Update on Antimicrobial Agents

Review of the Pharmacology, Pharmacokinetics, and Clinical Use of Cephalosporins

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The cephalosporins have emerged as one of the most widely prescribed classes of antibiotics in the United States. The tremendous growth of this group of drugs has been accompanied by great confusion as to their appropriate use. Improper use of cephalosporins has resulted in bacterial resistance, clinical failures, and excessive costs. This article reviews the pharmacology of the cephalosporins and outlines their appropriate clinical use.

Spectrum

The cephalosporins are separated into 3 classes (generations) according to their spectrum of activity (Table I).

The currently available 1st-generation cephalosporins are cefazolin, cephapirin, and cephalothin for intravenous use and cephalexin, cephradine, and cefadroxil for oral use. All of these cephalosporins are similar in spectrum (Tables II and III). They are very active against gram-positive cocci. They have limited activity against gram-negative bacteria, although most strains of *Escherichia coli*, *Klebsiella* species, and *Proteus mirabilis* are sensitive. They are inactive against methicillin-resistant *Staphylococcus aureus* (MRSA) and methicillin-resistant *Staphylococcus epidermidis* (MRSE), as well as enterococci, *Listeria monocytogenes*, *Bacteroides fragilis*, *Citrobacter*, *Enterobacter*, *Proteus* (other than *mirabilis*), *Providencia*, *Pseudomonas*, and *Serratia* organisms. Gram-positive anaerobes such as *Peptostreptococcus* and non-penicillinase-producing *Bacteroides* species are usually susceptible.

The second-generation cephalosporins are cefamandole, cefonicid, ceforanide, and cefuroxime. Although cefoxitin, cefotetan, and cefmetazole are also included in this class, these agents are technically considered cephamycins because of their methoxy side chain at C7 (Fig. 1).[1] Cefaclor and cefuroxime axetil are the only orally available 2nd-generation cephalosporins. These antibiotics are usually active against the same organisms as the 1st-generation cephalosporins, but they have more activity against certain aerobic gram-negative bacteria and *Haemophilus influenzae*. Cefaclor is generally less active against gram-negative bacteria than the other agents. In vitro, cefmetazole and cefotetan have been shown to be slightly less active than cefoxitin against *Bacteroides* species,[2] especially those in the so-called "DOT" group (*B. distasonis*, *B. ovatus*, and *B. thetaiotaomicron*). Moreover, with the exceptions of cefamandole, cefuroxime, and cefmetazole, the 2nd-generation drugs are less active against staphylococci than the 1st-generation drugs. Second-generation cephalosporins are inactive against enterococci, *L. monocytogenes*, MRSA, MRSE, and *Pseudomonas* species. Cefotetan is more active than the other 2nd-generation agents against aerobic gram-negative bacilli.

Third-generation cephalosporins include cefoperazone, cefotaxime, ceftazidime, ceftizoxime, ceftriaxone, and moxalactam (a 1-oxa-β-lactam). The only orally available 3rd-generation cephalosporin is cefixime, which has an advantage over other oral cephalosporins because of its greater β-lactamase stability and its potent gram-negative coverage. It has poor activity against staphylococci and is only marginally active against pneumococci. The parenteral 3rd-generation cephalosporins are

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TABLE I. Classification of Cephalosporins

1st-Generation

Oral
- Cefadroxil (Duricef®, Ultracef®)
- Cephalexin (Keflex®)
- Cephradine (Anspor®, Velosef®)

Parenteral
- Cefazolin (Ancef®, Kefzol®)
- Cephalothin (Keflin®)
- Cephapirin (Cefadyl®)
- Cephradine (Velosef®)

2nd-Generation

Oral
- Cefaclor (Ceclor®)
- Cefuroxime axetil (Ceftin®)

Parenteral
- Cefamandole (Mandol®)
- Cefmetazole (Zefazone®)
- Cefonicid (Monocid®)
- Ceforanide (Precef®)
- Cefotetan (Cefotan®)
- Cefoxitin (Mefoxin®)
- Cefuroxime (Kefurox®, Zinacef®)

3rd-Generation

Oral
- Cefixime (Suprax®)

Parenteral
- Cefoperazone (Cefobid®)
- Cefotaxime (Claforan®)
- Ceftazidime (Fortaz®, Tazidime®, Tazicef®)
- Ceftizoxime (Cefizox®)
- Ceftriaxone (Rocephin®)
- Moxalactam (Moxam®)

generally less active against staphylococci susceptible to 1st-generation cephalosporins, but they have an expanded spectrum of activity against gram-negative bacteria. Ceftizoxime and cefotaxime exhibit some activity against *B. fragilis* and other anaerobes.[3,4]

Cefoperazone and, especially, ceftazidime are the only cephalosporins with reliable activity against *Pseudomonas aeruginosa*. The 3rd-generation cephalosporins (along with the 1st and 2nd generations) are inactive against enterococci, *L. monocytogenes*, MRSA, and MRSE.

