

MEDICAL INTELLIGENCE



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BETA-LACTAM ANTIBIOTICS

(First of Two Parts)

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It has been said that curing all cancers would add 2 years to the life expectancy of Americans but that the introduction of antibiotics added 10 years.¹ The agent most responsible for this remarkable effect is penicillin, the prototypic beta-lactam antibiotic. The beta-lactam antibiotics include penicillins, cephalosporins, monobactams, and carbapenems. All have a beta-lactam ring, which is essential for antibacterial activity. In general, these agents have very favorable ratios of therapeutic to toxic effects, and the newer agents have enhanced antibacterial spectrums or favorable pharmacokinetic characteristics.

MECHANISM OF ACTION

Beta-lactam antibiotics are bactericidal because they inhibit bacterial cell-wall synthesis. Their basic method of action is the interruption of the transpeptidation process that links the individual peptidoglycan components of the bacterial cell wall to each other. Although the specific mechanisms involved remain incompletely understood, several basic elements in the process have been defined.²⁻⁶ Beta-lactam antibiotics bind to and inactivate specific targets on the inner surface of the bacterial cell membrane, the penicillin-binding proteins (PBPs).⁵⁻⁹ The PBPs are enzymes (transpeptidases, carboxypeptidases, and endopeptidases) that are involved in the terminal stages of assembling the bacterial cell wall and in reshaping the cell wall during growth and division. Beta-lactam compounds have different affinities for the various PBPs and, depending on the specific PBP bound, have different effects on bacteria.¹⁰⁻¹³ The inactivation of some PBPs (PBP 1A, 1BS, 2, and 3) causes bacterial cell death. In contrast, other PBPs (PBP 4, 5, and 6) are not essential for bacterial viability, and their in-

activation by beta-lactam molecules is not lethal to the bacteria.¹⁴⁻¹⁸ Other factors are involved in the process of bacterial lysis. It is currently theorized that beta-lactams binding to PBPs inactivate endogenous inhibitors of bacterial autolysins.¹⁹⁻²² The autolysins can then disrupt covalent bonds in the bacterial cell wall and cause bacterial lysis. The growth of certain organisms that lack autolysins can be inhibited by beta-lactam antibiotics, but such organisms are not killed (the phenomenon of bacterial tolerance).²³

MECHANISMS OF BACTERIAL RESISTANCE

Bacterial resistance to beta-lactam antibiotics may occur at any of the steps involved in the activity of the agents. Beta-lactam molecules must first be able to penetrate the bacterial cell wall. Although the peptidoglycan components of the cell wall of gram-positive bacteria can be penetrated easily, the outer cell wall of gram-negative organisms, which consists of lipids, proteins, and polysaccharides, may prevent beta-lactam antibiotics from reaching their PBP targets.²⁴ Channels through the cell walls of gram-negative bacteria are formed by proteins called porins, which allow diffusion of materials into the interior of the bacterium.²⁵ These porin channels may block the passage of beta-lactam compounds, depending on their size, charge, and hydrophilic properties.²⁶⁻²⁸ There are pathways across the bacterial cell wall that are not associated with porins, but they remain ill defined.^{29,30} The barrier properties of the cell wall may represent inherent characteristics of a given bacterium or may result from changes in cell-wall structure due to exposure to antibiotics.³¹⁻³⁴

Alterations in the binding characteristics of PBPs for beta-lactam compounds may result in the development of resistance, and such changes have been demonstrated in *Escherichia coli*,³⁵ *Streptococcus faecium*,³⁶ *Haemophilus influenzae*,³⁷ *Streptococcus pneumoniae*,³⁸ and methicillin-resistant *Staphylococcus aureus*.³⁹⁻⁴¹

The most important mechanism of bacterial resistance to the beta-lactam antibiotics is bacterial production of beta-lactamases, enzymes that hydrolyze the cyclic amide bond of the beta-lactam ring and render it inactive.⁴²⁻⁴⁶ Beta-lactamases are made by many gram-positive and gram-negative organisms and are encoded either chromosomally or extrachromosomally by means of plasmids or transposons.⁴⁷⁻⁵⁵ The ease of transfer of the plasmids and transposons plays a leading part in the spread of antibiotic resistance from one bacterial strain to another.

