Update on Antimicrobial Agents

Penicillins, Monobactams, and Carbapenems

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To help physicians choose among a bewildering array of antimicrobial agents, this article reviews 3 groups of β-lactam antibiotics: 1) the penicillins, an extremely familiar drug group that includes a wide range of derivatives; 2) the monobactams, a newer class of antibiotics that provides only 1 commercially available drug, aztreonam; and 3) the carbapenems, which also provide only 1 commercially available drug, imipenem.

Because the basic structure of all penicillins, monobactams, and carbapenems (as well as cephalosporins) is a 4-membered β-lactam ring, these drugs are known as β-lactam antibiotics (Fig. 1). The other moieties attached to the β-lactam ring determine these agents' penetrability through the outer membrane of gram-negative bacilli, their resistance to β-lactamases, and, thus, their activity against various bacteria. Because the integrity of the β-lactam ring is a determinant of activity, a major mechanism of bacterial resistance is disruption of the ring by β-lactamases.

Mechanisms of Action and Resistance

β-lactams are bactericidal antibiotics that inhibit the final stages of cell-wall synthesis; hence, they are effective only against organisms that are proliferating and actively producing cell-wall constituents. Laboratory studies indicate that these antibiotics do not kill nonproliferating organisms. During the past several decades, extensive studies of the β-lactams' mechanisms of action have helped reveal the complexities of the structure and metabolism of pathogenic bacteria. For a β-lactam to kill an organism, the drug must be able to penetrate the outer cell-wall structures and reach the site of cell-wall synthesis; it must also resist enzymatic destruction by β-lactamases and bind to the enzymes associated with cell-wall synthesis (transpeptidases, carboxypeptidases, and endopeptidases), which are known as penicillin-binding proteins (PBPs). Organisms may become β-lactam resistant by 1) altering their outer-membrane permeability, 2) producing β-lactamases, or 3) altering their PBPs.

Key words: *Antibiotics; bacterial infections; carbapenems; drug resistance, microbial; drug therapy, combination; monobactams; penicillins*

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Permeability

The outer cell-wall structures of gram-positive and gram-negative bacteria differ in complexity. Most gram-positive bacteria have a relatively simple outer cell-wall structure, consisting of a cytoplasmic membrane (where the PBPs are located) covered by peptidoglycan strands. Hence, β-lactams can penetrate gram-positive organisms with little difficulty. Among such organisms, altered membrane permeability has not been recognized as a mechanism of resistance.

Gram-negative bacilli have a more complex outer cell-wall structure (Fig. 2). The outer membrane impedes the passage of β-lactams; it does, however, contain channels known as porins, which allow the passage of large molecules including β-lactams and nutrients. Three characteristics of antibiotics can increase the drugs' ability to pass through these porins: sufficiently small size, low hydrophobicity (that is, an affinity for water), and positive charge. For example, the antistaphylococcal penicillins (such as oxacillin, nafcillin, and others) are ineffective against gram-negative bacilli, because these drugs consist of molecules that are too large to pass through the porin channels.

Gram-negative bacilli may develop resistance to β-lactams by altering their membrane permeability. This mechanism of resistance has been detected in strains of *Pseudomonas aeruginosa*, *Citrobacter* and *Enterobacter* species, *Serratia mar-*

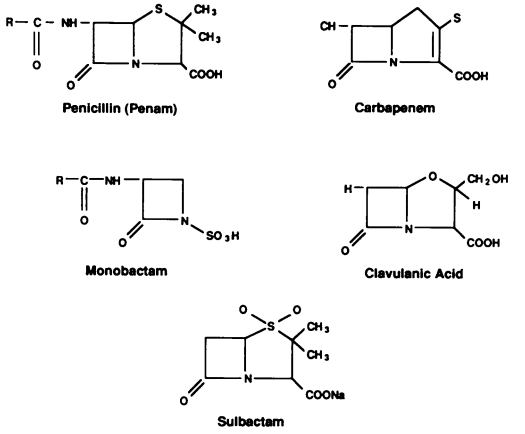

Fig. 1 *Chemical structures of selected β-lactams.*

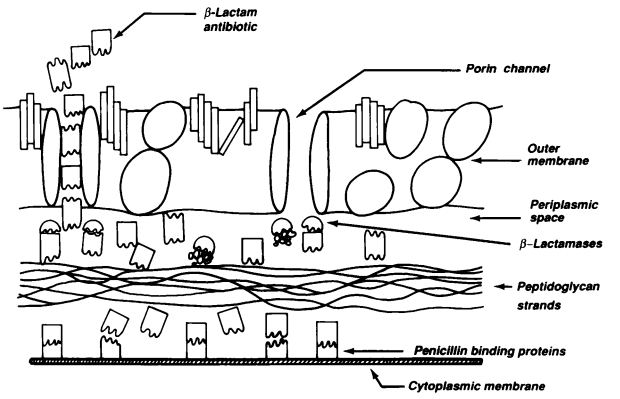

Fig. 2 *Diagrammatic representation of the cell wall of a gram-negative bacillus.*

cescens, and *Neisseria gonorrhoeae*. For example, some *P. aeruginosa* develop resistance to imipenem during therapy by altering membrane permeability. This mechanism of resistance can be overcome by designing β-lactams with different permeability characteristics.

β-lactamases

β-lactamases are bacterial enzymes that open the β-lactam ring, thereby inactivating the antibiotic.[1] β-lactamases are prevalent in most bacteria, including gram-positive cocci and gram-negative bacilli, as well as *Mycobacterium*, *Nocardia*, and *Legionella* organisms. Essentially all pathogenic gram-negative bacteria have strains that produce β-lactamases. Each β-lactamase is specific for certain β-lactam antibiotics.

The β-lactamases of gram-positive cocci differ from those of gram-negative bacilli. Production of most gram-positive coccal β-lactamases is mediated by plasmids and is inducible; that is, the organism produces the enzyme only in the presence of a β-lactam. Generally, the enzyme is produced in large amounts and dispersed extracellularly; this fact is important, because these organisms have no significant barriers to antibiotic penetration. The β-lactamases of gram-positive cocci usually provide clear-cut resistance to susceptible β-lactams. For example, β-lactamase-producing strains of *Staphylococcus aureus* are resistant to penicillin G, aminopenicillins (ampicillin), carboxypenicillins (ticarcillin), and ureidopenicillins (piperacillin), but are susceptible to methicillin and isoxazolyl penicillins (oxacillin).

Production of the β-lactamases of gram-negative bacilli may be plasmid or chromosomally mediated and may be inducible or constitutive. Constitutive enzymes are produced whether or not a β-lactam is present. Generally, β-lactamases are produced in small quantities and are located in the periplasmic space near the antibiotic's target. Multiple β-lactamases may be present in the same organism; they may or may not provide resistance, and their effect may vary with different antibiotics.

Drug manufacturers can circumvent the effect of β-lactamases by producing antibiotics resistant to destruction. Examples are the antistaphylococcal penicillins that kill penicillin-G-resistant *S. aureus*. Recently, investigators have discovered certain substances that can specifically inhibit β-lactamases. Two of these, clavulanic acid and sulbactam, will be discussed later.

Penicillin-Binding Proteins

The term penicillin-binding proteins (PBPs) is a misnomer, since the cell produces these enzymes to complete the cross-binding of peptidoglycan strands, the final stage of cell-wall synthesis, not to bind to penicillins. The variety of PBPs present depends upon the organism. Seven PBPs have been identified in *Escherichia coli*, 5 have been seen in *Streptococcus pneumoniae*, and 6 in *Clostridium perfringens*. Each enzyme performs a specific function, and not all are essential to the organism's survival.[2] Different β-lactams bind to different PBPs. In *E. coli*, for example, many penicillins bind to PBP1A, whereas imipenem binds preferentially to PBP2, and aztreonam binds to PBP3.