Mode of Action and Pharmacodynamics

The cephalosporin antibiotics interfere with cell-wall synthesis of bacteria, leading to lysis of the infectious organism. To achieve this effect, the antibiotic must cross the bacterial cell wall and bind to the penicillin-binding proteins.[5] These proteins are actually enzymes (transpeptidases) involved in the cross-linking of peptidoglycan polymers. The cephalosporins' lack of activity against the enterococcus is due to the fact that these drugs bind poorly to the organism's penicillin-binding proteins. Furthermore, differences in binding to penicillin-binding proteins may explain the cephalosporins' differences in activity against *P. aeruginosa* and the various Enterobacteriaceae.[6]

The structure activity relationships of the cephalosporins account for their various spectra of activity and pharmacokinetic properties (Fig. 1). Differences in the side chain substitutions at position C7 alter the spectrum of activity and the degree of β-lactamase stability. Changes at the R2 side chain affect the

TABLE II. Antimicrobial Spectrum of Selected Cephalosporins against Gram-Positive Cocci

	Staphylococcus aureus	***Staphylococcus epidermidis***	***Streptococcus pneumoniae***	***Streptococcus pyogenes***	***Streptococcus agalactiae***
Cefazolin	+++	++	+++	+++	+++
Cephalexin	+++	+	+++	+++	++
Cefuroxime	+++	++	+++	+++	+++
Cefamandole	+++	++	+++	+++	+++
Cefaclor	++	0	+++	+++	+++
Cefotaxime	+++	++	+++	+++	+++
Cefoxitin	+++	0	++	+++	+++
Cefmetazole	+++	0	+++	+++	+++
Ceftizoxime	+++	++	+++	+++	+++
Cefoperazone	++	++	+++	+++	+++
Ceftazidime	0	0	++	++	++
Cefixime	0	0	+++	+++	+++

Interpretation: +++ = > 90% susceptible; ++ = 50-90% susceptible; + = < 50% susceptible; 0 = poor to no activity.

TABLE III. Antimicrobial Spectrum of Selected Cephalosporins against *Haemophilus, Bacteroides, P. aeruginosa,* and Enteric Gram-Negative Bacilli

	Escherichia coli	*Haemophilus influenzae*	*Bacteroides fragilis*	*Proteus vulgaris*	*Serratia* species	*Enterobacter cloacae*	*Citrobacter freundii*	*Pseudomonas aeruginosa*
Cefazolin	+++	++	0	0	0	0	0	0
Cephalexin	+++	++	0	0	0	0	0	0
Cefuroxime	++	+++	0	0	0	++	0	0
Cefamandole	+++	++	0	0	0	0	+	0
Cefaclor	+++	+++	0	0	0	0	0	0
Cefoxitin	+++	+++	++	++	0	0	0	0
Cefotetan	+++	+++	++	+++	+++	+	+++	0
Cefmetazole	+++	+++	++	+++	0	0	0	0
Cefotaxime	+++	+++	+	++	+++	++	+++	0
Ceftizoxime	+++	+++	++	+++	+++	++	+++	0
Cefoperazone	++	+++	+	++	++	++	+++	++
Ceftazidime	+++	+++	0	+++	+++	++	+++	+++
Cefixime	+++	+++	0	++	+	+	0	0

Interpretation: +++ = > 90% susceptible; ++ = 50-90% susceptible; + = < 50% susceptible; 0 = poor to no activity.

pharmacokinetic disposition and may produce toxicity. For example, the N-methylthiotetrazole moiety found in several cephalosporins (e.g., cefamandole, cefoperazone, and cefotetan) has been associated with hypoprothrombinemia and disulfiram-like reactions (see Adverse Reactions). Other structural alterations such as the addition of a methoxy group at position C7 (cephamycins) or the substitution of an oxygen for sulfur in the dihydrothiazine ring (moxalactam) increase the drugs' stability against hydrolysis by β-lactamases, including some types produced by *Bacteroides* species.[1]

The postantibiotic effect causes bacterial growth to be suppressed after a brief exposure to antimicrobial agents.[7] The precise mechanisms of this effect are unknown. Many antibiotics, including cephalosporins, produce a postantibiotic effect against gram-positive organisms; however, only aminoglycosides, fluoroquinolones, tetracycline, chloramphenicol, and rifampin reliably produce such an effect against gram-negative organisms. Cephalosporins have minimal or no postantibiotic effects against gram-negative bacteria.[8] According to experimental data generated in animals (especially those rendered neutropenic), the best results in the treatment of gram-negative infection occur when β-lactam serum (and tissue) concentrations are maintained at or above the minimal inhibitory concentration (MIC) for as much of the dosing interval as possible. Concentration-dependent killing is not found to occur. Achievement of a large serum (tissue) concentration-to-MIC ratio, however, may help prevent the emergence of resistance.[9]

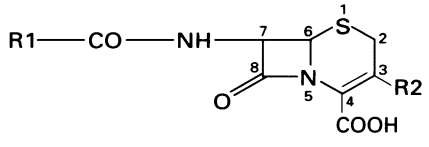

Fig. 1 *Cephalosporin structure.*

Mechanisms of Resistance

Resistance to cephalosporins results from a variety of mechanisms: β-lactamase production, alteration of penicillin-binding proteins, and alteration of the cell-wall permeability of gram-negative bacteria.[5]

Richmond-Sykes (RS) Type-1 β-lactamases are produced either inductively or constitutively. Inducible enzymes are found in *P. aeruginosa, Enterobacter, Serratia,* indole-positive *Proteus,* and *Citrobacter* species.[10] Induced production is transient and ceases when the inducing compound is removed from the system. Potent inducers of β-lactamase production are cefoxitin, imipenem, clavulanic acid, and ampicillin.[11,12]

