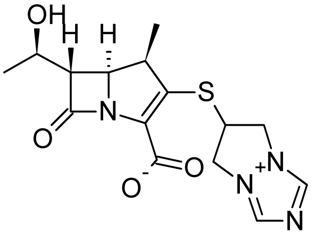
to be less epileptogenic than imipenem when the two agents are used in the treatment of bacterial meningitis.

Biapenem

Biapenem is a newer second-generation carbapenem with chemical and microbiological properties similar to those of meropenem.[67] Thus, it has broad-spectrum antibacterial activity that includes most aerobic Gram-negative and Gram-positive bacteria and anaerobes. Biapenem is stable to DHP-I[67] and resistant to most β-lactamases.[68] It is claimed to be less susceptible to metallo-β-lactamases than either imipenem or meropenem. It is not active orally.



CEPHALOSPORINS

Historical Background

The cephalosporins are β-lactam antibiotics isolated from *Cephalosporium* spp. or prepared semisynthetically. Most of the antibiotics introduced since 1965 have been semisynthetic cephalosporins. Interest in *Cephalosporium* fungi began in 1945 with Giuseppe Brotzu's discovery that cultures of *C. acremonium* inhibited the growth of a wide variety of Gram-positive and Gram-negative bacteria. Abraham and Newton[68a] in Oxford, having been supplied cultures of the fungus in 1948, isolated three principal antibiotic components: cephalosporin Pl, a steroid with minimal antibacterial activity; cephalosporin N, later discovered to be identical with synnematin N (a penicillin derivative now called penicillin N that had earlier been isolated from *C. salmosynnematum*); and cephalosporin C.

The structure of penicillin N was discovered to be D-(4-amino-4-carboxybutyl)penicillanic acid. The amino acid side chain confers more activity against Gram-negative bacteria, particularly *Salmonella* spp., but less activity against Gram-positive organisms than penicillin G. It has been used successfully in clinical trials for the treatment of typhoid fever but was never released as an approved drug.

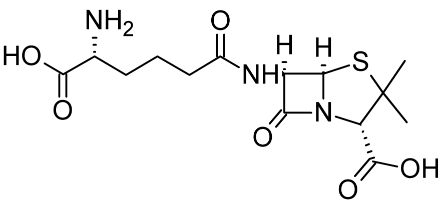
Cephalosporin C turned out to be a close congener of penicillin N, containing a dihydrothiazine ring instead of the thiazolidine ring of the penicillins. Despite the observation that cephalosporin C was resistant to *S. aureus* β-lactamase, early interest in it was not great because its antibacterial potency was inferior to that of penicillin N and other penicillins. The discovery that the α-aminoadipoyl side chain could be removed to efficiently produce 7-aminocephalosporanic acid (7-ACA),[69,70] however, prompted investigations that led to semisynthetic cephalosporins of medicinal value. The relationship of 7-ACA and its acyl derivatives to 6-APA and the semisynthetic penicillins is obvious. Woodward et al.[71] have prepared both cephalosporin C and the clinically useful cephalothin by an elegant synthetic procedure, but the commercially available drugs are obtained from 7-ACA as semisynthetic products.

Nomenclature

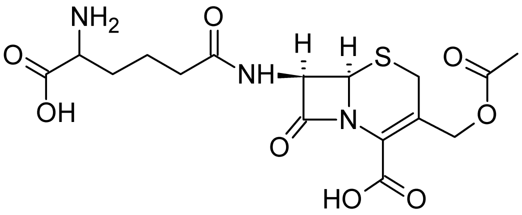
The chemical nomenclature of the cephalosporins is slightly more complex than even that of the penicillins because of the presence of a double bond in the dihydrothiazine ring. The fused ring system is designated by *Chemical Abstracts* as 5-thia-1-azabicyclo[4.2.0]oct-2-ene. In this system, cephalothin is 3-(acetoxymethyl)-7-[2-(thienylacetyl)amino]-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid. A simplification that retains some of the systematic nature of the *Chemical Abstracts* procedure names the saturated bicyclic ring system with the lactam carbonyl oxygen *cepham* (cf., *penam* for penicillins). According to this system, all commercially available cephalosporins and cephamycins are named *3-cephems* (or Δ^3-cephems) to designate the position of the double bond. (Interestingly, all known 2-cephems are inactive, presumably because the β-lactam lacks the necessary ring strain to react sufficiently.) The trivialized forms of nomenclature of the type that have been applied to the penicillins are not consistently applicable to the naming of cephalosporins because of variations in the substituent at the 3-position. Thus, although some cephalosporins are named as derivatives of cephalosporanic acids, this practice applies only to the derivatives that have a 3-acetoxymethyl group.

Semisynthetic Derivatives

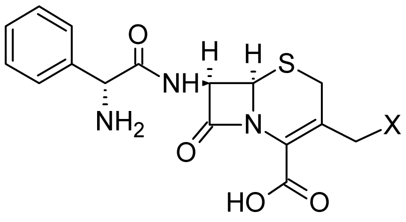
To date, the more useful semisynthetic modifications of the basic 7-ACA nucleus have resulted from acylations of the 7-amino group with different acids or nucleophilic substitution or reduction of the acetoxyl group. Structure–activity relationships (SARs) among the cephalosporins appear to parallel those among the penicillins insofar as the acyl group is concerned. The presence of an allylic acetoxyl function in the 3-position, however, provides a reactive site at which various 7-acylaminocephalosporanic acid structures can easily be varied by nucleophilic displacement reactions. Reduction of the 3-acetoxymethyl to a 3-methyl substituent to prepare 7-aminodesacetylcephalosporanic acid (7-ADCA)



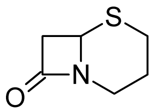
Penicillin N



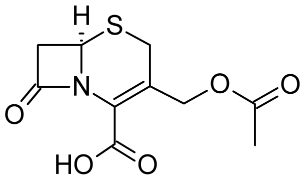
Cephalosporin C



Cephalosporin



Cepham



Cephalosporanic Acid

derivatives can be accomplished by catalytic hydrogenation, but the process currently used for the commercial synthesis of 7-ADCA derivatives involves the rearrangement of the corresponding penicillin sulfoxide.[72] Perhaps the most noteworthy development thus far is the discovery that 7-phenylglycyl derivatives of 7-ACA and especially 7-ADCA are active orally.

In the preparation of semisynthetic cephalosporins, the following improvements are sought: (a) increased acid stability, (b) improved pharmacokinetic properties, particularly better oral absorption, (c) broadened antimicrobial spectrum, (d) increased activity against resistant microorganisms (as a result of resistance to enzymatic destruction, improved penetration, increased receptor affinity, etc.), (e) decreased allergenicity, and (f) increased tolerance after parenteral administration.