Bacteria can develop β-lactam resistance by altering their PBPs. To do this, the organisms can 1) decrease their affinity to β-lactams, 2) overproduce a critical PBP, or 3) produce a new PBP. Penicillin resistance in *S. pneumoniae* and methicillin resistance in *S. aureus* have been associated with the production of new PBPs. Other organisms that have developed resistance because of altered PBPs include *Streptococcus faecalis*, *Streptococcus faecium*, *Staphylococcus epidermidis*, *E. coli*, *P. aeruginosa*, *N. gonorrhoeae*, and *Bacteroides* species. Although the physician may be able to overcome this by using another β-lactam that binds to other PBPs, it is usually necessary to rely on other types of antibiotic therapy.

General Side Effects

Because the mechanism of action of β-lactam antibiotics is directed against the synthesis of the bacterial cell wall, and because human cells have no such structure, these antibiotics are among the least toxic in our armamentarium. Many β-lactam antibiotics share side effects in common, and these reactions will be discussed in this section. Side effects unique to a specific antibiotic will be discussed in the section concerning that antibiotic. Major categories of side effects include hypersensitivity reactions, as well as gastrointestinal, hematologic, renal, hepatic, and neurologic sequelae. β-lactams interfere with some laboratory tests and may interact with concomitantly administered drugs.

Hypersensitivity Reactions

Hypersensitivity reactions to β-lactam antibiotics include mild-to-severe rashes, eosinophilia, fever, serum sickness, and anaphylaxis. Most serious reactions follow parenteral administration, but anaphylaxis has also been reported to follow oral penicillin therapy. Although acute allergic reactions require previous exposure, penicillins have been so widely used, in both human beings and animals, that few Americans remain unexposed. Sensitization may be directed toward penicillin itself but is more often directed toward the drug's degradation products, which serve as haptens that form a complex with proteins.

Penicillin allergy is greatly over-diagnosed, especially by patients, and physicians should determine what a patient means when claiming to be "allergic to penicillin." Such an allergy is more likely to occur in patients with a history of asthma or some other type of allergy. About 30% of patients with anaphylaxis have experienced a previous immediate-type hypersensitivity reaction. The faster the drug is absorbed, the greater the likelihood of an anaphylactic reaction. Half of such reactions are explosive, and another 35% occur within 15 minutes of antibiotic administration.

As Table I shows, hypersensitivity reactions can be divided into 4 types. Anaphylaxis, the most serious reaction, occurs in 0.004% to 0.05% of the patients and is associated with a mortality of 2% to 5%. It occurs most frequently after exposure to penicillin G. Because acute anaphylaxis is potentially fatal, patients should be kept under observation for an hour after receiving the 1st penicillin dose, and emergency treatment should be readily available. Penicillins should not be administered to patients with a history of anaphylaxis, urticaria, or other serious skin rashes. Skin sensitivity testing and desensitization can be performed.

About 2% of the patients who receive penicillin G experience serum sickness, manifested by fever, malaise, urticaria, joint pains, and lymphadenopathy. Erythema nodosum and exfoliative dermatitis occur much less frequently. Hematologic side effects include transient neutropenia, leukopenia, thrombocytopenia, maturation arrest, and Coombs'-positive hemolytic anemia. All of these side effects are attributed to hypersensitivity reactions, but some occur only at high doses. A coagulation disorder related to impaired platelet aggregation has been associated with high-dose penicillin-G therapy (> 24 million units daily) but is more common with carbenicillin and ticarcillin.

Gastrointestinal side effects, which primarily follow oral administration of penicillins, consist of nausea, vomiting, abdominal cramps, and diarrhea. Some of these effects can occur after parenteral administration, especially of carbenicillin or imipenem. Pseudomembranous colitis can occur with these antibiotics, but it is no more common than with other classes of antibiotics and is usually associated with broader-spectrum derivatives. Hepatotoxicity, which is primarily manifested by transient abnormalities in the results of liver-function tests, is more likely to occur with some of the semisynthetic agents than with penicillin G.

Acute interstitial nephritis may occur 7 to 14 days after the initiation of therapy and is most likely a hypersensitivity reaction. It is manifested by fever, proteinuria, hematuria, azotemia, eosinophilia, and rash formation. In most cases, the problem resolves when the drug is discontinued. Electrolyte disturbances occur in patients receiving high penicillin

TABLE I. Hypersensitivity Reactions to Penicillins

Type	Mediator	Time of Occurrence	Manifestations
I	IgE antibodies	Immediate (< 1 hr); accelerated (1–72 hrs)	Anaphylaxis, asthma, angioedema, urticaria, laryngospasm, hypotension
II	IgM or IgG antibodies	Late (weeks)	Hemolytic anemia, agranulocytosis, leukopenia
III	Immune complexes	Late (7–10 days)	Serum sickness, drug fever, interstitial nephritis, vasculitis, Arthus phenomenon
IV	T cells	Delayed or late (> 48 hrs)	Skin rashes

doses, which are usually administered as sodium salts. Hypokalemia and edema are the most common sequelae.

Because penicillins are potentially irritating to the central nervous system, side effects may occur when high doses are administered or when renal function is impaired. Neurologic side effects are most prevalent with imipenem therapy. Symptoms include generalized seizures, hallucinations, confusion, lethargy, twitching, hyperreflexia, myoclonus, and coma. Because of penicillin's direct irritative effects, intrathecal administration should be avoided. Cardiopulmonary bypass may predispose a patient to penicillin-G neurotoxicity. When penicillins are used to treat syphilis, Jarisch-Herxheimer reactions occur relatively often. To prevent permanent neurovascular damage, special care should be taken when penicillins are injected intramuscularly near major peripheral nerves or blood vessels.

Drug Interactions

Penicillins are chemically incompatible with aminoglycosides; therefore, they should not be mixed in the same container. Although such a mixture produces no important interaction in the bloodstream of normal hosts, penicillins can inactivate aminoglycosides to a significant extent in patients with severe renal failure. Concomitant administration of bacteriostatic antibiotics should also be avoided, since it may result in drug antagonism; the clinical significance of such antagonism in vitro, however, is debatable. Concomitant probenecid therapy results in heightened serum concentrations of β-lactams, whose renal excretion occurs predominantly by means of tubular secretion. Nonsteroidal anti-inflammatory agents can delay renal excretion of penicillins, and some penicillins can decrease the effect of estrogenic contraceptives.

Laboratory Test Interference

Penicillins interfere with some laboratory test results, including those involving serum, urine, cerebrospinal proteins, glucose, and uric acid. These drugs may also alter the results of tests for phenylketonuria and folic acid, which depend on microorganisms. Penicillins can interfere with human lymphocyte antigen (HLA) typing and the detection of δ-aminolevulinic acid (lead poisoning).

The Penicillins

In 1929, Alexander Fleming serendipitously discovered that the mold *Penicillium notatum* produced a substance that inhibited the growth of gram-positive cocci.[3] However, the efficacy of penicillin for the treatment of staphylococcal and streptococcal infections was not demonstrated until 12 years later by Florey and associates.[4] Because of its far-reaching impact, Fleming's initial discovery was a monumental event in medical history.

The basic structure of penicillin is a 4-membered β-lactam ring attached to a thiazolidine ring. In 1959, Batchelor and associates[5] discovered that, by using bacterial enzymes, they could produce large quantities of the basic penicillin structure (6-aminopenicillanic acid) with no side chain. This breakthrough opened the way to the synthesis of a wide variety of derivatives, with different spectra of activity.

The penicillins can be divided into 3 main groups. The 1st group consists of those agents whose activity is limited primarily to gram-positive organisms. This group can be further subdivided into 1) limited-spectrum agents such as penicillin G and 2) antistaphylococcal penicillins. The 2nd major group comprises penicillins that have activity against gram-negative bacilli. These drugs can be divided into 1) limited-spectrum agents such as ampicillin and 2) antipseudomonal penicillins. The 3rd main group consists of penicillins combined with β-lactamase inhibitors. Figure 3 shows the chemical structures of representative β-lactams.