Older (1st-generation) cephalosporins are relatively resistant to staphylococcal penicillinases, although recent data[13] suggest that cefazolin is less stable to hydrolysis by certain types of penicillinases than are other cephalosporins. Second- and (especially) 3rd-generation cephalosporins are very stable to hydrolysis by most commonly encountered β-lactamases of gram-negative bacteria. These include RS types II, III, IV, and V enzymes. Even though the

3rd-generation cephalosporins are relatively stable to RS Type-I enzymes in cell-free systems, the slow diffusion of these drugs across gram-negative cell-wall membranes leads to hydrolysis and, thus, inactivation of the cephalosporins. In a population of *Enterobacter cloacae*, for example, $1:10^6$ to 10^8 bacteria will constitutively produce enzymes in large quantities. This small number of organisms is difficult to detect, because standard MIC determinations test about 10^5 organisms and the resistant isolates may be missed. These mutants are highly resistant to 3rd-generation cephalosporins; when the susceptible members of the inoculum are eradicated by the addition of a cephalosporin, the resistant organisms overgrow—possibly resulting in clinical failure.[14-17] These resistant organisms may become stable in the environment and lead to hospital-wide resistance. Testing a larger inoculum of organisms ($> 10^7$), as suggested by Jimenez-Lucho,[18] may be 1 way to help detect these resistant colonies before the initiation of therapy.

Alterations of penicillin-binding proteins occur by means of genetic mutation and have been associated with β-lactam resistance in *S. aureus* (MRSA) and in *Streptococcus* species such as *S. faecium* (enterococcus).[6] Fortunately, this type of resistance is easily detectable with standard MIC techniques.

Cell-wall impermeability is often postulated as a means of resistance when other mechanisms have been discounted; nevertheless, there is evidence that the cell-wall structure of gram-negative (but not gram-positive) organisms may exclude certain cephalosporins or allow only slow diffusion across the outer membrane.[19]

Pharmacokinetics

Oral Cephalosporins (Table IV)

In general, the oral cephalosporins are absorbed rapidly and well. Cephalexin, cefadroxil, cephradine, and cefaclor are absorbed almost completely, whereas cefuroxime axetil and cefixime are absorbed to a lesser extent.[20] These agents achieve therapeutic concentrations in most tissues, including pleural and synovial fluids, and bone. Their degree of central nervous system penetration is not adequate to treat meningeal infections. In the gastrointestinal tract and in serum, cefuroxime axetil is rapidly hydrolyzed to cefuroxime—the active parent compound. Except for cefixime, the oral agents are primarily eliminated unchanged in the urine. Cefixime is excreted chiefly by nonrenal mechanisms,[20] so dosage adjustment is not necessary in cases of renal impairment. Because cephalexin, cephradine, and cefaclor have shorter half-lives than cefadroxil and cefuroxime axetil, they must be given every 8 hours instead of every 12 hours. The main advantage of cefixime is its long half-life, which allows administration once daily.

TABLE IV. Pharmacokinetic Parameters of Oral Cephalosporins

Antibiotic	Absorption (%)	Half-Life (hours)	CP_{max} (mg/L)	Renal Excretion (%)	Protein Binding (%)
Cephalexin	> 95	0.5-1.2	23.4	91	6-15
Cephradine	> 95	0.7-2.0	21.3	85	6-20
Cefadroxil	> 95	1.1-2.0	13.7	95	20
Cefaclor	> 95	0.5-1.0	13.1	50-80	25
Cefixime	40	3.0-4.0	4.8	18	67
Cefuroxime axetil	37-52	1.0-2.0	6.3	36	33-50

CP_{max} = maximum plasma concentration after oral administration

Parenteral Cephalosporins (Tables V and VI)

The parenteral cephalosporins can be given intravenously or intramuscularly. These drugs are widely distributed to the tissues and fluids, including the cerebrospinal, pleural, and synovial fluids and bone. Although the total excretion of most drugs in the bile is low, therapeutic concentrations of the cephalosporins are generally obtained if biliary obstruction is not present. Only cefoperazone and ceftriaxone are eliminated primarily in bile. Generally, only small amounts of the 1st- or 2nd-generation cephalosporins diffuse into the cerebrospinal fluid, even in the presence of inflamed meninges; however, cefotaxime, ceftazidime, ceftizoxime, ceftriaxone, and cefuroxime do achieve therapeutic concentrations in the cerebrospinal fluid, especially when the meninges are inflamed. The cephalosporins cross the placenta, and low concentrations are distributed into breast milk.[21]

Cefazolin, cefonicid, ceftazidime, ceftizoxime, and cefuroxime are minimally metabolized. Cefamandole nafate is rapidly hydrolyzed to its parent compound, cefamandole. Cephalothin, cephapirin, and cefotaxime are partially metabolized to a desacetyl metabolite, which has some antibacterial activity. Numerous reports have shown that the desacetyl metabolite of cefotaxime interacts synergistically in vitro with its parent compound, cefotaxime, against several types of bacterial strains, including anaerobes.[3,22-25] Ceftriaxone is partially metabolized to inactive products in the gastrointestinal tract. Cefoperazone is excreted primarily by biliary excretion; therefore, no dosage adjustment is necessary in patients with renal failure. Because of its high biliary concentrations, cefoperazone has been promoted for use in patients with biliary tract infections. For prophylaxis or treatment of sepsis from a biliary source, however, serum and