STRUCTURE-FUNCTION RELATIONS

Several excellent reviews have outlined the principal structure-function relations of the beta-lactam antibiotics.⁵⁶⁻⁵⁸ The basic beta-lactam structure consists of a four-membered beta-lactam ring fused to a second ring. Biochemical modifications have been made in attempts to increase penetration through bac-

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terial cell walls, to decrease susceptibility to bacterial beta-lactamases, or to increase binding to PBPs.

In the penicillins, the beta-lactam ring is fused to a five-membered thiazolidine ring (Fig. 1). Modifications of the penicillin molecule take place on the acyl side chain attached to the C₆ carbon (R¹). Most of the newer penicillins are modifications of ampicillin⁵⁷ (Fig. 1a). Substitution of a carboxy group for the amino group of ampicillin on the acyl side chain produced carbenicillin and ticarcillin (Fig. 1b and 1c). The substitution of this acidic side group in these compounds decreased binding to PBPs of *Streptococcus faecalis*, thereby decreasing activity against this organism. However, there was more activity against gram-negative rods, including *Pseudomonas aeruginosa*, partly because of increased penetration of the drug through the bacterial cell wall.^{2,59} Substitution of ureido groups (—NH—C(=O)—N—R²) for the carboxy group produced the ureido penicillins — piperacillin, azlocillin, and mezlocillin (Fig. 1d) — which main-

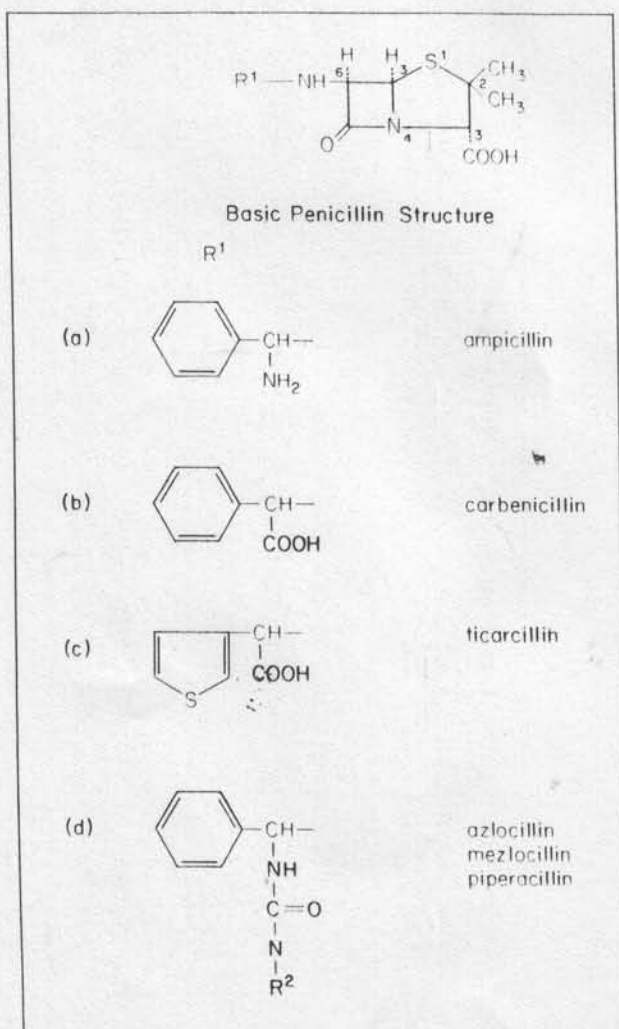


Figure 1. Chemical Structure of the Penicillins. Substitutions at the R¹ site create the extended-spectrum penicillins (a to d).

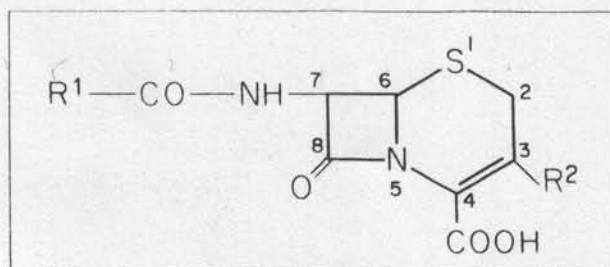


Figure 2. Chemical Structure of the Cephalosporins. Position 1, R¹, R², and C₇ are the sites of potential biochemical manipulation.

tained ampicillin's activity against *Strep. faecalis* and *Strep. faecium* and increased its activity against gram-negative bacilli and anaerobes by means of greater penetration through bacterial cell walls and greater affinity for PBPs.^{60,61}