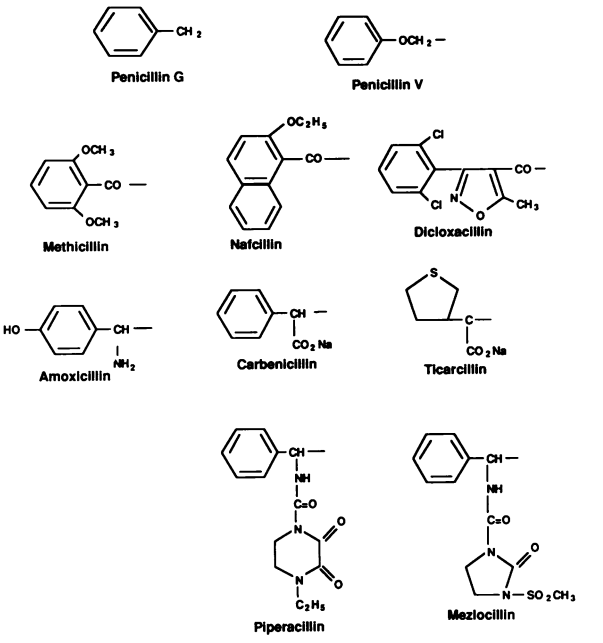

Fig. 3 *Side chains of selected penicillins.*

Anti-Gram-Positive Penicillins

Limited-Spectrum Agents. Penicillin G, or benzylpenicillin, the commercially available purified penicillin, is manufactured as a sodium or potassium salt. It is also available in depot forms as procaine penicillin and benzathine penicillin. These drugs are often prescribed in dosages expressed as units rather than as weights. One unit of sodium penicillin G is equal to 0.6 μg. Table II shows the β-lactams' spectra of activ-

ity against common pathogens.[6] Penicillin G remains highly active against nearly all strains of *Streptococcus pyogenes* (group A). Other β-hemolytic streptococci, including groups B (*Streptococcus agalactiae*), C, F, and G are sensitive to the drug. Most isolates of *S. pneumoniae* (pneumococcus) remain quite sensitive (minimal inhibitory concentration [MIC] < 0.01 μg/mL). Nevertheless, relatively resistant strains (MIC = 0.1 to 2.0 μg/mL) and resistant strains (MIC > 2.0 μg/mL) are being identified with increasing frequency; these represent a serious problem in some areas outside the United States. With a few exceptions, those species of α-hemolytic streptococci known collectively as viridans streptococcus remain susceptible. "Nutritionally variant" streptococci may be penicillin tolerant—that is, inhibited but not killed by penicillin G. Enterococci are also penicillin tolerant, having an MBC:MIC ratio* of greater than 32. Nonenterococcal strains of group-D streptococci are penicillin-G sensitive.

Staphylococcus aureus was uniformly sensitive to penicillin G when the drug was 1st introduced, but resistance has become widespread in both nosocomial and community strains. Most strains of *S. epidermidis* and related coagulase-negative species are resistant to penicillin G. Most aerobic gram-positive bacilli, including *Corynebacterium diphtheriae*, *Bacillus anthracis*, and many *Listeria monocytogenes*, are sensitive. Pathogenic anaerobic gram-positive cocci (*Peptococcus, Peptostreptococcus*) and bacilli (*Clostridium* species) are sensitive to the drug, although some strains of *Clostridium* species (for example, *C. innocuum*) have developed resistance.

Among the gram-negative cocci, *Neisseria meningitidis* remains sensitive; in some areas of the United States and elsewhere, however, a sizable number of the strains of *N. gonorrhoeae* are relatively or completely resistant to penicillin G. Most aerobic gram-negative bacilli are resistant, with a few exceptions such as *Pasteurella multocida* and some strains of *Haemophilus influenzae*. Among the anaerobic gram-negative bacilli, *Bacteroides fragilis* is resistant, whereas oral anaerobes (*Fusobacterium, Capnocytophaga*), including most isolates of other *Bacteroides* species, are sensitive. Some strains of *Bacteroides* and *Fusobacterium* species produce β-lactamases and are resistant. Other organisms sensitive to penicillin G include actinomycetes, treponema, lepto-

*Minimal bacterial concentration-to-minimal inhibitory concentration ratio.

TABLE II. Susceptibility of Common Pathogens to β-Lactam Antibiotics

Organism(s)	PenG	Anti-Staph	Amino	Ticar	Mez	Azlo	Pip	Amino+BLI	Ticar+BLI	Aztr	Imip
Streptococcus	++	+	+	+	+	+	+	+	+	–	+
Enterococcus	+	–	++	+	+	+	+	++	+	–	+
Staphylococcus aureus	–	++	–	–	–	–	–	+	+	–	+
Clostridium	++	+	+	+	+	+	+	+	+	–	+
Meningococcus	++	+	+	+	+	+	+	+	+	+	+
Escherichia coli	–	–	+	+	+	+	+	+	+	++	++
Klebsiella	–	–	–	–	+	+	+	+	+	++	++
Enterobacter	–	–	–	+	+	+	+	–	+	++	++
Serratia	–	–	–	+	+	+	+	–	+	++	++
*Proteus**	–	–	–	++	++	++	++	–	++	++	++
Pseudomonas aeruginosa	–	–	–	++	++	++	++	–	++	++	+
Bacteroides fragilis	–	–	–	–	–	–	–	+	+	–	+

– = not effective
\+ = effective, but not a drug of choice
++ = a drug of choice, but alternatives may exist

Amino = aminoglycoside; Anti-Staph = antistaphylococcal penicillin; Azlo = azlocillin; Aztr = aztreonam; BLI = β-lactamase inhibitor; Imip = imipenem; Mez = mezlocillin; PenG = penicillin G; Pip = piperacillin; Ticar = ticarcillin

*Other than *mirabilis*

spira, *Borrelia*, *Streptobacillus moniliformis*, and *Spirillum minus*.

Penicillin G is usually administered intravenously, but it can also be given intramuscularly. The drug has a short serum half-life (0.5 hr) and is excreted in the urine, predominantly by means of tubular secretion. This secretion can be blocked by concomitant probenecid therapy, but such therapy is infrequently prescribed. Penicillin G is unstable in acid and is therefore unsuitable for oral administration, because only one-third of a dose is absorbed. The drug is well distributed into all body compartments except the eye. It crosses inflamed meninges satisfactorily but uninflamed meninges poorly. In the absence of obstruction, biliary concentrations generally exceed serum concentrations. Table III lists the usual dosages of β-lactams.

Procaine penicillin is a penicillin-G preparation designed for intramuscular use. Its administration is less painful than that of aqueous penicillin G, and absorption continues for up to 24 hours, permitting once- or twice-daily dosing. Benzathine penicillin is an intramuscular repository form that maintains low serum concentrations for 1 to 3 weeks. It is used for the treatment of *S. pyogenes* infections and syphilis, and for the prophylaxis of rheumatic fever and endocarditis.

The major uses of all these penicillin-G preparations are for the treatment of *S. pyogenes* and other β-hemolytic streptococcal infections, pneumococcal pneumonia, meningitis, meningococcal infections, gonococcal infections (except where resistance is prevalent in the community), syphilis, clostridial infections (including tetanus), leptospirosis, Lyme disease, rat-bite fever, anthrax, diphtheria, actinomycosis, and *P. multocida* and *Capnocytophaga* (DF-2) infections, as well as for the prophylaxis of rheumatic fever. Penicillin G should be used in combination with an aminoglycoside for treating endocarditis caused by viridans streptococcus, enterococci, or "nutritionally deficient" streptococci. Combination therapy may also be more effective against group-B streptococcal infections.

Phenoxymethyl penicillin (penicillin V), a penicillin-G derivative that is available as an oral preparation, has a spectrum of activity similar to that of penicillin G. Peak serum concentrations are reached within 1 hour, and 20% to 40% of an administered dose is excreted in the urine within the 1st 6 hours. The drug's use is limited to mild-to-moderate streptococcal infections, prolonged therapy after initial response to parenteral preparations, urinary tract infections caused by susceptible organisms, and prophylaxis.