TABLE V. Pharmacokinetic Parameters of Parenteral Cephalosporins

Antibiotic	Half-Life (hours)	CP_{max} (mg/L)	Renal Excretion (%)	Protein Binding (%)	CSF Penetration (%)
1st-Generation					
Cefazolin	1.2-2.2	188	100	80	1.0-4.0
Cephalothin	0.5-1.0	30	60-95	65	0-50
Cephapirin	0.3-0.5	67	70-94	50	N/A
2nd-Generation					
Cefamandole	0.5-2.1	139	60-80	65-75	2.0-8.6
Cefuroxime	1.0-2.0	38-64	90-100	33-50	11.6-13.7
Cefoxitin	0.7-1.1	125	85	50-80	0.8-22
Cefotetan	2.8-4.6	79-132	80	76-91	28
Cefmetazole	1.0	130	85	85	N/A
3rd-Generation					
Cefoperazone	1.6-2.6	153	15-30	93*	0.8-11.5
Cefotaxime	0.9-1.7	102	40-60	13-38	4.0-54
Ceftazidime	1.4-2.0	69	80-90	5-24	14
Ceftizoxime	1.4-1.9	85	28-31	58-92	22.6
Ceftriaxone	5.4-10.9	23-150	33-67	93-96*	1.5-7.0

*Percentage of protein binding is dose dependent.

CP_{max} = maximum plasma concentration after administration by intravenous 15- to 30-min infusion; CSF = cerebrospinal fluid; N/A = not available

Table VI. Dosage Adjustment in Renal Failure

Drug	Dosage Interval in Patients with Normal Renal Function	Dosage Interval in Renal Failure Creatinine Clearance (mL/min)		
		>50	10-50	<10
1st-Generation				
Cefazolin	8	8	12	24-28
Cephalothin	6	6	6-8	12
Cephapirin	6	6	6-8	12
2nd-Generation				
Cefamandole	6	6	6-8	8
Cefuroxime	6-8	8	8-12	12
Cefoxitin	6-8	8	8-12	24-48
Cefotetan	12	12	24	48
Cefmetazole	6	12	24	48
3rd-Generation				
Cefoperazone	12	NA	NA	NA
Cefotaxime	6-8	6-8	8-12	12
Ceftazidime	8	8-12	24	48
Ceftizoxime	8	8-12	12	24-48
Ceftriaxone	12-24	NA	NA	NA
Moxalactam	8	8	12	12-24

NA = no adjustment

tissue concentrations—not biliary concentrations—are most important for effective therapy.[26] Except for cefonicid, ceftriaxone, and cefoperazone, the cephalosporins are usually removed by hemodialysis.

Adverse Reactions

In general, the cephalosporins produce few adverse effects. Hypersensitivity reactions are the most common sequelae, yet they are rare. Most of these reactions manifest as maculopapular skin rashes after several days of therapy; they may be accompanied by eosinophilia and fever. Anaphylactic reactions are uncommon with cephalosporins. Cross-hypersensitivity with penicillins probably occurs in less than 2% of patients;[27] therefore, it is generally considered safe to give cephalosporins to patients with a history of penicillin allergy. Nevertheless, cephalosporins should not be given to patients who have a well-documented history of anaphylactic reactions to penicillins. Skin rash, associated with fever and arthritis (serum sickness-like syndrome), has been observed during cefaclor therapy, but this reaction is rare.[28]

Coagulopathy has been reported during treatment with cefoperazone, moxalactam, cefotetan, cefmetazole, and cefamandole. Each of these cephalosporins contains an N-methylthiotetrazole (NMTT) side chain associated with hypoprothrombinemia. This reaction is more of a problem in debilitated, malnourished, or vitamin-K-deficient patients.[1]

Nichols and colleagues[29] compared the incidence of coagulopathy associated with ceftizoxime, cefotaxime, and moxalactam therapy in patients with serious infections. Overall, moxalactam was associated with a higher incidence of hypoprothrombinemia than ceftizoxime or cefotaxime; moreover, patients receiving moxalactam had a higher average increase in prothrombin time than those receiving the other agents.

The prolongation of prothrombin time appears to result from the NMTT side chain's interference with vitamin K metabolism in the liver. Vitamin K reverses the hypoprothrombinemia and is useful when given prophylactically in patients receiving these cephalosporins. Welage and coworkers[30] have studied the in vivo production and pharmacokinetic disposition of NMTT in healthy subjects receiving the various drugs containing this moiety. These investigators found that the greatest amount of in vivo NMTT production occurred after cefoperazone administration and that substantially less NMTT was produced after cefotetan therapy and especially after cefmetazole therapy. It is unknown, however, whether the amount of NMTT production correlates with either the frequency or the severity of the adverse effect.

Disulfiram is used in the therapy of alcoholism, because it inhibits the metabolism of the alcohol metabolite acetaldehyde. When disulfiram and alcohol are administered simultaneously, there is a buildup of acetaldehyde, which results in flushing, headache, nausea, and vomiting. A dimer formed from the NMTT side chain of the cephalosporins is structurally similar to disulfuram. Therefore, a similar reaction can occur when alcohol is ingested with cefoperazone, cefamandole, moxalactam, cefotetan, or cefmetazole. This disulfiram-like reaction seldom needs specific treatment, but patients must be cautioned not to consume alcoholic beverages or take alcohol-containing medications for a few days after treatment with these cephalosporins.[31]