In cephalosporins, the beta-lactam ring is attached to a six-membered dihydrothiazine ring (Fig. 2). In contrast to the penicillin nucleus, the cephalosporin nucleus is inherently more resistant to beta-lactamases and is more active against beta-lactamase-producing (penicillin-resistant) bacteria, including *Staph. aureus* and *E. coli*. The cephalosporin molecule also provides more sites for potential manipulation. Therapeutically important modifications have been made at the sulfur atom at position 1, the acyl group attached to C₇ (R¹), C₇ itself, and the moiety attached to C₃ (R²).⁶²⁻⁶⁶

Two classes of compounds have structures markedly different from those previously described (Fig. 3). Carbapenems have a carbon instead of a sulfur on the five-membered ring attached to the beta-lactam ring. The small size and compact structure of these agents allow them to pass easily through gram-negative bacterial cell walls. Imipenem, the only carbapenem currently available, has a hydroxyethyl side chain rather than the classic acylamino moiety of penicillin and the cephalosporins. Marked resistance to hydrolysis by bacterial beta-lactamases is provided by the trans configuration of this group, which contrasts with the cis configuration of other beta-lactams.⁶⁷

The monobactams are a novel group of compounds in which the bicyclic structure characteristic of the other beta-lactams is absent. The core configuration is that of a beta-lactam ring. Since the 1-sulfonic acid group lowers the energy requirements needed for interaction of the beta-lactam molecule with PBPs, it is said to "activate" the molecule.⁶⁸ Side-chain substitutions at R¹ and R² confer antibacterial activity and resistance to beta-lactamase, as they do in the classic, two-ringed beta-lactam agents.⁶⁹ Aztreonam is the only member of this group currently available for therapy.

Beta-lactamase inhibitors such as clavulanic acid and sulbactam resemble penicillin structurally and enhance the in vitro activity of certain beta-lactam

antibiotics by protecting them from hydrolysis by beta-lactamases.⁷⁰⁻⁷⁵ They are termed "suicide inhibitors" because they bind to and inactivate bacterial beta-lactamases but are destroyed in the process.

EXTENDED-SPECTRUM PENICILLINS

Antibacterial Activity

The carboxy penicillins, carbenicillin (Geopen, Pyopen) and ticarcillin (Ticar), and the ureido penicillins, piperacillin (Pipracil), mezlocillin (Mezlin), and azlocillin (Azlin), are considered extended-spectrum penicillins because they inhibit a wide variety of aerobic gram-negative bacilli, including *Ps. aeruginosa* (Tables 1 and 2).⁷⁶⁻⁸⁷

The extended-spectrum penicillins are susceptible to staphylococcal beta-lactamases and are not reliable for treating staphylococcal disease. They are less active than penicillin and ampicillin against most gram-positive organisms,^{82,84,88} except that the ureido penicillins inhibit enterococci to a degree comparable to that achieved with ampicillin.⁸⁹⁻⁹¹

Table 1. In Vitro Activity of Extended-Spectrum Penicillins against Gram-Positive Cocci.*

GRAM-POSITIVE COCCI [†]	CARBENICILLIN	TICARCILLIN	AZLOCILLIN	MEZLOCILLIN	PIPERACILLIN
MIC ₉₀ in µg/ml (% strains susceptible)					
<i>Streptococcus</i> species					
Pyogenes	<0.2 (100)	<0.2 (100)	<0.2 (100)	<0.2 (100)	<0.2 (100)
Viridans group	16 (80)	8 (100)	<0.2 (100)	<2.0 (100)	<0.2 (100)
Pneumoniae	2 (100)	1 (100)	<0.2 (100)	<0.2 (100)	0.2 (100)
Faecalis	128 (0)	128 (50)	4 (90)	4 (90)	4 (90)

*Values were compiled from references 76 to 87. MIC₉₀ denotes the lowest concentration of an antibiotic inhibiting growth in 90 percent of the strains tested. Susceptibility break points for the extended-spectrum penicillins are ≤ 16 µg per milliliter for carbenicillin and ≤ 64 µg per milliliter for all others, as determined from in vitro activity and achievable serum drug concentrations.⁸⁶

[†]Ninety percent of strains of *Staph. aureus* are resistant. Minimal inhibitory concentrations of 0.5 to 1.0 µg per milliliter are noted for susceptible strains of this organism.

