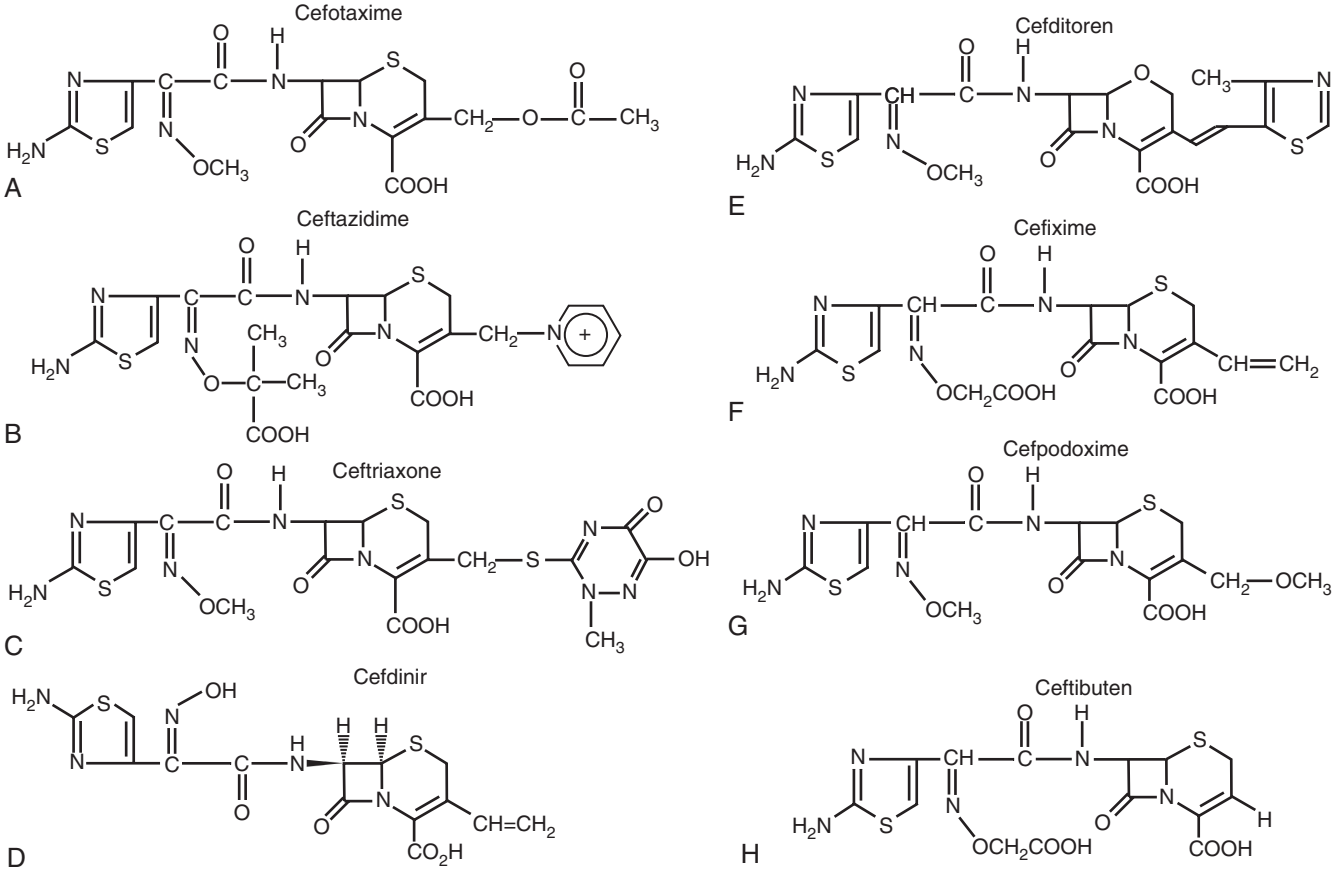

FIG. 21.4 Third-generation cephalosporins. (A) Cefotaxime. (B) Ceftazidime. (C) Ceftriaxone. (D) Cefdinir. (E) Cefditoren. (F) Cefixime. (G) Cefpodoxime. (H) Ceftibuten.

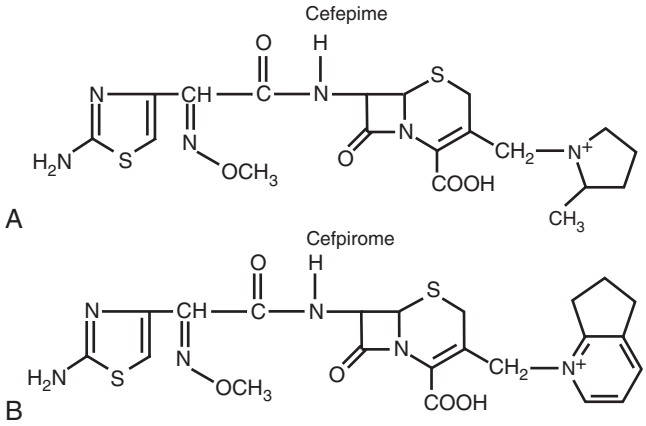

FIG. 21.5 Fourth-generation cephalosporins. (A) Cefepime. (B) Cefpirome.

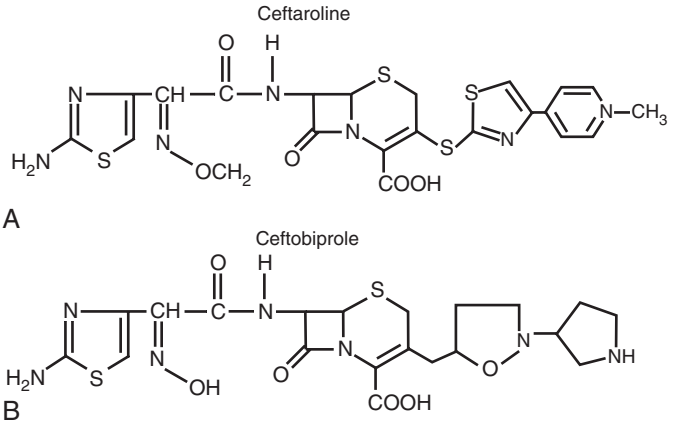

FIG. 21.6 Methicillin-resistant *Staphylococcus aureus*–active cephalosporins. (A) Ceftaroline. (B) Ceftobiprole.

spectrum of activity of the five groups. These drugs, such as cefepime and cefpirome, have activity against most gram-negative bacilli, including *P. aeruginosa,* and maintain their potency against gram-positive cocci. The third- and fourth-generation drugs combined are also called the extended-spectrum cephalosporins. The fifth group is referred to as the MRSA-active cephalosporins and currently includes ceftaroline and ceftobiprole. In addition to this unique activity against MRSA among the cephalosporins, these drugs also have enhanced activity against *Streptococcus pneumoniae* and *Enterococcus faecalis.* Their activity against gram-negative bacilli is similar to that of the third-generation cephalosporins. Ceftobiprole also has activity against *P. aeruginosa.*

More recently, a few cephalosporins susceptible to inactivation by extended-spectrum β-lactamases (ESBLs) have been combined with β-lactamase inhibitors (BLIs) to expand their activity against gram-negative bacilli. Ceftazidime is combined with avibactam, whereas ceftolozane is combined with tazobactam. The aforementioned siderophore cephalosporin and continued development of novel cephalosporin-BLI combinations with enhanced activity against drug-resistant gram-negative organisms exhibit mechanistic and spectrum novelties leading to distinct cephalosporin categories (see Table 21.1).

MECHANISM OF ACTION

The mechanism of antibacterial activity of cephalosporins is similar to that of other β-lactam drugs. Bacterial growth is inhibited by interference with the synthesis of the cell wall. The primary target of these compounds within the cell wall is the peptidoglycan cross-linkage structure.[28]

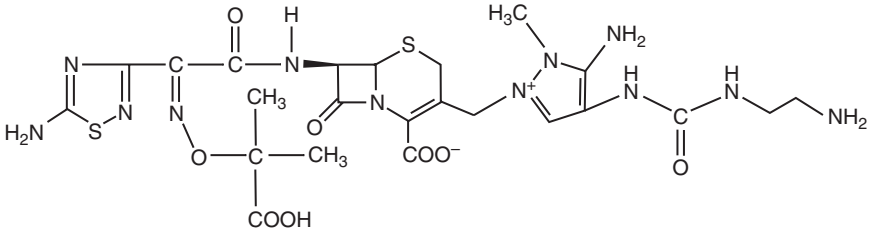

FIG. 21.7 Ceftolozane.

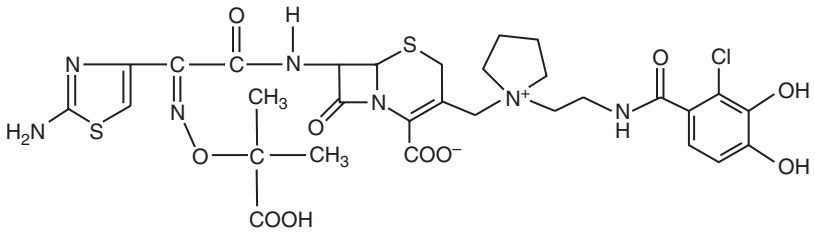

FIG. 21.8 Siderophore cephalosporin cefiderocol.

Peptidoglycans are polysaccharide chains consisting of alternating *N*-acetylglucosamine and *N*-acetylmuramic acid residues. The polysaccharide chains are cross-linked at the pentapeptide side chain of the *N*-acetylmuramic acid residues to form a netlike structure. These structures are inserted into the cytoplasmic membrane from the cytoplasm by the action of a group of enzymes that includes transpeptidases, carboxypeptidases, and endopeptidases. The lactam ring provides for penicillins and cephalosporins a conformation similar to the terminal D-alanine-D-alanine of the pentapeptide.[29] These antibiotics bind covalently to these enzymes, in particular to the transpeptidases, resulting in loss of enzyme activity.[28] The enzyme drug targets are referred to as penicillin-binding proteins (PBPs).[30,31]

The location of the PBPs relative to the extracellular space differs between gram-positive and gram-negative bacteria. The peptidoglycan of gram-positive bacteria is located on the outer surface of the cell. Conversely, a complex lipopolysaccharide (LPS) structure is located on the outermost surface of gram-negative bacteria such that a cephalosporin must first penetrate or diffuse across the LPS membrane to reach the PBPs. The PBP targets within bacteria vary by size and affinity for different β-lactam antibiotics. It is generally agreed the high-molecular-weight PBPs (PBP1A, PBP1B, PBP2, and PBP3) are the most critical for cellular function, and inhibiting more than one high-molecular-weight PBP can provide superior antimicrobial action.[32,33] At low concentrations cephalosporins preferentially bind to PBP3 in gram-negative bacilli, resulting in filament formation with septae.[33,34] At higher concentrations, many cephalosporins also bind to PBP1A, PBP1B, or both, resulting in spheroplast formation and rapid lysis.[33] Cephalosporins with enhanced gram-positive activity (e.g., cefazolin) likely owe their effects to high-affinity binding of both PBP2 and PBP3.[33] Finally, as mentioned previously, the MRSA-active cephalosporins maintain their activity by means of binding to the altered penicillin binding protein PBP2A′ (mecA gene product), which confers methicillin resistance.

In general, cephalosporins are considered to be bactericidal drugs. The rate of killing of bacteria by cephalosporins exhibits minimal dependence on the concentration of the antibiotic.[35] Maximal bacterial killing is observed at concentrations four times the minimal inhibitory concentration (MIC). Cephalosporins produce persistent suppression of bacterial growth (i.e., the postantibiotic effect) of several hours' duration with gram-positive bacteria, but they induce very short or no postantibiotic effects with gram-negative bacilli.[36,37] The duration of time during which drug concentrations exceed the MIC is the major determinant of the antibacterial activity of the cephalosporins.[37,38,39] Net stasis efficacy of cephalosporins against gram-positive pathogens, such as *S. aureus* or *S. pneumoniae,* is noted at free-drug concentrations exceeding the MIC (T>MIC) for 25% to 40% of the dosing interval. Conversely, stasis activity for cephalosporins against most gram-negative organisms, including *P. aeruginosa,* occurs at free-drug concentrations T>MIC of 35% to 45% of the dosing interval, and maximal effects at about 60% of the dosing interval.

SPECTRUM OF ACTIVITY

The cephalosporins are active against a wide variety of aerobic and anaerobic bacteria (Tables 21.2 and 21.3).[a] Most drugs are active against streptococci and staphylococci, which is expected given their similar structure to penicillins. However, there are important differences in potency among cephalosporin agents noted for penicillin-resistant pneumococci. Ceftaroline and ceftobiprole have the greatest potency against these organisms, followed by cefditoren, ceftriaxone, cefotaxime, cefepime, and cefpirome.[70,74] A few members have less activity against methicillin-susceptible staphylococci, including the cephamycins, ceftazidime, cefixime, and ceftibuten. Extensive surveillance susceptibility data are lacking for newer cephalosporin-BLI combinations in terms of gram-positive coverage, but it is likely that the same activity exists for these (ceftazidime-avibactam and ceftolozane-tazobactam) as is noted for ceftazidime, given the structural similarity. Although MRSAs are resistant to all the earlier cephalosporins, the new MRSA-active cephalosporins ceftaroline and ceftobiprole exhibit low MICs of 0.25 to 2 μg/mL.[70,74] Enterococci have also consistently been resistant to the cephalosporins, with most MICs greater than 32 μg/mL. However, the new MRSA-active cephalosporins have much lower MICs for ampicillin-susceptible strains. These have ranged from 0.12 to 4 μg/mL for both drugs.[70,74]

The first-generation cephalosporins are not very active against *Haemophilus influenzae* or *Moraxella catarrhalis.* The second-generation drugs are about fourfold more potent against these respiratory pathogens. The third-generation cephalosporins have the lowest MICs for *H. influenzae* and *M. catarrhalis*—10 to 100 times lower than those of the second-generation drugs. The first-generation cephalosporins also are not as active against *Neisseria* spp. as the second-, third-, and fourth-generation drugs.

Although all of the cephalosporins are considered to be active against *Escherichia coli, Klebsiella pneumoniae,* and *Proteus mirabilis,* the potency of the third- and fourth-generation drugs and the MRSA-active cephalosporins is 10- to 100-fold greater than that of the first- and second-generation cephalosporins. The increased potency of the later-generation

[a]References 16, 18, 40, 41-48, 49, 50-62, 63, 64, 65-73, 74, 75-82, 83, 84-87, 88, 89, 90, 91, 92, 93, 94, 95.

TABLE 21.1 Classification of Parenteral and Oral Cephalosporins

1ST GENERATION	2ND GENERATION	CEPHAMYCINS	3RD GENERATION	4TH GENERATION	5TH GENERATION (MRSA-ACTIVE CEPHALOSPORINS)	CEPHALOSPORIN–β-LACTAMASE INHIBITOR COMBINATIONS	SIDEROPHORE CEPHALOSPORINS
Parenteral Cephalosporins							
Cefazolin (Ancef, Kefzol) Cephalothin (Keflin, Seffin)[a] Cephapirin (Cefadyl)[a] Cephradine (Velosef)[a]	Cefamandole (Mandol)[a] Cefonicid (Monocid)[a] Cefuroxime (Kefurox, Zinacef)	Cefmetazole (Zefazone)[a] Cefotetan (Cefotan) Cefoxitin (Mefoxin)	Cefoperazone (Cefobid)[a] Cefotaxime (Claforan) Ceftazidime (Fortaz) Ceftizoxime (Cefizox)[a] Ceftriaxone (Rocephin) Moxalactam[a]	Cefepime (Maxipime) Cefpirome (Cefrom)[a]	Ceftaroline (Teflaro) Ceftibiprole (Zeftera)[a]	Ceftolozane-tazobactam Ceftazidime-avibactam	Cefiderocol
Oral Cephalosporins							
Cefadroxil (Duricef, Ultracef) Cephalexin (Keflex, Biocef, Keftab) Cephradine (Velosef)[a]	Cefaclor (Ceclor)[a] Cefprozil (Cefzil) Cefuroxime-axetil (Ceftin) Loracarbef (Lorabid)[a]		Cefdinir (Omnicef) Cefditoren (Spectracef) Cefixime (Suprax) Cefpodoxine (Vantin) Ceftibuten (Cedax)				

[a]No longer marketed in the United States.
MRSA, Methicillin-resistant *Staphylococcus aureus.*

TABLE 21.2 In vitro Activity of Cephalosporins Against Selected Gram-Positive Cocci, *Haemophilus Influenzae, Moraxella Catarrhalis,* and *Neisseria* Species