Renal dysfunction has been reported after cephalosporin use, with transient increases in blood urea nitrogen and serum creatinine levels. Cephaloridine was 1st implicated as a cause of nephrotoxicity in 1965.[32] In the presence of other complicating factors, high doses (> 12 g/day) of cephalothin can induce renal damage in humans. Cefazolin and cefamandole can induce proximal tubular necrosis in humans and have proved to be mildly nephrotoxic in rabbits.[33] Experimental data suggest that cephalexin, cephapirin, cefoxitin, cefoperazone, and cefotaxime can alter renal function, but this effect has only rarely been reported clinically. It has been suggested that cephalosporins may enhance the nephrotoxicity of aminoglycosides. This effect has been observed only during cephalothin therapy, however, and the trials involved actually supported the notion that penicillins offer protection from aminoglycoside toxicity, rather than supporting the notion that cephalosporins enhance nephrotoxicity.[34]

Hepatic damage has been noted, with transient increases in serum glutamic-oxaloacetic transaminase (SGOT), serum glutamic-pyruvic transaminase (SGPT), and alkaline phosphatase levels during treatment. Increased bilirubin and lactate dehydrogenase (LDH) levels have also been reported. Isolated cases of hepatomegaly have been observed during cephradine treatment. These hepatic effects are generally mild and reversible upon discontinuation of the drug.[35]

When gastrointestinal reactions such as nausea, vomiting, and diarrhea occur, they usually result from oral therapy. Tally and associates[36] have reported that cefixime causes diarrhea in 13.4% of recipients and stool changes in 12.8%. These numbers are significantly higher ($p < 0.0005$) than those associated with amoxicillin. In about half of the cefixime-treated patients who develop diarrhea, therapy must be discontinued. Other cephalosporins, especially cefoperazone, can also produce diarrhea and stool changes; however, these effects are usually mild and transient, and only rarely necessitate discontinuation of treatment. *Clostridium difficile* toxin-associated diarrhea can occur during cephalosporin therapy and appears to be more common with cefoxitin. A cholecystitis-

like syndrome, caused by formation of biliary sludge, has been observed occasionally during ceftriaxone therapy; the mechanism is not well understood, but it may result from precipitation of the calcium salt of ceftriaxone in the gallbladder.[35]

Local reactions after intravenous or intramuscular administration are common. Those associated with intramuscular injection include pain, tenderness, and induration. These effects appear to be less severe with cefamandole, cefazolin, ceforanide, ceftazidime, ceftriaxone, and cephapirin. Phlebitis and thrombophlebitis occur only rarely with intravenous administration.

Clinical Use

Oral Cephalosporins

Cephradine, Cefadroxil, Cephalexin, and Cefaclor. These 4 agents are indicated for the treatment of acute and chronic upper and lower respiratory tract infections related to *Streptococcus pneumoniae*, *H. influenzae*, *Klebsiella pneumoniae*, *S. aureus*, and *Streptococcus pyogenes*. These drugs are also useful for otitis media caused by β-lactamase-producing *H. influenzae* and *Branhamella catarrhalis*. In the treatment of infections produced by susceptible bacteria, however, these cephalosporins should be reserved as 2nd or 3rd choices, since they are not superior to other agents such as ampicillin and trimethoprim/sulfamethoxazole. Use of either erythromycin/sulfamethoxazole or amoxicillin/clavulanic acid is as efficacious and potentially less expensive than the use of oral cephalosporins against ampicillin-resistant strains of *H. influenzae* and *B. catarrhalis*.[20] The oral cephalosporins are often used in the treatment of skin and skin-structure infections that may be due to streptococci or staphylococci. These drugs are also valuable in treating urinary tract infections related to *E. coli*, *Klebsiella*, and indole-negative *Proteus* species in patients who cannot tolerate a penicillin or sulfonamide.

Cefuroxime Axetil. Compared to the older cephalosporins, cefuroxime axetil has increased activity in vitro against *E. coli* and other Enterobacteriaceae. It is as efficacious as cefaclor, amoxicillin/clavulanic acid, and cephalexin in the treatment of urinary tract infections. Cefuroxime axetil may be useful for uncomplicated urinary tract infections that are resistant to less expensive drugs, but serious urinary tract infections require other forms of therapy.[37]

Although cefuroxime axetil has exhibited activity against the major pathogens involved in otitis media, the lack of an oral liquid formulation limits the drug's use in the pediatric population, which most commonly experiences this type of infection.[37]

Cefuroxime axetil is not superior to amoxicillin/clavulanic acid or penicillin V in the treatment of upper respiratory tract infections; its role in lower respiratory tract infections remains unclear.[37]

Combined with probenecid, cefuroxime axetil is effective in a single dose for uncomplicated urethral, endocervical, and rectal gonorrhea.[38] It offers no advantages over other antimicrobial agents for skin and soft-tissue infections or for pharyngitis.

Cefixime. The 1st orally-administered 3rd-generation cephalosporin to be marketed in the United States, cefixime is structurally similar to cefotaxime. Once-daily administration has been effective in treating pharyngitis, acute otitis media, bronchitis, and urinary tract infections caused by susceptible pathogens.[39]

In otitis media infections, cefixime's efficacy is similar to that of cefaclor[40] and amoxicillin,[41] although cefixime treatment is accompanied by more gastrointestinal complaints. In comparison with amoxicillin, cefixime is somewhat more effective against *H. influenzae* and *B. catarrhalis* middle-ear infections, but is less active against *S. pneumoniae*.[42] On the basis of current evidence, cefixime does not appear to offer any clear advantages over older antimicrobial agents for treating otitis media. Moreover, the high frequency of diarrhea accompanying such therapy limits cefixime's use in the pediatric population.