Antistaphylococcal Penicillins

Methicillin was the 1st semisynthetic antistaphylococcal penicillin. Subsequently, oxacillin, cloxacillin, dicloxacillin, and nafcillin were introduced. Methicillin, oxacillin, and nafcillin are available as parenteral preparations; oxacillin, cloxacillin, dicloxacillin, and nafcillin are available as oral preparations.

These penicillins have similar spectra of activity, despite minor differences in their degrees of activity. They are effective against gram-positive and gram-negative cocci. Against susceptible isolates, however, penicillin G's activity is generally 20 to 50 times that of the antistaphylococcal penicillins. Enterococci are generally resistant to the antistaphylococcal agents. These drugs' major advantage over penicillin G is their resistance to degradation by the β-lactamases produced by *S. aureus* and *S. epidermidis*. Unfortunately, as of the past few years, at least 50% of the isolates of *S. epidermidis* are resistant to methicillin. Methicillin-resistant strains of *S. aureus* were common in Europe more than a decade ago but have only recently become a problem in the United States. In many tertiary-care centers, 10% to 15% of the *S. aureus* strains are methicillin resistant; at some institutions, the proportion exceeds 50%. Methicillin-resistant strains are also resistant to all the other penicillins.

The pharmacokinetic properties of the various antistaphylococcal penicillins differ (Table IV). Methicillin is unstable in acid and, therefore, is ineffective via the oral route. This agent is usually administered intravenously, because intramuscular injections are painful. Its degree of serum protein binding is lower than that of most other penicillins, and the drug is widely distributed in body fluids.

The isoxazolyl penicillins include oxacillin, cloxacillin, and dicloxacillin. Oxacillin is available both as an oral and as a parenteral preparation. Its extent of oral absorption varies; because some individuals achieve only barely detectable serum concentrations, other penicillin derivatives are more desirable for oral administration. In the United States, cloxacillin and dicloxacillin are available only as oral preparations. Dicloxacillin produces serum concentrations twice as high as those of cloxacillin. All of these isoxazolyl penicillins are excreted primarily in the urine, and to a certain extent in the bile. Active metabolites constitute about 10% of the total serum concentrations of these antibiotics, and these metabolites account for 10% to 20% of the drug amounts excreted in the urine. These penicillins, especially oxacillin, also undergo inactivation in the liver. All isoxazolyl penicillins are highly bound (> 90%) to serum proteins. The significance of such protein binding is unascertained.[7] Studies have indicated that the isoxazolyl penicillins diffuse relatively poorly into interstitial fluid, but there is no evidence that they are clinically less effective than methicillin.

Nafcillin is available for both oral and parenteral administration. Because this drug is not reliably ab-

TABLE III. Usual Dosages of β-Lactams

Drug	Route	Adults		Children		Renal Impairment		
						Creatinine Clearance (mL/min)		
		Total Daily Dose	Interval (h)	Total Daily Dose	Interval (h)	50-80	10-50	<10
Penicillin G	IV	2–20 million U	4–6	50,000–250,000 U/kg	6	NC	NC	50% dose
Procaine penicillin	IM	0.6–4.8 million U	6–12	500,000–1 million U/kg	24	NC	NC	NC
Benzathine penicillin	IM	1.2–2.4 million U	—	600,000–1 million U/kg	—	NC	NC	NC
Penicillin V	PO	1–2 g	6	25,000–100,000 U/kg	6	NC	NC	NC
Methicillin	IM, IV	4–12 g	6	100–200 mg/kg	6	1–2 g q6h	1–2 g q8h	1–2 g q12h
Oxacillin	IM, IV	2–12 g	4–6	100–200 mg/kg	2–12	NC	NC	NC
Cloxacillin	PO	1–2 g	6	50–100 mg/kg	6	NC	NC	NC
Dicloxacillin	PO	1–2 g	6	25–50 mg/kg	6	NC	NC	NC
Nafcillin	IM, IV	2–12 g	4–6	50–200 mg/kg	4–6	NC	NC	NC
Ampicillin	IV	2–8 g	4–6	100–200 mg/kg	4–6	NC	NC	NC
Amoxicillin	PO	0.75–2. g	6–8	20–40 mg/kg	8	NC	0.25-0.5 g q12h	0.25-0.5 g q12-24h
Bacampicillin	PO	0.8–1.6 g	12	800 mg	12	NC	NC	—
Cyclacillin	PO	1–2 g	6	50–100 mg/kg	6	NC	500 mg q12–18h	500 mg q24h
Carbenicillin	IV	8–30 g	4–6	200–600 mg/kg	4–6	NC	2–3 g q6h	Change
Ticarcillin	IV	4–24 g	4–6	200–300 mg/kg	4–6	NC	2–3 g q6–8h	2 g q12h
Mezlocillin	IV	6–24 g	4-6	100–300 mg/kg	4–6	NC	3 g q8h	2 g q8h
Piperacillin	IV	6–24 g	4–6	100–300 mg/kg	4–6	NC	3 g q8h	3 g q12h
Azlocillin	IV	8–24 g	4–8	100–450 mg/kg	4–6	NC	1.5–2 g q8h	1.5–3 g q12h
Augmentin®	PO	0.75–1.5 g	8	20–40 mg/kg	8	NC	0.25–0.5 g q12h	0.25–0.5 g q20–36 h
Unasyn®	IM, IV	4–8 g	6	—	—	1–2 g q8h	1–2 g q8h	1–2 g q12h
Timentin®	IV	12–18 g	4–6	200–300 mg/kg	4–6	NC	2–3 g q8h	2 g q12h
Aztreonam	IV	1.5–6 g	4–8	—	—	NC	1–2 g q12–18h	1–2 g q24h
Imipenem	IV	1–4 g	6	60–100 mg/kg	6	500 mg q6–8h	500 mg q8–12h	250–500 mg q12h

IM = intramuscular; IV = intravenous; NC = no change; PO = oral; U = units

TABLE IV. Pharmacokinetic Properties of β-Lactams

Drug	Route	Percentage of Protein Binding	Percentage Excreted in Urine at 6 hrs	Half-Life (hrs)	Percentage Metabolized	Percentage Absorbed from GI Tract
Penicillin G	IV	45–68	60	0.4–0.9	15–30	—
Penicillin V	PO	75–89	25–65	0.5	35–70	60–73
Methicillin	IV	30–50	32–80	0.4–0.5	10	—
Oxacillin	IV, PO	89–94	40–70	0.3–0.8	49	0–35
Cloxacillin	PO	90–96	30–62	0.4–0.8	22	37–60
Dicloxacillin	PO	95–99	33–49	0.6–0.8	10	35–76
Nafcillin	IV	70–90	27–31	0.5–1.5	60	—
Ampicillin	IV, PO	15–25	73–90	0.7–1.4	10–12	30–55
Amoxicillin	PO	17–20	43–80	0.7–1.4	19–33	74–92
Bacampicillin	PO	15–25	60–83	0.7–1.4	?	80–98
Cyclacillin	PO	18–25	50–77	0.5–0.8	15–19	>80
Ticarcillin	IV	45–65	80–93	1.0–1.4	10	—
Mezlocillin	IV	16–42	39–72	1.1	Min	—
Piperacillin	IV	16–22	42–90	0.8–1.6	Min	—
Azlocillin	IV	20–46	48–83	0.8	Min	—
Clavulanate	IV, PO	22–30	25–45	0.8–1.2	50	60
Sulbactam	IV	38	70	1.0	?	—
Aztreonam	IV	46–60	58–74	1.5–2.0	10–15	—
Imipenem	IV	13–21	70	1.0–1.5	20–30	—

GI = gastrointestinal; IV = intravenous; Min = minimal (exact amount is uncertain and unimportant); PO = oral

sorbed from the gastrointestinal tract, it is less useful than the isoxazolyl penicillins. About 30% of an intramuscular dose is excreted in the urine, 8% is excreted in the bile, and the remainder is inactivated in the liver. Methicillin, oxacillin, and nafcillin penetrate inflamed meninges adequately.