Structures of cephalosporins currently marketed in the United States are shown in Table 8.4.

Chemical Degradation

Cephalosporins experience various hydrolytic degradation reactions whose specific nature depends on the individual structure (Table 8.4).[73] Among 7-acylaminocephalosporanic acid derivatives, the 3-acetoxylmethyl group is the most reactive site. In addition to its reactivity to nucleophilic displacement reactions, the acetoxyl function of this group readily undergoes solvolysis in strongly acidic solutions to form the desacetylcephalosporin derivatives. The latter lactonize to form the desacetylcephalosporin lactones, which are virtually inactive. The 7-acylamino group of some cephalosporins can also be hydrolyzed under enzymatic (acylases) and, possibly, nonenzymatic conditions to give 7-ACA (or 7-ADCA) derivatives. Following hydrolysis or solvolysis of the 3-acetoxymethyl group, 7-ACA also lactonizes under acidic conditions (Fig. 8.5).

The reactive functionality common to all cephalosporins is the β-lactam. Hydrolysis of the β-lactam of cephalosporins is believed to give initially cephalosporoic acids (in which the R' group is stable, [e.g., $R' =$ H or S heterocycle]) or possibly anhydrodesacetylcephalosporoic acids (7-ADCA, for the 7-acylaminocephalosporanic acids). It has not been possible to isolate either of these initial hydrolysis products in aqueous systems. Apparently, both types of cephalosporanic acid undergo fragmentation reactions that have not been characterized fully. Studies of the in vivo metabolism[74] of orally administered cephalosporins, however, have demonstrated arylacetylglycines and arylacetamidoethanols, which are believed to be formed from the corresponding arylacetylaminoacetaldehydes by metabolic oxidation and reduction, respectively. The aldehydes, no doubt, arise from nonenzymatic hydrolysis of the corresponding cephalosporoic acids. No evidence for the intramolecular opening of the β-lactam ring by the 7-acylamino oxygen to form oxazolones of the penicillanic acid type has been found in the cephalosporins. At neutral to alkaline pH, however, intramolecular aminolysis of the β-lactam ring by the α-amino group in the 7-ADCA derivatives cephaloglycin, cephradine, and cefadroxil occurs, forming diketopiperazine derivatives.[75,76] The formation of dimers and, possibly, polymers from 7-ADCA derivatives containing an α-amino group in the acylamino side chain may also occur, especially in concentrated solutions and at alkaline pH values.

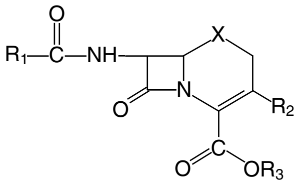
Oral Cephalosporins

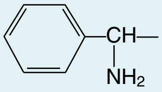
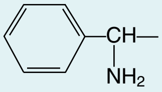
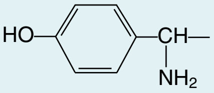
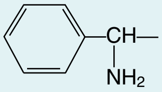
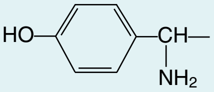
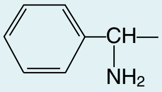
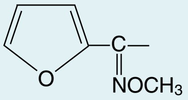
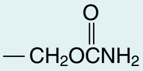
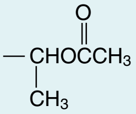
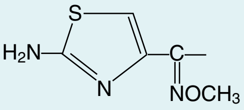
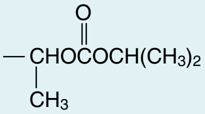
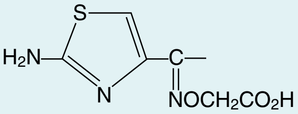
The oral activity conferred by the phenylglycyl substituent is attributed to increased acid stability of the lactam ring, resulting from the presence of a protonated amino group on the 7-acylamino portion of the molecule. Carrier-mediated transport of these dipeptide-like, zwitterionic cephalosporins[51] is also an important factor in their excellent oral activity. The situation, then, is analogous to that of the α-aminobenzylpenicillins (e.g., ampicillin). Also important for high acid stability (and, therefore, good oral activity) of the cephalosporins is the absence of the leaving group at the 3-position. Thus, despite the presence of the phenylglycyl side chain in its structure, the

(text continues on page 282)

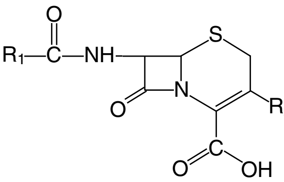
TABLE 8.4 Structure of Cephalosporins

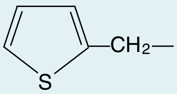
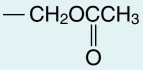
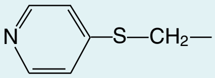
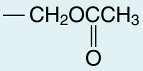
ORAL CEPHALOSPORINS

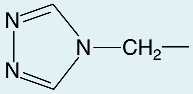
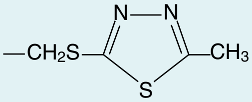
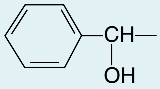
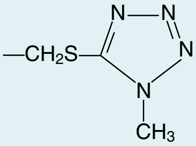
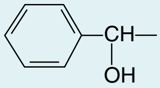
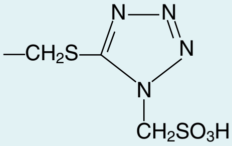
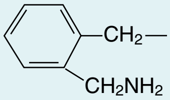
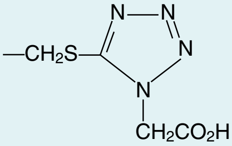
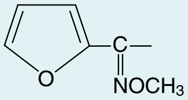
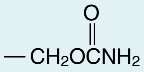
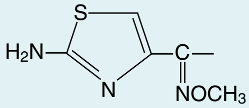
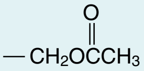
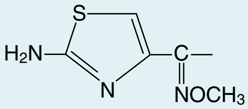
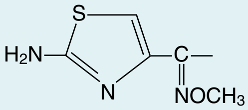
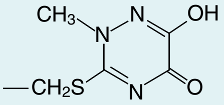
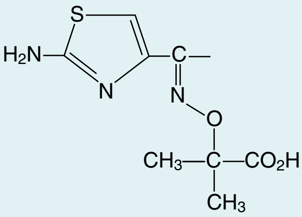
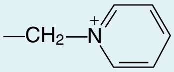
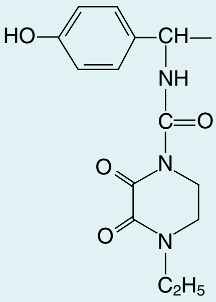
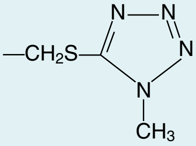