Because of its limited coverage of *S. pneumoniae*, cefixime may be less effective than amoxicillin for the treatment of bacterial bronchitis.[43]

Compared with other oral cephalosporins, cefixime has excellent in vitro activity against *E. coli* and other Enterobacteriaceae, so it should be effective for uncomplicated urinary tract infections. Cefixime has proved as effective as amoxicillin for treating urinary tract infections in adults.[44] Nevertheless, because of its high cost and adverse gastrointestinal effects, cefixime should be used only when other less expensive, equally appropriate antimicrobial agents cannot be given.

First-Generation Parenteral Cephalosporins

The 1st-generation cephalosporins are widely administered both preoperatively and postoperatively for clean, contaminated procedures such as cholecystectomy, vaginal hysterectomy, and cesarean section. These agents are also commonly used in patients undergoing clean operations such as cardiovascular or arthroplasty procedures, in which infection would result in substantially increased morbidity or mortality.[45]

The 1st-generation cephalosporins are alternative agents for treating soft-tissue and other infections caused by *Staphylococcus aureus* or *Streptococcus pyogenes*. Depending on the results of susceptibility tests, these agents may be used to treat serious lower respiratory tract, bone, and joint infections, as well as

bacteremias. Because of their narrow gram-negative coverage and relatively high cost, however, the value of 1st-generation cephalosporins in urinary tract infections is limited. Nevertheless, they are useful against *E. coli*, *Proteus*, or *Klebsiella* urinary tract infections when ampicillin or trimethoprim/sulfamethoxazole cannot be given. The 1st-generation cephalosporins are not helpful in patients with meningitis, since these agents do not achieve therapeutic concentrations in the cerebrospinal fluid.

Cefazolin. Cefazolin is generally preferred over other 1st-generation cephalosporins because of its longer half-life and higher serum concentrations. There are data to suggest, however, that cefazolin is more β-lactamase labile than cephalothin.[13] The clinical significance of this finding is unclear, but if a 1st-generation agent is to be used for a serious staphylococcal infection (e.g., endocarditis), cephalothin or cephapirin may be preferable.

Second-Generation Parenteral Cephalosporins

Cefoxitin. Cefoxitin is active against the *B. fragilis* group, as well as many gram-negative and gram-positive bacteria. Therefore, cefoxitin is valuable in treating intraabdominal and pelvic infections, since these are generally polymicrobial, involving gram-negative enteric bacilli and anaerobic bacteria. Cefoxitin is also commonly used as a prophylactic agent in patients undergoing colorectal or pelvic surgery. By itself, the drug appears to be as effective as the combination of clindamycin and an aminoglycoside in mild to moderately ill patients with community-acquired intraabdominal infections.[36,46-49] Cefoxitin plus doxycycline is preferred for women with pelvic inflammatory disease, because this regimen provides coverage against *Neisseria gonorrhoeae*, the Enterobacteriaceae, anaerobic bacteria, and *Chlamydia* species.

Cefoxitin has been valuable in treating uncomplicated and disseminated gonococcal infections caused by penicillinase-producing *N. gonorrhoeae* (PPNG) strains. However, the 3rd-generation cephalosporin ceftriaxone is generally more active and is therefore preferred.[50]

Cefoxitin may be prescribed for serious lower respiratory tract, urinary tract, bone, joint, skin, and soft-tissue infections or for bacteremias, provided that the organisms are susceptible and that agents equally efficacious, less toxic, and less expensive are unavailable. Cefoxitin has a fairly short half-life and therefore is given every 6 hours.

Cefotetan. Cefotetan has proved effective in treatment of intraabdominal, obstetric and gynecologic, skin and soft-tissue, complicated urinary tract, and lower respiratory tract infections caused by susceptible bacteria.[51] Less clinical experience has been gained with cefotetan than with cefoxitin, but the 2 drugs have proved comparable for the treatment of community-acquired intraabdominal infections in moderately ill patients,[52] as well as for obstetric and gynecologic infections,[53] skin and superficial soft-tissue infections,[54] and prophylaxis in colorectal surgery.[55] Thus, cefotetan appears to be an alternative to cefoxitin for these infections, which are frequently polymicrobial. Compared to cefoxitin, cefotetan has a wider spectrum of activity against aerobic gram-negative bacilli and a longer elimination half-life, which allows twice-daily administration. A possible disadvantage is cefotetan's NMTT side chain, as discussed earlier. Moreover, cefotetan is less active than cefoxitin against staphylococci.

Cefmetazole. Cefmetazole is as efficacious as cefoxitin for the treatment of intraabdominal and gynecologic infections.[56] Cefmetazole is also equally efficacious for surgical prophylaxis.[56-58] Therefore, cefmetazole appears to be an acceptable alternative to cefoxitin and cefotetan, although clinical experience with this agent has been very limited in the United States. Compared to cefoxitin, cefmetazole's only advantage is a longer half-life, which allows it to be administered 3 times daily. Alternatively, cefotetan can be administered twice daily, and its activity in vitro against aerobic gram-negative bacilli is superior to that of cefmetazole. Although cefmetazole is very active against staphylococci, the utility of this activity is unclear. Cefmetazole also has the NMTT side chain, but coagulopathy has been reported only rarely.