	STREPTOCOCCUS PNEUMONIAE (PSSP)	*S. PNEUMONIAE* (PRSP)	*STREPTOCOCCUS PYOGENES*	*STREPTOCOCCUS AGALACTIAE*	VIRIDANS STREPTOCOCCI GROUP	*STAPHYLOCOCCUS AUREUS* (MSSA)	*S. AUREUS* (MRSA)	*STAPHYLOCOCCUS EPIDERMIDIS*	*HAEMOPHILUS INFLUENAZAE*	*MORAXELLA CATARRHALIS*	*NEISSERIA MENINGITIDIS*	*NEISSERIA GONORRHOEAE*
First Generation												
Cefazolin	0.5/4	32/>32	0.12/0.12	0.12/0.12	0.12/0.12	0.5/2	—	0.5/>32	4/16	2/4	—	16/32
Cephalothin	0.12/0.25	8/16	0.05/0.10	0.12/0.5	0.25/0.50	0.12/0.5	—	0.5/32	4/8	4/8	0.25/0.5	8/32
Cefadroxil (O)	2/4	>32	0.12/0.25	0.25/2	—	2/8	—	4/>32	16/>32	2/4	—	8/64
Cephalexin (O)	1/2	>32	0.25/2	0.5/4	—	2/4	—	1/>32	8/16	2/8	2/2	4/16
Cephradine (O)	2/4	>32	0.25/2	0.5/2	—	1/4	—	4/>32	4/16	2/4	—	8/16
Second Generation												
Cefamandole	0.12/0.5	8/>32	0.12/0.12	0.12/0.5	0.12/4	1/1	—	0.5/>32	2/8	1/4	0.12/0.12	0.25/4
Cefonicid	0.5/1	4/>32	0.12/0.12	0.12/2	0.12/8	1/2	—	2/>32	0.5/1	1/4	0.12/2	0.06/0.5
Cefuroxime	0.12/0.25	4/>32	0.12/0.12	0.12/0.12	0.12/0.5	1/2	—	0.5/>32	1/2	0.5/2	0.12/2	0.015/0.25
Cefaclor (O)	0.5/1	16/>32	0.06/0.5	0.5/2	—	1/8	—	1/>32	2/32	0.5/2	0.06/0.25	0.25/16
Cefprozil (O)	0.12/0.5	8/>32	0.03/0.12	0.06/0.25	—	0.5/2	—	0.25/32	2/16	1/8	—	0.12/4
Loracarbef (O)	0.5/2	>32	0.5/2	0.5/2	—	1/4	—	4/>32	1/4	0.5/4	0.12/0.25	0.5/4
Cephamycins												
Cefmetazole	2/16	>32	0.5/0.5	2/2	2/4	4/16	—	8/>32	1/4	0.12/0.5	0.12/0.12	0.25/4
Cefotetan	8/16	>32	2/4	4/8	2/8	8/16	—	32/>32	1/2	0.12/2	0.12/0.25	0.25/2
Cefoxitin	2/4	32/>32	1/2	2/2	4/16	4/8	—	2/>32	1/4	0.25/0.5	0.12/0.25	0.25/4
Third Generation												
Cefoperazone	0.06/0.12	4/16	0.12/0.12	0.12/0.25	0.5/1	2/4	—	2/>32	0.015/0.25	0.12/2	0.12/0.5	0.03/0.06
Cefotaxime	0.015/0.06	0.5/2	0.015/0.015	0.03/0.25	0.06/0.25	2/2	—	4/>32	0.008/0.015	0.5/1	0.004/0.008	0.004/0.008
Ceftazidime	0.25/1	16/>32	0.12/0.25	0.25/0.5	1/2	8/32	—	8/>32	0.06/0.12	0.03/0.5	0.015/0.06	0.03/0.06
Ceftizoxime	0.25/1	16/32	0.015/0.015	0.12/0.12	0.25/2	4/8	—	4/>32	0.015/0.03	0.03/0.5	0.008/0.03	0.008/0.015
Ceftriaxone	0.03/0.06	0.5/2	0.015/0.03	0.03/0.06	0.06/0.25	2/4	—	4/>32	0.008/0.015	0.25/0.5	0.008/0.015	0.002/0.004
Moxalactam	1/1	—	1/2	—	—	8/16	—	8/>32	0.03/0.12	0.03/0.12	0.008/0.06	0.015/0.06
Cefdinir (O)	0.06/0.12	2/8	0.015/0.03	0.03/0.06	—	0.25/0.5	—	0.25/>32	0.12/0.5	0.06/0.25	0.06/0.25	0.008/0.06
Cefditoren (O)	0.015/0.03	0.5/2	0.008/0.015	0.06/1	—	0.25/1	—	0.25/>32	0.008/0.015	0.25/1	<0.06/0.06	0.004/0.06
Cefixime (O)	0.25/1	32/>32	0.06/0.25	0.12/0.25	—	16/>32	—	16/>32	0.015/0.12	0.03/0.5	<0.06/0.06	0.015/0.06
Cefpodoxime (O)	0.015/0.06	2/>32	0.06/0.12	0.03/0.12	—	2/4	—	2/>32	0.015/0.12	1/2	<0.06/0.06	0.06/0.06
Ceftibuten (O)	4/8	>32	0.5/2	4/16	—	16/>32	—	16/>32	0.06/0.12	2/4	0.06/0.25	0.015/0.5
Fourth Generation												
Cefepime	0.06/0.12	0.5/2	0.015/0.12	0.05/0.05	0.016/0.03	2/4	—	2/>32	0.06/0.12	1/4	0.03/0.06	0.03/0.06
Cepirome	0.03/0.12	0.5/2	0.008/0.06	0.06/0.06	0.06/0.25	1/2	—	1/>32	0.06/0.12	0.5/2	0.06/0.06	.015/0.12
Fifth Generation												
Ceftaroline	≤0.016/≤0.016	0.12/0.25	≤0.016/≤0.016	≤0.016/≤0.016	≤0.016/0.03	0.25/0.25	0.5/1	0.25/1	1/4	0.06/0.12	0.002/0.004	0.008/0.03
Ceftobiprole	≤0.06/≤0.06	0.25/0.5	≤0.06/≤0.06	0.06/0.12	≤0.06/0.25	0.25/0.5	0.5/2	0.12/2	0.5/4	0.12/0.5	0.002/0.004	0.03/0.06

Minimal inhibitory concentration (MIC) for 50% and 90% of strains in µg/mL.
MRSA, Methicillin-resistant *Staphylococcus aureus; MSSA,* methicillin-susceptible *S. aureus; O,* oral; *PSRP,* penicillin-resistant *Streptococcus pneumoniae; PSSP,* penicillin-susceptible *S. pneumoniae.*

TABLE 21.3 In vitro Activity of Cephalosporins Against Selected Aerobic and Anaerobic Gram-Negative Bacilli

	ESCHERICHIA COLI	*KLEBSIELLA PNEUMONIAE*	*PROTEUS MIRABILIS*	*ENTEROBACTER AEROGENES*	*ENTEROBACTER CLOACAE*	*CITROBACTER FREUNDII*	*SERRATIA* SPP.	*PSEUDOMONAS AERUGINOSA*	*MORGANELLA* SPP.	*BACTEROIDES FRAGILIS*	*SALMONELLA* SPP.	*SHIGELLA* SPP.
First Generation												
Cefazolin	2/16	2/>16	4/16	>32	>32	>32	>32	>32	>32	>32	2/4	2/8
Cephalothin	4/8	1/16	8/16	>32	>32	>32	>32	>32	>32	>32	2/4	4/8
Cefadroxil (O)	4/>16	8/>16	16/>32	>32	>32	>32	>32	>32	>32	>32	8/>16	4/16
Cephalexin (O)	8/>16	8/32	16/>32	>32	>32	>32	>32	>32	>32	>32	4/16	8/>16
Cephradine (O)	4/>16	4/>16	16/>32	>32	>32	>32	>32	>32	>32	>32	4/>16	8/>16
Second Generation												
Cefamandole	1/2	1/8	1/2	4/>32	2/>32	2/>32	16/>32	>32	4/>32	32/>32	0.5/4	0.5/2
Cefonicid	2/8	2/8	1/2	4/>32	8/>32	8/>32	>32	>32	16/>32	32/>32	2/8	2/8
Cefuroxime	2/8	2/16	2/4	8/>32	8/>32	8/>32	>32	>32	32/>32	8/>32	4/8	2/4
Cefaclor (O)	2/>16	2/32	2/4	>32	>32	>32	>32	>32	>32	>32	2/8	4/16
Cefprozil (O)	2/8	1/>32	2/2	>32	>32	16/>32	16/>32	>32	16/> 32	>32	2/8	4/16
Loracarbef (O)	1/>16	0.5/8	0.5/2	16/>32	16/>32	4/>32	>32	>32	32/>32	>32	0.5/8	0.25/8
Cephamycins												
Cefmetazole	0.5/1	1/2	2/4	>32	>32	>32	16/>32	>32	4/8	8/>32	0.5/2	1/2
Cefotetan	0.12/0.5	0.12/0.5	0.12/0.5	32/>32	8/>32	0.5/>32	1/8	>32	2/4	8/>32	0.12/0.12	0.12/0.5
Cefoxitin	2/8	2/8	2/4	>32	>32	>32	16/>32	>32	8/16	8/32	2/4	2/4
Third Generation												
Cefoperazone	0.12/8	0.25/8	0.5/1	0.25/8	0.25/8	0.5/32	2/8	4/>32	1/8	32/>32	0.5/4	0.25/1
Cefotaxime	0.06/0.25	0.06/0.25	0.06/0.25	0.12/16	0.25/32	0.25/>32	0.25/2	16/>32	0.25/4	8/>32	0.06/0.12	0.06/0.25
Ceftazidime	0.06/0.25	0.25/1	0.06/0.5	0.25/32	0.25/32	0.5/>32	0.25/2	2/16	0.12/0.5	>32	0.12/0.5	0.06/0.25
Ceftizoxime	0.03/0.12	0.03/0.12	0.008/0.015	0.06/16	0.06/16	0.25/>32	0.12/0.5	32/>32	0.25/2	16/>32	0.015/0.25	0.008/0.25
Ceftriaxone	0.06/0.12	0.06/0.25	0.008/0.03	0.25/16	0.25/>32	0.12/>32	0.25/4	32/>32	0.008/0.25	8/>32	0.06/0.25	0.03/0.12
Moxalactam	0.12/0.25	0.12/0.25	0.25/0.5	0.25/16	0.5/8	0.25/8	0.25/4	32/>32	0.25/0.5	2/32	0.12/0.25	0.12/0.25
Cefdinir (O)	0.12/0.25	0.06/0.25	0.06/0.12	0.5/>32	0.5/>32	0.25/>32	4/32	16/>32	4/16	16/ >32	0.12/0.25	0.25/0.5
Cefditoren (O)	0.25/0.5	0.25/1	0.12/1	0.5/>32	1/>32	1/>32	2/32	>32	—	4/>32	0.25/0/5	0.25/0.5
Cefixime (O)	0.12/0.25	0.03/0.12	0.008/0.03	0.5/>32	0.12/>32	2/>32	2/>32	>32	2/32	16/>32	0.06/0.25	0.25/0.5
Cefpodoxime (O)	0.25/1	0.5/2	0.06/0.12	2/>32	4/>32	2/>32	1/8	>32	2/>32	16/>32	0.5/1	0.12/0.25
Ceftibuten (O)	0.12/0.25	0.06/0.25	0.015/0.03	1/32	2/>32	1/>32	0.5/8	>32	0.25/8	16/>32	0.06/0.25	0.06/0.25
Fourth Generation												
Cefepime	0.03/0.06	0.03/0.25	0.06/0.12	0.06/0.5	0.06/2	0.06/2	0.12/0.5	2/16	0.03/0.12	>32	0.06/0.12	0.03/0.06
Cefpirome	0.06/0.12	0.06/0.25	0.06/0.12	0.06/0.5	0.12/4	0.03/2	0.25/2	2/16	0.03/0.12	32/>32	0.06/0.25	0.06/0.12
Fifth Generation												
Ceftaroline	0.06/0.5	0.06/0.25	0.06/4	0.12/8	0.12/1	0.5/8	0.06/16	16/128	0.06/2	8/>32	0.12/0.25	0.03/0.12
Ceftobiprole	0.06/0.12	0.06/>8	0.03/0.12	0.03/>32	0.12/>32	0.12/4	0.06/2	4/16	—	16/>64	0.03/0.06	0.03/0.06
Cephalosporin–β-Lactamase Inhibitor												
Ceftolozane-tazobactam	0.12/0.5 (all) 0.5/4 (ESBL)	0.25/8 (all) 0.5/64 (ESBL) ≥32/≥32 (KPC)	0.25/0.5 (all) 1/8 (ESBL)	0.25/8	0.25/8	0.25/8	0.5/1	0.5/2 (all) 4/>32 (MDR)	—	1/4	—	—
Ceftazidime-avibactam	0.06/0.12 (all) 0.12/0.25 (ESBL)	0.12/0.5 (all) 0.25/1 (ESBL) 0.25/1 (KPC)	0.06/0.12	0.25/0.5	0.25/1	0.25/0.5	0.25/0.5	2/8 (all) 4/32 (MDR)	0.06/0.12	4/32	0.25/0.5	—

Minimal inhibitory concentration (MIC) for 50% and 90% of strains in μg/mL.
ESBL, Extended-spectrum β-lactamase producing organisms; *KPC, Klebsiella pneumoniae* carbapenemase–producing organisms; *MDR,* multidrug-resistance; *O,* oral.

drugs extends to strains of *Enterobacter, Serratia, Citrobacter,* and *Morganella* spp., which are usually resistant to the first- and second-generation drugs. Several cephalosporins, such as ceftazidime, ceftolozane, cefoperazone, cefepime, cefpirome, and ceftobiprole, are active against many strains of *P. aeruginosa.* The addition of β-lactamase inhibitors (e.g., avibactam and tazobactam) significantly increases the activity of cephalosporin-BLI combination drugs (e.g., ceftazidime-avibactam and ceftolozane-tazobactam) against drug-resistant gram-negative rods.

The third- and fourth-generation cephalosporins also exhibit enhanced potency against strains of *Salmonella* and *Shigella.* Many cephalosporins are active against penicillin-susceptible gram-positive anaerobes, such as peptostreptococci.[96,97] Among the cephalosporins, the best activity against *Bacteroides fragilis* is with the cephamycins and the cephalosporin-BLI combinations. Many of the drugs are active against spirochetes, including the agents of Lyme disease and syphilis.[98,99] As a group, the cephalosporins have very poor activity against *Chlamydia, Mycoplasma,* and *Listeria* spp.[100-102]

MECHANISMS OF RESISTANCE

Four general mechanisms can result in resistance to cephalosporin antibiotics: (1) antibiotic destruction by hydrolyzing β-lactamase enzymes, (2) reduced penetration of the antibiotic through the LPS membrane to the PBP target, (3) enhanced efflux of the drug from the periplasmic space, and (4) alteration in the PBP target, resulting in reduced binding affinity. Most often, resistance in a bacterial population is caused by a single mechanism; however, an increasing percentage of organisms, particularly Enterobacteriaceae and *P. aeruginosa,* exhibit multiple mechanisms.[103,104,105,106,107]

Production of β-lactamase enzymes that hydrolyze the β-lactam ring is a common resistance mechanism for many gram-negative bacteria. Although all gram-negative bacilli produce β-lactamase enzymes, the type and amount of enzyme vary among organisms. These enzymes are located in the periplasmic space between the outer and inner membranes that comprise the gram-negative cell wall. The penetration of drugs across the outer membrane is through water-filled channels formed by various membrane proteins, termed *porins.* Movement through porin channels depends on the size, shape, charge, and hydrophilic properties of the compound. Drugs that are able to penetrate the outer membrane via porins are then subject to degradation by β-lactamase enzymes before being able to reach the PBP target. The net antimicrobial activity of cephalosporins against gram-negative bacilli is dependent on both the rate of penetration across the outer membrane (i.e., rate of movement through porins) and the stability of the drug to the various hydrolyzing β-lactamases. The concentration of a drug with a slow rate of penetration is low relative to the amount of β-lactamase within the periplasmic space. In this case, if there are sufficiently active β-lactamase enzymes present, the result would be near-complete antibiotic inactivation. Conversely, a drug can penetrate so rapidly that even if active β-lactamase enzymes exist, the antibiotic can remain active because the enzymatic capacity for degradation is overwhelmed. For example, the zwitterion of cefepime enhances movement across the membrane, resulting in very high concentrations in the periplasmic space and a relative net resistance to drug hydrolysis.[108]

The number of unique β-lactamases is markedly increasing, with more than 1000 distinct enzymes; even a single amino-acid difference from one enzyme to another may affect phenotype. These proteases may be genetically encoded chromosomally or extrachromosomally (i.e., mobile elements). Stable derepression of a chromosomal mutation is a common genotypic scenario. This is observed predominantly in *Enterobacter* spp., *Serratia* spp., *Citrobacter freundii,* and *P. aeruginosa.*[109] Transmissible plasmids are the largest and most common reason for resistance in Enterobacteriaceae, especially for *E. coli* and *K. pneumoniae.* Multiple classification schemes have been devised; the simplest is the molecular or Ambler classification (see Chapter 18 for further details).[110] Examples of the most relevant β-lactamase enzymes resulting in cephalosporin resistance are discussed here.

Class A β-lactamases TEM (Temoneira) and SHV (sulfhydryl variable) confer resistance most commonly to penicillins and earlier classes of cephalosporins. However, newer enzyme variants have arisen as the result of amino-acid substitutions related to point mutations in the common β-lactamase genes (i.e., TEM and SHV). These are capable of inactivating many third- and fourth-generation cephalosporins.[111,112] These enzymes have been observed most commonly in *K. pneumoniae* and *E. coli* and are referred to as extended-spectrum β-lactamases (ESBLs). The new MRSA-active cephalosporins are also susceptible to inactivation by ESBLs.[113,114] More recently, the cefotaxime/ceftazidime-hydrolyzing (CTX-M) family of β-lactamases, derived from the chromosomal enzyme of *Kluyvera* spp., have spread into *K. pneumoniae* and *E. coli.*[115] CTX-M enzymes commonly confer resistance to cephalosporins including extended-spectrum cephalosporins, such as ceftazidime and cefepime. Indeed, CTX-M variants have been responsible for the massive explosion of ESLB-positive clinical isolates of *E. coli* throughout the world.[116,117] Finally, the first enzyme member responsible for carbapenem resistance in Enterobacteriaceae (now commonly termed CRE) was the KPC (*Klebsiella pneumoniae* carbapenemase) variant, which breaks down nearly all traditional β-lactam therapies including cephalosporins and carbapenems.[118,119] As discussed later, there have been successful efforts to combat class A β-lactamases that confer extended-spectrum β-lactam resistance (i.e., CTX-M) and carbapenem resistance (i.e., KPC) with newer cephalosporin therapies.

Class B β-lactamases are termed the *metallo-β-lactamases* owing to the dependence of zinc ions for activity rather than serine found in the other classes. VIM (Verona integron-encoded metallo-β-lactamase), NDM (New Delhi metallo-β-lactamase), and IMP (imipenemase) are examples and are all members that produce the carbapenem-resistant phenotype similar to KPC enzymes. Cephalosporins are rendered inactive, and unfortunately, novel cephalosporin antimicrobials remain inactive against the metallo-β-lactamases.