The major clinical indications for antistaphylococcal penicillin therapy are susceptible *S. aureus* and *S. epidermidis* infections. Because these drugs are less active than penicillin G, they should not be used preferentially for treating penicillin-G-susceptible infections. In cases of presumed gram-positive coccal infection, the antistaphylococcal penicillins provide adequate coverage, so the former practice of administering penicillin G plus an antistaphylococcal penicillin until the infecting organism was identified is no longer necessary. Whether an aminoglycoside should be included for the treatment of staphylococcal endocarditis has not yet been determined.

Interstitial nephritis, apparently related to hypersensitivity, is most frequently associated with methicillin usage, especially when the drug is administered in high doses for prolonged periods. Such dosages can also cause hemorrhagic cystitis. If either of these complications occurs, the drug should be discontinued. Oxacillin is the antistaphylococcal penicillin most likely to cause hepatotoxicity, as manifested by fever, nausea, vomiting, and elevated liver-function test results. When nafcillin is administered in high doses, hypokalemia and alkalosis may occur.

Anti-Gram-Negative Penicillins

Limited-Spectrum Agents. Ampicillin is the 1st semisynthetic penicillin to have substantial activity against gram-negative bacilli. This activity is the result of the addition of an amino group to the side chain of penicillin G, which alters the drug's charge and facilitates passage through the outer membrane of gram-negative bacilli. Amoxicillin resembles ampicillin, except that in amoxicillin, a hydroxyl group is added to the benzyl ring of the side chain, thereby altering the pharmacokinetic properties. Cyclacillin and bacampicillin are newer alternatives that offer better oral absorption.

In general, ampicillin's spectrum of activity against gram-positive cocci resembles that of penicillin G, but ampicillin is more active than penicillin G against enterococci. It is susceptible to destruction by staphylococci-produced β-lactamases. Coagulase-negative staphylococci such as *Staphylococcus saprophyticus*, which cause urinary tract infections in women, are usually sensitive. Ampicillin is also effective against aerobic and anaerobic gram-positive bacilli. Its activity against gram-negative cocci is similar to that of penicillin G.

Ampicillin's major advantage has been its usefulness against some Enterobacteriaceae. When the drug was introduced, more than 95% of the isolates of *E. coli* were sensitive to it. Now many nosocomial strains, as well as 20% to 40% of community strains, are resistant.[8] Resistance is usually mediated by β-lactamase production. *Proteus mirabilis* and *Arizona* species tend to be sensitive, but other *Proteus* species, as well as *Serratia*, *Enterobacter*, *Citrobacter*, *Edwardsiella*, *Providencia*, and *Yersinia* organisms, are resistant. Some strains of *Klebsiella* species were initially sensitive to ampicillin, but this sensitivity was subsequently lost. *Salmonella* species are usually sensitive, but resistant strains are being found with increasing frequency, especially among *Salmonella typhimurium*. Most *Shigella* organisms were sensitive to ampicillin when it was introduced, but resistance is now prevalent throughout the world. Other organisms that are usually sensitive to ampicillin include *Brucella* species, *Vibrio* species, and *H. influenzae*. In the recent past, ampicillin-resistant *H. influenzae* has unfortunately become prevalent in some communities, thereby limiting the drug's usefulness.[9] Resistance is mediated by β-lactamase production.

Ampicillin is available both as an oral and as a parenteral preparation. About 30% to 55% of each oral dose is absorbed, and peak serum concentrations are achieved between 1 and 2 hours. If ampicillin is administered with food, its absorption is reduced by 50%. About 75% of a parenteral dose is excreted in the urine by means of glomerular filtration and tubular secretion. The drug is cleared more slowly by the kidneys than is penicillin G. Some ampicillin is excreted in the bile, and this portion may be reabsorbed from the gastrointestinal tract. About 10% is inactivated in the liver. Ampicillin is adequately distributed in most body tissues, including inflamed meninges. It penetrates bronchial secretions poorly.

Ampicillin was at one time used extensively for the treatment of urinary tract infections, but its efficacy has been limited by increasing resistance among *E. coli* organisms. Although uncomplicated *Salmonella* enteritis does not require treatment, antibiotic therapy is beneficial in cases of shigellosis. Widespread resistance to ampicillin makes it an unreliable agent for shigellosis at present. It can be used to treat bronchitis, community-acquired pneumonias that are not life-threatening, soft-tissue infections, otitis media, sinusitis, pertussis, meningitis, biliary tract infections, and gonorrhea. Widespread resistance among *H. influenzae* and other organisms has reduced ampicillin's usefulness for the initial therapy of meningitis, bronchitis, otitis media, and sinusitis. Penicillin-resistant gonococci are also resistant to ampicillin. With respect to activity, the differences between ampicillin and amoxicillin are of minimal clinical significance. Bacampicillin is hydrolyzed to ampicillin in vivo and, therefore, has the same spectrum of activity. Cyclacillin is substantially less active than ampicillin or amoxicillin in vitro, but it has a similar spectrum of activity.

In the United States, amoxicillin is available only as an oral preparation. The drug is well absorbed (75% to 90%) from the gastrointestinal tract, and serum concentrations are twice as high as with the same dose of ampicillin. The presence of food in the stomach decreases absorption, but to a lesser extent than with ampicillin. The serum half-life of amoxicillin is similar to that of ampicillin. Bacampicillin is absorbed more rapidly and more completely (80% to 98%) than ampicillin and is quickly converted to ampicillin by esterases in the intestinal wall. Its degree of absorption is comparable to that of amoxicillin, and food does not hinder its absorption. Cyclacillin is also rapidly absorbed from the gastrointestinal tract; peak serum concentration is reached at 30 minutes. This drug is rapidly cleared, however, so serum concentrations are low after 2 hours and virtually undetectable after 4 hours. In comparison with the serum concentrations of cyclacillin, those of amoxicillin are higher during the 1st 45 minutes after administration of similar doses, but are lower thereafter.

A high percentage (58% to 68%) of each amoxicillin dose is excreted unchanged in the urine. About 20% to 30% is metabolized in the liver. Urine is also the major excretory pathway for both bacampicillin and cyclacillin. About 50% to 75% of an oral dose of cyclacillin is excreted unchanged in the urine within 6 hours.

The indications for amoxicillin, bacampicillin, and cyclacillin are the same as those for ampicillin. Because amoxicillin and bacampicillin have a degree of activity similar to that of ampicillin and are more completely and reliably absorbed, they are preferred for oral administration.

Rashes occur more commonly with ampicillin than with any other penicillin; presumably, many of these rashes are not allergic reactions. Rashes are especially common (65% to 95%) in patients with infectious mononucleosis. A similar high frequency of rash formation has been reported in patients with leukemia and lymphoma. Diarrhea and other gastrointestinal side effects occur more frequently with oral ampicillin than with amoxicillin, bacampicillin, or cyclacillin. Clavulanic acid increases the frequency of amoxicillin-associated diarrhea.

Antipseudomonal Penicillins

Carboxypenicillins. The introduction of carbenicillin represented a significant advance in antibiotic therapy, because this was the 1st penicillin to have activity against *P. aeruginosa*, *Proteus* species in addition to *P. mirabilis*, and some other gram-negative bacilli.[10] An oral preparation, carbenicillin indanyl sodium, was subsequently introduced. Ticarcillin proved to be a more active drug, however, and eventually supplanted carbenicillin.

Carbenicillin differs from penicillin G only by the addition of a carboxyl group on its side chain, whereas ticarcillin has a different side-chain moiety (Fig. 3). In general, carbenicillin and ticarcillin have identical spectra of activity, except that ticarcillin has a greater degree of activity and can therefore be administered in lower doses that produce less toxicity.