Generic Name	R₁	R₂	R₃	X
Cephalexin		$-CH_3$	$-H$	$-S-$
Cephradine		$-CH_3$	$-H$	$-S-$
Cefadroxil		$-CH_3$	$-H$	$-S-$
Cefachlor		$-Cl$	$-H$	$-S-$
Cefprozil		$-CH{=}CHCH_3$	$-H$	$-S-$
Loracarbef		$-Cl$	$-H$	$-CH_2-$
Cefuroxime axetil		 $-CH_2O\overset{O}{\overset{\|}{C}}NH_2$	 $-\underset{CH_3}{\underset{\mid}{CH}}O\overset{O}{\overset{\|}{C}}CH_3$	$-S-$
Cefpodoxime proxetil		$-CH_2OCH_3$	 $-\underset{CH_3}{\underset{\mid}{CH}}O\overset{O}{\overset{\|}{C}}OCH(CH_3)_2$	$-S-$
Cefixime		$-C{=}CH_2$	$-H$	$-S-$

PARENTERAL CEPHALOSPORINS



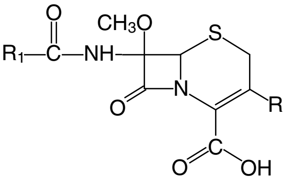
Generic Name	R₁	R₂
Cephalothin		 $-CH_2O\underset{O}{\underset{\|}{C}}CH_3$
Cephapirin		 $-CH_2O\underset{O}{\underset{\|}{C}}CH_3$

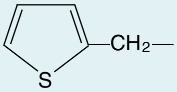
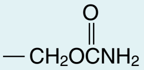
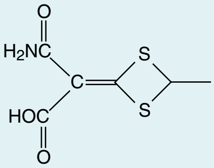
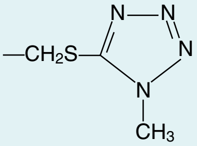
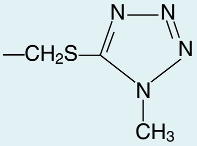
Generic Name	R_1	R_2
Cefazolin		
Cefamandole		
Cefonicid		
Ceforanide		
Cefuroxime		 $-CH_2O\overset{O}{\overset{\|}{C}}NH_2$
Cefotaxime		 $-CH_2O\overset{O}{\overset{\|}{C}}CH_3$
Ceftizoxime		—H
Ceftriaxone		
Ceftazidime		
Cefoperazone		

(table continues on page 282)

TABLE 8.4 Structure of Cephalosporins *(continued)*

PARENTERAL CEPHAMYCINS



Generic Name	R_1	R_2
Cefoxitin		$-CH_2O\overset{O}{\overset{\|}{C}}NH_2$
Cefotetan		
Cefmetazole	$NCCH_2SCH_2—$	

cephalosporanic acid derivative cephaloglycin is poorly absorbed orally, presumably because of solvolysis of the 3-acetoxyl group in the low pH of the stomach. The resulting 3-hydroxyl derivative undergoes lactonization under acidic conditions. The 3-hydroxyl derivatives and, especially, the corresponding lactones are considerably less active in vitro than the parent cephalosporins. Generally, acyl derivatives of 7-ADCA show lower in vitro antibacterial potencies than the corresponding 7-ACA analogs.

Oral activity can also be conferred in certain cephalosporins by esterification of the 3-carboxylic acid group to form acid-stable, lipophilic esters that undergo hydrolysis in the plasma. Cefuroxime axetil and cefpodoxime proxetil are two β-lactamase–resistant alkoximino-cephalosporins that are orally active ester prodrug derivatives of cefuroxime and cefpodoxime, respectively, based on this concept.

Parenteral Cephalosporins

Hydrolysis of the ester function, catalyzed by hepatic and renal esterases, is responsible for some in vivo inactivation of parenteral cephalosporins containing a 3-acetoxymethyl substituent (e.g., cephalothin, cephapirin, and cefotaxime). The extent of such inactivation (20%–35%) is not large enough to seriously compromise the in vivo effectiveness of acetoxyl cephalosporins. Parenteral cephalosporins lacking a hydrolyzable group at the 3-position are not subject to hydrolysis by esterases. Cephradine is the only cephalosporin that is used both orally and parenterally.

Spectrum of Activity

The cephalosporins are considered broad-spectrum antibiotics with patterns of antibacterial effectiveness comparable to that of ampicillin. Several significant differences exist, however. Cephalosporins are much more resistant to inactivation by β-lactamases, particularly those produced by Gram-positive bacteria, than is ampicillin. Ampicillin, however, is generally more active against non–β-lactamase-producing strains of Gram-positive and Gram-negative bacteria sensitive to both it and the cephalosporins. Cephalosporins, among β-lactam antibiotics, exhibit uniquely potent activity against most species of *Klebsiella*. Differential potencies of cephalosporins, compared with penicillins, against different species of bacteria have been attributed to several variable characteristics of individual bacterial species and strains, the most important of which probably are (a) resistance to inactivation by β-lactamases, (b) permeability of bacterial cells, and (c) intrinsic activity against bacterial enzymes involved in cell wall synthesis and cross-linking.

β-Lactamase Resistance

The susceptibility of cephalosporins to various lactamases varies considerably with the source and properties of these enzymes. Cephalosporins are significantly less sensitive than all but the β-lactamase–resistant penicillins to hydrolysis by the enzymes from *S. aureus* and *Bacillus subtilis*. The "penicillinase" resistance of cephalosporins appears to be a property of the bicyclic cephem ring system rather than of the acyl group. Despite natural resistance to staphylococcal β-lactamase, the different cephalosporins exhibit considerable variation in rates of hydrolysis by the enzyme.[77] Thus, of several cephalosporins tested in vitro, cephalothin and cefoxitin are the most resistant, and cephaloridine and cefazolin are the least resistant. The same acyl functionalities that impart β-lactamase resistance in the penicillins unfortunately render cephalosporins virtually inactive against *S. aureus* and other Gram-positive bacteria.