The prototypical class C β-lactamases are the AmpC enzymes, which are potent hydrolyzing enzymes for many cephalosporins.[120] The AmpC cephalosporinase is capable of inactivating almost all current cephalosporins, including the cephamycins. Emergence of this type of resistance is frequent when infections resulting from these organisms are treated only with broad-spectrum cephalosporins.[121,122] Cefepime, cefpirome, and ceftobiprole are less susceptible to inactivation by AmpC β-lactamases.[113,123,124]

Class D β-lactamases are termed OXA for their oxacillinase enzymatic activity. There are many OXA subgroups with varied phenotypic effects. A number of them, for example OXA-11 and OXA-15, hydrolyze cephalosporins including extended-spectrum cephalosporins, and resistance to numerous β-lactam drugs including carbapenems has been observed in organisms carrying OXA-48.[106,110]

Novel members of the cephalosporin class have been developed to combat β-lactamase resistance mechanisms. Ceftazidime-avibactam was developed specifically for activity against class A, C, and some class D enzymes.[91] The retained activity against these organisms is exclusively due to the presence of avibactam, a novel BLI developed in recent years. The result of this combination is an effective option for many of the most concerning epidemic types of β-lactamase-producing Enterobacteriaceae, which includes those that have the CTX-M or KPC enzymes. Although this is encouraging, not surprisingly, soon after release reports of resistance to ceftazidime-avibactam emerged.[125,126] Ceftolozane-tazobactam is similarly active against many class A and C enzymes, primarily though tazobactam activity.[16] The combination is active against many ESBL organisms, most importantly the CTX-M family, and maintains high stability in the face of AmpC β-lactamases, but unlike ceftazidime-avibactam, it does not have appreciable activity against KPC producers or class D enzymes (e.g., OXA). Finally, siderophore cephalosporins have demonstrated potent activity against class A, B, C, and D β-lactamases including carbapenemase enzymes such as KPC, NDM, IMP, VIM, and OXA.[127]

It is unlikely that deletion or mutation of porin proteins causes primary resistance to cephalosporins. However, such changes can alter the relationship between the concentrations of drug and β-lactamase in the periplasmic space, resulting in much more hydrolysis of the cephalosporin. For example, strains of *K. pneumoniae* containing ESBLs have been shown to be resistant to cephamycins because of the lack of an outer membrane porin protein.[128] Porin-deficient strains are especially high in *Enterobacter aerogenes.*[129] The endogenous AcrAB multidrug efflux system in *E. coli* affects the potency of penicillins but has little

effect on the activity of cephalosporins.[130] However, a major contribution to resistance in *P. aeruginosa* has been associated with porin-efflux pump systems, such as the MexAB-OprM efflux pump for ceftazidime and the MexXY-OprM efflux pump for cefepime and ceftobiprole.[131-134] The differences among these organisms in the impact of somewhat similar pumps are probably due to the markedly higher outer membrane permeability in *E. coli* compared with *P. aeruginosa*.[135]

Most cephalosporins, with the exception of cephaloridine, are poorly hydrolyzed by staphylococcal penicillinases. Thus, enhanced activity against many gram-positive organisms is noted for the early-generation cephalosporins in addition to some third- and fourth-generation cephalosporins such as ceftriaxone and cefepime. This differential activity of the cephalosporin class to gram-positive and select gram-negative pathogens is primarily due to differences in affinity to PBP2. Resistance to cephalosporins is therefore due almost entirely to alteration of the PBP2 target—for example, cephalosporin-resistant *S. pneumoniae,* MRSA, *H. influenzae,* and some *Neisseria gonorrhoeae* strains.

PHARMACOLOGIC PROPERTIES

The pharmacologic properties of selected cephalosporins are listed in Table 21.4.[b] Cephalosporins are polar, water-soluble compounds. Within each of the first-, second-, and third-generation classifications, there are both oral and parenteral formulations. The fourth- and fifth-generation compounds are available for parenteral use only. The parenteral formulations are available for both intravenous and intramuscular administration. All of the parenteral formulations, with the exception of cephradine, are stable in solution at room temperature for 24 hours or longer. Drug stability at room temperature facilitates use of these compounds for home intravenous therapy, including continuous infusions. Many of the parenteral compounds can also be administered by the intraperitoneal route for treatment of peritoneal infections associated with continuous ambulatory peritoneal dialysis.[169] Formulations of the oral cephalosporins are available as tablets, capsules, or suspensions.

In contrast to many other β-lactams, oral preparations of the cephalosporins are stable in the acid milieu of the upper gastrointestinal tract. Cephalosporins can be actively absorbed if their structure mediates transport by the dipeptide and tripeptide transport systems in the brush border membrane of the small intestine.[170] Cephalexin, cephradine, cefadroxil, cefaclor, cefprozil, and loracarbef have an aminobenzyl group or a similar group in the C7 position and have high oral bioavailability (80% to 95%). Ceftibuten, cefixime, and cefdinir have other groups in the C7 position and exhibit more variable bioavailability after oral administration. Absorption by the dipeptide and tripeptide transport systems appears to be both pH and calcium dependent.[170] Drugs that have low oral bioavailability can be esterified to enhance absorption; the ester prodrug is hydrolyzed after absorption in the intestinal epithelial cells. The esters commonly used include axetil, proxetil, and pivoxil formulations.[171] Ester prodrug formulations exist for cefuroxime, cefditoren, and cefpodoxime. Absorption of the ester is still not complete; in fact, the percent oral bioavailability of ester formulations is lower than that of most nonesterified compounds. Absorption of the ester formulations is enhanced by concomitant food intake[171] because food within the stomach delays gastric emptying and prolongs contact with the mucosal surface.

Distribution of cephalosporins within the body is governed by the lipid solubility of the drug and the extent of protein binding. β-Lactams bind almost exclusively to albumin. The extent of protein binding can vary from less than 10% to as much as 98%.[160] Because only unbound drug can pass through capillary pores into interstitial fluid or across cell membranes into intracellular fluid, avidly bound compounds tend to exhibit high serum concentrations and low tissue concentrations. In general, the cephalosporins are largely confined to the extracellular compartment. Drug concentrations in subcutaneous blisters, a model for extracellular drug penetration, are similar to those found in serum.[157,172] Techniques measuring extracellular drug concentrations in human tissues (e.g., microdialysis) have demonstrated that concentrations of unbound drug in interstitial fluid are also similar to those in serum.[173,174] The cephalosporins have relatively poor intracellular concentrations such that tissue homogenates, which mix intracellular and extracellular fluid, always provide concentrations that are lower than those in serum because of dilution by the larger intracellular volume.[172] This group of compounds does not achieve intracellular concentrations adequate to treat most intracellular pathogens (e.g., *Legionella* spp.).[175]

In the absence of infection, drug concentrations in the cerebrospinal fluid (CSF) and in the vitreous humor are low. None of the oral cephalosporins achieve therapeutic concentrations in the CSF. Penetration of most parenteral drugs from the first- and second-generation groups is similarly poor. Parenteral cefuroxime is an exception, and this drug also has the lowest MICs for common meningeal pathogens among the first- and second-generation cephalosporins.[160] The parenteral third- and fourth-generation drugs, such as ceftriaxone, cefotaxime, ceftazidime, and cefepime, achieve concentrations that would allow treatment of central nervous system infections.[161-166] The presence of an active transport system that transports many cephalosporins from the CSF back to serum contributes to the low drug levels in the CSF observed with many of the earlier-generation drugs. The transport protein involved in this system is similar to the protein involved in renal secretion of β-lactam antibiotics.[176] Ceftriaxone, cefotaxime, ceftazidime, and cefepime exhibit minimal renal tubular secretion and are poor substrates for the choroid plexus pump, contributing to higher CSF concentrations. Probenecid is a competitive substrate for this pump and can produce higher concentrations with drugs that are effluxed by this transport system.[177] Infection results in higher CSF levels because inflammation can enhance penetration and interfere with efflux by active transport.

Very few drugs from the cephalosporin class are extensively metabolized. The three exceptions are cefotaxime, cephalothin, and cephapirin, which undergo deacetylation of the acetoxymethyl side chain in the liver.[178,179] The metabolic desacetyl products still possess modest microbiologic activity. The elimination half-life of desacetylcefotaxime is significantly longer than that of the parent compound, allowing less frequent administration of this cephalosporin.[179] The remaining drugs in the cephalosporin class are excreted from the body unchanged.

Most cephalosporins are eliminated by the kidney, with half-lives of 1 to 2 hours. The major mechanism for renal excretion of many compounds is tubular secretion. This active transport process is largely unaffected by protein binding.[160] Probenecid inhibits this organic acid transport system and can prolong the half-life of these compounds. For several compounds, glomerular filtration is more important, and protein binding can significantly prolong their elimination half-life.[180] For some drugs, the elimination half-life is 3 to 8 hours, allowing for 12- and 24-hour dosing intervals. A few compounds with high protein binding and high molecular weights, such as ceftriaxone and cefoperazone, are eliminated to a large extent by the biliary route.[181] Between 50% and 70% of the active parent compound may be recovered in the bile and eventually in the feces.

The maximal daily doses of agents eliminated primarily by the kidney must be reduced for patients with renal impairment. Most often, this adjustment includes both a reduction in dose level and a lengthening of the dosing interval. Recommended dose adjustments for various degrees of renal impairment and for patients receiving dialysis are presented in Table 21.5 for the currently available cephalosporins.[182,183] For drugs eliminated by the biliary system, such as ceftriaxone, dose adjustments are unnecessary unless concomitant severe hepatic insufficiency and renal insufficiency are present.[182] Most of the cephalosporins excreted by the renal route are eliminated by hemodialysis. Between 20% and 50% of the parent compound is removed after a usual dialysis session. It is recommended that the drug be given again after hemodialysis. On the other hand, few cephalosporins are removed to any significant extent (<10%) by peritoneal dialysis, and additional dosing is not recommended after a peritoneal dialysis session. Continuous venous hemofiltration (CVH) is frequently used in critically ill patients. Compounds eliminated by the kidneys and by hemodialysis are also removed by CVH. Most often, the efficiency of drug removal is thought to be similar to a creatinine clearance of 10 to 30 mL/min, and appropriate dosing modification is recommended.[184]

[b]References 15, 16, 79, 91, 136-138, 139, 140-145, 146, 147-159, 160, 161-168.

TABLE 21.4 Pharmacokinetics of Cephalosporins

CEPHALOSPORIN	USUAL ADULT DOSING REGIMEN	PEAK SERUM CONCENTRATION (μg/mL)	HALF-LIFE (h)	SERUM PROTEIN BINDING (%)	ROUTE OF EXCRETION	CSF CONCENTRATION RANGE (μg/mL)	CSF PENETRATION (%)	STABILITY AT ROOM TEMPERATURE (h) OR ORAL BIOAVAILABILITY (%)
First Generation								
Cefazolin	0.5–1 g q8h	193 (1 g)	1.9	74–86	R (65%–100%)	<0.7	0–4	24
Cephalothin	0.5–2 g q4–6h	64 (1 g)	0.5–1.0	50–80	R (50%–70%)	0.16–0.31	1	24
Cephapirin	0.5–2 g q4–6h	70 (1 g)	0.6	50–60	R (60%–85%)	NS	NS	24
Cephradine	0.5–1 g q6h	50 (1 g)	0.7	8–17	R (75%–100%)	NS	NS	2–10
Second Generation								
Cefamandole	0.5–2 g q6h	88 (1 g)	0.7–1.3	50–78	R (80%)	0.35–7.4	0–8.6	24
Cefonicid	0.5–1 g q24h	221 (1 g)	4.4	98	R (95%)	NS	NS	24
Cefuroxime	0.75–1.5 g q8h	39 (1 g)	1.2–1.8	33–50	R (70%–100%)	0.35–22.5	11.6–13.7	24
Cephamycins								
Cefmetazole	2 g q8h	143 (2 g)	1.3–1.8	68	R (75%–85%)	NS	NS	24
Cefotetan	1–2 g q12h	158 (2 g)	3.5	76–90	R (80%)	1.1–4.8	0.8–3.6	24
Cefoxitin	1–2 g q6h	110 (1 g)	0.8–1	41–79	R (90%)	1.2–22	0.8–35	24
Third Generation								
Cefoperazone	1–3 g q8–12h	153 (1 g)	1.6–2.1	90	H (80%) R (20%)	<0.8–119	2.5–5.9	12
Cefotaxime	1–2 g q12h	102 (1 g)	1–1.2	35–40	R (50%–80%)	1–83	4–55	24
Ceftazidime	1–2 g q8–12h	107 (1 g)	1–2	17	R (80%–90%)	1.4–30	14–45	24
Ceftizoxime	1–2 g q6–12h	113 (1 g)	1.4–1.7	31	R (70%–100%)	<0.5–29	3–22.6	24
Ceftriaxone	1–2 g q12–24h	145 (1 g)	6.4	85–95	R (50%) H (40%)	2–20	1.5–7	72
Moxalactam	1–2 g q8h	70 (1 g)	2.2	50	R (67%–88%)	0.8–39	12–69	24
Fourth Generation								
Cefepime	1–2 g q12h	79 (1 g)	2	16–19	R (85%)	5.7	11.8	24
Cefpirome	1–2 g q12h	80 (1 g)	2	10	R (90%)	0.8–4.2	5–67	24
Fifth Generation (MRSA Active)								
Ceftaroline	0.6 g q8–12h	21 (0.6 g)	2.6	7–19	R (85%)	NS	NS	24
Ceftobiprole	0.5 g q8–12h	34 (0.5 g)	2.85	17	R (82%)	NS	NS	24
Cephalosporin-BLI Combinations								
Ceftolozane-tazobactam	1 g/0.5 g q8h	75/18	3.1/1.0	16–21/30	R (95%/80%)	NS	NS	24
Ceftazidime-avibactam	2 g/0.5 g q8h	90/15	2.8/2.7	10/8	R (80%–90%/97%)	NS	NS	12
Oral—First Generation								
Cefadroxil	0.5–1 g q12h	15 (0.5 g)	1.3–1.6	20	R (90%)	NA	NA	80%
Cephalexin	0.5–1 g q6h	5.8 (250 mg)	0.5–1.2	6–15	R (80%–100%)	NA	NA	90%
Cephradine	0.5–1 g q6h	15 (0.5 g)	1–2	10–20	R (80%–90%)	NA	NA	95%
Oral—Second Generation								
Cefaclor	250–500 mg q8h 375 mg q12h	6 (250 mg) 19.2 (400 mg)	0.5–1	25–50	R (50%–80%)	NA	NA	50%–90% FE
Cefprozil	500 mg q12h	9.3 (500 mg)	1.3	35–45	R (61%)	NA	NA	95%
Cefuroxime (axetil)	250–500 mg q12h	4.6 (250 mg)	1.2	33–50	R (66%–100%)	NA	NA	52%–68% FE
Loracarbef	200–400 mg q12h	8 (200 mg)	1.0	25	R (87%)	NA	NA	90%
Oral—Third Generation								
Cefdinir	300 mg q12h	2.9	1.5–1.7	60–73	R (18%)	NA	NA	25%
Cefditoren (pivoxil)	200–400 mg q12h	2.5 (200 mg)	0.8–1.6	88	R (16%–22%)	NA	NA	17% FE
Cefixime	200–400 mg q12–24h	2.8 (200 mg) –4.5 (400 mg)	3–4	65–70	R (50%) H (5%)	NA	NA	40%–50%
Cefpodoxime (proxetil)	200 mg q12h	2.2 (200 mg)	2.2–2.7	18–40	R (29%–33%)	NA	NA	50%–80% FE
Ceftibuten	400 mg q24h	15 (400 mg)	2.4	65–77	R (57%)	NA	NA	75%–90%

BLI, β-Lactamase inhibitor; *CSF,* cerebrospinal fluid; *FE,* food effect; *H,* hepatic; *MRSA,* methicillin-resistant *Staphylococcus aureus*; *NA,* not applicable because oral cephalosporins are not indicated for CSF-related infections; *NS,* not studied in robust human pharmacokinetic studies and/or limited to case reports without pharmacokinetic analyses; *R,* renal.

ADVERSE REACTIONS AND TOXICITIES

The safety profile of the cephalosporins as a class is generally favorable. The incidence of specific adverse reactions for these compounds is relatively similar among drugs within the class, with few exceptions (Table 21.6). As with other β-lactam drugs, hypersensitivity reactions are the most common adverse effect associated with cephalosporin therapy.[185,186] The frequency of hypersensitivity reactions to cephalosporins is less than that for penicillins. Various cutaneous rashes, often associated with eosinophilia and occasionally with fever, occur in 1% to 7% of patients receiving these drugs.[187] More severe hypersensitivity reactions, such as serum sickness, anaphylaxis, or angioedema, occur very infrequently. These immunoglobulin E (IgE)-mediated reactions are estimated to occur in fewer than 1 in 100,000 patients.[188] However, there have been reports of a strong association between serum sickness in children and use of cefaclor.[189]

Cross-reactivity among drugs from the cephalosporin class and other β-lactams has been extensively investigated.[190] Important to note, the risk appears to depend on the similarity of side chains on the molecule to those on penicillins or other cephalosporins.[191] For example, in patients with allergy to amoxicillin, cross-reactivity was observed in 38% of those receiving cefadroxil, which has a similar side chain, and in none of those receiving cefamandole, which has a different side chain.[192] Recent estimates suggest a cross-reaction frequency of 1% or less.[193,194,195] Cross-reactivity with second-, third- and fourth-generation drugs has been very low.[190,193,196]

Use of the penicillin skin test to predict cephalosporin reactions is unreliable. In a study of almost 100 individuals who were given a cephalosporin and had a history of reaction to the penicillin determinants used in skin testing, only 1 patient had a reaction.[197] The practical clinical decision to use a cephalosporin in a patient with a prior history of reaction to either a penicillin or another cephalosporin should be guided by the severity of the prior reaction and the cephalosporin to be used. In patients with prior nonsevere, non–IgE-mediated reactions to other β-lactams, use of a cephalosporin with a different side chain than the prior agent is considered safe.[190,191,196] Although the risk of a similar reaction is slightly increased, the reactions are rarely severe. However, in the setting of a prior severe IgE-mediated reaction with another β-lactam compound, use of a cephalosporin is discouraged.

Immunologically mediated reactions to cephalosporins may manifest as hematologic or renal toxicities. Eosinophilia is the most commonly reported laboratory abnormality.[198] Overt hematologic toxicity—such as anemia, leukopenia (e.g., neutropenia), or thrombocytopenia—with cephalosporin use is uncommon.[199] Hemolytic anemia due to cephalosporin use, in particular ceftriaxone, has been reported but is rare.[200-202] Although the results of Coombs laboratory tests are reported to be positive in a significant percentage of patients receiving many of the cephalosporins, these patients most often do not have hemolytic anemia[203] because this is a false-positive reaction related to cross-reactivity that occurs in up to 3% of treated patients. Neutropenia is a potential complication of high-dose or prolonged use of β-lactams including cephalosporins; however, the effects are limited to the antibiotic exposure period, and cell counts recover after discontinuation.[204-207] Acute interstitial nephritis (AIN) is a well-described form of kidney injury secondary to β-lactam use. Drug-induced AIN due to cephalosporins commonly manifests as an abrupt decline in renal function; urine sediment with white cells, red cells, and white cell casts; proteinuria; and eosinophiluria.[208] Classic symptoms attributed to AIN including skin rash, eosinophilia, and fever are not common, and many patients are asymptomatic; the mainstay of treatment is withdrawal of the offending agent. Direct cytotoxicity to renal tubular cells can occur, particularly with an older cephalosporin cephaloridine, but this is quite rare.[209,210]

Nonimmunologic hematologic toxicities have been reported with a similarly low frequency. Bleeding abnormalities have been related to two mechanisms. Impaired adenosine diphosphate–induced platelet aggregation has been reported with moxalactam[211] but not with other cephalosporins. Another coagulopathy is specifically associated with the MTT side chain present on cefamandole, cefotetan, cefoperazone, and moxalactam.[212] The MTT side chain can dissociate from the parent cephalosporin and act as a competitive inhibitor of the vitamin K–dependent carboxylase responsible for converting clotting factors II, VII, IX, and X to active forms.[213] In addition, other cephalosporin side chains may interact with warfarin and increase inhibition of vitamin K 2,3-epoxide reductase, which converts vitamin K to its active form.[214,215] These reactions can lead to prolongation of the prothrombin time and clinically significant bleeding. Patients with poor nutritional status, advanced age, or recent surgery on the gastrointestinal tract are at increased risk for clinically significant bleeding.[216-218] In addition, patients with renal failure may be at increased risk for bleeding because of the accumulation of the side chain.[219] Vitamin K administration rapidly reverses the abnormality in 24 to 36 hours.