The carboxypenicillins' major advantage is their activity against *P. aeruginosa* and indole-positive *Proteus* and *Morganella* species. Although these drugs have been widely used for 20 years, more than 90% of *P. aeruginosa* isolates remain susceptible. When resistance occurs, it may be due to altered outer-membrane permeability, β-lactamase production, or modified PBPs. Altered membrane permeability appears to be the most important mechanism of resistance at present. Ticarcillin is generally 2 to 4 times more active than carbenicillin, and cross-resistance is total. The carboxypenicillins all have similar spectra of activity against ampicillin-susceptible gram-negative organisms (*E. coli*, *H. influenzae*, meningococcus, and others). In addition, some strains of *Enterobacter* species and *S. marcescens* are susceptible, but the proportion of susceptible strains has diminished in recent years. *Klebsiella*, *Aeromonas*, *Yersinia*, and *Pseudomonas* species other than *aeruginosa*, as well as *Xanthomonas maltophilia*, are resistant. *Acinetobacter* species may be sensitive, but these organisms' antibiotic susceptibility varies substantially from 1 institution to another. Against anaerobes and gram-positive organisms, carboxypenicillins generally have the same spectrum of activity as penicillin G. Their degree of activity against these organisms, however, is substantially lower than that of penicillin G. β-lactamase-producing strains of *Bacteroides* and *Staphylococcus* species, as well as methicillin-resistant staphylococci, are resistant to carboxypenicillins.

High doses of these drugs are required for the treatment of systemic *Pseudomonas* infections (carbenicillin, 5 g every 4 hours; ticarcillin, 3 to 4 g every 4 hours). Carbenicillin and ticarcillin have comparable serum half-lives (Table IV). Both drugs are excreted almost entirely in the urine by means of glomerular filtration and tubular secretion. Concomitant probenecid therapy has less of an effect with these agents, because renal tubular maximum is exceeded at these high concentrations and glomerular filtration plays a more important role. The distribution of these 2 drugs in body fluids is similar to that of penicillin G. In bronchial secretions and inflamed meninges, drug concentrations are low.

Carbenicillin and ticarcillin are useful against infections caused by *P. aeruginosa* and *Proteus* species. Many physicians believe that these antibiotics should be combined with an aminoglycoside for treating serious *Pseudomonas* infections.[11] Carboxypenicillins can also be used to treat infections caused by other gram-negative bacilli. Many of these infections require lower doses than are needed for *Pseudomonas* infections. Carbenicillin and ticarcillin have been used extensively and successfully in combination with an aminoglycoside for the empiric therapy of nosocomial pneumonias, abdominal and pelvic infections, and fever in neutropenic patients.

Carbenicillin indanyl sodium is available for the oral treatment of urinary tract infections. In vivo, the drug is rapidly hydrolyzed to carbenicillin. Although 30% to 40% of an oral dose is absorbed, serum concentrations are inadequate; therefore, the drug's use is limited to the treatment of urinary tract infections caused by susceptible strains of *P. aeruginosa* and *Proteus* species. More appropriate drugs are available for treating urinary tract infections caused by other organisms. Carbenicillin may play a limited role in the treatment of chronic prostatitis caused by susceptible organisms.

Ureidopenicillins. Mezlocillin, piperacillin, and azlocillin are ureidopenicillins that provide either a broader spectrum of activity or a greater antipseudomonal activity than ticarcillin, because they have more complex side-chain moieties that enhance membrane permeability and intensify binding to PBPs (Fig. 3). Their activity against gram-positive organisms is somewhat less than that of penicillin G or ampicillin but is comparable to, or better than, that

of ticarcillin. Against enterococci, these 3 antibiotics are several times as effective as ticarcillin. They are also active against gram-negative bacilli susceptible to ticarcillin. Whereas piperacillin and azlocillin are the most effective penicillins against *P. aeruginosa*, the activity of mezlocillin resembles that of ticarcillin. Unlike ticarcillin, the ureidopenicillins have substantially less bactericidal activity than inhibitory activity. Piperacillin and mezlocillin are useful against *Klebsiella*, *Enterobacter*, *Citrobacter*, and some *Serratia* species. Azlocillin is less active than mezlocillin and piperacillin against these gram-negative bacilli. The ureidopenicillins are also active against *H. influenzae*, gram-negative cocci, and *Bacteroides* species. Nevertheless, these antibiotics are susceptible to the β-lactamases produced by an increasing number of these organisms.

In general, the ureidopenicillins' pharmacokinetic properties resemble those of carbenicillin and ticarcillin, despite some important differences (Table IV). The ureidopenicillins' serum half-lives are somewhat shorter, and these drugs are excreted primarily in the urine, although significant amounts are excreted in the bile. Because these antibiotics' serum half-lives are dose-dependent (that is, longer at higher dosages), larger-than-recommended doses should be administered with caution. Dose-dependent prolongation of the serum half-life may be more pronounced in patients with renal impairment.

The indications for ureidopenicillin use are similar to those for carboxypenicillin treatment. Against most infections, the ureidopenicillins are combined with an aminoglycoside. Although they have greater in vitro activity than ticarcillin, there is little to indicate that they are superior to ticarcillin against susceptible organisms, especially when combination therapy is used. Against mixed-organism infections in which enterococci may play a role, the ureidopenicillins may be more desirable than the carboxypenicillins.

Coagulation disorders—as manifested by a prolonged bleeding time, a prolonged prothrombin time, and abnormal platelet aggregation, with or without apparent bleeding—can result from the use of antipseudomonal penicillins, especially carbenicillin and ticarcillin. Although this may contraindicate the use of these drugs in surgical patients, it should not prevent their being administered to thrombocytopenic patients. Use of these penicillins may be accompanied by an unpleasant taste and smell that can lead to nausea and vomiting; this side effect occurs most often with carbenicillin. Transient elevations in liver-function test results are seen occasionally, but these elevations rarely indicate hepatic disease.

Hypokalemia (sometimes associated with alkalosis) and fluid overload are additional complications. Because all the antipseudomonal antibiotics are administered as sodium salts and in high doses, they produce a substantial sodium load. They are excreted by the kidneys, where potassium and hydrogen are exchanged for sodium. Hypokalemia and sodium loading are most problematic with carbenicillin, which is a disodium salt administered in high doses. Ticarcillin is also a disodium salt, whereas the other agents are monosodium salts.

Penicillins Combined with β-lactamase Inhibitors

The antistaphylococcal penicillins were the 1st penicillins to inhibit β-lactamases. Although researchers attempted to combine them with other penicillins for the treatment of gram-negative infections, this combination did not prove practical. Some of the newer β-lactam agents, such as aztreonam and imipenem, are β-lactamase inhibitors but also potent antibiotics. Two specific β-lactamase inhibitors, clavulanate and sulbactam, are now being used clinically. Clavulanate has been combined with amoxicillin (Augmentin, Beecham Laboratories; Bristol, Tennessee, USA) and ticarcillin (Timentin, Beecham); sulbactam has been combined with ampicillin (Unasyn, Pfizer Incorporated [Roerig Division]; New York, New York, USA).

Combining a β-lactamase inhibitor with a penicillin (or a cephalosporin) can potentially convert resistant organisms to sensitive ones if the mechanism of resistance is β-lactamase production. Of the many β-lactamases that have been identified, not all are inhibited by clavulanate or sulbactam; specifically, the chromosomally-mediated β-lactamases produced by some strains of *P. aeruginosa*, *Enterobacter* organisms, *Citrobacter* species, and *S. marcescens* are not susceptible. Fortunately, however, these combination drugs do inhibit the most frequently occurring plasmid-mediated β-lactamase, which has been transmitted to many pathogens. Both clavulanate and sulbactam are distributed into body tissues and reach sites of infection, and both have the same effect, as has been demonstrated in vitro.