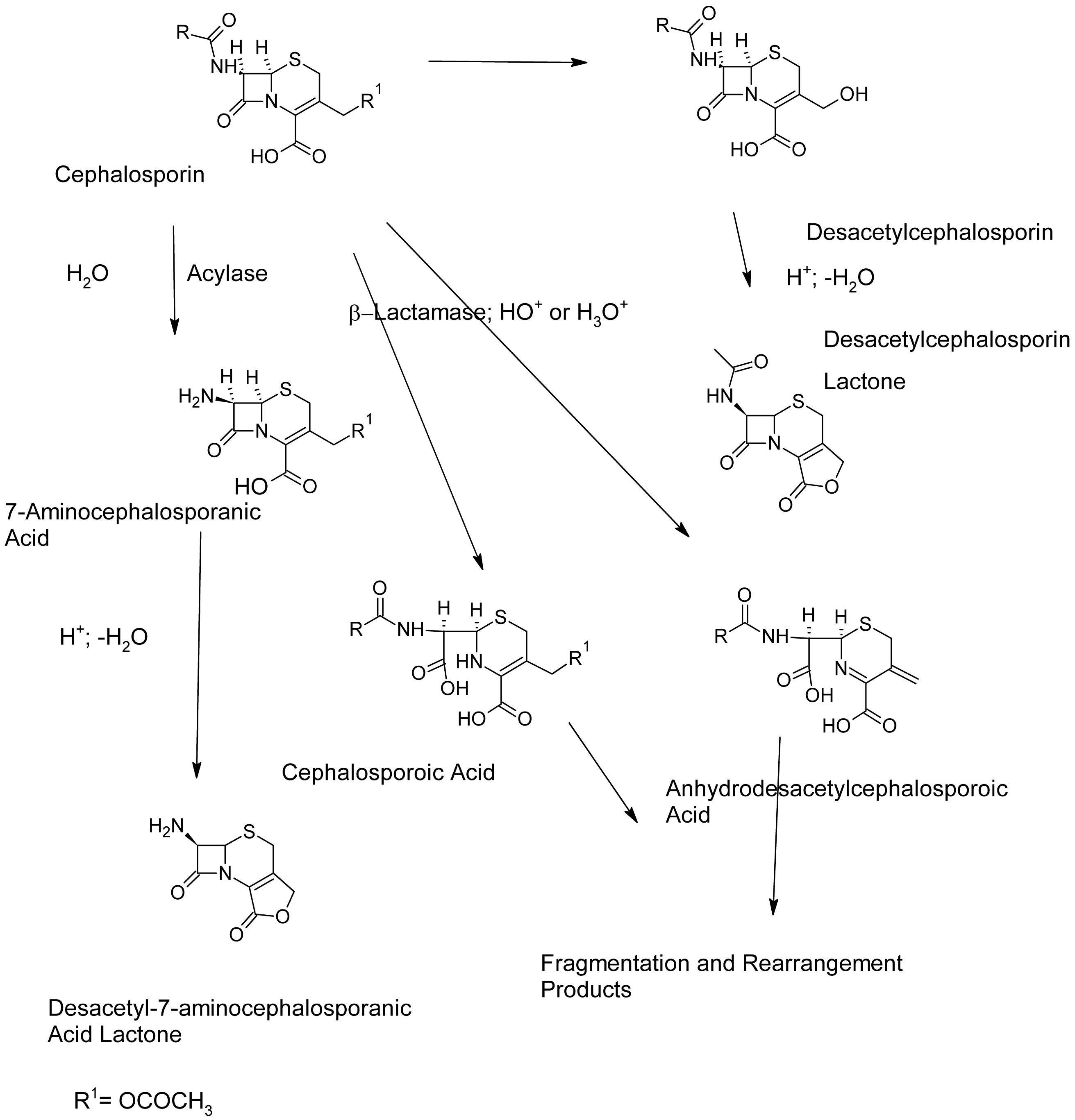


Figure 8.5 ● Degradation of cephalosporins.

β-Lactamases elaborated by Gram-negative bacteria present an exceedingly complex picture. Well over 100 different enzymes from various species of Gram-negative bacilli have been identified and characterized,[25] differing widely in specificity for various *β*-lactam antibiotics. Most of these enzymes hydrolyze penicillin G and ampicillin faster than the cephalosporins. Some inducible *β*-lactamases belonging to group C, however, are "cephalosporinases," which hydrolyze cephalosporins more rapidly. Inactivation by *β*-lactamases is an important factor in determining resistance to cephalosporins in many strains of Gram-negative bacilli.

The introduction of polar substituents in the aminoacyl moiety of cephalosporins appears to confer stability to some *β*-lactamases.[78] Thus, cefamandole and cefonicid, which contain an *α*-hydroxyphenylacetyl (or mandoyl) group, and ceforanide, which has an *o*-aminophenyl acetyl group, are resistant to a few *β*-lactamases. Steric factors also may be important because cefoperazone, an acylureidocephalosporin that contains the same 4-ethyl-2,3-dioxo-1-piperazinylcarbonyl group present in piperacillin, is resistant to many *β*-lactamases. Oddly enough, piperacillin is hydrolyzed by most of these enzymes.

Two structural features confer broadly based resistance to *β*-lactamases among the cephalosporins: (a) an alkoximino function in the aminoacyl group and (b) a methoxyl substituent at the 7-position of the cephem nucleus having *α* stereochemistry. The structures of several *β*-lactamase–resistant cephalosporins, including cefuroxime, cefotaxime, ceftizoxime, and ceftriaxone, feature a methoximino acyl group. *β*-Lactamase resistance is enhanced modestly if the oximino substituent also features a polar function, as in ceftazidime, which has a 2-methylpropionic acid substituent on the oximino group. Both steric and electronic properties of the alkoximino group may contribute to the β-lactamase resistance conferred by this functionality since *syn*-isomers are more potent than *anti*-isomers.[78] β-Lactamase–resistant 7α-methoxylcephalosporins, also called cephamycins because they are derived from cephamycin C (an antibiotic isolated from *Streptomyces*), are represented by cefoxitin, cefotetan, cefmetazole, and the 1-oxocephalosporin moxalactam, which is prepared by total synthesis.

Base- or β-lactamase–catalyzed hydrolysis of cephalosporins containing a good leaving group at the 3-position is accompanied by elimination of the leaving group. The enzymatic process occurs in a stepwise fashion, beginning with the formation of a tetrahedral transition state, which quickly collapses into an acyl-enzyme intermediate (Fig. 8.6). This intermediate can then either undergo hydrolysis to free the enzyme (path 1) or suffer elimination of the leaving group to form a relatively stable acyl-enzyme with a conjugated imine structure (path 2). Because of the stability of the acyl-enzyme intermediate, path 2 leads to transient inhibition of the enzyme. Faraci and Pratt[79,79a] have shown that cephalothin and cefoxitin inhibit certain β-lactamases by this mechanism, whereas analogs lacking a 3′ leaving group do not.