The MTT side chain can also produce a disulfiram-like reaction with ethanol ingestion that may persist for several days after antibiotic administration.[27,220] The disulfiram reaction manifests with flushing, tachycardia, headache, sweating, nausea, vomiting, hypotension, confusion, or blurred vision. The reaction is caused by a block in alcohol metabolism at the acetaldehyde step, which results in the accumulation of acetaldehyde and subsequent symptoms.

A variety of adverse reactions within the gastrointestinal tract have been reported with variable frequency. Diarrhea is the most commonly reported side effect, with rates ranging from 1% to 20%.[187] Upper gastrointestinal symptoms occur much less frequently. Mild and transient hepatic toxicity has been reported with most compounds from the class and manifests as twofold to fourfold elevations in transaminase levels in up to 7% of patients.[221] Obstructive biliary toxicity has also been reported with ceftriaxone.[222,223] The high biliary ceftriaxone concentrations cause crystallization of a ceftriaxone-calcium salt and the clinical syndrome of biliary pseudolithiasis. This biliary abnormality has been reported most often in children who were receiving high doses of ceftriaxone and in patients with preexisting biliary abnormalities.[224] The syndrome is reversible and in most reports has cleared within 10 to 60 days after discontinuation of the drug. It was recommended that ceftriaxone and calcium-containing products not be mixed in vials or infusion lines for therapy in neonates younger than 28 days because of the risk of precipitation in their plasma. This warning was later retracted because other cephalosporins had a similar low precipitation risk.[225]

Adverse reactions in the nervous system are uncommon and are similar in nature to those reported with other β-lactams.[226,227] The main mechanism of neurotoxicity is inhibition of γ-aminobutyric acid A.[227] Encephalopathy and seizures have been reported primarily in patients with renal insufficiency who were receiving high doses of these drugs, in particular with cefepime use.[226-231] Decreased protein binding and inhibition of the choroid plexus pump occur with uremia and may contribute to enhanced toxicity in patients with renal impairment. Local phlebitis reactions related to intravenous administration of the parenteral compounds have been reported with variable frequency, ranging from 1% to 5%.[232] On the other hand, pain associated with intramuscular administration is common with all of the parenteral compounds.[233] The local discomfort can be reduced by the use of 1% lidocaine in diluent. With the exception of once-daily intramuscular ceftriaxone and cefepime, most parenteral cephalosporins are administered by the intravenous route.

The cephalosporins have not been studied extensively in pregnancy. All drugs within the cephalosporin group are placed in pregnancy category B.[234] All of the compounds are secreted to a small degree into breast milk, but as a class they are considered safe for use in this situation.

In addition to the false-positive Coombs test result, laboratory abnormalities in urine glucose and serum creatinine have been reported with certain cephalosporins. False-positive results on glucosuria tests performed with the copper reduction technique (Clinitest) have been reported with cefaclor, cefadroxil, cefamandole, cefonicid, cefotaxime, cefoxitin, and ceftazidime.[235] Similarly, false increases in serum creatinine were reported in patients receiving cefoxitin or cephalothin in laboratories using the Jaffe technique.[236]

Because the cephalosporins have broad-spectrum activity, superinfection or overgrowth of *Candida* in the gastrointestinal and vaginal tracts can occur.[237,238] Similarly, overgrowth of *Clostridioides difficile* (formerly *Clostridium difficile*) in the gastrointestinal tract with diarrhea

TABLE 21.5 Dosing Adjustments of Commonly Used Cephalosporins in Adult Patients With Renal Insufficiency

CEPHALOSPORIN	USUAL ADULT DOSING REGIMEN[a]	DOSING REGIMEN WITH RENAL INSUFFICIENCY				DOSING REGIMEN WITH DIALYSIS	
		GFR 51–90 mL/min	GFR 31–50 mL/min	GFR 11–30 mL/min	GFR ≤10 mL/min	INTERMITTENT HEMODIALYSIS	CAPD
Intravenous: First Generation							
Cefazolin	1–2 g q8h	NC	NC	1–2 g q12h	1 g q24h	0.5–1 g q24h[b] or 2 g 3 times weekly[b]	0.5 g q12h
Intravenous: Second Generation							
Cefuroxime	0.75–1.5 g q8h	NC	NC	0.75–1.5 g q12h	0.75–1.5 g q24h	0.75–1.5 g q24h[b]	0.75–1.5 g q24h
Intravenous: Cephamycin							
Cefoxitin	2 g q6h	NC	2 g q8h	2 g q12h	1 g q12–24h	0.5–1 g q24–48h and supplemental dose after each dialysis (usually 1 g)	1 g q24h
Intravenous: Third Generation							
Cefotaxime	2 g q6–8h	NC	2 g q8–12h	2 g q8–12h	2 g q24h	1–2 g q24h[b]	1 g q24h
Ceftazidime	2 g q8h	NC	1 g q12h	1 g q24h	0.5 g q24h	1 g q24h[b]	0.5 g q24h
Ceftriaxone	1–2 g q24h	NC	NC	NC	NC	NC	NC
Intravenous: Fourth Generation							
Cefepime	2 g q8–12h	NC	2 g q12–24h	1–2 g q24h	0.5–1 g q24h	1 g q24h[b]	2 g q48h
Intravenous: Fifth Generation (MRSA Active)							
Ceftaroline	0.6 g q12h	NC	0.4 g q12h	0.3 g q12h	0.2 g q12h	0.2 g q12h[b]	0.2 g q12h
Ceftobiprole	0.5 g q8h	NC	0.5 g q12h	0.25 g q12h	0.25 g q12h	0.25 g q12h[b]	0.25 g q12h
Intravenous: Cephalosporin–β-Lactamase Inhibitor Combinations							
Ceftolozane-tazobactam	1.5 g q8h	NC	0.75 g q8h	0.375 g q8h	NA	0.75 g load, then 0.15 g q8h[b]	NA
Ceftazidime-avibactam	2.5 g q8h	NC	1.25 g q8h	0.94 g q12h	0.94 g q24h	0.94 g q24[b]	NA
Oral: First Generation							
Cefadroxil	500 mg q12h	NC	NC	500 mg q24h	500 mg q36h	500 mg 3 times weekly[b]	500 mg q24h
Cephalexin	500 mg q6h	NC	500 mg q12h	250 mg q8–12h	250 mg q24h	500 mg q24h[b]	500 mg q24h
Oral: Second Generation							
Cefprozil	500 mg q12h	NC	NC	250 mg q12h	250 mg q12h	500 mg q24h[b]	250 mg q12h
Cefuroxime (axetil)	500 mg q12h	NC	NC	500 mg q24h	250 mg q24h	250 mg q24h and supplemental dose after each dialysis (usually 250 mg)	250 mg q24h
Oral: Third Generation							
Cefdinir	300 mg q12h	NC	NC	300 mg q24h	300 mg q24h	300 mg 3 times weekly[b]	300 mg q24h
Cefditoren	400 mg q12h	NC	200 mg q12h	200 mg q24h	200 mg q24h	NA	NA
Cefixime	400 mg q12–24h	NC	300 mg q24h	200 mg q24h	200 mg q24h	300 mg q24h[b]	200 mg q24h
Cefpodoxime	200-400 mg q12h	NC	NC	200–400 mg q24h	200 mg q24h	200–400 mg 3 times weekly[b]	200 mg q24h
Ceftibuten	400 mg q24h	NC	200 mg q24h	100 mg q24h	100 mg q24h	400 mg 3 times weekly[b]	100 mg q24h

[a]For intravenous administration, the dosing regimen is based on the standard infusion time recommended in package insert.
[b]Doses given on the day of dialysis should be given after the dialysis session.
CAPD, Continuous ambulatory peritoneal dialysis; *GFR,* glomerular filtration rate; *MRSA,* methicillin-resistant *Staphylococcus aureus*; *NA,* not applicable or no data; *NC,* no change.

TABLE 21.6 Potential Adverse Effects of Cephalosporins

EFFECT TYPE	SPECIFIC EFFECT	FREQUENCY (%)
Hypersensitivity	Rash	1–3
	Urticaria	<1
	Serum sickness	<1
	Anaphylaxis	0.01
Gastrointestinal	Diarrhea	1–19
	Nausea and vomiting	1–6
	Transient transaminase elevation	1–7
	Biliary sludge	20–46[a]
Hematologic	Eosinophilia	1–10
	Neutropenia	<1
	Thrombocytopenia	<1–3
	Hypoprothrombinemia	<1
	Impaired platelet aggregation	<1
	Hemolytic anemia	<1
Renal	Interstitial nephritis	<1–5
Central nervous system	Seizures	<1
	Encephalopathy	<1
False-positive laboratory results	Coombs positive	3
	Glucosuria	Rare
	Serum creatinine	Rare
Other	Drug fever	Rare
	Disulfiram-like reaction[b]	Rare
	Superinfection	Rare
	Phlebitis	Rare

[a]Ceftriaxone.
[b]Cephalosporins with thiomethyl tetrazole ring side chain.

and colitis has been associated with increased use of broad-spectrum cephalosporins.[239,240,241]

MAJOR CLINICAL USES OF CEPHALOSPORIN ANTIBIOTICS

The usual dosing regimens for adults and children for the various cephalosporins by generation are listed in Table 21.7. The daily doses recommended to treat serious infections are also listed. It should be noted that prolonged-infusion and continuous-infusion β-lactam therapy has become common at many institutions. The rationale behind this is the optimization of the time that drug concentrations remain above MIC (T>MIC) for the dosing period.[37,38,39] In providing a slow, prolonged infusion rate, drug concentrations can remain above the MIC for a longer period of time, especially for drugs with relatively short half-life in which dosing intervals are either every 6 hours or every 8 hours. This dosing strategy can increase the chances of pharmacokinetic and pharmacodynamic target attainment while potentially decreasing the total daily dose necessary.[242] Important to note, outcomes in general have been either equivalent or improved with a prolonged-infusion dosing strategy in comparison with standard infusion rates, and this has been particularly useful for cefepime.

First-Generation Cephalosporins

The first-generation cephalosporins available in the United States are cefazolin, cephalexin, and cefadroxil. The first-generation cephalosporins have been extensively used as alternatives to penicillin for susceptible staphylococcal and streptococcal infections. Most commonly, these include skin and soft tissue infections and more severe infections such as streptococcal and methicillin-susceptible *S. aureus* bacteremia. Cefazolin is not metabolized and is eliminated more by glomerular filtration than by tubular excretion.[180] Its moderate protein binding slows the glomerular filtration of the drug, resulting in a half-life of 1.5 to 2 hours, which allows dosing every 8 hours and every 12 hours. With coadministration of probenecid, cefazolin has been effective in skin and soft tissue infections with once-daily dosing.[243] Cefazolin is still recommended in penicillin-allergic patients for more serious staphylococcal infections, such as endocarditis, even though the drug is more readily hydrolyzed by staphylococcal β-lactamase than other first-generation cephalosporins.[244,245] Cefazolin is recommended as the prophylactic antibiotic of choice for foreign-body implantation and for many clean and clean-contaminated surgical procedures in which there is a high risk of infection.[246] These include cardiac and vascular surgery, insertion of orthopedic devices, head and neck surgery that crosses the oropharyngeal mucosal barrier, vaginal and abdominal hysterectomy, high-risk cesarean section, and high-risk gastroduodenal and biliary tract procedures. Because of its poor activity against *Bacteroides* spp., cefazolin alone is not recommended for intraabdominal procedures that involve the intestine.

The oral first-generation cephalosporins, cephalexin and cefadroxil, have very high oral bioavailability. Cefadroxil has a slightly longer half-life than cephalexin, which allows twice-daily dosing instead of the usual four times a day.[137] These drugs provide appropriate outpatient therapy for many skin and soft tissue infections. However, they are not effective for animal bites and scratches involving *Pasteurella multocida*.[247] The drugs are quite active against *Streptococcus pyogenes* and provide effective therapy in streptococcal pharyngitis.[248,249] They have poor activity against penicillin-resistant pneumococci, *H. influenzae,* and *M. catarrhalis* and are not recommended for sinusitis, otitis media, or lower respiratory tract infections. The drugs are effective against some Enterobacteriaceae and because of renal excretion are effective in uncomplicated urinary tract infections; however, they are less effective than trimethoprim-sulfamethoxazole or fluoroquinolones.[250]

Second-Generation Cephalosporins

The second-generation cephalosporins currently available in the United States include two true cephalosporins, cefprozil and cefuroxime, and one cephamycin, cefoxitin. The two groups of drugs have different spectra of antimicrobial activity and different clinical uses. Because of their activity against *S. pneumoniae, H. influenzae,* and *M. catarrhalis,* the true second-generation cephalosporins, such as cefuroxime, have been used extensively for treatment of various respiratory tract infections in hospitalized patients.[251] Cefuroxime can also be used to treat meningitis caused by penicillin-susceptible pneumococci, *H. influenzae,* or *Neisseria meningitidis*.[252] However, its use has been largely supplanted by third-generation cephalosporins, which result in faster eradication of bacteria from the CSF.[253] Cefuroxime was in the past one of the recommended agents for empirical therapy of community-acquired pneumonia (CAP) in hospitalized patients.[254] Although cefuroxime has good activity against penicillin-susceptible and penicillin-intermediate strains of *S. pneumoniae,* its activity against most penicillin-resistant strains is suboptimal. In an observational study of 844 patients with pneumococcal bacteremia, mostly resulting from pneumonia, resistance to cefuroxime was associated with significantly greater mortality.[255] The latest recommendations on CAP list ceftriaxone or cefotaxime for initial empirical therapy.[256] Cefuroxime provides effective therapy for other serious infections caused by susceptible pathogens, including skin and soft tissue infections, epiglottitis, complicated sinusitis, and gynecologic infections.[257,258] Cefuroxime is also an important cephalosporin for surgical prophylaxis for many of the same surgical procedures for which cefazolin is recommended.[246] Cefuroxime should not be considered for empirical therapy of nosocomial pneumonia or other nosocomial infections because of its poor activity against most strains of *Enterobacter, Citrobacter, Serratia, Morganella,* and *P. aeruginosa.*

The cephamycins have inferior activity against staphylococci but enhanced antibacterial activity against certain Enterobacteriaceae and especially for their activity against anaerobic bacteria such as *B. fragilis.* Given this, cephamycins are important adjuncts to surgical prophylaxis for colorectal procedures and appendectomies.[246] For elective colorectal surgery, cefoxitin is commonly administered even when an oral bowel preparation with erythromycin and neomycin is used. Cephamycins are also used for the treatment of intraabdominal, pelvic, and gynecologic infections; infected decubitus ulcers; diabetic foot infections; and mixed aerobic-anaerobic soft tissue infections.[259,260,261,262] They also demonstrate good in vitro activity against ESBL-producing strains of *E. coli* and *K. pneumoniae*; however, their reliability in treating infections caused by ESBL-producing strains has not been proven. It is important to note though that as many as 15% to 20% of *B. fragilis* strains are resistant to the various cephamycins, and drugs with better anaerobic activity

TABLE 21.7 Dosing Regimens for Cephalosporins in Adults and Children

	ADULT		CHILDREN
CEPHALOSPORIN	**USUAL DOSE**	**SEVERE DISEASE**	**USUAL DOSE**
First Generation			
Cefazolin	0.5–1 g q8-12h	2 g q6–8h	12.5–33 mg/kg q6–8h
Second Generation			
Cefuroxime	0.75–1.5 g q8h	1.5 g q8h	12.5–60 mg/kg q6–8h
Cephamycins			
Cefotetan	1–2 g q12h	2-3 g q12h	Not recommended
Cefoxitin	1–2 g q6h	2 g q4–6h	20–25 mg/kg q4–6h
Third Generation			
Cefotaxime	1 g q8–12h	2 g q4–8h	25–30 mg/kg q4–6h
Ceftazidime	1 g q8–12h	2 g q8h	30–50 mg/kg q8h
Ceftriaxone	1 g q24h	2 g q12–24h	50–100 mg/kg q24h
Fourth Generation			
Cefepime	1 g q12h	2 g q8–12h	50 mg/kg q8h
Cefpirome	1 g q12h	2 g q12h	Not recommended
Fifth Generation (MRSA Active)			
Ceftaroline	0.6 g q12h	0.6 g q8h	Not recommended
Ceftobiprole	0.5 g q12h	0.5 g q8h	Not recommended
Cephalosporin–β-Lactamase Inhibitor Combination			
Ceftolozane-tazobactam	1.5 g q8h	1.5 g q8h[b]	No safety or efficacy data, ongoing trials
Ceftazidime-avibactam	2.5 g q8h	2.5 g q8h	No safety or efficacy data, ongoing trials
Oral: First Generation			
Cephalexin	250–500 mg qid	1 g qid	6.25–25 mg/kg qid
Cefadroxil	500 mg bid	1 g bid	15 mg/kg bid
Oral: Second Generation			
Cefprozil	250–500 mg bid	500 mg bid	7.5–15 mg/kg bid
Cefuroxime (axetil)	250–500 mg bid	500 mg bid	10–15 mg/kg bid
Oral: Third Generation			
Cefdinir	300 mg bid or 600 mg qd	300 mg bid or 600 mg qd	7 mg/kg bid or 14 mg/kg qd
Ceditoren	200–400 mg bid	400 mg bid	Not recommended
Cefixime	200 mg bid or 400 mg qd	400 mg bid	4 mg/kg bid or 8 mg/kg qd
Cefpodoxime	200–400 mg bid	400 mg bid	5 mg/kg bid
Ceftibuten	400 mg qd	400 mg qd	9 mg/kg qd

[a]These dosing regimens are for standard infusion rates.
[b]Studies for higher doses including 3 g q8h are currently ongoing for ceftolozane-tazobactam.
MRSA, Methicillin-resistant *Staphylococcus aureus.*

should be used for empirical therapy of serious *Bacteroides* infections.[263,264] All of the cephamycins are active against *N. gonorrhoeae,* including penicillin-resistant strains. However, recommended therapy for infections with this organism is with ceftriaxone, which is effective as a single dose.[265] However, resistance of *N. gonorrhoeae* to ceftriaxone is increasing worldwide.[266] Cefoxitin in combination with doxycycline provides effective therapy for pelvic inflammatory disease.[267] Cefoxitin is also a useful addition to combination regimens for certain atypical mycobacterial infections, such as those caused by *Mycobacterium abscessus.*

The oral second-generation cephalosporins, including cefuroxime axetil and cefprozil, are effective for treatment of a variety of mild-to-moderate community-acquired infections. Double-tap studies in acute otitis media and acute maxillary sinusitis demonstrated that bacterial eradication was related to the drug's ability to produce serum concentrations exceeding the MIC of the infecting pathogen for 40% to 50% of the dosing interval.[268,269] In this regard, cefuroxime axetil and cefprozil are the best agents for *S. pneumoniae* and are effective against penicillin-susceptible isolates and most penicillin-intermediate strains. None of the oral second-generation cephalosporins provides optimal therapy for penicillin-resistant pneumococci. For *H. influenzae* and *M. catarrhalis,* cefuroxime axetil would be a better choice than cefprozil. Clinical and bacteriologic outcomes have demonstrated that 5- to 10-day courses of therapy with the second-generation cephalosporins are equivalent to or more effective than 10 days of therapy with penicillin V for the treatment of group A β-hemolytic streptococcal pharyngitis.[270,271] Cefuroxime axetil is also a recommended alternative to doxycycline and penicillin for treatment of early Lyme disease.[272]

Third-Generation Cephalosporins

Third-generation cephalosporins available in the United States are cefdinir, cefditoren, cefixime, cefotaxime, cefpodoxime, ceftazidime, ceftibuten, and ceftriaxone. The third-generation cephalosporins are major drugs for the treatment of many important infections because of their high antibacterial potency, wide spectrum of activity, low potential

for toxicity, and favorable pharmacokinetics (e.g., enhanced drug concentrations in the CSF). They have been especially useful in infections resulting from gram-negative bacilli that are resistant to other β-lactam antibiotics. However, their superior activity against the Enterobacteriaceae is being challenged by the increasing frequency of organisms with β-lactamase–mediated resistance. New AmpC β-lactamases, ESBLs, and carbapenemases, which inactivate third-generation cephalosporins, present a distinct threat to the continued utility of these agents.