There are small differences in the pattern of activity of these agents against gram-negative organisms. Ticarcillin is two to four times more active than carbenicillin against *Ps. aeruginosa*.^{78,82} Piperacillin is more potent than ticarcillin against *Ps. aeruginosa* and klebsiella, but has activity similar to that of ticarcillin against most other gram-negative pathogens. Azlocillin is as active as piperacillin against *Ps. aeruginosa* but is less active against most other gram-negative organisms.^{86,87,89-91} Mezlocillin is similar to ticarcillin in regard to antimicrobial spectrum, but it has more activity against klebsiella. The extended-spectrum penicillins are often more susceptible to beta-lactamases produced by gram-negative bacteria than are the third-generation cephalosporins. All the extended-spectrum penicillins are highly active against anaerobes.^{79,92,93}

Pharmacologic Features

The pharmacologic features of the extended-spectrum penicillins are summarized in Table 3. The dosage schedules, peak serum concentrations, and serum half-lives of the agents are very similar. For the ureido penicillins, biliary excretion accounts for 20 to 30 percent of elimination, allowing for less adjustment of doses in patients with renal failure.^{100,101,106}

Toxicity

The extended-spectrum penicillins are relatively nontoxic, although hypersensitivity reactions, neutropenia, seizures, and elevations in liver-enzyme levels have been reported.^{78,79,98,107-109} Carbenicillin and ticarcillin induce dose-dependent abnormalities in platelet aggregation involving both primary and secondary adenosine diphosphate-induced responses.¹¹⁰⁻¹¹² This phenomenon occurs most often at dosages higher than 300 mg per kilogram of body weight per day. Prolongation of bleeding time and abnormalities in platelet aggregation have been attributed to the ureido penicillins, but the problems have been quantitatively less severe than those noted with the carboxy penicillins.^{113,114} The extended-spectrum penicillins may inactivate aminoglycosides in a manner that depends on the time of exposure and the concentration of penicillin.^{115,116} This may

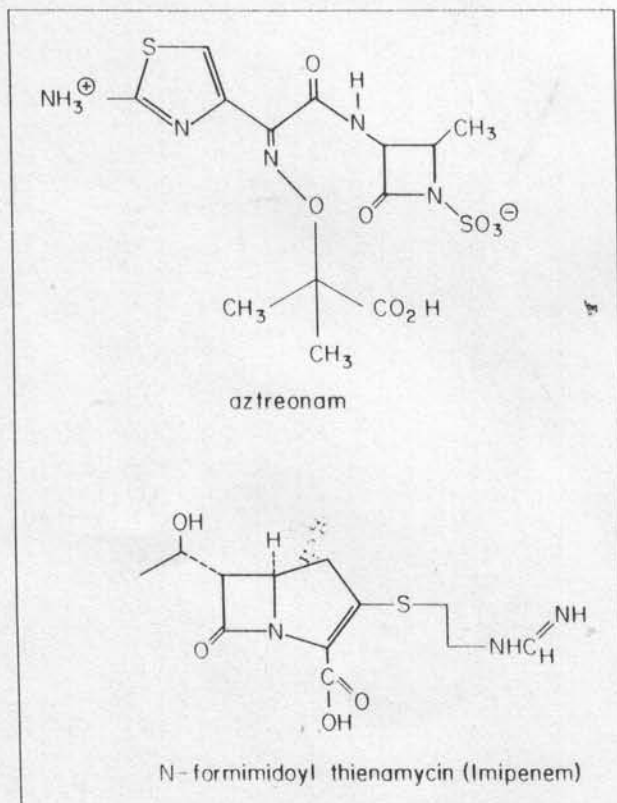


Figure 3. Chemical Structure of Aztreonam and Imipenem. These agents are representative of the monobactam and carbapenem classes of drugs, respectively, whose chemical structures differ markedly from those of the penicillins and cephalosporins.

Table 2. In Vitro Activity of Extended-Spectrum Penicillins against Gram-Negative Organisms and Anaerobes.*