Antipseudomonal Cephalosporins

Species of *Pseudomonas*, especially *P. aeruginosa*, represent a special public health problem because of their ubiquity in the environment and their propensity to develop resistance to antibiotics, including the β-lactams. The primary mechanisms of β-lactam resistance appear to involve destruction of the antibiotics by β-lactamases and/or interference with their penetration through the cell envelope. Apparently, not all β-lactamase–resistant cephalosporins penetrate the cell envelope of *P. aeruginosa*, as only cefoperazone, moxalactam, cefotaxime, ceftizoxime, ceftriaxone, and ceftazidime have useful antipseudomonal activity. Two cephalosporins, moxalactam and cefoperazone, contain the same polar functionalities (e.g., carboxy and *N*-acylureido) that facilitate penetration into *Pseudomonas* spp. by the penicillins (see carbenicillin, ticarcillin, and piperacillin). Unfortunately, strains of *P. aeruginosa* resistant to cefoperazone and cefotaxime have been found in clinical isolates.

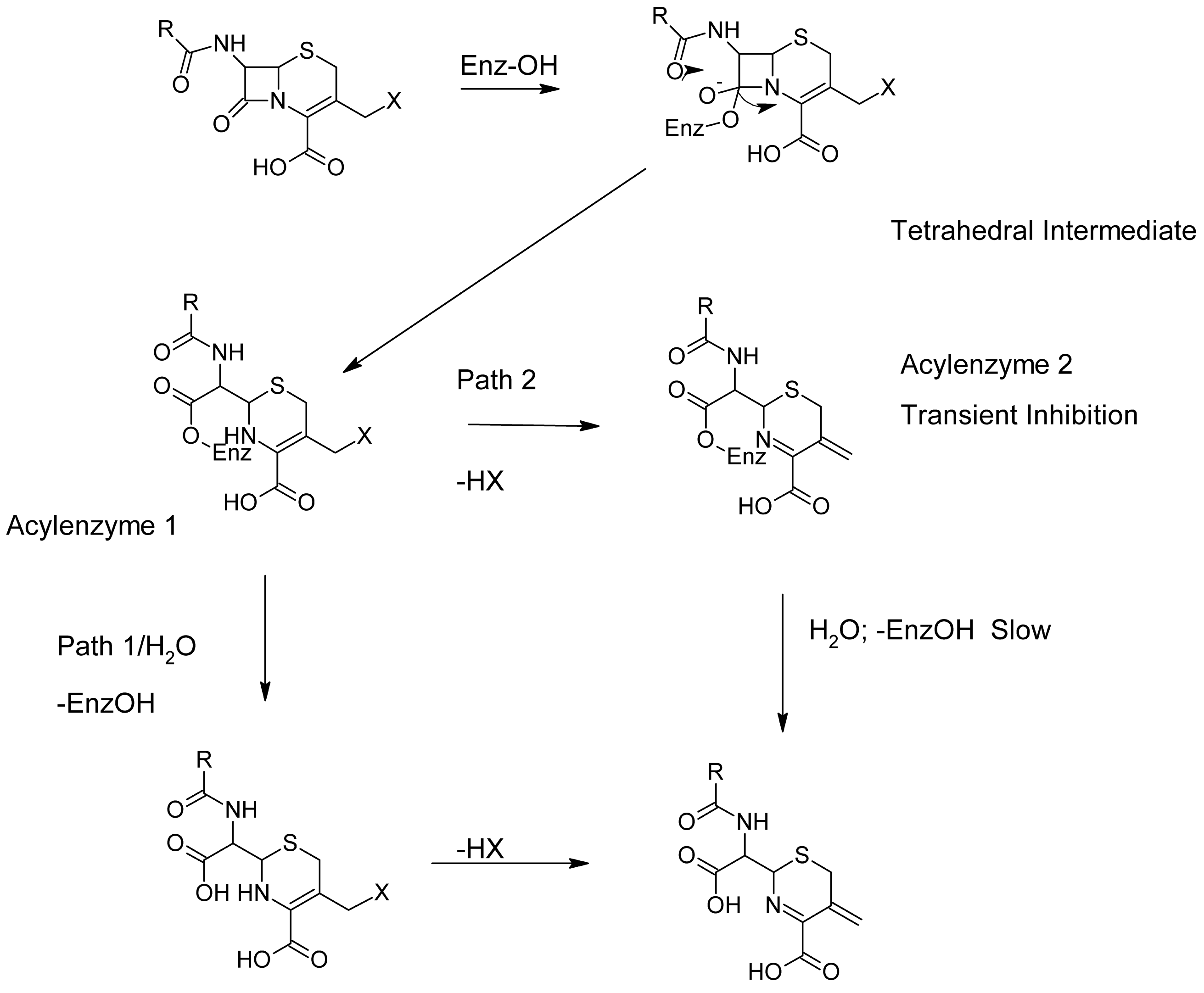


Figure 8.6 • Inhibition of β-lactamases by cephalosporins.

Adverse Reactions and Drug Interactions

Like their close relatives, the penicillins, the cephalosporin antibiotics are comparatively nontoxic compounds that, because of their selective actions on cell wall cross-linking enzymes, exhibit highly selective toxicity toward bacteria. The most common adverse reactions to the cephalosporins are allergic and hypersensitivity reactions. These vary from mild rashes to life-threatening anaphylactic reactions. Allergic reactions are believed to occur less frequently with cephalosporins than with penicillins. The issue of cross-sensitivity between the two classes of β-lactams is very complex, but the incidence is considered to be very low (estimated between 3% and 7%). The physician faced with the decision of whether or not to administer a cephalosporin to a patient with a history of penicillin allergy must weigh several factors, including the severity of the illness being treated, the effectiveness and safety of alternative therapies, and the severity of previous allergic responses to penicillins.

Cephalosporins containing an *N*-methyl-5-thiotetrazole (MTT) moiety at the 3-position (e.g., cefamandole, cefotetan, cefmetazole, moxalactam, and cefoperazone) have been implicated in a higher incidence of hypoprothrombinemia than cephalosporins lacking the MTT group. This effect, which is enhanced and can lead to severe bleeding in patients with poor nutritional status, debilitation, recent GI surgery, hepatic disease, or renal failure, is apparently because of inhibition of vitamin K–requiring enzymes involved in the carboxylation of glutamic acid residues in clotting factors II, VII, IX, and X to the MTT group.[80] Treatment with vitamin K restores prothrombin time to normal in patients treated with MTT-containing cephalosporins. Weekly vitamin K prophylaxis has been recommended for high-risk patients undergoing therapy with such agents. Cephalosporins containing the MTT group should not be administered to patients receiving oral anticoagulant or heparin therapy because of possible synergism with these drugs.