Cefotaxime, ceftriaxone, and ceftazidime are the major parenteral third-generation cephalosporins in clinical use for the treatment of nosocomial infections caused by susceptible gram-negative bacilli. Cefotaxime and ceftriaxone are also two of the most potent cephalosporins against penicillin-resistant pneumococci. Because of its high protein binding, ceftriaxone has the longest half-life and is usually administered once daily. Ceftazidime is administered two or three times daily, and effective dosing of cefotaxime, which has the shortest half-life, has varied from every 4 hours to twice daily. Ceftazidime is usually reserved for infections that are likely to involve *P. aeruginosa.*

Monotherapy with cefotaxime or ceftriaxone has provided effective treatment for a variety of nosocomial infections caused by susceptible gram-negative bacilli, including complicated skin and soft tissue infections, prosthetic joint infections, pneumonia, complicated urinary tract infections, and intraabdominal infections such as peritonitis.[273-276,277] However, cephalosporin monotherapy for infections caused primarily by *Enterobacter, Citrobacter, Serratia, Morganella, Proteus,* and *Providencia* spp. can be complicated by the emergence of stably derepressed resistant mutants.[120,278,279] Combination antimicrobial therapy may be beneficial in reducing this emergence of resistance, which results from increased chromosomal β-lactamase production. Organisms containing ESBLs have also been observed to result in failed therapy with third-generation cephalosporins, even when the organism was judged susceptible in laboratory tests.[280] The carbapenems are the recommended drugs for these ESBL-producing strains.

Cefotaxime and ceftriaxone have provided effective therapy for meningitis caused by a variety of different bacteria.[281-283,284] They are the drugs of choice for meningitis caused by *H. influenzae* and various Enterobacteriaceae.[285] Cefotaxime and ceftriaxone also provide effective therapy for meningitis caused by *N. meningitidis* and against pneumococci that have MICs of 1.0 μg/mL or less. Organisms with higher MICs have resulted in failed monotherapy with these cephalosporins. Therefore, empirical therapy with cefotaxime or ceftriaxone is combined with vancomycin (with or without rifampin) until the laboratory determines the susceptibility of the pneumococcal isolate.[285] If the organism is susceptible to cefotaxime or ceftriaxone, the vancomycin (and rifampin) can be discontinued. Treatment of meningitis requires maximal doses of these cephalosporins, such as 2 g every 12 hours in adults and 50 mg/kg twice daily or 100 mg/kg once daily in children for ceftriaxone, and 2 g every 4 to 6 hours in adults or 100 to 150 mg/kg every 6 to 8 hours in children for cefotaxime.

Cefotaxime and ceftriaxone continue to be active against most bacteria producing CAP. In a large observational study of pneumococcal bacteremia, resistance to cefotaxime and ceftriaxone was not associated with higher mortality.[255] Cefotaxime and ceftriaxone were also effective in treating patients with nonmeningeal pneumococcal infections, mostly pneumonia, caused by strains with MICs as high as 2 μg/mL.[286] The Clinical and Laboratory Standards Institute (CLSI) has created higher susceptibility and resistance breakpoints for pneumococci causing nonmeningeal infections than for *S. pneumoniae* causing meningitis.[287] As a result of these changes, cefotaxime and ceftriaxone are considered active against most penicillin-resistant pneumococci and are recommended, in combination with a macrolide, for empirical therapy for CAP requiring hospitalization.[256] Single intramuscular doses of ceftriaxone are also highly effective in eradicating *H. influenzae* and penicillin-susceptible strains of *S. pneumoniae* from middle ear fluid.[288] However, three daily doses of ceftriaxone were required in one study to eradicate penicillin-resistant pneumococci.[289]

The oral third-generation cephalosporins, which include cefdinir, cefditoren pivoxil, cefixime, cefpodoxime proxetil, and ceftibuten, are approved for oral therapy of mild-to-moderate respiratory infections, such as otitis media, sinusitis, and acute exacerbations of chronic bronchitis. These drugs have very potent activity against *H. influenzae,* but their activity against pneumococci is more variable.[290-292] Cefdinir, cefditoren, and cefpodoxime have activity similar to that of cefuroxime or cefprozil and are active against penicillin-susceptible and most penicillin-intermediate strains of *S. pneumoniae*. Cefixime is active only against penicillin-susceptible strains, and ceftibuten is marginal even for penicillin-susceptible pneumococci. Short courses of most of these drugs have also provided equivalent rates of eradication in group A β-hemolytic streptococcal pharyngitis.[293-295] Their increased potency over other oral cephalosporins for *E. coli, K. pneumoniae,* and *Enterobacter, Citrobacter,* and *Serratia* spp. enhances their utility for treatment of complicated urinary tract infections.[296]

Ceftazidime is the third-generation cephalosporin used for serious infections in which *P. aeruginosa* is documented or highly likely. It is one of the recommended drugs, either alone or in combination with an aminoglycoside, for initial empirical management of febrile neutropenia.[297] However, ESBLs and AmpC β-lactamases have reduced the utility of ceftazidime for monotherapy, and therefore cefepime has largely supplanted its use for empiric therapy in neutropenic fever. Ceftazidime has been effective for the treatment of acute exacerbations of chronic pulmonary infections in patients with cystic fibrosis.[298] The drug penetrates into CSF and is one of two cephalosporins as treatment of choice for meningitis caused by *P. aeruginosa.*[299]

Third-generation cephalosporins have also become established therapy for a variety of specific infections. Ceftriaxone 250 to 500 mg intramuscularly is highly active against *N. gonorrhoeae,* including penicillin- and quinolone-resistant strains. It is the drug of choice for all forms of gonococcal infection and is used in combination with a single oral dose of azithromycin.[265] A single oral dose of cefixime is also highly effective for uncomplicated gonococcal infections of the cervix, urethra, and rectum.[265,300,301] However, because of increasing resistance, it is no longer recommended as first-line therapy.[302] Single-dose intramuscular ceftriaxone is recommended therapy for chancroid.[265] Ceftriaxone and cefotaxime are recommended therapy for treatment of early Lyme disease in patients with neurologic involvement or third-degree atrioventricular heart block.[303] These drugs are also recommended in Lyme disease patients with both arthritis and objective evidence of neurologic disease and for those with late neurologic disease affecting the central or peripheral nervous system. Ceftriaxone is considered as alternative therapy in penicillin-allergic patients with syphilis.[265,304] Ceftriaxone is a recommended alternative therapy for typhoid fever and for severe infections caused by *Shigella* spp. or by non-*typhi* spp. of *Salmonella*.[305] Third-generation cephalosporins have provided effective therapy for focal *Salmonella* infections, brain abscess caused by gram-negative bacilli, and endocarditis caused by fastidious gram-negative coccobacilli.[306,307] Single doses of ceftriaxone are highly effective in eradicating nasopharyngeal carriage of *N. meningitidis.*[308,309] The long half-life of ceftriaxone, which allows for once-daily dosing, has enhanced its use in the outpatient setting for both streptococcal and staphylococcal infections. Ceftriaxone has been effective for the outpatient treatment of staphylococcal and streptococcal skin and soft tissue infections, including osteomyelitis and prosthetic joint infection.[277,310,311] The drug is also effective as monotherapy for the outpatient treatment of nonenterococcal streptococcal endocarditis.[312]

Fourth-Generation Cephalosporins

Cefepime is the only fourth-generation cephalosporin available in the United States. The fourth-generation cephalosporins have the widest spectrum of all the cephalosporins. They have enhanced activity against certain gram-negative bacilli, such as *Enterobacter, Citrobacter,* and *Serratia* spp. These drugs are zwitterions, which cross the outer membrane of gram-negative bacilli more rapidly than other cephalosporins. They are also less susceptible to inactivation by AmpC β-lactamases. As a result, about 75% to 80% of the Enterobacteriaceae resistant to third-generation cephalosporins are susceptible to the fourth-generation drugs, and they are the treatment of choice for serious infections caused by AmpC inducible-resistant strains.[313,314] They are active against *P. aeruginosa* and, unlike ceftazidime, maintain good potency against gram-positive cocci, most notably methicillin-susceptible *S. aureus, S. pneumoniae* (including most penicillin-resistant strains), and other streptococci.[54,315-318] Only two fourth-generation agents have been

developed so far. Cefepime has a slightly longer half-life than ceftazidime and is usually administered twice daily, although 8-hour dosing is recommended for documented *P. aeruginosa* infections. Cefpirome, which is not available in the United States, has a pharmacokinetic profile very similar to that of cefepime.

At some hospitals, the fourth-generation agents have largely replaced third-generation cephalosporins for treatment of serious gram-negative bacillary infections. They have proved to be effective in a variety of serious gram-negative infections, such as bacteremia, pneumonia, skin and soft tissue infections, prosthetic joint infections, and complicated urinary tract infections.[313,314,320,321,322] With continuous infusion of cefepime, optimal efficacy was observed when serum concentrations were at least fourfold greater than the MIC.[323] Comparative trials with ceftazidime or other agents have generally demonstrated equivalent efficacy.[324-327] Cefepime therapy for ESBL-producing organisms with maintained cefepime susceptible MICs is controversial.[328] Both clinical failures and successes have been noted against these organisms, and studies have highlighted the importance of achieving pharmacodynamic target (i.e., appropriate time above MIC) and inoculum effect or severity of infection as important parameters.[328] Cefepime is recommended as monotherapy or in combination for initial empirical therapy in febrile neutropenic patients.[297] The drug is one of the recommended agents for the empirical treatment of severe CAP, for health care–associated pneumonia, and for ventilator-associated pneumonia, especially when *P. aeruginosa* or resistant Enterobacteriaceae are suspected.[254,329] The drug's activity against pneumococci is similar to that of ceftriaxone in patients with CAP requiring hospitalization.[330,331] The drug penetrates well into the CSF and produces outcomes similar to those of cefotaxime in acute bacterial meningitis.[332,333] However, it is not approved for treatment of meningitis in the United States. Resistance is an increasing issue for cefepime, and many of the new ESBL and carbapenemase enzymes (usually class A or class B) can inactivate these fourth-generation drugs.[124]

A meta-analysis of cefepime versus other β-lactam drugs in the treatment of febrile neutropenia and other serious infections reported that all-cause mortality with cefepime was higher than with other cephalosporins or with a β-lactam–BLI combination.[335,336] An additional report suggested that the difference in mortality in patients with febrile neutropenia was caused by greater progression of underlying disease in the cefepime arm.[337] A meta-analysis by the Center for Drug Evaluation of the US Food and Drug Administration (FDA) using a larger database of both published and unpublished comparative studies did not find a significant increase in mortality in cefepime-treated patients compared with those treated with other antibacterials.[338]

Fifth-Generation Cephalosporins (MRSA-Active Cephalosporins)

The MRSA-active cephalosporins have unique activity compared with other cephalosporins. They have excellent activity again MRSA and against ampicillin-susceptible strains of *E. faecalis.*[70,73] They also exhibit potent activity against pneumococci with multiple mutations in genes encoding PBP1A, PBP2B, and PBP2X. MIC_{90} values that were as high as 4 and 8 μg/mL to the most active third-generation cephalosporins were fourfold to eightfold lower with the MRSA-active cephalosporins.[339,340] On the other hand, the activity of these drugs against gram-negative bacilli is similar to that of many of the third-generation cephalosporins. The first approved drug in this group (in a few countries, but not the United States) was ceftobiprole medocaril, the prodrug for ceftobiprole. The US-approved MRSA-active cephalosporin is ceftaroline fosamil, the prodrug for ceftaroline. Ceftobiprole is more resistant than ceftaroline to inactivation by AmpC β-lactamase[113] and has activity against strains of *P. aeruginosa* that is similar to that of ceftazidime. However, the maximal doses of ceftobiprole studied so far are fourfold lower than those of ceftazidime.

The MRSA-active cephalosporins have exhibited comparable efficacy to vancomycin plus a broad-spectrum β-lactam in patients with complicated skin and skin-structure infections.[341,342,343] The results with ceftobiprole and ceftaroline were similar to those obtained with vancomycin in the large number of patients with MRSA infections. Studies with ceftaroline and ceftobiprole have shown efficacy in hospitalized patients with CAP similar to that of comparators.[344-346] Ceftobiprole also has shown similar efficacy in hospital-acquired pneumonia (excluding ventilator-associated pneumonia) to that of ceftazidime plus linezolid.[347] Ceftaroline has been effective in patients with soft tissue infections complicated by MRSA bacteremia and in other small studies of complicated bacteremia with or without endocarditis.[348,349,350] Ceftaroline also increases the membrane binding of daptomycin against daptomycin-nonsusceptible MRSA, resulting in enhanced killing and improved clinical outcome.[351,352] Little is known about the CSF penetration of ceftobiprole and ceftaroline in humans or whether the enhanced activity of these drugs against pneumococci will be useful in treating meningitis. These drugs may also become useful agents for treating severe enterococcal infections in penicillin-allergic patients.[353]

Cephalosporin and β-Lactamase Inhibitor Combinations

Efforts have been focused on combining cephalosporins with BLIs to combat increasing drug resistance. Ceftolozane-tazobactam and ceftazidime-avibactam are the first successful agents to make it to clinical use thus far.

In the case of ceftazidime-avibactam, the novel BLI avibactam targets class A, class C, and some class D enzymes and completely restores full susceptibility (MIC ≤1 mg/L) for most strains producing ESBLs, AmpCs, or both.[91,354] For *P. aeruginosa,* avibactam reduces the MIC_{90} fourfold and produces MICs less than or equal to 8 mg/L for 60% of multidrug-resistant strains.[355] Avibactam has minimal effect on ceftazidime MICs for *Acinetobacter baumanii* and most anaerobic bacteria.[91,356] Clinically, the combination of avibactam and ceftazidime has resulted in comparable efficacy to carbapenems in complicated urinary tract infections and in complicated intraabdominal infections.[357-359] Small uncontrolled studies have demonstrated encouraging outcomes for patients with CRE[360,361,362,363]; however, reports of development of resistance to ceftazidime-avibactam have emerged.[125,126]

Tazobactam is the BLI that is being combined with ceftolozane, a new cephalosporin with enhanced activity against strains of *P. aeruginosa.* The MICs of ceftolozane against *P. aeruginosa* are 4- to 16-fold lower than ceftazidime.[364,365] The drug also appears to have earlier in vitro killing and more rapid in vivo killing than ceftazidime.[366,367] Although tazobactam has a minimal effect on ceftolozane's activity against *P. aeruginosa,* it does enhance its activity against other gram-negative bacilli producing primarily class A and class C β-lactamases.[16] At a concentration of ceftolozane and tazobactam of 8 and 4 mg/L, respectively, 70% to 76% of *Enterobacter* strains that are AmpC hyperproducers or producing ESBLs are susceptible to the drug combination.[368] Thus, the combination is active against many ESBL organisms, most importantly the CTX-M family. Its main difference from ceftazidime-avibactam is that it does not have appreciable activity against KPC producers and is therefore not effective against most CRE organisms. Clinically, ceftolozane-tazobactam has been approved for complicated urinary tract infections and, along with metronidazole, for complicated intraabdominal infections based on large randomized studies.[369,370,371] These studies also demonstrated high efficacy for those isolates that were ESBL positive.[372] Retrospective studies examining outcome for patients infected with multidrug-resistant *P. aeruginosa*, including carbapenem-resistance, treated with ceftolozane/tazobactam are encouraging, but prospective, randomized controlled trials are needed.[373,374] As with ceftazidime-avibactam, resistance to ceftolozane-tazobactam has been documented during therapy in a small number of cases.[374,375]

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The complete reference list is available online at Expert Consult.