	CARBENICILLIN	TICARCILLIN	AZLOCILLIN	MEZLOCILLIN	PIPERACILLIN
MIC ₅₀ in µg/ml (% strains susceptible)					
Gram-negative organisms					
<i>E. coli</i>	4 (80)	4 (82)	8 (82)	2 (85)	2 (85)
<i>Klebsiella</i> species	>64 (8)	>64 (12)	>64 (50)	8 (80)	8 (88)
<i>Serratia</i> species	16 (76)	16 (80)	64 (65)	8 (75)	4 (85)
<i>Enterobacter</i> species	16 (70)	16 (60)	16 (60)	8 (90)	8 (90)
<i>Proteus</i>					
Indole positive	8 (80)	4 (80)	64 (70)	2 (85)	1 (90)
Indole negative	2 (100)	2 (100)	4 (100)	4 (100)	1 (100)
<i>Ps. aeruginosa</i>	32 (80)	16 (85)	4 (95)	16 (80)	4 (95)
<i>Pseudomonas</i> species	256 (40)	>64 (40)	16 (85)	16 (90)	4 (97)
Anaerobes					
<i>Bacteroides</i>					
<i>fragilis</i> (group) [†]	16 (85)	32 (80)	16 (90)	16 (90)	16 (95)
<i>fragilis</i>	64 (85)	64 (85)	32 (95)	16 (100)	8 (92)
<i>Clostridium perfringens</i>	0.25 (100)	0.5 (100)	<0.13 (100)	<0.13 (100)	0.25 (100)
<i>Clostridium</i> species	2 (81)	4 (86)	0.5 (95)	1 (95)	1 (95)
<i>Peptococcus/pepto-</i> <i>streptococcus</i>	1 (92)	2 (90)	<0.25 (75)	<0.25 (95)	<0.25 (75)
<i>Fusobacterium</i>	<0.13 (100)	<0.13 (95)	<0.13 (95)	<0.13 (95)	0.12 (95)

*Values were compiled from references 76 to 87. In many cases, at least 10 to 15 percent of strains will show resistance to the agents listed; thus, data on minimal inhibitory concentrations required to inhibit growth in 90 percent of strains (MIC₉₀) are not helpful.

[†]The *Bacteroides fragilis* group includes *B. distasonis*, *B. fragilis*, *B. ovatus*, *B. thetaiotaomicron*, and *B. vulgatus*.

occur in vitro when drugs are mixed together in the same bottle, or in vivo in patients with renal failure in whom high concentrations of penicillin may accumulate.

Clinical Use

The extended-spectrum penicillins are most useful for infections caused by *Ps. aeruginosa*, other aerobic gram-negative rods, and anaerobes. When used as single agents, these drugs have produced overall response rates of 60 to 80 percent in patients with bacteremias, intraabdominal infections, infections of the female genitourinary tract, bone and soft-tissue infections, and pneumonias.^{78,79,96,107,109,117-128} Comparative trials have shown no differences in efficacy among the extended-spectrum penicillins.^{122,124,125,129} Therapy with a single agent has been associated with colonization by resistant organisms in 6 to 39 percent of cases,^{96,109,119,130} superinfection in 7 to 12 percent of cases,^{96,131,132} and failure to eliminate organisms, even in patients who improve clinically, in 25 to 50 percent of cases.^{107,117,131,133} Extended-spectrum penicillins

have yielded poor responses when used as single agents in compromised hosts.^{134,135} Therefore, for serious infections, these agents are usually used in combination with an aminoglycoside. This combination provides in vitro synergy against 30 to 60 percent of strains of *Ps. aeruginosa* and 20 to 50 percent of Enterobacteriaceae and has been proved effective in a variety of clinical situations.^{61,136-138} In compromised hosts, especially those with neutropenia, response rates of 56 to 97 percent have been reported.¹³⁹⁻¹⁴⁵ In patients with cystic fibrosis and pulmonary infection, clinical responses are more favorable and rates of resistance are lower with combination therapy than with therapy with one agent.¹⁴⁶⁻¹⁵³

Other pseudomonas infections that can be successfully treated with the combination of an aminoglycoside

and an extended-spectrum penicillin include bacteremia, endocarditis, osteomyelitis, malignant otitis externa, keratitis, and central nervous system infections.^{136,154,155}

Because of their activity against anaerobes, the extended-spectrum penicillins have been used in intraabdominal and pelvic infections, as well as in mixed aerobic-anaerobic infections of the lung, and have produced response rates of 70 to 90 percent.¹⁵⁶⁻¹⁶² Therapy with a single agent has been associated with recurrences in up to 20 percent of patients; combination therapy with an aminoglycoside is therefore suggested.¹⁶⁰ When extended-spectrum penicillins are used in patients with pelvic inflammatory disease, specific antichlamydial therapy with a tetracycline should be added.¹⁶³

The ureido penicillins are as effective as ampicillin against the enterococci in vitro and have shown synergy with aminoglycosides.⁶¹ However, because of the wider experience with the combination of penicillin or ampicillin and an aminoglycoside (gentamicin or streptomycin), this regimen remains the therapy of