The MTT group has also been implicated in the intolerance to alcohol associated with certain injectable cephalosporins: cefamandole, cefotetan, cefmetazole, and cefoperazone. Thus, disulfiram-like reactions, attributed to the accumulation of acetaldehyde and resulting from the inhibition of aldehyde dehydrogenase–catalyzed oxidation of ethanol by MTT-containing cephalosporins,[81] may occur in patients who have consumed alcohol before, during, or shortly after the course of therapy.

Classification

Cephalosporins are divided into first-, second-, third-, and fourth-generation agents, based roughly on their time of discovery and their antimicrobial properties (Table 8.5). In general, progression from first to fourth generation is associated with a broadening of the Gram-negative antibacterial spectrum, some reduction in activity against Gram-positive organisms, and enhanced resistance to β-lactamases. Individual cephalosporins differ in their pharmacokinetic properties, especially plasma protein binding and half-life, but the structural bases for these differences are not obvious.

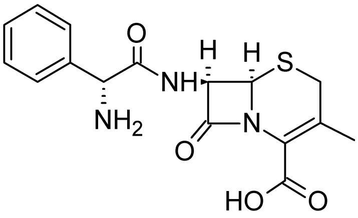
TABLE 8.5 Classification and Properties of Cephalosporins

Cephalosporin	Generation	Route of Admin.	Acid Resistant	Plasma Protein Binding (%)	β-Lactamase Resistance	Spectrum of Activity	Antipseudomonal Activity
Cephalexin	First	Oral	Yes	5–15	Poor	Broad	No
Cephradine	First	Oral, parenteral	Yes	8–17	Poor	Broad	No
Cefadroxil	First	Oral	Yes	20	Poor	Broad	No
Cephalothin	First	Parenteral	No	65–80	Poor	Broad	No
Cephapirin	First	Parenteral	No	40–54	Poor	Broad	No
Cefazolin	First	Parenteral	No	70–86	Poor	Broad	No
Cefaclor	Second	Oral	Yes	22–25	Poor	Broad	No
Loracarbef	Second	Oral	Yes	25	Poor	Broad	No
Cefprozil	Second	Oral	Yes	36	Poor	Broad	No
Cefamandole	Second	Parenteral	No	56–78	Poor to avg.	Extended	No
Cefonicid	Second	Parenteral	No	99	Poor to avg.	Extended	No
Ceforanide	Second	Parenteral	No	80	Average	Extended	No
Cefoxitin	Second	Parenteral	No	13–22	Good	Extended	No
Cefotetan	Second	Parenteral	No	78–91	Good	Extended	No
Cefmetazole	Second	Parenteral	No	65	Good	Extended	No
Cefuroxime	Second	Oral, parenteral	Yes/No	33–50	Good	Extended	No
Cefpodoxime	Second	Oral	Yes	25	Good	Extended	No
Cefixime	Third	Oral	Yes	65	Good	Extended	No
Cefoperazone	Third	Parenteral	No	82–93	Avg. to good	Extended	Yes
Cefotaxime	Third	Parenteral	No	30–51	Good	Extended	Yes
Ceftizoxime	Third	Parenteral	No	30	Good	Extended	Yes
Ceftriaxone	Third	Parenteral	No	80–95	Good	Extended	Yes
Ceftazidime	Third	Parenteral	No	80–90	Good	Extended	Yes
Ceftibuten	Third	Oral	Yes	?	Good	Extended	No
Cefepime	Fourth	Parenteral	No	16–19	Good	Extended	Yes
Cefpirome	Fourth	Parenteral	No	–	Good	Extended	Yes

Products

Cephalexin

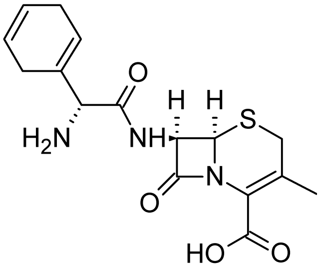
Cephalexin, 7α-(D-amino-α-phenylacetamido)-3-methylcephemcarboxylic acid (Keflex, Keforal), was designed purposely as an orally active, semisynthetic cephalosporin. The oral inactivation of cephalosporins has been attributed to two causes: instability of the β-lactam ring to acid hydrolysis (cephalothin and cephaloridine) and solvolysis or microbial transformation of the 3-methylacetoxy group (cephalothin, cephaloglycin). The α-amino group of cephalexin renders it acid stable, and reduction of the 3-acetoxymethyl to a methyl group circumvents reaction at that site.



Cephalexin occurs as a white crystalline monohydrate. It is freely soluble in water, resistant to acid, and absorbed well orally. Food does not interfere with its absorption. Because of minimal protein binding and nearly exclusive renal excretion, cephalexin is recommended particularly for the treatment of urinary tract infections. It is also sometimes used for upper respiratory tract infections. Its spectrum of activity is very similar to those of cephalothin and cephaloridine. Cephalexin is somewhat less potent than these two agents after parenteral administration and, therefore, is inferior to them for the treatment of serious systemic infections.

Cephradine

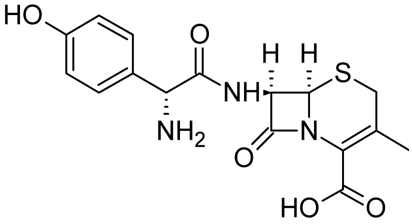
Cephradine (Anspor, Velosef) is the only cephalosporin derivative available in both oral and parenteral dosage forms. It closely resembles cephalexin chemically (it may be regarded as a partially hydrogenated derivative of cephalexin) and has very similar antibacterial and pharmacokinetic properties.



It occurs as a crystalline hydrate that is readily soluble in water. Cephradine is stable to acid and absorbed almost completely after oral administration. It is minimally protein bound and excreted almost exclusively through the kidneys. It is recommended for the treatment of uncomplicated urinary tract and upper respiratory tract infections caused by susceptible organisms. Cephradine is available in both oral and parenteral dosage forms.

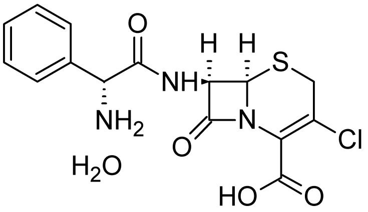
Cefadroxil

Cefadroxil (Duricef) is an orally active semisynthetic derivative of 7-ADCA, in which the 7-acyl group is the D-hydroxylphenylglycyl moiety. This compound is absorbed well after oral administration to give plasma levels that reach 75% to 80% of those of an equal dose of its close structural analog cephalexin. The main advantage claimed for cefadroxil is its somewhat prolonged duration of action, which permits once-a-day dosing. The prolonged duration of action of this compound is related to relatively slow urinary excretion of the drug compared with other cephalosporins, but the basis for this remains to be explained completely. The antibacterial spectrum of action and therapeutic indications of cefadroxil are very similar to those of cephalexin and cephradine. The D-p-hydroxyphenylglycyl isomer is much more active than the L-isomer.