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22 Ertapenem, Imipenem, Meropenem, Doripenem, and Aztreonam

Yohei Doi

SHORT VIEW SUMMARY

ERTAPENEM
- Usual adult dose: 1 g daily intravenously
- Renal and hepatic failure: decrease dose in renal failure
- Cerebrospinal fluid penetration: no human data
- Adverse effects: diarrhea, nausea, infused vein complication
- Contraindications: prior allergy
- Drug-drug interactions: avoid probenecid, valproic acid

IMIPENEM
- Usual adult dose: 0.5 g every 6 hours or 1 g every 8 hours intravenously
- Renal and hepatic failure: decrease dose in renal failure
- Cerebrospinal fluid penetration: moderate
- Adverse effects: seizure, diarrhea, nausea, phlebitis
- Contraindications: prior allergy
- Drug-drug interactions: avoid probenecid, valproic acid, ganciclovir

MEROPENEM
- Usual adult dose: 0.5 to 1 g every 8 hours intravenously
- Renal and hepatic failure: decrease dose in renal failure
- Cerebrospinal fluid penetration: moderate
- Adverse effects: diarrhea, nausea/vomiting, headache, inflammation of injection site
- Contraindications: prior allergy
- Drug-drug interactions: avoid probenecid, valproic acid

DORIPENEM
- Usual adult dose: 0.5 g every 8 hours intravenously
- Renal and hepatic failure: decrease dose in renal failure
- Cerebrospinal fluid penetration: moderate
- Adverse effects: diarrhea, headache, nausea, rash, phlebitis
- Contraindications: prior allergy
- Drug-drug interactions: avoid probenecid, valproic acid

CARBAPENEMS

Four carbapenems—imipenem, meropenem, ertapenem, and doripenem—are approved for clinical use in the United States. In addition, panipenem is available in Japan and China, tebipenem in Japan, and biapenem in Japan, China, and Thailand. Carbapenems are active against a broad range of gram-positive and gram-negative aerobic and anaerobic bacteria due to their efficient penetration through the bacterial outer membrane, their high affinity for multiple penicillin-binding proteins (PBPs), and their stability against most β-lactamases, including class A extended-spectrum β-lactamases (ESBLs) and class C β-lactamases (AmpCs).

Chemistry

Carbapenems are derivatives of thienamycin, an antibiotic produced by the soil organism *Streptomyces cattleya.* They differ from penicillins by a carbon atom replacing the sulfur at position 1 and a double bond between C2 and C3 in the five-membered thiazolidine ring (Fig. 22.1). The *trans*-1α-hydroxyethyl side chain in the *trans*-configuration at C6 confers the excellent β-lactamase stability, which is associated with the broad spectrum of activity of carbapenems. Thienamycin was chemically too unstable, which prompted the development of its *N*-formimidoyl derivative imipenem. However, imipenem is degraded in vivo by mammalian renal dehydropeptidase (DHP-I) and must be coadministered with cilastatin, a selective antagonist of this enzyme. Meropenem, ertapenem, and doripenem differ from imipenem by having a 1β-methyl, 2-thiopyrrolidinyl substituent at C2. The 1β-methyl constituent is believed to provide stability to DHP-I, which allows it to be administered without a DHP-I inhibitor, unlike imipenem.

Mechanism of Action

Carbapenems inhibit cell wall synthesis by binding to most high-molecular-weight PBPs. They traverse the outer membrane of gram-negative bacteria through specific outer membrane proteins (OMPs) to reach the periplasmic space. The most significant OMP is OprD in *Pseudomonas aeruginosa.* Although variations exist depending on the specific agent, carbapenems preferentially bind to PBPs 1a, 1b, 2, and 4 and to a lesser extent PBP3, which is the primary target of aminopenicillins and cephalosporins. This low affinity with PBP3 is thought to be responsible for the formation of sphere forms without the production of long filaments on bacterial lysis. The affinity of carbapenems to multiple PBPs of various bacteria contributes to the broad spectrum of activity of these agents.

Resistance

Resistance to carbapenems is mediated by one or a combination of the following mechanisms: (1) production of β-lactamase that hydrolyzes carbapenems; (2) diminished permeability due to impaired expression of certain OMPs; (3) efflux of drug across the outer membrane; and (4) production of an altered or low-affinity target, which is more relevant in gram-positive bacteria. In gram-negative bacteria, although a single mechanism may not be sufficient to cause a clinically relevant degree of resistance, frank resistance occurs through an interplay involving β-lactamase production, impaired permeability, and enhanced efflux.

Carbapenems are readily hydrolyzed by Ambler class B β-lactamases, which are zinc-dependent metalloenzymes.[1] Some lactose-nonfermenting species, including *Stenotrophomonas maltophilia* and *Elizabethkingia meningoseptica,* are intrinsically resistant to carbapenems due to class B β-lactamase production. In addition, acquired class B β-lactamases, such as Verona integron-encoded metallo-β-lactamase (VIM) and New Delhi metallo-β-lactamase (NDM), confer resistance in a wide array of gram-negative bacteria. Several Ambler class A β-lactamases hydrolyze carbapenems. In particular, *Klebsiella pneumoniae*–type carbapenemases (KPCs) have emerged as an important carbapenem resistance determinant in gram-negative bacteria worldwide, mostly in *K. pneumoniae.*[2] Ambler class D oxacillinase β-lactamases (OXAs) that hydrolyze carbapenems are also found frequently in *Acinetobacter baumannii* and are emerging in *K. pneumoniae* in certain geographic areas.[2]

Downregulated production or absence of porin protein OprD is responsible for resistance to carbapenems in *P. aeruginosa* when combined with background production of AmpC β-lactamase.[3,4] Imipenem is the preferred substrate of OprD and is affected most, whereas the effect of the lack of OprD on resistance is less pronounced for meropenem and

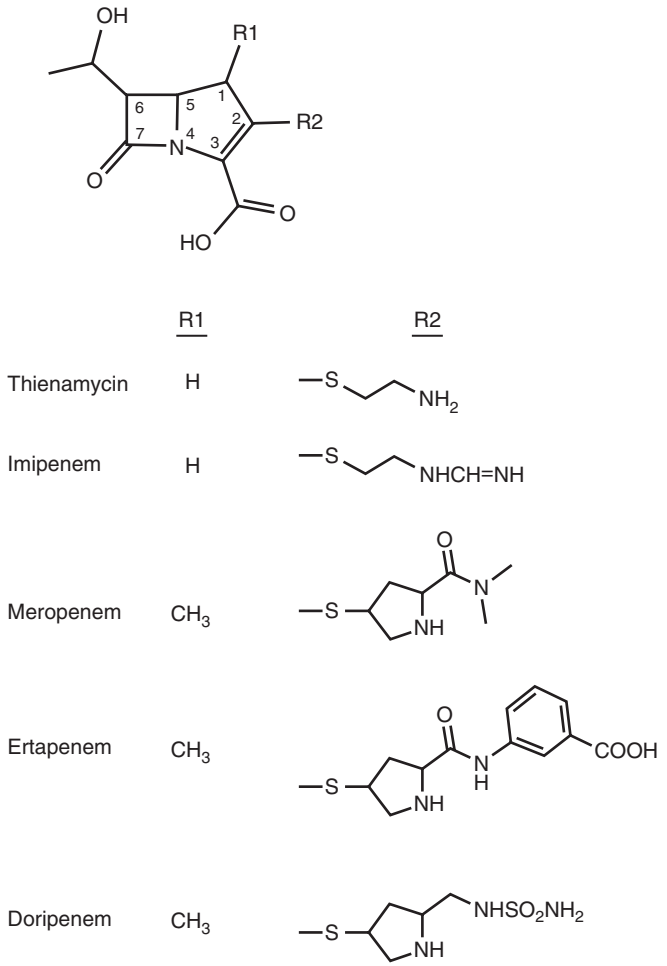

FIG. 22.1 Core structure and substituents for carbapenem antibiotics. They differ from penicillins by a carbon atom replacing the sulfur at position 1 and a double bond between C2 and C3 in the five-membered thiazolidine ring. The *trans*-1α-hydroxyethyl side chain in the *trans*-configuration at C6 confers the β-lactamase stability.[28]

doripenem.[5,6] Likewise, decreased expression of OmpK35 and OmpK36 for *K. pneumoniae* and OmpC and OmpF for *Enterobacter* spp. has been associated with carbapenem resistance.[5,7–9]

Meropenem and doripenem, but not imipenem, are substrates of the tripartite multidrug efflux system MexA-MexB-OprM in *P. aeruginosa*.[10,11] Here, MexB is the cytoplasmic protein, OprM is the outer membrane component forming channels, and MexA is the membrane fusion protein linking the two membrane proteins. Upregulation of this efflux system augments resistance to meropenem and doripenem.

Production of a low-affinity PBP may mediate β-lactam class resistance, including carbapenem resistance in gram-positive bacteria. Examples include PBP2a in oxacillin-resistant staphylococci[12] and PBP5 in *Enterococcus faecium*.[13] Approximately 50% of *Staphylococcus aureus* clinical strains are resistant to oxacillin and by extension to carbapenems, whereas 90% of *E. faecium* clinical strains are resistant to ampicillin and by extension to carbapenems due to low-affinity PBPs.[14,15]

CARBAPENEM-RESISTANT ENTEROBACTERIACEAE

Increasing incidence of carbapenem-resistant Enterobacteriaceae, including those producing NDM-1 and KPC, has aroused concern about erosion of utility for this important class of antibacterial agents.[2] Equally concerning is the difficulty encountered in detecting carbapenem-resistant Enterobacteriaceae in the routine diagnostic laboratory. In 2011, the Clinical and Laboratory Standards Institute decreased the carbapenem breakpoints of Enterobacteriaceae fourfold for imipenem, meropenem, and ertapenem.[16] This change was made to accommodate carbapenem resistance mechanisms that were remaining undetected at the higher 2010 breakpoints. Automated susceptibility testing systems do contain low drug concentrations to account for the lowered breakpoints, but manufacturers are not permitted to change the interpretive criteria on their instrument without approval by the US Food and Drug Administration (FDA) of the revised system. Before implementing new interpretive criteria onto FDA-approved instruments, microbiology laboratories are required to conduct rigorous in-house validation. The revised breakpoints negate the need to do phenotypic carbapenemase detection tests (e.g., Modified Hodge Test, modified Carbapenem Inactivation Method, Carba NP test) unless warranted by epidemiologic and infection control purposes. Carbapenem resistance in Enterobacteriaceae by current standards may be missed if susceptibility testing is only done on automated systems for which the laboratory did not implement the updated breakpoints.

Antibacterial Activity

The carbapenems have similar antibacterial spectra.[17,18] All have excellent in vitro activity against gram-positive cocci in general (Table 22.1). For *Streptococcus pneumoniae,* the minimal inhibitory concentrations (MICs) are less than 0.03 μg/mL for penicillin-susceptible strains and around 0.5 μg/mL for penicillin-resistant strains, which are far exceeded by plasma levels. β-Hemolytic streptococci are exquisitely susceptible to carbapenems. Oxacillin-susceptible strains of *S. aureus* and coagulase-negative staphylococci are inhibited at carbapenem concentrations of less than 0.5 μg/mL, but oxacillin-resistant strains are highly resistant to currently available carbapenems. *Enterococcus faecalis* is typically susceptible to imipenem, with MICs of 2 μg/mL or less, but is more resistant to ertapenem, meropenem, and doripenem. None of the carbapenems is active against *E. faecium*.

Neisseria gonorrhoeae and *Neisseria meningitidis* are highly susceptible to carbapenems, with MICs typically less than 0.1 μg/mL. Ceftriaxone-resistant *N. gonorrhoeae* remains fully susceptible to ertapenem.[19] MICs of *Haemophilus influenzae* are 0.1 μg/mL or less for ertapenem, meropenem, and doripenem and 1 μg/mL or less for imipenem, including β-lactamase–producing strains. Most Enterobacteriaceae are inhibited by imipenem at concentrations of 1 μg/mL or less, whereas *Morganella* and *Proteus* strains have slightly higher MIC values. Corresponding MICs of ertapenem, meropenem, and doripenem are typically 0.1 μg/mL or less, including for strains producing ESBLs. Carbapenemase-producing *K. pneumoniae* strains are typically resistant to all carbapenems, with MICs of 8 μg/mL or greater. Carbapenemase-producing *Escherichia coli* are inhibited at lower carbapenem concentrations, between 1 and 4 μg/mL.

Doripenem is the most active carbapenem against *P. aeruginosa,* including strains hyperproducing AmpC β-lactamase, with typical MICs of 0.5 μg/mL or less compared with 1 μg/mL for meropenem and 2 μg/mL for imipenem. Ertapenem has no activity against *P. aeruginosa*. Carbapenem-susceptible strains of *A. baumannii* are inhibited by less than 1 μg/mL of imipenem, meropenem, and doripenem, but resistance to carbapenems is increasingly reported in this species. Ertapenem is not active against *A. baumannii.* All *S. maltophilia* and most *Burkholderia cepacia* strains are resistant to carbapenems.

Carbapenems are highly active against most obligately anaerobic species, including anaerobic gram-positive cocci, *Bacteroides fragilis,* non-*fragilis* species of *Bacteroides, Clostridium* spp. with the exception of *Clostridioides difficile* (formerly *Clostridium difficile*) *Fusobacterium* spp., *Prevotella* spp., *Porphyromonas* spp., and other species with MICs of 1 μg/mL or less.

Nocardia spp. are inhibited by carbapenems, but *Nocardia farcinica* and *Nocardia otitidiscaviarum* may be resistant.[20] *Actinomyces* spp. are susceptible to carbapenems.[21] Susceptibility of rapidly growing *Mycobacterium* spp. to imipenem is variable.[22] *Mycobacterium tuberculosis* and *Mycobacterium avium* are considered resistant to carbapenems, but in vivo efficacy of imipenem has been proposed.[23]

Pharmacology

Ertapenem, imipenem, meropenem, and doripenem are formulated as parenteral agents because they are absorbed poorly after oral ingestion. Imipenem, meropenem, and doripenem are pharmacologically similar. A 30- to 60-minute infusion of 500 mg of any of these agents in healthy

TABLE 22.1 Comparative Activity of Ertapenem, Imipenem, Meropenem, and Doripenem Against Selected Aerobic and Anaerobic Bacteria

	MIC_{90} (μg/mL)				
ORGANISM	**Ertapenem**	**Imipenem**	**Meropenem**	**Doripenem**	**REFERENCES**
Gram-Positive Organisms					
Staphylococcus aureus, oxacillin susceptible	0.25	0.12	0.12	0.06	52–54, 55–56
Staphylococcus aureus, oxacillin resistant	>16	>16	>16	>16	52, 55, 57
Coagulase-negative staphylococci, oxacillin susceptible	0.25	0.12	0.12	0.03	56, 58
Coagulase-negative staphylococci, oxacillin resistant	>16	>16	>16	>16	55, 59
Streptococcus pneumoniae	0.06–0.5	0.06–0.25	0.06–1	0.06–0.5	53, 55, 56
β-Hemolytic streptococci	0.06	0.06	0.06	0.06	53, 55, 56
Viridans group streptococci	0.12	0.03	0.03	0.06	53, 55, 56
Enterococcus faecalis	8	1	8	4	53, 55
Enterococcus faecium	>8	>8	>8	>8	53, 55, 56
Bacillus anthracis	—[b]	0.12	0.05	—[b]	60, 61
Gram-Negative Organisms					
Listeria monocytogenes	0.25	0.06	0.12	0.12	18, 62, 63
Haemophilus influenzae	0.03	0.25	0.06	0.12	55–56, 57, 64
Moraxella catarrhalis	0.03	0.25	0.03	0.03	56, 57
Neisseria gonorrhoeae	0.06	0.25	0.03	0.05	19, 65, 66
Neisseria meningitidis	0.03	0.03	0.03	0.06	18, 65, 67
Escherichia coli	0.06	0.5	0.03	0.03	52, 53, 55, 56
Escherichia coli, ESBL producing	0.06	0.5	0.06	0.06	52, 55, 56
Salmonella spp.	0.06	≤0.5	0.03	0.06	56
Shigella spp.	0.06	≤0.5	0.03	0.06	56
Klebsiella pneumoniae[c]	0.12	0.5	0.12	0.12	52, 53, 55
Klebsiella oxytoca	0.06	0.5	0.12	0.12	55
Enterobacter cloacae	0.06	0.5	0.12	0.12	52, 54, 64
Enterobacter aerogenes	0.06	0.5	0.12	0.12	55, 64
Morganella morganii	0.06	8	0.12	0.5	63, 68, 69
Citrobacter spp.	0.06	0.5	0.12	0.12	55, 56, 70
Serratia marcescens	0.06	0.5	0.12	0.12	55, 64
Proteus mirabilis	0.06	1	0.12	0.12	55, 56
Aeromonas spp.	0.25	0.5	0.12	0.5	56
Pseudomonas aeruginosa[c]	>8	1–>8	0.5–>8	0.5–8	53–54, 55–56
Acinetobacter baumannii[c]	4–>8	0.5–>8	0.5–>8	0.25–>8	55, 56, 71
Stenotrophomonas maltophilia	>8	>8	>8	>8	55, 56
Burkholderia cepacia	>8	>8	4	8	56
Anaerobic Organisms					
Peptostreptococcus spp.	0.125	0.25	0.125	0.125	53, 72
Fusobacterium spp.	0.03	0.12	0.03	0.03	73
Bacteroides fragilis	0.5	0.5	0.25	0.5	72
Clostridium perfringens	0.06	0.5	0.06	0.06	72
Clostridioides difficile (formerly *Clostridium difficile*)	4	2	2	2	72, 74

[a]Values less than 0.03 μg/mL are rounded up to 0.03 μg/mL.
[b]No specific data available.
[c]Susceptibility varies widely on the basis of local epidemiology.
ESBL, Extended-spectrum β-lactamase; *MIC_{90},* minimal inhibitory concentration for 90% of isolates.

persons produces mean peak serum concentrations of approximately 25 μg/mL and areas under the plasma concentration-time curve (AUCs) of 30 to 45 μg•h/mL.[24–26] A 1-g dose of ertapenem administered intravenously produces a peak serum concentration of approximately 150 μg/mL and an AUC of greater than 500 μg•h/mL.[27] The plasma half-life is 1 hour for imipenem, meropenem, and doripenem and 4 hours for ertapenem. The longer half-life of ertapenem is due to extensive protein binding (>90%) compared with imipenem (20%), meropenem (2%), and doripenem (8%) and permits once-daily dosing. Imipenem is typically administered every 6 hours, and meropenem and doripenem are given every 8 hours. All carbapenems undergo extensive renal elimination and thus require dosage adjustment in patients with reduced renal function, but not in patients with impaired liver function. Between 30% and 50% of ertapenem, imipenem, meropenem, and doripenem is removed by hemodialysis. Between 25% and 50% of imipenem, meropenem, and doripenem is removed during continuous venovenous hemofiltration or hemodiafiltration.

Imipenem is subject to degradation by DHP-I located in the brush border of renal tubules; thus, it is coformulated with the selective competitive DHP-I antagonist cilastatin.[24] Ertapenem, meropenem, and doripenem do not require a DHP-I antagonist because they are not substrates of this enzyme.