Cefamandole. Cefamandole's value is limited because of its narrow activity and heightened potential for adverse effects. Nevertheless, it can be used for respiratory tract, urinary tract, skin, bone, and joint infections caused by susceptible bacteria, provided that equally efficacious, less toxic alternatives are unavailable. Because of cefamandole's greater stability to penicillinases, some authorities believe that it is superior to cefazolin for cardiovascular surgical prophylaxis. The data concerning this application are conflicting.

Cefamandole has been used as an alternative to ampicillin and chloramphenicol for infections caused by *H. influenzae*, but clinical failures have been reported.[59] This is due to the drug's relative instability to β-lactamases. Cefamandole is not effective in the treatment of meningitis: its penetration into the cerebrospinal fluid is limited, resulting in breakthrough meningitis in patients being treated for periorbital cellulitis or epiglottitis.[59,60]

Cefuroxime. Cefuroxime is widely prescribed for community-acquired infections such as pneumonia, and for bone and joint infections. The drug is active against *H. influenzae* type B (including β-lactamase-producing strains), pneumococci, *Streptococcus pyogenes*, and *Staphylococcus aureus*. Because of its

coverage of *H. influenzae* and its degree of penetration into the cerebrospinal fluid, it has also been used to treat meningitis in the pediatric population. However, reports of delayed sterilization of the cerebrospinal fluid, treatment failure, and relapse in patients with *H. influenzae* type-B infection[61-63] have raised concerns about the use of cefuroxime in meningeal infections. Third-generation cephalosporins are considered superior to earlier generations for meningeal infections because of their greater potency, superior penetration, and resultant higher bactericidal titers in the cerebrospinal fluid.

Cefonicid. Structurally similar to cefamandole, cefonicid has the longest elimination half-life among the 1st- and 2nd-generation cephalosporins, therefore allowing once-daily administration. It has been prescribed for mild to moderately severe infections, including community-acquired pneumonias, urinary tract infections, and skin and soft-tissue infections.[64] Published comparative clinical studies are somewhat limited to date. There is concern over the efficacy of cefonicid in serious *S. aureus* infections such as endocarditis, since the drug's use has resulted in failures.[65] Cefonicid is not recommended for the treatment of meningitis. The drug holds no meaningful advantages over other cephalosporins.

Third-Generation Parenteral Cephalosporins

Cefotaxime and Ceftizoxime. Cefotaxime is a preferred agent in the treatment of meningitis caused by susceptible gram-negative bacilli (*E. coli*, and *Klebsiella* and *Proteus* species). The drug is effective against meningitis caused by β-lactamase-producing *H. influenzae* type B and is as effective as ampicillin in combination with chloramphenicol.[66] It is active against *H. influenzae*, *Neisseria meningitidis*, and *S. pneumoniae*—the organisms that commonly cause meningitis in infants and young children—and therefore is often used for empiric therapy of meningitis in these age groups. Ampicillin is given in combination with cefotaxime for coverage of *L. monocytogenes*. The role of ceftizoxime in treating meningitis caused by *H. influenzae* and susceptible enteric gram-negative bacilli looks promising, but clinical experience has been more limited with ceftizoxime than with cefotaxime.

Cefotaxime and ceftizoxime are effective against serious gram-negative bacillary infections such as lower respiratory tract, complicated urinary tract, intraabdominal, and gynecologic infections; skin, bone, and joint infections; and bacteremias. These drugs are also useful against infections caused by organisms resistant to penicillins or older cephalosporins; as alternatives to aminoglycosides in some cases; and in infections resulting from *K. pneumoniae* against which 3rd-generation cephalosporins are the most active agents.[67-69] Because ceftizoxime and cefotaxime provide some anaerobic coverage, they have an advantage over other 3rd-generation cephalosporins. One advantage of ceftizoxime is its longer elimination half-life, which allows for 8- to 12-hour dosing intervals, compared to the 4- to 6-hour intervals necessary with cefotaxime.

All 3rd-generation cephalosporins are subject to rapid development of resistance during therapy for infections related to *Enterobacter*, *Citrobacter*, or *Serratia* organisms.[70] Therefore, these agents should be used judiciously.

Ceftriaxone. Ceftriaxone's long half-life allows once-daily dosing, which gives this agent a potential advantage over other 3rd-generation cephalosporins. Its activity is excellent against *N. gonorrhoeae*, including PPNG, chromosomally-mediated resistant *N. gonorrhoeae*, and tetracycline-resistant *N. gonorrhoeae*. A single 250-mg intramuscular dose can be highly effective against uncomplicated gonorrhea (including urethral, endocervical, anorectal, and pharyngeal forms) in adults.[71,72] Ceftriaxone is also effective in the treatment of chancroid.[73]

Because ceftriaxone is highly active against pathogens that cause meningeal infections in infants and young children (*H. influenzae*, *N. meningitidis*, and *S. pneumoniae*), it is used instead of ampicillin plus chloramphenicol for empiric therapy.[74-78]

Ceftriaxone is commonly prescribed for empiric monotherapy against lower respiratory tract, complicated urinary tract, skin, bone, and joint infections, as well as bacteremias secondary to organisms resistant to older cephalosporins. Once-daily ceftriaxone therapy has proved as efficacious in serious bacterial infections as cefotaxime, given every 4 to 8 hours.[79,80]

Ceftriaxone and other 3rd-generation cephalosporins have been used successfully to treat salmonellosis caused by ampicillin- and chloramphenicol-resistant strains.[81] Ceftriaxone may also be useful for eradicating pharyngeal carriage of *N. meningitidis*.[82]

Because ceftriaxone permits once-daily dosing, it is commonly used in the outpatient setting.