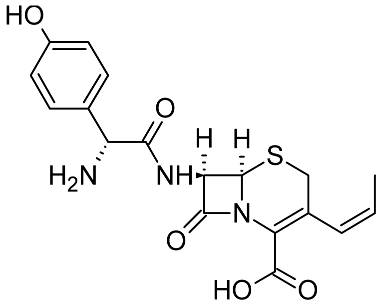
Cefaclor

Cefaclor (Ceclor) is an orally active semisynthetic cephalosporin that was introduced in the American market in 1979. It differs structurally from cephalexin in that the 3-methyl group has been replaced by a chlorine atom. It is synthesized from the corresponding 3-methylenecepham sulfoxide ester by ozonolysis, followed by halogenation of the resulting β-ketoester.[82] The 3-methylenecepham sulfoxide esters are prepared by rearrangement of the corresponding 6-acylaminopenicillanic acid derivative. Cefaclor is moderately stable in acid and achieves enough oral absorption to provide effective plasma levels (equal to about two-thirds of those obtained with cephalexin). The compound is apparently unstable in solution, since about 50% of its antimicrobial activity is lost in 2 hours in serum at 37°C.[83] The antibacterial spectrum of activity is similar to that of cephalexin, but it is claimed to be more potent against some species sensitive to both agents. Currently, the drug is recommended for the treatment of non–life-threatening infections caused by *H. influenzae*, particularly strains resistant to ampicillin.



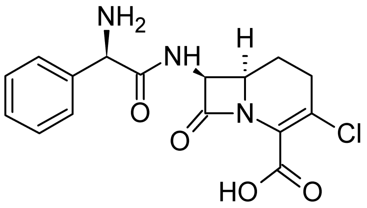
Cefprozil

Cefprozil (Cefzil) is an orally active second-generation cephalosporin that is similar in structure and antibacterial spectrum to cefadroxil. Oral absorption is excellent (oral bioavailability is about 95%) and is not affected by antacids or histamine H_2-antagonists. Cefprozil exhibits greater in vitro activity against streptococci, *Neisseria* spp., and *S. aureus* than does cefadroxil. It is also more active than the first-generation cephalosporins against members of the Enterobacteriaceae family, such as *E. coli*, *Klebsiella* spp., *P. mirabilis*, and *Citrobacter* spp. The plasma half-life of 1.2 to 1.4 hours permits twice-a-day dosing for the treatment of most community-acquired respiratory and urinary tract infections caused by susceptible organisms.



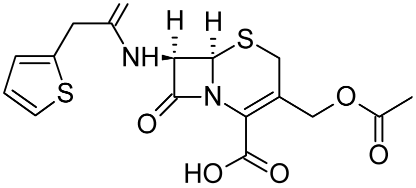
Loracarbef

Loracarbef (Lorabid) is the first of a series of carbacephems prepared by total synthesis to be introduced.[84] Carbacephems are isosteres of the cephalosporin (or Δ^3-cephem) antibiotics in which the 1-sulfur atom has been replaced by a methylene (CH_2) group. Loracarbef is isosteric with cefaclor and has similar pharmacokinetic and microbiological properties. Thus, the antibacterial spectrum of activity resembles that of cefaclor, but it has somewhat greater potency against *H. influenzae* and *M. catarrhalis*, including β-lactamase–producing strains. Unlike cefaclor, which undergoes degradation in human serum, loracarbef is chemically stable in plasma. It is absorbed well orally. Oral absorption is delayed by food. The half-life in plasma is about 1 hour.



Cephalothin Sodium

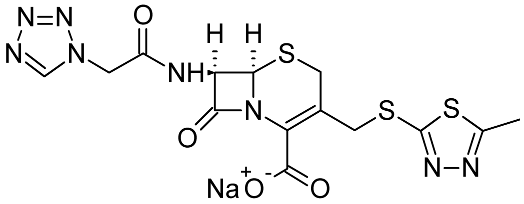
Cephalothin sodium (Keflin) occurs as a white to off-white, crystalline powder that is practically odorless. It is freely soluble in water and insoluble in most organic solvents. Although it has been described as a broad-spectrum antibacterial compound, it is not in the same class as the tetracyclines. Its spectrum of activity is broader than that of penicillin G and more similar to that of ampicillin. Unlike ampicillin, cephalothin is resistant to penicillinase produced by *S. aureus* and provides an alternative to the use of penicillinase-resistant penicillins for the treatment of infections caused by such strains.



Cephalothin is absorbed poorly from the GI tract and must be administered parenterally for systemic infections. It is relatively nontoxic and acid stable. It is excreted rapidly through the kidneys; about 60% is lost within 6 hours of administration. Pain at the site of intramuscular injection and thrombophlebitis following intravenous injection have been reported. Hypersensitivity reactions have been observed, and there is some evidence of cross-sensitivity in patients noted previously to be penicillin sensitive.

Cefazolin Sodium, Sterile

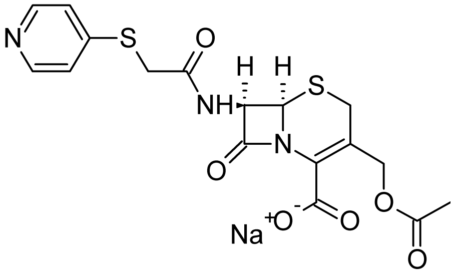
Cefazolin (Ancef, Kefzol) is one of a series of semisynthetic cephalosporins in which the C-3 acetoxy function has been replaced by a thiol-containing heterocycle—here, 5-methyl-2-thio-1,3,4-thiadiazole. It also contains the somewhat unusual tetrazolylacetyl acylating group. Cefazolin was released in 1973 as a water-soluble sodium salt. It is active only by parenteral administration.



Cefazolin provides higher serum levels, slower renal clearance, and a longer half-life than other first-generation cephalosporins. It is approximately 75% protein bound in plasma, a higher value than for most other cephalosporins. Early in vitro and clinical studies suggest that cefazolin is more active against Gram-negative bacilli but less active against Gram-positive cocci than either cephalothin or cephaloridine. Occurrence rates of thrombophlebitis following intravenous injection and pain at the site of intramuscular injection appear to be the lowest of the parenteral cephalosporins.