Table 3. Pharmacologic Features of the Extended-Spectrum Penicillins.*

	CARBENICILLIN 400-500 mg/kg/day (5 g EVERY 4 HR)	TICARCILLIN 200-300 mg/kg/day (3-4 g EVERY 4-6 HR)	AZLOCILLIN 200-300 mg/kg/day (3-4 g EVERY 4-6 HR)	MEZLOCILLIN 200-300 mg/kg/day (3-4 g EVERY 4-6 HR)	PIPERACILLIN 200-300 mg/kg/day (3-4 g EVERY 4-6 HR)
Peak serum concentrations (µg/ml) [†] (dose)	223 (3 g)	210 (3.5 g)	214 (3 g)	263 (3 g)	240 (4 g)
Half-life (hr)	1.1	1.2	0.8	0.8	0.9
Renal excretion (%)	95	80	50-70	55	70
Hepatic excretion (%)	0	0	20-30	20-30	20-30
Removed by hemodialysis	Yes	Yes	Yes	Yes	Yes
Sodium (mmol/g)	4.7	5.1	2.17	1.85	1.85

*Values were compiled from references 90 and 94 to 105. Dosages given are the maximal adult dosages.

[†]After a 30-minute intravenous infusion.

choice for serious enterococcal infections such as endocarditis.¹⁶¹ Ureido penicillins are effective prophylactic agents for use in pelvic, intraabdominal, and biliary surgery. However, they are no better than regimens using first-generation cephalosporins, which are less expensive.¹⁶⁵⁻¹⁷¹

PENICILLINS AND BETA-LACTAMASE INHIBITORS

Clavulanic acid in a fixed combination with ticarcillin (Timentin — 3 g of ticarcillin and 100 mg of clavulanic acid) increases the activity of ticarcillin against 60 to 80 percent of ticarcillin-resistant strains of Enterobacteriaceae, beta-lactamase-producing strains of *H. influenzae* and *Staph. aureus*, and bacteroides species. No increased activity is provided against *Ps. aeruginosa*.¹⁷²⁻¹⁷⁵ The combination, given intravenously every four to six hours, is more useful than ticarcillin for treating infections in which *Staph. aureus*, beta-lactamase-producing aerobic gram-negative bacilli, or bacteroides species are implicated.¹⁷⁶⁻¹⁷⁹

The combination of clavulanic acid and amoxicillin (Augmentin — 250 or 500 mg of amoxicillin plus 125 mg of clavulanic acid) provides an oral preparation with enhanced activity against beta-lactamase-producing strains of staphylococcus, *Branhamella catarrhalis*, *H. influenzae*, *Neisseria gonorrhoeae*, and bacteroides.¹⁸⁰⁻¹⁸³ Most beta-lactamase-producing strains of *E. coli*, *Proteus mirabilis*, and klebsiella species will be susceptible only to concentrations of the combination present in urine.¹⁸¹ Oral administration of amoxicillin and clavulanic acid (every eight hours) is effective for treatment of human-bite infections and animal-bite infections in which *Pasturella multocida*, streptococci, staphylococci, anaerobes, and *Eikenella corrodens* are potential etiologic agents.^{185,186}

Sulbactam is a semisynthetic beta-lactamase inhibitor with activity against a broad range of beta-lactamases, including those produced by bacteroides, haemophilus, klebsiella, *E. coli*, and *N. gonorrhoeae*.^{71,187,188} It is currently available as a parenteral preparation in combination with ampicillin (Unasyn — 2 g of ampicillin and 1.0 g of sulbactam). Given every six hours, the combination has been successful in the treatment of a variety of infections, including intraabdominal and pelvic infections, infections of the skin, soft tissue, and bones and joints, and uncomplicated urethritis caused by penicillin-sensitive and penicillin-resistant *N. gonorrhoeae*.¹⁸⁹⁻¹⁹¹ Overall, clinical experience with sulbactam remains limited.

AMIDINOCILLIN

Amidinocillin (Coactin), previously known as mecillinam, is a semisynthetic derivative of beta-amidopenicillanic acid that binds specifically to PBP 2,¹⁹⁵ in contrast to most other beta-lactam antibiotics, which bind primarily to PBP 1 and 3. This agent has activity against most of the Enterobacteriaceae and may be used to treat urinary tract infections. It acts synergistically with other beta-lactam compounds against cer-

tain gram-negative rods; however, its clinical role is unclear.^{12,196}

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