Carbapenems are well distributed to various body compartments and penetrate well into most tissues.[28]

As β-lactam agents, the most important pharmacodynamic parameter predicting bacteriologic and clinical efficacy of carbapenems is the time of free plasma drug concentration exceeding the MIC (*f*T > MIC) of the infecting organism.[29] For bacteriostatic and bactericidal activity in vivo, *f*Ts greater than MICs of 20% and 40% of the dosing interval, respectively, are required.[29]

Adverse Reactions

Carbapenems are generally well tolerated. There seems to be no particular propensity for them to cause major adverse effects, *C. difficile*–associated colitis, coagulation abnormalities, nephrotoxicity, or hepatotoxicity. The most common adverse events possibly, probably, or definitely related to the carbapenems are nausea, vomiting, diarrhea, rash, headache, and phlebitis, occurring in 1% to 3% of patients. All carbapenems have been associated with seizures, believed to be related to their structural similarity with γ-aminobutyric acid and antagonism at the receptor site.[30] Although the overall incidence is low, the risk is elevated in patients with renal failure and neurologic comorbidities. Seizures are more common with imipenem (1%–2%) than ertapenem, meropenem, and doripenem (0.1%–0.3%). Drug interactions are uncommon, though the combination of valproic acid and carbapenems leads to grossly subtherapeutic valproic acid levels.[31]

The incidence of imipenem and meropenem hypersensitivity has been estimated to be less than 3% in the general population.[32] Carbapenems have been considered potentially cross-allergenic with penicillins. The occurrence of hypersensitivity reactions to a carbapenem has ranged between 0% and 11% of patients with documented or self-reported history of penicillin allergy.[33–35] Most of the reactions observed were maculopapular rash. However, studies using skin testing suggest that patients with a positive skin test to penicillins for immunoglobulin E–mediated (i.e., immediate) hypersensitivity rarely have a positive skin test to carbapenems (<1%), and those with a negative skin test tolerate graded challenge doses of imipenem or meropenem.[36–38] Therefore administration of a carbapenem is considered safe in patients with a history of penicillin immediate hypersensitivity if their skin test is negative for that carbapenem. In the absence of skin testing, it appears prudent to administer carbapenem in graded doses until extended safety data on up-front administration of full doses to patients with a history of penicillin immediate hypersensitivity become available.

Clinical Use

Carbapenems display broad-spectrum activity covering gram-positive, gram-negative, and anaerobic bacteria and thus are useful for treatment of a wide variety of moderate to severe infections, including bacteremia, hospital-acquired pneumonia, intraabdominal infections, complicated urinary tract infections, bone and soft tissue infections, and obstetric and gynecologic infections. Meropenem is the only carbapenem approved by the FDA for treatment of bacterial meningitis. Imipenem should be avoided because of its propensity to cause seizures.

Carbapenems are generally active against cephalosporin-resistant Enterobacteriaceae producing ESBLs and AmpC β-lactamases but not those producing KPC β-lactamases. Recently developed β-lactamase inhibitors capable of inhibiting KPC β-lactamase as well as ESBLs and AmpC β-lactamases can be combined with a carbapenem to restore its activity against KPC β-lactamase–producing strains. One such combination (meropenem-vaborbactam) has been approved for clinical use in the United States[39] (also see Chapter 20). Ertapenem has only limited activity against enterococci and lactose-nonfermenting gram-negative species, including *P. aeruginosa.* Carbapenems other than ertapenem are drugs of choice for treatment of infections caused by multidrug-resistant strains of *A. baumannii* that remain susceptible to carbapenems; however, resistance to carbapenems is rapidly increasing.[40]

Imipenem, meropenem, and doripenem are therapeutically equivalent and interchangeable in most clinical situations, with imipenem being slightly more active against gram-positive organisms (especially *E. faecalis*) than meropenem and doripenem, and meropenem and doripenem being slightly more active against gram-negative organisms than imipenem.[28] In *P. aeruginosa,* however, predominant mechanisms of resistance can be different for imipenem (most affected by downregulation of OprD but not substrate for multidrug efflux pumps) and meropenem and doripenem (substrates of MexAB-OprM efflux pump but less affected by downregulation of OprD). Consequently, resistance to imipenem is not always predictive of resistance to meropenem or doripenem, and vice versa.[41] Doripenem is the most active carbapenem against *P. aeruginosa* in vitro. Imipenem, meropenem, and doripenem are all appropriate for use in the treatment of hospital-acquired infections because of their antipseudomonal activity. However, doripenem carries an increased risk of death and lower cure rates compared with imipenem when used to treat patients with ventilator-associated pneumonia, which is not an approved indication. *S. maltophilia, E. meningoseptica,* and *Chryseobacterium indologenes* are intrinsically resistant to all carbapenems because of chromosomal production of metallo-β-lactamase.

The recommended adult dose of imipenem for patients with creatinine clearance of greater than 50 mL/min is 250 to 500 mg every 6 hours or 1 g every 8 hours intravenously. The pediatric dose is 15 to 25 mg/kg every 6 hours. The recommended adult dose of meropenem for patients with creatinine clearance greater than 50 mL/min is 500 mg to 1 g every 8 hours. For treatment of severe infections, doses of up to 6 g/day have been used safely. The pediatric dose is 10, 20, or 40 mg/kg every 8 hours, with the highest dose indicated for treatment of meningitis. The recommended adult dose of doripenem for patients with creatinine clearance greater than 50 mL/min is 500 mg every 8 hours. The pediatric dose has not been established for doripenem. The doses should be adjusted according to the creatinine clearance for patients with renal impairment.

Ertapenem differs from other carbapenems in two important respects: it has a long half-life permitting once-daily dosing, and it has relatively poor activity against *P. aeruginosa* and *A. baumannii.* Like all carbapenems, ertapenem has excellent antianaerobic activity and thus is especially useful in a single daily dosage regimen for polymicrobial infections. Ertapenem is active against ESBLs and AmpC-producing Enterobacteriaceae and can be used for infections caused by these organisms. The recommended adult dose of ertapenem for patients with creatinine clearance greater than 30 mL/min is 1 g daily. The pediatric dose is 15 mg/kg twice daily.

MONOBACTAMS

Monobactams are monocyclic β-lactam agents characterized by the presence of a 2-oxoazetidine-1-sulfonic acid moiety. Aztreonam is the only monobactam currently approved by the FDA. Aztreonam is a synthetic monocyclic β-lactam, the core structure of which was originally isolated from *Chromobacterium violaceum* (Fig. 22.2). It has high affinity for PBP3 of gram-negative bacteria, causing their filamentation, bacterial lysis, and death.[42] It has a broad spectrum of activity against gram-negative bacteria but has no activity against gram-positive or anaerobic bacteria.[43] Aztreonam readily penetrates the outer membrane of gram-negative

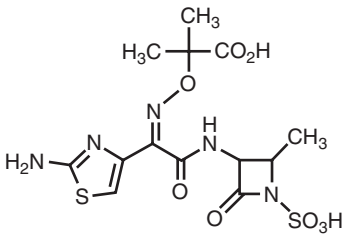

FIG. 22.2 The structure of aztreonam. The core structure is monocyclic, unlike penicillins and cephalosporins, which are bicyclic. The 1-sulfonic acid group activates the β-lactam, whereas the 4α-methyl group provides stability against β-lactamases. The aminothiazole oxime moiety on the acyl side chain is responsible for the activity against aerobic gram-negative bacteria.[77]

bacteria. It is resistant to hydrolysis by all class B β-lactamases and most class A and D β-lactamases but is hydrolyzed by KPC β-lactamases, ESBLs, and also AmpC β-lactamases when they are produced in large amounts.

Aztreonam inhibits most Enterobacteriaceae at concentrations less than 0.5 μg/mL (Table 22.2). Some *P. aeruginosa, Enterobacter cloacae,* and *Citrobacter freundii* strains are resistant. Most *P. aeruginosa* strains are inhibited by less than 16 μg/mL of aztreonam. Most *B. cepacia, S. maltophilia,* and *A. baumannii* strains are resistant.

Aztreonam is not absorbed from the gastrointestinal tract. A 1-g intravenous dose of aztreonam produces serum concentrations of approximately 50 μg/mL at 1 hour.[44] Aztreonam is 56% protein bound and distributes well in tissues and fluids throughout the body. Mean cerebrospinal fluid concentration in the presence of inflamed meninges after a single 2-g dose is 2 to 3 μg/mL; higher concentrations can be achieved after multiple doses.[45]

Aztreonam is renally excreted, with 60% to 65% recovered in urine.[44] In adults with normal renal and hepatic function, the elimination half-life is 1.7 hours.[44] In neonates 7 days old, the half-life of aztreonam is approximately 6 hours.[46] The rate of serum clearance of aztreonam is linearly related to the rate of urinary creatinine clearance. The half-life of aztreonam is approximately 6 hours at creatinine clearances of 10 mL/min or less. The half-life of aztreonam is slightly prolonged in patients with hepatic impairment; dose adjustment is not necessary in patients with chronic hepatic disease if renal function is not impaired. Aztreonam is cleared by continuous venovenous hemofiltration, hemodialysis, and peritoneal dialysis. Standard hemodialysis removes about half of a 1-g dose given just before dialysis.[47]

Aztreonam is well tolerated. Local reactions, including phlebitis, occur in less than 2% of patients. Diarrhea, nausea, vomiting, and rash can occur in about 1% of patients.[48] Cross-reactivity with penicillins and cephalosporins is extremely rare, even in patients with immunologically proven hypersensitivity to other β-lactams,[49] though caution is still recommended in the setting of repeated exposure to aztreonam.[50]

TABLE 22.2 Activity of Aztreonam Against Selected Aerobic Bacteria

ORGANISM	MIC_{50} (μg/mL)	MIC_{90} (μg/mL)	REFERENCES
Haemophilus influenzae	0.06	0.12	75
Moraxella catarrhalis	0.12	0.25	75
Neisseria gonorrhoeae	0.125	0.25	76
Neisseria meningitidis	≤0.06	≤0.06	77
Escherichia coli	≤0.12	0.25	78
Escherichia coli, ESBL producing	4	>16	78
Salmonella spp.	≤0.12	0.25	78
Shigella spp.	≤0.12	≤0.12	78
Klebsiella spp.	≤0.12	0.5	78
Klebsiella spp., ESBL producing	>16	>16	78
Enterobacter spp.	≤0.12	>16	78
Citrobacter spp.	≤0.12	>16	78
Serratia spp.	≤0.12	0.5	78
Proteus mirabilis	≤0.12	≤0.12	78
Aeromonas spp.	≤0.12	0.25	56
Pseudomonas aeruginosa	8	>16	56
Acinetobacter spp.	>16	>16	56
Stenotrophomonas maltophilia	>16	>16	56
Burkholderia cepacia	16	>16	56

ESBL, Extended-spectrum β-lactamase; *MIC_{50},* minimal inhibitory concentration for 50% of isolates; *MIC_{90},* minimal inhibitory concentration for 90% of isolates.

Aztreonam is rarely used alone empirically because its spectrum of activity is limited entirely to aerobic gram-negative bacteria. Aztreonam has been used safely and effectively in conjunction with agents that have gram-positive and anaerobic activity. Its greatest utility is for definitive treatment of infections caused by aerobic gram-negative bacteria, which are susceptible to aztreonam, in a patient who has severe allergy to penicillin or other β-lactams. It may also have a role in combination therapy of infections caused by metallo-β-lactamase–producing gram-negative bacteria, although these strains often produce other β-lactamases that hydrolyze aztreonam.[51] The usual dose is 1 to 2 g every 6 to 8 hours intravenously or intramuscularly, with a daily dose for serious infection of up to 6 g. The pediatric dose is 30 mg/kg every 6 to 8 hours.

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The complete reference list is available online at Expert Consult.

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23 Antibiotic Allergy

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The majority of adverse drug events are not immunologically mediated allergic reactions but rather what are categorized as type A drug reactions, referring to predictable, dose-dependent events secondary to the pharmacologic action of the drug. Only 10% to 15% of reactions are defined as type B, which are seemingly random and unrelated to pharmacologic effects and include the development of drug hypersensitivity and other idiosyncratic reactions. Antibiotics are the most important cause of allergic drug reactions for infectious disease specialists. Maculopapular exanthems and urticaria account for most of these, but more severe reactions may also occur.

Correct labeling of an adverse drug reaction as a pharmacologic side effect of the drug versus a true immunologic event is essential for prevention of erroneous allergy labels. Improving the accuracy of antibiotic allergy reporting is required in order to reduce the impact of antibiotic allergy labels.

PATHOPHYSIOLOGY

According to the Gell and Coombs classification, there are four main pathophysiologic mechanisms that result in allergic drug reactions. Immunoglobulin E (IgE)-mediated immediate reactions (type 1) are relatively common and may manifest as symptoms of urticaria and angioedema or anaphylaxis. Cytotoxic reactions (type 2) are exemplified by drug-induced hemolytic anemia or thrombocytopenia and are a relatively uncommon reaction from antimicrobial agents. Immune complex reactions (type 3) are serum sickness–like reactions with rashes, fever, and arthralgias and typically occur several days after initiation of the culprit drug. Finally, delayed-type hypersensitivity reactions (type 4), induced by T-cells, represent the most common manifestation of antimicrobial drug reactions as exemplified by the maculopapular exanthem.

Four additional subclassifications have been introduced for type IV reactions that highlight the heterogeneous T-cell response and clinical variability in these delayed drug reactions.[1,2] Reactions of the type IVa subclassification are Th1-mediated reactions involving macrophage activation and occur as an exanthem; type IVb reactions are Th2 mediated with eosinophil-rich exanthems or bullous lesions; type IVc reactions are cytotoxic reactions with bullous exanthems or pustular reactions; and type IVd reactions are neutrophil-rich pustular reactions, such as acute generalized exanthematous pustulosis (AGEP).

Although this hypersensitivity classification system is still used today in the management of drug hypersensitivity, many drug reactions do not neatly fit into this system. Pseudoallergic reactions cause reactions similar to IgE-mediated reactions but are due to IgE-independent mast cell activation. Red man syndrome from vancomycin is an example. Recently, the human G protein–coupled receptor MRGPRX2 has been identified as a mast cell specific receptor critical for pseudoallergic drug reactions to drugs such as ciprofloxacin.[3] Delayed severe cutaneous adverse drug reactions (SCARs) have unclear mechanisms that may involve classic features of delayed-type hypersensitivity and also other mechanisms.

Approach to a Patient With an Antibiotic Allergy

The accurate diagnosis of drug allergy is important not only to prevent serious reactions secondary to further exposure but also to avoid the unnecessary restriction of a drug to which the patient may not truly be allergic.

The clinical history is integral in evaluating the likelihood of a drug allergy, because only a small percentage of patients with a reported reaction have a history compatible with actual hypersensitivity. Even in the presence of a consistent history, the proportion of true reactors is low.

Key historical features to seek out include a detailed description of the nature and timing of the reaction, and concomitant ingestion of other medications. A clinical history of anaphylactic shock has the highest predictive value for IgE-mediated allergy, with a fourfold increase in risk.[4] In addition, taking a thorough medical history for underlying risk factors (e.g., viral infections, prior drug reactions, atopy) is crucial for evaluating antibiotic allergy.

Information to Be Obtained When Taking a History of Antibiotic Allergy

Concerns regarding the reaction include:

- Timing of the reaction in relation to drug administration
- Symptoms and evolution of the reaction
- Description of cutaneous symptoms (e.g., maculopapular, urticarial, bullous)
- Involvement of mucosal surfaces or internal organs
- Treatment administered, response, and duration of reaction
- History of prior exposure to the implicated agent
- Other medications ingested at the time of the reaction
- Whether the medication or similar medications were taken (and tolerated) thereafter
- Whether there are potential confounders (e.g., underlying viral or bacterial infections)
- History of other drug reactions and allergies (many patients with multiple drug intolerance syndrome do not have true drug allergies)
- Whether the patient has experienced recurrent, similar reactions without known exposures (e.g., chronic urticaria)
- The likelihood of future need of the medication

CLINICAL MANIFESTATIONS

The clinical spectrum of antibiotic allergy is extremely heterogeneous. There are two broad entities based on timing and pathophysiologic mechanism.

Immediate (Immunoglobulin E–Mediated or Pseudoallergic) Drug Reactions

Immediate IgE-mediated reactions result from the interaction of drug antigens with preformed drug-specific IgE antibodies bound to mast cells or basophils, with the consequent release of preformed mediators (histamine, proteases, and chemotactic factors) and newly generated mediators (prostaglandins, leukotrienes, and platelet-activating factor). These reactions usually occur within 1 hour of drug administration and clinically manifest as urticaria, angioedema, rhinitis, bronchospasm, or anaphylaxis. IgE-mediated reactions require prior sensitization to the drug or structurally related drugs, typically from prior exposure. Pseudoallergic reactions may also result in immediate reactions, often with first exposure to the drug. These reactions are due to nonspecific (IgE-independent) activation of mast cells and can cause reactions clinically indistinguishable from IgE-mediated reactions. The mast cell receptor MRGPRX2 has been identified as an important receptor in

pseudoallergic reactions to several drugs.[3] It is also possible for drug-specific IgG to activate complement, which results in acute rashes and non–IgE-mediated mast cell activation.

Nonimmediate Drug Reactions

Nonimmediate drug reactions have been further subdivided as accelerated (predominantly urticaria) or late reactions. By definition, they occur more than 1 hour and within 7 days after the last drug administration. Although drug reactions can involve multiple organs, cutaneous reactions are the most common. There are numerous cutaneous manifestations of drug reactions, which include maculopapular exanthems, bullous lesions, and pustules, to name a few. Severe cutaneous adverse reactions (SCARs), including Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), may include internal organ involvement. It should be kept in mind that a significant proportion of maculopapular or urticarial reactions labeled as drug reactions are secondary to the underlying infection itself, without any contribution by the suspected agent.[5] In other situations, the incriminated antibiotic may cause allergic manifestations only in the presence of a specific underlying predisposing factor (e.g., ampicillin-induced rash in Epstein-Barr infection; increased risk for sulfonamide-related rashes in people infected with human immunodeficiency virus [HIV] and CD4 lymphopenia).

Drug Rash With Eosinophilia and Systemic Symptoms

Drug rash with eosinophilia and systemic symptoms (DRESS), also known as drug (induced) hypersensitivity syndrome (DHS or DiHS), is a systemic reaction that is distinguished from other antimicrobial reactions by a delayed appearance after a 2- to 10-week exposure to several antibiotics, including sulfonamides and vancomycin. Clinical characteristics include rash, fever, lymph node swelling, hepatitis, or involvement of other organs. Facial swelling is a common feature and may be confused with IgE-mediated angioedema; some patients have signs of a capillary leak syndrome. Interesting to note, patients may develop disease flares after discontinuation of the culprit drug, which may result in other medications being falsely labeled as causing a drug reaction. In addition, the course is characterized by relapses that have been attributed to the reactivation of latent viral infection, in particular human herpesvirus 6.[6] DRESS reactions are also atypical in that clinical manifestations may worsen despite drug withdrawal, and symptoms may persist for months and in some cases require immunosuppressive therapies.