Cephapirin Sodium, Sterile

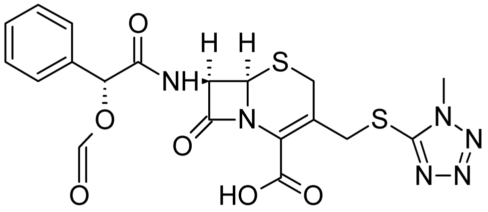
Cephapirin (Cefadyl) is a semisynthetic 7-ACA derivative released in the United States in 1974. It closely resembles cephalothin in chemical and pharmacokinetic properties. Like cephalothin, cephapirin is unstable in acid and must be administered parenterally in the form of an aqueous solution of the sodium salt. It is moderately protein bound (45%–50%) in plasma and cleared rapidly by the kidneys. Cephapirin and cephalothin are very similar in antimicrobial spectrum and potency. Conflicting reports concerning the relative occurrence of pain at the site of injection and thrombophlebitis after intravenous injection of cephapirin and cephalothin are difficult to assess on the basis of available clinical data.



Cefamandole Nafate

Cefamandole (Mandol) nafate is the formate ester of cefamandole, a semisynthetic cephalosporin that incorporates

D-mandelic acids as the acyl portion and a thiol-containing heterocycle (5-thio-1,2,3,4-tetrazole) in place of the acetoxyl function on the C-3 methylene carbon atom. Esterification of the α-hydroxyl group of the D-mandeloyl function overcomes the instability of cefamandole in solid-state dosage forms[85] and provides satisfactory concentrations of the parent antibiotic in vivo through spontaneous hydrolysis of the ester at neutral to alkaline pH. Cefamandole is the first second-generation cephalosporin to be marketed in the United States.

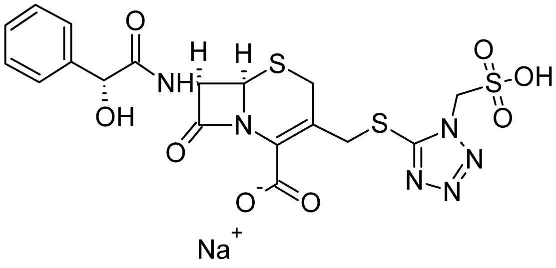


The D-mandeloyl moiety of cefamandole appears to confer resistance to a few β-lactamases, since some β-lactamase–producing, Gram-negative bacteria (particularly Enterobacteriaceae) that show resistance to cefazolin and other first-generation cephalosporins are sensitive to cefamandole. Additionally, it is active against some ampicillin-resistant strains of *Neisseria* and *Haemophilus* spp. Although resistance to β-lactamases may be a factor in determining the sensitivity of individual bacterial strains to cefamandole, an early study[86] indicated that other factors, such as permeability and intrinsic activity, are frequently more important. The L-mandeloyl isomer is significantly less active than the D-isomer.

Cefamandole nafate is very unstable in solution and hydrolyzes rapidly to release cefamandole and formate. There is no loss of potency, however, when such solutions are stored for 24 hours at room temperature or up to 96 hours when refrigerated. Air oxidation of the released formate to carbon dioxide can cause pressure to build up in the injection vial.

Cefonicid Sodium, Sterile

Cefonicid Sodium (Monocid) is a second-generation cephalosporin that is structurally similar to cefamandole, except that it contains a methane sulfonic acid group attached to the N-1 position of the tetrazole ring. The antimicrobial spectrum and limited β-lactamase stability of cefonicid are essentially identical with those of cefamandole.

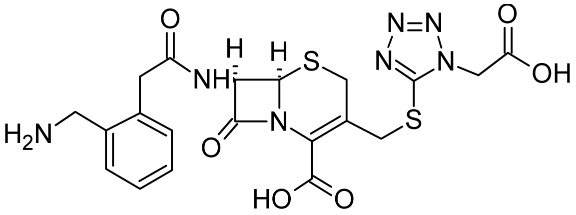


Cefonicid is unique among the second-generation cephalosporins in that it has an unusually long serum half-life of approximately 4.5 hours. High plasma protein binding coupled with slow renal tubular secretion are apparently responsible for the long duration of action. Despite the high fraction of drug bound in plasma, cefonicid is distributed throughout body fluids and tissues, with the exception of the cerebrospinal fluid.

Cefonicid is supplied as a highly water-soluble disodium salt, in the form of a sterile powder to be reconstituted for injection. Solutions are stable for 24 hours at 25°C and for 72 hours when refrigerated.

Ceforanide, Sterile

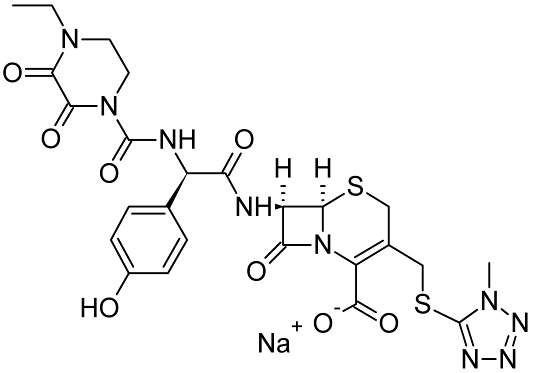
Ceforanide (Precef) was approved for clinical use in the United States in 1984. It is classified as a second-generation cephalosporin because its antimicrobial properties are similar to those of cefamandole. It exhibits excellent potency against most members of the Enterobacteriaceae family, especially *K. pneumoniae*, *E. coli*, *P. mirabilis*, and *Enterobacter cloacae*. It is less active than cefamandole against *H. influenzae*, however.



The duration of action of ceforanide lies between those of cefamandole and cefonicid. It has a serum half-life of about 3 hours, permitting twice-a-day dosing for most indications. Ceforanide is supplied as the sterile, crystalline disodium salt. Parenteral solutions are stable for 4 hours at 25°C and for up to 5 days when refrigerated.

Cefoperazone Sodium, Sterile

Cefoperazone (Cefobid) is a third-generation, antipseudomonal cephalosporin that resembles piperacillin chemically and microbiologically. It is active against many strains of *P. aeruginosa*, indole-positive *Proteus* spp., *Enterobacter* spp., and *S. marcescens* that are resistant to cefamandole. It is less active than cephalothin against Gram-positive bacteria and less active than cefamandole against most of the Enterobacteriaceae. Like piperacillin, cefoperazone is hydrolyzed by many of the β-lactamases that hydrolyze penicillins. Unlike piperacillin, however, it is resistant to some (but not all) of the β-lactamases that hydrolyze cephalosporins.



Cefoperazone is excreted primarily in the bile. Hepatic dysfunction can affect its clearance from the body. Although only 25% of the free antibiotic is recovered in the urine,