Ceftazidime. Ceftazidime's primary advantage over other cephalosporins is its activity against *P. aeruginosa*. Although ceftazidime has this advantage over cefoperazone, it has less activity against staphylococci than the other cephalosporins and generally should be combined with antistaphylococcal agents for empiric therapy.

Because of its superior antipseudomonal activity, ceftazidime is frequently used for empiric therapy in neutropenic patients with unexplained fever. It should be combined with an aminoglycoside in febrile patients with profound neutropenia (< 100/mm^3) or in those infected with *P. aeruginosa*.[83,84] Ceftazidime appears to be valuable against hospital-acquired gram-negative infections,[85] but its useful-

ness for single-therapy treatment of intraabdominal and gynecologic infections is limited because of its lack of activity against the *Bacteroides* species. In some studies, breakthrough infections with gram-positive bacteria have been frequent when ceftazidime was used alone.[86,87]

Ceftazidime has excellent penetration into the cerebrospinal fluid and may, therefore, be useful against *P. aeruginosa* meningitis;[88] however, clinical studies in this area are lacking. Ceftazidime is also used in treating meningitis caused by gram-negative enteric bacilli such as *E. coli*, and by *Klebsiella* and *Proteus* species,[89] but experience with cefotaxime is more extensive.

Like other 3rd-generation cephalosporins, ceftazidime is not indicated for infections that can be treated effectively with less-expensive, narrower-spectrum 1st- or 2nd-generation cephalosporins.

Cefoperazone. Cefoperazone has better activity against *P. aeruginosa* than the other 3rd-generation cephalosporins, except ceftazidime. Nevertheless, cefoperazone is not recommended as the sole therapy of serious *P. aeruginosa* infections.[90]

The drug has been effective in treating lower respiratory tract, complicated urinary tract, skin, bone, and joint infections, as well as bacteremia.[90-93] Compared with other 3rd-generation cephalosporins, however, cefoperazone has inferior in vitro activity against most Enterobacteriaceae and is associated with more undesirable sequelae (see Adverse Reactions). Moreover, cefoperazone exhibits a variable degree of penetration into the cerebrospinal fluid and therefore should not be used for meningitis.

Cefoperazone offers no advantage over the other 3rd-generation cephalosporins in the treatment of biliary tract infections (see Pharmacokinetics).

Moxalactam. Moxalactam's clinical use is questionable because the drug has been associated with a high incidence of serious bleeding episodes (some involving fatalities) in a number of patients.[94,95] With

TABLE VII. Investigational Cephalosporins

Drug	Administration	Advantage(s)	Potential Indications	Comments
BMY 28100 (Cefprozil)	Oral	Excellent GPC and GNB coverage including *H. influenzae, Klebsiella* species, and *E. coli*; no *B. fragilis* or *P. aeruginosa* coverage	Otitis media, skin and soft-tissue infections, and lower respiratory tract infections	Similar to cefaclor for GNB; superior to cefaclor for GPC
LY 164846 (Loracarbef)	Oral	β-lactamase stable; good activity against respiratory pathogens; no *B. fragilis* or *P. aeruginosa* coverage	Oral therapy of respiratory-tract infections	Comparable to cefaclor
SCH 39720 (Ceftibuten)	Oral	β-lactamase stable; very active against GNB and poor against *Staphylococcus*, anaerobes, *P. aeruginosa*, and enterococci	Oral therapy of infections involving GNB and some GPC	Similar to cefixime but broader spectrum
Cefpodoxime	Oral	Broad spectrum against GPC, GNB, MSSA, *E. coli, Streptococcus, H. influenzae, B. catarrhalis*, and *Proteus* species	Oral therapy of infections involving GNB and GPC (not MRSA or MRSE)	Inoculum effect with β-lactamase plus *H. influenzae*
BMY 28142 (Cefepime)	Parenteral	β-lactamase stable; broad spectrum antibiotic against GPC and GNB, including *P. aeruginosa*	Bacteremia; skin/soft-tissue and lower respiratory tract infections	Better activity against *Enterobacter* species than other currently available drugs
HR 810 (Cefpirome)	Parenteral	β-lactamase stable; as active as 1st-generation cephalosporins against GPC, and highly active against GNB	Bacteremia; skin/soft-tissue and lower respiratory tract infections	Similar to ceftazidime

GPC = gram-positive cocci, GNB = gram-negative bacilli; MSSA = methicillin-sensitive *Staphylococcus aureus*; MRSA = methicillin-resistant *Staphylococcus aureus*; MRSE = methicillin-resistant *Staphylococcus epidermidis*

the availability of other, less toxic cephalosporins, its usefulness has greatly diminished, and it should probably no longer be prescribed.

Investigational Agents

Table VII provides a brief list of cephalosporins undergoing development. For the most part, these are duplicative agents designed to capture a share of the vast cephalosporin market. A few of these new agents, however, notably cefepime and ceftibuten, offer important advances with regard to spectrum of activity, pharmacokinetics, or both. Numerous other compounds are being developed whose introduction into the marketplace will no doubt enhance the potential for confusion.

Conclusion

The cephalosporins are the most commonly prescribed antimicrobial agents in the United States. These clinically "attractive" compounds offer a broad spectrum of activity, relative safety, and proven effectiveness. Because of some subtle, as well as major, differences in the individual cephalosporins' pharmacologic and microbiologic characteristics, however, physicians must understand these agents thoroughly in order to apply them optimally.

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