DIAGNOSIS AND MANAGEMENT OF ANTIBIOTIC ALLERGY

Many antibiotic-associated adverse drug reactions are unlikely to be true allergies that preclude drug therapy. Although the quantification of drug allergy risk through history is essential, this alone is grossly insufficient in clinical decision making. However, investigation is often hampered by lack of reliable immunologic tests, which are available for only a few drugs. Skin tests for most antimicrobial agents lack high negative predictive values. Therefore patients may be tested for drug tolerance via a drug challenge, or a desensitization procedure may be performed to induce temporary drug tolerance.

Tests for Immunoglobulin E–Mediated Immediate Reactions

Skin Testing: Prick and Intradermal Tests

The reagents used in skin testing are seldom standardized (except for penicillins, as detailed later); and in the majority of cases, the predictive value of skin testing remains indeterminate. Its use for various antibiotics is described in the sections on individual antibiotics.

In vitro Tests

Serum-specific IgE assays have been used for evaluating immediate reactions to β-lactams (mainly penicillins), with a relatively low sensitivity (~50%) compared with skin testing and a specificity approaching 90%.[7] The role of the flow cytometric basophil activation test (BAT) in the diagnostic evaluation of immediate reactions is still being investigated. The BAT detects the upregulation of activation markers CD63 and CD203c on the surface of basophils after incubation with the implicated drug. Multiple studies with BATs have been performed for β-lactams and fluoroquinolones and have found such testing to be highly specific but with low sensitivity. Commercially available assays have not undergone rigorous testing and are generally not recommended for use in making management decisions.

Drug Challenge (Drug Provocation Tests)

A drug challenge is generally accepted as the gold standard to establish tolerance to a drug. For clinical purposes, drug challenges are recommended when a true drug allergy is deemed unlikely based on the history and available diagnostic tests. In most cases, when the pretest probability is determined to be low for a drug allergy, drug challenges allow drug hypersensitivity to be excluded in a large percentage of patients.[8,9] Pretest probability is dependent on the nature of the reaction and the date of onset. The probability of true IgE-mediated allergy is high (20%–50%) in the setting of antibiotic-associated anaphylaxis within 3 months.[10] On the other hand, the risk of immediate hypersensitivity decreases to 1% to 2% with a distant (more than 10 years) history of benign symptoms. Unlike desensitization, challenge protocols are not designed to alter the immune response to a drug and merely confirm the presence or absence of sensitization. If the clinical question is whether a patient will tolerate a drug, a drug challenge is the appropriate procedure. Most drug challenges for immediate reactions are performed in a graded fashion with escalated dosing every 30 to 60 minutes. A common protocol is to start with $\frac{1}{10}$ of the therapeutic dose, followed by the final dose. Multistep challenges do not contribute further safety to the procedure.[11] If a patient tolerates the challenge, he or she may receive a therapeutic course of the drug. If the entire therapeutic course is tolerated without reaction, it is reasonable to remove the drug allergy label from the patient's chart.

For delayed reactions such as maculopapular exanthems and delayed-appearing urticaria, drug challenges are recommended when a true drug allergy is deemed unlikely based on the history and available diagnostic tests.[9,12] Protocols vary for delayed drug challenges. Some protocols are performed over days to weeks until a therapeutic dose is achieved. Similar to immediate drug challenges, a dose escalation starting with $\frac{1}{100}$ or $\frac{1}{10}$ of the final dose is performed, but the interval of dose escalation may be 2 to 3 days or a week, depending on the time interval between the drug intake and the index reaction. Another approach uses the immediate drug challenge approach, reaching a therapeutic dose in 1 to 2 hours. For more acute indications of antimicrobial agents, this latter approach may be more practical. Some experts suggest that multiday challenges do not appear to be any safer or more useful than single-dose challenges.[13] It is essential to update the patient's medical records and ensure that the antibiotic allergy label is removed after an uneventful challenge.

Contraindications to drug challenges include non–cutaneous-based reactions (e.g., hepatitis, cytopenias, and pneumonitis), serum-sickness reactions, drug-induced vasculitis, bullous eruptions, and SCARs, which include SJS and TEN, DRESS, and AGEP reactions. Although anaphylaxis is rare, equipment to treat anaphylactic reactions should be readily available, including epinephrine.

Skin and in vitro Tests for Nonimmediate Reactions

There is currently no established gold standard for the diagnosis of a delayed-type allergy.

Skin Testing: Delayed Intradermal and Patch Tests

Both delayed reading intradermal testing and patch testing have been used as in vivo methods for diagnosis of nonimmediate allergy, with various levels of sensitivity and specificity.[12,14]

Intradermal testing should not be performed in patients with SCARs owing to the risk of reactivation and an increased risk of systemic events. A multicenter study confirmed that patch tests are safe in patients with SCARs and have the highest sensitivity for DRESS (32%–80%) and AGEP reactions (58%–64%).[15] The negative predictive value for most drugs has not been well established. Thus a positive test result may suggest delayed hypersensitivity, but a negative test result does not exclude a drug allergy. According to European guidelines, patch testing

with suspect antibiotics should be used as first line of investigation in severe delayed reactions.[16] In the United States, few centers use drug patch testing in the evaluation of SCAR.

In vitro Tests

The lymphocyte transformation test (LTT), the lymphocyte activation test (LAT) evaluating for CD69 expression through flow cytometry, and enzyme-linked immunospot (ELISPOT) assays have been used to assess drug-specific, cytokine-producing T-cell activity in vitro.[17,18] Performance characteristics of these tests vary by laboratory, and they are mainly used for research purposes. Commercially available assays have not undergone rigorous testing and are generally not recommended for use in making management decisions.

Procedures to Induce Temporary Drug Tolerance

Drug Desensitization

In drug-allergic patients for whom no therapeutic alternative exists, a procedure to induce temporary drug tolerance can be considered.[19] These procedures are usually referred to as drug desensitizations. In contrast to drug challenges, which are merely a diagnostic test for tolerance to a drug, desensitization procedures actively induce tolerance through mechanisms that are still unclear but may involve internalization of high-affinity IgE receptors.[20] Desensitization procedures cause a state of temporary tolerance and allow a patient to receive an uninterrupted therapeutic course of an antimicrobial agent. It is critical to recognize that this "desensitized" state of drug tolerance is transient and that after cessation of the drug the patient's prior hypersensitive state returns. If the patient requires the drug again, a desensitization procedure will be required before each therapeutic course.

Desensitization protocols have been established for several different antibiotics in the event of documented (e.g., positive drug skin test result) or presumed IgE-mediated sensitization. Most protocols begin with a dilute concentration of drug (e.g., $\frac{1}{10,000}$ of dose), and the dose is typically doubled every 15 minutes until a full therapeutic dose is reached. Drug desensitizations for antibiotics are generally well tolerated, and anaphylactic reactions are rare. Antibiotic desensitizations should be conducted by personnel familiar with the procedure, equipment should be available to treat anaphylaxis, and close monitoring should be maintained. Owing to the requirement for close monitoring and frequent dose adjustments, desensitization procedures are often performed in an intensive care unit, although this is not a strict requirement. Desensitizations can be performed intravenously or orally. If feasible, an oral route is preferred because it may be a safer route of administration. The same aforementioned contraindications for drug challenges apply to drug desensitizations.

"Treating Through" Antibiotic-Associated Exanthems

"Treating through" refers to unchanged continuation of the antibiotic therapy despite the occurrence of maculopapular exanthem when the benefits of antibiotic therapy outweigh the risks. There are a very small number of reports describing this strategy and it must be conducted by an experienced allergist, with close monitoring of cutaneous symptoms and laboratory parameters.[21]

DRUG ALLERGY TO SPECIFIC ANTIMICROBIAL AGENTS

β-Lactams

β-Lactams represent the main cause of both immediate and nonimmediate allergic drug reactions. The four main groups share in common a four-membered β-lactam ring; and if this ring is fused to a thiazolidine ring, the β-lactam is classified as a penicillin. This includes piperacillin and the antistaphylococcal penicillins. The thiazolidine ring is replaced by a dihydrothiazine ring in the cephalosporin nucleus. In addition, penicillins have only one side chain (R1 group at 6-position), whereas cephalosporins have two side chains (R1 and R2 at the 3- and 7-positions, respectively). Monobactams contain a monocyclic ring structure, whereas carbapenems have a bicyclic nucleus composed of a β-lactam ring with an associated five-membered ring.

β-Lactams act as haptens and require conjugation to a carrier molecule to be recognized as a sensitizing molecule and to elicit an allergic response.

Penicillins

Epidemiology

The prevalence of self-reported penicillin allergy is high, at 10% to 15% among hospitalized patients. Because the diagnosis is often not substantiated by further testing, the use of suboptimal antibiotics contributes to worsening antibiotic resistance and increased health care costs. Recent literature suggests that up to 98% of patients with a history of penicillin allergy have negative findings on investigation.[22] This extreme discrepancy is secondary to the previously discussed factors of inaccurate history and compounding infectious causes that elicit similar reactions. Furthermore, IgE-mediated sensitivity to penicillins has been documented to wane over time, to less than 20% at 10 years after the reaction.[23] In a cohort of β-lactam allergic children (confirmed with drug provocation testing [DPT]), systematic follow-up DPT demonstrated tolerance at a mean of 3.5 years.[24]

Addressing the label of penicillin allergy has emerged as a significant public health risk. Several observational studies have reported clinical and economic outcomes associated with penicillin allergy, mostly focusing on inpatient admissions. In one institution, patients with reported penicillin allergy had a 51% increased risk of developing surgical site infections, primarily related to the substitution of non–β-lactam prophylactic antibiotics for cephalosporins.[25] King and colleagues calculated average savings of $297 per patient with a switch from a non–β-lactam antibiotic to a β-lactam antibiotic.[26] Macy and Contreras estimated indirect costs from associated complications in a study of 51,582 inpatients with a label of penicillin allergy, including increased use of non–β-lactam antibiotics, increased methicillin-resistant *Staphylococcus aureus* (MRSA) and vancomycin-resistant enterococci (VRE), and longer average hospital stay (0.59 days).[27] The authors presented calculations regarding potential cost savings with penicillin skin testing of $64.6 million by shortening the hospital stay by 0.59 days per patient (assuming negative skin test result in 95% of patients). This cost analysis was based on a single patient encounter, and the authors postulated that the cost throughout a patient's life would likely yield much larger differences.

Evaluation of Penicillin Allergy as Part of Antimicrobial Stewardship

Because penicillins are often the drug of choice for many infections, use of the label of penicillin allergy leads to more broad-spectrum antibiotic use, which leads to increased morbidity. The vast majority of patients with a label of penicillin allergy are not allergic; therefore addressing reported penicillin allergy has become an important part of antimicrobial stewardship. Recent position statements from the American Academy of Allergy, Asthma, and Immunology endorse that penicillin allergy testing should be done routinely in patients with self-reported penicillin allergy.[28] This will be discussed later in greater detail.

Pathophysiology

Two major mechanisms have been implicated in allergic reactions to β-lactams: IgE-dependent responses and T-cell–mediated reactions. In the event of the former, rapid and stable cleavage of the β-lactam ring results in the generation of defined epitopes that act as haptens, as described earlier. The major determinant derived from the β-lactam ring is known as benzylpenicilloyl (accounting for 95% of haptenated penicillin), and there are also minor determinants (of which only penicillin G is commercially available in the United States).[29] Furthermore, the R1 side chain is recognized as the antigenic determinant in the case of some reactions involving aminopenicillins, and these patients are selectively allergic to amoxicillin or ampicillin but tolerate other agents. This selective aminopenicillin allergy is commonly reported in European studies but is rarely reported in the United States. In addition, some patients react only to clavulanic acid, thereby tolerating amoxicillin but reacting to amoxicillin-clavulanate. Again, there are limited data on this phenomenon, and all are from southern Europe.

Clinical Manifestations

Penicillin allergy may manifest either as anamnestic responses to IgE formation or as delayed T-cell–mediated reactions. Maculopapular exanthems occur at a frequency of 2% to 3% during treatment, but SCARs may also develop. Amoxicillin is the most commonly used β-lactam in North America and Europe, and the most frequent drug involved in immediate and in nonimmediate reactions.

Diagnosis

Penicillin skin testing is an excellent diagnostic tool. The clinical history is known to be an unreliable predictor of skin test results.[30] The negative predictive value for skin testing with commercially available reagents (benzylpenicilloyl polylysine [PRE-PEN] and penicillin G) is approximately 97%. On the other hand, the positive predictive value of penicillin skin testing is unknown owing to ethical concerns regarding challenging patients who have positive reactions. Most practices follow a negative penicillin skin test result with an open challenge to amoxicillin, which increases the negative predictive value of the evaluation to almost 100%. Amoxicillin is commonly used to challenge after negative penicillin skin test results because it addresses the core β-lactam of penicillin and also side chain–specific reactions, which may not be detected through skin testing with penicillin itself. Although mainly indicated for immediate reactions, penicillin skin testing is often performed in patients with a history of delayed reactions because histories are often inaccurate and exclusion of the presence of penicillin IgE is important. It is typically recommended that penicillin skin testing be performed at least 6 weeks after a reaction (especially if anaphylactic) owing to the potential for false-negative skin test results. This recommendation is more theoretical and not evidence based. It is important to note that penicillin skin testing has no value in SJS and TEN, DRESS, and other noncutaneous organ-based reactions.

Studies have demonstrated uneventful direct oral challenges without skin testing in patients with a history of non–life-threatening reactions, particularly in the case of drug exanthems.[31] Furthermore, fatal anaphylaxis to penicillin is rare, with the majority of reported cases occurring in patients without a prior allergic reaction. Hence, a graded-dose challenge is often appropriate and usually well tolerated in these situations.[32] Recently, more data have been emerging regarding the safety of direct oral challenges without a preliminary negative skin test result in cases of low-risk phenotypes and nonanaphylactic symptoms, such as in patients with benign delayed-onset nonurticarial rashes. Studies in children and adults with histories predominantly of delayed reactions to penicillin have confirmed the safety of this approach.[33,34] This approach requires a skilled allergist and a reliable historian, and will need further confirmation in larger studies before it can become the new standard of care. A clinically significant delayed hypersensitivity to amoxicillin will typically manifest within 5 days of a single-dose oral amoxicillin challenge.[35]

Conversely, in vitro testing for anti-penicillin IgE vastly exaggerates sensitivity. Because anti-penicillin IgE has a poor correlation with clinically significant symptoms, commercially available serologic tests have little clinical usefulness.[36]

Desensitization

Patients with positive penicillin skin testing results should receive alternative agents, but if there are no alternative antibiotics indicated, desensitization procedures may be used. The procedure is typically successful, although 30% of patients tend to develop minor cutaneous reactions such as urticaria.

Cephalosporins

Pathophysiology

Cephalosporins form a heterogeneous group with five generations available in terms of antibiotic spectrum. Allergic reactions to cephalosporins may occur because of sensitization to antigenic determinants shared with penicillin or to unique cephalosporin haptens. In contrast to penicillins, cephalosporins undergo extensive fragmentation at the dihydrothiazine ring, with the consequent formation of a large number of degradation products, which has hindered the understanding of its haptenic determinants. However, the R1 group side chain is believed to contribute to most of the antigenicity. Consequently, IgE-mediated cephalosporin hypersensitivity is not necessarily a class hypersensitivity but rather is based on R1 side chain similarity.[37]

Clinical Manifestations

The majority of allergic reactions to cephalosporins are delayed rashes, but IgE-mediated urticaria and anaphylaxis can also occur.

Diagnosis

Evaluation of immediate reactions to cephalosporins may include skin testing with the suspected compound, along with other cephalosporins and penicillin determinants. However, even though skin tests with cephalosporins have been evaluated in various studies, they are not as well validated as with penicillin. In particular, the negative and positive predictive values are not fully established.[38] Testing with nonirritating concentrations (2 mg/mL) has been used to identify IgE-mediated allergy, although the exact sensitivity (ranging from 30.7% to 72% in various studies) and specificity of this skin test have not been determined.[39,40] In patients with a cephalosporin allergy, skin testing to structurally different cephalosporins appears to have good negative predictive value in indicating tolerance to other cephalosporins.[36] The role of skin testing is even less well defined with a history of delayed reactions to cephalosporins. Although intradermal and patch testing have been used, overall rates of sensitization are extremely low (~5%). In one study, most delayed skin manifestations attributed to cephalosporin treatment did not demonstrate positive skin test results, and subsequent challenges failed to reproduce the symptoms.[39] Thus, like patients with histories of penicillin allergy, many patients with histories of cephalosporin allergy appear to tolerate cephalosporins. Drug challenges are also appropriate to evaluate cephalosporin-allergic patients when the likelihood of true allergy is low.

Desensitization

Desensitization to cephalosporins may be considered for documented or presumed IgE-mediated reactions. Successful desensitization to cefotaxime and ceftazidime has been reported without major side effects.

Carbapenems

Current carbapenems available in the United States include imipenem-cilastatin, meropenem, doripenem, and ertapenem, and the incidence of associated hypersensitivity is estimated to be less than 3%.

Skin testing has not been well studied in carbapenem allergy, and thus the negative predictive value is unknown. Successful desensitization regimens to both imipenem and meropenem have been described, mostly as case reports, wherein carbapenems were the only antibiotic indicated.

Monobactams

Aztreonam is generally less immunogenic than other β-lactams because reactive haptenic breakdown products are less likely to be formed. It is considered a useful therapeutic alternative to patients with sensitivity to other β-lactams. Aztreonam does not cross react with other β-lactams except for ceftazidime, with which it shares an identical R-group side chain.

Cross-Reactivity Among β-Lactams

There has been a definite paradigm shift in the use of cephalosporins among the penicillin-allergic population. It is now recognized that cross-reactivity is not equal among all β-lactams, with most recent studies describing much lower rates of potential cross-reactivity.[16] Cross-reactivity between cephalosporins and penicillins is especially rare for cell-mediated reactions.[41] In most instances, positive in vitro testing results suggestive of potential cross-reactivity between penicillins or cephalosporins do not translate into clinical reactions.[42] In addition, penicillin allergy predisposes to a threefold higher risk for reactions to structurally unrelated antibiotics, and a concomitant cephalosporin allergy does not necessarily indicate cross-reactivity.

For patients with histories of nonsevere reactions to penicillin, the likelihood of reacting to cephalosporins is approximately 0.2%, based on retrospective evaluations of patients with reported allergy.[43,44] If