Clavulanate alone has no clinically significant antibacterial activity. The addition of this drug to amoxicillin or ticarcillin extends the spectrum of activity against gram-positive and gram-negative cocci to include β-lactamase-producing strains of *S. aureus*, *S. epidermidis*, and *N. gonorrhoeae*.[12] Methicillin-resistant staphylococci are resistant, but these combinations extend the gram-negative bacillary spectrum to include most *Klebsiella* species, amoxicillin-resistant strains of *E. coli*, and *Proteus* species, as well as salmonellae and shigellae. Other susceptible organisms include β-lactamase-producing strains of *H. influenzae*, *Moraxella (Branhamella) catarrhalis*, and *Bacteroides* species. The activity of these drug combinations against *Enterobacter* species, *S. marcescens*, *Citrobacter* species, *Providencia* species, and

Morganella species is variable, because many of the β-lactamases present in these organisms are not inhibited by clavulanate; however, some of these strains are susceptible to ticarcillin. Ticarcillin plus clavulanate (Timentin) also combats *P. aeruginosa* infections, but most ticarcillin-resistant strains of *P. aeruginosa* are resistant to this drug combination.

Amoxicillin-clavulanate (Augmentin) is available for oral administration only, either as 250 mg of amoxicillin plus 125 mg of clavulanate, or 500 mg of amoxicillin plus 125 mg of clavulanate. When using this combination, a 500-mg dose of amoxicillin should not be administered via two 250-mg tablets, since this would cause the clavulanate dose to be doubled, thereby increasing toxicity without enhancing efficacy. Ticarcillin-clavulanate (Timentin) is available only as an intravenous preparation.

The addition of clavulanate does not affect the pharmacokinetics of amoxicillin or ticarcillin. The percentage of clavulanate absorbed from the gastrointestinal tract is variable, but averages 60%. The drug combination has a serum half-life of 1 hour. Absorption of both amoxicillin and clavulanate is minimally affected by food in the stomach; therefore, to reduce gastrointestinal side effects, the combination is best given before the patient eats. About half of an intravenous dose of clavulanate is excreted unchanged in the urine, mainly by means of glomerular filtration. The other half appears to be metabolized in the body.

Augmentin has the same indications for use as amoxicillin and should be substituted for this drug when resistance secondary to β-lactamase production is likely. Augmentin has been used successfully for treating urinary tract infections, upper and lower respiratory tract infections, and gonorrhea. It is useful for skin and soft-tissue infections, especially those involving a bite wound or a diabetic foot. Timentin has the same indications as ticarcillin and should replace this drug for the empiric therapy of serious infections in which ticarcillin-resistant organisms are likely to be present.

Sulbactam is a penicillanic acid sulfone that is less potent than clavulanate but has inherent activity against *N. gonorrhoeae*, *Acinetobacter* species, and some *Pseudomonas* organisms (other than *aeruginosa*).[13] This agent has been combined with ampicillin (Unasyn) for intravenous administration. Because Unasyn has the same mechanism of action as clavulanate, its spectrum of activity is similar to that of Augmentin, except in a few cases. Unasyn is less active against some β-lactamase-producing *E. coli* organisms but is more active against *S. marcescens*, *Morganella* organisms, and *Providencia* species.

Unasyn is available for parenteral administration in a 2:1 ratio of ampicillin to sulbactam. Sulbactam does not interfere with ampicillin's pharmacokinetics. After intravenous administration, the 2:1 ratio is maintained in peak serum concentrations; after intramuscular injection, however, the sulbactam concentration is somewhat higher, making the ratio closer to 1.5:1. Sulbactam has a serum half-life of 1 hour and is excreted primarily in the urine by means of both glomerular filtration and tubular secretion. A certain percentage of the drug is excreted in the bile, and some is probably inactivated in the liver.

Because of its broader spectrum of activity, Unasyn has a wider range of indications than ampicillin. It is useful against serious soft-tissue and urinary tract infections and is especially suitable for the therapy of mixed-organism infections such as those involving the abdomen or pelvis. Unasyn should not be administered alone if *P. aeruginosa* is a possible causative pathogen (as is increasingly the case in nosocomial respiratory infections, even in community hospitals).

Monobactams: Aztreonam

Monobactams are a new class of β-lactam antibiotics, whose name refers to the fact that they contain a "naked" β-lactam ring (Fig. 4). Naturally occurring monobactams have only weak antibacterial activity. Aztreonam, the only commercially available monobactam, is a completely synthetic product. Unlike most other β-lactam antibiotics, it binds preferentially to PBP3, thereby adversely affecting septum formation in proliferating bacteria. Although this drug is resistant to destruction by most β-lactamases, recently a β-lactamase has been identified that inactivates aztreonam.

Aztreonam's spectrum of activity resembles that of an aminoglycoside.[14] It is inactive against gram-positive organisms and anaerobic bacilli, because it binds poorly to their PBPs. It is active against most aerobic gram-negative organisms, including *P. aeruginosa*, *H. influenzae*, and *Neisseria* species, even β-lactamase-producing strains. It is also active against many gentamicin- and carbenicillin-resistant strains of *P. aeruginosa*. Resistant gram-negative bacilli in-

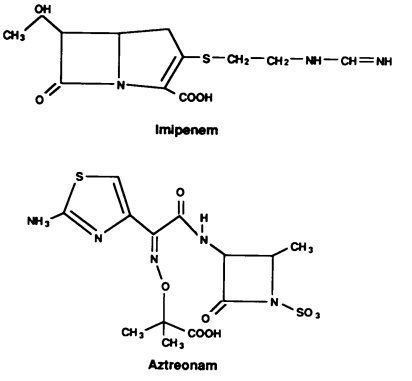

Fig. 4 *Chemical structures of imipenem and aztreonam.*

clude *Acinetobacter*, *Alcaligenes*, and *Pseudomonas* species other than *aeruginosa*.

Aztreonam is available only as a parenteral preparation. Intramuscular and intravenous administration result in similar serum concentrations. The drug's serum half-life is 1.7 hours and appears to be biphasic, with a distribution phase of 0.2 to 0.7 hours. Aztreonam diffuses well in body tissues; in the presence of inflamed meninges, about 17% of the serum concentration is achieved in the cerebrospinal fluid. About 70% of the drug is excreted in the urine by means of glomerular filtration and tubular secretion. About 10% to 15% is metabolized to inactivated compounds that are excreted in the urine and feces.

Aztreonam can be used to treat serious nosocomial infections caused by gram-negative bacilli. In potential mixed-organism infections involving gram-positive organisms or anaerobic bacilli (as seen in the lower respiratory tract, abdomen, or pelvis), an antimicrobial agent with activity against these organisms must be included. Aztreonam combined with vancomycin has been used successfully for the initial therapy of fever in neutropenic patients.

One of the major advantages of aztreonam is its lack of cross-allergenicity with other β-lactam antibiotics. Animal and human studies indicate a lack of cross-reactivity to aztreonam with antibodies produced against penicillin G and vice versa. Therefore, aztreonam is a reasonable alternative for patients with penicillin or cephalosporin allergies. Nevertheless, allergic reactions can be caused by aztreonam itself.

Carbapenems: Imipenem

Olivanic acids and thienamycin were the 1st carbapenem antibiotics to be discovered. Because the latter agent was chemically unstable in concentrated solution, researchers developed the N-formimidoyl derivative, imipenem (Fig. 4). This antibiotic is metabolized by a naturally occurring dihydropeptidase in the renal brush border. The metabolite is inactive and potentially nephrotoxic. Consequently, imipenem is administered with cilastatin, which inhibits the dihydropeptidase. In the commercial preparation, the 2 components are present in a 1:1 ratio.

Imipenem has the broadest spectrum of activity of any antibiotic currently available.[15] It is also the only β-lactam to have a significant postantibiotic effect against gram-negative bacilli. ("Postantibiotic effect" denotes an antibiotic's ability to inhibit the proliferation of an organism after the drug is no longer present in the environment.) All β-lactam antibiotics have a postantibiotic effect against gram-positive cocci but not against gram-negative bacilli. Imipenem is a potent inducer of β-lactamase production in gram-negative bacteria; these β-lactamases can destroy other antibiotics but not imipenem itself. The clinical significance of this phenomenon is unclear, since these bacteria are destroyed by imipenem. Because of the drug's broad spectrum of activity, resistant organisms are easier to enumerate than susceptible ones. Resistant species include methicillin-resistant staphylococci, *S. faecium* (which accounts for about 10% of enterococcal infections), *Clostridium difficile*, corynebacteria, *X. maltophilia*, the *Chlamydia*, *Mycoplasma*, and *Mycobacterium* organisms, and some strains of *Pseudomonas cepacia*. Cross-resistance between imipenem and penicillins or cephalosporins has not been reported.

Imipenem is not absorbed from the gastrointestinal tract and is available only as an intravenous preparation. Because of a potential increased risk of side effects, the maximum daily dose should not exceed 50 mg/kg or 4 g, whichever is less. The drug's serum half-life is approximately 1 hour, and 70% of an administered dose is excreted in the urine, predominantly by means of glomerular filtration. Some of the drug apparently is metabolized in the kidney because the concentration of cilastatin does not completely inhibit the dihydropeptidase. Higher concentrations of cilastatin can inhibit this enzyme more completely, but they can also lead to the accumulation of cilastatin in patients with impaired renal function. Imipenem is widely distributed in body tissues.

Imipenem can be used for the therapy of serious nosocomial infections. It appears to be less active against *P. aeruginosa* infections than against those caused by other pathogens, especially if the patient has previously received another β-lactam antibiotic.[16] In 15% of the isolates of *P. aeruginosa*, resistance has emerged during therapy, although some patients have recovered from their infections. Consequently, combination therapy with an aminoglycoside may be advisable against serious *Pseudomonas* infections. Imipenem is a potentially useful agent for mixed-organism infections of the abdomen or pelvis. It has been used alone for the initial therapy of fever in neutropenic patients. Little experience has been gained in using this drug to treat gram-negative meningitis. There is little justification for using it in the treatment of community-acquired infections.

Imipenem/cilastatin may cause nausea and vomiting severe enough to necessitate discontinuation of the drug, although these side effects can usually be ameliorated by slowing the rate of infusion. Seizures or myoclonus episodes occur in about 2% of the patients who receive this antibiotic. Most of these patients have preexistent neurologic disorders or renal failure, or receive relatively high doses. Nevertheless, occasional patients have no identifiable predisposing factor. Patients with seizures usually respond promptly to anticonvulsants, and the seizures cease after the drug is discontinued.

Overview of Indications

Because so many antibiotics are available, physicians tend to become confused about the current roles of penicillins, monobactams, and carbapenems.

Penicillin G remains the drug of choice against infections caused by susceptible gram-positive organisms, since this drug, along with ampicillin and amoxicillin, is the most active antibiotic. Penicillin G is also preferred for treating pneumococcal pneumonia; in many areas, however, community-acquired pneumonia is frequently caused by other organisms, so penicillin G therapy is inadequate if the diagnosis is unknown. Penicillin G is still the drug of choice against syphilis, but no longer against gonorrhea. Moreover, gonorrhea is frequently associated with other venereal diseases (e.g., chlamydial and mycoplasmal infections) that are not susceptible to penicillin. Penicillin G is the best antibiotic for treating anthrax, actinomycosis, gingivitis, leptospirosis, and rat-bite fever, as well as infections caused by *Clostridium* species, *P. multocida*, and the meningococcus. The drug is not effective for the prophylaxis of meningococcal infections. It can be used to treat Lyme disease, Whipple's disease, and listeriosis. In combination with an aminoglycoside, it is effective against enterococcal endocarditis.

The antistaphylococcal penicillins remain the drugs of choice for treating susceptible staphylococcal infections. These agents are preferable to penicillin G or the aminopenicillins for the empiric therapy of infections that may involve gram-positive cocci, including staphylococci. Because they are less active than penicillin G, they should not be used as penicillin-G substitutes for the treatment of penicillin-susceptible organisms. Vancomycin should be administered empirically at centers where methicillin-resistant staphylococci are prevalent. For oral therapy, cloxacillin or dicloxacillin is the drug of choice. For parenteral administration, some physicians prefer nafcillin to oxacillin or methicillin, because nafcillin is less toxic.

Ampicillin is the only aminopenicillin available for parenteral administration. Because of their superior degree of absorption, amoxicillin and bacampicillin are the drugs of choice for oral administration. These antibiotics have been used extensively for the treatment of upper and lower respiratory and urinary tract infections. In many areas, however, the emergence of β-lactamase-producing strains of *H. influenzae*, *M. (Branhamella) catarrhalis*, and *E. coli* has limited these drugs' usefulness. Moreover, more of the pneumonias are being caused by organisms such as *Legionella*, *Chlamydia*, and *Mycoplasma* species that are not susceptible to β-lactam antibiotics. Aminopenicillins are the drugs of choice against enterococcal and listerial infections. Amoxicillin is generally recommended for chronic typhoid carriers. Because of the high frequency of resistance, aminopenicillins should be used for treating serious infections only if the responsible organism is known to be susceptible.

The antipseudomonal penicillins are usually administered in combination with an aminoglycoside for treatment of serious nosocomial or community-acquired infections, especially of the lungs, abdomen, or pelvis. These drug combinations have also been widely used for the empiric therapy of fever in neutropenic patients. They are especially useful for the empiric treatment of infections that may involve multiple organisms, as well as those caused by *P. aeruginosa*, indole-positive *Proteus* species other than *mirabilis*, anaerobes, or enterococci. Other agents are preferable for treating gram-negative meningitis and infections known to be caused by *Enterobacter* species, *Citrobacter* organisms, or *S. marcescens*. All of the penicillins are ineffective against most staphylococci, and ticarcillin and azlocillin are ineffective against *Klebsiella* species. Ticarcillin plus clavulanate offers the broadest spectrum of activity (including efficacy against methicillin-sensitive staphylococci, *B. fragilis*, and *Klebsiella* species); ticarcillin provides the narrowest. Piperacillin and mezlocillin are relatively active against enterococci, and this advantage may be important in some abdominal infections. Azlocillin and piperacillin have the greatest activity against *P. aeruginosa* (although ticarcillin has greater bactericidal activity), but there is little clinical evidence to indicate that any one of these antibiotics is superior, unless resistance is prevalent.

When ampicillin, amoxicillin, or ticarcillin is combined with a β-lactamase inhibitor, its spectrum of activity is expanded to include staphylococci, *B. fragilis*, *Klebsiella* species, and some other aerobic gram-negative bacilli. β-lactamase inhibitors, however, do not increase the penicillins' activity against penicillin-susceptible organisms. A combination of a β-lactamase inhibitor with the penicillin should replace the penicillin alone when β-lactamase-producing organisms such as *H. influenzae* are prevalent. These agents are especially useful for mixed-organism infections such as those involving a bite wound, a diabetic foot, or the respiratory tract, abdomen, or pelvis. Unasyn and Augmentin cannot be used when *P. aeruginosa* is a suspected or proven pathogen.

For empiric therapy, aztreonam must be combined with an agent that has anti-gram-positive and anti-anaerobic activity. Aztreonam has been suggested as an aminoglycoside replacement, and this application may be appropriate if the aminoglycoside is selected as the only agent to provide activity against aerobic gram-negative bacilli. There is minimal evidence to suggest that aztreonam can be substituted for an aminoglycoside when the latter drug is being included for additive or synergistic interaction with another β-lactam. Aztreonam's major indications in-

volve its usefulness as a substitute for other β-lactams in allergic patients or as a substitute for aminoglycosides in elderly patients, in those with impaired renal function, and in those receiving other nephrotoxic agents.

Imipenem should be reserved for the treatment of serious nosocomial infections. Its major indication is the need for broad-spectrum coverage when multiple organisms are likely to be involved. When the infectious organism is known, however, narrower-spectrum antibiotics are generally preferable. Imipenem has been used successfully as a single agent for the empiric therapy of fever in neutropenic patients; nevertheless, its use should be avoided in patients with renal impairment or preexistent neurologic disorders because of the risk of seizures.

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